Sex differences and sleep apnoea

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Although obstructive sleep apnoea is a highly prevalent disorder with major public health ramifications for both men and women, very little is known about sex differences in the pathogenesis of this disorder. Initial studies[1–3] indicated that sleep apnoea was much more common in men than in women. It was originally thought that the male to female ratio for obstructive sleep apnoea was approximately 8:1.[1–3] However, more recent and rigorous epidemiological studies[2 4] have shown that the male to female ratio for sleep apnoea is in the range of 2:1. Young and colleagues[4] reported that the prevalence of obstructive sleep apnoea associated with excessive daytime sleepiness in the 30–60 year old population is 4% in men and 2% in women. Gislason and coworkers[2] estimated that the lower limit of the prevalence of sleep apnoea in middle aged Icelandic women was 2.5%. These studies indicate that sleep apnoea is common in women. Moreover, studies have shown that the clinical presentation of sleep apnoea is similar in men and women, although the prevalence is higher in men.[5] One reason for the higher prevalence in men may be that women are less likely to report symptoms associated with sleep apnoea.[6] However, several studies[7–10] have demonstrated sex differences in the structure and physiological behaviour of the upper airway. Such data imply that sex differences in the prevalence of sleep apnoea are not solely related to the under-reporting of symptoms but rather are related to pathological differences in the presentation of this condition in men and women.

What are the possible mechanisms underlying the differences in the pathogenesis of obstructive sleep apnoea in women and men? Two important determinants of upper airway luminal calibre are the activity of the upper airway dilator muscles, which tend to increase airway dimensions, and the anatomy of the oropharynx. Upper airway size presumably reflects a balance between these two factors, and women differ from men in both of them. Studies have found that during wakefulness women have augmented genioglossal muscle activity compared with age matched men.[7] Theoretically, increased activity of the genioglossus muscle would result in greater upper airway stability. Moreover, female hormones (possibly progesterone) have been shown to have an impact on genioglossus muscle activity.[8] If this augmented genioglossus muscle activity persists during sleep, the upper airway of women may be less likely to collapse or narrow than that of men. Thus, one possible explanation for the reduced prevalence of sleep apnoea in women is that upper airway dilator muscle activity is increased, making upper airway closure less likely to occur during sleep.

In addition to changes in upper airway motor tone, the configuration and anatomical structure of the upper airway appear to be different in men and women. Differences in upper airway shape between men and women could theoretically increase the risk for sleep apnoea by making the airway more likely to collapse during sleep.[11] Studies in normal subjects using acoustic reflection have shown that the upper airway is larger in men than in women.[9 10] However, when the pharyngeal cross sectional area was normalised for body surface area there were no significant differences between men and women.[10] Body surface area, however, may not be the appropriate control. A more recent study[12] using acoustic reflection did not find sex related differences in the average cross sectional airway between supine men and women. Unfortunately, acoustic reflection is not an ideal upper airway imaging modality since the mouth is opened during imaging (once the mouth is opened the soft palate elevates from the tongue altering pharyngeal anatomy).[13] Computed tomography (CT) and magnetic resonance imaging (MRI) provide a better anatomical representation of the upper airway than acoustic reflection.[13] Schwab and colleagues[14] performed dynamic computed tomography (electron beam) to evaluate respiratory related changes in the upper airway during wakefulness. No significant differences in upper airway calibre during respiration were noted between normal men and women but the sample size was too small (10 men and five women) to draw definitive conclusions. Studies of pharyngeal resistance have not shown any differences between men and women, which suggests that upper airway calibre is similar in the two sexes.[7] The data from all these studies[7 9 10 12 14] are conflicting as to whether or not there are truly sex related differences in upper airway calibre.

In order to answer this fundamental question more definitively, Whittle and colleagues have used MRI to examine upper airway and soft tissue differences in normal men and women and their results are reported in this issue of *Thorax*.[15] Magnetic resonance scanning is an ideal modality to examine sex related differences in upper airway anatomy since it provides excellent airway and soft tissue resolution (including adipose tissue), accurately determines cross sectional area and volume, and provides the capability of imaging in the axial, sagittal and coronal planes.[13] They examined normal men and women matched for age and body mass index but found no sex related differences in the minimum cross sectional area. The mean cross sectional area was similar in men and women in the palatal region but was significantly greater in men in the subpalatal region. These data indicate that upper airway calibre may be similar in men and women, at least in certain anatomical regions. However, upper airway volume or regional volumes (retropalatal and retroglossal) may be a more definitive measurement than upper airway area but these were not determined in this investigation. Further studies are still needed to determine whether volumetric differences in upper airway calibre exist between men and women.

In addition to upper airway calibre, Whittle *et al*[15] studied sex related differences in upper airway soft tissue structures in normal men and women. It is critical to examine upper airway soft tissue and bony structures since these structures are the determinants of upper airway calibre (examination of the doughnut rather than the hole in the doughnut). The primary determinants of upper airway calibre are thought to arise from three domains: upper airway adipose tissue, craniofacial morphology, and size of the surrounding soft tissue structures (tongue, soft palate, lateral pharyngeal walls).[13] Women are known to have a smaller neck size than men so it would be reasonable to hypothesise that craniofacial structure, upper airway fat deposition, and size of the critical soft tissue structures should be smaller in women than in men.[12] The data presented by Whittle and colleagues[15] lend partial support to such a hypothesis.

Obesity is known to predispose to obstructive sleep apnoea[16] so it has been hypothesised[17 18] that increased upper airway adipose tissue, specifically deposited in the lateral parapharyngeal fat pads, results in airway narrowing. Indeed, upper airway imaging studies have found that the size of the lateral parapharyngeal fat pads is increased in obese patients with apnoea.[17 18] Increased adipose tissue surrounding the upper airway has been demonstrated in obese and non-obese patients with sleep apnoea.[19] Upper airway MRI studies[18 20] have confirmed that the total volume of fat in the lateral parapharyngeal fat pads is greater in patients with sleep apnoea than in normal subjects. In addition, it is known that fat distribution is different in men and women.[21 22] Men tend to have predominantly upper body fat whereas women have lower body fat distribution.[21 22] It would therefore be reasonable to hypothesise that upper airway fat deposition and, specifically, lateral parapharyngeal fat pad size is greater in men than in women. However, the data reported by Whittle and colleagues[15] do not support this hypothesis. No significant differences between normal men and women were found in the volume of upper airway fat, and the deposition of upper airway fat was greater in men than in women only in the anterior segments inside the mandible in the palatal region.

The major finding from the investigation by Whittle *et al*[15] was that total neck soft tissue volume was significantly greater in men than in women. Since they found fat volumes to be similar in men and women, the increased tissue volume in men was related to enlargement of upper airway soft tissue structures. They found that the mean cross sectional area of the tongue and soft palate was larger in men than in women. Unfortunately, the lateral pharyngeal walls, a key mediator or upper airway calibre, were not specifically examined. Schwab and coworkers[20] have shown that the thickness of the lateral pharyngeal muscular walls is an important anatomical factor in airway narrowing in subjects with sleep apnoea. These lateral walls, if measured, may have been part of the increased tissue found in the upper airway of men by Whittle and colleagues.[15] Volumetric imaging of the tongue, soft palate, and lateral walls should now be performed to determine definitively whether sex related differences exist in the upper airway soft tissue structures and to establish which of these structures is the most important. It is not known why the upper airway soft tissue structures are larger in men than in women, but it is possible that obesity (increased fat and fat free tissue), genetic, or hormonal factors underlie this process.[13 20]

Craniofacial morphology may also be important in examining sex differences in upper airway size and structure. Studies have shown certain craniofacial morphometric features of women with mild sleep apnoea, including a narrow hard palate, overjet, triangular chin, and class II malocclusion.[3] Further studies are needed to evaluate these and other morphometric characteristics of men and women. Such information may be useful in screening populations for sleep disordered breathing.

Why is the upper airway different in men and women? I do not believe we entirely understand the answer to this question although upper airway soft tissue structures (tongue, soft palate, possibly lateral pharyngeal walls) appear to be larger in men than in women. However, sex is likely to be only one of several important factors which mediate upper airway calibre and increase the risk for sleep apnoea. Other important factors are thought to include age,[12] race,[23] and genetics.[13] These factors may interact and be intimately affected by regional obesity. It will be critical in the future to understand the various risk factors for sleep apnoea so that suitable screening techniques can be used. Volumetric imaging studies may provide the tools to examine these risk factors. Sex will undoubtedly be an important factor in such an equation.

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