Periodic Breathing Triggered by Hypoxia in Normal Awake Adults*

Modification by Naloxone

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Breathing patterns in six normal awake subjects were monitored noninvasively during progressive hypoxia accomplished with the administration of nitrogen at 2, 4, 6, and 8 L/min by nasal cannula. The lowest value of arterial oxygen saturation (SaO₂) of 88 ± 4 percent (mean ± SD) was achieved with nitrogen at 8 L/min. At baseline, tidal volume (VT) and frequency were fairly regular; with nitrogen at 2 and 4 L/min, some subjects showed minor fluctuations of VT. At 6 and 8 L/min, periodic breathing with marked oscillations of VT, apneas, hypopneas, and intermittent large tidal breaths were consistently observed. Inspired oxygen concentration fluctuated because of the variations of tidal breaths provoked when periodic breathing took place and enhanced fluctuation in SaO₂. A randomized, double-blind crossover design was used to assess the effect of pretreatment with naloxone on this periodicity. In contrast to the irregular breathing pattern observed with pretreatment with placebo, the breathing pattern after pretreatment with naloxone was regular during nasal administration of nitrogen except at 8 L/min, when minor fluctuations in VT with occasional hypopneas and large tidal breaths occurred. On another day, irregular and periodic breathing with apneas or hypopneas (or both) produced by nasal nitrogen at 8 L/min was eliminated or blunted by short-term intravenous administration of naloxone. On another day, electroencephalographic monitoring corroborated visual observations made in the previous studies that the hypoxic subjects were awake during the breathing alterations. Thus, awake adults develop irregular and periodic breathing during induction of mild hypoxia produced by nasal administration of nitrogen. The irregularity in breathing appears to be mediated through release of endorphins, since the effect is blunted or eliminated by pretreatment or short-term treatment with naloxone.

Periodic breathing with apnea during sleep commonly occurs in adult male sojourners at high altitudes and in infants breathing 15 percent oxygen when monitoring of breathing pattern is obtained with noninvasive devices. The mechanism of these alterations in the breathing pattern under hypoxic conditions has not been defined, nor has it been demonstrated whether periodic breathing occurs during wakefulness.

The localization of opioid receptors in the area of the brain stem, and their well-known respiratory depressant action have led to the belief that endogenous opiates may modulate respiratory center activity. Furthermore, there appears to be an association between hypoxia and activity of endorphins. In infants and animals, endogenous opioids have been implicated in the pathogenesis of apneas during hypoxia. Wardlaw et al. found that β-endorphin-like activity in cord arterial blood from human fetuses was inversely related to its arterial oxygen pressure (PaO₂) and to the one-minute Apgar score of birth. Chernick et al. reported that the duration of primary apnea in asphyxiated newborn rabbits was reduced by pretreatment with naloxone, a specific endorphin antagonist, suggesting that endorphins were released by this stress. In normal awake adults, administration of naloxone did not affect the ventilatory response to hypoxemia and hypercapnia, but rhythmicity of breathing pattern was not analyzed. Other investigators have not noted changes in breathing rhythmicity in awake hypoxic adults who were breathing on a mouthpiece with the nose clipped, which in itself alters breathing pattern.

The purpose of the present study was to monitor natural breathing with the noninvasive device, the respiratory inductive plethysmograph, during mild hypoxia in awake normal adults and to assess whether naloxone alters rhythmicity under such circumstances. Hypoxia was produced by nasal administration of nitrogen, rather than mouthpiece breathing of hypoxic gas mixture, in order to avoid the effect of the mouthpiece on breathing patterns; this mode of producing hypoxia promotes fluctuations in inspired oxygen concentration with breathing if tidal volume (VT) varies because of entrainment of different volumes of room air.

MATERIALS AND METHODS

Four male and two female normal subjects with a mean age of 28

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years (range, 21 to 35 years) were enrolled in the study. None had a history of cardiopulmonary disease, and all were nonsmokers. Informed consent was obtained from all subjects, and they received financial remuneration for their participation in the study.

Tests of Pulmonary Function

Evaluation of baseline pulmonary function consisted of spirometry, measurements of airway resistance (Raw), specific airway conductance (Gaw/Vt), and functional residual capacity (FRC) by body plethysmography, and distribution of ventilation by the single-breath nitrogen test.

Respiratory Inductive Plethysmography

A detailed description of the respiratory inductive plethysmograph (Respiracine) and of the technique of calibration using the least-squares method has been published previously.14,20

Transcutaneous Oxygen Tension

The transcutaneous oxygen tension (tcPO2) was measured by a monitor (Lifespan 100). The tcPO2 sensor was applied in the infraclavicular area at a temperature of 38°C to 40°C and was continuously recorded during the period of study. At these temperatures the response time for the tcPO2 sensor is 10 to 20 seconds, and the correlation coefficient with PaO2 is r = 0.98 at rest and during exercise, but tcPO2 is lower than PaO2.4,20

Arterial Oxygen Saturation

The arterial oxygen saturation (SaO2) was measured with an ear oximeter (Hewlett-Packard 47201A).

Protocol

Days 1 and 2. The study was designed in a randomized double-blind crossover design. After calibration and validation of the respiratory inductive plethysmograph, the subjects lay in the supine position within a quiet room for 15 minutes. Subjects were instructed to keep their eyes open, to watch television, and to breathe nasally at all times. They then donned a plastic nasal cannula (Hudson 1104), through which they inhaled air at ambient pressure while tcPO2 was monitored continuously. On the first day, after completion of the rest period, either 2 mg of naloxone diluted in 10 ml of physiologic saline solution or else 10 ml of saline solution (placebo) was injected intravenously. Collection of data was begun five minutes after injection in order to provide a baseline period of ten minutes; then the subjects received 100 percent nitrogen via the nasal cannula at 2, 4, 6, and 8 L/min, followed by compressed air as a sham at 6 L/min for ten minutes each while breathing pattern and tcPO2 were continuously monitored. After exposure to the air sham, breathing patterns were collected for another ten minutes of recovery period while breathing room air. On the second day the same protocol was repeated after pretreatment with that which had not been received on the first day.

Day 3. After calibration and validation of the respiratory inductive plethysmograph, an intravenous infusion was started with 5 percent dextrose in water at 25 ml/hr in each subject to maintain vein patency. Long tubing was used such that the infusion bag in another room was located out of sight of the subject. The subjects donned a nasal cannula through which they inhaled compressed air at ambient pressure while tcPO2 was monitored continuously. After a period of ten minutes, the baseline breathing pattern and tcPO2 were monitored for ten minutes. The subjects then breathed 100 percent nitrogen at 8 L/min by nasal cannula for five minutes. Two milligrams of naloxone diluted in 10 ml of physiologic saline solution was then injected into the indwelling infusion tubing from outside the room without the subject being aware of the injection, and breathing pattern monitored for another ten minutes.

Day 4. The mean values of tcPO2 and SaO2 with an ear oximeter were measured simultaneously while the subjects breathed room air and 100 percent nitrogen at 2, 4, 6, and 8 L/min by a nasal cannula in the supine position in order to relate tcPO2 values to SaO2.

Day 5. In four subjects, three electrodes in the C4, O2, and A4 position2 were placed to record the electroencephalogram (EEG); and after calibration and validation of the respiratory inductive

Table 1—Breathing Patterns and tcPO2 at Baseline, after Inhalation of 100 Percent Nitrogen at Various Flow Rates, after Air Sham Exposure, and after Recovery after Placebo (A) and after Naloxone (B)*

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Room Air)</th>
<th>Inhalation of 100 Percent Nitrogen</th>
<th>Air Sham Exposure at 6 L/min</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 L/min</td>
<td>4 L/min</td>
<td>6 L/min</td>
<td>8 L/min</td>
</tr>
<tr>
<td>VT, L/min†</td>
<td>6.05 ± 1.32</td>
<td>6.29 ± 1.20</td>
<td>6.14 ± 1.40</td>
<td>6.19 ± 1.44</td>
</tr>
<tr>
<td></td>
<td>6.32 ± 1.29</td>
<td>6.09 ± 1.37</td>
<td>6.27 ± 1.42</td>
<td>6.38 ± 1.47</td>
</tr>
<tr>
<td>VR, ml†</td>
<td>396 ± 74</td>
<td>381 ± 86</td>
<td>376 ± 74</td>
<td>389 ± 104</td>
</tr>
<tr>
<td></td>
<td>375 ± 69</td>
<td>389 ± 90</td>
<td>383 ± 75</td>
<td>390 ± 53</td>
</tr>
<tr>
<td>Frequency, breaths/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>16.1 ± 2.9</td>
<td>16.5 ± 2.9</td>
<td>16.2 ± 2.7</td>
<td>16.7 ± 3.9</td>
</tr>
<tr>
<td>B</td>
<td>16.3 ± 2.4</td>
<td>16.7 ± 1.4</td>
<td>16.4 ± 1.4</td>
<td>16.8 ± 2.0</td>
</tr>
<tr>
<td>T1, sec</td>
<td>1.57 ± 0.37</td>
<td>1.60 ± 0.29</td>
<td>1.50 ± 0.22</td>
<td>1.53 ± 0.40</td>
</tr>
<tr>
<td></td>
<td>1.61 ± 0.40</td>
<td>1.58 ± 0.30</td>
<td>1.51 ± 0.29</td>
<td>1.52 ± 0.45</td>
</tr>
<tr>
<td>Tt/Ttot</td>
<td>0.420 ± 0.030</td>
<td>0.422 ± 0.035</td>
<td>0.421 ± 0.031</td>
<td>0.420 ± 0.041</td>
</tr>
<tr>
<td></td>
<td>0.421 ± 0.032</td>
<td>0.420 ± 0.032</td>
<td>0.420 ± 0.039</td>
<td>0.423 ± 0.034</td>
</tr>
<tr>
<td>VR/T1, ml/sec†</td>
<td>261 ± 36</td>
<td>276 ± 51</td>
<td>255 ± 43</td>
<td>265 ± 89</td>
</tr>
<tr>
<td></td>
<td>243 ± 40</td>
<td>262 ± 29</td>
<td>280 ± 40</td>
<td>275 ± 54</td>
</tr>
<tr>
<td>tcPO2, mm Hg</td>
<td>67 ± 4</td>
<td>62 ± 3</td>
<td>52 ± 3</td>
<td>45 ± 5</td>
</tr>
</tbody>
</table>

*Table data are means ± SD.
†Body temperature and pressure, saturated.

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plethysmograph, subjects donned a nasal cannula and rested in the supine position for 15 minutes. This study was performed several months after the preceding investigations. Breathing pattern and EEG were monitored at baseline and while breathing air with a nasal cannula at 8 L/min and 100 percent nitrogen at 8 L/min followed by air at 8 L/min. Subjects were instructed to stay awake and breathe nasally. They were also monitored continuously on a video screen outside the room by a remote-controlled infrared camera.

**Analysis of Data.** Data for study of the breathing pattern were collected and analyzed with a Z-80A-based microprocessor system (Resplicomp). The system measured the amplitude, the inspiratory and expiratory times for each breath of the ribcage, and the abdominal excursions and their sum and calculated in a variably compressed time scale on a breath-by-breath basis the following components: minute ventilation (Vi), VT, inspiratory time (Ti), fractional inspiratory time (VT/TI), and mean inspiratory flow (VT/TI). Tidal volumes were accumulated minute by minute, rather than averaged from breath-by-breath values to account for the presence of apneas. The VT was then calculated as the sum of the values for VT for each minute and the frequency from the number of breaths counted.

**Statistical Analysis**

The mean ± SD of breathing pattern components of baseline were compared to values obtained after various exposures to 100 percent nasal nitrogen, after exposure to the air sham, and after recovery using block analysis of variance and Newman-Keuls pairwise comparison with p<0.05 taken as statistically significant.

**Results**

**Days 1 and 2**

Tissue oxygen tension fell progressively from baseline as the nasal flow of nitrogen was increased, and the magnitude of the fall shows no differences between placebo and naloxone (Table 1). There were no significant changes from baseline on either the day of placebo or the day of naloxone for frequency, VT, and VTi (Table 1) nor other components of the breathing pattern. On the day of placebo, the coefficient of variation of VT while breathing nasal nitrogen at 6 and 8 L/min (Table 2) was significantly greater than baseline or the sham exposure of 6 L/min of compressed air administered by nasal cannula. On the day of naloxone, no significant difference in the coefficient of variation of VT
Baseline pattern of VT is regular. Minor fluctuations in VT are seen at higher flows of nasal nitrogen. No apneas are observed.

On the day of administration of placebo (saline), the VT and frequency at baseline were regular, as depicted in a representative subject (Fig 1). With nasal nitrogen at 2 L/min, minor fluctuations in VT developed, but no apneas were seen. With a greater increase in the flow of nitrogen and thus a decrease in tcPo2, the amplitude of VT fluctuated widely. At 8 L/min of nasal nitrogen, periodic breathing with marked oscillations in VT and apneas developed in this subject (Fig 1). During air sham exposure and the recovery period, VT and frequency became regular as during baseline. In the same subject, after naloxone, there were fewer fluctuations in VT, and no apneas were noted while breathing nasal nitrogen at 2, 4, and 6 L/min (Fig 2). At 8 L/min of nasal nitrogen, minor fluctuations of VT were observed with occasional hypopneas but no apneas. The VT and frequency became regular during air sham and the
recovery period.

Figure 3 depicts the breathing pattern of all six subjects during nasal administration of nitrogen at 8 L/min on the day of placebo. This was present throughout the ten-minute exposure period. All subjects show marked oscillations in VT with intermittent apneas or hypopneas (or both). Two subjects showed crescendo-decrescendo VT with intermittent apneas. In three subjects, frequent breaths greater than 1.0 L were seen. The apneas were central in type because both abdominal and rib cage movements ceased, and there was no paradoxic motion between the two compartments. On the day of naloxone, the same six subjects breathing nasal nitrogen at 8 L/min showed

Figure 4. Tidal volume recorded by sum signal of respiratory inductive plethysmograph in six subjects while breathing nasal nitrogen at 8 L/min on day of naloxone. Minor fluctuations in VT are seen with occasional large breaths, but no apneas or hypopneas are seen.

Figure 5. Tidal volume recorded by sum signal of respiratory inductive plethysmograph in six subjects while breathing nasal nitrogen at 8 L/min showing periodic breathing with apneas or hypopneas (or both). After intravenous injection of 2 mg of naloxone (arrows), VT and frequency became regular, with disappearance of hypopneas, apneas, and fluctuations in VT.
minor fluctuations in \( V_t \) with occasional large breaths but did not develop apneas nor hypopneas (Fig 4).

On both days, subjects were checked frequently for wakefulness by visual inspection. At all times, they were watching television with their eyes open.

**Day 3**

Figure 5 shows the breathing pattern in six subjects while breathing nasal nitrogen at 8 L/min and immediately after injection of naloxone. All subjects developed periodicity in \( V_t \) with intermittent apneas or hypopneas (or both) after administration of nasal nitrogen at 8 L/min for ten minutes. After injection of 2 mg of naloxone, \( V_t \) and frequency in all subjects became regular, with the disappearance of hypopneas, apneas, and fluctuations of \( V_t \). The regularity of \( V_t \) and frequency lasted for the ten-minute observation period, at which time monitoring was discontinued. None of the subjects was aware of the timing of the injection of naloxone.

**Day 4**

The \( tcPO_2 \) (mean ± SD) of 69 ± 5 mm Hg on room air corresponded to \( SaO_2 \) (mean ± SD) of 98 ± 4 percent, and \( tcPO_2 \) of 38 ± 6 mm Hg while breathing 100 percent nitrogen nasally at 8 L/min corresponded to a \( SaO_2 \) of 88 ± 4 percent. The latter fluctuated widely with respiration, but \( tcPO_2 \) did not because of the slow time response of its monitoring device.

**Day 5**

Figure 6 shows the breathing pattern and EEG recording in a representative subject while breathing air, nasal nitrogen at 8 L/min, and then followed by air. All subjects remained awake during the study period, as demonstrated by stage-0 EEG (Fig 6), and had their eyes open during video monitoring. They developed periodicity in \( V_t \) with intermittent apneas along with fluctuations of \( SaO_2 \). There were no significant changes from baseline for any of the components of the breathing pattern. The coefficient of variation for \( V_t \) increased significantly from baseline while breathing nasal nitrogen but not while breathing air.

**Discussion**

Mild hypoxia produced by nasal administration of nitrogen was associated with periodic and irregular breathing in awake normal adults when monitoring was carried out noninvasively with respiratory inductive plethysmography. Fluctuations of \( SaO_2 \) which occurred during periodic breathing with this method of inducing hypoxia were greater than observed in clinical Cheyne-Stokes respiration; namely, there was a difference of 10 to 15 percent of \( SaO_2 \) from high to low.
values in our normal subjects vs 4 to 8 percent in ten patients with Cheyne-Stokes respiration. The latter fluctuations were similar to those found in other patients with Cheyne-Stokes respiration. This accentuation of the usual fluctuations in SaO₂ with periodic breathing is in part due to varying degrees of entrainment of room air through the nose of the subjects in the present study which alters inspired oxygen concentration. In this respect, our method for inducing hypoxia differs from altitude chambers or breathing hypoxic gas mixtures from a gas reservoir with a mouthpiece or mask; however, alveolar hypoxia would be expected to fluctuate in all models of hypoxia when periodic breathing takes place.

Values of breathing pattern components on air breathing did not differ from values obtained in a large group of normal subjects reported previously. The electroencephalographic and visual observations suggested that the irregular breathing patterns during hypoxia took place in the waking state. These changes appeared to have been mediated through release of endogenous endorphins, since naloxone, a specific opioid antagonist, blocked or blunted this effect. Despite periodicity of breathing with apneas and hypopneas, the frequency, Vₚ, and ventilation on a minute-by-minute basis were not altered from baseline.

Berssenbrugge et al' monitored breathing pattern by noninvasive respiratory inductive plethysmography in normal adults placed within a high-altitude chamber (mean barometric pressure, 455 mm Hg). These investigators noted that during wakefulness, five of six subjects developed mild oscillations in Vₚ with occasional apneas, whereas one subject showed periodic breathing with a large number of apneas. The fluctuations in Vₚ and number of apneas were lower in their study than ours, but the degree of hypoxia induced was more severe; namely, mean SaO₂ was 78 ± 1.2 percent in the investigation by Berssenbrugge et al' and 88 ± 4 percent at our most severe level of hypoxia. Hypoxic ventilatory stimulation which increased ventilation from 5.9 ± 0.4 L/min to 8.6 ± 1.0 L/min in the study of Berssenbrugge et al' might have masked changes in periodicity, whereas the less severe hypoxia in our investigation did not alter ventilation. Furthermore, the greater fluctuations in inspired oxygen concentration, once periodic breathing developed in our awake subjects, might have made the respiratory center more unstable than in the altitude exposures.

Brusil et al' and Waggerer et al° described periodic breathing in normal adults sojourning at high altitude and placed within a high-altitude chamber, respectively. These investigators employed magnetometers to monitor breathing pattern and instructed their subjects to keep their eyes open but noted that some fell asleep. Since the studies did not obtain EEGs for staging sleep, it is not possible to ascertain how many of their subjects were awake and asleep when the periodic breathing developed.

Other investigations of the effect of hypoxia on ventilation in awake adults°° have not noted changes in rhythmicity of breathing, but they have been done with greater hypoxia and under isocapnic conditions while breathing on a mouthpiece with the nose clipped. The latter promotes slowing of respiratory frequency, elevation of Vₚ, and variable changes of respiratory drive.°°°° In anesthetized newborn rabbits, hypoxia initially stimulates ventilation, but with time, respiratory depression occurs; the latter is reversed by naloxone, thereby implicating endorphin release.°°°° Administration of enkephalin in newborn rabbits causes periodic breathing which is abolished by naloxone infusion.°°°° Cherrick et al°°°° reported that duration of primary apneas in asphyxiated newborn rabbits is reduced by pretreatment with naloxone, suggesting that endorphins are released during asphyxia. In unanesthetized conscious dogs monitored by noninvasive barometric plethysmography, intracranial injection of enkephalin induces periodic breathing with apneas.°°°° Morphine and related narcotic drugs often produce irregular and periodic breathing in normal human men, even with therapeutic doses.°°°° In our study, the observed effects of naloxone on breathing pattern were related to endorphin blockade during hypoxia, rather than a direct respiratory stimulant effect, since naloxone does not alter the volume, timing, or periodicity of the breathing pattern in normal subjects breathing room air.°°°°

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