Physiologic Effects of Noninvasive Ventilation

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Noninvasive ventilation (NIV) has a number of physiologic effects similar to invasive ventilation. The major effects are to augment minute ventilation and reduce muscle loading. These effects, in turn, can have profound effects on the patient's ventilator control system, both acutely and chronically. Because NIV can be supplied with PEEP, the maintenance of alveolar recruitment is also made possible and the triggering load imposed by auto-PEEP can be reduced. NIV (or simply mask CPAP) can maintain upper-airway patency during sleep in patients with obstructive sleep apnea. NIV can have multiple effects on cardiac function. By reducing venous return, it can help in patients with heart failure or fluid overload, but it can compromise cardiac output in others. NIV can also increase right ventricular afterload or function to reduce left ventricular afterload. Potential detrimental physiologic effects of NIV are ventilator-induced lung injury, auto-PEEP development, and discomfort/muscle overload from poor patient–ventilator interactions. *Key words: invasive ventilation; noninvasive ventilation; minute and alveolar ventilation; ventilation distribution; ventilation-perfusion matching; control of ventilation; ventilatory muscles; work of breathing; patient–ventilator interactions; ventilator-induced lung injury.* [Respir Care 2019;64(6):617–628.

Introduction

Noninvasive ventilation (NIV) is the process of supporting respiration using devices that do not require an artificial airway. While a variety of external chest devices meet this definition, this discussion will focus on positive-pressure devices with a mask interface to either totally or partially

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provide O_2 and CO_2 transport between the environment and the pulmonary capillary bed.[1,2] NIV is often coupled with PEEP to maintain positive airway pressure throughout the ventilatory cycle. The primary desired effect of NIV is to maintain adequate levels of P_{O_2} and P_{CO_2} in arterial blood while also unloading the inspiratory muscles.

NIV has many of the same physiologic effects as invasive ventilation (ie, through an artificial airway). However, there are important differences. First, because of inherent leaks, NIV systems cannot always supply volumes and pressures comparable to invasive ventilation, despite sophisticated leak-compensation features. These leaks can also affect triggering sensitivity and patient–ventilator synchrony during flow delivery and breath cycling. Second, NIV is applied to the oronasal pharynx that connects to the esophagus as well as the trachea. Despite the presence of gastroesophageal sphincters, high positive esophageal pressures can lead to gastric distention. Third, the unprotected trachea, especially in the setting of a distended stomach, is exposed to significant aspiration risk. Fourth, the absence of an artificial airway also limits the effectiveness of airway suctioning and pulmonary toilet. Fifth, with single-lumen circuits relying on controlled leaks for exhalation, the potential for CO_2 re-breathing exists, especially if flow settings are low. Finally, inspiratory pressure settings on many dedicated NIV systems are referenced to atmosphere, which can lead to confusion in clinicians more familiar with invasive ventilation devices where inspiratory pressure is referenced to set expiratory pressure (PEEP).

There are also important advantages to NIV vs invasive ventilation. By using a noninvasive mask interface instead of an artificial translaryngeal airway, preservation of glottic function may, in fact, reduce aspiration risk from pharyngeal material. Intermittent breaks from NIV are possible, which allows talking and swallowing, and this, coupled with the absence of an irritating trans-laryngeal airway, may improve comfort and reduce sedation needs compared to invasive ventilation.[3] NIV can also be helpful in maintaining patency of upper-airway obstruction in patients with obstructive sleep apnea and can reduce venous return and pulmonary edema in selected patients with congestive heart failure.[4,5] Importantly, like invasive ventilation, NIV can also injure the lungs if used inappropriately.[6-8] The specific physiologic effects of NIV on both the respiratory system as well as important non-respiratory systems (ie, neurologic and cardiovascular) are reviewed below.

NIV Can Augment Minute Ventilation

By adding pressure and flow to the mask interface using NIV, tidal volumes can be either created during a controlled (ie, machine time-triggered) breath or augmented during assisted (ie, patient effort-triggered) breaths.[9] Either way, the minute ventilation ($\dot{V}_E$) delivered to the patient can be increased substantially.

Unless there is a marked increase in dead space ($\dot{V}_D$) with positive-pressure ventilation, an increased $\dot{V}_E$ from NIV usually translates to an increased alveolar ventilation ($\dot{V}_A = \dot{V}_E - \dot{V}_D$). The net effect of an increased $\dot{V}_A$ is to provide additional O_2 to and remove additional CO_2 from alveolar gas. Mathematically, the relationship of $\dot{V}_A$ to alveolar gas partial pressures are:

$$P_{aO_2} = P_{IO_2} - (\dot{V}_{O_2}/\dot{V}_A) \times k$$

$$P_{aCO_2} = (\dot{V}_{CO_2}/\dot{V}_A) \times k$$

where P_{IO_2} is inspired oxygen, $\dot{V}_{O_2}$ is total body oxygen consumption, $\dot{V}_{CO_2}$ is total body CO_2 production, and k is a constant. These relationships are depicted in Figure 1 and show that, as $\dot{V}_A$ increases, alveolar P_{O_2} asymptotes on the P_{IO_2} and alveolar P_{CO_2} asymptotes on zero.[10]

Gas transport across the alveolar capillary membrane is driven by gradients between alveolar and venous blood gas tensions and alveolar capillary membrane diffusing properties. In general, with a normal blood transit time in the capillary bed of < 1 s, gas diffusion is sufficiently rapid and equilibration of both CO_2 and O_2 in the alveolus and capillary bed is complete.[11-12]

The ultimate P_{O_2} and P_{CO_2} in pulmonary venous blood entering the left atrium, however, depends not only on $\dot{V}_A$ and alveolar-capillary gas transport, but also on ventilation perfusion matching ($\dot{V}/\dot{Q}$) relationships throughout the millions of lung units into which the $\dot{V}_E$ distributes.[11-13] Factors affecting this distribution include regional resistances, compliances, functional residual capacities, and the machine-delivered pressure/flow pattern (square vs decelerating vs variable flow; with or without an inspiratory pause; with or without expiratory pressure). In general, positive-pressure breaths will tend to distribute more to units with high compliance and low resistance and away from obstructed or stiff units. This creates the potential for regional overdistention of healthier lung units in heterogeneous disease states, even in the face of normal tidal volumes (see ventilator-induced lung injury discussion below). $\dot{V}_E$ distribution is also affected by body position (eg, gravitational forces tend to distend non-dependent regions) and the presence or absence of inspiratory muscle activity (eg, an actively contracting diaphragm tends to distribute gas to dependent regions better).[14-15]

$\dot{V}/\dot{Q}$ effects are different for CO_2 and O_2.[11,12] Because CO_2 is very soluble in blood and CO_2 content is essentially linearly related to P_{CO_2}, the ultimate P_{CO_2} in pulmonary venous blood is a flow-weighted average of all lung units in which alveolar gas came into at least some contact with capillary blood (ie, $\dot{V}_A$). On the other hand, the ultimate P_{O_2} in pulmonary venous blood is not a flow-weighted average but

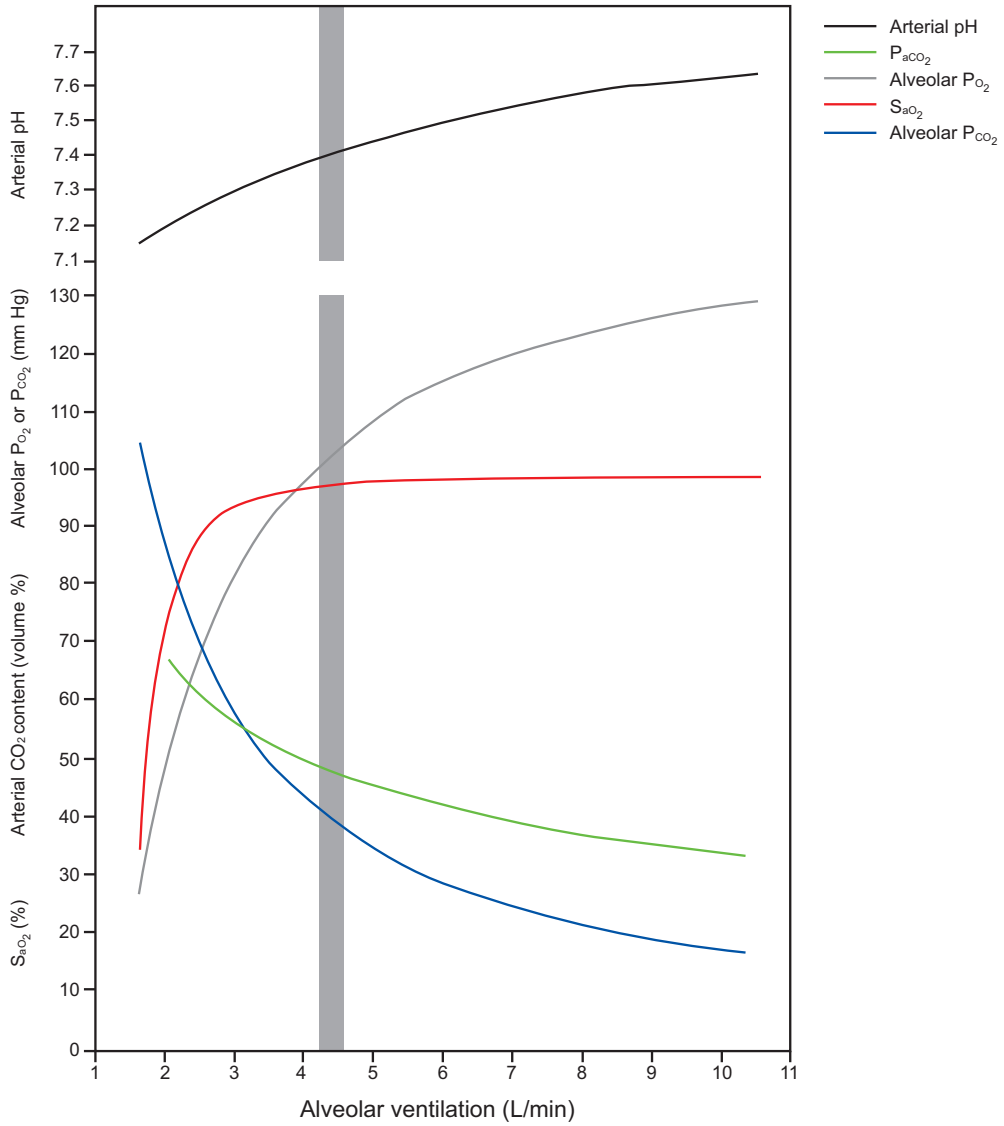

Fig. 1. Relationship of alveolar ventilation to alveolar P_{O_2} and P_{CO_2} and to the ultimate S_{aO_2} and P_{aCO_2} with an assumed oxygen consumption of 250 mL/min and CO_2 production of 200 mL/min. The shaded area represents a normal alveolar ventilation. Note that as alveolar ventilation increases, alveolar P_{CO_2} decreases exponentially, and P_{aCO_2} follows. In contrast, as alveolar ventilation increases, the alveolar P_{O_2} increases and approaches the inspired P_{O_2}. However, because hemoglobin saturation is virtually complete at P_{O_2} values $>$ 70–80 mm Hg, arterial oxygen content rises little at alveolar P_{O_2} above this. Data from Reference 10.

depends heavily on regional $\dot{V}/\dot{Q}$ matching. This is because O_2 is poorly soluble in plasma and because hemoglobin, the major O_2-carrying molecule in blood, is fully saturated when capillary P_{O_2} values are $>$ 70–80 mm Hg. Under these circumstances, raising the capillary P_{O_2} has little effect on capillary blood oxygen content, and thus a lung unit with a high $\dot{V}/\dot{Q}$ ratio does not have much "extra" oxygen to compensate for a lung unit with a low $\dot{V}/\dot{Q}$ ratio. In summary, systemic oxygen content depends heavily on hemoglobin and $\dot{V}/\dot{Q}$ matching and tends to plateau as $\dot{V}_E$ and $\dot{V}_A$ are increased with NIV. In contrast, systemic arterial CO_2 content depends less on $\dot{V}/\dot{Q}$ and falls steadily as $\dot{V}_E$ and $\dot{V}_A$ are increased with NIV (see Fig. 1).

NIV Unloads Ventilatory Muscles

The simplified equation of motion defines the necessary pressure (P_{tot}) required to overcome the loads of respiratory system elastic recoil (P_{el}) and airway resistance (R_{res}) for a given flow ($\dot{V}$) and volume change (ΔV):

$$P_{tot} = P_{el} + P_{res}$$

$$P_{tot} = (\Delta V/C_{RS}) + (R_{aw} \times \dot{V})$$

where C_{RS} is respiratory system compliance, and R_{aw} is airway resistance.[16]

Individual contributions of inertness and lung tissue resistance also impact the equation of motion, but these contributions are small and are generally disregarded. When present, overcoming intrinsic PEEP contributes to the pressure requirements to breathe. Note that P_{tot} is supplied entirely by the ventilatory muscles (P_{mus}) during unassisted breathing. In contrast, during machine-triggered controlled mechanical ventilation, P_{tot} is supplied entirely by the ventilator. During interactive assisted breathing, P_{tot} is a combination of P_{mus} and machine-applied airway pressure.

Although intercostal muscles contribute to P_{mus}, the most important ventilatory muscle is the diaphragm. This musculotendinous sheet of skeletal muscle separating the thoracic and abdominal cavities is the primary muscle of ventilation and is the most used skeletal muscle.[17] Although many of the physiologic principles of skeletal muscle can be applied to the diaphragm, including the length–tension relationship, unique adaptations exist. Compared to limb muscles, the diaphragm has a greater proportion of fatigue-resistant type I muscle fibers with increased mitochondrial density, oxidative capacity, and maximal oxygen consumption.[17,18] These smaller muscle fibers have an increased capillary density that facilitates more efficient O_2 diffusion, and they have the potential to augment blood flow up to 4 times more than limb muscles while shifting regional blood supplies from other skeletal muscle beds.[18]

Ventilatory muscle capabilities are determined by inherent strength and endurance properties, which can be profoundly diminished in critically ill patients with metabolic derangements associated with the systemic inflammatory response syndrome.[19-21] Capabilities can also be diminished as a consequence of lung hyperinflation literally flattening the diaphragm and thereby placing it at a substantial mechanical disadvantage through an unfavorable length–tension relationship.[18] Limitations in energy supply imposed by hypoperfusion, anemia, hypoxia, malnutrition, or the inability to extract oxygen, such as that seen in sepsis and cyanide poisoning, also predispose to ventilatory muscle failure.[22,23] Weak muscles are also less efficient and require more energy in relation to their maximum energy consumption to perform a given task.[19]

Ventilatory muscle failure is the loss of the ability of ventilatory muscles to generate the necessary P_{mus} to provide for the patient's ventilatory needs. This failure has 2 mechanisms: one is actual muscle fatigue from muscle overload, and the other is a reduction in ventilatory drive to protect muscles from fatigue. Regardless of mechanism, ventilatory muscle failure with its ensuing alveolar hypoventilation and hypercapnia is ultimately related to an imbalance in ventilatory muscle capabilities versus the loads placed on those muscles.[22-24]

Mechanical loads can be described as a single value for work or pressure-time product.[24] Work is the integral of pressure over change in volume, and the pressure-time product is the integral of pressure over inspiratory time. The pressure-time product, with its reliance on the pressure-time component of loading, better correlates with ventilatory muscle energetics and O_2 consumption than does work and is thus increasingly used clinically to measure the energy demands on ventilatory muscles.[25-27]

Load tolerance or the load/capacity balance can be expressed by a tension-time index (TT_{max}). The TT_{max} incorporates pressure as a fraction of maximum inspiratory pressure (P_{Imax}) and couples this with the fraction of the ventilatory duty cycle devoted to muscle contraction (ie, T_I/T_{tot})[25]:

$$TT_{max} = (P_I/P_{Imax})(T_I/T_{tot})$$

In a normal subject at rest, TT_{max} values are generally < 0.05, and even at high levels of exercise TT_{max} rarely exceeds 0.1. However, TT_{max} values > 0.15 for the diaphragm and > 0.3 for rib cage muscles are related to the development of ventilatory muscle failure.[25]

All of the components of TT_{max} are likely abnormal in patients with respiratory failure due to lung disease. In patients with high resistive loads (eg, those with COPD, asthma, or large airway obstructions) or patients with high elastic loads (eg, those with interstitial lung disease, cardiogenic pulmonary edema, or ARDS), the required inspiratory pressures (P_I) can be substantial. The imposed loads from asynchronous patient–ventilator interactions can also contribute to a need for a high P_I. The low P_{Imax} in respiratory disease reflects the reduced capabilities of ventilatory muscles in the setting of critical illness noted above. Finally, in acute respiratory failure, the higher minute ventilation requirement may be associated with an increased tidal volume (V_T) and shortened T_{tot} (ie, faster breathing frequency). This combination can greatly increase T_I/T_{tot}. Taken together, all of the components of TT_{max} often change unfavorably in the setting of acute respiratory failure and likely contribute to ventilatory muscle failure.

NIV can unload the ventilatory muscles in 2 ways. First, NIV reduces the number of required patient efforts; second, for a given V_T, NIV reduces the muscle load during an interactive assisted breath (Fig. 2).[28] These effects, in turn, can reverse fatigue and the reduced neural drive to prevent fatigue. There is controversy surrounding the amount of unloading that is ideal. Clearly total unloading is undesirable because it increases the risk for ventilator-induced diaphragmatic dysfunction or diaphragm atrophy.[29] At the other extreme, inadequate unloading potentiates muscle failure and may lead to permanent muscle damage.[30]

A recent concept has been the notion that intermittent (eg, nocturnal) resting of overloaded muscles in patients with chronic respiratory acidosis may improve muscle function and lower P_{aCO_2}, even during the periods when NIV is not in use. The amount of support required to accomplish this is not

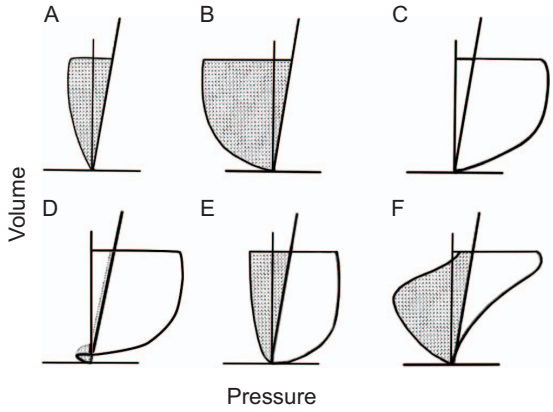

Fig. 2. Pressure-volume plots illustrating loading and unloading ventilatory muscle with positive-pressure breaths. Pressure is on the horizontal axis, and volume is on the vertical axis. The solid diagonal line represents the passive respiratory system compliance. Pressures to the left of this line are patient-generated, and pressures to the right of this line are machine-generated. The area of the pressure volume plot represents work (shaded for patient work, open for machine work). A: Represents a normal subject with normal work. B: Represents a diseased patient with excessive work. C: Represents the same diseased patient being totally unloaded by a machine breath (ie, no patient work). D: Represents the patient only doing enough work to trigger a machine breath that provides most of the work to breath. E: Represents the patient and the ventilator interacting to share the work in a fashion that resembles the normal subject work pattern in A. F: Represents a poorly interactive breath in which inadequate unloading by the machine produces excessive loading of the patient. Conceptually, E would seem ideal. From Reference 41, with permission.

clear, but some studies suggest that a substantial duration of high-level NIV (eg, $P_I > 20$ cm H_2O) may be necessary.[31,32]

In summary, overloading already impaired ventilatory muscles is a major contributor to muscle task failure and hypercapnia in respiratory disease. Properly applied, synchronous, assisted NIV is very effective at reducing muscle loading and facilitating muscle recovery. Moreover, some evidence suggests that chronic muscle overloading can be alleviated by nocturnal use of NIV with improved muscle function during the day.

NIV Resets the Ventilatory Control System

The ventilatory pattern (tidal volume, frequency, and inspiratory/expiratory ratio) is controlled by a collection of neurons, known as the ventilatory control center (VCC), located in the brainstem. The VCC has an inherent respiratory rhythm generator that interacts with several inputs. Two important inputs come from chemoreceptors (ie, P_{O_2}, P_{CO_2}, and pH receptors) located in the great vessels and the fourth ventricle of the brain, and from mechanoreceptors (ie, stretch and irritant receptors) in the thorax and ventilatory muscles (Fig. 3).[33-35] The optimum ventilatory pattern generated by a normal VCC is generally the one that provides adequate gas exchange (ie, a physiologic pH and a P_{O_2} that fully saturates hemoglobin) with the least amount of ventilatory muscle loading and air trapping.[36] Cortical inputs (eg, pain, anxiety, stress, artificial airway presence, and some central nervous system injuries) can also influence this pattern (loop gain), usually stimulating overall ventilatory drive.[33,35] In contrast, drugs, such as sedatives and opioids, and many other central nervous system injuries can depress the overall ventilatory drive. The sleep state can also modulate these responses.[33,35]

The ability of NIV to provide adequate gas exchange and unload muscles can have profound effects on the VCC. Reducing acidosis and hypoxemia will decrease the intensity and frequency of the VCC output.[37] Muscle unloading will alter the mechanical inputs into the VCC with variable effects that often reduce intensity and timing depending upon the types of load (ie, compliance, resistance) being sensed by the VCC.[38] Mechanoreceptors can also sense overventilation and overdistention, which often leads to shortening of neural inspiratory time and even activation of expiratory muscles.[38,39] As noted above, nocturnal unloading of chronically overloaded muscles may reset the VCC targets for a more normal P_{aCO_2} and V_A during the day.[30,31]

Imposed loads from inappropriate NIV settings can also affect the VCC through their effects on muscle loading.[33-35,40] Delayed or missed triggers are sensed as an uncomfortable isometric load leading to increased effort intensity and pronounced dyspnea.[41] If excessive muscle loading is sensed during flow delivery, this usually leads to alterations in the spontaneous ventilatory pattern to reduce this loading (eg, rapid shallow breathing) and also is often accompanied by dyspnea.[33-34,39]

Ventilator breath cycling criteria can also impact the VCC.[33-35,42-45] A mechanical breath termination shorter than the neural inspiratory time (machine $T_I <$ neural T_i) can lead to muscle activity beyond the machine's flow delivery phase, which can lead to high muscle loading, excessive tidal volumes, or triggering of a second breath. In contrast, when mechanical breath cycling terminates after the inspiratory effort has ended (machine $T_i >$ neural T_i), dyspnea and expiratory muscle recruitment may occur in an effort to terminate the breath. It is also worth noting that, because asynchronous interactions often results in anxiety and dyspnea, which can stimulate overall ventilatory drive, improving synchrony in one area (eg, triggering) can help facilitate achieving synchrony in other areas (eg, flow demand).[44,45]

In summary, NIV can affect the VCC in a variety of ways. Improving gas exchange, reducing muscle loads, and reducing dyspnea can all result in a more normal ventilatory pattern. Importantly, central nervous system abnormalities can complicate this scenario, and a poor setup of NIV with significant imposed loading may provoke VCC responses that serve only to worsen the situation.

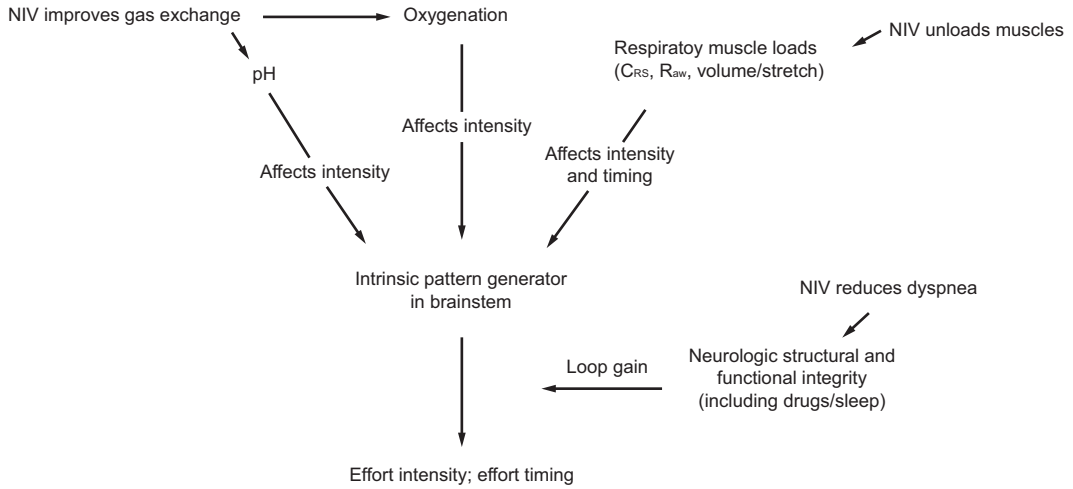

Fig. 3. Noninvasive ventilation (NIV) has effects on the ventilatory control center (VCC) in the brainstem. The VCC has an intrinsic pattern generator with important inputs from gas exchange sensors and from mechanical load sensors. The output from the VCC controls ventilatory muscle inspiratory muscle intensity and timing. Importantly, this output can be modulated by cortical influences and drugs, an effect sometimes referred to as a loop gain. Positive-pressure NIV can affect the VCC in a variety of ways that include beneficial (and sometimes harmful) effects on gas exchange, ventilatory muscle loading, and even cortical influences that are affected by the sense of dyspnea/anxiety. C_{RS} = compliance of the respiratory system; R_{aw} = airway resistance.

Alveolar Recruitment and Gas Exchange

Parenchymal lung injury produces $\dot{V}/\dot{Q}$ mismatching and shunts because of alveolar inflammation, flooding, and collapse.[46-48] In many of these disease processes (but not all), substantial numbers of collapsed/atelectatic alveoli can be recruited during the NIV-delivered V_T. Additional recruitment can sometimes be provided with the use of formal recruitment maneuvers, although this is much more commonly done with invasive ventilation than during NIV.

Once alveoli are recruited, PEEP can be applied during NIV to prevent de-recruitment. PEEP is generally produced by expiratory circuit valves or by continuous flow provided during the expiratory phase (applied PEEP). PEEP can also be produced as a consequence of short expiratory times in lung units with long expiratory time constants (intrinsic or auto-PEEP in highly compliant, highly obstructed lung units).[49,50] Importantly, applied PEEP is generally distributed uniformly throughout the lungs, whereas intrinsic/auto-PEEP predominantly develops in lung units that may need it the least (eg, emphysematous or severely obstructed lung units).[51]

Alveoli prevented from de-recruiting by PEEP provide several potential benefits. First, recruited alveoli improve $\dot{V}/\dot{Q}$ matching and gas exchange throughout the ventilatory cycle.[47] Second, patent alveoli throughout the ventilatory cycle are not exposed to the risk of injury from the shear stress of repeated opening and closing.[46-48] Third, PEEP prevents surfactant breakdown in collapsing alveoli and thus improves lung compliance.[52]

PEEP, however, can also be detrimental. Because the tidal breath is delivered on top of the baseline PEEP, end-inspiratory pressures are usually raised by PEEP application (although this increase may be less than the actual increased PEEP level because of PEEP-induced improved compliance). This increase must be considered if the lung is at risk for regional overdistention. Moreover, because parenchymal lung injury is often quite heterogeneous, appropriate PEEP in one region may be suboptimal in another and yet excessive in another.[48,53,54] Optimizing PEEP is thus a balance between recruiting the recruitable alveoli in diseased regions without over-distending previously recruited alveoli in healthier regions. Another potential detrimental effect of PEEP is that it raises mean intrathoracic pressure, which can compromise cardiac filling in susceptible patients (see below).

Other Physiologic Effects of NIV: Intended and Unintended

Maintaining Upper-Airway Patency

A common indication for NIV (either with PEEP or as simple CPAP) is for managing upper-airway collapse in patients with obstructive sleep apnea. The underlying physiologic principle is that the positive upper-airway pressure literally splints open the collapsed upper-airway structures during sleep.[4] Often only simple CPAP is required, although some patients do better with the addition of inspiratory positive pressure.

Reducing Imposed Triggering Loads From Auto-PEEP

The PEEP applied with NIV can also help with assisted breath triggering in patients with a significant triggering load imposed by auto-PEEP.[55-57] In this setting, patients must first decrease alveolar pressure below the auto-PEEP level before mask pressures will fall to trigger the assisted breath. This can be an intolerable isometric-like load on inspiratory muscles leading to respiratory failure. By providing applied PEEP below the auto-PEEP level, the gradient between alveolar pressure and mask pressure is reduced, thereby reducing the imposed triggering load.

Cardiac Interactions: Both Beneficial and Harmful

Application of elevated intrathoracic pressure from NIV can have profound effects on cardiovascular function.[5,58-61] In general, as mean intrathoracic pressure is increased, venous return is decreased and cardiac output/pulmonary perfusion consequently decreases. This may be compounded by increased right ventricular afterload. Of note, however, increased intrathoracic pressures may also result in better left ventricular function due to an effective reduction in left ventricular afterload.[5,61] Thus, in patients with left heart failure, elevated intrathoracic pressure may actually improve cardiac function, and intrathoracic pressure removal may produce weaning failure.[61]

Intrathoracic pressures can also influence distribution of perfusion. The relationship of alveolar pressures to perfusion pressures in the West three-zone lung model help explain this.[11,12,62] Specifically, the supine human lung is generally in a zone 3 state (ie, permanently distended capillaries with low and normal $\dot{V}/\dot{Q}$ units). As intra-alveolar pressures rise, however, zone 2 (ie, intermittently distended capillaries and high $\dot{V}/\dot{Q}$ units) and zone 1 (ie, collapsed capillaries and dead space) regions can appear.

Positive-pressure mechanical ventilation can affect other aspects of cardiovascular function. Specifically, dyspnea, anxiety, and discomfort from inadequate NIV support can lead to stress-related catechol release with subsequent increases in myocardial oxygen demands and risk of dysrhythmias.[5,58-61] In addition, coronary blood vessel oxygen delivery can be compromised by inadequate gas exchange from the lung injury coupled with low mixed venous P_{O_2} due to high oxygen consumption demands by the inspiratory muscles.

Ventilator-Induced Lung Injury

The lung can be injured when it is stretched excessively by positive-pressure ventilation, whether applied either invasively or noninvasively. The most well recognized injury is that of alveolar rupture presenting as extra-alveolar air in the mediastinum (pneumomediastinum), pericardium (pneumopericardium), subcutaneous tissue (subcutaneous emphysema), pleura (pneumothorax), and vasculature (air emboli).[63] The risk for extra-alveolar air increases as a function of the magnitude and duration of alveolar overdistention. Thus, interactions of respiratory system mechanics and mechanical ventilation strategies (eg, high regional V_T and PEEP, both applied and intrinsic) that produce regions of excessive alveolar stretch (ie, transpulmonary distending pressures in excess of 40+ cm H_2O) for prolonged periods create alveolar units at risk for rupture.

A parenchymal lung injury not associated with extra-alveolar air can be produced at lower transpulmonary pressures in the setting of excessive maximal lung stretch (ie, end-inspiratory transpulmonary pressures exceeding physiologic maximums), excessive tidal lung stretch (ie, V_Ts exceeding the physiologic range), or collapse-reopening of injured alveoli.[6-8,64] Frequency of stretch, acceleration of stretch, and vascular pressures may also be involved. These forms of ventilator-induced lung injury manifest pathologically as diffuse alveolar damage[6,8,64] and are associated with cytokine release[65,66] and bacterial translocation.[67]

The risk of ventilator-induced lung injury can be reduced during NIV with the use of lung-protective settings: transpulmonary end-inspiratory pressures $<$ 30 cm H_2O, tidal volumes $<$ 8 mL/kg ideal body weight (or perhaps V_T driving pressures $<$ 15 cm H_2O), and judicious use of PEEP balancing end-inspiratory distending pressures and F_{IO_2} to meet a P_{aO_2} target.[68,69] A clinical challenge with NIV (and invasive ventilation) occurs when ventilator settings are minimal, yet a vigorous patient effort results in potentially harmful transpulmonary pressures and volumes.[70] Under these circumstances, of course, reversible causes of a vigorous inspiratory effort (eg, pain, acidosis, anxiety) must be addressed. Beyond that, however, management of such patients without obvious causes is problematic.[70,71] Some argue that an inappropriate excessive respiratory drive should be blunted with sedatives or opioids to prevent self-induced lung injury. Others counter that self-induced lung injury is a controversial concept and that the use of sedating drugs should be avoided to facilitate the ventilator withdrawal process.

Production of Auto-PEEP

High levels of $\dot{V}_E$ from NIV support can lead to the development of auto-PEEP, especially in patients with inadequate expiratory times or lung units with excessively long expiratory time constants.[72] If pressure-controlled NIV is being used, auto-PEEP results in progressively smaller V_T delivery; if volume-controlled NIV is being used, this results in the buildup of high inspiratory pressures.[55]

The development of auto-PEEP can be particularly problematic in patients with severe obstruction who are receiv-

ing pressure support because the slow inspiratory flows can markedly delay the reduction in flow needed to cycle the breath off. This problem can be addressed by simply changing the flow-cycling threshold or by using pressure assist with a set time-cycling mechanism.[9]

Patient-Ventilator Interactions

Although NIV can be delivered as pure controlled positive-pressure ventilation (ie, no patient activity present), it is usually provided as an interactive form of support to facilitate comfort and partial muscle unloading. Unfortunately, the presence of leaks and mask dead space volume reduces the sensitivity and responsiveness of ventilator effort-sensing capabilities and flow responsiveness. This can create significant triggering delays or missed triggers, flow delivery mismatches with effort, and cycling asynchronies (both premature and delayed). Moreover, like invasive ventilation, premature cycling as well as leaks can lead to auto triggering. All of these can produce considerable patient discomfort and excessive muscle loading.[41,73]

Newer modes addressing asynchrony include proportional assist ventilation and neurally-adjusted ventilator assistance.[41,74,75] Proportional assist ventilation tracks patient flow demand and modulates delivered flow and pressure to augment that demand. Neurally adjusted ventilator assistance controls ventilator flow and pressure according to a monitored diaphragmatic electromyographic signal. Both modes can be used with NIV, and while both modes have been shown to improve patient–ventilator synchrony, neither has been shown to improve clinically meaningful outcomes in either invasive or noninvasive settings.

Summary

NIV has a number of physiologic effects similar to invasive positive-pressure ventilation. The major effects are to augment minute ventilation and reduce muscle loading. These effects, in turn, can have profound effects on the patient's VCC, both acutely and chronically. Because NIV can be supplied with PEEP, the maintenance of alveolar recruitment is also made possible and the triggering load imposed by auto-PEEP can be reduced. NIV (or simply mask CPAP) can maintain upper-airway patency during sleep in patients with obstructive sleep apnea. NIV can have multiple effects on cardiac function. By reducing venous return, it can help in patients with heart failure or fluid overload, but it can compromise cardiac output in others. NIV can also increase right ventricular afterload, but it can also function to reduce left ventricular afterload. Potential detrimental physiologic effects of NIV are ventilator-induced lung injury, auto-PEEP development, and discomfort/muscle overload from poor patient–ventilator interactions.

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Discussion

Davies: Neil [MacIntyre], you referred to the fact that patient effort can have an unintended consequence of adding to the transpulmonary pressure, and I think of some of the patients I see on NIV who really seem to be struggling. In the battle of trying to provide lung-protective ventilation, I do wonder about transpulmonary pressure, especially in some of those patients who have a high respiratory drive.

MacIntyre: I didn't have time to go into it, but thank you for bringing that up. Especially in the setting of asynchrony, where patients are struggling to trigger and/or get more flow or longer durations of flow, you may have only have a small pressure applied by the machine. However, if you were to look in the pleural space with an esophageal balloon or other technology, you may see enormous pressure swings taking place. It may appear from patient observation that the lung is not excessively inflating, so maybe it's not a big deal. Well, the problem is that it's a regional phenomenon, and yes, maybe your global V_T is not huge, but these huge pressure swings have the potential to pull gas into the healthier lung units and cause a regional overdistention injury. Yoshida and colleagues[1] have shown that this high inspiratory effort in the setting of bad mechanics or poor flow delivery can create a pendelluft effect. You can literally suck gas out of one region of the lung and overinflate another region even without delivering a V_T at all. The idea of aggressive patient inspiratory effort is a very complicated issue, and it's one that is grossly underappreciated because, in the absence of obvious discomfort, it can be hard to appreciate from simple patient observation. You also may not appreciate it from circuit measurements, and these vigorous patient efforts may be generating potentially dangerous levels of transpulmonary pressures and creating regional overdistention even though V_T, the global total volume, is not excessive. I assume you'll talk about this Bhushan [Katira]—I hope I'm not contradicting you.

Katira: Yes, I will talk about this, and you are not contradicting me at all.

Kacmarek: I just think it's a general concern with any patient who is breathing spontaneously and is being mechanically ventilated, whether it's NIV or invasive. We have a false sense of security if the patient's gas exchange is reasonable, and we commonly fail to appreciate the amount of effort that patients are putting forth. Even with good gas exchange, if patients look like they're using every accessory muscle they have, the decision to provide controlled ventilatory support is not made when it should be made. We do a lot of patients a disservice by allowing them, when they look uncomfortable, to continue to ventilate that way instead of providing control of ventilatory support. Because we're not going to know the transpulmonary pressure, since we do not put esophageal balloons in every patient, and we do not have electrical impedance tomography available, our clinical judgment must guide us.

Davies: How many times have you approached a resident or even a fellow to let them know a patient appears uncomfortable, and their immediate response is to treat the numbers? That is, "The patient must be okay since his numbers are okay." It's exactly what you were saying: the failure to recognize that something bad is going on. We just can't show what it is other than by clinical assessment.

MacIntyre: Let me give you a clinical scenario. You have a COPD patient who's getting better, who has been weaned down to 5 cm H_2O of pressure support, but you don't want to take the tube out yet because secretions are still a concern and the patient is not as awake as you'd like. Despite providing only 5 cm H_2O of pressure support, the patient looks comfortable but the V_T is 11 mL/kg. There's no clear right answer here—I'm just curious what the experts here might do. Would you reach for the dexmedetomidine and say we need to blunt this drive, or would you leave everything alone? Blood gases are OK, there is no metabolic acidosis, there is no sign of pain. So how many would reach for a drug, pick whichever one you like, to blunt that 11 mL/kg V_T? [Pause for panel response, during which no one raised a hand].

Kacmarek: Not as the first choice.

MacIntyre: Alright, you do all the things that Bob [Kacmarek] wants you to do to make the ventilator better, and still same scenario. [Pause for panel response; still no hands raised]. Everybody would let them ride? Interesting.

*** Hess:** I think the important question is why is this patient desiring a V_T of 11 mL/kg? Is the patient acidotic, is the patient in pain, is the patient anxious?

MacIntyre: I already stated that there was no obvious cause—no pain, no acidosis. You are messing up my survey!

Kacmarek: It's not a good survey!

*** Hess:** It's not so black and white.

MacIntyre: Rarely is clinical management black or white, and I agree with you there are many things that must be assessed in making clinical decisions. But there are patients, and I think if you're honest with yourself you've seen them—I know I've seen them. They look pretty darn good, they're comfortable, so why are they demanding such high V_T? There's this notion that, in the systemic inflammatory response syndrome, you get brain dysfunction that alters that loop gain I mentioned earlier to the point where there is a demand for a higher V_T. The neurologic patients do this all the time—there is this drive for a bigger than normal V_T. This invokes this notion of self-induced lung injury (SILI), which I think is a very reasonable concept. Dean [Hess] and Bob, you're absolutely right, of course you go through a checklist: why would this patient be demanding such a large V_T? But once you've gone through a checklist, there are patients who remain who just seem to like a big V_T. And what do we do with them?

Hill: One of the reasons my hand didn't go up is you gave us a COPD patient, and if you gave us somebody with hypoxemic respiratory failure I might have made a choice. But I don't see 11 mL/kg too often in COPD patients who are on a ventilator.

MacIntyre: Maybe COPD was a bad example, and in fact I see this more in the neurologic unit than I do in my medical ICU. So if I gave you a neurologic patient, would that change your mind?

Hill: No.

MacIntyre: I still can't get anybody to sedate this patient! By the way, based on what I know about the trade-offs of sedation versus the potential for SILI, I would not sedate under these conditions either.

Benditt: I deal with a lot of spinal cord-injured patients and because of interruption of baroreflexes and perhaps other physiologic abnormalities, they often desire a much higher V_T—in fact, it can be really big on occasion. I've done many things to try to reverse that without any effect; I have had spinal cord-injured patients who have been on 15 mL/kg for years with no effects. It makes me wonder whether we should do a survey of spinal cord-injured patients because many of them show these large V_Ts.

Hill: It's not just spinal cord-injured patients either, it's also chronic neuromuscular disease patients. I've had some over the years who like large V_Ts and they're ventilated at $>$10 mL/kg for years. Endurance athletes will ventilate themselves with high V_Ts sometimes for 24–48 h depending on what crazy thing they're doing, and they don't get any significant lung injury. I think when you have a vulnerable lung, if you have acute lung injury, then you're at risk if you ventilate at higher lung volumes. But I think patients who don't have acute lung injury are not necessarily at high risk.

MacIntyre: I accept all the points everyone has made, but there is literature out there that self-induced lung injury is real. The postoperative arena is, I think, an interesting one, where postoperative pulmonary complications are increased with use of large V_Ts, even though the lungs are near normal and end-inspiratory distending pressures are not excessive. Some fascinating animal data going back 30 years demonstrated that modest hyperventilation for 72 h with end-inspiratory volumes well below total lung capacity created tremendous lung injury.[2] I don't know who these athletes are who go 48 h with high V_T ventilation—that's impressive. There are marathon and triathletes who I know will go 6–8 h.

Hill: We did some studies on Iron Man triathletes. We enrolled about 40 subjects—this was before institutional review boards were as stringent. We published an article in one of the sports journals.[3] They had a slight reduction in V_T, and people think they may get a bit of edema, but these guys were going anywhere from 8–16 h and they were fine. The V_Ts during the event were at least double or more of what they would breathe at rest.

Kacmarek: The data that are out there show the type of injury you're talking about occurs in the hypoxemic respiratory failure patient, and I think that's the patient we're all concerned with. Every one of us sees this type of patient; if we cannot correct the ventilatory pattern in any other way, we would sedate that patient. Or, if it is a noninvasively ventilated patient, we would elect to intubate that patient. But the animal data are pretty much from ARDS models.

MacIntyre: Mascheroni's were normal sheep.[2]

Kacmarek: Kolobow's were normal sheep but affected their central nervous system.[4]

MacIntyre: But he did get a whopping lung injury. And again I go back to the postoperative patient who does have normal lungs and is at higher risk for postoperative complications.

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*** Hess:** Back to Nick's [Hill] point, I believe there was a study a number of years ago where the authors took elite athletes and exercised them to the maximum of whatever they could do and then they did bronchoalveolar lavage.[5] There were red cells in the bronchoalveolar lavage suggesting there was injury, either on the vascular side or on the lung side, or both, which to me suggests there was some injury there.

Hill: That's different than the endurance situation; you're going to an extreme level of exertion. It's sort of like a thoroughbred horse.

*** Hess:** That has blood in its sputum at the end of a race.

Hill: Right, you give racehorses a diuretic like furosemide beforehand, it reduces the hemoptysis. If you stretch the lung enough and increase pulmonary artery pressures enough, it's going to be injured. I think it's a matter of degree; if you're not at that level of extreme exertion, I think the normal human lung can endure much higher tidal volumes than we target in the ICU for hypoxemic respiratory failure patients.

MacIntyre: Xiaofei Cong at Mayo has done some interesting work[6] that may address this question. He showed that if you took the lungs slowly over time to a larger volume, it adapted to those larger volumes. So it's conceivable that in these long-term neurologic patients they actually might adapt to a larger V_T and it's this stretching phenomenon over time that allows it to go on. And that would not occur, or would be less likely to occur, in the acute setting.

Hill: The Operation Everest II study,[7] which was a simulated ascent of Everest in an Army research decompression chamber about 5 miles from where I live, had previously healthy, relatively athletic young men go through a 40-d simulated ascent to the summit of Everest where they put them on exercise bikes. Do you know what their minute volume was at the summit of Everest? It was 180 L/min on average to drive the CO_2 down so they could oxygenate, and they sustained that, not necessarily at the full 180 L/min, but certainly at extremely high volumes and frequencies for probably at least a couple of weeks at higher altitudes.

MacIntyre: I had the privilege of going to Nepal earlier this year, and I was fascinated with the Everest phenomena. I did not climb Everest (no surprise there!), but I did tour in a helicopter and was especially intrigued with the Everest basecamp situated around 17,500 ft above sea level. Climbers use the base camp as a place to adapt to hypoxemia, a process that takes several weeks and involves multiple mechanisms affecting hemoglobin and cellular metabolism. But perhaps it's also a place to adapt to hyperventilation and the stretch injury that might occur otherwise. It took 40 d to reach the summit in that simulated model, and maybe that's long enough to create some adaptation to not only hypoxemia but hyperventilation.

† Branson: Sometimes these discussions trigger old memories. There was a time when one of the original oxygen concentrator companies, OECO (Oxygen Enrichment Company, Schenectady, NY), would routinely treat racehorses by connecting them to that device through a nasal catheter. The key attribute of the OECO device was it only provided 30% oxygen but it provided 100% relative humidity at a very high flow. It may actually be the first high-flow nasal cannula ever used.

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