Electrically-activated dilator muscles reduce pharyngeal resistance in anaesthetized dogs with upper airway obstruction

H. Bishara, M. Odeh, R.P. Schnall, N. Gavriely, A. Oliven


ABSTRACT: There is current controversy as to whether electrical stimulation of upper airway musculature can be used as a beneficial treatment modality in patients with obstructive sleep apnoea syndrome. Increased upper airway (UAW) muscle activity decreases UAW resistance (R_uaw) in isolated UAW of dogs. In the present study, we evaluated the effect of UAW muscle contraction on UAW patency in anaesthetized dogs in vivo breathing spontaneously through partially and completely obstructed UAW.

Airflow and supraglottic pressure were measured to obtain R_uaw. R_uaw could be regulated by inhalation of a rubber balloon implanted transcutaneously in the pharyngeal submucosa to produce partial or complete obstruction. Wire electrodes were implanted bilaterally into the genioglossus (GG), geniohyoid (GH), sternothyroid (ST), and sternohyoid (SH) muscles for electrical stimulation (ES), and into the alae nasi for electromyographic (EMG) recording. Three levels of electrical stimulation were delivered to each muscle before and during partial or complete UAW obstruction.

Genioglossus and geniohyoid stimulation both resulted in a significant reduction in R_uaw, which was most pronounced during partial obstruction, reducing R_uaw from 54±11 to 14±3 and from 74±12 to 31±5 cmH_2O·L⁻¹·s, respectively. At low voltage, stimulation of the genioglossus was more effective than stimulation of the geniohyoid in reducing R_uaw. Furthermore, electrical stimulation of the genioglossus but not of the geniohyoid released total obstruction. In contrast, electrical stimulation of the sternothyroid and sternohyoid produced no significant change in R_uaw.

These findings demonstrate that selective UAW dilatory muscle contraction in spontaneously breathing anaesthetized dogs reduces R_uaw in the presence of UAW obstruction and releases UAW occlusion, with the genioglossus being the most effective muscle. This favours further attempts to investigate the benefits of electrical stimulation of selected upper airway muscles in the treatment of obstructive sleep apnoea syndrome.

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The obstructive sleep apnoea syndrome (OSAS) is a common disorder characterized by intermittent inspiratory closure of the upper airway (UAW) during sleep, resulting in troubled sleep frequently interrupted by arousals, daytime fatigue and hypersomnolence. Furthermore, the resultant hypoxaemia which develops during apnoea could trigger cardiac arrhythmias and produce systemic and pulmonary hypertension [1–5].

The mechanism(s) leading to UAW occlusion and cessation of airflow have been the subject of intensive research. Anatomical abnormalities and mechanical narrowing of the UAW each play an important role in OSAS. However, functional factors are obviously essential in maintaining UAW patency during inspiration, since even in the presence of severe obesity or anatomical abnormalities, apnoeas occur only during sleep, presumably due to decrease in UAW dilator muscle tone [5–10].

Previous studies have shown that enhanced UAW muscle activity during respiratory stimulation decreases UAW resistance (R_uaw) in the isolated UAW model [11, 12]. Similarly, electrical stimulation (ES) of the UAW muscles which shift the hyoid bone anteriorly, and stimulation of the genioglossus (GG), have been shown to decrease R_uaw [13–15] and collapsibility [15–17] in various models of the isolated UAW. Based on these findings, ES was assessed as a treatment modality in patients with OSAS [18–23]. Whilst some studies reported beneficial effects [19, 20], the clinical efficacy is as yet unclear, and reports by different investigators are not unequivocal [21–23]. The discrepancy between results of animal studies and the results obtained in patients with OSAS could be explained in several ways. For example, the effects of ES of UAW muscles on R_uaw and stability had not been examined in the intact, spontaneously breathing animal, nor had the effects of ES been studied in the presence...
of UAW obstruction. Therefore, the present study was undertaken to examine the effects of ES induced UAW muscle contraction on UAW patency in spontaneously breathing anaesthetized dogs. UAW muscle contraction was induced both before and during the introduction of mechanical flow impedance in the pharyngeal lumen, and the relative contribution of each muscle in reducing resistance and preventing obstruction was evaluated.

Methods and materials

Eight healthy mongrel dogs, weight 16±1.5 kg (mean±SEM), were studied in the supine position. The dogs were anaesthetized with 20 mg·kg⁻¹ chloralose, and additional anaesthesia was administered as needed during the surgical preparation. The dogs were spontaneously breathing room air. The head of each dog was tethered to maintain fixed positioning, the tongue was secured under mild tension to the lower jaw with tape, and the mouth was held open with a small rubber block situated between the front teeth. Upper and lower tracheostomies were performed, and the cervical trachea was bypassed via a polyethylene tube with a pneumotachograph through which the dogs breathed. The flow signal was electronically integrated to obtain tidal volume. Supraglottic pressure was continuously recorded through the tracheal tube via a thin polyethylene tube positioned 5–10 mm above the vocal chords (Validyne ±50 cmH₂O). End-tidal carbon dioxide tension (PETCO₂) was continuously monitored with an infra-red gas analyser (Mijnhardt Corp. Bunik, Holland). The femoral artery was cannulated for monitoring of blood pressure and for sampling arterial blood for gas analysis. Body temperature was monitored and maintained at 38°C with a heating pad.

Teflon-coated stainless steel electrodes with hooked bare tips were implanted transcutaneously into the alae nasi for electromyographic (EMG) signal recording. The signal was band-pass filtered, amplified, and integrated with a moving time averager to obtain the signal envelope. Similar electrodes were also implanted bilaterally into the genioglossus (GG), geniohyoid (GH), sternohyoid (SH), and sternothyroid (ST) for ES. Stimulation was performed using tetanic 50 Hz stimuli of 0.2 ms spike duration, given throughout the inspiratory phases of each of five successive breaths. ES was initiated at the start of each inspiratory phase using a computer controlled stimulator, which was triggered by the alae nasi EMG (ANEMG), which slightly precedes inspiratory muscle activity [24]. Stimulation was programmed to start before the onset of inspiratory airflow, and to continue throughout the inspiratory and early expiratory phase, to limit muscle fatigue. Airflow, tidal volume, transpharyngeal pressure, ANEMG, systemic blood pressure and the end PETCO₂ were recorded on a chart recorder (Graphite WR 7700).

Protocol

To alter Rₜₕₑₑₐₑ, a small rubber balloon connected to a thin tube was implanted transcutaneously under the pharyngeal submucosa via a small midline incision at the upper neck. The balloon was positioned medially behind the ventral oropharyngeal wall, below the tongue and above the glottis. Depending on dog size, 1–2 cm long (unstretched) balloons were used, which could be inflated by up to 10 mL with water. Stepwise inflation of the balloon increased Rₜₕₑₑₑ until complete occlusion occurred at the point when the mucosa-covered balloon reached the dorsal oropharyngeal wall. Rₜₕₑₑₑ was initially increased by attempting to raise the pharyngeal pressure approximately fourfold, and subsequently the balloon was inflated until complete occlusion occurred.

GG, GH and ST+SH together, were stimulated before obstruction (baseline), during partial obstruction, and during complete UAW obstruction. The efficacies of each of the individual UAW muscles in decreasing Rₜₕₑₑₑ and releasing occlusion were assessed during ES. For each muscle, three levels of ES were used: 1) The lowest ES at which muscle contraction could be observed; 2) ES of about twice this intensity; and 3) ES which provided maximal muscle contraction without current spread and apparent contraction of adjacent muscles. The same levels of ES were used before and during partial obstruction.

Data analysis

Rₜₕₑₑₑ was calculated by dividing peak negative inspiratory pharyngeal pressure by peak airflow. Data from five consecutive breaths were averaged and each stimulation trial was performed in triplicate. Significance of changes in Rₜₕₑₑₑ during ES of each UAW muscle were determined using t-test for paired data and accepted as significant at a p-value of <0.05.

Results

Changes in upper airway resistance (table 1)

GG stimulation. Figure 1 illustrates tracings from GG ES trials in one dog before obstruction, during partial pharyngeal obstruction and during complete obstruction. In the absence of exogenously applied obstruction, ES reduced transpharyngeal pressure. Partial obstruction resulted in marked increase in transpharyngeal pressure, reduction in airflow and a rise in ANEMG and PETCO₂. ES immediately reversed these changes (EMG signals were automatically terminated during ES for technical reasons). UAW occlusion, with almost complete cessation of airflow and a massive increase in transpharyngeal pressure and in ANEMG, was released by GG ES, which in this case restored baseline pressure-flow relationships.

Figure 2 shows the relationship between Rₜₕₑₑₑ and the intensity of GG stimulation. In the baseline state, without UAW obstruction, an average of 6±1 V stimulation caused no significant reduction in Rₜₕₑₑₑ. However stimulation at 12±2 V decreased resistance significantly from...
When the submucosal balloon was inflated, causing partial occlusion of the UAW and raising the resistance to 54±11 cmH₂O·L⁻¹·s, GG stimulation of 6±1 V lowered \( R_{\text{uaw}} \) to 30±5 cmH₂O·L⁻¹·s, and at 12±2 V stimulation resistance fell to 14±3 cmH₂O·L⁻¹·s (\( p < 0.01 \) for both). However, increasing ES to 20±2 V had no additional significant effect on \( R_{\text{uaw}} \). During complete UAW obstruction only 20±2 V GG ES released the obstruction with \( R_{\text{uaw}} \) falling to 29±3 cmH₂O·L⁻¹·s.

### Table 1. Effects of electrical stimulation of upper airway dilator muscles on upper airway resistance

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>GG ES stimulation V</th>
<th>Upper airway resistance cmH₂O·L⁻¹·s</th>
<th>GH ES stimulation V</th>
<th>SH + ST ES stimulation V</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 6±1 12±2 20±2</td>
<td>0 8±1 16±2 24±2</td>
<td>0 10 20 30</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>9 9 4 4</td>
<td>15 5 6 5</td>
<td>11 11 12 11</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11 11 10 6</td>
<td>19 7 5 6</td>
<td>10 10 8 10</td>
<td></td>
</tr>
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<td>3</td>
<td>10 8 5 4</td>
<td>21 20 19 15</td>
<td>8 8 8 5</td>
<td></td>
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<tr>
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<td>15 14 6 4</td>
<td>21 13 5 5</td>
<td>16 17 17 16</td>
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<tr>
<td>5</td>
<td>23 20 7 7</td>
<td>25 25 24 19</td>
<td>20 18 16 19</td>
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</tr>
<tr>
<td>6</td>
<td>9 8 6 5</td>
<td>9 9 9 7</td>
<td>8 8 6 6</td>
<td></td>
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<tr>
<td>7</td>
<td>3 2 1 1</td>
<td>5 5 4 4</td>
<td></td>
<td></td>
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<tr>
<td>8</td>
<td>25 25 15 10</td>
<td>28 29 17 17</td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>13.1 12.2 6.8* 5.0*</td>
<td>17.9 14.1 11.8* 9.7*</td>
<td>12.2 12.0 11.2 11.2</td>
<td></td>
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<tr>
<td>±SEM</td>
<td>±2.7 ±2.6 ±1.4 ±0.8</td>
<td>±2.8 ±3.3 ±2.7 ±2.2</td>
<td>±2.0 ±1.8 ±1.9 ±2.2</td>
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</tr>
</tbody>
</table>

Values are presented as individual and group mean±SEM. V: voltage stimulation; GG: genioglossus; GH: geniohyoid; SH: sternohyoid; ST: sternothyroid; ES: electrical stimulation; \*: \( p < 0.05 \); **: \( p < 0.01 \) as compared to the nonstimulated resistance. When the submucosal balloon was inflated, causing partial occlusion of the UAW and raising the resistance to 54±11 cmH₂O·L⁻¹·s, GG stimulation of 6±1 V lowered \( R_{\text{uaw}} \) to 30±5 cmH₂O·L⁻¹·s, and at 12±2 V stimulation resistance fell to 14±3 cmH₂O·L⁻¹·s (\( p < 0.01 \) for both). However, increasing ES to 20±2 V had no additional significant effect on \( R_{\text{uaw}} \). During complete UAW obstruction only 20±2 V GG ES released the obstruction with \( R_{\text{uaw}} \) falling to 29±3 cmH₂O·L⁻¹·s.

![Fig. 1. Tracing illustrating the effect of electrical stimulation (ES) at 20 V of the genioglossus muscle (GG) on transpharyngeal pressure (P), airflow (V'), alae nasi integrated electromyogram (ANEMG) and end-tidal carbon dioxide tension (PETCO₂) in one dog. a) baseline; b) partial obstruction; c) complete occlusion. See text for explanation. au: arbitrary units.](image-url)
GH stimulation. The relationship between $R_{\text{uaw}}$ and the intensity of GH stimulation is shown in figure 3. In the unobstructed state ($R_{\text{uaw}} 18\pm3 \text{ cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}$), an average stimulation of $8\pm1 \text{ V}$ produced no significant changes, whilst $16\pm2 \text{ V}$ stimulation resulted in significant reduction in $R_{\text{uaw}}$ to $11\pm3 \text{ cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}$ ($p<0.05$). With partial obstruction which raised the resistance to $74\pm12 \text{ cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}$, $8\pm1 \text{ V}$ stimulation reduced $R_{\text{uaw}}$ to $64\pm11 \text{ cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}$ ($p=\text{NS}$), and only at $16\pm2 \text{ V}$ did stimulation reduce $R_{\text{uaw}}$ significantly to $31\pm5 \text{ cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}$ ($p<0.01$). Increasing intensity of stimulation to $24\pm2 \text{ V}$ caused no additional significant change. When complete UAW occlusion was produced, release of occlusion was achieved only at levels of stimulation that caused current spread with simultaneous contraction of GG and other muscles.

ST and SH stimulation. The results of the combined ST and SH stimulation are shown in figure 4. ES of both muscles with intensities of 10, 20 and 30 V, causing intense muscle contraction, caused no significant change in $R_{\text{uaw}}$, in either the unobstructed state or during partial obstruction. Likewise, ES of these two muscles did not release total occlusion.

Changes in tidal volume, end-tidal carbon dioxide tension and ANEMG

Tidal volume was not affected by ES during the baseline, unoccluded state. For example, the tidal volume was $272\pm19$ before and $278\pm21 \text{ mL}$ during ES of the GG muscle. Partial occlusion, however, significantly decreased tidal volume to $194\pm16 \text{ mL}$ ($p<0.01$), and maximal GG stimulation restored tidal volume to the original level of $283\pm25 \text{ mL}$ ($p<0.05$). Similarly, the $\text{P}_{\text{ET,CO}_2}$ prior to obstruction (38±3 mmHg) was not affected by ES, but increased during partial occlusion to $46\pm4 \text{ mmHg}$ ($p<0.05$), and with maximal GG stimulation decreased to $39\pm3 \text{ mmHg}$. ANEMG envelope amplitude increased from baseline 12±2 arbitrary units (au) to 18±2 au ($p<0.01$) during partial occlusion, and reached 21±3 au during total obstruction ($p<0.01$).

Discussion

The results of this study indicate that electrical stimulation of the genioglossus and geniohyoid muscle reduces $R_{\text{uaw}}$ in spontaneously breathing anaesthetized dogs both before and during partial occlusion of the pharyngeal airway. During partial occlusion, UAW dilator muscle stimulation also restored tidal volume and $\text{P}_{\text{ET,CO}_2}$ to normal baseline levels. GG stimulation improved UAW patency beginning with low voltage stimulation, whilst reduction in $R_{\text{uaw}}$ during GH ES was observed only at higher intensities of stimulation. During complete UAW occlusion, ES of GG but not of GH released the obstruction. In contrast, ES of either sternohyoid or sternothyroid did not affect $R_{\text{uaw}}$.

The methodology used to measure $R_{\text{uaw}}$ in the present study is similar to that described by Widdicombe and
Changes in head, lower jaw and tongue position can substantially affect $R_{uaw}$ [5, 6, 10]. We, therefore, tethered the heads of the dogs to maintain a constant jaw position and taped the tongue under mild tension. This led to better reproducibility of results in repeated experiments in the individual dog. In previous studies [15], we observed that without this precaution, changes in head or jaw position and variable prolapse of the tongue resulted in highly variable baseline values before ES. During GG and GH ES, on the other hand, the level of $R_{uaw}$ with and without tethering was similar. Hence, tethering of the tongue to prevent its prolapse into the pharynx resulted in some underestimation of the effect of ES.

The possibility of some degree of current spread between GH and GG and possible mild activation of one muscle during high intensity stimulation of the other could not be completely ruled out. Activation of these muscles may be only crudely gauged by palpation. However, since no sign of such muscle activation was noted during the high intensity stimulation, it seems reasonable to assume that current spread during stimulation with lower voltages must have been minimal, and the mechanical effects were, thus, due mainly to contraction of the directly stimulated muscle. Therefore, we believe that the effects observed can be attributed directly to the specific muscles stimulated and, thus, demonstrate their specific effects on UAW patency.

Stimulation of the ST and SH was evaluated, since previous studies have reported a beneficial effect on UAW patency in experimental models using isolated UAW [15–17]. However, in the anaesthetized dog breathing spontaneously through the UAW, we found no significant change in $R_{uaw}$ both before and during partial occlusion, despite producing maximal contraction of the muscles. Furthermore, stimulation of these muscles also failed to release total obstruction.

Since the pharynx is a collapsible tube, it has the properties of a starting resistor [26]. Reduction of crosssectional area due to anatomical abnormalities increases flow velocity, and, hence, transmural pressure due to the Bernoulli effect. This causes a further decrease in crosssectional area, thus producing a vicious cycle leading to collapse. Therefore, lowering $R_{uaw}$ and/or stiffening the pharynx is crucial for preventing larger transmural pressures from developing and causing UAW collapse. The decrease in $R_{uaw}$ during ES indicates dilatation of the UAW, an effect that could easily be seen during the ES experiments.

The present study differs from previous ones, in that the effects of UAW muscle contraction were studied in a model in which animals breathed spontaneously through the UAW tract. Obviously, the model of mechanical pharyngeal obstruction used in the present study differs from anatomical abnormalities common in patients with OSAS. These anatomical abnormalities include hypertrophic tonsils, uvula and soft palate, macroglossia, micrognathia, nasal deformities and nonspecific narrowing of the pharyngeal airway [1, 2, 6, 10]. The submucosal inflatable balloon used in the present study may simulate a swelling at the ventral supra laryngeal, subglottic area, a rather uncommon pathology. Nevertheless, this model may help elucidate the role of UAW muscle contraction in improving UAW patency in the presence of obstacles to airflow. We found that under these conditions, with contraction caused by ES, the GG muscle was the most effective muscle in reducing $R_{uaw}$ and overcoming occlusion.

The ability of the electrically-stimulated GG to dilate the pharynx sufficiently to release the pharyngeal occlusion was particularly impressive, as the combined spontaneous intrinsic contraction of the UAW dilator muscles failed to achieve this effect. In four dogs, we applied sustained prolonged obstruction by inflating the submucosal balloon, and observed that the dogs remained obstructed despite maximal rise in ANEMG, suggesting similar activation of other UAW dilating muscles. When asphyxia-induced bradypnoea and decrease in blood pressure began, ES of the GG immediately released the obstruction and facilitated adequate ventilation.

Several studies have previously evaluated the effect of ES of UAW dilator muscles on $R_{uaw}$ and/or collapsibility in anaesthetized animals. These were based on various types of isolated UAW models, with the animals ventilated through a tracheostomy. In dogs, all investigators found a decrease in resistance and collapsibility during ES [13–16]. GG stimulation was most effective in reducing $R_{uaw}$ and collapsibility [15]. In rabbits, ES of ST and SH improved UAW stability [17]. In cats, however, GH and SH stimulation had no effect on $R_{uaw}$ [27]. Recently, hypoglossal nerve stimulation was found to reduce upper airway collapsibility in the isolated feline and canine upper airways [28, 29].

Attempts to use ES of UAW muscles in the treatment of OSAS were first undertaken by REMMERS et al. [7], who reported that apnoea could be interrupted by GG stimulation in an obese patient using intramuscular wire electrodes. Subsequently, MIKI et al. [19] found significant reduction in sleep-apnoeas in patients with OSAS when submental ES was applied using surface electrodes, and SCHWARTZ et al. [20] reported similar findings. However, other reports were unable to confirm these studies. INSALACO et al. [21] found submental ES to be of benefit in only 2 out of 9 patients. EDMONDS et al. [22] reported that submental ES failed to enlarge the UAW as observed on computed tomography (CT) during wakefulness, and was unable to revert OSAS without causing arousal. STROHL and co-workers [23, 24] came to the same conclusion, and found that even direct hypoglossus nerve stimulation failed to prevent OSAS.

The difference between these results and animal experiments may be due to species differences. It is most likely, however, that pain sensitivity during sleep, in contrast to anaesthesia, prevented satisfactory ES induced muscle contraction in patients with OSAS. An important factor could be the location of stimulation. SCHNALL et al. [30] showed that sublingual ES (which contracts the GG) but not submental stimulation (which activates mainly the GH) reduced pharyngeal resistance in awake humans with raised $R_{uaw}$.
Furthermore, only if ES was performed at the sublingual location, could $R_{\text{uaw}}$ be lowered during sleep without causing arousal [31]. A further possible explanation for the discrepancy between previous animal studies and studies in patients with OSAS was that animal studies were all performed on isolated intact UAW models.

The present study has shown that improved upper airway patency can be obtained with electrical stimulation of upper airway muscles in dogs breathing through the upper airway with partial and complete upper airway obstruction. Furthermore, this study provides additional support for the superiority of genioglossus stimulation in releasing upper airway obstruction. These results suggest that electrical stimulation of selected upper airway muscles could be a beneficial treatment modality in patients with obstructive sleep apnoea syndrome.

References