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Review Article

Respiratory Patterns in Neurological Injury, Pathophysiology, Ventilation Management, and Future Innovations: A Systematic Review

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Abstract

Traumatic brain injuries (TBI), ischemic stroke, hemorrhagic stroke, brain tumors, and seizures have diverse and sometimes overlapping associated breathing patterns. Homeostatic mechanisms for respiratory control are intertwined with complex neurocircuitry, both centrally and peripherally. This paper summarizes the neurorespiratory control and pathophysiology of its disruption. It also reviews the clinical presentation, ventilatory management, and emerging therapeutics. This review additionally serves to update all recent preclinical and clinical research regarding the spectrum of respiratory dysfunction. Having a solid pathophysiological foundation of disruptive mechanisms would permit further therapeutic development. This novel review bridges experimental/physiological data with bedside management, thus allowing neurosurgeons and intensivists alike to rapidly diagnose and treat respiratory sequelae of acute brain injury.

Introduction

Homeostatic mechanisms for respiratory control are diverse, sophisticated, and redundant, thus relying on both central and peripheral mechanisms. However, the orchestrated process of breathing under both physiological and pathologic conditions (*i.e.*, stressors and/or illnesses) relies on intact neurological anatomy and physiology. The overarching goal is the titrated ventilatory rate, depth, and rhythm to achieve proper gas exchange. The clinical syndrome known as Cushing's triad (intracranial hypertension, bradycardia, and irregular respirations) is a classic teaching point of the devastating clinical consequences of neurological deterioration.[1] Not only do patients with acute brain damage show abnormal breathing patterns, including periodic, irregular, and rapid respirations, but one-third of moderate-severe traumatic brain injury (TBI) patients will go on to develop acute lung injury.[2,3] The lungs may be the organ system most adversely affected by isolated acute brain injury with neurogenic pulmonary edema (NPE), ventilator-associated pneumonia, and acute respiratory distress syndrome (ARDS) being the main culprits.[4] Recent research has aimed to identify the physiologic cause of the disruptions and develop novel interventions. This paper summarizes the neurological basis and regulation of breathing as well as pathologic perturbations of this process. The exact mechanisms behind respiratory disruptions are incompletely understood and ongoing research presented acts to update the current understanding. The review also highlights ventilatory management and clinical challenges. Lastly, this paper provides an update regarding the preclinical and proposed investigative treatment approaches for respiratory distress in the context of neurologic injury.

Keywords: Respiration; Ventilation; Common review; Central nervous system.

Abbreviations: ARDS, acute respiratory distress syndrome; BBB, blood brain barrier; CNS, central nervous system; CPB, central periodic breathing; CSF, cerebral spinal fluid; DRG, dorsal root ganglia; ICU, intensive care unit; NPE, non-cardiogenic pulmonary edema; SAH, subarachnoid hemorrhage; SUDEP, sudden unexpected death in epilepsy syndrome; TBI, traumatic brain injury; TV, tidal volume; VRG, ventral respiratory group.

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Neurorespiratory control

Respiratory outputs: expiration vs inspiration

While increasingly complex with a multitude of neural pathways and communication systems, we attempted to focus on what a clinician should understand when caring for neurological patients. The medullary respiratory center is the focus of the central command of breathing. Simply and succinctly described by Costanzo,[5] it consists of a dorsal respiratory group (DRG) housing inspiratory neurons

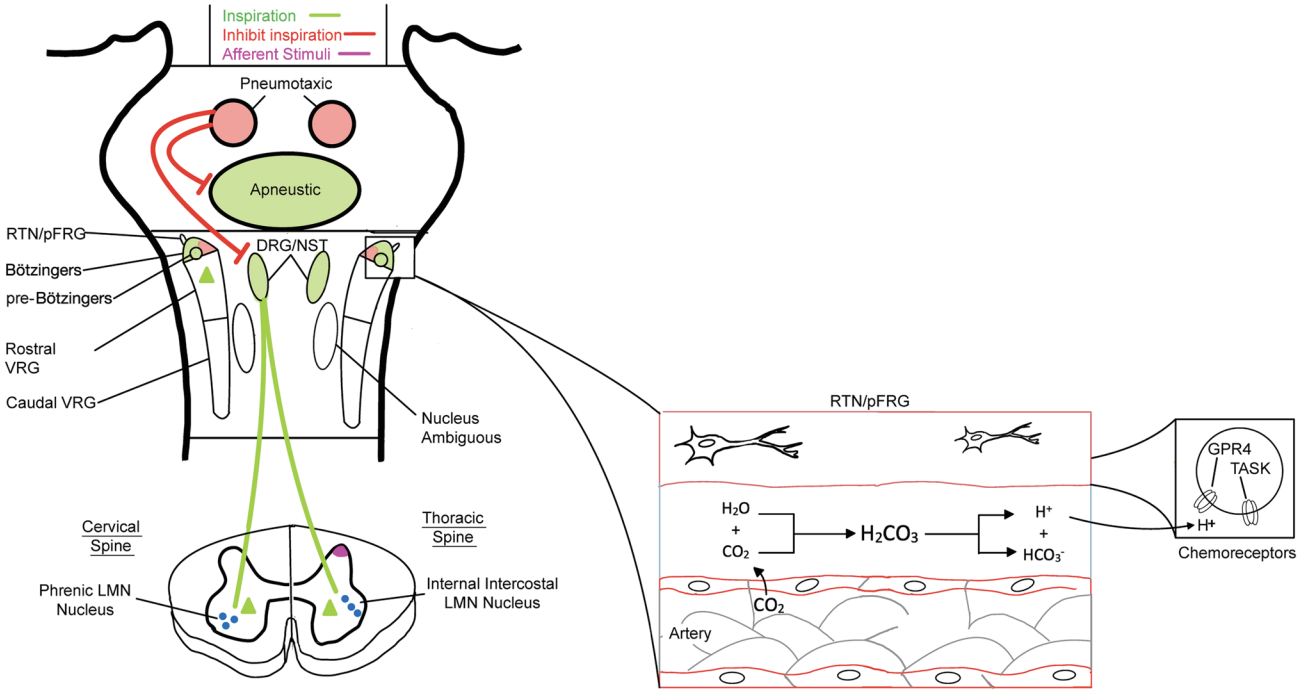

Fig. 1. Central respiratory controls and brainstem circuitry. (a) Demonstrates the brainstem inspiratory control activated by the apneustic center (green) and inhibited by the pneumotaxic center (Red). Intercommunication between these pontine respiratory centers is also shown in red. Pneumotaxic mediates switch from inspiration to expiration via the connections drawn in red; (b) chemoreceptive GRP4 and TASK receptors (in RTN) responding to H+ in CSF in the ventral nedulla and subsequently activating the respiratory compensation to the acidosis. DRG, dorsal respiratory group; NST, nucleus of the solitary track; pFRG, parafacial respiratory group; RTN, retrotrapezoid nucleus; VRG, ventral respiratory group.

and a ventral respiratory group (VRG) housing mainly an expiratory (and some inspiratory) neuron. The DRG is situated in the nucleus of the solitary tract, while the VRG consists of the retrotrapezoid nucleus/parafacial respiratory group (RTN/pFRG), Bötzinger's complex, pre-Botziner complex, rostral VRG, and caudal VRG (Fig. 1a).[6] It should be noted, however, that the exact anatomic origin of the rhythmic generation of respiration remains unclear.[6]

Inspiration is accomplished primarily via DRG medullary neurons communicating with spinal cord motor afferents to both the diaphragm (phrenic nerve) and external intercostal muscles. Additional inspiratory effort can be achieved by recruiting accessory muscles like the scalenes and sternocleidomastoid.[7] As the frequency of the action potential increases, the force of contraction of these muscle fibers increases due to more motor units being recruited.[8] Furthermore, the thoracic pressure drops due to an increase in the chest cavity volume resulting in a driving force of air from the environment to the airway. Additionally, during the inspiratory phase, the laryngeal and pharyngeal muscles are contracted allowing the glottic diameter to increase.[8]

Smooth inspiration over a period of approximately 2 s is followed by expiration lasting around 3 s.[8] To facilitate a smooth tidal volume entrance into the lung, inspiratory neurons depolarize in a fashion that results in a "inspiratory ramp". This ramp is a result of steady, continuous depolarization from the inspiratory neurons allowing for a smooth tidal volume entrance into the lungs, rather than abrupt, sudden inspiratory gasps. Switching to expiration is achieved by the cessation of the inspiratory neurons accomplished by the pneumotaxic center and various peripheral receptors (stretch receptors).

Under resting conditions, expiration is a passive process accomplished by the intrinsic elastic force of the lungs. However, expiration may become a more voluntary or forced process with the help of the VRG. Specifically, Botzinger's complex located most rostrally in the VRG is known to send impulses to internal intercostals and abdominal muscles (rectus, obliques, and transverse abdominus), while also inhibiting the inspiratory drive from the VRG and DRG neurons.[5–7] This helps compensate for insufficient expiration occurring due to either intrinsic lung parenchymal issues (*i.e.*, emphysematous lungs) or extrinsic stressors (*i.e.*, exercise).[5,8]

Central inputs to breathing

Respiration occurs constantly without any required attention. This predominantly autonomic process is fine-tuned to maintain metabolic homeostasis without any awareness. Perhaps the most well-known natural trigger for ventilation seen often in clinical practice is acidemia. Ventilation triggered by acidemia is considered one of the many autonomic mediators of respiration, whereas others include peripheral visceral inputs detailed in the prior section. Conscious control of respiration is also possible albeit limited. Moreover, intentional respiratory control involves different neural circuitry than the rhythmic autonomically driven breathing; we will discuss both these issues independently in the following sections.

This can be explained by increases in blood [H^+] that lead to increased blood cerebrospinal fluid (CSF) [CO_2]. The ultimate by-product of this is increased [H^+] in the CSF. These protons can also directly bind to central chemoreceptors located in the ventral medulla near cranial nerve (CN) IX/X which ultimately stimulate the DRG.[9] Two of the most heavily studied central chemoreceptors are TASK2 and GPR4, which are located in the RTN (Fig. 1b).[10]

Two centers located in the pons help augment the process of

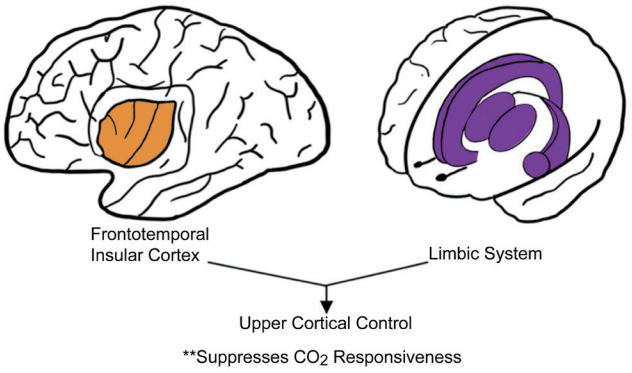

Fig. 2. The gross circuitry involved in the control of respiration above the brainstem.

breathing by either stimulating (apneustic center; lower pons) or inhibiting inspiration (pneumotaxic center; upper pons) (Fig. 1a). Not only do these centers communicate with the solitary nucleus in the DRG, but also with each other. Apneusis (severely prolonged inspiratory effort) has been reported in transection experiments, in which the higher pneumotaxic center is unable to inhibit the lower apneustic pons and medullary DRG neuron networks. Interestingly, this phenomenon is dependent on the non-intact vagus nerve.[6] Nevertheless, these pneumotaxic neurons were proposed as the main contributor to switching from an inspiratory to expiratory phase of breathing. As pneumotaxic center depolarization increases, inspiration is diminished, thus decreasing the inspiratory time and tidal volume while increasing the respiratory rate. The converse is also true.

Regarding the neurocircuitry involved in the conscious control of ventilation, less is understood. Feedback neural loops prohibit prolonged voluntary control as partial pressure of carbon dioxide (pCO_2) changes.[6] Nevertheless, increasing evidence points to both cortical and limbic locations as areas in which "higher" brain circuits for respiration are located.[11] Intracranial EEG (iEEG) recorded breath coherence values saw caudal-medial frontal, premotor, orbitofrontal, and motor cortex, insula, superior temporal gyrus, and amygdala being involved with volitational breathing and the anterior cingulum, premotor, insula, hippocampus were involved with attentive breathing (Fig. 2).[11] Higher cortical centers additionally function to modulate brainstem respiratory homeostasis. Under normal conditions, reflexive responsiveness to CO_2 is inhibited. This protective mechanism prevents apnea following hyperventilation.[12]

Peripheral inputs to breathing

Sensory afferents communicate with the central nervous system (CNS) (specifically near the nucleus of the solitary tract located in the DRG) via a variety of messengers, including glutamate, monoamines, purines, peptides, or other volatile co-transmitters.[13] These sensory afferents come from a variety of locations, including aortic and carotid bodies, pulmonary stretch receptors (PSR), muscles and joints, and airway epithelial cells.[6,14,15] CN IX is responsible for carrying afferent information from the carotid bodies located at the bifurcation of the external and internal carotid arteries (Fig. 3). The most important triggers to remember include

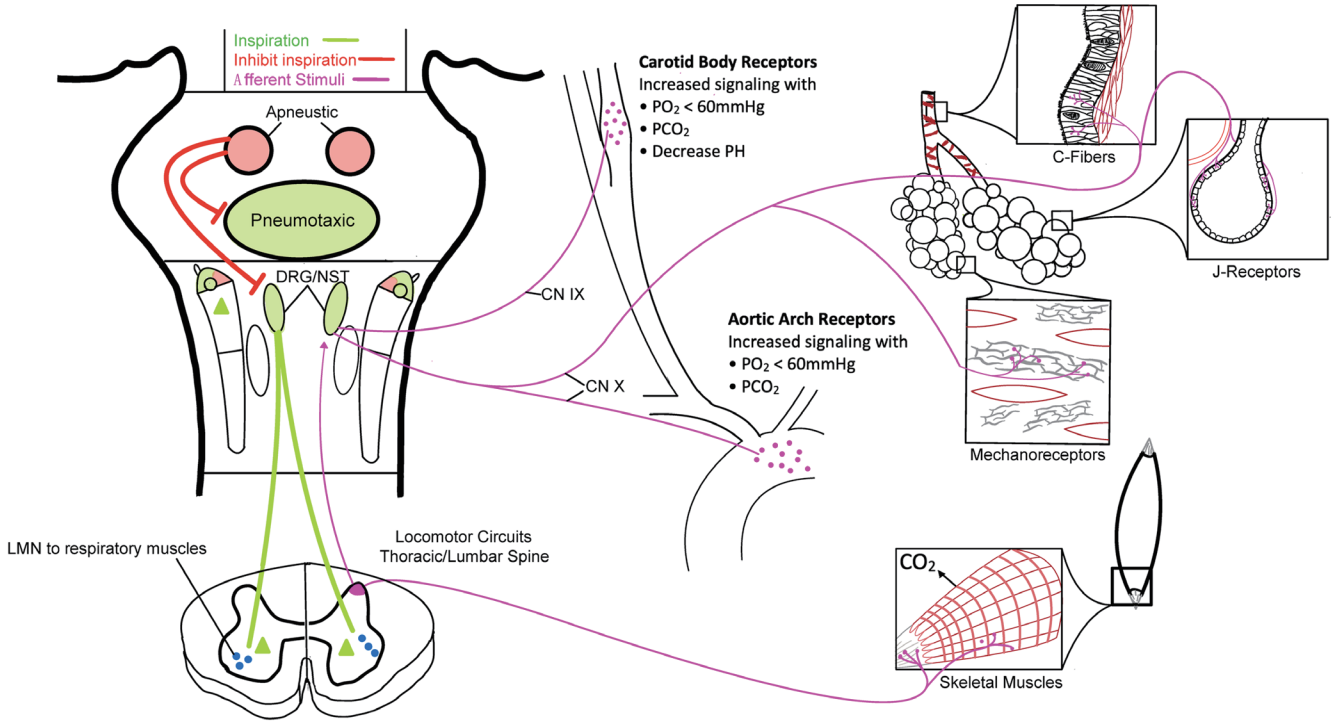

Fig. 3. Peripheral respiratory controls and brainstem circuitry. Peripheral inputs to the breathing arriving at the brainstem respiratory centers via CN IX (carotid bodies), CN X (aortic bodies and pulmonary receptors), and spinal locomotor circuits (muscle/tendon) are represented by the pink lines. All afferents terminate near the nucleus of the solitary track within the DRG and work in concert to modulate respiration. The brainstem communicates the LMN in the anterior horn of the spinal cord represented by the green lines. CN, cranial nerve; DRG, dorsal respiratory group; LMN, lower motor neurons; NST, nucleus of the solitary track.

decreased partial pressure of oxygen (PO_2) <60 mmHg, increased PCO_2, and decreased arterial pH.[16] Very similar to this is CN X, which relays the presence of diminished PO_2 and increased PCO_2 from the aortic bodies located in the aortic arch.

Irritants, mechanoreceptors, and metaboreceptors

The sophisticated orchestra of breathing must be dialed precisely to external environmental stimuli. The smooth muscle of the airways responds to the increased stretch (via vagal afferent mechanoreceptors) by decreasing the breathing rate (Hering-Breuer reflex).[5,15] This is accomplished by prolonging the expiratory time; however, this mechanism may only be applicable to human physiology at tidal volumes >800 ml.[5,6] The vagus nerve not only carries information from the peripheral chemoreceptors, stretch receptors, and mechano/metaboreceptors, but also from irritant receptors.

As mentioned before, switching to expiration is a complex process involving synchronous interactions between slowly adapting pulmonary stretch receptors (SAPR) and the central respiratory control centers. The "ramp" like increase in inspiratory activity is due to the abrupt inhibitory release mediated by the ventrorostoral medulla.[17] Visceral afferent signals from the SAPRs are relayed to the central control centers in the brainstem to facilitate the transition to expiration. Experimental data conducted on rats demonstrated that during lung inflation, the SAPRs released both adenosine triphosphate and glutamate from their central terminal at the dorsal medullary nucleus of the solitary track.[18]

Nuclei outside of the brainstem have also been found to contribute to the complex switching mechanisms. The medial parabrachial nucleus (mPBN) acts as an autonomic sensory relay station in the thalamus, whose role in this switch has been recently investigated.[19] Recent animal studies on beagles demonstrated the mPBN plays a role in attenuating the PSR mediated reflex.[20]

In addition, bronchopulmonary C-fibers located between the airway epithelia respond to the contact with noxious substances (*i.e.*, ammonia; cigarette smoke), consequently resulting in bronchial smooth muscle constriction, respiratory rate increase, and mucus production.[6,15,21] Lastly, juxtacapillary (J) receptors found in the alveolar walls respond to capillary distention and increased interstitial fluid volume by increasing the breathing rate (Fig. 2). This may underscore the subjective sense of breathlessness found in patients suffering from heart failure induced volume overload.

Limb movements can also activate both the mechanoreceptors and metaboreceptors in the joints, muscles, and tendons of the extremities which communicate with the DRG to increase the respiratory rate.[5,6,9] Different fiber types mediate the afferent inputs to the respiratory centers. Muscle spindles are transported by type Ia fibers, golgi tendon organs by type Ib fibers, muscular mechanical stimulation by type III fibers, and intramuscular metabolic changes by type IV fibers. Exercise hyperpnea involves a ventilatory response to submaximal exercise that is immediate and proportional to the metabolic rate.[22] Moreover, the exact mechanism of respiratory modulation is poorly understood, but evidence points toward afferent signals from the type III/IV fibers being the primary mediators of exercise hyperpnea. As a result, the afferent input is relayed via spinal locomotor circuits in the lumbar and thoracic spinal cord. Feedback from these peripheral inputs synergistically interacts with other stimulatory inputs to the central respiratory neuronal pool to modify respiration appropriately to meet the metabolic demands.[22]

CNS insults, pathophysiology, and clinical manifestations

Traumatic brain injuries (TBIs), ischemic stroke, hemorrhagic stroke, brain tumors, and seizures have diverse and sometimes overlapping associated breathing patterns. Respiratory dysfunction can be secondary to a localized lesion (stroke; trauma) or systemic dysfunction (metabolic; edema). In the following section, we will detail each insult's pathophysiology and clinical manifestations. Understanding and recognizing specific secondary clinic signs of respiratory decompensation can permit earlier intervention aimed to improve the patients' outcomes. Here we will discuss specific insults to the central nervous system and how these pathological disruptions interfere with respiratory control. The main problems often involve secondary systemic responses to a central injury, including catecholamine surges and inflammatory cascade activation. Therapeutic interventions discussed in the final section attempt to mediate these secondary insults.

TBI

TBIs are one of the leading causes of long-term disability in the United States. At the extremes of age (<17 and >55), TBI's are secondary to falls, contrary to adolescence and early adulthood (14–44), where motor vehicle collisions are most commonly responsible.[6] TBIs induce systemic changes extending far beyond the central and peripheral nervous system. The consequences are wide-reaching and highly complex, but of all the extracranial organs, the respiratory system is the most effected (81%).[23] TBI can directly induce devastating conditions like ARDS and NPE.[24]

Following brain trauma, there is a bi-phasic inflammatory response involving both innate and adaptive immune activation. The primary insult activates the innate immunity when the inflammasome proteins NLRP1 and NLRP3 increase. Once activated, IL-1β is produced for the purpose of CNS repair. Inflammatory pyroptotic cell death and glial activation potentiates the second phase of immune mediated damage.[25] NLRP1 is believed to be the primary contributor of initial neuroinflammation. This inflammation should be contained within the blood-brain barrier (BBB), but inflammation itself breaks this seal. Traumatic priming of microglia and astrocytes by fibrinogen, thrombin, and albumin lead to increased levels of transforming growth factor beta (TGF- β), glutamate, reactive oxygen species (ROS), vascular endothelial growth factor (VEGF), Tumor necrosis factor alpha (TNF-β), and interleukin-1β (IL-1β). These mediators upregulate the cellular adhesion molecules and neutrophil extravasation across the BBB.[26] Dysregulation of BBB permits the systemic release of inflammatory cytokines and partially contributes to the intricate systemic changes.

Systemic inflammation throughout the entire body incites conditions like ARDS and NPE. ARDS is a common complication in an intensive care unit (ICU) and frequent cause of death; Mortality rates range from 35–46%.[27] This is defined by noncardiogenic acute respiratory failure within a week of an inciting event. There is extensive medical literature on the multitude of conditions that also cause ARDS (pancreatitis, trauma, and uremia), and all etiologies induce a severe systemic inflammatory response flooding the lungs.[28] Alveolar capillaries also suffer extensive damage increasing vascular permeability. Air exchange is impossible as fluid suffocates the oxygen exchange interface and progressive atelectasis intensifies hypoxia. TBI with the Glasgow coma scale (GCS) <9 is associated with ARDS 20–30% of the time, which occurs most often 2–3 days after initiating the mechanical ventilation or 7–8 days post insult.[29] Experimental studies have demonstrated a synergistic detrimental effect of ARDS and acute intracranial hypertension (AICH). This hypothesis was tested on porcine animal models showing increased hippocampal and cerebral edema exacerbated

by ARDS alongside AICH.[30] However, ARDS is not exclusive to TBI and is notably present in 15–40% of patients with subarachnoid hemorrhage (SAH).[31]

NPE is like ARDS, but a distinctly different respiratory complication of TBI. More extensive research is warranted to fully understand the pathophysiology behind NPE. Recognizing NPE is difficult due to its nonspecific presenting symptoms and is currently considered a diagnosis of exclusion.[32] In addition, it has been theorized that an abrupt increase in ICP causes a systemic catecholamine release and vasoconstriction (Cushing effect). Intravascular hydrostatic engorgement induces endothelial injury further increasing pulmonary fluid extravasation.[30] The pathophysiology may extend beyond the mechanical capillary hyperextension driving fluid. Its suggested extracellular damage-associated molecular patterns (DAMP) and cytokine damage could contribute to alveolar damage. Like ARDS, clinical manifestation occurs in a bimodal fashion. Bilateral infiltrates on a chest X-ray may appear immediately (within minutes) following injury or 12–24 hours later.[30] Other CNS pathology inducing NPE includes seizure, infection, stroke, and spinal cord injury.[33]

An alternative mechanism of TBI induced respiratory dysfunction does not originate cytokines nor hyperadrenergic changes. Impact apnea, defined as complete cessation of the respiratory effort, has been demonstrated in animal models studying TBI. The arrest of breathing has been attributed to acute electrophysiological changes, as opposed to the delayed respiratory compromise seen in mechanical/biochemical disruption.[34]

Ischemic and hemorrhagic stroke

Like other lesions, strokes alter respiration that is largely dependent on the anatomical location and magnitude of the stroke. Up to one in six deaths in cardiovascular disease are due to stroke, and the most common subtype is ischemic stroke 87% of the time.[35] Neurogenic stunned myocardium is present in 20–40% of ischemic or hemorrhagic stroke.[36,37] Other stroke associated respiratory patterns are detailed below.

Central periodic breathing (CPB), also known as Cheynes-Stokes respiration, was first described in the context of heart failure, but also occurs secondary to stroke, brain tumors, and head trauma. This dysrhythmic breathing is characterized by regularly recurring oscillation of apneas and pre-apneas.[13] CPB has been seen in 53% of patients with acute ischemic stroke.[38] Nevertheless, there has been no clear association between the anatomical location and development of CPB, and the lack of localization suggests a nonspecific widespread respiratory control circuit. Only the increased size of ischemic tissue and presence of a mass effect has been correlated with CPB. It is speculated that larger lesions have a proportionally higher cytokine burden, thus increasing cortical dysfunction. Under normal physiological conditions, higher cortical centers inhibit respiratory reflexes. Following a stroke, cortical inhibition is damaged and respiratory reflexes (CO_2 responsiveness) are heightened. This led to the appearance of apneic episodes in 26% of patients within the first 24 hours of a stroke.[13] Periodic hypoxia and secondary reflexive sympathetic surges could increase the oxygen demand and worsen the ischemic tissue damage in both the heart and CNS. Recognition and management of CPB and other sleep dysrhythmias are now believed to be crucial in the prevention of secondary stroke.

Sleep disordered breathing (SDB) is another all-encompassing term for CPB alongside other sleep disturbances, including obstructive/central sleep apnea, hypoxemia/hypercapnia, and CPB. Most patients (50–70%) experience SDP following acute stroke. Notably, prevalence is higher among male patients following cryptogenic or recurrent strokes.[39] Research has also shown that SDP is associated with brain tumors.

Subarachnoid hemorrhage

A SAH is a potentially deadly brain bleed impacting 9/1,000,000 patients. SAH is a medical emergency, which most are caused by a ruptured cerebral aneurysm; prehospital mortality rates are as high as 15%.[40] As mentioned before, there is a high prevalence of ARDS following the traumatic inflammatory response induced by SAH. Systemic inflammatory changes may alter ventilation centrally in addition to the sites of gas exchange (*e.g.*, ARDS; NPE). Spontaneous hyperventilation may also be present following SAH and complicated care.

A retrospective analysis of 207 patients with SAH found 55% experienced spontaneous hyperventilation (hyperventilation without secondary cause). The presence of this spontaneous respiratory pattern was associated with diffuse cerebral edema and poor neurological outcomes.[40] Another study of 220 patients investigated hyperventilation hypocapnia and associated secondary ischemia. The results demonstrated an increased risk of delayed cerebral ischemia in diffusion restricted lesions (ex. watershed zones) and that a lower pCO_2 was independently associated with a greater risk of in-hospital death.[41] The exact pathophysiology behind this respiratory pattern is poorly understood, but it has been theorized that systemic inflammation induced by SAH contributes to this issue.

Systemic inflammatory response syndrome (SIRS) is seen in over 50% of those in the ICU.[20] Other theories suggest that extensive cortical inhibitory input is disrupted in severe brain injury, and absence of inhibition results in the hyperactivity of the central respiratory control center in the brainstem.[42]

Neurogenic stunned myocardium (NSM) is another potential cause of respiratory failure following SAH. NSM can precipitate acute cardiogenic pulmonary edema following SAH. Arrythmias of some form occur in up to 100% of SAH patients significantly more than prevalence with stroke with most occurring within the first week. Additionally, disruption of the diencephalic nuclei located in the brainstem are implicated in cardiogenic dysfunction.[43] These nuclei are inhibited from higher cortical areas within the insular cortex and hypothalamus. In the context of SAH, it has been hypothesized that severe increased intracranial pressure (ICP) damages upper respiratory modulatory centers resulting in catecholamine surges specifically at the sympathetic myocardium terminals.[36]

Seizure

Seizures are caused by an abnormal synchronous electrical discharge across one or multiple cerebral hemispheres. A considerable portion of the population would have a seizure throughout their lifetime (10%), but most people never develop epilepsy. Seizure prevalence has increased, thus theorized to be secondary of an increased survival rate following the CNS insults.[44] The hierarchy of seizure classification will not be discussed here, as we will focus on generalized tonic-clonic seizures (GTCS) and associated respiratory consequences. GTCS cause 1–3 m of cyclic sustained muscle contracture (tonic phase) followed by rhythmic jerking (clonic phase). Acutely in the tonic phase, patients may grow or cry as turbulent air is forced by the vocal cords.[45]

Patterns were studied in comparison to patients having non-epileptic seizures; the most common difference was found in the postictal respiratory patterns. Those having epileptic seizures exhibited

deep, prolonged inspiratory and expiratory phases. These breathing patterns were also regular and loud. Comparatively those having psychogenic non-epileptic seizures demonstrated rapid and shallow breathing patterns.[46] In true epileptic seizures, post-ictal breathing is driven by acidemia. Moreover, prolonged dystonic contractions result in increased serum lactic acid concentrations lowering the PH. Physiological countermeasures would also respond to decreased CSF PH by increasing the respiratory rate, and the tachypneic respiratory response would attempt to maintain the physiological acid base status. Similar concepts have driven counterregulatory respiration in early acidic stages of patients suffering from diabetic ketoacidosis, an acidic state that can occur in diabetics with uncorrected hypoglycemia before Kussmaul's respirations begin.[47,48]

Sudden unexpected death in epilepsy (SUDEP) is a common cause of death among epileptic populations. It is defined as a sudden, unexpected, non-traumatic, non-drowning death in an individual with epilepsy.[49] Respiratory dysfunction is a core component of SUDEP, and although little is known, its theorized to involve amygdala activation. Electrical stimulation of the amygdala in animal models resulted in apnea, but in human observational studies amygdala seizures were only sometimes associated with ictal apnea. In a small study monitoring 10 cases of SUDEP, further clinical manifestations of this respiratory pattern were detailed. Patients initially demonstrated tachypnea (18–50 breaths/m) immediately followed by GTCS. Within 3 m into the post-ictal state, terminal apnea and severe bradycardia were witnessed. This study demonstrated a 3-m window period for therapeutic intervention prior to cardiopulmonary arrest.[49] Further neuroimaging studies are thus warranted to elucidate the etiology of SUDEP, including investigating other pathophysiology at the brainstem respiratory network. Etiology aside, awareness and vigilance for apnea in the context of status epilepticus could prevent respiratory failure related mortality.[50]

Neoplasia

Brain tumors produce a diverse spectrum of respiratory effects depending on the tumor size, location, and characteristics. Tumors interfering with brainstem function have historically been associated with apnea and SDB, but recent studies have demonstrated similar respiratory effects of isolated cerebellar tumors. Sleep functional imaging was analyzed in posterior fossa tumor patients and abnormal signaling in cerebellar peduncles was correlated with SDB with most significant changes in the inferior cerebellar peduncle.[51]

Any growth disrupting CSF homeostasis has the potential to increase ICP and contribute to a herniation risk. Tumors in the third and fourth ventricle (colloid cyst, ependymoma, and meningioma) disrupt CSF drainage, consequently inducing obstructive hydrocephalus.[52] ICP elevation could additionally be secondary to cerebral edema caused by increased vessel permeability and blood-brain-barrier disruption. Late in tumor progression, any combination of hydrocephalus, edema, and mass effect could cause the feared consequence of brain herniation. Notably, of all the herniations, central herniations involving the midbrain cause devastating respiratory collapse.[53] Posterior fossa tumors also force the caudal medulla downward inducing life-threatening cardiopulmonary arrest.

A rare neoplastic respiratory complication is central neurogenic hyperventilation seen in primary central nervous system carcinomas.[54] Hyperventilation is not universally present and additional symptoms, include altered mental status (AMS), blurry vision, and gait disturbances. This is a diagnosis of exclusion once all other hypercapnic etiologies have been omitted.

Cushing reflex

One of the most well-known and widely observed respiratory patterns in neurological injury is the Cushing reflex. Clinically, this breathing pattern is presented with the classic triad of widened pulse pressure, bradycardia, and irregular respirations. The father of American neurosurgery, Dr. Harvey Cushing, first described these findings in 1901. The common provoking factors were severe increases in ICP, but the etiology of this increase varies widely. Characteristic respirations are shallow breaths with occasional periods of apnea.[55] It is important to note, this triad occurs in three distinct stages: initially hypertension, followed by bradycardia, and finally breathing alterations. Observation of >2 of the triad indicates impending herniation, and this has been associated with almost two-fold higher mortality.[55] With respiratory irregularity being the last of the triad, the presence of the cardiovascular dyad warrants immediate intervention. Notably, of the CNS insults reviewed, the Cushing reflex was not regularly seen in seizures. Hence, the presence of such reflex may indicate a secondary cause of the seizure (mass effect; trauma) opposed to a primary seizure disorder.

Ventilatory management

Severe brain injuries, TBI, or stroke are a frequent cause of ICU admissions requiring mechanical ventilation.[56,57] Mechanical ventilation is widely used to protect the airway against aspiration and to prevent hypoxemia and hypercapnia, two important contributors to secondary brain injury. A comprehensive set of ventilator settings criteria, including tidal volume (TV) or positive end-expiratory pressure (PEEP), are a topic of contention and until recently had not received adequate research. In recent years, there has been increased investment to understand respiratory management of neuro-ICU patients to improve the outcomes and reduce mortality secondary to respiratory complications.

Protective ventilation, using TV, high PEEP, permissive hypercapnia, prone positioning, recruitment maneuvers (RM), and extracorporeal membrane oxygenation (ECMO) have all been shown to be beneficial in patients with ARDS.[58–61] Managing TBI with ARDS can be challenging because the pulmonary and neurologic goals of oxygenation (hypercapnia vs hypocapnia) and maintaining perfusion pressures could be conflicting.

Prone positioning and high PEEP improve pulmonary gas exchange and respiratory mechanics by lowering the V/Q mismatch and opening collapsed alveoli, which reduces the intrapulmonary shunt.[58,62,63] These interventions may, however, be linked to the development of intracranial hypertension due to an obstructed jugular venous outflow and impaired cerebral venous return to the right atrium.[58,62–64] Furthermore, these measures could raise ICP and lower the mean arterial pressure, both of which lower CPP.[58,65]

In addition, recent studies evaluated ventilator settings attempting to achieve a middle ground in the concomitant management of respiratory distress in patients with TBI. A statistically significant drop in CPP was observed with increased PEEP in a retrospective investigation of 341 patients, but CPP remained within the therapeutic target.[66] However, in this study, the patients' volume status was not factored. Attention to volume status would also be vital because PEEP could affect CPP in hypovolemic patients. When the volume is overloaded, intrathoracic pressure increases, which may impede venous return and promote a further decrease in CPP. In another trial, the PEEP was increased to 15 cmH_2O in patients with TBI and ARDS. The results showed ICP and CPP were not significantly altered, while there was a considerable improvement

in brain tissue oxygenation with increased ventilatory PEEP.[31] In conclusion, assuming that ARDS patients with brain injury have volume stability, an increase in PEEP would appear to be safe and could even have favorable cerebral benefits.

Regarding TV, in both ARDS and brain damage patients, TV was a critical variable in ventilatory management. Low TV was a protective ventilation strategy used to manage ARDS in the ICU, which could lead to hypercapnia. Furthermore, high $PaCO_2$ would be detrimental for patients with a neurologic compromise, as this would cause cerebral vasodilation and thus result in an increased ICP; a high tidal volume was thought to be a more appropriate strategy.[56] Protective low TV (6–8 ml/kg of ideal predicted body weight) was evaluated in brain injury patients in the ICU. The results showed an improvement in the number of ventilator-free days during the intervention period.[57,67–69] If $PaCO_2$ was regulated within the physiological range, low TVs had no effect on the ICP or patient outcomes.[57,63,67,68] As a result, reducing the respiratory rate rather than the tidal volume could be a preferable method for managing respiratory distress in brain damage without jeopardizing the lung integrity or increasing secondary brain injury. The TV should be 6–8 ml/kg and RR regulated according to the defined target of CO_2, which would depend on the ICP and brain oxygenation. Extubation management, tracheostomy, and ECMO are other ventilatory management procedures that are less well understood in the context of brain injury.[25,58,70–73] The European Society of Intensive Care Medicine reviewed current physician practices and concluded that the intact protective airway reflexes, understanding of the underlying neurological insult, and patient's level of consciousness remained the most important factors for extubating success. Exactly when a more invasive tracheal intubation would be warranted is still debated due to a lack of data.[74]

Another ongoing global study, VENTIBRAIN, is investigating the effects of ventilator settings in brain injury patients with or without acute respiratory distress, as well as ventilator settings to manage intracranial hypertension.[70] This study would offer unique insights that would have the potential to fill the current gaps in the clinical management of ARDS in the setting of TBI. This study could additionally provide clarification for the efficacy of ventilation modalities like timely extubation, tracheostomy, and ECMO.

Current clinical management and emerging therapeutics

ARDS

Although the primary modalities currently used to treat ARDS are centered around ventilator management with the strategy aimed at reducing ventilator induced lung injury, there has been an increasing presence in the literature of therapeutic modalities that have aimed to prevent the pathophysiologic sequelae of ARDS.[75] These therapies include pharmacological approaches to mitigating damage secondary to the inflammatory response in ARDS and the use of cell-based therapies to support lung cellular architecture and increased recovery.[76,77]

The severity of the inflammatory response is a critical factor in respiratory and other associated organ failure that may occur during ARDS. Steroid use has also long been a target of study in the literature with lots of debate regarding their potential to reduce proinflammatory cytokines versus increased risk by obtunding the immune response in the setting of infection. A multicenter study in 2020 demonstrated that patients who received a high dose of dexamethasone earlier had more ventilator-free days as well as reduced mortality.[74] Immunomodulators have also become increasingly studied as potential therapeutic agents in curbing the inflammatory response. Moreover, Imatinib is a tyrosine kinase inhibitor that is being investigated as a potential form of adjuvant therapy during ARDS due to its antioxidant capability and its ability to reduce vascular permeability and attenuate the inflammatory response.[59] Bevacizumab, a vascular endothelial growth factor antibody, is also being studied for its potential ability to reduce pulmonary edema during ARDS.[78] This has been demonstrated in mice models. Finally, Pirfenidone, an NLRP3 inflammasome inhibitor has shown significant reduction in mortality, pulmonary edema, and neutrophile infiltration in mouse models.[76,79] This is thought to occur as NLRP3 inflammasome plays a direct role in proinflammatory cytokine activation, including caspases and IL-1β.[79] Other pharmacotherapies that are aimed at reducing the pathophysiologic insults of ARDS, include low dose inhaled carbon monoxide gas, which has been shown in preclinical studies to reduce oxidative stress and lung injury,[80] Solnatide, an alveolar sodium channel activator that demonstrated a reduction in interstitial lung fluid and reduced ventilation pressure,[80] and ACE2, which inactivates angiotensin II by reducing its implication in the inflammatory cascade as well as reducing post ARDs interstitial fibrosis.[81] All these pharmacotherapies have shown promise in preclinical trials, among others, and are currently being targeted for efficacy in clinical trials as adjuvant treatment of ARDS.[76]

Another area that is now being studied for potential therapy in ARDS is the use of pluripotent/multipotent progenitor cells to aid in the recovery and mitigate secondary damage to ARDS.[77] Embryonic stem cells, which are derived from blastocyte with the potential to differentiate into nearly any cell line and "induced pluripotent stem cells", which are derived from adult fibroblast cells that have been reprogrammed with transcription factors to differentiate into other cell lines, offer great potential for the treatment of ARDS.[77] The devastating implications of ARDS could last long after patients have recovered. In certain cases, particularly severe ones, patients are left with reduced respiratory capacity and post ARDS fibrosis.[75] Pluripotent cells would therefore provide an avenue for lung repair by differentiating into alveolar cells and replacing ones that are injured, thus helping reduce the impact of post ARDS.[82] The potential benefit of these cells is not limited to direct replacement, but their paracrine effect on native alveolar cells has been shown to potentially cause immunomodulation and curb the inflammatory damaging effects. These stem cells do this by providing direct support to native cells through cell-to-cell contact which mediates protein, organelle, and nucleic acid transport via macrovesicles.[77] Mesenchymal stem/stromal cells, although less capable in their ability to differentiate, have also been shown to have a profound ability to modulate the immune system by directly affecting the macrophages, lymphocytes, and neutrophiles thought growth factor and cytokine release.[77,82,83] Currently, these approaches have been shown to be effective in ARDS models and preclinical trials. Additionally, several new studies are now aimed at evaluating their efficacy in clinical trials.[79]

Although these modalities have shown promise in preclinical trials, many have yet to be proven efficacious in clinical trials and results may yet be several years away due to the need of RCTs and multi-phase trials.[75] The complex nature of ARDS also makes it difficult to create preclinical models that are representative of the array of factors that affect ARDS progression, such as the timing of the insults, patient specific demographics, and the presence of ongoing comorbidities.[76] This results in multiple confounders, and as a result, positive findings may not be seen when applied to human subjects. As a consequence, these obstacles make adjuvant

therapies still far from clinical practice, however as better preclinical models and more specified clinical RCTs are being employed, we may yet see many new medical therapies being employed in the treatment of ARDS in the coming decades.

Neurogenic pulmonary edema

There have been recent investigations into therapeutics for NPE. With many being unfamiliar with handling this condition, this has proven to be a chaotic and difficult complication to handle.[32,84] Current treatments for NPE are aimed to reduce intracranial pressure and control sympathetic hyperactivity related to lung injury. Sympathetic hyperactivity has been a promising target of multiple innovative NPE treatments. Sevoflurane acts as a sympatholytic and has known neuroprotective effects on CNS injuries. Prior studies have additionally demonstrated sevoflurane's antioxidant, metabolic, and hemodynamic benefits, and it is hypothesized to have the clinical utility in improving neurological and pulmonary functional outcomes in NPE.[32,84] Likewise, atropine has received attention for similar sympatholytic properties. A hypothesis has been introduced that high doses of atropine could prevent NPE by attenuating the baroreflexive bradycardic response to increased systemic blood pressure.[85] Atropine was suggested to provide additional benefits of bronchial dilatation and pulmonary venous relaxation, hence adventitious in improving respiratory function. As such, both of these interventions have promise for disrupting the cascade autonomic dysregulation core to NPA pathophysiology.

Another innovative preclinical therapy target for NPE is aimed at suppressing inflammatory apoptosis, an aspect of NPE that has not yet been investigated. The sympathetic hyperactivity would initiate NPE, but inflammation is thought to maintain and aggravate the edema by increasing the capillary permeability. For the first time ever, a compound was proven to prevent lung cell apoptosis in NPE after SAH in an animal study. A model of SAH was created using endovascular perforation of the left anterior cerebral artery in mice. A high dose (10 mg/Kg) of a capsase-1 inhibitor Ac-YVAD-CMK inhibited pulmonary endothelial cell apoptosis and significantly reduced NPE. Additional preclinical trials are warranted to further understand the mechanism and drawbacks of capsase-1 targeted therapy.[86]

Central breathing disturbances

Little is known regarding the influence central breathing disturbances have on stroke recovery, and CPAP therapy is often not tolerated.[87] There are few available pharmacological treatments for central breathing disturbances. A series of agents modifying both the central and peripheral respiratory drive has been researched. Acetazolamide and mirtazapine have been investigated for treating CSA in the context of spinal cord injury. Acetazolamide also showed efficacy in reducing CSA severity and is a promising target for patients unable to tolerate positive airway pressure therapy. The findings have suggested that acetazolamide alters the central respiratory drive by widening the CO_2 reserve and decreasing the propensity to develop sleep apnea.[88] Mirtazapine is another agent with the potential to reduce CSA severity by widening the CO_2 reserve. Existing clinical and preclinical trials have demonstrated modulation of serotonin receptors could decrease the susceptibility to SDB. In a recent study done in Michigan, USA, administration of 15 mg of mirtazapine for one week resulted in a significant decrease in the positive airway pressure requirement compared to a placebo. Mirtazapine's mechanism of improving sleep disturbances is complex and requires further assessment.[89] Triazolam is a centrally acting benzodiazepine shown to decrease sleep apneas and improve daytime psychomotor performance and alertness.[90] Unilateral phrenic nerve stimulation is another new therapeutic strategy that has shown some promise in heart failure induced central breathing disturbances but requires further large-scale data collection.[91] Furthermore, a recent study investigating transvenous phrenic nerve stimulation (TPNS) investigated a new clinically relevant endpoint differing from the traditional apnea-hypopnea index (AHI). Investigators focused on the nocturnal hypoxia burden, an endpoint believed to be more predictive of mortality. This was measured with time spent with an oxygen saturation below 90% (T90). A pivotal trial conducted on 151 randomized patients demonstrated TPNS improved the average nocturnal oxygen saturation and T90. Nonetheless, more trials are warranted to assess the TPNS' effect on long-term outcomes.[92]

Neurogenic stunned myocardium

There are proposed mechanisms of preventing cardiogenic shock following neurological injury. A study done in 2013 was the first to demonstrate that beta blockers (β-blockers) administration prior to admission was associated with a reduced risk of developing NSM. It was theorized that pretreatment with β-blockers effectively blocked the effect of SAH induced catecholamine surges sparing myocardial tissue damage.[93] In the context of NSM, traditional inotropes are often ineffective at restoring cardiac stability and may worsen catecholamine surplus induced arrythmias. High dose insulin therapy has also been shown to increase hemodynamics by offsetting increasing the glucose uptake into cardiomyocytes.[20] Likewise, hyperinsulinemia-euglycemic therapy has proven effective in case studies and warrants further clinical evaluation.[94]

Sudden unexpected death in epilepsy syndrome

Regarding preventing SUDEP, increased attention has been drawn to pharmacological variables. Many commonly prescribed medications have been theorized to alter the risk of SUDEP, but clinical data is still lacking. A population-based control study in Sweden investigated the association of an automated external defibrillator (AED), selective serotonin reuptake inhibitors (SSRI), neuroleptics, β-blockers, and statins with SUDEP. The results showed that AED polytherapy significantly reduced the risk of SUDEP (most commonly carbamazepine and lamotrigine). Of the monotherapies, levetiracetam was the sole agent associated with significantly lowering the risk of SUDEP. A reduced risk was also reported with concurrent statin use, but none was reported with other analyzed agents. Notably, none of the investigated medications were associated with an increased risk of SUDEP.[95]

As neuromodulatory interventions for refractory epilepsy continue to be utilized, their effect on SUDEP must be evaluated. Vagal nerve stimulation (VNS) has been used for over 30 years and continues to be the most used form of neurostimulation to treat epilepsy.[45] Recent population studies found the rate of SUDEP to be significantly lower in VNS, ANT-DBS (anterior nucleus of the thalamus-deep brain stimulation), and RNS (responsive neurostimulation of the epileptogenic zone) therapy.[96]

For those with secondary SUDEP to Dravet syndrome, recent use of targeted augmentation of nuclear gene output technology (TANGO) has shown to reduce the incidence of SUDEP in mouse models. This intervention worked by utilizing antisense oligonucleotides to increase the expression of the Scn1a transcription,

Table 1. Each respiratory insult alongside the pathophysiology and spectrum of the treatments covered in this review

Respiratory dysfunction	Symptoms	Pathophysiology	Proposed Treatment
ARDS	Acute respiratory failure 2–3 days post ventilation initiation of 7–8 days post insult	Increased alveolar membrane capillary permeability	Ventilatory support, bevacizumab, pirfenidone, low dose carbon monoxide gas, solnatide, ACE3, stem cell modalities
NPE	Nonspecific and difficult to diagnose	Catecholamine surge mediated increase in hydrostatic pressure	Sevoflurane, atropine, and capsase-1 inhibitors
CBD	Highly variable depending on specific CBD	Damage to higher cortical breathing centers heightening respiratory reflexes	CPAP, acetazolamide, mirtazapine, TPNS
NSM	Cardiogenic pulmonary edema within first week of insult	Catecholamine surges at myocardial terminals of sympathetic circuitry	Prophylactic β -Blockers, hyperinsulinameic euglycemia therapy
SUDEP	Tachpnea followed by GTCS. Terminal apnea or severe bradycardia in post-ictal state	GTCS induced compromise of cardiopulmonary function	Preventative measures including VNS, ANT-DBS, and RNS therapy. TANGO therapy for Dravet syndrome

ARDS; acute respiratory distress syndrome; CBD, central breathing disorders; CPAP, continuous positive airway pressure; NPE; neurogenic pulmonary edema; NSM, neurogenic stunned myocardium; SUDEP, sudden unexpected death in epilepsy; TPNS, transvenous peripheral nerve simulator.

consequently preventing SUDEP in 97% of mice up to 90 days after injection.[97]

Future directions

Systemic changes following CNS injury cause significant pulmonary damage. Despite the heterogeneity of each detailed respiratory dysfunction, innovative therapeutic research has shown a conceptual overlap (Table 1). In ARDS and NPE, targeting the inflammatory cascade with immunomodulatory drugs (imatinib, pirfenidone, Ac-YVAD-CMK, and steroids) offer future promise. For NSM and NPE, it has been hypothesized that mitigating sympathetic hyperactivity and catecholamine surges have therapeutic potential (β-Blockers, sevoflurane, and atropine). Innovative treatment for chronic respiratory dysfunction following injury has also received increasing attention. Investigative treatments for conditions like SUDEP and CBD both utilize emerging neuromodulatory interventions (VNS, ANT-DBS, RNS, and TPNS). Therefore, the long-term outcome data from currently implanted devices and the integration of emerging implantable technology offers significant therapeutic potential. Current evidence from retrospective and preclinical trials exists, but additional clinical trials are warranted. As patient survival improves following neurological injury, preventing and treating secondary respiratory dysfunction is an important topic for continued research.

Conclusions

Neurological conditions cause complex and overlapping patterns of respiratory dysfunction. Understanding the underlying neurological respiratory pathophysiology would provide clinicians and researchers with a foundation to identify and create innovative therapeutic targets. Early recognition of symptoms and proper ventilatory management would remain vital for improving patients' outcomes, but there has been significant preclinical research investigating additional interventions. In addition, there is significant interventional potential for the prevention and management of ARDS, NPE, CBD, NSM, and SUDEP, but further preclinical and clinical trials are warranted to strengthen the available evidence.

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Conflict of interest

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References

[1] Heymans C. The control of heart rate consequent to changes in the cephalic blood pressure and in the intracranial pressure. Am J Physiol Legacy Content 1928;85(3):498–506. doi:10.1152/ajplegacy.1928.85.3.498.
[2] North JB, Jennett S. Abnormal breathing patterns associated with acute brain damage. Arch Neurol 1974;31(5):338–344. doi:10.1001/archneur.1974.00490410086010, PMID:4411797.
[3] McDonald SJ, Sharkey JM, Sun M, Kaukas LM, Shultz SR, Turner RJ, *et al*. Beyond the Brain: Peripheral Interactions after Traumatic Brain Injury. J Neurotrauma 2020;37(5):770–781. doi:10.1089/neu.2019.6885, PMID:32041478.
[4] Clinical Gate. Control of Ventilation. Available from https://clinicalgate.com/control-of-ventilation/. Accessed September 6, 2022.
[5] Costanzo LS. Physiology (6th Edition). Elsevier; 2017.
[6] Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic Brain Injury: An

overview of epidemiology, pathophysiology, and medical management. Med Clin North Am 2020;104(2):213–238. doi:10.1016/j.mcna.2019.11.001, PMID:32035565.
[7] De Troyer A, Boriek AM. Mechanics of the respiratory muscles. Compr Physiol 2011;1(3):1273–1300. doi:10.1002/cphy.c100009, PMID:23733642.
[8] Gosselink R. Breathing techniques in patients with chronic obstructive pulmonary disease (COPD). Chron Respir Dis 2004;1(3):163–72. doi:10.1191/1479972304cd020rs, PMID:16281658.
[9] Webster LR, Karan S. The Physiology and Maintenance of Respiration: A Narrative Review. Pain Ther 2020;9(2):467–486. doi:10.1007/s40122-020-00203-2, PMID:33021707.
[10] Guyenet PG, Stornetta RL, Souza GMPR, Abbott SBG, Shi Y, Bayliss DA. The Retrotrapezoid Nucleus: Central Chemoreceptor and Regulator of Breathing Automaticity. Trends Neurosci 2019;42(11):807–824. doi:10.1016/j.tins.2019.09.002, PMID:31635852.
[11] Herrero JL, Khuvis S, Yeagle E, Cerf M, Mehta AD. Breathing above the brain stem: volitional control and attentional modulation in humans. J Neurophysiol 2018;119(1):145–159. doi:10.1152/jn.00551.2017, PMID:28954895.
[12] Cherniack NS, Longobardo G, Evangelista CJ. Causes of Cheyne-Stokes respiration. Neurocrit Care 2005;3(3):271–279. doi:10.1385/NCC:3:3:271, PMID:16377843.
[13] Shevtsova NA, Marchenko V, Bezdudnaya T. Modulation of Respiratory System by Limb Muscle Afferents in Intact and Injured Spinal Cord. Front Neurosci 2019;13:289. doi:10.3389/fnins.2019.00289, PMID:30971888.
[14] Guyenet PG, Bayliss DA, Stornetta RL, Kanbar R, Shi Y, Holloway BB, *et al*. Interdependent feedback regulation of breathing by the carotid bodies and the retrotrapezoid nucleus. J Physiol 2018;596(15):3029–3042. doi:10.1113/JP274357, PMID:29168167.
[15] Alheid GF, McCrimmon DR. The chemical neuroanatomy of breathing. Respir Physiol Neurobiol 2008;164(1-2):3–11. doi:10.1016/j.resp.2008.07.014, PMID:18706532.
[16] Ziaka M, Exadaktylos A. Brain-lung interactions and mechanical ventilation in patients with isolated brain injury. Crit Care 2021;25(1):358. doi:10.1186/s13054-021-03778-0, PMID:34645485.
[17] von Euler C. On the central pattern generator for the basic breathing rhythmicity. J Appl Physiol Respir Environ Exerc Physiol 1983;55(6):1647–1659. doi:10.1152/jappl.1983.55.6.1647, PMID:6363361.
[18] Chiang MC, Bowen A, Schier LA, Tupone D, Uddin O, Heinricher MM. Parabrachial Complex: A Hub for Pain and Aversion. J Neurosci 2019;39(42):8225–8230. doi:10.1523/JNEUROSCI.1162-19.2019, PMID:31619491.
[19] Chiang MC, Bowen A, Schier LA, Tupone D, Uddin O, Heinricher MM. Parabrachial Complex: A Hub for Pain and Aversion. J Neurosci 2019;39(42):8225–8230. doi:10.1523/JNEUROSCI.1162-19.2019, PMID:31619491.
[20] Zygun DA, Kortbeek JB, Fick GH, Laupland KB, Doig CJ. Non-neurologic organ dysfunction in severe traumatic brain injury. Crit Care Med 2005;33(3):654–660. doi:10.1097/01.CCM.0000155911.01844.54, PMID:15753760.
[21] Chandler BT, Pernu P. Hyperinsulinaemic euglycaemic therapy use in neurogenic stunned myocardium following subarachnoid haemorrhage. Anaesth Intensive Care 2018;46(6):575–578. doi:10.1177/0310057X1804600607, PMID:30447666.
[22] Bruce RM, Jolley C, White MJ. Control of exercise hyperpnoea: Contributions from thin-fibre skeletal muscle afferents. Exp Physiol 2019;104(11):1605–1621. doi:10.1113/EP087649, PMID:31429500.
[23] Zuperku EJ, Hopp FA, Stuth EAE, Stucke AG. Interaction between the pulmonary stretch receptor and pontine control of expiratory duration. Respir Physiol Neurobiol 2021;293:103715. doi:10.1016/j.resp.2021.103715, PMID:34126261.
[24] Mascia L, Zavala E, Bosma K, Pasero D, Decaroli D, Andrews P, *et al*. High tidal volume is associated with the development of acute lung injury after severe brain injury: an international observational study. Crit Care Med 2007;35(8):1815–1820. doi:10.1097/01.CCM.0000275269.77467.DF, PMID:17568331.
[25] Bortolotti P, Faure E, Kipnis E. Inflammasomes in Tissue Damages and Immune Disorders After Trauma. Front Immunol 2018;9:1900. doi:10.3389/fimmu.2018.01900, PMID:30166988.
[26] Chodobski A, Zink BJ, Szmydynger-Chodobska J. Blood-brain barrier pathophysiology in traumatic brain injury. Transl Stroke Res 2011;2(4):492–516. doi:10.1007/s12975-011-0125-x, PMID:22299022.
[27] Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, *et al*. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372(8):747–755. doi:10.1056/NEJMsa1410639, PMID:25693014.
[28] Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, *et al*. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818–824. doi:10.1164/ajrccm.149.3.7509706, PMID:7509706.
[29] Hu PJ, Pittet JF, Kerby JD, Bosarge PL, Wagener BM. Acute brain trauma, lung injury, and pneumonia: more than just altered mental status and decreased airway protection. Am J Physiol Lung Cell Mol Physiol 2017;313(1):L1–L15. doi:10.1152/ajplung.00485.2016, PMID:28408366.
[30] Colice GL, Matthay MA, Bass E, Matthay RA. Neurogenic pulmonary edema. Am Rev Respir Dis 1984;130(5):941–948. doi:10.1164/arrd.1984.130.5.941, PMID:6388446.
[31] Robba C, Ball L, Battaglini D, Iannuzzi F, Brunetti I, Fiaschi P, *et al*. Effects of positive end-expiratory pressure on lung ultrasound patterns and their correlation with intracranial pressure in mechanically ventilated brain injured patients. Crit Care 2022;26(1):31. doi:10.1186/s13054-022-03903-7, PMID:35090525.
[32] Lozada-Martínez ID, Rodríguez-Gutiérrez MM, Ospina-Rios J, Ortega-Sierra MG, González-Herazo MA, Ortiz-Roncallo LM, *et al*. Neurogenic pulmonary edema in subarachnoid hemorrhage: relevant clinical concepts. Egypt J Neurosurg 2021;36(1):27. doi:10.1186/s41984-021-00124-y, PMID:34988372.
[33] Rajagopal R, Ganesh S, Vetrivel M. Neurogenic Pulmonary Edema in Traumatic Brain Injury. Indian journal of critical care medicine: peer-reviewed. ISCCM 2017;21(5):329–331. doi:10.4103/ijccm.IJCCM_431_16.
[34] Paek D, Kwon DI. A review on four different paths to respiratory arrest from brain injury in children; implications for child abuse. J Forensic Leg Med 2020;71:101938. doi:10.1016/j.jflm.2020.101938, PMID:32342908.
[35] CDC WONDER Online Database. Underlying Cause of Death, 1999-2020. Available from https://wonder.cdc.gov/ucd-icd10.html. Accessed September 6, 2022.
[36] Ali A, Ahmad MQ, Malik MB, Alvi ZZ, Iftikhar W, Kumar D, *et al*. Neurogenic Stunned Myocardium: A Literature Review. Cureus 2018;10(8):e3129. doi:10.7759/cureus.3129, PMID:30345188.
[37] Nguyen H, Zaroff JG. Neurogenic stunned myocardium. Curr Neurol Neurosci Rep 2009;9(6):486–91. doi:10.1007/s11910-009-0071-0, PMID:19818236.
[38] Rowat AM, Wardlaw JM, Dennis MS. Abnormal breathing patterns in stroke: relationship with location of acute stroke lesion and prior cerebrovascular disease. J Neurol Neurosurg Psychiatry 2007;78(3):277–279. doi:10.1136/jnnp.2006.102228, PMID:17060339.
[39] Hepburn M, Bollu PC, French B, Sahota P. Sleep Medicine: Stroke and Sleep. Mo Med 2018;115(6):527–532. PMID:30643347.
[40] Yokoyama S, Hifumi T, Okazaki T, Noma T, Kawakita K, Tamiya T, *et al*. Association of abnormal carbon dioxide levels with poor neurological outcomes in aneurysmal subarachnoid hemorrhage: a retrospective observational study. J Intensive Care 2018;6:83. doi:10.1186/s40560-018-0353-1, PMID:30574334.
[41] Hextrum S, Minhas JS, Liotta EM, Sorond FA, Naidech AM, Maas MB. Hypocapnia, ischemic lesions, and outcomes after intracerebral hemorrhage. J Neurol Sci 2020;418:117139. doi:10.1016/j.jns.2020.117139, PMID:32949919.
[42] Zheng RZ, Lei ZQ, Yang RZ, Huang GH, Zhang GM. Identification and Management of Paroxysmal Sympathetic Hyperactivity After Traumatic Brain Injury. Front Neurol 2020;11:81. doi:10.3389/fneur.2020.00081, PMID:32161563.
[43] Estañol Vidal B, Badui Dergal E, Cesarman E, Marin San Martin O, Loyo M, Vargas Lugo B, *et al*. Cardiac arrhythmias associated with subarachnoid hemorrhage: prospective study. Neurosurgery 1979;5(6):675–680. doi:10.1227/00006123-197912000-00005, PMID:534076.

[44] Falco-Walter J. Epilepsy-Definition, Classification, Pathophysiology, and Epidemiology. Semin Neurol 2020;40(6):617–623. doi: 10.1055/s-0040-1718719, PMID:33155183.
[45] Pack AM. Epilepsy Overview and Revised Classification of Seizures and Epilepsies. Continuum (Minneap Minn) 2019;25(2):306–321. doi:10.1212/CON.0000000000000707, PMID:30921011.
[46] Bergen DC. Diagnosing pseudoseizures: don't hold your breath. Epilepsy Curr 2008;8(6):154–155. doi:10.1111/j.1535-7511.2008.00277.x, PMID:19127309.
[47] Gallo de Moraes A, Surani S. Effects of diabetic ketoacidosis in the respiratory system. World J Diabetes 2019;10(1):16–22. doi:10.4239/wjd.v10.i1.16, PMID:30697367.
[48] Nass RD, Zur B, Elger CE, Holdenrieder S, Surges R. Acute metabolic effects of tonic-clonic seizures. Epilepsia Open 2019;4(4):599–608. doi:10.1002/epi4.12364, PMID:31819916.
[49] Maguire MJ, Jackson CF, Marson AG, Nolan SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). Cochrane Database Syst Rev 2016;7:CD011792. doi:10.1002/14651858.CD011792.pub2, PMID:27434597.
[50] Park K, Kanth K, Bajwa S, Girgis F, Shahlaie K, Seyal M. Seizure-related apneas have an inconsistent linkage to amygdala seizure spread. Epilepsia 2020;61(6):1253–1260. doi:10.1111/epi.16518, PMID:32391925.
[51] Lee A, Chen ML, Abeshaus S, Poliakov A, Ojemann JG. Posterior fossa tumors and their impact on sleep and ventilatory control: a clinical perspective. Respir Physiol Neurobiol 2013;189(2):261–271. doi:10.1016/j.resp.2013.05.027, PMID:23727229.
[52] Alentorn A, Hoang-Xuan K, Mikkelsen T. Presenting signs and symptoms in brain tumors. Handb Clin Neurol 2016;134:19–26. doi:10.1016/B978-0-12-802997-8.00002-5, PMID:26948346.
[53] Esquenazi Y, Lo VP, Lee K. Critical Care Management of Cerebral Edema in Brain Tumors. J Intensive Care Med 2017;32(1):15–24. doi:10.1177/0885066615619618, PMID:26647408.
[54] TarulliAW,LimC,BuiJD,SaperCB,AlexanderMP.Centralneurogenichyperventilation: a case report and discussion of pathophysiology. Arch Neurol 2005;62(10):1632–1634. doi:10.1001/archneur.62.10.1632, PMID:16216951.
[55] Dinallo S, Waseem M. Cushing Reflex. StatPearls Publishing; 2022. PMID:31747208.
[56] Esteban A, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, *et al*. Characteristics and outcomes in adult patients receiving mechanical ventilation: A 28-day international study. JAMA 2002;287(3):345–355. doi:10.1001/jama.287.3.345, PMID:11790214.
[57] Asehnoune K, Mrozek S, Perrigault PF, Seguin P, Dahyot-Fizelier C, Lasocki S, *et al*. A multi-faceted strategy to reduce ventilation-associated mortality in brain-injured patients. The BI-VILI project: a nationwide quality improvement project. Intensive Care Med 2017;43(7):957–970. doi:10.1007/s00134-017-4764-6, PMID:28315940.
[58] Della Torre V, Badenes R, Corradi F, Racca F, Lavinio A, Matta B, *et al*. Acute respiratory distress syndrome in traumatic brain injury: how do we manage it? J Thorac Dis 2017;9(12):5368–5381. doi:10.21037/jtd.2017.11.03, PMID:29312748.
[59] Rizzo AN, Sammani S, Esquinca AE, Jacobson JR, Garcia JG, Letsiou E, *et al*. Imatinib attenuates inflammation and vascular leak in a clinically relevant two-hit model of acute lung injury. Am J Physiol Lung Cell Mol Physiol 2015;309(11):L1294–L1304. doi:10.1152/ajplung.00031.2015, PMID:26432864.
[60] Fanelli V, Vlachou A, Ghannadian S, Simonetti U, Slutsky AS, Zhang H. Acute respiratory distress syndrome: new definition, current and future therapeutic options. J Thorac Dis 2013;5(3):326–334. doi:10.3978/j.issn.2072-1439.2013.04.05, PMID:23825769.
[61] Parsons PE, Eisner MD, Thompson BT, Matthay MA, Ancukiewicz M, Bernard GR, *et al*. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med 2005;33(1):1–6.doi:10.1097/01.ccm.0000149854.61192.dc,PMID:15644641.
[62] Sud S, Friedrich JO, Adhikari NK, Taccone P, Mancebo J, Polli F, *et al*. Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ 2014;186(10):E381–E390. doi:10.1503/cmaj.140081, PMID:24863923.
[63] Gattinoni L, Pelosi P, Crotti S, Valenza F. Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med 1995;151(6):1807–1814. doi:10.1164/ajrccm.151.6.7767524, PMID:7767524.
[64] Robba C, Bragazzi NL, Bertuccio A, Cardim D, Donnelly J, Sekhon M, *et al*. Effects of Prone Position and Positive End-Expiratory Pressure on Noninvasive Estimators of ICP: A Pilot Study. J Neurosurg Anesthesiol 2017;29(3):243–250. doi:10.1097/ANA.0000000000000295, PMID:26998650.
[65] Georgiadis D, Schwarz S, Baumgartner RW, Veltkamp R, Schwab S. Influence of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure in patients with acute stroke. Stroke 2001;32(9):2088–2092. doi:10.1161/hs0901.095406, PMID:11546901.
[66] Boone MD, Jinadasa SP, Mueller A, Shaefi S, Kasper EM, Hanafy KA, *et al*. The Effect of Positive End-Expiratory Pressure on Intracranial Pressure and Cerebral Hemodynamics. Neurocrit Care 2017;26(2):174–181. doi:10.1007/s12028-016-0328-9, PMID:27848125.
[67] Nemer SN, Caldeira JB, Santos RG, Guimarães BL, Garcia JM, Prado D, *et al*. Effects of positive end-expiratory pressure on brain tissue oxygen pressure of severe traumatic brain injury patients with acute respiratory distress syndrome: A pilot study. J Crit Care 2015;30(6):1263–1266. doi:10.1016/j.jcrc.2015.07.019, PMID:26307004.
[68] Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, *et al*. Epidemiology, Patterns of Care, and Mortality for Patients with Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 2016;315(8):788–800. doi:10.1001/jama.2016.0291, PMID:26903337.
[69] Roquilly A, Cinotti R, Jaber S, Vourc'h M, Pengam F, Mahe PJ, *et al*. Implementation of an evidence-based extubation readiness bundle in 499 brain-injured patients. a before-after evaluation of a quality improvement project. Am J Respir Crit Care Med 2013;188(8):958–66. doi:10.1164/rccm.201301-0116OC, PMID:23927561.
[70] Robba C, Poole D, McNett M, Asehnoune K, Bösel J, Bruder N, *et al*. Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus. Intensive Care Med 2020;46(12):2397–2410. doi:10.1007/s00134-020-06283-0, PMID:33175276.
[71] Borsellino B, Schultz MJ, Gama de Abreu M, Robba C, Bilotta F. Mechanical ventilation in neurocritical care patients: a systematic literature review. Expert Rev Respir Med 2016;10(10):1123–1132. doi:10.1080/17476348.2017.1235976, PMID:27635737.
[72] Serpa Neto A, Hemmes SN, Barbas CS, Beiderlinden M, Biehl M, Binnekade JM, *et al*. Protective versus Conventional Ventilation for Surgery: A Systematic Review and Individual Patient Data Meta-analysis. Anesthesiology 2015;123(1):66–78. doi:10.1097/ALN.0000000000000706, PMID:25978326.
[73] Pelosi P, Ferguson ND, Frutos-Vivar F, Anzueto A, Putensen C, Raymondos K, *et al*. Management and outcome of mechanically ventilated neurologic patients. Crit Care Med 2011;39(6):1482–1492. doi:10.1097/CCM.0b013e31821209a8, PMID:21378554.
[74] Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, *et al*. Dexamethasone treatment for the acute respiratory distress syndrome: A multicentre, randomised controlled trial. Lancet Respir Med 2020;8(3):267–276. doi:10.1016/S2213-2600(19)30417-5, PMID:32043986.
[75] Fan E, Brodie D, Slutsky AS. Acute Respiratory Distress Syndrome: Advances in Diagnosis and Treatment. JAMA 2018;319(7):698–710. doi:10.1001/jama.2017.21907, PMID:29466596.
[76] Horie S, McNicholas B, Rezoagli E, Pham T, Curley G, McAuley D, *et al*. Emerging pharmacological therapies for ARDS: COVID-19 and beyond. Intensive Care Med 2020;46(12):2265–2283. doi:10.1007/s00134-020-06141-z, PMID:32654006.
[77] Maron-Gutierrez T, Laffey JG, Pelosi P, Rocco PR. Cell-based therapies for the acute respiratory distress syndrome. Curr Opin Crit Care 2014;20(1):122–131. doi:10.1097/MCC.0000000000000061, PMID:24300620.
[78] Watanabe M, Boyer JL, Crystal RG. Genetic delivery of bevacizumab to suppress vascular endothelial growth factor-induced high-permeability pulmonary edema. Hum Gene Ther 2009;20(6):598–610. doi:10.1089/hum.2008.169, PMID:19254174.
[79] Li Y, Li H, Liu S, Pan P, Su X, Tan H, *et al*. Pirfenidone ameliorates lipopol-

ysaccharide-induced pulmonary inflammation and fibrosis by blocking NLRP3 inflammasome activation. Mol Immunol 2018;99:134–144. doi:10.1016/j.molimm.2018.05.003, PMID:29783158.

[80] Jahn N, Lamberts RR, Busch CJ, Voelker MT, Busch T, Koel-Simmelink MJ, *et al*. Inhaled carbon monoxide protects time-dependently from loss of hypoxic pulmonary vasoconstriction in endotoxemic mice. Respir Res 2015;16:119. doi:10.1186/s12931-015-0274-7, PMID:26415503.

[81] Krenn K, Lucas R, Croizé A, Boehme S, Klein KU, Hermann R, *et al*. Inhaled AP301 for treatment of pulmonary edema in mechanically ventilated patients with acute respiratory distress syndrome: a phase IIa randomized placebo-controlled trial. Crit Care 2017;21(1):194. doi:10.1186/s13054-017-1795-x, PMID:28750677.

[82] Németh K, Leelahavanichkul A, Yuen PS, Mayer B, Parmelee A, Doi K, *et al*. Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. Nat Med 2009;15(1):42–49. doi:10.1038/nm.1905, PMID:19098906.

[83] Lee JW, Gupta N, Serikov V, Matthay MA. Potential application of mesenchymal stem cells in acute lung injury. Expert Opin Biol Ther 2009;9(10):1259–70. doi:10.1517/14712590903213651, PMID:19691441.

[84] Yang A, Liu B. May sevoflurane prevent the development of neurogenic pulmonary edema and improve the outcome? Or as a new sedation method for severe brain injury patients. Med Hypotheses 2020;137:109538. doi:10.1016/j.mehy.2019.109538, PMID:31911369.

[85] Sedý J, Zicha J, Kunes J, Syková E. Atropine may prevent the development of neurogenic pulmonary edema. Med Hypotheses 2009;73(1):42–44. doi:10.1016/j.mehy.2008.12.051, PMID:19269749.

[86] Suzuki H, Sozen T, Hasegawa Y, Chen W, Zhang JH. Caspase-1 inhibitor prevents neurogenic pulmonary edema after subarachnoid hemorrhage in mice. Stroke 2009;40(12):3872–3875. doi:10.1161/STROKEAHA.109.566109, PMID:19875734.

[87] Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, *et al*. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. Eur Respir J 2017;49(1):1600959. doi:10.1183/13993003.00959-2016, PMID:27920092.

[88] Ginter G, Sankari A, Eshraghi M, Obiakor H, Yarandi H, Chowdhuri S, *et al*. Effect of acetazolamide on susceptibility to central sleep apnea in chronic spinal cord injury. J Appl Physiol (1985) 2020;128(4):960–966. doi:10.1152/japplphysiol.00532.2019, PMID:32078469.

[89] Prowting J, Maresh S, Vaughan S, Kruppe E, Alsabri B, Badr MS, *et al*. Mirtazapine reduces susceptibility to hypocapnic central sleep apnea in males with sleep-disordered breathing: a pilot study. J Appl Physiol (1985) 2021;131(1):414–423. doi:10.1152/japplphysiol.00838.2020, PMID:34080920.

[90] Bonnet MH, Dexter JR, Arand DL. The effect of triazolam on arousal and respiration in central sleep apnea patients. Sleep 1990;13(1):31–41. doi:10.1093/sleep/13.1.31, PMID:2406849.

[91] Randerath W, Deleanu O, Schiza S, Pepin JL. Central sleep apnoea and periodic breathing in heart failure: prognostic significance and treatment options. Eur Respir Rev 2019;28(153):190084. doi:10.1183/16000617.0084-2019, PMID:31604817.

[92] Oldenburg O, Costanzo MR, Germany R, McKane S, Meyer TE, Fox H. Improving Nocturnal Hypoxemic Burden with Transvenous Phrenic Nerve Stimulation for the Treatment of Central Sleep Apnea. J Cardiovasc Transl Res 2021;14(2):377–385. doi:10.1007/s12265-020-10061-0, PMID:32789619.

[93] Liang CW, Chen R, Macri E, Naval N. Preadmission beta-blockers are associated with decreased incidence of neurogenic stunned myocardium in aneurysmal subarachnoid hemorrhage. J Stroke Cerebrovasc Dis 2013;22(5):601–607. doi:10.1016/j.jstrokecerebrovasdis.2011.10.006, PMID:22105019.

[94] Devos J, Peeters A, Wittebole X, Hantson P. High-dose insulin therapy for neurogenic-stunned myocardium after stroke. BMJ Case Rep 2012;2012:bcr2012006620. doi:10.1136/bcr-2012-006620, PMID:23175002.

[95] Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Pharmacologic treatment and SUDEP risk: A nationwide, population-based, case-control study. Neurology 2020;95(18):e2509–e2518. doi:10.1212/WNL.0000000000010874, PMID:32967928.

[96] Han Z, Chen C, Christiansen A, Ji S, Lin Q, Anumonwo C, *et al*. Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome. Sci Transl Med 2020;12(558):eaaz6100. doi:10.1126/scitranslmed.aaz6100, PMID:32848094.

[97] Han Z, Chen C, Christiansen A, Ji S, Lin Q, Anumonwo C, *et al*. Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome. Sci Transl Med 2020;12(558):eaaz6100. doi:10.1126/scitranslmed.aaz6100, PMID:32848094.