Augmenting expiratory neuronal activity in sleep and wakefulness and in relation to duration of expiration

JOHN OREM
Department of Physiology, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas 79430

Orem, John. Augmenting expiratory neuronal activity in sleep and wakefulness and in relation to duration of expiration. J. Appl. Physiol. 85(4): 1260–1266, 1998.—Augmenting expiratory cells (n = 23) were recorded in the rostral medulla of five cats in sleep and wakefulness. The objective was to determine the relationship of their activity to the duration of expiration (TE) and, particularly, to TE in rapid-eye-movement (REM) sleep, when expirations are short and may even cause fractionated breathing. Correlation analysis (Kendall’s τ) showed no consistent relationship in any state between the breath-by-breath mean activity of augmenting expiratory cells and TE. This result contradicts predications of an inverse relationship between augmenting expiratory activity and TE. Some cells (11 of 23) were more active in REM than in non-REM sleep and were active during fractionated breathing. This suggests that fractionated breathing in REM sleep is caused by short expiratory phases and not by intermittent inhibition of an ongoing inspiration.

METHODS

Electrodes for recording electroencephalograhic (EEG) and electromyographic (EMG) activity were implanted in five adult cats. In addition, tracheal fistulas were created, and a headcap was attached to the skull. Surgical procedures. The animals were anesthetized with acepromazine maleate (2.5 mg) and ketamine (30 mg/kg) and 1–5% halothane in oxygen. A midline incision was made from below the cricoid cartilage to just above the suprasternal notch, and the sternothyroid, sternohyoid, and sternomastoid muscles were retracted to expose the trachea. The trachea was opened longitudinally for a length of five cartilaginous rings. The cut edges of the rings were sewn to the skin on the corresponding side to create a fistula. The animals were placed in a stereotaxic frame, and a midline incision was made to expose the dorsal skull. EEG electrodes and 4–40 stainless steel electrodes were threaded into the skull and secured with dental cement.

A third objective was to learn more about the erratic pattern of breathing characteristic of REM sleep. In particular, inspiratory efforts sometimes occur as a series of rapid and brief efforts, as if a single breath were fractionated into several parts (13). It has been proposed that this fractionated pattern of breathing is the result of a descending inhibition associated with pontogeniculooccipital waves (13). Alternatively, it may be that fractionated breaths are brief but complete respiratory cycles in which both phases, inspiratory and expiratory, are present. If the latter is the case, then expiratory neurons should discharge during the brief breaks in inspiratory activity that are seen during fractionated breathing.

The results show that the prediction of a positive relationship between TE and the discharge rate of augmenting expiratory cells is not supported, that some augmenting expiratory cells are excited in REM sleep and may account in part for the pattern of breathing in that state, and that fractionated breathing in REM sleep is the result of short, but complete, respiratory cycles.

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sessions were required before the animals would sleep in the laboratory.

After adaptation and in a second operation under general anesthesia (as above), a small craniotomy (~5 mm diameter) was made in the occipital bone. The craniotomy allowed passage of microelectrodes through the cerebellum into the brain stem.

To consolidate sleep to the daytime hours when recordings were made, the animals were housed overnight in a cold (0°C) environment.

For recording of intratracheal pressures, a small Silastic tube was inserted through the fistula into the trachea. This tube was connected to a pressure transducer. In two of five animals in the study, the trachea was intubated with an 18-Fr endotracheal tube, and pressures within the tube and instantaneous airflow rates were measured. Only four augmenting expiratory cells were recorded from these two animals. Accordingly, the results were obtained primarily from animals that breathed normally through the upper airways rather than through an endotracheal tube. EEG and EMG activity and intratracheal pressures (PT5A volumetric pressure transducer, Grass Instruments) were recorded on an analog tape recorder (Hewlett-Packard) and on a chart recorder (MT9500, Astro-Med). The EEG was band-pass filtered [1–35 cycles/s (cps)] and amplified (wideband alternate current preamplifiers, Grass Instruments). EMG signals from the nuchal muscles were led to a high-impedance probe (Grass HP511) and to an amplifier (Grass P511) set to pass frequencies from 300 to 10,000 cps.

Tungsten microelectrodes (impedances 1–10 MΩ) were used to record single medullary respiratory neurons. The microelectrodes were mounted to a hydraulic microdrive and driven through the cerebellum and into the medulla. Signals were led to a high-impedance probe (Grass HP511) and to a preamplifier (Grass P511) and were recorded on the Astro-Med and analog tape recorders.

The recording sessions lasted 4 h. Non-REM (NREM) and REM sleep and wakefulness were defined on the basis of standard EEG criteria.

Data analysis. All analyses were performed off-line. Data were played back from the tape recorder into a PS/2 486 computer with a LabWindows data-acquisition system (National Instruments). Cycle-triggered histograms and the signal strength and consistency of the respiratory component of the activity of a cell (η² values) were determined for each cell. Procedures for constructing cycle-triggered histograms and calculating the η² value of the activity of a cell have been published (18). The η² values can vary from 0.0 to 1.0. The respiratory component can vary in different states; the η² values used to categorize the cells in this study were obtained from activity occurring during relaxed wakefulness or NREM sleep. Discharge rates of the cell and the duration of inspiration (Ti) and Te were calculated breath by breath in wakefulness and in NREM and REM sleep. Discharge rates were calculated from interspike intervals of <300 ms, an arbitrary value chosen to exclude intervals during the inactive phase of the cells. Rank order and Pearson product-moment correlation coefficients were calculated to determine the relationship between Ti and the mean discharge rate of the cells by breath.

Histology. After fixation in Formalin (10%), frozen sections (40–80 µm in thickness) of the medulla were cut, stained with cresyl violet, and examined for evidence of microelectrode penetrations.

RESULTS

Characteristics of augmenting expiratory cells. Twenty-three augmenting expiratory cells were recorded in five adult cats. They were located in the ventral respiratory group from the retrofacial nucleus to 1–2 mm rostral to the obex. Their activity augmented throughout expiration and ceased at the onset of inspiration. Eleven had a distinct period of activity at the end of inspiration or beginning of expiration (Fig. 1, see also Ref. 10, 20, 24). The η² values of the cells varied by 10.220.33.4 on September 22, 2017 http://jap.physiology.org/ Downloaded from
from 0.45 to 0.94 and averaged 0.74 ± 0.16 (SD). Average discharge rates in NREM sleep varied from 4.5 to 64.6 cps.

Behavior of augmenting expiratory cells in REM sleep. Eleven cells were more active in REM than in NREM sleep. Of these, two were significantly less active in REM sleep (n = 9) or had similar mean rates in both states (n = 3) (Fig. 2, Tables 1 and 2). The group average χ² value was 0.82 ± 0.15 (Table 1). These cells were active during all expirations in REM sleep, regardless of whether the breathing pattern was regular or irregular (Fig. 4). The activation was sustained throughout REM sleep, but there was much variability, and, on some breaths, rates were equivalent to those in NREM sleep (Fig. 5).

Nine cells were significantly less active in REM sleep than in NREM sleep. The average discharge rate of this group of cells in NREM sleep was 24.9 ± 19.5 cps and decreased to 13.7 ± 18.3 cps in REM sleep. The average ratio of REM activity to NREM activity across cells was 0.46 ± 0.31. The coefficients of variation of discharge rates were greater in REM sleep (1.84 ± 1.52) than in NREM sleep (0.31 ± 0.28). The group average χ² value was 0.65 ± 0.14 (Table 2).

Three cells had similar discharge rates in REM sleep (44.9 ± 12.7 cps) and NREM sleep (45.5 ± 18.5 cps). Their average χ² value was 0.75 ± 0.7, and coefficients of variation of their discharge rates were greater in REM sleep (0.43 ± 0.01 cps) than in NREM sleep (0.15 ± 0.02 cps). Activity of augmenting expiratory cells during active expirations in wakefulness. Large expiratory intrathoracic pressures sometimes occurred on arousal and were associated with movement of the animal. These

Fig. 2. Discharge rates of augmenting expiratory cells in wakefulness and REM sleep normalized to discharge rates in NREM sleep. Solid lines plot results for cells that were more active in REM than in NREM sleep. No. of lines showing relationship of discharge rates in wakefulness to those in NREM sleep are fewer than for relationship between NREM and REM sleep because no data in wakefulness were available for 3 cells. Dotted lines show data for cells that were less active in REM than in NREM sleep or for cells the discharges rates of which were not different in the two states. Again, here data are incomplete and no. of lines for NREM sleep-wakefulness relationship do not correspond to no. of lines for NREM-REM sleep relationship. This figure shows diverse behaviors of augmenting expiratory cells in REM sleep.

Fig. 3. Transition from NREM to REM sleep showing an increase in discharge rate of an augmenting expiratory cell in REM sleep. Note that this cell is active during even very short expirations in REM sleep. EEG, electroencephalogram; Prin, intrathoracic pressure. Negative pressures (inspiration) signaled by upward deflections.

Fig. 4. Activity of an augmenting expiratory cell in REM sleep (A) and in wakefulness (B). Note that cell discharges in association with each positive (downward) Prin deflection (expiration) during rapid and erratic breathing in REM sleep. In wakefulness (B), cell is silent or only weakly active during expiratory events associated with body movements (note artifacts on EEG) and during a swallow (arrow). Expiratory efforts at beginning of this episode are large and produce large voltage changes that cause oscillation of amplifier. Those episodes in which there are expiratory efforts were commonly seen as part of a sequence that comprised also an augmented breath and swallows.
movements generally preceded an augmented breath (e.g., Fig. 6). Some augmenting expiratory cells \( (n = 5) \) were intensely active during these movements associated with large expiratory pressures, and they were active also during swallowing (Fig. 6), whereas others \( (n = 10) \) were not (Fig. 4). In eight cases, these movements were not observed.

Comparisons between augmenting expiratory cells with increased activity in REM sleep and other augmenting expiratory cells. Cells that had higher discharge rates in REM sleep had significantly \( (t\)-test, \( P < 0.05 \)) higher \( \gamma^2 \) values than did cells that were less active or unchanged in that state. The coefficient of variation of the activity in REM sleep was also significantly less for cells that were more active in that state than for other cells. The mean discharge rate in NREM sleep tended to be higher for the cells that were more active in REM than in NREM sleep (38.2 vs. 24.9 cps), but this difference was not significant at the 0.05 level.

Only 1 of the 11 cells that were more active in REM sleep, but 4 of the 9 cells that were less active in that state, discharged during active expirations in wakefulness. The number of cases is too small for statistical analysis of this association; nevertheless, the results suggest a relationship between behaviors in REM sleep and during active expirations.

Early expiratory bursting was not related to the direction of the change in cellular discharge from NREM to REM sleep. Approximately one-half of the cells (5 of 11) that were more active in REM sleep and one-half of the cells (5 of 9) that were less active in REM sleep had early expiratory peaks in their cycle-triggered histograms.

Relationship between mean discharge rate of augmenting expiratory cells and \( T_E \). Kendall’s rank order coefficient \( (\tau) \) was calculated to determine the relationship between the mean discharge rate of the cells and \( T_E \) breath by breath. A total of 64 \( \tau \) values were calculated from samples in wakefulness and NREM and REM sleep.

In REM sleep, 10 of 23 cells showed a small but significant relationship. In five cases the relationship was positive, which indicates that expirations with longer durations were associated with higher discharge rates; in five cases the relationship was negative. Values of \( \tau \) varied from 0.16 to 0.48 and averaged 0.25. These small but significant correlations between discharge rate and \( T_E \) were found in 4 of 11 cells that were more active in REM sleep and 6 of 9 cells that were less active in REM sleep. Five of six correlations of the latter cells were positive, whereas only one of four correlations of the former cells was positive. One cell

Table 1. Characteristics of augmenting expiratory cells that were more active in REM than in NREM sleep

<table>
<thead>
<tr>
<th>Cell Name</th>
<th>( \gamma^2 )</th>
<th>Wakefulness Mean, cps SD n</th>
<th>NREM Mean, cps SD n</th>
<th>REM Mean, cps SD n</th>
<th>REM Mean/NREM Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>st38</td>
<td>0.94</td>
<td>56.9 3.4 36</td>
<td>50.6 4.1 31</td>
<td>72.6 21.7 119</td>
<td>1.43</td>
</tr>
<tr>
<td>st49</td>
<td>0.94</td>
<td>59.6 16.7 36</td>
<td>64.6 6.4 60</td>
<td>79.3 17.1 30</td>
<td>1.22</td>
</tr>
<tr>
<td>st120</td>
<td>0.92</td>
<td>40.9 16.1 160</td>
<td>35.3 4 76</td>
<td>45.1 28 164</td>
<td>1.27</td>
</tr>
<tr>
<td>dx25</td>
<td>0.92</td>
<td></td>
<td>27.6 6.3 50</td>
<td>33.1 7 33</td>
<td>1.19</td>
</tr>
<tr>
<td>st84</td>
<td>0.91</td>
<td>53.6 12.8 55</td>
<td>62.9 7.1 47</td>
<td>76.4 15.1 115</td>
<td>1.21</td>
</tr>
<tr>
<td>st45p</td>
<td>0.9</td>
<td>60.2 10.2 31</td>
<td>55.6 7.5 28</td>
<td>90.1 23 53</td>
<td>1.62</td>
</tr>
<tr>
<td>st41</td>
<td>0.79</td>
<td>37.7 21.1 160</td>
<td>43.4 8.7 28</td>
<td>75.4 23.5 125</td>
<td>1.73</td>
</tr>
<tr>
<td>st34</td>
<td>0.78</td>
<td></td>
<td>27.4 7.2 48</td>
<td>35.8 23.1 46</td>
<td>1.30</td>
</tr>
<tr>
<td>dx69</td>
<td>0.72</td>
<td></td>
<td>24.4 6.1 35</td>
<td>45.9 21.6 74</td>
<td>1.88</td>
</tr>
<tr>
<td>dx35</td>
<td>0.71</td>
<td>6.9 8.2 75</td>
<td>16.4 7.2 69</td>
<td>25.4 15 288</td>
<td>1.54</td>
</tr>
<tr>
<td>os58</td>
<td>0.45</td>
<td>8.8 9.5 41</td>
<td>11.9 10.5 38</td>
<td>30.1 13.1 137</td>
<td>2.52</td>
</tr>
<tr>
<td>Mean</td>
<td>0.82</td>
<td>40.6 38.2</td>
<td>38.2</td>
<td>55.4</td>
<td>1.54</td>
</tr>
</tbody>
</table>

REM, rapid-eye-movement sleep; NREM, non-REM sleep; \( \gamma^2 \), signal strength and consistency of respiratory component of activity of a cell; cps, cycles/s; Mean, mean discharge rate; SD, SD of the discharge rate; n, no. of breaths analyzed. REM Mean/NREM Mean, ratio of REM discharge rate to NREM discharge rate.

Table 2. Characteristics of augmenting expiratory cells that were less active in REM than in NREM sleep

<table>
<thead>
<tr>
<th>Cell Name</th>
<th>( \gamma^2 )</th>
<th>Wakefulness Mean, cps SD n</th>
<th>NREM Mean, cps SD n</th>
<th>REM Mean, cps SD n</th>
<th>REM Mean/NREM Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>st55p</td>
<td>0.85</td>
<td>52.2 11.5 33</td>
<td>57.4 10.8 33</td>
<td>48.4 16.7 58</td>
<td>0.843</td>
</tr>
<tr>
<td>dx42</td>
<td>0.80</td>
<td>41.5 8.0 33</td>
<td>54.0 6.8 60</td>
<td>41.8 14.2 61</td>
<td>0.774</td>
</tr>
<tr>
<td>st110</td>
<td>0.80</td>
<td>35.0 19.7 27</td>
<td>37.0 6.5 44</td>
<td>0.6 2.1 32</td>
<td>0.016</td>
</tr>
<tr>
<td>d1120</td>
<td>0.70</td>
<td>18.6 9.3 98</td>
<td>17.2 5.1 27</td>
<td>1.0 2.7 29</td>
<td>0.058</td>
</tr>
<tr>
<td>d193</td>
<td>0.50</td>
<td>17.7 5.9 42</td>
<td>17.1 4.9 60</td>
<td>12.4 6.5 25</td>
<td>0.725</td>
</tr>
<tr>
<td>hm57</td>
<td>0.60</td>
<td>23.8 3.1 90</td>
<td>13.4 3.1 90</td>
<td>5.3 9.0 493</td>
<td>0.396</td>
</tr>
<tr>
<td>hm63</td>
<td>0.51</td>
<td>18.2 3.9 66</td>
<td>13.1 3.3 56</td>
<td>7.3 7.9 73</td>
<td>0.573</td>
</tr>
<tr>
<td>st40</td>
<td>0.55</td>
<td>11.4 2.6 28</td>
<td>10.5 2.0 25</td>
<td>5.4 9.0 62</td>
<td>0.514</td>
</tr>
<tr>
<td>os54</td>
<td>0.50</td>
<td>11.1 6.3 38</td>
<td>4.7 4.9 71</td>
<td>1.1 5.2 115</td>
<td>0.234</td>
</tr>
<tr>
<td>Mean</td>
<td>0.65</td>
<td>25.5</td>
<td>24.9</td>
<td>13.7</td>
<td>0.459</td>
</tr>
</tbody>
</table>
with comparable rates in NREM and REM sleep showed a significant negative correlation. Figures 3 and 4 illustrate an augmenting expiratory cell that was active during even very short expirations in REM sleep. Mixed results were obtained also for correlations in NREM sleep. Seven of twenty-two cells for which there were NREM sleep data showed significant correlations: five correlations were positive, and two were negative. The average $t$ value of the significant correlations in NREM sleep was 0.29.

Six of nineteen cells studied in wakefulness showed significant correlations between mean discharge rate and TE. All but one of these six significant correlations were negative. The average $t$ value of the significant correlations in wakefulness was 0.31.

Linear regression lines of discharge rate as a function of TE were determined from data across states for each of the 23 cells (Fig. 7). The slopes were in some cases negative and in others positive. This result followed from the behaviors of the cells in REM sleep: cells that were more active in REM sleep, when TE is short, had primarily negative correlations to the TE (Fig. 7C). Cells less active in REM sleep had mostly positive correlations. (Fig. 7B).

**DISCUSSION**

Characteristics of rostral augmenting expiratory cells. The cells in this study were located in the rostral medulla. This area contains respiratory motoneurons that innervate upper airway muscles and propriobulbar as well as bulbospinal respiratory neurons. Some rostral augmenting expiratory cells have widespread inhibitory actions on other respiratory neurons, including phrenic motoneurons and augmenting and decrementing expiratory and inspiratory cells in both the dorsal and ventral medullary respiratory groups (5, 9, 11). Other rostral augmenting expiratory cells excite expiratory premotoneurons in the caudal brain stem (2, 9), and there are projections back to the region of rostral augmenting expiratory cells from this caudal area (26). Thus there are several different types of cells with augmenting expiratory patterns in the rostral medulla.

Augmenting expiratory cells in the rostral medulla display different discharge patterns during active expirations. Some are inactive during sneezing (17) or during expiratory efforts induced by chemical stimulation of caudal expiratory premotoneurons in anesthetized animals (3). In contrast, other studies find that rostral expiratory neurons are active during vomiting (12) and coughing (25). In the present study, some rostral augmenting expiratory cells were active during active expirations, and others were not. The augmenting expiratory cells that are active during active expiration may be motor, premotor, or pre-premotor cells, and those that are inactive may be part of the network that produces rhythmogenesis.

The three-phase theory. A current theory contends that the respiratory cycle comprises three phases: an inspiratory phase and an early and a late expiratory phase (22). According to this theory, TE depends on activity in the third phase. The theory contends that shortening of expiration occurs by reducing or eliminating the late expiratory phase. (e.g., Ref. 21). Augmenting expiratory cells are members of the class of cells that define the late expiratory phase. As stated by Parkes et al. (21), there should be “elimination of the stage II (late expiratory) phase of expiration as seen in the membrane potential changes in all classes of respiratory neurone, and in the loss of discharge in stage II expiratory neurones, as the respiratory rate increases” (Ref. 21, p. 136).

In the present study, Kendall’s $\tau$ and Pearson’s product-moment correlation coefficients were calculated to determine the relationship between TE and the mean discharge rate of augmenting expiratory cells. Pearson’s product-moment correlation coefficients were calculated on the combined data from wakefulness and NREM and REM sleep. These showed relationships that followed from the behaviors of the cells in REM sleep. If a cell was more active in REM sleep than in NREM sleep, the correlation to TE was negative; if the cell was less active in REM sleep, the correlation was positive. This result could be interpreted as partial support of the three-phase theory. Additional support
comes from observation that five of nine cells that were less active in REM sleep showed a small but significant positive correlation between mean discharge rate and TE within REM sleep. However, this interpretation does not explain why correlations between the activity of other augmenting expiratory cells and TE were negative or not significant.

Values of $\tau$ were calculated within states for each cell. Most $\tau$ values were not significant. This indicates that there was not a monotonic relationship between the discharge rate of a cell and TE. Of the $\tau$ values that were significant, 11 were positive (the direction predicted by the three-phase theory) and 12 were negative. The $\tau$ values of significant correlations were small (0.2–0.3). These cannot be interpreted in the same way as Pearson product-moment correlation coefficients, but the possible range of $\tau$ values, like correlation coefficients, is $-1.0$ to $+1.0$, indicating complete disagreement and complete agreement, respectively, in the rank order of the two variables.

Because most $\tau$ values were not significant and because significant $\tau$ values were evenly divided between those showing a positive and those showing a negative relationship, we conclude that the predictions of the three-phase theory cannot be supported by our observations. On a qualitative basis alone, it is difficult to see how the persistence of augmenting expiratory neuronal activity during extremely rapid and irregular breathing in REM sleep (Fig. 4) can be reconciled with the predictions of the three-phase theory.

Fractionations. Diaphragmatic activity in REM sleep appears at times interrupted or fractionated (13). It was originally proposed that these interruptions were the result of a phasic descending inhibition that was related to the occurrence of pontogeniculocippital waves and that bypassed medullary respiratory neurons to affect directly phrenic motoneurons (13). Subsequent studies have found that fractionations can occur in the absence of pontogeniculocippital waves and that they can have significant depressive effects on ventilation (7, 8). Although we did not record the activity of the diaphragm in this study, intratracheal pressures (and/or airflow traces) showed patterns consistent with fractionations. These patterns were rapid alternations from negative (inspiratory) to positive (expiratory) pressures (Fig. 4A). Augmenting expiratory cells discharged during these reversals of inspiratory pressures even when they were very brief. This suggests that fractionations may be extremely rapid breathing during which respiratory cycles are complete, progressing rapidly through all the phases of inspiration and expiration and involving respiratory cells of all types, including augmenting expiratory cells.

Excitatory effects on the respiratory system in REM sleep. The variable that distinguished augmenting expiratory cells that were more active in REM sleep from those that were less active was the $\gamma^2$ value of their activity. All of the cells in this study except one had $\gamma^2$ values $\geq 0.5$, but cells that were more active in REM than in NREM sleep had significantly higher $\gamma^2$ values than did cells that were less active in REM sleep. The $\gamma^2$ values of some of the augmenting expiratory cells are among the highest we have seen in recordings of many different types of respiratory neurons in chronic animals. The meaning of the association of high $\gamma^2$ values with activation in REM sleep is not known.

This is the first evidence of excitation of augmenting expiratory neurons in REM sleep. Previous studies have shown that augmenting and late inspiratory neurons increase their discharge rates in REM sleep.
compared with NREM sleep (14, 15), and that diaphragmatic EMG activity has a greater rate of rise in that state (16). This excitation may be a compensatory response to changes in compliance and resistance of the respiratory system during REM sleep, or it may result from state-specific processes that cause excitation throughout the nervous system. The increase in the activity of some augmenting expiratory cells in REM sleep may explain the increase in rate of breathing and in the rate of rise of inspiratory activity in that state. If the augmenting expiratory cells that are excited in REM sleep are those that have widespread inhibitory actions, then they may cause more rapid breathing because of strong inhibition of inspiratory cells and then postinhibitory rebound excitation of the same cells. Indeed, simulations of a network model have found that increased augmenting expiratory activity causes an increase in inspiratory activity (1), just as has been observed in previous studies (14, 15).

Conclusions. Augmenting expiratory cells in the rostral medulla are a heterogeneous group that includes cells that are excited in REM sleep. Their mean discharge rates are poorly related or unrelated to the TE. The activity of some of them indicates that fractionated breathing consists of inspirations alternating rapidly with brief expirations. The oscillator in REM sleep has an inspiratory bias (the TI/TE ratio is large), and inspiratory neurons have a greater rate of rise of activity that may be caused in part by brief but intense augmenting expiratory activity.

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Address for reprint requests: J. Orem, Dept. of Physiology, School of Medicine, Texas Tech Univ. HSC, Lubbock, TX 79430 (E-mail: phyjmo@ttuhsc.edu).

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