Upper Airway Disorders and Noninvasive Mechanical Ventilation

Rationale and Approaches

Antonio M. Esquinas
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Preface

Successful airway management has always been, and still remains, a critical maneuver for the optimal treatment of a significant number of patients in Medicine. Maintaining adequate oxygenation levels through mechanical or non-mechanical ventilation is of utmost significance in cases where breathing function is insufficient or entirely lost. In modern medicine, various techniques of ventilation may be utilized either for emergency medical conditions, such as trauma or acute breathing disorders, or more manageable conditions, such as endotracheal intubation during scheduled operation procedures. The maintenance of a patent airway path emerges as a very important duty and physicians often need to utilize any means necessary in order to preserve the patient's adequate oxygenation.

While performing mechanical ventilation, the thorough anatomical knowledge of the structures, forming the upper airway, is critical for successful ventilation. The oral cavity, the nasal cavity, the pharynx, and the larynx are such structures through which air flows during normal function of breathing. Comprehension of these anatomical elements, as well as their functionality, is essential for the usage of specified instruments during ventilation, such as tracheal or naso-tracheal tubes. Furthermore, these structures may often present significant number of anatomical disorders or anatomical variations. Such abnormal disorders may cause significant difficulty while performing proper airway management. Trained physicians, such as anesthesiologists, must be prepared to overcome such obstacles, directly and efficiently. Various anatomical classifications, such as the "Mallampati Score," along with other specific maneuvers, such as the "Jaw—Thrust" maneuver may predict difficulties during intubation and are routinely used nowadays.

One of the most demanding tasks which concerns patients with acute or chronic pulmonary diseases is the application of "Non-Invasive Ventilation" techniques (NIV). Such tasks also require early diagnosis and efficient management, combined with continuous follow-up. Physicians must obtain analogous expertise, accompanied with the necessary facilitation support, when it is considered obligatory. "NIV" applications consist rather beneficial ventilation methods against acute and chronic respiratory failure management, taken into account that such manifestation may evolve with numerous different pathological clinical conditions. "NIV" does not require endotracheal intubation while it may be performed in every clinical department which provides standard medical equipment and is constituted with adequately trained nursing and medical staff with expertise. "NIV" appliance must follow the

current international guidelines, such as the "British Thoracic Society" (BTS) guidelines, accompanied with continuous observation and monitoring, 24 h/day.

Proper knowledge of the physiological mechanisms, activated during breathing function, is very important. Physiology of the anatomical structures, the breathing function, as well as the "Gas-Exchange" mechanism constitute important role regarding maintenance of adequate oxygenation. Chronic breathing disorders, such as "Chronic Obstructive Pulmonary Disorder" (COPD), affect normal ventilation procedures and must always be taken into account, especially during potential non-mechanical ventilation or weaning. Furthermore, various ventilation parameters, such as "Positive Pressure" or "Tidal Volume," may need to adjust.

The following chapters provide thorough analysis of all the parameters that may hinder airway management and ventilation. In order to do so, indicative anatomy information of the elements that form the upper airway is cited, alongside commonly appeared structural and ethnic variations. The importance of anatomy knowledge for correct airway ensurement, as well as its significance for every physician, is emphasized, rather than providing detailed anatomical display of the structures involved. Moreover, most frequent acute and chronic upper respiratory disorders, alongside their implications against successful ventilation, are discussed, while the authors aim to suggest optimal solutions, in order to manage and overcome such emergency conditions.

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Part I

Upper Airways Anatomy and Applied Physiology

Upper Airway Structure

Lazopoulos Achilles, Gogakos Apostolos,
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Introduction

The upper airway structures are mainly responsible for transporting air to the lungs. Functionally, they consist of the nose and nasal cavity, the oral cavity, the pharynx and the larynx. Apart from transporting air, these structures are useful for phonation, humidification, cleaning and warming of the inspired air, swallowing and the sense of smell [1]. An adequate knowledge of the structural and functional anatomy of the upper airway plays a significant role for the anaesthesiologist during intubation and airway management [2].

Nose and Nasal Cavity

The nose is a pyramid-shaped structure located in the middle of the face, with its base facing the facial bones. It is formed by a combination of bones, cartilage and fibrous and fatty tissue which is mainly located in the nostrils. The bones that create the skeleton of the nose externally are the nasal bones, the frontal bone and the frontal processes of the upper maxillae. The cartilage framework of the nose includes the greater and lesser alar cartilages, two lateral nasal cartilages and the septal cartilage, which is part of the nasal septum. The nose has two distinct openings via which air enters the airway tract, the nostrils or nasal vestibules [3].

The nasal septum divides the nostrils and the nasal cavity vertically into two cavities, left and right. It consists of an anterior part formed by cartilage tissue and a posterior part formed by the ethmoid and vomer bones. The septum is a structure with common anatomic variations. Therefore, it's important for the physician to

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determine the more open side before introducing instruments, like nasogastric tubes, through the nasal passages [4].

The borders of the nasal cavity are formed by the ethmoid, the palatine bones, the maxillae and the vomer. The ethmoid bone forms the roof of the nasal cavity, whereas the palatine and the maxillae form the floor [5]. The anterior portion of the nasal cavity opens to the nostrils, and the posterior portion forms the nasopharynx which opens to the posterior nasal opening (conchae) [5]. The nasal conchae (turbinates) are, usually three, bony projections from the lateral nasal wall, in each side, that extend into the nasal cavity. From top to bottom, these are the superior, the middle and the inferior nasal conchae and are covered with respiratory epithelium [5]. They play a significant part in filtering, warming and humidifying the air that passes through the nose by increasing the surface area inside the nasal cavities [6]. The inferior conchae, which are the largest, direct the passage of the inhaled air through the nose cavity. The middle conchae protect the sinuses, while the superior conchae, which are the smallest, protect branches of the olfactory nerve [4].

Between the three conchae, three passages are formed, the inferior meatus, the middle meatus and the superior meatus. These passages are formed beneath each of the relevant conchae [7]. Of these three passages, the inferior meatus is the largest one. It is formed by the inferior concha and the base of the nasal cavity; it extends almost to the full of the nasal cavity's lateral wall and is used as a passage for instrumentation via the nasal cavity [8].

The paranasal sinuses are the frontal, ethmoid, sphenoid and maxillary sinuses and are named from the bone that they are located at. They are, usually asymmetrical, cavities filled with air within the corresponding bones and drain into the nasal cavity. They develop completely in adolescence, and they have many functions including lubricating the nose via mucus production and assisting in phonation [9].

The inward surface of the nostrils is covered with hairs, which play an important role in filtering the inhaled air and prevent large particles from moving towards the lungs. The nasal cavity and the sinuses are lined with a contiguous membrane, which is formed by stratified squamous epithelium in the anterior part of the nasal cavity and pseudostratified columnar epithelium in the posterior part, alongside with goblet cells. The main function of this membrane is to produce mucous which acts as a lubricant in the nasal cavity. Beneath this membrane lies the nasal submucosa, which contains capillaries, nerves and mucous-producing cells. Another significant structure in the nasal cavity is cilia. These are hair-like structure, but unlike the hair in the outer portion of the nostrils, they occupy the posterior part of the nasal cavity. With their continuous waveform movement, cilia move mucous and trapped fine particles away from the airway tract [10].

As mentioned above, smell is one of the primary functions of the nose and the nasal cavity. On the roof of the nasal cavity, there is an area which contains a special type of epithelium called olfactory epithelium, in the distal part of the nasal cavity, away from the nostrils. This epithelium contains olfactory receptor neurons. In humans, an average of six million olfactory receptors are present. The nerve supply to this area originates from the olfactory nerve. The sensory innervation of the nose

and the rest of the nasal cavity is derived from the trigeminal through its first and second branches [8].

The main arteries that supply blood to the nose and nasal cavity are the ophthalmic artery, through its ethmoidal branches, the internal carotid artery, the maxillary artery and the facial artery. All these arteries provide several branches that direct the blood flow to all the parts of the nasal cavity [11]. Because of this rich blood supply, nosebleeds (epistaxis) may, sometimes, be very difficult to control and may require medical assistance. Nosebleeds are categorized to anterior nosebleeds and posterior nosebleeds according to the point of origin [10]. Anterior nosebleeds, which are the most common, originate from vessels in the nasal septum. Many conditions may start a nosebleed, like trauma, infections, medications used for blood thinning, blood disorders, drugs, etc. [10]. Posterior nosebleeds originate from vessels deeper in the nasopharynx and the more common causes are medication, blood disorders or surgery [10].

Oral Cavity

The oral cavity is formed by the mouth, the palate, the teeth and the tongue. The roof of the mouth cavity is developed by the palate. The palate is divided into two distinct parts, the hard palate anteriorly and the soft palate posteriorly. The frontal boundaries of the mouth cavity are formed by the maxilla bone, which also plays a role in the creation of the nasal cavity, and the mandible. The lower surface of the mouth cavity consists of the tongue, mylohyoid and geniohyoid muscles and salivary glands [4].

The teeth are located in the arches of the maxillary and mandibular bones. There are 32 teeth in a normal mouth of an adult; 8 incisors, 4 canines, 8 premolars, 8 molars and 4 third molars (wisdom teeth). Half of them are located in the maxillary arc and the other half in the mandibular arc in a symmetric way. Each tooth is divided into two parts: the root and the crown. The crown is the part of the tooth that projects in the mouth cavity, while the root is the part that attaches the tooth to the bone. They are positioned in a symmetric, mirror-like way. By dividing the oral cavity in the middle with an imaginary sagittal plane, there are four incisors, two canine, four premolars and six molars in each side, half of them located in the mandible and half located in the maxilla [12]. During preoperative evaluation, the condition of the teeth must be examined and well-known, in order to avoid accidents like dislodging a loose tooth during insertion, manipulation or removal of airway devices, causing unnecessary bleeding or possible airway obstruction. It's also very important to identify any false teeth and remove them, or check their stability, before intubation. The most prone to teeth injury are the upper maxillary ones, especially the incisors, due to the pressure created sometimes by the laryngoscope or the rigid bronchoscope on the teeth in order to get a better view of the epiglottis and the larynx, especially in cases with difficult intubation. It's estimated that the danger of teeth injury during intubation is 20 times higher in patients with difficulty in intubation [8].

The superior surface of the mouth cavity is formed by the palate. Palate separates the nasal from the oral cavity. The hard palate is a horizontal plate formed by the corresponding (palatine) processes of the maxillary bones and the palatine bones. It facilitates the movement of food through the mouth towards the pharynx and the function of phonation [11]. A rare birth defect of the hard palate, called cleft palate, occurs when the left and right parts of this structure don't join in the middle as usual, forming a canal and allowing passage between the nasal and oral cavity. This condition impairs severely the ability to speak and is treated surgically at a young age. One of the most distinguished risk factors for this condition is excessive maternal smoking during pregnancy [13]. The fleshy soft palate (velum) consists of a mucous membrane that contains muscles which play an important role in swallowing, breathing and talking. Due to not having bony parts, it's a moveable structure that moves upwards and backwards and closes the nasal passages during swallowing. The uvula, which resembles a cone, hangs from the centre of the soft palate. The movement of the soft palate and the uvula is accomplished by five paired muscles [10]. Both the uvula and the soft palate play an important role during insertion of instrumentation in the oral cavity. Pressure in the uvula and the end of soft palate causes a strong gag reflex which may lead to aspiration of stomach contents in the airway. The anaesthesiologist must be sure that this reflex is suppressed before intubation in order to avoid unnecessary complications [11].

The tongue is a large muscular organ that occupies the mouth and forms the floor of the oral cavity. Its average length in adult humans is 10 cm and weighs around 60–70 g [10]. The terminal sulcus divides the tongue into an anterior and a posterior part. The anterior part (oral) consists of approximately the two thirds of the tongue and is visible as it's located in the mouth. The posterior (pharyngeal) part consists of the remaining one third of the tongue and is connected to the hyoid bone, to the epiglottis, to the soft palate and to the pharynx with a multitude of muscles and membrane processes. These two parts have different nerve supply for taste and sensation; the oral part is supplied by the trigeminal nerve, through a branch called lingual nerve, and the facial nerve, whereas the pharyngeal part is supplied by the glossopharyngeal nerve [14]. The lower surface of the tongue attaches to the floor of the mouth through a mucous membrane (frenulum) in which the major salivary glands excrete. The muscles of the tongue are divided into two categories, intrinsic and extrinsic [14]. There are four intrinsic muscles responsible for changing the shape of the tongue. The rest four extrinsic muscles are attached to bones and are responsible for the positioning of the tongue. The motor nerve supply of the muscles of the tongue is supplied by the hypoglossal and the vagus nerves. The main blood supply to the tongue comes from the external carotid artery through a branch called lingual artery. Secondary blood supply comes also from the facial and pharyngeal artery through corresponding branches. The lingual veins drain in the internal jugular vein [14]. Due to its rich blood supply and thin membrane, the base of the tongue is an ideal way of administering certain drugs, such as nitroglycerin. This helps for a speedy delivery by bypassing the gastrointestinal tract [10]. The tongue plays an important role in the sensory of taste. It's equipped with many taste buds (2000–4000 in adults), which consist of approximately 10–50 taste receptor cells

responsible for distinguishing different tastes like sweet, bitter, salty, sour and savoury, and through the trigeminal, facial and glossopharyngeal nerves, the stimuli reach the gustatory cortex in the brain. Such sensory cells are also found in the nasal cavity, the anterior aspect of the epiglottis and the upper quadrant of the oesophagus. The tongue also facilitates mastication by crushing food against the hard palate and by guiding the soft food towards the pharynx. Furthermore, by changing position and shape with the help of the intrinsic and extrinsic muscles, the tongue facilitates speech and especially articulation [10]. Due to its position inside the mouth, the tongue sometimes may fall back and restrict the airway in patients with no senses. This may become a problem also during the induction of anaesthesia. Ventilation in this case may be difficult and the anaesthetist must be ready for intubation or use special manoeuvres, like the jaw thrust [11].

Pharynx

The pharynx is the continuation of the oral and nasal cavities to the oesophagus and the larynx, starting at the base of the skull and extending to the level of the cricoid cartilage. It's shaped like a tube and contains circular and longitudinal muscles, with different functions [4]. The circular muscles are used to move masticated food towards the oesophagus and their nerve supply arises from the vagus nerve, while the longitudinal muscles are used to raise the larynx during swallowing, and they are innervated by the glossopharyngeal and vagus nerves [10]. The muscles that control the upper airway lumen may be generally divided into four groups. The first group contains the muscles that control the soft palate. The second group contains muscles that control the movement of the tongue. The third group is comprised of muscles that regulate the position of the hyoid bone and the fourth group regulates the movement of the pharyngeal walls [15]. The complex interaction of these muscles is responsible for the preservation of the airway during breathing. In anesthetized patients, these muscles lose their natural muscle tone and the pharyngeal structure collapses causing obstruction of the airway. The pharynx is divided into three different segments: the nasopharynx, the oropharynx and the laryngopharynx [15].

The nasopharynx is the superior segment and is located behind the nasal cavity, above the soft palate. Through the nasopharynx the air is moved from the nasal cavity towards the larynx. Nasopharynx also houses the pharyngeal tonsils (adenoids) [14]. Some conditions of the tonsils, like chronic inflammation, may cause them to enlarge and consequently obstruct the airway or cause difficulty to the passage of instruments [10]. Nasopharynx is connected to the middle ear through the Eustachian tubes. These canals have a bony segment formed by the tympanic cavity and a fibrocartilaginous segment that enters the lateral wall of the nasopharynx. These canals are a drainage system for the middle ear secretions to the nasopharynx and act as a system for equalizing the atmospheric and the inner ear pressures [14].

The middle segment of the pharynx is called oropharynx and extends from the soft palate to the level of the epiglottis. Nasopharynx and oropharynx communicate

through the pharyngeal isthmus, which closes during swallowing in order to prevent food from entering in the nasopharynx and the nasal cavity. Laterally, this section of the pharynx contains the palatine and lingual tonsils which, like the pharyngeal tonsils, may become enlarged and obstruct the passage of food and air from the oral cavity to the oesophagus [11]. The palatine tonsils sit in the lateral wall between two arches, the palatine arches. The anterior arch is called the palatoglossal and the posterior arch is called the palatopharyngeal. Both these arches contain the corresponding muscles (palatoglossal and palatopharyngeal), which play a significant part in moving the soft palate and the uvula. In some cases of serious inflammation, abscesses may be created in the tonsils, which require immediate medical attention. Pharyngeal, palatine and lingual tonsils, together with the tubal tonsils, form a hypothetical ring of lymphoid tissue surrounding the nasopharynx and oropharynx, which is mostly known as Waldeyer's ring [14].

The inferior segment of the pharynx, the laryngopharynx or hypopharynx, extends from the epiglottis to the inferior border of the cricoid cartilage. After this level, the gastrointestinal tract continues with the oesophagus. Hypopharynx contains the piriform sinuses or fossa. These are located laterally to the larynx and are formed by the thyroid cartilage, the thyroid membrane and the aryepiglottic fold. The clinical importance of these spaces lies to the fact that food may be trapped there. This way food is not allowed to enter the larynx and it will not cause aspiration [15].

Swallowing can be divided into four different phases. In the oral preparatory phase, food is masticated with the help of the teeth and the movement of the mandible and the tongue and is mixed with saliva. During this phase breathing is accomplished through the nasal passageway, with the pharynx and larynx open. In the oral transit phase, as the food reaches the end of the oral cavity, the soft palate moves to close the passage towards the nasal cavity, while the pharynx is stimulated by sensory receptors and swallowing starts. In the pharyngeal phase, the movement of the soft palate is completed and the nasopharynx is protected from accidental food regurgitation. The hyoid bone and larynx move upwards and forwards to protect the airway, the pharynx elevates and the oropharynx closes. All these movements are accomplished with the appropriate musculature. In the meantime, the vocal cords in the larynx close and breathing stops. All these movements displace finally the food to the oesophagus. In the last phase, the oesophageal phase, food continues to move down the oesophagus, the larynx and pharynx return to their relaxed positions, and breathing is resumed [10].

Larynx

The larynx is the continuation of the pharynx and is considered the limit between the upper and lower airway tract. It is positioned anteriorly at the top of the neck and is a complex structure composed of cartilages, ligaments and muscles, which provide flexibility and allow larynx to perform many functions [16]. The borders of the larynx are the epiglottis anteriorly, the aryepiglottic folds laterally and the

interarytenoid folds posteriorly and inferiorly. It is divided functionally into three segments. The middle segment is called the glottis and contains the true vocal folds. Superiorly lies the supraglottis and inferiorly lies the subglottis. The supraglottis is comprised of the epiglottis, the aryepiglottic folds and the arytenoid cartilages and contains the false vocal cords. The subglottis lies inferior to the vocal cords and extends to the end of the cricoid cartilage [16].

The cartilaginous core of the larynx is composed of two different sets of cartilages. There are three full cartilages (the thyroid, the cricoid and the epiglottic cartilage) and three paired cartilages (the arytenoid, corniculate and cuneiform cartilage) [14].

From the full cartilages, the thyroid cartilage is in the middle and is the largest one. The superior one is the epiglottic and inferiorly sits on the cricoid cartilage. The laryngeal prominence, most commonly known as Adam's apple, is formed by the thyroid cartilage and can be palpated in the neck. It is considered as an important anatomical landmark, and it serves as a guiding point for several medical interventions such as percutaneous tracheostomy. Due to its size, the thyroid cartilage protects the glottis which contains the sensitive vocal cords from damage during trauma in the neck. The thyroid cartilage connects to the hyoid bone via the thyrohyoid membrane superiorly and with the cricoid cartilage via the cricothyroid ligament inferiorly [14]. The cricothyroid ligament plays a significant role during cricothyrotomies for securing airway passage in cases of obstruction above the level of the larynx, especially in emergency situations.

Immediately below the thyroid sits the cricoid cartilage, which is shaped like a ring surrounding the airway. It is the only cartilage in the larynx that forms a complete circle. The cricoid cartilage is connected to the first tracheal cartilage with the cricotracheal membrane and contains the part of the larynx below the vocal cords (subglottic) [14].

The epiglottis is located superiorly and acts as a valve between the gastrointestinal and the airway tract. It's located at the entrance of the larynx and plays a very important role in preventing aspiration during swallowing, as described above [15].

The three paired cartilages are the arytenoid, the corniculate and the cuneiform cartilages. The arytenoid cartilages are connected with the corniculate cartilages superiorly and the cricoid cartilage inferiorly. They are located at the posterior side of the larynx, behind the thyroid cartilage; they are shaped like a pyramid and have two processes, one muscular and one vocal. These processes serve as an attachment point for intrinsic musculature and ligaments of the larynx which control the movement of the vocal cords [14].

The corniculate cartilages, also known as cartilages of Santorini, are positioned superiorly to the arytenoid cartilages. Both corniculate and cuneiform cartilages form the posterior and part of the lateral border of the larynx entrance and are considered accessory cartilages. The cuneiforms, which sit near the arytenoepiglottic folds, superiorly to the corniculate, serve as support structures to the epiglottis and the vocal cords, whereas the corniculate cartilages facilitate the opening and closing of the vocal cords [11].

The larynx is supported by a number of intrinsic and extrinsic muscles. The intrinsic muscles facilitate the movement and fine-tuning of the vocal cords and several larynx ligaments during speech and phonation. The cricothyroid muscle, which arises from the cricoid cartilage towards the inferior margin of the thyroid cartilage, changes the thickness of the vocal cords. The thyroarytenoid muscle links the thyroid and arytenoid cartilages and mainly relaxes the vocal ligaments. The posterior cricoarytenoid muscles are located at the posterior aspect of the larynx and connect the cricoid and arytenoid cartilages. By lateral rotation of the arytenoid cartilages, these muscles help to increase the distance between the vocal cords; thus these are the prime surgical target in cases of vocal cord paralysis. The lateral cricoarytenoid muscles also connect the cricoid and arytenoid cartilages, in which they rotate medially, and serve as an opposite to the posterior cricoarytenoid muscles by narrowing the distance between the vocal cords. The oblique arytenoid muscles and the transverse arytenoid muscles connect the arytenoid cartilages of the opposite sides. Both these muscles help on increasing and decreasing the distance between the vocal cords [14].

The extrinsic muscles are responsible for the position of the larynx. The suprahyoid group raise the hyoid bone and subsequently the larynx during swallowing, widening the entrance of the oesophagus and facilitating the passage of food to the gastrointestinal tract. The infrahyoid group lower the hyoid bone and the larynx during speech [16].

The cricothyroid joint, between the cricoid and the thyroid cartilage, is an important synovial joint that allows regulation of the length and the tension of the vocal cords. This is accomplished by the function of this junction as a hinge point which facilitates tilting of the thyroid and cricoid cartilages. Another important synovial joint is the one between arytenoids and cricoid cartilage (cricoarytenoid). This joint allows rotation and sliding of the corresponding cartilages abducting or adducting the vocal ligaments. Pathologic conditions that affect these joints, such as trauma or arthritis, may cause these joints to fixate, resulting in immobilization of the vocal ligaments and speech or respiratory problems [15].

Inside the glottis, two projections of the lateral walls of the larynx form the vocal cords. These cords abduct and adduct with the help of the intrinsic muscles and the synovial joints of the larynx as described previously. The space between these cords is called rima glottides (glottic opening). Due to the heavy presence of ligaments and the lack of blood vessels, these folds have a distinct white appearance that makes them easy to identify during laryngoscopy. There are two sets of vocal cords. The false vocal cords are situated superiorly, in the supraglottic part of the larynx, and are separated from the true vocal cords with the laryngeal ventricle, which contains glands and provides lubrication for the true vocal cords via mucous secretion. Normally, these false vocal cords don't play any role in speech, although in some cases, such as patients with true vocal cord paralysis, they may approximate to the true ones during speech. The true vocal cords are located, as mentioned before, in the glottis segment and are responsible for the function of speech. By changing the size of the glottic opening, the larynx is the main structure of the upper airways that facilitates speech [17].

The main arteries that provide blood supply to the larynx are the external carotid artery and the subclavian artery through the superior and inferior thyroid arteries, respectively. The thyroid veins, superior, middle and inferior, are responsible for the venous drainage of the larynx and direct the blood flow to the left brachiocephalic and internal jugular veins. The pretracheal, prelaryngeal, paratracheal and deep cervical lymph nodes are responsible for the lymphatic drainage of the structure [15]. The innervation of the larynx originates from the vagus nerve via several branches including the recurrent laryngeal nerve. The recurrent laryngeal nerve originates from the vagus nerve in the thoracic cavity, loops around the aortic arch and exits the thoracic cavity via the thoracic inlet travelling upwards, towards the larynx. It is responsible for the innervation of the majority of the intrinsic muscles, which, as mentioned above, control the movement and shape of the vocal cords. The only intrinsic muscle that has different innervation is the cricothyroid muscle. Its nerve supply is provided by branches of the superior laryngeal nerve. Branches of the vagus nerve and the recurrent pharyngeal also provide the motor function of the lower pharynx. The sensory innervation of the larynx differs according to the level of the vocal cords. Superior laryngeal nerve provides branches for sensory function to the parts of the larynx above the glottis. Recurrent laryngeal nerve is responsible for the sensory function of the parts of the larynx below the vocal cords. Any lesion that may impair these nerves may cause vocal cord paralysis. Especially for the recurrent laryngeal nerve, due to its intrathoracic course, tumours of the left upper lobe of the lung, enlarged lymph nodes in the aorto-pneumonic window or aneurysms of the aortic arch may apply pressure to, invade or displace the nerve, impairing its function and causing cough, stridor or hoarseness [18].

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Upper Airways the Maxilar-Jaw Effect

Apostolos S. Gogakos, Thomas Rallis,
and Nikolaos Barbetakis

Airway Management

The upper airway is a vital passage composed of hard and soft tissue responsible for the human breathing [1].

Management of the airway is crucial in anesthesia. Difficulty or failure in airway management is the main cause of disability and mortality. Preoperative airway assessment plays an important role in physical examination by the anesthesiologist, where the anatomic parameters of the airways are determined in order to evaluate the extent of a possible difficult intubation. Throughout the world, about 600 patients every year are thought to die from such difficulties [2]. The relationship between a problematic airway, a difficult intubation, and a difficult laryngoscopy remains a challenge among clinicians. There are numerous preoperative evaluation tests and measurements that are commonly practiced. Measurements such as distance between canine teeth, thyromental distance, and the Mallampati test can be used to assess a potential difficult intubation. Preoperative measurements such as neck circumference at the level of the thyroid cartilage, width of mouth opening, body mass index (BMI), and sternomental distance are also performed [3, 4]. Despite good sensitivity, bedside tests cannot predict the possibility of intubation difficulties that may occur.9 Mallampati et al. suggested that there is an association between laryngeal and oropharyngeal appearance under direct laryngoscopy, which helps to identify any difficult intubation cases. Furthermore, classification of the interincisal gap, the sternomental and thyromental distances, and retrognathia are variables that can also predict the potential of a difficult intubation. Nowadays, the combination of these tests is used to assess the airway. The most routinely used is the Mallampati test, with a sensitivity and specificity of 28.6% and 93%, respectively [5].

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Cranial morphology is one of the factors that can directly affect the upper airways. Studies have found that disorders in the maxillofacial structure can lead to stenosis of the upper airway, causing obstruction symptoms [6]. Patients with maxillofacial structure of short body length, retrusion, or clockwise rotation of the mandible are among those with the highest odds of suffering from airway stenosis [7].

The 3:3:2 Rule

The 3:3:2 rule can be useful for elective endotracheal intubation where:

- The first "3" is a measurement of three fingers between the upper and lower teeth of the open mouth of a patient and indicates the ease of access to the airway through the oral opening.
- The second "3" is a measurement of three fingers from the anterior tip of the mandible to the anterior neck and provides an estimate of the volume of the submandibular space.
- The "2" is a measurement of two fingers between the floor of the mandible and the thyroid notch on the anterior neck and identifies the location of the larynx relative to the base of the tongue. If it's less than two fingers, that means the larynx is anteriorly located, and in these cases direct laryngoscopy (DL) will be difficult for endotracheal intubation. In such cases, direct visualization with a bronchoscope or fiber optics should be attempted [8].

Endotracheal intubation is used for major surgical procedures and for respiratory support. The proper identification of a difficult intubation can help clinicians prepare for complications where advanced airway management equipment is available [9].

The ability for the appropriate prediction and planning in case of a patient with a difficult airway is of vital importance in order to avoid the catastrophic "cannot intubate, cannot ventilate" scenario [10]. The likelihood of an event like this happens in fewer than 1/5000 elective procedures under general anesthesia. Moreover, the need for surgical airway rescue occurs in fewer than 1/50000 cases. As a result, major complications can arise, which account for 25% of anesthesia-related deaths [11].

What Is a Difficult Intubation?

Regarding the term "difficult intubation," the two most often used definitions in literature are the Cormack-Lehane grading scale and the Intubation Difficulty Scale [12]. The first describes how visible the vocal cords are during laryngoscopy, ranging from 1 (full view of vocal cords) to 4 (cannot see the epiglottis). The second is a scoring system that includes the Cormack-Lehane grading scale as well as other features, such as the number of intubation attempts, the doctors involved, the use of

advanced airway adjuncts, the increased lifting force that might be needed, the need for external laryngeal pressure, and whether the vocal cords are open or closed during laryngoscopy [13].

The safe management of the difficult airway has consistently been a core topic of interest in anesthesia and in clinical practice guidelines. The Difficult Airway Society published its latest guidelines in 2015 for managing difficult or failed tracheal intubation [14]. Although the number of deaths and brain damage during the induction of anesthesia has decreased dramatically over the past few decades, the risk stratification of, and response to, unanticipated difficult airways still exists [15].

The term "difficult airway" is far from being precise. It is not a disease, nor simply a specific anatomical characteristic of a patient, but an outcome of a combination of factors that include anatomy, clinical situation, clinician's level of expertise, and available airway equipment resources. Current guidelines of the ASA describe the following difficult domains:

- Difficult face mask ventilation
- Difficult laryngoscopy
- Difficult tracheal intubation
- Failed intubation
- Difficulties in the placement and use of supraglottic devices

Although these domains are clearly distinct from each other, the terminology is often misleading, with some studies trying to examine "difficult intubation" when they are strictly referring to "difficult laryngoscopy" [16].

As the definition of each of these domains is also not well clarified, varying prevalence rates occur between studies. Kheterpal et al. reported a frequency of 1141/53,401 (2.1%) for difficult face mask ventilation but only 77/53,401 (0.1%) for failed face mask ventilation [17]. In another study, the prevalence of difficult face mask ventilation was 917/94,006 (1.0%) but only 32/94,006 (0.03%) for impossible face mask ventilation [18]. These different prevalence rates may also be due to the use of neuromuscular blocking agents during face mask ventilation.

For difficult laryngoscopy, the four-grade scoring system introduced by Cormack and Lehane is commonly used, with a score of 3 (only epiglottis visible) or 4 (neither glottis nor epiglottis visible) usually referring to a difficult laryngoscopy. Although the reported frequency of difficult laryngoscopy ranges from 6% to 27%, the accuracy and clinical relevance of reporting the Cormack-Lehane scale have recently been questioned [19].

However, the clinical utility of these bedside screening tests is unclear. Despite the widespread use of these tests, a prospective cohort study of 2803 patients stated that the proportion of unanticipated intubation problems was 29 of 168 airway-related adverse events (17%) [20]. To date, four systematic reviews on airway examination tests have been previously published reporting:

- Insufficient published evidence to evaluate the predictive value of these tests
- Limited accuracy for predicting the difficult airway for the Mallampati test

- Inadequate performance of the modified Mallampati test
- Limited clinical value of bedside screening tests

However, these tests are still recommended by the clinical practice guidelines. The bedside index screening tests are:

- The Mallampati test
- Modified Mallampati test
- Wilson risk score
- The thyromental distance
- The sternomental distance
- The mouth opening
- The upper lip bite test (ULBT) [21]

Components of the Airway Examination

The American Society of Anesthesiologists has established 11 anatomical features that should be assessed prior to general anesthesia in order to identify potential patients at risk for difficult intubation. However, even during emergency situations when a thorough assessment of the oropharynx and neck is not possible, experienced clinicians might recognize anthropometric features that increase the likelihood of a difficult intubation [22].

History

A patient's history begins with a review of prior intubations and factors that may have altered the anatomy of the airway or neck. Examples include previous neck injury, radiation, surgery, or medical conditions including ankylosing spondylitis and diabetes. A history or symptoms suggestive of obstructive sleep apnea (OSA) should not be neglected, as OSA is associated with upper airway obstruction during sedation [23].

Physical Examination

Several physical signs and bedside tests have been assessed in clinical practice for the evaluation of a difficult airway. Physical examination should involve inspection of the oropharynx as well as calculation of anthropometric distances and mobility of the cervical spine and mandible [24].

Upper Lip Bite Test, Retrognathia, and Mandibular Protrusion

The upper lip bite test assesses the mandibular range of movement by asking patients to bite their upper lip with their lower incisors. The results of this test are described in terms of three grading classifications:

- Class 1: The lower incisors extend beyond the vermilion border of the upper lip.
- Class 2: The lower incisors bite the lip but cannot extend above the vermilion border.
- Class 3: The lower incisors cannot bite the upper lip at all (Fig. 1).

Patients without teeth are asked to try and raise the lower lip in order to cover the vermilion border of the upper lip. This is called "the upper lip catch test."

Retrognathia can either refer to a short mandible or to a mandible where the distance from the tip of the chin to the angle of the jaw is measured less than 9 cm. The anesthesiologist can also ask the patients to move their lower teeth past their upper teeth. This evaluation technique assesses the range of movement of the mandible and is called "mandibular protrusion" [25].

Thyromental and Hyomental Distance

The thyromental distance measures the distance between the upper border of the thyroid cartilage and the mentum, with the neck extended. Similarly, the hyomental distance is the distance between the hyoid bone and the mentum. The patient's height and overall size must always be taken into consideration when calculating the thyromental or hyomental distance, while adjustments should be made accordingly. For example, a patient who is 200 cm tall and has a thyromental distance of 6 cm is more likely to have a difficult intubation than a patient who is 160 cm tall with the same thyromental distance [26].

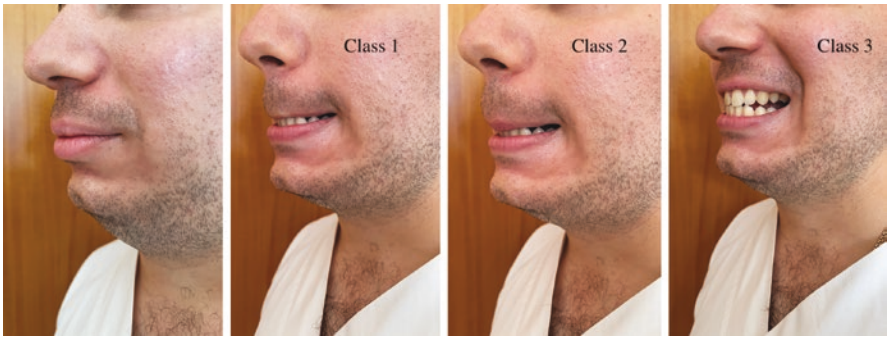

Fig. 1 Upper lip bite test

Cervical Spine Mobility and Sternomental Distance

Before proceeding to intubation, the anesthesiologist should assess the degree of cervical spine flexion and extension and be aware of possible neurological symptoms that may arise from the neck movement. The sternomental distance is measured from the upper border of the sternum to the tip of the jaw when the neck is fully extended. Patients with a normal spine tend to have a longer sternomental distance. A restricted cervical spine mobility, on the other hand, can make intubation more difficult [27].

Interincisor Gap and Modified Mallampati Score

The interincisor gap is measured with the mouth completely open and refers to the distance between the upper and lower incisors. The modified Mallampati score is a grading system used to rate the visibility of the structures in the oropharynx, including the uvula, faucial pillars, and soft palate. The original Mallampati score used a three-level classification system. Nowadays, a modified Mallampati score is used with a four-level system to classify which structures mentioned above are visible [28] (Fig. 2).

Abnormal Teeth

Abnormalities in teeth can make it sometimes impossible to visualize the vocal cords. Subjective assessments of prominent, loose, or missing teeth are strongly advised [23].

Composite Scores

The sum of all findings from the patient's history and physical examination can improve the predictive accuracy for difficult intubation. Composite scores include the El-Ganzouri score (which incorporates the modified Mallampati score, the interincisor gap, the thyromental distance, and the cervical spine mobility) and the Wilson score (which incorporates weight, cervical spine mobility, jaw mobility, degree of retrognathia, and the appearance of the incisors) (Table 1).

Several individual physical examination findings are predictive; however they cannot always reliably exclude the possibility of a difficult intubation. The most accurate individual bedside clinical assessment is upper lip bite test, which can be performed quite easily. Given the fact that the prevalence of a difficult intubation is estimated at about 10%, the inability to bite the upper lip with the lower incisors raises the probability of having a difficult intubation to more than 60% [23].

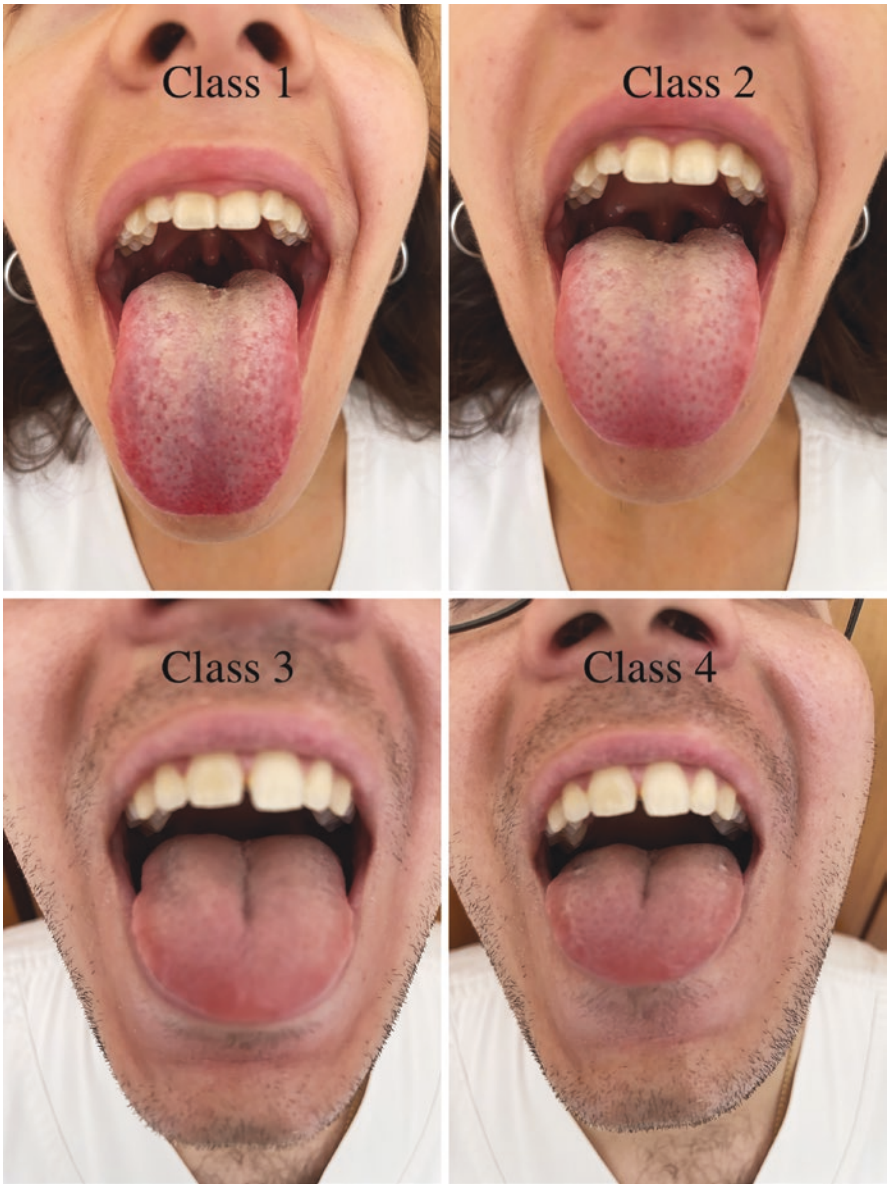

Fig. 2 Modified Mallampati score and mouth-opening capacity

Table 1 The Wilson score

	Score		
Parameter	0	1	2
Weight, kg	<90	90–110	>110
Cervical spine mobility	>90°	90°	<90°
Impaired jaw mobility	Interincisor gap ≥5 cm or able to protrude lower teeth past the upper teeth	Interincisor gap <5 cm and only able to protrude lower teeth to meet upper teeth	Interincisor gap <5 cm and unable to protrude lower teeth to meet upper teeth
Retrognathia	Normal	Moderate	Severe
Prominent incisors	Normal	Moderate	Severe

The Seven Airway Assessment Factors

Usually, the prediction of a difficult endotracheal intubation before anesthesia depends on the criteria that assess physical characteristics, such as the Wilson score and the LEMON method among others. A study by Seo et al. came up with seven factors for airway evaluation for predicting difficult endotracheal intubation; they include some of the Wilson score, body mass index (BMI), and the upper lip bite test (ULBT) [3].

The seven airway assessment factors were the following:

- Mallampati classification
- The thyromental distance
- The head and neck movement
- BMI
- The severity of buck teeth
- The interincisor gap
- ULBT

Each factor was given a 0, 1, or 2 points (for BMI, 0 or 1 point), and the total score was tallied and recorded as total airway score (TAS) (Table 2).

The severity of buck teeth was considered normal if the patient was able put his teeth together, while the upper teeth closed over the lower teeth without space. If the upper teeth protruded 0–0.5 cm more than the lower teeth, it was considered moderate. If the upper teeth protruded more than 0.5 cm compared to the lower teeth, it was considered severe.

The interincisor gap was measured by taking the distance between the upper and lower teeth when the mouth was opened as widely as possible.

Table 2 Rules for evaluating airway score

	Score		
Airway factors	0	1	2
Mallampati classification	Class I	Class II	Class III–IV
Thyromental distance (cm)	>6.5	6–6.5	<6
Head and neck movement	>90°	90°	<90°
BMI (kg/m^2)	<25	≥25	–
Buck teeth	No	Mild	Severe
Interincisor gap (cm)	>5	4–5	<4
ULBT	Class I	Class II	Class III

BMI body mass index, *ULBT* upper lip bite test

The LEMON method stands for the following five parameters [29]:

- Look (facial impairment, large front teeth, large tongue, beard/moustache)
- Evaluate (3:3:2 rule – interincisor gap, mental-hyoid distance, hyoid-thyroid distance)
- Mallampati score
- Obstruction
- Neck mobility

The LEMON method finds its use in emergency situations for simple and prompt difficult endotracheal intubation by looking and using fingers to measure lengths without the need for special tools.

Obstructive Sleep Apnea

The upper airway is 12 to 14 cm long. It is an irregular lumen including the nasopharynx, palatopharynx, glossopharynx, and hypopharynx. The narrowing of one or more of the above segments may result in breathing problems. Studies have reported that the skeletal profiles with malocclusion bring about a narrower upper airway and a higher risk of obstructive sleep apnea syndrome (OSAS) [30].

OSA is a common sleep disorder characterized by recurring collapse of the upper airway during sleep, resulting in sleep fragmentation and oxygen desaturation. OSA is defined as the occurrence of five or more episodes of complete (apnea) or partial (hypopnea) upper airway obstruction per hour of sleep. This is called the apnea-hypopnea index (AHI) and is estimated to occur in around 24% of men and 9% of women. Patients with OSA experience snoring, daytime sleepiness, and impaired quality of life. Nowadays, it is considered as an independent risk factor for cardiovascular diseases, stroke, as well as car accidents. The gold standard treatment for moderate-severe OSA is oxygen supply through a continuous positive airway pressure (CPAP) ventilator. Another method of treating OSA is the use of oral appliances (OAs). OAs are designed to improve upper airway configuration and prevent collapse through alteration of jaw and tongue position.

Degree of Mandibular Advancement

An abnormal bony facial structure is believed to be a substantial factor in the pathogenesis of OSA. This abnormality might be accompanied by abnormal behavior of the pharyngeal dilating muscles, such as a reduction in tone. OSA is usually associated with the degree of mandibular advancement. Generally, the greater the level of advancement, the better the treatment effect, although this must be balanced against potential increase in side effects [31].

It is generally agreed that mandibular advancement can widen the upper airway, and many oral appliances have been designed to move the mandible forward in treating OSA. Mandibular advancement should move forward not only the mandible but also the tongue and soft palate, because they are connected to each other; this will result in enlargement of the upper airway caliber. Furthermore, mandibular advancement might also elicit neuromuscular action, which would stiffen the upper airway wall [32].

Oral Appliance Treatment for Obstructive Sleep Apnea

A study of three levels of advancement (2, 4, and 6 mm) resulted in improvement of overnight oximetry (25%, 48%, and 65% of patients showing improvement >50% in desaturation, respectively). Assessment of the pharyngeal collapsibility during mandibular advancement has also reported a dose-dependent effect in improvement of upper airway pressures. However, in severe OSA, more patients achieved a successful treatment with 75% compared to 50% of maximum advancement (52% vs. 31%, respectively). Such evidence suggests that maximizing of the mandibular advancement may be highly effective in severe disease. A titration approach to determine optimal level of advancement over time is thought to optimize treatment outcome. The optimal advancement level can be found with titration that is guided by a combination of both subjective symptomatic improvement and objective monitoring by overnight oximetry. A newly available remotely controlled mandibular titration device is now available and can determine the maximal therapeutic level of mandibular protrusion during sleep. Identification of therapeutic protrusion level by this method may help reduce side effects produced by further unnecessary titration. It is also worth noting that the optimization of the mandibular advancement in patients is important for successful treatment, although no standardized titration procedure currently exists. In clinical practice, a follow-up sleep study to clearly verify optimal treatment is often not conducted. This is an area by which to improve clinical outcomes [33].

Degree of Vertical Opening

Opening of the bite occurs during OA treatment as all appliances have a certain thickness causing vertical jaw displacement. A crossover trial that compared two

levels of vertical opening (4 mm and 14 mm, equivalent advancement) found no severe impact on the AHI, although patient preference was in favor of the smaller degree of mouth opening. However, in the majority of OSA patients, increased vertical mouth opening has an adverse effect on upper airway patency. Therefore, the amount of bite opening should be minimized to improve patient tolerance and increase the beneficial effect on upper airway dimensions [34].

In conclusion, OAs are an effective treatment for OSA. They improve not only AHI but also a variety of physiologic and behavioral outcomes. Recent comparative trials have shown that the outcomes between CPAP and OA treatments are equivalent, even in severe OSA, despite greater efficacy of CPAP in reducing AHI. This likely reflects greater nightly adherence to OAs compared to CPAP therapy. Selection of appropriate patients who will respond to OAm treatment is an ongoing barrier to use. Establishing best quality devices that are objectively validated in terms of both efficacy and durability in selected patients will continue to optimize OAs as an effective and maybe a first-line treatment for OSA.

Malocclusions

In orthodontics, a malocclusion is a misalignment or incorrect fit between the teeth of the upper and lower dental arches as the jaws close. According to Angle, malocclusion is any deviation of the occlusion from the ideal [35].

Classification

- *Class I* (neutrocclusion): Here the molar relationship of the occlusion is normal but with incorrect line of occlusion or as described for the maxillary first molar but the other teeth having problems like spacing, crowding, over or under eruption, etc.
- *Class II* (distocclusion (retrognathia, overjet, overbite)): In this situation, the mesiobuccal cusp of the upper first molar is not aligned with the mesiobuccal groove of the lower first molar. Instead it is anterior to it. Usually the mesiobuccal cusp rests in between the first mandibular molars and second premolars. There are two subtypes:
  - Class II Division 1: The molar relationships are like that of Class II and the anterior teeth are protruded.
  - Class II Division 2: The molar relationships are Class II, but the central are retroclined, and the lateral teeth are seen overlapping the centrals.
- *Class III* (mesiocclusion (prognathism, negative overjet, underbite)): In this case the upper molars are placed not in the mesiobuccal groove but posteriorly to it. The mesiobuccal cusp of the maxillary first molar lies posteriorly to the mesiobuccal groove of the mandibular first molar, usually seen as when the lower front teeth are more prominent than the upper front teeth. In this case the patient very often has a large mandible or a short maxillary bone [36].

Obstructive processes of morphologic, physiologic, or pathologic nature, such as hypertrophy of adenoids and tonsils, chronic and allergic rhinitis, irritant environmental factors, infections, congenital nasal deformities, nasal traumas, polyps, and tumors, are predisposing factors to a blocked upper airway. When that happens, a functional imbalance results in an oral breathing pattern that can alter facial morphology and dental arch forms, generating a malocclusion [37].

Regarding the possible associations among respiratory function, facial morphology, and malocclusions, the literature is quite controversial. The ways in which different airflow patterns can influence growth and development are yet to be clarified. This occurs because of the methodological limitations related to the variety of factors that can cause a malocclusion, the limitations in the use of the cephalometric method, and the lack of longitudinal studies assessing the airway [38].

Many studies have assessed the relationship between craniofacial morphology and the pharyngeal airway using cephalometric radiographs. However, lateral teleradiographs are limited because they reproduce a three-dimensional structure in a two-dimensional way that does not allow the assessment of cross-sectional areas and volumes of these structures [39, 40].

An accurate diagnosis through novel techniques of the changes in the upper airway considering the morphology and volume is fundamental to ensure normal development of the craniofacial complex in growing subjects as well as the choice of an adequate treatment plan [41].

Class I and II

Facial growth changes not only are related to differences in the direction of condylar growth but also may result from differences in development of anterior and posterior facial height. These differences in vertical development may lead to rotational growth or positional changes of the mandible [42].

Kerr et al. reported that Class II malocclusion subjects presented with narrow nasopharyngeal airway space compared with Class I and normal occlusion subjects. However, the vertical skeletal pattern was not emphasized [43].

It is also known that the tongue position is more backward and that contact with the soft palate may result in a posterior location of the soft palate and narrowing of the oropharyngeal airway in subjects with mandibular retrognathism.

In addition, tonsil size is often related to the size of the mandible and the horizontal growth pattern in patients with nasal obstruction [44].

Class III

By combining progress in imaging and software in the medical field, the geometric changes in the form of a structure can be analyzed using landmarks that have actual anatomic significance. Statistical shape analysis is a modern geometric and morphometric method that uses the shape of organs or organisms as input data and has recently become popular [45].

In the treatment of subjects with Class III malocclusion characterized by maxillary deficiency during the growth period, a face mask (FM) is often applied with different intraoral anchorage units for the forward movement of the maxilla and correction of maxillomandibular relationship. Chun et al. introduced the tandem traction bow appliance, as an appliance more aesthetically acceptable, easy to use, and not affecting oral hygiene adversely, compared with other appliances used in the treatment of Class III anomalies. Atalay and Tortop modified the appliance and reported that the modified tandem traction bow appliance (MTTBA) was effective for patients with Class III malocclusion because of maxillary retrusion or a combination of maxillary retrusion and mandibular protrusion [46, 47].

Although there were no significant differences between the appliances, as a precaution in patients with Class III malocclusion with a narrower nasopharyngeal airway, FM might be the preferred choice. Conversely, MTTBA might be an alternative treatment choice in patients with a narrower oropharyngeal airway [47].

Surgical Considerations

Throughout literature sagittal and vertical growth pattern are closely related to different breathing patterns and airway sizes. Using computed tomography (CT) in patients presenting mandibular retrusion, a significant decrease in nasopharyngeal volumes was reported when compared to the ones presenting mandibular prognathism and also if compared to control group without retrognathism. On the contrary, significantly higher oropharyngeal volume was reported in Class III malocclusion patients when compared to Class I patients [48].

Moreover, significant improvements in breathing function were reported, following the effects of rapid maxillary expansion (RME) treatment. These changes were associated with substantial reduction in nasal obstructions and abnormal tongue position. Transitory increasing of facial height and in some Class II patients even a forward relocation of the mandible might occur after RME. The abovementioned mandibular effects could contribute to enlargement of the oropharynx volume with repositioning of the tongue and soft palate with an improvement of upper airway volume after treatment [49, 50].

In conclusion, appropriate orthodontic diagnosis and treatment, such as oral appliance, maxillomandibular advancement, and mandibular setback surgery, could improve lateral appearance, upper airway morphology, and hyoid bone position and alleviate the stenosis of the upper airway [1].

Advances in Upper Airway Imaging

There are several two-dimensional (2D) and 3D studies that focus on the relationship between upper airways and craniofacial patterns in normal breathing patients [51].

A vertical growth pattern is more likely to present with a narrower upper pharyngeal width regardless of skeletal differentiations [7]. Conventional CT imaging gives a very accurate evaluation of the airway and the surrounding tissues [52]. However, radiation dose is a limiting factor for everyday use. On the other hand, CBCT imaging provides an adequate image quality with lower radiation doses and a shorter time of exposure [53]. The scanning procedure is executed with the patient in an upright position. It has been reported that the upper airway size and shape change depending upon the position of the body. Moreover, Ingman et al. found that no significant changes occur either in nasopharyngeal or in hypopharyngeal soft tissues between the upright and supine positions. However, they noted a significant narrowing of the oropharyngeal region in supine position [54].

Nowadays, the dominating evaluation tool for upper airway imaging is the lateral cephalogram. CT however has proved superior in eliminating any shortcomings that lateral cephalograms may present. Nevertheless, exposure to radiation and its potential hazards still raise many concerns [53]. In addition, with the use of DICOM (Digital Imaging and Communications in Medicine) viewer programs, hollow structures such as the airway can now be visualized in 3D. Therefore, a whole new set of possibilities in the area of airway research is lying ahead [55].

The relationship between airway volume and different craniofacial patterns has also been evaluated, including Class I, II, and III subjects [53].

Latest advances in CBCT technology have created a growing need for 3D imaging of the craniofacial structures. It is evident that novel volumetric studies have provided a new perspective on airway studies as well. For this reason, a detailed analysis of volume and shape of the airway through imaging technology may prove to be a valuable diagnostic breakthrough [51].

Relationship Between Craniofacial Morphology and Respiratory Function

The relationship between craniofacial structure and respiratory function has been investigated since the beginning of twentieth century [25]. Some authors directly correlate patients with abnormal respiratory patterns with lip incompetency, increased anterior face height, maxillary constriction, protruded maxillary incisors with Class II molar relationship, open bite, and narrow external nares, so called adenoid facies [56].

However, the direct relation of skeletal and dental malocclusions only to airway pathologies is quite insufficient. Studies have been conducted on subjects with various skeletal abnormalities and no related upper airway disorders. Ceylan and Oktay investigated the pharyngeal size on lateral cephalometric head films and reported that the oropharynx areas of patients with ANB <1° were larger compared to subjects with ANB >5° [57]. In another study by Kirjavainen et al., the upper airway of 40 patients with Class II malocclusion was compared to 80 children with a Class I molar relationship. They concluded that the children with Class II malocclusion had a wider if not similar nasopharynx than the controls but narrower oropharyngeal

(OP) and hypopharyngeal areas [58]. Martin et al. also stated that the lower pharyngeal dimensions were increased in patients with Class III malocclusion [59].

Joseph et al. noted that hyperdivergent patients had a narrower pharyngeal dimension especially in the nasopharynx at the level of hard palate and in the oropharynx at the level of the tip of the soft palate and mandible [60]. In addition, Grauer et al. observed that patients with long faces tended to have an extremely narrow airway, when compared to patients with normal faces [61].

It has been reported that OP area decreases with the increase of the ANB angle [57]. This finding may suggest that the length of the mandible contributes more to the size and volume of the OP than its position. This agrees with Trenouth and Timms who indicated that OP airway was positively correlated with the length of the mandible [62].

Tso et al. also mentioned that the most constricted cross-sectional area of the airway and the total airway volume were highly correlated [63]. Therefore, the detection of restriction in the upper airways is of major clinical importance in order to understand the metrics of the pharyngeal airway as well as the therapeutic plan.

When the length of the mandible increases, the tongue appears to lie lower in the floor of the mouth. Vig and Cohen also stated that the decrease in the size of the tongue within the oral cavity is partly due to differential rates of maturation of the skeletodental and muscular elements [64].

It has been mentioned in the literature that the pharyngeal airway width is not always associated with the type of malocclusion [7]. However, Kim et al. and Palomo et al. stated that the total airway volume of patients with retrognathia was significantly smaller compared to patients with normal anteroposterior relationship [53, 55]. Grauer et al. also confirmed that airway volume and shape differed among patients with different anteroposterior jaw relationships [61]. In a previous study by the same authors, the relationship between different angle classifications and airway volume was evaluated. It was found that Class II subjects had lower OP airway volumes, but the answer to which jaw was responsible remained unclear [53]. Finally, in a 3D study by Kim et al., it was reported that the nasal airway volume of the Class I subjects was bigger than the Class II subjects, but it was not significant [55].

Conclusion

Management of the airway is crucial in anesthesia. Difficulty or failure in airway management is the main cause of disability and mortality. Preoperative airway assessment is one of the most important parts of a physical examination by the anesthesiologist, where the anatomic parameters of the airways are determined to evaluate the extent of expected difficulty in intubation. Craniofacial morphology is one of the factors that can affect the upper airways. Obstructive processes of morphologic, physiologic, or pathologic nature of the visceral skull, such as hypertrophy of adenoids and tonsils, chronic and allergic rhinitis, irritant environmental factors, infections, congenital nasal deformities, nasal traumas, polyps, and tumors, are

predisposing factors to a blocked upper airway. Techniques that allow the precise diagnosis of changes in the upper airway considering their morphology and volume are fundamental to ensure a normal development of the craniofacial complex in growing subjects and the choice of an adequate treatment plan.

Acknowledgments The figures of the present study are a copyright of the author himself.

Conflict of Interest None declared.

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Upper Airway Ethnic Variations

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Abbreviations

ACB/HP	Anterior cranial base/horizontal plane
AHI	Apnea-hypopnea index
ANCOVA	Analysis of covariance
ARDS	Acute respiratory distress syndrome
ASP	Average sleep propensity
BMI	Body mass index
COPD	Chronic obstructive pulmonary disease
EEG	Electroencephalography
ESS	Epworth Sleepiness Scale
ETI	Endotracheal intubation
MPH	Hyoid and the mandibular plane
MRI	Magnetic resonance imaging
MS	Mallampati oropharyngeal score
NC	Neck circumference
OHS	Obesity hyperventilation syndrome
OSA	Obstructive sleep apnea
OSAHS	Obstructive sleep apnea-hypopnea syndrome
RDI	Respiratory disturbance index
ROC	Receiver operator characteristic curves
TMA	Thyromental angle
TMD	Thyromental distance
TV/MV	Tongue/mandibular volume
UA	Upper airways

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Introduction

The upper airway (UA) anatomic segment includes four major anatomic compartments:

- Two distinct inlet cavities:
  - The nasal cavity, functional during nasopharyngeal breathing
  - The counterpart oral cavity, functional during oropharyngeal breathing
- The pharynx
- The larynx
- The trachea, and its prime functional point of separation, the main carina, located at the lower end of the tracheal tube

Unlike the lower conducting airways, several of which are the main, lobar, and segmental bronchi, UA do not present collateral ventilation, and it is comprised of "extra-thoracic" as well as "intrathoracic" anatomic segments. The "upper thoracic inlet" stands as the conceivable point of demarcation. This particular structural distinction proves to be functionally crucial, regarding the overall assessment of such patients, suspected of suffering from any kind of UA anatomic malformations, or functional obstruction.

The global variety and structural differences of the UA tract demonstrate distinguishing anatomical features among the principal ethnic racial populations, such as Caucasian, African, Asian, etc. In order to facilitate the documentation and subsequently comprehend each ethnicity's unique structural functionality, expert physicians perform numerous, specifically determined measurements, calculations, and further systematic evaluation. Many reports throughout the years indicate that specific racial anatomical characteristics, mainly focusing on the variance of craniofacial structure among populations, present important conclusions while investigating individuals presenting almost identical functionality behavior, or furthermore similar clinical symptomatology. The ongoing progression of any eventual pathological manifestations undergoes detailed documentation, additional to systematic alongside performance of routine physical examination [1]. In order for the necessary measurements to be reliable and properly conducted, an investigator performs random individual calculations. Otherwise, the investigator performs separate identical documentations between specific time intervals, thus providing necessary "intra-observer reliability." Additionally, similar measurements repeat in random order on duplicate images, in a blinded fashion, at another investigational center, providing "interobserver reliability." Such UA measurements include the following:

Craniofacial and Soft Tissue Measurements

The individual sits upright in a chair, straight-backed, maintaining natural head position while looking straight ahead. The principal craniofacial measurements are discussed in below:

Principal Craniofacial Measurements

- *Neck Circumference (NC)*. The physician uses a common tape measure, focusing at the level of the cricothyroid membrane.
- *Thyromental Distance (TMD)*. The physician uses a modified tape measure, presenting vertical attachment, thus calculating the horizontal distance between the thyroid prominence and a perpendicular drop from the soft tissue mentum.
- *Thyromental Angle (TMA)*. The physician measures TMA according to the angle, formed by the soft tissue plane of the anterior neck and the counterpart plane between the soft tissue mentum and the thyroid prominence. The measurement takes place after taking a lateral photo of the head and neck, while the individual maintains natural head position, looking straight ahead. The camera equipment mounts on a camera tripod, having the front of the photo lens oriented vertically. The distance between the horizontal adjusted photo lens and the individual's left ear, while it focuses at the same time on the left ear tragus, is constant and fixed at 2 m (6 feet). The abovementioned preferred angle captures adequately the features of both, obesity and abnormal craniofacial skeletal structures.
- *Mallampati Oropharyngeal Score (MS)*. MS is measured after instructing the individual to hold breath during the end-tidal inspiration interval, maintaining the mouth open wide, while the tongue protrudes to its maximal potential, without attempting elevation of the soft palate or additional phonation. The MS indicates five levels—"classes"—which are classified as:
  - *Class 0*: Any part of the epiglottis upon mouth opening and tongue protrusion can be seen.
  - *Class I*: The soft palate, fauces, uvula, and pillars are visible.
  - *Class II*: The soft palate, fauces, and uvula are visible.
  - *Class III*: The soft palate and the base of the uvula are visible.
  - *Class IV*: The soft palate is not visible at all.

Additional Craniofacial Measurements

- Measured distance between the hyoid and the mandibular plane (MPH)
- Tongue/mandibular volume (TV/MV)

Complementary Measurement Means

Polysomnography

Each individual undergoes full overnight polysomnography, for a time interval none less than 12 weeks after the initial evaluation, while basic analysis and calculations take place in separate centers under specific recommendations and measurement techniques according to everyday usual practice [2]. Systematic monitoring is performed, including electroencephalography (EEG), electrooculography, electrocardiography, leg and chin electromyography, oximetry, measurements of the thoracic

cage and the abdominal peristalsis during respiration, as well as airflow measurements, such as oronasal thermistor, pressure cannula, etc. Other indicators, such as the "apnea-hypopnea index" (AHI), document continuous recordings for intervals which exceed at least 5 h of sleep time. "Apneic" status is defined as a complete cessation of airflow for 10 s, while "hypopneic" status indicates airflow reduction, regarding normal airflow for 10 s, accompanied with at least 3% of oxygen desaturation or additional cortical arousal.

Upper Airway Collapsibility Determination

During such measurements, every individual is placed in supine position, with nasal mask that is attached to a heated "pneumotachograph" alongside a differential pressure transducer for optimal airflow recording, under mild sedation. An additional pressure transducer calculates the applied mask pressure. A modified CPAP device, attached to the mask, delivers both positive and negative airway pressure. The aim is to record every subsequent vital reaction, thus evaluating each individual's tendency for maintaining regular respiratory functionality, or the potentiality against eventual pathological clinical manifestations.

Upper Airway Imaging

Most frequently, each individual undergoes the following:

- *Upper airway CT scan*, during quiet tidal respiration, in supine position, accompanied with neutral head positioning. The head is placed according to the "Frankfurt plane," defined from the inferior margin of the orbit to the superior portion of the external auditory meatus, perpendicularly set to the table.
- *Abdominal CT scan*, performed after the abovementioned upper airway CT scan, aiming to measure underlying visceral fat volume by tracing its contour, during maximum inspiration from the individual.
- *Magnetic resonance imaging (MRI), lateral cephalometry*, etc. MRI exam successfully demonstrates that patients suffering from "obstructive sleep apnea" (OSA) frequently present larger tongue/oral cavity lateral, compared to healthy individuals, while lateral cephalometry is responsible for indicating significant imbalance between maxillo-mandibular size and the tongue, a rather useful contributing fact toward manifestation of OSA. Additional measured imbalance between the oral cavity and the tongue led to positive predictive evaluation toward mandibular advancement splint.

The Commonest Indexes Regarding Anthropometric Measurements

- *Calculation of body mass index (BMI),* a measure of body fat, based on every individual's height and weight, which applies to adult men and women. Obesity may affect the modification of the UA tract, evolving to an enlargement of the participating soft tissues, most frequently the human tongue.

- The *Epworth Sleepiness Scale (ESS)*, which is a self-administered questionnaire, consisted of eight questions. Participants must rate, on a 4-point scale, from "0" to "3," their everyday possible chance of "dozing off" or falling asleep, while they are engaged occasionally, although not necessarily, every day in eight different specific activities [3]. The "ESS" score may range from 0 to 24. The higher the score, the higher the individual's "average sleep propensity" (ASP) in daily life.

Further Statistical Analysis

A properly selected statistical plan aims at determining the most reliable craniofacial and anthropometric calculations in order for the acquired results to apply predictive value toward potential pathological estimations and clinical manifestations. The investigator performs numerous "Hotelling's T^2 analyses," regarding ethnic groups, sex, and other clinical variables. Additionally, "receiver operator characteristic curves" (ROC) are useful for comparison regarding sensitivity and specificity. Other "cross-validation" data analyses, along with complementary "analysis of covariance" (ANCOVA), or the "Kolmogorov-Smirnov" test, aim to determine whether the relationship between selected clinical variables and overall analysis is statistically significant.

The abovementioned ethnic variations of the UA tract structure may also consist of a major cause that contributes to numerous pathological manifestations, acute or chronic. Such clinical evolvements may present themselves as:

- Common everyday symptoms, such as snoring and/or potential daytime hypersomnolence
- Other, more persistent symptomatology, such as apnea during sleep, accompanied with acute pharyngeal occlusion, a major contributing effect that leads to "obstructive sleep apnea-hypopnea syndrome" (OSAHS)
- Notable high measurements of BMI manifesting typical "obesity hyperventilation syndrome" (OHS), etc.

Clinical Challenges

Obstruction of the UA tract, whether acute (from several seconds to a few minutes) or chronic (evolving and established for weeks or months), may result in a catastrophe for humans. Chronic obstructive pulmonary disease (COPD) may also evolve because of acute respiratory distress syndrome (ARDS), following progressive critical narrowing of the UA tract that eventually causes the obstruction, or after recurrent bleeding and/or mucus plugging events [4].

Any significant degree of obstruction may manifest at every functional topographic level along the UA tract and result clinically in acute sense of asphyxia, progressive dyspnea, exercise intolerance, respiratory distress, and eventual death.

It should be emphasized that early realization and recognition and furthermore immediate treatment prove to be lifesaving.

The nasal and oral cavities are rarely a site of any kind of UA obstruction, due to their specific parallel functionality, except from individual events or clinical situations of any occurrence of a massive facial trauma. An eventual obstructive cause may be dynamic/variable or anatomical, whose early identification can define the optimal therapeutic plan and support.

A variety of causes may lead to acute UA obstruction, such as:

- Infection of the UA tract
- Foreign body or substance aspiration
- Hemorrhage
- Iatrogenic causes
- Hemorrhage
- Inhalation injury
- Blunt trauma
- Angioedema
- Neuromuscular diseases

When the physician suspects chronic UA obstruction, the commonest causes, regarding differential diagnosis, are:

- Infection of the UA tract
- UA malignancy and/or mediastinal tumors
- Post-ETI syndrome
- Collagen vascular diseases
- Sarcoidosis and/or amyloidosis
- Several UA vascular abnormalities
- Several esophageal disorders
- Laryngeal dysfunction or paralysis
- Idiopathic causes
- Etc.

General Demographic Characteristics

According to standard craniofacial measurements, men demonstrate larger NC and higher AHI than women, with the female proportion being partially greater among Caucasians. Women patients present smaller neck dimensions, resulting in less severe UA pathological manifestations, especially OSA. Individuals who suffer from such conditions demonstrate, in order of importance, significantly high MS, large TMA, similarly large NC, and high BMI. Such patients are usually older than other, healthier ones [5]. The abovementioned craniofacial features relate directly toward structural narrowing of the UA, a fact that contributes directly toward manifestation of UA obstruction. A crowded posterior oropharynx and a steep thyromental plane represent the most useful diagnostic and clinical markers, while they

remain strong prognostic factors, even after the physician achieves to correct at least two of the most important confounding variables, such as ethnicity and obesity.

When individuals display significant accumulation of adipose tissue, accompanied with established central obesity, as well as featuring measurements of short TMD of the anterior cranial base, final calculations result in a large TMA. TMD does not significantly differ between men and women, as well as between healthy subjects and registered patients. Usually, non-healthy individuals demonstrate elements of high-grade obesity, combined with craniofacial abnormalities, thus explaining the reason that TMA measurement emerges as one of the most important diagnostic predictors, especially in cases of OSA. High measurements of MS are also indicative of demonstrating crowded posterior oropharynx, probably caused by craniofacial abnormalities and/or intense obesity as well. High obesity measurements may be responsible for potential tongue enlargement, UA lengthening, as well as "caudal hyoid displacement," after calculating the distance between the hyoid and the mandibular plane (MPH) [6]. Eventually, high measurements of MS, combined with large TMA features, prove their interactive predictive significance, having already adjusted other additional factors, such as ethnicity, BMI, NC, and AHI cutoff values toward each subject. Similarly, NC and BMI measurements have proven themselves quite indicative predictive factors for UA established pathological conditions, most frequently OSA.

The already established clinical symptomatology does not participate in favor of eventual early prediction and/or diagnosis, as its reliability does not especially differentiate among patients and healthy individuals.

Several UA soft tissue and bony abnormalities present significant potentiality, regarding OSA prediction. Such features include the presence—or absence—of tonsillar, uvular, and/or tongue enlargement, combined with low-lying soft palate, lateral pharyngeal narrowing, as well as retrognathia. Eventually, tonsillar enlargement, accompanied with lateral pharyngeal narrowing, remains the strongest predictive factors. Other features, such as "cricomental space," defined by the perpendicular distance alongside the neck skin, from the midpoint of a conceivable line that eventually joins the cricoid to the mentum, as well as the "pharyngeal grade," represent reliable measurements of the craniofacial profile, in order to include and develop the necessary clinical algorithms toward early and accurate diagnosis. Subsequently, there are adequate criteria, regarding necessary final prioritization for polysomnography performance among candidates.

Understanding the importance of the UA functionality and evolution, physicians constantly attempt to predict any eventual degree of difficulty, regarding endotracheal intubation (ETI) and its relationship with the overall ethnic anatomical variations. Anesthesiologists constantly use the MS measurement, in order to correlate connection between soft tissues, the posterior oropharynx, and its skeletal constraints. TMD represents the position of the chin, relative to the thyroid cartilage, which also relates to the length of the anterior cranial base. MS and TMD additionally correlate with both difficult ETI and OSA. Furthermore, studies of the craniofacial features indicate that abnormal measurements associate significantly with the severity and evolution of OSA disordered breathing. Other features, such as modified MS and increased BMI without, though, distinctive TMD evaluation, also

accompanied with various sizes of the tonsils, have presented themselves quite accurately, regarding the possibility of difficult eventual ETI. The abovementioned measurements account for approximately 20% of the "respiratory disturbance index" (RDI) range, although they do not demonstrate considerable potential interaction between BMI and the overall UA structural differences.

The most frequently recorded anatomical abnormalities of the UA tract focus mainly on inferiorly positioned hyoid bones, posteriorly placed and more protruded maxillae and mandible, enlarged tongues and soft palates, as well as smaller velopharyngeal cross-sectional areas. These craniofacial abnormalities are the commonest, especially among patients that suffer from OSAHS, or other relevant UA pathologies. Obese patients of different ethnic populations commonly present crowded posterior oropharynx, accompanied with steep thyromental plane, compared to the healthier individuals. Physicians must immediately recognize such abnormalities, regarding a patient's craniofacial profile, and remain alert toward the possibility of eventual OSA, or other progressive pathological situations.

Ethnicity Variations

Recent interethnic studies presented efficient amount of data, regarding participation of craniofacial abnormalities and characteristics, in terms of calculating the obesity degree and predicting acute and/or chronic established UA pathological manifestations, especially regarding OSA. Each ethnic population may demonstrate different measuring indexes and results, despite eventual similar obesity calculations, while studies against probable UA collapsibility evolve because of imminent interaction among UA anatomical particularities. Ongoing functional evolution of the UA tract resulted in the portrayal of shorter and steeper cranial base. This is a rather unavoidable adaptation which, although it has led to significant facilitation of speech acquisition, has also probably increased predisposition and eventual development of UA pathological syndromes, as well as potential UA collapsibility.

Local cultures, associated with ongoing environment interactions, are particularly responsible toward evolving modification of the initial, original morphological characteristics of each ethnic population, such as body fat deposition, associated with nutritional factors, BMI, and other similar participant factors. The most indicative ethnic populations alongside their unique morphological and anatomical features are the following:

Caucasians

Individuals of Caucasian ethnicities present significantly larger UA soft tissue, especially indicating enlarged tongue dimensions, fat pad, and pterygoid volumes. They also present considerable degree of imbalance regarding soft tissues and bony structures, shown by the greater tongue/mandibular volume (TV/MV) ratio, and this indicates strong determinant toward UA potential collapsibility, which remains independent of waist circumference [7]. Western diet or nutritional habits strongly

contribute to considerably high BMI and obesity measurements. Other additional features, such as UA length, MPH, and visceral fat volume, are quite similar between Caucasian and South American individuals. The abovementioned indicators strongly suggest that the imbalance between soft tissue and craniofacial dimensions demonstrates a rather significant role, related to potential UA collapsibility among Caucasians. Regarding comparisons of the UA caliber, there are no major differences between Caucasians and Asians, relative to the size of the retroglossal airway, and their mandibular corpus length is greater than any other ethnic group. The anteroposterior relationship between the mandible and maxilla is considered normal.

Asians

Individuals of Asian ethnicity frequently present higher MS and larger TMA, while their TMD is smaller than Caucasian ones. Such subjects show significant tendency toward manifestation of severe cases of OSA, compared to Caucasians. There is strong evidence that shorter TMD in Asians is a strong indicator for retrognathia, possibly due to the existence of shorter anterior cranial base, something that affects directly the evolution of their small anteroposterior facial dimensions. Asians demonstrate bigger "ANB angle" (including subspinale/nasion/supramentale measure point), while the "anterior cranial base/horizontal plane" (ACB/HP) is smaller than the Caucasian counterpart [8]. They also present small mandibular depth and large mandibular total lengths and ramus, accompanied with greater mandibular widths, compared to Caucasians.

Obese Asian individuals express greater tendency toward pathological UA manifestations, although being less obese than Caucasians, presenting, at the same time, anteriorly positioned maxilla and mandible, with shorter anterior cranial base dimensions, compared to them. Asian subjects demonstrate shorter TMD, but they may subsequently present larger TMA, accompanied with steeper thyromental plane, especially regarding patients suffering from OSA.

In addition to a higher MS, craniofacial anatomical abnormalities manifest frequently, due to structural narrowing of the UA tract. Higher MS in Asians reflects toward more severe oropharyngeal narrowing, a fact which also explains the cause, provoking more severe OSA, compared with Caucasians, when they match for age and BMI. Asians are considered to present severe predisposal to OSA or other UA clinical pathologies due to their craniofacial bony restriction while presenting shorter cranial base length compared to Caucasians. Asian patients present steeper cranial base angle that approximates the spine and posterior pharyngeal wall to the posterior portion of the tongue, a structure that defines the anterior border of the pharynx, thus leading to potential pharyngeal narrowing, accompanied with eventual increased collapsibility. These populations demonstrate significantly lower measurements of BMI, a feature that is without doubt relative with the specific nutritional habits of this vast geographic territory, while unexpectedly these indexes appear to be quite similar, compared to the Caucasian counterparts.

Asian subjects also present considerably small "total airway volume" and "cross-sectional area," accompanied with small retropalatal airway, mean and minimum

"cross-sectional area," minimum anteroposterior distance, and finally minimum lateral distance. Such patients also demonstrate smaller total and retropalatal airway sizes for all measures, accompanied with small retroglossal airway volume measurements. Regarding soft tissue structures, Asian characteristics include large soft palate volume, although no significant difference in lateral wall volumes exists between them and Caucasian counterparts. The mandible measurement in reference to the maxilla results as more "retrognathic," while the maxilla is wide, accompanied with shallow maxillary unit depth and large maxillary divergence. Asian individuals present long "hyoid-to-C_3" and "hyoid-to-sella" distances, while the "retropogonion-to-C_3" distance is short. They also present larger upper and anterior facial height, compared to Caucasians, with similar measurements toward the "oropharyngeal" and "nasopharyngeal area." Such patients present narrow UA, especially the ones concerning the retropalatal region, with large soft palate volume.

Africans

Numerous reports have already indicated several important risk factors, such as obesity, OSA family history, male sex, cerebral palsy, and sickle cell disease. These severe pathological conditions prove quite responsible for such outspread in African populations, especially in children. Some US studies connect severe OSA with high percentage of manifestation among African-American young individuals. In comparison to similar measurements, compared to Caucasian children, the African-American ones demonstrate significantly smaller volume between the uvula and the epiglottis. These elements of data indicate that children of African ethnicity present considerable risk of suffering from potential additional cardiovascular consequences in young age, with increased possibility of suffering from residual disease. UA anatomical characteristics present important differences between these two ethnic groups. African children demonstrate considerably smaller tongue base and hypopharynx volumes, due to several established features, such as lingual tonsillar hypertrophy, macroglossia, and/or glossoptosis. The abovementioned morphological facts explain higher dominance of obesity markers and measurements in the United States of America [9]. Additionally, recent researches focus on discovering the impact of evolving tongue base/hypolaryngeal obstruction and its degree of participation, regarding the overall evolution of OSA, especially in children, in favor of selecting efficient predictive strategy against progressive clinical manifestation and potential related complications, compared to other ethnic populations.

South Americans

South American individuals are also associated with such anatomical features, as small maxillary, mandibular, and cranial base lengths than Caucasians, while the mandibular volume is greater in South Americans. Regarding several soft tissue features, like lateral wall thickness or parapharyngeal fat, these appear to be similar indicators for both ethnic groups, as well as complementary obesity-related

measurements, such as BMI, neck and waist circumferences, and visceral fat. Usually, such individuals demonstrate low BMI, combined with less abdominal obesity measurements and shorter waist circumference [10]. Cranial base angle is of significant importance, regarding small craniofacial bony dimension functionality of this ethnic group. The abovementioned features of South American populations do not indicate contribution toward eventual UA collapsibility, in contrast with Caucasian individuals, who present different risk predictors.

Conclusions

The key to eventually understanding the variance and subsequent importance of ethnicity-specific differences of each population group is to focus on studying each UA-related anatomical characteristics and features and their relationship toward progressive clinical pathological manifestation, in order to successfully predict and improve an optimal treatment plan and reduce evolution of any potential clinical complications. Physicians obtain significant working tools for calculation and optimization of all the necessary variants under study. This task may prove particularly difficult, when it takes place in remote territories without adequate means and/or equipment. Overall accomplishments, though, demonstrate rather important prognostic and diagnostic data, which have the ability to provide immediate treatment options and improve quality of life.

Conflict of Interest None declared.

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Upper Airway Humidification: Physiology and Clinical Implications

Filipa Torres Silva and Bebiana Conde

Humidity is defined as the quantity of water carried by a certain gas, in the current context, the inspired air [1]. It can be expressed by relative humidity (the percentage of water vapor contained in a gas, relative to its maximum capacity—%) or absolute humidity (the total amount of water in a gas (mg of water in liters of gas—mg/L)) [2]. When comparing values of humidity, the temperature must be considered, since the amount of water a gas can contain increases with the temperature [1].

One of the main functions of the upper airway is to heat the inspired air until it reaches core body temperature and to saturate it to body humidity [1].

While breathing at room temperature, the exhaled air (with body temperature of 37 °C) leaves the body at 32 °C, giving the trachea mucosa 5 °C and 10.3 mg H_2O/L of humidity, as it passes through the upper airway. In the inspiratory phase, colder and drier air is progressively warmed and humidified, in a renovating airway humidifying cycle (nearly 25% is recycled) [1, 2]. The nose constitutes the main area where the air is heated, optimized by its narrow circuit, which generates a turbulent flow, maximizing the heating, humidification, and filtering [2]. The optimal temperature (37 °C) and humidity (100% relative) are achieved, usually, 5 cm below the carina (close to the fourth and fifth bronchial generation), with variances according to the heat and moisture content of the inspired air [1, 2].

When we consider the delivery of medical gases, these have 0% humidity, increasing the mucus blanket viscosity and inducing cilia damage, which, in turn, promotes secretion accumulation, increased airway resistance, and predisposition to infection. The same concept is applied, when endotracheal intubation is performed, bypassing the physiological heating and humidifying structures [1].

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There are several consequences of insufficient humidification, when administering artificial gases (ventilation, for instance). In order to warm the cooler inspired air, the body is required a higher heat production and transference, causing a core temperature drop, more clinically significant in infants, whose body temperature regulation is delicate. The same conception can be applied to moisturizing of the drier air, with a consequent moisture loss and, ultimately, dehydration. This airway dehydration promotes epithelial damage and impaired function, directly proportionate to the length of ventilation with dry gases. The epithelial injury leads to sputum accumulation and basement membrane damage, with reduced tissue elasticity, inducing bronchiole collapse and consequent atelectasis. When lowering the optimal temperature and humidity point (more than 5 cm below the carina), the lung function is altered, with a compromise of the residual capacity and an increase in alveolar arterial oxygen tension difference, resulting in hypoxemia. Furthermore, in patients with hyperactive airways, the dry air acts as a powerful bronchoconstrictor [1].

Even though the insufficient humidification is damaging, the excessive artificial humidification is also hazardous, in an opposite manner, with heat gain (with airway mucosal burning) and moisture gain (with increased secretion volume, for instance) [1].

Thus, when ventilating a patient (invasively or noninvasively), achieving optimal humidification levels is of the utmost importance [2].

On the other hand, the environment temperature and humidity can influence the prevalence and severity of upper airway-related symptoms. Reinikainen and Jaakkola (2003) studied the effect of humidity and temperature on upper airway symptoms. They concluded, when the relative humidity is increased (either by augmenting the absolute humidity with a fixed temperature or lowering the temperature with a fixed absolute humidity), the nasal dryness and congestion are alleviated [3]. However, Andersen et al. (1972) postulate that there is no significant change in nasal mucus flow and secretion between a 10 and 70% relative humidity if the temperature is stable at 23 °C, showing that the temperature is a predominant factor in secretion regulation, rather than humidity [4].

The application of the abovementioned concepts in ventilation strategies becomes paramount, in order to improve patient adherence and ventilation efficacy.

When using positive airway pressure, a unidirectional airflow is promoted (caused by mouth leaks), inducing an upper airway mucosa dryness. This increases the mucosal blood flux as a compensating mechanism and, thus, enhances the nasal resistance and consequently the upper airway symptoms [5]. The higher pressure may also deform the respiratory tissue and close the secreting cells, compromising natural lubrication [6].

Zhu et al. (2018) investigated the role of heated humidification on positive airway pressure (PAP) therapy adherence, in patients with obstructive sleep apnea. In this meta-analysis, the authors concluded that the humidification did not improve compliance to the PAP therapy [5]. These results were independent of the presence of upper airway symptoms, even though many studies have showed a reducing effect of humidification on these symptoms [5, 7, 8]. They attributed these results to

statistical inability to associate the reduction of upper airway symptoms to increased PAP therapy compliance [5].

The upper airway humidification dynamics is multifaceted, with many possible interference features. Its disturbance can promote upper and lower airway symptoms and jeopardize the management of invasive and noninvasive ventilation. Therefore, a proper balance is vital, in order to maximize patient adherence and ventilation efficiency.

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Upper Airway Thermoregulation and Airway Resistance

Thomas Kanteres, Eleni Tzitzili, and Nikolaos Barbetakis

Introduction

Respiratory system is one of the main systems of the human body and is responsible for a number of very important functions such as oxygen supply, removal of carbon dioxide, removal of excess heat (thermoregulation), and vocal communication [1]. The respiratory system is divided into the upper respiratory tract and the lower respiratory tract.

The upper respiratory tract consists of the external and internal nose and the nasal and oral parts of the pharynx and extends to the pharyngeal opening of the larynx.

The lower respiratory tract consists of the lower part of the larynx, the trachea, the two main bronchi, and the two lungs.

Thermoregulation is the ability of an organism to maintain its internal body temperature constant, even when the ambient temperature is different. Temperature regulation is a type of homeostasis and a means of keeping the body's internal temperature constant, regardless of changes in ambient temperature [2]. Thermoregulatory control of blood flow to the human skin is crucial for maintaining normal body temperatures. Sympathetic nervous control of blood flow in the skin involves the noradrenergic vasoconstrictor system and the sympathetic active vasodilator system, which is responsible for 80–90% of skin vasodilation that occurs in a heat stress [3]. Thermoregulatory physiology maintains health by keeping the body's core temperature at about 37°C with a deviation of 1 or 2 degrees, which allows normal physiological function. Failure of neural thermoregulatory mechanisms or exposure to extreme and prolonged temperatures that overwhelm body's thermoregulatory capacity can lead to potentially life-threatening deviations from

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normal temperature [4]. In order for the body to maintain its homeostasis, it is necessary to constantly monitor internal parameters, such as temperature, blood pressure, and levels of certain nutrients. Each parameter has a specific set point, whose value fluctuates around normal range. The master switch that acts as a thermostat to regulate the body's core temperature is located in one area of the brain, the hypothalamus. If temperature is too high, the hypothalamus can initiate several processes in order to reduce it and cool the body [5]. Information in the hypothalamus is transmitted through both peripheral and central thermoreceptors, which are distributed at various locations along the human body. There are different thermoreceptors for cold and warm detection, transmitting the corresponding information to the hypothalamus [6].

Mechanisms and Thermoregulation

There are three mechanisms of thermoregulation: afferent sensing, central control, and efferent responses [2]. Afferent sensing works through various receptors located along the entire body and can recognize if the body's temperature is too hot or too cold. Central control of thermoregulation is determined and regulated by the hypothalamus. Efferent responses are behaviors that depend on temperature fluctuations, so that the individual adds or removes clothing according to his body temperature. In addition to this, efferent responses are automatic movements made by the body to protect itself against changes in temperature. These movements include sweating, vasodilation, and shivering [6–8].

The functions of the upper airway consist of thermoregulation, heat and humidity exchange, and filtering of breathing air. Despite the fact that many studies have been carried out on the functions and the exact role of the upper airway, even today their mechanisms are not fully understood. Different environmental conditions affect to a different degree the individual in terms of thermoregulatory mechanisms. More specifically and in regard to the upper airway system, the gradient of heat and moisture seems to alter depending on the environment. For example, people who live in tropical conditions are unable to use their upper airway for thermoregulation, because heat and moisture content of inhaled air approaches full saturation at the body's temperature resulting in compensatory mechanisms [9]. Another important parameter that contributes to thermoregulation in addition to environmental conditions is exercise. Many studies have demonstrated that the upper airway is able to adapt to different conditions in order to maintain the homeostasis of the organism. These conditions include and depend on the ambient temperature, the ambient relative and absolute humidities, the state of individual's airway, and his breathing volumes. The airway has the ability to adapt to different environments, including extreme weather conditions. The majority of individuals could adapt to extreme weather conditions preserving their homeostasis. However, the upper airway of some people is more sensitive, thus reducing the range of fluctuations to which it could adapt [10].

When thermoregulation is malfunctioning, many organs are affected, but the most important among others is the heart as well as other parts of the circulatory system. The heart could experience decreased or increased work as high temperature increases both heart rate and cardiac output. The circulatory system could experience intravascular volume depletion, the lungs could become impaired due to ARDS (which is caused by hyperventilation, hyperpnea, and pulmonary vasodilation), and the brain could experience edema or ischemia. In total, electrolyte abnormalities such as hypoglycemia, metabolic acidosis, and respiratory alkalosis could occur during fluctuations of temperature and malfunction of thermoregulation. On the other hand, decreased cardiac function is one of the main causal factors of thermoregulation dysfunction, since the heart is unable to adequately pump blood to the surface as a cooling mechanism [2]. In addition to this, dehydration is a condition which also affects thermoregulation. When there is insufficient intravascular volume, the blood viscosity increases and the body loses its ability for cooling [2].

One of the main compensatory mechanisms of the upper airway involved in the process of thermoregulation is bronchospasm. The definition of bronchospasm refers to the tightness of bronchi (airways in the lungs), which leads to wheezing, coughing, and other symptoms [11]. Bronchospasm is a natural reflex of the body which sets the limits that a person is able to withstand exposure to cold or hot environment. As the demand for heat and moisture exchange increases with minute and tidal volume, so the limits of compensation are reached. A very simple example to understand this defense and thermoregulatory mechanism is that many people are able to tolerate a cold morning with low temperatures and a lot of humidity, while some other people cannot tolerate exercise in such an environment. Thus, they reactively develop bronchospasm as a defense mechanism that simultaneously signals their upper airway to limit exposure to heat and moisture [9, 12]. The amount of heat lost from the airway depends on basic physical principles and more specifically on the mass of expired gas, its specific heat, and the change in its temperature. In addition to these principles, the latent heat plays a significant role in changing the state of water from liquid to vapor. The specific heat of dry air is relatively low and even if temperature change is large, a small amount of heat is lost in the dry air. This is a very important phenomenon on the basis of understanding the way in which the heating of cold gases from the airway is carried out without any injury. The explanation is based on the fact that the absolute humidity of the cold gas is low, resulting in relative less heat requirements [13]. On the other hand, heat loss depends to a greater extent on the amount of water vapor in the exhaled gases. Considering that the specific heat of water is much higher, more heat is lost from the airway when the absolute humidity of expired gases is high, and moreover, respiratory heat loss is more dependent on absolute humidity than on temperature [9].

Temperature fluctuations during the process of inhalation and exhalation have been known for several years. In a study where an attempt was made to map the different temperatures along the length of the tracheobronchial tree, using sensors placed from the upper respiratory tract to the final bronchioles with the help of a bronchoscope. The results show that at room temperatures, the air has a temperature

of approximately 32 degrees Celsius, then it increases up to about 35 degrees Celsius, and, as long as the ventilation process continues, the temperature of the air decreases. Corresponding fluctuations in temperature changes occur in situations where there is cold air in the environment, with the temperature values ranging from 20 to 31 degrees Celsius [14]. These results are very important and demonstrate that the breathing air undergoes significant changes in its temperature and humidity, leading to the conclusion that the upper airway and the lungs themselves have a key role in the body's thermoregulatory ability. In addition, considering the importance of the bronchospasm's function, it's easy to understand that some people can tolerate extreme environments, while others can't. The function of bronchospasm results in decreasing and narrowing of the diameter of the bronchi and bronchioles, which inevitably lead to less and less air moving through them. In this way, the organism acts protectively in order to maintain its homeostasis by not allowing cold air to enter the body, which would sharply reduce its internal temperature leading to several unpleasant consequences. The bronchospasm warns the person to breathe more slowly in order to allow the air entering the body to acquire higher temperature and more humidity or in another case to change the environment and move somewhere warmer so that the breathing process is tolerable [13].

Another very important function of the respiratory system is the loss of heat through evaporation, and therefore it is possible to maintain the homeostasis of the organism and contribute to its thermoregulation. The best methods of increasing evaporative heat loss are panting, sweating, and saliva spreading. Despite the fact that panting is not a part of the thermoregulation mechanisms of humans and large mammals, there are studies that show its contribution to heat loss in other animals, and, indeed, in certain species it represents one of the main mechanisms for heat loss. However, panting is a mechanism which is applied by humans in certain conditions contributing to heat loss. The main goal of large organisms such as humans is to maintain a low temperature and avoid overheating the thermosensitive brain. This is achieved because most heat exchange takes place at the nasal epithelial lining, and venous drainage is directed to a special network of arteries at the base of the brain, which creates an opposite flow of the heat and therefore cooling of the brain.

Respiratory Evaporation

Often, it is perfectly natural for the function of the respiratory system to be limited to gas exchange and to overlook very important functions, such as the regulation of acid-base balance, vocalization, and thermoregulation. In order for the gas exchange to take place, the humidification of inhaled air is necessary, while an increase in ventilation (frequency of breathing) will increase the respiratory evaporation as long as there is no humidification and cooling of the inhaled air [15]. From an evolutionary point of view, it is possible that panting and saliva spreading may have been among the first mechanisms of heat loss that appeared and that used the latent heat from the evaporation of water in order to increase the heat loss. However, in order to maintain the necessary requirements for maintaining gas exchange and pH

homeostasis, the alveolar exchange of oxygen and carbon dioxide must be controlled. Thus, the increase in ventilation will have to be limited to the dead space, where in practice air humidification takes place without compromising the exchange of gases in the alveoli, a condition that can be achieved by increasing the respiratory frequency and the corresponding decrease in the exhaled volume (definition of panting) [16]. In an attempt to compare the mechanisms of heat loss (panting and sweating), it is often concluded that although the movement of air on the moist surfaces of the bones of the nasal cavity helps in the evaporation of water and heat loss, in a way that is not generally available on the surface skin of sweating species, heat loss from the panting mechanism is limited by the increase in respiratory muscle heat production. However, studies have shown that the heat loss of panting, which was measured as the difference in oxygen consumption between the thermoneutral and thermolytic zones, was found to be zero (most efficient mechanism) [17, 18]. This conclusion seems to be strengthened by the opinion of Hales, who compared the distribution of cardiac output before and during exposure to heat, concluding that the increase in blood flow to the respiratory muscles during panting was compensated by the decrease of blood flow to certain non-respiratory muscles [19]. All this leads to the conclusion that since blood flow and oxygen consumption are matched, the metabolism of the respiratory muscle may indeed be increased, but the total energy consumption is reduced, since it is compensated by the reduced metabolism of other non-respiratory muscles. An additional feature that contributes to the high energetic efficiency of panting is that the maximum panting frequency occurs at the resonant frequency of the respiratory system [20]. Because panting frequency is inversely related to the organism size, it is possible to explain the observation that larger species use more the mechanism of sweating relative to panting as a strategy for increased heat loss through evaporation [21]. So one can easily assume that panting represents a primitive form of evaporative heat loss used by early mammals, which were small in size, and the subsequent evolution of larger species required the development of a complementary form of evaporative heat loss, namely, sweating.

The loss of heat and water through respiration depends to a great extent both on the humidity of the environment and the minute ventilation. In very cold environments, heat loss through respiration and evaporation is largely uncontrolled resulting in an increase in both metabolism and respiratory ventilation for the benefit of thermal homeostasis. Thus, for example, mountaineers at high altitudes who are in a hypoxic environment with increased respiratory ventilation and inhaling air of low humidity face a double threat of heat and water loss, which can lead to hypothermia and dehydration. On the other hand, a reduction in minute ventilation during exposure to low temperatures may lead to hypercapnia and increased oxygen extraction from inhaled air [22]. Therefore, the respiratory system participates and is part of a series of reactions to the thermal environment in various ways, including hypoventilation in the cold and hyperventilation in the heat. Despite the fact that increases in ventilation by the panting mechanism are largely confined to dead space, a small but detectable increase in alveolar ventilation leading to hypoxemia is inevitable. In the event that the heat loss from evaporation is insufficient and body temperature

continues to rise, the volume of respiration increases, while the respiratory frequency decreases with the result that the subsequent alveolar hyperventilation leads to the progressive development of profound respiratory alkalosis [16].

Finally, regarding the respiratory stimulus that leads the organism to hyperventilation, several studies have been carried out, mainly in animals, and several mechanisms have been proposed which are called to interpret if the hyperventilation comes from the exercise of the muscles themselves (it is directly dependent on the intensity of the exercise), if it is related to the increase in the levels of lactic acid in the blood, or if it is part of the body's thermoregulatory response. The results converged to the conclusion that as body temperature increases (hyperthermia), there is a shift in the control level or set point of the arterial PCO_2 that compensates for any homeostatic conflict between thermolysis and pH control. A corresponding study concluded that in conditions of normocapnia with the addition of carbon dioxide, the mechanism of panting is reduced with a simultaneous increase in tidal volume, leading to the conclusion that the response of the chemoreceptor threshold to carbon dioxide was reduced by hyperthermia. These changes in the respiratory threshold or sensitivity to arterial PCO_2 play a particular role in species that use the mechanism of panting as a primary solution to heat loss through evaporation. As for humans, it is accepted that there is little or no evidence for panting as a heat loss mechanism. However, the work of Cabanac and White showed that change in breathing rate only occurs when the body's core temperature has increased to a value greater than a threshold [23, 24]. As soon as threshold temperature is exceeded, hyperventilation follows. This temperature threshold is significantly higher than the corresponding thresholds for sweat and increased skin blood flow, leading to the conclusion that the respiratory response to hyperthermia may not be proportional to the response by the panting mechanism. The hyperthermic hyperventilation observed in species that use the panting mechanism, such as dogs and sheep, may be analogous to that observed in humans that do not use this mechanism, suggesting that it is a fundamental property of the respiratory system of all species [25].

Airway Resistance

The term airway resistance refers to the change in transpulmonary pressure required to produce one unit of gas flow through the airways of the lungs. In simpler terms, the difference between the pressure of the mouth and the alveoli of the lung divided by the flow of air corresponds to the resistance of the airway. There are various factors that can affect airway resistance such as airflow velocity, airway diameter, and lung volume.

The diameter of the airway is one of the most important factors that can affect the resistance of the airway. The flow contrast can be described by dividing the air pressure by the flow rate. However, in case the airflow is turbulent or stratified, the resistance of the air duct may also be affected. Under normal conditions the flow of the air in the lungs is laminar, so Poiseuille's law can be applied to measure the airflow ($Q = \pi Pr4/8\eta l$, where Q = flow rate, P = pressure, r = radius, η = viscosity,

and l = length) [26]. According to this formula, the change in the diameter of the air duct is very important as a decrease or increase in the diameter has the effect of changing the flow rate by four times. There are forces that act on the lungs that help them expand and opposing forces that promote lung collapse. The natural elasticity of the lungs, wanting to assume the smallest possible size, and the lung surface tension contribute to the collapse of the lung and the creation of atelectasis. Additionally, pleural pressure acts in a similar manner through gravity contributing to atelectasis. Based on this, one can conclude that the pleural pressure is greater at the base of the lung and smaller at the apex. Thus, the resistance of the airflow will be higher at the base and smaller at the top of the lung. The natural elasticity of the chest wall tends to pull the lung toward the periphery of the thorax and, therefore, contributes to the expansion of pulmonary parenchyma. Type 2 pneumocytes, which produce surfactant, a substance that allows the alveoli to stay open, are also contributing to the expansion of pulmonary parenchyma. Finally, the difference between intrapulmonary and intrapleural pressure helps keeping the airways open and allows air to pass through the terminal bronchioles and alveoli.

The maximum airway pressure corresponds to the pressure required to move air through the lungs when the patient is intubated under mechanical ventilation. The greater the pressure required, the greater will be the resistance of the airway. The plateau pressure is the pressure point that corresponds to the pressure of the alveoli and can occur by performing an inspiratory pause. Normal airflow resistance is about 1 cm/HO/L/s, mild obstructive disease is about 5 cm/HO/L/s, and > 10 cm/HO/L/s corresponds to severe obstructive airway disease. In mechanically ventilated patients, airway resistance is calculated by subtracting the maximum airway pressure minus the plateau pressure. A pressure difference smaller than 5 cm/HO/L/s is considered acceptable, whereas as the resistance increases, the gap between the two pressures will increase. With the use of alveolar pressure, it is possible to calculate the pressure needed in order to overcome the resistance of the airway and ventilate the patient. Since the airflow is directed from areas with higher pressure to the areas of lower one, a destruction of the alveoli implies that higher pressures must be applied in order to overcome the resistances and achieve ventilation of the lungs. A more accurate way to measure alveolar pressure is as follows:

$$\mathrm{PO} = \left(\mathrm{FiO} \times \left(P - P\right)\right) - \left(\mathrm{PCO} / \mathrm{RQ}\right)$$

PO is the alveolar pressures, FiO is the fraction of inspired oxygen (0.21 at normal room air), P is the atmospheric pressure (usually 760 mmHg at sea level), P is water vapor pressure in alveoli (usually 45 mmHg), PCO is the partial pressure from carbon dioxide (usually 40 mmHg), and finally, RQ is the respiratory quotient (usually 0.8) [27].

Lung volume has an inversely proportional relationship with airway resistance. When lung volume increases above functional residual capacity (FRC), this has minimal impact on airway resistance, which increases minimally. In the event that there is a reduction in functional residual capacity (FRC), airway resistance increases very quickly and approaches residual lung volume. One of the main factors involved in this process is the loss of lung elastic recoil. During the reduction of

lung volume, the elastic recoil of the lungs is reduced, which contributes to the maintenance of lung expansion. On inhalation, airway resistance decreases as the lungs and airways expand, while on exhalation airway resistance increases as the lung and airways deflate, narrowing the airways [28].

According to Bernoulli's principle, when a gas flows through a pipe whose diameter decreases, its flow velocity increases, while the pressure of the volumetric flow decreases (as long as the temperature and density of the air are kept constant). Under normal conditions, the airway is divided and becomes smaller and smaller, so in order to maintain volumetric flow, the flow velocity will increase with each further division of the airway, which leads to an increase in turbulent flow, resulting in greater resistance to the airflow. In clinical practice, this is particularly important when trying to ventilate a patient whose airways have either collapsed or contracted (bronchospasm) [29].

Thermoregulation and Airway Resistance

The role of the upper airway in maintaining body homeostasis and thermoregulation is a subject of constant study in recent years. It is known that inhalation of cold air can trigger bronchoconstriction, especially in asthmatic patients. The mucous membrane of the upper airway has a particular sensitivity to the effect of cold air. When the person is in an environment with cold air, various thermoregulatory mechanisms get activated, limiting the heat difference. Microclimate refers to the parameters of temperature, relative humidity, and wind speed, which affect the exchange of heat between the individual and the environment, while under certain circumstances it can hinder thermoregulation mechanisms. A typical example is the high humidity values during summer period, increasing a person's heat-related discomfort. The high concentration of water vapor in the atmosphere prevents the evaporation of water in sweat, exacerbating this feeling. This explains why in environments with high humidity values, some individuals tolerate less heat and perceived temperature discomfort than the actual ambient temperature. Wind can increase the feeling of discomfort associated with cold because it increases the rate at which body loses heat. Breathing cold air through the nose results in the swelling of the venous sinuses of the submucosa, which leads to nasal congestion, sneezing, and rhinorrhea, both in healthy individuals and in patients with pre-existing nasal inflammation. However, hyperpnea with cold air causes bronchoconstriction, especially in people with asthma, in children, and in young adults [30].

There are plenty of studies that try to explain this mechanism. In some of these, which were carried out on animals, it was shown that certain sensory receptors located in the lower airways are more sensitive to cold, causing bronchoconstriction. Vasoconstriction of bronchial smooth muscle vessels also appears to play a fundamental role in this mechanism. In addition to bronchoconstriction, hyperventilation with cold air causes coughing, especially in people with pre-existing sensitive upper airways. Cough and bronchoconstriction appear to be independent responses, since pretreatment with salbutamol prevents cold air-induced bronchoconstriction, while having no effect on cold air-induced cough [31]. Long-term

consequences and responses of the exposure to cold air include all airway alterations, both anatomical and increased bronchoalveolar lavage fluid granulocytes in healthy humans, loss of squamous epithelium of the respiratory mucosa, thickening of the lamina propria with increased concentrations of inflammatory cells, hyperresponsiveness, and airway obstruction [32]. Finally, it appears that reflex bronchoconstriction induced by cooling of the face or upper airway is too mild to cause respiratory distress in a person with normal lung function. However, in individuals with severe lung function impairment, these responses may have particular clinical significance [33]. The respiratory system is affected by exposure to cold air, as inspired air has to be conditioned before participating in peripheral lung gas exchange, with an associated loss of heat and water. Exposure to cold air can cause significant changes in the airways even in people without respiratory system diseases. When a person is exposed to cold air, the number of granulocytes and macrophages in the lower airways increases. Additionally, an infection of the respiratory system associated with cold air can disrupt the clearance of contaminants from the respiratory mucosa, disrupting the function of an important defensive mechanism. It is a fact that in environments with extremely low temperatures, people tend to congregate in closed spaces, resulting in the transmission of infectious diseases and subsequent damage to the airways [34].

Conclusion

Although upper airway is considered to be a part of the respiratory system that contributes to the process of breathing, it is proven throughout the years that this structure is involved in and is one of the main components of complex tasks such as thermoregulation, filtering of breathing air, and vocalization. Another very important function of the upper airway is the heat exchange which is achieved through evaporation, driving heat loss and therefore contributing to body homeostasis. Additionally, upper airway has the ability to change its diameter and its resistance to the airflow (airway resistance), and this particular function is one of the main defensive mechanisms that is involved in the process of thermoregulation, especially in individuals exposed to cold air environments. Despite the fact that many studies have focused on the functions of the upper airway and its role in thermoregulation, even today its exact role is not fully understood, and further research is needed.

Conflict of Interest None declared.

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Work of Breathing in Upper Airway Respiratory Failure

Bruno Matos Gomes

Introduction

NIV is the process of supporting respiration using devices that do not require an artificial airway.

Since the *1940s NIV* has been used to treat patients with acute respiratory failure, and nowadays there many other indications in the acute or chronic patient. The main difference between *NIV* and invasive mechanical ventilation is the existence of an artificial airway.

The Upper Airway: Basic Anatomical and Physiological Concepts

The airway, or respiratory tract, describes the organs of the respiratory tract that allow airflow during ventilation. The airway can be subdivided into the upper and lower airway.

The upper airway consists of the nose and nasal cavity, the pharynx, and the larynx. These structures allow us to breathe and speak.

The nasal cavities are chambers of the internal nose; the posterior region leads into the nasopharynx and to the pharynx. The region is defined as a mucous membrane-lined portion of the airway between the base of the skull and the esophagus.

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Finally the larynx is the portion of the airway between the pharynx and the trachea. Formed by a cartilaginous skeleton of nine cartilages, it includes the epiglottis and the vocal cords which are the opening to the glottis.

The muscular aspect of the upper airway is crucial and it is related to the action of swallowing. The muscles of the pharynx and larynx provide the structure and support of the upper airways and are composed of striated muscles under visceral and somatic control.

The innervation of these structures is via cranial nerves, so the pharynx is innervated by cranial nerves VII, IX, X, and XII, and the larynx is supplied by the vagus nerve (cranial nerve X).

The importance of the upper airway assessment is paramount in both emergency, respiratory, and anesthetic scenarios. Lack of airway management in situations where it may be required can lead to reduced blood oxygen levels in individuals and can be life-threatening.

Considering all of these, the upper airway has a critical role in the normal respiration, involving a highly detailed neurophysiologic process that allows the airflow to reach the lower airway.

Regarding the anatomical concept of *NIV*, it is applied on the oronasal pharynx which connects to the esophagus as well as the trachea. Despite the presence of gastroesophageal sphincters, high positive esophageal pressures can lead to gastric distention and an increased risk of aspiration.

In sum and according to several studies aiming the factors that contribute to *NIV* failure, the main causes are a low experience medical team and patient–ventilator asynchrony.

The Work of Breathing: General Concepts

Work of breathing (*WOB*) is defined as the amount of energy (O_2 consumption) needed by the respiratory muscles to produce enough ventilation and respiration to meet the metabolic demands of the body.

Under normal resting circumstances, the *WOB* is about 5% of $V.O_2$ max. In individuals with pulmonary problems, *WOB* may exceed 50% of $V.O_2$ max, reducing their energy reserve and exercise capacity and stressing other systems to compensate.

WOB varies according to the metabolic demands aiming adequate ventilation. The *WOB* could be more or less demanding depending by how much force the respiratory muscles must exert to overcome the resistance to airflow to deliver an adequate lung volume each respiratory cycle. The final determinant of *WOB* is the respiratory rate, which defines how hard and how fast the respiratory muscles must contract to generate force.

Impact of the Upper Airway Respiratory Failure on the *WOB*

Acute respiratory failure is caused by a wide range of etiologies. Therefore, one of the primary goals of airway management is to provide adequate ventilation and oxygenation.

Upper airway obstruction may occur from anatomical causes such as choanal atresia, pathological causes such as a tonsillar abscess, or adverse effects from patient management such as loss of airway patency during the administration of sedation and/or analgesia. It is important to recall that, according to the *British Thoracic Society* (BTS) guidelines on *NIV*, having a fixed airway obstruction is an absolute contraindication to use *NIV*.

There are also subsets of patients that are more prone to develop upper airway obstruction. The muscles of the upper airway are under both voluntary and involuntary control. Their function is affected by sleep, which abolishes voluntary control which can lead to suppression of involuntary or reflex control of the muscles. As a result, upper airway function is vulnerable during sleep, and respiration is predisposed to dysfunction in that state; specially patients with obesity are at significant risk for upper airway obstruction due to altered upper airway anatomy. Pharyngeal tissues have increased fat deposition causing excess upper airway tissue and an increased likelihood of pharyngeal wall collapse resulting in airway obstruction. This can be exacerbated when patients have other comorbidities, such as *obstructive sleep apnea (*OSA) and/or *obstructive hypoventilation syndrome* (OHS).

The literature available about the impact of the upper airway respiratory failure on the *WOB* is limited; however there are a few studies that can provide us more knowledge about this matter. *Oppersma* et al., *in 2013*, published a paper called "Noninvasive ventilation and the upper airway: should we pay more attention?" in *Critical Care journa*l. The investigators referred to a previous paper that studied (T*ela* et al. *in 2001 – Modulation of laryngeal and respiratory pump muscle activities with upper airway pressure and flow*) the effect of pressure and flow in isolated piglet upper airway. They concluded that the presence of negative pressure in the upper airway and flow during inspiration results in phasic respiratory activity of the posterior cricoarytenoid muscle above tonic levels, which results in glottic widening during inspiration and reduces resistance to airflow allowing the inspiratory muscles to unload. Positive pressure and flow during expiration results in phasic activity of the thyroarytenoid muscle, resulting in glottic narrowing and therefore increased resistance to the expiratory flow. Accordingly, this study shows that, at least in an animal model, respiratory flow patterns affect the activity of the upper airway muscles.

Oppersma et al. concluded that respiration and in particular patency of the upper airway rely on a complex relation between several inhibitory and excitatory pathways. Physical conditions such as pressure, flow, and temperature affect upper airway patency. *NIV* may affect these physical characteristics and therefore affect patency of the upper airway.

There is a study with interesting results called the *Work of breathing during spontaneous ventilation in anesthetized children: a comparative study among the face mask, laryngeal mask airway and endotracheal tube* from Keidan et al. and published in the *Anesthesia & Analgesia* journal. They concluded that the inspiratory *WOB* using general anesthesia in spontaneously breathing children was markedly increased with a face mask without oral airway as a result of narrowing of the pharyngeal airway. The insertion of an oral airway significantly decreased *WOB* by improving the patency of the upper airway. An addition of relatively low *CPAP* (5–6 cm H_2O) significantly decreased *WOB* with all three airway apparatuses. This decrease in *WOB* was apparently a result of further improvements of upper airway patency, probably because of stenting of the pharyngeal airway against collapse by inspiratory negative pressure.

EPAP (expiratory positive airway pressure) is the pressure delivered by the ventilator while the patient is exhaling.

EPAP assists with maintenance of the upper airway patency in sleep, which may be important in patients with an unstable upper airway (*OSA*) and helps to recruit/maintain lung volume, improving oxygenation.

Pathophysiological Implications of *NIV* in the Upper Airway

The use of *NIV* has increased over the last years in patients with acute respiratory failure due to the reduction of the complications related to invasive ventilation. As said before, the main difference between invasive ventilation and *NIV* is the role of the upper airway.

However, failure rates of *NIV* range between 5 and 50% and most of these patients require endotracheal intubation.

Despite medical evolution in respiratory support, the pathophysiology of *NIV* failure is incompletely understood.

During *NIV* the patency of the upper airway plays a critical role in the efficiency of delivered ventilation.

Keeping in mind that the main goal of *NIV* is to decrease the work of breathing and by that improving oxygenation and ventilation of the patient, we must identify and correct the patient–ventilator asynchronies.

A careful selection of patients, a properly timed intervention, and a comfortable and well-fitting interface will reduce the air leaks allowing the adequate supply of volumes and pressures to the patient.

These leaks can also affect triggering sensitivity and patient–ventilator synchrony during flow delivery and breath cycling.

Final Thoughts

Recalling *Oppersma* et al.'s study, the data on the effects of *NIV* on upper airway physiology in patients with acute respiratory failure is very limited.

Nevertheless, they emphasize the synchrony with the upper airway muscles in ventilator cycles, because it will improve efficiency of ventilation. Upper airway patency is linked to neural respiratory drive. Therefore, improved synchrony between the ventilator and respiratory drive may improve ventilation partly by limiting wasted ventilation at the level of the upper airway. They concluded that, currently, it would be preliminary to provide recommendations on how the level of assist, level of positive end-expiratory pressure, and flow pattern should be adapted to enhance patency of the upper airway in patients with acute respiratory failure.

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Noninvasive Positive and Negative Pressure Effects in Upper Airway Respiratory Failure

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Introduction

Noninvasive ventilation (NIV) is becoming more common in patients with acute respiratory failure, such as exacerbations of chronic obstructive pulmonary disease or acute heart failure [1]. One of the main goals of NIV is to prevent endotracheal intubation, which reduces the risks of invasive ventilation [2]. NIV failure rates range between 5% and 50%, with the majority of these patients requiring endotracheal intubation.

The endotracheal tube bypasses the upper airway during invasive ventilation, and the cuff of the endotracheal tube creates an airtight seal in the trachea. On the other hand, the upper airway may affect how ventilation works during NIV [1].

Upper Airway

The nose, oral cavity, pharynx, and larynx make up the upper airway. The upper airway is used for chewing, swallowing, speaking, and smelling, and its principal roles are to act as an air conductor, humidify and warm the inspired air, and keep foreign materials out of the tracheobronchial tree [3]. The nose and oral cavity are

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mostly static in their conducting role, but the pharynx and larynx are mostly muscular organs that can change the upper airway's patency [4].

During inspiration, glottic constriction increases upper airway resistance, which may impede effective breathing.

The presence of negative pressure in the upper airway and flow during inspiration results in a phasic respiratory activity of the posterior cricoarytenoid muscle above tonic levels, which results in glottic widening during inspiration and decreases resistance to airflow in isolated piglet upper airways. The inspiratory muscles are successfully unloaded as a result of this response. During expiration, positive pressure and flow cause phasic activation of the thyroarytenoid muscle, which causes glottic constriction and hence higher resistance to the expiratory flow. As a result, at least in an animal model, respiratory flow patterns influence upper airway muscle activity [5].

The upper airway is a collapsible tube vulnerable to closure during breathing because this region of the breathing apparatus is surrounded by a complex anatomical arrangement of skeletal muscles and soft tissues, unlike other regions of the respiratory tract such as the trachea and bronchi that are supported by a more rigid cartilaginous structure. The muscular and soft tissue composition of the pharyngeal airway provides the necessary support for a variety of essential non-respiratory functions such as vocalization, suckling, chewing, and swallowing, i.e., behaviors that require dynamic changes in airway size to move air, liquids, and solids. However, this property of a collapsible tube compromises the essential respiratory function of the upper airway; the airway must remain open during breathing, in all postures, to allow for adequate lung ventilation and gas exchange [5].

From a mechanical standpoint, the upper airway behaves as a Starling resistor, in which the pharyngeal airway represents the collapsible segment and is situated between two noncollapsible structures (larynx and nasopharynx). The flow pattern depends on the forces applied inside and outside the collapsible segment. The transmural pressure gradient is the net pressure difference between all of these opposite forces. The collapsing forces are represented by the negative inspiratory transmural pressure gradient and the pressure applied by upper airway tissue. The contraction of upper airway stabilizing muscles (upper airway dilators) is the main dilating force, the other being represented by tracheal traction. So, the amount and timing of the neuromuscular activation process of the muscles that help keep the upper airway stable, as well as the mechanical properties of the tissues in the upper airway, play a big role in deciding how stable the upper airway is [6].

Apart from the influence of the extent of phasic activation of upper airway muscles, the dynamic profile of this phasic activity plays a key role in the maintenance of upper airway patency. The upper airway muscles are activated first and reach their peak value before the respiratory muscles. Phasic activity and the preactivation delay increase with increasing central respiratory activity and with decreasing upper airway pressure. This activation pattern decreases upper airway resistance and prevents upper airway inspiratory collapse. The occurrence of upper airway obstruction in normal awake subjects when this preactivation of upper airway stabilizing muscles is lost (as with diaphragmatic pacing, phrenic nerve stimulation, or iron

lung ventilation) further supports the importance of the upper airway muscle preactivation pattern in maintaining upper airway patency. The link that exists between ventilatory and upper airway stability could result from the common activation process of respiratory and upper airway stabilizing muscles originating from the central pattern generator that would be responsible for the fine-tuning in the amplitude and activation pattern of these different muscle groups [6].

The Upper Airway's Interaction with Noninvasive Ventilation

In awake lambs, the influence of NIV on glottal constrictor (thyroarytenoid) and dilator (cricothyroid) muscle activity was studied. Both the thyroarytenoid and cricothyroid muscles are active during spontaneous breathing, with the thyroarytenoid muscle activity peaking at the end of inspiration. However, when pressure support is used during NIV, inspiratory cricothyroid activity decreases, but thyroarytenoid muscle activity increases. As evidenced by respiratory inductance plethysmography [7], this causes glottal constriction and limited breathing.

A subsequent study demonstrated that increased glottal constrictor muscle activity during NIV depends mainly on the activation of bronchopulmonary receptors. After a bilateral vagotomy, the increase in inspiratory activity of the thyroarytenoid muscle that was seen before when the support got stronger during NIV did not happen [8].

In humans, there is limited evidence of a similar response to NIV. Rodenstein and colleagues subjected healthy volunteers to escalating amounts of NIV assistance while monitoring their glottis with a fiber-optic bronchoscope. The narrower the glottic aperture and the greater the airway resistance, the higher the amount of support. This effect resulted in a gradual decline in the percentage of tidal volume reaching the lungs, which was attributed at least in part to the glottis' behavior [9]. In conclusion, research on both animals and people shows that positive pressure breathing makes the upper airways less open when trying to breathe in.

Maintaining Airway Patency in the Upper Airway

The upper airway collapse in patients with obstructive sleep apnea is a typical indication of NIV (either with PEEP or as simple CPAP). According to the fundamental physiologic concept, positive upper airway pressure splints open the collapsed upper airway structures during sleep. Even though adding inspiratory positive pressure can help some people, CPAP on its own is often enough for most.

Positive pressure and negative pressure techniques are used to provide noninvasive ventilation. Positive pressure is put on the airway to directly fill the lungs with air, and negative pressure is put on the abdomen and thorax from the outside to pull air into the lungs through the upper airway.

By avoiding intubation, the risk of upper airway trauma, patient discomfort, and the need for sedation are all reduced. It also keeps the airway clear and helps the

patient swallow; it also allows oral patency and intermittent ventilation, which lets the patient eat, drink, and talk normally. It also lets the patient take breaks from ventilation, which lets them eat, drink, and talk normally [10].

Monitoring Muscles of the Upper Airway

During mechanical ventilation, the need for monitoring inspiratory muscle activity has been emphasized in the literature [11]. Less is known about the role of upper airway activity monitoring during NIV. This is likely because it is hard to see how these patients' upper airways work.

Activation of intrinsic laryngeal muscles alters glottis opening, which affects flow resistance into and out of the lungs. Because the phasic activity of upper airway dilator muscles goes up when breathing is restricted, like in patient-ventilator asynchrony, it could be clinically important to watch how upper airway dilator muscles work when breathing in [12].

MR imaging with tagging of the upper airway in healthy patients revealed that not only the genioglossus muscle but also nonmuscular soft tissues surrounding the upper airway move before the commencement of inspiratory flow. The movement of particular reference sites on the genioglossus muscle was greater during normal inspiration than during loaded inspiration, suggesting that the increased muscle activity during loaded inspiration causes rigidity of the upper airway rather than dilatation [13]. Furthermore, it has been proven that nonmuscular soft tissue movement impacts upper airway patency. The movement of nonmuscular soft tissue and the activation of the genioglossus muscle have a complex interplay.

Although electromyography of laryngeal muscles (such as the genioglossus or cricothyroid muscle) is possible during NIV [14], electromyography does not provide information on nonmuscular soft tissue movement. As a result, additional procedures should be utilized to assess upper airway patency. Magnetic resonance imaging is the most reliable way to get information, but it is also the most expensive and takes the most time, especially for people with NIV.

Although the upper airway can be viewed with ultrasound, the utility of using this technology to measure upper airway patency has not been investigated [14]. Endoscopy has also been used to measure upper airway patency, but it should preferably be utilized at several levels in the upper airway.

Conclusion

Future research and clinical relevance increasing the success rate of NIV are critical from a clinical standpoint. In contrast to invasive ventilation, NIV relies heavily on the upper airway as a conductor of air. Recent research shows that during NIV, it is important for the ventilator to have synchronization with the muscles in the upper airway to make sure there is enough ventilation.

The effects of NIV on upper airway physiology in patients with acute respiratory failure are currently unknown. When the ventilator cycles in time with the upper airway, it is fair to predict that ventilation efficiency will improve. The neuronal respiratory drive is linked to upper airway patency. As a result, better synchronization between the ventilator and respiratory drive may increase ventilation by reducing wasted ventilation at the upper airway level. At this time, it would be premature to provide recommendations on how to adjust the level of assistance, the level of positive end-expiratory pressure, and the flow pattern to improve upper airway patency in patients with acute respiratory failure [7].

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Part II

Upper Airways Noninvasive Ventilator Management

Nasal High Flow: Rationale and Indications

Zuhal Karakurt and Erdem Yalçınkaya

Patients with Upper Airway Disorders: Nasal High Flow—Rationale and Indications

Nasal high flow (NHF) includes the administration of warmed, humidified air at a flow rate of up to 60 L/min for adults and 8 L/min for newborns, which may be infused with oxygen [1]. NHF increases expiratory resistance as nasal cannula size increases, but by a decrease in inspiratory effort of breathing, respiratory rate, and minute volume, it can lower the work necessary to overcome upper airway resistance [2–4]. Respiratory failures caused by abnormalities of the upper airway may necessitate high-flow nasal assistance. Despite the significantly changed geometric configuration of the upper respiratory tract during NHF, efficient gas cleansing persists. In the upper airway space, gas is cleared more quickly from the front nasal cavities than the posterior nasal cavities, and this is proportional to the NHF rate [5]. Clearing the nasal portion of the anatomical dead space with NHF therapy is a quick process that can substantially reduce CO_2 rebreathing [5].

NHF uses are as follows:

1. After extubation
2. Hypoxemic respiratory failure with upper airway disorders
3. Sleep breathing disorders (obstructive sleep apnea [OSA])
4. Swallowing disorders
5. Combination delivery of aerosolized drugs into the airways
6. Tracheostomized patients

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NHF Use After Extubation

The use of NHF instead of traditional oxygen support following extubation significantly reduces the rate of reintubation in the first 72 h due to all-cause and respiratory failure in patients at low risk of reintubation, according to a randomized, controlled research [6].

The criteria for low reintubation risk are as follows:

1. Age under 65
2. The absence of heart failure as the key indication for mechanical ventilation [7, 8]
3. The absence of severe to moderate chronic obstructive pulmonary disease [9]
4. Less than 12 points on the Acute Physiology and Chronic Health Evaluation (APACHE) II on the day of extubation [7, 8]
5. A body mass index of less than 30 (determined by dividing weight in kilos by height in meters squared) [10, 11]
6. The lack of airway patency issues, including a high risk of developing laryngeal edema [8]
7. The capacity to control respiratory secretions (sufficient cough reflex or suctioning), as well as a significant risk of developing laryngeal edema [8]
8. The capacity to control respiratory secretions (sufficient cough reflex or suctioning 2 in 8 h)
9. Simple weaning, less than two comorbidities, and no prolonged mechanical ventilation, defined as greater than 7 days [12]

After extubation, physicians should prefer respiratory support with noninvasive mechanical ventilation (NIMV) over NHF for patients with persistent hypercarbic respiratory failure, patients receiving long-term NIMV at home, and hypercapnia development after a T-tube trial for spontaneous breathing [11].

NHF Use in Hypoxemic Respiratory Failure with Upper Airway Disorders

In acute and progressive hypoxemic respiratory failure (PaO2/FiO2 200 mmHg), the use of NHF and NIMV may fail, and the risk of intubation and mortality is increased [13]. For acute hypoxemic patients who require a higher airway pressure due to respiratory muscle fatigue, NHF cannot offer the same mean airway pressure as NIMV, which is associated with a twofold risk of intubation [14].

Recent ERS Task Force for Clinical Practice Guideline for the use of high-flow nasal cannula in acute respiratory failure has been published [15]. In this guideline, the risks and benefits associated with the administration of NHF in several clinical settings, such as hypoxemic, hypercapnic acute respiratory failure, postoperative and post-extubation acute respiratory failure, and pandemic related to SARS-CoV-2 pneumonia (COVID-19), were evaluated [15]. This guideline summarizes the use of NHF in eight recommendations suggesting using (1) NHF over conventional oxygen therapy in hypoxemic acute respiratory failure (*conditional recommendation,*

moderate certainty of evidence), (2) NHF over NIMV in hypoxemic acute respiratory failure (*conditional recommendation, very low certainty of evidence*), (3) NHF over conventional oxygen therapy during breaks from NIV *(conditional recommendation, low certainty of evidence)*, (4) either NHF or conventional oxygen therapy in postoperative patients at low risk of pulmonary complications *(conditional recommendation, low certainty of evidence),* (5) either NHF or NIV in postoperative patients at high risk of pulmonary complications (conditional recommendation, low certainty of evidence), (6) NHF over conventional oxygen therapy in nonsurgical patients at low risk of extubation failure *(conditional recommendation, low certainty of evidence)*, and (7) NIV over NHF for patients at high risk of extubation failure unless there are relative or absolute contraindications to NIV *(conditional recommendation, moderate certainty of evidence)* and (8) trialling NIV prior to use of NHF in patients with chronic obstructive pulmonary disease (COPD) and hypercapnic acute respiratory failure *(conditional recommendation, low certainty of evidence)* [15].

NHF Use in Sleep Breathing Disorders (Obstructive Sleep Apnea [OSA])

Obstructive sleep apnea (OSA) is occurring during sleep when upper airway collapses associated with intermittent hypoxemia in both adult and children. Due to upper airway collapse, administering continuous positive airway pressure (CPAP) seems to be most effective treatment. However CPAP adherence is suboptimal for some OSA patients; in this circumstance, the use of HFO can keep open and hydrated the upper airway during sleep, increasing compliance in both adult and children with OSA [16–19]. OSA patients can well tolerate when flow rate is 18 L/min and decreased ratio of both for apnea-hypopnea and oxygen desaturation: The percentage of slow-wave sleep significantly increased, and quality of sleep was better [19]. In obese patients with OSA, the use of 20 L/min flow with 40% oxygen concentration in pre-post-operational period with head of bed elevation can be an alternative respiratory support in which standard care and CPAP therapy are denied, or unsuitable [20].

NHF Use in Swallowing Disorders

During ischemic stroke, swallowing can be impaired. For acute respiratory support, CPAP compliance was poor and under CPAP the cerebral blood flow is uncertain [21, 22]. In those patients the use of nasal CPAP may lead to inhibit swallowing functions and increase risk of aspiration pneumonia [23, 24]. NHF oxygen therapy at the therapeutic flow rate (50–60 L/min) is beneficial in lowering OSA severity in post-acute ischemic stroke patients fed via a nasogastric tube, particularly when OSA severity is moderate to severe [25]. Due to low acceptability, NHF oxygen therapy may be a temporary therapeutic option for OSA, and nasal CPAP therapy is recommended after dysphagia improves and nasogastric tube is removed [25].

NHF Use During Combination Delivery of Aerosolized Drugs into the Airways

During NHF therapy, bronchodilator medications could also be used. Nebulizers positioned within an NHF circuit just upstream from the humidification chamber have the potential to facilitate the delivery of clinically significant quantities of aerosol to the lungs [26]. It is expected that this technique of nebulization will create a bronchodilatatory effect in adults during normal breathing; however, this effect may also be produced in rapid inspiratory flows, such as those encountered during respiratory distress [26]. Because there would be no additional gas flow to potentially interfere with the inspired oxygen fraction, it seemed as though the use of a vibrating mesh nebulizer would be appropriate for this purpose. On the other hand, a jet nebulizer is an option that could be examined [26]. These findings could provide the groundwork for future clinical investigations into the efficacy of nebulization during NHF in adult patients.

NHF Use in Tracheostomized Patients

When high-flow oxygen is delivered through a tracheostomy (HFOtracheal), its effects differ, and this effect has not been well described [27, 28]. Recently, a randomized crossover study was conducted to evaluate the effects of HFOtracheal uses at different gas flow rates on gas exchange, tracheal pressure, and respiratory rate, as well as to determine whether the increase in airway pressure generated by high-flow oxygen is different when administered via nasal cannula or tracheostomy [29]. This study demonstrates that HFOtracheal has milder effects than HFOnasal. The researcher stated that the interface is entirely accessible. Limiting the negative swing in inspiratory airway pressure is possible with HFOtracheal, but the dead space washout and creation of positive expiratory pressure are limited. The findings of this study indicate that a minimum gas flow rate of 50 L/min should be used during HFOtracheal in order to significantly increase oxygenation and decrease respiratory rate compared to normal oxygen. In tracheostomized patients, resistance is reduced and pressure created is negligible. This matter ought to be investigated further.

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Noninvasive Ventilation: Rationale and Indications

Ana Rita Catarino Ferro

Noninvasive ventilation (NIV) refers to the delivery of ventilatory support into the lungs without an invasive artificial airway (endotracheal tube or tracheostomy tube), usually through a mask [1].

Since the first studies of NIV in critical care around 1980, thousands of reports have been published exploring different clinical applications, modalities, interfaces, and comparisons with other therapies [2].

Before starting NIV, it is crucial to recognize if the patient is a good candidate. The indications for NIV vary according to the underlying cause, severity of illness, and complicating factors [1].

NIV can be used as ventilatory support for patients with acute or chronic respiratory failure. In fact, NIV is widely used in the acute care setting for acute respiratory failure (ARF) across a variety of etiologies. Its effectiveness has been proven for common clinical conditions in critical care, such as exacerbation of chronic obstructive pulmonary disease (COPD) with hypercapnic respiratory acidosis and acute cardiogenic pulmonary edema (ACPE). It is also used as a home care therapy in patients with other chronic pulmonary diseases or sleep disorders.

In ARF, inclusion criteria for NIV are dyspnea, tachypnea (respiratory rate > 25 breaths per minute), increased work of breathing, and hypercapnic respiratory acidosis ($PaCO_2$ > 45 mmHg, pH <7.35) [3].

In acute exacerbation of COPD, bilevel NIV should be started when pH <7.35 and $PaCO_2$ > 45 mmHg persist or develop despite optimal medical therapy. Bilevel NIV remains the preferred choice for patients with COPD who develop acute respiratory acidosis during hospital admission. There is no lower limit of pH below which a trial of NIV is inappropriate, but the lower the pH, the greater the risk of failure. Patients must be very closely monitored with rapid access to endotracheal intubation and invasive ventilation if not improving [4, 5].

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In ACPE, either bilevel NIV or continuous positive airway pressure (CPAP) improves respiratory mechanics and facilitates left ventricular work by decreasing left ventricular afterload.

In acute asthma, there is not enough evidence to support the use of NIV [4].

Surgery, particularly that approaching the diaphragm, may have deleterious effects on the respiratory system, causing hypoxemia, decrease in lung volume, and atelectasis. Bilevel NIV and CPAP are frequently used in these clinical situations [4].

CPAP is the first-line treatment for obstructive sleep apnea (OSA), because it eliminates obstructive apneic and hypopneic events, resulting in improved daytime symptoms and reducing adverse cardiovascular outcomes [1, 6].

NIV is considered a significant treatment option for patients with obesity hypoventilation syndrome (OHS). Volume-assured modes of providing NIV may be more effective when high inflation pressures are required [1].

Home NIV can be used in conditions that can lead to chronic ventilatory failure such as scoliosis, kyphosis, thoracoplasty, muscular dystrophy, and motor neuron diseases [1].

NIV is currently used in a wide range of settings, from the ICU to home care. The appropriate selection of patients and the capacity of the team and the patients to achieve a proper adaptation to the technique are the bottom line for success [7].

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The Mask Interface Designs

Bshayer Ramadan Alhamad

Introduction

The use of noninvasive ventilation (NIV) therapy has increased in the last two decades, in both the critical care unit and home setting [1]. It is used as a first-line management for acute exacerbation of chronic obstructive pulmonary diseases and cardiogenic pulmonary edema [2]. NIV can also be used in the management of other diseases like asthma, chest wall deformity, and neuromuscular diseases [3, 4]. Studies have shown that NIV can reduce the risk of intubation and decrease the mortality rate and the cost [5–7]. It uses positive pressure most commonly in a form of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) to be applied noninvasively to a patient via different forms of interfaces. Interface is an adjunct device that holds the NIV tubing on a patient' face. The success of NIV therapy depends on multiple factors and one of these factors is selecting the appropriate interface for a patient [8]. In order to help the healthcare providers in selecting the appropriate NIV interface to a patient with least interface-related complications, this chapter will discuss the interface and its types, and it will compare the designs of the interfaces. It will also describe the effect of the type of interface on the upper airway dynamics. In addition, the chapter will explain interface fitting and the relationship between the interface type and carbon dioxide rebreathing. Finally, it will list the common interfaces' problems and some practical solutions.

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Interface

Interface is either factory-manufactured, semi-customized, or customized. Factory-manufactured interfaces differ in shape, design, size, and material. Silicone is the most commonly used material to construct an interface [9]. Semi-customized interfaces are factory-manufactured and then customized to fit the individual [10]. For example, some manufacturers use gel to construct the interface which will help to adapt the interface to the contours of the patient's face [9]. No studies compared this type of interfaces with the standard ones [10]. Customized interfaces are created by centers specializing in NIV. Customized interface is an interface, made for a certain patient [10]. Due to the advancement of medical technology and the availability of 3D medical printing, 3D-printed custom interface can be developed for both adults and children [11]. For example, patients who have craniofacial malformation can benefit from having customized interfaces that are created specific to them.

Types of Interfaces

This section lists and describes the different types of interfaces commonly available in the market:

Nasal Pillow or Nasal Prongs

It has two soft nasal tubes that fit into the nostrils. It is held in place by a strap that wraps around the back of the head. It is preferred to be used with patients who have skin allergy [12] or those who find nasal or oronasal mask uncomfortable or those who have skin breakdown on the nasal bridge since it has least contact with the skin [9]. It is also preferred with those who are suffering from claustrophobia [12].

Nasal Mask

It covers the nose only from its bridge down to the upper lip. It is recommended to be used with patients who have good nasal breathing and facial symmetry. The nasal mask is discouraged to be used with patients who have facial anatomical deformations or facial paralysis [12].

Oronasal Mask or Full-Face Mask

It covers the nose and the mouth and rests on the chin. The cushion of a typical oronasal mask is triangular in shape. The top of the triangle should be placed on the

nasal bridge, whereas the bottom of the triangle should be placed between the lower lip and the mentum. It is preferred to be used with patients who have acute respiratory failure since they breathe through their mouth to bypass the nasal resistance and with other kinds of patients who have considerable mouth breathing. It is also indicated with patients who have nasal obstruction [12]. To prevent rebreathing in case of ventilator malfunction, recent advances added quick-release straps and anti-asphyxia valves to the oronasal mask [13].

Oral Mask or Mouthpiece

It fits inside the mouth and is placed between the patient's teeth and lips; thus; it requires active participation of the patient [9]. It is indicated commonly to support daytime ventilation for patients with neuromuscular diseases [14].

Total Face Mask

It covers the whole face, including the nose, mouth, and eyes. It is mainly used with acute respiratory failure [9].

Helmet

It is a transparent latex-free polyvinyl chloride hood that covers the entire head and all or part of the neck with no contact with face or head and has a soft collar neck seal. It is a valuable interface for the management of acute hypoxemic respiratory failure and acute cardiogenic pulmonary edema in certain countries [15].

Comparisons of the NIV Interfaces

An ideal NIV interface is the one that has the following characteristics: transparent, leak-free, lightweight, good stability, non-allergenic material, durable, nontraumatic, minimal dead space, low resistance to airflow, available in several sizes, adaptable to variations in facial anatomy, easy to clean and disinfect, connectable with any ventilator, easy to secure and take off in order to avoid aspiration, nondeformable, and affordable [16, 17]. In reality, there is no universally ideal interface. Each of the aforementioned NIV interface has advantages and disadvantages. It is important for clinicians to understand them in order to select the appropriate interface for a patient. These are summarized in Table 1.

Many studies had an interest to compare the efficacy of different types of interfaces during NIV therapy. The following section will present these studies:

Table 1 Comparisons of the NIV interfaces

Interface	Advantages	Disadvantages
Mouthpiece	• Less claustrophobic • No pressure on the nasal bridge	• Less effective for acute respiratory failure • Requires nasal or oronasal interface when sleeping • Nasal leak
Nasal mask	• Less claustrophobic • Coughing and expectoration are easier • Speaking and eating are easier • Less danger in case of vomiting • No risk of asphyxia in case of ventilator malfunction • Gastric distension is less likely	• Nasal patency required • Mouth leak • Mouth dryness • Nasal irritation and rhinorrhea • Contraindicated with nasal obstruction or malformation, mouth breather, or soft palate surgery
Nasal pillows	• Less claustrophobic • Coughing and expectoration are easier • No pressure on the nasal bridge • Speaking is easier	• Nasal patency required • Mouth leak • Mouth dryness • Nasal irritation and rhinorrhea • Contraindicated with nasal obstruction or malformation
Oronasal mask	• Better mouth leak control • More effective in mouth breather	• More claustrophobic • Increased aspiration risk • Speaking, eating, and expectoration are difficult • Asphyxiation with ventilator malfunction • Contraindicated with patients who have vomiting or claustrophobia
Total face mask	• No pressure on the nasal bridge • Easier to fit • More comfortable for some patients	• High level of noise • Eye irritation
Helmet	• No pressure on the nasal bridge • Speaking is easier • Can be applied regardless of the facial contour, facial trauma, or edentulism • Coughing is easier • More comfortable for some patients	• High level of noise • High gas flow required to prevent rebreathing • Hearing loss • Poor patient-ventilator synchrony • Contraindicated with patients who have tetraplegia or claustrophobia

Data from [16–18]

Mouthpiece vs. Nasal Mask

Nicolini et al. [14] compared the effectiveness of two interfaces (open mouthpiece [angled mouthpiece without lip seal fixation] and nasal mask) on improving arterial blood gases and breathing frequency after 2 h of NIV therapy and then after 12, 24, and 48 h in patient with mild to moderate acidosis due to exacerbation of chronic

obstructive pulmonary disease. Fifty participants were enrolled in the randomized study, and they were found to have similar trends in arterial blood gases and breathing frequency in both mouthpieces and nasal mask. However, more patients accepted mouthpiece over the nasal mask when analyzing the survey with the Likert scale ($p < 0.01$).

Nasal Mask vs. Oronasal Mask

Kwok et al. [19] found no differences between oronasal mask and nasal mask in terms of improvement in clinical data, such as vital signs, gas exchange, and avoiding intubation. However, nasal mask was less tolerated by the participants than oronasal mask when they are used to manage acute respiratory failure caused by chronic obstructive pulmonary disorder and cardiogenic pulmonary edema in emergency department or intensive care unit.

In a meta-analysis study that included five randomized and eight non-randomized trials, Andrade et al. [20] found that oronasal mask is associated with higher level of CPAP with an average of 1.5 cmH_2O, more residual apnea/hypopnea index with an average of 2.8 events/h, and less adherence with 48 min/night, when compared to nasal mask with participants who have obstructive sleep apnea.

A systematic review and individual participant data meta-analysis compared the effect of nasal and oronasal mask on home NIV efficacy and adherence in patients with COPD and obesity hypoventilation syndrome. Thirty-four prospective randomized control trial participants were recruited between 1994 and 2019 with at least 1-month duration of NIV therapy. The study reported that oronasal mask was used more for home NIV compared to nasal mask; however, there was no difference in the NIV efficacy or tolerance between the two used interfaces [21].

Majorski et al. [22] compared oronasal mask and nasal mask in terms of quality of sleep using objective and subjective measurements with the nocturnal NIV in COPD patients. The randomized crossover trial found a tendency toward improved sleep efficiency and sleep stages III and IV with the oronasal mask ($p = 0.054$ and $p < 0.001$, respectively). Subjective mask preference was independent from the objective measures, but it is associated with nocturnal dyspnea.

Nasal Pillow vs. Nasal Mask vs. Oronasal Mask

In a randomized control crossover trial, Goh et al. [23] investigated the effect of interface type on the adherence and efficacy of CPAP treatment on patients with moderate to severe obstructive sleep apnea. Three interfaces were compared: nasal pillow, nasal mask, and oronasal mask. The study reported that participants with CPAP and nasal mask were more adherent than those with nasal pillow and nasal mask. Additionally, they found that higher apnea/hypopnea is associated significantly with oronasal mask. Moreover, participants who have less nasal obstruction

and a proportionally increased chin-lower lip distance to midface width had better adherence to oronasal mask.

Blanco et al. [24] compared the impact of three different interfaces, nasal pillow, nasal mask, and oronasal mask on the effectiveness of and adherence to unattended home-based CPAP titration in patients with obstructive sleep apnea. In this retrospective study, nasal mask was selected by most of the participants and had the lower leak rates, and nasal pillows presented a similar performance.

Total Face Mask vs. Helmet

In a single-center randomized control trial of 83 patients with acute respiratory distress syndrome, helmet was compared to total face mask in terms on intubation rate. The study found that helmet significantly reduced intubation rate and 90-day mortality [25]. Another single-center randomized control study was conducted with similar purpose as the aforementioned study in 60 COVID-19 patients. The study reported that helmet also was associated with reduction in intubation rate, better oxygenation, greater patients' comfort, and shorter ICU length of stay compared to face mask [26]. Both studies recommended further research with large sample size and multi-centers to confirm the findings.

Effect of the Type of NIV Interface on the Upper Airway Dynamics

During NIV therapy, it has been thought that upper airway obstruction can be induced by nasal obstruction, pharyngeal collapse, and/or glottis closure [27]. However, Vrijsen et al. [28] reported a case in which oronasal mask can induce obstructive events in the upper airways, which resulted in decreased sleep and NIV efficiency.

Ebben et al. [29] compared the nasal mask and the oronasal mask on the retroglossal and retropalatal anterior-posterior space in patients suffering from obstructive sleep apnea and using CPAP. Ten participants were imaged with real-time cine magnetic resonance imaging with the aforementioned interfaces at different CPAP (5, 10, and 15 cmH_2O) in the supine position along the sagittal plane while awake. The study found that oronasal mask produced significantly less airway opening in the retropalatal region of the upper airway compared to the nasal mask.

In a retrospective four case series, Ng et al. [30] reported that nasal mask should be considered when obstructive sleep apnea is incompletely controlled by CPAP with oronasal mask and/or surprisingly when patients require high CPAP with evidence of residual upper airway obstruction. The four patients were on CPAP with oronasal mask, and when they were switched to nasal mask, there was significant reduction in the average of residual apnea-hypopnea index. In two of the four cases, the patients required much lower CPAP.

Similarly, another prospective study found that nasal mask is superior than oronasal mask in preventing upper airway obstruction, specifically pharyngeal collapse, under the same pressure in 13 participants who underwent drug-induced sleep endoscopy exam with positive airway pressure [31].

Therefore, it is recommended to use the oronasal mask in acute settings, and once the patient's condition becomes stable, switching to nasal mask is preferred, if tolerated [9].

Interface Fitting

After selecting the appropriate interface to the patient, it is crucial to select the correct size to increase patient's tolerance and decrease complications resulted from skin breakdown [8]. To help select the correct size, fitting gauge is usually provided by the manufacturer of the interface and it can be used as a guide [9]. After selecting the appropriate size, it is important to maintain the interface in its place by a well-fitted headgear. The headgear should be made of soft material that allows sweating [32]. The headgear should be fixed symmetrically on a patient according to the instruction. It is also recommended to always permit one to two fingers of distance beneath the headgear to avoid pressure-related skin lesions [33]. Additionally, air leak should be checked around the interface by hands or via the NIV monitoring to ensure the interface is well-fitted [18].

Interface and Carbon Dioxide Rebreathing

It is crucial when selecting the interface to be familiar with the type of the ventilator's circuit that will be used and which type of mask (vented mask or non-vented mask) is suitable with it. NIV can be applied either via closed dual-limb circuit (it has inspiratory limb and expiratory limb and inspiratory and expiratory valves, such as those used with critical care ventilator) or single-limb circuit (it has one limb for both inspiration and expiration) [9].

For the closed dual-limb circuit, a non-vented mask must be used to maintain the closed circuit. In this case, expiration occurs through the exhalation port or filter in the expiratory limb of the circuit. By contrast, single-limb circuit requires either a vented mask (a mask built-in exhalation port) or a non-vented mask and an additional exhalation valve in the circuit. When using a vented mask, expiration occurs through the holes in the mask. If a non-vented mask will be used with the open single-limb circuit, an additional exhalation valve in the circuit must be added to allow carbon dioxide (CO_2) washout. In this case, the exhalation valve is open during expiration to permit CO_2 removal and closed during inspiration to avoid loss of delivered tidal volume. It is recommended to have the exhalation valve near the patient to minimize CO_2 rebreathing [9, 17, 18].

The interface itself can act as additional dead space to the system. Theoretically, the internal volume of the interface can play a role in increasing CO_2 rebreathing.

An in vitro study found that increasing internal volume of an interface can increase CO_2 rebreathing when the face mask (inner volume of 165 mL) is compared to total face mask (inner volume of 875 mL) [34]. The study also reported the position of the exhalation port can affect the CO_2 rebreathing, too. Face mask with a built-in exhalation port (i.e., vented mask) demonstrated lesser CO_2 breathing compared to face mask with an exhalation valve in the circuit [34]. Another study concluded that effective dead space is not related to the internal gas volume of the interface since they found that the effective dead space differed only modestly (110–370 mL) among the three interfaces (oronasal mask, integral mask, and helmet) that had been tested although their internal volumes were markedly different (110–10,000 mL) [35]. The study suggested that internal volume of the interface should not be considered as a limiting factor for their efficacy during NIV [35]. In vivo studies reported that no apparent dead space effect was observed on minute volume, work of breathing, and arterial CO_2 level despite using four interfaces with different internal volumes: two face mask (internal volume of 977 mL and 163 mL), oronasal mask (84 mL), and mouthpiece (virtually no internal volume) [36]. The study suggested that with the exception of mouthpiece, facial interfaces may be interchangeably used in clinical practice with the adjustment of the ventilatory device parameters [36].

Common Interfaces' Problems and Practical Solutions

Problems related to NIV interface is not uncommon. The section below will cover the most common problems such as air leak, skin breakdown, mucosal dryness, eye irritation, and noise. Healthcare providers should be familiar with these problems and how they can be prevented or reduced to optimize the success of NIV therapy.

Air Leak

One of the common interface-related problems is air leaks. Leak can be around the edge of the interface or through the mouth with nasal pillow or nasal mask, or it can be through the nose when the patient uses mouthpiece [9]. Small air leak can irritate the patient. Large air leak interferes with the effectiveness of NIV therapy and then can lead to NIV failure. The large leak can lead to patient-ventilator asynchrony by affecting trigger functions which causes auto-triggering since it can cause a significant drop in the delivered intra-alveolar pressure that reduces the delivered tidal volume [37].

Leak can be prevented by using an appropriate type, size, and headgear of interface. After fitting the mask, it is recommended to place the back of the hand around the interface to assess the presence of leak [18]. Asking the patient about how comfortable they are with the interface and about the eye irritation is also an important step after fitting the interface and throughout the treatment [18]. Regular monitoring of the amount of the unintentional leak on the panel of NIV is recommended.

Additionally, monitoring the flow-time waveform can help in detecting the presence of leak, particularly in dual-limb circuit. When inspiratory tidal volume is similar to the expiratory tidal volume, it is expected to observe that the length of inspiratory flow is comparable to the expiratory flow. In case there is a difference between the length of inspiratory flow and that of expiratory flow in the flow-time waveform, then leak is suspected [38]. The optimal unintentional leak is zero. Small air leak can be compensated by modern ventilators designed for NIV to a variable extent [39]. Sometimes, small air leak does not disturb the patients and can be accepted [18].

Patients who are using nasal mask or nasal prongs and are mouth breather can have leak through the mouth. In this case, using chinstraps can be a solution, but this strategy is not recommended to be used for a long period of time since it can cause jaw or teeth pain and patients' discomfort and can increase snoring due to returning the jaw backward which narrows the airways [12]. Instead, it is recommended to change the interface to a one that covers the mouth, such as oronasal mask. When a leak comes from the nose when a patient uses mouthpiece, nasal clip can be used to prevent the leak [40].

Skin Breakdown

Skin breakdown can be caused by prolonged pressure resulted from the NIV interface or its headgears at the site of skin contact. The affected skin areas depend on the type of interface chosen. However, the most common areas are the bridge of the nose, forehead, and sides of the interface (cheeks, mentum, etc.) [1].

The skin breakdown ranges from transient erythema, prolonged erythema, to skin necrosis in the very severe cases. Pediatric population can experience facial flattening due to pressure from the interface on the growing face. It can be resulted in maxilla underdevelopment that leads to midface flattening and malocclusion of the teeth [10]. To reduce facial flattening, it is advised to change the interface periodically which can alternate pressure points. Additionally, reducing the number of ventilation hours if the patient's condition is allowed can help in reducing facial growth restriction [40, 41].

To prevent skin breakdown related to the interface, it is crucial to select an appropriate mask type and size to the patient as well as appropriate headgear and optimal tension when fitting the interface and headgear to the patient. Regular assessment of skin integrity especially in the pressure points of the interface is also important to identify early any skin breakdown and to take immediate intervention to avoid further severe skin lesions [18].

To maintain a good seal of the interface without pressurizing the skin, most masks have a cushion [12]. Using water to fill the cushion of a face mask showed delay in the appearance of facial ulcer compared to that filled with air [42].

To reduce or prevent skin damage, pressure relief dressing such as hydrocolloid dressing can be used to improve the situation [43]. Alternating between two types of interface can be another solution to vary the area of skin insulted. Additionally, taking regular breaks from the mask can be another strategy [44].

Mucosal Dryness

Dryness of nasal and oral mucosa is one of the most complained-about issues by the patient which can be caused by either dry, cold air coming from the NIV ventilator or by the unintentional leak [45, 46]. If the cause of mucosal dryness is air leak, then decreasing air leak will help to reduce the dryness. Heated humidification is recommended if the patient reports mucosal dryness or if the secretions are thick and tenacious, making it difficult to be expectorated [44]. Although there is no clear evidence to support using nasal topical treatments (nasal rinses, topical corticosteroids, or decongestants), they have shown to be effective in controlling the nasal symptoms (nasal dryness, inflammation, and irritation) [47].

Eye Irritation

Leak from the interface toward the eye can cause eye irritation and redness, such as conjunctivitis [18]. Therefore, it is important to check the good seal fit of the interface and do regular assessment of interface fit during NIV therapy. In case eyes are affected, artificial tears can be applied [18].

Noise

Noise can be caused by either the leak or by using the high flow system, such as helmet. If the noise is caused by the leak, then the interface must be refitted. If the noise is caused by the high flow system, then earplug can be used [18].

Summary

Effectiveness of NIV therapy depends on selecting the appropriate interface. Different types of NIV interfaces are available. Therefore, healthcare providers should be familiar with the advantages and disadvantages of each interface to help them select the appropriate interface for a patient, taken into consideration the other related factors, such as underlying disease, facial characteristics, patient preference, breathing pattern, staff experiences, and compatibility of the interface with the used ventilator circuit. Proper interface fitting is also challenging; therefore, clinicians should select the appropriate size by using interface's size guide and the appropriate headgears. Additionally, it is crucial to be aware with the problems related to the interfaces to reduce or prevent them by using the recommended strategies. Regular assessment of the interface fitting and its associated related adverse effects is needed throughout the NIV therapy to take early actions, if needed, to optimize the patient's adherence and satisfaction which at the end can lead to successful NIV therapy.

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Relationship Between Mask Interface and Upper Airway Anatomy and Physiology

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Abbreviations

ARF	Acute respiratory failure
EMG	Electromyography
GG	Genioglossal activity
NIV	Noninvasive ventilation
OSA	Obstructive sleep apnoea

Introduction

Upper airway functions are controlled by both voluntary and involuntary complex neuromuscular systems. They perform numerous functions and are a duct for the air; they have a role in heating and humidifying the air, in the sense of smell and in the coordination between ventilation and swallowing. They also represent a primary defence against infections and involuntary food aspiration and play a fundamental role in speech. The upper airways depend on the surrounding soft tissues for support and have a natural tendency to collapse [1]. The neuromuscular systems' activities that control its patency are represented by cough, hiccups, recovery of aspiration, vomiting and sneezing during wakefulness and sleep. Their failure can lead to obstructive sleep apnoea (OSA) and sequelae. *Sleep* is a particularly vulnerable moment in which the protective reflexes of the upper airways are attenuated, leaving the upper airways susceptible to collapse [2]. These protective or tone-maintaining reflexes are further compromised during pathological states that can affect both the lung and the chest wall.

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Anatomy and Physiology

The upper airways are a complicated structure usually divided into four anatomical subsegments:

- Nasopharynx – between the nostrils and the hard palate
- Velopharynx or retropalatal oropharynx – between the hard and soft palates
- Oropharynx – from the soft palate to the epiglottis
- Hypopharynx – from the base of the tongue to the larynx

This entire structure forms a passage for air movement from the nose to the lungs and participates in other physiological functions such as speech and swallowing. The airflow through the airways is finely regulated according to function, varying from complete patency during breathing to closing during swallowing. More than 20 upper airway muscles surrounding the airways actively constrict and dilate the upper airway lumen. They can be classified into four groups – muscles that regulate the position of the soft palate (alae nasal, palatine tensor, levator palatini), tongue (genioglossus, geniohyoid, hyoglossus, styloglossus), hyoid apparatus (hyoglossus, genioglossus, digastric, geniohyoid, sternohyoid) and the posterolateral pharyngeal walls (palatoglossus, pharyngeal constrictors) [3]. All muscles make a complex interplay aimed at determining the patency of the airways. Soft-tissue structures form the upper airway walls, including the tonsils, soft palate, uvula, tongue and lateral pharyngeal walls. The main craniofacial bone structures that determine the size of the airways are the mandible and the hyoid bone; these presumably act by providing the anchoring structures to which muscles and soft tissues attach. However, it is clear that complex relationships also occur in these structures, as some of these, such as the hyoid bone, have no attachment to other bone or cartilage structures. The muscle groups act as levers where the contraction, instead of moving the structure, causes the elongation of the adjacent soft tissues (e.g. tracheal traction). In nonobese subjects, the mean minimum cross-sectional area over multiple upper airway segments was measured using different techniques: estimates range from 320 ± 450 mm^2 (acoustic reflection) [12 ± 14], 59 mm^2 (fast CT at FRC), 64 mm^2 (MRI), 144 mm^2, 188 mm^2 to 138 mm^2 (conventional CT) [4]. This wide range of sizes reflects differences due to individual variability. Still, it is also due to different measurement positions, changes in position (sitting/supine) and differences imposed by choice of imaging modality. There is a substantial overlap in measurements between normal subjects and those with adult apnea obstructive syndrome (OSAS). However, it is essential to remember that most of the measurements reported were made while awake, so they combine anatomical properties (such as bone structure and fat deposition) and activation of the upper airway dilator muscles. The minimum calibre of the upper airway in the waking state is mainly in the retropalatal oropharynx, making it a site of interest as a potential site of collapse during sleep. The anterior wall oropharynx comprises the soft palate, tongue and lingual tonsils.

In contrast, the posterior wall is bounded by a muscular wall consisting of the upper, middle and lower constricting muscles. The lateral pharyngeal walls are

composed of several muscles (hypoglossal, styloglossus, stylohyoid, stylopharyngeal, palatoglossus, palatopharyngeal, pharyngeal constrictors), lymphoid tissue and pharyngeal mucosa. This complexity of the interactions between these different muscles makes the oropharynx a complicated structure to assess. The landmarks are bone, fat, muscle, and airways. Upper airway imaging techniques have also been used to identify and visualise the airway lumen and define its anatomical and spatial relationships with surrounding structures [5].

In awake subjects, Schwab et al. demonstrated that normal upper airways have a longer lateral dimension than the AP using magnetic resonance techniques [6]. Furthermore, using fast cine CT, they also demonstrated that airway size remains relatively constant during inspiration and reaches a minimum during the end of expiration, suggesting that muscle stabilization of the airway lumen during inspiration against negative intraluminal pressure is more critical than actual dilation. As previously believed, according to these authors, most of the changes related to breathing (i.e. the loss of diameter at the end of exhalation) are predominantly in the lateral dimension. In describing the dynamic behaviour of the airways during cyclic breathing, it is helpful to use various physical and mathematical models to reduce this complex structure to a simpler and more understandable one. From a simplistic point of view, the airway is considered a rigid tube and the resistance is analysed. A more realistic model considers "resistance" as a variable during the inspiratory cycle consisting of a dynamic interaction between flow and pressure. The validity of this complex model is evident when it is observed that negative intrathoracic pressure transmitted to the passive upper airways during inspiration promotes a reduction in pharyngeal cross-sectional area [7]. According to the concept of "pressure balance", the airways' size (and therefore the resistance) depends on the balance between the collapsing intraluminal pressures generated during inspiration by the subatmospheric pressures in the chest and the forces of contraction towards the outside of the upper airway dilator muscles. In this analysis, airway patency depends on transmural pressure (Ptm), the difference between the negative intraluminal pressure induced by inspiratory efforts and the positive dilating pressure from the upper airway musculature. To better understand this "dynamic collapse", an alternative, a complementary approach has been to describe the upper airway as a non-fixed system. This model better deals with the dynamic collapse described above and helps explain why airway calibre can increase associated with lung inflation [8]. This collapsible tube model can examine multiple components that influence susceptible airway collapse. These factors include at least the following: guiding respiratory pressure across the collapsing region, determined by negative intrathoracic inspiratory pressure and any fixed resistances of anatomical structures (e.g. the nose); intrinsic properties of the airway wall (this is called the "tube law" and is determined by the size, collapsibility and longitudinal tension of the tube); and neural input to the upper airways, which determines the behaviour of the dilating/stabilizing musculature [9]. The upper airways are rich in neural receptors, which play a role in controlling basic genioglossus tonic EMG. Any loss of this EMG tone, which occurs early in sleep, likely contributes to increased pharyngeal resistance [10].

The role of topical receptor mechanisms in the nasopharynx on the dilator muscle activity has been investigated during upper airway anaesthesia. Moreover, a

reduction of phasic and tonic genioglossal activity (GG) was observed during stomal breathing compared to nasal breathing in tracheostomized subjects, suggesting the influence of local upper airway stimuli [11]. In addition it has been also observed the phasic inspiratory activity of many upper airway dilator muscles during inspiration, including the genioglossus and geniohyoid, in human and animal models. This phasic activation of the upper airway muscles has been shown to occur before the muscular activity of the diaphragm and intercostal muscles, suggesting preactivation of these muscles in onset of negative pressure. In experimental situations, upper airway dilator muscles may widen the airways by shortening muscle fibres. The presence of a dilating force concomitant with upper airway activation during early inspiration was demonstrated in sealed isolated upper airways in a dog model. Recently, the relationship between genioglossus EMG and pharyngeal size has been investigated in laryngectomized patients breathing through a tracheal stoma. In this study, inspiration-related muscle activation was associated with widening of the glossopharyngeal airways, all in the absence of flow through the upper airways due to tracheostomy. Despite the above data, it is unclear whether the activity of the "dilator" muscles is actually to dilate the airways or whether these increases in muscle tone act to stabilize the airways [12].

NIV and Upper Airways

NIV can affect these physical characteristics and thus affect the patency of the upper airway. Regarding the interaction of the upper airways with noninvasive ventilation, Moreau-Bussière and colleagues investigated the effect of NIV on glottal constrictive muscle activity of the glottis (thyroid) and dilator (cricothyroid) in awake lambs [13]. During spontaneous breathing, both the thyroarytenoid muscle and the cricothyroid muscle are active: the activity of the thyroarytenoid muscle occurs mainly at the end of inspiration. However, with the application of pressure support during NIV, the inspiratory cricothyroid activity disappears as the activity of the thyroarytenoid muscle increases. This results in glottal narrowing and limited ventilation, as evidenced by the respiratory inductance plethysmography. A subsequent study showed that the increase in glottal constrictor muscle activity during NIV mainly depends on the activation of bronchopulmonary receptors. After bilateral vagotomy, the previously observed increase in inspiratory activity of the thyroarytenoid muscle with increasing support during NIV was absent. Limited data are available on humans. Rodenstein et al. assessed through a fibre optic bronchoscope glottis patency of healthy subjects exposed to increasing levels of support with NIV [14]. Animal and human studies indicate that positive pressure ventilation reduces upper airway patency during neural inspiration. Neurally adjusted ventilatory assist (NAVA) is a relatively new modality of NIV support. The key features of NAVA are that the ventilator is cycled by the diaphragm's electrical activity, thereby improving patient-ventilator synchrony. The level of support is proportional to the diaphragm's electrical activity. The diaphragm's electrical activity is measured by a series of bipolar electrodes mounted on a nasogastric tube [15]. Contrary to PSV, glottal

constrictor muscle activity does not increase with NAVA during inspiration in lambs. The use of NAVA leads to a reduced glottal closure and increased synchronous ventilation and may be advantageous over PSV during NIV. A possible mechanism underlying the absence of constrictive glottal activity during NAVA inspiration is that increased pressure mimics the normal progressive recruitment of diaphragmatic motor units, while during PSV ventilator insufflation is performed at a level of constant pressure (decelerating flow pattern), often with a short inspiratory rise time to decrease the patient's inspiratory work further. The resulting rapid non-physiological increase in airway pressure at the onset of PSV inspiration could be responsible for the reflex activation of the inspiratory activity of the glottal constricting muscles and thus limits the efficiency of NIV [16]. Regardless, further studies are required to support this hypothesis. The importance of monitoring inspiratory muscle activity during mechanical ventilation has been highlighted in the literature. On the other hand, the role of monitoring upper airway activity during NIV is poorly understood, possibly related to the complexity of monitoring upper airway function in these patients. Activation of intrinsic laryngeal muscles affects the opening of the glottis and thus affects the resistance to flow in and out of the lungs. Monitoring upper airway dilator muscle recruitment during inspiration may be clinically relevant considering that the phasic activity of upper airway dilator muscles increases with respiratory constraints, as in patient-ventilator asynchrony [17]. Cheng and colleagues studied the upper airways in healthy subjects using magnetic resonance imaging. This study showed that the genioglossus muscle and the non-muscular soft tissues surrounding the upper airways move before inspiratory flow. The entourage of movement of certain landmarks on the genioglossus muscle was greater during normal inspiration than during charged inspiration, suggesting that increased muscle activity during charged inspiration does not translate into dilation but a stiffening of the upper airway area. Furthermore, this study demonstrated that the movement of non-muscular soft tissues affects the patency of the upper airways. There is a complex interaction between the movement of non-muscular soft tissues and the genioglossus muscle activity. Although electromyography of the laryngeal muscle (e.g. genioglossus or cricothyroid muscle) is feasible during NIV, it should be noted that electromyography does not provide information on the non-muscular soft-tissue movement. Therefore, additional techniques should be used to assess upper airway patency. MRI probably provides the most reliable information, but it is expensive and cumbersome, particularly in patients with NIV. A recent study supports the role of ultrasound in the assessment of the upper airway, although the role of evaluating upper airway patency with this technique has not been studied. Additionally, endoscopy has been used to assess upper airway patency, but ideally, it should be used at different levels in the upper airway [18].

Increasing the success rate of NIV is of great clinical importance. In contrast to invasive ventilation, the upper airways are important as air conductors during NIV. Available pieces of evidence suggest that during NIV, it is essential for the ventilator to act in synchrony with the upper airway muscles to allow for adequate ventilation. In animal models, the patency of the upper airways is affected by ventilator-induced changes in pressure and flow. However, we do not know if this

phenomenon can be extrapolated to humans. The reflexes involved are similar in humans to those in newborn lambs but are thought to be less pronounced. Today, data on the effects of NIV on upper airway physiology in patients with acute respiratory failure are limited [17]. The neural respiratory drive is crucial in maintaining the patency of the upper airways. Therefore it is logical to think that when the ventilator is activated synchronously with the upper airways, these will not collapse, and ventilation will be more efficient.

Mask Interface and Upper Airways

The purpose of NIV is to decrease the work of breathing and/or improve oxygenation and ventilation. The most commonly used NIV mode is pressure support ventilation (PSV). The ventilator should work in sync with the patient's neural respiratory drive for the most effective release of the inspiratory muscles. Although the activation and cycling of mechanical support during PSV depend on the patient's respiratory effort, frequently asynchrony between patient and ventilator appears often. Several types of asynchronies and dyssynchrony have been identified between the patient's neural thrust and ventilator support. Suboptimal synchrony between patient and ventilator can be affected by respiratory mechanics, breathing pattern, neural thrust, ventilator settings, interface type and air leak [19]. The impacts of patient-ventilator asynchrony are poorly comprehended, but a high incidence of asynchrony is correlated with distress and a protracted time of NIV. The types of asynchronies discussed above are related to the interaction between inspiratory muscle activity and ventilator response. Indeed, this is sufficient for patients who require invasive ventilation. However, it is also important during NIV that the ventilator is synchronized with the upper airway muscles. Narrowing the glottis during inspiration increases upper airway resistance and limits adequate ventilation [20]. This type of asynchrony will be examined after briefly citing the details of upper airway physiology connected to the topic of this review. In recent years, device manufacturers have developed a greater variety of interface types, styles and materials. This allows you to find a suitable interface for almost any patient in most situations, but having to manage many different interfaces and being able to select the most appropriate one can be difficult for clinical staff. There are six main classes of interfaces commercially disposable in various sizes, all with advantages and disadvantages. Custom aligners are another option, but in the acute setting with critically ill patients, there is usually not enough time to manufacture them. The choice of interface is mainly influenced by patient characteristics (e.g. facial anatomy, breathing pattern and individual comfort level) and clinical efficacy, but staff experience, equipment availability, and wait. cheap. In the studies that compared various types of interfaces used in NIV for acute respiratory failure (ARF), respiratory parameters such as dyspnoea and respiratory rate but also the objective parameters derived from performing arterial blood gas analyses were similar in the various groups. Therefore, there is currently no strong scientific evidence that one type of mask has any improvement in terms of clinical efficacy for some patients over others. Although

patients with ARF often breathe through the mouth, and although they may start with a nasal mask, many patients need to switch to an alternative interface that covers the nose and mouth if air leaks from the mouth occur. The most common initial interface for ARF treatment with NIV is, therefore, an oronasal mask in clinical practice [20]. This was reflected in a large web-based survey in Europe and North America, with oronasal masks (70%) being the first choice, followed by full face masks, nasal masks and helmets. The ability to quickly try on different types and sizes of masks can increase tolerance as patients who don't fit well on one type of mask may conform to another. Therefore, it is considered advantageous to have different types, materials and sizes of masks to be connected to the patient and the ventilator, even if financial constraints may lead to influence the choice of available interfaces. Most masks come with proper gauges to avoid selecting a too large or too small mask, and doctors are encouraged to use them to reduce complications. The mask must not touch the corners of the eyes or lips. Altering the interface can decrease NIV failure and is always worth a try if large leaks are observed and shown on the ventilator software or if the patient does not accept the interface type well, but the interface test should not be delayed. When switching to a different mask, it is necessary to check the sensitivity of the trigger, the level of pressurization and compatibility with the circuits. In the long term, nasal masks are classified as more comfortable than other types of masks and less often cause skin problems. If the patient is stable and there are no large air leaks from the mouth, it may be reasonable to switch to a nasal mask or nasal tip. Patients in the post-acute setting may sometimes be encouraged to continue NIV by switching to a less claustrophobic interface. The in vivo effect is limited, except for the helmet; face masks are generally interchangeable. At the beginning of NIV, the first few hours of acute NIV are critical, and the time spent on mask fitting and building patient confidence is well invested. Having a mask fastened on the face immediately can be very scary for a breathless patient in ARF, particularly if the person is naive to NIV [21]. Explain to the patient in advance the need for using NIV, how its use will proceed and that it is a procedure with the possibility of immediate interruption at his will, and describe what the patient will feel during and after using NIV. Monitoring can be clinical and instrumental, so we try to give the patient a feeling of tranquillity. A good rule of thumb to increase patient compliance to ventilatory treatment is to start with low pressures making sure the mask is not then immediately strapped to the patient's head to allow the patient to remove it at any time and learn to manage its use; logically this can be done in the patient who does not have severe acidemia. Once the patient can tolerate the mask, it can be secured with the head straps. Regarding the prevention and management of side effects related to the use of the mask, the clinician must obtain a good seal of the mask providing the best possible comfort and preventing complications related to skin pressure of the mask or the fastening systems. Initially, reducing air leaks is the main goal of applying the mask. Still, the longer the treatment lasts, the more likely complications will occur, including erythema of the facial skin, skin lesions, rashes, conjunctivitis or dryness of the mucous membrane. There are varying degrees of small air leaks, and a small number of air leaks can be tolerated as long as the leak does not bother the patient. In addition to

using an appropriate interface with the correct size and headgear, there are many other ways to decrease air leaks [22]. To improve interface tolerance and ventilation efficiency, it is advisable not to overtighten the head straps, as would be natural, but sometimes loosening the head straps and removing the mask from the face to give the patient a break may have a better effect than press without causing more pressure on the face which, in addition to making NIV ineffective, can predispose to the development of skin ulcers. For example, masks that incorporate non-rigid dual system pillows will fit and seal better if the pillows are filled with air and not pressed hard against the face. Several types of mask pillows are also available, such as hydrogel or foam pillows, and replacing the pillow can sometimes improve the fit of the mask. Additionally, you can try support rings for masks, thin silicone or cotton comfort flaps, mask liners and hydrogen or foam seals. If the patient's chin continues to recede, aligners with chin rests are a useful alternative. With nasal masks or nasal tips, air leaks through the mouth can become problematic. Although the use of a chin strap or mouth patch has been suggested, it is usually essential to switch to a type of mask that shields the mouth and nose. Chin straps can successfully decrease air leakage through the mouth in select chronic patients, but they are not constantly accepted, and there is little evidence to reinforce their use in ARF. Additionally, chin straps can cause discomfort and pain in the jaw or teeth, and their use should not be used to prolong ineffective treatment. In a chronic physiological study, the oral dressing was shown to reduce air loss from the mouth but cannot be recommended in ARF for obvious safety reasons. Suppose a troublesome air leak cannot be controlled by other means, and it is not possible to switch to a different interface type. You can try to slightly reduce the inspiratory pressure peak or switch from a volume-controlled ventilation mode to a pressure-controlled mode. Conversely, increasing pressure with pressure-targeted ventilation or tidal volume with volume-targeted ventilation can improve minute ventilation despite increased leakage, as long as the patient tolerates this strategy. The additional volume will add to the leak but can still increase minute ventilation [23]. Small air leaks near the eyes can cause irritation or conjunctivitis if not noticed. Evaluating small air leaks by positioning the back of the hand over the area and asking the patient for frequent eye irritation during therapy and each time the mask is used can help prevent this complication. Artificial tears can be used if the eyes are affected. If air leaks make noise, the mask must be reassembled, and a liner can be counted on to seal it. There are no issues with air leaks with the helmet interface, but the high-flow system creates a higher noise level within the device than other interfaces, and it may be helpful to provide earplugs for the patients. Some pressure is usually required to hold the NIV mask in place and seal it, but a tight fit is not required. Excessive pressure of the interface causing discomfort and compromising tolerance and success of or causing failure of NIV contributes to the breakdown of the skin. One of the most unpleasant and painful complications related to the iatrogenic interface in NIV is facial pressure ulcers. These are visible in high-pressure areas, mainly on the bridge of the nose, but can develop anywhere where the mask or headgear comes into contact with the skin. The registered event rate in ARF varies, depending on the study period, patient population, masks and skin protection strategies used. Reports from previous NIV

studies range from 5% to 56%; although improvements in mask design have helped reduce the problem, the most recent reports still range from 3% to 87% [24]. Increasing the indications and the use of NIV may partly clarify this for more seriously ill patients at risk of pressure ulcers, ventilation with higher inspiratory pressures that favour air leaks and the number of costs an increasing number of staffed NIV services they are originally less experienced and only a small sample of the available masks. The fact that the respiratory support necessary for the patient is considered more priority by medical personnel than local skincare also contributes to the persistence of the problem. Interface-related pressure ulcers are medical device-related pressure ulcers, and the longer the treatment lasts, the more likely they are to develop. The main cause of these ulcers, according to the literature, is usually associated with a lack of understanding of how and how often to remove devices and examine the skin and how to make sure the device fits appropriately to minimize friction and pressure. Most patient-dependent risk factors cannot be changed, but when mask fit is considered, regular evaluation and skin protection from initiation of therapy are tailored to the individual patient's needs. It is possible to avoid or reduce skin lesions in many cases. The most important strategy in pressure ulcer prevention is to keep the pressure applied to the skin as low as possible. Of course, it can be complicated to find the ideal strap tension and mask fit that permits for both a good seal and low pressure on the skin. A physiological study on a head model indicated that a mask pressure against the face of approximately 2–3 cmH_2O beyond the peak inspiratory airway pressure is adequate to prevent expansive air leaks. Unfortunately, the tension on the face cannot be objectively measured in daily care or any type of mask and does not provide information on individual high-pressure points, for example, the nose bridge. Therefore, clinicians applying the mask should be guided by patient feedback about their interface tolerance and by the clinician's experience in evaluating possible leak points or future pressure points, all considering the need to use the best ventilation with minor complications. The correct size of the mask and headgear with a larger number of attachment points will help disperse the pressure more evenly around the rim of the mask. Tighten the mask straps until the air leak is only barely controlled, either purposely leaving a minimal air leak or leaving enough room for at least two fingers to pass under the strap. It can also help avoid over-tightening the head straps. Skin protection strategies include making the skin clean and dry, releasing pressure regularly, utilizing special face masks and applying bandages to the skin to redistribute pressure and decrease friction. For patients with very well-known anatomy or at high risk of developing pressure ulcers, masks with more delicate pads (e.g. hydrogel pillows or dual-spring air pillows, or both) may be used. An adjustable forehead spacer can also help distribute pressure more evenly across the face and reduce it across the bridge of the nose. For complex cases, it is advisable to choose a very comfortable mask that can be cost-effective if it avoids intubation. Providing the skin with regular breaks from interface pressure, ideally every 2–4 h, is essential to relieve pressure and allow for examination of the skin under the mask. Otherwise, severe skin and tissue damage can occur, as demonstrated in a case report of a patient where the mask was not removed for 0.90 consecutive hours. The switch from a full-face mask

to a full-face mask allows for an even pressure effect on the nose bridge. Other non-contact interfaces with the nose bridge can also be tried, such as masks with an opening on the bridge of the nose or nose tips. In patients at high risk of pressure ulcers, the mask cycle should be started from the onset. The routine use of other protective covers applied to areas with the highest pressure can reduce the occurrence of pressure ulcers. Foam pads, hydrocolloids or gels distribute pressure, reduce friction and at the same time can reduce even small air leaks. They are suggested for patients at high risk of pressure ulcers from the beginning of NIV or, at the latest, when the first signs of redness emerge on the skin. It is essential not to create more pressure on the skin when positioning the dressing [25]. The helmet is the only interface that does not create pressure ulcers on the face and is a practical choice for expert centres if the effects of pressure on the face become a limiting problem for NIV. The use of the helmet can create abrasion to the skin along the shoulder straps in the underarm region or around the neck due to the inflating system. Cases of venous thrombosis of the arm due to pressure on the vessel by the fixation straps have been described in cachectic patients.

The high pressure from the lower mask strap can sometimes cause or aggravate obstruction of the upper airway by pushing the lower jaw back. This usually is not a problem when the mask is initially mounted in an upright or semi-recumbent position but may be seen in some patients in the supine position or during sleep with rapid eye movements. The obvious solution is to loosen the straps, reassemble the mask or slightly increase the positive airway pressure. When a secure fit of the mask cannot be achieved without increased strap tension, adding a stiff collar or rolled towel under the chin may be considered to help keep the upper airways open. To decrease the risk of skin irritation, it is essential to keep the skin and mask clean and dry during the entire treatment. If reddening, rash or blistering occurs, you can try switching to a silicone- and latex-free mask pillow, apply a barrier cream and cover damaged skin to protect it when the mask is in place. If an allergic rash appears, the mask cushion should be modified to a different material, and the application of steroid cream may be considered. Regular reevaluation, movement, sweating, changes in fluid status and the tendency of the Velcro straps to gradually loosen over time can change the fit of the mask. Therefore, no matter how well the interface adapts to the onset of NIV, it is essential to monitor for air leaks and skin condition regularly and re-evaluate the mask's fit during treatment. Oral and nasal dryness and stuffy nose are frequent complaints during NIV with an occurrence rate of 10–50%. They indicate air leaks through the mouth or around the mask, but even without an air leak, patients may be disturbed by these symptoms. The cold and dry air from the ventilator, often caused by an improved oxygen fraction, promotes the release of inflammatory mediators in the nasal mucosa, improves the blood flow of the mucosa and therefore increases the resistance of the nasal airways and causes congestion. Treatment options include topical nasal application of saline, hyaluronic acid, steroids, decongestants or antihistamines, regular mouth care and adding heat/moisture exchangers and an external heated humidifier to the circuit [26]. The use of active humidification of inspired gas is mandatory for patients with tracheostomy, but its use in NIV is not always necessary. However, it should be added to the circuit

with a low threshold, especially if there are leaks or a high fraction of oxygen delivered. It can mitigate the increased resistance in the nasal mucosa, decrease dryness and improve comfort and tolerance of the nose. Ventilation with a mask is also recommended to bypass thickened and stubborn secretions. Other noncontact interfaces with the nose bridge can also be tried, such as masks with an opening on the bridge of the nose or nose tips. In patients at high risk of pressure ulcers, mask rotation should be initiated from the beginning [27]. This usually is not a problem when the mask is initially mounted in an upright or semi-recumbent position but may be seen in some patients in the supine position or during sleep with rapid eye movements. The obvious solution is to loosen the straps, reassemble the mask or slightly increase the positive airway pressure. When a secure fit of the mask cannot be achieved without increased strap tension, adding a stiff collar or rolled towel under the chin may be considered to help keep the upper airways open.

Conclusion

Recommendations on modulating the level should be provided to adapt the level of care, the level of end-expiratory positive pressure and the flow pattern to improve upper airway patency in patients with acute respiratory failure. Therefore, future research should investigate the effect of different ventilator modes and settings on upper airway patency in patients. For example, NAVA ventilation in lambs has decreased glottal constrictor muscle activity relative to PSV during NIV. Ventilator settings such as rise time, trigger sensitivity and pressure support level and positive end-expiratory pressure should also be subject to further research. The settings can restrict ventilation as they affect the behaviour of the upper airways. To date, a study is specifically investigating these aspects, namely, the effect of ventilator settings during NIV on patency of the upper airway in patients with exacerbation of chronic obstructive pulmonary disease (ClinicalTrials.gov ID: NCT01791335). Further research recommendations focus on inspiration, but exhalation can also be affected by the patency of the upper airway.

In conclusion, we demonstrated that NIV is complex and influenced by upper airway regulation. These latest findings are mainly based on animal data. Understanding laryngeal reactions during the different modalities and settings of NIV in patients will be critical in determining whether impaired upper airway patency contributes to NIV failure. Improving the success rate of NIV is of significant clinical implication. The upper airway plays an essential role as a conductor of air during NIV. Current literature suggests that during NIV, the ventilator must act in synchrony with the upper airway muscles to allow adequate ventilation. In lambs and piglets, the upper airway patency is influenced by ventilator-induced changes in pressure and flow. We know that the reflexes involved in maintaining patency of the airways are similar between humans and newborn animals but less pronounced. Today we have a wealth of data that shows a limitation on the effects of NIV on the upper airways in acute respiratory failure. Thus, it is fair to think that synchronous activation of the patient's upper airway ventilator will improve ventilation

efficiency. In a preliminary way, it would be indicated to provide recommendations on how to proceed with the adaptation of the patient in NIV as regards the level of assistance with a set of positive pressures and also indications about the management of the interface to improve the acceptance of NIV and to not have negative effects on upper airway patency.

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Noninvasive Ventilation in Upper Airways: Pressure, Airflow, and Volume Waveform Monitoring

Ana Sofia Alves Correia and Sara Daniela Soeima

Introduction

Mechanical ventilation is a ventilatory support method indicated for treating patients with acute or chronic respiratory failure. Positive airway pressure is delivered via an interface (in noninvasive ventilation) or a prosthesis in the airway (in invasive ventilation) [1].

The upper airway is located outside the thorax and consists of the nasal cavities, pharynx, and larynx, and its main functions are to conduct, humidify, and warm the air up to the lungs [2].

The pharynx and larynx are predominantly muscular structures, which may compromise upper airway permeability. This alteration may result in its intermittent obstruction [2, 3].

Its collapse causes oropharyngeal obstructive events as a result of insufficient expiratory positive airway pressure (EPAP). This mechanism may be present in patients with unstable upper airways, namely, those with obstructive sleep apnea syndrome (OSAS) and SOH [2, 4].

This collapse corresponds to cyclic hypocapnia-induced glottis obstruction and is characterized by decreased or suppressed inspiration. Glottic narrowing during inspiration increases upper airway resistance and may limit effective ventilation [2].

To compensate for the alterations described, the use of NIV causes air to enter the lungs. This transition occurs using a positive pressure gradient, i.e., through the cyclical formation of a supra-atmospheric pressure value [5].

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In NIV, when compared to IR, two important characteristics can be found: the fact that we are in the presence of a non-hermetic circuit and also the fact that the ventilator-lung set cannot be considered as a single system, as the variable resistance of the upper airway must be considered [6].

It is useful to remember that in NIV there is a wide range of parameters and ventilator configurations and knowledge of them allows a more correct understanding and interpretation of the patient-ventilator interaction. The ventilator performance, the chosen ventilatory mode, the ramp, the triggers, and the existence or not of an end-expiratory pressure are factors that will have physiological repercussions. The existence of a high leak and the variation in resistance of the upper airways are also factors to be considered, to understand that by applying a higher volume or a higher inspiratory pressure, we may not be increasing the ventilation of the lung. These two factors will influence the characteristics of the respiratory tracings when we evaluate the flow and pressure curves [6]. Monitoring becomes central to the assessment of patients with acute respiratory failure, but it is still necessary to define or prioritize certain variables and signs [7].

Pressure-Time Curve in Superior Airway

The pressure-time curve will guarantee a necessary tidal volume for the patient. The positive end-expiratory pressure (PEEP) corresponds to a pressure curve, by administering enough upper airway pressure to open the airway because it may collapse during inspiration.

Positive end-expiratory pressure (PEEP) will allow the opening of alveoli, previously collapsed or partially opened, substantially improving their recruitment and improving ventilation. This mechanism promotes an increase in functional residual capacity, which results in improved blood oxygenation and reduced inspiratory effort.

The pressure curve allows parameters such as compliance and resistance to inspiration to be calculated and various practical information to be obtained.

The analysis of its morphology can reveal the ventilatory mode that we are using, as the pressure curve is squarer.

In pressure mode, obstruction is suspected if there is a reduction in inspiratory and expiratory flow amplitude on the total flow and patient flow curves without any change in the pressure curve.

The Flow-Time Curve in the Upper Airway

The flow-time curve will allow us to analyze the patient's ventilatory mechanics. It is characterized by the presence of a positive portion which indicates the flow of air toward the lungs (i.e., inspiratory phase) and a negative final portion which indicates the flow of air toward the ventilator (i.e., expiratory phase) [5].In the expiratory

phase, low expiratory peaks indicate obstruction, as does the delay in returning to the basal line. These two indicators allow understanding that there is a greater difficulty in exhaling the air from the lungs (it is retained). This may contribute to the formation of auto-PEEP, also called intrinsic PEEP [1, 5, 8].

PEEP (Positive End-Expiratory Pressure)

The initial PEEP adjustment, in the patient under mechanical ventilation and/or endotracheal intubation, is considered adequate, with a value of at least 5 cm H_2O since the glottis is unable to maintain this expiratory pressure and the ventilator is responsible for generating the positive end-expiratory pressure (PEEP) [5].

PEEP with higher values is also used to reduce pulmonary edema and in alveolar recruitment maneuvers. Increased intrathoracic pressure may lead to consequences such as an increase in intracranial pressure and a decrease in venous return and cardiac output [5].

With increased pulmonary pressures, air trapping generates a pressure higher than the desired PEEP, which we call auto-PEEP. This occurs mainly in patients with airway obstruction, such as in patients with lung disease [5].

We can find many diseases where this increase in exhalation resistance may occur, such as chronic obstructive pulmonary disease (COPD), asthma, and bronchospasm. Self-PEEP may also be associated with high tidal volume, high respiratory rate, and low inspiratory flow, by inversion of the inspiration/expiration (I:E) ratio to values lower than 1:2 [5].

Air trapping is related to the increase of auto-PEEP. This may lead to hemodynamic instability and reduction in tidal volume with a progressive increase in pressures when the expiratory phase time is not sufficient [5].

The increase in intrapulmonary pressure associated with auto-PEEP will originate a high risk of hemodynamic complications, ventilatory asynchronies, barotrauma, and an increase in dead space (ventilated but not perfused regions—increase of hypercapnia) [5].

The presence of auto-PEEP will also cause an increase in respiratory work, forcing the respiratory system to generate a negative pressure greater than auto-PEEP to trigger inspiration, in assisted/spontaneous ventilation modes. It also causes muscle fatigue, unnecessary effort, respiratory discomfort, and increased hemodynamic instability [5].

To calculate the auto-PEEP, the physician must perform an expiratory pause of at least 3 seconds. The difference between the final PEEP observed after the pause and the PEEP visualized on the monitor corresponds to auto-PEEP. Indirectly, by the pressure-time graph on the ventilator, it is possible to identify the presence of auto-PEEP and estimate the value [5, 8].

To solve the increase in auto-PEEP, the safest procedure is to increase the expiratory time, allowing time for the trapped air to be exhaled, and to maintain the PEEP up to 80% of auto-PEEP, which reduces the inspiratory effort.

In case of imminent risk of life, the patient can be disconnected for a few seconds and wait for the air to empty. After that, reconnect the patient, observing the O_2 saturation values and remaining vital signs.

Volume-Time Curve

The main function of the volume-time curve is to assess tidal volume loss. Irregularities in this curve demonstrate asynchrony in the patient's ventilation [5].

Once again, I believe the pictures were to be erase once you didn't get the authorization to publish constitutes the tidal volume. A decrease in this area indicates a low tidal volume and consequently the presence of self-PEEP, high leakage, or even a fault in the circuit [5] (Fig. 1).

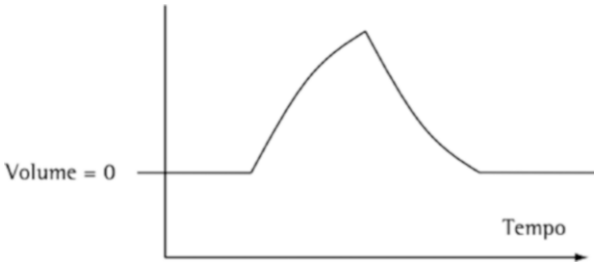

Fig. 1 The volume graph represents, in its ascending portion, the inspired lung volume and, in its descending curve, the expired total lung volume. The volumes are equal unless there is a leak, circuit disconnection, or air trapping. Source: III Consenso Brasileiro de Ventilação Mecânica Mechanical ventilation [1]

Conclusion

- Although the importance of individual assessment of the flow, volume, and pressure curves is well known, it will be more advantageous when analyzed together (Fig. 2) [1].
- Its analysis, besides the advantage of being a noninvasive method, has proven to be a reliable ally in detecting asynchronies that hinder ventilator-patient interaction [9].
- The correct analysis of these curves is important for optimizing therapy and also the knowledge and experience of the health professional in interpreting them.

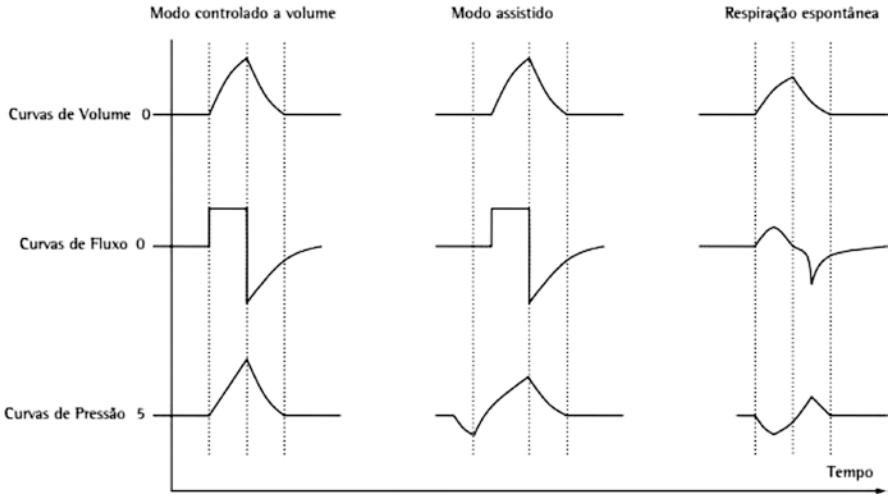

Fig. 2 Association of volume, flow, and pressure curves. Source: III Consenso Brasileiro de Ventilação Mecânica Mechanical ventilation [1]

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Noninvasive Ventilation Success and Failure Risk Factors: The Role of Upper Airways

Domenica Di Costanzo and Mariano Mazza

Abbreviations

ALS	Amyotrophic lateral sclerosis
ARF	Acute respiratory failure
cmH_2O	Centimeters of water
COPD	Chronic obstructive pulmonary disease
EPAP	Expiratory positive airway pressure
FiO_2	Fraction of inspired oxygen
HMEs	Heat-moisture exchangers
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
IPAP	Inspiratory positive airway pressures
NIV	Noninvasive ventilation
PSRs	Pulmonary stretch receptors
PVA	Patient-ventilator asynchrony
RARs	Rapidly adapting receptors
UA	Upper airways

Introduction

Noninvasive ventilation (NIV) refers to the provision of ventilatory support through the patient's upper airways (UA) using a mask or similar device. This technique is distinguished from those which bypass the upper airways with a tracheal tube, laryngeal mask, or tracheostomy and are therefore considered invasive.

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The use of NIV to treat respiratory failure has spread widely throughout the world with a wide spectrum of pathologies treated and settings of application [1–3].

Over the past 20 years, several studies were designed to assess the outcome of NIV and several factors have been identified that increase its success rate.

Similarly, NIV failure, defined as need for intubation or death, relies on numerous factors. However, the pathophysiology of NIV failure is incompletely understood.

An important difference in the application of NIV versus invasive ventilation is, evidently, the involvement of the upper airways. During invasive ventilation the endotracheal tube bypasses the upper airways, and the cuff of the endotracheal tube provides an airtight seal in the trachea; in contrast, during NIV the upper airways may play a role in the efficiency of delivered ventilation [4].

Noninvasive Ventilation Failure

Over the past 20 years, several studies have been designed to assess the outcome of NIV. Failure of NIV is usually defined as (a) need for intubation because of lack of improvement in arterial blood gas tensions and clinical parameters after 1–3 h of ventilation; (b) clinical deterioration and subsequent intubation during hospital stay, and (c) death [5].

The failure rate of NIV varies from 5 to 60% of the treated cases, depending on numerous factors, including the type and severity of acute respiratory failure (ARF), the timing of NIV application, inappropriate ventilation pressures, the patient's clinical condition (i.e., the coexistence of other organ failures besides respiratory failure), the expertise of the team, and the intensity of care provided by the environment [6].

Based on data from randomized controlled trials, NIV failure occurs in three identified time points: (1) immediate failure (within minutes to <1 h), due to weak cough reflex, excessive secretions, intolerance, agitation or hypercapnic encephalopathy syndrome, and patient-ventilator asynchrony; (2) early failure (from 1 to 48 h), due to poor arterial blood gas and the inability to promptly correct them, increased severity of illness, and the persistence of a high respiratory rate with respiratory muscles distress; and (3) late failure (after 48 h), which can occur after an initial favorable response to NIV and may be related to sleep disturbances and severe comorbidities [5].

Immediate Noninvasive Ventilation Failure

Patients with a depressed cough reflex are unable to spontaneously clear their airways, thus creating an excessive burden of respiratory secretions which is likely to cause NIV failure [7].

In such a clinical scenario, adequate secretion management with manual or mechanical techniques may be advisable before NIV is declared failed or

contraindicated: particularly, the suction of secretions with fiber-optic bronchoscopy performed by an experienced team may increase the chance of NIV success [8, 9].

Patients undergoing NIV often present with a heterogeneous spectrum of neurological alterations (from psychomotor agitation and confusion to soporous status, delirium, and coma) which may potentially lead to NIV intolerance.

Paradoxically, if the sensorium is severely depressed, NIV is more likely tolerated, but as patient awakens, a status of agitation and/or delirium frequently occurs, especially in elderly patients, and induces patient to refuse remaining on ventilation [10].

Especially in the first few minutes of adaptation to this "new mode" of breathing, patient tolerance has been shown to be critical for NIV feasibility and success, while the presence of psychomotor agitation induces the lack of necessary cooperation in patients who do not tolerate the mask and the pressurized air pushed by the ventilator. In these conditions, despite the assistance provided also by an experienced nurse team, severe patient-ventilator asynchrony, major air leaks, and patient's attempts in removing the interface may make impossible for the physician to provide an adequate NIV [11].

An integrated strategy based on explaining the technique, asking the patient's preference for the interface, and initiation at low pressures followed by stepwise increases may be helpful to overcome agitation.

However, the use of judicious sedation may be beneficial in some patients for symptom relief and improved patient tolerance and compliance. Physicians should aim to achieve an ideal sedation level that keeps the patient awake or easily arousable, and comfortable. Sedation must be performed by a highly experienced team providing a close monitoring and prompt availability of intubation since an unduly delay may increase the risk of serious systemic complications and, eventually, of death [12].

Patient-ventilator asynchrony (PVA) can be defined as a lack of coordination between the patient and the ventilator [13].

The PVA prevalence is variable since it depends on numerous factors, including timing and duration of observation, detection technique, patient population (e.g., severity of illness, underlying diagnosis), type of asynchrony, ventilation mode and settings (e.g., trigger, flow, and cycle criteria), and confounding factors (e.g., state of wakefulness, sedation) [14].

Several factors affect the occurrence of PVA and they can be related to patient characteristics (e.g., respiratory mechanics, effort) and to the ventilator (e.g., trigger asynchrony, flow asynchrony, cycle asynchrony, mode asynchrony). Moreover, the interface used can be a potential cause of PVA through two mechanisms: (1) it promotes air leaks, and (2) the interface can contribute to mechanical dead space and rebreathing, thus increasing respiratory drive and dyspnea [15].

Asynchrony can easily be detected by an evaluation of symptoms and a physical examination of the patient, particularly taking into account number of spontaneous breaths vs. ventilator-delivered breaths and accessory muscle use. Also, the close observation of the flow, volume, and pressure waveforms on the ventilator can be used to assess for patient-ventilator interactions [16].

The systematic research for asynchronies may be useful in driving the operators' choices and allows an "optimized ventilation," driven by the analysis of the waveforms generated by ventilators, which may have a positive effect on physiological and patient-centered outcomes [17].

Patient-ventilator asynchrony is a potential cause of NIV failure since it causes a series of adverse clinical effects and is associated with unwanted outcomes, such as discomfort, dyspnea, increased/wasted work of breathing, worsening of pulmonary gas exchanges, increased respiratory effort, diaphragmatic injury, decreased quantity and quality of sleep, increased need for sedation, prolonged mechanical ventilation, and longer ICU and hospital stay [14].

Late Noninvasive Ventilation Failure

Late failure can occur after an initial favorable response to NIV and may be related to severe comorbidities and sleep disturbances including an abnormal electroencephalographic pattern, disruption of the circadian sleep cycle, and decreased rapid eye movement sleep [18].

The occurrence of sleep disturbances during noninvasive ventilation is related to different factors. First, during sleep physiological parameters (muscle tone, heart rate, breathing, blood pressure, and metabolic rate) change and may interfere with the efficacy of ventilation [12].

Vice versa, the influence of mechanical ventilation on the quality of sleep is not entirely unambiguous. Mechanical ventilation can cause sleep disruptions through various mechanisms like the occurrence of PVA which can increase respiratory effort, the sedation's effect on sleep architecture, and noise-related sleep fragmentation. However, even if there is a consensus in the literature that mechanical ventilation is probably a factor causing sleep disruptions, it must be considered that sleep disturbances are also related to the severity of disease and noninvasive ventilation can reduce patient effort, improve gas exchange, and thus indirectly improve their quality of sleep [19].

Noninvasive Ventilation Intolerance

Although NIV is generally perceived as more comfortable for patients than IMV, the rate of NIV failure due to patients' intolerance is reported to be variable between 9 and 25% [11, 20–23].

As described above, neurological alterations and the presence of PVA could be cause of NIV intolerance and consequent failure. Moreover, as the duration of NIV increases, patients may develop ventilation-related complications which may lead them to refuse ongoing NIV prompting its discontinuation and subsequent requirement for endotracheal intubation. Ventilation-related complications can be divided into major NIV complications (pneumonia, barotrauma, hemodynamic effects) and minor NIV complications which include interface-related complications (arm

edema and deep venous thrombosis, carbon dioxide rebreathing, claustrophobia, discomfort, facial skin lesions, noise, and patient-ventilator asynchrony) and air pressure- and flow-related complications (air leaks, nasal or oral dryness and nasal congestion, lower airway dryness) [24].

In expert hands, potential remedies can be considered to avoid some minor complications and to reduce the risk of NIV failure, need for IMV, or the chance of death. Discomfort is mainly related to the interface since different models of NIV masks can produce different levels of tolerance. Moreover, all attachment systems were considered variably uncomfortable against the skin, and tolerance may decrease by tightening the straps in an attempt to reduce air leaks. This condition may require a change to a different strap system or mask in order to reduce the discomfort. Air leakage is virtually universal during NIV and depends on sealing features of the interface. Large air leaks decrease the FiO_2 and arterial oxygen saturation and increase ventilation asynchronies and rebreathing of exhaled gas, all of which increase chances of NIV failure. Hence, air leaks must be monitored closely and taken care of promptly. During NIV, nasal or oral dryness is usually indicative of air leaking through the mouth with consequent loss of the nasal mucosa capacity to heat and to humidify inspired air. Nasal mucosa progressively dries and releases inflammation mediators that increase nasal congestion and resistance, thus reducing tidal volume and patient comfort. Strategies to decrease the airway dryness and congestion during NIV should be carefully considered from the beginning of NIV.

During NIV, cool and dry gases alter the tracheobronchial mucosa inducing airway dryness. By drying secretions and desquamating mucosal epithelium, NIV may cause mucous plugging and atelectasis. To avoid this problem, humidification devices, heated humidifiers and HMEs, are used for both short-term and long-term humidification during NIV [24, 25].

It shall be considered that, in order to provide patient comfort as to optimize the chances of success during NIV, judicious use of sedation during NIV can be a valuable option for some patients at risk of intubation due to mask intolerance, because of pain, discomfort, claustrophobia, or agitation. This reasoning is helpful within the first few hours of NIV when the patient needs to adapt and later when prolonged ventilation is required [26].

Sedation can facilitate ventilation, calms anxiety, promotes sleep, and modulates the autonomic system responses to stress, such as tachycardia and hypertension, with a final improvement of patient's adaptation to NIV [26, 27].

Previous studies have addressed the efficacy of sedation during NIV, using dexmedetomidine [28–30], midazolam [30], propofol [31], and remifentanil [32].

The intrinsic characteristics and clinical effects of the various pharmacological categories must be considered when choosing the drug, especially regarding the effects exerted on patient's own respiratory drive.

Benzodiazepines should preferentially be avoided in the elderly due to the risk of a paradoxical state of delirium [33].

In addition, the benzodiazepines' pharmacokinetics profile is prone to accumulation in the case of obese patients or in those subjects with renal injury or low albumin levels [34].

Propofol has a rapid pharmacokinetic profile, but sedation regimen dose must be decided carefully since it has shown to adversely affect the breathing pattern, the respiratory drive, and gas exchange, proportionally to the rate of its infusion [35].

Dexmedetomidine, a selective α2 agonist with intrinsic properties of sedative and analgesic effects, may be useful thanks to its limited effect on the respiratory pattern. Its main adverse effects are bradycardia and hypotension, and in literature there is evidence of it being superior to midazolam in terms of pharmacokinetics manageability [27].

Remifentanil is a short-acting opioid that has also proven to be safe and effective to achieve optimal sedation in case of intolerance to NIV [32].

Regardless of the drug adopted, evaluation for agitation before starting therapy and subsequent sedation assessments are of pivotal importance during NIV. The use of subjective scales (e.g., Richmond Agitation-Sedation Scale) at regular time intervals allows to provide the desired target of sedation [12].

The Role of Upper Airway in the Failure of NIV

Noninvasive Ventilation and Upper Airway Physiology

Currently, the relationships between NIV efficiency and upper airways (UA) are not completely understood. On one side, ventilator settings during NIV affect physical conditions such as pressure, flow, and temperature which contribute to determine the patency of the UA. On the other side, this effect implies that deviant behavior of the UA may play a role in the failure of NIV.

Therefore, to achieve optimal management of ventilated patients, it is of utmost importance to understand the normal anatomy and physiology of UA and the changes induced by pressure, flow, and temperature.

The UA comprise the nose, oral cavity, pharynx, and larynx. The nose and oral cavity are mainly static in their conducting function, whereas the pharynx and larynx predominantly are muscular structures and thus may alter the patency of the UA [4].

Receptors in the upper and lower airways modulate activity of the UA muscles. The most prominent receptors are the bronchopulmonary C-fiber receptors, rapidly adapting receptors (RARs), and slowly adapting pulmonary stretch receptors (PSRs).

C-fiber receptors are excited both by large mechanical deformations and chemical stimuli. Their activation evokes inhibitory effects (apnea or bradypnea; hypotension and bradycardia) and can result in closing of the UA by glottic narrowing by activation of laryngeal muscles.

RARs respond in reaction to mechanical and chemical stimuli and produce mainly excitatory effects such as tachypnea. When the laryngeal mucosa is stimulated, RAR reflexes elicit laryngoconstriction and bronchoconstriction, which may be part of the glottal closure seen during cough.

PSRs do not affect patency of the UA but modulate the respiratory cycle: they terminate inspiration and extend expiration. PSRs are activated by stretching the airway wall and fire throughout the respiratory cycle (tonic activity) or in response to lung inflation (phasic activity).

Respiration and in particular patency of the UA depend on a complex, but incompletely understood, interplay between several inhibitory and excitatory pathways [36–40].

NIV may affect some physical conditions such as pressure, flow, and temperature and therefore affects patency of the UA [41].

Previous studies have tested the impact of NIV-derived positive pressure with a nasal interface in the UA of healthy subjects. The protocol included the delivery of three different levels of inspiratory positive airway pressures (IPAP: 10, 15, and 20 cmH_2O), in the presence of 5 cmH_2O of expiratory positive airway pressure (EPAP), using controlled and spontaneous modes. The authors concluded that incremental IPAP does not always lead to improvements in lung ventilation, so they suggest that the use of a two-level positive-pressure ventilator in controlled mode is less predictable and less stable compared to volumetric ventilators. This observation may be explained by the significant narrowing of the glottis caused by adduction of the vocal cords for all patients undergoing positive pressure [42, 43].

Another study evaluating glottis patency in the acute exacerbation of COPD with NIV found that high pressures using different ventilatory modes did not cause UA obstruction, but increased respiratory volume, perhaps because the protective and normal reflex response at high pressures does not occur in COPD patients. The main reason invoked is the alteration of the C-fiber receptors' response to chemical stimulus with narrowing of the glottis, due to chronic inhalation of carbon dioxide. Therefore, this may be the reason for the high-intensity ventilation effectiveness in COPD patients [44].

In addition to the positive pressure delivered by the ventilator, the interface used can also induce changes in the patency of the UA. Particularly, caution needs to be used when applying oronasal masks because this can cause posterior displacement of the tongue inducing partial obstruction of the oropharyngeal airway. On the contrary nasal masks are thought to produce a differential pressure gradient between the nasopharynx and oropharynx, thus causing a pneumatic splinting, and this phenomenon pushes the soft palate and the tongue anteriorly away from the posterior pharyngeal wall [45, 46].

Another important aspect to consider is that positive-pressure ventilation can induce hyperventilation and cyclic hypocapnia. This effect has been shown to promote intermittent obstruction of the UA through active glottis closures in normal subjects when either awake or asleep [47, 48].

Asynchronies are generally related to the interaction between the activity of the inspiratory muscles and the ventilator response; however, as far as explained so far, it is evident that during NIV it is also important that the ventilator acts in synchrony with the UA muscles [4, 49].

Noninvasive Ventilation and Upper Airway Pathology

The efficacy of NIV delivery can be also greatly compromised by alterations in the UA patency or spasticity.

In patients with obstructive sleep apnea or obesity hypoventilation syndrome, soft tissue collapse of UA can significantly decrease their diameter and increase airflow resistance, particularly in the supine position, thus provoking oropharyngeal obstructive events [44, 50].

Neuromuscular patients with upper motor neuron involvement and impairment of bulbar function, particularly amyotrophic lateral sclerosis (ALS), are more likely to fail NIV due to UA spasticity [51, 52].

The alteration common to neuromuscular disease patients is respiratory muscle weakness, which varies highly according to the underlying disease. Weakness may affect three main muscle groups: inspiratory muscles (diaphragm, parasternal, scalene, and accessory muscles), expiratory muscles (external intercostal and abdominal muscles), and muscles of the upper airways (palatine, pharyngeal, and genioglossal muscles) [53].

Patients with bulbar muscle weakness present epiglottic flapping which may be an explanation for the failure of NIV therapy per se. Moreover, the way NIV is applied can aggravate this condition since the use of high-pressure values could worsen the epiglottic dysfunction and result in the occlusion of the laryngeal space [54, 55].

Predictors of Noninvasive Ventilation Success

Several factors have been identified that increase the success rate of NIV. These factors include careful selection of patients, properly timed intervention, a comfortable and well-fitting interface, coaching and encouragement of patients, careful monitoring, and a skilled and motivated nursing team.

The prediction of NIV success inevitably depends even on the ability to predict its failure.

From the beginning of NIV usage, several tries have been made to predict NIV success, as early intubation may reduce hospital mortality, in patients experiencing NIV failure. Different scores, more or less easy to apply, have been tried.

In 2017, a composite score, the HACOR score, which includes heart rate, acidosis, state of consciousness, oxygenation, and respiratory rate, recorded after the first hour of treatment, has shown to predict NIV failure with high sensitivity and high specificity, in patients suffering from hypoxemic respiratory failure. The study results indicate that the HACOR score can be used in patients with different disease severity; then, though the NIV failure rate is different between patients who have received different diagnoses and also for different ages, the HACOR score achieves a good predictive power independently from them. The HACOR score shows moreover lower values in patients who successfully undergo NIV, but it does not improve after 1 h in patients with NIV failure. Therefore, it can be also used to assess the efficacy of NIV. A HACOR score of 5 as cutoff value has a good predictive power

for NIV failure. At 1 h after NIV initiation, 87.1% of patients with a HACOR score of >5 required intubation, and 81.6% of patients with HACOR score ≤ 5 did not require intubation. These values indicate that the risk of NIV failure is high in patients with a HACOR score of >5. Further, the high-risk patients who receive early intubation meet lower hospital mortality than those who receive a late intubation. Thus, the HACOR score can be used to establish the necessity for intubation too and so avoid late intubations [56].

In the year 2020, a small monocenter study, inspiring to HACOR score, enrolls 329 patients suffering from respiratory failure of various etiology who need to be treated with assisted mechanical ventilation, and try to pack a score composed by five items, collected at the beginning of hospitalization in an emergency department and before starting the NIV, to predict its failure. These, in order of weight on the score, were the presence of lactacidemia greater than 8 mmol/L, a pH below 7.30, a systolic blood pressure below 90 mmHg, a heart rate greater than 110 beats per minute, and a peripheral oxygen saturation of less than 90%. Three risk classes have been then identified, low (score 0–1), moderate (score 2–4), and high (score > 5), which have shown a sensitivity to predicting noninvasive mechanical ventilation failure of 72.27% [57].

In another study with a larger cohort of nonsurgical patients, from 127 different US centers, who underwent NIV as the first ventilation methodology for the treatment of respiratory failure due to various causes, not later than 2 days after hospitalization, 10 items were evaluated, which included the number of organ failure, principal diagnosis, acute physiological parameters, and chronic disease comorbidities. This score applies regardless of the cause of respiratory failure and stratifies patients into three risk classes, high, intermediate, and low; it does not require the evaluation of laboratory parameters, so it can be applied to all patients, even in the earliest stages of hospitalization, who are immediately subjected to NIV. Among its weaknesses, however, there is the lack of control of the same entry parameters after 1 or 2 h, a time universally considered to evaluate the effectiveness of NIV. The use of this score is however to be considered innovative, because in other works have been prepared scores that tried to predict the failure of the NIV, but in specific pathology settings [58].

Conclusions

Noninvasive ventilation failure, defined as need for intubation or death, relies on numerous factors like weak cough reflex, neurological alterations, patient-ventilator asynchrony, sleep disturbances, and severe comorbidities. A poor tolerance and compliance can also be responsible for NIV failure.

An important difference in the application of NIV versus invasive ventilation is, evidently, the involvement of the upper airway which might play a role in the efficiency of delivered ventilation.

Currently, the relationship between noninvasive ventilation outcome and upper airway is not completely understood.

It is known that respiration and in particular patency of the UA depend on a complex, but incompletely understood, interplay between several inhibitory and excitatory pathways.

On one side, ventilator settings during NIV affect physical conditions such as pressure, flow, and temperature which contribute to determine the patency of the upper airway.

On the other side, this effect implies that deviant behavior of the UA may play a role in the failure of NIV.

Careful selection of patients, properly timed intervention, a comfortable and well-fitting interface, coaching and encouragement of patients, careful monitoring, and a skilled and motivated nursing team are factors that can increase the success rate of NIV.

Several tries have been made to predict NIV success, as early intubation may reduce hospital mortality, in patients experiencing NIV failure. Different scores, more or less easy to apply, have been tried, and their use, regardless of which one is chosen, must become an integral part of the daily evaluation of the patient in NIV, even in non-ICU settings, as the prediction of NIV success inevitably depends even on the ability to predict its failure.

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Humidification in Noninvasive Mechanical Ventilation and High-Flow Oxygen

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The human airways have an important role in heating and humidifying inspired gas and recovering heat and moisture from expired gas. The amount of water vapor in a gas mixture can be measured as absolute humidity (AH) or relative humidity (RH) in relation to the temperature. AH is the total water present in the gas (mg H_2O/L) and RH is the amount of water present expressed as the percentage of maximum carrying capacity at a given temperature. The human airways must provide gas at core temperature and 100% RH at the alveolar surface, in order to optimize gas exchange and protect lung tissue. The percentage (%) of water vapor contained in a gas, relative to its maximum carrying capacity, represents the better relative humidity. Absolute humidity is the total amount of water vapor contained in a gas, expressed in milligrams of water suspended in liters of gas (mg/L) (Table 1).

Table 1 Relationships between the gas temperature, absolute humidity, and water vapor pressure

Gas temperature (°C)	Absolute humidity (mg/L)	Water vapor pressure (mmHg)
0	4.85	4.6
5	6.8	6.5
10	9.4	9.2
15	12.8	12.8
30	30.4	31.7
34	37.6	39.8
36	41.7	44.4
37	43.9	46.9
40	51.1	55.1

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Table 1 Relationships between the gas temperature, absolute humidity, and water vapor pressure [1]

When there is respiratory failure, a clinical condition characterized by the inability of the respiratory system to ensure adequate gas exchange, both in resting conditions and under effort, resulting in hypoxemia (type I respiratory failure) and, sometimes, hypercapnia (type II respiratory failure), the available therapies are represented by oxygen therapy and mechanical ventilation.

Type I can be carried out through low-flow systems (e.g., nasal cannula, nasal catheter, simple mask, reservoir mask, or transtracheal cannula) or high-flow systems (e.g., Venturi mask, T-tube, humidified high-flow nasal systems humidified high-flow nasal cannulas (HFNC)), while type II required mechanical ventilation.

Oxygen supplementation often takes the form of a low-flow nasal cannula (LFNC) [2]; however, there are limitations to this supplemental oxygen intervention. A traditional nasal cannula can effectively provide only up to 4–6 L per minute of supplemental oxygen. This equates to a FiO_2 of approximately 0.37–0.45.

The efficacy of LFNC is limited, because of nasal mucosal irritation, there is an increased potential for bleeding with prolonged use, and also there are high levels of leaking air around the oxygen source.

High-flow nasal cannula (HFNC) therapy is an oxygen supply system carried out through dedicated devices or through mechanical ventilation, and it is capable of delivering up to 100% humidified and heated oxygen [3].

The delivering system includes:

- A flow generator (up to 60 L/min)
- A room air/oxygen mixer (which allows you to deliver a FiO_2 up to 100%)
- A gas humidification and heating system
- A heated disposable circuit
- Special small, pliable nasal prongs with an internal diameter greater than those commonly used for conventional oxygen therapy that enhance patient comfort and allow oral feeding

To carry out the HFNC titration, it is necessary to set two parameters: flow (L/min), first to be set, from 20 to 35 L/min (range from 5 to 60 L/min), and FiO_2 21–100% range to reach target peripheral SpO_2.

The possibility of heating and humidifying inspired air facilitates the clearance of airway secretions, avoids airway desiccation and epithelial injury, decreases work of breathing, and reduces risk of bronchospasm and microatelectasis.

The washout of nasopharyngeal dead space improves oxygen delivery and increases alveolar ventilation (reduced VD/VT) with possible reduction in respiratory rate.

Finally the persistence of the high flow during exhalation induces the appearance of low PEEP levels that reduce the work of breathing and recruit poorly ventilated areas, improving V/Q ratio.

HFNC allows the increase, in proportion to the increase in airflow, of the pressure of the nasopharyngeal airways, which reaches its peak at the end of exhalation.

There will therefore be a reduction in auto-PEEP (if any) and a reduction in respiratory work.

Each increase of 10 L/min of the flow generated about 0.7 cmH_2O with mouth closed and about 0.35 cmH2O with mouth open.

The indications regarding the use of HFNC are not absolute, and there hasn't been consistent evidence of improvement in clinically significant outcomes (mortality, orotracheal intubation rate, length of hospitalization).

Unquestionably the use of HFNC is correctly indicated in patients with severe hypoxemic respiratory failure (PaO_2/FiO_2 ratio < 300 mmHg), as a first choice; it's also useful in patients who have difficult adaptation to mechanical ventilation, in patients with a lot of bronchial secretion, and in the weaning phases from the mechanical ventilation itself.

Finally, HFNC therapy also has contraindications and side effects. It cannot be used in case of maxillofacial anatomical alterations; surgery of the face, nose, or airways (because of a theoretical risk that high pressure may cause venous thromboembolism); altered state of consciousness; hemodynamic instability; and respiratory arrest.

The side effects are represented by gastric and/or abdominal distension, suction, and rarely barotrauma with pneumothorax (PNX).

HFNC therapy may be used also in pediatric settings, like in the care of bronchiolitis. There have been some small retrospective trials examining its benefit with asthma; the heated and humidified oxygen may be beneficial to further prevent airway inflammation and bronchospasm. Other uses may include pneumonia.

Mechanical ventilation is a therapy carried out through a device, the ventilator, which supports or replaces the effort that the respiratory muscles must make to support the respiratory work. This is possible by applying a positive pressure to the airways or a subatmospheric pressure to the outside of the chest (negative pressure ventilation).

Mechanical ventilation is a therapy that is used in the treatment of type II respiratory failure or hypoxemic-hypercapnic respiratory failure or in cases where the respiratory musculature is not sufficiently adequate to support respiratory acts, with the onset of fatigue.

There are various ventilation modes, such as pressure support ventilation (PSV), assist-control ventilation (A/C), and synchronized intermittent mandatory ventilation (SIMV), which must be used according to the different clinical pictures presented by patients; therefore, there are no more effective or less effective ways.

In order for ventilotherapy to have the desired success, it is necessary to follow certain rules:

-Select the most appropriate patient-ventilator interface, to ensure the greatest possible comfort and prevent side effects such as excessive air leakage, claustrophobia, skin decubitus, and conjunctival irritation.

The available interfaces can be nasal, oronasal, helmet, snorkel, and tracheostomy cannula (to be used in case of invasive ventilation); they are commercially available in standard sizes (small, medium, large, extra-large, and pediatric sizes) or custom-made, by facial impression or cast.

- Use a correct tidal volume (VT), to avoid excessive distension of the pulmonary parenchyma (VT = 4–6 mL/kg) [4].
- Set the correct PEEP (positive end-expiratory pressure) value, which allows you to recruit collapsed areas of pulmonary parenchyma [5].

While in the literature there is a clear standardization of the parameters of the use of ventilation in respiratory failure, there are no clear indications on the timing of use of noninvasive ventilation, which must be started as early as possible, to avoid the progression of the clinical picture and a possible recourse to intubation.

Finally, humidification is of great importance, even if often underestimated, both during therapy with HFNC and during ventilation therapy [6].

Repeated inhalation by the patient of a flow of cold and dry air is able to give rise to side effects, which often undermine the patient's compliance with the therapy.

Pharyngodynia, dry mouth, nasal congestion, rhinorrhea, nosebleeds, and cough are preventable complications, adding a humidification system into the circuit.

There are two main classes of humidifiers, cold humidifiers, called HME (heat and moisture exchangers), and hot humidifiers (HH), which have both advantages and disadvantages, which will be explored in depth during this chapter.

Humidification in NIV, Why? How?

Noninvasive ventilation (NIV) is a mechanical ventilation modality that does not utilize an invasive artificial airway (endotracheal tube or tracheostomy tube). NIV is usually delivered through a nasal or oronasal mask, so the inspired gas passes through the upper airway where it is conditioned. Like during spontaneous breathing, patients under NIV require adequate humidification and heating of the inspired air (i.e., gas conditioning). NIV delivers inspired air at high flow rates, which may overwhelm the usual airway humidification mechanisms [7].

Adequacy of ventilation during treatment with noninvasive ventilation (NIV) is dependent on providing sufficient airflow to maintain a pressure gradient from the ventilator, through tubing and from the mask to the patient's nasopharynx and subsequent airways. Justin M. Tuggeya et al. [8] demonstrated that a poorly fitting nasal mask can lead to discomfort and interface leak. Leak is particularly common during sleep in patients receiving NIV and may be associated with increased sleep fragmentation and failure of NIV in those receiving long-term ventilation. Other studies using continuous positive airway pressure (CPAP) have demonstrated that during periods of mouth leak, there is high, unidirectional, nasal airflow. This can cause the release of inflammatory mediators, increased mucosal blood flow, and increased nasal airway resistance. Richards et al. [9] demonstrated that during CPAP, this increase in resistance can be largely attenuated using heated humidification. Furthermore, equipping patients receiving CPAP for obstructive sleep apnea with heated humidification reduces side effects and enhances comfort and compliance. Provision of either a full face mask or chinstrap can reduce mouth leak. No similar

studies have been performed during NIV applied through the nose. There are significant differences in terms of airway mechanics, physiological responses, and treatment goals between NIV and CPAP. NIV, is used to treat ventilatory failure and, therefore, increases in nasal resistance as may occur during mouth leak, particularly during pressure-targeted NIV, a significant pressure drop across the nasal passages may result, with a reduction in intra-alveolar pressures. This could have deleterious effects on nocturnal ventilation and daytime arterial blood gas tensions, which may be attenuated by the use of heated humidification [10].

Two types of devices for conditioning inspired gases in the presence or absence of an artificial airway are available: heat and moisture exchangers (HME) (Fig. 1) and active humidifiers.

Regardless of which device is chosen, it should infallibly meet the minimum requirements to replace the function of the upper airway, which, according the American Association for Respiratory Care, are:

– 30 mg/L absolute humidity, 34 °C, and 100% relative humidity for HME
– Between 33 and 44 mg/L absolute humidity; between 34 °C and 41 °C; 100% relative humidity for active humidifiers

Passive Humidifiers (See Fig. 1)

The working principle for these devices is based on their capacity to retain heat and humidity during expiration and to deliver at least 70% of them to the inhaled gas during subsequent inspiration. This "passive" function can be achieved by different mechanisms, and the classification of these devices is based on their mechanisms:

Fig. 1 Example of HME *Simplifying we can describe HME as a moisture catcher*

(a) Heat and moisture exchangers
(b) Hygroscopic condenser humidifiers (HCHs) or hygroscopic heat and moisture exchangers (HHME)
(c) Heat and moisture exchangers with filter
(d) Combined heat and moisture exchangers

The passive humidifiers are used especially in invasive mechanical ventilation (iMV).

Active Humidifiers (Heated Humidifiers)

Active humidifiers are devices composed of an electric heater on which is placed a plastic casing with a metallic base in which sterile water is stored. When the base is warmed, the water temperature increases by convection. Some active humidifiers are self-regulated by a mechanism consisting of a heating wire (heated-wire breathing circuit) that keeps the gas temperature constant during its passage through the circuit and a wire with two temperature sensors connected to the exit of the heater (distal) and to a part of the circuit (close to the patient) to control the system temperature.

It should be taken into account that while heated-wire breathing circuit keeps the temperature stable throughout its route and decreases the condensation, the lack of control exposes the patient to risks such as a higher incidence of occlusion of the artificial airway.

Types of Active Humidifiers

Bubble Humidifiers (See Fig. 2)

Bubble humidifiers rely on the bubble-water interface to enrich the inspired gas with water.

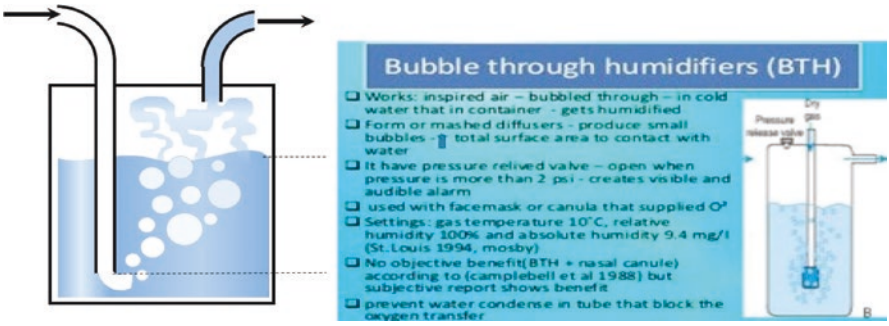

Fig. 2 Bubble humidifiers
Bubble humidifiers are safe and easy to use. The bubblers moisten the inhaled oxygen. The goal here is to prevent the nose from drying out. This can prevent nasal irritation caused by inhaling oxygen

Pass-Over Humidifiers (See Fig. 3)

The airflow passes over the water surface, which is hot, and the circulating gas gains heat and humidity from the gas-water interface formed. In comparison with the previously described device, pass-over humidifiers have lower resistance. It is important to consider that the water temperature in the enclosure will be a determining factor for humidity.

A variant of the pass-over humidifier is the "wick" humidifier, in which a porous membrane that absorbs humidity (such as blotting paper) is dipped into water surrounded by the heating element, keeping the membrane constantly saturated with water vapor. The dry gas enters the chamber, makes contact with the wick, and is loaded with more water vapor than in the basic system because the gas-liquid interface is larger.

Another variant is the hydrophobic membrane humidifier, where dry gas passes through the membrane, and, due to the membrane properties, only water vapor passes through. The dry gas is loaded with water vapor and exits the chamber.

To conclude in *RESPIRATORY CARE* [11], there were the following recommendations:

- Humidification is recommended on every patient receiving invasive mechanical ventilation.
- Active humidification is suggested for NIV, as it may improve adherence and comfort.
- When providing active humidification to patients who are invasively ventilated, it is suggested that the device provide a humidity level between 33 mg H_2O/L and

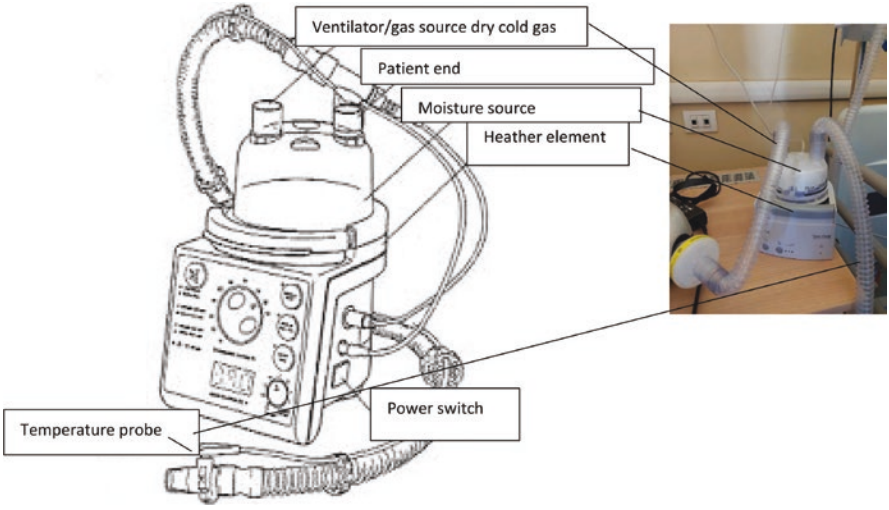

Fig. 3 Examples of active/pass-over humidifier
When the pass-over humidifier is used, the air coming from the pulmonary ventilator touches the water contained in the "bell" and gains heat and humidity, which can also be associated with thermoregulated circuit

44 mg H_2O/L and gas temperature between 34 °C and 41 °C at the circuit Y-piece, with an RH of 100%.
- When providing passive humidification to patients undergoing invasive mechanical ventilation, it is suggested that the HME provide a minimum of 30 mg H_2O/L.
- Passive humidification is not recommended for NIV.
- When providing humidification to patients with low tidal volumes, such as when lung-protective ventilation strategies are used, HME are not recommended because they contribute additional dead space, which can increase the ventilation requirement and $PaCO_2$.
- It is suggested that HME are not used as a prevention strategy for ventilator-associated pneumonia.

Humidification in High-Flow Oxygen, Why? How?

The traditional oxygen therapy with mask or nasal prongs system delivering dry gas and cold air can cause mask discomfort, nasal dryness, oral dryness, eye irritation, nasal and eye trauma, gastric distension, and aspiration.

Primary mechanical pulmonary defense mechanisms are sneezing, coughing, gagging, and the use of natural filters, i.e., nasal hairs. The second line of defense is the mucociliary transport system which traps and neutralizes inhaled contaminants (in mucus) and transports them up and out of the airway, keeping the lung free from infection-causing pathogens. This critical defense system is very sensitive to humidity. Loss of humidity can be a problem in itself.

In the clinical settings, there are several situations where moisture is reduced. It is the case of delivering gas from an artificial flow source, such as piped oxygen, or the utilization of an endotracheal or tracheostomy tube bypassing the upper airway where the majority of humidification would naturally occur. These factors deplete the airway mucosa of heat and moisture, and this can have significant adverse effects on the function of the mucociliary transport system and lead to impaired airway defense and gas exchange:

1. The mucus layer becoming thick and tenacious
2. The thickness of the aqueous layer decreasing, causing cilia to slow down or stop
3. Heat loss from the epithelium cells, making cilia beat less frequently

Nasal high-flow oxygen is part of this context and may have an important role [12]. In fact the need to heat and humidify supplemental oxygen has been long debated. In comparison to high-flow face mask oxygen, some studies have found better comfort, tolerance, and oxygenation and lower respiratory rate with HFNC.

Chanques et al. [13], in a study including 30 patients treated with high-flow oxygen therapy, showed that bubble humidifiers delivered poor levels of humidity and were associated with significant discomfort; however the use of a heated humidifier in patients with high-flow oxygen therapy was associated with a decrease of dryness

symptoms mediated by increased humidity levels. Because high flows of cold and dry oxygen used during HFNC therapy increase the airway resistance, the addition of heat and humidity is compulsory with HFNC.

The heated humidifier system may also indirectly affect non-oxygenation. Active humidification improves mucociliary function, facilitates secretion clearance, and decreases atelectasis formation which improves the ventilation-perfusion ratio and oxygenation. In a study by Sztrymf et al. [14] about the impact of high-flow nasal cannula oxygen on intensive care unit patients with acute respiratory failure, there were no reported interruptions of HFNC therapy because of discomfort. In another study in which HFNC was used for an average of 2.8 ± 1.8 days (maximum 7 days), intolerance never caused HFNC to be discontinued, and no unexpected side effects were reported. Therefore, it's demonstrated that HFNC could be considered very comfortable, especially because all the patients chose to continue with HFNC, there is better control of FiO_2, and there is better mucociliary clearance. In addition, other proposed mechanisms of action may include the ability to more accurately control the patient's FiO_2 and better mucociliary clearance [15].

Delivering essential humidity through HFNC can prevent drying of the airway, avoiding the inflammatory response caused by the drying of the mucosa. Conditioning of the gas can also minimize airway constriction, reducing the work of breathing, which helps to maintain effective delivery of oxygen to the lungs. By delivering optimal humidity, patients can maintain the function of the mucociliary transport system, clearing secretions more effectively and reducing the risk of respiratory infection. This can be particularly important for patients with secretion problems such as those with COPD. All these beneficial effects are directly related to humidification, hence the name of active humidification.

To conclude there are physiological effects of HFNC [16]:

- Pharyngeal dead space washout
- Reduction of nasopharyngeal resistance
- Positive end-expiratory pressure (PEEP) effect
- Alveolar recruitment
- Humidification, great comfort, and better tolerance
- Better control of FiO_2 and better mucociliary clearance

Technical Issues

HFNC devices require three components: a patient interface, a gas delivery device to control flow and FiO_2, and a humidifier (Figs. 4 and 5).

Patient Interface

Several manufacturers provide cannulas with standard dimension prongs which are designed for high-flow applications. These cannulas can accommodate a high inlet flow of at least 60 L/min.

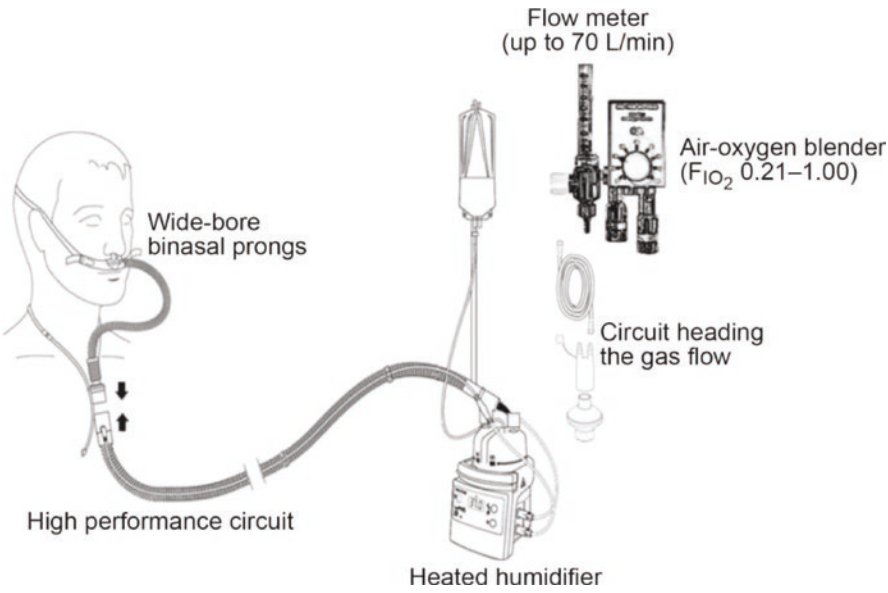

Fig. 4 HFNC hospital system

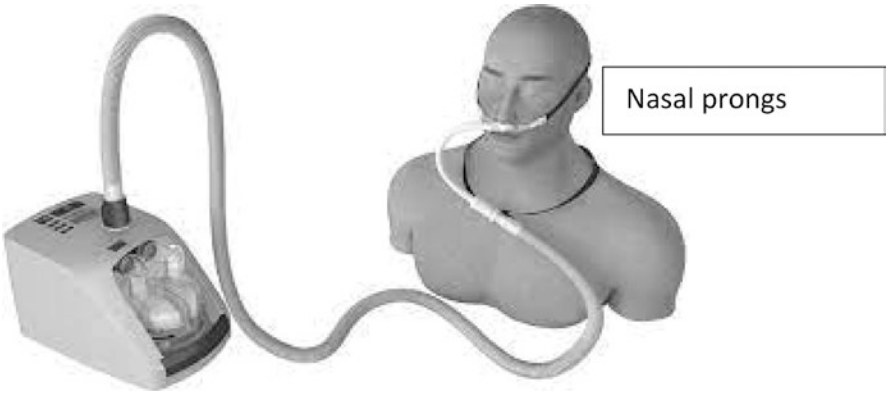

Fig. 5 HFNC home system
High-flow nasal cannula (HFNC) oxygen therapy is carried out using an air/oxygen blender, active humidifier, single heated tube, and nasal cannula. Able to deliver adequately heated and humidified medical gas at flows up to 60 L/min, it is considered to have a number of physiological advantages compared with other standard oxygen therapies, including reduced anatomical dead space, PEEP, constant FIO_2, and good humidification

Controlling Flow and FiO_2

We need to use commercially available calibrated high-flow (0–70 L/min) oxygen flow meters. To allow independent adjustment of FiO_2 less than 1.0, separate high-flow air and oxygen flow meters can be connected via a "Y-piece" adapter. High-flow air/O_2 proportioner valve blenders or high-flow "Venturi" air mixing valves can be used. In any case, an oxygen analyzer is needed to confirm the FiO_2 is appropriate.

Humidifiers

A key element for clinical use of HFNC is effective humidification. The two most popular commercial HFNC devices are the Fisher & Paykel Optiflow and the Vapotherm Precision Flow HFNC. They have different characteristics and technology development (see Figs. 4, 5, and 6).

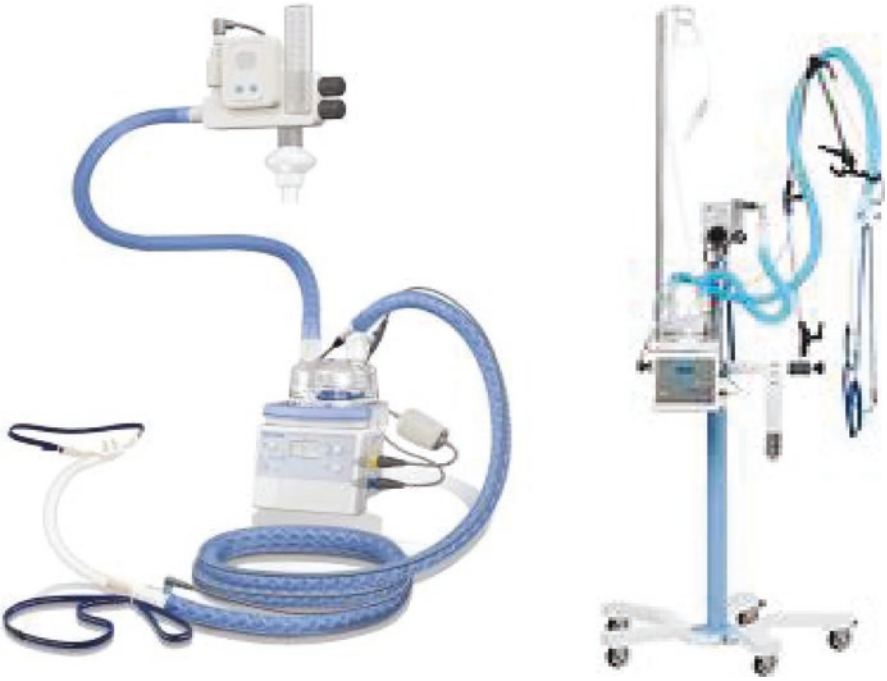

Fig. 6 Different examples of HFNC system (by web)

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Part III

Clinical Indications in Upper Airways Disorders

Noninvasive Approaches to Supraglottic and Vocal Cord Dysfunction

Yunus Emre Tunçdemir and Kamil Cintan

Introduction

Ventilation is of vital importance to human beings. Ventilation is defined as the delivery of the outside air to the alveoli and the discharge of the alveolar air to the outside through the respiratory tract. Thus, oxygenation of the cells and elimination of carbon dioxide from the body are provided. The respiratory system begins with the nose and mouth and ends with the alveoli [1].

The larynx is a very important anatomical component of this system. Pathologies of the larynx may present with various clinical manifestations, such as congenital anomaly obstruction. These pathologies can cause very different clinical presentations like hoarseness, odynophagia, and even death [2].

In case of moderate to severe respiratory failure, some medical intervention may be required. This intervention can be invasive and noninvasive. The noninvasive method is to provide ventilation support without endotracheal intubation [3]. In noninvasive approaches, supportive ventilation is usually provided with a mask or similar device [4].

Mechanical ventilators have become an integral part of noninvasive interventions. In recent years, further progress has been made with different complex modes of microprocessor mechanical ventilators. Some modes of advanced mechanical ventilators are also used in noninvasive approaches.

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Supraglottic and Vocal Cord Pathologies

- Congenital anomalies
- Laryngeal acute infections
- Chronic infections
- Inflammatory diseases causing laryngeal involvement
- Laryngeal malignancies
- Vocal cord paralysis

Congenital Anomalies

The upper airway extends from the nasal opening to the subglottis. Different congenital anomalies may occur along the tract which may cause anatomical or functional obstruction. Laryngomalacia, vocal cord paralysis, and subglottic stenosis are the most common congenital anomalies. Laryngomalacia is the most common congenital laryngeal anomaly. Inspiratory stridor usually develops 2 weeks after birth and resolves by 18 months of age.

Most cases can be managed with mindful nutrition support. Clinically severe cases require surgical intervention. Bilateral vocal cord paralysis is usually idiopathic. In severe cases, endotracheal intubation and tracheostomy may be required. Congenital subglottic stenosis is the third most common laryngeal anomaly. It is defined as a diameter less than 4 mm in a premature baby. It is the most common laryngeal anomaly requiring tracheotomy [5].

Laryngeal Acute Infections

Acute Laryngotracheobronchitis

Laryngotracheobronchitis is inflammation of the larynx, trachea, and bronchi. Usually, viruses are responsible for the etiology. Although it is more common in children, it can rarely be seen in adults [6–8]. On physical examination, the vocal cords are edematous, and intense purulent secretions can be seen in the larynx and trachea. Hoarseness and dyspnea are the main symptoms [9]. In treatment, oxygen support, hydration, and if necessary epinephrine can be given. Dexamethasone can be used in persistent acute respiratory failure. If secondary bacterial infection is suspected, antibiotics should be added to the treatment. Intubation may be required in 1% of patients [10].

Acute Epiglottitis

Acute epiglottitis, also known as acute supraglottis, is a life-threatening mortal disease due to the risk of laryngospasm and irreversible loss of the airway. There is edema due to inflammation in the epiglottis. Mortality is higher in adults than in children. The most common causative agent is *Haemophilus influenzae* type b. Fever, dysphonia, odynophagia, dysphagia, and dyspnea are the most common

symptoms [11]. The patient should be hospitalized, and antibiotherapy, hydration, and anti-inflammatory treatment should be applied. If the airway is obstructed, noninvasive or invasive airway relief-opening maneuvers should be tried depending on the severity of the disease [12].

Laryngeal Diphtheria

Diphtheria caused by *Corynebacterium diphtheriae* is an extremely rare disease due to the widespread use of the diphtheria vaccine. It is characterized by gray membranes that may bleed when lifted. The presence of membranes in the larynx can lead to acute airway obstruction. Penicillin group antibiotics and antitoxins are used in treatment [13].

Chronic Infections

Laryngeal Tuberculosis

Laryngeal tuberculosis is rare. It may be primary laryngeal tuberculosis or secondary to pulmonary tuberculosis. Patients usually present with symptoms such as hoarseness, dysphagia, fever, or localized pain [14]. Laryngeal tuberculosis commonly involves the supraglottic region. It may cause severe dyspnea depending on the extent of the lesions. Long-term antituberculosis treatment is required [15].

Laryngeal Syphilis

Syphilis is a sexually transmitted disease caused by *Treponema pallidum*. Laryngeal syphilis is rare. Granulomatous diseases such as tuberculosis, sarcoidosis, and laryngeal carcinoma take place in differential diagnoses [16]. Syphilis causes ulcers, nodules, and erythematous plaques in the larynx. In untreated cases, it can lead to complications such as laryngeal scarring and chronic chondritis, which can cause airway obstruction. High-dose penicillin is used in treatment [17].

Laryngeal Leprae

Leprae caused by *Mycobacterium leprae* is a disease that classically affects the skin and peripheral nerves. Involvement of the testis, eye, lymph node, liver, spleen, bone, bone marrow, muscle, and larynx is rare. Laryngeal involvement presents with cough, hoarseness, shortness of breath, and rarely life-threatening airway obstruction. It causes erythematous and edematous nodular lesions. Especially epiglottis and glottis are affected. Long-term dapsone and rifampicin treatment is used [18, 19].

Laryngeal Fungal Infections

Primary fungal laryngitis is extremely rare [20]. Symptoms are usually nonspecific. Fungal laryngitis is often confused with leukoplakia and other granulomatous lesions of the larynx [21]. Clinical conditions such as long-term antibiotic use, inhaled steroid use, and laryngopharyngeal reflux may predispose to fungal infections of the larynx. It may present with hoarseness, odynophagia, and dyspnea due

to laryngeal edema and granulations. Fungal laryngitis often mimics granulomatous disease, gastroesophageal reflux disease, and malignant lesions [22]. The most commonly isolated fungi are *Candida*, *Aspergillus*, *Cryptococcus*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*. Mucosal ulcers, intense edema, and inflammation are seen in tissue. If untreated, it can cause mortal airway obstruction [23].

Prompt treatment and appropriate precautions prevent the morbidity of fungal laryngitis. Laryngeal fungal infection is treated with antifungal drugs and the elimination of risk factors [24]. Fluconazole, itraconazole, ketoconazole, topical nystatin, or intravenous amphotericin B is used for the primary treatment of fungal laryngitis [25].

Inflammatory Diseases Causing Laryngeal Involvement

Rheumatoid Arthritis

Rheumatoid arthritis is a common autoimmune disease affecting 3% of the adult population and 35 per 100,000 of the pediatric population [26, 27]. It is a devastating systemic disease that affects all joints in the body. The course of the disease is characterized by remissions and exacerbations. It is characterized by the formation of both articular and extra-articular lesions, especially small joints [28, 29].

On laryngoscopic examination, arytenoids are edematous and hyperemic. In the chronic phase, mucosal thickening and arytenoid fixation can be seen [30]. Although it can be asymptomatic, symptoms such as odynophagia, dysphagia, changes in voice quality, side ear pain, dyspnea, and stridor can also be seen [31].

Amyloidosis

Amyloidosis includes a heterogeneous group of diseases characterized by the accumulation of amyloid protein in various organs. Extracellular accumulation of amyloid leads to organ damage and failure [32]. Larynx involvement is rare. Vocal cords are most commonly involved. Hoarseness and stridor are the most common symptoms [33].

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune collagen vascular disease that causes widespread damage to many organs. Few studies have been reported on the laryngeal involvement of SLE [34]. Laryngeal involvement in systemic lupus erythematosus (SLE) can range from mild ulcerations to airway obstruction due to edema, to vocal cord paralysis to necrotizing vasculitis [35]. If it causes a limitation of movement in the vocal cords, respiratory distress may occur. High-dose steroids are the main treatment [36].

Sarcoidosis

Sarcoidosis is common in young women. The most frequently involved organs are lungs, hilar-mediastinal lymph nodes, and the liver. It is also a chronic

granulomatous disease that tends to involve the eyes, skin, bones, and nervous system. Laryngeal sarcoidosis is rare. It can cause hoarseness, dysphagia, dyspnea, and life-threatening airway obstruction [37]. Corticosteroids are helpful in treatment. Rarely, a tracheotomy may be required due to severe dyspnea [38].

Laryngeal Malignancies

Laryngeal cancers account for one-third of head and neck cancers. It is an important cause of morbidity and mortality [39]. Laryngeal cancers can develop from any of the epithelial and non-epithelial structures of the larynx. Squamous cell carcinoma is the most common histological variant and accounts for 85–95% of all malignant tumors of the larynx [40]. Verrucous carcinoma, adenoid cystic carcinoma, or sarcomas may occur less frequently. Larynx cancers may originate from potentially malignant leukoplakia or erythroplakia [41]. It is more common in men older than 40 years. Male predominance has been considered to be associated with increased exposure to risk factors. Although the etiology is unknown, it is considered it could be strongly associated with frequent exposure of the larynx mucosa to a wide variety of ingested and inhaled exogenous carcinogenic agents. Smoking and alcohol consumption are the two most important risk factors for the development of laryngeal squamous cell carcinoma [42, 43].

Symptoms may differ according to the localization of the lesion. Dysphagia in supraglottic laryngeal cancers, hoarseness in glottic cancers, and shortness of breath in subglottic cancers are the main symptoms. Also, there may be symptoms such as odynophagia, ear pain, and swelling in the neck [44].

In early-stage disease, treatment with surgery or radiation monotherapy is highly curative. However, advanced laryngeal cancer has a poor prognosis and requires multimodal treatment. Speech rehabilitation methods have been developed for patients requiring laryngectomy [39].

Bilateral Vocal Cord Paralysis

The vocal cords have two functions: phonation and protection of the lower airways by the glottis. Symptoms vary depending on the underlying etiology of bilateral vocal cord paralysis and the position of the vocal cords. Management of the disease depends on the underlying etiology and vocal cord position [45].

Benninger et al. estimated that etiologically, bilateral vocal cord paralysis cases can be attributed to surgical trauma in 44%, malignancies in 17%, secondary to endotracheal intubation in 15%, neurological disease in 12%, and idiopathic causes in 12% [46]. Although surgical intervention is indicated in patients with bilateral vocal cord paralysis, treatment of the underlying etiology is essential. Corticosteroids are effective in sarcoidosis, polychondritis, and Wegener's granulomatosis. Regulation of glucose is mandatory to prevent neuropathy development in patients with diabetes mellitus. Reflux treatment is usually recommended during the

recovery period to minimize unwanted stimulation of the larynx. More than 50% of children will spontaneously improve their symptoms in the first 12 months of life [47].

If the patient has increased respiratory effort or significant stridor, surgical intervention may be required to improve the airway, even if spontaneous recovery is expected. Depending on the course of the prognosis, a reversible procedure such as botulinum toxin injection or tracheostomy should be performed. If minimal or no improvement is expected, laryngeal surgery may be considered to decannulate the patient [48].

In glottic and supraglottic dysfunctions, regardless of the etiology, the patient may present with acute respiratory failure. In this case, noninvasive approaches can be used.

Noninvasive Approaches

Acute Oxygen Therapy

Oxygen is widely available in the hospital and nonhospital medical institutions. It can be lifesaving when used correctly and on time. But it should never be forgotten that it is a drug. The use of oxygen should be decided by the clinician, because oxygen has adverse effects like any other drug [49]. The most common indication for oxygen therapy is hypoxemia. The main goal is to correct hypoxia at the tissue level. Oxygen can be given by nasal cannula, simple oxygen mask, oxygen mask with reservoir, nasal or oropharyngeal catheter, tracheostomy mask, diffuser mask, or proportional gas distribution mask [50].

Venturi Mask

A Venturi mask provides a constant mixing of room air and oxygen. Thus, it allows the patient to breathe oxygen at a constant concentration. Gas flow in this mask is usually greater than the patient's inspiratory gas flow. Oxygen reaches the patient without being affected by the patient's respiratory rate and inspiratory airflow rate. It consists of a simple mask and different colored adapters that allow different amounts of oxygen to pass through. Different ratios of FIO_2 can be provided with these adapters [50].

High Flow Nasal Cannula (HFNC) Oxygen Therapy

High flow nasal cannula (HFNC) oxygen therapy is performed using an air/oxygen mixer, active humidifier, single heated tube, and nasal cannula. It is an application

that can deliver sufficiently heated and humidified medical gas at flows up to 60 L/min. Although few large randomized clinical trials have been conducted, particularly in adults, HFNC is being considered alternative respiratory support in critically ill patients. Several published reports have shown that HFNC reduces respiratory effort and tachypnea. However, exact indications for HFNC and criteria for initiation or discontinuation of therapy remain unclear. Despite these uncertainties, HFNC has emerged as an innovative and effective method for the early treatment of adults with various respiratory failures [51].

Newly published data suggest that HFNC should be used as a potentially superior alternative to conventional simple oxygen masks in patients with acute respiratory failure without hypercapnia [52].

Noninvasive Mechanical Ventilation Method

Noninvasive mechanical ventilation (NIMV) is an application of external ventilation without intubating a patient. It is increasingly used in acute and chronic respiratory failure. NIMV provides ventilation support to the patient through the upper airway with a mask or similar device [4]. Noninvasive mechanical ventilation is an effective ventilation practice that is frequently used.

Face masks are gold standard equipment for NIMV. Nasal or mouth ventilation can be done with masks of different sizes [53].

Mechanical ventilators provide ventilation with bilevel positive airway pressure (BIPAP) modes that can determine inspiratory/expiratory pressure levels and continuous positive airway pressure (CPAP) [54].

NIMV should primarily be considered as an alternative to avoiding endotracheal intubation. The use of NIMV as an alternative to tracheal intubation in patients with acute respiratory failure has increased in recent years [4]. As a result of the studies, the noninvasive approach is as effective as the invasive approach, and if there are no contraindications, NIMV should be applied first to all patients presenting with acute respiratory failure [55, 56].

Conclusion

Pathologies that cause dysfunction in the glottis and supraglottis, which are important components of the larynx, were discussed. The etiology of these pathologies may have different causes such as congenital anomalies and paralysis. Patients may present with different clinical symptoms.

It was discussed which noninvasive interventions can be used in order to ensure airway safety in dysfunctions that cause moderate to severe respiratory failure. The types of noninvasive interventions used to ensure airway safety in dysfunctions leading moderate to severe respiratory failure were discussed.

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Noninvasive Ventilation in Dynamic Airway Collapse

Pragadeshwaran Rajendran and Habib Md Reazaul Karim

Introduction and Definition

Dynamic airway collapse (DAC) is a benign entity characterized by tracheal collapse entirely because of the laxity of the posterior membranous portion of the trachea with structurally intact tracheal cartilage [1].

Tracheal dimensions are largely preserved during inspiration, and the airway collapse predominantly occurs during expiration in a patient with DAC. In normal airways, the diameter of the trachea can be reduced up to 50% during a cough [2]. The exaggeration of the normal narrowing of the trachea to more than 50% during expiration can be aptly referred to as excessive dynamic airway collapse (EDAC) [3]. This exaggeration occurs when intrathoracic pressure increases, resulting in a clinical picture of coughing, difficulty clearing secretions, dyspnea, stridor, and respiratory insufficiency.

Large airway collapse is also seen in tracheomalacia, which is relatively grave. The trachea collapse in tracheomalacia happens due to abnormality in the fibrocartilaginous part. Therefore, differentiation of DAC from tracheomalacia is of prime importance, as tracheomalacia warrants aggressive treatment, portends a poor prognosis, and avoids mistreatment.

Pathophysiology

The usual collapse is accentuated in increased intrathoracic pressures because of changes in the velocity of airflow along the airways, i.e., trachea. As explained by Bernoulli's principle, a focal area of increased airflow may result in increased

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transmural pressure, ultimately resulting in collapse. In chronic airway diseases, loss of elastic recoil combined with positive pleural pressures, especially during exercise or vigorous expiratory maneuvers, can increase the propensity to airway collapse. Thus, EDAC should be viewed as comorbidity rather than a primary pathological problem or disease state per se. Patients usually have respiratory insufficiency, and a reduction in the maximum voluntary ventilation is the nearly consistent finding in the pulmonary function tests of such patients [1]. In dynamic bronchoscopy or computed tomography, the tracheal shape is better maintained in inspiration than expiration. While DAC patients show laxity of the posterior membranous parts, tracheomalacia patients show laxity of the cartilaginous part leading to distorted shape and diameter of the trachea [1].

Etiology

DAC commonly occurs in patients with chronic airway inflammation. The prevalence is unknown because of the significant overlap with tracheomalacia and differences in the diagnostic threshold. Important causes include, but are not limited to, chronic obstructive pulmonary disease, asthma, emphysema, recurrent respiratory infections, gastroesophageal reflux disease, obesity, relapsing polychondritis, inhalation of chemical irritants, and chronic use of inhaled corticosteroids [4]. The increased risk in obese patients at risk of obstructive sleep apnea (OSA) is attributable to mechanical compression and airway inflammation. The severity of OSA in the general population is independently associated with increased expiratory tracheal collapse [5].

Diagnosis

Dynamic (functional) bronchoscopy and paired inspiratory–expiratory dynamic CT images are now routinely used to diagnose dynamic central airway collapse and differentiate DAC from tracheobronchomalacia. Dynamic bronchoscopy entails real-time observation of the central airways in response to various maneuvers and is performed under conscious sedation when patients can follow instructions [6]. While several drugs like propofol, dexmedetomidine, and local anesthetics can be used, ketamine is usually avoided as it increases secretion and causes a hallucinosis-type state where the required patient cooperation for the dynamic bronchoscopy might be lost. Recently, noninvasive diagnostic imaging modalities like dynamic computed tomography (CT) and magnetic resonance imaging have shown good promise in assessing airway morphology and its relation during inspiration and expiration [7]. Dynamic CT imaging correlates well with dynamic bronchoscopy findings, offers an excellent display of anatomic detail of the airway and adjacent structures, and provides objective interpretation and quantitative measurement of the degree of airway collapse [8]. There is no universally accepted cutoff, but many published articles used the 50% reduction in circumference criterion during forced exhalation [9].

Treatment

Both medical and surgical modality of treatment is considered [4]. Initial treatment of symptomatic EDAC includes supportive treatment and optimal management of comorbidities. If an infection is suspected, appropriate empiric followed by a specific antibiotic as per the culture sensitivity report should be initiated. Nebulization using bronchodilators and pulmonary hygiene with airway clearing devices such as flutter valves could be utilized. Maximization or escalation of medical therapy for concomitant diseases such as obstructive sleep apnea, asthma, or COPD, along with proper education about inhalers for such patients, is essential. Furthermore, patients are trained in using pursed-lip breathing and referred to pulmonary rehabilitation, humidified oxygen therapy, and weight loss program as appropriate. Airway stenting with silicone or metallic stents is also an option but is associated with stent migration, infection, and mucus plugging risks.

Regardless, the detection and characterization of EDAC are essential, given that several studies have now highlighted clinically meaningful improvements in exercise tolerance and quality of life with targeted intervention, e.g., with the application of continuous positive airway pressure [10] and tracheobronchoplasty [11].

Stenting of the trachea has also been described [4]. Such a patient might develop mucus plug due to poor secretion clearance. Secretion management in patients with ineffective airway clearance is challenging yet feasible using various noninvasive techniques even during NIV [12]. The high-frequency chest wall oscillator is used for the clearance of secretion in patient with EDAC treated with metal stenting [13]. However, stenting is frequently useless when the EDAC is diffuse, but NIV might be beneficial in such cases [14].

Role of Noninvasive Ventilation in EDAC

An experimental study has shown that the application of continuous positive airway pressure (CPAP) of more than 6 cmH20 leads to a significant improvement in collapse [15]. Therefore, CPAP or other noninvasive ventilation modes are used for pneumatic stenting of the airway. It is a better alternative for patients at high risk for surgical management, such as patients with OSA. Expiratory positive airway pressure (EPAP) provides the pneumatic stenting that prevents the expiratory collapse of the airway. However, NIV is only a temporal measure to prevent and/or treat EDAC. It is regarded chiefly as bridging therapy in severe cases till definitive surgery or intervention is planned. It can also be applied to the patients who are not a candidate for the definitive procedure or deny to undergo surgeries and need palliation of the severe symptoms.

Patients with EDAC also present with weaning difficulty [16], and extubation on NIV is effective in such difficult to wean cases [15].

EDAC in the Perioperative Period

EDAC has been reported to contribute to postoperative respiratory failure anecdotally [17]. The increasing prevalence of COPD and obesity and the need for surgical care for such patients increases the likelihood of getting such patients in the perioperative period as EDAC is prevalent in COPD and morbid obesity [18]. People at high risk for EDAC like smokers, female sex, COPD, OSA, and the elderly are identified preoperatively. Symptomatic EDAC should be subjected to diagnostic testing to assess the severity of obstruction. Patients with critical narrowing (i.e., more than 70%) should undergo definitive surgical treatment for EDAC [4]. Risk mitigation should include smoking cessation, minimizing airway secretions, and bronchodilator therapy.

Nevertheless, EDAC has been shown to present as the cause of increased peak airway pressure with shark-fin pattern capnogram resistant to bronchodilator therapy [19]. General anesthesia, muscle relaxation, and mechanical ventilation should be tailored as they precipitate airway collapse. Vigilance for intraoperative airway collapse should be there with regional techniques as well. Postoperative NIV may be instituted either prophylactically or therapeutically to prevent respiratory failure.

Conclusion

DAC is a distinct entity of tracheal collapse, which is probably less evaluated and diagnosed by clinicians. High suspicion of the condition is required in patients having risk factors and showing the expiratory problem with respiratory insufficiency or difficult weaning. Dynamic bronchoscopy or dynamic CT can help in diagnosis. Noninvasive ventilatory approaches might help severe EDAC patients as a bridging, adjunct, and palliative therapy. Further, NIV can even be used for weaning from invasive mechanical ventilation for patients having EDAC and difficulty in weaning. However, there is still a lack of randomized trials and even well-controlled studies. Future studies will be required to ascertain the extent of the benefit.

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Noninvasive Approaches in Tracheobronchomalacia

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Introduction

Tracheobronchomalacia (TBM) is a central airway disease, defined by a tracheal weakness extended to the mainstem bronchus, due to softening or destruction of the tracheobronchial cartilage and/or hypotonia of the elastic fibers. This causes an excessive compliance and collapsibility of the central airways, which will result in amplified narrowing of the tracheal lumen during expiration and excessive widening during inspiration. It can cause symptoms like dyspnea, cough, wheezing, and recurrent pneumonia due to accumulated secretions [1]. The word tracheomalacia is used when only the trachea is involved and bronchomalacia when the weakness is limited to one or both of the mainstem bronchi [1, 2].

TBM can be morphologically classified into three categories based on the shape of the trachea: saber-sheath type, circumferential type, or crescent type [3]. The crescent type occurs when the anterior cartilaginous wall is softened and results in excessive narrowing of the sagittal airway diameter. The saber-sheath type is due to weakness of the lateral walls and excessive narrowing of the transverse airway diameter. Circumferential type, also called combined type, is characterized by anterior and lateral airway wall collapse.

It can be congenital or acquired, being that acquired is more common than congenital in adults. Some of the congenital causes include polychondritis, dyschondroplasia, Ehlers-Danlos syndrome, Hunter syndrome, trisomy 9 and 21, Williams-Campbell syndrome, etc. [4] Mounier-Kuhn syndrome is often diagnosed in adulthood, with 75% of diagnosis made in patients over 28 years old. The pathogenesis is related to congenital defects or atrophy of the muscle and elastic tissue of

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the trachea and central bronchi, resulting in diffuse dilation of the airway [4]. Acquired tracheomalacia can be secondary to tracheostomy or endotracheal intubation, chest trauma, thoracic surgery, chronic infections/recurrent bronchitis, chronic inflammatory disease like relapsing polychondritis, and chronic compression of the trachea [5].

TBM seems to have a male predominance, occurring primarily in smokers and middle-aged to elderly people [6]. It has a progressive nature and can be asymptomatic, but symptoms will typically develop as the severity of narrowing progresses. It is underdiagnosed, because there are asymptomatic patients and patients whose symptoms are attributed to other respiratory diseases. The most common symptoms are dyspnea, cough, and sputum production [1]. Patients may feel wheezing or hear stridor. These symptoms are not exclusive to this disease and can be caused by alternative diagnosis like bronchitis, asthma, or bronchiectasis. Tracheobronchomalacia can coexist with several of these conditions and symptoms may be amplified because of that. It's typically a benign disease but can be associated with important morbidity and respiratory failure and death in some cases.

Diagnosis

Flexible bronchoscopy with observation of dynamic airway collapse is considered the gold standard for diagnosis [1]. During dynamic bronchoscopy, the airways can be visualized with the patient in different positions and during maneuvers like cough, deep inspiration, and forced expiration. There are several classifications of the severity of the airway collapse, but there isn't a standard method to quantify it. Some authors classify the obstruction as mild if the lumen narrows 51–75%, moderate if there is a reduction of 76–90%, and severe if it narrows >90% [7]. Dynamic CT scan during expiration and inspiration may also be helpful as a diagnosis tool. *Aquino* et al. showed that a change greater than 18% in cross-sectional area (CSA) in the middle trachea between inspiration and end expiration was associated with 89–100% probability of tracheomalacia [8].

Pulmonary function tests can support the diagnosis, but are not diagnostic. Dynamic airway obstruction is suspected when a notch is visible on the flow-volume loop. There is a sudden decrease of the flow at the beginning of expiration when the airways collapse. Other findings may include diminished expiratory flow, biphasic flow-volume loop, flow oscillations, and obstruction [9]. Endobronchial ultrasound (EBUS) using a radial probe can be helpful in identifying an etiology, for example, showing compression due to vascular rings and tumors, and can identify the depth of tracheobronchial wall abnormalities and the absence of cartilage layers [1].

Treatment

Treatment will depend on severity of symptoms, etiology, and degree of airway collapse. Patients who are asymptomatic do not require therapy. In symptomatic patients, we should start by trying to identify the underlying cause if existent and

treat it (optimized medical treatment for asthma or COPD and gastroesophageal reflux, steroids for relapsing polychondritis). If the cause can't be identified or the patient has persistent symptoms, the treatment can pass for three different therapeutic approaches: noninvasive ventilation, bronchoscopic interventions (stents), and surgery [1, 4].

Noninvasive Ventilation

Noninvasive positive pressure ventilation can help maintain the airway open acting as a pneumatic stent [4]. It decreases pulmonary resistance and work of breathing by helping reducing the inspiratory transpulmonary pressures and improves expiratory flow. This all contributes to reduce symptoms like dyspnea.

The use of continuous positive airway pressure (CPAP) for TBM was first described in 1980, in a newborn infant with Larsen's syndrome [10]. CPAP has shown to improve dyspnea, cough, and secretion drainage in patients with TBM. *Ferguson et al*. showed that nasal CPAP improved spirometry values (forced vital capacity, disappearance of flow-volume loop notching), helped with sputum clearance, diminished atelectasis, improved exercise tolerance, and reduced need for medical care. Addition of nasal CPAP eliminated airway collapse during passive expiration and improved airway collapse during active expiration to a normal or mild level in this study. Although the improvement in forced vital capacity could be due to increased lung volumes because of CPAP, there was no change in slow vital capacity which suggests that the improvement was due to improved airway patency. The optimal pressure that allowed airway patency was 10 cm H_20 [11].

A study with 40 children with TBM evaluated the effect of positive expiratory pressure in expiratory flow and cough efficiency. Patients performed spirometry with expiratory pressures of 0, 5, 10, and 15 cmH_20. Cough expiratory flow between 25 and 75% of vital capacity was calculated to represent the effectiveness of cough at midline lung volume. In patients with TBM, CEF25-75 increased by a mean of 18.8%, 1.7%, and 0.5% at PEP of 5, 10, and 15 cm H_2O, respectively, but decreased by 2.4% at PEP of 20 cm H_2O [12].

Bronchoscopy assisted with noninvasive ventilation can be used to identify the level of pressure needed to maintain airway patency. Pressures can be gradually increased until airway caliber during exhalation is considered sufficient [13]. Positive pressure ventilation can be used as a bridge to stabilize patients before more definitive treatment like surgery.

The use of automatically adjusting positive airway pressure (APAP) should be done with caution because the minimum pressure may not be sufficient. Bilevel positive airway pressure can be used if hypercapnic respiratory failure exists or patients cannot tolerate high CPAP pressures, but it has to be assured that the EPAP applied is sufficient to ensure airway patency during expiration [14]. Vézina et al. reported a case of a 1-month-old infant with severe tracheobronchomalacia which was successfully adapted to home high flow nasal cannula (HFNC) therapy, but more studies are needed to evaluate the efficiency of HFNC in patients with tracheobronchomalacia [15]. *Patout et al.* reported a case of the use of portable CPAP,

which could be a safe therapeutic option for patients with dyspnea, exercise limitation, and tracheobronchomalacia, but it has to be validated by further studies [16].

There aren't studies that evaluated the long-term effects of CPAP and the evidence is based on small case series. The optimal pressures and duration of treatment are not yet determined, but some authors recommend intermittent nasal CPAP during the day and continuous by night [1].

Conclusion

Although treatment with CPAP/noninvasive ventilation is not a definitive or curative therapy for tracheobronchomalacia, it can be useful and benefic in some patients, including those who are not surgical candidates or cannot tolerate airway stents, and can be a temporary solution before definitive treatment like surgical intervention. More studies are needed to evaluate its effect on long term.

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Upper Airway Noninvasive Ventilation in Acute Hypoxemic Respiratory Failure

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Abbreviations

ABG	Arterial blood gas
AHF	Acute heart failure
AHRF	Acute hypoxemic respiratory failure
ARDS	Acute respiratory distress syndrome
BiPAP	Bi-level positive airway pressure
BMI	Body mass index
CF	Cystic fibrosis
CHRF	Chronic hypercapnic respiratory failure
COPD/AECOPD	Chronic/acute exacerbation of chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPD	Chronic pulmonary diseases
CPE	Cardiogenic pulmonary edema
CWD	Chest wall disease
ETI	Endotracheal intubation
FiO_2	Fraction of inspired oxygen
FRC	Functional residual capacity
GBS	Guillain-Barré syndrome
HFNC	High-flow nasal cannula
HVS	Hyperventilation syndrome
ICU	Intensive care unit
MG	Myasthenia gravis
MI	Myocardial infarction

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MRI	Magnetic resonance imaging
MV	Mechanical ventilation
NAVA	Neurally adjusted ventilatory assist
NCPAP	Nasal continuous positive airway pressure
NIPPV	Noninvasive intermittent positive pressure ventilation
NIV	Noninvasive ventilation
NMPD	Neuromuscular pathological disorder
OHS	Obesity hypoventilation syndrome
PaO_2	Partial pressure of oxygen
pCO_2	Partial pressure of carbon dioxide
PCU	Pediatric care unit
PEEP	Positive end-expiratory pressure
PIF	Peak inspiratory flow
PRC	Palliative respiratory care
P-SILI	Patient self-inflicted lung injury
PSRs	Slowly adapting pulmonary stretch receptors
PSV	Pressure support ventilation
RARs	Rapidly adapting receptors
RF	Respiratory failure
SAHS	Sleep apnea-hypopnea syndrome
SB	Spontaneous breathing
SMA	Spinal muscular atrophy
TD	Tidal volume

Introduction

Acute hypoxemic respiratory failure (AHRF) is a medical condition that emerges under specific conditions of respiratory system failure against the necessary needs of proper gas exchange maintenance [1]. AHRF's main clinical manifestation is a rather progressive evolution, followed by such clinical symptoms, of moderate to rapidly developing severe acute hypoxemia. The commonest cause of AHRF is the abnormal interaction between the CO_2 production and its pressure effect in the arterial blood, estimated through the partial pressure of CO_2 (pCO_2) and the CO_2 amount which is eventually eliminated through alveolar ventilation by the pulmonary parenchyma. When the patient establishes "hypercapnic respiratory status," the nonfunctional respiratory muscles fail to ensure adequate alveolar ventilation, in order to prevent eventual increase of arterial pCO_2 measurements, leading to an additional decrease of the arterial blood pH, known as "respiratory acidosis," an overall clinical condition, otherwise referred to as "respiratory pump failure."

Principal Noninvasive Treatment in Acute Hypoxemic Respiratory Failure (AHRF)

When a patient transcends AHRF status, the options for adequate noninvasive respiratory support consist of the use of the following means [2]:

- *Delivery of O_2 standard treatment*, through usage of a standard face mask in early progressing AHRF-suffering patients, usually the ones who do not manifest metabolic acidosis (low ABG pH measurements). Unfortunately, when respiratory needs advance, ventilator support, along with the "fraction of inspired oxygen" (FiO_2), is limited and inadequate to support efficiently, while the mucociliary clearance suffers further impairment.
- *Noninvasive ventilation (NIV) respiratory support*, a noninvasive supportive technique that involves the usage of a specific device complex, whose goal focuses on maintaining optimal ventilation and oxygenation and hemodynamic stability, while it reduces the manifestation of potential complications, related to endotracheal intubation (ETI).
- *Additional usage of high-flow nasal cannula (HFNC) O_2 therapy*, most commonly applied in pediatric care units (PCU) and preterm with significant manifested premature apnea or severe acute respiratory distress syndrome (ARDS) [3]. The HFNC system provides a gas mix of O_2 and air, carefully humidified 100% and heated to normal body temperature, via specific nasal prongs, with the aim to provide adequate, constant, and accurate FiO_2 range, between 0.2 and 1.0 according to the patient's needs. The system maintains low levels of positive pressure, average gas flow between 1 and 60 L/min, and efficient rinsing of the upper airways' dead space. The majority of ICU ventilators present the option of enabling a connection with a HFNC system device, if estimated necessary.

Noninvasive Ventilation in Acute Hypoxemic Respiratory Failure (AHRF)

NIV is a noninvasive supportive treatment, applied via bi-level positive airway pressure through the upper airways, under ICU environment for a known four-decade chronological period [4]. The main goals of systematic NIV treatment focus on:

- Improvement and facilitation of the respiratory functionality
- Improvement of oxygenation
- Improvement of ventilation

In comparison with standard O_2 treatment, numerous data stand in favor of NIV appliance over typical O_2 therapy. During spontaneous breathing (SB), it is quite possible that rapidly increased respiratory muscle functionality may lead to lung aggravation and/or potential injury, provoking "patient self-inflicted lung injury" (P-SILI); therefore supportive strategies aim mainly to unload distressed respiratory effort, while they must ensure adequate oxygenation improvement.

According to NIV's main principle, the technique performs administration of positive pressure through a proper external interface that necessarily connects to supportive equipment, aiming to assist the spontaneous effect of the respiratory functionality, consisted of the following:

- Humidification system, which may provide at least 5–30 mg/L, depending on each system's type
- Heated humidifier, or a heat and moisture exchanger
- Ventilator

One of the NIV technique's most important advantages focuses on the absence of any kind of obstruction in the upper airways, especially during expiration, which may lead to eventual generation of additional positive nasopharyngeal pressure, something that is possible to occur during HFNC appliance due to the use of the large nasal prongs.

According to each selected NIV mode used, in order to achieve maximum unloading of the inspiratory muscles, the ventilator has to synchronize effectively with the patient's respiratory effort [5]. This proves to be a rather challenging task, having in mind that asynchrony between the patient and NIV ventilator is a frequent occurrence. Most often, the reasons for the unachieved synchrony, which eventually leads to patient discomfort and NIV prolongation, are:

- The patients' respiratory mechanics
- The patients' neural drive
- The established breathing pattern
- The ventilator's system settings
- The type of NIV interface
- The overall percentage of air leakage
- Suboptimal interaction of the inspiratory muscles' activity and the ventilator's functionality

Having available the proper equipment, set up on time for immediate NIV appliance, and checking upon its trigger sensitivity and its functionality toward optimal provision of positive end-expiratory pressure and overall pressure support ensure the necessary conditions for an optimal outcome of any selected supportive intervention.

Some of the most important contributing conditions, responsible for successful NIV application and prevention of ETI, are without doubt the following [6]:

- Optimal and accurate selection of the patients who will receive NIV, according to current guidelines, excluding the ones that indicate strong predictors for NIV failure. Individuals with low (acidic) pH measurements (pH <7.25), high (hypercapnic) pCO_2 measurements (pCO_2 > 45 mmHg), and/or aggravated clinical respiratory status are most commonly selected.
- Thorough time selection for proper intervention.
- Availability of adequately trained and skilled ICU staff.
- Adequate ICU technological equipment for monitoring and support, providing optimal interface, aiming to minimize complications, such as decubitus injuries, anxiety, claustrophobia, and/or delirium, and close access for eventual ETI, if needed [7]. Indications, such as pH acute measurements' improvement during initiation of NIV (first 1–2 h), stand as very positive predictive factor toward the patient's outcome.
  - Recent studies indicate that the usage of a NIV delivery system that includes the appliance of a specifically modified helmet, with the aim to provide increased comfort and tolerance from the patient's side, has led to improved rates of NIV success, providing potentiality for further alveolar recruitment, as well as lung parenchyma protection.
- Continuous patient coaching and motivation.

The commonest NIV modes of application, individually or combined, are the following:

- Pressure support ventilation (PSV) through bi-level positive airway pressure (BiPAP).
- Continuous positive airway pressure (CPAP), especially during the expiratory phase. The two main types of CPAP mode, according to the selected gas flow, are:
  - Nasal continuous PAP (NCPAP), delivered through a ventilator or a CPAP system, with a positive end-expiratory pressure (PEEP) valve responsible to control the proper flow delivery
  - Variable-Flow NCPAP, a system that generates CPAP using a dual injector, responsible for the maintenance of constant pressure and gas delay, when necessary
- Noninvasive intermittent positive pressure ventilation (NIPPV), which is usually applied, combined with NCPAP.
- Neurally adjusted ventilatory assist (NAVA).

BiPAP mode under NIV may provide proper ventilation, depending on monitored patient-triggered breaths, while it may achieve combined delivery with PEEP, when muscle unloading is suboptimal, having already determined the preset levels above it. The abovementioned intervention indicates significant positive patient outcomes, compared to individual PSV or PEEP appliance, with important decrease of the respiratory drive. A great deal of attention must be taken into account, regarding establishment of high tidal volumes (TD), especially under measurements between

6 and 8 mL/kg, combined with low range of PEEP, in order to prevent potential lung injury.

The greatest benefit that NIV technique ensures is that, the FiO_2 delivery level provides oxygenation and ventilation with 0% air leakage, due to high-pressure conditions within the system and the face mask. The achieved low positive upper airway pressure leads to a PEEP effect generation, responsible for recruitment of the alveoli, thus significantly improving overall gas exchange, due to increased FiO_2. The abovementioned PEEP effect indicates decreased results, compared to HFNC appliance. CPAP system appliance achieves significant analogic improvement of the PaO_2/FiO_2 ratio (increasing PEEP, even up to 10 cm H_2O, as well as the PaO_2/FiO_2 ratio), an effect that is absent even in systematic PSV.

When NAVA via NIV mode is applied, the ventilator synchronizes with the diaphragm's electrical activity, which is calculated through use of bipolar electrodes, attached to a nasogastric feeding tube, thus providing optimal conditions for successful patient-ventilator synchrony. NAVA achieves less glottal constriction, which benefits in favor of synchronous ventilation, providing advantage compared to PSV via NIV mode, whereas PSV ventilation establishes a constant environment of non-physiological increasing pressure, accompanied with decreased inspiratory interval, which may lead to induced respiratory function from the patient's side by triggering glottal constrictive reflex.

A major difference between NIV and ETI is without doubt the participation of the upper respiratory airways. ETI manages to bypass the upper airways, by applying the endotracheal tube, while the pathway is airtight sealed thanks to the tube cuff [8]. During NIV appliance, upper airways participate toward the efficient ventilation and oxygenation delivery. The physician must always be alert for any level of affection of the upper airway's patency, in order to prevent eventual NIV failure that may lead to unavoidable ETI. An almost perfect synchronization between the NIV ventilator system and upper respiratory airway muscles is a major requirement for successful ventilation and oxygenation; however the glottis narrowing during inspiration, which may easily cause upper airway resistance, leads to ineffective ventilation.

Monitoring the respiratory muscles' functionality during NIV appliance also is a rather important task, in addition to registering the upper airway activity. In several cases, digital magnetic resonance imaging (MRI) with additional tagging provides important data about the relevance of the laryngeal dilator muscle functionality and their phasic activity during inspiration, contributing to regular flow delivery and therefore the evolution regarding patient-ventilation synchrony. Other muscles and additional surrounding soft tissues, such as the genioglossus muscle, participate actively throughout the inspiratory flow, affecting upper airway patency. Laryngeal muscle electromyography, upper airway ultrasound, and additional endoscopic interventions may provide sufficient data, regarding the proper muscle behavior, as well as airway patency maintenance.

Upper Respiratory Airways and NIV Participation

Upper respiratory airways consist of:

- The nose
- The oral cavity
- The pharynx
- The larynx

Upper airways have significant roles regarding conduction, warming, and humidification of the breathing air, as well as preventing entrance of any foreign objects into the tracheobronchial tree. The oral cavity and the nose participate throughout static function, while the larynx and the pharynx demonstrate active functionality due to their muscular structure.

In normal breathing conditions, when a person inhales, the upper airways submit to an environment of negative pressure, combined with phasic respiratory activity, while the posterior cricoarytenoid muscle functions above tonic level, resulting to glottis widening, decreased airflow resistance and unloading of the respiratory muscles. On the contrary, when the person exhales, the thyroarytenoid muscle commences phasic activity, leading to glottis narrowing and eventually increase of the expiratory flow resistance.

The role of the pressure and flow neuro - muscular receptors, known also as "Thermoreceptors" participate significantly against the Upper Airways' muscle activity during the respiratory function, in relation to changes of the environmental and room temperature. Some of the most important and functional neuromuscular receptors are:

- The bronchopulmonary "C-fiber" receptors, divided into two:
  - *Pulmonary "C-fiber" receptors*, detected between pulmonary capillaries and the epithelium of the alveoli
  - *Bronchial "C-fiber" receptors*, functioning along the conducting airway

  "C-fiber" receptors react mainly to chemical stimulations, manifestation of progressive pulmonary edema due to rapid increased production of the interstitial fluid and increase of body temperature, and they are also responsible for provoking inhibitory functions, such as bradycardia, hypotension, bradypnea, and/or apnea. They are also responsible for immediate participation of the laryngeal muscles through glottis narrowing, under circumstances of inspiration of irritating gas proportions, in order to protect the respiratory tract.
- *The Rapidly Adapting Receptors (RARs)*. They are detected throughout the respiratory tract, under the respiratory epithelium. Their functionality focuses on reacting very sensitively against mechanical and chemical stimulations, while they are responsible for generating excitatory actions, such as tachypnea. The

RARs of the larynx, otherwise known as "irritant" receptors, are the main reason behind cough and violent expiration activities when irritated by various stimulating factors, followed by laryngo- and bronchconstricting effects, leading to necessary glottal closure.

- *The Slowly Adapting Pulmonary Stretch Receptors (PSRs)*. They are responsible for participating in modulating the overall respiratory function, terminating the inspirational effect while extending expiration. They take action under conditions of airway wall stretching (tonic participation), or lung inflation (phasic participation), known otherwise as the "Hering-Breuer reflex" (a respiratory "on-off" switch), an overall action whose aim is to decrease the TD, preserve constant ventilation, and protect the lung parenchyma from hyperinflation.

Multiple recorded data indicate that during NIV appliance, most commonly with PSV, the cricothyroid muscle's functionality, toward glottal dilatation and furthermore inspirational support, decreases until its disappearance, while the thyroarytenoid muscle's counterpart activity, toward glottal constriction, increases, thus being in constant functional cooperation with the diaphragmatic respiratory participation. The abovementioned effect does not apply during spontaneous breathing, when all participant upper airway muscles maintain activity, especially toward the final stage of inspiration. Bronchopulmonary "C-fiber" receptors are mainly responsible for glottal constriction effect, a fact that indicates the importance of constantly surveilling the glottis behavior for optimal oxygenation and ventilation, while protection of the upper airway patency remains a similarly significant task.

Acute Hypoxemic Respiratory Failure (AHRF) and NIV Benefits

AHRF remains one of the severest respiratory clinical manifestations that usually follows acute exacerbation of chronic obstructive pulmonary disease (AECOPD), due to the decreased capacity of the "respiratory pump," in addition to already established loss of balance between increased elastic and resistive load. AHRF may as well evolve as typical complication of other severe clinical conditions, such as chronic respiratory hypercapnia, metabolic acidosis, acute heart failure (AHF), etc. Such patients who manifest AHRF status may generate "peak inspiratory flow" (PIF) that varies from 30–40 L/min to 60 L/min and possibly exceeds to approximately 120 L/min, resulting in reduced FiO_2 rates, not more than 0.7.

AHRF usually leads to clinically high respiratory drive, accompanied with heavy labored breathing function, especially noticeable when the patient strives to inhale, leading to upcoming hypoventilation. According to the imminent ABG measurements, respiratory functionality initially evolves to combined status of hypocapnia (when levels of $pCO_2 \leq 35$ mmHg) and hyperventilation syndrome (HVS, 20–30 breath attempts/min), symptoms which eventually may end up to hypercapnic status (when levels of $pCO_2 \geq 45$ mmHg), due to established respiratory muscle fatigue [9].

The main diagnostic references that are most indicative in order to establish presence of AHRF are:

- When the level of $PaO_2 < 60$ mmHg on room air, after measuring arterial blood gas (ABG)
- When the level of $SpO_2 < 91\%$ under conditions of room air environment, using a pulse oximetry
- When the P/F (arterial pO_2/fraction of inspired $O_2 \rightarrow PaO_2/FiO_2$) ratio measurement receives indication under the level of 300

A rough evaluation of a patient's current respiratory status is possible to estimate, according to the following:

- When the P/F ratio ≥ 400, and $pO_2 \geq 80$ (under conditions of room air environment), respiratory status is considered "normal."
- When the P/F ratio ≤ 400 and pO_2 is measured 60–79, respiratory status is considered "hypoxemic."
- "Respiratory failure" (RF) is established when the P/F ratio ≤ 300 and pO_2 is measured 50–59.
- "Severe respiratory failure" (severe RF) is established when the P/F ratio ≤ 250 and pO_2 is measured 40–49.
- "Critical respiratory failure" (critical RF) is established when the P/F ratio ≤ 200 and $pO_2 < 40$.

AHRF mainly categorizes as:

- "Type I" (hypoxemic) AHRF, when pO_2 measurements are calculated <60 mmHg, while the corresponding pCO_2 measurements are normal or low
- "Type II" (hypercapnic) AHRF, when pCO_2 measurements are calculated >60 mmHg, while the corresponding pO_2 measurements are normal or low

One of the most crucial therapeutic challenges throughout the last decades, considering the progress and optimal treatment in patients suffering from respiratory failure, is always the provision of every available means and support in order to avoid eventual ETI. The most beneficial aim of not proceeding to ETI intervention focuses on reducing development of eventual complications that connect directly to invasive ventilation and may lead to increased hospital mortality. In addition to the above, reduced percentage of hospitalization in the intensive care unit (ICU) or, equally mentioned, decreased eventual hospital and/or ICU readmissions, as well as reduced possibility for applying an eventual tracheostomy procedure, indicates the significance of selecting the optimal supportive and/or therapeutic action against AHRF.

As long as the overall clinical status allows the physician to perform such strategy and primary disease does not progress toward a negative path, the patient may continue to receive noninvasive respiratory support. Nevertheless, each selected strategy that aims for the most beneficial oxygenation should not misguide the physician, under the manifestation of "hidden" clinical symptoms, or the existence of an already established aggravated personal medical history. Thus, when the needs

for ETI reach "nonnegotiable" level, such following intervention must take place immediately [10].

The commonest indicative clinical symptoms and/or situations that demand immediate respiratory assistance and support are:

(i) *AECOPD*, which consists of the commonest pathological symptomatology, and is already described above, progressively leading to AHRF.

(ii) *Cardiogenic pulmonary edema (CPE)*. CPE is another critical medical condition that may lead to AHRF manifestation, especially regarding patients who already have developed early clinical signs of hypercapnia ($pCO_2 > 60$ mmHg) or suffer from other chronic pulmonary diseases (CPD). Approximately 50% of the individuals with severe CPD manifest hypercapnia, a negative prognostic factor, according to the future evolution of the CPD, as well as a significant higher risk for eventual ETI. Nevertheless, NIV interventions present high rate of success, which may reach a percentage over 95%, while CPAP appliance takes over as first choice of treatment. CPAP appliance aims to increase "functional residual capacity" (FRC), while it supports discharge of the "flooded" alveoli, especially when the respiratory functionality leads to progressive failure. NIV interventions have notably reduced the amount of eventual ETIs, the evolution of sudden myocardial infarctions (MI), as well as the rate of hospital mortality. When a patient receives NIV in time, established AHRF clinical symptoms improve sooner, thus presenting higher rates of positive clinical outcomes. Finally, approximately 20% of the patients who receive NIV appliance after CPE present chronic respiratory disorders, a fact that indicates the importance of an early NIV intervention.

(iii) *Chest wall diseases (CWD) combined with neuromuscular pathological disorder (NMPD)*. Patients suffering from such severe clinical conditions usually manifest reduced respiratory muscle strength, due to suboptimal ventilation of the alveoli, in addition to existence of weakened expiratory muscle groups that lead mainly to deficient clearance of the respiratory airway secretions. Additionally, such patients present chest wall deformities, combined with altered thoracic cage compliance, leading to laborious situations such as chronic hypercapnic respiratory failure (CHRF) that may evolve to life-threatening manifestations. NMPDs combined with AHRF are divided into slowly progressive NMPDs, accompanied with intervals of acute outbursts of CHRF, and rapidly progressive NMPDs. Some of the most frequent slowly progressive NMPDs are spinal muscular atrophy (SMA), various motor neuron diseases, and other inherited myopathies. Subsequently, myasthenia gravis (MG) and "Guillain-Barré syndrome" (GBS) are the commonest rapidly progressive NMPDs, with significant potential to reverse. The most beneficial treatment includes nocturnal NIV appliance in addition to mechanically assisted coughing provocation. Ten percent of the overall ICU admissions consist of individuals with NMPDs, combined with AHRF symptomatology, who may undergo emergency tracheostomy performance at a 30% rate due to neuromuscular respiratory failure. When NIV appliance is

performed with additional tracheostomy, especially when several myasthenic crises occur, the treatment's effectiveness reaches quite satisfactory rates, as well as avoidance of potential ETI. "Chronic" NIV treatment remains the optimal choice for standard care.

(iv) *Obese patients, accompanied with hypoventilation clinical symptomatology*. Obesity is a rather frequent condition among patients, suffering from COPD, "sleep apnea-hypopnea syndrome" (SAHS), allergic asthma, or less commonly "obesity hypoventilation syndrome" (OHS), including measurements of body mass index (BMI) over 30 kg/m^2. These patients demonstrate tendency of manifesting chronic alveolar hypoventilation that usually leads to severe hypercapnia. Their clinical status presents complex respiratory symptomatology, various complementary chronic pulmonary defects, and severe sleep-related disorders, a clinical picture that leads to impaired central respiratory functionality. Patients who suffer from AHRF, combined with OHS, may receive successful NIV intervention, leading rather soon to improved pCO_2 measurements, while they eventually avoid ETI, with subsequent minor rates of hospital mortality or hospital readmissions and higher 1-year survival percentage. OHS degree, in addition to existing "difficult upper airways" presents negative prognostic criteria for NIV failure, although the overall clinical outcomes maintain positive progression. The commonest NIV mode used is CPAP. Patients with OHS, combined with COPD, usually receive identical NIV treatment.

(v) *Weaning, following ETI*. Patients undergoing ETI, mechanical ventilation (MV), and eventually prolonged intubation usually have higher mortality and morbidity rates. ICU physicians strive to resolve primary, underlying clinical conditions that led to AHRF and ETI, before they proceed with withdrawal of MV. The acceleration of the weaning process, along with shortening the patient's ICU stay, remains one of the most challenging tasks in favor of the improvement of the individual's overall prognosis. Patients who manifest ventilator-dependent hypercapnia, combined with COPD, receive continued weaning, in addition to immediate NIV, quite successfully, accompanied with satisfactory rates of decreased inspiratory drive, while ABG measurements additionally improve, leading to subsequent shorter duration of IMV and decrease of ICU stay and hospital mortality, along with increase of post-extubation survival period over 3 months. Patients with preexisting CPD also demonstrate positive post-extubation indications with analogous clinical rates.

(vi) *Difficult intubated patients due to "difficult upper airway."* The main goal focuses on avoidance of any further potential tissue damage, or eventual brain injury caused by brain anoxia. The term "difficult intubation" is defined as the difficult visualization of the epiglottis during placement of the endotracheal tube, while clinical signs, such as hypotension, hypoxemia, severe acidosis, or even right ventricular failure, may occur during the peri-intubation interval, despite technically easy tube placement. Bronchoscopy is highly recommended in similar situations; should there be lack of proper equipment or

there be absence of specifically trained physicians, NIV appliance stands as an imminent alternative, compared to invasive MV, which proves to be quite beneficial. The principal NIV benefits during ETI are the following:

- Pre-oxygenation, with aim to prolong time interval before desaturation during ETI, through positive pressure appliance
- Maintaining proper gas exchange during apneic interval, preventing arterial blood desaturation
- Preventing alveolar de-recruitment
- Maintaining upper airway patency, thus protecting the respiratory tract from potential obstruction
- Preserving hemodynamic stability
- Decrease of the respiratory stress level
- When patients with severe respiratory failure must undergo emergency ETI, NIV appliance can provide temporary stabilization until final preparations for safer ETI. The use of a full face mask increases delivered FiO_2, limiting potential air leakage through the oral cavity, maintaining satisfactory levels of PEEP. The procedure must be carefully applied, having in mind that the patient lies in supine position, a fact that favors eventual upper airway obstruction due to the tongue's posterior displacement. Other individuals who require higher level of respiratory pressure in order to achieve optimal tidal volume (TV) need the BiPAP NIV mode, or subsequently the CPAP variation. Patient monitoring is an essential and mandatory issue in order to determine if the procedure reaches the acquired proper TV levels. ETI procedures combined with NIV appliance may include laryngeal mask, fiber-optic bronchoscope equipment accompanied with endoscopy "Patil" mask, Boussignac valves, additional nasal interface, etc. The presence of a well-adjusted and fully functional organized equipment and participation of well-trained physicians are necessary requirements toward successful procedure, in addition to thorough and careful selection of potential candidates. Other contraindications for NIV during ETI include the presence of blood, vomit, and/or excessive mucus and salivary secretions, as these cause eventual pulmonary aspiration.

(vii) *Prevention of post-extubation failure toward previously intubated patients*. One of the most troubling clinical matters that requires constant effort toward its solution is post-extubation failure, especially for patients presenting prolonged hypercapnia and/or AECOPD after the removal of the endotracheal tube. Individuals who receive NIV treatment, especially those who endure NIV for at least a 48 h interval, express lower rates of reintubation, along with decreasing overall ICU mortality.

(viii) *Palliative respiratory care (PRC) toward patients, contraindicated for ETI*. NIV appliance is preferable toward critically ill patients, presenting end-stage diseases, in order to facilitate and relatively improve the already permanently established dyspneic respiratory function. Such patients most commonly include cancer patients, or other ones with severe CPD, as a component of an overall palliative care plan. The desired goal is mainly relief,

accompanied with potential peaceful end of life, especially when hypercapnia takes over, as long as the patient tolerates the treatment and does not develop additional prolonged complications. Similar criteria are valid for patients who manifest AHRF but refuse to receive ETI or undergo tracheostomy procedure, a rather frequent picture during recent SARS-CoV-2 days. Those individuals, who usually manifest complementary respiratory acidosis, receive NIV with additional therapeutic goal, leading to quite satisfactory survival rates.

(ix) *PRC toward significantly elderly patients*. Such individuals, who are usually over 80 years old, represent approximately 15% of the overall ICU admissions. Although hospital mortality is significantly higher among this specific age group, the effectiveness of NIV appliance does not vary from the one that patients with CPD receive and similar rates address to NIV failure and ETI clinical outcomes. It is commonly accepted that, above all matters, such patients often find themselves at the lower places of the NIV selection criteria table, due to their age range.

(x) *PRC toward patients suffering from*:
- Community-acquired pneumonia, with no significantly different rates of efficiency, compared with COPD patients
- Post-ETI ventilator-associated pneumonia, where NIV treatment may provide satisfactory beneficial level

(xi) *Respiratory care toward future transplantation candidates*, especially toward individuals suffering from severe chronic respiratory conditions, leading to progressive irreversible airway obstruction that demands immediate lung transplantation, such as cystic fibrosis (CF). Such patients, who manifest severe AHRF, benefit from NIV appliance that improves the respiratory stress and prevents ETI and its eventual complications.

Conclusions

Although the percentage of NIV appliance failure maintains a range between 20 and 30%, throughout the years it is proven that this method has significantly decreased the frequency of ICU complications, ETI interventions, hospitalization, and mortality rates. NIV interventions depend significantly upon the level of the patient's tolerance and compliance. According to the latest data, NIV intolerance reaches approximately 20–25% of the selected individuals, while 10% of them undergo eventually ETI. Additionally, absence of a fully functional humidification system leads to less comfort and increased oral dryness, especially for patients under long periods of NIV. Noninvasive ventilation remains the optimal choice toward severe acute clinical pathologic manifestations, such as AHRF, as long as physicians are able to realize when the proper moment will emerge, in order to proceed to the patient's treatment through ETI and MV.

Conflict of Interest None declared.

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Noninvasive Approaches in Difficult Endotracheal Intubation

Jaritzy Lagunez Caramon and Ricardo Guzman Rojas

Introduction

Basic Concepts of Difficult Airway

There is no exact terminology to define a difficult airway [1]. Therefore, the International Colleges of Anesthesiologists, in search of implementing concepts that help unify criteria and develop guidelines that allow the creation of better strategies for the management of difficult airway, have proposed the following concepts:

Difficult airway: is the difficulty in ventilating the upper airway despite the intervention of an experienced anesthesiologist using a face mask, tracheal intubation, or both

Difficult ventilation with a facial mask or supraglottic device: inadequate ventilation because of the impossibility of adequate sealing of a face mask or supraglottic device, allowing excessive air leakage favoring hemodynamic changes induced by hypoxemia and hypercapnia

Difficult laryngoscopy: impossibility to visualize the vocal cords despite multiple attempts with conventional laryngoscopy [2]

Failure in ventilation: impossibility of the placement of an endotracheal tube despite multiple attempts

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Failure or difficulty with invasive airway: impossibility or difficulty in placing a successful airway in the trachea because of features or abnormalities in the anatomy of the neck [3].

Basic Concepts of Noninvasive Ventilation

Acute respiratory failure (ARF) is the result of dysfunction in the pump mechanism of the muscles involved in breathing, or of a dysfunction of the lung. When either of these two mechanisms is affected, it results in ARF due to hypercapnia or an ARF due to hypoxemia, respectively [4].

One of the strategies for the treatment of ARF is noninvasive ventilation (NIV), which is considered first-line treatment in pathologies such as exacerbation of chronic obstructive pulmonary disease (COPD), pulmonary edema of cardiogenic origin, and pulmonary infiltrates in immunocompromised patients and in patients withdrawn from mechanical ventilation, after having presented ARF for hypercapnia.

The indications for initiating this type of ventilatory modality are the following:

- $PaO_2/FiO_2 < 200$ mmHg
- Hypercapnia and respiratory acidosis, $PaCO_2 > 45$ mmHg, pH < 7.35
- Use of accessory respiratory muscles
- Respiratory rate > 24

Contraindications to NIV that should not delay intubation and initiation of mechanical ventilation are as follows:

- Altered neurological status
- Respiratory arrest
- State of circulatory shock
- Abundant secretions in the airway
- Facial injury that prevents the placement of nasal or facial masks [5].

NIV bases its principle on the administration of positive pressure ventilation by means of an external interface that can be traversed by:

- Total face masks
- Full face masks
- Nasal masks
- Nozzles
- Nasal cannulas
- Helmets or hoods [6].

There is no standardized terminology for the modes of NIV, so they depend on each manufacturer and can thus be a cause of confusion during their use. Some of these modalities are listed below.

1. *Mandatory Controlled Ventilation:* This does not require patient effort. The inspiratory pressure and/or tidal volume is established, as well as the respiratory rate and time of each breath.
2. *Assisted/Controlled Ventilation:* A predetermined number of breaths is set in the absence of patient effort, which are synchronized if there are breaths initiated by the patient to avoid patient-ventilator asynchrony.
3. *Ventilation with Pressure Support (PS):* The ventilator is activated or deactivated by the effort of the patient. In this way, the respiratory rate and the time of each breath are determined by the patient. Sometimes, given the poor effort of the patient, it does not happen.
4. *Continuous Positive Pressure in the Airway:* This modality allows a continuous flow throughout the respiratory cycle, with which the respiratory effort decreases; it always needs a high air flow for its own functionality.
5. *Two-Level Pressure Support*: In this modality the two modalities described above are combined, PS and CPAP; ventilation is produced by inspiratory positive airway pressure; expiratory positive airway pressure recruits and acting compensating the intrinsic PEEP.
6. *Proportionally Assisted Ventilation:* Flow and volume are adjusted to measure strength and compliance, respectively [7].

NIV: A Support Device?

To facilitate endotracheal intubation in patients with difficult airway, various benefits have been observed with the use of support devices, such as noninvasive mechanical ventilation. More often in the preoxygenation of the patient, the NIV allows alveolar recruitment, decreases respiratory work, and increases the permeability of the upper airway, avoiding the obstruction of the velopharynx, through the application of positive pressure, which prevents the leakage of air out of the oropharynx [8].

The critical patient has a potentially difficult airway, with hypoxemia being the main complication. Twenty percent of the complications related to respiratory tracts occur in the intensive care unit [9]. The presence of $spO_2 < 70\%$ increases the risk of arrhythmias, cerebral ischemia, and death. It is a challenge to ensure the airway without reaching the period of critical hypoxia and thus allow the safe placement of the endotracheal tube [10]. Preoxygenation improves hypoxemia during intubation, with better results by combining support pressure + PEEP, thus reducing alveolar collapse and atelectasis [11].

Methodology of Noninvasive Ventilation in the Difficult Airway

Preoxygenation Strategies with NIV + Pressure Support, High-Flow Nasal Cannula

In the rapid intubation sequence, specifically during preoxygenation carried out in a conventional way with the use of a mask and bag or also called inflatable self-bag,

a considerable number of episodes of severe hypoxemia occur [12]. Therefore, an attempt has been made to introduce new preoxygenation strategies with the aim of reducing these episodes by focusing mainly on two strategies for preoxygenation. The first of these is the NIV + support pressure, which bases its principle on the increase of alveolar recruitment using the positive pressure of the airway. The second strategy is the use of the high-flow nasal cannula in which a continuous flow in the airway is used, which increases the functional residual capacity. There are few studies where the previous strategies have been used, so making a recommendation is difficult; however, in the FLORALI-2 study where these two strategies were compared in patients who presented ARF, performing a preoxygenation of 3–5 min using for NIV a PEEP 5 cmH_2O, a support pressure until reaching a Tidal Volume of 6–8 mL/kg, FiO_2 100% and for the strategy with HFNC flow of 60 L/min was used, FiO_2 100%, a lower number of episodes of severe hypoxemia was demonstrated in patients with the NIV strategy compared to patients who used HFNC. However, both strategies presented fewer episodes of severe hypoxemia when compared with the preoxygenation strategy with the conventional method. Thus, a lower amount of desaturation during preoxygenation was reported when combining both NIV and HFNC strategies [13], since during the removal of the interface used in NIV, the nasal cannulas provide a constant uninterrupted flow guaranteeing the administration of oxygen during apnea, which is known as apneic oxygenation, which is the period from laryngoscopy to intubation [14].

Approach to the Difficult Airway with NIV

By maintaining the positive pressure in the airway, access is facilitated through various techniques. In the description of Barjaktarevic et al., they performed orotracheal intubation by means of flexible bronchoscopy. At the time of the procedure, they changed the interface for a nasal mask. In addition to the positive pressure, they used FiO_2 >70% for a minimum period of 30 min prior to the intervention. A previous trial found no difference between the use of nasal masks and full face masks to pre-oxygenate [15]. However, no medical procedure is harmless; the risk of gastric aspiration related to the pressure applied during preoxygenation is a potential complication. To avoid this, it is recommended not to exceed 15 cm H_2O of total pressure (pressure support + PEEP) [16]. The success rate of orotracheal intubation by videolaryngoscope is 85–100%, and by flexible endoscope, a success of up to 78 and 100% was described [3]. The structure of the MACOCHA score is seven items that identify risk factors for difficult intubation in critical patients with ICU stay. The MACOCHA score predicts the risk of difficult intubation with a score ≥ 3 [17]. Noninvasive ventilation is an option to improve functional breathing capacity. There was no improvement in the results by extending the preoxygenation for more than 4 min [18].

Conclusions

The more strategies you perform in a procedure or an intervention, the higher the success rate and the lower the number of failures, positively impacting the reduction of mortality.

Therefore, introducing noninvasive mechanical ventilation strategies in preoxygenation will significantly reduce episodes of severe hypoxemia. From its physiological point of view, the use of noninvasive mechanical ventilation is an alternative for difficult airway treatment. Many clinical studies could support the results observed in current clinical studies, managing to standardize strategies in difficult airway intubation protocols.

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Noninvasive Approach in Extubation Respiratory Failure

Elena Rosalía Díaz Rivera

Introduction

Noninvasive mechanical ventilation (NIMV) has shown effectiveness in the treatment of acute respiratory failure (ARF) and in weaning from mechanical ventilation; therefore it would also be useful in post-extubation ARF, which is defined as the appearance of respiratory failure within 48 h of extubation.

Post-extubation acute respiratory failure as a result of extubation failure is reported between 10% and 20% and generates an increase in morbidity and mortality of patients and costs of health services; consequently weaning from mechanical ventilation and successful extubation are a fundamental objective in intensive care and must be protocolized in each hospital. NIMV in this context is an effective ventilatory support option to avoid reintubation in these patients and also prevent the short- and medium-term risks that reintubation entails.

Rescue NIMV is defined as noninvasive ventilatory support implemented within the first 48 h after extubation in the event of a diagnosis of ARF I or II and/or upper airway obstruction.

In prolonged mechanical ventilation, previous failed extubation, and neuromuscular pathology acquired in intensive care, NIMV can be used on a scheduled basis and immediately after extubation to reduce the risk of possible reintubation. At the same time, post-extubation NIMV should not delay orotracheal intubation due to the need for reintubation.

The results of studies show that NIMV is more effective in preventing post-extubation acute respiratory failure than in treating it once this complication has set in.

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Mild to moderate work of breathing, optimal or clearly improving oxygenation indices, neurological status that allows good airway management, a systematic evolution, and intensive monitoring allow us to recognize the success of post-extubation NIMV or the need for immediate reintubation.

Diagnosis of the cause of extubation failure and its severity are the starting point for defining a patient as a candidate for NIMV.

Causes of Extubation Failure

- Upper airway obstruction (UAO) due to edema, laryngospasm, or subglottic obstruction
- Hypoxemia (post-extubation aspiration syndrome, fall in functional residual capacity, atelectasis, bronchospasm)
- Post-obstructive pulmonary edema
- Dysfunction or paradoxical mobility of the vocal cords- fibroscopic diagnosis
- Unilateral or bilateral paralysis of the vocal cords

Noninvasive Mechanical Ventilation in Post-extubation Respiratory Failure

The most used interfaces are oronasal mask, total face mask, and helmet, but they will depend on the patient, comorbidities, current diagnosis, and availability of masks.

Acute respiratory failure Post-extubation	Noninvasive mechanical ventilation Partial ventilatory support BiPAP		
Setting	Initial setting	Limit setting	Systematic and permanent evolution
EPAP	5 cm H_2O	7 cm H_2O	• Glasgow Coma Scale >12 points • Effective swallowing reflex • Effective cough reflex • Stable hemodynamics • Regular ventilation pattern • Optimal management of secretions • Optimal treatment of pain and anxiety • Vital signs monitoring • Gasometric monitoring at the first hour
IPAP	10 cm H_2O	<20 cm H_2O	
Breathing	15	20	
Trigger	2	2	
FiO2	Acute hypoxemia SO_2 = 94% Chronic hypoxemia SO_2: 88–92%	100%	
I:E	1: (2, 3)	1: (2, 3)	

Failure of noninvasive mechanical ventilation: need for endotracheal intubation in the first 48 h

Persistent or increased respiratory distress, hypoxemia, decreased level of consciousness, upper airway obstruction, hemodynamic instability, and failure to protect the airway define NIMV failure.

Key Points

- The use of elective and prophylactic NIMV in patients with a high risk of failed extubation is transcendental.
- The use of NIMV is an effective option in patients with mild to moderate post-extubation acute respiratory failure.
- Early recognition of NIMV failure is necessary to avoid delaying the installation of invasive ventilatory support.
- There is not solid scientific evidence to predict respiratory failure after extubation.
- The etiological diagnosis of extubation failure and its severity are the starting point for defining a patient as a candidate for NIMV.
- Noninvasive ventilatory modalities used in post-extubation acute respiratory failure are partial support.

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Upper Airway Disorders and Noninvasive Mechanical Ventilation: Rationale and Approaches

Bruno Matos Gomes

Introduction

Every man's life ends the same way. It is only the details of how he lived and how he died that distinguish one man from another.—Earnest Hemingway

Over the last 50 years, thanks to advances in medical science and improved social care, life expectancy has been increasing across the world [1].

And so, the medical community has a new challenge that involves not only scientific knowledge but also difficult bioethical questions.

Physicians and other healthcare professionals may find certain concepts vague and hard to understand. Furthermore, there must be a balance between two extremes: a treat-at-all-costs vitalism, on the one hand, and a too-rapid withdrawal of potentially beneficial treatments on the other [2].

Noninvasive Ventilation in Do Not Intubate Patients

The use of noninvasive ventilation (NIV) as a first-line supportive therapy for acute respiratory failure (ARF) is increasing [3].

The use of NIV as a palliative treatment for respiratory failure and chronic dyspnea has become increasingly common. NIV also has a strong impact on the concept of "do not intubate" (DNI) orders.

A variety of factors may drive patients to the acute care setting when nearing the end of life. Dyspnea is one of the most distressing symptoms experienced by dying patients, and it is a common reason for such patients to seek emergency care [4].

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Piroddi et al. published a paper named *Non-invasive mechanical ventilation in elderly patients*; in this narrative review, there are many interesting thoughts about *NIV* support in *DNI* patients. The researchers referred that "DNI" cannot be considered as an indication for NIV; however, the use of *NIV* as a palliative measure is increasing. The authors stated that *NIV* has emerged as an additional, albeit controversial, tool in the management of impending respiratory failure and dyspnea near the end of life [3].

NIV Application in Palliative Patients: A Burning Issue

Palliative *NIV* encompasses a range of applications, from symptom-based intervention concurrent with disease-directed treatment to purely palliative treatment delivered at the end of life. Ideally, decisions about all potentially life-sustaining therapies, from endotracheal intubation and cardiopulmonary resuscitation to oxygen and *NIV*, should be carefully considered in the outpatient setting for patients in whom death as a result of respiratory failure is anticipated.

Taking in mind that *NIV* application is controversial in palliative setting, *Vilaça* et al. designed a study to determine the health-related quality of life (*HRQOL*) impact of regular use of NIV outcomes on DNI patients in the emergency department (*ED*) [4].

The results were clear; they found that almost 50% of the DNI patients were alive 90 days after hospital discharge; however none of them experienced a noteworthy change in HRQOL. On the other hand, in patients who received NIV only for symptom relief, more than 50% did not experience significant improvement of symptoms. All patients in this group died within 90 days of discharge [4].

Schortgen et al. identified an important aspect that could have an impact on the survival rates. Their research led them to conclude that the survival of very old patients depends heavily on the context in which NIV is applied. A leading role for *NIV*, as comfort treatment or palliative care, is recognized for very old patients suffering from *ARF* [5].

On the same page as their colleagues, *Scala and Esquinas* suggested that DNI activities for very old patients admitted for *ARF* (ventilated at home with severe dependence in their daily activities) should be performed in an open or half-open place out of *ICU* [6].

Another interesting paper on this matter was published by *Vargas* et al. in *Aging Clinical and Experimental Research* journal in 2014. The researchers affirmed that very old *DNI* patients with *ARF* could be treated with *NIV* in a half-open geriatric ward with trained physicians and nurses [7].

An important aspect that must be emphasized in this research is the role of the patients' family in these critical situations. The authors stated that the presence of family members might improve patients' comfort and reduce anxiety levels even at the end of life. In sum, they concluded that the specialized respiratory care setting is a more appropriate setting for the *DNI* patient than the *ICU* [7].

Recently *Steindal* et al. published in the *British Medical Journal* a protocol review of noninvasive ventilation in the palliative care of patients with *COPD*; they concluded that the findings regarding the use of *NIV* in palliative care are conflicting and previous systematic reviews only included quantitative studies [8].

Final Thoughts

Anticipation is key in palliative medicine, especially regarding patients with chronic respiratory failure. Mantaing Quill et al. summarized this idea very well in series of clinical cases published in the *Journal of Palliative Medicine*. They affirmed that, ideally, decisions about all potentially life-sustaining therapies, from endotracheal intubation and CPR to oxygen and NPPV, would be carefully considered in the outpatient setting for patients in whom death due to respiratory failure can be anticipated [9].

Piroddi et al. finished their narrative review with an interesting conclusion. Firstly, they affirmed that more diverse patient groups now benefit from *NIV* and even more important is that age does not exclude benefits from *NIV* in a variety of settings [3].

In the same line of research, *Scala and Esquinas* made a couple of enthusiastic statements by suggesting that *DNI* activities for very old patients admitted for *ARF* should be performed in an open or half-open place out of *ICU*. The authors considered that the place where the patients were ventilated could be important in reducing anxiety and depressive symptoms and to improve pain and psychological morbidity "related to *DNI* and end-of-life context" [6].

In sum, this is a controversial topic and future research is needed; however many authors suggested that NIV could be helpful in an appropriate environment and a family-centered strategy.

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Upper Airway in Anesthesiology: Basic Relationships

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Introduction

A "difficult airway" is defined as the problem of maintaining the airway patency without intubation or performing the intubation [1]. A tendency to upper airway collapse and the anatomical structure are predisposing factors for difficult intubation and upper airway obstruction during anesthesia [2]. In this case, good perioperative airway management that requires basic anesthetic skills should be performed since difficulties may develop in maintaining airway patency and intervention may be required. It is also estimated that there are no significant differences between sleep and anesthesia in upper airway changes. The patient's sleep history provides important information for the anesthetist about the unprotected upper airway. Preanesthesia identification of patients with potential anatomical or functional risk for upper airway obstruction in anesthesia is important to ensure good airway management. Additionally, changes in upper airway during anesthesia might be useful in predicting the changes during sleep. Thus, this may be predictive in identifying patients at risk for obstructive sleep apnea (OSA). It can also determine the collapse area and identify suitable patients for surgical treatment [3].

Sites with Upper Airway Collapsibility

The upper airway is a complex structure, starting from the mouth to nose and ending with the larynx, which has respiratory, alimentary, and linguistic functions. These functions are provided by the compatible interaction of soft tissue, bone, and neuromuscular structures which can importantly affect the flexibility of the upper airway.

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The patency of the whole upper airway is dynamically controlled by these systems during respiration. Major dilator muscles (alae nasi, intrinsic palatal, genioglossus, posterior cricoarytenoid, and pharyngeal constrictor muscles) in the upper airway are responsible for the airway patency [4–7]. When the upper airway is not adequately supported by the bone, cartilage, or neuromuscular system, it may collapse by losing its rigidity with loss of muscle tone during sleep or anesthesia. Therefore, estimating whether the upper airway has the potential to collapse during anesthesia is restrictive and requires skill in wakefulness. This includes evaluating the changes in the upper airway with loss of tone during sleep and anesthesia, identifying potential collapsed narrow segments, and evaluating the adequacy of dynamic factors such as airflow in providing passage opening.

Regions with high risk of collapsibility are the narrowest and loosest anatomical regions of the upper airway. The most common collapsed airway regions vary according to the underlying pathologies in adult and childhood. While tonsil hypertrophy is the most common cause of upper airway obstruction in children, the velopharynx is the narrowest region in adults which is vulnerable to collapse [8]. The most common place of collapse in adults during sleep and anesthesia, especially in patients with obstructive sleep apnea (OSA), is the velopharynx, and collapse can be seen at many different points depending on the underlying anatomical or functional pathology [9]. The levels of upper airway collapse have been demonstrated with several radiological images and pharyngeal manometric measurements under various anesthetic agents in several studies [10]. In a recent study by Eastwood et al., it was determined in patients who undergo minor surgical procedures that the soft palate was the most common level of upper airway collapse and retroglossal collapse was less frequent. In addition to that, it was reported that the collapse sites of upper airway were unaffected by the depth of anesthesia [11]. On the other hand, previous studies associated the upper airway obstruction with a retrolingual obstruction during general anesthesia [12, 13]. This difference suggests that the level of collapse may differ according to the underlying anatomical or functional pathologies of the patients.

Changes in Upper Airway During Anesthesia

Structurally, the upper airway consists of two rigid passages, nasal and trachea, and a relatively flaccid pharynx between them. The mechanism of collapse that can develop in the pharynx is basically explained by the Starling resistor model, which has been validated in humans during anesthesia in previous studies. The Starling model is mainly based on the pressure–flow relationship [1, 11, 14]. According to the model, the flow through the collapsed segment depends on the pressure gradient between upstream–downstream and the surrounding tissue. A limited flow may occur when the tissue pressure is greater than the pressure of downstream end of the collapsible segment but less than the pressure of the upstream end. If the pressure of tissue exceeds the pressure of the upstream end, the flow will stop, and a collapse will occur in that segment [1].

The major dilator muscles that are responsible for the patency of upper airway are controlled by central and peripheral mechanoreceptors and chemoreceptors, which are affected by dynamical factors such as intraluminal pressure, airflow, systemic oxygen and carbon dioxide changes, and temperature [8, 15, 16]. These factors resist the airway constriction with the help of the tone of these muscles when the pharyngeal intraluminal pressure decreases during inspiration. The activity of these muscles is partly dependent on reflexes and central impulses controlled by the brain stem. The activity of upper airway muscles reduces during anesthesia due to decreased cortical effects, decreased chemosensitivity, and directly inhibited neural activity and upper airway muscles via laryngeal respiratory mechanoreceptors. The decrease in upper airway muscle activity leads to a decline in the resistance of the muscles against airway narrowing and collapse [1, 17].

Underlying Pathologies Associated with Upper Airway Collapsibility

All these changes increase the sensitivity of collapse during anesthesia and make the development of collapse almost inevitable when the underlying pathologies causing upper airway stenosis are accompanied. Basically, the factors, which can narrow the pharynx, decrease intraluminal pressure, and increase tissue pressure, may predispose to airway obstruction. These factors may be related with the airway passage, wall, or surrounding area. This can lead to a decline in the resistance of the muscles to airway narrowing and collapse [1]. The underlying pathologies that predispose to airway obstruction include space-occupying pathologies in the airway passage such as foreign body, hypertrophic tonsil, pharyngeal tumors, neuromuscular diseases affecting the muscle tone in the pharyngeal wall and connective tissue, endocrine and storage diseases affecting the diameter of the airway passage, laryngomalacia, and edema. There is a risk for airway occlusion during anesthesia in patients with OSA and head, neck, and craniofacial anomalies (acromegaly, Down syndrome, etc.) accompanied by pharyngeal fat pads, macroglossia, and micrognathia. Additionally, several habits such as sedative consumption, smoking, and alcohol are facilitator factors for collapse due to their effects on muscle tone of the upper airway.

Anesthetic Agents

The dynamics of upper airway during anesthesia vary according to the type of the anesthetic agent. Results of measurements obtained with imaging studies, upper airway pressure, endoscopic evaluation, genioglossus electromyography, polysomnography, and clinical signs of obstruction vary [18]. They generally act by neuromuscular blockade and inhibition of skeletal muscle activity. It has been shown that they have greater depressant effects on respiratory muscles such as intercostal muscles and the diaphragm than effects on respiratory muscles [19–21]. Therefore, it

can be seen that inspiratory effort continues during the inhibition of upper airway activity, since the upper airway muscles are more sensitive to anesthetics than the respiratory muscles [11].

Propofol is a commonly used anesthetic agent for induction and maintenance of anesthesia. It can be used for sedation at lower doses. However, adverse effects of propofol on the airway are more common than other anesthetic agents [22]. Sedation due to propofol is associated with upper airway obstruction and pharyngeal dysfunction [10, 23]. Upper airway collapsibility is known to be associated with increased depth of propofol anesthesia because of the extended inhibition of genioglossus muscle activity [11]. However, a dose–response relationship has not yet been clearly defined for several agents. In a systematic review by Ehsan et al., which investigate anesthetic agents (topical lidocaine, propofol, dexmedetomidine, midazolam, desflurane, pentobarbital, sevoflurane, ketamine, and opioids), it was suggested that all agents caused airway collapse at varying degrees. According to that study, sevoflurane, isoflurane, and propofol have dose-dependent effects unlike dexmedetomidine when evaluated with magnetic resonance imaging [18].

Isoflurane does not have a precise dose–response relationship at anesthetic concentrations. Swallowing disturbance may occur with isoflurane at subanesthetic concentrations, suggesting a mild pharyngeal dysfunction. Therefore, this could be a dose–response at subanesthetic drug levels [1].

Mishima et al. studied the passive mechanical upper airway collapsibility and compensatory response against acute partial upper airway obstruction using three different sedative drugs, namely, propofol, dexmedetomidine, and ketamine. Their results have demonstrated that ketamine may be more advantageous than other anesthetics in maintaining the passive upper airway patency and may also be more suitable than propofol for sedation during invasive procedures due to its synergistic effect with local anesthesia [24].

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Pharmacology in Upper Airway Physiology

Savino Spadaro and Gaye Sensoz Celik

The Effect of Anaesthetic Drugs on the Upper Airway

Intravenous Sedative Agents

The upper airway integrity is well maintained in a conscious state, regardless of the position of the head and neck. On the contrary, the upper airway diameter, muscle activity and reflexes are diminished in an anaesthetized state. The alterations are influenced by the dose and the agent used.

Propofol

Propofol is a hypnotic and sedative drug which also has antiemetic and amnestic properties. It is indicated in induction and maintenance of anaesthesia, sedation for short procedures like endoscopy and sedation in mechanically ventilated intensive care unit (ICU) patients.

Effect of Propofol on the Upper Airway

Propofol impairs upper airway dilator muscle tone and increases upper airway collapsibility [1]. It also decreases laryngeal reflexes. It causes a diminished response to increased carbon dioxide levels and decreased partial oxygen levels.

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The studies show upper airway obstruction was observed more frequently with the use of propofol than with dexmedetomidine in patients who underwent DISE [2, 3]. However, the site of obstruction is controversial, although there is one study that shows that at similar levels of sedation there is no difference between pharyngeal critical pressures during sedation with dexmedetomidine or propofol, either the low or moderate infusion rates [4]. Also, there is a retrospective study that supports that there is no significant difference in the degree of upper airway obstruction with propofol when compared to dexmedetomidine [5].

Dose-dependent elevation of end-tidal carbon dioxide ($ETCO_2$) via carbon dioxide insufflation reverses airway collapsibility in patients who are sedated with propofol [6]. Upper airway collapsibility also depends on the dose of propofol, as the dose is increased, the collapsibility increases [7, 8]. Moreover, in children who underwent propofol anaesthesia, it is seen that with the increased depth of anaesthesia, the upper airway dimension is decreased [9]. Head elevation with the mouth closed can be applied to ensure upper airway patency by decreasing airway collapsibility [10].

In perioperative management of children with upper respiratory tract infection (URTI), intravenous induction with propofol reduces the occurrence of respiratory adverse effects [11]. For magnetic resonance imaging sleep study in children, the need for artificial airway support is significantly great with propofol when compared to dexmedetomidine [12]. The most affected area of the upper airway from propofol anaesthesia is found to be the epiglottis in children aged 2–6 years old [9]. In infants, with increasing depth of anaesthesia, a generalized narrowing was seen at each anatomical level [13]. In low-dose propofol sedation, the narrowest part of the pharyngeal airway was found to be the base of the tongue [14].

Upper airway closing pressure and genioglossus muscle activity, which is the primary airway dilator, during airway occlusion did not differ between sevoflurane and propofol anaesthesia [5]. Midazolam and propofol were found to have similar upper airway obstruction propensity when compared to mild to moderate sedation levels [15]. Tracheal intubation with propofol anaesthesia causes lower airway resistance than with thiopental or etomidate anaesthesia [16].

Patients with obstructive sleep apnoea (OSA) are more prone to upper airway obstruction than patients who do not have OSA with propofol sedation [17].

Benzodiazepines

Benzodiazepines are in the group of hypnosedative drugs. It has several indications like procedural sedation, anxiety disorders, seizure, spastic disorders, Tourette's syndrome, alcohol withdrawal, delirium and delirium tremens. Benzodiazepines should be used with caution in respiratory disorders and pregnant patients. There are pharmacological agents that have agonistic effects on benzodiazepine receptors, named Z-drugs. Examples are zaleplon, zolpidem and eszopiclone.

Effects of Benzodiazepines on the Upper Airway

Benzodiazepines are respiratory depressants. They reduce the ventilatory response to carbon dioxide. Therefore ventilation should be monitored in patients who are receiving benzodiazepines.

Midazolam administration causes a significant increase in upper airway resistance, and midazolam-induced apnoeas are initially central, and later it is obstructive in character. Oral diazepam use causes a significant depression in the sensitivity of the upper airway reflexes. There is no recent study on the effect of diazepam on the upper airways.

The upper airway reflex sensitivity is depressed with intravenous administration of midazolam or diazepam [18], although there is no increase in pharyngeal collapsibility and OSA severity with low doses of diazepam and midazolam. Therefore, benzodiazepines are found appropriate to use in patients with airway diseases. In patients with OSA, critical closing pressure in natural sleep and low-dose midazolam-induced sleep were found similar [19]. Midazolam sedation results in airway obstruction, and patients need to be constantly aroused or to restore airway patency; jaw thrust manoeuvre may be necessary [20]. Transient apnoea may occur after the rapid injection of large doses of midazolam, especially in the presence of preoperative medication that includes an opioid [21].

Midazolam versus midazolam with propofol sedation was compared in an early study, and the minimum diameter of the pharyngeal airway was smaller in the group which receive midazolam with propofol sedation. There is no difference found between midazolam and propofol in the negative pressure resulting in upper airway obstruction [15].

Zolpidem increases the responsiveness of the genioglossus muscle to upper airway narrowing; on the other hand, with temazepam use, the genioglossus muscle responsiveness is preserved with upper airway narrowing. Neither zolpidem nor temazepam impairs passive airway collapsibility [22]. Zopiclone does not reduce the activity of the genioglossus muscle and its responsiveness in patients with OSA [23].

In children who receive oral midazolam and nitrous oxide inhalation, significant upper airway obstruction may be seen, especially in those with enlarged tonsils. Therefore, in preoperative assessment, it is important to evaluate the tonsil size [24].

Barbiturates

Barbiturates are hypnotic-sedative drugs. There are different kinds of barbiturates depending on the structure. While oxybarbiturates (pentobarbital, secobarbital) contain oxygen at the second position, thiobarbiturates (thiopentone, thiamylal) have a sulphur atom. They are indicated in epilepsy, induction of anaesthesia, preoperative anxiety treatment, withdrawal syndrome and insomnia. It is also used to induce coma in patients with increased intracranial pressure (ICP) because it reduces ICP by decreasing cerebral blood flow.

Effects of Barbiturates on the Upper Airway

Thiopentone affects activity of the tongue, the infrahyoid muscles and the scalene muscles in a dose-dependent manner; with incremental doses, the muscle activity decreases. Induction with barbiturates may cause a higher incidence of cough and hiccups than propofol [25]. Thiopentone is less effective at suppressing pharyngeal reflexes than propofol.

Genioglossus muscle phasic activity may be increased by pentobarbital in rats [26]. However, there are recent studies that show, in awakeness, pentobarbital did not affect genioglossus muscle activity but in sleeping adults pentobarbital caused an increase in phasic genioglossus activity prior to arousal. Also, pentobarbital has no effect on critical closing pressure [27].

Positioning of the patient can impact airway resistance. The airway impedance increased after lithotomy positioning with thiopentone anaesthesia, but it remains unchanged with propofol anaesthesia [28]. Children who undergo computed tomography or magnetic resonance imaging under sedation with rectal thiopentone have not shown any respiratory depression; however, some of them had an event of desaturation which was corrected immediately after repositioning of the neck [29].

Thiopentone mixture with propofol, compared to propofol alone in patients who were inserted with laryngeal mask airway (LMA), has a higher incidence of gag reflex, inadequate jaw relaxation and coughing [30]. A recent study also shows that the incidence of gag reflex with propofol is lower than thiopentone and the incidence of laryngospasm was found higher with thiopentone; however, there was no statistically significant difference in the incidence of coughing between these two drugs [31]. Also, fewer post-operative complications, like sore throat and dysphagia, were seen in patients who were anaesthetized with propofol when compared to thiopentone after the use of LMA [32].

Opioids

Opioids are mainly used in pain control. They are used in acute and chronic pain, especially in cancer patients. They are contraindicated in known hypersensitivity to opioids, respiratory insufficiency, known substance use disorder that are not in remission period and acute psychiatric disorder.

Effects of Opioids on the Upper Airway

Opioids have numerous effects on the airways. They cause a diminished response in the airways to stimuli. The upper airway patency is reduced with opioid use. The airway resistance may increase, although the cough reflex is reduced. They cause depression of the supraglottic airway which results in airway obstruction. They cause central nervous system depression which results in depression in ventilation and a decreased response to increased carbon dioxide levels [33]. Reduced response to hypoxia and hypercapnia as a result of opioid use could cause a decrease in upper airway dilator muscle neural output, which results in the collapse of the airway [34]. Patients with severe OSA have an increased risk of respiratory depression with opioids [35, 36]. A recent study shows that there is no reduction in pharyngeal muscle activity with morphine administration. However, the respiratory response is

decreased with the use of morphine in the presence of hypercapnia. Morphine does not alter the genioglossus muscle activity [37]. On the other hand, fentanyl has been shown to cause a decrease in genioglossus activity, and it can be reversed by naloxone [38].

Opioids can also cause vocal cord closure which is a life-threatening condition. This may be seen with tramadol use, which is a weak opioid agonist [39]. It is also seen with the use of sufentanil at induction of anaesthesia. Cough and dyspnoea were observed more frequently in patients who did not receive sedation when compared to patients who are sedated with a combination of midazolam and alfentanil during bronchoscopy [40].

Comparing remifentanil with propofol, studies show that respiratory events, such as bradypnoea, desaturation and apnoea, had higher incidence with propofol sedation [41]. The addition of fentanyl to propofol anaesthesia causes depression in airway reflexes in a dose-dependent manner, except for apnoea with laryngospasm, although the duration of laryngospasm becomes shorter as the cumulative doses of fentanyl increase [42]. In spontaneously breathing patients, the addition of remifentanil to propofol infusion reduces the haemodynamic response caused by upper airway stimulation [43].

Fentanyl reduces airway irritability in children who receive desflurane as maintenance anaesthesia followed by thiopental induction [44]. The optimal effect-site concentration of fentanyl to prevent the emergence cough was given to patients who underwent laparoscopic cholecystectomy either with sevoflurane or desflurane anaesthesia; however, there was no significant difference [45].

Alpha-2 Agonists

Alpha-2 agonists are in the group of adrenergic drugs. Their main effect is stimulation of alpha-2 receptors, which causes adrenergic and cholinergic nerve inhibition, platelet aggregation, vascular smooth muscle contraction, inhibition of lipolysis and secretion of insulin. Dexmedetomidine is highly lipid-soluble and a rapidly distributing drug. Therefore its onset of action is rapid, but it has a short duration of action, which makes it useful for infusions. They are metabolized in the liver and excreted by the kidneys. They can be given through oral, IV, IM, sublingual and intranasal routes. Dexmedetomidine is used for initially intubated and mechanically ventilated patients during treatment in an intensive care setting and non-intubated patients prior to and/or during surgical and other procedures. Moreover, it can be used in treatment of delirium, insomnia treatment in the ICU and treatment of alcohol withdrawal.

Effects of Alpha-2 Agonists on Upper Airway

Dexmedetomidine has minimal effects on the respiratory system. In particular patients with airway compromise like OSA and obese patients, dexmedetomidine provides a good sedation without airway collapse and respiratory depression [46]. An earlier study showed that there is no significant difference in airway dimensions between dexmedetomidine and propofol anaesthesia in children [47]. However, it is the preferred anaesthetic in children because of its minimal effect on airway [48].

Recent studies show dexmedetomidine anaesthesia provides better airway patency than propofol. The majority of the studies identified dexmedetomidine as the preferred pharmacologic agent for drug-induced sleep endoscopy (DISE) due to an overall safer and more stable profile based upon haemodynamic stability. However, propofol causes more airway obstruction and this results in oxygen desaturations [49]. In another study, sedation with propofol or dexmedetomidine was given to the patients, and lower numbers of upper airway obstruction were seen in the dexmedetomidine group [50].

In a series of paediatric DICE, dexmedetomidine and ketamine combination is compared to propofol alone or to propofol with sevoflurane combination; the results show that dexmedetomidine and ketamine combination has lower respiratory incidents and a higher rate of completion success than the other groups [51].

Critical closing pressure and upper airway resistance did not significantly differ between dexmedetomidine and propofol anaesthesia [4, 52]. However, in coblation-assisted upper airway procedure, propofol causes more airway obstruction and apnoea than dexmedetomidine [53]. In patients who underwent inguinal hernia repair, dexmedetomidine is found to be safer than midazolam sedation because of its minimal effect on the airways [54].

In children with OSA, with increasing doses of dexmedetomidine, the airway dimensions are slightly increased or do not change at all. In children without OSA, dose-dependent changes in airway were minimal [47]. In children with severe OSA, the need for artificial airway is less with dexmedetomidine when compared to propofol [12]. In children with Down syndrome and OSA, dexmedetomidine does not cause an alteration in upper airway reflexes, and the airway patency is maintained [55].

Clonidine causes a reduced sensitivity to hypocapnic central apnoea; however it does not cause a significant effect on upper airway mechanics [56]. Also, there is no effect seen on the upper airway resistance with a single dose of oral clonidine either with awakeness or sleep [56].

Ketamine

Ketamine is a non-gamma-aminobutyric acid sedative with analgesic properties. It is used in procedural sedation, general anaesthesia, analgesia, reversal of opioid tolerance, asthma exacerbations and severe bronchospasm with no response to other medications.

Effects of Ketamine on the Upper Airway

Ketamine decreases airway resistance, causes bronchodilation and has minimal effect on the central respiratory drive [57]. Therefore, it is a preferred sedative agent in patients with asthma. Ketamine does not significantly alter pharyngeal and laryngeal reflexes; therefore spontaneous breathing is maintained [58]. This feature can be helpful in patients with expected difficult intubation. The activity of the muscles of the tongue, anterior neck and scalene does not change significantly after sedation with ketamine [20]. Upper airway patency with less collapsibility is maintained by

ketamine sedation. The compensatory neuromuscular mechanisms for upper airway obstruction remain intact during ketamine sedation [52].

The combination of dexmedetomidine and ketamine cause fewer oxygen desaturations compared to propofol or a combination of sevoflurane with propofol, during endoscopy under sedation [51]. In children who receive dexmedetomidine anaesthesia, the addition of ketamine does not cause any signs of airway obstruction [59].

Apnoea incidence is found to be lower in patients who receive ketamine-fentanyl combination compared to propofol-fentanyl combination [60]. However, if given IV and rapidly, it can cause apnoea. The time to resumption of spontaneous breathing is longer with the combination of alfentanil-propofol compared to ketamine-propofol combination [61].

Inhalational Agents

Inhalational agents are used in induction and maintenance of anaesthesia. Inhalational anaesthetics affect both the upper and lower airways. The pharyngeal airway collapse is primarily caused by loss of muscle function; therefore, upper airways are affected indirectly by volatile agents. Inhalational anaesthetics, except desflurane, are known to produce bronchodilation.

Sevoflurane

Sevoflurane decreases airway resistance. It decreases the airway resistance of at least or even more than isoflurane or halothane [62]. Sevoflurane depresses the pharyngeal dilator muscle activity in a dose-dependent manner [63]. It causes a reduction in airway diameter in children, and the decrease in airway diameter is dose-dependent [64]. It may reduce airway patency [65, 66]. Sevoflurane decreases airway resistance more than isoflurane and halothane either used alone [62]. Sevoflurane causes less airway irritation than halothane in children [67]. It also causes less airway irritation than desflurane and isoflurane [68]. The critical closing pressure is higher with sevoflurane than with halothane. Sevoflurane depresses the pharyngeal dilator muscle activity more than halothane, and this indicates that airway patency is better achieved with halothane [69]. There is no significant difference in the incidence of coughing at induction of anaesthesia between sevoflurane and desflurane; however, sevoflurane is better at depressing the cough reflex to cuff inflation than desflurane [70, 71].

The removal of the laryngeal tube in the anaesthetized state with sevoflurane may result in upper airway obstruction in children. On the other hand, if the removal of the laryngeal tube is done when the child is awake, it could lead to airway complications like laryngospasm, coughing and desaturation [72].

Desflurane

Desflurane does not increase adverse respiratory events when compared to sevoflurane [73, 74]. However, a recent meta-analysis shows that the risk of respiratory

events with desflurane has a higher incidence when compared to sevoflurane [75]. The incidence of coughing does not significantly differ between desflurane and sevoflurane during induction and emergence from anaesthesia. However, overall, the incidence of coughing is higher in the desflurane group [71, 76]. Moreover, the incidence of laryngospasm and breath holding did not differ between sevoflurane and desflurane [77]. Desflurane provides a rapid wakening and more rapid return or airway reflexes than sevoflurane [78]. In smokers, desflurane anaesthesia increases airway resistance [79].

The administration of desflurane during anaesthesia also provides a rapid wakening, although it results in a higher incidence of airway complications than sevoflurane [80]. In infants who have a history of prematurity, the incidence of apnoeas did not show any difference between sevoflurane and desflurane [81].

Isoflurane

Isoflurane anaesthesia results in a decrease in muscle activity and an increase in the collapsibility of the upper airway. Under isoflurane anaesthesia, genioglossus muscle activity is depressed; however decreasing airway pressure does not cause electromyographic changes in the activity of genioglossus muscle [82]. Isoflurane provides higher tonic and phasic genioglossus muscle activity in rats when compared to propofol [83]. Isoflurane decreases the ciliary movements in the airway when the minimum alveolar concentration (MAC) reaches 3 [84]. Isoflurane reduces the response to acute hypoxia; this reduction may be reversed by antioxidant use [85]. In patients with asthma or chronic obstructive pulmonary disease (COPD), isoflurane may slightly increase airway resistance [86].

Enflurane

The administration of enflurane wither with laryngeal mask airway or face mask causes upper airway complications like cough, holding breath, laryngospasm, bronchospasm or excitement [87]. When MAC reaches 3, enflurane is shown to cause decrease in the ciliary movements of the airway [84].

Neuromuscular Blocker Agents

Neuromuscular blockers (NMB) are used in general anaesthesia to facilitate tracheal intubation and to improve surgical conditions. They act on nicotinic acetylcholine receptors; therefore smooth muscles are not affected by neuromuscular blockers. The most resistant muscles to NMB are the diaphragm and laryngeal muscles. Neuromuscular blockers facilitate the management of the airways. They are very useful in maintaining airway patency in the presence of positive pressure ventilation.

Total muscle paralysis results in airway collapse. Minimal neuromuscular blockade (train of four (TOF) ratio: 0.5–1) increases upper airway collapsibility by impairing upper airway dilator muscles' compensatory responses to negative airway pressures [88]. This may lead to upper airway obstruction and, therefore,

desaturation. Early extubation may result in upper airway collapse and respiratory arrest; therefore it is vital to monitor the level of neuromuscular blockade. Partial neuromuscular blockage (TOF ratio 0.5–0.8) is associated with a decreased response to normal increase in anteroposterior diameter of the airway during forced inspiration, a decrease in genioglossus muscle activity during maximum voluntary tongue protrusion and unchanged airway size during expiration [89].

Reversal Agents for Neuromuscular Blockers

1. **Sugammadex** is a cyclodextrin derivative. Its mechanism of action is encapsulation of the steroidal neuromuscular blockers.
2. **Cholinesterase inhibitors**, like neostigmine, pyridostigmine and edrophonium, cause a reduction in the breakdown of acetylcholinesterase; therefore cholinergic system remains active. They are associated with the reconstruction of neuromuscular transmission. However, the administration of cholinesterase inhibitors also causes muscarinic effects on the cardiovascular system, exocrine glands and smooth muscles. In order to block these parasympathomimetic effects, co-administration of antimuscarinic (anticholinergic) drugs is necessary.

   A residual neuromuscular block may be seen in patients who receive neuromuscular blocking agents intraoperatively, even if a reversing agent has been used. Residual block may cause unwanted critical respiratory events postoperatively, like reduced pharyngeal muscle activity, upper airway obstruction, pulmonary aspiration and even respiratory arrest. The most common critical respiratory events seen are severe hypoxemia, upper airway obstruction and mild hypoxemia [90]. Residual neuromuscular blockade can be detected by neuromuscular monitoring, and it can be reversed by reversal agents.

   Reversal of neuromuscular blockade either with sugammadex or neostigmine does not have significant difference in respiratory complications such as laryngospasm, increase in upper airway secretions and coughing [91]. Also, there is no statistical significance found between sugammadex and neostigmine in respiratory complications in elderly patients [92]. In patients who underwent major abdominal surgery, post-operative pulmonary complication incidence did not differ between neostigmine and sugammadex [93].

   After reversal of neuromuscular blockade, the upper airway dilator muscle activity is significantly impaired in patients who are given neostigmine. However, this effect is not seen with sugammadex [94].

   Inappropriate use of cholinesterase inhibitors may impair genioglossus activity, upper airway dilator muscle activity, diaphragmatic function and breathing after the reversal of neuromuscular blockers [95]. The administration of neostigmine with glycopyrrolate after recovery from neuromuscular blockade may result in upper airway collapsibility and impaired genioglossus muscle activity [96].
3. Antimuscarinic drugs block the binding of acetylcholine to muscarinic receptors, which results in an anticholinergic response. The primary effect of antimus-

carinic agents on airways is smooth muscle relaxation, i.e. bronchodilation. The muscarinic receptor activation has been shown to reduce the genioglossus muscle activity, therefore impairing upper airway integrity during rapid eye movement (REM) sleep. This reduction may be reversed by local antimuscarinic use [97]. Inhalational antimuscarinics, such as ipratropium bromide, cause an increase in airway diameter. However, the degree of bronchodilation is not equal all over the airways; it is greater in distal airways than proximal airways with the use of inhalational antimuscarinics [98, 99]. Inhalational ipratropium is shown to reduce upper airway secretions [100]. The use of glycopyrrolate parenterally also reduces airway secretions. However, glycopyrrolate and atropine use does not diminish the incidence of coughing [101, 102]. Moreover, the use of anticholinergic drugs may result in hypertension.

There are many recent studies investigating the effect of a noradrenergic agent and antimuscarinic combination on the upper airway. The combination of reboxetine with hyoscine butyl bromide improves upper airway function in healthy people. This combination also reduces upper airway resistance [103]. The combination also increases tonic genioglossus muscle responsiveness during non-rapid eye movement (non-REM) sleep [104]. The combination of selective norepinephrine reuptake inhibitor and atomoxetine with solifenacin succinate improves airway patency during sleep [105]. Atomoxetine and fesoterodine combination improves airway collapsibility in patients with OSA [106]. Atomoxetine alone and in combination with oxybutynin improve upper airway collapsibility [107].

Local Anaesthetics

Local anaesthetics (LA) are weak base molecules that have several properties.

Effect of Local Anaesthetics on Upper Airway

Local anaesthetics may cause irritation in airway mucous membranes with high doses.

Topical lidocaine impairs glottic function and increases airway resistance. It reduces the incidence of coughing [108]. Viral upper respiratory tract infection causes an increase in the sensitivity of upper airway reflexes. Nebulized lidocaine reduces the increased sensitivity of the reflexes [109]. Topical lidocaine is known to reduce the incidence of post-operative laryngospasm. IV lidocaine reduces airway reactivity and facilitates the placement of the endotracheal tube.

Antihistaminic Drugs

Histamine is an organic compound which takes part in allergic reactions and immunological responses and acts as a central neurotransmitter. There are four classes of histamine receptors, H-1, H-2, H-3 and H-4. H-1 receptors are primarily involved in

allergic reactions, and H-2 receptors are involved in the acidification of gastric fluid. Histamine release is associated with vasodilation and increased capillary permeability. The increase in capillary permeability allows the proteins and cells like leucocytes to reach the inflammation site. It also causes the symptoms of allergic upper airway diseases, like runny nose and sneezing. Antihistaminic drugs are used in the treatment of histamine-mediated conditions. H-1 receptor antagonists are used to treat allergies. H-2 receptor antagonists are used in the treatment of gastric conditions that are caused by excessive acid. First-generation antihistaminics can cross the blood-brain barrier and antagonize H-1 receptors; as a result they can cause central nervous system side effects.

Effect of Antihistaminic Drugs on Upper Airways

Antihistamines reduce the oedema in upper airways especially in allergic reactions and in upper airway disorders. They are used in combination with corticosteroids in emergency conditions like urticaria and angioedema to reduce the oedema in the upper airways.

First-generation antihistamines reduce the incidence of cough in upper airway cough syndrome [110]. Fexofenadine a second-generation antihistamine does not cause/affect cough reflex sensitivity, even in patients with upper respiratory tract infection [111]. The first-generation antihistamine diphenhydramine is also shown to reduce cough reflex sensitivity during respiratory tract infection [112]. The combination of first-generation diphenhydramine with pseudoephedrine does not affect genioglossus responsiveness; however they cause a slight improvement in upper airway collapsibility in patients with OSA [113].

Corticosteroids

Corticosteroids (CSs) are synthetic derivatives of steroid hormones which are produced by the adrenal glands. Adrenal steroid hormones are cortisol, aldosterone and sex steroids. The effects of CSs are dependent on their degree of glucocorticoid and mineralocorticoid properties. Glucocorticoids have anti-inflammatory, immunesuppressive vasoconstrictive effects, whereas mineralocorticoids have an effect on water and electrolyte balance.

Inflammation causes an increase in capillary permeability, impairs vascular integrity and causes exudation of vascular content to tissues. CSs suppress the effects of inflammation. The effectiveness of CSs depends on the type, dose of the CS and the severity of the inflammation. They are the cornerstone therapy for allergic diseases.

Effect of CSs on Upper Airway

CSs are the cornerstone treatment of upper airway diseases. The upper airway obstruction which is caused by oedema and inflammation may resolve to some degree with the use of CSs. The combination of inhaled CSs and long-acting beta-agonist agent may be more effective in reducing inflammation. They can reduce

post-extubation laryngeal oedema. Moreover, prophylactic use of CSs before extubation may benefit in preventing post-extubation airway complications, although prophylactic use of CSs could be restricted to patients who are at high risk of post-extubation airway obstruction. This risk can be detected by cuff leak test [114]. In critically ill children, dexamethasone reduces the post-extubation airway obstruction [115].

The use of intranasal steroids has been shown effective in allergic rhinitis; they are the first-line treatment; however, the side effects should be well identified. Peak nasal inspiratory flow is significantly improved in patients with allergic rhinitis who are receiving intranasal CS therapy [116]. Intranasal CSs have no effect on nasal mucociliary activity. Inhaler CSs are not effective in common cold in adults, although they may be effective in children with wheezing if given in high doses. CSs may reduce sore throat.

Adrenergic Agents

Adrenergic agents are a group of drugs that exerts their effect by binding alpha (α_1, α_2) or beta receptors (β_1, β_2, β_3).

Effects of Adrenergic Agents on Upper Airways

Non-selective α-agonists, such as xylometazoline, have decongestant effect on the mucosa.

Selective α_1-agonists, such as phenylephrine and oxymetazoline, cause vasoconstriction; therefore they have decongestant effect. Resolving the oedema of the mucosa contributes to airway patency. However, α-agonists may cause rhinitis medicamentosa in prolonged use. In allergic rhinitis, the combination with corticosteroid therapy provides better upper airway patency. And CSs may reverse the rebound congestion and tachyphylaxis [117].

B_2-agonists are well-known bronchodilators; moreover, they increase mucociliary activity and cause inhibition of the release of inflammatory mediators.

Epinephrine decreases mucosal swelling due to its vasoconstrictive properties. The upper airway obstruction due to mucosal swelling could be treated by epinephrine; thus with the resolution of oedema, the upper airway patency is maintained. It also reduces haemorrhagic events.

Pseudoephedrine decreases nasal congestion and opens nasal passage. A combination of an oral antihistamine with nasal pseudoephedrine causes an increase in peak nasal airflow due to the resolution of the inflammation and congestion [118]. Aspirin and pseudoephedrine together provide an effective treatment for pain relief and decongestant effect in patients with upper respiratory tract infections. Moreover, this combination provides a better analgesic and decongestant effect than aspirin or pseudoephedrine alone [119].

Vasoactive adrenergic drugs may cause cardiovascular side effects like tachycardia, bradycardia and hypertension; therefore they should be given precautiously.

Antipsychotic Agents (Neuroleptic Agents)

Antipsychotic agents are a group of drugs that are used to treat psychosis. They are used in schizophrenia, schizoaffective disorders, acute mania, delusional disorders, major depression with psychotic features, borderline personality disorder, dementia, delirium and Tourette's syndrome.

Effects of Antipsychotics on Upper Airway

Antipsychotics may cause airway obstruction due to their side effects, especially extrapyramidal ones. They can cause respiratory muscle spasms which may result in asphyxia. The use of antipsychotic agents, especially haloperidol, quetiapine, prochlorperazine and risperidone, may result in acute respiratory failure in patients with COPD [120]. Quetiapine can cause respiratory depression by unknown mechanisms [121]. They may cause respiratory depression by reducing consciousness.

Antidepressant Drugs

Antidepressant drugs are used in treatment of major depression and other disorders such as anxiety disorders, panic disorder, social phobia, post-traumatic stress disorder, obsessive compulsive disorder and chronic pain conditions. They affect certain neurotransmitters and thus affect mood and behaviour. The first-line antidepressant drugs are selective serotonin reuptake inhibitors (SSRIs).

The neurotransmitters play an important role in the regulation of sleep. Especially many studies have been done about serotonin and noradrenaline. Serotonin levels are lower than the awake state; therefore, in the state of sleep, the activity of the upper airway dilator muscles is decreased and upper airway becomes prone to obstruction. The treatment with antidepressants may cause an increase in serotonin levels in the synapse; as a result, serotonergic activity will increase, and the dilator effect will be seen in upper airway muscles, especially in OSA patients.

Effects of Antidepressant Drugs on the Upper Airway

Paroxetine increases the activity of the genioglossus muscle as a result of hypoglossal nerve innervation. SSRIs decrease the apnoea-hypopnoea index (AHI) in patients with OSA.

Mirtazapine reduces AHI in patients with OSA [122]. However the effect of mirtazapine on OSA severity is controversial; a randomized controlled trial has shown that there is no effect of mirtazapine on OSA severity [123]. Atomoxetine, a selective noradrenaline reuptake inhibitor, causes pharyngeal hypotonia by changing the activity of potassium channels. Moreover, a combination of atomoxetine with an anticholinergic agent may reduce OSA severity [124]. A combination of duloxetine with an anticholinergic agent improves the upper airway collapsibility; however milnacipran, which is also an SNRI, combination with the same anticholinergic agent does not cause an improvement in upper airway collapsibility [125].

Desipramine, a tricyclic antidepressant (TCA), causes an increase in genioglossus muscle activity in non-REM sleep and causes a decrease in critical collapsing pressure of the upper airway; therefore, it improves the upper airway patency [126, 127].

Mucoactive Agents

Mucoactive agents are used in disorders which cause abnormal mucus secretion and transportation. They decrease mucus secretion and facilitate expectoration.

Effects of Mucoactive Agents on Upper Airway

Mucoactive agents affect the ciliary movement; they generally increase the movement, therefore clearance. They are effective in reducing cough symptoms. N-acetylcysteine (NAC) diminishes the adhesion ability of bacteria to the oropharyngeal epithelium [128]. In addition to its mucoactive properties, NAC is also an anti-inflammatory and antioxidative agent. Thiamphenicol glycinate acetylcysteine, which is a combination of an antibiotic and acetylcysteine, is effective in enhancing mucociliary clearance and inhibiting bacterial adhesion and biofilm formation [129]. NAC and carbocisteine reduce the viscosity of the mucus; they are especially useful in patients with COPD and bronchitis.

Drug	Effect on the upper airway	↑↓↔
Propofol	Upper airway collapsibility	↑[a]
	Critical closing pressure	↑
	Laryngeal reflexes	↓
	Ventilatory response to hypercarbia	↓
	Phasic GG activity	↓
Benzodiazepines	Upper airway collapsibility	↑
	Pharyngeal collapsibility	↔[b]
	Upper airway resistance	↑
	Ventilatory response to hypercarbia	↓
Barbiturates	Upper airway muscle activity	↓
	GG muscle activity	Dependent on sleep/awake status
	Pharyngeal reflexes	↓
Opioids	Upper airway patency	↓
	Ventilatory response to hypoxia and hypercapnia	↓
	GG activity	Depends on the agent
	Vocal cord closure	↑
	Airway irritability	↓
Alpha-2 agonists	Upper airway patency	↔
	Upper airway reflexes	↔
	Upper airway resistance	↔

Drug	Effect on the upper airway	↑↓↔
Ketamine	Upper airway muscle activity	↔
	Airway resistance	↓
Sevoflurane	Airway patency	↓
	Pharyngeal dilator muscle activity	↓[a]
	Airway resistance	↓
	Airway irritation	Low
Desflurane	Coughing incidence	↑
	Airway resistance in smokers	↑
Isoflurane	Upper airway collapsibility	↑
	Airway muscle activity	↓
	GG activity	↓
	Ciliary movements	↓
	Airway resistance	↑
Neuromuscular blockers	Upper airway patency	↓
	Pharyngeal muscle activity	↓
Reversal agents	Upper airway patency	↑
Antimuscarinics	Airway diameter	↑
	GG activity	↓
	Airway secretions	↓
Lidocaine	Airway resistance	↑
	Airway reflexes	↓
	Laryngospasm	↑
Antihistaminics	Upper airway collapsibility	↓
	Coughing incidence	↓
	GG responsiveness	↔
	Upper airway oedema	↓
Corticosteroids	Upper airway inflammation	↓
	Post-extubation airway obstruction	↓
	Nasal mucociliary activity	↔
Adrenergic agents	Upper airway patency	↔
	Airway oedema	↓
	Mucosal swelling	↓
Antipsychotics	Airway obstruction	↑
Antidepressants	Upper airway collapsibility	Dependent on the agent
	Pharyngeal hypotonia	↑
	Apnoea-hypopnoea index (AHI)	↓
Mucoactive agents	Ciliary movement	↑
	Cough symptoms	↓

[a]Dose-dependent
[b]At low doses, GG, genioglossus muscle

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Upper Airway Disorders and Postoperative Respiratory Failure

Ferhat Çetinkaya and Dilek Özcengiz

Respiratory failure occurs as a result of the respiratory system's inability to provide the oxygen needed by the tissues and/or the inability to remove carbon dioxide, which is a product of metabolism [1].

Acute respiratory failure, pathophysiologically, is classified as hypoxemic respiratory failure (type 1), hypercapnic respiratory failure (type 2), perioperative respiratory failure (type 3), and shock-induced respiratory failure (type 4) [2].

Type 3 respiratory failure is called perioperative respiratory failure. The basic mechanism is atelectasis. In the perioperative period, atelectasis develops with the effect of gravity, especially in the lower lobes, when the functional residual capacity falls below the closure volume abnormally in patients [3]. It can also occur due to surgery-related reasons such as suppression of the respiratory center (sedatives, anesthesia, and opioids), diaphragm paralysis, and phrenic nerve damage. The location of the surgery is also important. While vital capacity decreases by 50% in the first 24 h in upper abdominal surgery and returns to normal on the seventh day, in lower abdominal surgery, the vital capacity decreases by 25% in the first 24 h and returns to normal on the third day [4]. It has been reported that it may take several months for the reduction of up to 30% in all lung volumes to recover after coronary artery bypass operations [5]. It has been reported that there is a decrease of up to 30% in vital capacity in the first 24 h after thoracotomy [6].

Postoperative respiratory failure occurs in more than 20% of all patients receiving respiratory support [7, 8]. Respiratory failure requiring unplanned reintubation in the postoperative period is associated with high morbidity and causes prolonged hospital stay and increased 30-day mortality [9–11].

Postoperative respiratory failure may occur due to atelectasis, bronchospasm, pneumonia, and exacerbation of chronic lung disease. However, pleural effusions,

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chemical pneumonia, pulmonary edema, hypoxemia due to abdominal compartment syndrome, tracheal rupture and acute upper airway obstruction, and respiratory failure due to worsening obstructive sleep apnea may also be seen.

Acute upper airway obstruction typically occurs immediately after surgery. It usually manifests itself as stridor if the obstruction is partial and as aphonia, if it is complete. Patients may also develop dyspnea, tachypnea, tachycardia, sweating, and respiratory distress. Causes of postoperative acute upper airway obstruction include the following:

- Pharyngeal muscle weakness (obstruction from the tongue or other soft tissues).
- Airway edema (laryngeal edema).
- Laryngospasm.
- Iatrogenic vocal fold paralysis.
- Cervical hematoma can be counted.

Pharyngeal muscle weakness. The residual effect of long-acting neuromuscular blocking agents is the most common cause of upper airway obstruction after anesthesia [12–14]. Other factors that may contribute to pharyngeal muscle relaxation include the effects of opioids, volatile anesthetics, or other agents with sedative properties [15].

Residual paralysis of the pharyngeal muscles (or relaxation during sleep) causes the base of the tongue and tissues of the posterior oropharynx to move toward each other and block the supraglottic inlet. During inspiration, the negative pressure created in the thorax brings the pharyngeal tissues closer together, further obstructing the airway. It manifests as a lack of airflow into the trachea, retraction in the sternum notch, and paradoxical movement of the abdominal musculature. Severe upper airway obstruction results in oxygen (O_2) desaturation, atelectasis, and respiratory failure. This is more likely in patients with obesity, obstructive sleep apnea (OSA), or tonsillar or adenoid hypertrophy due to excess pharyngeal or nasal soft tissue.

Airway edema. Risk factors for airway edema include airway or major neck surgery, decreased venous drainage due to prolonged head-down or prone position and excess volumes of fluid resuscitation [16]. Moreover, patients who are attempted multiple or traumatic intubations may develop pharyngeal or laryngeal edema.

Other causes, such as angioedema or anaphylaxis, are considered in patients with airway edema and none of the abovementioned risk factors. Angioedema may occur in the perioperative setting due to latex, radiocontrast agents, fibrinolytic agents, calcium channel blockers, opioids, or nonsteroidal anti-inflammatory drugs.

Laryngospasm. Laryngospasm is the prolonged continuation of the glottic closure reflex due to stimulation of the superior laryngeal nerve.

Laryngospasm may occur immediately after extubating in a patient who is not alert enough to disable laryngeal reflexes in response to vocal cord irritation from the removal of the endotracheal tube, secretions, blood, or foreign body in the upper airway.

Vocal cord paralysis. Vocal cord paralysis due to unilateral or bilateral laryngeal nerve damage may occur after otolaryngology, thyroidectomy, parathyroidectomy,

surgery of the aortic arch or its branches, or rigid bronchoscopy [17]. In addition, an inflated endotracheal tube cuff in the subglottic larynx can compress the anterior branch of the recurrent laryngeal nerve between the cricoid and thyroid cartilage, causing nerve damage [18].

Bilateral recurrent laryngeal nerve injury may present in much the same way as laryngospasm. Diagnostic laryngoscopy shows that the vocal cords are in apposition in the midline. Intubation attempts in this setting are traumatic and often unsuccessful. Emergency tracheostomy is the appropriate first intervention [19, 20].

Cervical hematoma. After carotid endarterectomy, thyroidectomy, parathyroidectomy, or other neck surgery, hematoma compressing the upper airway may occur. A retropharyngeal hematoma may occur after anterior cervical spine surgery [21]. Although many neck hematomas can be treated conservatively, the patient should be closely monitored for signs of airway obstruction. A rapidly expanding hematoma may cause supraglottic edema due to venous and lymphatic obstruction or cause tracheal deviation or directly compress the tracheal lumen below the level of the cricoid cartilage [22]. Symptoms may not occur until the lumen is <5 mm, but compression can quickly become life-threatening, resulting in the need for urgent airway management and reoperation.

In conclusion, upper airway pathologies should always be kept in mind in patients who develop postoperative respiratory failure, since postoperative respiratory failure constitutes more than 20% of all patients receiving respiratory support and respiratory failure requiring reintubation in the postoperative period is associated with high morbidity. Moreover, a detailed preoperative evaluation may guide us for postoperative respiratory failure, which may be caused by upper airway pathologies such as obesity, obstructive sleep apnea, and tonsillar or adenoid hypertrophy. It might be prevented without the need for invasive methods by using NIMV or appropriate techniques.

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Tracheostomy in Upper Airway Disorders

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Introduction

Respiratory failure is one of the major causes of tracheostomy indication. In the intensive care setting, patients dependent on invasive ventilation for more than 10 days are indicated for tracheostomy. In cases of prolonged intubation, tracheostomy is the most viable strategy, as it favors comfort, reduces the need for sedation, facilitates airway management, and provides the return home of patients dependent on invasive ventilation. Among the most common indications for tracheostomy placement, acute respiratory failure with the expected need for prolonged mechanical ventilation is the most indicated. Failure to wean from orotracheal intubation, upper airway obstruction, copious secretions, brain trauma or severe neurological disease, and neuromuscular diseases are common causes for the use of a tracheostomy tube [1].

Other implications of tracheostomy are related to respiratory changes due to the presence of secretions, communication difficulties, and swallowing. In the literature review conducted by Barros et al. [2], the authors describe the factors that compromise respiratory functions of communication and swallowing. Among the causes of physiological changes, the presence of the CUFF was mentioned, which is fundamental for the maintenance of the pressurized respiratory system for the safety of

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ventilation, but the constant presence of this device causes stasis of secretions in the upper airways, negatively impacts the pharyngeal phase of swallowing, and decreases the pressure to the upper airways, which causes a decrease in the closure of the vocal fold and subglottic pressure [1].

This chapter describes the alterations and consequences of tracheostomy and presents some strategies used in the current literature on noninvasive ventilation as decannulation strategies.

Swallowing Disorders in Patients with Tracheostomy

Relationship Between Breathing and Swallowing

In the last decade, the relationship between the lower airway and swallowing began to be understood. It is known that breathing and swallowing are highly correlated, not only by sharing structures and anatomical regions but also by their similarity in neural control [3, 4]. The pharyngeal phase occurs during the expiratory breathing cycle [4–6]. The pause during swallowing occurs between the mean and low expiratory lung volumes in quiet breathing [7, 8], bringing physiological advantages, including facilitation in the elevation and closure of the larynx (position of the paramedian vocal fold) and the generation of subglottic pressure [5, 6, 9].

Impact of Tracheostomy on Swallowing Physiology

The insertion of a tracheostomy tube into the trachea divides the upper and lower airways, diverting the airflow and directing it to the stoma. The tracheostomy tube nullifies the trans-laryngeal airflow that helps in the maintenance of pharyngolaryngeal functions, such as phonation and swallowing, contributing to incoordination swallowing-breathing; thus, dysphagia becomes a very common disorder in patients undergoing tracheostomy, and it is estimated that 11–93% of these patients have swallowing problems [10]. Tracheostomy is related to isolated changes in the physiology of swallowing, including reduced laryngeal sensitivity [11], changes in laryngeal reflexes [12], reduced cough strength [13], decreased elevation of the larynx during swallowing [14], esophageal compression [15], and decreased subglottic pressure [16]. Historically, these isolated changes are confused with the relationship between tracheostomy and dysphagia, but it should be noted that, although these isolated changes have been studied and are widely described in the literature, the origin of dysphagia in patients with tracheostomy is a misunderstood subject today. The literature does not support the idea that these isolated physiological changes actually translate into clinically significant swallowing difficulties [10, 17–19].

Causal Relationship Between Tracheostomy and Dysphagia: Myths and Evidence

Studies that include an instrumental evaluation of swallowing before tracheostomy placement are very important for the study of the causal relationship between tracheostomy and aspiration. Leder and Ross [17] performed a flexible endoscopic evaluation of swallowing (FEES) before tracheostomy, after tracheostomy, and before decannulation in 20 patients in the intensive care unit. In this study, 19 of 20 (95%) patients had the same aspiration status before and after tracheostomy placement. Specifically, the 12 (100%) patients who aspirated prior to tracheostomy continued to aspirate after their placement. Also, seven out of eight (88%) patients who did not aspire before tracheostomy continued without aspiration after placement. The same authors conducted a direct replication study in 25 hospitalized patients [18]; the FEES was also performed before tracheostomy, after tracheostomy, and before decannulation. Three patients started to present aspiration after tracheostomy placement due to worsening of clinical conditions. Also, four patients stopped aspirating after tracheostomy placement, due to the improvement in clinical conditions. Excluding these patients, all nine subjects who aspirated pre-tracheostomy continued to aspirate after, and the nine patients who did not aspirate pre-tracheostomy continued without aspirating after [18]. These studies support the idea that tracheostomy placement is not related to increased aspiration.

Another study aimed to evaluate the effects of the presence of the tracheostomy tube on the superior and anterior movement of the hyoid bone and larynx in seven patients [14]. The results showed that the presence/absence of the tracheostomy tube did not significantly alter the hyo-laryngeal movement and none of the evaluated subjects presented aspiration. This study did not support the idea that tracheostomy ties the larynx to the neck, preventing the elevation of the hyo-laryngeal complex and the protection of the airways [14].

The pharyngeal and upper esophageal sphincter (UES) pressures were evaluated in 11 individuals in two conditions: (a) with the tracheostomy tube open and (b) with the tracheostomy tube closed. This small study failed to demonstrate that tracheostomy tube occlusion improves pharyngeal and UES pressures [20]. Kang et al. [21] evaluated the effects of decannulation on swallowing kinematics assessed by video fluoroscopy in 13 patients. The results showed that the removal of the tracheostomy tube did not affect any swallowing parameter or the status of penetration/aspiration. Another study evaluated swallowing using FEES in 37 patients undergoing tracheostomy with the tracheostomy tube in situ and after tube extraction; the study showed that, after tube removal, the status of penetration and aspiration changed in 95% and 78% of cases, respectively. Thus, in most cases, the removal of the tracheostomy tube made no difference in the status of penetration or aspiration [22].

Recently, Vergara et al. [23] evaluated the effect of the weight of closed suction circuits and heat and humidity exchange filters (when attached to the tracheostomy tube) on the hyo-laryngeal displacement, using ex situ theoretical models. This small study without humans demonstrated that, although the connection of these circuits increases the weight of the tracheostomy tube, this did not translate into reduced hyoid displacement. Therefore, the idea that the weight of the tracheostomy attaches the larynx to the neck and hinders the protection of the airways is a hypothesis that continues to be rejected [14, 23].

Tracheostomy placement is a medical intervention often used for people with complex respiratory conditions. The procedure is performed mainly in the context of the intensive care unit, in critically ill patients, with a history of prolonged endotracheal intubation, polytrauma, and multiple comorbidities. There is cumulative evidence that bases the etiology of dysphagia on individual and clinical factors, such as the history of prolonged intubation, the presence of comorbidities, and the chronicity/severity of the disease [10, 17–19, 21, 22]. Additionally, the evidence does not support the idea that swallowing will improve when the tracheostomy tube is removed.

Voice, Communication, and Tracheostomy

Voice and communication problems can be evidenced in patients with tracheostomy, since the tube reduces the flow of the trans-laryngeal air and contributes to the atrophy of the vocal muscles and the reduction of subglottic pressure, fundamental aspects for voice production [24]. In addition, those patients with a history of prolonged intubation may have structural problems that may include vocal fold paralysis, granulomas, stenosis, and laryngeal edema, among others [24]. It is known that the restoration of voice and communication in tracheostomized patients increases the quality of life [25], given that the patients may have greater interaction with the family, caregivers, and health professionals, facilitating participation in decision-making about their own treatment [26].

Currently, several strategies for voice and communication in tracheostomized patients have been documented in the literature. In this chapter, we present the strategies most used by speech therapists for the restoration of voice and communication in tracheostomized patients, including those on mechanical ventilation.

Speech Valve

The speech valve can be used in patients who are breathing spontaneously, as well as those who are on mechanical ventilation. It is indicated for those patients who tolerate total cuff disinflation, a small tube size, reduced secretion aspiration, airway patency, and optimal structural condition (e.g., no vocal fold paralysis, no stenosis). Patients should be alert and have communication skills that facilitate phonation and communication. An evaluation with the speech therapist and the respiratory therapist is indispensable for the placement of the speech valve in any clinical context.

Total or Partial Occlusion of the Tube

Occluding the tube will allow the trans-laryngeal airflow to be reactivated, facilitating the movement of the vocal fold. It is important that the speech therapist educate the patients and their families, as well as the multidisciplinary team, about the occlusion methods that can be used. These methods may include total or partial occlusion of the tube with occlusion devices (e.g., collusion valves), as well as digital occlusion using gloves or the sanitized hand [23].

Above Cuff Vocalization (ACV)

This technique consists of introducing external subglottic airflow (e.g., medical air or oxygen) in those patients who have cannulas with subglottic aspiration port [26]. The technique has been used mainly in patients who are dependent on mechanical ventilation and who do not tolerate cuff deflation and adaptation of the in-line speech valve. The airflow that is directed to the larynx and oropharynx during the ACV has shown benefits in communication, swallowing, quality of life, and cough [27].

Electronic Larynx

Since the last century, the electronic larynx has been used in patients with tracheostomy [28]. Although this device was created mainly for patients with total laryngectomy after laryngeal cancer, new studies have evaluated its use in intensive care units in patients with tracheostomies. Rose et al. [29] demonstrated that patients classified their own communication as "easier" during the use of the electrolarynx, which reduced anxiety. However, speech intelligibility with this device can be reduced, especially in patients with muscle weakness.

Alternative and Augmentative Communication

Augmentative and alternative communication (AAC) strategies are ideal for those patients who are unable to communicate orally using the aforementioned tools. However, subjects who are using an oral communication method may also use AAC strategies to maximize the possibilities of interaction with family members and the team. These strategies can be high-tech, low-tech, and without technology. For example, devices that can be used manually may be useful for patients with some degree of upper extremity dexterity [30].

Strategies for Decannulation of Tracheostomized Patients

The process of removing the tracheostomy tube is known as decannulation. Commonly, the procedure can be performed in the intensive care unit, hospitalization, and outpatient clinic. Several health professionals participate in this process, including (but not limited to) physicians, nurses, speech therapists, and respiratory therapists. It has been proven that the structuring of a multidisciplinary team improves the results of decannulation [31].

The decannulation process requires the patient to comply with several clinical criteria, including (but not limited to) independence of ventilation and air humidifying systems, Glasgow >8, evaluation of the risk of aspiration, airway permeability, cough strength (> 300 L/min), management of secretions (including saliva swallowing and good sputum), oxygen saturation above 90% in ambient air, good alert, and conscious state [32, 33].

Modifications in the tracheostomy (e.g., reduction of cannula size, fenestrated cannula, reduction of cuff pressure (deflation), and/or partial or total occlusion of the tube) are strategies widely used during the decannulation process [10]; although there is no evidence that these modifications can generate improvements in the swallowing function, it is believed that it has the potential to facilitate tracheostomy weaning. These modifications are described below.

Cuff Deflation

From the moment the patient tolerates cuff deflation, he must remain deflated permanently, aiming at decannulation [34]. Partial and progressive deflation can be considered in patients who do not tolerate total deflation. Those who have fenestrated cannula can benefit from opening the fenestra (even with the cuff inflated) for voice rehabilitation and swallowing exercises, as well as during feeding.

Use of the Speech Valve

The speech valve allows the exhaled air to be directed to the upper airway, allowing the reestablishment of subglottic pressure and upper airway functions. Some studies have used the speech valve as a strategy for tracheostomy decannulation, showing positive results [31, 35]. Bach et al. [36] suggests that the CUFF should be deflated to allow air passage. The author conducted a study in which 104 patients were evaluated in the respiratory rehabilitation program. Of these, 91 were selected to use the deflated cuff and 24 were inflated. Clinical parameters were evaluated as pulmonary gases, oximetry, and PCO_2 expired by capnography. The result showed a decrease in saturation in six patients, but without major changes in PCO_2 (maximum of 47 mmHg). In this study, he concluded that patients with good lung compliance and satisfactory oropharyngeal muscle strength are candidates for tracheostomy without CUFF insufflation, and the speech valve is a device that facilitates decannulation.

Use of Fenestrated Cannulas or Reduction of Cannula Size

Although decannulation protocols are variable, a viable and safe alternative to decannulation is the use of fenestrated cannulas. Patients who meet the decannulation criteria may use cannulas with smaller calibers. This strategy allows the passage of air next to the cannula and fenestra; the objective of this strategy is to increase the airflow toward the upper airway by reducing the cannula caliber or the opening of fenestra, facilitating the adaptation to the physiological breathing pattern [37].

Total or Partial Occlusion of the Cannula

Tube occlusion is indispensable for the decannulation process. Following the patient's tolerance to breathing in ambient air with the occluded cannula (for a period that may range from 24 to 72 h), the patient may be effectively decannulated. Occlusion failure suggests problems in upper and/or lower airway permeability and requires evaluation through imaging exams, such as laryngoscopy and/or bronchoscopy [32].

The use of the strategies mentioned above should be evaluated on a case-by-case basis, considering the clinical conditions of the patient and the resources of the institution. The detailed description of the decannulation process is not part of the scope of this chapter; we suggest that readers review the articles by Medeiros et al. [32] and Singh et al. [37] for further study on the subject.

Noninvasive Ventilation as Decannulation Strategy

Noninvasive ventilation (NIV) has been widely used as a weaning strategy in patients with difficult disconnection from invasive ventilation, especially in hypercapnic patients, favoring the success of extubation in the intensive care environment; but its use as a decannulation strategy in patients dependent on invasive ventilation through tracheostomies still seeks solid scientific evidence of the difficulty of weaning tracheostomized patients. This is associated with an imbalance between the workload and the effectiveness of the ventilatory pump force, very common in patients on prolonged controlled mechanical ventilation or in patients with neuromuscular diseases. The major limitation of the transfer of tracheostomy to noninvasive ventilation is the weakness present in the upper airways (e.g., bulbar dysfunction, low cough efficiency, vocal cord dysfunction, and airway stenosis and/or edema) or respiratory muscle weakness. The advantages of using NIV as a decannulation strategy include, but are not limited to, reduction of inspiratory effort and respiratory work, as well as the recruitment of collapsed alveoli, which increases dynamic compliance [38]. Another factor for the success of NIV as a decannulation strategy in neuromuscular patients is the possibility of remaining with the support even after tracheostomy removal, allowing speech and even swallowing, since NIV

Table 1 Description of the protocol for the use of NIV as a decannulation strategy removed from Ceriana et al. 2019

Phases	Description
1	Proper NIV mask placement
2	Decrease by 1 mm the internal diameter of the cannula without fenestration to leave more pericannular space in order to facilitate airflow from the upper airways during NIV
3	Daytime verification of patient tolerance and adherence to NIV with the cannula capped
4	Increasing nocturnal periods of NIV with the cannula capped, aiming at least 4 consecutive hours of NIV. After two nights of good NIV adherence, patients are transferred to a two-level home fan
5	Daily arterial blood gas analysis, recording of NIV time, verification of air leaks and asynchronies through analysis of the fan microchip

applies positive pressure, helping to maintain upper airway permeability, preventing oropharyngeal collapse, and minimizing the effects of vocal cord dysfunction [39].

Ceriana et al. [40] evaluated whether a combined protocol of NIV and decannulation in tracheostomized patients requiring prolonged mechanical ventilation was feasible and what would be the result in 1 year.

Patients dependent on invasive mechanical ventilation with the following inclusion criteria were studied: (a) tolerance of at least 8 h of respiration without support, (b) hypercapnia/progressive acidosis after interruption of invasive ventilation, (c) good adaptation to NIV, and (d) favorable criteria for decannulation. These patients were switched from IMV to NIV and decannulated. In the study, 82% of the patients were discharged and remained on NIV. The NIV adaptation protocol for decannulation had strategies to minimize the loss of respiratory strength imposed by prolonged invasive ventilation [40] (Table 1).

The study highlights the role of NIV as a decannulation strategy in patients on prolonged mechanical ventilation, given the improvement in respiratory mechanics and blood gases [39].

The Choice of the Ideal Mask for Decannulation

Noninvasive ventilation uses external devices to generate positive pressure. Among the most indicated interfaces are the nasal and oronasal mask, in addition to the use of mouthpiece. Nocturnal NIV is also indicated in sleep disorders, such as obstructive and central apnea; the latter can be caused by diaphragmatic weakness, obesity, or various diseases of the chest wall. The nocturnal NIV has also been widely used for patients with respiratory muscle weakness [41].

The choice of mask is an influencer of success in the adaptation of ventilatory support. The use of nasal mask and mouthpiece facilitates speech, swallowing, and removal of bronchial secretions. Bach et al. [41] conducted a prospective study in 49 patients, including 37 tracheostomized neuromuscular patients. As a strategy for the removal of the tracheostomy tube, transfer to the fenestrated cannula, occlusion, and progression to noninvasive ventilation by nasal mask were performed. As a result, decannulation was successful in 32 of the 37 patients studied.

In addition to volume and pressure adjustments, the choice of mask is fundamental to the success of decannulation with NIV, particularly in patients with neuromuscular diseases and NIV-dependent patients. Schellhas et al. [42] studied 212 patients who initiated NIV support with an oronasal mask. There was a high prevalence of upper airway obstruction in this group, especially in patients with amyotrophic lateral sclerosis (ALS). In 2021, Dorça et al. [43] presented two cases in which they evaluated the impact of the use of nasal and oronasal masks in ALS patients. The study was performed using videofluoroscopy images (Fig. 1). The decrease in the

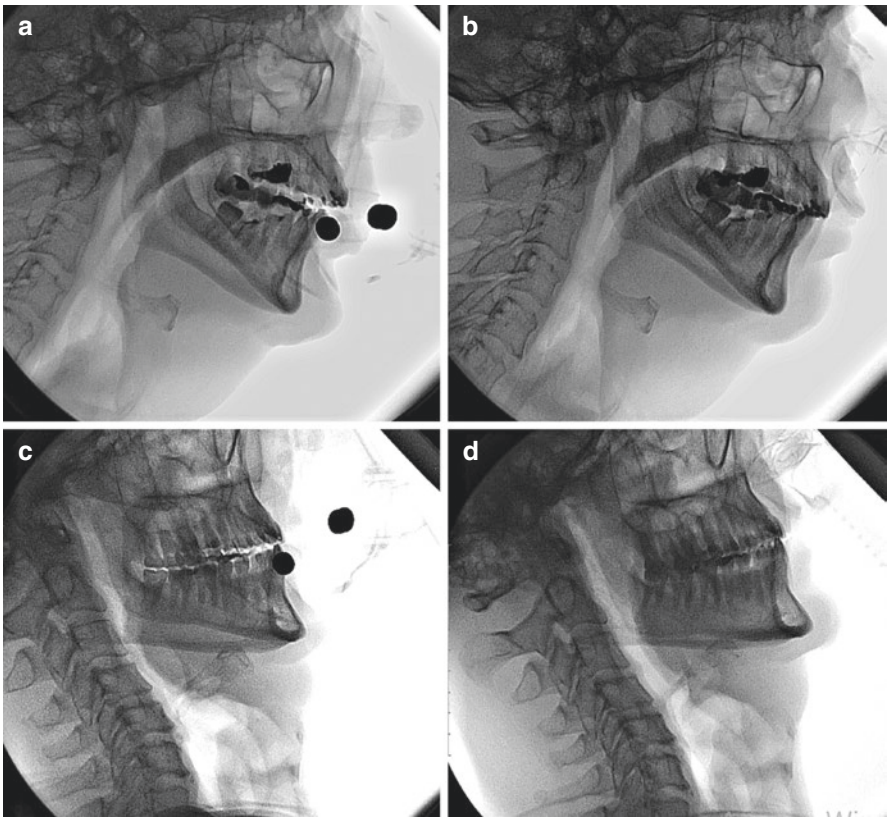

Fig. 1 Clinical data, ventilation details, and pharyngeal area measurements. Patient 1 is a 64-year-old male, diagnosed with ALS 1.5 years ago, ALSFRS-R of 32 points, functional vital capacity of 69%, ventilated with a ResMed Stellar 150 (ET mode; IPAP 12 cmH_2O; EPAP 4 cmH_2O; inspiratory time 0.7–1.2 s; respiratory frequency, 16 bpm; cycle, medium; rise time, 250 ms; fall time, 100 ms). Using an oronasal mask ResMed AirFit F20, he presented a pharyngeal area (squared C2–C4, as proposed by Stokely et al.) of 8.91 cm^2 (**a**) and with an intranasal mask ResMed AirFit P10 of 8.74 cm^2 (**b**). Patient 2 is a 48-year-old male, diagnosed with ALS 8 years ago, ALSFRS-R of 6 points, functional vital capacity of 12%, ventilated with a ResMed Stellar 150 (ET mode; IPAP 17 cmH_2O; EPAP 6 cmH_2O; inspiratory time, 0.8–1.5 s; respiratory frequency, 16 bpm; cycle, medium; rise time, 300 ms; fall time, 200 ms). Using an oronasal mask ResMed AirFit F20, he presented a pharyngeal area (squared C2–C4) of 2.29 cm^2 (**c**) and with an intranasal mask ResMed AirFit P10 of 6.21 cm^2 (**d**). (Dorça et al. 2019)

upper airway space in both patients studied was observed, but the patient with bulbar weakness presented airway obstruction with nasal oronasal mask.

The case report presented by Vrijsen et al. [44] suggests that the use of oronasal masks in patients with ALS requires further studies to understand their potential therapeutic use and possible adverse effects. Vrijsen et al. [44] observed that the oronasal mask caused a tongue posteriorization movement, causing obstructive events and decreased oxygen saturation, an interrupted sleep architecture, and persistent hypercapnia in a patient with ALS. We recognize that more studies are needed to understand the effects of NIV interfaces on the airways; however, these preliminary results suggest that the type of mask, as well as the ventilatory strategy, may be complicating the failure of decannulation in patients with bulbar weakness.

Peak Cough Flow and Decannulation

Cough capacity is an easy measure to evaluate cough flow. The values are dependent on the expiratory muscle forces and the effective coaptation of the glottis. In addition to being a useful measure to evaluate protective function in patients with neuromuscular disorders, it is rarely used in clinical practice for patients without these disorders [45]. The measure is useful to predict markers of laryngeal function, abdominal muscle strength PFT, and a strong marker of success in decannulation. A PCF above 160 L/min is required for an effective cough, and less than 270 L/min is associated with increased secretion retention and risk of infection. Factors that may cause a decrease in the peak cough flow include reduced respiratory muscle strength, lack of coordination of glottal closure and opening, airway obstruction, and changes related to age and activity.

The evaluation of cough has been shown to be correlated with other measures of lung function in neuromuscular disorders and in the prediction of extubation failure. Parkinson's disease patients have a reduced PFT even in the early stages [46]. Sequential studies in patients with dysphagia associated with stroke have reported that the measurement of cough was correlated with risk of respiratory infection and results of formal swallowing evaluations [46]. Studies in patients with dysphagia associated with stroke have reported that PFT evaluation was correlated with risk of respiratory infection and results of formal swallowing evaluations and peak cough flow for safe decannulation [47].

The measurement of cough flow is an easy method to evaluate the safety of decannulation and is also widely used in decannulation of neuromuscular patients on continuous ventilation or in cases of transfer of invasive to noninvasive support. The measurement can be performed by the mouth, using the cuff of the deflated tracheotomy, and thus effectively predict the flow passage to the upper airway, glottal strength, and safety in the removal of secretion [46, 47].

Conclusion

Tracheostomy is a necessity in situations of severe respiratory changes; there are several functional changes in the mechanics of swallowing, breathing, and speech caused by the placement of the tracheostomy tube in the airway. Decannulation should be a multiprofessional objective, defined by the use of methods and tools based on the best available evidence.

End Practical: Key Messages

- The impacts of tracheostomy on speech, swallowing, and breathing functions are still poorly understood and require further studies. Professionals should keep up to date to ensure correct management of the tracheostomized patient as new evidence becomes available.
- There is cumulative evidence (but with several methodological limitations) on the potential use of NIV in the decannulation process. We advise that its use be based on a case-by-case basis, with multiprofessional discussions.
- The evaluation of peak cough flow has been shown to be a relevant criterion during the decannulation process. It is recommended that institutions use this measure in decision-making throughout the decannulation process.

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Videofluoroscopy and Swallowing Evaluation and Pattern of Inhalation Injury. Implications for Noninvasive Ventilatory Approach

Tullio Valente

Introduction

Key Facts

Dysphagia and aspiration syndromes are strongly related.

Dysphagia and aspiration may be silent.

VFSS provides a comprehensive evaluation of the oral, palatal, pharyngeal, and pharyngoesophageal segments of deglutition.

Swallowing is an array of synergistic interdependent movements, initiated by a complex set of sensory inputs that generate pressures and forces for propelling ingested materials through the upper aerodigestive tract and simultaneously protect the upper airway [1].

Respiration and swallowing utilize a common passageway, and the two activities must be coordinated so that mutual compromise does not occur. A high degree of coordination between respiration and swallowing is required to maintain adequate ventilation without causing pulmonary aspiration [2]. In an advanced stage of neuromuscular disorders or multisystem diseases with respiratory muscle dysfunction, swallowing disorders due to deficiency of upper airway muscles are frequently observed and can lead to aspiration and malnutrition. Furthermore, dysphagia is an increasing problem with age (presbyphagia) and one of the most critical problems in patients with long-term, progressive congenital or acquired diseases (Table 1) [3].

Dysphagia and aspiration syndromes are strongly related, may be overt or silent, and lead to severe consequences, such as malnutrition, dehydration, pneumonia, or airway obstruction. Aspiration is defined as "the inhalation of oropharyngeal or gastric contents into the laryngeal or lower respiratory tract" [4]. A prompt assessment

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Table 1 Causes of dysphagia

Neurologic
Immunologic
Gastroesophageal
Congenital
Oncologic
Endocrine
Psychiatric
Infectious
Traumatic
Postsurgical

of the swallowing function is crucial to organize proper interventions and prevent complications in dysphagic patients. Dysphagic patients are 3 times, and those with confirmed aspiration 11 times, more likely to develop aspiration pneumonia [4]. Macroaspiration can cause a wide spectrum of airways/lung diseases with various clinical presentations and can be overt or silent, and its content can be variable (e.g., oropharyngeal or gastric).

Dysphagia is of great interest to radiologists because the dynamic radiological examination of swallowing, the videofluoroscopic swallowing study (VFSS), is considered the gold standard not only for a diagnostic purpose (helps to identify the causes of aspiration, often treatable) but also for planning the rehabilitation therapy and type of nutrition, and for the results of the therapy evaluation [5–7].

Since 1988 the fiber-optic endoscopic evaluation of swallowing (FEES) has appeared alongside VFSS and has become increasingly employed [8]. Due to availability, expertise needed, patient compliance, and the evolution of the swallowing disorder, sometimes rapidly progressive, an instrumental examination should be performed on every patient with suspected dysphagia. A better understanding of the swallowing problems associated with these disorders may help in guiding treatment, choosing technical aids, modifying the consistency of foods, swallowing rehabilitation, and nutritional support by the nonoral route.

Anatomic/Physiological Background and VFSS Technique

Eating, swallowing, and breathing are tightly functionally coordinated systems. Swallowing is a complex physiologic act consisting of simultaneous and sequential contractions of orofacial, pharyngeal, laryngeal, and esophageal muscles to propel ingested materials through the upper aerodigestive tract with simultaneous protection of the airways. It involves approximately 50 paired muscles and virtually all levels of the central nervous system (cerebral cortex, brain stem swallowing center, motoneurons, and sensory receptors in the oropharynx, larynx, and esophagus by cranial nerves V, VII, IX, X, XII).

Schematically, in normal swallowing, it is possible to distinguish (Fig. 1) the following:

- An *oral preparatory* phase: the bolus is manipulated by lingual motion, mixed with saliva, and masticated, sized, shaped, and if necessary, also tasted or savored. All the actions of this phase are conscious and voluntary, the swallow reflex is absent, and the airway remains open for the usual purpose of respiration.

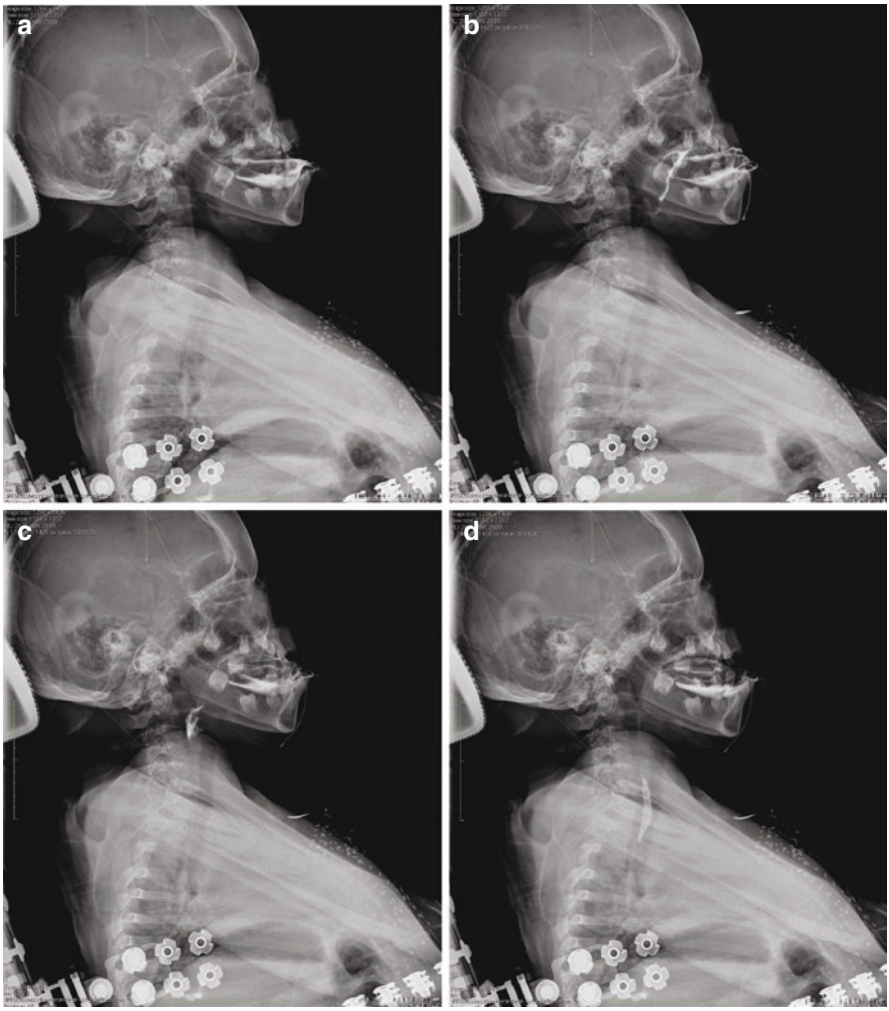

Fig. 1 A technically complex videofluoroscopic swallow study (VFSS) in an 25-year-old boy with Cornelia de Lange syndrome. Functional anatomy of the phases of swallowing. (**a**) LL views of a normal oral, (**b**) early pharyngeal, (**c**) hypopharyngeal, and (**d**) esophageal phases of swallowing are shown

- An *oral propulsive* phase: the tongue starts to squeeze the bolus between the soft palate and itself. A groove or channel becomes evident in the tongue, and its pressure conveys the food bolus posteriorly into the back of the mouth. As the bolus passes the posterior faucial pillars, the involuntary swallow reflex occurs [9].
- A *pharyngeal* phase: five main physiologic events can be distinguished:
  - Nasopharyngeal seal
  - Elevation and anterior displacement of the larynx and hyoid bone
  - Laryngeal closure
  - Bolus compression and propulsion
  - Cricopharyngeal opening
- An *esophageal* phase: a normal primary peristalsis as an aboral contraction wave that progressively obliterates the esophageal lumen is appreciable.

Pathophysiological Mechanisms of Dysphagia

Symptoms of dysphagia have been reported in about 60% of institutionalized elderly people [10]. The altered swallowing mechanism of elderly people is in part related to sarcopenia, the age-related loss of skeletal muscle mass, and can lead to diminishing lingual pressure, with consequent disorders in pharyngeal swallowing or to reduced pharyngeal constrictor muscle contractility with delay in pharyngeal transit.

Other two main pathophysiological mechanisms operate in these patients:

1. The triggering of the swallowing reflex for the voluntarily initiated swallows is delayed, disordered, and eventually absent.
2. The cricopharyngeal sphincter muscle of the pharyngoesophageal segment became hyper-reflexic and hypertonic.

Delayed bolus transit, palatal weakness predisposing to nasal regurgitation, decreased laryngeal elevation, and bolus residue after swallowing are other mechanisms that determine swallow impairment and aspiration. The weakness and the impaired coordination of facial, oral, and pharyngeal muscles compromise all the phases of swallowing [11]. As a result, the laryngeal protective system and the bolus transport system of deglutition lost their coordination during voluntarily initiated oropharyngeal swallowing.

Pathological VFSS Findings

Lateral (LL) and Anteroposterior (AP) Direct Neck Radiograph

Ideally all patients should be examined in both lateral and frontal (AP) positions. In the real life, the examination starts and ends only in latero-lateral (LL) projection with the bedside or wheelchair patient and should always begin with the assessment without contrast medium.

Laryngeal thyroid, cricoid, and most of the arytenoid are hyaline cartilages that undergo enchondral ossification over aging both in males and in females and may cause VFSS misdiagnosis.

VFSS on LL Projection

Latero-lateral projection best allows documentation of the contrast medium passage in the laryngeal vestibule (penetration) and/or in the trachea (aspiration). Small and then gradually increasing amounts of contrast medium of different texture are administered. This allows the radiologist to identify the food textures responsible for aspiration [12]. In more severe deficits, the contrast agent (barium, gastrografin) can be administered through a syringe connected to a tube placed in the oral cavity.

Aspiration-Induced Lung Disease (AILD)

Key Facts

Aspiration into the airways and lung can cause a wide spectrum of pulmonary diseases with various clinical presentations.
Aspiration-induced lung diseases are often underdiagnosed in the clinical setting.
Noninvasive ventilation may have a beneficial impact on these inhalational injuries.

Aspiration represents a broad spectrum of diseases, with patterns of tracheobronchial tree and lung injury that overlap, both pathologically and radiographically, finally leading to respiratory distress [13–16].

These patterns are determined by the aspirated content and volume, the chronicity, as well as host defenses (Table 2). Microaspiration, or silent aspiration, is commonly suspected in patients with refractory respiratory symptoms, including unexplained chronic cough, asthma, chronic obstructive pulmonary disease, bronchiolitis, bronchiectasis, and idiopathic pulmonary fibrosis. In very ill patients, inability to ventilate (diaphragm weakness and chest wall stifness) and decreased airflow velocity usually restrict secretion clearance, and decrease coughing limits airway clearance. On the past few years, the importance of cough augmentation and airway clearance has been increasingly recognized. Diagnostically, it may be

Table 2 Spectrum of aspiration-induced lung diseases (AILDs) and imaging patterns

Acute-subacute	Subacute-chronic
Tracheobronchial foreign body	Diffuse aspiration bronchiolitis (DAB)
Aspiration pneumonia (infectious origin)	Bronchiectasis
Aspiration pneumonitis (chemical origin)	Organizing pneumonia (OP)
Mendelson's syndrome	Chronic interstitial lung disease (chronic-ILD)
Near drowning	Chronic exogenous lipoid pneumonia
Abscess formation	
ARDS	

helpful to distinguish respiratory disorders directly caused by macroaspiration, such as diffuse aspiration bronchiolitis (DAB), aspiration-related organizing pneumonia (OP), acute respiratory distress syndrome (ARDS), and exogenous lipoid pneumonia, from respiratory conditions in which microaspiration is more likely to play an indirect aggravating role, such as in chronic cough, asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), non-CF bronchiectasis, and idiopathic pulmonary fibrosis (IPF). Evaluation for aspiration-induced lung diseases (AILDs) usually entails visualization of the airways with laryngoscopy or bronchoscopy and pulmonary function testing. AILDs, such as aspiration pneumonitis, aspiration pneumonia, and exogenous lipoid pneumonia, are generally diagnosed by clinical and radiologic findings.

Aspiration Pneumonia (with or Without Abscess Formation)

Because of its low pH, gastric contents are sterile under normal conditions. Thus, aspiration is required but not sufficient for the formation of aspiration pneumonia that refers to an infectious process secondary to aspiration of colonized oropharyngeal secretions [17, 18]. It usually results in localized segmental or lobar airspace consolidations in dependent portions of lung, with or without an associated parapneumonic effusion. In supine patients, the material is most commonly aspirated into the right middle lobe, into the posterior segments of the upper lobes, or into the superior and posterior basal segments of the lower lobes. This primarily happens because of the larger caliber and more vertical course of the right main bronchus compared with the left [13, 19]. These secretions or food debris-filled airways cause airspace opacities that can become more confluent and appear as consolidation, with patent airways within these regions appearing as air bronchograms (Fig. 2).

Heterogeneous opacities on CXR and thin-slice CT usually represent small areas of atelectasis caused by distal airway obstruction by aspirated material [20]. Aspirated material can also be seen filling the airways, which is an important clue to the diagnosis. In normal individuals resolution is commonly observed within 24–48 h as mucociliary action and coughing clear the airways, and persistent opacities for more than 4–5 days suggest superimposed infection. In addition, depending on the bacterial contents of the aspirate, abscess formation, cavitation, or empyema may result. The differential diagnosis (DD) includes other causes of segmental or lobar consolidation, such as community-acquired pneumonia, pulmonary contusion or hemorrhage, or pulmonary infarct [20].

Aspiration Pneumonitis and Mendelson Syndrome

Aspiration pneumonitis is caused by the acute inhalation of a large volume of acidic gastric contents, resulting in chemical lung injury. A cascade of inflammatory response follows this initial injury and includes recruitment of inflammatory cells and release of various inflammatory mediators. This disorder is known as Mendelson

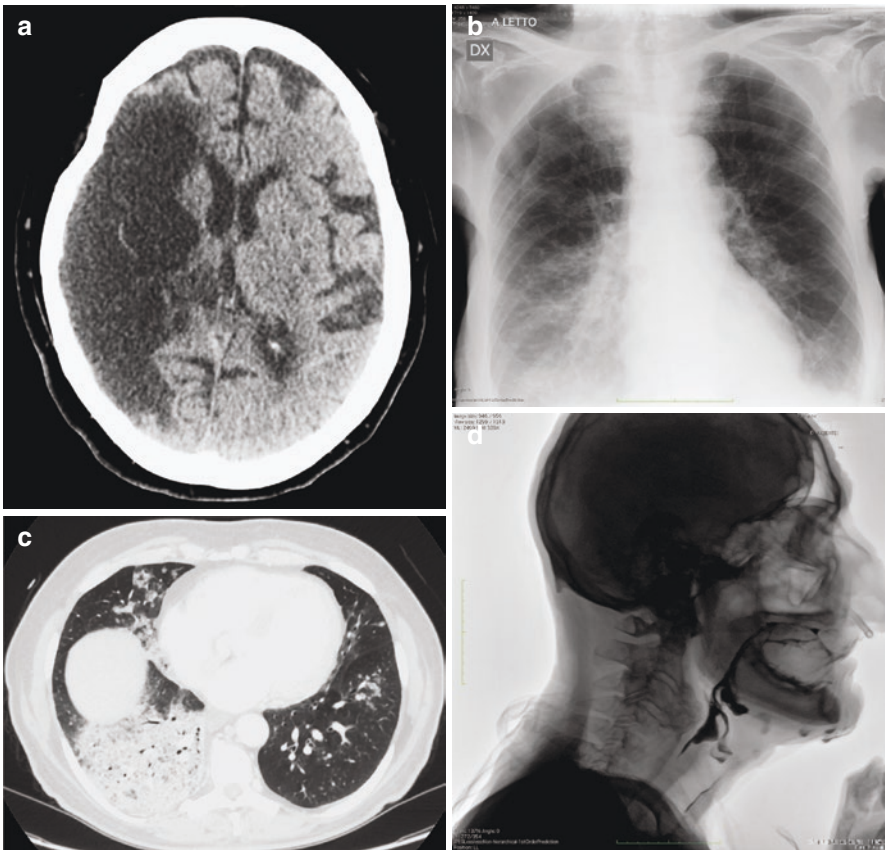

Fig. 2 Dysphagia after stroke and aspiration pneumonia. (**a**) Acute right MCA territory infarct in a 63-year-old man. (**b**) After 8 months at emergency department, a bedside CXR shows a lower right lobe consolidation in this patient with recurrent fever, chills, and productive cough. HRCT chest axial image (**c**) confirms lower right lobe consolidation. (**d**) VFSS shows posterior oral leakage, vallecular and sinus residue, and tracheal aspiration. Dysphagia affects more than 50% of stroke survivors. Fortunately, only 15–20% of these patients remain dysphagic after 6 months

syndrome when the acute aspiration is massive and when aspirated contents have a pH of <2.5 [21]. First described in association with obstetric anesthesia, it is now known to occur in patients with markedly decreased levels of consciousness from multiple causes (drug overdose, following head trauma, seizures). Recurrent small-volume aspirations of refluxed gastric contents during sleep appear to result in chronic and less severe forms of lung injury, such as diffuse aspiration bronchiolitis or chronic exogenous lipoid pneumonia (when oil-based substances [e.g., mineral oil laxative] are aspirated). On imaging, the severity of the resulting lung injury depends on the pH and volume of the aspirate, including airway thickening with ground-glass opacities and nodules in a centrilobular and peribronchovascular distribution. Because of dispersion of the aspirate by coughing, the distribution can be

diffuse, bilateral, and symmetric. The DD of diffuse aspiration pneumonitis includes aspiration pneumonia, community-acquired pneumonia, cardiogenic or noncardiogenic pulmonary edema, pulmonary hemorrhage, and acute hypersensitivity pneumonitis [14].

Bronchiectasis

Bronchiectasis, defined by irreversibly widened bronchi due to damage to the bronchial walls, usually arises from some combination of bronchial obstruction and infection [22]. Bronchiectasis is a well-known sequela of chronic pulmonary aspiration that can result in significant respiratory morbidity and death (Fig. 3) [23].

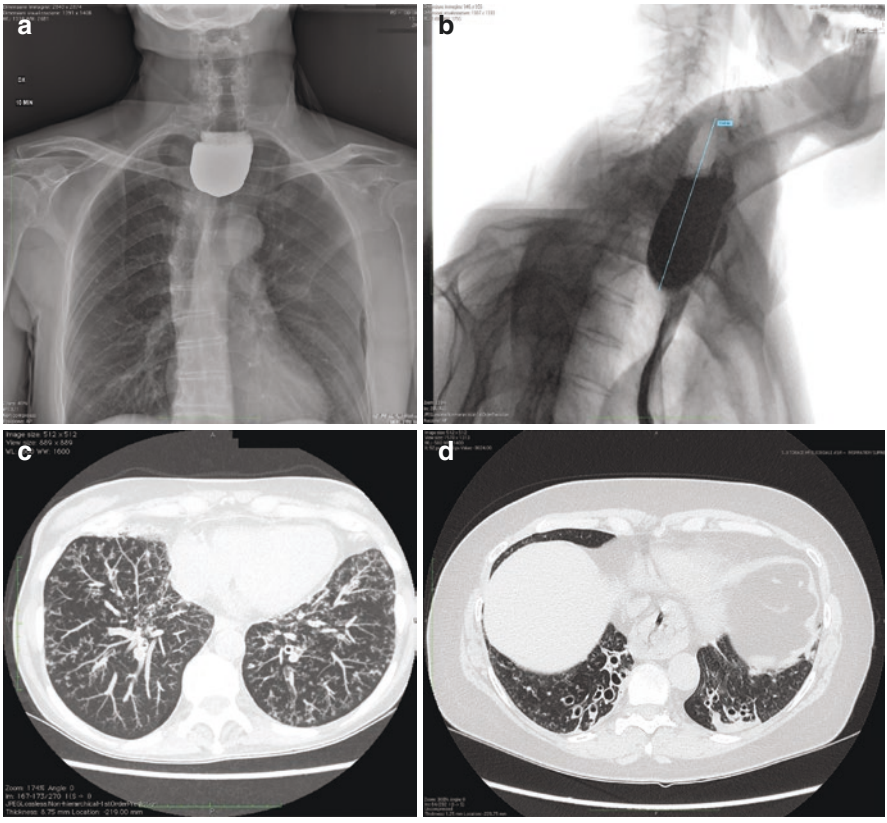

Fig. 3 Zenker diverticulum. **(a, b)** VFSS examination in a 68-year-old man with dysphagia, cough, and halitosis. AP and LL views show a large Zenker diverticulum, extending inferiorly and compressing the cervical esophagus. **(c, d)** HRCT chest axial images show multiple bilateral centrilobular nodules and cylindrical bronchiectasis in the lower lobes. Uncoordinated swallowing, impaired relaxation, and spasm of the cricopharyngeus muscle leads to an increase in pressure within the distal pharynx, so that its wall herniates through the point of least resistance

Diffuse Aspiration Bronchiolitis (DAB)

Bronchiolitis refers to a broad spectrum of disorders characterized by inflammation and fibrosis of the bronchioles (internal diameter of ≤2 mm). DAB describes the resultant inflammation of bronchioles secondary to aspiration. There is a high association of DAB with oropharyngeal dysphagia, bedridden status, dementia, and neurological disorders. Its onset is often insidious, making it difficult to establish a direct association with food intake. On imaging, DAB resembles diffuse panbronchiolitis, typically manifesting as unilateral or bilateral centrilobular nodules, tree-in-bud nodularity, bronchial wall thickening, and poorly marginated acinar areas of increased attenuation (Fig. 4) [24]. Mosaic attenuation or segmental and subsegmental air trapping can be seen in expiratory imaging. In contrast to asthma, imaging findings are often concentrated in the lower lobes or dependent aspects of the

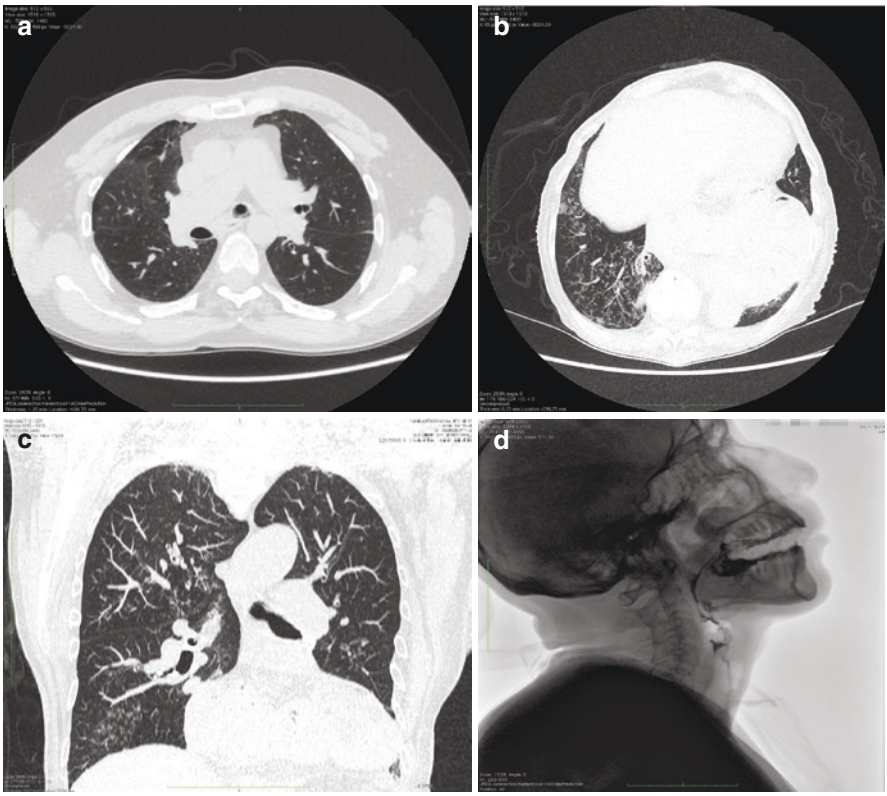

Fig. 4 Hiatal hernia, GERD, and diffuse aspiration bronchiolitis (DAB) in a 58-year-old woman with fever. HRCT chest axial images (**a, b**) and coronal reconstruction (**c**) show a large hiatal hernia in (**b**) and diffuse lobular bronchioles dilatation filled by mucus and pus (tree-in-bud pattern). This pattern is a known manifestation of various entities as aspiration of infected oral secretions or other irritant material into small airways. (**d**) VFSS lateral view shows associated tracheal aspiration

lungs. Associated imaging findings include an esophageal mass, hiatal hernia, or air-fluid level in the esophagus. DD for this pattern is broad and includes other causes of small airway disease, such as infectious bronchiolitis, diffuse panbronchiolitis, cystic fibrosis, allergic bronchopulmonary aspergillosis, and collagen vascular disorders [25].

Tracheobronchial Foreign Body

Big-sized foreign body aspiration may result in obstruction of the central airway and sudden death from asphyxiation. In a small-sized inhaled and retained foreign body, most patients present with a nonresolving cough, sometimes associated with exertional dyspnea, chest pain, or hemoptysis. Imaging findings can include postobstructive atelectasis or rarely hyperinflation, air trapping, recurrent pneumonia, bronchial wall thickening, and bronchiectasis; complications are distal abscess formation and parenchymal necrosis. Chest CT scanning often provides additional diagnostic information including demonstration of an intrabronchial mass, which may be mistaken for an endobronchial malignancy [26]. Expiratory images may show air trapping in the affected segment (or lobe). When bronchial obstruction is chronic, consolidative opacities from postobstructive pneumonia may be demonstrated along with bronchiectasis. On high-resolution computed tomography (HRCT) of the chest, lentil aspiration pneumonia manifests as centrilobular nodules, some with a tree-in-bud configuration [27]. Pill aspiration represents a unique type of foreign body aspiration because some pills such as potassium and iron preparations may dissolve in the airways, causing intense bronchial inflammation and stenosis [28]. DD for this pattern is similar to that described for aspiration bronchiolitis. An additional concern in adults is that aspiration of undigested food can have similar imaging characteristics to an endobronchial neoplasm and can be associated with lymphadenopathy and lobar collapse when chronic.

Near Drowning

In near drowning, defined as severe asphyxia caused by submersion in water but not resulting in death, chemical and organic contaminants in the aspirated water are thought to cause adult respiratory distress syndrome. Radiographic findings are often presented as scattered ground-glass opacities that progress to patchy airspace consolidation over the next several days. Mild cases may present as perihilar ground-glass opacity, progressing to coalescent opacities in severe cases. Ground-glass opacities and consolidation likely represent pulmonary edema and adult respiratory distress syndrome, largely secondary to fluid entering the alveoli from the blood or disruption of the surfactant production.

Chronic Exogenous Lipoid Pneumonia

The aspiration of oily material, whether mineral, vegetable, or animal, commonly mineral oil, leads to exogenous lipoid pneumonia. The severity of the reaction depends largely on the amount of free fatty acid in the aspirate. The lung parenchyma in these cases may show fibrosis, as well as a histiocytic reaction involving the accumulation of lipid-laden macrophages. Radiographically, the distribution is predominantly basilar and paramediastinal. Early in the disease course, centrilobular or panlobular ground-glass opacities are identified, which progress to volume loss and interlobular septal thickening. When present, airspace consolidation or mass-like opacities with attenuation values of ≤10HU are diagnostic of this condition and can be seen in either the acute or chronic setting. Ground-glass opacities associated with interlobular septal thickening in a "crazy paving" pattern have also been described [13]. The DD of focal consolidation or mass-like opacity can include carcinoma and acute bacterial pneumonia or OP. The differential for a "crazy paving" pattern is broad and includes alveolar proteinosis, pneumocystis pneumonia, and diffuse alveolar damage or hemorrhage.

Chronic Interstitial Lung Disease (Chronic-ILD) and Organizing Pneumonia

Chronic aspiration may be asymptomatic or present nonspecifically with symptoms such as chronic cough or dyspnea. Gastroesophageal reflux disease (GERD) with repeated reflux of gastric contents into the superior esophagus and pharynx also likely contributes to chronic microaspiration.

Secondary aspiration organizing pneumonia (OP) pattern is often basilar predominant and peripheral or bronchovascular in distribution. A suggestive imaging finding of OP is the reverse halo sign, also called the atoll sign or fairy ring sign. Another pattern that may be related to chronic aspiration is a usual interstitial pneumonia (UIP) pattern of pulmonary fibrosis [29].

Implications for Noninvasive Ventilation (NIV) Approach

Breathing-swallowing coordination is one of the most important airway defense mechanisms. Swallowing normally occurs during expiration, and the subsequent respiration reinitiates with expiration; this expiration-swallow-expiration (E-SW-E) pattern at mid-to-low lung volumes poses significant physiologic advantages for hyolaryngeal anterior-superior movement, airway closure, and pharyngoesophageal segment opening, preventing the pharyngeal contents from invading the lower airway. Expiration-followed swallow is a mechanism helpful in clearing the

pharyngeal recesses of foreign residues before subsequent inspiration and may prevent low-grade recurrent aspiration. Moreover, when swallowing interrupts in the expiratory phase of the respiratory cycle, the elastic recoil of the lungs and the chest wall can generate a subglottic positive pressure which is considered as a key component of swallowing efficiency [30]. Patients with respiratory insufficiency due to either chronic obstructive pulmonary disease (COPD) or neuromuscular diseases (NMD) equally swallow during the expiratory and inspiratory phases of respiration. The use of a patient-controlled NIV during swallowing significantly improved breathing-swallowing coordination in ventilated dysphagic patients with severe respiratory failure by increasing the pattern of expiration-followed swallowing and reducing dyspnea and aspiration.

Breathing-swallowing discoordination more frequently occurs in dysphagic patients [2]. Respiration after swallowing is more frequently resumed with inspiration in patients with COPD than in healthy subjects, which may predispose patients to aspiration-related exacerbation [31]. In noninvasive ventilation continuous positive airway pressure (CPAP) decreases the swallowing-inspiration frequency and alleviates the risk of aspiration in patients with COPD [32, 33]. NIV use significantly improved swallowing fragmentation (defined as the number of respiratory interruptions of the swallowing of a single bolus) and breathing-swallowing synchronization with a significant increase of swallows followed by an expiration [34]. The use of patient-controlled NIV improves swallowing parameters in patients with severe neuromuscular respiratory failure requiring daytime NIV, without impairing swallowing comfort [34].

Multidisciplinary Team

Dysphagia affects most patients with NMD, and each patient with dysphagia is different owing to the underlying neurological impairment. Aspiration can cause a wide spectrum of pulmonary diseases (AILD), is often silent/occult and undetected clinically, and has the potential for dire consequences. Etiologic diagnosis is possible by VFSS and by knowledge of the chest imaging patterns, and the radiologist plays an important role in suggesting the diagnosis when proved by VFSS. A multidisciplinary management is needed, including neurologist, respiratory physician, intensivist, ENT specialist, nutritionist, speech pathologist, and last but not least radiologist.

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Hypercapnic Chronic Obstructive Pulmonary Disorder

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Introduction

The respiratory system is responsible for the gas exchange process that allows for sustaining human life. The process of respiration starts with the oxygen entering from the outside air to the human body through the lungs with inhalation. After oxygen is extracted from the atmosphere, it is transferred to all tissues and organs through the bloodstream, and carbon dioxide is removed with expiration. Poor gas exchange with a compromised respiratory system will result in inadequate exchange between oxygen and carbon dioxide.

Chronic obstructive pulmonary disease (COPD) refers to a chronic inflammatory lung disease that causes limitation and obstruction of the airflow. COPD is a progressive disease that makes breathing difficult. People are usually asymptomatic in the early stages. As the disorder progresses, symptoms develop and become more prominent. Main symptoms of COPD include shortness of breath and chronic cough with or without mucus production. Early on, dyspnea might occur only during exercise and other activities, and people usually associate it with other factors and not seek medical attention. Furthermore, many people avoid activities that may cause dyspnea delaying the establishment of the diagnosis even more. As the disease worsens though, dyspnea will be present in the most basic daily activities affecting severely the quality of life. Cough can also be ignored and attributed to other causes such as smoking leading to delayed diagnosis and treatment.

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Chronic obstructive pulmonary disease is the third leading cause of death worldwide [1]. The most common cause of COPD is tobacco smoking, especially in developed countries. Other risk factors include air pollutants, exposure to dust and fumes, and genetics (alpha-1-antitrypsin deficiency). In developing countries, common sources of indoor air pollution are the use of coal and biomass such as wood and dry dung as fuel for cooking and heating [2].

People with COPD are at increased risk of developing a variety of conditions such as heart disease, lung cancer, and many others.

COPD Phenotypes

The two most common conditions of COPD are emphysema and chronic bronchitis, and they have been the two classic COPD phenotypes [3].

Emphysema refers to the damage of lung tissue, specifically the breakdown of the walls of the alveoli, and develops gradually over time. This leads to the reduction of the alveolar surface that participates in gas exchange causing low oxygen in the blood.

There are four types of emphysema. Three types—centrilobular or centriacinar, panlobular or panacinar, and paraseptal or distal acinar emphysema—are related to the anatomy of the lobules of the lung and are not associated with fibrosis (scarring) [3]. The fourth type is known as paracicatricial emphysema or irregular emphysema that involves the acinus irregularly and is associated with fibrosis [4]. Centrilobular and panlobular types are associated with significant airflow obstruction.

Chronic bronchitis refers to the irritation and inflammation of the bronchi resulting in increased mucus production and poor gas exchange. This is usually due to long-term exposure to irritants such as cigarette smoking that damage the airways.

There are two types: acute and chronic. Acute bronchitis develops from a respiratory tract infection and goes away after few weeks, while chronic bronchitis develops over time and is a more serious condition. Even though acute bronchitis is usually caused by bacterial and viral infections, repeated exposure to infections can lead to chronic bronchitis.

Pathophysiology

Hypercapnia

Carbon dioxide (CO_2) is a metabolic product of the many cellular processes within the body to process lipids, carbohydrates, and proteins [5]. The term hypercapnia is used when the partial pressure of carbon dioxide ($PaCO_2$) in the blood is elevated above the value of 45 mmHg.

Through the process of gas exchange, the respiratory system eliminates CO_2 from the body. If this exchange process is affected, the relationship between the rate

of CO_2 production and the portion of CO_2 eliminated by the lung will be affected as well. Carbon dioxide is then hydrated with the formation of carbonic acid that subsequently dissociates with release of hydrogen ions (H+) in the body fluids [6]. The increased H+ concentration will lead to the development of respiratory acidosis.

The CO_2 is regulated by various physiological mechanisms. One of these mechanisms is the pH buffering system that exists between CO_2 and hydrogen carbonate (HCO_3). Elevated CO_2 levels above the normal range will cause acid-base balance disturbances. The body's homeostatic mechanism will then activate as an effort to minimize the changes in pH and compensate for the increased CO_2 by increasing bicarbonate levels.

COPD

As mentioned already, COPD is a progressive lung disease in which chronic, incompletely reversible poor airflow (airflow limitation) and inability to breathe out fully (air trapping) exist. Mucociliary clearance is particularly altered with a dysregulation of cilia and mucus production [7]. The increased mucus secretion will lead to chronic productive cough, but not all COPD patients will have hypersecretion of mucus. The hypersecretion is due to squamous metaplasia, increased numbers of goblet cells, and increased size of bronchial submucosal glands in response to chronic irritation by noxious particles and gases [8].

Inflammation and scarring of the lungs cause narrowing of the airways leading to a reduction of airflow during expiration. This results in air from the previous breath getting trapped inside and causing abnormal lung air volume in the alveoli. During exercise, shortness of breath might occur as the lungs are partially filled with air, making breathing more difficult.

The main mechanism behind abnormal gas exchange is the ventilation-perfusion mismatch. It is mainly a consequence of the anatomical changes that occur in COPD. Pulmonary hypertension may develop at late stage of COPD as a result of the severe impairment of the gas exchange process and lead to right ventricular dysfunction. Both emphysema and chronic bronchitis may result in pulmonary heart disease also classically known as cor pulmonale [9].

Decreased ventilation together with the anatomical changes that occurs from COPD will disturb the gas exchange process and lead to low O_2 levels and high CO_2 levels in the blood. High CO_2 levels will change the pH balance of the blood, making it too acidic. This can happen slowly or suddenly. When it happens slowly, the body may be able to balanced by renal compensation. This is possible by increasing urinary excretion of hydrogen ions and resorption of HCO_3 to help keep the body's pH level balanced. This process occurs over several days and it is relatively slow. The pH will reach normal values, but HCO_3 levels and BE will be increased. During acute increase of CO_2 levels, such as exacerbation episodes, the kidneys cannot handle the spike. Acute hypercapnic episodes are a life-threatening emergency.

Management of COPD

There is no cure for COPD but the progression of the disease may slow down. Main objectives include management of the symptoms, avoidance of exposure to irritants, as well as healthier lifestyle and decent quality of life. Spirometry is the best tool to measure airflow obstruction in COPD and is required for diagnosis of COPD.

Cessation of smoking should be the primary focus. For those who smoke, stopping smoking is the only measure shown to slow down the worsening of COPD [10]. It is crucial because it can reduce the rate of which the lung function declines and reduce risks of cancer-related disorders, such as cardiovascular conditions.

Pharmacological management options include bronchodilators, corticosteroids, as well as antibiotics. Bronchodilator use is recommended as needed; using them on a regular basis is not recommended. The two main types used are beta-2 adrenergic agonists and anticholinergics. Corticosteroids are especially effective on exacerbation events.

Oxygen therapy at home, known as long-term oxygen therapy (LTOT), is recommended in patients with low oxygen levels at rest. Standard LTOT criteria are related to COPD patients who have PaO_2 <60 mmHg, are in a clinical stable situation, and are receiving optimal pharmacological treatment [11]. Long-term oxygen therapy (LTOT) is the treatment proven to improve survival in chronic obstructive pulmonary disease (COPD) patients with chronic respiratory failure [11]. This treatment approach seems to lower the number of patients requiring hospitalization, increase effort capacity, and improve the quality of life.

Pulmonary rehabilitation is also recommended. It is aimed to help patients to manage daily activities, work, and social outings as well as reduce anxiety and symptoms of depression. Following hospital admission, pulmonary rehabilitation has been shown to significantly reduce future hospital admissions and mortality and improve quality of life [12].

COPD patients are at a high risk for respiratory tract infections. Vaccines against influenza an annual basis and pneumococcal vaccination are recommended to reduce exacerbation episodes from infections especially in older adults >65 years old.

COPD Exacerbation

Exacerbations of COPD refer to an acute situation in which the symptoms of the disease worsen and may require additional treatment. It is usually a result of infections of the respiratory tract or exposure to pollutants which trigger the episodes. During these episodes there is inflammation of the airways, increased mucus and sputum, as well as trapped air inside the lungs. These episodes may require medical treatment with antibiotics, inhaled agents, and/or hospital admission. The duration of COPD exacerbation can vary and persist for days or even weeks and usually is associated to severity.

The most important risk factor for subsequent exacerbations is a history of previous episodes. Other risk factors for exacerbations include low-baseline lung function, increased symptom burden, radiographic evidence of emphysema, and a history of chronic bronchitis [13].

In mild episodes, there is only no or a minimal increase in airflow obstruction, while during severe exacerbations, there is increased mismatch between ventilation and perfusion due to worse gas exchange, and that will lead to respiratory muscle fatigue. The worsening ventilation-perfusion ratio results in reduced ventilation, and in response, the hypoxic pulmonary vasoconstriction (HPV) mechanism reduces blood flow due to hypoxia-affecting perfusion. Hypoxia and respiratory acidosis from hypoventilation and respiratory muscle fatigue can also lead to pulmonary vasoconstriction, thus increasing the load on the right heart.

Acute exacerbations are typically treated by increasing the use of short-acting bronchodilators including a combination of a short-acting inhaled beta-agonist and short-acting anticholinergic [14].

Severe exacerbations with acute hypercapnic respiratory failure (AHRF) may warrant admission to the intensive care unit (ICU) for noninvasive ventilation (NIV) [15]. It is usually used for acute exacerbations, because such episodes may be managed and reversed quickly. NIV seems to respond well in hypercapnic patients during acute exacerbation. Patients surviving such a respiratory crisis are at high risk for readmission and death [15].

As already mentioned, hypercapnia and respiratory acidosis are very serious. If left untreated or treatment is delayed, it can lead to complications such as confusion and altered mental status that can progress to loss of consciousness and coma. Furthermore it can cause cardiac arrhythmia, hypoxemia, and tissue death causing irreversible brain damage and finally death.

Noninvasive Ventilation

NIV is usually the first choice in treating severe exacerbations of COPD that require respiratory support. Exacerbations with acute hypercapnic respiratory failure with acidosis can lead to death if not treated early. Noninvasive ventilation (NIV) is often used in preference to invasive mechanical ventilation [16]. Endotracheal intubation may be deemed necessary if NIV cannot be used at the medical center, either due to the patient being unresponsive and/or unconscious, or it is not available at that moment, or there is a lack of knowledge and experience of the treating physician.

Despite the issues that follow NIV such as leaks and poor tolerance from many patients, there are various benefits when NIV can be successfully used including reduced complications from infections and length of hospital stay, avoiding airway trauma from intubation, reduced mortality, as well as reduction in costs for the healthcare system.

NIV is used mainly as an intermittent mode providing respiratory support and is usually used for a few hours throughout the day. When the patient condition will require longer periods of support, mask tolerance becomes an issue, and NIV might fail. The success of NIV application will depend on its ability to improve alveolar ventilation, while reducing the patient's work of breathing and improving the gas exchange process.

The need for NIV in acute exacerbations of COPD itself continues to be a poor prognostic factor [17].

Upper Airway

The upper airway consists of the nose, oral cavity, pharynx, and larynx. The upper airway participates in the process of chewing and swallowing, has a role in speech and smell, and stops foreign materials from entering the lungs.

Airflow enters and navigates through the upper airway to the lower respiratory tract. Therefore it is only expected that conditions and disorders that affect the upper way will also affect breathing and amount of air and oxygen that reaches the lungs as well as the amount exhaled from the lungs. These conditions can be either congenital or acquired and may have severe implications either in the progression of the disease or the treatment. This is especially important in patients that suffer from COPD or any pulmonary disorder for that matter.

While during ETI the tube goes past the upper airway bypassing it completely, upper airway can have a substantial role in the successful use of NIV. There are many disorders of the upper airway that can influence the success of NIV. Conditions that affect the anatomy of the structures that are involved in the upper airway can cause obstruction and cause breathing difficulties or prevent the correct fitting of the mask and prevent the use of NIV in those patients. These conditions can be congenital or acquired.

Examples of congenital condition include Pierre Robin syndrome which is a rare congenital birth defect that is characterized by an underdeveloped jaw, backward displacement of the tongue, and upper airway obstruction. Treacher Collins syndrome is another genetic condition that affects the proper development of the head and results in facial anomalies. Down's syndrome is another genetic disorder that predisposes to upper airway obstruction due to midface hypoplasia, macroglossia, a shortened palate, and a narrow nasopharynx. Micrognathia is another example of a condition that might lead to failure of NIV.

Examples of acquired conditions may include morbid obesity, obstructive sleep apnea (OSA), airway infections such as Ludwig's angina, rheumatoid arthritis, ankylosing spondylitis, and tumors that involve the airway. Trauma is another cause that will prevent correct application of NIV.

Discussion

Chronic obstructive pulmonary disease (COPD) is associated with high mortality and morbidity all over the world. Correct and timely treatment as well as following instructions as given will improve the symptomatology and quality of life for the patients. Exacerbations can be very serious and lethal. It is crucial to seek medical attention as soon as possible.

Patients may not be able to prevent all exacerbations, but there are measures to be taken in order to reduce the frequency and the severity of the episodes. Smoking cessation, annual vaccines, avoidance of environmental pollutants, adopting a heathier lifestyle, and a balanced weight can reduce the rate of lung function deterioration and improve quality of life.

NIV can have many advantages over endotracheal intubation (ETI) when it can be avoided together with the complications that follow ETI such as respiratory infections, ventilator-associated pneumonia (VAP), lung injury, etc. Although NIV is the first choice of managing exacerbations, it cannot replace ETI when there are indications for it.

It is important to distinguish the patients that can benefit from early use of NIV during acute exacerbations and patients that will need early intubation to prevent further lung function deterioration. A physician should seek to predict NIV failure. Many factors may lead to failed NIV application. Using a single variable, it is difficult to predict NIV failure with high accuracy [18]. The patient's outcome does not depend only on the patient but also on the physician monitoring the patient. Knowledge and practical skills regarding the use of NIV are critical components in the patient's care.

Early management and correct treatment can improve survivability, reduce exacerbation episodes, and lead to a better quality of life. By reducing the number of hospital admission, we reduce the burden on the healthcare system on a global basis as well.

Key Messages

- Chronic obstructive pulmonary disease (COPD) is associated with high mortality and morbidity all over the world
- Exacerbations with acute hypercapnic respiratory failure with acidosis can lead to death if not treated early
- NIV is usually the first choice in treating severe exacerbations of COPD that require respiratory support
- Upper airway can have a substantial role in the successful use of NIV
- There are measures to be taken in order to reduce the frequency and the severity of exacerbations

Conflict of Interest None declared.

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Upper Airway Neuromuscular Disorders and Noninvasive Ventilation

Bebiana Conde and Filipa Torres Silva

Introduction

The upper airway acts as a gateway, protecting the lower airway from foreign-body aspiration, injury, and dehydration [1]. This protective mechanism, already present in other species, evolved in humans, allowing, as well, for other fine purposes, such as phonation. The consequent fine-tuned rapid movements made the laryngeal inlet a potential major point of airflow resistance [1].

The protective upper airway reflexes are commonly disturbed in neuromuscular disorders. These diseases affect the function of bulbar innervated muscles, causing malfunctioning in muscle coordination; weakness and/or spasm, which ultimately impairs speech; cough; and swallowing [1]. Both afferent and efferent pathways can be compromised, resulting in hypo- or hyperresponsive reflex circuits [2].

Severe bulbar dysfunction and consequent glottic dysfunction most commonly occur in patients with amyotrophic lateral sclerosis (ALS), spinal muscle atrophy (SMA) type 1, and other uncommon neuromuscular disorders, such as x-linked myotubular myopathy and pseudobulbar palsy of central nervous system etiology [3].

An effective cough is essential for the pulmonary secretion's clearance, a mechanism which is impaired in neuromuscular disorders. Combined with the hypoventilation frequently seen in these patients, the upper airway disturbance also contributes to lower respiratory tract infection, atelectasis, and chronic lung disease [4].

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Interaction Between Mechanical Insufflation-Exsufflation Devices and the Upper Airway

To assist this condition, mechanical insufflation-exsufflation (MIE) devices were developed. These have shown to boost peak cough flow in patients with neuromuscular disorders and could help in maintaining lung volume, both crucial for effective secretion clearance [4].

Although mechanical insufflation-exsufflation and noninvasive ventilation (NIV) devices are thoroughly used in neuromuscular patients, the understanding of upper airway response to these therapies is still weak.

In patients with bulbar dysfunction, a laryngeal adduction of glottis was observed during insufflation, compromising an adequate lung filling, paramount in the first phase of the cough reflex. These findings were more common in predominantly spastic disease. In contrast, the insufflation in hypotonic patients promoted a backward movement of the tongue base, contributing to a hypopharynx obstruction [5]. Similarly, due to the loss of the muscle tone, the exsufflation causes an upper airway collapse, which is partially beneficial for increasing linear airflow velocity and propelling proximally the secretions but can also provoke anatomical prejudicial movement of larynx structures, compromising an adequate cough mechanism [6]. Bearing this in mind, slow titration of inspiratory pressures and increasing the inspiratory time may help to attain an adequate insufflation volume [5, 7]. Furthermore, the larynx reset after each cycle is crucial. As such, an increased time interval between each cough cycle can be implemented [6].

In order to pinpoint which adjustments are necessary individually, upper airway endoscopy may be useful, knowing strategies to improve ventilation and cough assistance efficacy and, ultimately, the patient prognosis. This technique can identify which structures are functionally compromised, with and without NIV or MIE devices, and also allow for individual parameter customizing [8, 9].

Noninvasive Ventilation Efficiency and Bulbar Dysfunction

Besides the compromised cough mechanisms, these patients might also respond inappropriately to external pressures provided during NIV.

Some studies reported an upper airway obstruction induced by NIV from the tongue base movement and by NIV-induced hypocapnia, with an ineffective response to expiratory positive airway pressure increase [10, 11].

When bulbar dysfunction is present, it constitutes a vital feature in the ineptitude of NIV in neuromuscular disorders, instead of the respiratory muscle weakness. Although the ineffectiveness has been postulated, the ability to prolong survival is still controversial. Bourke et al., in the only randomized control trial of NIV in ALS, found that in severe bulbar dysfunction, no survival improvement was observed. However, NIV adherence in this trial was low, and MIE devices were only used in the end of the trial [12]. Sancho et al. (2018) opposed these results, with a higher survival rate, since the included patients were NIV tolerant and performed adequate

secretion clearance. In order to do so, great efforts should be undertaken to achieve the lowest possible % sleepS_pO_2 <90 index, since it will increase the ventilation effectiveness and prolong survival. As such, the authors concluded a positive effect of NIV in survival, postulating the severity of bulbar dysfunction and % sleep-S_pO_2 < 90 index as prognostic factors for NIV failure in ALS patients [13].

Effects on the Upper Airway During Sleep and NIV

During sleep, all these disturbances are aggravated. The upper airway hypotonia and pharyngeal neuropathy are described in several neuromuscular disorders [14]. When considering the bulbar dysfunction, unexpectedly, obstructive events appear to be rare, possibly due to the predominance of diaphragm events or the reduced ability to generate negative pressure to induce the airway collapse. Thus, the sleep disturbance in these patients seem to be more central than obstructive events [15].

However, while bulbar dysfunction is not considered a contraindication to NIV, it still carries a certain challenge. Although NIV can improve oxygenation and sleep quality, these benefits are less apparent when the bulbar disturbance is severe, suggesting that a precocious initiation is preferable [14]. Furthermore, according to Dorst and Ludolph (2019), the adherence seems to be lower [16], and NIV with continuous positive pressure can be deleterious, since respiratory muscles may become exhausted as disease progresses [16, 17].

Conclusion

The physiopathology of neuromuscular disorders is extremely complex. The hypoventilation and secretion clearance, highly affected by the diaphragm and intercostal muscle hypotonia, have often unclear effects on the upper airway, although it significantly alters the breathing dynamics. As such, the research of the physiopathology of this anatomic segment and the creation of protocols to better customize the MIE and NIV devices are of utmost importance, allowing a better lower airway dynamic, but without the counterproductive effects in the upper airway.

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Sleep Obstructive Apnea Syndrome

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Epidemiology

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder with an estimated prevalence in adults aged 30–69 years of nearly 1 billion worldwide, and the number of people with moderate to severe obstructive sleep apnea is estimated to be almost 425 million [1].

The prevalence of OSA increases with age [2, 3], and the ratio between men and women is approximately two to one, but this disparity seems to fade in older age groups, given the greater prevalence in postmenopausal women [3, 4].

It can occur in any racial and ethnic group, but studies have shown a higher prevalence in younger and elderly black individuals [5]. Asian individuals seem to have a similar prevalence to Caucasians, despite lower rates of obesity, which can be explained by anatomical features such as a narrower airway that increases the probability of obstructive sleep apnea [6, 7].

The prevalence of OSA appears to be increasing, and the obesity epidemic and the aging population are likely to contribute to the rising prevalence [1].

Pathophysiology of Upper Airway Obstruction

The major determinants of upper airway patency are structural and neuromuscular factors [8]. Structural determinants include craniofacial structure and the surrounding soft tissue, with a variety of anatomic abnormalities associated with OSA, including retrognathia, micrognathia, overjet, high-arched palate, increased tongue size, increased size of lateral pharyngeal walls, enlarged tonsils, and increased total

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soft tissue volume [9]. These may be heritable traits, which can explain the familial predisposition to OSA [10]. Nonetheless, obesity remains the main contributing factor for OSA, with abnormal craniofacial structure most relevant in nonobese patients with OSA [8].

These anatomic abnormalities are correlated with higher collapsibility of the upper airway, which can be measured by the passive pharyngeal critical closing pressure (Pcrit) technique [11]. The more positive the Pcrit is, the more collapsible the pharynx is. While in normal adults Pcrit is estimated to be around −13.3 ± 3.2 cm H_2O, in patients with OSA, Pcrit is approximately 2.5 ± 1.0 cmH2O [11–13].

Currently, the severity of OSA is defined by apnea-hypopnea index (AHI) [14], which gives an estimate of the frequency of pharyngeal obstructions; nevertheless, it does not take into account the severity of these obstructions, and Pcrit can provide an estimate of the forces that cause these obstructions [15].

Regarding neuromuscular factors, sleep is accompanied by multiple physiologic changes, such as the loss of the wakefulness drive to breathe and a subsequent decrease in ventilatory motor output to respiratory muscles, including upper airway muscles [16]. Upper airway dilators have a critical role in maintaining pharyngeal patency, and upper airway narrowing or obstruction during sleep is associated with a sleep-related decrease in upper airway muscle activity, such as the levator palatini, tensor palatini, palatoglossus, geniohyoid, and genioglossus, among others [17–20].

During sleep we also assist to a decrease in the reflex that causes an increase in the upper airway muscle activity when there is an application of negative pressure to the upper airway [21, 22].

Clinical Features

The most common complaints of patients with OSA are daytime sleepiness, reports of loud snoring, gasping, choking, sleep maintenance insomnia, morning headaches, and nocturia [23–26].

Daytime sleepiness is a frequent feature of OSA and results from sleep fragmentation, interfering with the patient's quality of life. Sometimes, it may be underestimated because of its insidious onset and chronicity [24]. Daytime sleepiness should be differentiated from fatigue and has a weak correlation with the number of respiratory events [25]. The Epworth Sleepiness Scale (ESS) is used to quantitatively document the patient's perception of sleepiness, with an ESS score >9 indicating abnormal sleepiness that should lead to further testing [25, 27]. Also, nearly one-third of patients with OSA complain of insomnia rather than daytime sleepiness, mainly females [26, 28].

Snoring is associated with a high sensitivity for the diagnosis of OSA, but its specificity is relatively lower [23]. The absence of snoring, especially when the patient has no risk factors such as obesity, reduces the probability of a diagnosis of OSA [23, 29].

Morning headaches may last for several hours after awakening in the morning and are due to vasodilation secondary to hypoxemia, hypercapnia, increased intracranial pressure, and impaired sleep quality [30].

Nocturia may be associated with the release of atrial natriuretic peptide due to hypertension following obstructive events [31, 32].

Some patients may present symptoms of associated conditions and complications such as neuropsychiatric symptoms (depression, impaired concentration, and irritability) or nocturnal cardiovascular events including palpitations due to atrial fibrillation [23].

Cardiovascular Impact

The cardiovascular effects of OSA include hypertension, atrial fibrillation, stroke, heart failure, and pulmonary hypertension. These are related to OSA-induced changes in endothelial dysfunction, oxidative stress, sympathetic hyperstimulation, and systemic inflammation [33]. The main trigger of cellular damage underlying cardiovascular risk is intermittent hypoxia, the pathophysiological hallmark of OSA [17]. There is a direct correlation between OSA severity and the cardiovascular risk, and therefore, patients with severe OSA are the most affected [33].

OSA is highly prevalent in hypertensive patients (30–50% have comorbid OSA), particularly in patients with resistant hypertension, among whom the prevalence can reach 80% [34].

OSA is an independent risk factor for atrial fibrillation [35]. Beyond atrial fibrillation, OSA is associated with other cardiac rhythm disturbances, and an increased risk of sudden cardiac death has been reported in patients with severe OSA [36].

Pulmonary hypertension in OSA patients is generally mild in the absence of other cardiopulmonary diseases and seems to be a result of hypoxia-induced pulmonary arteriolar vasoconstriction [37].

OSA has also been associated with metabolic syndrome, insulin resistance, and type 2 diabetes [38].

Obstructive Sleep Apnea and COVID-19

A systematic review found that the risk factors and comorbidities associated with OSA are the same as those of the individuals who have poor COVID-19 outcomes, and, therefore, OSA patients may have an increased risk of mortality and morbidity associated with COVID-19 [39–41].

Patients with OSA often have high levels of angiotensin II, aldosterone, and the angiotensin-converting enzyme 2 (ACE2), which has been identified as the incoming receptor for the SARS-CoV-2 virus [42]. Also, chronic inflammation status in OSA patients, particularly in obese ones, contributes to the worsening of the cytokine storm in patients with severe forms of COVID-19 [43].

Diagnosis

In-laboratory polysomnography (PSG) is the gold standard diagnostic test for OSA; however, for patients without significant comorbidities and a high pretest probability of moderate to severe OSA, home sleep apnea testing with a type 3 device is a reasonable alternative [44, 45]. According to the third edition of *International Classification of Sleep Disorders* [46], the diagnosis of OSA requires 5 or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or respiratory effort-related arousals [RERAs]) per hour of sleep when associated with typical symptoms or comorbidities of OSA or 15 or more predominantly obstructive events per hour of sleep even in the absence of symptoms or comorbidities.

The severity of OSA syndrome is classified according to the number of apnea-hypopnea index (AHI) or the respiratory disturbance index (RDI), which also includes RERAs – mild OSA, 5–14 events/hour; moderate OSA, 15–29 events/hour; and severe OSA, 30 or more events/hour [15].

Treatment

The objectives of OSA treatment are to improve symptoms of OSA and sleep quality and normalize the AHI and oxyhemoglobin saturation levels. OSA should be treated as a chronic disease, requiring long-term and multidisciplinary management [47].

The patient should be educated about the risk factors and potential consequences of OSA. They should be warned about the increased risk of accidents associated with untreated OSA [48].

Obesity is an important risk factor and obese patients should be encouraged to lose weight. A 10% weight loss was observed to be associated with a 26% improvement in the AHI, while a 10% weight gain induces a 32% increase in the AHI [49].

All patients should avoid alcohol because it can depress the central nervous system, exacerbate OSA, worsen sleepiness, and promote weight gain [50]. They should also be advised that some medications may worsen their OSA, such as benzodiazepines [51].

Patients with positional obstructive sleep apnea are those in whom the AHI is at least twice as high while sleeping in the supine as in the non-supine position [52]. The American Academy of Sleep Medicine (AASM) task force on adult obstructive sleep apnea recommends positional therapy as an effective secondary therapy for people with positional OSA [53]. The European Respiratory Society task force on non-CPAP therapies in OSA refers that positional therapy can lead to a moderate reduction in the AHI; however, positional therapy is inferior to continuous positive airway pressure (CPAP) but may be recommended for selected patients [54]. Several devices are available for positional therapy, including semirigid backpacks, full-length pillows, a tennis ball attached to the back of nightwear, and electrical sensors

with alarms that indicate change in position. These therapies may be an alternative, especially in those for whom adherence with CPAP therapy is poor [55, 56].

Positive airway pressure (PAP) therapy is the current gold standard of treatment for OSA, reducing the frequency of respiratory events, improving symptoms, and reducing cardio- and cerebrovascular risk [57]. The AASM task force recommends PAP as the treatment of choice for moderate and severe OSA and an option for mild OSA in patients symptomatic enough to cause impairment in quality of life, after lifestyle advice and other treatment options have been unsuccessful [53, 58].

The most common modes of positive airway pressure administration include continuous positive airway pressure (CPAP), auto-titrating positive airway pressure (APAP), and bilevel positive airway pressure (BPAP). CPAP delivers positive airway pressure at a level that remains constant throughout the respiratory cycle. APAP increases or decreases the level of positive airway pressure in response to a change in airflow or circuit pressure, generally indicating a variation in upper airway resistance [59]. BPAP delivers a preset inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP), and it is indicated in cases of OSA syndrome that did not improve with CPAP/APAP, in patients intolerant to high pressures of CPAP/APAP, or with associated hypoventilation. Patients who initiate treatment with positive airway pressure should be frequently monitored, especially during the first weeks of therapy [53], so that any side effects that may develop can be managed, since this may affect long-term adherence [60].

Oral appliances, such as mandibular advancement devices, induce mandibular advancement, allowing the permeabilization of the pharyngeal lumen, and can represent an alternative for patients with mild or moderate OSA who decline or fail to adhere to positive airway pressure therapy [61].

The surgical approach in this syndrome can be considered when positive airway pressure or an oral appliance is declined or ineffective, after at least a 3-month trial of therapy [62]. Tonsillar hypertrophy, adenoid hypertrophy, or craniofacial abnormalities are examples of surgically correctable alterations that may obstruct the upper airway.

Hypoglossal nerve stimulation with an implantable neurostimulator device is an option in selected patients who have failed continuous positive airway pressure [63, 64].

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Sleep Breathing in Heart Failure

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Introduction

Sleep-disordered breathing (SDB) is common in patients with cardiovascular diseases, including in heart failure (HF) [1]. Patients with HF often have sleep problems due to periods of pulmonary fluid overload, which leads to classical symptoms of orthopnea, paroxysmal nocturnal dyspnea, and nocturia. A recent position paper of the European Society of Cardiology showed that almost 75% [2] of patients with HF report some degree of sleep disruption. Despite that, many patients remain undiagnosed in our current clinical practice.

SDB is associated with **several major pathophysiological abnormalities** [3], which include the following:

1. **Intrathoracic pressures swings** (which contribute to changes in ventricular repolarization and increased risk of sudden cardiac death)
2. **Sleep reduction and fragmentation** (decreased sleep efficiency and increased inflammation)
3. **Cyclical hypoxemia and reoxygenation**
4. **Sympathetic system activation** (worsened by coexisting HF)
5. **Endothelial dysfunction and increased thrombosis**

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Due to the increased risk of cardiovascular events as a consequence of these abnormalities, an adequate approach is crucial. In reality, several studies [3–5] showed that coexisting HF and sleep apnea increase the risk of developing malignant ventricular arrythmias leading to increased risk of sudden cardiac death.

SDB can be divided in **two main groups**: (1) **obstructive sleep apnea (OSA)** and (2) **central sleep apnea (CSA)**. Both OSA and CSA disrupt the normal sleep-heart interaction and impose similar autonomic, chemical, mechanical, and inflammatory burden in the cardiovascular system. In addition, OSA and CSA **can co-occur** in the same patient, increasing the difficulty in establishing a diagnosis and treatment scheme.

Despite OSA and CSA having a different etiology, they share a common pattern of recurring cycles of apnea, hypoxia, hypercapnia, and arousal from sleep, and both appear to be associated with increased sympathetic activity. As a consequence, a myocardial oxygen mismatch of demand and supply can occur, and the already debilitated heart just isn't able to deal with this increased workload, which paves the way to the establishment of ischemia or arrhythmias [1, 3, 4]. As HF becomes more severe, prevalence of OSA and CSA becomes more and more common leading to an increased risk of complications.

Obstructive Sleep Apnea

Definition

Over 50% of patients with HF have SDB [1], which includes obstructive, central, or mixed sleep apnea. OSA prevalence varies between 20 and 60% in this population and is typically more associated with heart failure with preserved ejection fraction (HFpEF). However, it may contribute to the progression of both heart failure with reduced (HFrEF) and preserved ejection fraction, potentially reflecting **an important modifiable risk factor** [6].

Sleep apnea is characterized by **repeated breathing pauses (apneas or hypopneas)** that may result in sleep fragmentation, excessive daytime sleepiness, and blood oxygen desaturation. According to the American Academy of Sleep Medicine, apneas are defined as a drop of at least 90% in respiratory flow from baseline during at least 10 s and hypopneas as a drop of at least 30% during at least 10 s accompanied by an oxygen desaturation of at least 3% or by an arousal [7]. In OSA, contrarily to what happens in CSA, **there are thoracoabdominal excursions**, generating a negative intrathoracic pressure that will be central to its pathophysiological consequences.

Pathophysiology

OSA is a heterogenous disorder with both anatomical and functional mechanisms occurring separately or in combination and contributing to upper airway occlusion.

They can be roughly divided into **four phenotypic traits** [8]: **high loop gain**, **reduced pharyngeal dilator muscle activity**, an **anatomically narrow pharyngeal airway**, and a **low respiratory arousal threshold** leading to recurrent awakenings.

Loop gain reflects the magnitude of change in respiratory drive-in response to a given disturbance. When it is excessive, like in OSA, a minor increase in $PaCO_2$ provokes an excessive increase in ventilation (may cause the inward suction of the upper airway muscles). The consequent fall of $PaCO_2$ results in an also exaggerated reduction of the respiratory drive that may well be an apnea if it drops below the apneic threshold. On the other hand, these patients also exhibit a low CO_2 reserve, which is defined as the difference between eupneic $PaCO_2$ and the apnea threshold, and that is generally associated with a ventilatory overshoot that will precipitate a central apnea [1, 8].

Predisposing factors for upper airway collapse like old age, male sex, obesity, high neck circumference, and retrognathism are also relevant in HF-related OSA. However, the tendency for obstruction is even more pronounced in HF owing to pharyngeal edema caused by rostral fluid shift during sleep. The pharyngeal dilator muscle activity exerted by the genioglossus is also reduced during sleep, increasing even more the risk of airway collapse.

Pathophysiological Consequences

Obstructive sleep apnea may accelerate HF progression through various mechanisms. The **negative intrathoracic pressure** generated by the respiratory muscles trying to inspirate against a closed airway **increases venous return** to the right heart and, consequently, the preload, causing the septum to move leftward. The same negative pressure is also responsible for **increasing transmural pressure and left ventricular afterload**. As a result, left ventricular function can be seriously compromised in OSA [1, 3].

Apnea and hypopnea are also responsible for other mechanisms that affect the cardiovascular functioning, like **sympathetic nervous system activation** (acutely related to arrhythmias and ischemia, chronically to left ventricle hypertrophy), **hypoxemia** (related to oxidative stress and inflammation), and **pulmonary vasoconstriction** (may cause *cor pulmonale*) [9].

Diagnosis

The **gold standard test** [1, 3] for sleep disorders is the **in-hospital polysomnography** (PSG). However, this is a costly exam that requires specialized personnel and facilities and, as such, is not widely available. **Multichannel sleep polygraphy** (PG) or **home sleep apnea test** (HSAT) with oxygen saturation are other options that have the advantage of being performed out of the hospital and without the need of attending personnel. They have some important limitations that should be known

in order to avoid underdiagnosis. Firstly, the sleep data is less precise with a HSAT and doesn't allow the calculation of the apnea-hypopnea index (AHI). In its place, we calculate the respiratory event index (REI). Secondly, hypopnea with arousal but without significant desaturation cannot be picked up without an electroencephalogram monitoring. Thirdly and finally, PSG allows an easier identification of periods of wakefulness, and therefore AHI can be recorded during sleep only, whereas in PG AHI is calculated throughout the recording period regardless of sleep pattern, and this may lead to an underestimation of the severity of the sleeping disorder [1, 3].

A diagnosis of OSA requires **at least an AHI/REI of 5/h**. Then the disease severity is categorized in three groups according to the AHI/REI cutoffs: mild between 5 and 15, moderate between 15 and 30, and severe with more than 30 events per hour [1, 3].

However, it's difficult to identify which patients should be tested for OSA, as most of them don't present with typical symptoms like daytime sleepiness thanks to the overactivated sympathetic nervous symptoms, rendering screening questionnaires like the Epworth Sleepiness Scale useless. Patient's characteristics and risk factors and input from a bedpartner can be a good starting point. On a next step, a **recording of nocturnal oxygen saturation via a finger probe** can indicate those who have to undergo a more thorough sleep study (those who present with **at least 12.5 desaturations/hour** are at bigger risk of developing sleep-disordered breathing) [1, 3].

Treatment

Ideally, each patient should be treated according to his/her phenotype.

High Loop Gain

Two medications have been used to treat OSA without HF and were previously used to treat CSA associated with HF. **Acetazolamide reduces loop gain** by increasing plant gain but also increases chemosensitivity to CO_2 [10]. Some studies indicated increased carbonic anhydrase activity is reportedly associated with severity of OSA and related hypoxemia [11]. As such, a combination of three effects (decreasing plant gain, being a mild diuretic, and moving the alkalotic pH toward normal values, further improving periodic breathing) can make this agent a useful weapon against OSA, but more trials are needed.

Oxygen is another drug therapy that **downregulates the loop gain**. However, the few studies that do exist did not include OSA patients with HF [10].

Reduced Pharyngeal Dilator Muscle Tone

Hypoglossal nerve stimulation is currently somewhat popular as a therapeutic target, but it has been used mainly to treat OSA in the general population or in patients who reject or don't tolerate positive airway pressure (PAP) devices.

Treatment with noradrenergic agonists (e.g., tricyclic antidepressants) may represent another possible therapeutic target, as **noradrenergic withdrawal may be responsible for the pharyngeal hypotonia** that occurs during the non-rapid eye movement sleep. However, associated c**ardiotoxicity may limit their use** in the population with HF.

Tongue and pharyngeal training may also be considered [10].

Anatomically Narrow Airway

Oral appliances have been used to treat OSA, including in patients with HF. These include the **mandibular advancement splints** (MAS) that work by lifting the mandible forward and stabilizing the upper airway and that can be particularly useful with patients with retrognathism [3, 5].

Upper airway surgery may also be considered, but the current evidence is mixed. Recently, patients with moderate or severe OSA who didn't tolerate or refused PAP or MAS that underwent surgery reported an improvement regarding the daytime sleepiness, but evidence is still scarce [3].

Low Respiratory Arousal Threshold

This might represent the more controversial therapeutic target. The idea behind the **use of hypnotics like trazodone** is that if the arousal could be delayed, the dilator muscles could be recruited and reestablish normal breathing. However, concerns regarding possible deleterious effects of prolonging the obstructive events are valid and can't be, at the moment, excluded.

Multimodal Approaches

Exercise and weight loss probably have a pleotropic effect, reducing the rostral movement of fluid and promoting the stabilization of the ventilation. **Optimization of the medical therapy should also not be forgotten**, as it will also reduce the rostral movement of fluid and improve cardiac output [10].

PAP devices, which include continuous (CPAP) and bilevel (BiPAP) devices, constitute the **most effective treatment option** for patients with OSA and HF, even if their long-term adherence is still very problematic.

CPAP is probably the more used modality, and its efficacy can be explained by **various mechanisms**, which include prevention of the pharynx collapse, generation of a positive end-expiratory pressure that prevents alveoli collapse secondary to pulmonary edema, reduced work of breathing, higher alveolar recruitment, improved gas exchanges, and reduced right to left intrapulmonary shunting of the blood. Besides that, the reduction of both left ventricle preload and afterload may improve cardiac function in some patients.

However, it should be noted that the vast majority of the evidence that nowadays supports the use of CPAP in patients with HF concerns HFrEF and not HFpEF that may actually be more prevalent in patients with OSA. As such, more trials in this particular subpopulation are needed [1, 9, 10].

Central Sleep Apnea

Definition

In a simple way, we can define CSA as the **cessation of breathing without thoracoabdominal effort**. It is characterized by a **breathing instability** with a periodic **crescendo-decrescendo pattern alternating with central apneas** [12] (cycle length superior to 40 s), often with some upper airway narrowing.

Prevalence

According to the literature [3–5, 9], the incidence of SDB is 53% and 48% in HFrEF and HFpEF, respectively. As the severity of HF increases, the episodes of CSA become increasingly more common, and its severity rises. However, despite the prevalence of CSA in HF being strikingly high, this condition continues to be seriously underdiagnosed.

Some studies showed a prevalence of 29–40% in HFrEF. In contrast, CSA in HFpEF remains less acknowledged, with some studies reporting an incidence of only 17%.

Regarding the risk factors [12] to SDB and mainly CSA, the ones that have been implied so far are **age** (older people), **gender** (male), **genetics** (gene-dependent development of respiratory center has been implied to play a role in SDB), **obesity** (a classic risk factor for OSA), **atrial fibrillation**, **hypocapnia**, **leptin** (low levels), and **smoking**.

Pathophysiology

Complex pathways of medullary and aortic receptor chemosensitivity are the key mechanisms of CSA. Simply put, its pathogenesis reflects an **amplified chemoreflex** and a **prolonged circulation delay** [8, 12] between the chemoreceptors localized in the carotid artery and the pulmonary capillaries. Cyclic periods of hyperventilation lead to decreased levels of CO_2, which will fall below apnea threshold, causing apnea/hypopnea.

Another mechanism implied in CSA is related with the **fluid shift** that occurs at nighttime. During the day, fluid tends to accumulate in the legs due to gravity, but when the patient is sleeping, a redistribution of fluids in the body happens. With the increased rostral fluid shift, some of it may additionally accumulate in the lungs, leading to hyperventilation and hypocapnia. As a result, this mechanism will drive $PaCO_2$ below the apnea threshold and cause CSA-Cheyne-Stokes breathing [3, 12].

In short, patients with HF are more vulnerable to the development of CSA because the increased chemosensitivity leads to an excessive ventilation during arousals, lowering $PaCO_2$ excessively. When sleep occurs again, the levels of $PaCO_2$ are below the apnea threshold, causing central apnea—**high loop gain mechanism** [3, 4].

Diagnostic Criteria

The diagnosis of CSA should **fulfill all the following criteria** [12]:

(a) **Presence of symptoms** (one or more of the following, sleepiness, difficulty initiating or maintaining sleep, awakenings, snoring, witnessed apneas, and awakening short of breath) **or atrial fibrillation/flutter, congestive HF, or a neurologic disorder**.
(b) **Polysomnography findings** (should present all the following, >5 central apneas and/or central hypopneas per hour of sleep, central events >50% of total events, and pattern of ventilation with criteria for Cheyne-Stokes breathing).
(c) The **disorder cannot be explained by another cause**.

One interesting evolution in the last years is the increasing use of cardiac device algorithms to detect and quantify SDB. As the number of HF patients with **cardiac implantable devices** increases, they are **being used more frequently** [1] to detect this kind of sleep abnormalities with reasonable sensitivity for moderate/severe SDB.

Consequences of CSA

CSA induces a cascade of cyclic variations in heart rate, blood pressure, respiratory volume, partial pressure of oxygen, and carbon dioxide that leads to **long-lasting structural changes** (like left and right ventricular hypertrophy). Hypoxia itself induces overactivation of the sympathetic nervous system (SNS), which leads to peripheral vasoconstriction (PV). The presence of **persistent overactivation of the SNS and PV leads to microcirculatory changes** [8, 12] causing cardiac electrical instability (such as atrial and ventricular arrythmias). Furthermore, oxidative stress precipitates a state of inflammation and endothelial dysfunction. All these changes potentiate progressive deterioration and increased mortality in HF patients.

Treatment

Current guidelines do not provide a unique way of approaching treatment for CSA. In addition, some clinical trials using positive airway pressure suffered from significant deficiencies, casting doubt on their results. All of these factors raised questions about how to best treat these patients.

Nowadays, we can divide the **treatment of CSA in four major pillars**: lifestyle modifications, pharmacological treatment, devices inducing positive airway pressure, and neurostimulation. The authors will explore each one of these points, focusing our attention on the use of positive airway pressure in CSA.

Lifestyle Modifications

Lifestyle modifications [2, 8, 12, 13] in OSA are clearly beneficial, but the advantages in CSA remain uncertain. **Weight loss** benefits on CSA have not been demonstrated, but it should be included in the treatment strategy of CSA patients. In addition, **exercise training and physical activity** should be implemented and incremented in HF patients with CSA to decrease symptomatic burden.

Pharmacological Treatment

Optimizing guideline-directed medical therapy for HF is the first step toward CSA treatment. Pharmacological therapy aims to minimize volume overload and improve functional capacity.

Each drug contributes to reduce the burden of CSA by its own distinct mechanism [13]:

- **Diuretics** are used to reduce nocturnal fluid shift and decrease the cardiac filling pressure, which is helpful in OSA and CSA.
- **Beta-blockers** are extremely useful because they decrease the nocturnal cardiac sympathetic activation. Carvedilol should be the preferred beta-blocker due to the lack of effect in melatonin inhibition, improving sleep quality and diminishing the CSA severity to some extent.
- **Angiotensin-converting enzyme inhibitors** contribute to CSA improvement thanks to the ability to reduce ventricular afterload and improve cardiac output.
- **Angiotensin receptor-neprilysin inhibitors** have also a clear benefit in the reduction of CSA symptoms due to their ability to reduce pulmonary congestion.
- Two other potential drugs, with limited evidence, are **theophylline and acetazolamide** [2, 3, 8, 12]. Theophylline has been able to decrease the periodic breathing and the AHI, while acetazolamide acts by reducing pulmonary congestion and lowering the apneic threshold through neural plasticity. These drugs should **only be considered after optimization with standard medical therapy and imply a cautious follow-up due to their potential side effects** (e.g., risk of arrythmia with the use of theophylline due to its narrow therapeutic window).

Although it is not a pharmacological strategy, **resynchronizing therapy** may also have beneficial effects on CSA, as the improvement of cardiac pumping function causes a considerable decrease in AHI in CSA patients.

Nonpositive Airway Pressure Modalities

We can divide these interventions in **two main modalities** [12]: nocturnal oxygen supplementation and nocturnal supplemental CO_2.

(a) **Nocturnal oxygen supplementation**: by improving oxygen delivery to cardiomyocytes and influencing controller gain and by decreasing hypoxemia and increasing the cerebral CO_2, this therapy could decrease AHI by 50%. Current evidence is scarce, and the recent LOFT-HF trial was not able to further clarify

the outcomes of this strategy on hospital admissions and mortality (the study was terminated because of lack of funding).

(b) **Nocturnal supplemental CO_2** [12]: in theory, this approach leads to suppression of CSA by shifting pCO_2 above the apneic threshold. Despite that, **CO_2 therapy is not recommended for clinical use**.

Positive Airway Pressure Modalities

We can divide these interventions in **three main modalities** [3, 4, 8, 12, 14]: continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), and adaptive servoventilation (ASV).

(a) **CPAP:** it is considered the **gold standard for the initial treatment of CSA** [8, 12, 13] related to HF, as it reduces AHI and improves the saturation profile. Patients classified as responders showed decreased AHI, virtually nonexistent oxyhemoglobin desaturation, and decreased nocturnal ventricular arrhythmias when compared with nonresponders. This allows patient division in two major groups with important repercussions on treatment strategy. Indeed, it seems likely that the hemodynamics of the cardiovascular system predict patient response to CPAP.

However, the benefits of this strategy in CSA are less well-established when comparing with OSA. Some of the main trials and their results are exposed in the fourth point of this chapter.

(b) **BiPAP:** ST mode should **only be considered if there isn't any clinical response with CPAP, ASV, and oxygen supplementation** [12]. BiPAP facilitates expiration and increases tidal volume. However, the latter mechanism may cause hypocapnia and provoke periodic or worsened CSA, effects that may be even more pronounced when there is a large difference between inspiratory and expiratory pressures (>7 cm H_2O). Despite the scarce data regarding BiPAP in CSA, the contradictory results of the studies raise questions about the utility of BiPAP in this setting.

(c) **ASV:** it is a modality aimed to deliver optimal positive pressure to maintain ventilation. Early studies showed a potential benefit with this modality (lower AHI and left ventricular ejection fraction recovery). However nowadays this modality, thanks to the results of the SERVE-HF trial [15], is considered unacceptable for patients with HFrEF. This study revealed an increased risk of cardiovascular events, but further reviews raised questions about its methodology (lack of information regarding right ventricular function, poor compliance of the patients, obsolete algorithm in the ASV device). In conclusion, ASV is **only indicated for the treatment of CSA in patients with ejection fraction >45%** [8, 12]**.**

Neurostimulation

A new modality of therapy, **unilateral phrenic nerve stimulation** [2, 3, 12, 13], has emerged as a potential strategy for this kind of patients. HF European Society of Cardiology Guidelines stated that "implantable phrenic nerve stimulation **can be**

considered for symptomatic relief," with some trials revealing an improvement in CSA that was associated with reduction in sleep arousals, better sleep quality, and improvement in quality of life.

Main Clinical Trials: Heart Failure and Noninvasive Ventilation

The use of noninvasive positive pressure ventilation can improve hemodynamics and ultimately be considered an adjuvant treatment in HF. Several clinical trials were published in the last years, some of them generating doubts about their findings among the scientific community. Tables 1 and 2 present the main findings of the major clinical [5, 13, 15] trials performed in HF patients with SDB.

Table 1 Main clinical trials in OSA

Trials in OSA	Main findings
CERCAS	• 725 non-sleepy patients with moderate/severe OSA • CPAP versus no active intervention • CPAP did not reduce the incidence of hypertension or cardiovascular events during a follow-up of 3 years
SAVE	• 2687 patients with established cardiovascular or cerebral disease • CPAP + usual care versus usual care • CPAP did not reduce the endpoint of major cardiovascular events
RICCADSA	• 244 patients with moderate/severe OSA after coronary revascularization • CPAP versus control • No difference in cardiovascular endpoints
ISAACC	• 1262 patients with acute coronary syndrome and moderate/severe OSA • CPAP versus control • No difference in cardiovascular endpoints

Table 2 Main trials in CSA

Trials in CSA	Main findings
CANPAP	• 258 patients with HF and CSA • CPAP versus no CPAP • CPAP group had greater reductions in apneas/hypopneas and greater increases in the mean nocturnal oxygen saturation and distance walked in 6 min • No differences in extending survival
SERVE-HF	• 1325 patients with HF and CSA • ASV versus medical therapy alone • ASV increased the risk of cardiovascular death
CAT-HF	• 126 patients recruited • ASV + medical therapy versus medical therapy alone • Trial was terminated when the SERVE-HF trial results were released • No improvement in 6-month cardiovascular outcomes in patients receiving ASV
ADVENT-HF	• Ongoing trial • Promising data regarding the use of ASV in HFrEF patients with CSA

The reasons why these trials failed to demonstrate cardiovascular benefits were intensely discussed, with the consensus being that the need for better phenotyping of SDB and poor CPAP adherence were important *biases* found in all of them.

Despite these findings, post hoc analysis of CERCAS, SAVE, and RICCADSA trials showed reduction of cardiovascular events in patients who had CPAP adherence >4 h per night.

Promising data was revealed during the 2022 European Society of Cardiology Congress regarding ADVENT-HF trial, as the usage of ASV (focused in peak flow targeted adaptative servoventilation) in CSA didn't result in increased cardiovascular events. However, a cautious approach to these findings is warranted, as the data has not been published and peer reviewed until the moment this chapter was redacted.

Nasal High-Flow Therapy in CSA

Nasal high-flow (NHF) therapy is a promising treatment strategy to reduce CSA. Thanks to the absence of the negative effects associated to intrathoracic pressure, this modality combines the positive effects of a mild level of continuous positive pressure with the use of oxygen therapy. Moreover, the pressure reached in the oropharyngeal cavity is actually very low [16] (maximum of 5 cm H_2O), and this fact will translate into even lower intrathoracic pressures. On the other hand, arterial carbon dioxide pressures decrease with this treatment (washout of dead space area), leading to potential central apnea induced by hypocapnia and its subsequent cardiovascular events. In line with this finding, one small study [16] showed an increased risk of cardiac arrythmias in patients treated with NHF. Although only five patients were included, it did raise questions about the safety of this therapeutic strategy. It is therefore necessary to conduct clinical trials for further clarification on possible benefits of this strategy.

Heart Failure with Preserved Ejection Fraction and Sleep Breathing Disorders

Some recent clinical trials [3, 4, 12] revealed that ASV can improve diastolic function and symptoms and decrease the level of natriuretic peptides concentration in patients with HFpEF and CSA. Current treatment recommendations with positive airway pressure devices are similar to the ones used in patients with HFrEF, the main difference being that **ASV is indicated for treatment of CSA related with HF in patients with ejection fraction >45%** [3, 12, 13]. Despite that, no robust clinical trials have yet been conducted to evaluate the true impact of this type of noninvasive ventilation on the cardiovascular outcomes.

Conclusion

SDB is found in at least 50% (some estimates point to 75%) of patients with HF and is associated with a worse prognosis. Pathophysiological mechanisms found in SDB include cyclic hypoxemia and sympathetic nervous system activation, although OSA is associated with thoracoabdominal excursions while CSA is not. The gold standard for its diagnosis is the PSG, but simpler or more accessible methods like PG or recording of nocturnal oxygen saturation via a finger probe can also be used and are still very helpful. CPAP and optimized medical therapy remained as the therapeutic cornerstones for both OSA and CSA, but newer strategies are being pursued and studied.

Key Points

- SDB is still highly prevalent in patients with HF, despite all the various clinical breakthroughs in the last decades.
- Untreated severe sleep apnea increases the risk for cardiovascular events (ischemia and arrythmias).
- Positive airway pressure treatment is useful both in OSA and CSA.
- The ADVENT-HF trial should bring us new data regarding the use of ASV in patients with HFrEF and CSA.
- There is scarce data about the use and benefits of nasal high-flow therapy in HF patients with CSA.

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Obesity Hypoventilation Syndrome

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Definition

Obesity hypoventilation syndrome (OHS) is defined as the combination of obesity (body mass index >30 kg/m^2), sleep-disordered breathing (SDB), and awake daytime hypercapnia ($PaCO_2$ > 45 mmHg), after excluding other causes for hypoventilation [1], such as severe obstructive pulmonary disorders, restrictive chest wall deformities, severe hypothyroidism, neuromuscular disorders, or central hypoventilation syndromes [2].

The definitive test for diagnosing alveolar hypoventilation is room air arterial blood gas, with an increased carbon dioxide level [3]. Although the definition of OHS suggests a diurnal pathology, polysomnography is required to determine the pattern of SDB and hypoventilation to better tailor treatment. Approximately 90% of patients with OHS have coexistent obstructive sleep apnea (OSA); the remaining 10% of patients have nonobstructive sleep-dependent hypoventilation [1].

Additionally, the levels of serum bicarbonate (>27 mEq/L) and/or calculated base excess of greater than 2 mmol/L have also been debated as a possible diagnostic criteria, since it represents longer-term measures of exposure to elevated levels of $PaCO_2$ and, unlike $PaCO_2$ and PaO_2, is improbable to change with a few breaths of hypoventilation or hyperventilation [2]. Although there is still no consensus, it is widely accepted that an elevated serum bicarbonate level should alert the clinician to consider the hypothesis of OHS.

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Epidemiology

The prevalence of OHS in the general population is currently unknown, although estimates based on obesity and OSA rates suggest that 0.3–0.48% of the general adult population may be affected [4], and it is likely to increase concurrent with the epidemic of obesity. Multiple studies have reported a prevalence of OHS between 8% and 20% in obese patients referred to sleep clinics [1].

Pathophysiology

Although the pathophysiology of OHS is not fully understood, what is apparent is that OHS represents a failure of the normal compensatory mechanisms that should be activated to compensate the consequences of excess weight on the respiratory system [2].

Individuals with OHS exhibit more marked reductions in lung volumes, impaired respiratory muscle performance, and greater reductions in respiratory system compliance compared to those with eucapnic obesity. These changes are at least in part attributable to a more central pattern of fat distribution seen in OHS, restricting diaphragm excursion and contributing to a high work of breathing [4]. Individuals with OHS adopt a pattern of breathing characterized by low tidal volume and increased respiratory rate, which increases anatomic dead space leading to CO_2 accumulation. Ventilation/perfusion (V/Q) mismatching in obese individuals may also contribute to CO_2 accumulation and hypoxemia in patients with OHS [5]. The CO_2 elevation stimulates renal absorption of bicarbonate each night, and sustained elevations in serum bicarbonate levels lead to increased CO_2 buffering capacity, attenuating the decrease in cerebrospinal fluid pH and consequently blunting the hypercapnia ventilatory response leading to diurnal hypercapnia. In summary, persistence of elevated bicarbonate level not only reflects the state of chronic hypercapnia but also contributes to perpetuate it [6].

Additionally, both leptin and insulin-like growth factor-1 (IGF-1) have been proposed as potential contributors to altered ventilatory control in OHS. Leptin has been shown to be a respiratory stimulant, and OHS patients appear to be leptin resistant [2]. Monneret and colleagues [7] found a significant reduction of IGF-1 in OHS patients compared with the obese control group. Serum IGF-1 levels were inversely associated with $PaCO_2$, and reductions in IGF-1 were directly correlated with reductions in forced vital capacity and inspiratory capacity.

Clinical Manifestations

The clinical manifestations of OHS are nonspecific and more reflective of the manifestations of obesity, coexistent obstructive sleep apnea, including daytime sleepiness, snoring, witnessed apnea, or complications, such as pulmonary hypertension

with right heart failure, presenting with dyspnea on exertion, elevated jugular venous pressure, peripheral edema, and, less commonly, facial plethora from polycythemia [8].

Treatment

Noninvasive positive airway pressure (PAP) together with weight loss are the first-line therapies for patients with OHS [1]. Approximately 90% of patients with OHS have coexisting obstructive sleep apnea, in which case continuous positive airway pressure (CPAP) is the initial mode of choice. For patients with OHS and sleep-related hypoventilation and patients with acutely decompensated OHS, bi-level positive airway pressure (BiPAP) is usually the initial mode of choice. Patients with OHS and OSA who fail or do not tolerate CPAP are also treated with BiPAP. For those who fail or do not tolerate BiPAP, a hybrid mode (average volume-assured pressure support) or, less commonly, volume-cycled ventilation may be chosen [9].

Bariatric surgery is also an option, especially for patients with class 2 or 3 obesity, in whom lifestyle modifications alone may be insufficient, or for those who wish to discontinue or reduce the need for PAP therapy [2].

Oxygen should not be administered as a sole therapy for OHS, since it may increase hypercapnia. In situations in which a patient with OHS requires supplemental oxygen (e.g., for comorbid chronic obstructive pulmonary disease, severe nocturnal desaturations unresponsive to noninvasive positive airway pressure therapy), it should be used concurrently with optimally titrated PAP therapy. Monitoring the need for oxygen is important since hypercapnia may improve and diurnal oxygen requirements may decrease with adherence to PAP therapy [10].

Other treatment options such as tracheostomy are now rarely necessary, since the introduction of noninvasive PAP therapy. Also, pharmacological therapy with respiratory stimulants (i.e., progestins and acetazolamide) are adjunctive therapies that are a last resort for patients who continue to have serious alveolar hypoventilation despite PAP therapy and weight lost, as they have potentially serious side effects [9].

Prognosis

Early identification and treatment of OHS is considered crucial given the significant health consequences, with high rates of morbidity and mortality in untreated patients [8].

Systemic inflammation, endothelial dysfunction, and insulin resistance are more pronounced in people with OHS compared to eucapnic obesity, resulting in the development of cardiovascular and metabolic comorbidities [11], such as hypertension and congestive heart failure, and may be present years prior to the diagnosis of OHS. Up to two-thirds of patients with OHS have pulmonary hypertension, which is negatively associated with exercise capacity [4].

The impact of therapy, particularly noninvasive positive airway pressure, on cardiovascular complications and mortality is uncertain and appears limited and based on extrapolated data from patients with OSA. However, even when sleep-disordered breathing is treated with positive airway pressure therapy, mortality in those with severe OHS remains substantially worse than individuals with OSA alone [12].

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Noninvasive Ventilatory Approaches in Neonatology

Ana Freitas

Characteristics of the Newborn's Airway

The anatomy of the newborn's upper airway has some particularities that differentiate it from that found in adults.

There is a relative higher proportion of the newborn's head in relation to the body. The greater prominence in the occipital region causes the newborn to adopt a flexed cervical posture when in supine, with consequent airway obstruction. To optimize the neonatal airway, the shoulders should be elevated so that the head is in a neutral or slightly extended position (the "sniffing posture").

The newborn's tongue occupies the entire space of the oral cavity and extends into the hypopharynx. Direct contact of the tongue with the posterior palate provides sealing and creates vacuum favoring nasal breathing. For this reason, newborns are preferred nasal breathers during the first weeks to months of life. They can breathe through their nose during feeding and also swallowing without aspiration [1].

The newborn's epiglottis is proportionately longer, wider, and less flexible, and the laryngeal inlet axis is angled anteriorly toward the base of the tongue. These anatomic characteristics favor upper airway obstruction in sedated newborns. The anterior displacement of the mandible and/or tongue minimizes this obstruction.

The larynx has also a more superior location, with the vocal cords positioned at C3 level. The narrowest portion of the upper airway in the newborn is at the cricoid cartilage, while in the adult it is at the level of the epiglottis. The aryepiglottic folds are located closer to the midline and may impede visualization of the vocal cords. The arytenoids and the corniculate and cuneiform cartilages are proportionally larger in relation to the size of the laryngeal inlet. The vocal cords are inserted more

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inferiorly on the anterior surface of the larynx, also causing an angulation of the anterior commissure. These factors make the neonatal intubation more prone to failure.

Repeated intubations pose a substantial risk of edema and airway obstruction in the newborn. The epithelium in the subglottic portion is columnar epithelium with less adhesion to the submucosal tissue, which further increases the risk of edema.

Neonatal respiratory physiology also presents numerous particularities that place the newborn in a special position of vulnerability for respiratory failure.

After birth, transition to extrauterine life is triggered by the first inspirations. The pulmonary fluids that occupied the respiratory tree are expelled through the upper airways or absorbed by the pulmonary blood and lymphatic vessels during the first hours of life. Progressive alveolar expansion is potentiated by the effect of surfactant produced by alveolar cells. Lung compliance undergoes a gradual increase during this process.

The rib cage recoil and lung recoil are both reduced in the newborn, but the first is more pronounced due to the cartilage structure and immaturity of the respiratory muscles. There is a natural tendency toward a lower functional residual capacity (FRC) and airway closure in the newborn. To maintain FRC, the newborn truncates exhalation before reaching static FRC and closes the glottis during exhalation to maintain positive teleexpiratory pressure.

The newborn's lung volumes are also disproportionately smaller in relation to body size and metabolic rate. The compensatory mechanism to maintain adequate ventilation is to increase the respiratory rate, as is normally observed in the newborn.

Neurological status changes and/or sedation inhibits the compensatory mechanisms and has the potential to dramatically reduce FRC. Optimization of airway patency and continued positive airway pressure through invasive or noninvasive mechanical ventilation are essential to maintain FRC in these situations.

The small caliber of the neonatal airways causes greater airway resistance in the newborn. According to Poiseuille's law, resistance to airflow is inversely proportional to the fourth power of the airway radius with laminar flow and to the fifth power during turbulent flow. When edema causes a halving of the airway lumen, airflow resistance increases by 16-fold. Any degree of airway obstruction places the newborn at high vulnerability for respiratory failure.

The protective coughing and swallowing reflexes are still immature in the newborn. On the contrary, there is a propensity to respond to mechanical and irritative airway stimuli with apnea, laryngospasm, and bradycardia. The response to hypoxia is also different from children and adults, since newborns can have initial hyperventilation period followed by a sustained ventilatory depression if the hypoxia persists. The initial hyperventilation response can be completely abolished if there is hypothermia, even if mild. Hypoxic ventilatory depression associated with bradycardia is more frequent and prolonged in preterm infants.

Upper Airway Anomalies in the Newborn

Newborns may present with a wide spectrum of upper airway disorders that may be congenital or acquired. These pathologies presenting with airway obstruction above the glottis can be categorized according to the level of obstruction at which they occur:

- Nasal obstruction, such as choanal atresia
- Oropharyngeal obstruction due macroglossia, micrognathia, and/or glossoptosis
- Laryngeal obstruction, such as laryngomalacia

Nasal Obstruction

Newborns are preferred nasal breathers, due to the mechanisms already described. Any nasal obstruction in the first weeks of life can lead to respiratory distress or failure.

Congenital choanal atresia is the paradigm of neonatal nasal obstruction, characterized by the posterior occlusion of the nostrils through a membranous or bony septum. It is a rare entity [2, 3] but can be fatal if the obstruction in complete. In cases of bilateral choanal atresia, newborns present with cyanosis when at rest, which resolves with crying through mouth breathing [1].

Incomplete choanal atresia, pyriform aperture stenosis, or nasal mass such as nasolacrimal duct cyst, hemangioma, or nasal dermoid can also cause congenital nasal obstruction, but with milder manifestations. Edema of the nasal mucosa resulting from infection or trauma is the main cause of acquired nasal obstruction.

The approach to choanal atresia is surgical resection of the atretic plates that can be done through endoscopic or non-endoscopic procedures [4]. Management of complete nasal obstruction, as occurs in bilateral choanal atresia or nasal agenesia, is a medical emergency in the newborn immediately after birth. It often requires the placement of tracheal tube and invasive mechanical ventilation as a bridge to surgical correction. However, the noninvasive approach to maintain airway patency must be considered. The use of a Guedel airway or a sectioned endotracheal tube in a oropharyngeal position is a transient alternative, but it can be poorly tolerated by the non-sedated newborn after the first few days of life [5, 6]. Other ingenious ideas have been described: the McGovern nipple with an open tip and secured to the oral cavity maintains oral airway temporarily until surgical intervention is reported by Kumar et al. [7] or a specially designed pacifier used by Stromiedel et al. [6] that is open at the tip and has a wet nose of a tracheostomy tube attached to the rear end allowing simultaneous breathing and suction to the newborn.

Oropharyngeal Obstruction

Oropharyngeal airway obstruction is mainly due to macroglossia, micrognathia, and/or glossoptosis. The pharyngeal negative pressure generated during inspiration causes posterior displacement of the tongue and airflow obstruction.

Macroglossia and micrognathia make it difficult to completely accommodate the tongue in the oral cavity, which is evidenced by the protrusion of the tongue between the lips of the newborn at rest. Congenital macroglossia can be focal or generalized. Focal macroglossia can be caused by tongue cyst, tumor, hemangioma, or lymphatic malformation. Generalized macroglossia can be idiopathic or secondary to systemic disorders such as Beckwith-Wiedemann syndrome, Down syndrome, hypothyroidism, or mucopolysaccharidoses.

Micrognathia in the newborn can cause upper respiratory obstruction due to glossoptosis and/or relative macroglossia. The paradigm of congenital micrognathia with glossoptosis is Pierre Robin sequence (PRS). It occurs when, before the tenth week of gestation, mandibular hypoplasia causes the tongue to be displaced upward and posteriorly, preventing the closure of the palatal shelves [8]. Pierre Robin sequence is, therefore, characterized by the triad micrognathia, glossoptosis, and airway obstruction. It is associated with cleft palate in 90% of the cases [8, 9]. It can be isolated, but in more than half of the infants, it is syndromic and mostly associated with Stickler syndrome and velocardiofacial syndrome [10]. Micrognathia can also be seen in other syndromes associated with craniodysostosis or craniosynostosis, such as Treacher Collins, Pfeiffer, Apert, and Crouzon syndromes.

The clinical presentation of the newborn with oropharyngeal airway obstruction is variable and may include signs of severe respiratory distress and apnea or only noisy breathing with stertor (low-pitched "snoring-like" sound) during sleep or respiratory difficulty during feeding. Respiratory symptoms are usually positional, improving in prone position. During sleep in dorsal decubitus, the more posterior position of the tongue aggravates the symptoms of obstruction (Cielo 2016 19). Some newborns appear to have no symptoms, but later poor weight gain can happen because of the increased caloric expenditure related to increased work of breathing [10, 11]. Pulmonary hypertension and *cor pulmonale* are also potential long-term complications of the chronic upper airway obstruction [10].

Infants with craniofacial malformations and/or macroglossia have higher incidence of obstructive sleep apnea [12–15]. Midface and mandibular hypoplasia and the volume of the tongue and of the pharyngeal lateral walls contribute to the obstructive sleep apnea in these infants [13, 16]. But, in syndromic patients, these factors are not the only predictor since OSA has multifactorial etiology [14].

Although rare, oropharyngeal obstruction in the neonatal period can lead to death especially when comorbidities exist, such as prematurity or other congenital malformations [8, 17, 18].

Facial growth is expected to help the natural resolution of the upper airway obstruction, but measures to minimize it in the first year of life are important to ensure normal systemic growth and neurocognitive development. A nonsurgical approach can be effective in many infants, regardless of presence of a clinical

syndrome [10, 19–21]. The appropriate approach should be centered in the individual characteristics and associated comorbidities of the patient, along with the experience of a multidisciplinary team.

Lateral or prone positioning of the newborn with oropharyngeal obstruction due to macroglossia or glossoptosis can be effective in reducing respiratory symptoms. It causes the tongue to fall forward and relieves the obstruction to the airflow. Although clinical effectiveness is reported [18–20], polysomnographic studies about the effect of position in PRS are lacking [13, 22]. Other pointed disadvantages of this approach are the lack of long-term efficacy on symptoms and on mandibular growth, along with the risk of sudden infant death syndrome and aspiration.

Nasopharyngeal tube can be used to act as a stent of the upper airway, pushing the tongue anteriorly and preventing oropharyngeal obstruction. Its long-term efficacy and tolerability have been reported, allowing hospital discharge and management at home [23–29]. The use of the nasopharyngeal tube does not favor mandibular growth, is not effective in all cases, and can have complications like obstruction from secretion plug, risk of displacement, or nasal trauma [22, 25].

Palatal plates have also report favorable results in infants with PRS, which if tough to act through an improvement in tongue function resulting in mandibular growth [22, 30]. A recent upgrade in palatal plates is the pre-epiglottic baton plate, which has a velar extension that dislodges the base of the tongue forward [31]. This device can reduce obstructive sleep apnea without significant adverse effects [32, 33].

Noninvasive ventilation though continuous positive airway pressure (CPAP) or noninvasive intermittent positive pressure ventilation (NIPPV) delivered by a nasal interface is also a therapeutic approach for infants with oropharyngeal airway obstruction [34]. The airflow acts as a virtual stent that prevents airway collapse. Noninvasive ventilation in patients with PRS was found to reduce respiratory effort, sleep hypoxemia, and hypercapnia and allows hospital discharge and home management [35, 36]. Ventilatory support from noninvasive interface allows for shorter hospital length of stay than the observed in patients with tracheostomy [36, 37]. Most of the patients with oropharyngeal airway obstruction were discontinued from noninvasive ventilation because of clinical and respiratory improvement, supporting the excepted favorable evolution of the craniofacial growth. The challenges of noninvasive ventilation in newborns and infants with craniofacial disorders are related to the difficulty in the fit of the interface and the need for longer hours of ventilation since sleep occupies most of the hours of the day. There should be a close follow-up and family/caregiver education to prevent side effects. Although adherence to NIV is generally good, a recent study from Amaddeo et al. [38] showed the high-flow nasal cannula as a potential rescue therapy in infants with craniofacial malformations who were non-compliers with CPAP.

The noninvasive measures in the approach of oropharyngeal airway obstruction should also take into account the important impact of gastroesophageal reflux and discoordination in the sucking and swallowing functions [8, 39]. Feeding tube, support from feeding therapy, and empiric therapy for gastroesophageal reflux are needed in some infants [21, 40].

When noninvasive approach is not effective to resolve respiratory distress related to airway obstruction, surgical management should be sought [13]. It may include partial glossectomy, mandibular distraction osteogenesis, tongue-lip adhesion, or tracheostomy [8].

Laryngeal Obstruction

Airflow through a restricted larynx leads to an increase in flow resistance and an exponential increase in airflow velocity, due to the Poiseuille law and the Venturi effect. It generates a decrease in the pressure exerted on airway walls (Bernoulli principle), resulting in the collapse of the airway walls. This turbulent laryngeal airflow and the airway collapse cause the inspiratory high-pitch stridor that is the main manifestation of laryngeal obstruction [41]. In cases of severe obstruction, stridor occurs along with respiratory distress, cyanosis, and apnea episodes in the newborn. Chronic stridor in the newborn suggests laryngomalacia, vocal fold paralysis, subglottic stenosis or mass, vascular ring, or glottic web.

Laryngomalacia is the most common congenital anomaly of the larynx. It is characterized by collapse of the supraglottic structures during inspiration. The etiology is still on debate and could be related to delayed maturation, redundant supraglottic soft tissue, tight aryepiglottic fold, supraglottic edema due to inflammation, or associated neuromuscular disease. It can occur in an isolate form or in association with congenital genetic syndromes or other non-airway anomalies [42].

Vocal fold paralysis is the second most common cause of neonatal stridor [43]. Vocal folds are immobile in paramedian position without proper abduction-adduction movements due to a disfunction in the laryngeal motor nerve supply from the vagus nerves. The main cause is iatrogenic related to cardiothoracic surgery, surgical repair of tracheoesophageal fistula or esophageal atresia, or extracorporeal membrane oxygenation [43–46]. It can also be caused by central nervous system disorders, mediastinal masses, birth-related trauma, or idiopathic congenital anomalies.

Subglottic stenosis is the narrowing of the cricoid lumen to less than 4 mm in the full-term newborn or less than 3 mm in the premature infant [47]. It can be congenital due to incomplete canalization of the cricoid ring or acquired and related to airway trauma or instrumentation. Congenital subglottic stenosis typically has less severe symptoms than when it is acquired. Prolonged intubation can result in posterior glottic scaring and stenosis and vocal fold tether by the cricoarytenoid joints, especially when there is a large endotracheal tube, excessive patient movement, and gastroesophageal reflux disease [43].

Laryngeal obstruction symptoms are related to the degree of obstruction. Some patients can present symptoms only during upper respiratory infections behaving like recurrent croups, while others can present with mild respiratory effort at rest or progress to respiratory failure and failure to thrive [48–50]. Inspiratory stridor is the main neonatal manifestation [51–53]. Laryngomalacia can get worse during feeding, in the sleep period, in supine positioning, and during upper respiratory tract

infections [49, 54]. Diagnosis is confirmed by laryngoscopy, which can also assess the severity and airway-associated anomalies.

Larynx and epiglottis maturation and growth cause natural and spontaneous resolution of the neonatal laryngeal obstruction symptoms, except in cases of neuromuscular disorders or genetic syndromes. Laryngomalacia resolution rate is about 90%, typically resolving between 12 and 18 months of age [55, 56].

Mild and intermittent stridor due to laryngeal obstruction usually resolves spontaneously [50, 57]. Patients who can breathe and eat safely can have a conservative management with close monitoring during the period of natural and spontaneous recovery. When respiratory distress, apnea, cyanosis, feeding difficulty, or poor weight gains are present, adequate treatment should be sought [50].

Noninvasive respiratory support can have an important role in the management of infants with moderate to severe symptoms of laryngeal obstruction. It is best studied in laryngomalacia, where it is demonstrated that noninvasive ventilation increases tidal volume and reduces all indices of respiratory effort (esophageal pressure swing, esophageal pressure time product, and diaphragmatic pressure) [58, 59]. NIV relieves the load imposed in the respiratory system by the laryngeal obstruction. Long-term home noninvasive ventilation in infants with laryngomalacia has been reported with good compliance and beneficial effects on growth and sleep [58]. Noninvasive ventilation can be used in patients with isolated laryngeal partial obstruction or when it is part of a congenital syndrome, mainly when it is associated with sleep-related breathing disorders, respiratory failure, or poor weight gain as an alternative to tracheostomy allowing for the larynx to grow and improve symptoms. In more severe cases, surgical intervention can be necessary [60]. NIV can still be used as a bridge to surgery or when surgical intervention fails to improve symptoms [61, 62].

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Upper Airway Disorders in Pediatric. Noninvasive Ventilatory Approaches

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Abbreviations

AHI	Apnea-hypopnea index
BIPAP	Bi-level positive airway pressure
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
HFNC	High-flow nasal cannula
IPAP	Inspiratory positive airway pressure
NIV	Noninvasive ventilation
OSA	Obstructive sleep apnea
PSG	Polysomnography
UAO	Upper airway obstruction

As known, children are not miniatures of adults. Their airway anatomical structures show developmental differences compared to adult patients, and as a result, the airway problems encountered will also differ.

Anatomically, upper airway is described as the area above the intrathoracic part of the trachea, and the nasal cavity, oral cavity, pharynx (nasopharynx, velopharynx, oropharynx, and hypopharynx), larynx, and trachea to the major bronchi are located in this area [1, 2].

In pediatric patients, upper airway disorders can be analyzed under two headings: congenital and acquired lesions. Congenital lesions include anatomical

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abnormalities (such as nasal atresia, choanal atresia, and craniofacial anomalies), macroglossia, subglottic stenosis, laryngeal clefts, laryngeal webs, cysts, laryngocele, laryngomalacia, tracheomalacia, trachea-esophageal fistula, and vascular ring. On the other hand, acquired lesions contain infections (such as croup syndrome, epiglottitis, bacterial tracheitis, retropharyngeal abscess, peritonsillar abscess), chemical and thermal burns, internal or external trauma, foreign body aspiration, extrinsic compression due to lymphadenopathy and tumors, hypertrophic tonsils and adenoids, laryngeal papillomatosis, hemangioma, and vocal cord paralysis [1]. The characteristic feature of these disorders is that they may cause upper airway obstruction (UAO), and this obstruction can lead to life-threating situations by further narrowing the already narrow airway for children.

Knowledge of the anatomy of the upper airway plays a very important role in planning the treatment. Depending on the developmental levels of children, acute UAO can occur at several anatomical levels. Infants have obligatory nasal breathing. Therefore nasal obstruction causes airway distress. However, infants can compensate for this obstruction with open-mouth breathing. In addition to nasal obstruction, UAO can also occur at lower levels, such as the oropharynx, larynx, and hypopharynx. Although the subglottic segment of the larynx is the narrowest part of pediatric airway, acute UAO is most common in the supraglottic and glottic region in children [3, 4].

Upper airway obstruction leads to hypoxemic and hypercapnic respiratory failure as a result of increased inspiratory muscle load and reduced alveolar ventilation [5, 6]. The classical treatment of airway obstruction includes antibiotic therapy, steroids, sympathomimetic agents, and for life-threatening situations, artificial airway placement such as endotracheal intubation or tracheostomy. These approaches to the airway, especially tracheostomy, may cause some complications in pediatric patients. In recent years, developments in noninvasive treatment modalities have led to a decrease in the application of invasive methods due to their possible complications [5]. However, this treatment method cannot be applied to all of the abovementioned causes of UAO. In this section, noninvasive ventilation methods that can be applied to a limited number of UAO will be focused.

Obstructive Sleep Apnea and Noninvasive Respiratory Support

Obstructive sleep apnea (OSA) is a disease in the spectrum of sleep-disordered breathing and is characterized by recurrent partial or complete UAO (hypopneas, obstructive, or mixed apneas) that disrupts normal oxygenation and ventilation during sleep [7, 8]. The prevalence of OSA in children varies between 0.1 and 13%, and this range can be up to 50% in obese children [7, 9]. OSA can affect neurocognitive, metabolic, and cardiovascular morbidity in children.

Adenotonsillar hypertrophy is seen as the main cause of OSA in children. Other reasons are craniofacial anomalies and syndromes, including Down syndrome, Pierre Robin syndrome, and Prader-Willi syndrome, and neuromuscular diseases [9].

The pediatric OSA criteria have been determined by *International Classification of Sleep Disorders-Third Edition* as follows: snoring, labored/obstructed breathing, or daytime consequences (sleepiness, hyperactivity, and so forth) [10]. The standard method for diagnosis of OSA is overnight polysomnography (PSG), which can be applied to a limited number of children. The other diagnostic methods are drug-induced sleep endoscopy and cine magnetic resonance imaging.

The primary treatment of OSA in children is surgical approaches that include adenotonsillectomy. Adenotonsillectomy is an effective treatment method, especially in children aged between 5 and 7 years. Medical treatment options are as follows: positive airway pressure ventilation, anti-inflammatory drugs (intranasal corticosteroids, leukotriene receptor antagonists), sleep supporting drugs and devices, orthodontic oral appliances, myofunctional therapy, and lifestyle changes [9].

Since 1984, noninvasive ventilation (NIV) has been used for pediatric OSA treatment. Generally, NIV is administered to maintain airway patency as supportive therapy when surgical treatment is contraindicated or respiratory failure after surgery or as a supportive treatment until appropriate stage for surgical intervention [11]. Continuous positive airway pressure (CPAP), bi-level positive airway pressure (BIPAP), adaptive servo-ventilation, and auto-titrating continuous positive airway pressure are the NIV methods used for this purpose. However, CPAP and BIPAP as noninvasive method will be discussed in this section. Additionally, high-flow nasal cannula (HFNC) therapy as an alternative method for respiratory support will also be mentioned.

Continuous Positive Airway Pressure and Bi-level Positive Airway Pressure

CPAP, which may be applied any age, is generally the preferred NIV method for treatment of OSA. CPAP does not treat underlying reason; it only contributes to maintaining airway patency. In these patients, CPAP is applied during sleep. However, pediatric patients who are undergoing CPAP should have a minimal ventilatory autonomy during awake periods. Invasive method should not be ignored in children with weak autonomy, especially in newborns.

Criteria of CPAP initiation are a matter debate. The European Respiratory Society suggests that CPAP can be considered in children with an apnea-hypopnea index (AHI) > 5 episode/hour after adenotonsillectomy [12]. In a retrospective study, authors stated that CPAP/NIV may be initiated in acute, subacute, and chronic setting with most children having an association of overnight gas exchange abnormalities and abnormal sleep study parameters [13]. Another issue is "where to start CPAP?." Generally, current guidelines recommend overnight hospitalization of children initiated on CPAP therapy. However, Amaddeo et al. presented a different viewpoint, suggesting that initiating CPAP in an outpatient setting is viable and beneficial for eligible children. The authors argued that the hospital environment can be stressful for children with chronic conditions and their families. Moreover,

the other negative features of this approach are the shortage of hospital beds, limited access to polysomnography, and economic limitations [14].

CPAP settings are adjusted according to the child's development and the underlying disease. The Pediatric Assembly of American Thoracic Society recommends titration of the CPAP level with PSG and periodic reassessment [15]. However, these may be difficult to implement routinely in children. Clinical guidelines of the American Academy of Sleep Medicine pointed out that the minimum recommended starting CPAP value should be 4 cm H_2O in pediatric patients, the maximum recommended CPAP value should be 15 cm H_2O in pediatric patients <12 years and 20 cm H_2O in pediatric patients >12 years, and CPAP should be raised by at least 1 cm H_2O at intervals of not less than 5 min until clinical improvement [16]. In infants, however, the situation may be slightly different due to minimal airway diameter, and even a minimal change in the CPAP level may cause different clinical outcomes in them. A retrospective study offered a different perspective, and the authors noted that physiological setting of CPAP values based on the monitoring of the esophageal and gastric pressures was more successful than the clinical setting based on clinical parameters in terms of an improvement in breathing pattern and respiratory effort in infants with UAO [17].

It is noninvasive respiratory support that can be applied in BIPAP other than CPAP. BIPAP provides two pressure levels: inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP). The American Academy of Sleep Medicine states that if the patient is uncomfortable or cannot tolerate high CPAP levels, BIPAP may be used. However, it does not mean that BIPAP is superior to CPAP at maintaining upper airway patency [16]. Similarly, a study comparing the efficacy of CPAP and BIPAP in infants with severe UAO showed that improved respiratory efforts were achieved with both noninvasive ventilation methods [18]. Other suggestions for the use of BIPAP in pediatric patients are as follows: the recommended minimum initial pressure value for IPAP and EPAP should be 8 cm H_2O and 4 cm H_2O, respectively. Applied pressures should be increased until clinical improvement is achieved. Maximum IPAP value is recommended as 20 cm H_2O [16].

Another important point for noninvasive methods is the choice of interface. The age and characteristics of patients, especially in children with craniofacial malformations, are influential in the selection of interfaces. İnterfaces include nasal prongs, nasal mask, nasobuccal mask, and total face mask. Depending on the equipment applied, nose, nose and mouth, or face is covered. It should be preferred that the equipment used is minimally invasive, hypoallergenic, easy to apply, and lightweight and provides optimal pressure without leakage.

For these methods, which are mostly applied at home, parents and children should be educated and followed closely afterward. Monitoring standards are uncertain due to the child's underlying disease, socioeconomic considerations, and healthcare system. In general, the recommendations can be listed as follows: follow-up visits should be made more frequent, especially as infants grow rapidly and their clinical condition change rapidly, and medical and technical support should be uninterrupted for these children and their families [19].

High-Flow Nasal Cannula Therapy

In recent years, HFNC has begun to gain attention in noninvasive respiratory support. HFNC, which is included in many treatment protocols, is used as an alternative respiratory support to CPAP and BIPAP for OSA treatment in pediatric patients. However, there are limited studies on this subject in the literature. The working principle of HFNC is based on delivering a high flow of heated and humidified air through the nasal cannula of an oxygen fraction which can be adjusted from 21% to 100%. Additionally, in terms of usage, HFNC oxygen therapy is less invasive and more comfortable than CPAP [20]. It has also been noted that the nasal masks of CPAP may lead to midface hypoplasia in infants and young children [21].

The titration of HFNC is adjusted according to the patients' work of breathing and oxygen saturation. HFNC flow rates in infants are recommended from 4 L/min to 8 L/min [22]. The flow rate of HFNC varies proportionally with the child's growth, and there are publications that recommend an initial minimum flow rate of 5 L/min and a maximum flow rate of 20 L/min with titration [23].

There are limited studies with a small sample size about HFNC therapy for children with OSA. Airway tone is low in children with OSA; therefore, it is difficult to maintain airway patency. The defect of nasal airflow sensation contributes to increased nasopharyngeal resistance, which negatively affects OSA. High flow rate, which is the main component of HFNC therapy, may activate or reactivate the protective airway reflex through the nasopharyngeal mechanoreceptor or thermoreceptor and help reverse the reduction in upper airway patency. Moreover, HFNC can decrease physiologic dead space and thus improve gas exchange [20, 23]. All these features of HFNC enable it to play an active role in the treatment of OSA.

Tracheomalacia and Noninvasive Respiratory Support

The pathogenesis of tracheomalacia includes an increased tracheal compliance that occurs in the intra- or extrathoracic trachea and inability to maintain airway lumen patency. Dynamic collapse usually occurs during the inspiration period in extrathoracic tracheomalacia and during the expiration period in intrathoracic tracheomalacia.

Tracheomalacia can be examined under two headings: congenital and acquired tracheomalacia. Symptoms of tracheomalacia include dyspnea, cough, apnea, shortness of breath, and cyanotic spells, especially during physical activity. In children with tracheomalacia, the ability to clear airway secretions is reduced; therefore, the risks of infections such as bacterial bronchitis or pneumonia are increased. There are currently no standardized diagnostic criteria for tracheomalacia. However, physical examination, pulmonary function testing, radiographic imaging techniques such as tracheograms, dynamic magnetic resonance imaging, and direct bronchoscopy may help for diagnosis. Treatment protocols include pharmacotherapy, noninvasive respiratory support therapy, and surgical intervention.

The function of CPAP during the treatment of tracheomalacia is to minimize airway collapse; this process is achieved by the correction of inspiratory mechanics by reducing expiratory resistance and maximal expiratory flow in patients [24, 25].

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Noninvasive Ventilation and Upper Airway Obstruction in Neuromuscular Disease

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Introduction

The upper airway is part of a comprehensive and vitally important system that ensures an efficient airflow passage into the lungs at the lowest possible energy cost, while preventing the entry of liquids and solids into the bronchial tree. The upper airway is a passage that provides air into and out of the lungs; heats, humidifies, and filters the air; and is involved in coughing, swallowing, and speaking. The complex muscular structure of the upper airway that produces speech and swallowing in humans also modulates respiratory airflow throughout the respiratory cycle, but it is vulnerable to functional problems that may compromise breathing. Even in non-compromised people, there is some upper airway collapse and increased upper airway resistance during sleep [1].

Obstructive sleep apnea is a process in which upper airway collapse is so great that breathing compromise promotes the awakening from sleep to restore adequate ventilation. A substantial proportion of people with this disorder have sleep disturbance and hypoxia, resulting in daytime sleepiness and neuropsychological and cardiorespiratory morbidity. Also, functional abnormalities of the larynx may occur, including prolonged laryngeal respiratory dysfunction, brief upper airway dysfunction, expiratory laryngeal dysfunction, or factitious asthma [1].

Upper airway weakness can impair the effectiveness of mechanical insufflation-exsufflation (MI-E) devices. Andersen et al. [2] proposed to determine the effect of a collapsible tube. The larynx has become increasingly recognized in respiratory

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therapy as an important potential source of airflow obstruction, playing a crucial role in controlling airflow resistance during exercise, protecting the lungs from aspiration, and performing precise movements in phonation and singing, and also in an effective cough [1, 3–5]. In this way, a defective larynx may set the flow generation for restricted airflow delivery to the lungs.

Normal cough is a highly dynamic and compound maneuver that strongly engages the upper airway. As Andersen et al. [2] point out, usually, coughing begins with an initial laryngeal abduction that allows air to enter the lungs during deep inspiration, followed by a rapid laryngeal closure phase to allow an increase in intrathoracic driving pressure. A secondary abrupt laryngeal abduction will result in a high expiratory airflow [6], creating a "fluid-structure interaction" within the upper airway. In healthy individuals, the laryngeal cough responses to MI-E are as described above [7].

The use of the cough device and its relationship with laryngeal movements has been the object of studies. Abduction of the vocal cords occurs during insufflation while adduction occurs during exsufflation, which in some patients may cause obstructive laryngeal movements, such as narrowing of the vocal cords, epiglottic retroflexion, constriction of the hypopharynx, and backward movement of the base of the tongue [7, 8]. The effect of airflow geometry on the large conducting airways has yet to be explored.

The purpose of this chapter is to describe upper airway disorders and strategies to minimize dysfunction in this region, including noninvasive ventilation (NIV) use and breathing exercises.

Dynamic Upper Airway Compliance

To move the respiratory system during normal breathing, a force (pressure) must be applied that is sufficient to overcome the elastic, resistive (frictional), and inertial components of different parts of that same system (lungs, airways, and chest wall). Dynamic compliance is the ratio between the change in air volume and the change in pressure used to keep the respiratory system stable. Volume and pressure changes also affect the collapsibility of the upper airway, and the end-expiratory volume becomes responsible for maintaining airway compliance affecting the upper airway stability [9].

Critical pharyngeal closure pressure has emerged as the gold standard for assessing upper airway mechanics based on the work of Schwartz and Smith et al. [10]. It can be done passively or actively and measures upper airway collapsibility using airway pressure drops.

Upper airway mechanics assessment has been performed using several techniques, although each has some limitations. Upper airway resistance can be quantified but becomes complicated during inspiratory flow limitation. Negative pressure pulses have been used to calculate collapsibility or collapsibility index but depend

on assumptions about resistive pressure drop down to a minimum flow. The active technique is based on gradual reductions in continuous positive airway pressure (CPAP) over several minutes, allowing time for the upper airway dilator muscle recruitment and end-expiratory lung volume (EELV) balance. The lung volume manipulation reflects a decrease in pharyngeal space, favoring upper airway collapse [9]. Airway resistance (Raw) is determined by the ratio between the resistive pressure change ΔP and its corresponding flow change ΔV, during normal breathing ($R = \Delta P/\Delta V$). Mead et al. [11] divided the respiratory system into seven structures, among them the oropharynx compliance determined by the effects of the cheek distensibility, mouth floor, and the air into the oropharynx.

There are also subgroups of patients more prone to develop upper airway obstruction, such as obese patients who are at significant risk for upper airway obstruction due to the altered anatomy of the upper airway [12, 13]. Since the pharyngeal tissues have increased, fat deposition may cause excess upper airway tissue and a greater probability of pharyngeal wall collapse resulting in airway obstruction. This can be exacerbated when patients with obesity receive medications that depress the central nervous system or have other comorbidities such as obstructive sleep apnea syndrome (OSAS) and obstructive hypoventilation syndrome (OHS). These syndromes may be associated with increased sensitivity to the respiratory depressant effects of sedatives and opioids, increasing the tendency for airway obstruction.

Upper Airway Resistance

The larynx determines upper airway resistance and accounts for 25–30% of airway resistance. Vocal fold abduction during inspiration produces a contraction of the cricoarytenoid muscles and adduction during expiration. The sensory innervation of the upper airway is responsible for the phasic and tonic activity of the pharyngeal dilators and laryngeal adductors. Hypercapnia or hypoxia can interfere with these reflexes.

Neuromuscular diseases may occur with bulbar muscle weakness and trigger resistance changes in the oropharyngeal and supra-tracheal regions. The association between low lung capacity and bulbar weakness is a strong predictor of bronchoaspiration pneumonia and early indication of tracheostomies affecting the quality of life. Dysphagia and dysarthria are functional alterations caused by this impairment. The swallowing alteration favors factors that decrease survival, such as weight loss, social isolation, dehydration, and saliva aspiration. The non-intelligibility of speech favors the loss of family and work relations, besides causing depression [14].

Bulbar weakness represents one of the causes of nocturnal apneas and contributes to the difficulty in adapting to ventilatory support. Maintenance of tidal volume and the stabilization of the respiratory rate are fundamental strategies in the use of noninvasive support, in such a way the muscular rest and the preservation of the elastic component of the thorax provide maintenance of respiratory functions such as speech, swallowing, sleep, and breathing [15].

Noninvasive Ventilation (NIV) and Upper Airway Obstruction (UAO)

The upper airway is a complex structure involving the oropharyngeal muscles, airway dilator muscles, and tongue muscles for keeping the airway open during sleep. Noninvasive ventilation (NIV) is characterized by maintaining a positive pressure from the upper airway to the lungs and is the option for keeping the airway open during obstruction situations [16]. In obstructive sleep apnea and progressive neuromuscular diseases, the dilator muscles of the upper airway lose their capacity to maintain permeability during sleep. The genioglossus muscles are the main ones responsible for maintaining the pharynx opening, helping with tongue projection, and preventing airway collapse during sleep [17]. NIV at night is indicated in sleep-related breathing disorders, including central sleep apnea (CSA), obstructive sleep apnea syndrome (OSAS), and sleep-related hypoventilation. The obstruction may be caused by diaphragmatic weakness, obesity, or various chest wall and neuromuscular disorders.

The lung volume reduction during sleep leads to loss of tone, reduced lung volume, and upper airway constriction. The ideal mask choice is a determining factor for a good adaptation to noninvasive ventilation.

Types of Masks and Their Relation to Upper Airway Obstruction (UAO)

The oropharyngeal muscles are the main ones responsible for neutralizing and minimizing airway collapse during sleep, especially the genioglossus muscle, which is responsible for the pharynx and oropharynx dilation and tongue projection [17]. During normal breathing, the caudal movement of the diaphragm produces increased lung volume and creates traction on the mediastinal structures. These movements of the lower airway muscles result in the stiffening of the pharyngeal walls and stabilize the permeability of the upper airway; for the realization of noninvasive ventilation, a range of interface nasal and oronasal mask models are proposed (Fig. 1).

Oronasal masks have been used for continuous positive airway pressure (CPAP) treatment in patients with obstructive sleep apnea (OSA). However, the study performed by Deshpande et al. [18] showed that the use of oronasal masks requires higher pressure to overcome the resistance imposed by the upper airway. Some studies have found upper airway pressure flow correlating with ease of ventilation and adaptation. Response to increased tidal volume, as well as increased chest mobility, is a predictor of successful adaptation.

Oronasal masks are preferred for patients with neuromuscular disorders since nasal masks can cause mouth leakage and compromise sleep quality. During NIV use, the highlighted causes of airway obstruction are nasal obstruction, pharyngeal collapse, and glottis closure [19].

Vrijsen et al. [19] also published a case report regarding oronasal mask use and upper airway obstruction, concluding that progressive neuromuscular weakness and

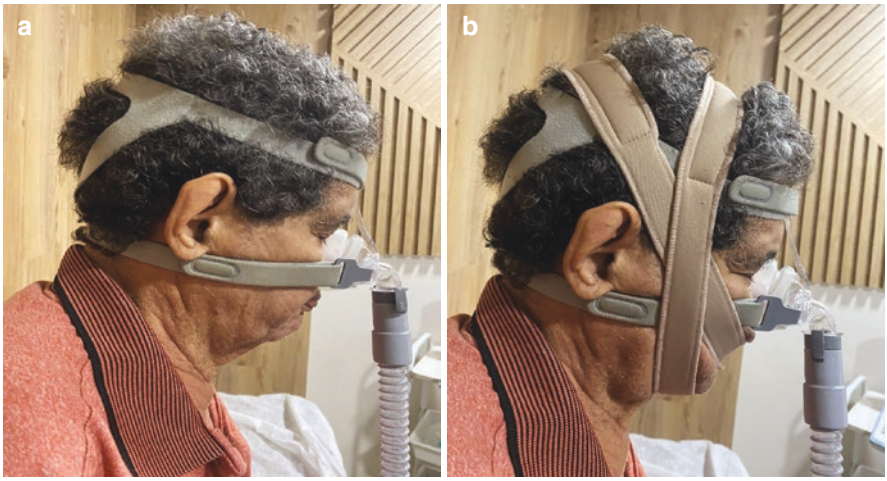

Fig. 1 A chin brace example for mandible traction and upper airway opening. Effect in mandible position before (**a**) and after (**b**) chin brace

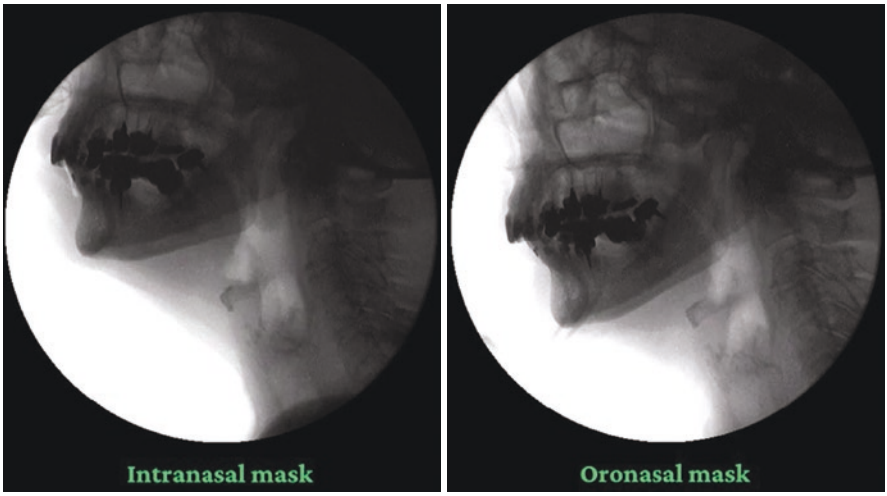

Fig. 2 Videofluoroscopic image using a nasal and oronasal mask. Female patient, diagnosed with ALS, 78 years old, vital capacity (FVC 69%), PImax 62 cm/h20, PEmax 59 cm/h20, peak cough flow 190 L/min

airway obstruction (caused by the tongue backward movement) may start even in successful NIV users, requiring more caution in mask indication. Detail in Fig. 1. Brace example for mandible traction and upper airway opening.

Schellhas et al. [16] evaluated the effects of inspiratory pressure in 212 patients in whom NIV was initiated with an oronasal mask and demonstrated that an oronasal interface use may promote obstructive events in some patients with neuromuscular disease (NMD) and amyotrophic lateral sclerosis (ALS). One hundred

seventy-six patients underwent overnight polysomnography and transcutaneous capnometry. Obstructive apnea was determined by an apnea index greater than 5 h. The authors concluded that the oronasal mask may be associated with obstructive nocturnal events, especially in neuromuscular patients.

Dorça et al. [20] evaluated the interface influence on the upper airway of ASL patients through videofluoroscopy in two different functional impairments (bulbar and appendicular). Details in Fig. 2. Videofluoroscopic—a nasal and oronasal mask. The patients were awake, and it was observed that during the use of the oronasal mask, the patient with appendicular impairment showed a slight increase in upper airway space, while the bulbar patient showed a significant decrease in the pharyngeal area.

The upper airway is made of muscles that neutralize collapse during sleep. In obstructive sleep apneas, the dilator muscles maintain permeability during sleep. The genioglossus is an important airway dilator, and its function is to dilate the pharynx, project the tongue, and dilate the oropharynx [21].

The diaphragm muscle has a caudal movement that favors the generation of lung volume and creates traction of the structures. The lung volume generated by the force of the respiratory muscles, inspiratory (diaphragm), external intercostals, and expiratory (abdominal) results in increased pressure in the oropharyngeal region, stiffening the pharyngeal wall and stabilizing the upper airway [22].

Respiratory muscle training exercises improve the performance and strength of upper and lower airway muscles providing muscle positioning, tension, and strength of oropharyngeal and soft tissue muscles [23].

Gaziano et al. [24] concluded that management strategies to improve vestibule closure, expiratory force generating pressure, and cough force may increase airway protection during swallowing in individuals with ALS.

Plowman et al. [25] evaluated the feasibility and impact of expiratory muscle strength training (EMST) on expiratory force-generating capacity, swallowing kinematics, cough physiology, and airway protection in individuals with ALS. The findings indicated that EMST training is feasible, safe, and well-tolerated in this small cohort of ALS patients and led to immediate gains in expiratory force and greater hyoid displacement during swallowing. In this study, a 5-week moderate-load EMST program led to increases in maximal expiratory force generation skills and hyoid displacement during swallowing. Maintaining subglottic air pressure generation skills is highly relevant in patients with ALS who have a severely diminished ability to generate adequate expiratory pressures to produce an effective cough and protect their airways. Therefore, EMST likely engaged this muscle complex that is primarily responsible for the anterior and superior excursion of the hyoid during swallowing. Displacement of the hyoid is an important kinematic event during swallowing, as the anterior and superior movement passively assists the relaxation and opening of the upper esophageal sphincter to allow effective transit of the food bolus from the pharynx into the esophagus. Improved hyoid displacement is relevant for ALS individuals who may have upper esophageal sphincter dysfunction, which can lead to significant residue in the piriform sinuses and further increases the risk of aspiration.

Torres-Castro et al. [26] performed a systematic review of inspiratory (power breath) and expiratory (EMT) muscle training for obstructive sleep apnea treatment; the use of the training devices demonstrated that inspiratory training therapy improves sleep quality and daytime sleepiness.

Dorça et al. [27] conducted a pilot study on expiratory muscle training technique preceded by volume recruitment (Fig. 3) in eight patients diagnosed with ALS. The authors aimed to measure the technique's acute effects on the upper airway using videofluoroscopy. Details in Figs. 4 and 5 demonstrated that the technique promoted acute effects on increasing pharyngeal constriction, pharyngeal expansion, retropalatal airway space size, and narrower postlingual airway size, significantly moving the retrolingual and retropalatal spaces.

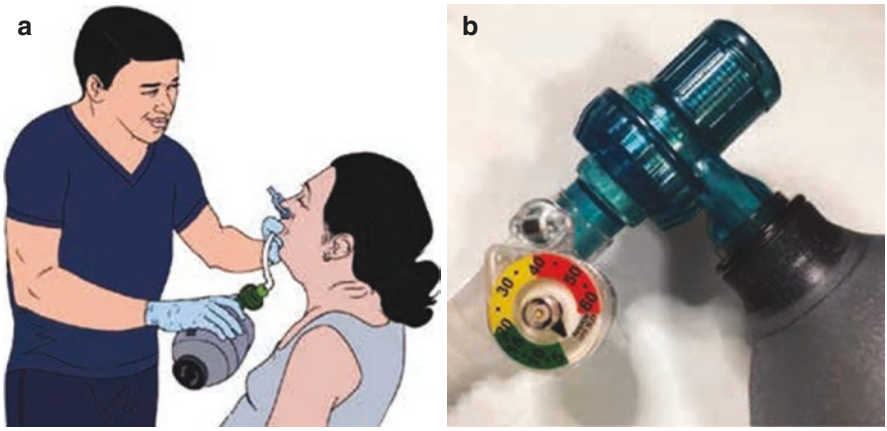

Fig. 3 (**a**) An example of technique execution [**a, b**—Ventlogos, Brazil, with permission], (**b**) Bag-mask ventilation mounted with a VUP valve and manometer

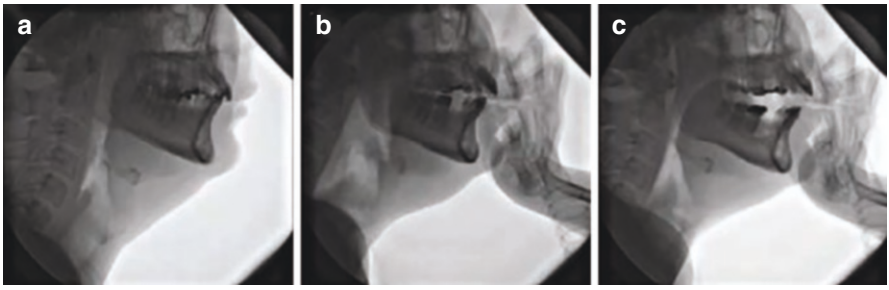

Fig. 4 Details of key videofluoroscopic frames of interest analyzed. Overview of differences across the pharyngeal constriction area during rest and respiratory training. (**a**) Example of rest position in which pharyngeal area at rest measurements were made; (**b**) example of maximum pharyngeal expansion (MPE) during VUP technique; (**c**) example of maximum pharyngeal constriction (MPC) during VUP technique

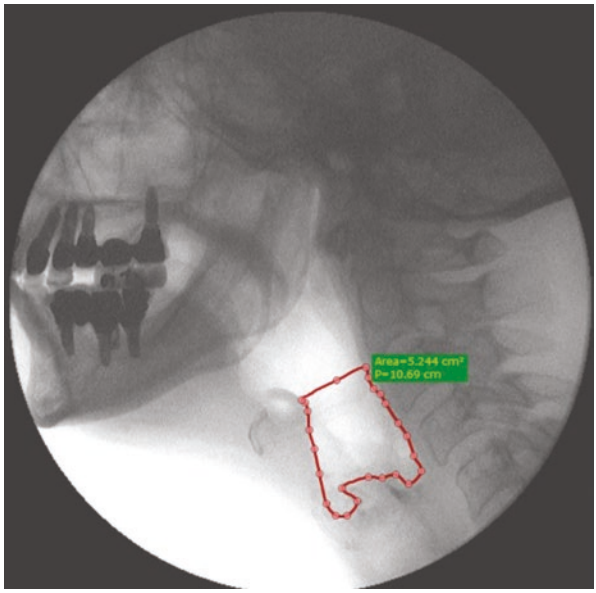

Fig. 5 Measurement of the pharyngeal area during the exercise of increasing capacity with Ambu and expiratory training

Conclusion

Many studies have looked into the better evaluation and understanding of the upper airway. Knowledge of mechanical changes in resistance and compliance can point to the best adaptation of NIV and the benefits of breathing exercises in upper airway obstructions. This chapter assists in building knowledge about the best mask and exercise indications for progressive neuromuscular disease and obstructive apnea patients.

End Practical: Key Messages

- Noninvasive ventilation (NIV) is widely indicated in neuromuscular diseases and obstructive sleep apneas; changes in compliance and resistance oropharyngeal area can interfere with speech, swallowing, and coughing. Clinicians must keep up to date to ensure the correct management of these structures as new evidence becomes available.
- There is limited evidence on the best NIV mask and the impact on upper airway opening. We advise that its use be based on a case-by-case basis, with multi-professional discussions.
- Breathing muscle training exercises are proving to be a great strategy for strengthening the oropharyngeal muscles and are showing positive impacts on speech, swallowing, and coughing.

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Transesophageal Echocardiography from Upper Respiratory Endoscopic Processes

Arzu Esen Tekeli and Mehmet Kılıç

Introduction

Today, transesophageal echocardiography (TEE) is a technological device that has started to be used in the emergency, intensive care unit, operating room, and even for the prehospital rapid diagnosis of unconscious patients [1, 2]. TEE is a semi-invasive procedure that has an important place in the perioperative management of cardiac surgery and in guiding diagnosis and treatment in hemodynamically unstable patients [3]. In appropriate indications, it can be performed by a trained echocardiologist who is aware of possible complications or by a trained physician/anesthesiologist/intensive care physician [1, 3]. Evaluation of cardiac anatomy and function began in the 1950s. After the 1980s, the use of TEE has become widespread in intensive care and emergency services, especially in the operating room [2]. The esophageal M-mode probe was first introduced in 1976 by Dr. Leon Frazin and contributed significantly to the development of TEE [4].

TEE shows the anatomy of the heart and thoracic aorta and evaluates general cardiac functions well. TEE, which is frequently used in cases where perioperative transthoracic echocardiography (TTE) is insufficient to evaluate the structure and functions of the heart valves, is an important technological tool in guiding diagnosis and treatment [1]. TEE is used to evaluate heart valve functions and to detect the presence of intracardiac air during cardiac surgery [1, 5]. TEE is also used when TTE is insufficient in hemodynamically unstable intensive care unit (ICU) patients.

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It is necessary to have sufficient knowledge about the device in order to use TEE correctly and effectively and to increase the image quality. Today, TEE has become one of the standard practices in the intraoperative management of patients undergoing noncardiac major surgery such as lung and liver transplantation [3]. The American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography reported relative and absolute contraindications for probe insertion in perioperative TEE practice guidelines [6, 7]. In fact, TEE is thought to be used in situations that cannot be diagnosed with TTE. However, there are limited indications for TEE to be the first choice: aortic pathology, heart valve dysfunction, cardiac interventions other than coronary artery disease, infective endocarditis, and atrial fibrillation [7–9].

It should be kept in mind that TEE, which is a semi-invasive diagnostic technique that can be applied safely although the indication is determined correctly, may rarely lead to the development of serious and life-threatening complications.

Transesophageal Echocardiography Device

Echocardiography provides information about heart anatomy with two-dimensional (2D) and motion (M)-mode imaging technique. Information about blood flow is obtained using Doppler and color flow imaging ultrasound (USG) [1]. Briefly, TEE is an ultrasonic device that produces digital images by reflecting sound waves sent from the transducer to the medium through which they pass, according to tissue density [1, 10]. It is shown in Fig. 1.

Fig. 1 (**a**) Transesophageal echocardiography unit; (**b**) display of the transesophageal echocardiography unit

TEE Equipment as Cardiac Ultrasound

TEE is a kind of cardiac ultrasound. This device consists of a transducer, a screen-recording unit, and an echocardiography unit. Simply put, the TEE probe is a modified gastroscope with an ultrasound tip [1]. There are control buttons in the middle of the probe body. While the probe tip is inserted into the mouth, oropharynx, and esophagus, it should be kept in a neutral position, while being pulled back and forth and/or turned to the right or left to avoid tissue damage [1, 11]. The frequency of the TEE probe varies between 3.5 and 7.5 MHz. The tip of the probe can be rotated in an angle range of 0–180° [1]. In addition, new-generation probes have electrocautery, reducing artifacts and providing better images. Adult- and pediatric-type probes are available. The pediatric-type probe is 5–7 mm in diameter and is more flexible and smaller [1, 3], shown in Fig. 1.

Display Screen and Recording Unit (Unit)

The display screen to be formed in TEE is in the form of a triangle area, and there is a transducer at the top of this triangle. When the transducer is in the mid-esophagus (at 0°), the patient's right side is seen on the left side of the screen, and the patient's left side is on the right side of the screen. When necessary, the screen image is frozen and can be saved and stored in digital memory [12]. If desired, the image can be printed out. Images taken in the digital system can also be shared electronically. In TEE, an image is generally in three color tones; fluid and blood appear black. Myocardium is medium-grey. Pericardium and calcifications are seen in bright white on the gray line [1, 12], shown in Fig. 2.

Fig. 2 Photo of a transducer. (**a**) Transducer bad, (**b**) handle, control wheels, and brake; (**c**) printer unit; (**d**) recording unit

Echocardiography Unit

Before the TEE procedure, device controls, electrocardiography, and pulse oximetry monitoring of the patient should be performed. Patient identification information must be entered; presets must be made by selecting the appropriate probe. The frequency of the TEE probe is usually between 3.5 and 7.5 MHz. As the frequency increases, the resolution increases, while the depth and penetration decrease. However, as the frequency decreases, the resolution decreases and the penetration increases [13]. For 2D images, the highest frequency that provides adequate penetration should be used. Focusing can be made to optimize the image resolution [1, 13].

TEE Indications

TEE is used to evaluate the anatomical structure, pressure, and function of the heart valves, aorta, atrium and ventricles, atrioventricular septum, pulmonary vein, and pulmonary arteries. Indications for TEE are summarized in Table 1 [2, 14]. TEE provides more reliable and accurate visualization of the natural and prosthetic mitral

Table 1 Indications

A. Outpatients
1. Natural heart valve evaluations: mitral regurgitation, follow-up of patients who underwent mitral balloon valvuloplasty, evaluation of aortic valve and subaortic membrane, evaluation of tricuspid and pulmonic valves (TEE has little benefit)
2. Prosthetic valve: it is very useful in the evaluation of prosthetic mitral valve; TEE evaluation is indicated in prosthetic aortic valve, prosthetic valve endocarditis, obstruction, and dysfunction when TTE is not diagnosed
3. Endocarditis: evaluation in terms of vegetation, abscess, and valve perforation, evaluation for endocarditis in prosthetic valves (such as abscess-cavitation, mycotic aneurysm)
4. In the diagnosis of intracardiac masses (atrial myxomas and heart tumors)
5. In the investigation of thrombus in the right atrium and left atrium for the etiology of pulmonary embolism and systemic embolism and in the diagnosis of patent foramen ovale
6. Investigation of left atrial thrombus before cardioversion in atrial fibrillation
7. Thoracic aortic examination (such as aortic root dilatation or intramural hematoma)
8. In the diagnosis of congenital heart diseases (ASD, VSD, abnormal pulmonary venous return)
9. Coronary artery stenosis and anomaly research
B. Perioperative period/intensive care unit
1. In the diagnosis of acute myocardial infarction complications in the intensive care unit
2. Investigation of the etiology of hemodynamic instability of the critically ill patient
3. Detection of ischemia during CABG in cardiac surgery, guiding diagnosis, and treatment in valve operations
4. Guiding treatment during operation for ASD closure and coarctation of the aorta
5. Investigation of the etiology of perioperative MI and ischemia in ventricular dysfunction developing in noncardiac surgeries
6. In cases where TTE is insufficient to diagnose (conditions such as COPD, obesity, and chest deformities)

valve compared to TTE [14]. In addition, TEE is very useful in the detailed evaluation of left atrium and left atrial appendage, mitral valve, and subvalvular calcifications. TEE guides catheter and balloon placement during the mitral balloon valvuloplasty procedure. In addition, it has an important place in investigating the heart valve movements and the presence of thrombus in the left atrium in these patients [14, 15]. With TEE, mitral valve prolapse is easily distinguished from vegetations [16]. Endocarditis vegetations that cannot be seen with TTE are more easily recognized with TEE. TEE is very useful in detecting the presence of an intra-atrial thrombus prior to cardioversion when medical therapy fails to treat arrhythmia [14]. Intraoperative TEE is very important in guiding the treatment/surgery for heart valve repair or replacement in cardiac surgery and increasing the chance of success of the surgery [2, 14].

TEE in the Perioperative Period

TEE is significant in demonstrating myocardial segment wall abnormalities in patients undergoing bypass grafting in case of perioperative myocardial ischemia [14, 15, 17]. Abnormal segment contraction in patients undergoing bypass grafting may be due to inadequate revascularization or cardioplegia. TEE is useful to provide information about the diagnosis of myocardial abnormality caused by inadequate revascularization and the necessity of placing additional intraoperative grafts. TEE is successful in evaluating valvular functions and demonstrating valvular regurgitation before and after valvular surgery in the perioperative period. In addition, it can prevent unnecessary intervention in a normally functioning valve and also guides the surgical plan to be made for valve insufficiency. TEE is one of the most appropriate tools to guide the surgeon in the perioperative periods, both in bypass grafting and valve surgery [14]. TEE provides valuable information in the detection of intraoperative ischemia in noncardiac surgical operations and especially in patients at high risk for cardiac complications [3].

TEE in Intensive Care Unit

Transthoracic echocardiography may sometimes be insufficient in the evaluation of echocardiographic functions in critically ill patients. TEE provides more accurate information in the evaluation of cardiac function and anatomy in hemodynamically unstable patients and in investigating possible causes [3, 18]. Among the causes of hemodynamic instability, many causes such as hypovolemia, valve dysfunction, papillary muscle rupture, ventricular septal defect, left or right ventricular failure, massive pulmonary embolism, or pericardial tamponade can be listed. TEE provides fast and necessary information at the bedside for the management of patients who are hemodynamically unstable for any reason [3].

Intensive care units are also places where patients with brain death are diagnosed. Pretransplant TEE may be useful to evaluate the cardiac function of organ

Table 2 TEE contraindications

A. Absolute contraindications
1. Esophageal obstruction (mass, severe stenosis, etc.)
2. Esophageal perforation
3. Esophageal diverticulum
4. Undiagnosed active upper gastrointestinal (GI) bleeding
5. Unstable cervical vertebral fractures
6. Patients with a full stomach (oral intake <4 h)
7. Uncooperative patients
B. Relative contraindications
1. Those who have undergone radiotherapy to the thorax
2. Rigidity of the neck or inability to flex it
3. Patients with bleeding diathesis

donors diagnosed with brain death. In addition, TEE is one of the diagnostic tools in the etiology of high fever of unknown origin or when infective endocarditis (IE) is suspected. Contraindications of TEE are given in Table 2 [3, 19].

Transesophageal Echocardiography Safety

Complication rates related to TEE performed in the outpatient clinic, perioperative period, and intensive care units vary. Major complications of TEE performed in outpatient settings are rare. The mortality rate due to TEE is thought to be below 0.01% [3]. However, complications related to TEE performed in the intensive care and intraoperative period may be slightly higher. It is thought that this situation is caused by manipulation problems while placing the TEE probe in patients under the influence of muscle relaxants. When patients cannot swallow and the probe encounters resistance, the patient's stimulating effect disappears [3]. In a study investigating complications related to intraoperative TEE, data of 7200 patients were evaluated, and the morbidity rate was 0.2%, and the mortality rate was 0% [18]. In another study, complications such as upper gastrointestinal (GI) laceration, bleeding, or perforation associated with TEE were reported [20]. There are studies reporting the overall incidence of TEE-related minor oropharyngeal injuries (including lip-tooth injuries, hoarseness, sore throat, dysphagia, or odynophagia) as 0.1–13% [3, 18, 21].

Dysphagia rates were found to be particularly high in cardiac surgery patients who underwent TEE (compared to those without TEE) [22]. Dysphagia in these patients has been associated with the development of additional problems such as aspiration, pneumonia, need for tracheostomy, and increased length of stay in the intensive care unit [3, 22]. Hogue et al. reported in their study that the use of intraoperative TEE is an independent risk factor for dysphagia [22]. In addition, other studies have reported that the rates of sore throat or odynophagia due to TEE (in patients undergoing cardiac surgery) did not differ significantly between groups [23, 24]. There are case-based case reports such as dislocation of dental prostheses due to TEE probe placement or positioning and tooth-tongue injury [3, 21, 25]. TEE-related upper GI perforations are estimated to have an incidence of 0.01–0.04%

after surgery in pediatric and adult patients [3]. Serious complications with mortality rates ranging from 10 to 56% have been reported, depending on the time elapsed until the diagnosis of upper GIS perforation and the type of treatment [3]. Deep sedation and general anesthesia applications in intraoperative or intensive care units may delay the diagnosis of upper GIS perforation after TEE in patients, because in cases under sedation or general anesthesia, the triple symptom of spontaneous esophageal perforation may be difficult to notice: vomiting, pain, and subcutaneous emphysema. In case of suspicion of upper GI perforation, investigation of the presence of blood coming from the nasogastric tube, dyspnea, agitation, fever, and subcutaneous emphysema may be useful for diagnosis. It should not be forgotten that 33% of the first chest radiographs taken in esophageal perforation are within normal limits [3, 19]. When the TEE probe is inserted through the oral cavity, pharynx, hypopharynx, and into the upper esophagus and when resistance is encountered, it should be considered that the probe is placed in one of the pyriform fossae or that there may be resistance in the upper esophageal sphincter. In this case, when force is applied to the probe, perforation may occur in the parapharyngeal area or the posterior cervical esophagus wall. Such complications have been encountered in studies [26]. Perforation risk is exacerbated in conditions such as Zenker's diverticulum, esophageal stricture, esophageal mass, esophageal varices, tracheoesophageal fistula, and congestive heart failure [26, 27].

The incidence of major upper GI bleeding associated with TEE is estimated to be between 0.02% and 1.0%, but the consequences can be serious [3, 28]. These hemorrhages usually develop due to esophageal trauma of the TEE probe. In addition, bleeding may occur in places such as the thoracic aorta and lung tissue other than the esophagus. Hematoma occurring after submucosal bleeding in the oropharynx and hypopharynx may cause serious complications such as airway obstruction. Anticoagulant use and developing coagulopathies in the perioperative period of cardiac surgery are risk factors for severe upper airway and upper GI bleeding associated with TEE [3, 28]. In addition, in cirrhotic patients with esophageal varices, the risk of bleeding can be evaluated by performing endoscopy before TEE [3]. TEE complications are summarized in Table 3 [2, 3, 14, 26].

Table 3 TEE-associated complications

1. Oral cavity injuries	2. Dysphagia
3. Oro-hypopharyngeal minor bleeding, discomfort	4. Severe odynophagia
5. Hoarseness, laryngospasm, bronchospasm	6. Major bleeding in the esophagus, perforation
7. Tracheal placement and occlusion of the probe	8. Stomach perforations
9. Malposition of the endotracheal tube	10. Pulmonary aspiration
11. Cardiac arrhythmias (AF, VF, VT, NSVT, AVB)	12. Spleen laceration
13. Transient hypotension	14. Accidental extubation

AF atrial fibrillation, *AVB* atrioventricular block, *NSVT* nonsustained ventricular tachycardia, *VF* ventricular fibrillation, *VT* ventricular tachycardia

TEE-Related Cardiovascular and Respiratory Complications

Cardiovascular complications (such as cardiac arrhythmias) after TEE are rare. The most common of these complications are atrial fibrillation, ventricular-supraventricular tachycardias, and atrioventricular blocks [3]. Those with structural heart disease are more likely to have these complications. Cardiac arrhythmias may develop as a result of hypoxemia and hypercarbia due to sedation in non-intubated patients [3]. Considering TEE-related respiratory complications, displacement of the intraoperative endotracheal tube within the trachea or unwanted extubation may be observed [18]. Complications associated with TEE in intensive care unit non-intubated patients include hypoxia, hypercarbia, need for unplanned endotracheal intubation, tracheal intubation with probe, bronchospasm, and laryngospasm in non-intubated patients. Another TEE-related complication is thermal injuries due to tissue absorption of heat generated by the piezoelectric crystal vibration at the probe tip [3]. Although the risk of these injuries is low, necessary precautions should be taken. During the procedure, the stylus can be kept in an unlocked and unbent position when not in use. There is a thermistor at the tip of the new-generation probes that is sensitive to temperature increase [2]. By this thermistor, the probe tip temperature will automatically turn off when it reaches the threshold temperature (42–44 °C). Thus, the risk of thermal damage is reduced [3].

Infectious Diseases and Chemical Complications

Another complication associated with TEE is infectious infections and chemical damage [3, 29]. Liquid chemicals are used in current standard disinfection applications. TEE probe and unit are sterilized with and without aldehyde solutions and then rinsed and reused. Thus, infection rates are reduced. However, it should not be forgotten that these chemical solutions carry a risk in terms of tissue damage [29].

TEE Procedure and Probe Placement

One of the necessary preparations before the TEE procedure performed in the intraoperative or intensive care unit is that the patient has been fasting for at least 4–6 h. The patient's hemodynamic parameters should be monitored [3, 7, 14]. Necessary equipment should be available for emergency intervention in cardiovascular unstable patients. Once the patient has been adequately sedated (who may benefit from direct rigid laryngoscopy/videolaryngoscopy if resistance is encountered), the probe should be inserted into the esophagus in the neutral position [21, 30]. It should never be done while the probe is in the locked position. A mouthpiece should be placed to prevent biting. Applying gel to the tip of the probe facilitates placement. When the endotracheal intubation tube interferes with the advancement of the probe, this

obstacle can be removed with the aid of direct/videolaryngoscopy [21]. Severe mucosal tears or perforations of the oral cavity, oro-hypopharynx, esophagus, and stomach; it is usually the result of rapid advance or removal of the probe after excessive force is applied to the probe and rapid rotations of the probe while locked in extreme anteflexion. However, even well-placed probes can cause injury during manipulation. Tissue damage or necrosis due to TEE probe compression is not expected [3, 30, 31]. In cases where TTE is insufficient in intensive care patients (especially in small endocardial lesions), the diagnostic effect of TEE is gradually increasing. Continuous TEE monitoring can be performed in critically ill patients in the ICU [29, 32, 33]. ICU patients are often worried about complications associated with TEE due to their major hemodynamic instability, being sedated, coagulopathy, being noncooperative, sepsis, and septic shock. However, studies have shown that TEE is safe in these patients [3, 34, 35]. There are also studies reporting no serious complications and an overall complication rate of 1.6% [3]. The use of TEE in pediatric patients younger than 7 years of age began with the development of smaller (5.9 mm diameter) probes after the 1990s [3, 36]. Today, with the developing technology, TEE probes are designed in a suitable size for use with infants and newborns [27, 36]. TEE has been used more and more as a guide for interventions performed in the perioperative period in pediatric cardiac surgery. In pediatric patients, TEE is usually performed under endotracheal intubation and general anesthesia [3]. There is a concern about the development of complications related to TEE in this age group. Hemodynamic disturbances may develop, especially due to compression or obstruction of the TEE probe to the airway or mediastinal structures [3, 37]. However, there are also studies reporting that no hemodynamic deterioration is observed [38].

Complications are more likely to be seen in low weight and young infants [36, 38]. Today, TEE is used safely in all age groups, even newborns. Adult TEE probes are used in all patients over 20 kg. However, there are also studies reporting that adult TEE probes can be used up to 14.7 kg [36]. Complication rates in pediatric patients are variable, and overall complication rates have been reported between 1.8% and 20.4%. In addition, complications encountered in the studies may be in the form of mild mucosal damage such as erythema, edema, erosion, and hematoma in the esophagus due to intraoperative TEE [3, 39]. In summary, choosing an appropriately sized probe for TEE in pediatric patients, careful placement, and appropriate manipulations will reduce complication rates. In some cases where TEE cannot be used, TTE or epicardial echocardiography can be used as an alternative, both in the ICU and in the perioperative period [3]. Epicardial echocardiography and epiaortic echocardiography during cardiac surgery are noninvasive and good options when there are contraindications for TEE or the TEE probe cannot be inserted into the esophagus (especially in pediatric cardiac surgery) [3, 39]. The applicability of TEE and alternative echocardiography devices is increasing day by day due to increasing technological developments. It is necessary to do specialization training in this field or to increase the necessary certified training programs.

Conclusion

Today, TEE is a device that guides clinicians in guiding diagnosis and treatment in emergency services, perioperative period, and intensive care unit safely at almost every age and every weight, thanks to its probes whose designs have improved with the effect of technological developments. It gives valuable information in evaluating the anatomy and functions of the heart and its arteries. TEE is not worrisome in terms of complications; fatal complications and mild complications are also rare. Most of the complications of TEE are associated with probe insertion and manipulation. Complications can be significantly avoided if the practitioner takes due care for high-risk patients with probe placement and manipulation. In cases where TEE is absolutely contraindicated, we recommend using alternative echocardiographic imaging methods.

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Part IV

Diagnosis and Monitoring

Functional Procedures in Upper Airway Disorders

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Endotracheal Intubation

Endotracheal intubation is the introduction of a tube through the patient's mouth and into their airway. The usual reason this is done is to secure and facilitate airway flow and oxygenation for patients who will undergo general anesthesia and patient who suffer from severe pulmonary disorders that requires support from a ventilator. It is preferred for the patient to be unconscious in order to perform the rather uncomfortable procedure.

Procedure

Assess intubation difficulty using the Mallampati and LEMON [1] scores. Prepare adequately. After loss of consciousness by the patient, adequate oxygenation is required to compensate for the lack of respiration during the respiration attempt. This is especially true for patients whose intubation may prove difficult and therefore take more time.

The head of the patient is placed in a position of extension [2], whenever it is possible, using the left hand of the physician. While the left hand of the physician keeps the head stable, the mouth is opened with the right hand. Then keeping the head stable and the mouth open with the right hand, the physician introduces the blade of the laryngoscope in the right side of the mouth and subsequently moves it toward the midline, moving the tongue along until the epiglottis is visible.

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The laryngoscope then is to be lifted in direction anterior and inferior to the patient. This way the larynx can be best visualized and the vocal cords exposed. Care must be taken to avoid rotation of the laryngoscope that may inadvertently cause damage to the patient's dental structures. An assistant can apply gentle pressure to the cricoid cartilage to assist with the visualization of the larynx [3].

Finally with the larynx and vocal cords exposed, the endotracheal tube is inserted into the trachea under direct vision. Optimal length from the tip of the endotracheal tube to the patient's dental structures varies depending on patient's height, but 23 cm for men and 21 cm for women can be used as a rule of thumb [2]. The blade of the laryngoscope is removed. The cuff of the tube is inflated and the oxygenation of the patient can resume. The physician performing the procedure must check that the tube is indeed placed correctly, usually by auscultating for bilateral breathing sounds and lack of gargling sounds in the stomach. Capnography can also be used, when available.

If for any reason difficulties are presented during the procedure, the performing physician needs to stop after due time, in order to oxygenate the patient, before resuming effort to prevent hypoxia. Adequate oxygenation is more important than intubation. Continuous monitoring of oxygen levels is mandatory when possible. In difficult cases an elastic bougie may be used as a guide for the tube. A video laryngoscope may also be used to provide vision in difficult intubations [2, 4].

Emergency Cricothyrotomy

Cricothyrotomy is the procedure of gaining surgical access to the trachea with the purpose of securing the function of the airway. Whenever bag-mask or supraglottic ventilation is unfeasible and intubation of the patient is not possible [5] (CICO, an acronym, meaning cannot intubate, cannot oxygenate, may commonly be used to describe the situation), a cricothyrotomy can offer direct access to the upper trachea in order to achieve vital oxygenation, performed usually on the patient's bedside, during admission, or during transportation to the emergency unit. Cricothyrotomy should be avoided in children under the age of 12. The underdeveloped larynx of children is thinner and more prone the permanent damage due to the operation. Cricothyrotomy should also be avoided in individuals with laryngotracheal injuries, as it may worsen their condition. Tracheostomy should be considered as an alternative to cricothyrotomy in these cases.

Procedure

The goal of cricothyrotomy is to gain access to the trachea through the cricothyroid membrane. After placing the patient's head in overextension whenever possible, the anatomical landmarks of the operation need to be identified. After the suprasternal notch, the thyroid cartilage, and the cricoid cartilage are located, the physician

performing the cricothyrotomy can palpate the cricothyroid membrane in the indentation between the thyroid and cricoid cartilages.

A 2 cm vertical incision is performed on the midline of the neck along the previously palpated cricothyroid membrane. The incision is further deepened with sharp dissection under guidance by palpation of the membrane using a finger. Due to the emergent nature of the procedure, slower blunt dissection and a more traditional slower surgical approach are discouraged [6].

After the cricothyroid membrane is located, it is incised horizontally. The incision is further dilated with the use of the physician's finger or that of Kelly forceps. An endotracheal tube can now be placed to provide oxygenation and ventilation assisted by the use of an elastic bougie guide.

Complications [7, 8]

During procedure:

- Bleeding
- Injury of the thyroid gland
- Laryngeal/vocal cord injury
- False passage through tissue
- Pneumothorax or subcutaneous emphysema
- Esophageal/mediastinal injury along perforation of the posterior tracheal wall
- Aspiration

After procedure:

- Dysphonia or voice changes
- Infection
- Hematoma
- Persistent stoma
- Scarring
- Laryngeal, glottic, or subglottic stenosis
- Tracheoesophageal fistula
- Tracheomalacia

Tracheostomy

A tracheostomy is the surgical bypass of the majority of the superior airway via incision of the trachea. It is performed to allow the placement of an endotracheal tube in conditions of upper airway blockage, where traditional intubation is unfeasible, or to secure the airway in cases of prolonged ventilatory support, where tracheomalacia is likely to develop. Gas exchange into and out of the lung is facilitated

through this surgical opening and diverted away from the nasal and oral orifices, commonly performed in the operating theater, under total anesthesia.

A tracheostomy is usually performed under these circumstances [9]:

- Complete or partial obstruction of the upper airway (may warrant emergent approach).
- Allow access to the lower trachea, in order to facilitate a surgical procedure (e.g., removal of foreign body too big or too dangerous to pass safely though the larynx).
- Need of safe, secure, and easy airway access for oxygenation (e.g., oxygenation during facial surgery).

Upper airway disorders that may require intervention with tracheostomy are as follows:

- Severe facial, neck, or laryngeal trauma
- Exposure to fire or smoke that may lead to airway damage
- Foreign body aspiration
- Cancer of the upper airway
- Subglottic stenosis
- History of laryngectomy
- Congenital defects of the upper airway
- Extended periods of ventilatory support and tracheomalacia
- Vocal cord paralysis (bilateral)
- Infections, leading to increased secretions and/or swelling of the epiglottis or the larynx

Procedure [10, 11]

The patient is placed under general anesthesia. Oxygenation of the patient is carried out by traditional endotracheal intubation when possible or different means, like nasal insufflation catheter when normal intubation is not feasible. The patient's neck is placed in a position of extension, using special pillows or sandbags, when possible. In cases of trauma where compromise of the cervical spine is suspected or evident, the patient's head must remain linear to avoid serious damage to the spinal cord and possible disability [12].

Using palpation, the performing physician identifies the landmarks of the sternal notch, the thyroid notch, and cricoid cartilage. The skin is incised 1–2 cm inferior to the cricoid cartilage. The incision may be vertical or horizontal, with a span of 3–4 cm.

The deep facia is to be vertically opened using electrocautery. Using blunt dissection, prepare and retract the strap muscles laterally. The thyroid isthmus may be divided or retraced inferiorly to provide sufficient area to operate. The later maneuver will expose the tracheal facia and the trachea beneath it.

The tracheal facia must be opened vertically, exposing the tracheal rings. After palpating the cricoid cartilage and counting the tracheal ring, the performing physician must choose the appropriate location to perform the tracheotomy. In adults the second and third rings are usually the site of the opening, and in prepubescent patients, the third and fourth rings are optimal. Congenital abnormalities and tumors may affect this choice.

After the location is identified, the performing physician can trace the shape of the tracheotomy before carefully incising it using a scalpel. The shape may be circular, square, or a vertical incision (preferably in prepubescent patients). Creating a flap to assist closure of the tracheal opening is optional.

Finally, after the trachea is opened, the endotracheal tube used to oxygenate the patient is retracted just enough to allow for the placement of a tube through the tracheal opening. After the ventilation of the patient is assumed using the tracheostomy, the distal ends of the incision are sutured and the tube stabilized on the patient's neck.

Alternative Procedure

In an alternative approach, the procedure can be performed using Seldinger's [13] principle. Patient position remains the same, and the performing physician gains access to the trachea in the same way. After the trachea is exposed, a needle is used to perforate the trachea between the second and third rings. The needle must be directed caudally with great care taken to avoid puncture of the posterior aspect of the trachea. Suction of air indicates correct positioning. For this approach to be possible, the anesthesiologist must maintain the endotracheal tube at the level of the vocal cords or lower larynx.

A guide wire with a j-tip can be presented through the needle, and the needle is subsequently removed. Dilation of the trachea is carried out using the guide wire and the appropriate dilator [14]. The tracheostomy tube is inserted and the guide wire removed.

Simultaneous bronchoscopy may be used to identify the optimal site for needle perforation (using the bronchoscope's light as a guide) and to assure correct placement of the tracheostomy tube as described by Marelli et al. [15]

Complications related to tracheostomy:

- Bleeding
- Tracheal damage or scaring
- Aspiration
- Infection or pneumonia
- Accidental removal of the tracheostomy tube
- Pneumothorax, pneumomediastinum or subcutaneous emphysema
- Esophageal damage or dysphagia
- Tracheoesophageal or tracheoarterial fistula
- Injury to the recurrent laryngeal nerve
- The tracheostomy tube can be obstructed by blood clots or excretions

Tracheal or Laryngeal Dilation

In cases of tracheal or laryngeal stenosis, tracheal or laryngeal dilation is an effective treatment option. Under endoscopic guidance a dilation procedure can be undertaken using either a balloon catheter [16] or a series of progressively larger laryngeal dilators over the span of multiple dilation. Usually lower occurrences of stenosis are adequately treated with a balloon catheter, while upper tracheal and laryngeal stenoses are better treated with dilators.

Vocal Cord Paralysis

Vocal fold paralysis can produce difficulty in breathing. Bilateral paralysis can be especially life-threatening as the vocal flaps may cover the entirety of the laryngeal outlet. The same effect can be observed in individuals with vocal cord fixation. To resolve this issue, a patient can undergo different procedures.

Posterior Commissuroplasty

During this procedure the physician uses endoscopic guidance to create small incisions on the posterior aspect of both vocal cords, thus increasing airflow and improving breathing, without the need for a more severe tracheostomy, and preserving voice functionality better than a transverse cordotomy [17].

Transverse Cordotomy

In a transverse cordotomy, after similar approach using endoscopic means [18], one of the two vocal cords is entirely dissected, to create passage and restore airway function. The incision is made anterior to the vocal process. An endoscope with 30-degree viewing capability can be used to ensure that the incision is performed at adequate length. This approach obviously hinders an individual's ability to vocalize and therefore must be weighed against voice-sparing interventions, like Commissuroplasty and tracheostomy.

Arytenoidectomy

Arytenoidectomy may be partial or total. In the partial version of the procedure, only the most median part (2–3 mm, or more depending on the severity of the obstruction) of the arytenoid cartilage is removed. On the total version, the entirety of the cartilage is removed, following similar approach to the partial procedure. Total arytenoidectomy may also be performed in an open manner. Both arytenoidectomy and transverse cordotomy yield similar results [17].

Foreign Body Removal

Aspiration of foreign bodies is a condition most commonly encountered in younger children, predominantly male, and constitutes a significant percentage of the cases that present to an emergency unit [19]. Foreign body aspiration can also present to the adult population, most often in the form of accidental hard food particle inhalation [20] (e.g., dry nuts or fish bones). The education of the population to the correct use of the Heimlich maneuver minimizes mortality in cases of acute airway obstruction but must be reserved in cases of partial obstruction, due to the risk of dislodging the foreign object deeper in the airways, causing complete obstruction.

Presentation

The presence of a foreign body in the respiratory system can produce choking of the airways. The introduction of a foreign body in the components of the upper airways may present with coughing, wheezing, dyspnea that might be severe, or even loss of consciousness, as the complete blockade of the upper airway eliminates all airflow to the lungs. Objects of smaller dimensions may also be inhaled or pushed during unsuccessful retrieval attempts further down the airways, into the lower airway components causing bronchial blockage. Anatomically the right bronchus is the most likely site of such event in adults by a big margin, yet not so much in children, whose underdeveloped anatomy presents a more even spread, maintaining the right bronchus as the most common site of aspiration by a slimmer margin (<60%).

Preoperative

The diagnosis of aspiration can present difficulty to the attending doctor since a definitive diagnosis may only be achieved through direct visualization of the object that may require the procedure of rigid bronchoscopy under total anesthesia [21]. Accurate patient anamnesis during the time of the incident, patient consciousness, the patients age, and the location of the inhaled object lead to variation of patient presentations. A patient may present with mild cough or cardiac arrest. Radiopaque bodies can be detected in the traditional chest X-ray but constitute only a minority of the offending objects aspirated. Unilateral airflow decrease auscultated by stethoscope or presented in radiographic findings along with emphysema is indicative of bronchial compromise [22, 23].

Securing adequate airway function is critical, and emergency cricothyroidotomy may need to be performed, prior to transporting the patient to the operating theater to remove the object. Otherwise tracheostomy may be required to facilitate proper anesthesia and oxygenation during the extraction of objects lodged in the larynx.

Complications of inhaled foreign bodies include chronic cough scarring of affected tissues, lung abscess, emphysema and/or edema secondary to obstruction, bronchial rupture or fistula, bronchial stricture, pneumothorax, and mediastinitis.

Procedures

Outpatient Office

Bodies located in the nasal cavity, the nasopharynx, and the oropharynx may be removed with the use of forceps under direct visualization, with the optional assistance of a tongue depressor, only when the patient is conscious and cooperative, to reduce the potentially catastrophic risk of pushing the object toward the hypopharynx and larynx. Before any intervention the patient should first be encouraged to cough aggressively, while assisted by percussive strokes on the back to provoke the forceful exhalation of the offending object.

Laryngoscopy

Bodies lodged in the larynx require the patient to receive total anesthesia. Oxygenation is secured via nasally inserted insufflation catheter that doesn't travel below the hypopharynx. In cases of complete laryngeal blockage, use of a tracheostomy is critical. With a laryngoscope the larynx and the object are visualized, and the object is subsequently removed with the use of a fitting forceps. After a successful removal, careful reexamination of the larynx is undertaken, along with auxiliary rigid bronchoscopy to eliminate the possibility of secondary objects or the primary object fractured.

Bronchoscopy

For removal of tracheobronchial objects, rigid bronchoscopy is required. In such cases the ventilation of the patient is carried out through the bronchoscope itself. Before any attempt is to be made, the patient first needs to be oxygenated with 100% O_2 to compensate for the decreased airflow that is to be expected during any retrieval attempt. The foreign object needs to be visualized and located. The rigid bronchoscope must be laid adjacent to the object that is to be extruded. Careful and gentle suction around the object may be required for better visualization. After the object is grasped, the rigid bronchoscope, the forceps used, and the foreign object are carefully pulled as one entity. After securing the foreign object, the rigid bronchoscope is immediately reinserted to provide oxygenation and examine the possibility of secondary foreign bodies [24].

Sharp object must have their perforating aspects rotated distally when possible to facilitate safety during extraction [25]. Exceptionally sharp objects, like safety pins, may require sheathing of their tip before extraction is attempted, least they became engaged and embedded in the mucosa. Unsuccessful attempts or the foreign object itself can cause inflammation of surrounding tissues that embeds the object into the mucosa. In such cases waiting 48–72 h for the inflammation to subside may be necessary (depending on degree of obstruction), as alternative to potential approach through thoracotomy.

Conclusion

The function of the upper airway is crucial to the act of respiration. Therefore any reduction to the ability of this function may prove life-threatening in short amounts of time. Securing of the airway function to facilitate oxygenation is of paramount importance and a constant concern to the practicing physicians in emergency cases. The procedures of the upper airway are often performed in an emergent state, with patient oxygenation in an unsure state. Procedures that require general anesthesia may further be complicated by the presence of obstruction and the inability to intubate, in order to provide adequate ventilation. The application of these procedures by appropriately trained physicians provides high success rates and low occurrence of complications.

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Sleep Breathing Disorders in Upper Airway Disorders Implications for Noninvasive Ventilation

Júlia Silva and João Portela

Introduction

Sleep is a heterogeneous process that apparently goes through multiple cycles during a given night. These cycles occur in typical non-rapid eye movement (NREM) and rapid eye movement (REM) sleep patterns, with a single cycle lasting approximately 90–120 min [1].

Sleep is a quiet resting period, characterized by a decreased responsiveness, limited movement, a decreased metabolic rate, loss of the wakefulness drive to breathe and a subsequent decrease in ventilatory motor output to upper airway muscle and other respiratory muscles [1, 2].

Sleep breathing disorders can be described as a group of disorders that affect breathing during sleep; they are characterized by abnormal breathing patterns that occur only during sleep [1, 2].

It has been estimated that one of five adults experiences at least some degree of sleep-related breathing disturbance [3].

Sleep breathing disorders can be divided into four groups: obstructive sleep apnea syndrome (OSAS), central sleep apnea syndrome (CSAS), sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder, according to the third edition of the *International Classification of Sleep Disorders* (ICSD) [4].

The Upper Airway

The upper airway is quite complex; it is composed of the nasal and oral cavities, nasopharynx, oropharynx, larynx, vocal cords, and glottis [5].

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Upper airway muscles play a key role in such important orofacial behaviors (food and fluid ingestion, swallowing, sneezing, phonation), including their important role as accessory respiratory muscles [6].

During sleep there is a loss of the wakefulness drive to breathe [2], decreasing the ventilatory motor output to respiratory muscles, including upper airway muscle. This loss of wakefulness makes breathing during sleep dependent on the level of chemoreceptor and mechanoreceptor stimuli [7] and therefore increases susceptibility to upper airway obstruction and central apnea.

Upper airway obstruction can be partial or complete, so it is fundamental to take a complete clinical history and perform a physical exam to determine the etiology of the obstruction and the subsequent management [5], because it can have significant long-term or fatal effects if not treated.

Decreased ventilatory motor output is associated with a reduction in upper airway muscle activity, especially in muscles that display tonic activity (regardless of breathing phase). In the case of the tensor palatine, for example, there is an immediate decrease in activity with the onset of sleep, which is associated with a reduction in inspiratory flow [8, 9].

The glottis is the most affected site of the adult airway and the most common cause of upper airway obstruction in OSAS [5].

Sleep Breathing Disorders (SBDs)

There is a high prevalence of respiratory disorders during sleep phase, which have significant health implications.

In the adult population, the estimated prevalence of SBD can range from 9 to 38% and reach until 49% [10–13].

Male gender, age, ethnicity, genetics, obesity, craniofacial anomalies, alcohol consumption, and smoking are considered increased risk factors for the development of these disorders [13, 14].

In healthy individuals, during sleep, there is a reduced metabolic demand, resulting in lower respiratory and pulse rates and changes in breathing patterns and muscle tone [15], so, typically, slight variations in arterial oxygen saturations occur, a decrease of about 2%, and there's a small increase in partial pressure of carbon dioxide, around 4–6 mmHg [16].

In REM sleep stage, there is a reduction in lung capacity to the lowest level, which makes the upper airways more susceptible to resistance and collapse [16].

This condition can have serious implications in some diseases, such as chronic obstructive pulmonary disease or in neuromuscular patients, since they need the intercostal and accessory muscles to maintain an acceptable level of ventilation [1].

The pathogenesis of SBD remains unclear, in spite of the well-stablished relationship with SBD and an increased risk for cardiovascular morbidity and mortality [17].

Sleep disorders can be divided into obstructive sleep apnea syndrome (OSAS), central sleep apnea syndrome (CSAS), sleep-related hypoventilation disorders, and sleep-related hypoxemia disorder, in which the most common are OSAS and CSAS [4].

Obstructive Sleep Apnea Syndrome (OSAS)

The prevalence of adult OSAS in industrialized countries is about 3–7% [11]; however, it is known that still it is an undiagnosed situation.

This condition affects predominantly middle-aged and elderly males [18, 19], and it is characterized by obstructive apneas, hypopneas, and/or respiratory effort caused by repetitive collapse of upper airway during sleep.

OSAS is most common among older males, but the incidence rises following menopause such that rates are similar in postmenopausal individuals [20].

The physiopathology of OSAS is multifactorial; in this condition a collapse of the upper airway occurs in association with multiple factors like gender, race, obesity, and upper airway dimensions [11].

Obstructive sleep apnea is a common disorder of repetitive pharyngeal collapse during sleep, which may be complete (causing apnea) or partial (causing hypopnea).

Oxygen desaturation, hypercapnia, and sleep fragmentation may occur due to disturbances in gas exchange, which contribute to the increase in cardiovascular, metabolic, and neurocognitive effects [21].

OSA is defined broadly as an apnea-hypopnea index (AHI) ≥ 5 events per hour plus symptoms or AHI ≥ 15 events per hour [2].

OSAS may lead to cognitive dysfunction and excessive daytime sleepiness, which are risk factors for driving and workplace accidents [21, 22]. It is through these indirect effects that OSAS represents a global health problem [21] and may cause premature mortality.

Treatment Options for Obstructive Sleep Apnea Syndrome

OSAS can increase the cardiovascular risk (stroke, hypertension, atrial fibrillation, myocardial infarction) and even pulmonary hypertension, so its treatment is fundamental [21].

Pharmacological and non-pharmacological measures should be used for its adequate management and treatment.

Continuous positive airway pressure (CPAP) is the gold standard treatment for OSAS, because it decreases the apnea-hypopnea index (AHI) and improves overall health and metabolic parameters.

The use of CPAP stabilizes the upper airway through increased end-expiratory lung volume and maintains a positive pharyngeal transmural pressure so that the intraluminal pressure exceeds the surrounding pressure [21].

The most commonly used PAP modes include continuous positive airway pressure (CPAP), auto-titrating CPAP (APAP), and bi-level (BiPAP). Many clinicians prefer to use CPAP as initial therapy, but generally the APAP mode is being used more.

Some patients, particularly those with expiratory pressure discomfort, prefer to use BiPAP as it may help in relieving expiratory pressure; however several clinical trials have not shown any significant benefit compared to continuous positive airway pressure [23].

It is also possible to use APAP, which seems to be beneficial in some patients who need different pressures according to sleep stage or posture; however some studies suggest that auto-titrating positive airway pressure has worse results, apparently because changes in intrathoracic pressure lead to sleep arousal and hemodynamic instability [24].

Some patients have poor adherence to PAP therapy, due to the discomfort of using them. In those cases it is possible to use positional oral appliances (such as mandibular advancement devices); others may be candidates for surgery such as tonsillectomy or adenoidectomy [25].

There are also some patient diagnoses with positional OSAS; these kinds of patients have upper airway obstruction during sleep in supine position; this condition can be improved if the patient sleep in a non-supine position, and there are many commercial devices to prevent it [26].

However, this option should not be used as primary therapy [26] and should be reviewed on a case-by-case basis. Non-pharmacological measures include patient's education, weight loss and exercise, promotion of a good sleep hygiene, and avoiding caffeine and alcohol before bedtime [27].

OSA treatment aims to improve sleep quality and normalize the apnea-hypopnea index, with a consequent reduction in healthcare costs, decrease cardiovascular morbidity and mortality, and improve quality of life [28].

Central Sleep Apnea Syndrome (CSAS)

CSAS is a sleep breathing disorder characterized by a lack of drive to breathe during sleep, which results in repetitive cessation or decrease of airflow and ventilatory effort [4].

CSA is less prevalent in the general population than OSA. In a population-based study of adults aged ≥40 years, the overall prevalence of CSA on PSG was 0.9% [29].

Central sleep apnea describes the pattern of an individual event and the clinical disorder characterized by repeated episodes of apnea during sleep resulting from the temporary suspension of ventilatory effort [30].

A central apnea is defined as a period of at least 10 s without airflow due to absence of evident inspiratory effort, which often produce arousals from sleep, which can lead to difficulty sustaining sleep and to daytime somnolence [29].

CSAS results from a decrease in $PaCO_2$ to a level below the apnea threshold during sleep, through the reflex inhibition of central respiratory drive.

Diagnosis of central sleep apnea generally requires a full-night polysomnographic evaluation, ideally including measurement of esophageal pressure.

The CSA comprises many different disorders, and criteria for diagnosis of a CSA vary according to the pathology:

1. Central sleep apnea with Cheyne-Stokes breathing
2. Central sleep apnea due to a medical disorder without Cheyne-Stokes breathing
3. Central sleep apnea due to high-altitude periodic breathing
4. Central sleep apnea due to a medication or substance
5. Primary central sleep apnea
6. Primary central sleep apnea of infancy
7. Primary central sleep apnea of prematurity
8. Treatment-emergent central sleep apnea [4]

Treatment Option for Central Sleep Apnea Syndrome

The treatment of CSAS must be individualized and directed, as much as possible, toward the underlying cause of the ventilatory instability, which may result in CSA improvement (i.e., opioids use, neurological disorder, heart failure).

CSAS treatment aims to normalize sleep breathing patterns, normalize AHI and avoid oxygen desaturations, decrease daytime symptoms, and improve quality of sleep [21].

CPAP can be used in the majority of CSAS patient, because it may decrease the central apnea frequency. There is no evidence of an ideal starting pressure, so its titration is useful to determine the minimal pressure required to solve respiratory events, which should be performed in a laboratory setting with polysomnographic monitoring.

For patients with hypoxemia during sleep, the use of supplemental oxygen may be used as an adjuvant therapy, or it can be used in patients who do not tolerate the use of PAP therapy [21, 22].

Sleep-onset central apneas do not require treatment unless they are frequent and result in desaturation or repetitive arousals.

Central sleep apnea with Cheyne-Stokes breathing is best managed with CPAP or in combination with adaptive servoventilation.

Idiopathic central sleep apnea and high-altitude periodic breathing often respond to oxygen or acetazolamide.

Complex sleep apnea often improves over time with consistent CPAP use. Hypercapnic respiratory failure usually requires noninvasive nocturnal ventilation. Thus, the cause of breathing disorder must be clarified, to optimize management and treatment.

In patients with CSA due to neurological disorder or use of respiratory depressant drugs, the first-line therapy is BiPAP.

Sleep-Related Hypoventilation Disorders

Sleep-related hypoventilation disorders are characterized by the presence of hypoventilation. This is defined by the American Academy of Sleep Medicine (AASM) as the presence of one of the following criteria during sleep: an increase in the arterial $PaCO_2$ > 55 mmHg for ≥10 min and a ≥ 10 mmHg increase in $PaCO_2$ during sleep (in comparison to an awake supine value) to a value >50 mmHg for ≥10 min [24].

Sleep-related hypoventilation disorders consist in a vast group, which can be divided into the following pathologies:

1. Obesity hypoventilation syndrome (OHS)
2. Congenital central alveolar hypoventilation syndrome
3. Late-onset central hypoventilation with hypothalamic dysfunction
4. Idiopathic central alveolar hypoventilation
5. Sleep-related hypoventilation due to a medication or substance
6. Sleep-related hypoventilation due to a medical disorder [1]

OHS is the most common of this group and will be discussed separately.

Obesity Hypoventilation Syndrome (OHS)

OHS is defined as the presence of awake alveolar hypoventilation in an obese individual which cannot be attributed to other conditions [4].

Diagnosis criteria requires a daytime elevation of $PaCO_2$ (>45 mmHg) in a patient with a body mass index [BMI] >30 kg/m^2, as well as no other underlying cause for hypoventilation (i.e., medications, neuromuscular disease, lung disease, deformities of chest wall) [4].

This disorder is associated with increased cardiovascular morbidity and mortality, so it is essential for an early detection and treatment to decrease these adverse effects.

The major risk factor for OHS is obesity (BMI >30 kg/m^2), in particular, severe obesity (BMI >50 kg/m^2); in this case, prevalence may be as high as 50%.

The clinical manifestations of OHS are nonspecific and reflect the manifestations of obesity, coexistent OSA (present in 90% of OHS), or OHS-related complications (e.g., pulmonary hypertension).

PSG with continuous nocturnal carbon dioxide monitoring is the gold standard for the evaluation of patients suspected of OHS.

Obesity Hypoventilation Syndrome Treatment

All patients with OHS should make lifestyle modifications to lose weight, because it may improve alveolar ventilation, reduce the risk of cardiorespiratory complications, improve nocturnal oxyhemoglobin saturation, decrease the frequency of respiratory events, and improve pulmonary function.

Noninvasive positive airway pressure (PAP) together with weight loss are the initial first-line therapies for patients with OHS.

The majority (90%) of OHS patients has coexisting OSAS; in such cases CPAP is the first-line therapy, except those who fail or do not tolerate CPAP; these can also be treated with BiPAP [31].

In patients with OHS and sleep-related hypoventilation, usually the initial mode of choice is BiPAP. For those who fail or do not tolerate BiPAP, they may use a hybrid mode like average volume-assured pressure support (AVAPS) or, less commonly, volume-cycled ventilation.

Some studies reported a reduction of sleep-related and awake arterial carbon dioxide tension ($PaCO_2$) as well as quality of life improvements after the initiation of CPAP, although normalization of $PaCO_2$ is not universal.

Sleep-Related Hypoxemia Disorder

There are many lung diseases that can cause or exacerbate abnormal breathing due to hypoventilation or hypoxemia. The most common are chronic obstructive pulmonary disease (COPD) and asthma but also interstitial lung diseases [31].

COPD is usually associated with OSA, CSA, breathing problems, and sleep-related hypoventilation and hypoxemia in up to 40% of patients.

The prevalence of nocturnal hypoxemia increases proportionally to disease severity and is defined by a reduction in PaO2 > 10 mmHg or an SpO2 < 88% over a period longer than 5 min [32].

Thus, polysomnographic study with nocturnal pulse oximetry (in asymptomatic patients) is important to diagnose this sleep-related hypoxemia [32].

Treatment Options of Sleep-Related Hypoxemia Disorders

After excluding other SBD, the treatment of sleep-related hypoxemia is guided by the severity and duration of hypoxemia and associated clinical features.

The use of nocturnal oxygen supplementation varies around the world, but according to Medicare, the criteria are as follows:

1. $PaO_2 \leq 55$ mmHg or $SpO_2 \leq 88\%$
2. Associated symptoms or signs reasonably attributed to hypoxemia (erythrocytosis, pulmonary hypertension, impaired cognition, morning headaches)
3. Decreased in $SpO_2 > 5\%$ for at least 5 min during sleep
4. Absence of another cause of sleep-related hypoxemia

The supplemental oxygen is supplied by nasal cannula at a flow rate sufficient to maintain the $SpO_2 > 90\%$ [33, 34]

The effectiveness of oxygen use is highly proven; however, the risk of hypoventilation cannot be eliminated with supplemental oxygen, as about 20% of patients may worsen hypoventilation during sleep, although increased CO_2 rarely results in

hypercapnia or acidosis in the morning. Still, in some patients, the use of BiPAP may attenuate the worsening of hypoventilation [35].

So, it is essential to diagnose SBD as early as possible, in order to reduce the associated morbidity and mortality, not neglecting an appropriate management and treatment for each clinical condition and respecting and taking into account the individual characteristics of each patient.

It is very important to promote continued research in this area in order to find viable alternatives for the treatment of these patients, many of whom have multiple comorbidities that can affect treatment adherence. Recent studies showed that high-flow nasal cannula (HFNC) with or without supplemental oxygen can assist ventilation of patients with chronic respiratory and sleep disorders, which may be an alternative treatment for patients intolerant of CPAP [36].

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Swallowing Disorder and Upper Airway Relationships During Noninvasive Ventilation

Mehmet Yasir Pektezel and Leyla Das Pektezel

Introduction

Swallowing is a complex process that needs to be regularly coordinated [1]. Although it is consciously started, only a few stages of swallowing can be voluntarily controlled [1]. The brain stem consisting of crucial cranial nerves such as facial, glossopharyngeal, and vagal nerves is the most fundamental area while this reflex is being achieved [2]. A lot of physiopathological disorders involving the brain stem, its extensions, and/or the route from mouth to stomach might cause dysphagia [1]. Causes of dysphagia are detailed in Table 1.

The process of swallowing is divided into two stages as oropharyngeal and esophageal phases [1]. Especially, oropharyngeal dysphagia puts the patients at risk by not only having the patient immunocompromised secondary to weight loss, malnutrition, and sarcopenia [3] but also giving rise to aspiration pneumonia which might be seen up to two-third of patients with dysphagia [4].

Because the relationship between esophageal dysphagia and noninvasive mechanical ventilation is not the scope of the chapter, only oropharyngeal causes of dysphagia will be further discussed in ongoing pages.

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Table 1 Causes of dysphagia

Nonstructural
Oropharyngeal dysphagia
Cerebral cortical/subcortical disorders
Stroke
Dementia (Alzheimer, Parkinson, Huntington, vascular, normal pressure hydrocephalus)
Amyotrophic lateral sclerosis
Brainstem/cerebellar disorders
Motor neuron diseases: Kennedy's variant
Motor neuron diseases: Fazio-Londe/Violetti syndromes
Multiple sclerosis
Guillain-Barre: Miller Fisher variant
Neuromuscular junction disorders
Myasthenia gravis
Muscular disorders
Dermatomyositis/polymyositis
Other myopathies (LGMD, dystrophinopathies, OPMD, MD, etc.)
Esophageal dysphagia
Gastroesophageal reflux disease
Functional esophageal disorders
Structural conditions
Esophageal stricture
Foreign body
Malignancy
Schatzki ring
Esophageal motility disorders
Achalasia
Diffuse esophageal spasm
Jackhammer esophagus
Infection
Candida esophagitis
Cytomegalovirus esophagitis
Herpes simplex virus esophagitis
Rheumatologic conditions
Systemic sclerosis
Structural disorders
Non-oral disorders
Head/neck cancer
Radiation
Zenker diverticulum/cricopharyngeal bar
Goiter
Pharyngeal/parapharyngeal abscess
Oral disorders
Poor dentition
Dry mouth

Noninvasive Ventilation Use in Swallowing Disorders

Noninvasive mechanical ventilation might be used in swallowing disorders by various different purposes. For instance, respiratory distress occurring secondary to aspiration pneumonia is mostly the main factor for using noninvasive mechanical ventilation in patients with degenerative cerebral/cerebellar diseases [1, 4], while supporting failed muscular chest power becomes the primary driving factor in patients with neuromuscular disorders [5]. Furthermore, its use is of importance, while a support for compensating the increased resistance through oro(naso)pharyngeal/hypopharyngeal area is needed especially in patients with structural involvements [6, 7].

Different uses of noninvasive mechanical ventilation related to swallowing disorders, which are the scope of the chapter, mostly include pneumonia occurring secondary to dysphagia; thus it will be reviewed by major examples of the categories divided as structural and nonstructural disorders (Table 1).

Nonstructural Disorders

Stroke, myasthenia gravis, and Guillain-Barre syndrome are handled as major diseases of nonstructural disorders.

Dysphagia might accompany up to 78% of patients with stroke, and it is a very close problem to stroke-associated pneumonia, which is seen in 14% of all stroke patients [4]. About 20% of patients with myasthenia gravis experience a myasthenic crisis [5]. Although supporting failed muscular chest power becomes the primary driving factor for using noninvasive mechanical ventilation in these patients, still a failure might be seen in up to 60% of patients with myasthenic crisis [7]. Dysphagia can accompany almost all patients with myasthenia gravis unless treated [8], and thus aspiration pneumonia accompanies nearly 30% of patients with myasthenia gravis [5]. On the other hand, in Guillain-Barre syndrome, the status is a little bit different. Due to the fact that supporting failed muscular chest power is not the same as in myasthenia gravis, extreme caution should be provided before the decision of using noninvasive mechanical ventilation in these patients. Still, pneumonia may occur in almost 40% of patients being followed secondary to Guillain-Barre syndrome independent of the type of mechanical ventilation (either invasive or noninvasive) [9]. Noninvasive mechanical ventilation can be applied to those patients if they are suitable according to criteria summarized in Table 2 [10, 11].

Table 2 General factors should be prompted before commencing noninvasive mechanical ventilation

Acceptable mental status (mostly a Glasgow Coma Scale (GCS) of greater than 9)
Cooperation of patient
Supporting a fractional O_2 level of lesser than 0.6
Intact medulla oblongata (brainstem) function
No obstacle on face interrupting noninvasive mask use
A pulmonary compliance providing an acceptable alveolar tidal volume with an IPP (inspiratory positive pressure) of lesser than 40 cm-H_20

Due to the fact that lack of certain benefit regarding noninvasive mechanical ventilation use in community-acquired pneumonia is a confusion [12], noninvasive mechanical ventilation should be cautiously used in patients with pneumonia occurring secondary to abovementioned disorders. An objection, which has to be kept in mind is that pneumonia is not the only cause respecting respiratory failure seen in this population, however pulmonary edema, respiratory distress syndrome, venous thromboembolism, etc. may also become important offending causes which must not to be neglected [13].

Structural Disorders

Noninvasive mechanical ventilation use differs from the abovementioned group by especially its palliative side and only a bridging therapy while an invasive respiratory pathway is being prepared [6].

Structural diseases occupying space through the oro(naso)pharyngeal/hypopharyngeal area might cause dysphagia in a wide range of patients, depending on its localization [7]. It is reported that a third of patients with tongue cancer show dysphagia [14]. On the other hand, aspiration pneumonia can be seen in 21% of patients with head/neck masses [15]. As in other nonstructural diseases, noninvasive mechanical ventilation is able to be used with caution in either population.

Key Messages

- Aspiration pneumonia, supporting failed muscular chest power, and compensating the increased resistance through oro(naso)pharyngeal/hypopharyngeal area are the main factors for using noninvasive mechanical ventilation in patients with swallowing disorders.
- Noninvasive mechanical ventilation should be cautiously used in patients with swallowing disorders.

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Monitoring Upper Airway Disorders and Noninvasive Ventilation Approach Pulse Oximetry and Capnography

Jaritzy Lagunez Caramon

Introduction

Noninvasive ventilation programming includes the clinical context of the patient, comfort, tolerance of the interface, respiratory rate, capnography, pulse oximeter, and finally, the most invasive, the gold standard for the monitoring of gases, arterial blood gas [1]. Noninvasive ventilation programming should be based on the results obtained from arterial gases. They must be extracted several times a day, due to changes in ventilatory patterns that modify the current volume [2].

Ventilatory monitoring performs a continuous evaluation of the patient to guide medical treatment. No monitoring saves life but the actions that are taken when you get the results of the same [3].

In the critical patient, alterations in gas exchange occur frequently. This can threaten the well-being of the same person. Monitoring identifies this type of disorder to give an immediate solution and avoid complications [4]. It must be established from the beginning of noninvasive mechanical ventilation until its withdrawal. The objective is to monitor the dead space, including the identification of disconnections, hypoventilation, obstruction of the airways, and cardiopulmonary resuscitation, among others. This is where its significance resides [5].

The Reliable Oxygen Monitor: Pulse Oximetry

Pulse oximetry is a commonly used noninvasive technique for monitoring oxygen saturation in the blood [6]. It is the gold standard for clinical monitoring; a cheap and easy to use instrument, it measures the saturation of hemoglobin in real and

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continuous time, through the spectrograph mechanism; it is a very useful tool in the programming of the ventilator and the inspiration fraction of oxygen. However, when this is overcome, oxygenation problems can be hidden [7]. The oxygen transported in the arterial blood is reversibly bound to the hemoglobin molecules. This can adsorb light. The pulse oximeter emits various wavelengths, red light and infrared, to differentiate between oxygenated and deoxygenated hemoglobin [8] (oxyhemoglobin and deoxyhemoglobin). As a result, it will give the percentage of oxygenation [9].

The dissociation curve of oxyhemoglobin is manifested in a sigmoidal way until the PO_2 reaches 80 mmHg or more and the SPO_2 is maintained at 100%, but even though the partial pressure of oxygen increases, the SPO_2 will not be modified, so that in pulse oximetry an evaluation cannot be obtained after the complete saturation of hemoglobin; it cannot detect hyperoxia.

Plethysmography is graphed with a systolic wave and a second diastolic wave, secondary to the pulsatile component of the absorption of light from arterial blood and examined tissues, plus venous blood volume. These are related to systemic vascular resistance and local perfusion [10] (Fig. 1, plethysmography wave).

In the presence of dis hemoglobinemia, carbon monoxide poisoning, or methemoglobinemia, SPO_2 values are overestimated. In patients with alterations of the base acid or alveolar ventilation, SPO_2 could be normal if you have an extra supply of oxygen. Low cardiac output directly affects peripheric tissue perfusion even though oxygen saturation by pulse oximetry is normal [8].

The efficiency of noninvasive ventilation is based on the results of arterial gas measurements and the clinical behavior of the patient while this therapy is established. In its diurnal phase, in the nocturnal phase, pulse oximetry and transcutaneous capnography are useful. In a clinical way, obstruction can be observed with an increase in respiratory effort, being suggestive of obstruction of the airway [11].

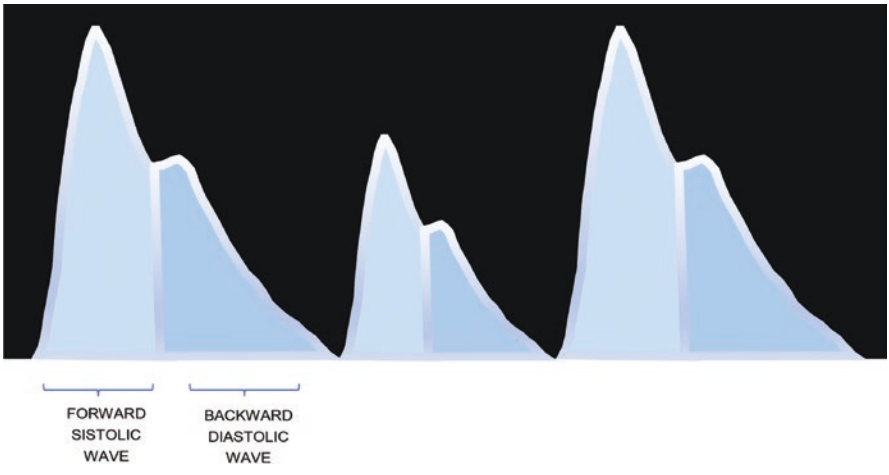

Fig. 1 Plethysmography wave [10]

Monitoring of plethysmography allows paradoxical pulse recognition, which correlates with airway obstruction [12].

The respiratory rate in an adult is 12–20 breaths per minute and varies according to the context of the disease and clinical state. The presence of tachypnea may indicate hypoxia, acidosis, agitation, pain, etc. Bradypnea or decreased respiratory rate (<12 breaths per minute) is indicative of hypoxia or alteration of neurological status. When complemented with plethysmography and capnography, a comprehensive evaluation can be carried out; variations in respiratory pattern can be identified and pathological states detected [13].

The pulse oximeter does not give exact measurements and, for the improvement in the result, should adhere to the specifications issued by the manufacturer and continuously evaluate its operation at least every 2 years for the improvement in accuracy. You should objectively interpret the results and be aware that SPO_2 does not necessarily reflect the supply of oxygen to the tissues [8].

Capnography in Noninvasive Mechanical Ventilation

Capnography is the graphic interpretation of the partial pressure of CO_2 as a function of time or volume. Graphs can identify alterations at the level of the respiratory tract, such as obstruction, apnea, return of spontaneous circulation, and patient exertion [4]. The fractional concentration of CO_2 is shown on the graph-dependent axis and is proportional to the time of the exhaled volume [14].

The capnograph is a CO_2 monitor that displays the numerical value and waveform, plotting the change in CO_2 concentration during the respiratory cycle over time [15] (Fig. 2, time-based capnography).

In noninvasive capnography, the interface of the oral-nasal cannula is used, which allows CO_2 sampling and the supply of low-flow O_2. Increased $EtCO_2$ can identify hypoventilation, tube obstruction, and patient strain [16] (Fig. 3,

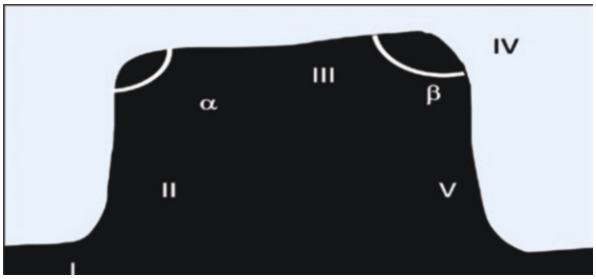

Fig. 2 Time-based capnography. (I) Baseline, CO_2 from zero, start of expiration. (II) Transition phase, increased CO_2, mixture of alveolar gas and dead space. (Angle α) Change from transition gas to alveolar gas. (III) Alveolar gas or alveolar plateau. (Angle β) Change from exhalation to inspiration. (IV) CO_2 at the end of expiration. (V) Rapid decrease in CO_2 and onset of inspiration [4, 14, 15]

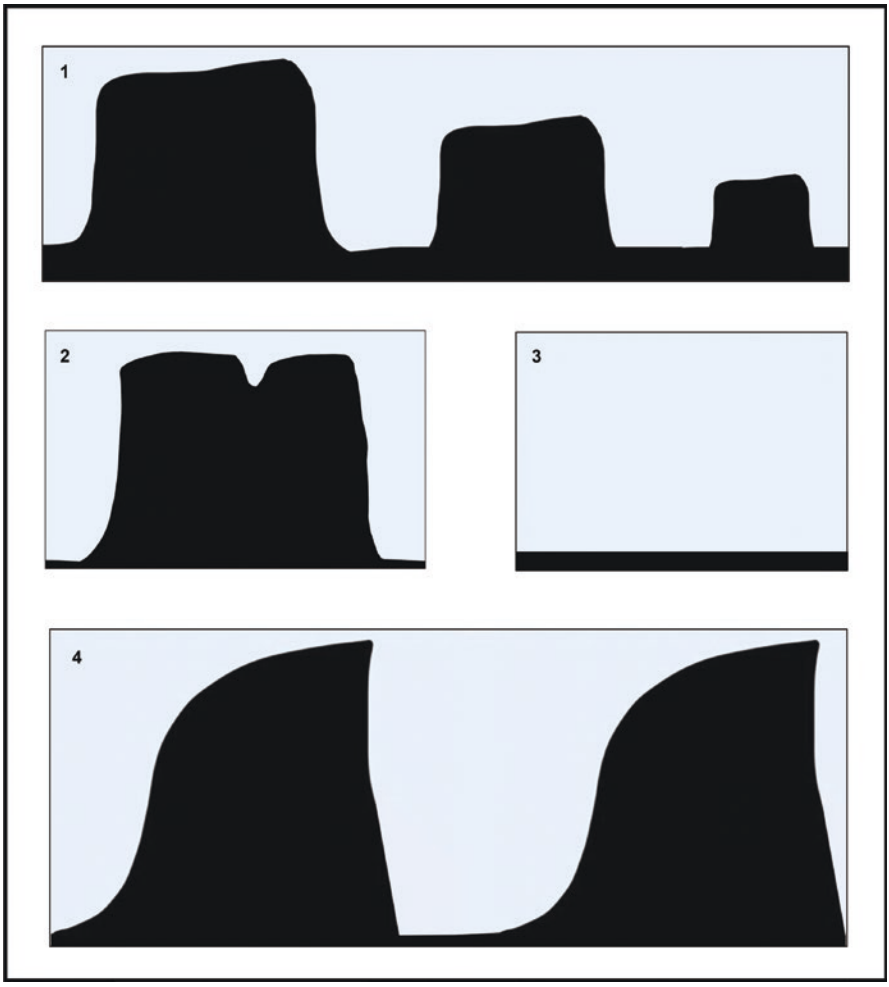

Fig. 3 Capnography disorders. (1) Hypoventilation, (2) patient effort, (3) disconnection of the circuit, (4) airway obstruction, bronchial spasm [16]

capnography disorders). Bohr's definition refers to the measurement of physiological dead space.

Volumetric capnography dynamically represents the elimination of CO_2 and allows knowing the ventilatory efficiency to monitor mechanical ventilation [17] (Fig. 4, volumetric capnography).

The anesthesiologist Bjørn Ibsen described that the increase in arterial CO_2 was secondary to the reduction of alveolar ventilation. This theory was confirmed by finding acidosis in the Ph measurements, a basic discovery to determine that positive pressure increases alveolar ventilation and reduces PCO_2 values.

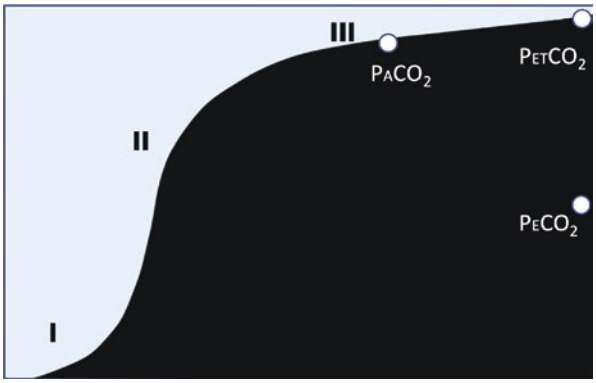

Fig. 4 Volumetric capnography is schematized in a graph in which 3 phases can be appreciated: phase 1, the emptying of the anatomical dead space is observed; the exhaled CO_2 is close to zero. Phase 2 represents the mixture of gas from anatomical dead space and alveolar gas containing CO_2. Phase 3 means the emptying of the alveoli or alveolar plateau [17]

The difference between $PetCO_2$ and $PaCO_2$ is approximately 2–5 mmHg of $petCO_2$ due to alveolar dead space [18]. Alveolar ventilation can be known by obtaining the measurement of $PaCO_2$ in arterial blood, to estimate the effectiveness of ventilation. There are noninvasive ways to monitor CO_2 and measure final expiratory carbon dioxide ($PetCO_2$) and cutaneous carbon dioxide ($PcCO_2$). In patients undergoing noninvasive mechanical ventilation, leaks must be avoided for the $PetCO_2$ measurement to be reliable, or skin measurement must be used [19].

Dilution of exhaled gas by the ventilator in noninvasive mode can affect the accuracy of the $PetCO_2$ measurement.

Therefore, enough gas must reach the cell to exert the measurement before positive expiratory pressure reaches it. Transcutaneous monitoring of carbon dioxide and oxygen is performed with a sensor fixed to the skin and that radiates heat to vasodilate the capillaries and facilitate the diffusion of gases. $PtcCO_2$ and $PtcO_2$ provide estimates of $PaCO_2$ and PaO_2, respectively; measurements may be overestimated due to sensor site metabolism and other factors [9].

Systems have been designed with nasal adapters that avoid erroneous measurements secondary to the continuous flow of oxygen, performing CO_2 monitoring while it is supplied [20]. In patients with noninvasive mechanical ventilation, the measurement of CO_2 exhaled by the structure of the therapy is difficult. Specific characteristics of patients, oral ventilators, obesity, and erroneous measurements can be found. The use of nasal cannulas with oral guides for the measurement of CO_2 is currently being studied. Studies are in the process of development to find the best way to measure it [21].

Conclusions

Monitoring is essential in patients with noninvasive mechanical ventilation. It must be maintained throughout the ventilatory therapy to identify complications and the support devices, capnograph and pulse oximetry completed with clinical data, to avoid errors in interpretation.

The results can be improved, avoiding difficulties on the part of the operator, making a timely diagnosis of anomalies in the airway and pathologies that could endanger the patient's life, without forgetting that they are friendly elements, easily accessible, mostly portable, and within reach of almost all hospital centers.

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Diagnosis and Evaluation of Upper Airway Disorders in Noninvasive Ventilator Support: Endoscopy Evaluation

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Introduction

As noninvasive ventilation (NIV) is the application of ventilator support using the natural airway defined. The efficacy of NIV can be greatly affected by the anatomy and coexisting abnormalities or dysfunction of the upper airway structures. More specifically, the upper airway's patency and elasticity or spasticity play a predominant role in the ventilatory support achieved through the application of NIV. In addition, pathophysiological changes of the upper airways function can be caused by certain body positions, obesity, sedation, and exercise. Characteristic examples are the obstructive sleep apnea syndrome (OSAS) and the obesity hypoventilation syndrome (OHS) [1]. Endoscopic evaluation of such patients can be key in deeply understanding the pathophysiological mechanisms that are at play in such patients and, hence, optimizing their treatment [2]. Moreover, chronically ventilated patients with persistent upper airway obstruction or restrictive respiratory disorders may benefit from endoscopic evaluation through its contribution in the identification of the mechanisms of the underlying disorders, although the currently published information on this topic are scarce and the indication of endoscopy in those patients is currently on debate.

Endoscopy Evaluation in Patients with OSAS

As already state above, the pathophysiological mechanisms of reduced upper airway patency involve both the skeletal and the soft structures of the anatomical region. In patients with obstructive sleep apnea syndrome (OSAS), the collapse of

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the soft palate or other upper airway structures is recurrent and characteristically exacerbated when the patient is asleep and in the supine position. Apart from anatomical abnormalities, other contributing factors include insufficient respiratory central control and reduced activity of the laryngeal dilatator muscle. Special mention should be made in regard to obesity as a risk factor in the development of OSAS, mainly due to increased volume of the upper airway soft tissues [3]. The severity of the disease is frequently measured by the apnea-hypopnea index, which is the number of incidents of apnea or hypopnea during 1 h of sleep. The endoscopic evaluation, however, especially when sleep induced, offers a more accurate assessment of the grade of the reduction of the upper airway diameter and can detect the anatomical site of obstruction. Studies of drug-induced sleep endoscopy (DISE) in patients with OSAS have revealed that the obstruction of the upper airway can be due to the collapse of various structures (epiglottis, soft palate, lateral pharynx wall, base of the tongue) or a combination of those. More specifically, DISE has identified the collapse of the epiglottis in 12–30% of the cases [2]. In addition, it has been shown that epiglottis collapse responds to positional therapy, while tongue base obstruction occurs frequently in the non-supine position [4]. Endoscopy contributes also to the appropriate choice of an interface, while evaluating directly the effect of each mask to the airway patency correspondingly [5].

Endoscopy Evaluation in Patients with ALS

Patients suffering from ALS often experience UA obstruction caused by upper motor neuron dysfunction and impairment of the bulbar function. This, in turn, leads to spasticity of the UA structures, significantly reducing the effectiveness of NIV in some cases. The negative prognostic impact of persisting obstructive events and the consequential hypoventilation have been proven [6]. Andersen et al. studied the impact of the different levels of pressures provided by mechanical insufflation-exsufflation (MI-E) in patients with ALS with different levels of bulbar involvement [7]. The authors showed that even slight changes in pressure levels produced significant reduction of the laryngeal diameter that could be avoided with stricter regulation and appropriate adjustment of pressure settings. Azkona et al. determined in a prospective study that in 6% of the cases studied with ALS evaluated by dynamic endoscopy, the application of NIV alone caused laryngeal obstruction, while patients with bulbar involvement where more prone to UA obstruction both spontaneously and while receiving NIV [8]. While endoscopy is not routinely part of the evaluation of the UA of patients with ALS receiving NIV, patients with bulbar involvement demonstrating severe residual obstruction events could greatly benefit by the adjustment of ventilation settings after endoscopic evaluation.

Endoscopic Evaluation in Patients Treated with NIV Support

The data in the literature regarding the study and more specifically the endoscopic evaluation of the upper airway in patients treated with NIV support is scarce. The efficacy of NIV can be greatly affected by disorders of the upper airway compromising the airway patency. Endoscopic evaluation of the upper airway in patients receiving NIV support can provide important information regarding the possible causes of residual obstructive events or persistent hypoventilation, the possible soft tissue collapse location, and the role of the body position and, hence, contribute to the selection of the most appropriate interface mask for each patient. Although it has been shown that obstructive or hypoventilation effects that result in hypoxia have a significantly negative prognostic impact, little research can be found on the underlying pathophysiological mechanisms and the role of the endoscopy in their identification.

Among the proposed pathophysiological dysfunctions responsible for such events are the collapse of the soft palate, obstruction at the tongue base or at the level of the epiglottis [2]. Ventilator settings can also affect the patency of the upper airway. Recent studies have shown that patient-ventilator asynchrony is associated with decreased diameter of the glottis, which in turn increases upper airway resistance. Suboptimal synchronization between the ventilator support and the patient's neural drive and upper airway muscle movement has been associated with significantly reduced efficacy of the ventilation and prolonged treatment with NIV [9]. The effect of NIV on the constrictor and dilator muscles of the glottis has been studied by Moreau-Bussière et al. on nonsedated lambs [10]. The researchers showed that when pressure support during NIV was applied, the activity of the cricothyroid muscle (dilator) disappears and that of the constrictor muscle (thyroarytenoid) increases, therefore causing a decrease of the glottal diameter and reduced ventilation.

A similar response in humans has been shown in some studies where the researchers exposed normal subjects to NIV and then monitored the patency of the glottis and the effects on airway resistance. Rodenstein et al. monitored the effects of NIV on the upper airway patency through fiber-optic bronchoscopy and showed the glottic aperture decreased proportionally to the increase of the positive pressure support applied [11]. Though limited data can be found in the literature, it is indicated that endoscopy can provide critical information in determining the upper airway patency in patients receiving NIV and contribute to optimizing the ventilation parameters and, therefore, the ventilation efficacy.

Endoscopy: Setting the Indication for Surgical Treatment

Upper airway video endoscopy may also be useful in setting the indication for operative treatment patients with upper airway obstruction. The flexible pharyngoscopy with Müller maneuver was first introduced by Sher et al. as a diagnostic tool in the

selection of patients eligible for uvulopalatopharyngoplasty. During the Müller maneuver, the patient attempts to inhale with his mouth and nostrils closed, which causes the airway to collapse. The process is monitored via flexible fibroscopy of the pharynx to identify the collapse of the airway and isolated weakness spots [12]. Drug-induced sleep endoscopy (DISE) has more recently been proposed as a valuable method in the selection of patients for surgical treatment of upper airway obstruction.

The technique includes the administration of a sedative agent that should ideally stimulate natural sleep without affecting the upper airway collapse. Such an ideal sedative agent does not yet exist, but most commonly propofol, midazolam, and dexmedetomidine are being used [13]. Issues have been raised in the literature concerning the assessment of the information obtained from DISE, as drug-induced sleep is not identical to the natural sleeping process. The update on the European position paper on DISE, published in 2017, indicates the use of this method in patients with socially disturbing snoring and OSAS not eligible for or not tolerating continuous positive airway pressure (CPAP) therapy and in patients where CPAP therapy and surgery have previously failed [14].

There is constant development in the field of endoscopic evaluation of the upper airway. De Vito et al. compared in a prospective randomized controlled study the conventional DISE to the target controlled infusion sedation endoscopy (TCI-DISE), where a manual bolus injection of the sedative agent is administered to induce with increased accuracy snoring and obstruction patterns comparable to natural sleep. A complete apnea event was recorded in 30% of the patients in the DISE group compared to 81% in the TCI-DISE group. The authors proposed the use of the TCI-DISE technique as method of first choice in patient selection for surgical treatment as it proved more accurate and safer [15]. Other techniques that are currently under research are awake procedures, such as fiber-optic nasopharyngoscopy with modified Müller maneuver, nasal snoring endoscopy, and oral snoring endoscopy [16]. In some studies, the results where promising and comparable to those obtained from the DISE technique [17]. However, more data is required regarding the techniques' accuracy in predicting the level and grade of the airway collapse and their effectiveness as a diagnostic tool in patient selection for surgical therapy.

Classification Systems

Some objective classification systems for the evaluation of the endoscopic findings have been proposed. De Vries et al. introduced the VOTE classification aiming to objectively describe the endoscopic findings during drug-induced endoscopy of the upper airway. The VOTE classification evaluates the degree of obstruction and the configuration of the obstruction related to the most commonly involved structures in the upper airway collapse. The structures included in the classification are the velum, the tongue base, the oropharyngeal lateral walls, and the epiglottis [18]. Although the VOTE classification is commonly used among physicians, no consensus has been reached regarding the use of one specific classification system, but it is

strongly recommended that the level, degree, and configuration of the obstruction are evaluated [14]. The assessment of the nose, nasopharynx, and glottis is not of the highest priority in adult patients, but no agreement has been reached on the exact structures that should be individually assessed or the number of levels that should be described during the endoscopic evaluation. As to the severity of the obstruction, it has been graded by some systems with only three degrees of obstruction, while others apply the use of percentages to more precisely evaluate the degree of the obstruction. Regarding the configuration, agreement has been reached on the three forms of obstruction: anteroposterior, lateral, and concentric.

Use of NIV During Endoscopic Evaluation of the Upper Airway

Endoscopic procedures for the evaluation of the upper airways are frequently performed in patients with reduced respiratory reserve due to the underlying condition. Important reference should be made to the use of simultaneous noninvasive ventilatory support during the performance of such procedures to prevent the development of hypoxia and respiratory failure in patients at high risk. In addition, the development of such symptoms often leads to interruption of the procedure before obtaining the necessary diagnostic information, which can be prevented with the use of NIV [19].

Periprocedural NIV has been used to improve oxygenation and avoid general anesthesia. Thanks to technological advancements, new masks that allow the insertion of an endoscopic probe for diagnostic purposes or even the conduction of interventional procedures are now available [20]. Routinely, the parameters that are closely monitored for patients treated with NIV during endoscopic procedures are electrocardiography, pulse oximetry and capnography, noninvasive arterial pressure measurement, respiratory rate, and minute ventilation, when possible [21].

Although most commonly the use of NIV in endoscopic procedures is indicated for patients undergoing a transesophageal echocardiography (TEE) assessment, it also has a role in the endoscopic evaluation of the upper airway structures [22].

Despite the advantages of applying NIV during the performance of endoscopic procedures and thus avoiding general anesthesia, it could also expose the patient to a higher risk of aspiration, while leaving the airway unprotected. Therefore, individual patient factors should be considered while choosing the applied approach during the endoscopic evaluation of the patient [23].

Conclusion

The pathogenetic mechanisms involved in upper airway disorders are various and include both anatomical and functional disorders. Among the diagnostic tools at the physician's disposal, endoscopy holds an important position. In the primary evaluation of patients with UA obstruction and OSAS, drug-induced endoscopy offers valuable information regarding the pathogenesis of the obstruction. A direct

evaluation of the level of the obstruction and the structures involved can be obtained, thus contributing to the prediction of the response to positioning therapy or ventilation support therapy and the choice of the most suitable interface for its application. Especially in patients with ALS, research has proven the negative prognostic effect of obstructive events of the upper airway. Evaluation of patients at high risk for such events, in particular those with bulbar involvement, could greatly benefit from dynamic endoscopic evaluation and adjustment of ventilation settings accordingly.

Treatment-induced upper airway obstruction or residual events and persisting obstruction in chronically ventilated patients and patients currently undergoing NIV therapy reduce the efficacy of ventilation support and pose a complex problem in the treatment of such patients. Endoscopy can provide invaluable information as to the type of obstruction caused, determining the anatomical structures involved and the degree of the reduction of the airway patency. More importantly, it can associate the UA disorder with the ventilation parameters under direct observation and identify a possible patient-ventilator asynchrony, hence guiding the titration of the positive pressure and other ventilation settings.

While, overall, the contribution of endoscopy in the evaluation of the patient with UA disorders is long known and valued, still to this day, no consensus has been reached regarding the classification system of the endoscopic findings.

In some studies, the assessment of endoscopic findings has been used as a diagnostic tool in the selection of patients eligible for uvulopalatopharyngoplasty with promising results. While the most extensively studied method in this regard is DISE, more recently, awake endoscopy procedures are being implemented with promising results, although more research is needed in this field. The synchronous application of NIV during the endoscopic procedures has achieved the conduction of such examinations on patients at high risk of hypoxia and respiratory failure, exposing them, though, at the same time to an increased risk of aspiration. The need for further optimization of such procedures and for individual planning of the diagnostic and treatment course still remains of utmost importance.

Conflict of Interest The authors have no conflict of interest to declare.

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