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DISCHARGE OF VAGAL PULMONARY RECEPTORS DIFFERENTIALLY ALTERS NEURAL ACTIVITIES DURING VARIOUS STAGES OF EXPIRATION IN THE CAT

BY WALTER M. ST JOHN AND DAN ZHOU

From the Department of Physiology, Dartmouth Medical School, Hanover, NH 03756, USA

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SUMMARY

1. The purpose was to evaluate the hypothesis that neural expiration is composed of two phases: I, a post inspiratory period; and II, the period at which expiratory activities of spinal nerves reach peak values. We hypothesized that the discharge of pulmonary stretch receptors might differentially alter neural activities during these two phases.

2. Activities of the phrenic nerve, intercostal nerve and nerves innervating the thyroarytenoid muscle of the larynx and triangularis sterni muscle of the chest wall were recorded in decerebrate and paralysed cats.

3. The experimental animals were ventilated with a servo-respirator which produced changes in tracheal pressure, and lung volume, in parallel with alterations in integrated activity of the phrenic nerve.

4. In order to assess the influence of the discharge of slowly adapting pulmonary stretch receptors upon neural activities during expiration, lung volume was held at end-expiratory or end-inspiratory levels for individual respiratory cycles.

5. When pulmonary inflation was prevented, phrenic activity increased, as did activity of the thyroarytenoid nerve during early expiration. In contrast, activities of the triangularis sterni and intercostal nerves during mid- to late expiration declined.

6. Holding the lungs at end-inspiratory levels caused a reduction of thyroarytenoid activity and increases in peak triangularis sterni and intercostal activities. Neural expiration typically continued as long as the lungs were maintained at the end-inspiratory level.

7. Responses were qualitatively similar in hypocapnia, normocapnia and hypercapnia, but the magnitude of changes in neural activities was typically augmented with elevations in end-tidal fractional concentrations of CO_2.

8. We conclude that the discharge of slowly adapting pulmonary stretch receptors inhibits neural activities during early expiration and augments activities during mid- to late expiration. Hence, our data support the concept that neural expiration is composed of two stages in which neural activities may be differentially controlled.

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INTRODUCTION

In a model for the neural control of ventilatory activity, Richter (1982) has proposed that expiration be divided into two phases. Phase I is considered to correspond to the period of post-inspiratory activity of the diaphragm and laryngeal adduction. Peak activity of expiratory spinal nerves occurs during phase II. Neural activities during these two phases of expiration are hypothesized to be differentially controlled (Richter, 1982; Remmers, Richter, Ballantyne, Bainton & Klein, 1986; Richter, Ballantyne & Remmers, 1986). This hypothesis has received support from recent studies in this laboratory (St John & Zhou, 1989).

As indices of phases I and II, we recorded activities of the nerves innervating the thyroarytenoid muscle of the larynx, a primary adductor, and the triangularis sterni muscle of the chest wall. When phrenic activity was prematurely terminated by stimulations of the superior laryngeal nerve or pontile pneumotaxic centre, thyroarytenoid activity typically rose while that of the triangularis sterni fell. Stimulations of the superior laryngeal nerve during phase I retarded expiration in this phase; a normal period of triangularis sterni activity followed the termination of stimulation (St John & Zhou, 1989).

The appropriateness of thyroarytenoid and triangularis sterni activities as indices of phase I and phase II is discussed in our report (St John & Zhou, 1989). Briefly, while Richter and his colleagues had defined phase I from the depolarizations of post-inspiratory medullary respiratory neurons, these depolarizations parallel those of motoneurons innervating the thyroarytenoid (see discussion in Remmers *et al.* 1986). Since the discharge of these post-inspiratory medullary respiratory neurons is envisaged to inhibit the discharge of expiratory bulbospinal neurons, triangularis sterni activity would represent phase II since it only commences in mid- to late expiration. However, it must be emphasized that the total durations of thyroarytenoid and triangularis discharges cannot be considered as exact determinants of the durations of phase I and phase II since these discharges may overlap (Fig. 1).

The present study was undertaken to further evaluate the control of neural activities during the two phases of expiration. In decerebrate cats, changes in the pattern of lung inflation and, hence, the discharge of pulmonary stretch receptors were found to alter differentially thyroarytenoid and triangularis sterni activities. These changes in thyroarytenoid activity confirm and extend those of our previous study (Huang, Zhou, St John & Bartlett, 1989) and an earlier report in which laryngeal motoneuronal activities were recorded (Barillot & Dussardier, 1976). These data support the concept of two separate phases comprising neural expiration.

METHODS

Sixteen adult cats of either sex were used. The surgical preparation has been described in detail previously (St John, 1979; Huang *et al.* 1989; St John & Zhou, 1989). Under halothane anaesthesia, the trachea was cannulated and catheters were placed in femoral arteries and veins. The brain stem was transected at an intercollicular level (Kirsten & St John, 1978); halothane anaesthesia was then discontinued. The following nerves were exposed and sectioned, and their activities recorded by procedures described previously: phrenic nerve, branch of the recurrent laryngeal nerve innervating the thyroarytenoid muscle, branch of the intercostal nerve innervating the triangularis

sterni, internal intercostal nerve (St John, 1979; Gauthier, Barillot & Dussardier, 1980; Huang *et al.* 1989; Zhou, Huang, St John & Bartlett, 1989; St John & Zhou, 1989). Neural activities were integrated by identical resistance–capacitance circuits.

The animals were paralysed and artificially ventilated by a servo-respirator described previously (Daubenspeck, Pichon, Bartlett & St John, 1989). This servo-respirator produced changes in tracheal pressure and lung volume in parallel with changes in integrated activity of the phrenic nerve. Since animals had bilateral pneumothoraces as a result of exposures of the intercostal nerves, the respirator was initially adjusted so that a positive end-expiratory pressure (PEEP) of approximately 2 cmH_2O was maintained. The initial volume delivered by the respirator was such as to produce an end-tidal fractional concentration of CO_2 (F_{ET,CO_2}) which was at a slightly hypocapnic level of 0·04; the inspired gas was 100% O_2. To produce normocapnia (F_{ET,CO_2} of approximately 0·05) or hypercapnia, CO_2 was added to the inspired gas. With any elevations of F_{ET,CO_2}, peak phrenic activity rose as did tracheal pressure and the volume of lung inflation.

Tracheal pressure, F_{ET,CO_2}, arterial blood pressure and rectal temperature were monitored as described previously (St John, 1979). Mean arterial pressure was at least 80 mmHg with a solution of metaraminol and dextran being infused intravenously, if required, to raise pressure. Rectal temperature was maintained at 37–39 °C by heating pads.

At each level of F_{ET,CO_2}, neural activities were recorded during control ventilatory cycles in which the lungs were inflated. These activities were also recorded during cycles in which inflation was held at the end-expiratory (no inflation) and end-inspiratory (maintained inflation) levels. There were approximately five of these inflation and non-inflation manoeuvres at each level of F_{ET,CO_2}; a minimum of ten control cycle intervened between any of these manoeuvres.

Data were analysed by a laboratory computer. Neural activities were quantified for the first ventilatory cycle without pulmonary inflation or with maintained inflation and for the preceding cycle during which inflation had been delivered. For phrenic activity, the time between the onset to the rapid decline of activity (neural inspiration T_I) and the time to the next onset of phasic discharge (neural expiration T_E) were determined, as was the peak integrated height. For the other neural activities, the following were determined: the peak heights, the times of onset of phasic activity during neural expiration, and the durations of phasic activities. In addition, for activity of the whole intercostal nerve, maximum values of peak integrated activity during phase I (the period of thyroarytenoid activity) and phase II (the period of triangularis sterni activity) were determined. For trials in which no thyroarytenoid or triangularis sterni activity could be discerned, phase I was considered to be the period prior to the commencement of triangularis sterni activity and phase II the period after the termination of thyroarytenoid discharge. As noted in the Introduction, such determinations of the durations of phase I and phase II can only be considered as approximate due to the slight overlap of thyroarytenoid and triangularis sterni activities in some animals. Since there were trials in which no phasic neural activities could be discerned, integrated neural activities have been expressed as a percentage of the maximum levels attained; separate maxima were defined for trials of non-inflation and maintained inflation.

Statistical evaluations of data were by the non-parametric Wilcoxon test and one-way analysis of variance. Statistical significance was taken as $P < 0·05$.

RESULTS

Examples of the discharge patterns of the phrenic and intercostal nerves and nerves to the thyroarytenoid and triangularis sterni muscles are shown in Fig. 1. Exclusive of the intercostal activity, which was recorded in twelve animals, all other neural activities were recorded in the sixteen experimental animals.

During cycles with lung inflation at F_{ET,CO_2} of 0·04, phasic phrenic and intercostal activities could be discerned in all animals whereas phasic thyroarytenoid activity was found for eleven of sixteen cats and phasic triangularis sterni activity was recorded in thirteen of sixteen animals. For all animals, the positive-end expiratory pressure (PEEP) averaged $2·3 \pm 0·4$ cmH_2O (mean ± S.E.M.); the peak pressure at end-inspiration averaged $5·0 \pm 0·5$ cmH_2O.

For these cycles with lung inflation, thyroarytenoid activity commenced immediately upon the fall of phrenic activity from its peak level. This phase of thyroarytenoid activity was concomitant with post-inspiratory phrenic discharge (Fig. 1*A*). Such post-inspiratory discharge was also observed in trials for which there

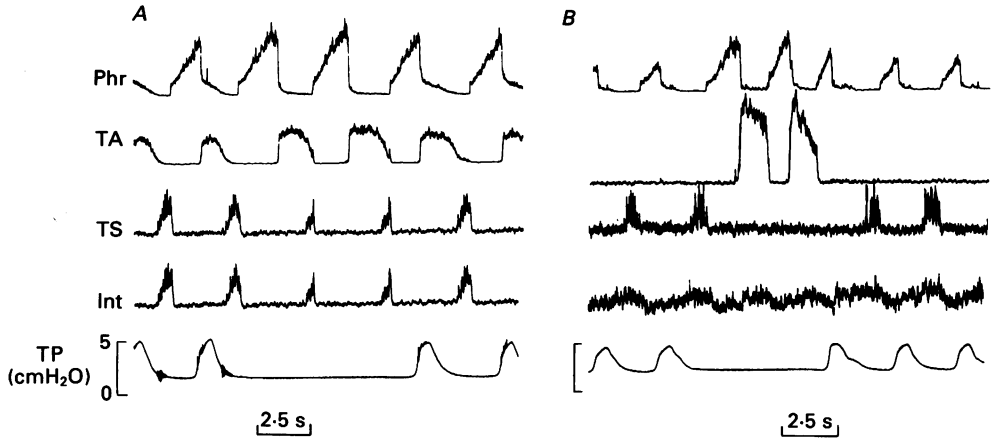

Fig. 1. Alterations of inspiratory and expiratory neural activities upon withholding phasic lung inflation. Records were obtained at end-tidal fractional concentrations of CO_2 (F_{ET,CO_2}) of 0·04 in two decerebrate cats (*A* and *B*). Note that peak thyroarytenoid (TA) activity during the early portion of neural expiration rose during non-inflation cycles whereas peak activities during the late portion of expiration declined for the nerve to the triangularis sterni (TS) and the intercostal nerve (Int). Peak integrated phrenic activity (Phr) increased during the non-inflation cycles and its post-inspiratory activity declined. TP, tracheal pressure. Non-inflation is indicated by the absence of changes of tracheal pressure during periods of phrenic activity.

was no phasic thyroarytenoid discharge (Fig. 1*B*). Activity of the triangularis sterni did not begin until most or all of the phase of post-inspiratory phrenic activity and thyroarytenoid discharge had been completed. Intercostal discharge in some animals was distributed across all of neural expiration with peak activity being attained late in the phase.

Responses to withholding lung inflation

Upon withholding inflation (tracheal pressure = PEEP level of 2·3 cmH_2O) at F_{ET,CO_2} of 0·04, peak integrated phrenic activity and T_I both significantly increased, the latter to 147% of values during control cycles with inflations. Neither T_E (average of 83% of control) of T_{TOT} (100% of control) was systematically altered. Peak thyroarytenoid activity was increased significantly (Figs 1 and 2) and a phasic discharge became evident in three of the animals for which no such activity was recorded during cycles with lung inflations. Concomitant with such augmentations in thyroarytenoid activity, post-inspiratory activity of the phrenic nerve was greatly reduced or completely eliminated (Fig. 1).

As opposed to the changes in phrenic and thyroarytenoid activity, peak triangularis sterni activity declined significantly upon withholding lung inflation. Indeed, such phasic activity disappeared in one cat. Compared to cycles with

inflations, mean levels of intercostal activities rose during phase I and fell during phase II but these changes did not achieve statistical significance (Figs 1 and 2).

The proportion of T_E occupied by thyroarytenoid activity was significantly increased from 46% during inflation cycles to 77% during cycles in which

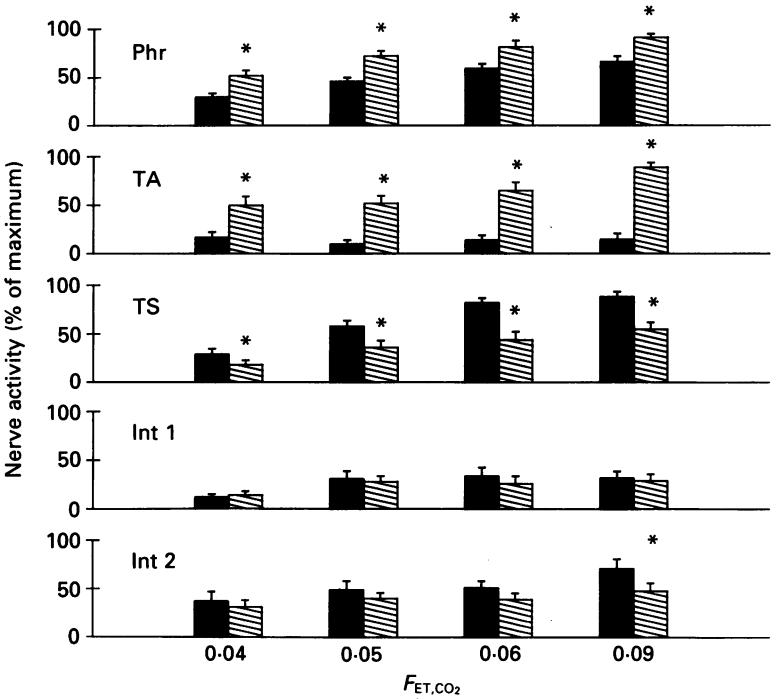

Fig. 2. Changes in inspiratory and expiratory neural activities upon withholding pulmonary inflations. Mean values and standard errors of values for peak integrated neural activities are shown at the designated levels of end-tidal fractional concentration of CO_2 (F_{ET,CO_2}). Phr, phrenic nerve activity; TA, thyroarytenoid activity; TS, triangularis sterni activity; Int 1, intercostal activity during phase I of expiration; Int 2, intercostal activity during phase II of expiration. Filled bars are values during cycles with lung inflations; hatched bars are non-inflation cycles. * = $P < 0{\cdot}05$ compared to cycles with lung inflations. Neural activities were recorded in sixteen cats, except for intercostal activity which was recorded in twelve animals.

pulmonary inflation was withheld. Under similar experimental conditions, the mean duration of triangularis sterni discharge fell from 53 to 32% of T_E, but the decline did not achieve statistical significance. There were no significant changes in times of commencement of either thyroarytenoid or triangularis sterni activity for animals in which these nerves has phasic discharges both during cycles with and without inflations. The absence of significant changes for triangularis sterni activity reflected variability in data.

Results similar to those at F_{ET,CO_2} of 0·04 were also obtained at normocapnia and hypercapnia (Fig. 2). With elevations of F_{ET,CO_2} levels to 0·05, 0·06 and 0·09, peak tracheal pressure during control cycles increased to average values of 5·8, 6·2 and 6·2 cmH_2O, respectively. At each level of F_{ET,CO_2}, withholding lung inflation resulted

in significant rises of peak integrated phrenic and thyroarytenoid activities whereas peak triangularis sterni activity declined. These declines were such that phasic triangularis sterni activity disappeared in three cats at F_{ET,CO_2} of 0·05 and in one cat each at F_{ET,CO_2} levels of 0·06 and 0·09.

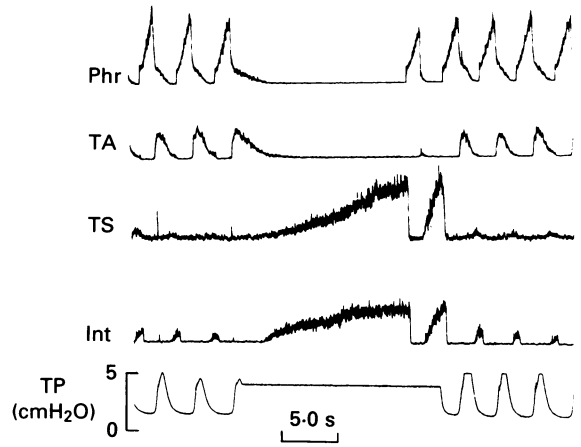

Fig. 3. Influence of sustained lung inflation upon inspiratory and expiratory neural activities. Records were obtained at F_{ET,CO_2} or 0·04 in a decerebrate cat. Note that sustained lung inflation caused a sustained expiratory phase marked by greatly augmented activities of the nerve to the triangularis sterni (TS) and the intercostal nerve (Int). Peak thyroarytenoid (TA) activity was slightly lower during this cycle with sustained inflation; phrenic (Phr) was similar to control levels. TP, tracheal pressure.

Changes in intercostal discharge phases I and II were not as consistent as those of the thyroarytenoid and triangularis sterni. Thus, for example, at F_{ET,CO_2} of 0·05, intercostal discharge during phase I rose in only half of the experimental animals; changes in phase II were more consistent with declines in discharge being observed in all but three cats. Similar results were also observed at F_{ET,CO_2} levels of 0·06 and 0·09 with only changes during phase II at F_{ET,CO_2} of 0·09 being significant. Concerning the level of F_{ET,CO_2} *per se*, analysis of variance revealed a significance influence upon peak phrenic and triangularis sterni activity during cycles with lung inflations and upon peak thyroarytenoid and triangularis sterni activities during cycles in which inflations were withheld.

Responses to maintaining lung inflation at end-inspiration

When the lungs were maintained at the end-inspiratory volume, neural expiration was greatly prolonged and, in some trials, continued as long as the inflation was maintained (Fig. 3). Thus, at F_{ET,CO_2} of 0·04, T_E was significantly increased to 494% of control values whereas T_I was not significantly changed (106% of control). Tracheal pressure averaged 4·56 cmH_2O when the lungs were held at end-inspiration. Phasic thyroarytenoid activity was eliminated in one animal during the maintained inflation and, for the entire group, peak thyroarytenoid activity was significantly reduced (Fig. 4). The duration of thyroarytenoid activity, expressed as a percentage of the T_E of control cycles with lung inflation, was not significantly different from that which had been recorded during these control cycles. Since T_E was greatly

prolonged during sustained inflations, the duration of thyroarytenoid activity, expressed as a percentage of this T_E, was significantly lower than that of control cycles.

During cycles in which inflation was held at the end-inspiratory level, triangularis

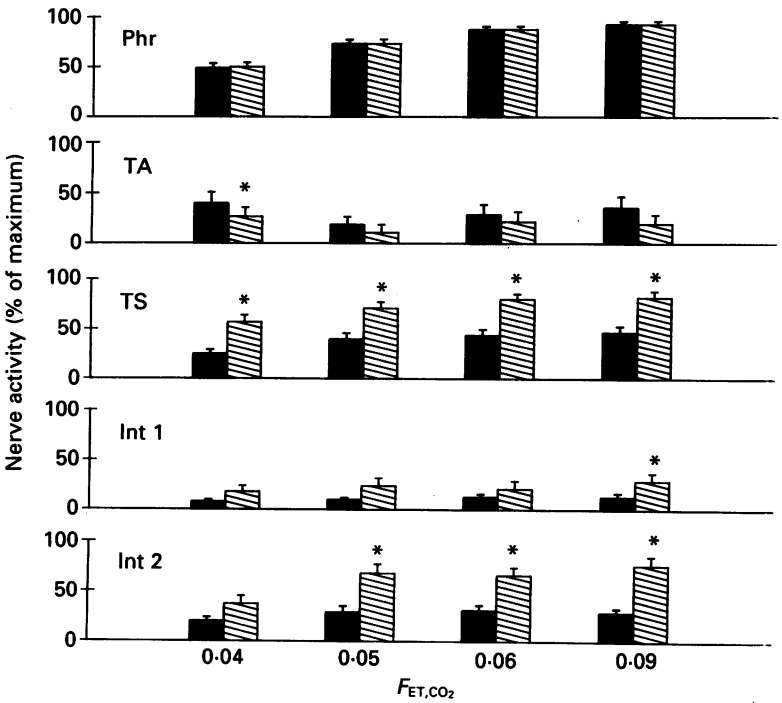

Fig. 4. Changes in inspiratory and expiratory neural activities upon holding the lungs at the end-inspiratory level during neural expiration. Mean values and standard errors of values for peak integrated neural activities are shown at the designated levels of end-tidal fractional concentration of CO_2 (F_{ET,CO_2}). Phr, phrenic nerve activity; TA, thyroarytenoid activity; TS, triangularis sterni activity; Int 1, intercostal activity during phase I of expiration; Int 2, intercostal activity during phase II of expiration. Filled bars are values during cycles with lung inflations; hatched bars are non-inflation cycles. * = $P < 0{\cdot}05$ compared to cycles with lung inflations. Neural activities were recorded in sixteen cats, except for intercostal activity which was recorded in twelve animals.

sterni activity commenced at a time, expressed either in milliseconds or as a percentage of T_E, which was not significantly different from control cycles. For animals in which phasic thyroarytenoid activity was evident, triangularis sterni activity began after most or all of the period of thyroarytenoid activity was completed. If no thyroarytenoid activity was recorded, there was still a delay, corresponding to post-inspiratory phrenic activity, between the termination of phrenic activity and the start of triangularis sterni discharge. Triangularis sterni, and also intercostal, activity were prolonged greatly. The peak integrated triangularis sterni activity was significantly greater than during control cycles. Changes in intercostal activities were less consistent although peak activities did increase in the majority of animals during both phase I and phase II.

Results similar to those at F_{ET,CO_2} of 0·04 were obtained at the other levels of

F_{ET,CO_2} examined (Fig. 4). At each, holding lung inflation at the end-inspiratory level resulted in no change or reductions of thyroarytenoid discharge and significant augmentations of triangularis sterni and intercostal activities during phase II of expiration. Peak intercostal activities during early expiration were not significantly altered, except at F_{ET,CO_2} of 0·09. However, these phase I intercostal activities did increase in the majority of animals at all levels of hypercapnia. Analysis of variance revealed no significant influence of the level of F_{ET,CO_2} upon these neural responses to sustained lung inflation.

DISCUSSION

The major conclusion of this study is that the discharge of slowly adapting pulmonary stretch receptors differentially influences neural activities during the two phases of expiration. When the lungs are inflated during the period of the phrenic burst, the augmentations in the discharge of these receptors caused diminutions in the discharge of the thyroarytenoid nerve. In contrast, pulmonary inflations caused augmentations in activities of the triangularis sterni and intercostal nerves during the mid- to late phase II period of expiration. These data support the concept of a differential control of neural activities during the two portions of expiration and the concept of two expiratory phases *per se*.

A fundamental question concerning these conclusions is whether activities of the nerves to the thyroarytenoid and triangularis sterni muscle are adequate representatives of phases I an II of expiration. As noted in the Introduction, phase I is considered to correspond to the period of post-inspiratory activity of the diaphragm and concomitant period of laryngeal adduction (Richter, 1982). An important controller of these laryngeal and diaphragmatic activities is envisaged to be the discharge of post-inspiratory medullary respiratory neurons (Richter, 1982; Ballantyne & Richter, 1984; Remmers *et al.* 1986; Richter, Ballantyne & Remmers, 1987). The depolarizations of these post-inspiratory medullary respiratory neurons parallel those of vagal motoneurons having post-inspiratory discharge patterns (Remmers *et al.* 1986). Moreover, the discharge of these post-inspiratory neurons is hypothesized to inhibit the discharge of inspiratory and expiratory bulbospinal neurons (Richter, 1972).

The augmentations of thyroarytenoid activity and diminutions of post-inspiratory phrenic activity and triangularis sterni discharge when lung inflation was withheld are in complete accordance with the hypothesized function of post-inspiratory medullary respiratory neurons. This hypothesized function is also supported by the finding that, during sustained lung inflations, thyroarytenoid discharge fell while post inspiratory phrenic and triangularis sterni discharges rose. Thus, data of the present study and our previous report (St John & Zhou, 1989) do support the concept that thyroarytenoid and triangularis sterni discharges are reasonable representatives of the state of phase I and phase II activities, as defined by the discharge of post-inspiratory medullary neurons. However, it is also obvious that the discharge of post-inspiratory neurons do not uniquely define phase I and phase II activities of thyroarytenoid, triangularis sterni or other motor nerves.

During cycles with lung inflations, there could be a complete absence of thyroarytenoid discharge and yet appreciable phase I activity as evidenced by the

delay in onset of triangularis sterni discharge. The finding that withholding lung inflation caused no statistically significant changes in phase I or phase II intercostal nerve activity, except at the highest levels of hypercapnia, also demonstrates that activities of motor nerves are defined by multiple factors.

The absence of significant changes in intercostal discharge concomitant with those of the thyroarytenoid nerve raises the possibility that our results do not reflect differences between control of neural activities during phases I and II but rather, simply, differences between cranial and spinal neural activities. The latter interpretation is not compatible with data showing comparable changes during the same phase. Thus, withholding lung inflation causes diminutions of phase II activities of the branch of the laryngeal nerve to the posterior cricoarytenoid muscle (Zhou *et al.* 1989) as well as the triangularis sterni, as described herein. This phase II triangularis sterni activity rose during sustained lung inflation as did activities of laryngeal motoneurons during the later portions of expiration (Barillot & Dussardier, Figs 8 and 9).

Concerning responses to sustained lung inflation, it was surprising that even though peak tracheal pressures in neural inspiration were the same, peak thyroarytenoid activity was significantly lower during cycles in which the lungs were held at the end-inspiratory levels than during control cycles. This finding implies that the influence of pulmonary stretch receptor discharge decays slowly during neural expiration. Likewise, since the lungs were inflated only during neural inspiration under control conditions, the influence of such inflations in neural expiration is another manifestation of the dependence of neural expiration upon activities during the preceding inspiration (see Euler, 1986 for review). Although phrenic activity was changed by lung inflation, phrenic activity *per se* would not appear to directly define neural events in expiration. The most obvious evidence in support of this conclusion is the lack of correlation between either the magnitude or duration of phrenic activity and comparable variables of expiratory neural activities. Thus, for example, similar declines of spinal neural activities during phase II followed reduction of phrenic activity by stimulations of the superior laryngeal nerve or pneumotaxic centre (St John & Zhou, 1989) and, as reported herein, augmentations of phrenic activity by withholding lung inflation.

Since expiratory neural activities are profoundly influenced by lung inflation during neural inspiration (Huang *et al.* 1989) and by end-expiratory lung volume (*e.g.* Bishop & Bachofen, 1973), variability in the magnitude or pattern of lung inflation might have accounted for some of the variability in these expiratory neural activities. Hence, there were differences in the peak levels of pulmonary inflation during neural inspiration and the levels of positive end-expiratory pressure. Also, the servo-respirator was not always perfectly adjusted and the lag between the onset of phrenic activity and start of lung inflation was several hundred milliseconds in some trials.

Attempts to correlate the presence and magnitude of thyroarytenoid or triangularis sterni activities with peak inflation pressures, PEEP or timing of inflations in various animals were unsuccessful (see also Huang *et al.* 1989). For example, at F_{ET,CO_2} of 0·04, phasic thyroarytenoid activity was present during cycles with lung inflation in cats having the lowest (1·8 cmH_2O) and highest (9·5 cmH_2O) peak inflation pressures but was absent in some animals having peak inflation

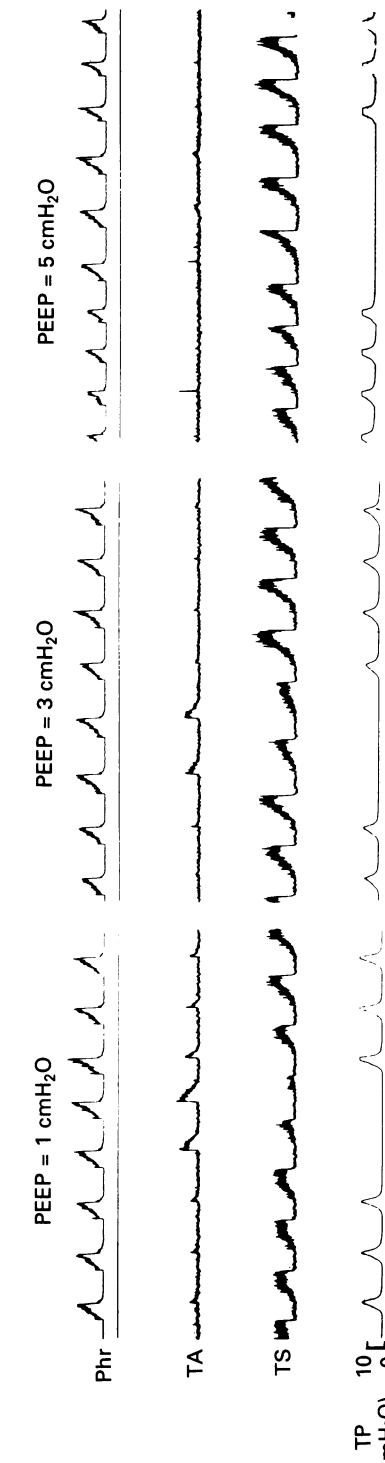

Fig. 5. Influence of changes in end-expiratory lung volume upon activities of the phrenic nerve (Phr) and nerves to the thyroarytenoid (TA) and triangularis sterni (TS) muscles. End-expiratory lung volume was elevated by changes in positive-end expiratory pressure (PEEP) in a cat with bilateral pneumothoraces. TP, tracheal pressure; non-inflation is indicated by the absence of changes of tracheal pressure during periods of phrenic activity. End-tidal fractional concentration of CO_2 was 0·05 at all levels of PEEP.

pressures between 3·9 and 5·4 cmH_2O. However, in preliminary studies with four cats, we did find that augmentations in PEEP and peak inflation pressure could significantly alter the magnitude of thyroarytenoid and triangularis sterni activity. As shown in Fig. 5, elevations in PEEP caused reductions in thyroarytenoid activity during both inflation and non-inflation cycles. Activity of the triangularis sterni fell during non-inflation cycles at PEEP levels of 1 and 3 cmH_2O but rose when inflations were withheld at PEEP of 5 cmH_2O; peak inflation pressures had also risen at this highest levels of PEEP. The changes in triangularis sterni activity with alterations in inflation pressures and PEEP are similar to the 'reversal phenomenon' which Cohen, Feldman & Sommer (1985) have reported for the influence of pulmonary inflations upon the activities of bulbospinal expiratory neurons and the internal intercostal nerve. These investigators reported that moderate augmentations in lung volume increased these expiratory activities whereas larger volumes depressed these activities. The PEEP and peak inflations pressures at which this reversal occurred in the study of Cohen *et al.* (1985) differed from those of the present report. Yet, this difference may be due to the variability *between* animals, as discussed above, or to the use of a cycle-triggered pump by Cohen *et al.* (1985) in which the rate of lung volume at the start of neural inspiration was much more rapid than in the present study using a servo-respirator.

In summary, results of the present studies demonstrate that the control of neural activities differs during the two phases of expiration. The data provided additional support for the three-phase theory for definition of the respiratory cycle (Richter *et al.* 1986).

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