AMERICAN UNIVERSITY OF BEIRUT

THE ROLE OF HYOID BONE POSITION IN MAINTAINING UPPER AIRWAY PATENCY

by
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ABSTRACT
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Corine Joseph Samaha for Master of sciences
Major: Orthodontics

Title: Role of Hyoid Bone Position in Maintaining Upper Airway Patency

The hyoid is a mobile bone located at the base of the tongue. It is the point of insertion for many of the muscles that control the geometry and mechanical properties of the upper airway (UA). Consequently, the hyoid is likely essential in maintaining upper airway patency, particularly when exposed to inspiratory negative pressures. Recurrent collapse of the upper airway during sleep is characteristic of obstructive sleep apnea (OSA), a highly prevalent respiratory sleep disorder with serious health risks. An inferiorly positioned hyoid is the most consistently observed anatomical difference between people with OSA and healthy controls. Surgical hyoid repositioning procedures are being performed to treat OSA patients, but outcomes are highly variable, primarily because of the lack of knowledge regarding the precise influence of hyoid position on upper airway function. The aim of this thesis is to determine the role of hyoid bone position in maintaining upper airway patency.

Seven anaesthetized, male, New Zealand White rabbits were tracheostomized and left to breath spontaneously via the caudal trachea (i.e. no UA airflow or muscle activity). The hyoid was repositioned within the mid-sagittal plane along cranial, caudal and anterior directions from baseline (0mm) to 5mm in 1mm increments, and along 30°, 45° and 60° cranial and caudal directions. These movement were performed using a custom-made device. The effect of hyoid position on upper airway patency was quantified using the upper airway closing pressure, Pclose (the negative pressure required to close the upper airway). On the basic premise that the more Pclose is negative, the less the upper airway is prone to collapse. Data were expressed as a change from baseline (0mm). Repeated measures ANOVA tests were performed to assess changes in key outcomes with hyoid displacement. Statistical significance was inferred for $p < 0.05$.

The baseline Pclose before any hyoid repositioning was -3.55 ± 0.95 cmH_2O (mean± SD). The anterior displacement of the hyoid resulted in the greatest decrease in Pclose amongst all directions ($p=0.002$). Pclose decreased progressively with each increment of anterior hyoid bone displacement, going down by 3.98 ± 1.31 cmH_2O at 5mm. In contrast, when the hyoid was moved cranially or caudally, Pclose did not change from the initial baseline value ($p= 0.723$ and $p=0.352$ respectively). When the hyoid was moved in anterior-cranial 45° and anterior-caudal 45° directions, Pclose decreased significantly ($p=0.001$ and $p=0.004$ respectively) and at similar magnitudes to the anterior direction ($p>0.05$). Also, the anterior-cranial 60° and anterior-caudal 60° directions decreased Pclose by 3.81 ± 0.78 cmH_2O and 4.29 ± 1.68 cmH_2O respectively, which is similar to the improvement obtained with the anterior direction. The anterior-

cranial 30° and anterior-caudal 30° improved Pclose to a lesser extent (2.22 ± 0.58 cmH_2O and 2.73 ± 0.85 cmH_2O respectively).

This is the first study to quantitatively examine the influence of hyoid bone position on upper airway patency. Study outcomes suggest that hyoid surgical interventions for OSA treatment and possibly mandibular advancement oral appliances should focus on increasing the amplitude of anterior hyoid repositioning as a main contributor to improved upper airway patency.

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CHAPTER 1

THE UPPER AIRWAY

1.1.General Structure and Function

The upper airway is a complex structure that participates in various physiologic functions including breathing, phonation and deglutition [1] . It has a dynamic control system that is composed of active (muscle activity, central drives) and passive (size, composition, and shape of the airway) components. Together they aim to maintain the equilibrium of forces applied on the upper airway during swallowing (that tends to constrict the UA) and during breathing (that tends to open the UA) [2]. The upper airway has a tube-like shape and is formed by the intricate arrangement of soft, cartilaginous and bony tissues, that collectively are often referred to as the peri-pharyngeal tissues. Due to its deformable mechanical properties, the upper airway is exposed to higher risk of closure, predominantly during inspiration when there is development of negative intraluminal airway pressure[3] . Hence, although a more rigid assembly would be more suited to maintain airway patency for breathing and speech, a compliant structure is necessary to allow passage of foods and fulfilling the other functions allocated for the upper airway.

The upper airway is divided along 4 cephalocaudal levels [1, 4, 5] (figure 1.1):

- The nasopharynx, extending from the posterior nasal choanae to the caudal margin of the hard palate.

- The velopharynx, running along the entire length of the soft palate from the caudal till the cranial margin. It is combined with the nasopharynx in some medical references [5], but due to its deformability, it constitute a major element of focus in upper airway pathophysiology (such as obstructive sleep apnea).

- The oropharynx or retroglossal segment extends from the tip of the soft palate to the epiglottis.

- The hypopharynx or laryngopharynx includes the epiglottis from its cranial margin to its base (level of the vocal cords)

The velopharynx is the most prone to closure followed by the oropharynx as they are the less supported sites [6, 7].

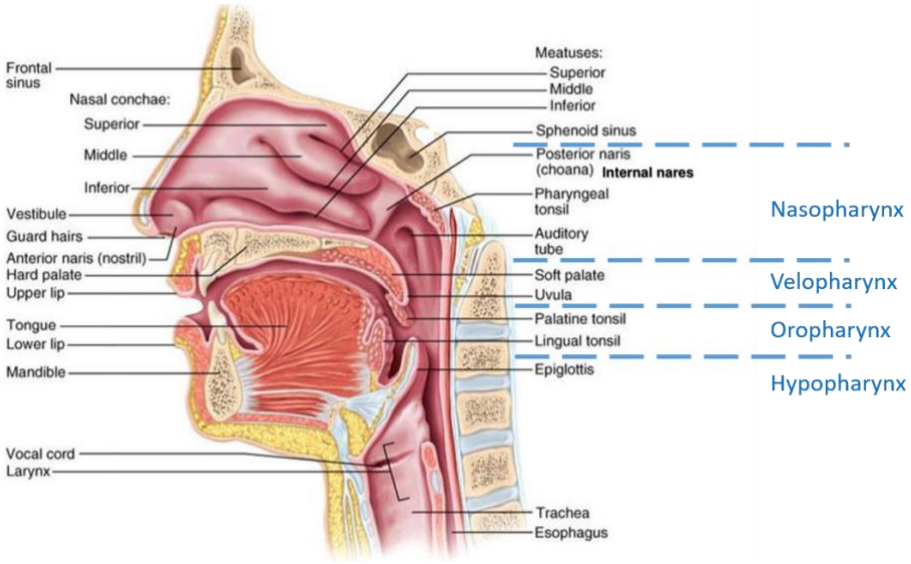


Figure 1. 1: Schematic representation of the midfacial section of the upper airway. Notice the main anatomical landmarks delineating the 4 parts of the pharynx: Nasopharynx, Velopharynx, Oropharynx and Hypopharynx. Adapted and modified from A. Zaghawa et al.(2019) [5].

1.2. Upper airway (or peripharyngeal, pharyngeal) tissues

The peripharyngeal tissues include bony tissues (hard palate, mandible and hyoid bone), cartilaginous tissue (thyroid and epiglottis) and the soft tissue (muscles and mucosa).

The mechanical properties of the peripharyngeal tissue modulate the conduct of the upper airway. Passive properties are related to the anatomical structure of the airway, whereas the active properties correspond to the muscular activity and pharyngeal reflexes that maintain the upper airway patency.

1.2.1. Bony structure (Passive component)

The bony tissue of the upper airway is composed of the hard palate, mandible and hyoid bone.

1.2.1.1. Hard palate

The **hard palate** is formed by the palatine process of the maxilla and horizontal plate of palatine bone. It separates the oral cavity from the nasal cavity (Figure 1.2).

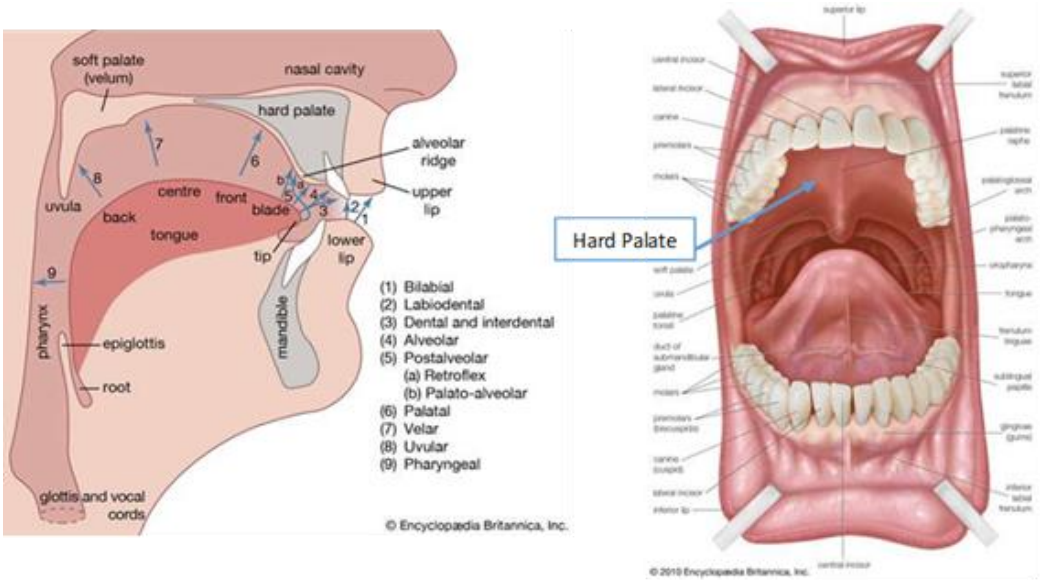


Figure 1. 2: Schematic drawing of the upper airway showing the hard palate from the side and the front view. On the left, side view. The hard palate, which is a part of the maxilla, is one of the bony components of the upper airway. Behind it is the soft palate. On the right, frontal view. The hard palate is visible behind the maxillary front teeth. Adapted and modified from Encyclopaedia Britannica (2010) [8].

1.2.1.2. Mandible

The **mandible** or lower jaw is a U-shaped bone that lies beneath the maxilla and articulates with the temporal bone forming the temporo-mandibular joint (Figure 1.3). This will allow the mandible to move downward, upward and sideways. It is formed of a horizontal part which is the body of the mandible supporting the teeth and a vertical portion extending at both ends of the mandibular body known as the mandibular rami.

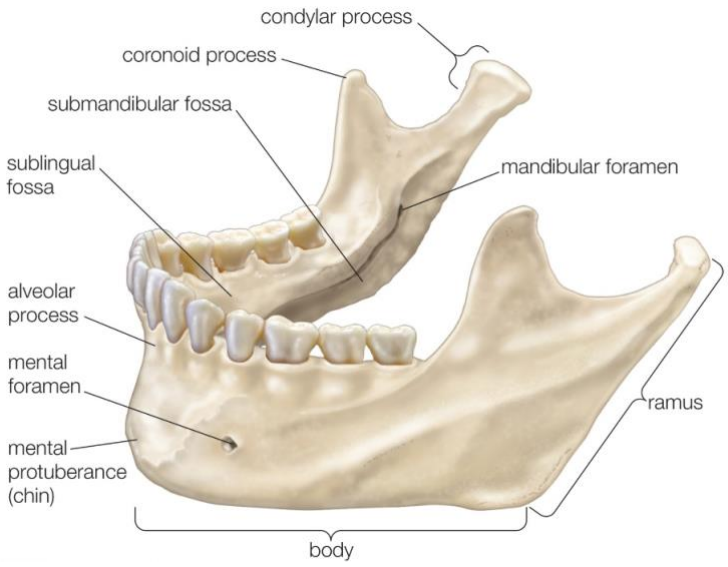


Figure 1. 3: Schematic drawing of the mandible, seen from a lateral view. The mandible constitutes a site of attachment of a number of the tongue and hyoid muscles. It is part of the anterior border of the upper airway. Adapted from the Encyclopaedia Britannica (2011).

1.2.1.3. Hyoid bone

The **hyoid bone** is a horseshoe-shaped bone situated at the base of the tongue at a midlevel between the mandible and the thyroid cartilage, and in front of

the third cervical vertebrae (C3) (Figure 1.4). It is formed of a central body from which the lesser and greater horns project. Those processes (eminences) serve as a support for muscle attachment. The lesser horns extend in a superior- posterior direction from the hyoid bone's body, while the greater horns extend in a predominantly posterior direction. Unlike other bones, the hyoid has no direct contact with other bones, it is only suspended by muscles or ligaments. The hyoid is anchored by muscles from the anterior, posterior and inferior directions that allow force transfer to the upper airway walls. This make the hyoid bone a fundamental element in studying the mechanics of the upper airway [5, 9]. The importance of this bone and its role in the upper airway function will be discussed in further details in chapter 3.

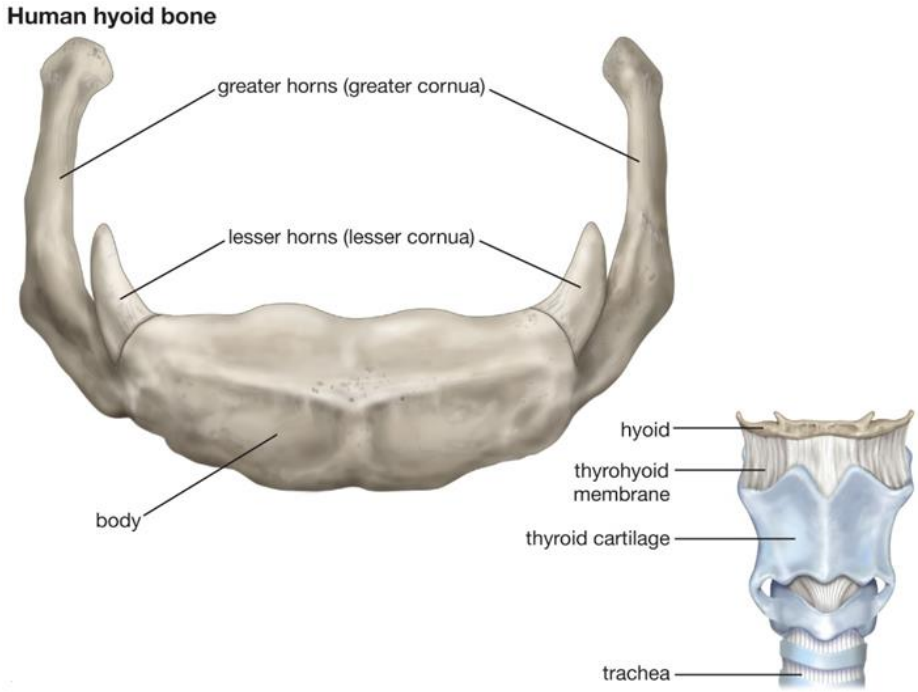


Figure 1. 4: Schematic drawing of the hyoid bone and its attachment to the thyroid cartilage via the thyrohyoid membrane. The hyoid is a mobile, freely suspended bone. It is attached to cartilaginous and connective tissue, as well as muscles that control its position. Adapted from Encyclopaedia Britannica, 2010 [8].

1.2.2. Soft tissue structures (passive)

The upper airway is delineated by a thin layer of mucosa that covers its entire inner surface and forms its boundaries at the airway gas interface. The soft tissue primarily includes glands, lymphoid and adipose tissue. Those structures affect upper airway patency through their relative sizes but do not participate actively in controlling the upper airway [10].

1.2.2.1. Soft Tissues - Muscles (Active component)

The upper airway muscles interact differently to constrict or dilate the upper airway lumen and maintain upper airway patency. They can be divided into 4 groups [1], depending on their anatomical and functional description, that include muscles controlling the position of 1) the tongue, 2) the soft palate, 3) the hyoid bone and 4) the posterolateral pharyngeal walls.

- *Muscles of the tongue*

The muscles controlling the tongue can be of intrinsic or extrinsic origin. The intrinsic muscles control the shape of the tongue and are primarily involved in changing the tongue shape [11]. The extrinsic muscles are the ones of importance in

affecting the upper airway lumen geometry. They include the genioglossus, hypoglossus, styloglossus and palatoglossus (Figure 1.5). They are responsible for the protrusion and retraction of the tongue [12, 13] .

The **genioglossus** is the leading protruder muscle of the tongue and the most extensively studied muscle of the upper airway. The genioglossus pulls the tongue anteriorly during inspiration in awake subjects. Its contraction stiffens and enlarges the pharyngeal airway [14]. During expiration, it relaxes posteriorly [2].

Upper airway dilator muscles, and the genioglossus in particular, increase their activity by 2 different mechanisms [14] :

- chemical stimulus: Low levels of oxygen (hypoxia) or high levels of carbon dioxide (hypercapnia) often as a result to breathing.

- mechanical stimulus: as a response to negative airway pressure generated during inspiration.

The styloglossus and hyoglossus are both tongue retracting muscles (pull the tongue backward and downward).

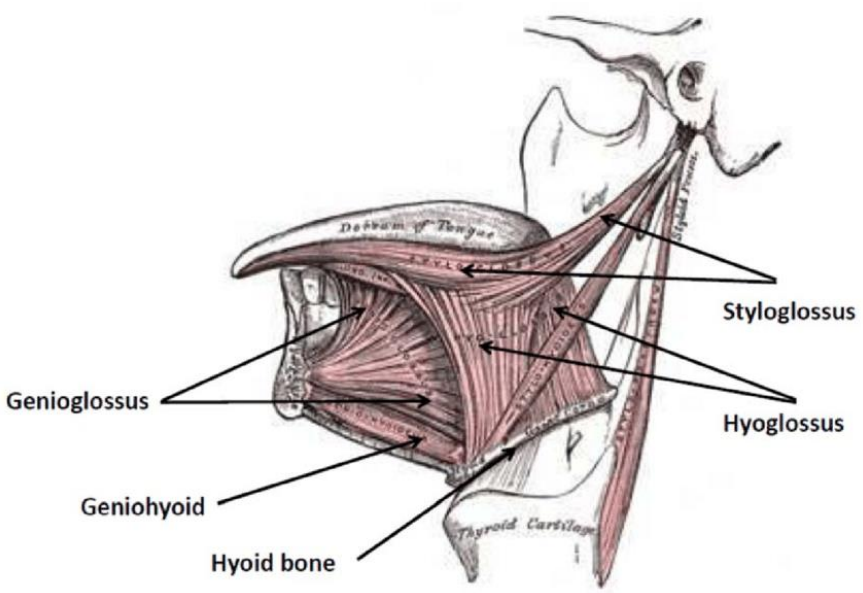


Figure 1. 5**:** Schematic drawing of the main extrinsic tongue muscles; styloglossus, hyoglossus and genioglossus. Adapted from Hermant et al. 2017 [13] .

- *Muscles of the soft palate*

The soft palate is composed of several muscles, principally the tensor palatini, levator palatini, palatoglossus, the palatopharyngeus and the musulus uvula (Figure 1.6). They act in harmony in order to close the velopharynx while swallowing (elevating the soft palate) and open it during nasal breathing (lowering the soft palate). For example, the activity of the levator palatini is more important during oral breathing in comparison to nasal breathing. In contrast, the palatoglossus, palatopharyngeus and tensor palatini open the nasal airway and facilitate nasal ventilation when activated. They pull the palate toward the tongue to have a proper oral seal [15] .

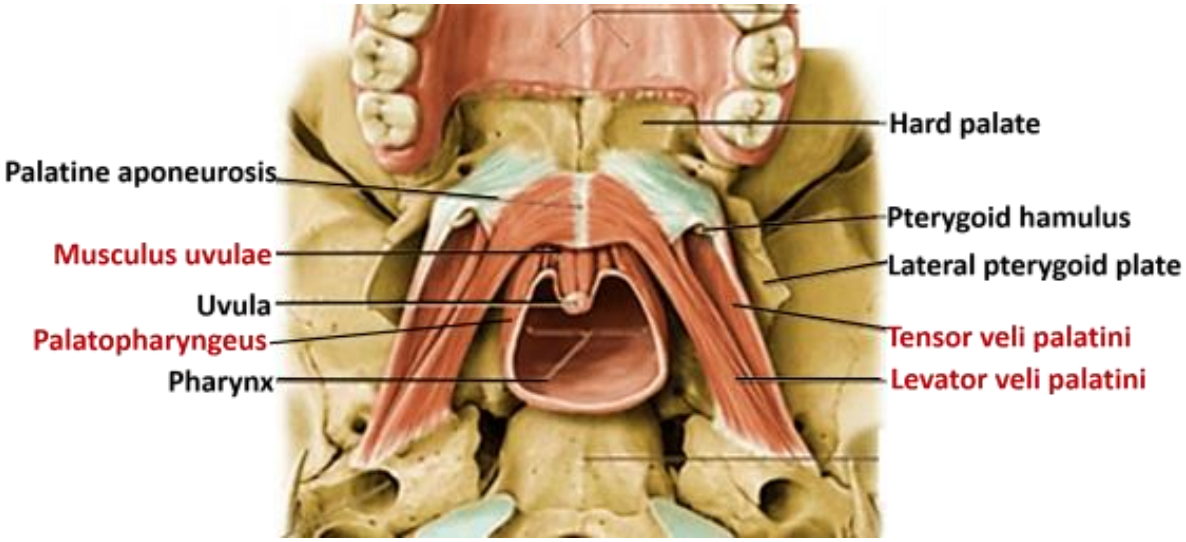


Figure 1. 6: Schematic drawing of the palatal muscles (written in red). Adapted from Perri et al. 2011.

- *Muscles of the hyoid bone*

The muscles connected to the hyoid bone control its position and can be divided based on their attachment location into infra-hyoid muscles (located below the hyoid) and supra-hyoid muscles (located above the hyoid).

The infra-hyoid muscles include the sternohyoid, sternothyroid, thyrohyoid and omohyoid. The supra-hyoid muscles consist of the geniohyoid, mylohyoid, stylohyoid and digastric (Figure 1.7).

The sternohyoid, omohyoid, and thyrohyoid apply a force in the inferior direction. When activated, these muscles pull the hyoid bone caudally.

The suprahyoid hyoid muscles act to elevate the hyoid bone. In addition, the geniohyoid, mylohyoid, and digastric muscles tend to pull the hyoid bone anteriorly as well, whereas the stylohyoid activity pulls the bone posteriorly [11, 16].

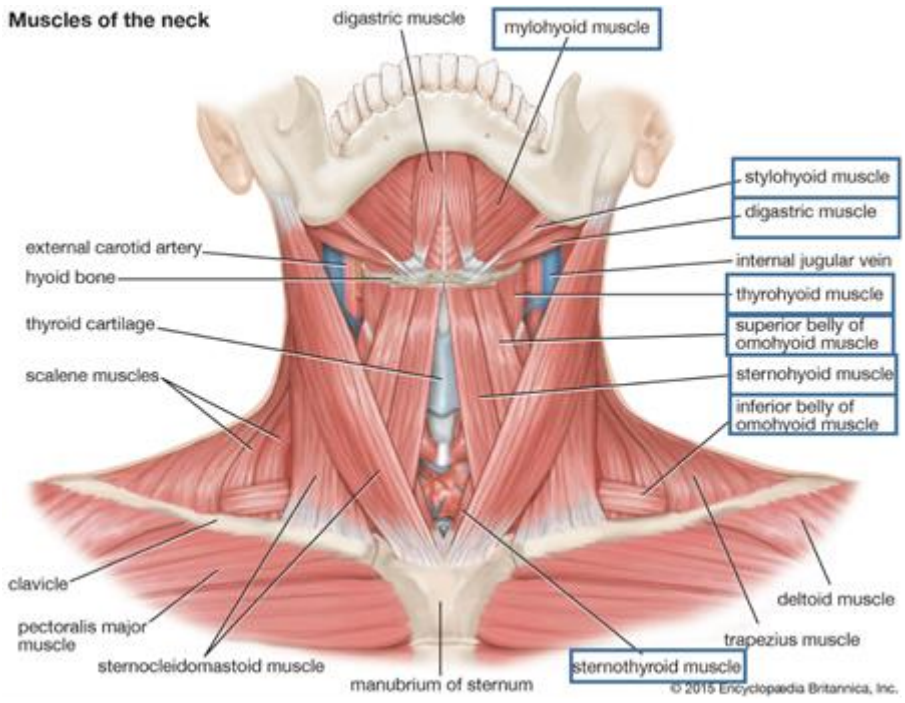


Figure 1. 7: Schematic drawing of the infra- and supra- hyoid muscles. The genioglossus is not located behind the mylohyoid muscle; thus it is not showing on this picture. Adapted and modified from the Encyclopedia Britannica (2010) [8].

- *Posterolateral pharyngeal walls muscles*

Posterolateral pharyngeal walls muscles are the pharyngeal constrictors (superior, middle, inferior), the stylopharyngeus and the salpingopharyngeus. These constitute the posterior and lateral wall of the upper airway that will provide, along with the posterior vertebral column, the main part of the support to prevent the collapse of this highly deformable structure. The constrictor muscles mostly narrow the upper airway

during the active phase of swallowing [17, 18]. Nevertheless, animal studies showed that the constrictors contribute to the stiffening of the upper airway [19].

The stylopharyngeus and salpingopharyngeus are two minor muscles that elevate the pharynx and larynx [12, 20].

Sleep effects on pharyngeal dilator muscles activity and control of the upper airway

The upper airway is predisposed to collapse at sleep onset due to several factors such as the reduction in muscle activity [21, 22]. This leads to a smaller upper airway lumen size and increased resistance [23]. Most upper airway muscles are considered as dilators, except for the constrictors muscles, the styloglossus and stylohyoid muscles. The research on the effect of sleep on upper airway muscle control has been focused on the genioglossus muscle, mainly due to its relatively ease of access for electromyography (EMG) measurement and because it occupies the tongue, which constitute a large part of the upper airway's anterior wall. During sleep, the genioglossus responsiveness to negative pressure and hypercapnia is reduced compared to wakefulness [4, 13].

In addition, there is a drop in the pharyngeal neurocompensatory reflexes, which are stimulated by negative intra-luminal pressure [24]. Those reflexes are responsible of the activation of neurologic pathways to promote breathing and stimulate dilator muscle activity [25].

On the other hand, during sleep the effort to breath is augmented, which means that there is a higher activity of the diaphragm and chest muscles [26]. As a result, the upper airway patency is maintained by the equilibrium between the respiratory

muscles (chest wall, diaphragm responsible of the increased negative pressure in the upper airway) and the upper airway dilatory muscles (compensatory muscles) [25, 27]. Thus, with this increased activation of the "negative pressure producing muscles" and a decreased activation of their opponent (dilatory muscles), the upper airway is at a greater risk to collapse during sleep.

In OSA patients, the activity of the pharyngeal dilator muscles is further reduced compared to normal at sleep leading to more apparent increase in airway resistance [25]. This often results in a reduction or complete loss of airway patency. Therefore, blood oxygen levels decrease alongside an increase in CO2 levels that stimulates respiratory drive. The genioglossus is activated in response to the negative airway pressure and changing blood gas pressures, but its activity often insufficient to reopen the airway, therefore arousal occurs and restore airway patency [12, 28, 29] . Patil et al observed that the capacity of the upper airway muscles to sufficiently counteract the increased negative pressure and stabilize the airway during sleep is reduced in OSA patients [30] .

1.3. Physiology and mechanical function

Several factors are utilized to assess the physiology and mechanics of the upper airway, such as upper airway lumen geometry (size, shape and length), compliance, collapsibility, stiffness, strain and peripharyngeal tissue pressure. These parameters are used to characterize the upper airway and will be discussed in the following section in order to provide a deeper understanding of the behaviour of the upper airway.

1.3.1. Upper Airway Geometry

Upper airway lumen size is a main indicator of the degree of airway patency. It can be quantified as the overall lumen size (volume) or based on cross sectional measurements at certain levels along the length of the upper airway. Various imaging techniques can be used to visualize and acquire data about the lumen geometry, particularly Magnetic Resonance Imaging (MRI)[31], Computed Tomography (CT), Cone Beam CT (CBCT)[32], fluoroscopy and video endoscopy [1, 33, 34]. MRI and CT provide precise anatomic examination of the airway and surrounding soft tissue structures[35].

Differences in reported upper airway dimensions may arise due to several factors including the body position during which the upper airway was visualized. For example, a CBCT is taken while being seated as opposed to a CT scan where the subject is placed in a supine position [36]. The upper airway dimensions tend to be smaller when the person is laying down due to the gravitational forces. Also, the upper airway lumen size varies with the head and neck angles.

The importance of lumen size metric is related to the fact that the size of the upper airway lumen determines the amount of airflow that can pass through it and the amount of negative inspiratory driving pressure to maintain required ventilation. There is a strong evidence for reduced upper airway space in adult OSA patients compared to control subjects [37], which could be due to craniofacial disharmony (retruded mandible narrows the airway space behind it) or enlarged soft tissues (e.g. long and thickened soft palate decreases space at the level of the velopharynx[38]) occupying more space. For instance, the thickness of the lateral pharyngeal wall was

proven to be the most important factor causing airway narrowing in OSA patients [1].

The upper airway lumen cross-sectional shape is approximated as an ellipsoid and is usually described by the ratio of its anteroposterior and lateral diameters [39].

The length of the upper airway has been linked with the severity of OSA [40]. A longer airway in males is associated with increased risk of developing OSA compared to females. Nevertheless, stretching of the upper airway, as occurring with increased lung volume during inspiration, may increase upper airway wall stiffness [41].

1.3.2. Upper airway compliance

Upper airway compliance is the amount of upper airway lumen size variation in relationship to the change in intra-luminal pressure. It is a parameter representing the functional radial stiffness of the upper airway. In other words, it indicates the resistance of the upper airway to the applied intra-luminal pressure load and determines its susceptibility to narrow and at what location this constriction will occur.

A compliant tissue implies that it can deform more easily than another less compliant tissue under the same applied loads. Different imaging and non-imaging techniques were traditionally developed to measure compliance. For example, in animals, a known volume of air is injected in the upper airway and the corresponding variation in the intra-luminal pressure is determined [42]. Compliance is then

concluded as the relationship between the injected volume and the change in the detected pressure. This change in pressure is reflective of a change in size which can be measured directly using imaging techniques. These offer the advantage of being able to obtain the compliance at different locations of interest (in a particular section of the upper airway or along the entire upper airway) [43]. A major limitation in using compliance to assess the upper airway mechanics is that it is affected by neuromuscular reflexes as the pressure/volume parameters of the pharyngeal airway are influenced by such mechanisms [39].

1.3.3. Upper airway collapsibility

Collapsibility is the tendency of the pharyngeal lumen to narrow or close under a certain pressure. It indicates how stable the upper airway is, or in other words how resistant it is to closure. It is frequently used to assess upper airway mechanics. Two main measures that characterize collapsibility are: closing pressure (Pclose) and critical closing pressure (Pcrit).

1.3.3.1. Pclose

When under negative pressure, the upper airway narrows until reaching a threshold pressure where it closes completely. This pressure is termed the closing pressure, or Pclose. Pclose is determined under static conditions where no airflow is allowed in the upper airway and with inactive upper airway muscles (i.e. passive upper airway). Therefore, Pclose characterizes the intrinsic peri-pharyngeal tissue properties causing the upper airway to collapse. The greater the negative value of

Pclose, the more the upper airway can undergo negative pressure before collapsing. The higher its value, the more it is prone to close at higher pressures.

Isono et al measured Pclose in humans (healthy and OSA patients) who underwent general anaesthesia and were mechanically ventilated. The upstream pressure was progressively decreased via a nasal mask and the upper airway surface variation with every pressure drop was recorded using videoendoscopy [7, 44]. A mathematical representation was then used to correlate pressure to area data and estimate Pclose. His results supported the anatomic hypothesis that apneics have a structurally narrowed and collapsible pharynx compared to healthy individuals [33].

In contrast, animal studies offer the advantage of measuring Pclose directly in a passive upper airway without the effect of cofounding factors (e.g. lung volume, muscle activity). This was initially performed by Roberts et al. [45] on rabbits where the trachea was sectioned and the upstream/ downstream pressures monitored while the downstream pressure was decreased (figures 1.8 and 1.9). The upstream pressure will decrease concomitantly with the downstream pressure in a patent upper airway. Once it is closed, the upstream pressure does not follow the downstream pressure drop anymore. The downstream pressure at which this initially happens is the Pclose [6].

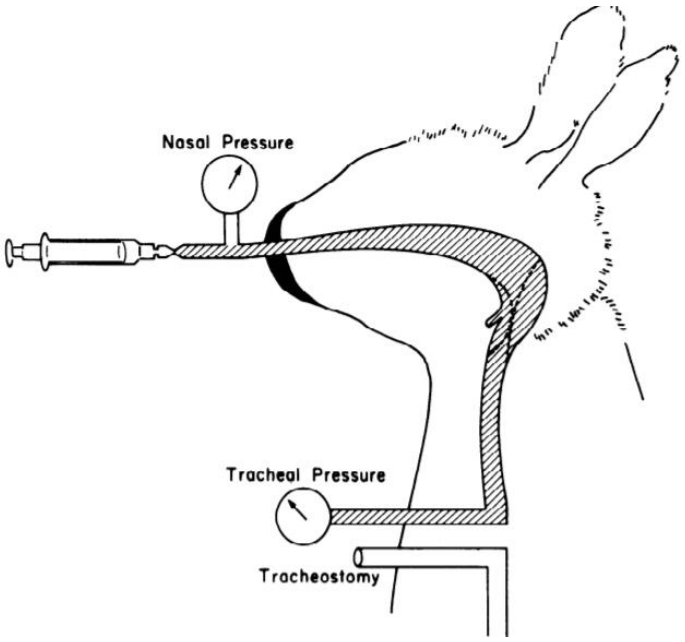


Figure 1.8**:** Schematic representation of the animal preparation in Roberts et al experiment on rabbits. A nasal syringe was used to deliver negative pressure in the upper airway. When the upper airway collapses under negative pressure, nasal pressure and tracheal pressure are no longer the same. Adapted from Roberts et al. 1984 [45].

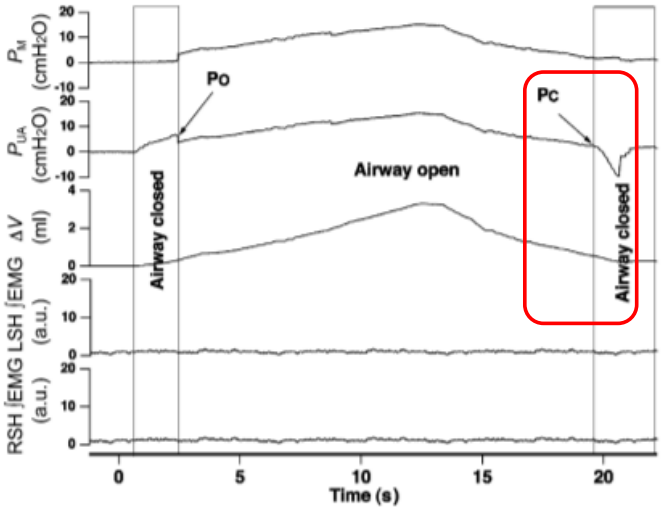


Figure 1. 9: Data recordings of a study by Kirkness et al, measuring the upper airway closing pressure (Pc) in rabbits. The pressure in the upper airway (P_{UA}) and at the

level of the mask (P_M) vary equally until the airway in closed then they become different. Pclose is then registered. [46].

1.3.3.2. Pcrit

Pcrit or the critical closing pressure is used frequently in human studies to characterize upper airway collapsibility, particularly during sleep [47-51]. A Starling resistor model developed by Schwartz and colleagues led to the definition of Pcrit. This model consisted of a collapsible tube interposed between two rigid segments modelling pressure-flow relationship in the airway (detailed in section 1.5). The critical closing pressure (Pcrit) of the passive airway is therefore the pressure inside the airway at which the airway collapses following flow limitation [52]. Flow limitation happens when airflow does not increase even with increased downstream inspiratory pressure. When this occurs, the upper airway is narrowed but not closed and the airflow is dependent on the pressure upstream to the constricted segment and the surrounding tissue pressure. Therefore, Pcrit is reflective of the tissue pressure that leads to upper airway closure. [39, 53, 54] .

"Passive" Pcrit is assessed during sleep and under conditions of complete muscle inactivity in paralyzed, anesthetized patients. In this case, it is reflective of the mechanical properties of the airway and its surrounding tissue.

"Active" Pcrit is a modification where upper airway muscle activities are not inhibited. It reflects active neuromuscular compensation for reduced intraluminal pressure. Active Pcrit measurements showed significant impairment in neuromuscular compensation in OSA patients [30].

In general, a value of Pcrit above 0 cmH_2O indicates that the upper airway closure pressure is above atmospheric pressure and is associated with a compromised anatomy and obstructive apneas. A value below -5 cmH_2O refers to healthy individuals. Between 0 and -5 cmH_2O, the patient is borderline [29]. The more negative the value of Pcrit is, the less collapsible is the upper airway, i.e. it can withstand more negative intraluminal pressure before closing.

Experimentally, the measure of Pcrit requires the use of pressure control systems connected to nasal masks that are capable of manipulating airway pressure in a stepwise fashion across a wide. Flow limitation is reached when by progressively decreasing the upstream pressure, the downstream pressure remains unchanged, the upstream pressure is then recorded. The same process is repeated at different flow rates and a line chart relating the recorded upstream pressure to the corresponding flow is generated. Pcrit is obtained by intercepting this line chart with the airflow axis (flow =0) [39] (Figure 1.10).

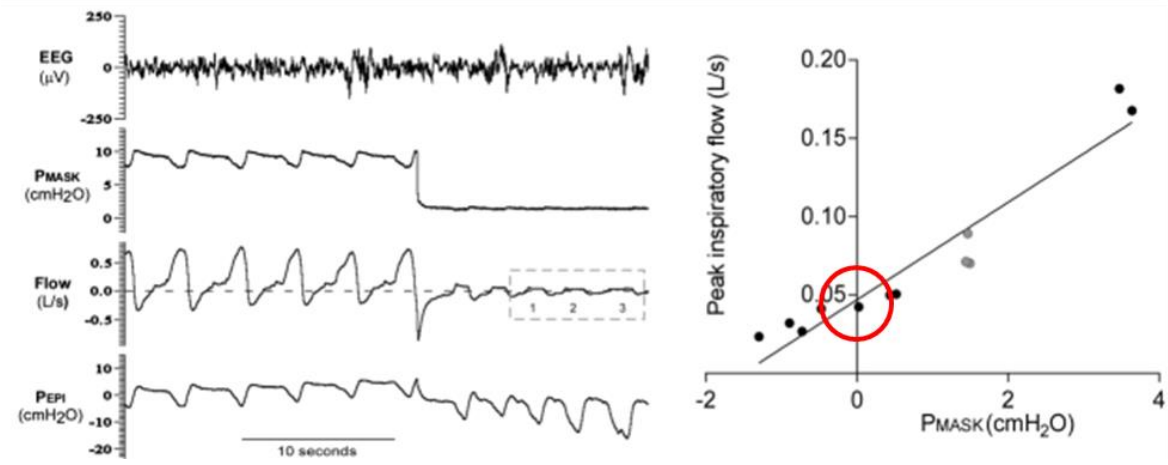


Figure 1. 10: Raw data of negative pressure pulse application for a 42-year-old OSA male patient. Flow recordings shows the three breaths used to plot the relationship to

calculate Pcrit (shaded in grey circles). Pcrit for this patient was -1.5 cmH2O indicating relatively mild airway collapsibility. Adapted and modified from Osman et al, 2019 [48].

1.3.4. Peripharyngeal Tissue Pressure

Peri-pharyngeal tissue pressure, also known as extra-luminal tissue pressure (ETP), is the pressure within the tissues surrounding the upper airway. ETP is a major component to be taken in consideration while studying upper airway mechanics since the upper airway patency is in balance between the intraluminal pressure and the tissue pressure. This is referred to as the transmural pressure. Measurement of the peri-pharyngeal pressure is difficult in human subjects as it requires invasive procedures. Accordingly, it, has only been directly measured in animal models.

The first measurements of peri-pharyngeal tissue pressure were performed on pig model by Winter et al. [55]. Later Kairaitis and colleagues studied ETP using anaesthetized rabbit model both anterior and lateral to the upper airway lumen. They found that ETP correlated with pharyngeal pressure and fluctuated with respiration, but it is uniformly present around the upper airway [56]. In addition, other factors such as the head/neck position[56], mandibular advancement [57, 58], caudal tracheal traction [59, 60], changes in lung volume[61], sternohyoid muscle stimulation [62], and increased peri-pharyngeal tissue volume [63] influence extraluminal tissue pressure.

1.4. Upper airway physiology and OSA – traits contributing to OSA

Poor anatomy of the upper airway bony or soft tissue structures is the first suspect when aiming to determine the pathophysiology of OSA. For instance, enlarged peri-pharyngeal tissues compress the upper airway walls and decrease upper airway size. Also, retruded or small mandible and maxilla tighten the retropalatal and retroglossal segments of the upper airway leading to crowding of soft tissues. This has been demonstrated in several imaging studies where they found reduced cross-sectionnal area of the upper airway in OSA patients when measured using magnetic resonance and computed tomography [10, 64]. Isono et al. observed increased closing pressure in OSA patients compared to healthy control when both were under general anesthesia and muscle paralysis [7].

In addition, the most observed anatomical feature in OSA patients is the inferiorly positioned hyoid bone. Several hypotheses were drawn around this finding to explain its potential effect on the upper airway. As a matter of fact, as the hyoid bone is the point of insertion of upper airway dilator muscle and alteration of its position might lead to muscle dysfunction in keeping the airway patent. This is due to the change in muscle's line of action and length/tension characteristics which cause the muscle to become less efficient in opening the upper airway [30, 65]. Current studies show that the capacity of the pharyngeal dilator muscles to adequately compensate for increased mechanical loads during sleep is lessened in OSA patients compared to healthy individuals [14]

On the other hand, some individuals have a high **respiratory arousal threshold** meaning that they would not wake up easily when faced with an increased respiratory demand. A higher arousal threshold provides more time for the

recruitment of the pharyngeal dilator muscles to counterbalance for a poor upper airway anatomical feature. OSA patients are often presented with a low arousal threshold which contributes to the development of the pathology [66].

The loop gain (LG) or ventilatory control system is the regulation of breathing via afferent feedback from chemoreceptors detecting the carbon dioxide (CO2) pressure. It is measured as the ventilatory response/ventilatory disturbance ratio. The instability of the ventilatory control system is also a cause for OSA in some patients. For instance, high loop gain indicates excessive ventilatory reaction to minor change in PaCO2. This leads to hypocapnia and therefore to a reduced stimulus to respiratory effort. Eventually, the upper airway collapses as a result to the high loop gain as it is the case in 30% of OSA patients [49] .

1.5. Factors Influencing Upper Airway Tissue Mechanical Properties

Several factors influence the mechanical behavior of upper airway tissues.

For instance, **fat deposit** in the neck area alter the passive tissue stiffness, narrow the airway and is associated with increased OSA risk and higher Pcrit [67]. Men and women also have different patterns of fat distribution that would also influence upper airway collapsibility. Men have more fat deposition around the neck area which expose them to a greater risk of airway collapse [68].

Caudal tracheal traction, following enlarged lung volumes during inspiration, increase the stiffness of the airway walls [69], and, equally, airway stiffness decrease when lungs are deflated [70]. Increased tracheal traction was studied in rabbits and it was demonstrated that it reduces collapsibility of the upper

airway [59, 71]. In addition, decreased lung volume can increase the severity of OSA [72] and/or increase required CPAP pressures. Possible explanation is that the upper airway wall tissues are elongated when the lung volume rises, thus increasing their stiffness and the opposite when the lung volume decreases [60, 73].

Posture has a pronounced effect on upper airway mechanics. The supine position, along with the gravitational force, challenges the upper airway, as the tongue tends to fall behind and close it. Indeed, some OSA patients have more apnoeic events when supine compared with the lateral position [74, 75]. In those patients, the treatment could consist of simply changing their sleeping position.

Head position can also influence upper airway collapsibility. Under anesthesia, head extension reduces airway collapsibility, and flexion increases collapsibility (37, 87) and can change the site of collapse (87). Head rotation did not affect collapsibility (87). These differences have been attributed to tracheal traction, although Isono and colleagues (37) suggest that the compliance of the airway walls decreased with neck extension due to increases in airway cross-sectional area.

Jaw position may also influence passive collapsibility, with an open mouth increasing collapsibility, likely by narrowing the oropharynx (37). Pharyngeal collapsibility also increases with age (24), but this is paralleled by an increase in obesity and airway resistance, so this appears likely to be related to airway narrowing rather than specific age-related changes in tissue mechanics.

In addition, advancement of the mandible, neck extension, and lateral position decreases closing pressure in subjects under general anaesthesia [33].

1.6. Models of Upper Airway Behavior

To understand a certain biological phenomenon or process, researchers develop and utilize different types of models to represent and simplify the systems they are dealing with. Each model is established with the aim to study a certain concept or test a specific hypothesis; therefore, no single model is expected to represent the entire biological, mechanical and physiological reality. Different forms of models were used to represent the upper airway such as the conceptual models, physiological models (human and animal), physical models, mathematical and computational models.

A summary of those models is presented below with the relative advantages and disadvantages of each model.

The **conceptual models** of the upper airway started with the balance of forces model developed by Remmers et al. to study the equilibrium of forces between intra-luminal pressures and the forces that act to open the airway, including dilator muscles [27] . It was further enhanced by Isono et al. who developed the balance of pressures model to study the passive mechanical properties of the pharynx [7] . A third major conceptual model is the Starling resistor model that simulated the upper airway to a collapsible tube fixed at both ends and floppy in the middle segment. The tube is surrounded by a chamber filled with air to represent peri - pharyngeal tissue pressure.

Thus, the conceptual model focuses on understanding the basic function of the upper airway without taking into consideration the anatomical and physiological

considerations. It provides rather a simple representation that could be integrated into more complex models.

Physiological models can use human or animal subjects.

In the **human model**, interventions are often safe and not invasive. Those studies should not cause harm to the patients, provide unnecessary treatment or prevent required treatment. Therefore, human studies are limited and not always possible due to ethical considerations. In upper airway studies, awake and anaesthetized human models were used to study upper airway mechanics and its dysfunction during sleep. Several studies used anesthetized subjects to simulate the upper airway in the sleeping state. There are mainly two types of anesthetized models in studying upper airway mechanics:

- The first consist of complete muscle paralysis (passive upper airway requiring mechanical ventilation). This was used to assess the collapsibility of the upper airway by measuring the closing pressure Pclose (Isono et al) [6, 7, 33].

- The second preserved muscle activity and respiratory reflexes but upper airway reflexes were abolished. This model was used to assess upper airway collapsibility by measuring the critical closing pressure Pcrit [48, 49, 51, 76].

Recently, there has been a focus on studying patients' response to OSA treatments, such as mandibular advancement and CPAP therapy in patients [51, 77, 78]. Additional examples of human models include those that stimulate snoring in the upper airway to study the effects of vibration on respiratory and cardiovascular functions [79].

In many cases, where the experiment requires the sacrifice of the subject or the use of invasive techniques, **animal models** are used instead. In addition, studies involving animals require a smaller sample compared to human studies because of the similarity (less variability) found between the animals of the same species. In many instances, the concepts generated in animal models can also be incorporated into other model types. Nevertheless, the animal model cannot provide answers all the time due to crucial anatomical and physiological differences sometimes with humans. Also, animal models are expensive and logistically difficult to achieve. In this thesis, we will be focusing on the animal model specifically the rabbit and elaborating its use in previous studies to understand the mechanics and physiology of the upper airway [57, 80-83].

The use of animals in upper airway studies is further detailed in the following section.

Physical, mathematical and computational models allow the examination of certain mechanisms and breaking down complex processes into simpler, consistent representations for a better understanding. Their advantage lies in allowing a high degree of control of multiple parameters without having the issue of biological variability. These parameters can comprise a wide range of values and combinations that may be impossible to perform physiologically.

Physical models have been used mainly to study airflow dynamics. They could be in the form of simplified representations such as the Starling resistor model or rigid-wall representations of the correct anatomical airway lumen geometry. The Starling resistor (Figure 1.11) is a model of collapsible tube relating airflow, intraluminal

pressure and peripharyngeal tissue pressure [2]. This model has provided insights into the development of the critical closing pressure measurement (Pcrit) and the mechanism of flow limitation (when increasingly negative pressure in a collapsible tube fails to increase airflow). The airflow pressure through the system is defined by the difference between the pressure upstream and Pcrit and is independent of the pressure downstream[84].

Major limitation of the Starling resistor is that it ignores the effect of the muscle activity and functional anatomy of the airway walls (the parts of the pharynx can behave independently, therefore they do not form a uniform collapsible tube required in simplistic models) [2].

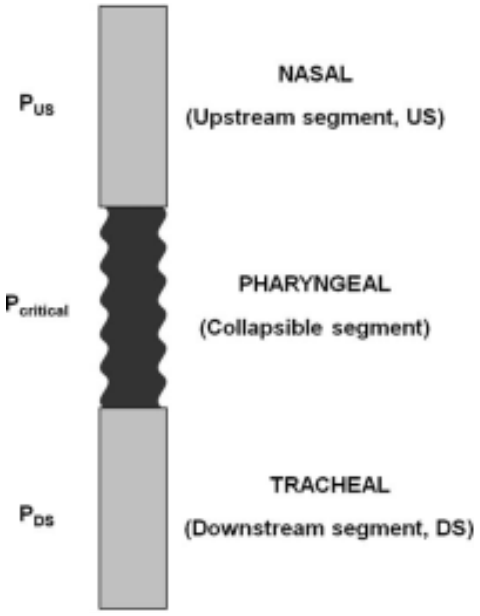


Figure 1. 11: Schematic representation of the Starling resistor model of the pharyngeal airway. The pressure needed to keep the airway patent (Pcritical) is a

function of the pressure upstream to the collapsing segment (PUS). Adapted from Susarla et al, 2010 [2].

Most of the mathematical upper airway models are used to predict airflow characteristics and cross-sectional area using one or more physiological variables. However, these models are often based on unrealistic assumptions and physiological simplifications that makes them far from the natural circumstances [26, 85].

Recently, more complex computational biomechanical models of the upper airway were developed. Many are based on imaging data and they represent the upper airway anatomical geometry in two- or three-dimensional views. Some focused on upper airway soft and hard tissues (finite-element models FEM), others on airflow (computational fluid dynamics models).

Amatoury et al. developed a two-dimensional (2D) computational finite element model (FEM) of the passive rabbit upper airway and peripharyngeal tissues [86, 87]. It was validated against physiological experimental data. The model predicts peripharyngeal tissue mechanics and upper airway lumen geometry changes related to mandibular advancement and lung volume in association to caudal tracheal displacement. This provided new insights into their mechanistic effect on upper airway function, as well as an implication to role for the hyoid bone.

New developments in computational modelling should allow the airflow and tissue compliance to be simulated together as well as models of muscle activity and mechanical properties of the tissues. Such models will help clarify the interaction between anatomical and mechanical properties of the upper airway tissues.

1.6.1. The Anaesthetized Rabbit model and Upper airway Physiology

Various animal species have been used to investigate upper airway physiology including dogs, cats, rats, mice and rabbits. Interventions included: stimulation of the upper airway muscles [43, 45, 62, 88]; stimulation of upper airway muscle innervating nerves, such as the hypoglossal nerve [89]; induction of hypoxia and/or hypercapnia and application of tracheal traction[59], mandibular advancement [58, 90, 91], tongue displacement and upper airway vibration[57].

Animal models used to study sleep disordered breathing are either spontaneous or induced. For example, English bulldogs were diagnosed with OSA by Hendricks and colleagues in 1987, as they have large soft palate and narrow oropharynx [92]. Also, the same was found in a kind of female pig in Guangxi, China, which were reported to have an abnormal narrowing upper airway anatomy. But due to the limited availability of those animals, interest rose in induced models, where OSA was provoked in animals without intrinsic OSA such as other breeds of dogs, cats or rabbits. This was done by invasive procedure (such as tracheotomizing the animals, or injection of silicone type substance at the base of the tongue in rabbit model to make it harder for them to breath) or non-invasive procedures by exposing the animals to hypoxic conditions for long periods that can last several months, allowing the investigation of chronic consequences as seen in human disease [80, 93]. However, the lack of an upper airway occlusion is a limitation of this latter model.

The rabbit is an ideal model to be used for upper airway investigations because it has many similarities with the human upper airway structure. First, the

rabbit has a mobile freely suspended hyoid bone which is not the case in remaining non-primate mammals. The hyoid bone is attached to the thyroid cartilage through the thyrohyoid membrane which is comparable to the human anatomy as presented in figures 1.12 and 1.13. The upper airway is divided into similar sections as the humans: nasopharynx, velopharynx oropharynx and hypopharynx. The velopharynx seems to be longer in the rabbits compared to human due to the lengthy soft palate in the rabbits which extends beyond the epiglottis [94] (Figure 1.14).

Second, the rabbit's airway is prone to collapse as is the case in humans because it has the same soft and hard tissue components [71, 80] . Third, the neurological and innervation similarity relative to the cranial nerve XII should also be noted [95] .

Despite the many advantages of the rabbit as an animal model, this species has not been widely used, probably due to limitations in terms of cost and availability. The cost of the animal itself as well as the space required to house it makes the rabbits more expensive to use than smaller species such as guinea pigs or mice.

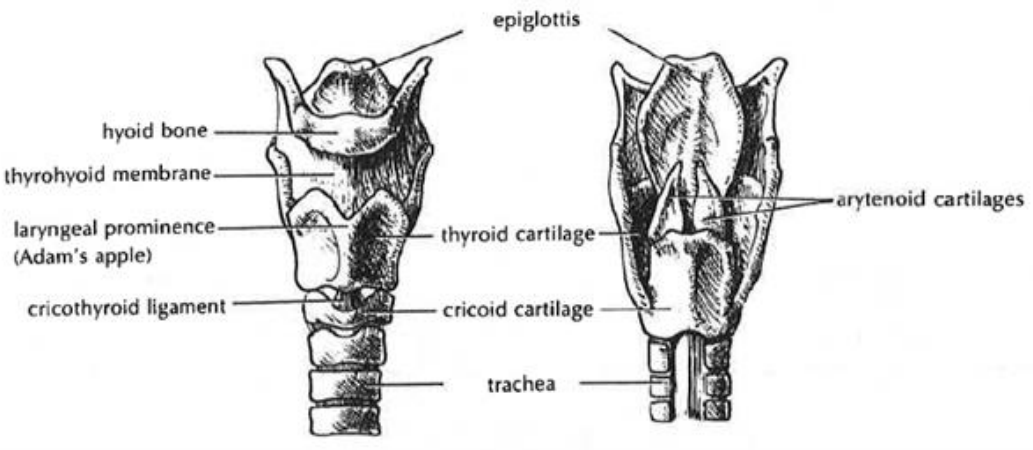


Figure 1. 12: Schematic drawing of the rabbit's larynx in the anterior (on the left) and posterior (on the right) views. Adapted from Wingerd, 1985 [94].

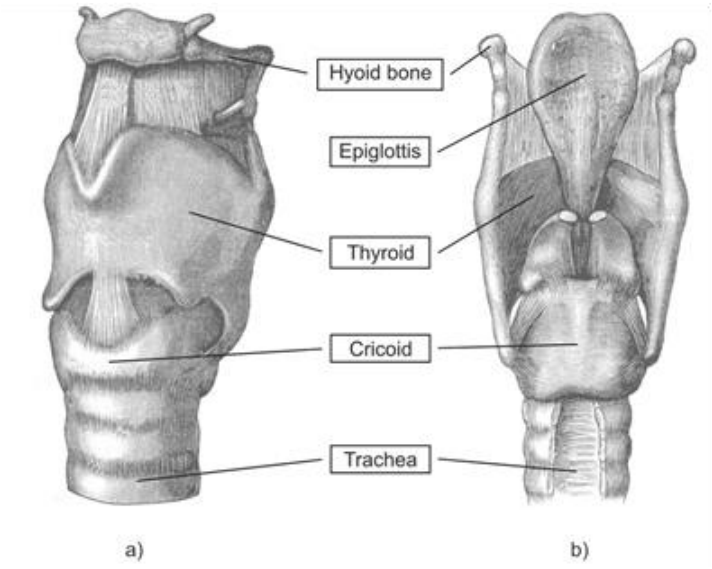


Figure 1. 13**:** Schematic drawing of the human larynx, a) anterior view, b) posterior view. Adapted and modified from Kniesburges et al, 2011 [96].

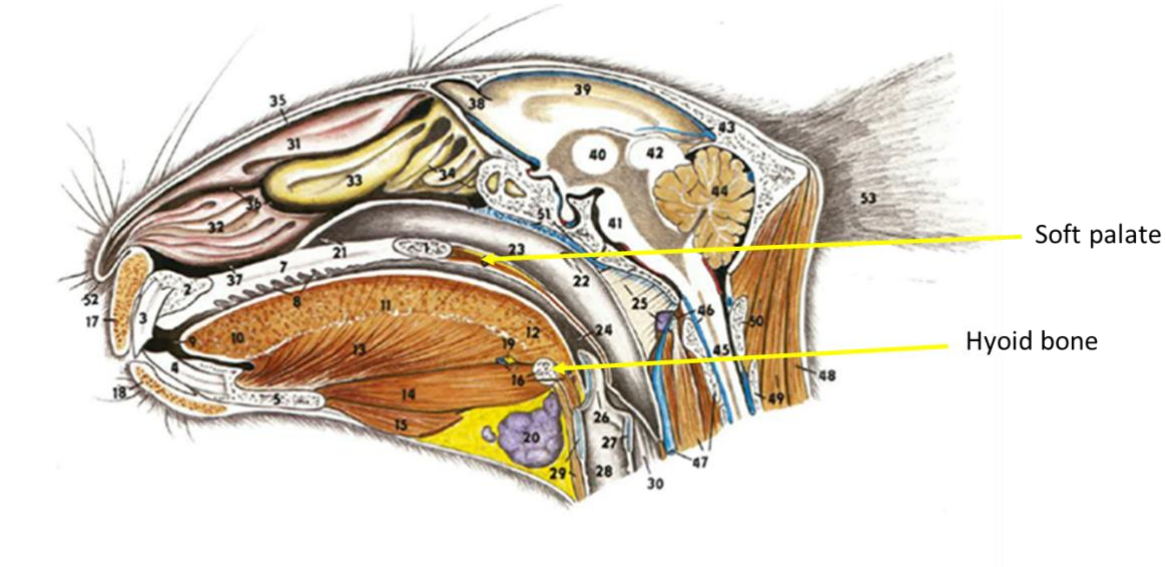


Figure 1. 14: Schematic drawing of the antero-posterior cross-sectional view of the head of the rabbit. The soft palate extends beyond the epiglottis, in contrast with human soft palate (presented in figure 1.1) Adapted from Cun

Summary

The upper airway is a collapsible structure but maintaining its patency is a necessity for breathing. Several factors such as the negative pressure during inspiration and the extra luminal tissue pressure will promote its closure. In contrast, other dilating forces such as the activity of the dilator muscles and the tracheal traction from the lungs expansion during inspiration will ensure its patency. The equilibrium of the dilating and collapsing forces is a necessity and the loss of this balance will lead to breathing disorders such as obstructive sleep apnea (OSA).

CHAPTER 2

OBSTRUCTIVE SLEEP APNEA

2.1. Definition and epidemiology

Obstructive sleep apnea is a sleep related disorder that is characterized by repetitive, total or partial closure of the upper airway during sleep. Total closure is referred to as an apnea and is clinically defined as a cessation of breathing lasting longer than 10 seconds. Whereas partial closure, or hypopnea, is a greater than 10s event associated with a reduction rather than complete cessation of airflow. These reductions in inspiratory airflow are usually associated with a decreased oxygen saturation leading to microarousals (brief awakening from sleep to resume breathing) [97, 98].

OSA is becoming increasingly prevalent affecting 9 to 38 % of the general population based on an AHI>5 events/hr [99] . Higher prevalence is found in the African American, Hispanic, and Asian ethnic groups and are increasing due to obesity and aging in the population [98] . It is found more in men than women. OSA is highly prevalent in the general population [97, 100] .

2.2. Symptoms and consequences

OSA is a heterogeneous condition whose symptoms vary amongst patients. Some with even moderate to severe OSA have few if any signs.

OSA patients complain usually of loud snoring, witnessed gasping, nocturnal choking, fatigue, and excessive daytime sleepiness (EDS). Other symptoms include sexual dysfunction, headache upon wakening, mood swings, irritability or depression, cognitive impairment such as difficulty with concentration or memory loss, and impaired quality of life [97, 101] .

The clinical consequences of OSA can be subdivided into neurocognitive, cardiovascular, metabolic and other comorbid conditions.

The neurocognitive symptoms are believed to result from sleep discontinuity ensuing from brain microarousals which reduces the quality of sleep and result in fragmented sleep as the patient fluctuates between wakefulness and sleep [102] . This leads to excessive daytime sleepiness, reduced attention, increased automobile and industrial accidents, and generally decreased quality of life. These effects can be reduced or stopped with treatment, which highlights the importance of early detection and appropriate treatment of OSA [103].

The cardiovascular outcomes are a product of the hypoxia when the normal airflow is lost during sleep. Cardiovascular consequences of OSA may include hypertension, myocardial infarction, heart failure, coronary artery disease, arrhythmias, and stroke. Other comorbidities are glucose intolerance, diabetes… Patients with moderate to severe OSA are at higher risk of developing those diseases at younger ages than the average. Although there is a strong epidemiological evidence supporting the

association between OSA and heart/vascular diseases, the cause effect relationship cannot be considered definitive at this time. Therefore, large-scale randomized trials are needed to confirm the post-treatment improvements on cardiovascular and metabolic systems [101].

2.3. Pathophysiology

The human pharynx can be simulated to a collapsible tube due to the presence of a mobile hyoid bone, a long upper airway whose walls are formed from soft tissue and muscles. It extends from the hard palate to the larynx without any rigid bony support.

As a matter of fact, the upper airway is subjected to different forces either promoting its collapse or preserving its patency (Figure 2.1)[39]. First, peripharyngeal, or extraluminal, tissue pressures surrounding the upper airway predispose the pharynx to collapse when it becomes greater than the intraluminal pressure (force opposing the tissue pressure). This is usually the case:

- during inspiration: which creates a negative pressure in the upper airway to help the air reach the lungs (↓ intraluminal pressure)

- With increased fat deposition and tissue weight in the area surrounding the upper airway (↑ extraluminal tissue pressure).

- A small mandible is thought to decrease the space in the upper airway enclosure and will compress the tissue to fit in a tight space (↑ extraluminal tissue pressure).

On the other hand, the pharyngeal dilator muscles preserve pharyngeal patency through reflex pathways [30] . Pharyngeal dilator muscles generally increase their activity in response to respiratory stimuli (increased CO_2 or decreased O_2) and to local stimulation, generally negative pressure.

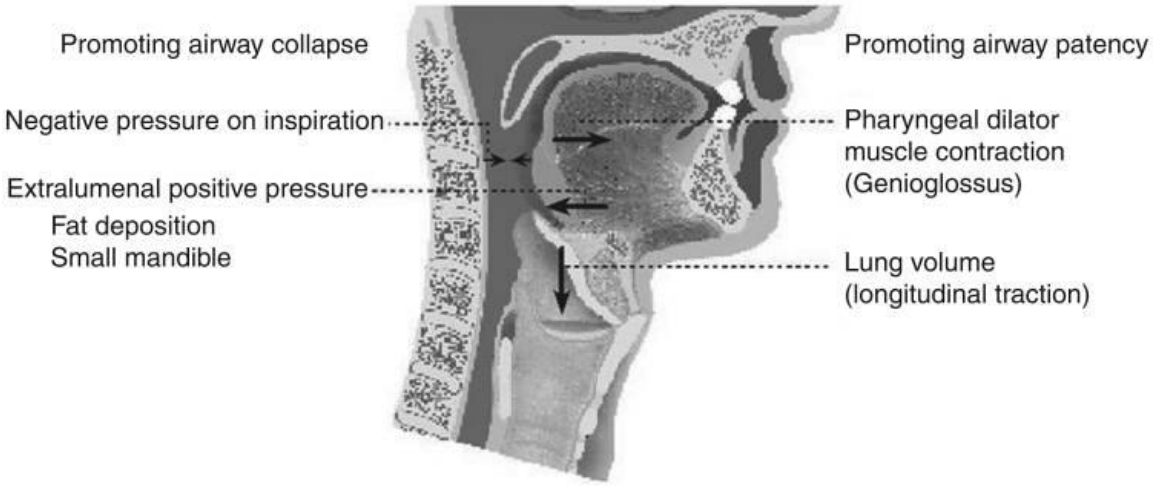


Figure 2. 1: Schematic drawing of the upper airway with the different factors promoting airway collapse on the left, and airway patency on the right [39].

Another protective mechanism is the longitudinal traction that happens with the increased lung volume during inspiration. When the lungs inflate, the upper airway walls become longer and subsequently more rigid [41].

These systems work efficiently in healthy and OSA patients during wakefulness. During sleep, there is a relative decrease in muscle activity and responsiveness to chemical and mechanical stimuli. Thus, the upper airway is more vulnerable and prone to collapse [98] . But in healthy subjects, the patency of the upper airway is maintained by different compensatory factors, i.e. a favorable upper airway anatomy will play a protective role against its collapse. In OSA patients, there is increased

pharyngeal collapsibility that is either due to altered anatomical components (increased external loads, narrow, collapsible airway), and/or non -anatomical factors related to dynamic neuromuscular responses [1, 30]. Therefore, the pathophysiological causes of OSA vary considerably between individuals. Major components are upper airway anatomy, the ability of the upper airway dilator muscles to respond to respiratory challenge during sleep, the tendency to wake from augmented respiratory drive during sleep (arousal threshold), the stability of the respiratory control system (loop gain) [102] .

- Anatomical factors

Although healthy and OSA patients show no difference in breathing capacities during wakefulness, OSA patients lose their upper airway patency during sleep. As a matter of fact, the cross-sectional area of the upper airway as measured by computed tomography and magnetic resonance imaging during wakefulness, is reduced in patients with OSA compared to healthy subjects [104] . In addition, enlarged tonsils and adenoids, lengthy soft palate extension, retruded mandible, inferior hyoid bone position… are commonly found in OSA patients (more details in the following section).

- Dilator Muscle Activity and Reflex

OSA patients have augmented genioglossus muscle activity to compensate for an abnormal anatomy or more collapsible pharyngeal airway when compared with healthy individuals. But since muscle activity is reduced during sleep, the

compensating mechanism is lost in OSA patients, and their upper airway patency is reduced or lost, leading to the occurrence of apnea and hypopnea events [1] .

- Arousal from sleep

Arousal from sleep to restore breathing after an apneic event was considered an important protective mechanism for airway reopening. In fact, studies by Younes et al. showed that normal airflow restoration happened in the absence of arousal in 17% of instances and before the arousal in 22% of the trials [105] . Even though OSA patients are able to restore ventilation without cortical arousal in some instances, it is to a lesser extent than healthy subjects [106] . This suggests that if OSA patients had enough time to restore normal breathing through compensatory mechanisms, this would prevent their awakening from sleep [107]. Delaying arousal in patients with low arousal threshold (meaning who are easily awaken) can be beneficial because it would give time to accentuate the stimuli (more Carbone dioxide and negative pressure to stimulate dilator muscles)[105]. But this can have deleterious effects on patients who already have high arousal threshold because it will lead to the toxic accumulation of carbon dioxide levels and increased negative pressure [108].

- Ventilatory Control Stability

The respiratory stability is controlled by the feedback control system known by the concept of loop gain. Every perturbation in the breathing pattern or cycle is detected by a series of sensors that sends signals to the brainstems that will in turn

react to stabilize the gas's fluctuations. There are two main constituents of the loop gain:

- controller gain referring to the chemoresponsiveness of the system (hypoxic and hypercapnic ventilatory responses),

- the plant gain refers to the ability to excrete CO2 within a certain ventilation level.

An individual with high loop gain has an excessive ventilatory response to a respiratory stimulus (disturbance in the CO2 levels). Therefore, the system will eliminate a more CO2 than required leading to hypocapnia and decrease in respiratory drive. This will result eventually in an unstable respiratory system.

A schematic representation of the accumulating factors leading to upper airway obstruction which in turn will lead to arousal and he different stages in the pathophysiology of OSA is shown in figure 2.2.

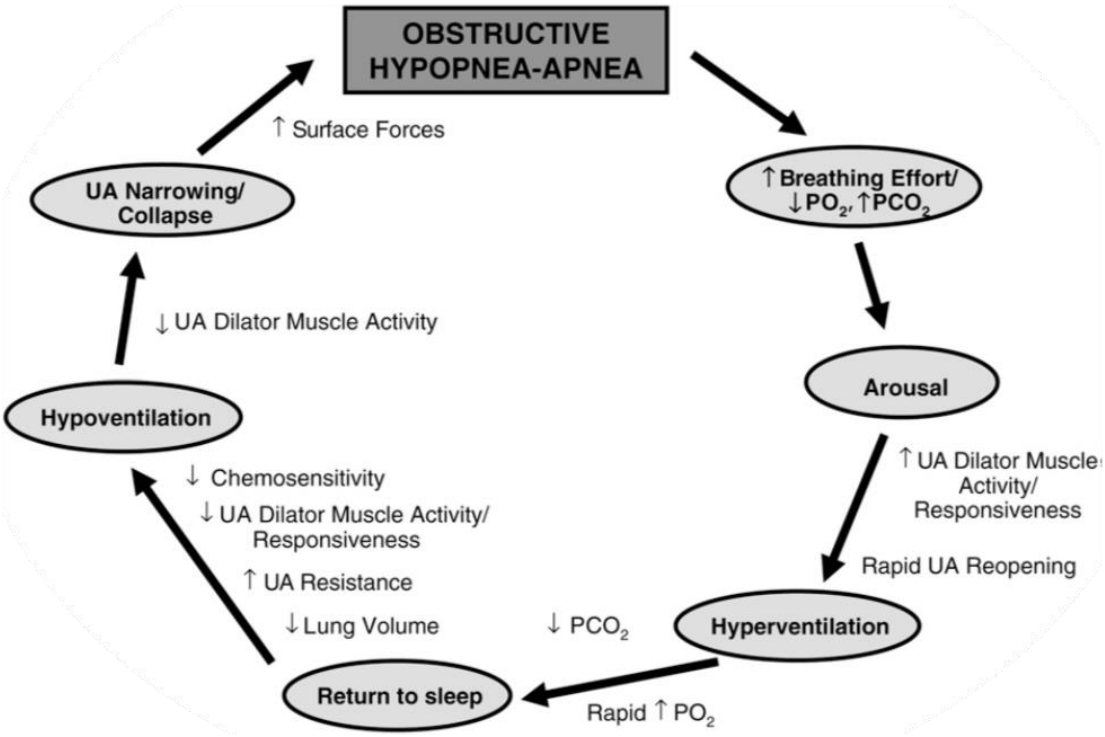


Figure 2. 2: Schematic representation of the physiological characteristics associated with OSA pathophysiology and leading to narrowing/ closure of the upper airway. Adapted from Eckert et a. 2008 [102].

2.4. Risk Factors

OSA major risk factors are obesity, male gender, aging and craniofacial anatomy [65, 99, 100].

- Obesity

Obesity is the strongest factor associated with the presence of OSA. This was well demonstrated in several recent studies where they showed higher AHI values in patients with higher body mass index (BMI) [54, 109, 110]. However, it is not only the high BMI, but how the fat is distributed in the body that is thought to contribute to OSA [73]. Excessive fat located in the soft tissues, tongue, and lateral pharyngeal walls increases external tissue pressure, thus increasing the collapsibility of the pharyngeal airway, and narrowing its size [54]. On the other hand, central adiposity leads to reduction in lung volume due to the external pressure exerted on the lungs. Thereby this will decrease the caudal traction forces and the upper airway walls will become less resistant, which translates into more collapsibility [111].

- Gender differences

OSA is two to three times more prevalent in men than women. This is thought to be associated with differences in body fat distribution, upper airway morphology and collapsibility, and female sex hormones protective effect [99].

- Aging

With increased age, sleep-related problems become increasingly common. A recent study reported 70% of men and 56%of women between 65 and 99 years of age had OSA (AHI > 10 events/hr) [112]. The Sleep Heart Health Study have shown

that disease prevalence increases with age until reaching a plateau after the age of 60 years. The prevalence of moderate and severe OSA remains relatively stable after the sixth decade of life [113].

Changes with age such as increased deposition of fat in the neck region, lengthening of the soft palate, and changes in body structures surrounding the pharynx are suggestive of the increase in OSA prevalence. Data on consequences attributable to obstructive sleep apnea in old patients has been inconsistent since they could be suffering from age-related cardiovascular problems even without the contribution of OSA. (Some studies concluding increased risk of adverse outcomes whereas others report little or no association.) Further studies are needed to investigate the association between OSA in older people and the increased morbidity and mortality [112].

- Craniofacial Anatomy

The alteration of craniofacial structures has been associated with OSA [110]. Soft and hard tissue may modify the mechanical properties of the upper airway rendering it less resistant to collapse thus increasing the tendency to develop obstructive sleep apnea.

Different imaging techniques (radiography, computerized tomography, and magnetic resonance imaging) were used to reveal anatomical and structural differences between healthy and OSA patients such as maxillary and mandibular retrognathism, enlarged tongue and soft palate, and tonsillar hypertrophy [53, 109, 114]. These factors will work to impinge on the posterior airway space [112]. Another common feature in OSA patients is an inferiorly positioned hyoid bone [50, 115], which will

be discussed further in chapter 3. A recent meta-analysis where several cephalometric parameters were evaluated on a 2D lateral cephalogram, confirms the strong association between the hyoid bone position and the collapsibility of the upper airway [37] .

Some of the variation in the prevalence of OSA across different racial groups is related to differences in craniofacial morphology. For example, Caucasians and African Americans show different cephalometric variables that are positively correlated with OSA severity. In Caucasians, the AHI is associated with the bony anatomy of the skull (brachycephaly), whereas in African Americans it is more associated with soft tissue size of the tongue and soft palate [112].

2.5. Clinical Diagnosis (polysomnography)

Polysomnography is the recommended test in the diagnosis of OSA. It consists of an in-laboratory, technologist-attended, overnight study where multiple physiologic signals are recorded during patient's sleep time [116] (Figure 2.3).

Recordings include monitoring of:

- sleep stages through electroencephalography (EEG), electro-oculography, chin electromyography,

- respiration through oronasal airflow and snoring recordings, pulse oximetry, thoracic and abdominal movement,

- cardiac arrhythmia through electrocardiography.

- body position and scoring periodic leg movements through electromyography [30, 97].

A trained technologist and sleep physician analyse the data, determine the distribution of sleep stages (REM/non-REM), and characterize breathing abnormalities seen during the night [30]. Episodes of apnea and hypopnea are visualized on a polysomnogram through a reduction in airflow (a cessation in airflow of at least 10 s for apneas) that is often accompanied by a decrease in oxygen saturation and terminated by an arousal (an interval of three seconds or longer of high frequency EEG) [116]. The total number of apnea and hypopneas per hour of sleep is calculated which corresponds to the AHI index (Apnea- hypopnea index) most commonly used to determine the severity of OSA. According to the American Association of Sleep Medicine (AASM), healthy subjects should score an AHI <5 episodes/hr, patients with mild sleep apnea have an AHI ranging between 5 and 15 (5 <= AHI <15 episodes/hr), moderate sleep apnea (15 <= AHI < 30 episodes/hr) and severe sleep apnea (AHI>=30 episodes/hr) [117] .

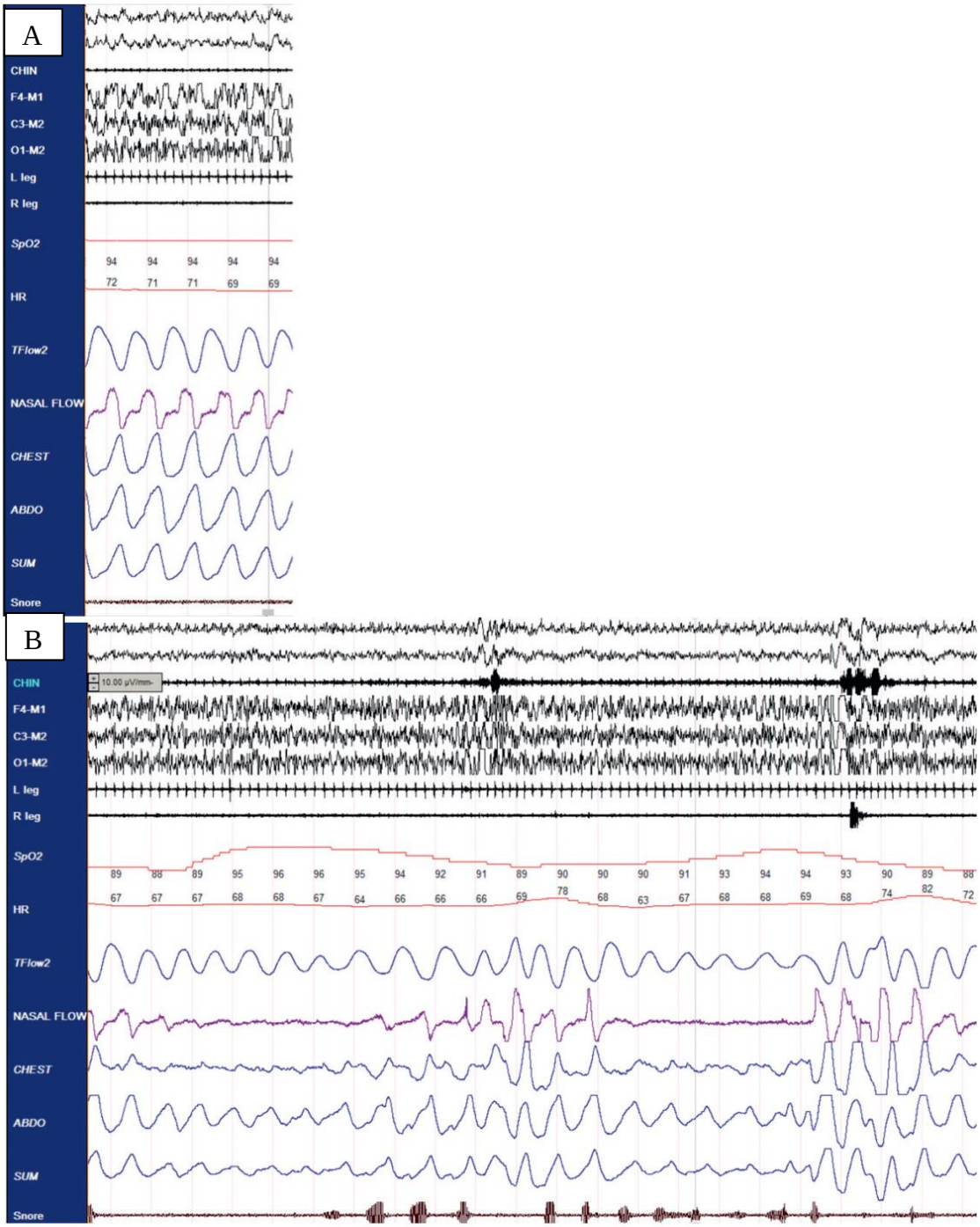


Figure 2. 3**:** Polysomnographic tracings in (A) patient with normal breathing (B) Patient with Obstructive sleep apnea. There is persistence of airflow during events on the thermistor (TFlow2) signal while the nasal pressure signal shows no flow. The event is therefore scored as a hypopnea because flow must be absent on both signals to score an apnea. Adapted from Kimoff et al. 2016 [97].

2.6. Current treatment approaches

There are several treatment options available for OSA, including weight loss, improved sleep hygiene, continuous positive airway pressure (CPAP), oral appliances and surgical interventions.

Weight loss was shown to be effective in reducing AHI in overweight patients, although to varying degrees between subjects, both with medical and surgical approaches. There are several reasons for this improvement variability, including baseline BMI and fat tissue distribution. Reduced craniofacial skeletal structure size may play a role on the effect of amount of weight loss on AHI improvement [49]. In a study held by Pepperd and colleagues, 10% weight gain predicted a 32% increase in AHI, whereas a 10% weight loss led to a 26% decrease in AHI. Strategies for weight loss include combined dietary, exercise, and behavior therapy [118].

Body position can increase OSA severity for most patients. Positional therapy aims to prevent supine sleeping position. This can be achieved by strapping a bulky object to the back or through an electronic device that vibrates when sleeping supine as an alert for the patient to shift to a lateral position. Those devices can be annoying, deranging sleep and cause back pain for patients therefore adherence to this kind of therapy is limited.

Changes in head/neck posture can also affect airway collapsibility as demonstrated by the decrease in Pcrit by approximately 13 cm H2O when head posture is in extension rather than flexion [49].

As for the continuous positive airway pressure and oral appliance therapies, they will be discussed separately below.

1.6.2. Continuous positive airway pressure (CPAP)

Continuous positive airway pressure (CPAP) was first described as a treatment for OSA by Sullivan et al. in 1981 [119]. CPAP therapy consists of a facial mask that provides positive pressure to the upper airway that prevents its collapse during sleep. It is highly successful in resolving OSA and is currently considered the gold standard OSA therapy [97]. The therapeutic pressure prescribed is the lowest value that maintains patency of the upper airway, which is manually determined during an overnight in-laboratory sleep study. Treatment with CPAP is recommended for patients with moderate to severe OSA [120, 121].

CPAP treatment has been consistently shown to improve sleep, reduce daytime sleepiness, neurocognitive function, and quality of life in most patients with moderate to severe OSA [97, 122]. However, despite these health-related improvements, many patients refuse the treatment or can only partially tolerate its use during the night, resulting in significant residual OSA. Therefore, compliance is a determining factor in the PAP clinical effectiveness. However, this is challenging for some patients, with long-term compliance estimates ranging from 30% to 85% [122] .

1.6.3. Oral appliance therapies

Oral appliance therapy or mandibular advancement splints (MASs) are a type of intraoral appliances that are used as a second line treatment after CPAP. Based on the American Academy of Sleep Medicine (AASM) practice guidelines, oral appliances are usually indicated for patients with mild-to-moderate OSA who prefer oral appliances over CPAP, or for patients with severe OSA who are unable to tolerate CPAP [123].

Mandibular advancement splints are designed to advance the mandible, which generally will increase the upper airway lumen dimensions, decrease pharyngeal collapsibility [76], and improve airflow [124] . The forward movement of the mandible will bring the tongue forward which will result in an increased anteroposterior dimension at the level of the oropharynx (Figure 2.4). This was demonstrated by measurements on two- dimensional lateral cephalograms [125] . However, consequent studies showed that mandibular advancement therapy produces lateral rather than antero-posterior airway expansion at the level of the velopharynx due to the stretching of tissues between the lateral walls and the ramus of the mandible [126].

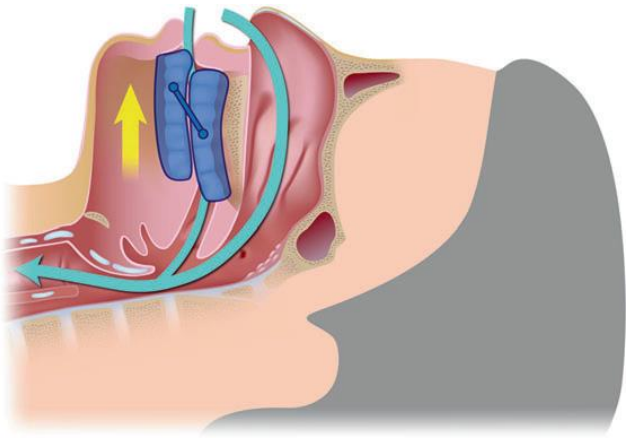


Figure 2. 4: Schematic drawing of the effect of the MAD as it advances the mandible and open the posterior airway space. Adapted from Alila Medical Library.

In general, a better treatment result is achieved with a greater level of advancement. In contrast, more advancement increases the risk of side effects. In a randomized clinical trial where mild-to- moderate OSA patients had their mandibles advanced either to 50% or 75% of maximum advancement, they found no difference between these levels in treatment AHI. However in patients with severe OSA, treatment success was higher with 75% compared to 50% maximum advancement (52% vs. 31%) [127] suggesting more advancement is needed in severe OSA patients. Mandibular advancement therapy is only effective in almost 50% of patients [128]. Without experimental testing in each patient [129, 130], there is currently no clinically-applicable predictors to the likelihood of oral appliance therapy success.

The side effects associated the use of the MADs include excessive salivation, mouth dryness, toothaches, migraines and temporomandibular joint distress. Long-term dental changes include tipping of the anterior teeth, intrusion of

the posterior teeth and occlusal problems [124]. Despite those adverse effects, MADs are generally tolerated by the patients [131].

MAD has been reported to be worn for a longer period of sleep time compared to CPAP [28]. Ultimately long-term studies of the comparative effectiveness CPAP and MAD are needed to provide robust evidence that supports substituting CPAP with MAD.

1.6.4. Surgical interventions (MMA, hyoid bone suspension, UPPP)

Multilevel surgeries addressing different levels of upper airway obstruction were developed as a surgical treatment option for the management of OSA.

1.6.4.1. Hyoid suspension

The hyoid bone is a mobile bone that is the insertion point of the major upper airway muscles for example the muscles of the tongue (hyoglossus, genioglossus, and the intrinsic muscles of the tongue). In addition, numerous muscles insert above (suprahyoid muscles) and below (infrahyoid muscles) the hyoid bone. Therefore, the hyoid bone plays a crucial role in the respiratory mechanics as we will be discussing in the following chapter.

It is justifiable that the hyoid bone has been of much importance in the treatment of OSA to expand the pharyngeal space, specifically the hypopharynx and the retrolingual airway when obstacles at these regions are suspected.

In an animal study using dogs in the 1980s, it was shown that anterior displacement of the hyoid body can expand the hypopharyngeal airway space [132]. Van de Graaf

and co-workers concluded through their studies on dogs that the anterior traction of the hyoid bone reduced significantly the airflow resistance. Therefore, the position of the hyoid is a major contributor to OSA as it affects the hyoid muscles activity [9].

At a later stage, Riley and colleagues noticed that most of the unsuccessfully treated patients with uvulopalatopharyngoplasty (UPPP), had an inferiorly positioned hyoid bone and they performed the first hyoid suspension surgery. Their technique consisted of suspending the hyoid to the lower border of the mandible. It was usually performed as a part of multilevel surgery.

In the early 1990s, Riley and Powell updated their technique to decrease the side effects associated with the original procedure (high morbidity and unfavorable cosmetic changes that could occur after advancement of the hyoid into the submental region). [133]. It consisted of suturing of the hyoid bone to the thyroid cartilage. This was referred to as “hyothyroidopexy” (figure 2.5) [134] .

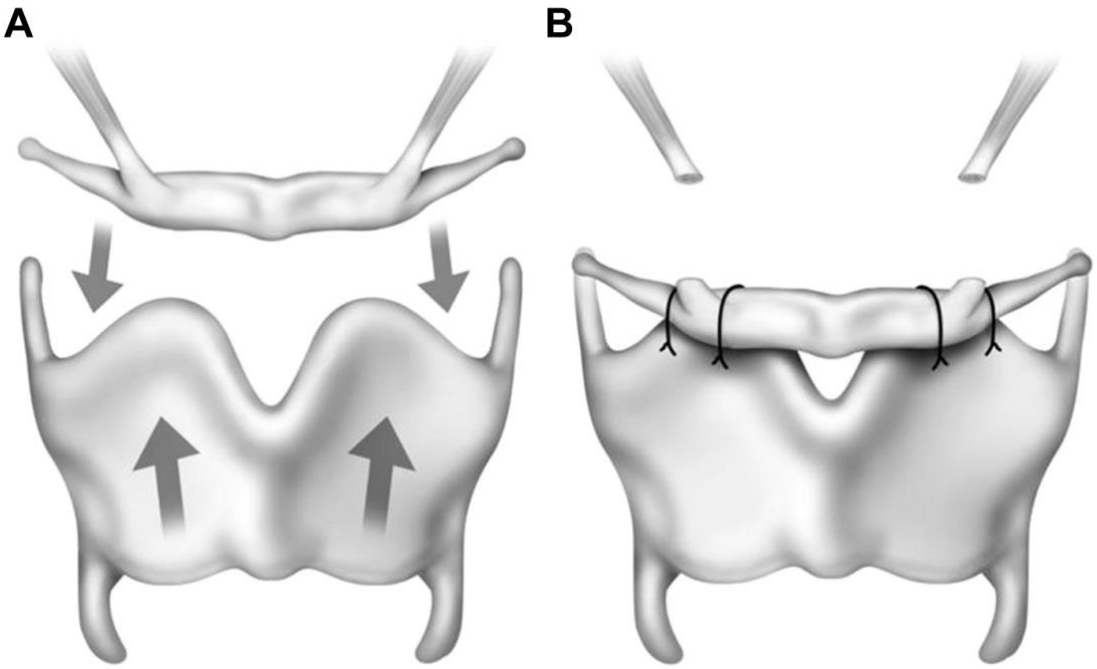


Figure 2. 5: Hyothyroidopexy: schematic drawing showing the position of the hyoid bone before (A) and after surgery (B). Adapted from Dorrity et al, 2016 [135].

Various approaches to this technique were developed afterwards, modifying the surgical cuts and dissection levels or combining it with different surgical procedures [135] . Nevertheless, the success rate of the modified hyoid suspension surgery remains low and vary between 30 to 60% [136].

Complications are uncommon and some impermanent distress in swallowing and feeling of neck tightness might be experienced by the patient, which the patient adjusts to with time [133] . The number of studies about this topic remains low and not conclusive.

1.6.4.2. Genioglossus advancement (GA)

It consists of advancing the genial tubercles which are the site of attachment of the genioglossus muscle (Figure 2.6). The genioglossus muscle (GGM) is the major dilator muscle in maintaining the patency of the upper airway. The aim of this intervention is to increase the tension at the base of the tongue, stretching the GGM and rearranging the muscle fibers. This leads to larger airways anteroposteriorly. It could be performed as a sole procedure or in combination with maxillomandibular advancement (MMA) procedure [118] . Alone, it is considered a limited intervention as it is dependent on the mandibular bone anterior thickness. [135] .

The surgical outcome of GA is variable. The average success rate ranges between 39 and 78% and it was demonstrated to be more efficient in patients with narrowing at the level of the lower pharyngeal airway. Postoperative complications are common with any other invasive surgery (wound infection, nonunion, and malunion of the fragments) [137] .

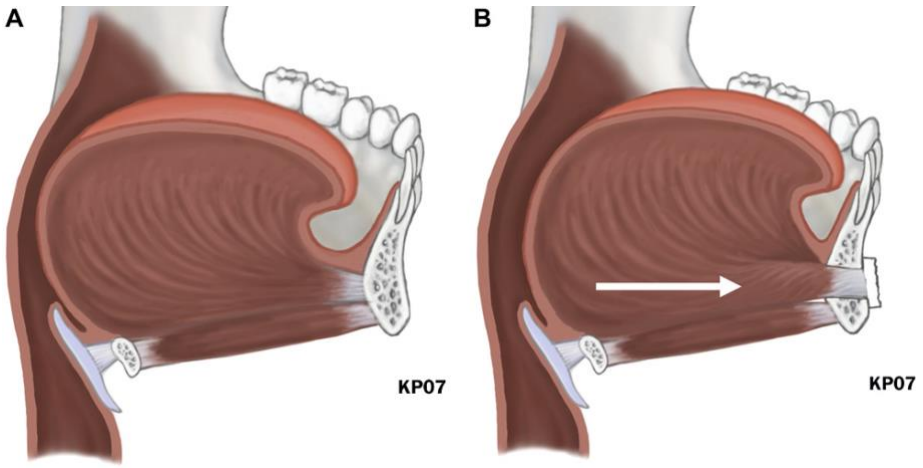


Figure 2. 6: Preoperative (A) and postoperative (B) sagittal views of the mandible, tongue and genioglossus muscle following GA surgery. [118]

1.6.4.3. Maxillomandibular Advancement (MMA)

Orthognathic surgery was originally aimed to treat dentofacial deformities and severe dental discrepancies. In 1980s, its application later extended to treat patients with severe OSA [138] . It is an invasive treatment option for OSA and most effective in expanding the upper airway. It is indicated in patients who had an incomplete or failed response to the first phase of less invasive interventions, specifically in patients with severe maxillomandibular facial deficiency [118] . According to Riley and Powell, a 10- mm advancement of the maxilla and mandibular resulted in an impressive 97% cure rate in patients who had failed phase I surgery [138]. Nevertheless, the effects of MMA on the upper airway were reported differently with the various utilized techniques and success rates range from 65% to 100% in some instances [134] . The surgical technique consists of a double jaw surgery targeting the maxilla and the mandible[118]. MMA surgery affects the entire length of the upper airway in the retropalatal and retrolingual space, thus increasing the posterior airway space. [139]

Potential complications of MMA are the same for any surgery (bleeding, infection, malunion of the segments…) as well as nerve lesion leading to transient or permanent sensory alteration and unfavourable facial changes. [140]

For optimal results, maximum advancement of both jaws while preserving functional occlusion and good aesthetics should be taken into consideration through an individualized treatment planning.[118]

1.6.5. Muscle function therapies

The pharyngeal muscles are primarily important in stiffening and dilating the UA therefore maintaining its patency.

The UA muscle activation is dependent on the respiratory stimuli (for example changes in negative or in the level of CO2 and oxygen) and this is known as muscle responsiveness. Over 30% of OSA patients have minor muscle responsiveness to negative pressure during sleep, which leads to UA collapse. Contrarywise, positive muscle responsiveness can guard patients with craniofacial impairment from OSA [66].

In cases where the pharyngeal dilator muscles are at fault, targeting the therapy towards improving muscle function by stimulation, training or through drug use provide novel treatment strategies for optimized outcome.

1.6.5.1. Hypoglossal Nerve stimulation

Hypoglossal nerve stimulation aims to activate the genioglossus muscle and other intrinsic and extrinsic muscles of the tongue that are responsible of the dilation of the upper airway. Thus, this will improve the upper airway patency and reduce OSA severity [141] . Successful treatment may be reliant on the patient's Pcrit at baseline (i.e. minimal negative pressure that closes the upper airway), the pharyngeal anatomy and site of obstruction [141, 142] . In a recent study, Benderro et al. (2018) tested the effects of hypoglossal nerve stimulation in the anesthetized rabbit before and after induced obstruction of the upper airway. They concluded that medial branch stimulation reduces airway resistance but it is less effective than anterior

advancement of the hyoid (which reduces the resistance more) [89] . Success rates are variable and are reported to be almost 65% [141] .

1.6.5.2. Drugs to increase muscle function

New research suggested the use of pharmacological substances to enhance the function of the upper airway dilator muscles, but there is lacking proof to support absolute utilization of medication in the treatment of OSA [143] . Positive outcome after the use of potassium channel blocker were reported in different animal studies in pigs and rats [144, 145] . Those chemicals tend to enhance the pharyngeal muscle function therefore increasing the upper airway patency.

Genioglossus muscle has a reduced function during sleep that increase the risks of collapse of the upper airway. Desipramine, along with other drugs, were tested and used to target this drop in activity. This would lessen OSA severity in patients by optimizing muscle effect [49, 143] . It is conceivable that better allocation of medications to patients based on the main causing factor to their OSA will prompt better outcomes and this likewise needs further examination. Currently, none of the previously investigated drugs is officially affirmed as a drug for OSA treatment.

Summary

OSA is a common disorder characterize by repetitive narrowing or collapse of the pharyngeal airway during sleep. The disorder is associated with major comorbidities including excessive daytime sleepiness and increased risk of cardiovascular disease. The underlying pathophysiology is multifactorial and may vary considerably between individuals. Important risk factors include obesity, male sex, and aging. However, the physiological mechanisms underlying these risk factors are not clearly understood. Treatment strategies include CPAP, mandibular advancement devices, MMA surgeries and hyoid suspension, in addition to hypoglossal nerve simulation and drug therapy are still currently being investigated to achieve better treatment outcomes.

CHAPTER 3

THE HYOID BONE AND UPPER AIRWAY FUNCTION

3.1. General function of the hyoid

The hyoid bone is a horseshoe-shaped bone, unpaired, symmetrical, located in the midline of the neck between the mandible and the thyroid cartilage. It is a freely suspended bone that does not attach to any other bone. It is connected to the base of the skull, the tongue, the larynx through a complex tendonomuscular arrangement. It provides attachments to the muscles of the floor of the mouth, to the tongue above, to the larynx below, and to the epiglottis and pharynx behind [9].

Even though it might have a simple anatomical shape, the hyoid bone is a crucial part of the human and animal body. It had gone through the evolutionary process and is considered a remnant of the second and third pharyngeal arches. It is involved in several prime human functions such as speech [146], chewing [147],swallowing [148], breathing and airway patency[149] due to its strategic location and characteristics. In addition, it is involved in the physiological set up to maintain pharyngeal patency.

It is present in animals as a part of the second pharyngeal arch or hyoid arch. In reptiles and amphibians, the hyoid bone is contained in the body of the tongue. However, in humans, it parted from the tongue as a result of a downward and backward movement of the face and lower jaw with the biological evolutionary adaptation of the human being [150].

3.2. Structure

The hyoid bone is composed of the hyoid body from which emerges two small eminences; the lesser horns and two bigger eminences; the greater horns. The evolution theory predicts that these eminences are the result of the forces applied from the muscles as they attach to the bone [150].

There are twenty muscles that are attached to the hyoid bone, ten on each side. They can be divided into two main groups: the suprahyoid muscles (four on each side) and the infrahyoid muscles.

The suprahyoid muscles attach the hyoid bone to the mandible, to the tongue, and to the temporal bone. They are the anterior and posterior digastric, stylohyoid, geniohyoid, and mylohyoid muscles.

The infrahyoid muscles are a group of four pairs of muscles located in the region between the hyoid bone and shoulder bones (clavicle and scapula). Those muscles are the sternohyoid, sternothyroid, thyrohyoid, and omohyoid muscle.

A summary of the supra and infrahyoid muscle origin, insertion and innervation is presented in tables 3.1 and 3.2.

Table 3. 1: Summary of the origin, insertion and innervation of the suprahyoid muscles. Adapted from Auvenshine et al, 2020 [1]

Suprahyoid muscles			
Muscle	Origin	Insertion	Innervation
Digastric (anterior belly)	Digastric fossa of mandible	Intermediate tendon	Mylohyoid nerve – branch of CN V3 (mandibular division of Trigeminal nerve)
Digastric (posterior belly)	Mastoid notch	Intermediate tendon	Facial nerve
Geniohyoid	Interior mental spine of symphysis menti	Hyoid	C1 via the hypoglossal nerve (XII)
Stylohyoid	Temporal styloid process	Hyoid	Facial nerve
Mylohyoid	Mylohyoid line of mandible	Hyoid	Mylohyoid nerve – branch of CN V3 (mandibular division of trigeminal nerve)

Table 3. 2**:** Summary of the origin, insertion and innervaion of the Infrahyoid muscles. Adapted from Auvenshine et al, 2020 [1].

Infrahyoid muscles			
Muscle	Origin	Insertion	Innervation
Sternohyoid	Posterior surface of manubrium sterni, adjoining part of clavicle and the posterior sternoclavicular ligament	Medial part of lower border of hyoid bone	Ansa cervicalis
Sternothyroid	Posterior surface of manubrium sterni and adjoining part of first costal cartilage	Oblique line of the thyroid cartilage	Ansa cervicalis
Thyrohyoid	Oblique line of the thyroid cartilage	Lower border of the body and the great cornu of the hyoid bone	Cervical spine nerve 1 via the hypoglossal nerve
Omohyoid (superior belly)	Intermediate tendon	Hyoid bone	Superior root of ansa cervicalis
Omohyoid (inferior belly)	Superior border of scapula	Intermediate tendon	Ansa cervicalis (C1–C3)

The hyoid bone is also suspended to ligaments such as the stylohyoid ligament (from the styloid process of the temporal bone) and the ligaments spreading from the thyroid cartilage. Its position is maintained by the equilibrium between the attached muscles and ligaments. Therefore, the hyoid bone musculature is a key factor in determining the limits of hyoid movement and position [151]. In other words, the amount of muscle traction and force exerted on the hyoid bone will dictate its position and movement. For instance, advancing the mandible also pulls the muscles attached to it forward and upward depending on their direction, and this force reaches the hyoid and lifts it upward. Likewise, breathing and lung volume changes is associated with vertical tracheal displacement (detailed in the next

section). These loads are transferred to the hyoid bone and affect its position [71] . When swallowing, the hyoid bone moves upward as the suprahyoid contract and the mandible is fixed in position, allowing the food to pass through the oropharynx and to the esophagus.

3.3. Hyoid - Swallowing and mastication

Mastication and swallowing require the interaction between the mandible, hyoid bone, and tongue. In Ishida et al.'s [152] study on the coordination of mastication and swallowing, they found that when subjects masticated solid food, a swallow is achieved with a upward then forward movement of the tongue and the hyoid bone while the tongue compresses the food against the palate several times. The forward movement of the hyoid was produced by contraction of the geniohyoid and anterior digastric muscles. Therefore, it is obvious that the masticatory muscles have a direct effect on the hyoid bone position (Figure 3.1).

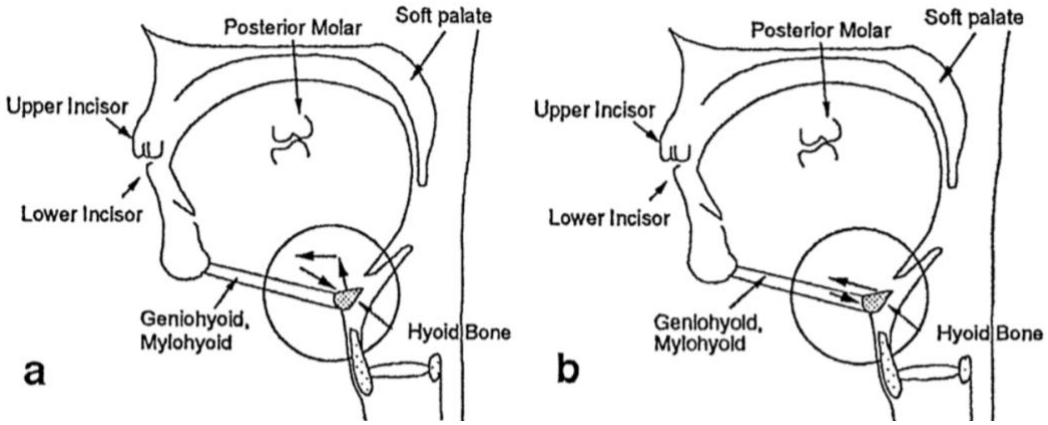


Figure 3. 1: Schematic representation of the human upper airway showing the hyoid bone movement during swallowing. The hyoid bone moves upward and forward when swallowing (a) then returns to its original position at the end of the swallow (b). The geniohyoid and mylohyoid are the main contributors to tis movement. Adapted from Ishida et al, 2002 [152].

Ekberg reported that the hyoid movement is precise with minimal variability between individuals and between swallows [153]. A number of studies emphasize on the importance of the hyoid movement as a component in the swallowing mechanism, with its role in the control of tongue movement [154], opening of the upper oesophageal sphincter [155], and tilting of the epiglottis [156].

Also, a significant correlation was found between the amplitude of the upward and forward movements of the hyoid and the volume of the swallowed bolus [156]. Jacob et al. [157] reported that the greatest extent of upward hyoid movement was significantly larger for bigger-volume liquid swallows (10 and 20 mL) than for small-volume (1 mL) liquid swallows. Forward movement was almost the same for all volumes, showing that hyoid movement is affected by bolus volume in the

upward rather than forward direction. Palmer et al. [158] reported on the movement of the hyoid bone during feeding on solid food. They found that the hyoid moves generally moved in parallel with the tongue. Maximal downward movement of the tongue and hyoid occurred with maximal jaw opening, while maximal upward displacement happened when the upper and lower jaws were brought together.

Thus, the hyoid bone movement is an important factor contributing to proper mastication and swallowing and the restriction of this movement might lead to problems, but this has not been well established yet.

3.4. Hyoid - airway

The airway dimension is dependent on soft tissue volumes and bony structure forming its borders. The tongue, along with the hyoid bone at its base, are major contributors in the maintenance of the airway and adaptation of oropharyngeal dimensions [159]. Knowing the importance of the hyoid bone as a determinant of upper airway patency, numerous studies focused of assessing the relationship between the hyoid bone and the other craniofacial structures[37, 114], as well as the relationship between the hyoid bone position and the upper airway dimensions, using CBCT imaging [32, 160], CT scans , 2D lateral cephalograms [115, 161]… In addition to the observations made following hyoid suspension surgeries aiming to improve breathing in OSA patients [134, 135].

In 1947, Mitchinson et al [162] showed that the hyoid bone moved anteriorly in humans during large breaths. Later in time, Roberts et al [45] used the rabbit model to test the efficacy of the sternohyoid and sternothyroid muscles (upper

airway muscles that connect to the hyoid bone) in maintaining the upper airway stability and patency. The effect of tension on those muscles with the animal's head at 90" is to pull the hyoid bone caudally. this caudal movement of the hyoid was associated with improved airway stability.

Brouillette and Thach[163] found that improvement in upper airway stability and dilation in the pharyngeal region seen when stimulating the genioglossus and geniohyoid muscles, was related to their effects on the hyoid bone. These muscles have the effect of shifting the hyoid bone toward the nose i.e more cranially. Reed et al. [164] obtained a similar finding when tension was placed on the hyoid bone simulating geniohyoid and genioglossus muscle contraction in infant cadavers

The observation that either movements of the hyoid bone has a similar effect on the pharyngeal dimensions may be explained by the small outward vector force away from the spine that could result from either cranial or caudal hyoid movement [45].

In a study by Rosenbluth et al, [165] they used a magnetic-based system to pull the hyoid bone 1cm anteriorly in five fresh cadaveric specimens and observed the improvement in the upper airway dimensions and airflow. Maximal airway opening was achieved with 2 N (0.5 lb) of anteriorly directed pull on the hyoid bone; airway patency was detected using fluoroscopy and CT imaging. The optimal force vector was perpendicular to the anterior neck contour, while pulling the hyoid anteriorly with a 30-degree caudal or rostral vectors showed less improvement. Nevertheless, this study did not determine the correlation between gradual anterior

repositioning of the hyoid bone and the amount of improvement in the airway patency at each position. In contrary, they linked the critical closing pressure to the amount of force they used to pull the hyoid bone. Also, it is unclear whether the magnitude of applied force or changes both in airway dimensions and upper airway airflow will be similar in live humans.

Following the previous findings, hyoid suspension was developed, as a surgical procedure designed so that the hyoid bone is suspended to the inferior border of the anterior mandible. This technique was later modified by Riley et al. where he attached the hyoid anteroinferiorly to the thyroid lamina rather than suspending it from the anterior mandible. The technique revision was based on animal studies by Van De Graaf et al. [9] where the hyoid arch was pulled ventrally in six anesthetized dogs. This lead to a reduction in the upper airway resistance showing that the position of the hyoid arch and its muscle attachments strongly affect upper airway patency and tongue position. Riley et al. [166] reported significant improvement in 15 patients with OSA treated with this revised technique.

Neruntarat [167] reported outcome for 32 patients treated with palate surgery (uvulopalatal flap) and hyoid suspension using the revised technique of Riley et al. Twenty-five (78%) of 32 patients achieved a successful outcome based on a 50% reduction in respiratory disturbance index (RDI).

Amatoury et al. [71] stated that the hyoid bone plays a pivotal role in redistributing the loads between the caudal and cranial segments and this affects the resultant upper airway geometry outcomes.

In a summary, data on the outcome of hyoid suspension surgeries is still limited with a small number of patients, and variable success rate between studies. Although different hyoid repositioning technique were considered, moving it cranially or caudally, the precise influence of this movement and the correlation between the amount/ direction of movement and the effect on the upper airway is still not well established.

3.5. Importance of the hyoid bone in OSA

The hyoid bone is considered a major contributor to upper airway function in OSA. This was proven in several human and animal physiological studies demonstrating the relationship between hyoid position and airway properties.

In patients with obstructive sleep apnea, the inferior position of the hyoid bone is considered the most consistently observed anatomical difference in comparison to healthy controls (Figure 3.2). It is associated with a more collapsible and resistant upper airway [37, 109, 115, 149, 161] . Tangugsorn et al. found that the hyoid bone was inferiorly placed at C4-C6 instead of the usual position at C4 in OSA patients. It was hypothesized that this was due either to increased mandibular plane angles or to thick fat pads in the submental, submandibular, and pharyngeal regions [168, 169] . On the other hand, displacement of the hyoid bone in a caudal direction following tracheal traction has an opposite effect on the upper airway as it was associated with decreased collapsibility [60].

Therefore, the precise influence of hyoid position on upper airway function is still not very well defined.

In addition, the hyoid bone position affects the upper airway muscles effectiveness by modifying the individual muscle contractile properties and force vector. The effect of a muscle when placed in a certain location in a certain direction is different that when the same muscle has another direction [170]. Therefore, the dilatory muscles attached to the hyoid bone follow the same principle. When the hyoid bone is at a lower level than where it should be, the dilatory muscles have a different direction, thus might not be as effective anymore in dilating the upper airway. This reduction in function does not mean that the muscle has a suboptimal function, as OSA patients often have more muscle activity than healthy subjects during wakefulness and sleep, but it might mean that the muscles are less effective in dilating the airway [21, 171] . This could be a main contributor to the development of OSA in patients with an inferiorly placed hyoid bone. Novel research in this field have shown that OSA patients have an inferior capacity in upper airway dilation compared to controls [126, 172] .

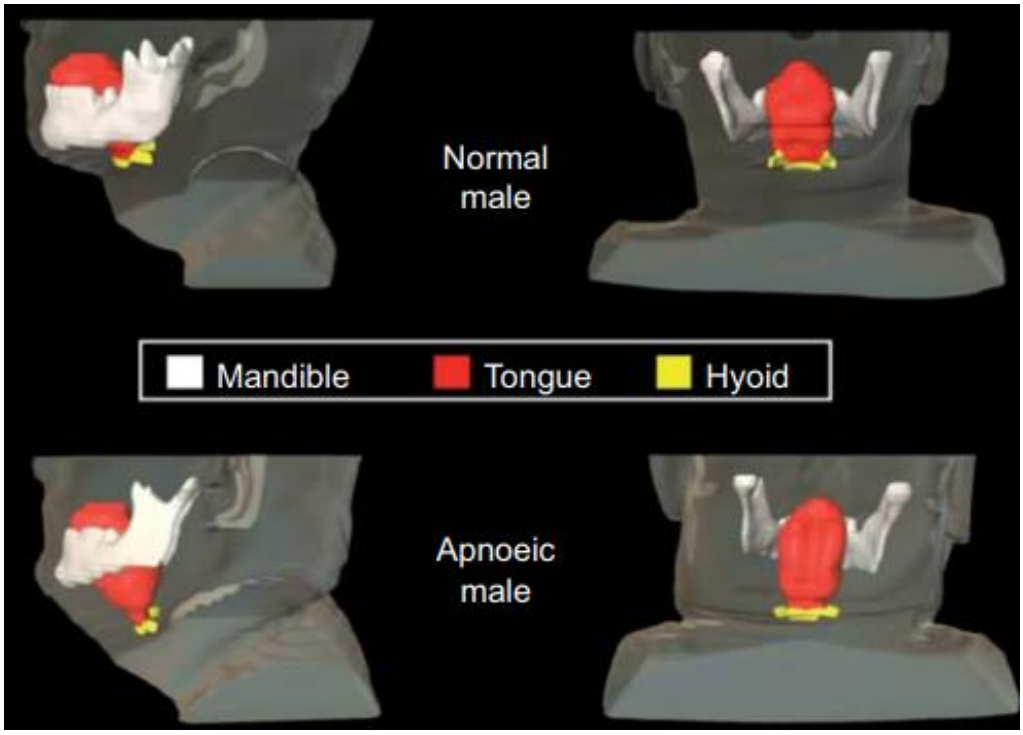


Figure 3. 2: Schematic drawing, based on CT scan imaging, showing the difference between the hyoid bone position between heathy and apnoeic patient. It is placed more inferiorly and posteriorly in OSA patient. Note that the tongue volume is greater in the apnoeic patient. Adapted from Chi et al, 2011. [109]

Genta et al. measured the critical closing pressure of the upper airway (Pcrit) on 34 male human subjects where they showed that the upper airway collapsibility is associated with the hyoid position. In addition, they discussed the effect of a larger tongue size, leading to a lower hyoid bone position and eventually to a longer pharyngeal length. When the upper airway length is increased, the pharyngeal collapsibility increases [50] .

3.6. Factors that alter hyoid position

Different factors affecting the upper airway dimensions and properties, are often directly or indirectly related to the hyoid bone (where it becomes an intermediate transmitting forces between the supra and infra hyoid regions). Those factors include head and neck positions, tracheal displacement and lung volume, obesity and mandibular advancement.

3.6.1. Head/neck/body position

Thompson et al. [173] stated that the hyoid muscle group contribute to the maintenance of head posture. This was demonstrated in electromyographic (EMG) studies, where the hyoid muscles were activated during head flexure [174]. Zheng et al. [151] examined a wide range of flexion/extension motion of the neck and the relative movement of the hyoid bone. It was hypothesized that the position of the hyoid bone in the sagittal plane is correlated with the motion of the head, jaw, and vertebrae. The position of the hyoid bone has been examined at its neutral posture. It was found to relate more closely to the curvature of the cervical spine than to the craniocervical relationship (e.g., the angle between the head and C2) [175].

The position of the hyoid bone in relation to the vertebral column had less variability than the hyoid position in relation to the maxilla and the mandible [176]. Furthermore, sex differences were found in hyoid bone shape and position [177]. Improved knowledge of hyoid bone movements with head and neck movement will help guide diagnosis and treatment of neck disorders, not just those related to the hyoid bone and muscles, but of the entire head neck region [151].

3.6.2. Tracheal displacement/lung volume

Variations in lung volume during inspiration and expiration are known to influence upper airway lumen dimensions. A reduction in pharyngeal collapsibility and an increase in airway patency is observed with increased lung volume in healthy individuals and obstructive sleep apnea patients, as it displaces the trachea caudally and stiffen the upper airway walls [178, 179] . In OSA patients, Kohno et al. reported that a 0.72 litre increase of the lung volume decreased the velopharyngeal closing pressures by 1.2 cmH_2O [73]. The reduction in lung volume during sleep which decreases the resistance of the upper airway is a major contributor to OSA in some patients [59] .

It was previously demonstrated in anaesthetized rabbits that increasing the caudal tracheal pull lead to a more resistant, less compliant upper airway tissue meaning that a more negative pressure in the peripharyngeal tissues is needed to close and reopen the airway [59] .

The effect of tracheal displacement on the upper airway is associated with movement of the hyoid bone (Figure 3.3). The hyoid bone position rest in a mechanical equilibrium between the lungs and the upper airway [73] . It moves caudally in response to the caudal tracheal traction. Many of the previous studies disregarded the importance of the hyoid bone movement with the tracheal displacement. But it was proven that its caudal movement causes increased tension in the upper airway tissues and improve the mechanical stability of the upper airway [71]. The graph below shows the hyoid bone in a rabbit model, as it is displaced caudally in a linear fashion, in response to the increased tracheal displacement.

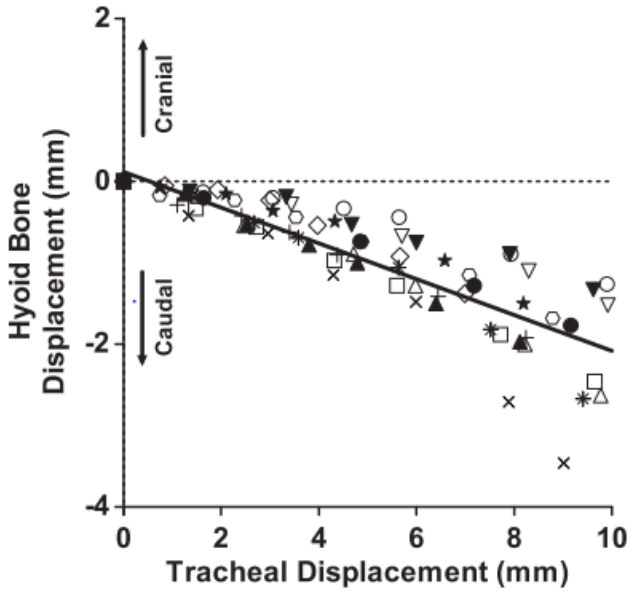


Figure 3. 3**:** Graph representing the data obtained from a rabbit following tracheal displacement. The hyoid bone is displaced caudally from 0 to -2mm with a tracheal displacement from 0 to 10mm. Adapted from Amatoury et al. 2014 [1].

When the trachea is displaced caudally, the hyoid bone is moved caudally, pulling thereafter the suprahyoid muscles, stretching and stiffening the peripharyngeal tissues. This will enlarge the airway anteriorly and laterally [71] (Figure 3.4). Therefore, a change in the hyoid bone position leads to upper airway lumen geometry changes.

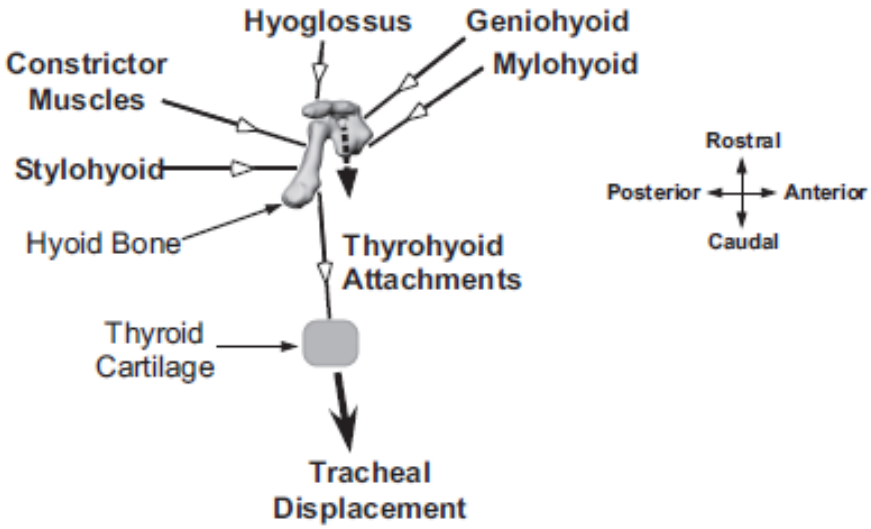


Figure 3. 4**:** Schematic drawing showing the effect of the tracheal displacement on the hyoid bone and therefore on the muscles attached to it. With the caudal tracheal displacement, the hyoid moves caudally, transferring the loads cranially to the suprahyoid muscles, stretching the peripharyngeal tissue leading to a stiffer upper airway. Adapted from Amatoury et al. 2014 [71] .

3.6.3. Obesity

Obesity is known to be a major risk factor for OSA. Increased fat pads and soft tissue volume in the region of the neck pushes the hyoid bone caudally because of tissue compression [73] . Even though the effect of obesity on the position of the hyoid bone is similar to that of the caudal tracheal displacement, the resultant force on the upper airway is different. The tension in the tissues below the hyoid bone is decreased, the upper airway becomes like a floppy tube in obese subjects. The caudal tracheal traction increases the resistance of the upper airway, as opposed to obesity

where there is increased collapsibility, narrowing and lengthening of the upper airway [71] .

On the other hand, central obesity at the level of the abdomen causes a decrease in the lungs volume due to compression. As discussed previously, smaller lung volume implicates more collapsible upper airway. This reflects a decreased tracheal pull as another potential cause leading to OSA linked to obesity[54, 110].

The upper airway collapsibility (Pcrit) was demonstrated to be associated with obesity (BMI, neck and abdominal circumferences). Tongue volume specifically, which is increased in obese patients, has been shown to be associated with higher AHI values [50, 73].

3.6.4. Mandibular advancement

Several studies in the recent literature have shown that mandibular advancement increases the pharyngeal patency by reducing airway resistance in both anesthetized and awake individuals. In OSA patients treated with mandibular advancement, the closing pressure of the upper airway is reduced compared to their baseline values, therefore it becomes less collapsible (–1.6 +-0.4 vs. –3.9 +-0.6 cm H2O, p 0.01) [76]. Amatoury et al. developed and validated a two-dimensional finite element model (FEM) of the passive rabbit UA and surrounding peri-pharyngeal tissues [86]. In this model, they examined the effect of mandibular advancement on the upper airway dimensions, collapsibility and peri-pharyngeal tissue deformation. Progressive mandibular advancement increases upper airway cross sectional area and

tissue stress and decreases upper airway length [180] . Adding tracheal displacement to the mandibular advancement optimized the results further more [87] .

However, there has been a lack in the knowledge about the process by which mandibular advancement improves upper airway patency. Earlier studies reported that mandibular advancement lead to an optimization of the genioglossus muscle activity and to a decrease in the extraluminal tissue pressure. It displaces as well the tongue anteriorly and widen the lateral pharyngeal walls [57]. In a recent study, Brown et al. studied upper airway tissue movement and deformation after mandibular advancement in healthy and affected subjects using magnetic resonance imaging (MRI). They concluded that the mandibular advancement increased the upper airway dimensions by expanding it laterally [126].

Nevertheless, mandibular advancement improves the upper airway properties even wih muscle paralysis, therefore, increased muscle activity and anterior displacement of the tongue are not the exclusive mechanism.

The mechanisms leading to upper airway changes with mandibular advancement, involve various interactions within the peripharyngeal tissues, including those associated with the movement of the hyoid bone. In their studies on rabbits, Amatoury et al. found that the hyoid bone moved in a cranial- anterior direction when advancing the rabbit's mandible (Figure 3.5) [58]. This is concordant with the results of other studies on human subjects [81, 181-183]. This movement will enhance the patency and stability of the upper airway.

The more the hyoid bone is displaced with mandibular advancement, the better is the effect in the upper airway lumen size in awake OSA subjects [181] .

When the mandible is advanced, the suprahyoid muscles, part of which are linking the hyoid to the mandible, are stretched. Those muscles will pull the hyoid cranial, which will stretch the infrahyoid tissue. This load will pull the thyroid cartilage cranially and stiffen the tissue in the area [58] . Thus the hyoid bone plays a pivotal role in conveying the mandibular advancement effect to the caudal peripharyngeal tissues. Thus, not just the position of the hyoid bone is a main factor as previously explained, but also the movement/mobility of the bone is to be considered. Restricting the hyoid bone from movement will not allow it to transfer the loads resulting from the mandibular advancement leading to a less enlarged and stiffened upper airway. Yet, It is still not well established whether moving the hyoid bone more caudally or cranially is responsible of the improvement seen with the advancement therapy [128, 184] .

On the other hand, the baseline position of the hyoid bone, which determines the effectiveness of the upper airway dilator muscles, might also affect the mandibular advancement outcomes. Thus, the hyoid bone original position might be a potential factor for mandibular advancement treatment success in OSA patients.

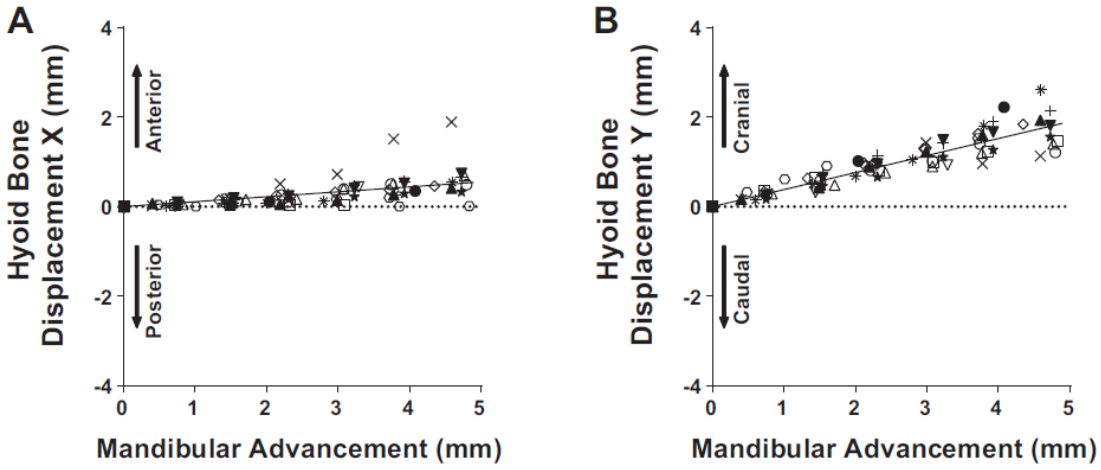


Figure 3. 5: The effect of mandibular advancement on the displacement of the hyoid bone in a passive rabbit model. The hyoid is displaced anteriorly and cranially with the progressive amounts of mandibular advancement. Adapted from Amatoury et al. 2014 [58] .

Summary

In this chapter, we discussed the importance of the hyoid bone and its contribution in different physiological functions, such as speech, swallowing, mastication and breathing. The hyoid bone movement is the main key factor to load distribution between the supra and infra hyoid regions. An abnormally positioned hyoid bone might lead to narrowing in the upper airway and ultimately to the occurrence of OSA.

While increased fat in the region of the neck leads to a more caudal position of the hyoid bone, increased lung volume also pulls the hyoid caudal via different mechanisms. In contrary, mandibular advancement lift the hyoid bone more cranially. Even though tracheal caudal displacement and mandibular advancement have different effect on the hyoid bone, they both decrease airway collapsibility and increase its stiffness. The mechanisms leading these processes is still not well established.

CHAPTER 4

RATIONALE AND AIMS

4.1. Summary and rationale

The upper airway is a complex structure that includes both dynamic (muscles, neuromuscular control) and static (bone, soft tissues) components [2]. Its patency is maintained by the equilibrium between collapsing and dilating forces. Whenever this equilibrium is lost, the upper airway becomes prone to obstruction and this imbalance can lead to serious breathing disorders such as obstructive sleep apnea (OSA).

OSA is a sleep-related disorder characterized by repetitive partial or complete closure of the upper airway that limit breathing. Untreated, OSA can cause major problems, such as excessive daytime sleepiness and increased risk of car and industrial accidents, cardiovascular disease, and neurocognitive dysfunction[65]. A multifactorial condition, OSA is mainly attributed to anatomical impairments that either lead to narrower upper airway dimensions such as increased fat pads in the neck region that reduce upper airway dimensions and promote its collapse [73] or affect the intrinsic properties of the airway tissues reducing their stiffness and enhancing collapsibility, whereby reduced lung volume and caudal tracheal traction cause the upper airway to become less rigid and reduce upper airway patency [41].

The inferior position of the freely suspended hyoid bone is an anatomical trait commonly observed in OSA patients [50, 53, 109]. Due to its strategic position at the base of the tongue, the hyoid bone plays an important role in the upper airway mechanics as the insertion anchor of several upper airway muscles. Therefore, the

bone contributes to determining the effectiveness of those muscles in maintaining upper airway patency. An abnormally positioned hyoid bone may affect muscle activity and reduce airway dilation by altering the muscles mechanical effectiveness [185]. Movement of the trachea and the mandible affect the position of the hyoid bone. Caudal tracheal displacement, which stiffens the upper airway, pulls the hyoid caudally [41, 71]. Also, mandibular advancement which is associated with increased posterior airway space and decreased upper airway collapsibility, pulls the hyoid bone anteriorly and cranially [58, 181]. Anterior movement of the hyoid bone was shown to stabilize the hypopharynx and reduce the tendency for collapse under negative intraluminal pressures[186]. When the hyoid complex was advanced in dogs, the upper airway resistance to airflow decreased by 57% [9]. Noting that the hyoid bone in dogs is fixed to the cranial base in contrast with human's hyoid bone. The advancement of the hyoid bone by 1cm in human cadavers resulted in improved upper airway dimensions and airflow [165].

Amatoury et al. [60] developed and validated a computational finite element model of the rabbit's upper airway. They observed that whenever the hyoid bone is moved cranially or caudally, it works on redistributing the loads throughout the upper airway between the supra- and infra- hyoid segments, maintaining therefore the stability of the upper airway.

In parallel, different clinical regimens focused on modifying the position of the hyoid bone, either directly through surgical hyoid repositioning (hyoid suspension), or indirectly via mandibular advancement (surgically or using splints). The hyoid suspension procedure anchors the hyoid bone more anteriorly and cranially to the inferior border of the mandible [167] or more caudally, to the thyroid

cartilage [166]. This method was efficient in some patients but the results were not ideal and consistent across patients [187]. The procedure also might cause dysfunction in speech and swallowing, including dysphagia [135]. Hyoid repositioning surgeries to treat OSA lack specific guidelines related to the amount and direction of displacement as well as the effect of the new hyoid position on the upper airway function [188, 189].

Despite repeated associations among the inferiorly placed hyoid bone, OSA and compromised upper airway function, the precise mechanical influence of hyoid position on OSA pathophysiology and on the upper airway mechanics remains unclear.

4.2.Aims

Quantitative studies are needed to provide proof of concept data to clarify the importance of the hyoid bone in the physiology of the upper airway in fulfilling its numerous functions, notably respiration. The study outcomes will also give additional insights on the role of the hyoid in OSA pathogenesis, while also improving our understanding to better treat this serious condition with improved and more targeted therapies.

The main aim of this thesis is to understand how the position of the hyoid bone influences upper airway patency from a quantitative perspective. Therefore, invasive interventions are needed that cannot be achieved in humans. The rabbit has a similar upper airway structure to humans particularly the freely suspended hyoid bone, unlike most non- primates in which the hyoid bone is fixed to the surrounding

structures. The rabbit model has been used in multiple studies in respiratory physiology and the outcomes were found applicable to humans. In addition, the inter-individual variations in animals (pure breed) reduces the number of research subjects needed.

Accordingly, the anesthetized rabbit is used as a physiological model to determine the effects of the hyoid bone repositioning on upper airway function. A passive airway lacking airflow or muscle activity is needed to eliminate cofounding factors and focus on the intrinsic properties of the upper airway and to simulate the sleeping state in which the airway dilator muscle activity is minimal.

The specific aims of this thesis are to:

1- Determine the impact of graded increments in hyoid repositioning on the upper airway collapsibility.

2- Determine the effect of different directions of hyoid pull on upper airway collapsibility.

3- Determine the presence of an interaction between cranial, anterior, and caudal directions in the angled direction increments.

The strategy to quantify the upper airway collapsibility is based on using the closing pressure metric, Pclose, with different hyoid bone positions following different angles going from the caudal, cranial, anterior, and 30, 45,60 degrees caudally and cranially.

CHAPTER 5

MATERIAL AND METHODS

5.1. Subjects

Studies were performed on a total of 7 adult, male, New Zealand White rabbits (weight= 3.14 Kg ± 0.39; n= 7), neck circumference (16.72 cm +- 1.83; n = 7) and height (37.83 cm +- 3.37; n = 7). Rabbits were bred and housed in the animal care facility at the American University of Beirut.

5.2. Ethics

The protocol was approved by the American University of Beirut Institutional Animal Care and Use Committee.

5.3. Anaesthesia

Anaesthesia was initially induced with an intramuscular injection of ketamine (35mg/kg) and xylazine (5mg/kg) and then maintained with a continuous intravenous infusion (through an ear vein) of ketamine (15 mg/kg/hr) and xylazine (4.5 mg/kg/hr) at an infusion rate of 0.025 ml/min/kg. The rabbit's ear was cannulated for anaesthetic maintenance using 24 G cannula in the lateral auricular vein no later than 30 minutes after the last intramuscular dose (Figure 5.1). Cannulated the other ear as a spare.

Animals were euthanized at the completion of each study by overdose of the intravenous ketamine/xylazine anaesthetic.

The details for the anthropometric parameters and anaesthetic dose for each rabbit are presented in table 5.1.

Table 5.1: Details of the male New Zealand White rabbits used in the experiments, including anthropometric parameters and anaesthetic dose.

#	Name	Experiment	Weight (kg)	Neck circumference	Height	Drug dose ketamine/xylazine	Infusion rate
1	JA01	JA01_HY01	3.60			1.3ml/0.85ml	5.5 ml/hr
2	JA02	JA02_HY02	3.70	20	44	1.3ml/0.9ml	6 ml/hr
3	JA03	JA03_HY03	2.90	16.5	37	1ml/0.75ml	4.5 ml/hr
4	JA04	JA04_HY04	3.30	17	38	1.3ml/0.75ml	5.5 ml/hr
5	JA05	JA05_HY05	2.60	16.8	38	1ml/0.75ml	4.5 ml/hr
6	JA06	JA06_HY06	2.75	15	34	1ml/0.75ml	5 ml/hr
7	JA07	JA07_HY07	2.50	15	36	1ml/0.75 ml	5 ml/hr

5.4. Preparation and surgery

The rabbit is chosen a day prior to the experiment and fasted for 12 hours prior to surgery. Before the start every surgery, the anaesthetic infusion, catheter instrumentation and the saline infusion set up were prepared. The pressure transducers were checked for proper calibration. The animal was then transported from the animal housing facility to the OR after initial anaesthetic intramuscular injection.

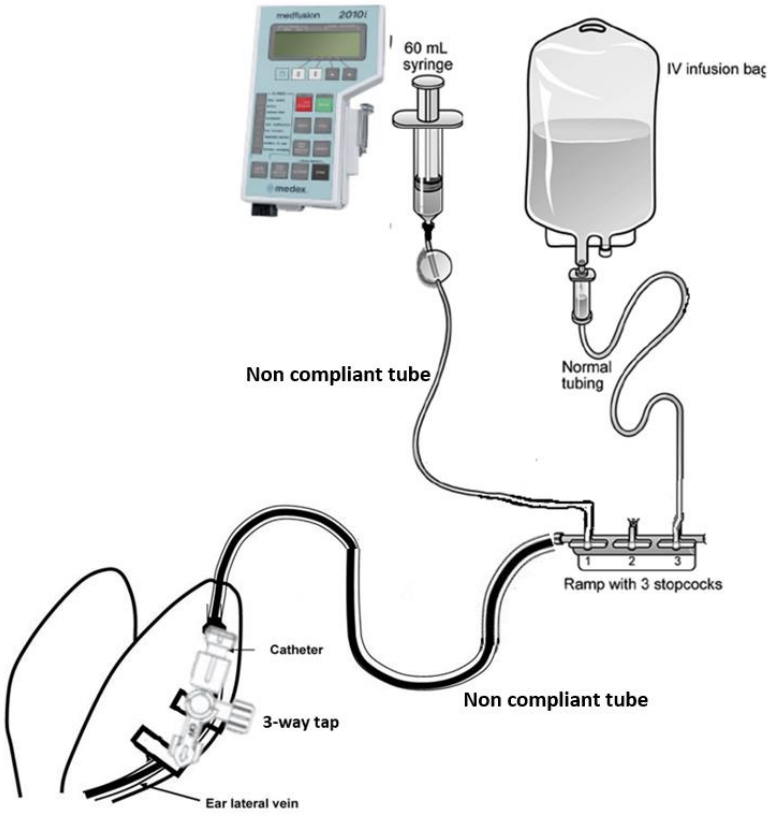


Figure 5. 1: Schematic drawing showing the anaesthetic and saline infusion set up, prepared the morning of the surgery. The saline bag and the anaesthetic syringe are connected to a ramp with 3 stopcocks from which a non-compliant tube emerges and is inserted in the way tap which forms the extension of the catheter.

5.5. Experimental Setup

Rabbits were studied in the supine position on a surgical platform. The rabbits' upper limbs were secured with tape to the bench in such a way as not to stress the thorax to alter resting heart rate the breathing. The head/neck position was

controlled, using an adjustable head rest, and measured using a protractor such that a line drawn from the tragus to the external nares was at 50 degrees to the horizontal.

A skin incision was made on the ventral surface of the neck and blunt dissection was used to expose the trachea. The baseline position of the trachea, taken between the fourth and fifth tracheal cartilage rings, was marked on the fixed experimental platform at the end of expiration. The skin incision extended to the level of the symphysis at the lower border of the mandible in order to expose the hyoid bone for setup of the hyoid bone re-positioning device (see below).

The upper airway was isolated via complete surgical transection of the trachea (between the 3rd and 4th tracheal cartilage rings), i.e. no airflow though the upper airway (rabbits breathing via caudal trachea) using diathermy (Valleylab Force 2 Electrosurgical Unit) (Figure 5.2). An L- shaped tube was inserted and secured (2.0 prolene, Johnson & Johnson) into the caudal tracheal segment, through which the rabbit breathed spontaneously. After transecting the trachea, the cranial segment was brought back to its baseline position by placing a suture around the cranial L shaped tube and connecting it to a vertical stand at the end of the bench to control the tracheal position.

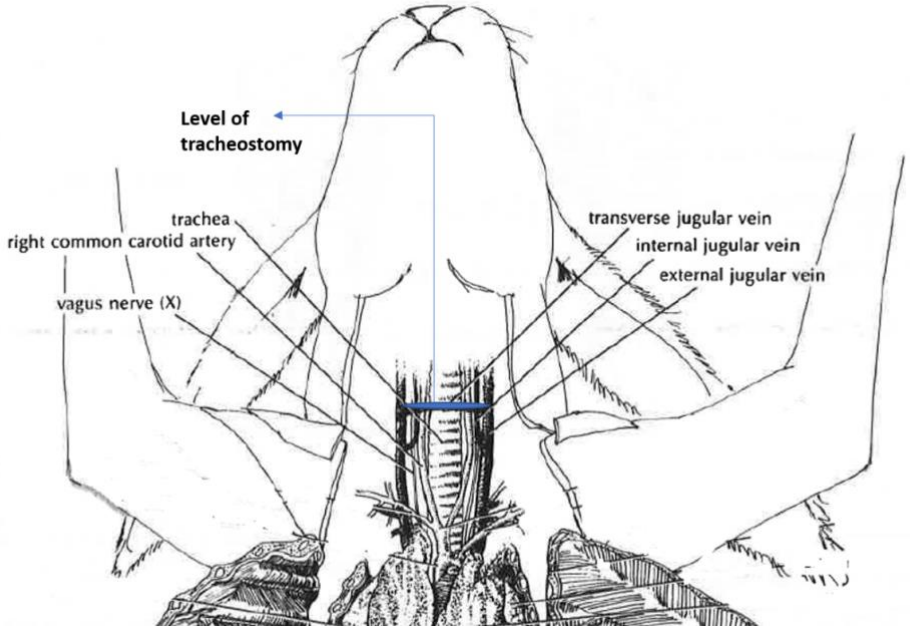


Figure 5. 2: Schematic drawing of the rabbit's trachea. The tracheostomy is performed between the 3rd and the 4th tracheal cartilaginous rings. Adapted and modified from Wingerd, 1985 [94].

The L – shaped tube was used to connect to the flow and pressure measuring devices. A custom-made L shaped tube was inserted into the cranial tracheal segment and secured using a suture (2.0 prolene, Johnson & Johnson). This tube was connected to a calibrated syringe and 100 cm volume extension (1*2.5mm), and a pressure transducer to measure upper airway pressure (Pua) (Figure 5.3).

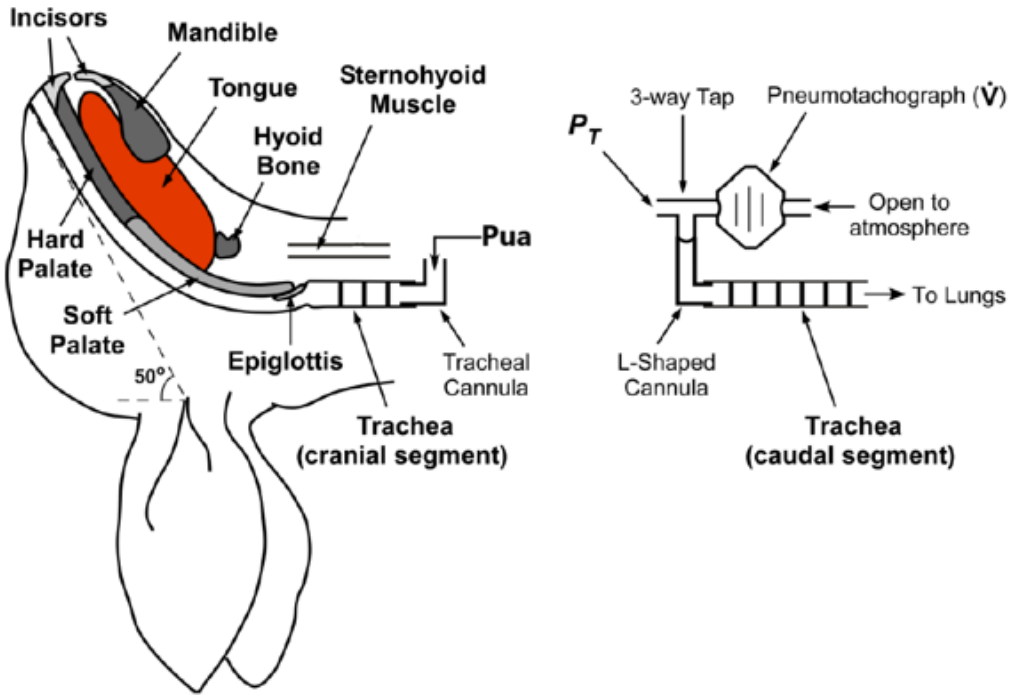


Figure 5. 3: Schematic of general experimental setup and monitoring. Pua: pressure at the level of the cranial end of the trachea, P_T: pressure at the level of the caudal end of the trachea, EMG: electromyography. Adapted and modified from J. Amatoury, Phd thesis, 2012.

A small modified conical animal anaesthetic mask (GaleMed VM-2, GaleMed, Taiwan) was fitted to the rabbit's snout to achieve a closed upper airway system for application of upper airway intra-luminal pressure and measurement of mask pressure. In order to achieve a proper seal around the rabbit's snout, an inflatable sleeve was incorporated into the mask (Figure 5.4). the inner sleeve consisted of a rubber tube segment (Penrose, flat size = 25mm).

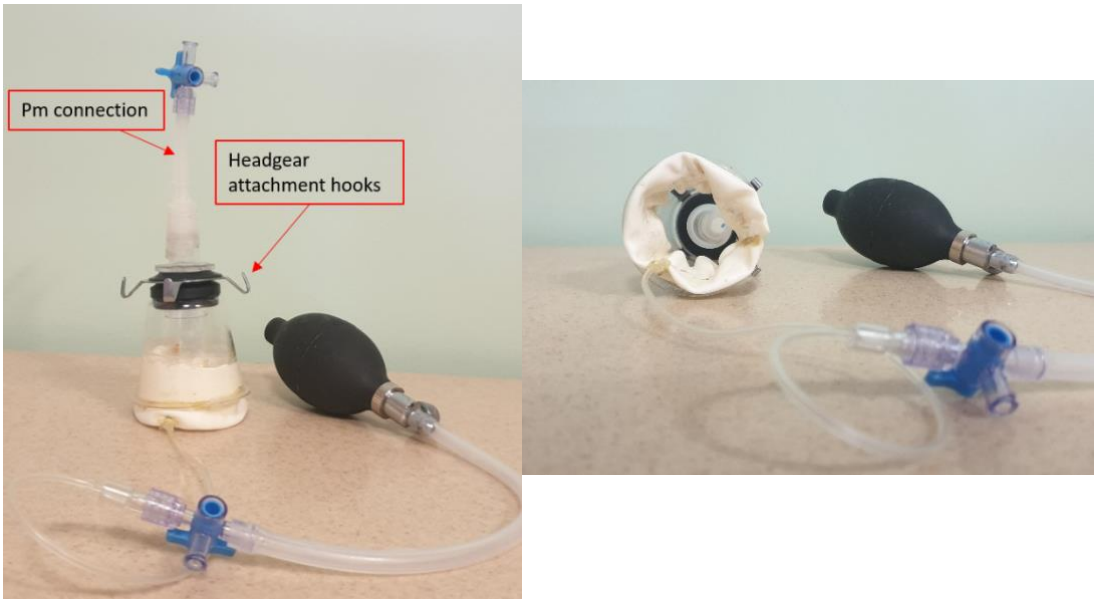


Figure 5.4: On the left, picture showing the mask in the vertical position with the connection tubing. On the right, the mask is shown from the bottom view with the Penrose tube deflated. The sleeve was inflated using a sphygmomanometer pump to provide seal when fitted on the rabbit's snout. Hooks around the top of the mask were used for attachment of a rubber custom-made headgear. A connection for the measurement pf mask pressure is also available.

A pressure transducer (mask pressure; Pm) was connected to the mask to measure the pressure at the level of the rabbit's face. We ensured that there is a complete mask seal by pressurizing the system using a syringe and noting any pressure leak (by increasing the pressure in the upper airway, it was detected similarly at the level of the mask and maintained over 20 seconds, Pmask = Pua) (Figure 5.5).

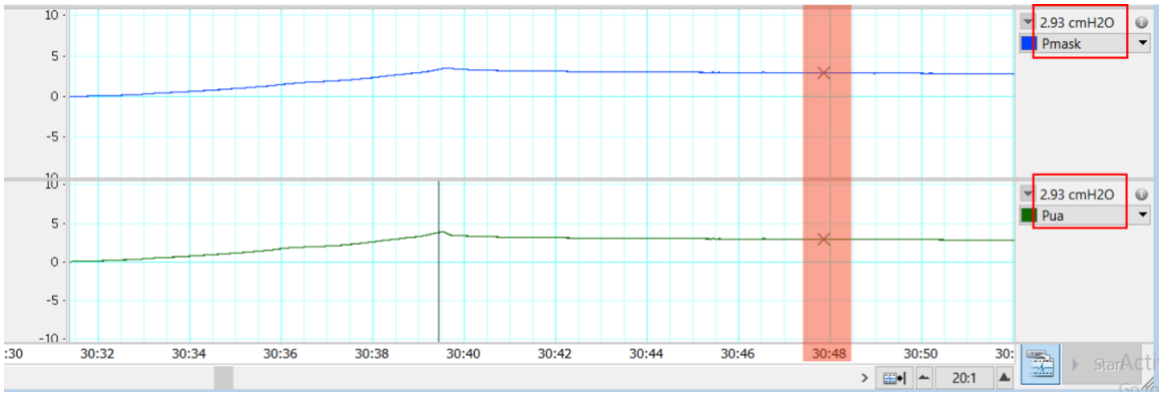


Figure 5.5: Recordings of Pua and Pmask while introducing positive pressure using a calibrated syringe in the upper airway. The pressure is the same and it is maintained (Pua = Pmask = 2.93 cmH_2O) as highlighted in red on the graph therefore no leakage in the upper airway system was detected.

5.6. Monitoring

Basic vital signals were monitored throughout the experiment to ensure the rabbit was in stable anesthetized state, and later to help confirm euthanasia.

- Electrocardiogram: A 3-lead electrocardiogram (ECG) was used throughout the study to monitor cardiac rhythm and heart rate. ECG electrodes were attached to the rabbit's paws after scrubbing them using sandpaper and placing ECG gel to reduce impendence [upper left paw (red -), lower left (black +), lower right (ground)].

- Tracheal pressure and flow: Tracheal pressure was measured from the caudal tracheal segment using a pressure transducer (Validyne DP45–32; Validyne Engineering, Northridge, CA) connected to the trachea via an L-shaped cannula, 3-way tap and extension tubing (Microbore hard extension set, length = 600mm,

internal diameter= 1mm , outer diameter= 2.5mm). Flow through the caudal tracheal airway was monitored using a heated pneumatograph (Fleisch 8300 A, range, 0–2 l/min range; Hans Rudolph, Kansas City, MO), attached to the 3-way tap and connected to a differential pressure transducer (Validyne DP45-32; Validyne Engineering Corporation, Northridge, CA, USA) by two identical polyethylene tubes. Both pressure transducers were coupled to a control unit (Validyne CD72-4) (Figure 5.6).

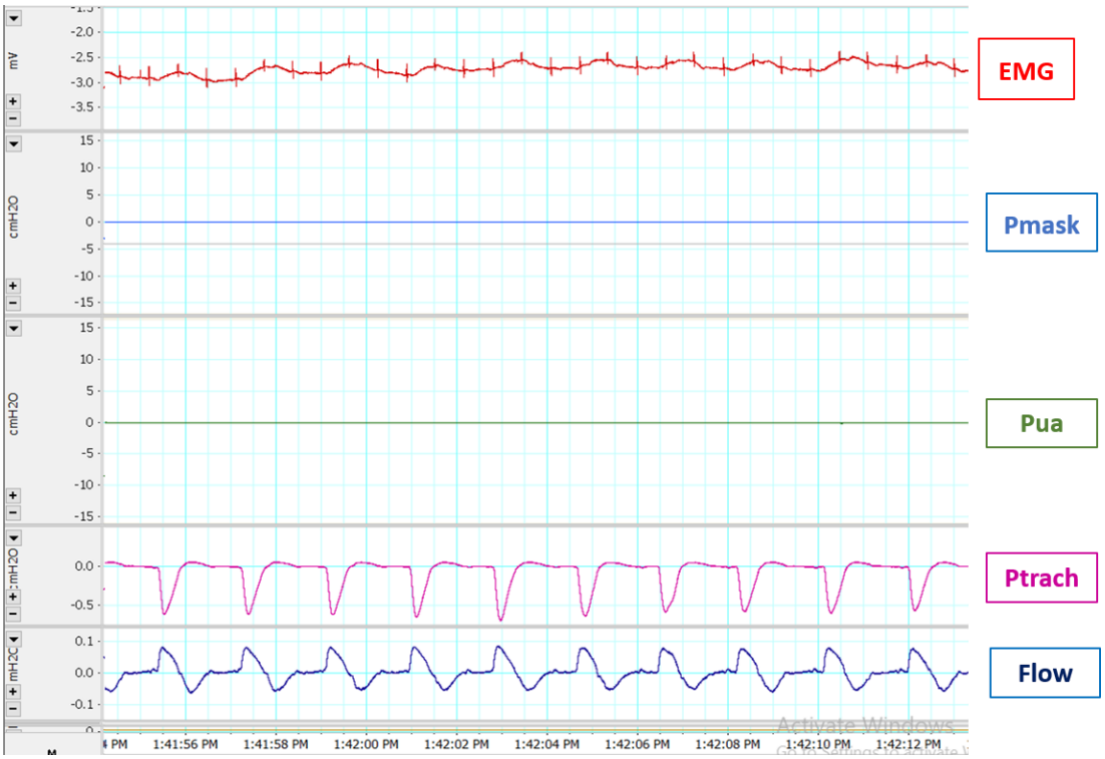


Figure 5.6: Baseline recording of acquired signals before the start of the protocol. Electrocardiography (ECG), Pressure at the level of the mask (Pmask), Pressure at the level of the upper airway (Pua), tracheal pressure (Ptrach), Flow of the upper airway,

5.7. Data acquisition

The hyoid bone was displaced caudally from 0 to 5mm at 1mm increments. At each position, the upper airway pressure is reduced progressively by pulling the syringe, creating a negative pressure inside the airway system. Since it is a closed system, the pressure detected at the level of the mask (Pm) is the same as the pressure induce at the level of the trachea (Pua). Pua and Pm were monitored carefully until reaching the point pressure leading to upper airway closure. This is when the pressures upstream and downstream diverge, where Pua continues to decease though Pmask no longer changes (Pm ǂ Pua). The minimal pressure value reached by Pm before diverging from Pua is equal to the closing pressure of the upper airway (Pclose) (Figure 5.7 and 5.8).

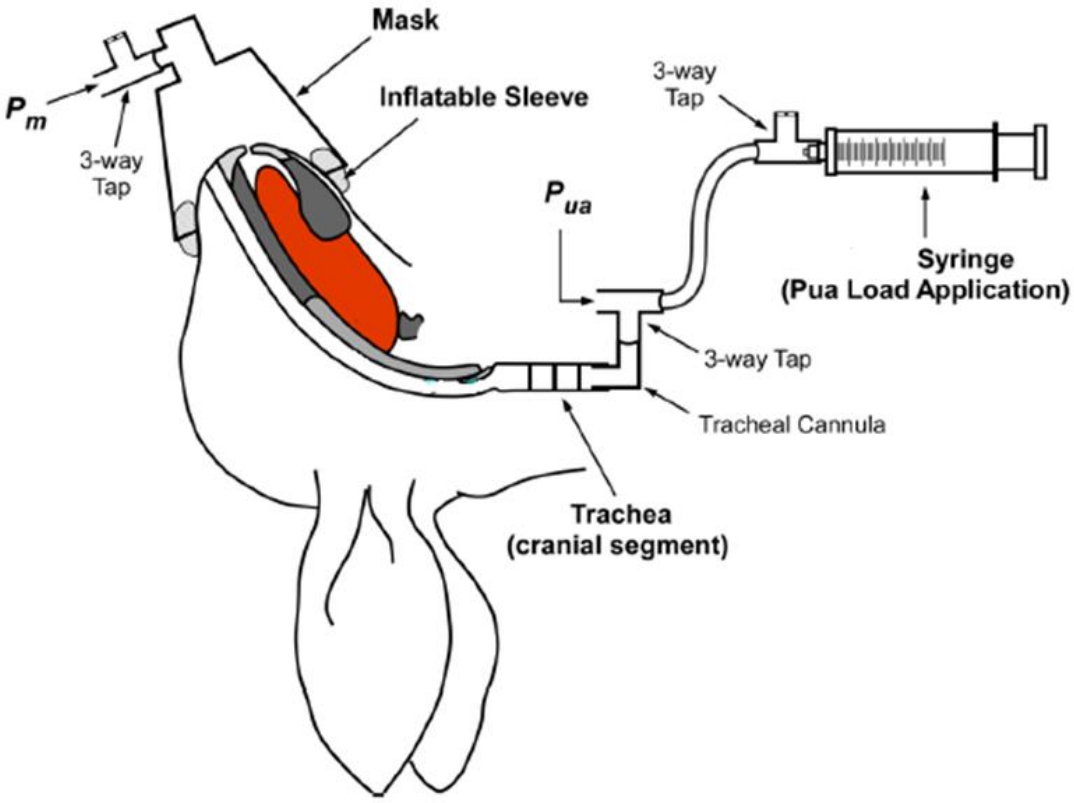


Figure 5. 7: Schematic of Experimental setup for upper airway intra-luminal pressure application. The syringe is pulled to create a negative pressure in the upper airway, which is detected at the level of the mask. Adapted from J. Amatoury, PHd thesis, 2012.

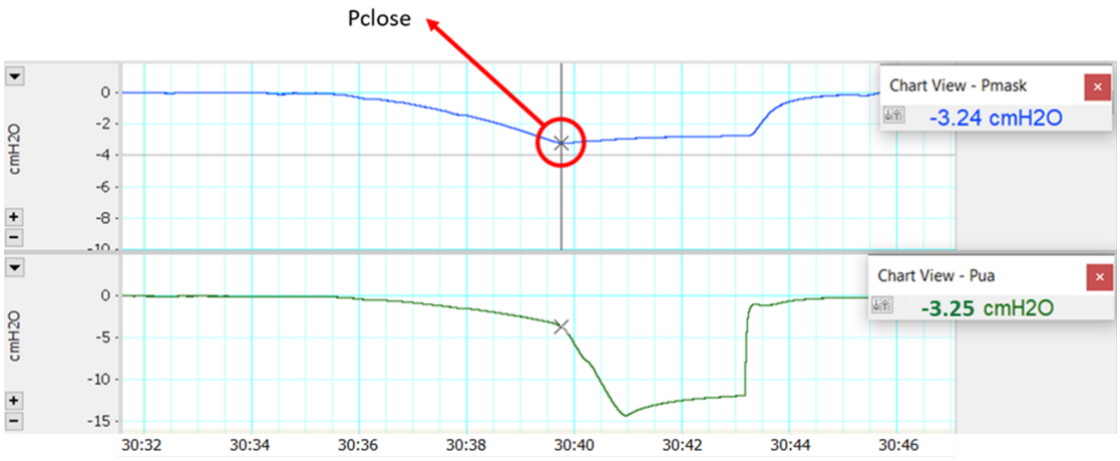


Figure 5.8: Screenshot of the Pmask and Pua recordings showing the Pclose value obtained when the hyoid was still at baseline position. Before the closure of the upper airway, Pmask and Pua decreased at the same rate as the negative pressure was applied in the upper airway. Notice the sudden drop in Pua once the upper airway was closed while Pmask was stabilized at -3.24 cmH2O until the upper airway was reopened to atmospheric pressure again, then Pmask and Pua were brought back to 0 cmH_2O (The 3-way tap connected to the calibrated syringe is opened to the atmosphere).

5.8. Baseline recordings

A starting point measurement was obtained by applying a negative pressure in the UA until reaching the closing pressure (Pmask differing from the Pua) and this was repeated it 3 times before setting up the hyoid device.

5.9. Hyoid device set-up

The hyoid device should be able to move the hyoid bone in small gradual increments, precisely and steadily, in different directions. The connection to the hyoid bone should be rigid, reproducible and with minimal damage on the muscles covering the hyoid body. To achieve this, an orthodontic miniscrew (RMO® Dual-Top, 2mm x 8mm) was inserted using a screwdriver into the body of the hyoid bone. The greater horns of the hyoid bone were held with surgical haemostats and rotated anteriorly to facilitate the placement of the miniscew at the centre of the hyoid body. In this way, the miniscrew is placed horizontally, at the midline of the hyoid body at the level of the basihyoideum.

The hyoid device consists of a horizontal beam supported by 4 vertical stands. A clamp extending from the horizontal part that attaches to the hyoid through the miniscrew and stability was tested by recording a video capturing the hyoid bone as it is moved (anteriorly, cranially and caudally) with the device to detect any movement between the clamp, the miniscrew and the hyoid.

Two callipers perpendicular to each other were used to calibrate the movement of the hyoid bone:

- vertical calliper with digital display: It was used to control the vertical position (anterior-posterior) of the hyoid. It was attached to a rod and a clamp (that attached to the miniscrew inserted in the hyoid body at the neutral position). This complex was fixed to a horizontal sliding beam.

- A horizontal calliper with digital display: It was used to control the craniocaudal position of the hyoid. Angles were constructed by a combination of the horizontal

and anterior movement of the hyoid. The hypotenuse of the formed triangle determined the linear movement of the hyoid and the angle was formed by the hypotenuse and the horizontal side of the triangle (Figure 5.9 and 5.10).

The device was fixed to the Perspex bench via four vertical stands that were held rigidly to the surgical platform by tightening the corresponding screws around them.

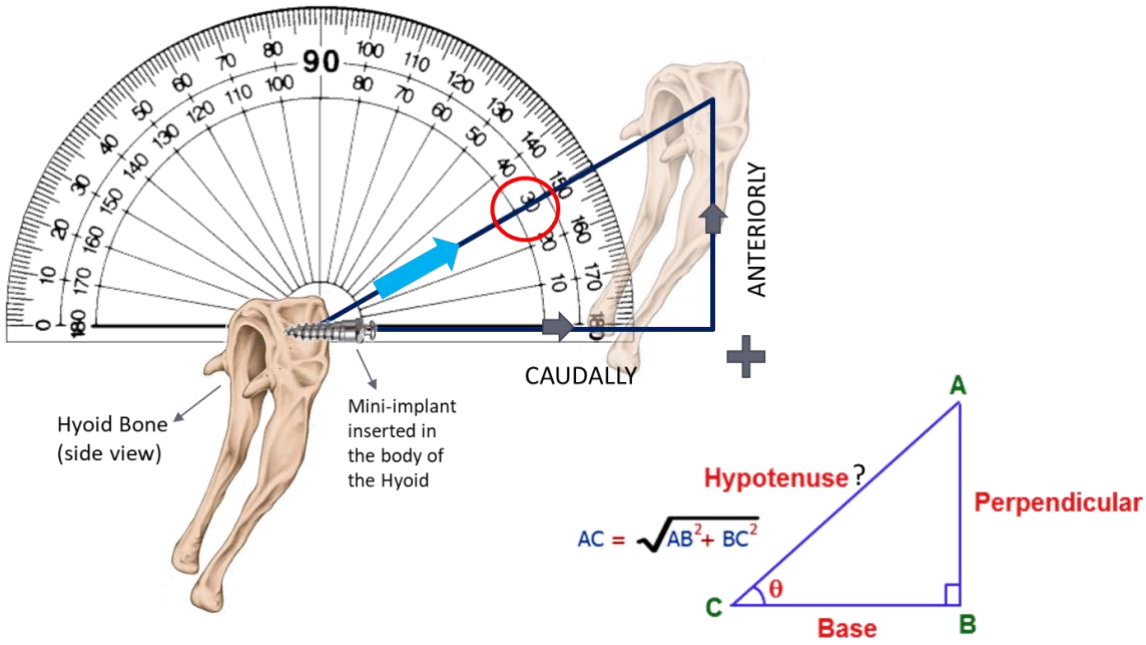


Figure 5.9: Schematic showing the initial and final positions of the hyoid bone as it is moved caudally and anteriorly to achieve an Ant-cranial 30° angle. The resultant linear movement of the hyoid is equal to the hypotenuse of the triangle formed by the base (BC) and perpendicular (AB) distances. It is calculated with the Pythagorean Theorem as the values of the triangle sides are known.

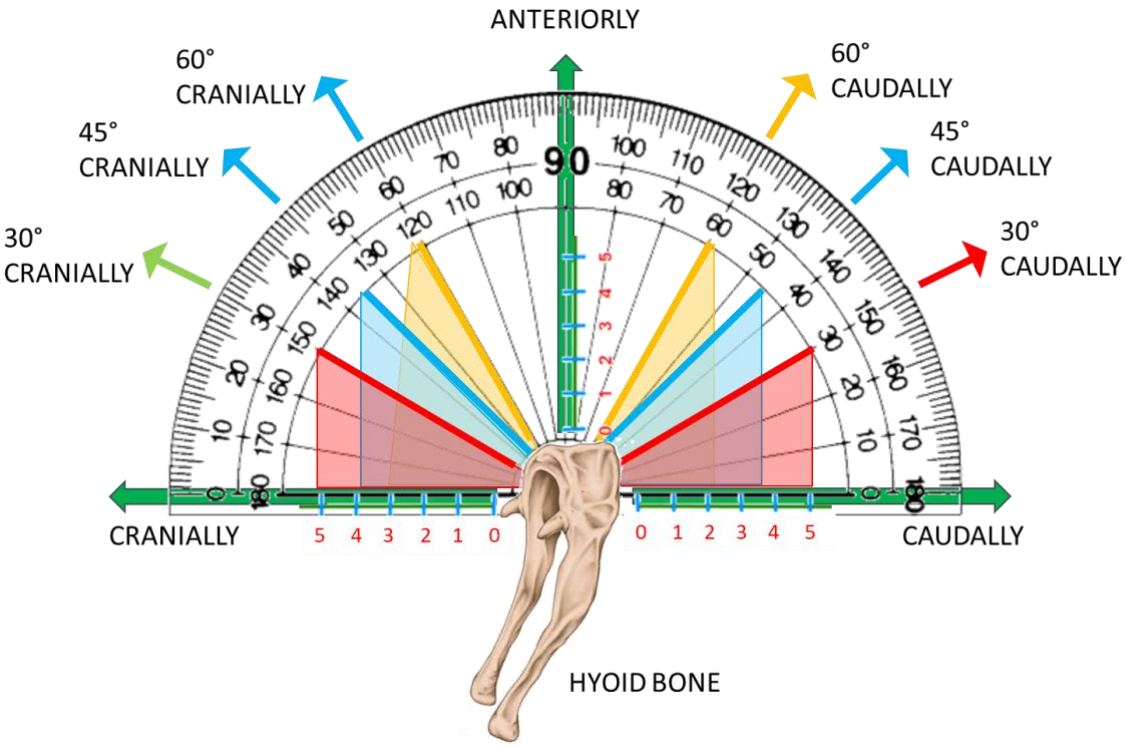


Figure 5.10: Drawing showing the different angles of hyoid bone movement during the experiment: cranially, caudally, anteriorly, ant-caudal 30,45, 60 and ant-cranial 30, 45, 60. The hyoid bone was displaced from 0 to 5mm at 1mm increments in all the directions (shown only here for the anterior, caudal and cranial directions).

5.10. Protocol

The measurement at baseline position is taken before the start of every set of measurements (hyoid moved in a different direction).

The same intervention was repeated in different directions and positions of the hyoid bone as it was displaced from 1 to 5mm at 1mm increments, following this order:

- Caudal

- Cranial

- Anterior

- Ant- cranial 45°

- Ant- caudal 45°

- Ant- cranial 30° (Table 5.2)

- Ant- caudal 30° (Tables 5.3)

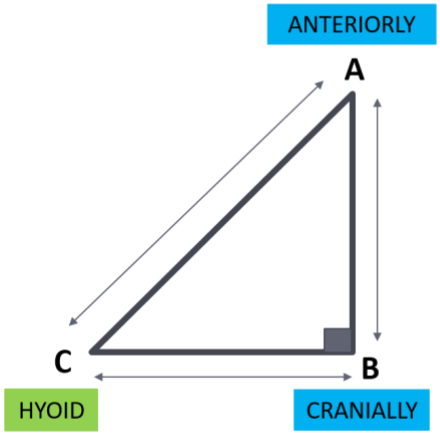
- Ant- cranial 60° (Table 5.2)

- Ant- caudal 60° (Tables 5.3).

The whole cycle of measurements was repeated 3 times.

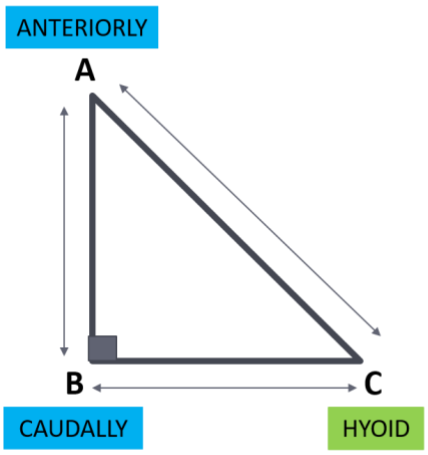
The measurements were performed at 0.5mm increments in 4 rabbits to test for differences in the outcome and to have precise data about the variation in Pclose. Nevertheless, the additional information was not relevant when weighed against the importance of obtaining Pclose for all the directions and repeating them 3 times (which took most of the time that we could have for each surgery).

Table 5. 2: Cranial and anterior positions which are combined respectively to generate a 30- and 60-degree cranial movement of the hyoid bone from 1 to 6 mm at 1mm increments.



Angle (°)	Hypotenuse (AC) (mm)	Side (AB) (mm)	Side (BC) (mm)
30° cranially	1	0.5	0.865
	2	1	1.73
	3	1.5	2.6
	4	2	3.5
	5	2.5	4.36
	6	3	5.2
60° cranially	1	0.865	0.5
	2	1.73	1
	3	2.6	1.5
	4	3.5	2
	5	4.36	2.5
	6	5.2	3

Table 5. 3: Caudal and anterior positions which are combined respectively to generate a 30- and 60-degree caudal movement of the hyoid bone from 1 to 6 mm at 1mm increments.



Angle (°)	Hypotenuse (AC) (mm)	Side (AB) (mm)	Side (BC) (mm)
30° caudally	1	0.5	0.865
	2	1	1.73
	3	1.5	2.6
	4	2	3.5
	5	2.5	4.36
	6	3	5.2
60° caudally	1	0.865	0.5
	2	1.73	1
	3	2.6	1.5
	4	3.5	2
	5	4.36	2.5
	6	5.2	3

5.11. Upon completion

The rabbit was euthanized using an overdose of ketamine/xylazine and it was confirmed by:

- The flattening of ECG and respiratory signals

- Checking reflexes

- Clamping and releasing tongue to see if arterial fill occurs

- Gel like look eyes.

5.12. Statistical Analysis

All the measurements were repeated 3 times in each rabbit. The repeated values (for each hyoid position and for each direction) were averaged to obtain individual rabbit data, which were then pooled and expressed as group mean ±SD. A two-way ANOVA with Benferroni post-hoc test was used to analyse the effect of the two independent variables (directions and increments) in each intervention (hyoid repositioning anteriorly, caudally, cranially, and ant-caudally 30°, 45°, 60° and ant-cranially 30°, 45°, 60°) on the outcome Pclose (dependant variable) as well as the interaction between the independent variables (SPSS v20, IBM). Statistical significance for all the above analyses was inferred for p less than 0.05.

CHAPTER 6

RESULTS

Data were acquired from a total of seven rabbits for anterior, cranial, caudal, ant-cranial 45 and ant-caudal 45 directions. For a subset of these rabbits (n=3), data were acquired for ant-cranial 30 and 60 and ant-caudal 30 and 60 directions and were excluded from statistical analyses.

The results are expressed as the change from baseline values (ΔPclose) to facilitate the interpretation as we are concerned mainly with the change that the hyoid bone movement is causing in the upper airway collapsibility.

6.1. Average baseline Pclose

The average Pclose before the hyoid device set up was -3.72±0.7 cmH_2O and immediately after connecting the device to the hyoid bone, it was -3.55 ± 0.95 cmH_2O ($p>0.05$). This difference is not statistically significant.

The average baseline Pclose for each direction is presented in table 6.1. The sequence of measurements followed the same order in each surgery, starting with the caudal, cranial, anterior, antero-caudal 45 and antero-cranial 45. At the end, a series of measurements for the antero-cranial 30 and 60 and antero-caudal 30 and 60 were performed.

Table 6.1: Average baseline Pclose for each direction

Direction	**Ant**	**Caudal**	**Cranial**	**Ant-cranial 45**	**Ant-caudal 45**
Pclose (cmH_2O) ±SD	-3.1± 1.17	-3.39± 0.86	-3.19± 1.00	-2.71± 1.16	-2.97± 1.38
Direction	**Ant-cranial 30**	**Ant-cranial 60**	**Ant-caudal 30**	**Ant-caudal 60**	
Pclose (cmH_2O) ±SD	-1.86± 0.7	-1.75± 1.04	-1.7± 0.99	-1.73± 0.89	

6.2. Anterior Hyoid Displacement

Pclose decreased progressively with increasing anterior displacement of the hyoid bone for all the rabbits. This reduction was significant between all the increments ($p<0.05$) except between 4 and 5 ($p=0.062$) (Table 6.2, Figure 6.1-A).

At maximum anterior displacement (5mm), Pclose reached -7.26 ± 1.17 cmH_2O (i.e a reduction of 3.98 ± 1.31 cmH_2O relative to baseline Pclose) (p=0.002 <0.05) (Figure 6.2).

Table 6.2: Repeated Measures ANOVA for comparison of ΔPclose in the anterior position among different increments

Increment 1 (mm)	Increment 2 (mm)	Mean difference (1-2)	SE	p value
1	2	0.873	0.088	0.001
	3	1.688	0.175	0.001
	4	2.541	0.268	0.001
	5	3.234	0.411	0.002
2	3	0.815	0.132	0.008
	4	1.669	0.236	0.004
	5	2.361	0.385	0.009
3	4	0.853	0.139	0.008
	5	1.546	0.271	0.012
4	5	0.693	0.168	0.062

6.3. Cranial and Caudal Hyoid Displacement

There was no main effect in the caudal movement of the hyoid bone on Pclose (P=0.352). Thus, the variation in Pclose when the hyoid bone was displaced caudally

from 0 to 5mm is not significant (Figure 6.1-B). Similarly, when the hyoid was moved cranially, Pclose remained almost the same or varied slightly at each position. (p=0.723>0.05) (Figure 6.1-C).

6.4. Ant-cranial 45° and Ant-caudal 45° Hyoid Displacement

Pclose decreased progressively with increasing ant-caudal 45° and ant-cranial 45° hyoid bone displacement for all the rabbits.

Pclose varied significantly at all levels when the hyoid was displaced in the ant-cranial 45° direction except between 3 and 4 mm (p=0.149) (Table 6.3). At maximum ant-cranial 45° displacement (5mm), Pclose reached -7.08 ±1.12 cmH_2O which is equal to -4.36 ± 0.87 cmH_2O reduction relative to baseline Pclose (p=0.001 <0.05) (Figure 6.2).

Pclose was significantly different at all levels in the antero-caudal 45° direction except between 2 and 3mm and between 4 and 5 mm (p=0.078 and p=0.057 respectively) (Table 6.4). At maximum ant-caudal 45° displacement (5mm), Pclose reached -7.6 ±1.4 cmH_2O which is equal to -4.58 ± 1.51 cmH_2O reduction relative to baseline Pclose (p=0.004 <0.05) (Figure 6.2 E).

Table 6.3: Repeated Measures ANOVA for comparison of ΔPclose in the antero-cranial 45° position among different increments

Increment	Increment	Mean difference (1-2) (cmH_2O)	SE	p value
1	2	0.937	0.130	0.004

	3	1.715	0.180	0.001
	4	2.486	0.312	0.002
	5	3.390	0.381	0.001
2	3	0.778	0.142	0.016
	4	1.549	0.252	0.009
	5	2.452	0.310	0.002
3	4	0.771	0.228	0.149
	5	1.674	0.298	0.014
4	5	0.903	0.111	0.002

Table 6.4: Repeated Measures ANOVA for comparison of ΔPclose in the antero-caudal 45° position among different increments

Increment	Increment	Mean difference (1-2) (cmH_2O)	SE	p value
1	2	0.894	0.111	0.002
	3	1.844	0.234	0.002
	4	2.910	0.339	0.001
	5	3.726	0.519	0.004
2	3	0.950	0.242	0.078
	4	2.015	0.316	0.007
	5	2.832	0.498	0.013
3	4	1.065	0.156	0.005
	5	1.882	0.305	0.008
4	5	0.817	0.195	0.057

6.5. Ant-cranial 30°/ Ant-caudal 30°/Ant-cranial 60°/ Ant-caudal 60° Hyoid Displacement

When the hyoid was displaced along 30° and 60° directions, Pclose decreased progressively with increased hyoid displacement (Figure 6.1 D, F, G, and I). Despite the limited number of rabbits, the response to the hyoid displacement in those directions was similar between rabbits. There was a greater improvement in the Pclose with the ant-caudal 60° and ant-cranial 60° compared to the ant-caudal 30° and ant-cranial 30°. The amplitude of the angle affected Pclose but not the direction (no difference between ant-caudal and ant-cranial with respect to the different angles).

When the hyoid bone was displaced, from 0 to 5mm, at:

- 30° angle caudally, Pclose decreased 2.73 ± 0.85 cmH_2O (Figure 6.2-D)
- 30° angle cranially, Pclose decreased 2.22 ± 0.58 cmH_2O (Figure 6.2-G)
- 60° angle caudally, Pclose decreased 4.29 ± 1.68 cmH_2O (Figure 6.2-F).
- 60° angle cranially, Pclose decreased 3.81 ± 0.78 cmH_2O (Figure 6.2-I)

6.6. Comparison between directions

The improvement in Pclose following the anterior displacement of the hyoid bone, was not significantly different than that obtained following the ant-caudal 45° ($p=0.679$) and ant-cranial 45° ($p=0.995$) displacements (Table 6.5). Also, the ant-caudal 45° hyoid displacement was not significantly different than the ant-cranial 45° displacement ($p=0.847$). On the other hand, when the anterior, ant-caudal 45° and

ant-cranial 45° hyoid displacements were compared to the cranial and caudal directions, Pclose was significantly different ($p<0.05$) (Table 6.5).

Pclose obtained with the caudal and cranial hyoid displacement was significantly higher at all incremental levels, in comparison to Pclose obtained with the anterior, ant-cranial 45° and ant-caudal 45° displacement ($p<0.05$) (Figure 6.5).

A greater improvement in the upper collapsibility was observed when the hyoid bone was displaced ant-caudally 60° and ant-cranially 60° compared to the 30° angle. On the other hand, the change obtained with the ant-caudally 45° and ant-cranially 45° movement is similar to the change obtained with that obtained with the ant-caudal 60° and ant-cranial 60° and both have a greater change compared to the ant-caudal 30° and ant-cranial 30° with respect to the studied rabbit.

Table 6.5: Repeated Measures ANOVA for comparison of ΔPclose between the studied directions

Direction 1	Direction 2	Mean difference (1-2) (cmH_2O)	SE	p value
Anterior	Caudal	-2.696	0.333	0.002
	Cranial	-2.454	0.284	0.001
	Antero-caudal 45	0.26	0.259	0.679
	Antero-cranial 45	0.286	0.202	0.995
Caudal	Cranial	0.242	0.228	0.856
	Antero-caudal 45	2.956	0.253	0.000
	Antero-cranial 45	2.982	0.376	0.002
Cranial	Antero-caudal 45	2.714	0.204	0.000
	Antero-cranial 45	2.740	0.361	0.003
Antero-caudal 45	Antero-cranial 45	0.025	0.229	0.847

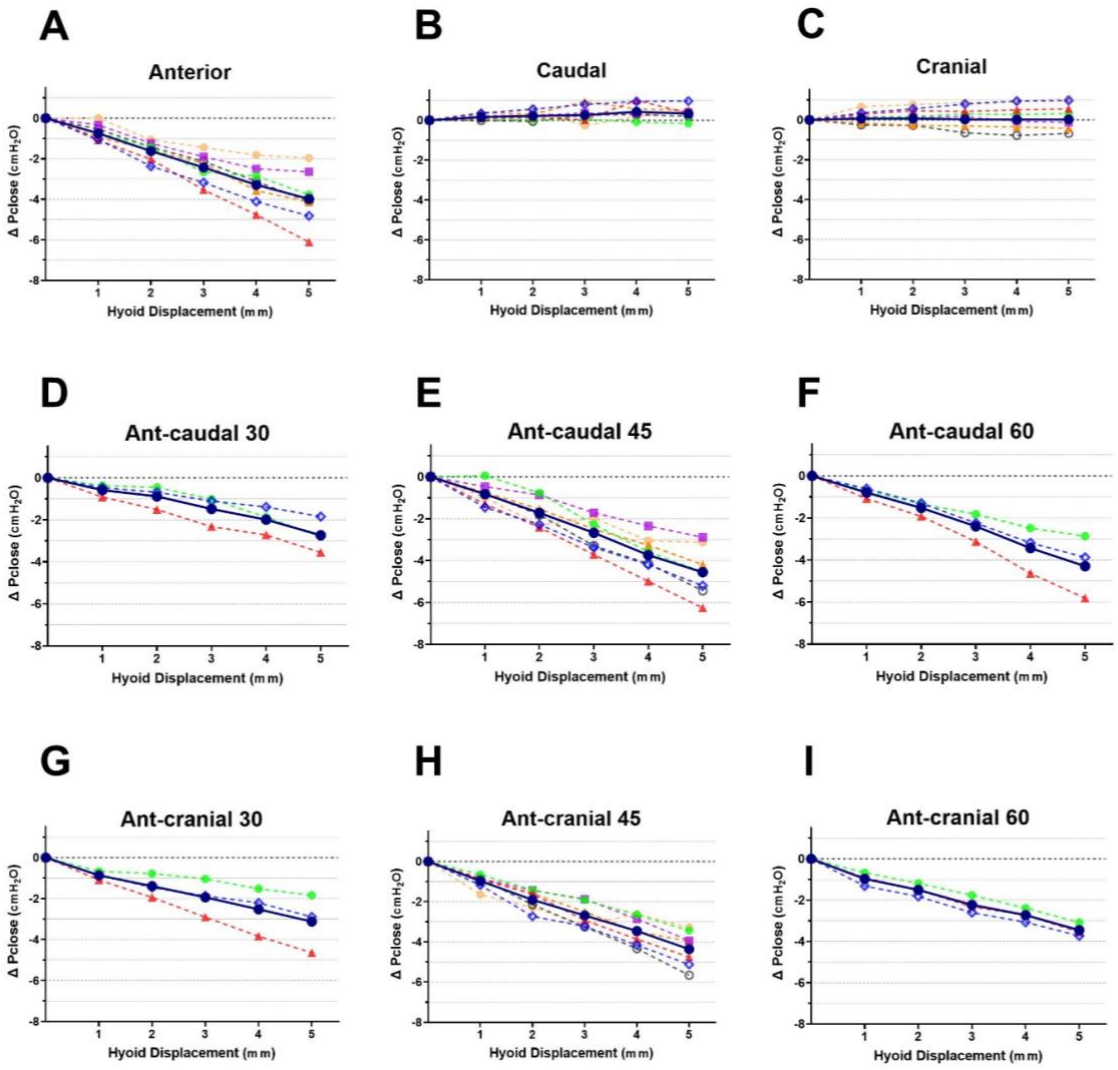


Figure 6.1: Graphical representation of the average ΔPclose obtained in the 7 rabbits (represented seperately) in each direction when the hyoid bone was moved, from 0 to 5 mm, anteriorly (A), caudally (B), cranially (C), ant-caudally 45 (E), ant-cranially 45 (H) . Pclose was obtained in 3 rabbits when the hyoid bone was moved, from 0 to 5 mm, ant-caudally 30° (D), ant-caudally 60° (F), ant-cranial 30° (G), ant-cranially 60° (I). Each study is represented by a dashed line and with a different color. Solid line refers to the average ΔPclose in each direction for all the rabbits.

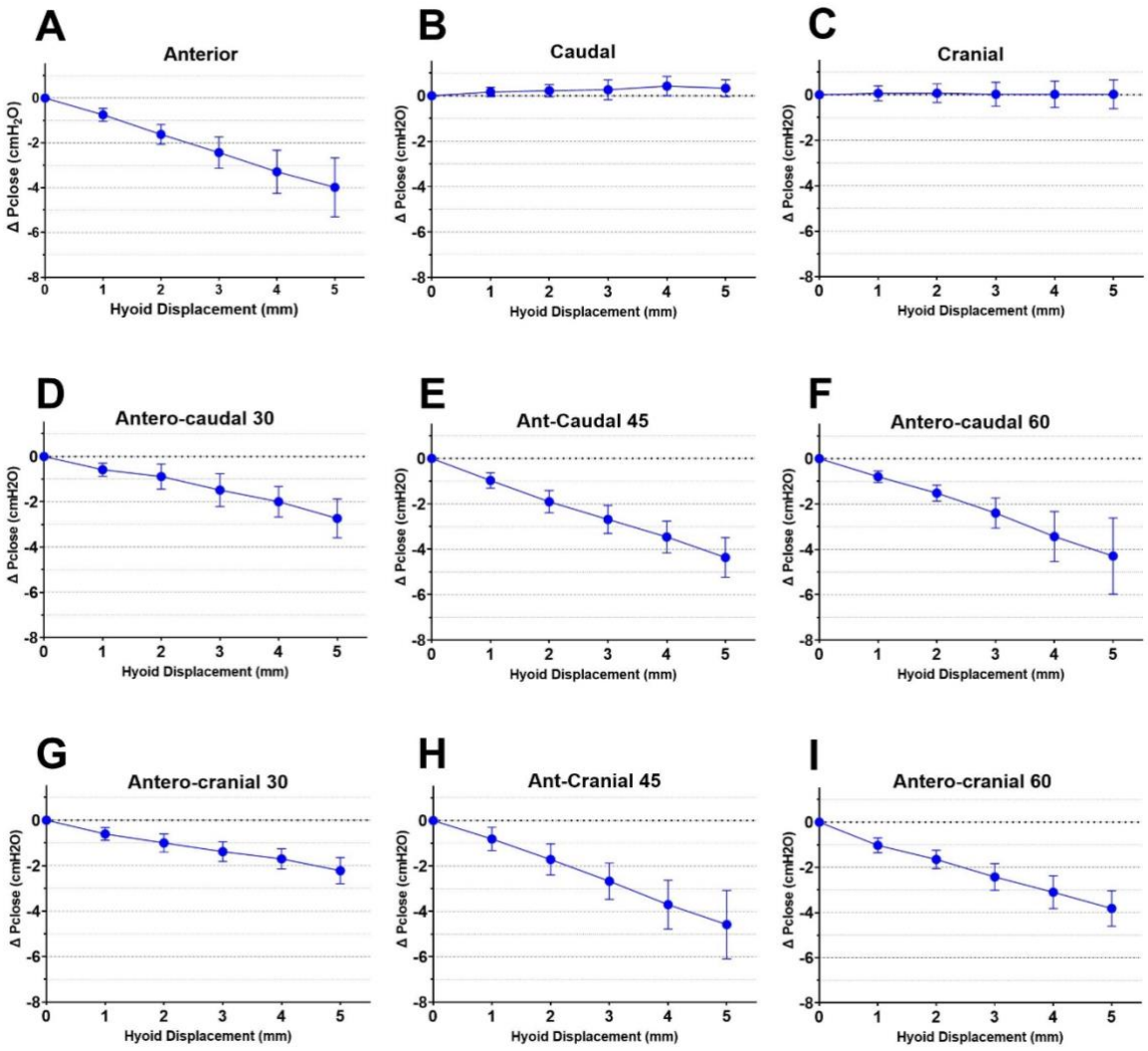


Figure 6.2**:** Graphical representation of the average ΔPclose and SD obtained in the 7 rabbits in each direction when the hyoid bone was moved, from 0 to 5 mm, anteriorly (A), caudally (B), cranially (C), ant-caudally 45 (E), ant-cranially 45 (H) . Pclose was obtained in 3 rabbits when the hyoid bone was moved, from 0 to 5 mm, ant-caudally 30° (D), ant-caudally 60° (F), ant-cranial 30° (G), ant-cranially 60° (I). Solid line refers to the average ΔPclose in each direction for all the rabbits. Notice the improvement of the upper airway collapsibility in the anterior (A), ant- caudal and ant-cranial directions (D, E, F, G, H and I), while it remains fairly unchanged in caudal and cranial directions (B and C).

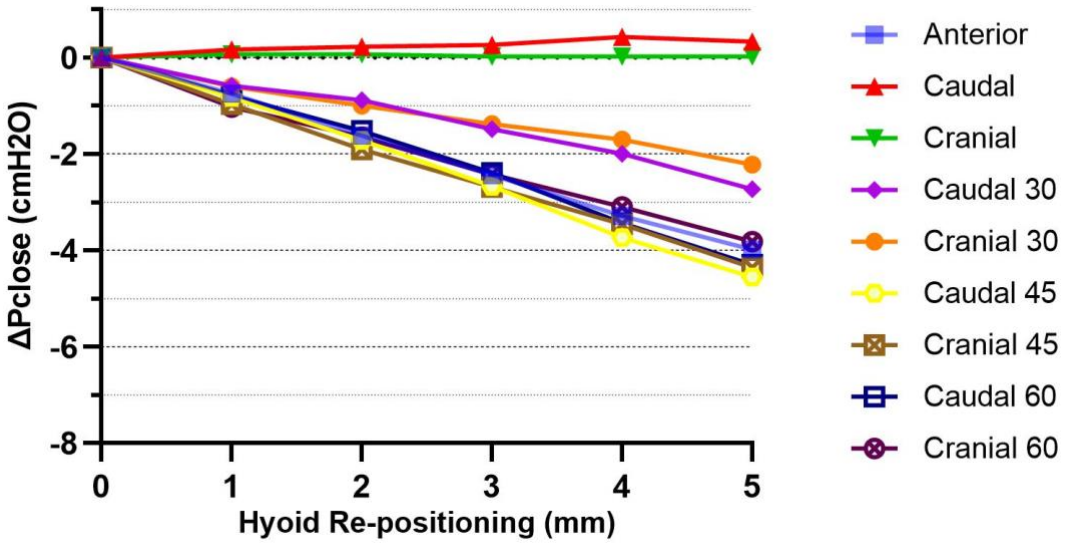


Figure 6.3: Graph representing the average ΔPclose variation, of the 7 rabbits, when the hyoid bone was moved from 0 to 5mm in all directions. Caudal and cranial directions did not affect Pclose significantly, whereas the change obtained with the angular measurements and the anterior directions is significant. Note that the ant-caudal 30 and ant-cranial 30 resulted in greater improvement of Pclose compared to cranial and caudal but less than the anterior, ant-caudal 45°, ant-cranial 45°, ant-caudal 60°, and ant-cranial 60°.

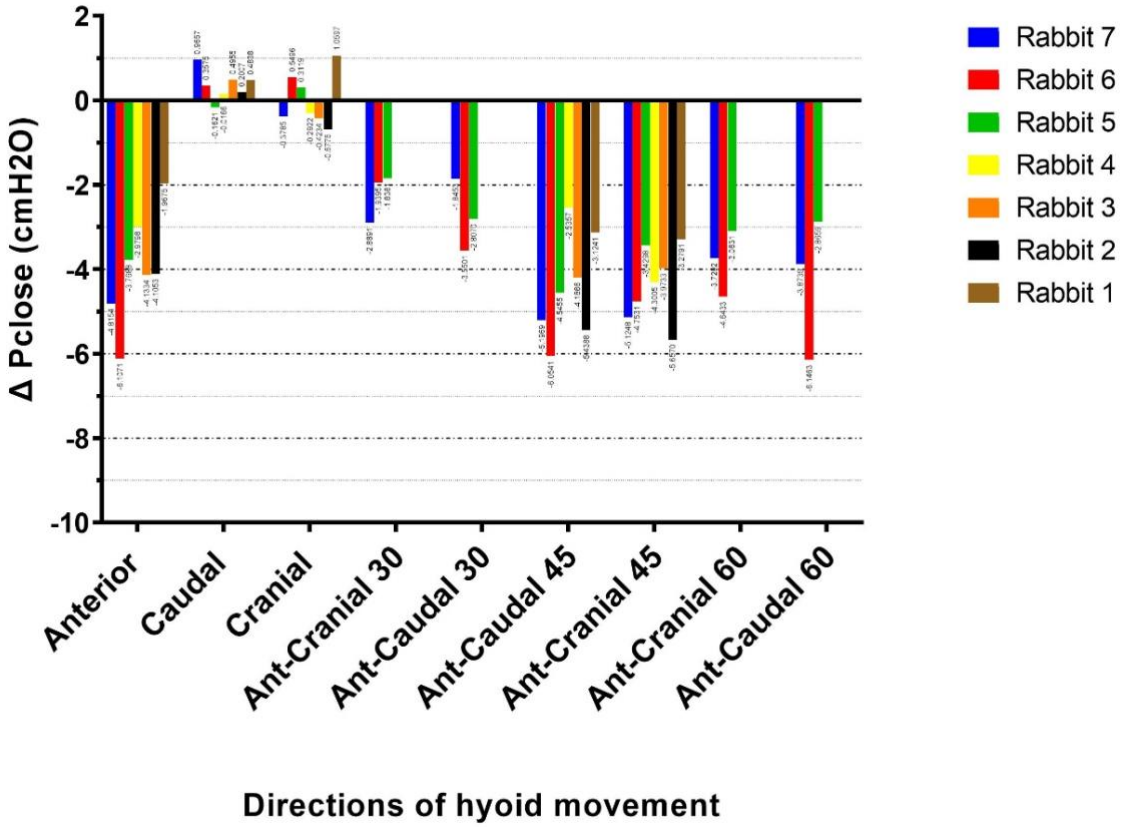


Figure 6.4**:** Bar chart representing the variation in Pclose obtained when the hyoid bone was moved 5mm in all directions (Anterior, caudal, cranial, antero-caudal 45°, antero-cranial 45° in the 7 rabbits and ant-cranial 30°, ant-cranial 60°, ant-caudal 30°, ant-caudal 60° in 3 rabbits). Note the significant improvement in Pclose in all the directions with an anterior component.

CHAPTER 7

DISCUSSION

This study is the first to investigate the effect of hyoid bone repositioning on upper airway collapsibility. Although the literature suggests a potential role for the hyoid bone to affect upper airway patency, no prior study has quantitatively assessed this effect.

The primary outcomes of this study were:

1) Anterior displacement of the hyoid bone is the main factor leading to decreased upper airway collapsibility. The more the hyoid bone was displaced anteriorly the less collapsible was the upper airway.
2) The caudal and cranial hyoid displacements did not affect the upper airway closing pressure.
3) The ant-caudal 45° and ant-cranial 45° displacements yielded similar outcomes as the absolute anterior displacement against collapsibility. The ant-caudal 60° and ant-cranial 60° movements were similarly efficient modification, and both were better than the ant-caudal 30° and ant-cranial 30°.

7.1. Assessment of methods

- Rabbit model

We chose the rabbit because of its upper airway anatomy and structure resemble that of the humans. In addition, the rabbit has a mobile, freely suspended hyoid bone, which is the site of insertion of several muscles and ligaments that control its position, similar to the human hyoid bone [190]. In contrast, rodents, dogs, and cats have a pharyngeal airway anatomy that is comparatively rigid, but their hyoid bones are firmly attached by cartilage to the styloid process and thyroid cartilage, making the airway less collapsible. The anaesthetized rabbit passive upper airway model has been employed extensively in previous studies of upper airway mechanics, including a number of early studies that established the mechanical effects of upper airway dilator muscles on the upper respiratory activity [42, 191-193], tracheal traction effects on upper airway in rabbits[59], sciatic nerve stimulation and its effects on upper airway resistance[194], effect of mandibular advancement on upper airway lumen size[91, 180]. The outcomes of those studies have repeatedly shown a high level of correlation with the outcomes of human studies, rendering the rabbit an ideal model for upper airway and respiratory studies requiring invasive procedures that cannot be performed in humans. Noteworthy is the fact that the rabbit has a normal pharyngeal structure which does not reflect the pathological setup of OSA. Nevertheless, our model helps explain the pathophysiology of OSA.

We chose the supine position because it would load the upper airway and cause the upper airway tissue to fall back under the effect of gravity recapitulating one aspect of the anatomical basis of OSA in humans (supine positioning leading to more pharyngeal obstruction).

- Passive upper airway

In the anesthetized rabbit model, muscle activity was minimized. The upper airway was isolated, thus eliminating the respiratory related upper airway reflexes induced by the pressure/flow changes. Those reflexes (increase in upper airway muscle activity) reappeared again when we applied negative pressure experimentally in the trachea to measure Pclose. Anaesthesia lowers the tone of the upper airway muscles and further promotes airway occlusion, simulating the effect of sleep on the upper airway [195]. We used a ketamine/xylazine mix for anaesthesia in the current study. The use of ketamine avoids the central suppressant effects produced by barbiturate anaesthesia and maintains airway patency [196]. However, ketamine promotes salivary secretion in both animals and humans which might stimulate muscle contraction [197]. To prevent excessive secretions from initiating swallow reflexes and affecting our results, we suctioned out the trachea and maintained a patent upper airway during the entire surgical time.

In veterinary anaesthesia, xylazine is often used in combination with ketamine. Xylazine has a sedative, muscle relaxant, and analgesic effects. Therefore, since we used ketamine and xylazine to anesthetize the rabbits, the upper airway muscle activity was reduced and the rabbit was maintained under deep anaesthesia throughout the surgery [198].

- Measuring Pclose

The closing pressure (Pclose) of the upper airway has been used in previous studies as a reproducible measure of upper airway collapsibility in animals and humans [45, 46, 163, 199-202]. It is the principal correlate with the frequency of nocturnal desaturations [201]. We used this metric to determine the effect of different hyoid positions on upper airway collapsibility. The methodology for the measurement of closing pressure used in the present study is based on that previously described in dogs [203] and rabbits [42, 192]. Lam et al, [3] measured in 10 supine anesthetized rabbits the upper airway closing pressure and obtained a baseline value of 3.8 (1.9–6.5) cmH2O. Abu-Osba at al [202] measured Pclose in rabbits under light and deep pentobarbital anaesthesia. Baseline Pclose values under light anaesthesia was +1.1±1.9cmH_2O. In contrast, in rabbit under deep anaesthesia, closing pressure was -4.9±1.4 cmH_2O concordant with our results. This finding supports the above discussion, that the rabbits were deeply anaesthetized, and that the upper airway was mostly passive. In humans, closing pressure of the velopharynx of patients with sleeping disorders was reported by Isono et al. [201] and ranged between 0.9 and 2.78 cmH_2O, which was significantly higher than that for the healthy subjects (-3.77 ± 3.44 cmH_2O). Pclose in healthy humans was similar to the rabbit's baseline Pclose (-3.72±0.7 cmH_2O, before hyoid displacement).

- Tissue stretch and deformation

After several negative pressure applications to the upper airway, composed of highly deformable tissue, a stretch phenomenon of those tissues can occur leading to a change in tissue elastance and consequently to collapse resistance [42]. Accordingly, we waited around 30 to 40 seconds between each measurement, to

allow the tissue to accommodate the stretch and return to its original state [2]. Despite this attention, the stretch of the upper airway soft tissues might be a reason for the absolute change of Pclose values between runs. However, the amount of change in Pclose (ΔPclose) relative to baseline for each intervention between runs remained relatively the same (see results for more details).

- Upper airway secretions

Repeated application of negative pressure to the upper airway can result in pharyngeal secretions (fluids in the upper airway, saliva, and mucus), that can increase the surface tension in the upper airway mucosal lining and thereafter increases collapsibility [192]. Such secretions also stimulate the swallow reflexes, which can affect the measurements. To avoid excess build-up of secretions, we cleared the upper airway between runs with suction through a syringe and a small diameter non-compliant tube. This manoeuvre was reported to be efficient to eliminate the pharyngeal fluids [45, 204].

Wilson et al. [205] observed a difference between airway closing pressure and airway reopening pressure and concluded that the collapsed airway walls are adherent. In the present study, airway wall adhesion was evident because the upper airway remained collapsed even after releasing the negative pressure from the airway system in 2 rabbits. Thus, surface forces impose a load inhibiting spontaneous airway reopening, necessitating the application of positive pressure in some instances as well as frequent suctioning of the airway to remove secretions. If left, those secretions can cause a great variability in the upper airway closing pressures mostly by increasing the pressure (i.e., more positive closing pressure) [45].

- Hyoid repositioning device

The hyoid repositioning device was custom designed in house for the current study. It attached via a clamp to a mini screw inserted in the hyoid bone. The stability of this connection was determined visually by verifying maintenance of the hyoid bone baseline position after clamping it to the device. In addition, markings on the clamp and the screw were placed and used as landmarks to ensure no slipping was occurring. To this end, a video was recorded at the beginning of the experiment when the hyoid bone was moved from 0 to 5mm anteriorly, cranially, and caudally. The purpose of this recording was to qualitatively ensure that no rotation or translation movement between the clamp and the mini screw while moving the hyoid bone, and that the connection was stable. The hyoid device was clamped onto the hyoid bone in the beginning and was unclamped at the end of the surgery. All measurements were performed with the same original clamping. Therefore, a minimal deviation from the original position while clamping the hyoid device can be accepted as it did not change throughout the study.

When the hyoid bone was fixed in the new position, it lost its physiological movement. This effect also occurs in hyoid repositioning surgeries when the hyoid bone is fixed to the mandible or the thyroid cartilage. However, during normal functioning (swallowing, speech, breathing), the hyoid moves in response to the contraction of various muscles. Experimentally, preserving the hyoid mobility after displacement is not feasible because it tends to return to its original position (muscles and ligaments attached to the hyoid bone pull the bone back to its baseline position). Nevertheless, hyoid mobility can be preserved in computational modelling after being validated based on our study outcomes.

7.2. Discussion of the results

- Anterior hyoid displacement

Advancement of the hyoid bone has long been recognized to offer potential benefit in the treatment of OSA. Rosenbluth et al [165] examined the effect of anterior displacement of the hyoid in human cadavers. They found that anterior hyoid advancement by 1cm produced airway opening and improvement in upper airway airflow by almost 4 fold (to 3.83 ± 1.93 L/min) [165]. Benderro et al, [89] found in a recent study on anesthetized rabbits that the anterior displacement of the hyoid bone (hyoid advancement, magnitude not mentioned) resulted in an increase in inspiratory flow and a decrease in the negative trans-upper airway pressure swing in inspiration and expiration.

Van de Graaf et al.[9] used anesthetized dogs to examine the effects of hyoid muscle stimulation and displacement of the hyoid arch on upper airway flow resistance. They found that forces controlling the position of the hyoid arch are important determinants of upper airway resistance. By manual anterior displacement of the hyoid bone (random amount, arbitrarily selected) or stimulation of the geniohyoid and thyrohyoid muscles (causing an anterior movement of the hyoid bone), the upper airway resistance decreased by 57 ± 15% and 52 ± 8% respectively during inspiration. It is thought that in humans, the anterior movement of the hyoid bone is due to simultaneous contraction of the supra and infra hyoid muscles, and OSA can

result from failure to move the hyoid bone outward as a consequence of reduced muscle activity [9] .

These findings are consistent with our results showing a reduction of Pclose whenever the hyoid bone was displaced anteriorly. This reduction reflects a more stable and less collapsible upper airway. This improvement varied with the range of hyoid displacement from 1 to 5mm; the greater the hyoid bone was displaced anteriorly, the more the value of Pclose was negative and the more stable was the upper airway.

- Caudal/cranial hyoid displacement

Studies are not available on the caudal and cranial displacement of the hyoid bone without any anterior vector component. In our study, the caudal and cranial directions did not have any significant effect on the upper airway closing pressure at all displacement increments.

This is in contrast with our expected outcomes, as we projected to observe a greater improvement with the caudal displacement of the hyoid bone since it stretches the tissues located in the suprahyoid region making it stiffer therefore less collapsible [41, 71]. However, a caudally displaced hyoid bone can lead to floppier tissue in the region below the hyoid bone (Figure 7.1, C). This occurrence might change the site of collapse in the upper airway, specifically in the infrahyoid region where the tissues are condensed now. Imaging would have been a useful tool to assess the area of obstruction, but technical and logistic factors prevented such

evaluation in our study. Also, the displacement of the hyoid bone in a cranial direction can lead to floppier tissue in the region situated above the hyoid bone, thus the upper airway may collapse in the suprahyoid region (Figure 7.1, B). This hypothesis remains to be proven. On the basis of this discussion, whenever a load is applied on the upper airway, and depending on the direction and amount of movement of the hyoid bone, a possible obstruction can occur above or below this bone where the tissue is less rigid. Roberts et al [9] used fiber-optic endoscope to visualize the site of airway closure in four living rabbits and five rabbits shortly after death. They observed that negative pressure application caused progressive narrowing at the level of the oro- and naso-pharynx then complete closure in the region 1-2mm above and below the free edge of the soft palate. We conclude that when that indeed the obstruction can occur in the supra or infrahyoid regions (the hyoid bone is located at the level of the free edge of the soft palate), and the position of the hyoid bone can contribute to determine the site of obstruction following the previously discussed mechanism.

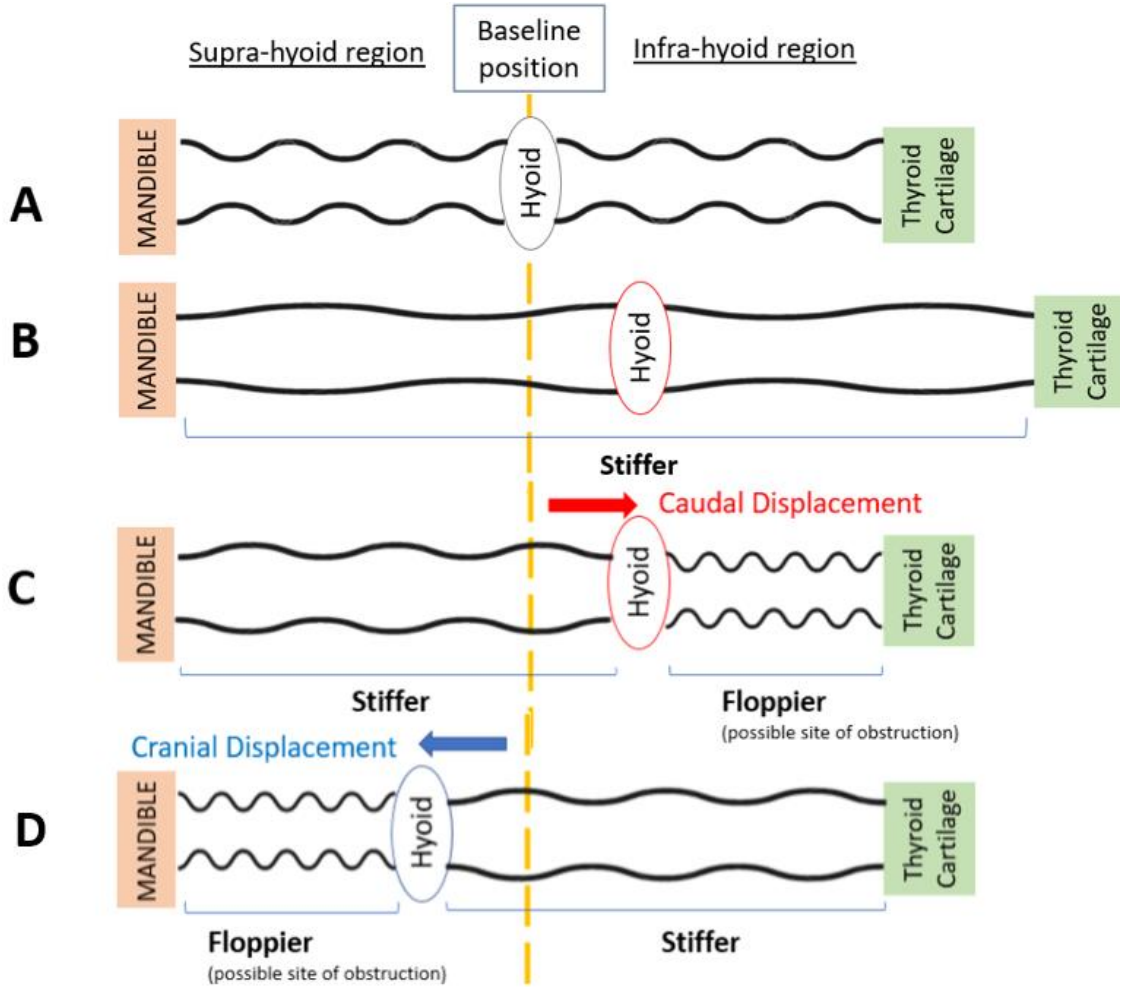


Figure 7.1: Schematic drawing of the hyoid displacement effect on the supra-hyoid and infra-hyoid anatomical configuration. A: When the hyoid is at its baseline position, the pharyngeal airway is patent and there is a distribution of tissue mass in the pharynx. B: Following tracheal displacement, the hyoid bone is moved caudally, and the upper airway tissues are stretched, and the airway walls are stiffened. C: Following caudal displacement of the hyoid bone, the tissue mass is jammed in the infra-hyoid region leading to a floppier segment in the infra-hyoid region, which promotes obstruction. The supra-hyoid segment of the pharynx is stiffer. D: Following cranial displacement of the hyoid bone, the tissue mass is squeezed in the

supra-hyoid region leading to a floppier segment that is more susceptible to collapse. The infra-hyoid segment of the pharynx is stiffer.

- Ant-caudal/ ant-cranial hyoid displacement

Ant-caudal and ant-cranial hyoid displacement studies have not been performed previously. However, muscle activation studies that move the hyoid bone in these directions suggest potential impacts. In a study by Roberts et al. [45] in 12 freshly killed rabbits, mechanical tension, mimicking the contraction of either the sternohyoid or sternothyroid, was achieved through direct pull on the hyoid bone or the thyroid cartilage in the direction of those muscles. This manoeuvre produced 1 to 2mm ant-caudal movement of the hyoid bone that was shown to improve airway stability widening of the pharynx. The increase in dimensions occurred in the oro- and nasopharynx and was caused by outward movement of the anterior, posterior, and lateral walls. Pclose improved by a mean of -2.6 ± 1.7 (SD) cmH_20 with sternohyoid stimulation, which was similar to the amount of Pclose reduction obtained with 2mm antero-caudal 45° hyoid displacement in our study (-1.92±0.68 cmH_2O). In addition, in the same animals (tracheostomized with passive upper airway rabbits) by Roberts et al, the upper airway closing pressures improved significantly during sternothyroid stimulation, which caused 1 to 2 mm ant-caudal hyoid movement. The mean change in the airway closing pressure was -4.3 ± 3.8 (SD) cmH_2O. Because thyroid cartilage has ligamentous attachments to the hyoid bone, contraction of the sternothyroid muscle also displaced the hyoid bone. The sternothyroid muscle stimulation was significantly more efficient in improving upper airway collapsibility in comparison to the sternohyoid muscle stimulation for the

same amount of hyoid movement. This finding may be associated with the size difference in the two muscles, with the sternohyoid having a greater cross-sectional area than the sternothyroid.

A similar change in airway dimensions was produced when tension was applied to the hyoid bone to simulate geniohyoid or genioglossus muscle contraction. Brouillette and Thach [163] found that the improvement in upper airway stability seen with genioglossus and geniohyoid contraction was related to the effects of these muscles on the hyoid bone. These muscles move the hyoid bone ant-cranially, but the amount of hyoid movement was not reported. Also, widening of the pharyngeal airway was obtained by Reed et al, [204] who visualized the upper airway using fiber optic endoscopy when tension was placed on the hyoid bone simulating geniohyoid and genioglossus muscle contraction in infant cadavers.

Based on our study and on the literature findings, the ant-caudal and ant-cranial movement (along 30°, 45° or 60° angles) improved the upper airway patency and stability, but the caudal or cranial movements did not produce this effect.

- Comparison of directions

The greatest improvement in Pclose in the current study was with the anterior displacement of the hyoid bone. The ant-caudal and ant-cranial hyoid displacements resulted in similar Pclose change as the anterior displacement. The caudal and cranial hyoid displacements did not change the upper airway collapsibility. Thus, the anterior movement of the hyoid bone is the major component leading to the improvement in the upper airway collapsibility [165]. When combining the caudal or

cranial displacement to the anterior movement, the collapsibility of the upper airway remained the same.

The greater improvement in the upper collapsibility was observed when the hyoid bone was moved at 60° angle then 45°, the least was at 30° angle. This finding seems logical considering a greater anterior vector for the same amount of hyoid displacement. These outcomes suggest that the greater the anterior displacement vector of the hyoid bone in ant-caudal or ant-cranial directions, the better the resistance to collapsibility. Nonetheless, these inferences from the variability of Pclose should be made with caution given the small sample size limitations for these detailed physiological investigations.

- Implications for hyoid suspension surgeries

The available hyoid surgical repositioning techniques have an anterior force vector combined with another vector applied either caudally (suspension to the thyroid cartilage) or cranially (suspension to the inferior border of the mandible). Initially, hyoid suspension was designed to the inferior border of the mandible. Riley et al. [139, 166] used and later revised this technique by securing the hyoid arch antero-inferiorly to the thyroid cartilage rather than suspending it from the anterior mandible. The rationale for surgery was based on the finding that the most commonly observed feature in OSA patients was the inferiorly positioned hyoid bone. However, the ‘low’ position was not properly defined in the literature as what is considered low for one patient might be normal for another. The advantages of the revised technique were the lower morbidity and avoidance of the unfavorable cosmetic changes that could occur after advancement of the hyoid into the submental

region. Riley et al [166] studied 15 patients with OSA treated with this revised technique and reported a significant improvement in sleep-related breathing disorders and excessive daytime sleepiness in 12 (80%) of 15 patients. Six (40%) of the 15 patients achieved surgical cure of OSA.

Neruntarat[167] reported data for 32 patients treated with palate surgery (uvulopalatal flap) and hyothyroidopexy. Twenty-five (78%) of 32 patients achieved a successful outcome based on a 50% reduction in the respiratory disturbance index (RDI). In a systematic review, Song et al [133] reported that in patients undergoing isolated hyoid surgery for OSA, hyoid suspension reduced the apnea-hypopnea index (AHI) by 38.3%, and hyothyroidopexy by 50.7%. This difference was not statistically significant. In another study by Bowdan et al [206] concluded that hyoid suspension alone is not an efficacious treatment for hypopharyngeal obstruction in OSA for most of the patients evaluated. Therefore, the literature is still not conclusive on the efficacity of the hyoid suspension surgery and hyothyroidopexy, whether performed alone or as part of a multilevel surgical procedure. Studies are limited to surgical reports that compare patients related outcomes rather than fundamental anatomical post-surgical changes.

Our study suggests that in both surgical procedures, it is the anterior vector that is mainly contributing to the improvement observed in obstructive sleep apnea patients who underwent hyoid repositioning surgeries. There is a greater anterior displacement of the hyoid bone with the hyoid suspension compared to the hyothyroidopexy (distance hyoid-mandible > distance hyoid-thyroid cartilage) (Figure 7.3). Nevertheless, several factors such as muscles rearrangement and

tissue concentration also play a role in determining the final outcome of those hyoid surgeries.

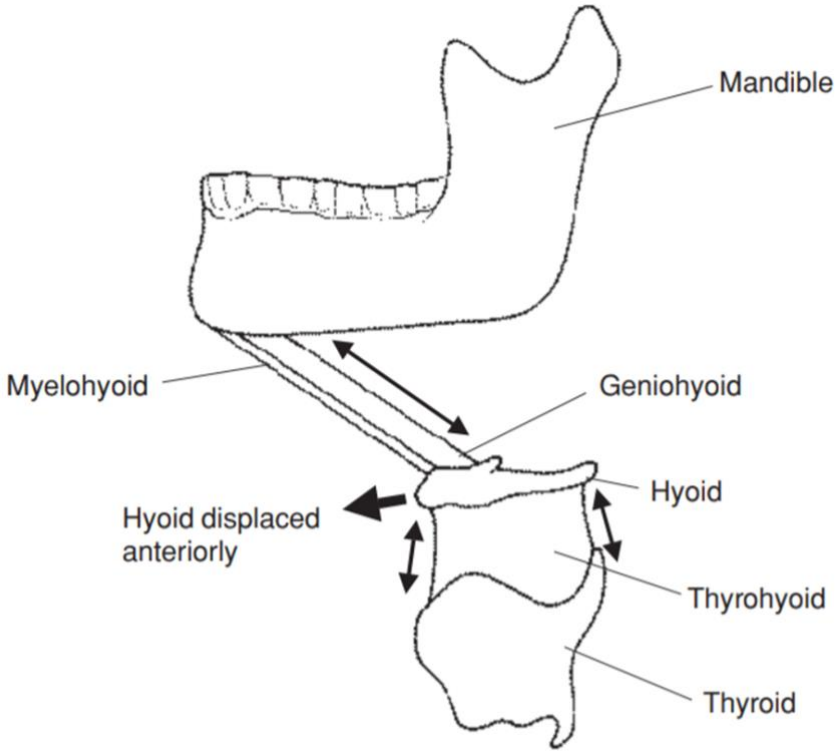


Figure 7. 2: Schematic drawing of the hyoid situated between the inferior border of the mandible and the thyroid cartilage. When performing the hyoid repositioning surgeries, the hyoid bone is displaced anteriorly, with a greater amplitude when the hyoid is fixed to the mandible in comparison to when it is fixed to the thyroid cartilage. Adapted and modified from Drummond, 1996 [195].

- Implications for mandibular advancement therapy

It is conceivable that mandibular advancement could indirectly target the hyoid bone, which in turn would be responsible for airway dilatation [28]. As the mandible

is advanced, the hyoid is displaced in an ant-cranial direction through its muscular connections to the body of the mandible. Such movement was found to improve the upper airway patency and stability. Also, an investigation in awake OSA subjects provides evidence that larger increments in hyoid bone displacement with mandibular advancement are linked to greater improvements in upper airway lumen size [181]. The greater the mandibular advancement, the greater improvement is expected in the upper airway patency as the hyoid bone will be displaced more anteriorly. In a recent study, Sutherland et al. [29] found that mandibular advancement reduces pharyngeal collapsibility in a dose-dependent manner without systematically changing genioglossus muscle function in a predominantly obese and severe OSA population. These findings indicate that the primary mode of action of mandibular advancement splint therapy is by enhancing passive pharyngeal anatomy. In support of treatment, the more anterior positioning of the hyoid bone could explain the improvement following mandibular advancement, the anterior hyoid advancement in a human cadaver (1cm) model produced airway opening and improvement in upper airway airflow [19]. Information on the behaviour of the hyoid during mandibular protrusion is both meagre and diverse, and the results of this manoeuvre on pharyngeal opening are not conclusive. Additional studies are needed to fully understand the physiological changes following mandibular advancement therapy and their relation to the hyoid bone. Considering that mandibular advancement in humans involves a downward vertical component, investigations should also address the effect of this component (whether rotation or translation) on the hyoid bone.

CHAPTER 8

CONCLUSION AND CLINICAL IMPLICATIONS

The incremental increase of the hyoid bone displacement was associated with a progressive reduction in the upper airway closing pressure leading to a less collapsible upper airway. This finding was only observed in the anterior and ant-cranial/ ant-caudal (30°, 45° and 60°) angles but not in the independant caudal or cranial directions.

- The anterior hyoid displacement was equally effective in decreasing the upper airway collapsibility as the ant-cranial 45° and ant-caudal 45° displacement.
- When the hyoid was displaced in the ant-caudally 60° or ant-cranially 60° directions, the improvement in collapsibility was almost the same as the anterior only or the 45° repositioning. The 45° and 60° setups yielded greater improvement than the ant-caudal 30° or ant-cranial 30° movement.
- These findings suggest that the hyoid repositionning surgeries should aim at maximizing the anterior hyoid displacement. Differences reported between the hyoid suspension and the hyothyroidopexy are more likely related to the surgical intervention itself or to other non-hyoid related factors rather than to the hyoid bone displacement effect.
- During mandibular advancement therapy, the hyoid bone moves in an ant-cranial direction which was proven to improve the upper airway patency. Increasing the amount of mandibular advancement (surgical or using a repositionning device) tends to increase the anterior displacement of the hyoid bone (following the force vectors). Therefore, different ranges of displacement of hyoid bone with mandibular advancement may explain differences in the pattern of improvement in upper airway collapsibility

between response groups in previous studies [51, 207]. Clinically, the practitioner should create a balance between the patient's comfort and the maximum mandibular advancement

Future Studies

Future studies should focus on determining the relation between hyoid bone position and the efficacy of therapies used to treat OSA such as mandibular advancement therapy using splints, hypoglossal nerve stimulation, and bimaxillary surgical advancement.

Also, new research should focus on the dose-dependent effects of hyoid repositioning on other pathophysiological traits contributing to OSA which may clarify the sources of variability in response to this treatment modality, with the ultimate goal of developing personalized approaches to patient selection.

The findings of this study are based on a animal model which has a highly similar upper airway structure to humans. Nevertheless, it would be ideal if non-invasive interventions can be tested in humans.

Finally, for an optimal physiological representation, a great addition to this study would be to find a way to preserve the hyoid bone mobility after displacement. This would help us understand more precisely the pathophysiology especially in OSA patients with an inherent inferiorly positionned hyoid bone.

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