Sleep apnea in obese miniature pigs

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Lonergan, Robert P., III, J. Catsby Ware, Richard L. Atkinson, W. Christopher Winter, and Paul M. Suratt. Sleep apnea in obese miniature pigs. J. Appl. Physiol. 84(2): 531–536, 1998.—We postulated that three extremely obese Yucatan miniature pigs would have more sleep apnea than three nonobese Yucatan miniature pigs. Pigs were studied with the use of electroencephalograms, inductance plethysmography, oximetry, expired nasal CO2, or thermistors. All of the obese pigs, but none of the nonobese pigs, had both sleep apnea (8.5, 10.3, and 97.0 in obese pigs vs. 0 apnea + hypopnea/h in all nonobese pigs; P < 0.05) and oxyhemoglobin desaturation episodes during sleep (9.4 ± 3.0 vs. 0 ± 0.53 [SD] mean desaturation episodes/h in obese pigs vs. nonobese pigs, respectively; P < 0.05). Two of the extremely obese pigs had obstructive sleep apnea, whereas the third obese pig had central sleep apnea. We conclude that sleep apnea occurs in extremely obese Yucatan minipigs and suggest that this animal can be used as a model for sleep apnea in obesity.

OBSTRUCTIVE SLEEP APNEA (OSA) is a common condition (27) that can cause significant morbidity and death (5). The etiology of OSA is unknown. Most patients with OSA are obese (14, 27), and weight loss in these subjects can eliminate this condition (17, 19, 24). Mechanisms proposed to explain how obesity causes OSA include 1) compression of the pharynx by either enlarged lateral pharyngeal fat pads (23a) or other adipose tissue in the neck (10, 11), 2) fat in the abdomen elevating the diaphragm and decreasing tracheal tug on the upper airway (25), or 3) fat altering respiratory control of the upper airway. It has not been possible to test whether these mechanisms cause OSA in humans, because testing would necessitate performing surgical procedures that may not be safe in humans. Development of an animal model of obesity-dependent OSA, however, would allow us to test these and other mechanisms.

Although the English bulldog has been shown to have OSA (6, 7), apnea in this animal is not thought to be related to obesity. Use of this animal has, however, significantly improved our understanding of upper airway muscle activation in OSA (8, 9).

After observing snoring and frequent arousals with snorts in an extremely obese pig, but no snoring and infrequent arousals in nonobese pigs, we postulated that extremely obese pigs would have more sleep apnea than nonobese pigs, just as obese humans have more sleep apnea than do nonobese humans. Therefore, we studied both extremely obese and nonobese Yucatan minipigs; we observed sleep apnea in the obese but not the nonobese pigs.

METHODS

We studied five extremely obese mature Yucatan female miniature pigs. We were able to obtain acceptable electroencephalograms (EEGs), which allowed us to score sleep and wakefulness, in only three of these obese pigs. Therefore we report data from only these three pigs. These pigs were being used in an ongoing obesity study (by R. L. Atkinson). We also studied, as controls, three mature male Yucatan miniature pigs that weighed considerably less than the extremely obese pigs. These pigs we will term nonobese. Morphometric characteristics of the pigs are shown in Table 1.

Sleep studies were performed between 1400 and 2000, lasting on average 3.2 h each. Pigs were studied until they had at least one complete sleep cycle (waking, non-rapid-eye-movement [NREM] and rapid-eye-movement [REM] sleep), and data from this study were used for comparisons with studies of other pigs. The obese pigs were studied twice and the nonobese pigs were studied three to five times until these conditions were met. Nonobese pigs also required several sham studies, without recordings, to acclimate them to the instrumentation. Pigs slept in both the prone position and on their sides. Sleep was monitored with two needle electrodes placed in the scalp subcutaneously, at a position approximating C1 and C2 in humans, with electrooculograms (EOGs) measured with needle electrodes placed cephad to each eye, and with electromyograms (EMGs) recorded from needle electrodes placed in the dorsal neck muscle — 2.5 cm lateral to the midline and 4 cm inferior to the base of the skull. Signals were processed by using standard techniques. The state of sleep or waking was scored as previously described for pigs (1, 16, 20, 22) by using both behavioral and EEG criteria. Awake state was characterized as having eyes open, being alert or moving, and having low-amplitude high-frequency waves or muscle artifact on the EEG. NREM sleep was characterized as having eyes closed, with no movement, and having high-amplitude slow waves on the EEG. REM sleep was characterized as having eyes closed, with frequent REM, multiple twitching of the muscles of the face and of the extremities, low-amplitude high-frequency waves on the EEG, and marked reduction in dorsal neck muscle EMG tonic activity. Arousals were noted when there was an abrupt shift in EEG frequency that lasted 3 s or longer. Arousal during REM also required an increase in the EMG signal.

Airflow was detected with the use of nasal prongs attached to a CO2 analyzer (Nelcor 1000, Hayward, CA) in the obese pigs and with thermistors in the nonobese pigs. Respiratory effort was detected with inductance plethysmography: one
followed by an increase in expired nasal CO₂ with a normally
Apneas and hypopneas were only counted when they were
decrease in flow to between 20 and 50% of baseline flow.

or longer. In the nonobese pigs, apnea was defined as a
of the curve, or by the curve's becoming dome shaped for 10 s

in obese pigs. A hypopnea was defined as the loss of the
ambient levels for
Episodes of desaturation were counted when oxyhemoglobin
saturation fell

3%. An apnea or hypopnea was said to be

$\geq 3\%$. An apnea or hypopnea was said to be 1) obstructive when it occurred despite paradoxical movement
of the chest wall and abdomen or 2) central when chest and
abdominal movement was absent (apnea) or decreased (hypop-
nea).

Oxygen saturation was measured with a Biox 3740 oximeter
(Ohmeda) with an Ohmeda 3470 probe attached to the
shaved and cleaned tail of the pig. Because of the pig's thick
skin, it was not possible to maintain an adequate signal
consistently throughout each study. We compared tail oxim-
metry values obtained with the Biox oximeter to saturation
values obtained from arterial blood in one anesthetized pig.
The pig was anesthetized with Telazol (6 mg/kg) and xylazine
(2 mg/kg) and ventilated with a Harvard ventilator. Desatura-
tion was produced by hypoventilating the pig to the desired
oxyhemoglobin saturation levels. When the oximeter oxyhe-
moglobin saturation level was stable for at least 25 s, an
arterial blood sample was obtained through a 20-gauge
catheter inserted in the right femoral artery. Samples were
obtained at oxyhemoglobin saturations ranging from 95 to
75% in intervals of 5% oxyhemoglobin saturation, as deter-
mined from the oximeter. Samples were drawn into heparin-
ized syringes, stored on ice for <40 min, and placed in a
blood-gas analyzer (Ciba-Corning 288, Medfield, MA) that
displayed $P_{O_2}$, $P_{CO_2}$, and pH. Oxyhemoglobin saturation
was determined from an oxygen-dissociation curve for porcine
whole blood (13).

Comparisons between obese and nonobese pigs were per-
formed with a nonparametric test, the Kruskal-Wallis test (21).

### RESULTS

The obese pigs appeared to be extraordinarily obese (Fig. 1). Their necks and cheeks were very prominent, and their cheeks bulged anteriorly toward their snout. Apneas or hypopneas occurred in all three obese pigs but not in the nonobese pigs ($P < 0.05$; Figs. 2–4, Table 2). Obese pigs, compared with nonobese pigs, also had more episodes of oxyhemoglobin desaturation/h of sleep ($P < 0.05$; Table 3). Oxyhemoglobin saturation in sleeping obese pigs, when they were not having apnea, was slightly lower than in sleeping nonobese pigs ($P < 0.05$; Table 4).

In two obese pigs (pigs 1 and 2), the apneic and hypopneic episodes were obstructive; however, in pig 3, the episodes were central. In the two pigs with obstructive episodes, the episodes occurred more often in REM sleep than in NREM sleep (Table 2). In pigs 1 and 2, 51% of the episodes were apneas and 49% were hypopneas, whereas in the pig with central episodes (pig 3), 100% of the episodes were apneas. In all three obese pigs with sleep apnea, the average length of apneas and hypopneas was $18.8 \pm 5.17$ s in NREM and $18.4 \pm 3.24$ s in REM. Whereas all pigs with apnea had episodes of desaturation during sleep, pigs with obstructive apnea had more episodes with lower saturation nadirs during the episodes than did the pig with central apneas (Table 3). All obese pigs were observed to snore during sleep, whereas none of the nonobese pigs were observed to snore. Arousals occurred at the termination of apnea and hypopnea episodes in 75% of episodes in pig 1, 23% of episodes in pig 2, and 13% of episodes in pig 3.

With onset of REM, obese pigs 1 and 2 twitched and struggled with each breath. Rhythmic respiratory movements (Figs. 2 and 3) became erratic and paradoxical, airflow decreased, and oxygen saturation declined. In some cases, after REM terminated with an arousal, respiratory movements became synchronous and saturation slowly returned to normal. In more severe cases of desaturation, the pig would be aroused, shake its head, and then return to sleep. After the arousal in this

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**Table 1. Morphological characteristics of pigs**

<table>
<thead>
<tr>
<th>Pig No.</th>
<th>Weight, kg</th>
<th>Length, m</th>
<th>BMI, kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese pigs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>102</td>
<td>1.21</td>
<td>69.8</td>
</tr>
<tr>
<td>2</td>
<td>107</td>
<td>1.31</td>
<td>62.1</td>
</tr>
<tr>
<td>3</td>
<td>107</td>
<td>1.24</td>
<td>69.1</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>105 ± 2.89</td>
<td>1.25 ± 0.051</td>
<td>67.0 ± 4.26</td>
</tr>
<tr>
<td>Nonobese pigs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>46.4</td>
<td>1.15</td>
<td>35.1</td>
</tr>
<tr>
<td>5</td>
<td>47.7</td>
<td>1.19</td>
<td>33.7</td>
</tr>
<tr>
<td>6</td>
<td>70.0</td>
<td>1.19</td>
<td>49.4</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>54.7 ± 13.3</td>
<td>1.17 ± 0.023</td>
<td>39.4 ± 8.69*</td>
</tr>
</tbody>
</table>

*Length was measured from tip of snout to base of tail; BMI, body mass index. *$P < 0.05$ compared with obese pigs.
circumstance, oxygen saturation quickly returned to its pre-REM level.

Oxyhemoglobin saturation values obtained with the Biox oximeter correlated significantly with saturation values obtained from arterial blood in the anesthetized pig (Fig. 5).

DISCUSSION

This study demonstrates that three extremely obese female Yucatan miniature pigs had apnea and oxyhemoglobin desaturation episodes during sleep, whereas three nonobese pigs did not. Apneas were obstructive in two pigs and were central in the third.

We observed no differences between the two pigs with obstructive apnea and the one with central apnea that might explain their different patterns of apnea. This phenomenon also occurs in obese humans, some of whom have obstructive apnea whereas others have central apnea. It is possible that the pig with central apneas had heart failure and Cheyne-Stokes respira-

![Fig. 2. Obstructive event showing apneic and hypopneic periods. During apneic period, there is no increase in expired CO₂, and there is paradoxical movement of rib cage and abdomen. During hypopneic period, there is loss of normal plateau on CO₂ curve and reduction in size of curve as well as paradoxical movement of rib cage and abdomen. Oxygen saturation decreases during episode. LOC/A1A2 and ROC/A1A2, left and right eye electrooculograms, respectively; C3/A1A2 and C3C4, electroencephalogram placements.](image1)

![Fig. 3. Obstructive hypopnea during rapid-eye-movement (REM) sleep. CO₂ signal shows loss of normal plateau and reduction in size of curve. Rib cage and abdominal movements are paradoxical. Oxygen saturation decreases during episode. REMs are present; dorsal neck EMG amplitude is low.](image2)
tion, although we did not observe in this pig the typical crescendo-decrescendo pattern of ventilation characteristic of this condition.

One of the pigs with obstructive apneas had more desaturation episodes than apneas (43 vs. 21, respectively). This pig may have hypoventilated in addition to having apneas. Our method of detecting airflow in these sleeping pigs may not have been sensitive enough to detect hypoventilation. Sleeping humans have also been occasionally observed to have more desaturation episodes than apneas (4, 23, 26). Zinkovska and Kirby (28) observed that, in spontaneously sleeping Yorkshire pigs, short 10-s apneas produced a fall in saturation during NREM from an average of 97.5 to 91.5%. Thus apneas shorter than 10 s probably also can produce desaturation episodes in sleeping pigs.

Apneas and hypopneas occurred more frequently in REM than in NREM sleep in the pigs with obstructive

![Figure 4. Central apnea during REM.](image)

**Table 2. Apneas plus hypopneas/h of sleep and type of sleep**

<table>
<thead>
<tr>
<th>Pig No.</th>
<th>All Sleep</th>
<th>NREM Sleep</th>
<th>REM Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese pigs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8.5 (2.48)*</td>
<td>3.2 (1.88)</td>
<td>25.0 (0.60)</td>
</tr>
<tr>
<td>2</td>
<td>10.3 (2.14)</td>
<td>8.9 (1.97)</td>
<td>29.4 (0.17)</td>
</tr>
<tr>
<td>3</td>
<td>97.0 (1.01)</td>
<td>93.8 (0.81)</td>
<td>110.0 (0.20)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>38.6 ± 50.6</td>
<td>35.3 ± 50.7</td>
<td>54.8 ± 47.8</td>
</tr>
<tr>
<td></td>
<td>(1.88 ± 0.77)</td>
<td>(1.55 ± 0.64)</td>
<td>(0.32 ± 0.24)</td>
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<tr>
<td>Nonobese pigs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0 (1.04)</td>
<td>0 (0.97)</td>
<td>0 (0.07)</td>
</tr>
<tr>
<td>5</td>
<td>0 (2.09)</td>
<td>0 (1.72)</td>
<td>0 (0.37)</td>
</tr>
<tr>
<td>6</td>
<td>0 (1.25)</td>
<td>0 (1.13)</td>
<td>0 (0.12)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0% (1.46 ± 0.56)</td>
<td>0% (1.27 ± 0.40)</td>
<td>0% (0.19 ± 0.16)</td>
</tr>
</tbody>
</table>

Values are apneas + hypopneas/h of sleep; nos. in parentheses are sleep time in h; NREM, non-rapid eye movement; REM, rapid eye movement. *P < 0.05 compared with obese pigs.

**Table 3. Desaturation episodes**

<table>
<thead>
<tr>
<th>Pig No.</th>
<th>Total Episodes</th>
<th>Episodes/h Sleep</th>
<th>65–69%</th>
<th>70–74%</th>
<th>75–79%</th>
<th>80–84%</th>
<th>85–89%</th>
<th>90–94%</th>
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<tr>
<td>Obese pigs</td>
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<tr>
<td>1</td>
<td>43</td>
<td>12.9</td>
<td>5</td>
<td>8</td>
<td>12</td>
<td>11</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>8.2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>7.2</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>13</td>
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<tr>
<td>Mean ± SD</td>
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<td></td>
<td>9.4 ± 3.0</td>
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<td>Nonobese pigs</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td>0.53 ± 0.92*</td>
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</table>

*P < 0.05 compared with obese pigs.
apnea. This predominance of apneas in REM sleep in pigs with obstructive apnea is similar to what has been observed in the English bulldog (7). These dogs had a mean of 27.4 sleep-disordered-breathing events/h of REM sleep and 7.4 events/h of NREM sleep. This is not dissimilar to our two pigs with obstructive apnea. They had 25.0 and 29.0 apneas and hypopneas/h, respectively, in REM sleep and 3.2 and 8.9 apneas and hypopneas/h, respectively, in NREM sleep.

Because apneas occurred in only the obese pigs, not in the nonobese pigs, it seems likely that sleep apnea in obese pigs is caused by their obesity. However, because the obese pigs were females and the nonobese pigs were males, we cannot exclude the possibility that sleep apnea occurs in female but not in male pigs.

Obtaining complete data on all pigs was an arduous task. We failed to obtain satisfactory EEGs from two pigs and consequently excluded them from the study. Interruptions during the studies were common when pigs woke up and moved around. Pigs slept better after acclimatization to the equipment and the study room. Obese pigs with sleep apnea required fewer study sessions for a successful sleep study than did the nonobese pigs.

Because these pigs were part of another ongoing study of obesity, we were limited in our ability to instrument them during sleep. Insertion of indwelling skull electrodes would have improved our ability to continuously monitor sleep. Although the needle electrodes provided adequate signals, they were difficult to insert in awake pigs and difficult to keep in place when an animal shook its head. Similarly, the flow signal was difficult to maintain. Investigators previously encountered this problem in the bulldog model (7). In an attempt to detect hypercapnia in obese pigs with sleep apnea, we used a CO2 analyzer to detect airflow, but we used a thermistor in the pigs without sleep apnea.

Both techniques are accepted qualitative methods of detecting apneas during sleep (12). Another problem was our difficulty in maintaining a continuous oximetry signal. Perhaps newer, brighter oximetry probes will eliminate this difficulty. However, the present study and others (3, 15, 18) have indicated that pulse oximetry can accurately detect changes in arterial oxyhemoglobin saturation in pigs.

An animal model for sleep apnea will allow investigators to perform pharmacological and surgical interventions that are not possible in humans. These interventions can be directed to understanding of the mechanism by which obesity contributes to sleep apnea as well as to development of better and more widely available treatment. There is no present treatment that can be used by all patients with this problem. The most effective and commonly used treatment for OSA, nasal continuous positive airway pressure, requires a patient to wear over the nose a mask through which air under pressure is delivered during sleep. Many patients are unable to tolerate nasal continuous positive airway pressure. There are no medications that are effective in OSA. Tracheostomy and mandibular advancement, the only surgical procedures that are effective in most patients, are either deforming or require a long surgical procedure with a painful postoperative course. Better treatment is clearly needed.

This study indicates that extremely obese female Yucatan micropigs can serve as a model for both OSA and central sleep apnea. This model can help us understand how obesity contributes to sleep apnea in humans and facilitate development of better treatment for this condition.

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