CRITICAL CARE

REVIEW

Noninvasive ventilation and the upper airway: should we pay more attention?

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Abstract

In an effort to reduce the complications related to invasive ventilation, the use of noninvasive ventilation (NIV) has increased over the last years in patients with acute respiratory failure. However, failure rates for NIV remain high in specific patient categories. Several studies have identified factors that contribute to NIV failure, including low experience of the medical team and patient–ventilator asynchrony. An important difference between invasive ventilation and NIV is the role of the upper airway. During invasive ventilation the endotracheal tube bypasses the upper airway, but during NIV upper airway patency may play a role in the successful application of NIV. In response to positive pressure, upper airway patency may decrease and therefore impair minute ventilation. This paper aims to discuss the effect of positive pressure ventilation on upper airway patency and its possible clinical implications, and to stimulate research in this field.

Introduction

Noninvasive ventilation (NIV) is increasingly used in acute respiratory failure, for instance in patients with exacerbation of chronic obstructive pulmonary disease or acute heart failure [1-3]. An important goal of NIV is to prevent endotracheal intubation and thereby reduce the complications related to invasive ventilation [1,4]. However, failure rates of NIV range between 5 and 50% [5,6] and most of these patients require endotracheal intubation [5-9]. 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 team [6,8,10]. In particular, careful selection is of major importance in patients with chronic obstructive pulmonary disease. A low pH (<7.25) is a strong predictor of NIV failure [10,11], but an improvement in pH 1 to 2 hours after the initiation of NIV accurately predicts NIV success [5,11-13].

Today, the pathophysiology of NIV failure is incompletely understood. How can ventilation be inadequate with NIV, but adequate with similar levels of support after endotracheal intubation? An important difference in the application of NIV versus invasive ventilation is, evidently, the involvement of the upper airway. During invasive ventilation the endotracheal tube bypasses the upper airway and the cuff of the endotracheal tube provides an air-tight seal in the trachea. In contrast, during NIV the upper airway might play a role in the efficiency of delivered ventilation. Indeed, ventilator settings during NIV affect the patency of the upper airway [14,15]. This effect implies that deviant behavior of the upper airway may play a role in the failure of NIV. The present concise review discusses the physiology and current understanding on the effects of NIV on upper airway patency. We will discuss the clinical relevance of the available studies and will list important points to stimulate research in this field.

Noninvasive ventilation and upper airway physiology

Patient–ventilator asynchrony

The aim of NIV is to decrease the work of breathing and/or improve oxygenation and ventilation. The most frequently used mode of NIV is pressure support ventilation (PSV). For the most effective unloading of the inspiratory muscles, the ventilator should cycle in synchrony with the patient's neural respiratory drive [16]. Although triggering and cycling of mechanical support during PSV depends on the patient's respiratory effort, asynchrony between the patient and ventilator occurs

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frequently [17]. Several types of asynchrony and dys-synchrony between the patient's neural drive and venti-lator support have been identified and are shown in Figure 1 [18,19]. Suboptimal synchrony between the pa-tient and the ventilator may be affected by respiratory mechanics, the breathing pattern, neural drive, ventilator settings, the type of interface and the amount of air leak [18,20-23]. The consequences of patient–ventilator asynchrony are poorly understood, but a high incidence of asynchrony is associated with discomfort and a prolonged duration of NIV [17].

The above-discussed types of asynchrony are related to the interaction between the activity of the inspiratory muscles and the ventilator's response. Indeed, this is suf-ficient for patients requiring invasive ventilation. How-ever, during NIV it is also important that the ventilator acts in synchrony with the upper airway muscles. Glottic narrowing during inspiration increases upper airway re-sistance and may limit effective ventilation. We will discuss this type of asynchrony after briefly summari-zing the knowledge of upper airway physiology relevant to the topic of this review.

Upper airway

The upper airway comprises the nose, oral cavity, pha-rynx and larynx. The upper airway is involved in che-wing, swallowing, speech and smell, and its primary functions are to act as a conductor of air, to humidify and warm the inspired air and prevent foreign materials from entering the tracheobronchial tree [24]. 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 upper airway [15,25]. A simplified representation

of the muscles of the upper airway is shown in Figure 2 and a view of the intrinsic muscles of the larynx shown in Figure 3 [26,27].

Stella and England studied the effect of pressure and flow in isolated piglet upper airway [28]. They showed that the presence of negative pressure in the upper air-way and flow during inspiration results in phasic respira-tory activity of the posterior cricoarytenoid muscle above tonic levels, which results in glottic widening du-ring inspiration and reduces resistance to airflow. This response effectively unloads the inspiratory muscles. 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.

Earlier, Sant'Ambrogio and colleagues showed that flow receptors actually respond to temperature changes from body to room temperature (thermoreceptors) [29]. Stella and England used these findings to analyze the laryngeal muscle response to continuous versus oscillating flow patterns and different body and room temperatures. They reported that a negative pressure and inspiratory flow re-sults in increased posterior cricoarytenoid activity (opening of the glottis), independent of the stimulus modality. Fur-thermore, positive pressure and expiratory flow increased the thyroarytenoid activity for all stimuli, although constant room air applied to the upper airway results in more activ-ity of the thyroarytenoid muscle than an oscillatory stimu-lus, implying that constant room air results in enhanced constriction of the glottis. Accordingly, both pressure and flow receptors play an important role in muscle activity of the upper airway during respiration [28,30].
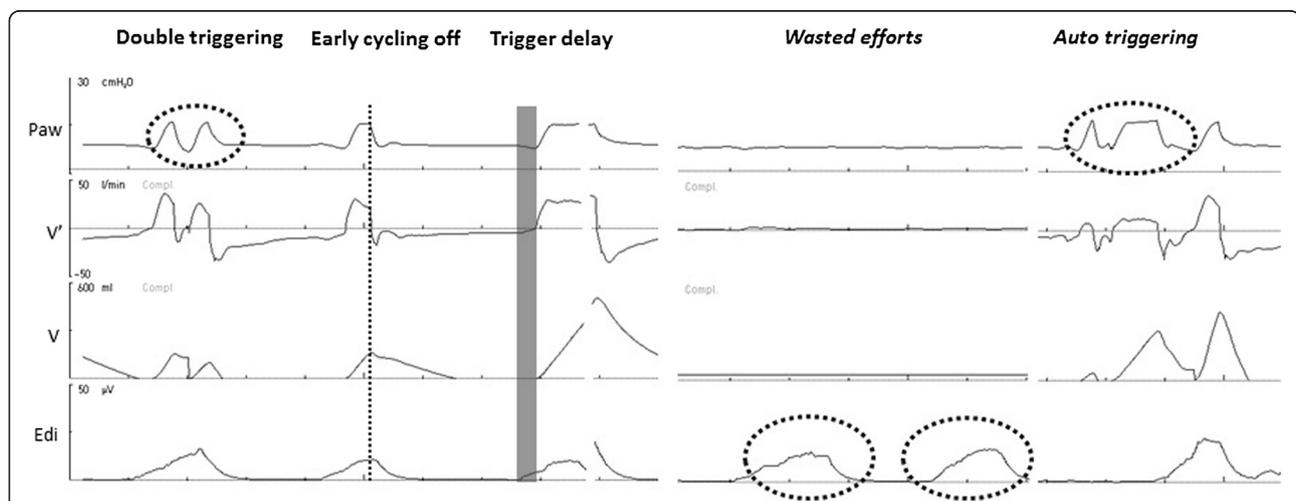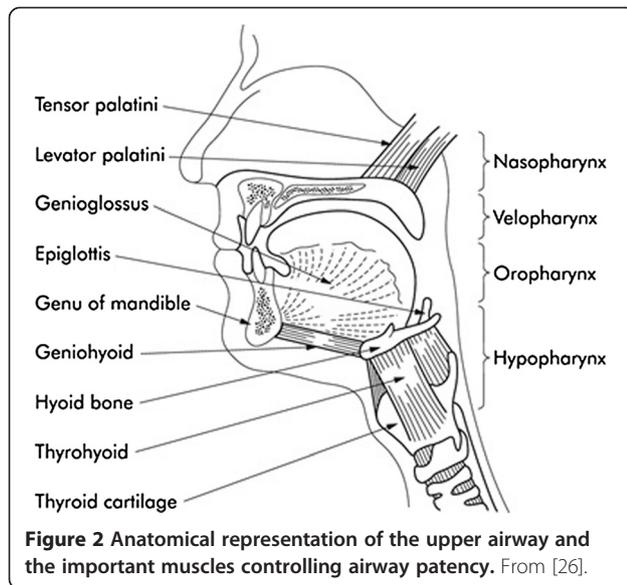

Figure 1 Screenshots from a ventilator in noninvasive ventilation pressure support mode. Tracings from top to bottom: airway pressure (Paw), airway flow (V'), tidal volume (V), and diaphragm electrical activity (Edi). Different types of patient ventilator asynchrony and dyssynchrony are shown: double triggering, early cycling off, trigger delay, wasted efforts and auto triggering [18,19].

Figure 2 Anatomical representation of the upper airway and the important muscles controlling airway patency. From [26].

Receivers in the upper and lower airway modulate activity of the upper airway muscles. The most prominent receptors are the bronchopulmonary C-fiber receptors, rapidly adapting receptors (RARs) and slowly adapting pulmonary stretch receptors (PSRs) (Table 1).

Pulmonary C-fiber receptors are located between the alveolar epithelium and the pulmonary capillaries, whereas bronchial C-fiber receptors have been identified in the conducting airway. The receptors' fiber endings extend into the space between epithelial cells or form a plexus immediately under the basement membrane. C-fiber receptors are excited by large mechanical deformations, chemical stimuli (for example, capsaicin and carbon dioxide), lung edema by increased interstitial fluid volume, or increased temperature [31,32]. C-fiber receptor activation evokes inhibitory effects (apnea or bradypnea;

hypotension and bradycardia). C-fiber receptor stimulation can result in closing of the upper airway by glottic narrowing to protect the respiratory system against inhalation of gaseous irritants, by activation of laryngeal muscles [33].

RARs are located in and under the epithelium throughout the respiratory tract from the nose to the bronchi. The receptors respond in reaction to mechanical (extremely sensitive) and chemical stimuli, and produce mainly excitatory effects such as tachypnea [33,34]. The RARs in the larynx are usually called irritant receptors because of their activation by inhaled irritants such as ammonia or cigarette smoke, and they probably cause cough and expiration reflexes. When the laryngeal mucosa is stimulated, RAR reflexes elicit laryngoconstriction and bronchoconstriction, which may be part of the glottal closure seen during cough. However, the exact modulation of laryngeal upper airway muscle activities by RARs is incompletely understood [31,33,34].

PSRs do not affect patency of the upper airway but modulate the respiratory cycle: they terminate inspiration and extend expiration [35]. PSRs are activated by stretching the airway wall and fire throughout the respiratory cycle (tonic activity) or in response to lung inflation (phasic activity). The discharge rate is progressively increased as a function of lung volume. PSRs are also widely known as the receptors responsible for the Hering–Breuer reflex, one of the first negative feedback loops in physiology. Hering and Breuer found that lung inflation decreases the tidal volume and increases the respiratory rate, thereby protecting the lungs from hyperinflation, while maintaining constant alveolar ventilation: an inspiratory off-switch [33,36].

To summarize, respiration and in particular patency of the upper airway depends on a complex, but incompletely understood, interplay between several inhibitory
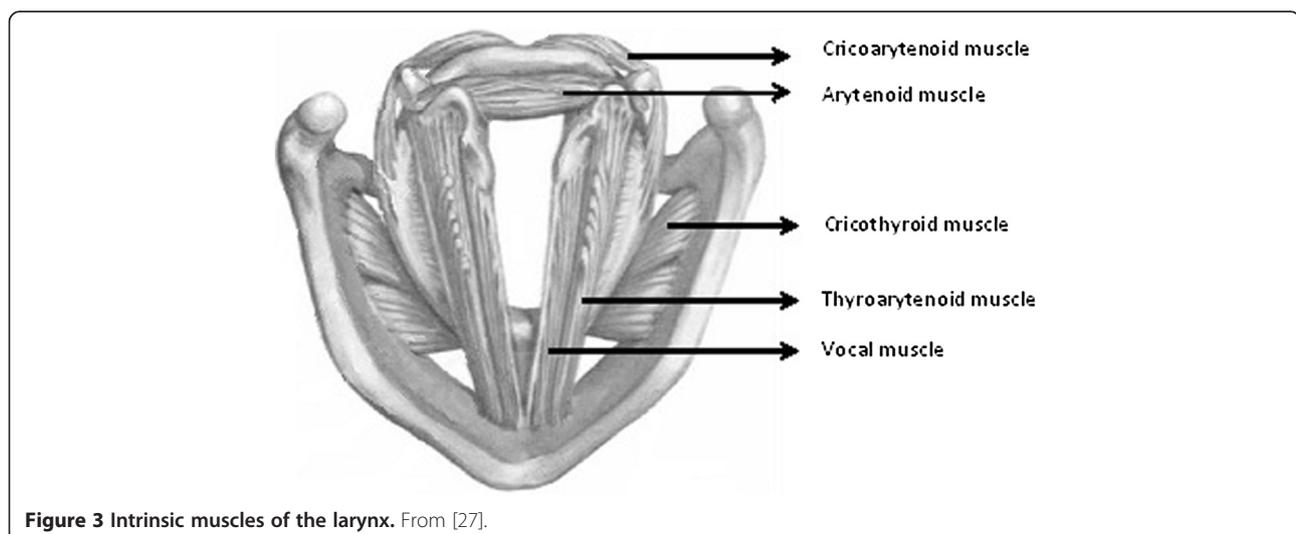

Figure 3 Intrinsic muscles of the larynx. From [27].

Table 1 Relevant respiratory receptors and their location and effect

Receptors		Location	Stimulus	Effect
C-fiber	*Pulmonary*	Between alveolar epithelium and pulmonary capillary	Large mechanical deformations, chemical stimuli and temperature increases	Inhibitory effects as apnea, hypotension and bradycardia
	Bronchial	In the walls of conducting airway		
Rapidly adapting		In epithelium close to bronchial venules	Very sensitive to mechanical stimuli and slow response to chemical stimuli	Irritant receptors cause cough and expiration reflexes
Pulmonary stretch		In close association with airway smooth muscle	Mechanical changes, stretch of airway wall	Terminate inspiration and extend expiration (Hering–Breuer reflex).

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.

Interaction between the upper airway and noninvasive ventilation

Moreau-Bussière and colleagues studied the effect of NIV on activity of the glottal constrictor (thyroarytenoid) and dilator (cricothyroid) muscles in awake lambs. Figure 4 shows thyroarytenoid, cricothyroid and diaphragm muscle activity during spontaneous breathing or NIV with PSV [37]. During spontaneous breathing, both the thyroarytenoid and cricothyroid muscles are active – thyroarytenoid muscle activity occurring primarily at the end of inspiration. However, with application of pressure support during NIV, inspiratory cricothyroid

activity disappears whereas activity of the thyroarytenoid muscle increases. This results in glottal narrowing and restricted ventilation, as reflected by respiratory inductance phlethysmography [37].

A subsequent study demonstrated that increased glottal constrictor muscle activity during NIV depends mainly on activation of bronchopulmonary receptors. After bilateral vagotomy, the increase in inspiratory activity of the thyroarytenoid muscle previously observed with increasing support during NIV was absent [14].

There are limited data that demonstrate a similar response to NIV in humans. Rodenstein and colleagues exposed healthy subjects to increasing levels of support with NIV while their glottis was continuously monitored through a fiberoptic bronchoscope. The higher the level of support, the narrower the glottic aperture and the higher the airway resistance. This effect led to
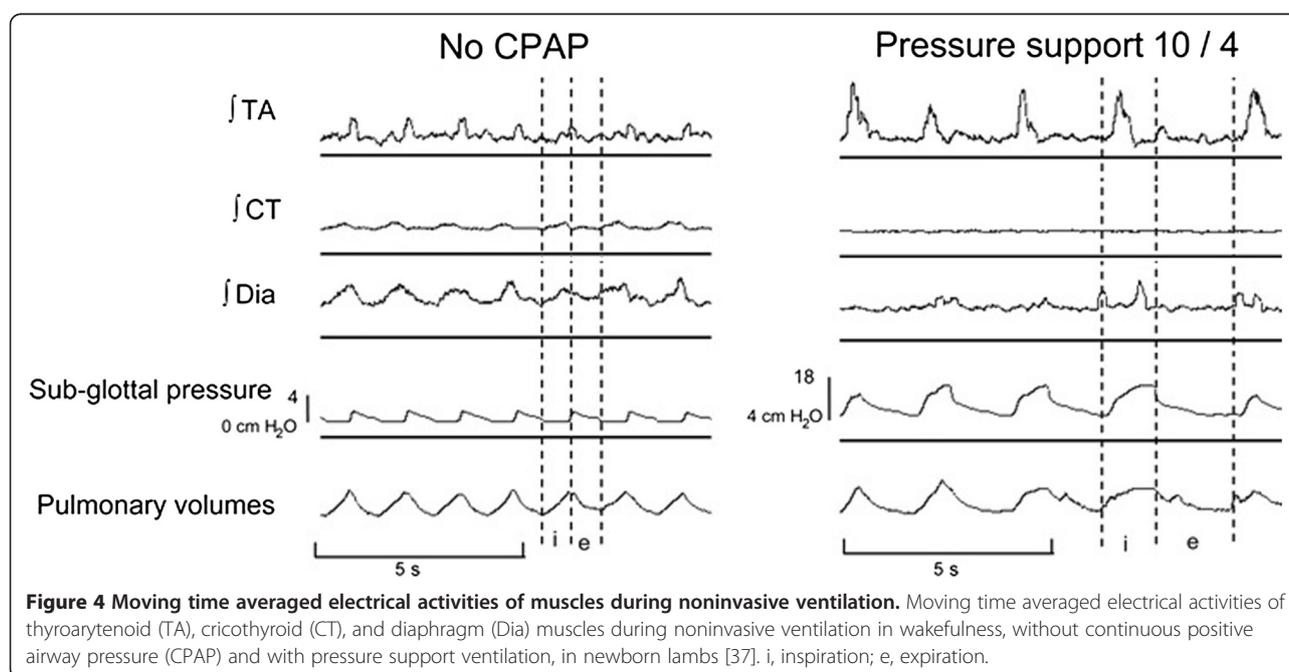

Figure 4 Moving time averaged electrical activities of muscles during noninvasive ventilation. Moving time averaged electrical activities of thyroarytenoid (TA), cricothyroid (CT), and diaphragm (Dia) muscles during noninvasive ventilation in wakefulness, without continuous positive airway pressure (CPAP) and with pressure support ventilation, in newborn lambs [37]. i, inspiration; e, expiration.

a progressive decrease in the percentage of tidal volume effectively reaching the lungs, apparently at least partly due to the behavior of the glottis [15,38,39].

In summary, studies in animals and humans indicate that positive pressure ventilation reduces patency of the upper airway during neural inspiration.

Neurally adjusted ventilator assist (NAVA) is a relatively new mode of noninvasive ventilatory support. The key features of NAVA are that the ventilator is cycled by diaphragm electrical activity, thereby improving patient–ventilator synchrony [40,41], and that the level of support is proportional to the electrical activity of the diaphragm [42]. The electrical activity of the diaphragm is measured by an array of bipolar electrodes mounted on a nasogastric feeding tube.

In contrast to PSV, glottal constrictor muscle activity does not increase with NAVA during inspiration in lambs [43]. Apparently, NAVA induces less glottal closure and more synchronous ventilation and may thus be advantageous compared with PSV during NIV. A possible underlying mechanism for the absence of glottal constrictor activity during inspiration with NAVA is that the pressure rise mimics the normal progressive recruitment of the diaphragmatic motor units, whereas during PSV insufflation from the ventilator is performed with a constant level of pressure (decelerating flow pattern), often with a short inspiratory rise time to further decrease the patient's inspiratory work. The consequent rapid nonphysiological rise in airway pressure at the onset of inspiration with PSV could be responsible for activating, in a reflex manner, the inspiratory activity of the glottal constrictor muscles and thus limits the efficiency of NIV [43]. This hypothesis should be the subject of further clinical research.

Monitoring muscles of the upper airway

The importance of monitoring inspiratory muscle activity during mechanical ventilation has been stressed in the literature [44]. In contrast, little is known about the role of monitoring upper airway activity during NIV – probably related to the complexity of monitoring the upper airway function in these patients.

Activation of intrinsic laryngeal muscles affects glottis opening and thus affects resistance to flow into and out of the lungs [28]. Monitoring the recruitment of upper airway dilator muscles during inspiration could be clinically relevant because the phasic activity of upper airway dilator muscles increases with respiratory constraints, as in patient–ventilator asynchrony [45,46]. Cheng and colleagues studied the upper airway in healthy subjects, using magnetic resonance imaging with tagging [47]. This study showed not only that the genioglossus muscle but also nonmuscular soft tissues surrounding the upper airway move before the onset of inspiratory flow [47].

Movement of certain reference points on the genioglossus muscle was greater during normal inspiration than during loaded inspiration, suggesting that the increase in activity of the muscle during loaded inspiration does not result in dilation but in stiffening of the upper airway [47]. Moreover, this study demonstrated that movement of nonmuscular soft tissue affects upper airway patency.

A complex interaction exists between movement of nonmuscular soft tissue and genioglossus muscle activity. Although laryngeal muscle (for example, genioglossus or cricothyroid muscle) electromyography is feasible during NIV [37,45], one should note that electromyography does not provide information about nonmuscular soft tissue movement. Additional techniques should therefore be used to evaluate upper airway patency. Magnetic resonance imaging probably provides the most reliable information but it is expensive and cumbersome, particularly in patients on NIV. Recently, a study showed that the upper airway could be visualized with ultrasound, although the value of assessing upper airway patency with this technique has not been studied [48]. In addition, endoscopy has been used to assess upper airway patency, but ideally should be used at different levels in the upper airway.

Clinical relevance and future research

Increasing the success rate of NIV is of major clinical importance. In contrast to invasive ventilation, the upper airway plays an important role as a conductor of air during NIV. Current literature suggests that during NIV it is important that the ventilator acts in synchrony with the upper airway muscles to allow adequate ventilation. In lambs and piglets, the patency of the upper airway is influenced by ventilator-induced changes in pressure and flow [14,30,37,43]. However, we do not know whether this phenomenon can be extrapolated to humans. The involved reflexes are similar in humans to those in newborn lambs, but are thought to be less pronounced.

Today, there are limited data on the effects of NIV on upper airway physiology in patients with acute respiratory failure. It is reasonable to assume that when the ventilator cycles in synchrony with the upper airway, this will improve efficiency of ventilation. As discussed, 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. 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.

Future research should therefore aim at studying the effect of different ventilator modes and settings on the patency of the upper airway in patients. For example, NAVA ventilation in lambs has been shown to decrease glottal constrictor muscle activity compared with PSV during NIV. Settings of the ventilator such as the rise time, trigger sensitivity, and the level of pressure support and positive end-expiratory pressure should also be the subject of further research. These settings could influence the behavior of the upper airway and potentially limit adequate lung ventilation. Currently, a study is investigating the effect of ventilator settings during NIV on upper airway patency in patients with an exacerbation of chronic obstructive pulmonary disease (Clinicaltrials.gov ID: NCT01791335). Our recommendations for further research focus on inspiration, but expiration could also be influenced by upper airway patency.

Conclusions

In conclusion, we have shown that regulation of the upper airway is complex and influenced by NIV. The latter findings are mostly based on animal data. Understanding of the laryngeal reactions during different modes and settings of NIV in patients will be crucial to determine whether a diminished upper airway patency contributes to NIV failure.

Abbreviations
NAVA: Neurally adjusted ventilator assist; NIV: Noninvasive ventilation; PSR: Pulmonary stretch receptor; PSV: Pressure support ventilation; RAR: Rapidly adapting receptor.

Competing interests
The authors declare that they have no competing interests.

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