

# Postoperative Respiratory Muscle Dysfunction

## Pathophysiology and Preventive Strategies

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### ABSTRACT

Postoperative pulmonary complications are responsible for significant increases in hospital cost as well as patient morbidity and mortality; respiratory muscle dysfunction represents a contributing factor. Upper airway dilator muscles functionally resist the upper airway collapsing forces created by the respiratory pump muscles. Standard perioperative medications (anesthetics, sedatives, opioids, and neuromuscular blocking agents), interventions (patient positioning, mechanical ventilation, and surgical trauma), and diseases (lung hyperinflation, obesity, and obstructive sleep apnea) have differential effects on the respiratory muscle subgroups. These effects on the upper airway dilators and respiratory pump muscles impair their coordination and function and can result in respiratory failure. Perioperative management strategies can help decrease the incidence of postoperative respiratory muscle dysfunction. Such strategies include minimally invasive procedures rather than open surgery, early and optimal mobilizing of respiratory muscles while on mechanical ventilation, judicious use of respiratory depressant anesthetics and neuromuscular blocking agents, and noninvasive ventilation when possible.

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POSTOPERATIVE pulmonary complications (PPC), defined as new onset or exacerbation of respiratory failure following surgery, occur frequently<sup>1–3</sup> and are associated with increased rates of short- and long-term mortality,<sup>4</sup> as well as increased cost.<sup>5</sup> A thorough understanding of the clinical effects of PPC is hindered by inconsistency in the definition of PPC among researchers. The diagnoses classically considered PPC include atelectasis, bronchospasm, pneumonia, pulmonary edema, and respiratory failure.<sup>6</sup> Respiratory failure itself is not clearly defined, although the most common criterion is failure to be extubated within 48 h of surgery.<sup>6</sup> Adding complexity to assessing the impact of PPC are recent studies which support expanding the definition to include acute upper airway obstruction,<sup>7–9</sup> complications from obstructive sleep apnea (OSA),<sup>10</sup> chemical pneumonitis,<sup>11</sup> and hypoxemia due to abdominal compartment syndrome.<sup>12,13</sup>

Estimating the incidence of PPC and respiratory failure is complicated for many reasons including the imprecise definitions; however, recent studies attempted exactly this by defining respiratory failure as unplanned reintubation and postoperative mechanical ventilation.<sup>3,14</sup>

For this small subset of the post-surgical population, the probability of PPC affecting their longevity is great. In 2005, National Surgical Quality Improvement Program data were queried and for patients who were unable to wean from mechanical ventilation after major surgery, the 30-day mortality was 29% (12 times greater than those not experiencing PPC).<sup>4</sup> In another cohort study, postoperative reintubation was associated with a 90-fold increase in mortality.<sup>14</sup>

Along with the huge mortality burden of PPC, there is a significant financial consideration. A 2004 study analyzing hospital cost at the University of Michigan identified PPC as the most expensive of the major postoperative complications. Moreover, when compared to the median hospital cost of \$5,015 for surgical patients without PPC, the \$62,704

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hospital expense for a surgical patient with a pulmonary complication was 12 times greater.<sup>5</sup>

One underappreciated factor in the development of PPC and respiratory failure is respiratory muscle dysfunction. Upper airway muscles play a vital role in maintaining the anatomic structure of the pharynx and laryngotracheal complex and ensure upper airway patency. Respiratory pump muscles create negative, and occasionally positive, pressure to ventilate and oxygenate. Research shows that even partial respiratory muscle paralysis may lead to more PPC.<sup>8,15</sup> In the upper airway, partial paralysis can lead to obstruction<sup>16</sup> and increased aspiration risk,<sup>17</sup> whereas respiratory pump muscle failure leads to weak cough<sup>18</sup> and increased incidence of pneumonia.<sup>19</sup> Finally, a 2-week long, preoperative inspiratory muscle training program reduced the incidence of PPC, further demonstrating the importance of respiratory muscle fitness in the prevention of PPC<sup>20</sup> and subsequent respiratory failure.

The aim of this article was two-fold: (1) to review the current concepts of postoperative pathophysiology as it pertains to respiratory muscle dysfunction, and (2) to discuss

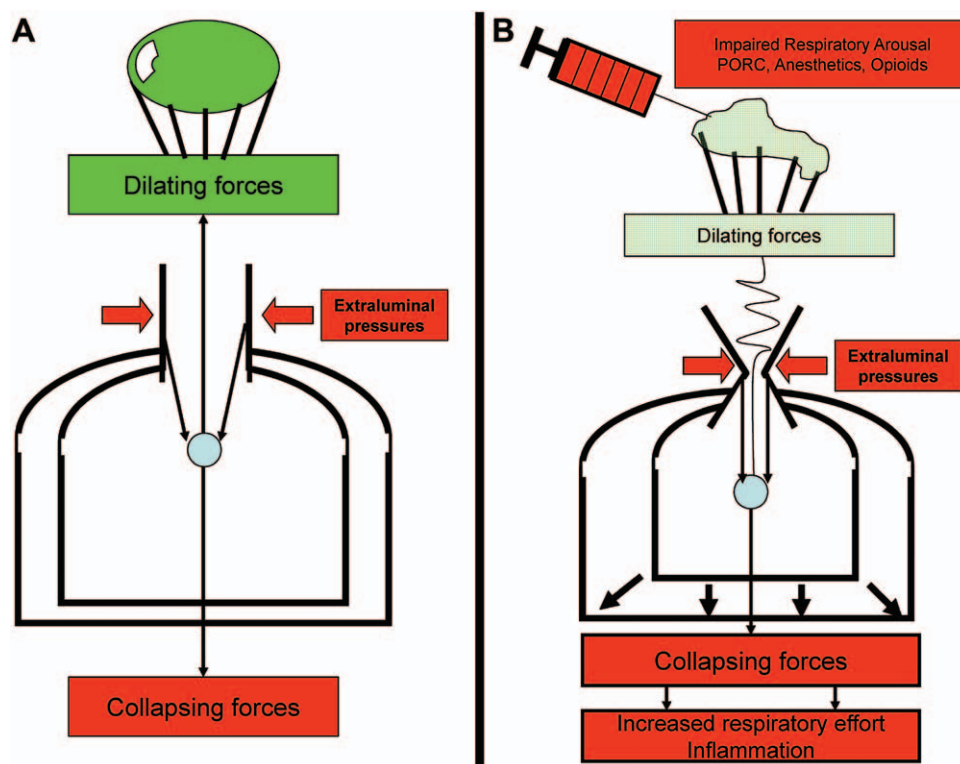
strategies to avoid respiratory muscle dysfunction during the perioperative period and critical illness.

## Anatomy and Physiology

The muscles involved in respiration are morphologically and functionally skeletal muscles and can be classified by their anatomic function into two groups: (1) upper airway dilators and (2) respiratory pump muscles. Upper airway dilator muscles counterbalance the negative inspiratory pressure generated by the pump muscle to permit airflow during inspiration. Respiratory pump muscles are the collection of muscles responsible for generating inspiratory and expiratory forces in the thorax.

### Upper Airway Patency

Patency of the upper airway is maintained by balancing collapsing and dilating forces (fig. 1). The primary upper airway collapsing forces are (1) negative intraluminal pressure generated by the respiratory pump during inspiration and (2) compressive extra-luminal forces from the surrounding tissues. These collapsing forces are opposed by the actions of the upper airway dilator muscles to maintain the airway.



**Fig. 1.** Perioperative relationship of upper airway patency and respiratory pump activation. (A) Schematic of the respiratory system under normal physiology. Upper airway dilator muscles counterbalance the collapsing forces imposed on the upper airway by extra-luminal pressures and negative inspiratory pressure generated by the respiratory pump muscles. The *green balloon* (labeled “dilating forces”) represents the forces generated by the upper airway dilator muscles which resist the anatomic and physiologic forces promoting collapse of the upper airway (represented by the orange counterweight labeled “collapsing forces”). (B) Respiratory system in the perioperative period. The “needle” represents the multitude of iatrogenic factors listed in the nearby *orange box* that can cause upper airway dilator muscle dysfunction. The lowest *orange counterweight* represents perioperative factors leading to increased respiratory pump muscle contractions. In the perioperative period, a patient’s physiology and anatomy are affected so that upper airway dilating forces are diminished and can no longer create enough force to resist the increased collapsing forces, thus leading to upper airway collapse. PORC = postoperative residual curarization.

**Upper Airway Dilator Muscles.** The actions of the upper airway dilator muscles keep the airway patent. There are many muscles involved in dilating the upper airway; however, the most extensively studied muscles of the upper airway dilators are the genioglossus and the tensor palatine, and experimentally these serve as surrogates for the others. Neurologically, the genioglossus receives a variety of inputs, including phasic (inspiratory) and tonic (non-inspiratory) drive which are distributed differentially across the hypoglossal motoneuron pool.<sup>21</sup> In response to negative pharyngeal pressure created by the respiratory pump during inspiration, the genioglossus reflexively stabilizes the upper airway in both humans<sup>22</sup> and rats.<sup>23</sup> This reflex is likely a product of signaling from inspiratory modulated motor units. Whereas the genioglossus responds to phasic input on top of its tonic (non-respiratory) activation, the tensor palatine is considered a tonic muscle with consistent tone throughout the respiratory cycle.<sup>24</sup>

**Extra-luminal Pressure.** The soft tissues of the pharynx are enclosed and stabilized by bony structures such as the mandible and the spine, and complete collapse of the pharyngeal airway ordinarily requires extra-luminal forces such as hematoma, edema, or peri-pharyngeal masses. Pharyngeal manifestation of obesity compresses the airway.<sup>25</sup> Craniofacial abnormalities can further increase the collapsing effects of excessive pharyngeal extra-luminal soft tissue in obese patients and lead to increased pharyngeal collapsibility and OSA<sup>26</sup>: a disorder involving intermittent nocturnal upper airway collapse. Thus, the extra-luminal soft tissue, and size and shape of the bony enclosure are determinants of the extra-luminal pressure that needs to be antagonized by the upper airway dilator muscle contraction during inspiration in order to avoid an upper airway obstruction-related apnea.<sup>26</sup>

**Body Position.** The effects of body position on upper airway patency have been extensively studied by Isono *et al.*<sup>27,28</sup> The upper airway is more vulnerable to collapse in the supine position than the lateral and sitting positions. Evidence for the lateral position is considerable and frequently based upon research involving subjects with OSA. In sleeping subjects with OSA, fewer obstructive events were reported in the lateral position than supine.<sup>29</sup> In anesthetized and paralyzed subjects with OSA, the patency of the passive pharynx was better maintained in the lateral and sitting positions than in the supine.<sup>27,28</sup> These improvements in airway patency caused by the lateral position are explained by a less obstructive orientation of the pharyngeal soft tissues.

**Respiratory Timing.** The length of the respiratory cycle ( $T_{\text{tot}}$ ) and variation in its component parts of inspiration ( $T_I$ ) and expiration can affect upper airway patency. Inspiratory duty cycle, also referred to as effective inspiratory time, is the ratio of inspiration to the total respiratory cycle ( $T_I/T_{\text{tot}}$ ), and this can be directly associated with airflow. In fact, increased inspiratory duty cycle can actually compensate for partial airway obstruction.<sup>30</sup>

**Effects of End-expiratory Lung Volume.** A less intuitive component of upper airway patency is lung volume. Higher end-expiratory lung volumes are associated with a decrease in upper airway resistance to airflow in awake healthy humans,<sup>31</sup> and an increase in upper airway lumen dimensions in subjects with and without OSA.<sup>32</sup> The mechanism for the interaction between upper airway patency and lung volume is thought to lie in the generation of longitudinal traction forces in the trachea.<sup>33,34</sup> Upon inspiration, the lung inflates and effectively forces the carina into a more caudal position, thus creating stretching forces on the fixed trachea.<sup>34</sup> These forces are transferred to the upper airway walls through assorted soft tissue connections, resulting in improved upper airway dilatation.<sup>33</sup> Effectively, tracheal traction allows the respiratory pump muscles to contribute to upper airway patency.

**Effects of Fluid Homeostasis on Upper Airway Patency.** Fluid overload can affect upper airway patency. In awake, healthy volunteers, the inflation of antishock trousers displaced so much fluid from the lower extremities that neck circumference increased, the pharynx narrowed,<sup>35</sup> and the upper airway had a lower threshold for collapse.<sup>36</sup> This concept is reinforced in studies of subjects with lower extremity venous insufficiency<sup>37</sup> and congestive heart failure.<sup>38</sup> These studies have shown that nocturnal redistribution of fluid from the lower extremities into the neck increases upper airway collapsibility<sup>37</sup> and the severity of central and OSAs.<sup>38</sup> Future studies in perioperative medicine will show if perioperative fluid restriction helps decrease the vulnerability of the upper airway to collapse.

### Respiratory Pump Muscle Activation

The respiratory pump generates the motorized action driving inspiration and expiration. It is the force that broadens the thoracic cavity and creates negative intrathoracic pressure to draw a breath in, and, when needed, positive intrathoracic pressure to exhale rapidly.

**Inspiratory Pump Muscles.** Inspiratory pump muscles are an anatomically diverse group, with the best studied being the diaphragm and those of the thoracic wall. The most important inspiratory muscle in healthy humans is the diaphragm, which accounts for 60–70% of lung volume change during simple respiration.<sup>39</sup> It is a thin, flat, musculotendinous structure subdivided into the crural diaphragm (originating at the lumbar vertebrae) and the costal diaphragm (originating at the inner surfaces of the lower six ribs); these two divisions function as one during respiration. During inspiration, the volume of the thoracic cavity increases as a result of contraction of the diaphragm and the external intercostal muscles. The lungs expand secondarily to the increased negative intrathoracic pressure generated by these phasic actions of the inspiratory pump muscles.

Inspiratory tone is present in muscles acting on the rib cage and helps to maintain negative intrathoracic pressure.<sup>40</sup> There is also inspiratory tone in the diaphragm and its likely purpose is to prevent abdominal viscera mechanically

from compressing the lungs.<sup>41</sup> The combination of an effective inspiratory tonicity of both the diaphragm and rib cage muscles acting upon the rib cage effectively increases functional residual capacity (FRC) by about 0.8 l.<sup>42</sup>

**Body Position.** Body posture has significant influence on the contribution of respiratory pump muscles to inspiration and lung function. When the torso is upright, the diaphragm is lower in the chest, and the chest circumference changes little compared to that in supine;<sup>43</sup> consequently, FRC is about 20% greater upright than supine in humans.<sup>44</sup> In the upright position, displacement of the rib cage accounts for approximately 60% of resting tidal volume and in this setting, thoracic wall muscles contribute greatly. In the supine position, rib cage displacement accounts for less than half of the upright tidal volume, and abdominal and diaphragmatic movement contributes significantly more.<sup>45</sup> Thus, supine position following surgery renders a patient particularly vulnerable to diaphragmatic dysfunction induced by perioperative medical interventions.

**Expiratory Pump Muscles.** The expiratory pump muscles include the internal intercostal, rectus abdominis, external oblique, internal oblique, and transverse abdominis muscles. Expiration at rest is usually passive, relying on the elasticity of the lungs and thorax to return to their equilibrium position. During high breathing effort (*i.e.*, exercise, sepsis, and dysfunctional pulmonary status), the expiratory muscles contract to increase the speed of exhalation, increasing inspiratory

duty cycle, in preparation for the next inhalation. Expiratory pump muscles are used in everyday life for speaking, coughing, and airway secretion clearance.

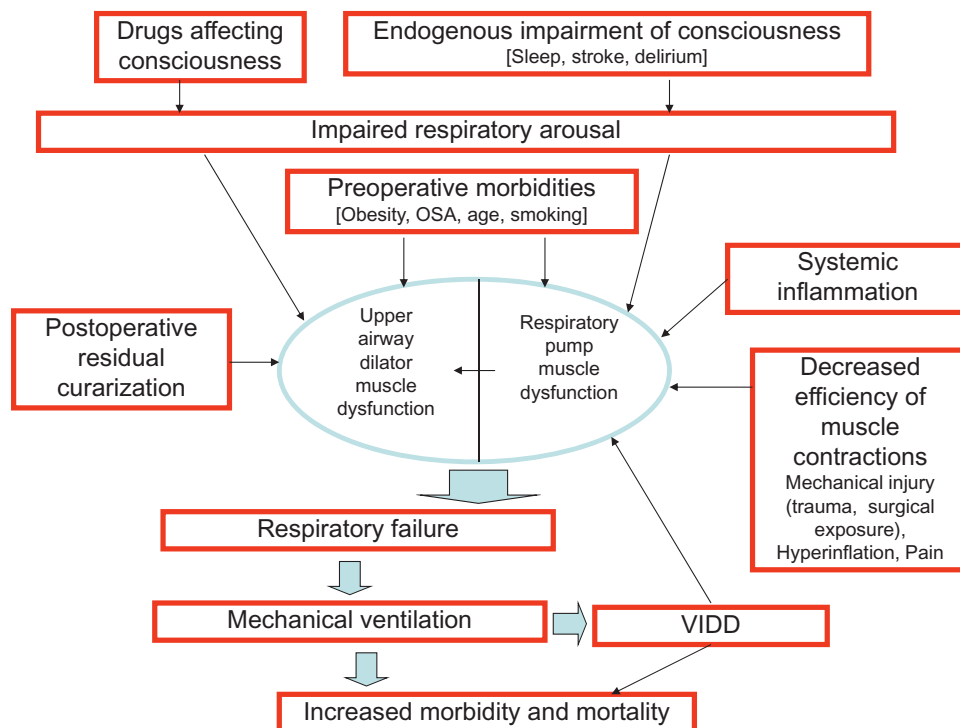
## Perioperative Pathophysiology, Treatments, and Interventions Contributing to Respiratory Muscle Dysfunction

Perioperative patients are a subset of the general population where respiratory muscle dysfunction occurs frequently and is often due to predictable causes (fig. 2).

### Surgery and Trauma

Surgery can be characterized as intentional penetrating trauma that can cause respiratory failure. Procedures on the foregut, the hepatopancreatobiliary region, and the aorta have the strongest association with respiratory failure<sup>46</sup>; length of surgery is also associated with greater incidence of PPC.<sup>47,48</sup> Surgery impairs respiratory pump muscles through a variety of different avenues, leading to increased atelectasis and decreased FRC and decreased vital capacity.<sup>49,50</sup> Moreover, the effects are not merely transient but can last from a day to a week,<sup>51,52</sup> to upward of a year with phrenic nerve damage.<sup>53</sup>

There are many mechanisms through which surgery can induce respiratory failure. Some of these reasons are



**Fig. 2.** Pathophysiology of postoperative respiratory failure emphasizing respiratory muscle dysfunction. Perioperative respiratory muscle dysfunction results from a multitude of factors, including preoperative comorbidities and perioperative interventions, each individually affecting upper airway dilator muscles, respiratory pump muscles, or both. Whereas a single factor rarely translates into respiratory failure, a combination of factors can cause pulmonary complications leading to respiratory failure. In the setting of respiratory failure requiring mechanical ventilation, ventilator-induced diaphragmatic dysfunction (VIDD) further compounds respiratory pump muscle dysfunction and contributes to increased morbidity and mortality. OSA = obstructive sleep apnea.



straightforward: functional disruption (cutting, tearing, and retracting) of respiratory muscles (intercostals or rectus abdominis),<sup>54–56</sup> postoperative pain leading to voluntary restrictions on respirations,<sup>57,58</sup> and phrenic nerve injury resulting in direct diaphragmatic dysfunction.<sup>53</sup> Following abdominal or thoracic surgery, patients typically experience a restrictive pattern respiratory abnormality due to impaired respiratory pump muscle function within the first postoperative day. When affected by this restrictive pathology, a patient breathes at reduced lung volumes and FRC diminishes. When FRC decreases below the lung volume where small airway closure generally occurs, entitled closing capacity, regions with low ventilation/perfusion ratios develop, leading to impaired gas exchange and possibly gas trapping and atelectasis.<sup>59</sup>

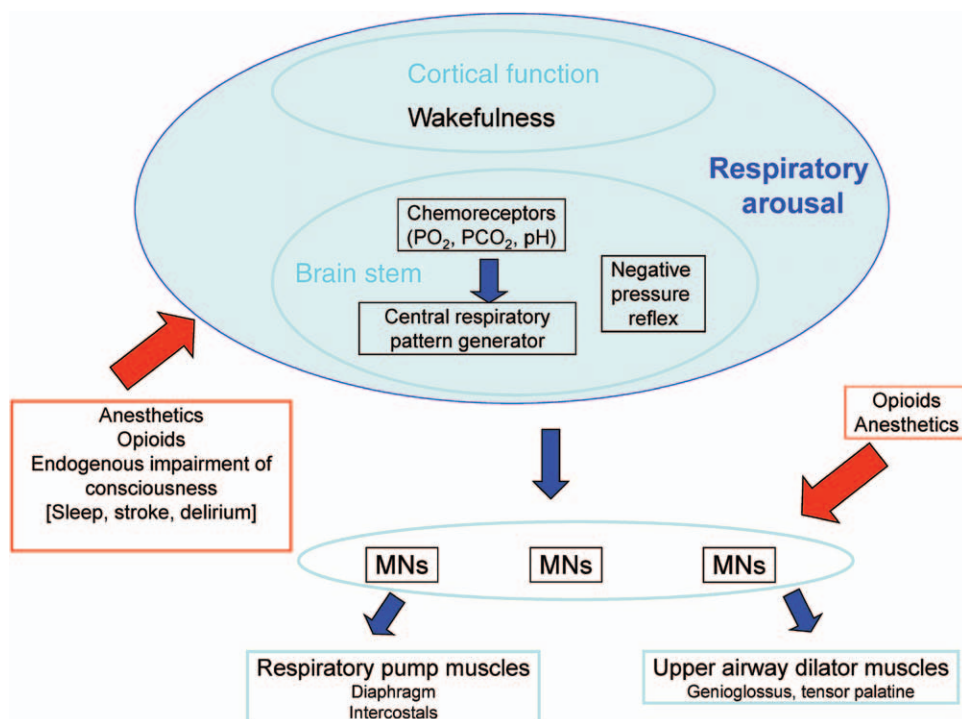
Other mechanisms underlying respiratory failure are physiologically more complex. It is well documented that diaphragmatic dysfunction occurs postoperatively,<sup>51,60</sup> but the exact mechanism is less certain. In rats, localized, postoperative inflammation has been shown to weaken diaphragm action within hours after exposure.<sup>61</sup> Another likely contributor to diaphragmatic dysfunction is the neural inhibitory response to surgical stimulation. In canines, surgical manipulation of the gallbladder has been associated with quick and profound reduction in function of the diaphragm; the rapid time-course of the effect suggests reflex inhibition via vagal afferents.<sup>62</sup>

In addition, surgery-associated conditions such as peritonitis, systemic inflammatory response syndrome, abdominal trauma, exploratory laparotomies, and fluid shifts following large resuscitations can cause respiratory failure by increasing the intraabdominal pressure, which leads to intraabdominal hypertension (intraabdominal pressure > 12 mmHg) and, in its extreme, abdominal compartment syndrome (intraabdominal pressure > 20 mmHg).<sup>63</sup> The external application of abdominal binders may also contribute to increased intraabdominal pressure.<sup>64</sup> The increase in intraabdominal pressure can decrease chest wall compliance and diaphragmatic excursion<sup>65</sup> which combine to affect respiratory mechanics and increase overall work of breathing for respiratory pump muscles.

Another contributor to respiratory failure is direct chest trauma and rib fractures. One of 13 patients with rib fractures from blunt trauma will have a flail chest, a condition with a 10–20% mortality rate.<sup>66</sup> With a flail chest, the negative intrathoracic pressure of inspiration generated by the contraction of the diaphragm and other respiratory muscles draws the flail segment inward, the opposite direction needed to inspire gas, resulting in increased work of breathing and an increase in oxygen consumption.<sup>67</sup>

### Respiratory Arousal

Respiratory muscle function is under both voluntary and involuntary control. Respiratory arousal, as defined by Berry *et al.*,<sup>68</sup> is arousal from sleep due to cumulative and



**Fig. 3.** Effects of respiratory arousal on upper airway dilator and respiratory pump muscles. Respiratory arousal is composed of three primary inputs: central respiratory pattern generator processing peripheral and central chemoreceptor afferents, reflex responsiveness to the magnitude of negative pressure in the airway generated by the respiratory pump muscles, and strength of the “wakefulness” drive. Inhibitory modulators are shown: anesthetics, opioids, and impaired consciousness of endogenous etiology. *Blue arrows:* excitatory; *Red arrows:* inhibitory; MNs = motor neurons.

progressive increases in stimuli related to breathing (hypoxia, hypercapnia, and respiratory effort). For our review focused on perioperative medicine, we broaden the definition of the term “respiratory arousal” to include awakening from sleep and other drug-induced or endogenous impairments of consciousness, as well as any neurally mediated restoration of sufficient upper airway and respiratory pump muscle tone independent of patient state of wakefulness.

Three primary inputs contribute to respiratory arousal: (1) peripheral and central chemoreceptors sensitive to partial pressures of oxygen and carbon dioxide,<sup>69</sup> (2) sensors in the upper airway responsive to negative pressure generated by the respiratory pump,<sup>22,23</sup> and (3) cortical stimulation directly related to state of consciousness or “wakefulness.”<sup>70</sup> For a visual representation of respiratory arousal, see figure 3.

Any of the three respiratory arousal inputs can restore respiratory muscle tone if the magnitude is great enough. Cortical awakening from sleep, identified by electroencephalogram signs of wakefulness, is an adequate stimulus for ventilation. Importantly, obstructive apneas, such as upper airway collapse in OSA, can be terminated by increased drive to the respiratory muscles not involving cortical arousal.<sup>71</sup> For example, hypercarbia resulting from sustained hypoxia<sup>69</sup> and elevated upper airway negative pressure<sup>22,23</sup> can independently restore tone to the respiratory muscles.

The magnitude of respiratory arousal provided to the respiratory muscles is dependent upon the summation of stimuli in the central respiratory pattern generator output, including peripheral and central chemoresponsiveness, reflex responsiveness to the negative airway pressure, and strength of the “wakefulness” drive. During the perioperative period, respiratory arousal is dampened by sedation, anesthesia, opioids, and endogenous impairment of consciousness. Consequently, the total level of stimulation to respiratory muscles decreases and the upper airway is more vulnerable to collapse and respiratory failure.

**Impaired Respiratory Arousal by Endogenous Impairment of Consciousness.** The wakefulness drive to the respiratory muscles can be reduced or eliminated by a variety of perioperative pathologies. Postoperative delirium is a common complication in patients aged more than 65 yr<sup>72</sup> and has been associated with failure to wean from the ventilator.<sup>73</sup> Stroke is an unfortunate intraoperative complication, with a relatively high incidence following cardiac surgery.<sup>74</sup> Strokes directly harm neuronal tissue and can afflict multiple sites, which may affect neuronal transmission of respiratory arousal, thereby causing respiratory muscle weakness that translates to a high incidence of respiratory failure.<sup>75</sup> Hypoglycemia,<sup>76</sup> hypothyroidism,<sup>77</sup> and adrenal insufficiency<sup>78</sup> also affect respiratory arousal and can be considered risk factors for respiratory failure in critically ill patients. Thus, endogenous conditions can impair respiratory arousal and are possible contributors to perioperative muscle dysfunction.

**Impairment of Respiratory Arousal by Anesthetics, Opioids, and Rapid Eye Movement Sleep Rebound.** Anesthetics, sedatives, and opioids are known respiratory depressants

and decrease motor drive to the upper airway dilator and respiratory pump muscles; functionally, they impair respiratory arousal by a variety of mechanisms including reducing chemoresponsiveness to hypoxia and hypercarbia,<sup>79–81</sup> suppressing the reflexive responsiveness to negative upper airway pressure,<sup>82</sup> and depressing the magnitude of wakefulness. In addition, anesthetics (similar to normal sleep) typically disturb the balance between upper airway dilator muscle and respiratory pump muscle activation upon initiation of unconsciousness.<sup>83,84</sup>

#### **Anesthetic and Sedative Effects on Respiratory Muscles.**

The effects of anesthetics upon respiratory function are dependent upon a variety of factors, including agent, dose, subject’s consciousness, and specific muscle group. Upper airway muscles are generally more affected by sleep, anesthetics, and sedatives than respiratory pump muscles. In 1984, the seminal paper written by Nishino *et al.*<sup>85</sup> described differential effects of anesthetics and sedatives on neural input to upper airway (hypoglossal nerve) and respiratory pump muscles (phrenic nerve) in ventilated, vagotomized cats. Anesthetic and sedative medicines from four classes were tested: volatile (halothane), barbiturate (thiopental), dissociative (ketamine), and benzodiazepine (diazepam). All showed a similar effect on respiratory muscles: decreased stimulation in both nerves. However, whereas halothane, thiopental, and diazepam significantly reduced neural input to upper airway muscles relative to that of the already dampened respiratory pump muscles, ketamine did not. Ketamine reduced the neural input to both the upper airway and respiratory muscles equally, but it reduced the neural input to the upper airway muscles less relative to the other classes of anesthetics.<sup>85</sup>

Recent animal research suggests that ketamine has no inhibitory effect upon genioglossus activity, but increases genioglossus muscle activity relative to wakefulness, slow wave, and rapid eye movement (REM) sleep.<sup>86</sup> Over a wide dose range, ketamine anesthesia maintains activity in the arousal areas of forebrain,<sup>87</sup> and it likely stimulates respiration by uncoupling the link between loss of consciousness and upper airway dilator muscle hypotonia.<sup>86</sup> Thus, ketamine, unlike other anesthetics, preserves a high level of upper airway dilator muscle activity ordinarily only found with consciousness<sup>87</sup>; this phenomenon may be in part linked to ketamine’s dose-dependent increase in duty cycle.<sup>86</sup> Based on the preclinical data as well as the long-term experience with ketamine as a drug that preserves respiratory function during anesthesia, it may prove to be a safe pharmacological choice for patients with upper airway comorbidities undergoing procedural sedation.

Additional evidence for compound- and muscle-specific effects of anesthetics comes from preclinical studies. In both pentobarbital<sup>84,88</sup> and isoflurane,<sup>89</sup> anesthetics that initially reduce upper airway muscle activity during the transition from wakefulness to unconsciousness dose dependently promote genioglossus phasic activity relative to the initial reduction. The neural pathways mediating the

dose-dependent activating effect of some anesthetics are not fully understood, but considering isoflurane's genioglossus stimulating effect is abolished in vagotomized rats, the vagus nerve is hypothesized to be the afferent limb.<sup>89</sup> Whereas isoflurane in a certain dose range may stimulate both upper airway dilator and respiratory muscles, barbiturates studied in the same model induced a different effect on these respiratory muscles. Pentobarbital increased genioglossus activity, while causing a dose-dependent decrease in diaphragmatic activity.<sup>84</sup>

Of all anesthetics studied, it appears that propofol has the greatest debilitating effect on the drive to both upper airway dilator and respiratory pump muscles. Compared to an equianesthetic dose of isoflurane, propofol elicited only one third the amount of phasic genioglossus activity in rats, and similarly depressed the drive to the pump muscles,<sup>90</sup> effects that could be reversed by conditions that increase the ventilatory drive (*i.e.*, hypoxia and hypercarbia).<sup>89</sup>

The majority of controlled studies evaluating the effects of anesthetics on the upper airway have been performed on animals. However, the preclinical results lend themselves to well-planned translational studies, which could lead to quality initiatives and the prevention of postoperative respiratory failure. One such study examined airway protection at subhypnotic doses of anesthetics and found that all anesthetics tested compromised pharyngeal function. Furthermore, propofol had the greatest effect upon pharyngeal contraction pattern,<sup>91</sup> a finding that agrees with the animal study.<sup>89</sup> Another clinical trial<sup>92</sup> suggests that ketamine has similar protective effects on ventilatory drive as that observed in preclinical trials.<sup>87</sup>

**Opioid Effects on Respiratory Muscles.** Opioids are the most common postoperative analgesic prescribed,<sup>93</sup> and they have a notable adverse effect profile including respiratory depression via upper airway dilator<sup>94,95</sup> and respiratory pump muscles<sup>96,97</sup> dysfunction. In animal models, opioids impair upper airway muscle function in a dose-dependent fashion.

This effect has been shown through reduced genioglossus activity in rats,<sup>94,98,99</sup> decreased vagal motor neuron activity in laryngeal abductors, and increased vagal motor neuron activity in laryngeal adductors.<sup>100</sup> These opioid-induced changes result in increased upper airway resistance and possibly vocal cord closure and pharyngeal airflow obstruction.<sup>100</sup> It is of clinical importance to note that patients with OSA may be more sensitive to the analgesic effects of opioids and should have doses adjusted accordingly.<sup>101,102</sup>

The effect of opioids on muscle function extends to those of the respiratory pump including muscles of the thorax and the diaphragm. Chest wall rigidity following opioid administration was first described in 1953,<sup>103</sup> and while usually associated with rapid injection, multiple agents, and large doses, it has also occurred when opioids were administered in a conservative fashion.<sup>104</sup> Opioid analgesia has also been shown to increase abdominal muscle activity,<sup>105</sup> and this persistent expiratory muscle activity produces a rapid decrease

in end-expiratory lung volume and FRC, contributing to a higher degree of atelectasis.<sup>106</sup> This opioid-induced expiratory muscle recruitment appears not to be related to airway obstruction.<sup>107</sup> Even the diaphragm is affected. In spontaneously ventilating rats, high-dose opioids led to diaphragm dysfunction and a reduction in phasic activity, leading to reduced tidal volume and minute ventilation;<sup>96</sup> similar effects have been seen in felines.<sup>100</sup>

**REM Rebound Effect on Respiratory Muscles.** Both surgery and anesthetics can affect sleep structure. Sleep following surgery is typically fragmented, reduced, and lacking in REM sleep.<sup>108,109</sup> The absence of REM sleep leads to a REM sleep deficit, and this deficit can only be repaid by increasing REM sleep relative to non-REM stages in subsequent nights.<sup>110</sup> Consequently, REM sleep returns abruptly a few nights after surgery in greater intensity and quantity than usual.<sup>111</sup>

During REM sleep, there is persistent voluntary muscle hypotonia, and electromyogram activity is at its lowest level of any stage of sleep.<sup>112</sup> Accordingly, the neural drive to the upper airway dilators is decreased and this relative hypotonia predisposes the patient to airway instability, leading to episodic hypoxemia.<sup>113</sup> In addition to the anatomic changes in the upper airway, REM affects respiratory physiology including reducing both the hypoxic ventilatory drive and the hypercarbic ventilatory response.<sup>112</sup> Thus, the postoperative return of REM sleep, labeled REM rebound, results in an even greater number of episodes of hypoxemia secondary to impaired respiratory arousal.<sup>114</sup>

However, not all surgeries and not all anesthetics have this effect. For surgery, the severity of the procedure performed affects loss of REM sleep<sup>115</sup> and implicitly the incidence of REM rebound. This concept holds true with minimally invasive surgery, as a laparoscopic cholecystectomy appears to have less effect upon postoperative REM quality and quantity than major abdominal surgery.<sup>116</sup>

As for anesthesia, different anesthetics and lengths of exposure have different effects upon REM sleep. For example, whereas 6 h of either isoflurane, sevoflurane, or halothane anesthesia caused both a REM deficit and REM rebound in mice,<sup>117</sup> 3 h of isoflurane general anesthesia in nonsurgical volunteers had no effect upon REM.<sup>118</sup> Benzodiazepines as a class reduce REM sleep and are known to cause REM rebound upon discontinuation.<sup>119</sup> On the opposite end of the spectrum is propofol which in preclinical trials appears to cause neither REM deficit<sup>120</sup> nor REM rebound.<sup>121</sup>

Accordingly, choice of anesthetic may help reduce occurrences of postoperative apnea both in the near term from immediate effects of anesthetics on the upper airway dilators and in the days into recovery by reducing or eliminating REM rebound.<sup>109</sup>

#### **Neuromuscular Blocking Agents (Postoperative Residual Curarization)**

Pharmacologic muscle relaxation through neuromuscular blocking agents (NMBA) is helpful to optimize surgical

conditions. Following completion of the procedure, patients often have this chemical paralysis reversed, but postoperative residual curarization frequently persists.<sup>122</sup> There is strong evidence that postoperative residual curarization not only results in physiologic impairment,<sup>16,17,123,124</sup> but also places patients at increased perioperative risk<sup>8,124,125</sup> and may increase costs.<sup>126</sup> Additionally, even patients whose “train of four” ratio is just less than unity still show significant distortion in their upper airway anatomy and function.<sup>123</sup>

It is well documented in preclinical and clinical trials that upper airway dilators are disproportionately sensitive to the effects of NMBA than the diaphragm,<sup>123,127,128</sup> and, similar to sleep,<sup>129</sup> the retropalatal region is the most collapsible part in the upper airway.<sup>123</sup> In healthy volunteers, even minimal neuromuscular blockade is associated with impairment of upper airway dilator muscle function, resulting in increased upper airway closing pressures and greater risk of collapse.<sup>123,124</sup> Even the use of modern intermediate-acting NMBA predicts an increased risk of postoperative desaturation as well as reintubation requiring unplanned admission to an intensive care unit.<sup>14</sup> Interestingly, increased upper airway closing pressures were also seen in healthy volunteers, who, after fully recovering from pharmacological paralysis, were administered reversal agents (neostigmine and glycopyrrolate),<sup>130</sup> and neostigmine reversal was also associated with increased postoperative respiratory complications.<sup>14</sup> These studies suggest that acetylcholinesterase inhibitor-based reversal agents can trigger the very symptomatology they are intended to prevent.<sup>14,130</sup>

Increased upper airway collapsibility may predispose patients to respiratory failure, particularly when coupled with other airway comorbidities such as obesity or increased airway secretions.<sup>8,15</sup> Additionally, postoperative residual curarization may cause negative pressure pulmonary edema secondary to excessive negative intrathoracic pressures generated by respiratory pump muscles contracting in the setting of upper airway obstruction.<sup>131</sup> Postoperative residual curarization may also lead to respiratory failure via increased aspiration risk secondary to impaired swallow reflexes.<sup>17</sup>

Accordingly, it is important to titrate NMBA carefully by using quantitative neuromuscular transmission monitoring. In addition, future goals for reducing the respiratory risks of non-depolarizing NMBA include the development and use of shorter-acting NMBA and new reversal agents that directly halt the effects of NMBA such that skeletal muscle strength can be fully restored at the end of the case.

### Systemic Inflammation

Systemic inflammation, whether a preoperative condition, a product of trauma,<sup>132</sup> or the surgery alone,<sup>133</sup> can have a serious effect upon the respiratory system. Traditionally, inflammation is associated with increased ventilatory effort due to increased metabolic demands, and direct cytotoxic effects upon the respiratory system.

**Imbalance between Energy Supplies and Oxygen Consumption.** Systemic inflammation places a patient into a catabolic state and a patient's metabolic demands markedly increase,<sup>134</sup> resulting in downstream effects of increased respiratory drive, increased respiratory pump work, and increased oxygen consumption. Both an animal model<sup>135</sup> and an observational study<sup>136</sup> have shown that severe, systemic inflammation can lead to body oxygen demand outstripping oxygen stores and leading to depressed performance of respiratory pump muscles and respiratory failure. Furthermore, the resulting lactate acidosis may also directly affect diaphragmatic contractility.<sup>137</sup>

**Cytotoxic Effects of Inflammatory Mediators.** In the setting of systemic inflammation, inflammatory mediators nitric oxide and tumor necrosis factor- $\alpha$  have been linked to respiratory muscle weakness, which contributes to severe sepsis-associated respiratory failure.<sup>138–141</sup>

### Mechanical Ventilation

Approximately 20–30% of patients have trouble weaning from prolonged mechanical ventilation<sup>142</sup> and this leads to increased healthcare costs.<sup>143</sup> Failure of respiratory pump muscles is a contributing factor to weaning delays.<sup>144,145</sup> Furthermore, controlled mechanical ventilation immobilizes the diaphragm and directly harms diaphragm function,<sup>146–148</sup> causing ventilator-induced diaphragmatic dysfunction and adding to the conditions perpetuating the respiratory failure.

Controlled ventilation is associated with the rapid onset of proteolysis in the diaphragm, leading to atrophy and diaphragm dysfunction in preclinical<sup>146,149</sup> and clinical studies.<sup>147,148</sup> Only 18 h of controlled ventilation resulted in diaphragm atrophy and contractile dysfunction in both laboratory animals<sup>146</sup> and humans.<sup>147</sup> Additionally, length of time on controlled ventilation is positively correlated with diaphragmatic thinning<sup>150</sup> as well as injury and atrophy.<sup>148</sup> Controlled ventilation appears to be a dose-dependent contributor to respiratory pump muscle dysfunction and may be responsible for delayed weaning from mechanical ventilation.

The addition of NMBA to controlled ventilation, in an attempt to reduce work of breathing and transpulmonary pressure ( $P_{\text{L}}$ ), and improve ventilatory synchrony, can further harm respiratory muscles making a risk–benefit assessment critical before prescribing NMBA in the setting of acute respiratory distress syndrome. The use of NMBA has been associated with intensive care unit-acquired weakness<sup>151–154</sup>—a condition linked to delayed weaning of mechanical ventilation.<sup>155</sup> The paralytic effects of NMBA persist long after their final dosing, with paralysis continuing from 6 h to 7 days in 44% of a group of critically ill patients treated with vecuronium.<sup>156</sup> Additionally, NMBA may compound the diaphragmatic damage done by mechanical ventilation; in rats, rocuronium with controlled ventilation has been linked to even greater diaphragmatic dysfunction than mechanical ventilation with placebo.<sup>157</sup>



Finally, NMBA block muscle function and eliminate volitional mobility. Physical mobilization historically has been associated with improved respiratory function.<sup>158</sup> Recent studies focusing on early mobilization have linked it to fewer ventilator days<sup>159</sup> and shorter intensive care unit and hospital lengths of stay.<sup>160</sup> Moreover, comprehensive early pulmonary rehabilitation consisting of inspiratory muscle training combined with early mobilization improved the 6-min walk distance, a fundamental measure of rehabilitation.<sup>161</sup> Early mobilization and pulmonary rehabilitation are likely cost-effective methods of improving respiratory outcomes. Recent data suggest that these data gathered in the medical intensive care units translate also to perioperative patients.<sup>162</sup>

### Preoperative Respiratory Morbidity

Respiratory muscle function can be affected in the postoperative period by patients' comorbid conditions unrelated to the operation.

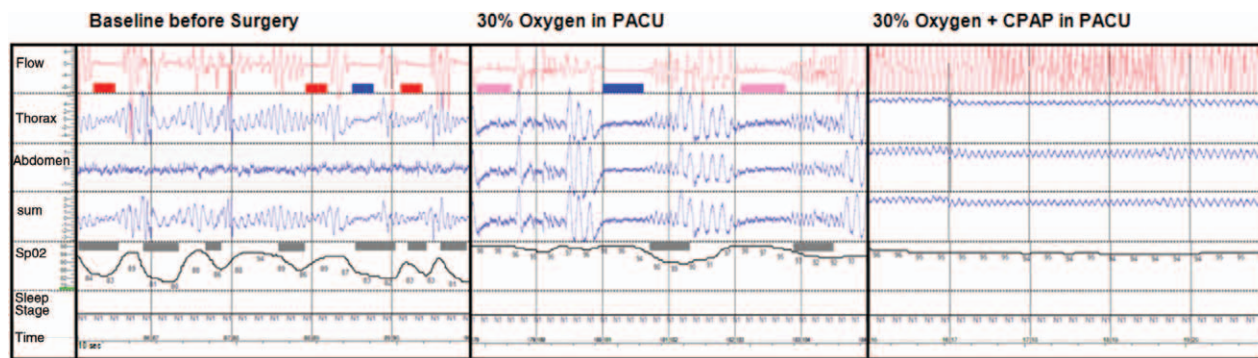
**Age.** Aging is an important preoperative predictor of the development of PPC<sup>163</sup> as it leads to reduced elastic recoil of the lung,<sup>164</sup> reduced chest wall compliance,<sup>165</sup> and decreased diaphragmatic strength.<sup>166</sup> These anatomic changes can impair gas exchange and increase work of breathing, thus leading to vulnerability to respiratory muscle fatigue, and impaired upper airway patency.<sup>167</sup> Furthermore, elderly patients are more sensitive to respiratory depressants<sup>168</sup> because of both decreased responsiveness to hypercarbia and hypoxemia,<sup>169</sup> and decreased metabolic clearance of anesthetics and opioids.<sup>168</sup> In combination, the anatomic and physiologic changes brought about by aging predispose the aged to respiratory muscle dysfunction in the perioperative setting.

**Obesity.** Over one third of the American adult population and one fifth of our children qualify as obese: obesity is an

omnipresent health problem.<sup>170</sup> Obesity affects both upper airway dilator and respiratory pump muscles. In the upper airway, obesity is associated with increased adipose around the pharyngeal airway which can overcome upper airway dilator muscles' efforts at maintaining patency.<sup>171</sup> This increased pharyngeal soft tissue in obese subjects predisposes the upper airway to collapse,<sup>172</sup> whereas in nonobese subjects, even during complete muscle paralysis through NMBA, the upper airway still requires  $-4$  cm H<sub>2</sub>O to collapse.<sup>173</sup> The excess truncal and abdominal adipose tissue found in obese subjects impedes the respiratory pump muscles by increasing the work required to expand the thorax during inspiration, thus leading to lower flow and volume.<sup>174</sup> Obese subjects also have an increased work of breathing compared with nonobese controls as demonstrated by a 16% reduction in oxygen consumption when obese subjects were placed on mechanical ventilation compared to no change with non-obese subjects.<sup>175</sup>

**Obstructive Sleep Apnea.** Body weight and obesity are strongly associated with OSA.<sup>176</sup> OSA is an increasingly common chronic disease in developed and rapidly developing nations, with a prevalence estimate of 3–7% in men and 1–4% in women;<sup>177</sup> this gender discrepancy may partially be related to women's more robust respiratory arousal elicited by negative pressures in the upper airway.<sup>178</sup> Along with obesity and male gender, OSA risk factors include aging,<sup>167</sup> smoking and alcohol consumption, craniofacial anatomy, and sundry heritable factors.<sup>177</sup>

In patients with OSA, upper airway obstruction during the perioperative period can result from alterations in either the passive structural pharyngeal properties or impaired respiratory arousal. During inspiration and expiration, the genioglossus muscle has significantly more activity in subjects with OSA than in control subjects.<sup>179</sup> However,



**Fig. 4.** Representative polysomnography recordings of an obese patient before and immediately after bariatric surgery. Respiratory recordings obtained through polysomnography in an obese patient. The first frame shows severe desaturations during sleep at patient's baseline prior to surgery resulting from a combination of obstructive and central events. In the second frame, immediately following surgery, patient was placed on 30% oxygen in the postanesthesia care unit and continues to have sleep-disordered breathing with mostly central apneas and desaturations. In the third block, again, immediately following surgery, patient was placed on 30% oxygen with continuous positive airway pressure (CPAP) at 10 cm H<sub>2</sub>O and there were no more apnea or desaturation events. Flow = respiratory flow; Thorax = thoracic respiratory effort; Abdomen = abdominal respiratory effort; Sum = respiratory effort of thorax and abdomen; SpO<sub>2</sub> = oxygen saturation; N1 = non-rapid eye movement (REM) sleep stage 1; red bar indicates obstructive apnea; blue bar indicates mixed apnea; pink bar indicates obstructive hypopnea; gray bar indicates desaturation; PACU = postanesthesia care unit.

the onset of sleep changes the control of the upper airway muscles. Specifically, the negative-pressure reflex resulting in increased upper airway contraction is substantially reduced during non-REM sleep and even further reduced during REM sleep.<sup>180,181</sup> Additionally, the “wakefulness” input to these muscles is lessened during sleep,<sup>70</sup> leaving the upper airway particularly vulnerable to collapse. Continuous positive airway pressure (CPAP) is the definitive standard treatment for OSA patients during sleep,<sup>182</sup> and CPAP has the potential to improve perioperative conditions as well<sup>183</sup> (fig. 4). Furthermore, usage of CPAP in the postoperative period may allow more patients with OSA to have ambulatory surgery rather than requiring overnight admission for respiratory observation.<sup>184,185</sup>

**Obstructive Respiratory Pathology.** Asthma and chronic obstructive pulmonary disease are two common respiratory pathologies and have been diagnosed in approximately 13 and 6% of American adults, respectively.<sup>186</sup> Both chronic obstructive pulmonary disease and asthma can lead to a pathologic increase in FRC termed hyperinflation. Hyperinflation prevents optimal generation of negative intrathoracic pressure through a variety of mechanisms—most affecting diaphragmatic function,<sup>187–190</sup> which may be an important pathophysiologic mechanism in the predisposition of chronic obstructive pulmonary disease patients to develop perioperative respiratory failure.<sup>191</sup>

**Smoking.** Active smoking is an independent risk factor for PPC.<sup>192</sup> Smoking increases airway hypersensitivity to chemical stimulants including desflurane,<sup>193</sup> retards pulmonary immune system defenses against infection,<sup>194,195</sup> and increases respiratory mucus production.<sup>196</sup> Together these

changes further reduce a patient’s physiological reserve to respond to perioperative respiratory challenges.

## Strategies to Prevent Postoperative Respiratory Failure

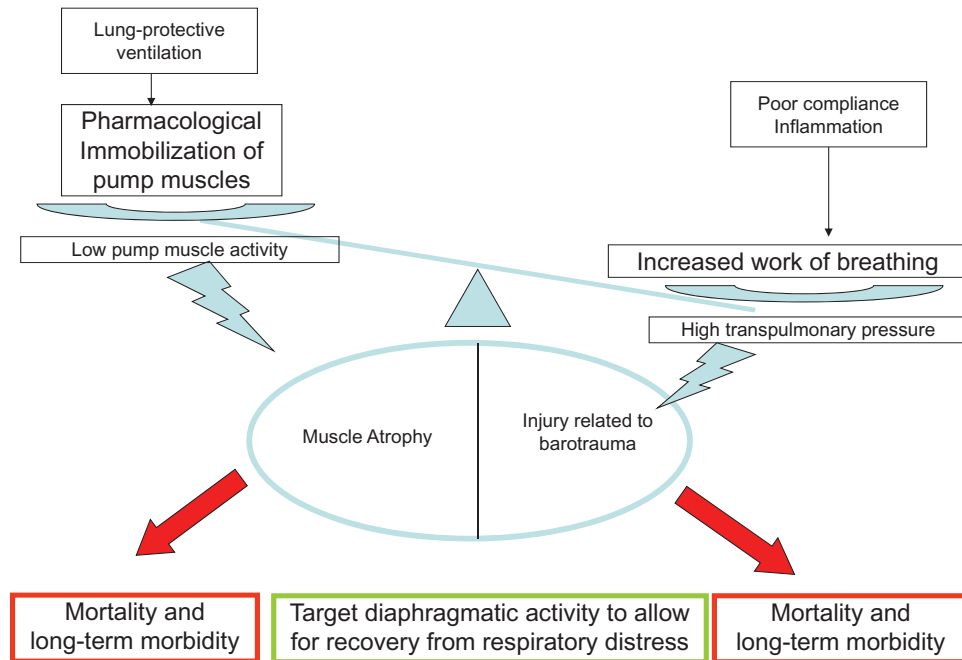
Postoperative hypoxemia complicates 30–50% of abdominal surgeries, and up to 8–10% of these patients require reintubation and mechanical ventilation.<sup>197</sup> Statistics such as these inspire research to predict which patients may need reintubation based on a variety of perioperative risk factors. The ideal algorithm for predicting the likelihood of reintubation would be based on preoperative characteristics<sup>198</sup> so patients could be triaged to appropriate postsurgical level of care. Furthermore, intraoperative events could be considered alongside a validated pretest probability, and only high-risk patients would be conservatively sent to higher care and higher cost units. Perioperative characteristics that have been associated with respiratory failure, and could be considered for an algorithm, include the following: American Society of Anesthesiologists physical status score, comorbid disorders, dependent functional status, emergency case, and type of surgery.<sup>3,6,46,198</sup>

Although predicting the likelihood of reintubation assists in the proper allocation of resources, preventing reintubation is the genuine goal and can be done by maintaining patients’ respiratory muscle function. A summary of preventative strategies for preserving respiratory muscle function can be found in table 1.

The effort to improve postoperative respiratory muscle function and avoid respiratory failure begins with surgical and anesthetic planning: minimally invasive techniques<sup>56,116,199</sup> and

**Table 1.** Avoiding Respiratory Muscle-related Postoperative Respiratory Failure

Mechanism of Respiratory Muscle Dysfunction	Possible Approach to Prevention	References
Tissue injury		
Surgery (laparotomy)	Minimally invasive surgical procedures	56
Trauma (flail chest)	Open reduction with internal fixation	205
	Regional anesthesia for breathing-dependent pain	200
Intraabdominal hypertension	Fluid restriction, decompression	65,206,207
Obesity/obstructive sleep apnea	Continuous positive airway pressure	171
Bronchial hyperreactivity	Avoid tracheal intubation, use noninvasive ventilation	208
	Rigorous bronchodilator treatment	209
Impairment of respiratory arousal		
Sedatives	Daily interruption of sedation	224
Opioids	Consider opioid sparing strategies of pain therapy	225
Sleep disorders	Sleep hygiene	226
Postoperative residual curarization	Quantitative neuromuscular transmission monitoring	125
	Limited use, particularly long acting	15
Inflammation	Rigorous diagnostic procedures—early and specific diagnosis and treatment	210
Barotrauma	Avoid excessive transpulmonary pressure (control respiratory pump muscle activity)	215,227
Diaphragmatic dysfunction	Minimize diaphragmatic immobility	147,157,228
	Respiratory muscle exercise	161



**Fig. 5.** Effects of respiratory pump muscle activity on the outcome of critically ill patients requiring mechanical ventilation. Acute respiratory distress syndrome (ARDS) typically is associated with an increased work of breathing due to poor respiratory system compliance and systemic inflammation. The associated increases in transpulmonary pressures ( $P_L$ ) may be sufficient to induce lung injury. Lung protective ventilation with low tidal volume is the standard of care in patients with ARDS. Temporary pharmacologic immobilization (opioids, sedatives, anesthetics, and rarely neuromuscular blocking agents) may be required to reduce or abolish breathing efforts, but even short-term (48 h) immobilization can lead to muscle atrophy. Thus, both muscle immobilization and excessive activation can lead to increased morbidity and mortality. The pulmonary health of the patient depends on seeking a fine balance between immobilization and activation.

regional anesthesia for pain aggravated by breathing<sup>200</sup> should be utilized when indicated. Regional anesthesia for postoperative pain control can result in improved pulmonary function. First, regional anesthesia can provide better overall pain control than intravenous administration of opioids<sup>201</sup> and potentially allow for deeper breaths and earlier ambulation. Additionally, regional anesthesia improves diaphragm muscle activity, likely by blocking nerves associated with an inhibitory reflex,<sup>202</sup> and increases FRC, through the caudal motion of the diaphragm and a decrease in the intrathoracic blood volume.<sup>203</sup> In total, these improvements in pain control and postoperative lung function may translate to decreased incidence of PPC.<sup>204</sup>

Furthermore, long-acting paralytics must be avoided,<sup>15</sup> and both paralytics<sup>8,124,125</sup> and reversal agents<sup>127</sup> must be precisely dosed and monitored by quantitative neuromuscular transmission monitoring.

In the setting of decreased efficiency of respiratory muscle contractions, such as flail chest, intraabdominal hypertension, and bronchial hyperreactivity, consider basing treatment on the property of the conditions; for example, open reduction with internal fixation and regional anesthesia for flail chest,<sup>200,205</sup> fluid restriction and decompression for intraabdominal hypertension,<sup>65,206,207</sup> and rigorous bronchodilator treatment and non-invasive ventilation for bronchial hyperreactivity.<sup>208,209</sup> During periods of systemic inflammation with increased respiratory

effort, identify and treat the underlying cause early.<sup>210</sup> Following any procedure, multimodal analgesic strategies to decrease opioid-induced respiratory muscle weakness should be employed.<sup>211</sup>

For obese patients with the diagnosis of OSA, and probably those without,<sup>212</sup> postoperative CPAP may reduce the risk of pulmonary complications.<sup>183</sup> Substituting CPAP and other forms of noninvasive mechanical ventilation may also be beneficial for patients with postoperative hypoxia or hypoventilation not requiring airway protection.<sup>208,213</sup>

When a patient is maintained on mechanical ventilation postoperatively or develops acute respiratory distress syndrome, it is important to minimize the immobilizing effect of mechanical ventilation on the respiratory muscles<sup>147,157</sup> and encourage passive mobilization as an initial step in pulmonary rehabilitation<sup>161</sup> (fig. 5). Therefore, spontaneous breathing efforts should be trialed while keeping the transpulmonary pressure ( $P_L$ ) in mind.<sup>214</sup>  $P_L$  is defined as the difference between airway plateau pressure ( $P_{plat}$ ) and pleural pressure ( $P_{pl}$ ), and it varies with respiratory pump effort when  $P_{plat}$  is constant.<sup>215</sup> Most importantly, increases in  $P_L$  from high respiratory effort and aggressive spontaneous breathing can result in barotrauma.<sup>216,217</sup>

One approach to managing  $P_L$  is utilizing controlled ventilation and prescribing NMBA<sup>216,218</sup>; however, it is important to avoid immobilizing the diaphragm unnecessarily,<sup>157</sup> especially when initial attempts to control  $P_L$  can be made

through titration and selection of sedatives and analgesics. Furthermore, partial support ventilatory modes that permit spontaneous breathing should be utilized as they reduce diaphragmatic harm in preclinical trials<sup>219–221</sup> and improve ventilation perfusion matching in clinical studies.<sup>222,223</sup>

## Conclusion

Proper respiratory muscle dysfunction is a key determinant of postoperative respiratory failure. Careful attention should be paid to the effect of perioperative interventions on respiratory muscles, particularly in patients at risk of postoperative respiratory failure. The type of surgical procedure, the anesthesia plan, the postoperative pain management, and the mechanical ventilation strategy can all incrementally push a patient toward or away from upper airway collapse or respiratory pump dysfunction: both of which increase the likelihood of postoperative respiratory failure.

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