Respiratory-related evoked potential elicited by expiratory occlusion

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Hammond, Carol Smith, Helen Gaeta, Christine Sapienza, and Paul W. Davenport. Respiratory-related evoked potential elicited by expiratory occlusion. J. Appl. Physiol. 87(2): 835–842, 1999.—Respiratory-related evoked potentials (RREPs) have been elicited by inspiratory loads in adults and children. The RREP was recorded over the somatosensory region of the cerebral cortex. It was hypothesized that a RREP could be recorded by using expiratory occlusion. Electroencephalographic activity was recorded in adults from 14 scalp locations, referenced to the linked earlobes. The occlusion was presented as an interruption of expiration. Epochs of expiratory occlusion-elicited potentials were recorded for each expiratory occlusion presentation. There were two occlusion trials and a control trial of 100 presentations each. The epochs in each trial were averaged and examined for the presence of short-latency, occlusion-related peaks. RREP peaks were observed bilaterally with expiratory occlusion and were absent in control unoccluded averages. A positive peak, P31, was observed at central and postcentral sites. A negative peak, N33, was observed at frontal and central sites. A second positive peak, P55, was observed at frontal and central sites. These results demonstrate that expiratory occlusion elicits a RREP. This suggests that expiratory occlusion-related sensory information activates the cerebral cortex similar to that for inspiratory loads.

SUBJECTS CAN CONSCIOUSLY PERCEIVE positive upper airway pressure. Williams et al. (35) demonstrated the detection of oral pressure differences of 1.5–2.0 cmH2O. Subjects can also detect expiratory resistive loads (34). Although these studies demonstrate that expiratory mechanical stimuli can elicit conscious sensations that presumably involve cerebral cortical processing, they do not provide information on the neural mechanisms mediating the sensory motor mechanisms involved with these processes.

METHODS

The Institutional Review Board, J. Hillis Miller Health Center, University of Florida, reviewed and approved the protocol of this study. All subjects were informed of the nature of the study before starting the experiment, and their consent was obtained. Twelve (n = 12) normal adult nonsmoking volunteers (5 women and 7 men, average age 23 yr), in good general health with no history of neurological or respiratory disease, participated in this protocol.

Subject preparation. Each subject was brought to the laboratory, and the general nature of the experiment was described. The subject chose a videotaped cartoon movie to watch during the experiment. Tin ear-clip electrodes were placed on both ears. The circumference of the head was measured, and an appropriately sized electrode cap with integral tin electrodes (Electro-Cap International) was placed on the head (Fig. 1). The electrode positions were based on the International 10-20 System (15). Scalp and electrode contact was made by application of electrode-conducting paste. The subject was prepared for recording on a 14-channel electroencephalograph (EEG) electrode montage of the following scalp positions: F3, F4, Fz, C3, Cz, C4, P3, P4, Pz, T3, T4, T5, and T6 referenced to the joined ear lobes. In 5 of the 12 subjects, recordings were also made from C3′ and Cz electrodes (2 cm posterior to C3 and Cz, respectively), which were also linked to the joined ears. Vertical electrooculogram (EOG) activity was monitored with bipolar electrodes placed on the upper and outer canthus of the left eye. The impedances were checked and adjusted to be <3 kΩ for all electrodes. In addition, the impedance of the ear-clip electrodes was within 0.4 kΩ of each other. The electrode cap was connected to a 16-channel EEG system (model 12 Neurodata Acquisition System, Grass). EEG activity was monitored on an oscilloscope. The EEG activity was band-pass filtered (0.3 Hz-3 kHz), amplified (50 k), digitized (2.5 kHz; model 1401, Cambridge Electronics Design), and led into an on-line signal-averaging computer system. The mouth pressure (Pm) signal was recorded by a differential-pressure transducer (model MP-45, Validyne Engineering), digitized, and led into the on-line signal-averaging computer system. Airflow (V) was recorded with a pneumotachograph connected to a differen-
tial pressure transducer. The Pm and V were also led to an oscilloscope monitored by the investigator. Pm and V were monitored continuously on the oscilloscope and used to time the presentation of the expiratory occlusions. A transistor-transistor logic (TTL) pulse generated by the expiratory occlusion valve controller triggered the collection of 50 ms of pretrigger and 350 ms of posttrigger EEG and Pm data. The duration of the occlusion was greater than the 350-ms posttrigger portion of the recorded epoch. Individual 400-ms epochs of EEG, EOG, and Pm data were collected, digitized at 3 kHz, and stored on disk for 50 ms pretrigger and 350 ms posttrigger.

Protocol. The subjects were studied semireclining in a lounge chair that provided full, comfortable support to the back, arms, neck, and head. The subjects respired through a mouthpiece and nonrebreathing valve with a nose clip in place. Care was taken to suspend the valve to minimize facial muscle activity. The expiratory port of the nonrebreathing valve was connected to the loading manifold, located outside of a sound-attenuated room and hidden from the subject’s view (Fig. 1). The occlusion valve was pressure activated with a closure time of 2 ms. The inspiratory port of the nonrebreathing valve was unobstructed and opened to room air. During the occlusion trial, the three-way valve was turned to close the room-air port, directing the expiration only through the occlusion valve in the expiratory circuit. The three-way valve was turned to include the room-air port in the expiratory circuit for a control trial. This allowed the occlusion valve to be activated without interruption of the expiratory airflow. The experimenter was in an adjacent room, which allowed observation of the subject via a video camera and television monitor.

Expiratory occlusion was generated by closure of a diaphragm valve in the expiratory line. Valve closure was triggered by a TTL pulse in response to a manual switch, which exposed the valve diaphragm to a positive-pressure source. The subject was given a few expiratory occlusions to become familiarized with the stimulus. The video movie was then turned on, and the protocol was initiated. Expiration was interrupted by manual activation of the valve after the onset of expiration as indicated by the Pm and flow signals on the oscilloscope. Any presentation with an EOG eye-blink artifact was rejected. The occlusion was a 350-ms interruption of expiration, presented every two to six breaths. The subject was not provided with any cues as to when the occlusion was presented. The occlusion was presented after the onset of expiration, usually during the first one-half of the expiration, timed by visual observation of the airflow pattern by the experimenter. A minimum of 100 occlusions were presented for the first experimental trial. The subject then removed the mouthpiece and was given a drink of water and allowed to rest. The cortical, ear, and eye electrode impedances were checked and, if necessary, reapplied to maintain values within the specified range. The subject continued watching the movie. The control trial was obtained by opening the port proximal to the occluder. The subject returned to breathing through the mouthpiece. One hundred activations of the occlusion valve were then presented, similar to the first occlusion trial. The control trial provided the same sounds and vibrations without the occlusion. The subject was again allowed a rest period when the control trial was complete. A second occlusion trial was then presented. The time required to complete the entire study session was <2.5 h.

Data analysis. The TTL pulse generated by the occlusion valve controller triggered the collection of 50 ms of pretrigger and 350 ms of posttrigger EEG and Pm data by the computer signal processor. The TTL pulse simultaneously electrically activated the occlusion valve. Each of the 400-ms epochs of the 100 expiratory occlusion presentations were stored on computer disk for off-line averaging and analysis.

The EEG activity and Pm were averaged for each experimental trial. Individual presentations were recalled from the computer stored file of the experimental trial and displayed. The first criterion for inclusion of an individual presentation in the average was if the onset of the occlusion-related change in Pm was present and coincident with preceding samples. The second criterion for inclusion was the absence of artifact in the EEG traces. Each trial of 100 presentations was
averaged in this manner, with a minimum of 65 presentations included in each average and with most trials consisting of 80–90 averaged presentations; the averages were stored on computer disk. For each subject, the averaged control trial was then subtracted from each averaged occlusion trial. This procedure removes any auditory or vibratory component in the waveform because these are equally represented in both the control and occlusion trials. The presence, latency, and amplitude of the peaks in the averaged, control subtracted occlusion trials were determined for each scalp electrode site. Peak latencies were measured as the time from onset of the occlusion as indicated by the rapid increase in Pm (Fig. 2) to the average of the prestimulus EEG baseline to voltage at the peak. The nomenclature for the peaks was based on previous reports for inspiratory occlusion elicited RREPs (4, 6, 32) with the P (positive) or N (negative) referring to the polarity of the peak. The peak nomenclature differs, with the subscripted number in the present study representing the approximate mean latency of the peak. Each scalp electrode location was analyzed for the presence, latency, and amplitude of the early peaks (peak latencies <110 ms) of the RREPs. There was no difference between the two occlusion trials, and one trial occlusion trial for each subject was used for analysis. The latencies and amplitudes were determined for each individual subject; group grand averages were not used to avoid the loss of peak resolution that accompanies averaging across subjects.

Descriptive statistics of peak latencies and peak amplitudes were determined. A repeated-measures ANOVA was used to test for differences in peak latencies and amplitudes. When significance was reported, a post hoc pairwise multiple comparison was performed by using the Student-Newman-Keuls method. This analysis was used for testing for differences in rostral-caudal distribution (F, C, C’, and P electrodes) and for bilateral (F3-F4, C3-C4, P3-P4, T3-T4, and T5-T6) differences in an horizontal plane. The criterion for acceptance was a significant difference set at P < 0.05.

RESULTS

Expiratory occlusion-related peaks in the RREP were observed bilaterally in the averaged response of 11 of 12 subjects (Fig. 3A). These peaks were not present in the averaged control trials (Fig. 3B). There were systematic regional differences in the RREP resulting in two distinct RREP waveforms. One waveform was observed in the frontal (F3, FZ, F4) and midline (FZ, CZ) electrode averages. The other waveform was observed more caudally in the C3, C4, P3, and P4 electrode averages.

Table 1 lists the electrode site and mean latencies and amplitudes for the short-latency peaks of the RREP found at each scalp position. Three peaks of the expiratory-elicited RREP were consistently observed in averaged expiratory occlusion traces; the peaks were identified according to their polarity (P or N) and mean latency. The three short-latency peaks found consistently in these subjects are marked with arrows in Fig. 3A: P34, N53, P95. These peaks were not found in the control trial (Fig. 3B).

The three short-latency peaks demonstrated systematic regional differences in distribution across the scalp. The P34 was predominant at central and postcentral electrode sites. In contrast, N53 and P95 were predominant at frontal and central electrode sites.

P34. An initial positive peak, P34, had an amplitude significantly greater at the central (C3, C4, CZ) and postcentral electrode sites (P3, P4, PZ) than at the frontal electrode sites (F3, F4, FZ). There was no significant difference in the P34 amplitude or latency between the central and postcentral electrode sites. The P34 was not observed in any of the subjects in the lateral temporal electrode sites (T3, T4, T5, T6). The P34 was found bilaterally, and there were no significant differences in bilateral peak latencies and amplitudes between left and right electrode pairs. The peak was present in both occlusion trials when averaged separately (Fig. 4A). Mean P34 peak latencies and amplitudes are summarized in Table 1. When the P34 was observed at frontal electrode sites (4 of 12 subjects), the mean latency was slightly shorter [25.7 ± 6.0 (SD) ms]. This peak was also found in C3’ and C4’ in the five subjects in whom these sites were used. The P34 amplitude and latency was not significantly different in the C3’ and C4’ than the central (C3, C4, CZ) and postcentral electrodes (P3, P4, PZ).

N53. The second peak, N53, was negative and had an amplitude significantly greater at the frontal (F3, F4, FZ) than at the central (C3, C4, CZ) electrode sites. This peak was not observed in the lateral temporal electrode sites (T3, T4, T5, T6). In addition, the N53 was not observed in the C3’ and C4’ electrodes. The N53 was observed bilaterally, and there were no significant differences between left and right electrode pairs in peak latencies and amplitudes. The peak was present in both occlusion trials when averaged separately (Fig. 4B). Mean N53 peak latencies and amplitudes are summarized in Table 1. When N53 was observed at postcentral sites (4 of 12 subjects), the mean latency was significantly longer [69.1 ± 13.8 (SD) ms] and the mean amplitude significantly reduced [1.6 ± 1.4 (SD) µV].

P95. The third peak, P95, was positive and had an amplitude significantly greater at the frontal (F3, F4, FZ) than at the central (C3, C4, CZ) electrode sites. This peak was not observed in the lateral temporal electrode sites (T3, T4, T5, T6). The P95 was observed bilaterally, with no significant differences between left and right electrode pairs in peak latencies and amplitudes. The

Fig. 2. Averaged Pm and EOG signal recorded during expiratory interruption occlusions for an individual subject. Positive pressure is plotted up y-axis. Dotted line, point of valve closure. Associated point of rapid change in Pm was used as time 0 for determining peak latencies.
peak was present in both occlusion trials when averaged separately (Fig. 4B). Mean P95 peak latency and amplitudes are summarized in Table 1.

DISCUSSION

The results of the present study demonstrate that a RREP can be elicited by expiratory occlusion in adults. The expiratory RREP was recorded in adult subjects and was similar to that reported previously in adults for inspiratory interruption occlusions (4, 30). Two waveforms were found, with one RREP waveform predominant in the central and postcentral sites. The second RREP waveform was predominant in frontal electrode sites.

The expiratory short-latency peaks of the RREP observed in this study were elicited by expiratory occlusion. Previous reports of RREPs used inspiratory occlusion or extrinsic loads (2, 4, 5, 13, 18, 30). Although the RREP waveforms are similar, the pressures are opposite, and the similarity of RREP waveform does not necessarily mean that the inspiratory and expiratory RREPs are mediated by the same mechanoreceptor.

Table 1. Group mean latencies and 0-peak amplitudes (0 voltage to peak voltage) of short-latency respiratory-related evoked potential peaks elicited by expiratory occlusion

<table>
<thead>
<tr>
<th></th>
<th>P34</th>
<th></th>
<th>N53</th>
<th></th>
<th>P05</th>
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<tbody>
<tr>
<td></td>
<td>Latency, ms</td>
<td>Amplitude, µV</td>
<td>Latency, ms</td>
<td>Amplitude, µV</td>
<td>Latency, ms</td>
</tr>
<tr>
<td>F3</td>
<td>33.1 ± 6.29</td>
<td>1.60 ± 0.97</td>
<td>52.9 ± 7.22</td>
<td>−2.67 ± 1.83</td>
<td>94.6 ± 11.5</td>
</tr>
<tr>
<td>F2</td>
<td>29.9 ± 7.06</td>
<td>1.29 ± 0.57</td>
<td>51.8 ± 7.78</td>
<td>−2.12 ± 2.09</td>
<td>96.5 ± 11.8</td>
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<tr>
<td>F4</td>
<td>34.1 ± 8.12</td>
<td>1.74 ± 0.47</td>
<td>53.6 ± 8.46</td>
<td>−2.26 ± 1.39</td>
<td>94.9 ± 13.2</td>
</tr>
<tr>
<td>C3</td>
<td>23.7 ± 7.60</td>
<td>1.65 ± 1.14</td>
<td>64.2 ± 15.44</td>
<td>−2.02 ± 1.97</td>
<td>93.0 ± 17.9</td>
</tr>
<tr>
<td>C2</td>
<td>37.0 ± 7.20</td>
<td>2.15 ± 1.25</td>
<td>66.2 ± 14.49</td>
<td>−2.38 ± 2.32</td>
<td>95.0 ± 13.3</td>
</tr>
<tr>
<td>C1</td>
<td>36.6 ± 7.20</td>
<td>1.23 ± 0.58</td>
<td>60.7 ± 13.76</td>
<td>−2.21 ± 1.56</td>
<td>95.4 ± 24.6</td>
</tr>
<tr>
<td>P3</td>
<td>36.7 ± 6.00</td>
<td>1.33 ± 0.78</td>
<td>66.7 ± 14.90</td>
<td>−2.38 ± 2.32</td>
<td>95.4 ± 24.6</td>
</tr>
<tr>
<td>P4</td>
<td>37.3 ± 5.98</td>
<td>1.52 ± 0.81</td>
<td>95.4 ± 24.6</td>
<td>1.86 ± 1.37</td>
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Values are means ± SD for 12 subjects.
population(s). The short-latency peaks of the RREP are the result of dipoles elicited by afferent activation of cortical neurons. These peaks are recorded at a distance from the cortical surface and only indicate that an afferent-elicited dipole is present in the vicinity of the recording electrode. This indicates that, whereas the short-latency peaks of the RREP are the result of sensory activation of cortical neurons by respiratory-related mechanoreceptors, the location and transduction properties of those receptors remain unknown. Expiratory occlusion has been used to elicit long-latency, endogenous peaks of the RREP (13). These long-latency components of the RREP are the result of respiratory-related mechanoreceptor activity. The protocol for recording these long-latency peaks is different from that for the short-latency peaks; in particular, it requires a minimum of 32–64 occlusion presentations to reduce the signal-to-noise ratio for recording the short-latency peaks (30). These long-latency peaks were not investigated in the present study.

The subjects in the present study were semireclined with relaxed quiet breathing. Expiration is generally a passive deflation in the quiet breathing state. The application of the expiratory occlusion by interruption of the deflation stops expiratory airflow and causes a rapid increase in the pressure of the airways. With the subject relaxed, there is probably no active expiratory muscle activity. The absence of expiratory muscle activ-
ity is supported by the stable occlusion pressure plateau (Fig. 2). This is in contrast to the continued decrease in occlusion pressure reported with inspiratory occlusion (5, 30). The expiratory occlusion pressure will thus be primarily due to passive elastic deflation forces generating a 6- to 8-cmH₂O positive-pressure pulse. This pressure will act primarily on the positive-pressure receptors of the airways, pharynx, and buccal cavity. The rate of rise in the pressure is a function of the closure time of the valve (2 ms) and time required for pressure equilibration throughout the respiratory tract. The magnitude of this pressure is well above the threshold for detection of positive oral pressure (35). Although the afferents activated by the expiratory interruption occlusion are unknown, it is likely that mechanoreceptors in the buccal cavity, pharynx, and airways may be mediating the expiratory RREP. Inspiration under similar recording conditions is an active process, and inspiratory occlusion produces mechanical changes in the respiratory tract and the inspiratory muscles. Thus there is a difference in the populations of mechanoreceptors that may be mediating the RREPs for inspiratory and expiratory occlusions. The similarity of the RREP waveforms is significant in marking the sensory activation of similar regions of the cerebral cortex, suggesting similar higher brain processing of expiratory and inspiratory mechanoreceptor information despite differences in pressure and mechanoreceptor populations. Future studies recording the RREP for inspiratory and expiratory occlusions in the same subjects will be necessary to understand the differences/similarities of these RREPs.

RREPs are evoked potentials elicited by respiratory mechanical loads (4, 5, 18, 32). The initial report of RREPs used occlusions presented at the onset of inspiration as the stimulus (5). The RREP was recorded from cephalic (C₂)-referenced electrodes over the so-matosensory region. The P₁ peak was the shortest latency initially positive peak. This peak was hypothesized to represent the initial activation of the somatosensory cortex by the occlusion-related respiratory mechanoreceptors. The amplitudes and distribution of the P₁ show a similar level of activity at the C₂ and C₄ referenced to C₁ (30). The P₃₄ peak in the present study corresponds to the inspiratory P₁ found with the joined-earlobe reference (4). This is consistent with a somatosensory source for the P₃₄ peak (7). This result is also consistent with the reports of mechanically elicited evoked potentials for the digits (17, 22, 28). This early positive activity in response to cutaneous mechanical stimulation has been suggested to be generated in the SI cortex (12). If the P₃₄ peak observed with expiratory occlusion has the same origin as the inspiratory P₁ and early positive cutaneous peak, then it is likely that this P₃₄ peak represents somatosensory cortical activity.

The RREP recorded with the precentral electrodes referenced to the joined earlobes had a uniquely different pattern from the postcentral electrodes. The shortest latency peak observed was a negative potential change, N₅₃, and occurred after the P₃₄ peak. The amplitude was greatest in the F₃ and F₄ electrodes, but the peak could also be discerned in the more caudal C₃ and C₄ electrodes. The presence and frontal distribution of the N₅₃ peak predominant in the frontal electrode sites suggest a second region of expiratory occlusion-related mechanoreceptor-mediated cortical activation. The topographic pattern of the frontal RREP elicited by expiratory occlusion is similar to that reported with inspiratory occlusion (4) and that reported by Peterson et al. (26). Intracortical recordings demonstrated that the epidural components were the result of separate generators (26). The origin of the P₃₄ and N₅₃ peaks in the present report may be related to dual neural generators that have separate thalamic pathways (7, 8). Future studies will be necessary to further characterize the generator source of these potentials.

The P₃₄ and N₅₃ peaks may be the electrophysiological marker of the arrival of the initial sensory signal to the cortex, which may represent one early stage in the higher cognitive processing of respiratory mechanical information. Cortical sensory processing of mechanosensory information involves thalamocortical and cortico-cortical connections that have been studied morphologically and electrophysiologically for the somatosensory, auditory, and visual systems (see Ref. 25 for review). The primary and secondary sensory areas are involved in the elementary analysis of incoming information to the cortex (24). The electrophysiological marker of this early sensory processing is a short-latency dipole generated by depolarization of neurons in the primary and secondary sensory cortex. This dipole produces the voltage changes recorded as short-latency peaks in the evoked potential. If the P₃₄ and N₅₃ peaks of the expiratory RREP are the result of cortical dipoles in the somatosensory and frontal cortices, respectively, then these short-latency peaks represent the initial stage of cerebral cortical processing of mechanical information related to expiratory occlusion. Cortical areas subjacent to the primary sensory regions are termed first-order parasensory areas while those beyond the first-order parasensory areas are designated as second-order or third-order association areas (3, 16). It is thought that for information reaching the cerebral cortex to be further elaborated on and ultimately lead to the execution of behavior, it must pass from the primary sensory areas through the different cortical association areas. The P₃₄ and N₅₃ peaks may represent the initial primary sensory step in this sequence of cortical processing. This process of advancing information within the cerebral cortex must also involve the interlinking of cerebral connections among different cortical and subcortical regions. Longer latency components of the evoked potential, such as the P₁₀₀ peak, represent markers of neural activity related to this cognitive processing. These cognitive-related peaks have been recorded with inspiratory loads and occlusion and have been demonstrated to be attention related (2, 13). In recent years it has been shown that, within a given modality, related cortical regions are interconnected in a stepwise fashion, beginning in the primary sensory area and progressing sequentially through post-Rolandic parasensory and multimodal areas and finally...
reaching frontal association and paralimbic regions (16, 23, 24, 33). The sequential nature of the flow of information through the long connections of association areas has been viewed as an important substrate for attention, sensory integration, learning, memory, as well as the performance of skilled behavior (1, 11, 14, 20, 21, 27). This study was designed to examine only the initial stage of that processing sequence: the initial activation of the cerebral cortex. Future studies are needed to elucidate the cortical sequential and cognitive processing of expiratory mechanosensory information.

Multichannel scalp recordings provide a measure of the distribution of scalp EEG activity. In the case of short-latency sensory components, the regional distribution acts as an indication of the activity of specialized areas of underlying cortical tissue. In past studies of mechanically and electrically stimulated somatosensory event-related potentials, multichannel topographies have indicated maximal responses occur over tissue contralateral to the side of stimulation (10, 17, 19, 22, 28, 29, 31). Expiratory occlusion is a stimulus, like inspiratory occlusion, that acts on the entire respiratory apparatus. This results in bilateral stimulation of respiratory mechanoreceptors. The bilateral symmetry of the RREP suggests a bilateral projection of theseafferents. The results, however, do not provide insight into the origin and central pathways for these afferents.

In summary, a RREP elicited by expiratory occlusion was observed in adult subjects. This RREP was recorded with joined-earlobe reference and exhibited two waveforms that were distinctly different in peak polarity, latency, and topography. One waveform, recorded from electrodes over the somatosensory region, was characterized by a short-latency, initially positive peak: P_{34}. The second waveform recorded from electrodes placed in the frontal region was characterized by a short-latency negative peak, N_{53}, followed by a positive peak, P_{95}. The waveform and distribution of the expiratory occlusion-elicited RREP are similar to the inspiratory occlusion-elicited RREP found by using the joined-earlobe reference. The mechanoreceptors and neural processing mechanisms mediating the expiratory occlusion RREP remain unknown.

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