The effects of a mixture of surface-active agents (Sonarex) on upper airways resistance and snoring in anaesthetized dogs

J. G. Widdicombe, A. Davies

ABSTRACT: We measured upper airways resistance from the trachea and from the pharynx to the atmosphere, EMG of the genioglossus muscle and the sound of snoring, in anaesthetized greyhounds, breathing spontaneously through the upper airways. Using extra-corporeally produced continuous flow we determined flow/pressure curves for the upper airways and resistances from the trachea and from the pharynx. We tested the effects of 0.9% saline and of Sonarex (a proprietary mixture containing sodium chloride, glycerol, polysorbate 80 and benzalkonium chloride). Both saline and Sonarex decreased upper airways resistance, but the latter did so more consistently. With Sonarex, genioglossus activity increased and the sound of snoring decreased. Flow/pressure curves 5-20 min after Sonarex showed a decrease in upper airways resistance and a smoother curve, whereas those with saline showed an increase in resistance. The sound produced by continuous flow through the upper airways was decreased by Sonarex but increased by saline. Thus, both Sonarex and saline decrease upper airways resistance, but Sonarex also reduces the sound of snoring and the resistance and sound of continuous airflow through the upper airways.

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We have described a method for measuring upper airways resistance, genioglossus electromyogram (EMG) and the sound of snoring in anaesthetized greyhounds [1]. The present paper describes the effects of saline and of a proprietary treatment for snoring (Sonarex) on these variables. The liquids were inserted into the oropharynx. Some of the results have been presented as an abstract [2].

Methods

Twelve adult greyhounds were used. Nine were the same dogs as described in a previous paper [1]. In brief, they were anaesthetized with pentobarbitone sodium (30 mg·kg⁻¹ initially), and blood pressure and tracheal airflow were measured. The latter was obtained from a plastic catheter, internal diameter 2 mm, was passed via the mid-cervical oesophagus into the oropharynx. This was used for pressure recording and for injection of liquids. The electromyogram of the genioglossus muscle was recorded via hook electrodes, and the sound of snoring was recorded from a microphone either attached to a canine tooth or mounted 2-3 cm away from the side of the mouth.

Two experimental procedures were performed. In the first the pneumotachograph connected the two tracheal cannulae so that the dog breathed through its upper respiratory tract. Airflow, tracheal and pharyngeal pressures, EMG and sound were all recorded on magnetic tape (Racal) and on recording paper (Gould).

In this condition some dogs did not snore but snoring could be induced by closing the nostrils with gentle manual pressure. To prevent the respiratory effects of nasal obstruction, this was performed for 1-2 breathing cycles about once every minute during experimental runs. On a few occasions the nostril on one side only was closed to induce snoring.

With the second procedure the dog breathed through the caudal tracheal cannula and the pneumotachograph. The cranial tracheal cannula was connected to a rotameter and a compressed air cylinder, and air was blown through the upper respiratory tract in steps of 10 l·min⁻¹ from 0-60 l·min⁻¹. Each step was held for about 20 s. At any constant flow rate, pressure varied with respiratory phase, and peak expiratory and inspiratory pressures were measured. This allowed the preparation of flow/pressure curves for the upper respiratory tract for inspiratory and expiratory phases. The procedure was carried out first with the nose open and then with the nose closed.

When the dog was either snoring spontaneously or because its nostrils were closed, a control record was made for several minutes, if necessary closing the nostrils for...
one or two breaths every minute. The two tracheal cannulae were then disconnected and flow/pressure curves of the upper respiratory tract were determined first with the nose open and then with the nose closed. Duplicates of each curve were made. The two tracheal cannulae were then reconnected via the pneumotachograph so that the dog again breathed through its upper respiratory tract.

After several minutes of recording, if necessary with closure of the nose, 0.5 or 1.0 ml of either Sonarex (see below) or saline was introduced through the pharyngeal catheter, which could not be used for pressure recording for about 30 s during this injection. The solution was blown in with air, and pressure recording was restored promptly. After recording variables with breathing through the upper respiratory tract for about a further 5 min, the two tracheal cannulae were again separated and flow/pressure curves of the upper respiratory tract were determined with nose open and nose closed, in duplicate. The whole procedure took about 20 min. Supplemental doses of anaesthesia were given at intervals of about 60 min, and never during a procedure as described above.

Saline was made up as 9 g·l⁻¹ sodium chloride. Sonarex is a mixture of sodium chloride (9 g), glycerol (85%, 3 g), polysorbate 80 (Tween 80, 2 g) and benzalkonium chloride (0.2 g), all quantities per litre of water; it was provided by Anasco GmbH. The choice of solution for the initial test in each dog was randomized, and the other solution was used subsequently. Usually at least 2 h were allowed between injections of liquids. In some experiments the oropharynx was cleaned out with gauze swabs between introductions of liquids. In some dogs a third injection of liquid was made about 2 h after the second. Results were analysed by analysis of variance and Student’s paired t-test.

**Results**

Figure 1 shows an example of the action of Sonarex on airflow, upper airway pressures and genioglossus EMG. Before Sonarex (A), the genioglossus contracted only in the inspiratory phase and there were rapid oscillations in inspiratory flow and pressure corresponding to snoring. Immediately after the application of Sonarex there was an increase in genioglossus activity in both inspiratory and expiratory phases (B). Within 30 s the rapid oscillations in flow and pressure had decreased (C), the pharyngeal and tracheal pressure swings were smaller especially in the inspiratory phase and flow was, if anything, greater. In other words there were decreases in upper airway resistances measured from the two sites concomitant with increased contraction of genioglossus.

Table 1 summarizes the percentage changes in upper airways resistance, measured from the trachea and pharynx, on insertion of saline and Sonarex into the oropharynx. There was considerable variation in response, as can be seen from the size of the standard errors of the means. However, both saline and Sonarex usually decreased upper airways resistances, especially those measured from the pharynx, whether the nose was open or closed.

Statistically Sonarex significantly decreased resistances in the inspiratory phase in all but one condition. Because of the high variance of control values, population means for Sonarex were no different from those for saline except for pharyngeal resistance in inspiration with the nose closed. However, with paired values, the responses to Sonarex were significantly greater than those to saline in half the conditions assessed (table 1).

![Figure 1](image-url)
Table 1. Changes in upper airways resistance on addition of saline or Sonarex to the oropharynx.

<table>
<thead>
<tr>
<th>Pressure</th>
<th>Nose</th>
<th>n</th>
<th>Control</th>
<th>Change</th>
<th>Control</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>kPa·l⁻¹·s</td>
<td>%</td>
<td>kPa·l⁻¹·s</td>
<td>%</td>
</tr>
<tr>
<td>Saline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheal</td>
<td>Open</td>
<td>11</td>
<td>0.69±0.16</td>
<td>-8±3.3</td>
<td>0.59±0.11</td>
<td>-1±3.4</td>
</tr>
</tbody>
</table>
|              | Closed   | 11 | 3.48±3.72| +1±8.4 | 8.58±7.12| -16±6.1*
| Pharyngeal   | Open     | 9  | 0.38±0.10| -14±7.6| 0.35±0.10| -15±10.6|
|              | Closed   | 9  | 3.21±2.86| -8±7.5 | 7.49±6.53| -4±12.2|
| Sonarex      |          |    |          |        |          |        |
| Tracheal     | Open     | 15 | 0.66±0.14| -19±9.7| 1.02±0.22| -11±4.9†|
|              | Closed   | 13 | 1.32±0.34| -17±7.0| 5.20±1.15| -28±8.9**|
| Pharyngeal   | Open     | 14 | 0.53±0.16| -9±3.5 | 0.62±0.15| -28±4.7**|
|              | Closed   | 12 | 1.28±0.26| -13±12.1| 3.99±1.15| -29±6.9***|

Values are means±SEM. * p<0.05; ** p<0.01 for change compared to control; † p<0.05 for Sonarex compared to saline, paired values.

Analysis of the results in terms of translaryngeal pressure, obtained by subtracting pharyngeal from tracheal pressures and calculating laryngeal resistance, showed that neither saline nor Sonarex had a significant effect on laryngeal resistance. Because of the relatively small sizes of laryngeal resistance [1] it was difficult to measure changes in this variable accurately.

Integrated sound and integrated genioglossus EMG were measured before and immediately after introduction of saline or Sonarex into the pharynx (table 2). Sonarex significantly decreased sound by -19%, whereas saline increased sound by 11% (ns). Both saline and Sonarex significantly increased genioglossus EMG in the inspiratory phase and this was significantly larger for Sonarex compared to saline. In only one of fourteen tests did Sonarex fail to increase genioglossus EMG.

Figure 2 illustrates the results of injection of Sonarex into the pharynx on genioglossus EMG and its integral, and on pharyngeal pressure and airflow. Sonarex increased the activity of genioglossus EMG in the inspiratory phase and this was significantly larger during expiration. Pressure swings in the pharynx were reduced although airflow values were maintained. Thus resistance measured from the pharynx was reduced.

Figure 3 shows curves relating pressure to flow measured simultaneously from the trachea and the pharynx with the nose open, in the inspiratory phase, in one experiment. A common feature of the relationships is that before Sonarex the flow/pressure curves are highly irregular in shape, usually showing a pronounced decrease in pressure (resistance) at the middle flow rates (see [1] and Discussion).

To compare results between dogs we normalized the curves. The flow/pressure curves before Sonarex or saline were drawn with the maximum pressure at maximum flow (60 l·min⁻¹) as 100%, and all the values at lower flows and after administration of Sonarex or saline are expressed as percentages of this value. The total number of pairs of curves is eight: pressures from pharynx and trachea, nose open and nose closed, inspiratory and expiratory phases. In figure 4 the effects of Sonarex (left) and saline (right) are shown for pharyngeal pressure with the nose closed in the expiratory phase. Sonarex displaced the curve downwards (i.e. reduced

Table 2. Changes in integrated sound and integrated genioglossus EMG on addition of saline or Sonarex to the oropharynx.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Condition</th>
<th>n</th>
<th>Change %</th>
<th>n</th>
<th>Change %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sound</td>
<td>Spontaneous flow, nose open</td>
<td>7</td>
<td>+11±19.0</td>
<td>10</td>
<td>-19±8.0*</td>
</tr>
<tr>
<td></td>
<td>Continuous flow, nose open</td>
<td>5</td>
<td>+10±8.7</td>
<td>9</td>
<td>-65±9.2**</td>
</tr>
<tr>
<td></td>
<td>Continuous flow, nose closed</td>
<td>5</td>
<td>+55±16.4*</td>
<td>7</td>
<td>-47±15.6†</td>
</tr>
<tr>
<td>EMG</td>
<td>Spontaneous flow</td>
<td>8</td>
<td>+16±5.4**</td>
<td>14</td>
<td>+55±15.4***</td>
</tr>
</tbody>
</table>

Means±SEMs. * p<0.05; ** p<0.01 for change compared with zero effect; † p<0.05 for response to Sonarex compared with that to saline.
airflow resistance) and the curve was smoother. By contrast, saline (right) displaced the curve upwards whilst also making it smoother. The other seven conditions gave similar patterns: Sonarex displaced the flow/pressure curves downwards whereas saline displaced the curves upwards. These changes were especially conspicuous in the middle part of the curves. However, statistical significance was not always as clear as in figure 4, possibly because N-values are sometimes smaller.

Analysis of genioglossus EMG activity during flow/pressure curves is not presented because genioglossus activity was often weak or absent when the animals were not breathing through the upper respiratory tract, and because imposition of flow through the upper airways often reflexly increased genioglossus activity [1, 3-5]. With regard to sound, figure 5 shows the effect of Sonarex, with a time interval of about 20 min between records. In (A), determination of the flow/pressure
Fig. 4. – Averaged and normalized curves for flow/pressure relationships for pressures measured with the nose closed and in the expiratory phase. On the left are shown averaged curves for controls (crosses) and after Sonarex (filled circles); on the right are shown curves for controls (crosses) and after application of saline (filled circles). Vertical lines are SEMs. * p<0.05 for paired values for Sonarex and saline compared with controls.

Fig. 5. – Effects of Sonarex on sound produced by airflow through the upper airways isolated in situ with the nose open. From above down: genioglossus EMG, sound from a microphone next to the mouth, airflow (V) and pharyngeal pressure (Pph). Flow was increased by steps of 10 l/min at each arrow, therefore increasing up to a maximum of 60 l/min for the furthest right-hand arrows. In (A), when airflow surpassed 40 l/min, sound started to be recorded reaching a maximum at 60 l/min. In (B), after administration of 0.5 ml of Sonarex into the pharynx, the same increments in airflow caused far less sound, starting at about 50 l/min, and the pressure increases due to flow were smaller.
relationship produced a conspicuous sound at flows greater than 40 l-min\(^{-1}\). In (B), after administration of Sonarex there was a smaller increase in pharyngeal pressure for each increment of flow and the sound was far smaller.

The effects of Sonarex and saline on the integrated sound during flow/pressure determinations of upper airways resistances were averaged (table 2). Sonarex decreased sound in each of the nine tests by a mean of -65% when the nose was open, and by -47% (n=7) when the nose was closed. By contrast, saline increased sound by 10% when the nose was open and by 55% when the nose was closed.

**Discussion**

We had hoped to conduct a blind cross-over study, but this proved impractical. The experimenter could distinguish between Sonarex and saline, since the former was slightly opalescent and its bubbles were stable. An attempt at a cross-over study did not give equal N-values for some variables. Pharyngeal pressure was often difficult to measure in tests with saline, although Sonarex invariably led to stable pharyngeal pressure records, presumably because of its lubricant and surface activities in the catheter and oropharynx. In dogs and conditions when there was no sound of snoring, or no genioglossus EMG, analysis of these variables was impossible. We have therefore included all results in the tabular analysis.

Sonarex is a proprietary treatment for snoring, subjects being instructed to instill four drops into each nostril (total about 0.5 ml) before sleeping [6, 7]. We found that it reduced upper airways resistance, decreased the sound of snoring, and increased genioglossus muscle activity. Some of these effects could be caused by changes in mechanical properties of the airways. For example, Sonarex could lower surface tension of any mucus or liquid lining the pharynx and would presumably reduce the adheriveness of the pharyngeal soft tissues. The opening and closing pressures of the pharynx of experimental animals and dead humans are influenced by tissue adheriveness [8, 9]. In an important study in man, phosphocholinamin (a surfactant consisting of lecithin in mineral oil) reduced the degree and frequency of occurrence of snoring [10]; upper airways resistances were not measured. It is not known to what extent the intensity and quality of snoring depend on the amount of secretions in the upper airways and on their rheology but, if these properties were changed by surface-active materials, snoring might also be affected. It is interesting that saline had the opposite effect to Sonarex on snoring; integrated sound was increased and the subjective impression was that this change was because of the introduction of a "bubbling" noise not heard after Sonarex.

Genioglossus activity was increased by Sonarex, which strongly suggests that a reflex was activated leading to greater pharyngeal dilatation. Reflexes from the upper airways which contract the pharyngeal dilator muscles are well established [3–5, 11, 12], although little is known about the natural stimuli to the nervous receptors that mediate them. The ingredients of Sonarex might have had a direct action on nervous receptors, or the reflexes might be influenced secondarily by induced mechanical changes. Genioglossus activity increased in both inspiratory and expiratory phases, consistent with the measured changes in upper airways resistances. Other studies have shown that the genioglossus, although an airway dilator muscle, can discharge in one or both respiratory phases depending on the position of the tongue [13, 14].

We have not attempted to identify which of the ingredients of Sonarex are active. Polysorbate 80 is a non-ionic surfactant which, in high concentrations, changes the permeability of rabbit oral mucosa [15] and removes lipids from the surface of the intestine [16]. It also increases the permeability of the intestine to small solutes [17]. Benzalkonium chloride is a cationic surfactant that increases the permeability of the intestine to small solutes [17–19] and changes the ultrastructure of the cornea [20]. Thus, both agents might work not only by their mechanical surface activity but also by altering epithelial function. There is little value in comparing concentrations with different methods, since the concentrations in our studies could only be determined by direct experiment or by knowing the dilution factor of the Sonarex added to any secretions already in the upper airways. With regard to glycerol, we have found no evidence that it might have either appreciable surface activity or a physiological effect on epithelia.

One important observation was that 0.9% sodium chloride solution was active in some respects. It frequently lowered upper airways resistance and increased genioglossus EMG, although considerably less than Sonarex. It did not, like Sonarex, decrease the sound of snoring but increased it; this may indicate that the surface activity of Sonarex is the more important factor influencing the sound of snoring. Our difficulty in interpreting these results is due to ignorance of the chemical and physical properties of the resting secretions in the pharynx. There could be considerable dehydration, especially if breathing is through the mouth as occurs in many snoring subjects. Thus, not only could the mucus be "thicker and stickier" than normal, but the osmolarity of the epithelial fluid could be higher than that of 0.9% saline. 0.9% saline could have an action on the adheriveness of mucus and of the airway soft tissue, and could have reflex actions in the nose and the larynx [4, 21]. An airway which had become acclimatized to epithelial fluid of high osmolarity due to evaporation might well respond to the introduction of "normal" saline as a non-physiological event.

The actions of Sonarex cannot be explained as being due solely to its saline base for two reasons. Firstly, as indicated above, the effects of saline on resistance were usually smaller and more variable than those of Sonarex; they were certainly far smaller on genioglossus EMG and were in the opposite direction on snoring. Secondly, when flow/pressure curves were determined at 5–20 min after application of saline or Sonarex and compared to controls, Sonarex produced a significant reduction in resistance whereas saline increased resistance. Sonarex also markedly decreased the irregularities of the flow/
pressure curves. These irregularities may well be due to sudden changes in the position of the epiglottis and the soft palate as flow is increased through the upper airways [1]. At this time Sonarex also decreased the noise of airflow through the upper airways. Saline may not have directly increased resistance assessed from flow/pressure curves because we did no controls without administration of either saline or Sonarex. The passage of time between determination of flow/pressure curves might have been enough to increase resistance by a drying out of the upper airways.

In conclusion, our results show that an animal model for studying snoring and upper airways obstruction can be used successfully to test physiological mechanisms. The results support human studies indicating that surface-active agents in the upper airways can reduce snoring [10], and animal studies indicating that upper airways resistance depends upon soft tissue adhesiveness [8, 9] and on the contraction of airway dilator muscles [3, 4].

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References


RÉSUMÉ: Nous avons mesuré les résistances des voies aériennes supérieures, à la fois au niveau de la trachée et du pharynx, par rapport à l’atmosphère, ainsi que l’electromyogramme du muscle gênieglosse et les bruits de renflements chez des lévriers anesthésiés. Nous avons déterminé également les courbes débit-pression pour les voies aériennes supérieures, en utilisant un débit continu de production extra-corporelle et nous les avons analysées en terme de résistance au niveau de la trachée et du pharynx. Nous avons étudié l’effet d’une solution saline à 0,9% et celui du Sonarex (un mélange commercial contenant du chlorure sodique, du glycérol, du polysorbate 80 et du chlorure de benzalkonium) sur les variables mesurées. Quand les chiens respirent au travers des voies aériennes supérieures, la solution saline isotonique ainsi que le Sonarex diminuent les résistances des voies aériennes supérieures mais le Sonarex le fait de façon plus régulière. L’activité du gênieglosse est augmentée et les bruits de renflements diminuent avec le Sonarex. Quand les courbes débit-pression sont déterminées, on observe de 5 à 20' après Sonarex une diminution de la résistance des voies aériennes supérieures et une courbe plus lisse alors que l’inhalation de solution saline entraîne une augmentation de la résistance. Les bruits produits par un débit continu au travers de voies aériennes supérieures sont diminués par le Sonarex mais aug­mentés par la solution saline isotonique. La résistance des voies aériennes supérieures est diminuée aussi bien par le Sonarex que par la solution saline mais le Sonarex diminue en outre les bruits de renflements ainsi que la résistance et le son entraînés par un débit continu d’air au travers des voies aériennes supérieures.