Update on Respiratory Management of Critically Ill Neurologic Patients

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Current Neurology and Neuroscience Reports 2005, **5:**476–482
Current Science Inc. ISSN 1528-4042

Respiratory failure complicates a number of acute neurologic conditions, most notably neuromuscular diseases (eg, Guillain-Barré syndrome and myasthenia gravis) and stroke. In addition, pulmonary complications, particularly pneumonia and atelectasis, are fairly common in patients with these diagnoses; their prevention and early recognition are crucial to avoid detrimental consequences. This review discusses recent studies related to predictors of respiratory failure and pneumonia, strategies of respiratory care and ventilatory support, functional prognosis, and withdrawal of mechanical ventilation in patients with acute neuromuscular respiratory failure and stroke.

Introduction

Respiratory failure and ventilatory support in patients with acute neurologic and neurosurgical diseases differ from those in other critically ill patients. Primary pulmonary illnesses are less commonly responsible for the initial intubation, and ventilatory strategies must be adjusted to the condition, prompting the requirement for mechanical support. Neuromuscular respiratory failure and impaired level of consciousness due to severe brain insults (stroke being the one most often encountered by general neurologists) are two of the most frequent causes for endotracheal intubation and mechanical ventilation in neurologic-neurosurgical intensive care units (ICU). Therefore, this review of recent evidence on the field focuses on advances in the management of acute neuromuscular disorders leading to ventilatory insufficiency and the treatment and prognosis of patients with stroke who require mechanical ventilation. Given its practical importance, this review also briefly discusses the factors that lead to withdrawal of mechanical ventilation in acute neurologic patients.

Neuromuscular Respiratory Failure

The two most common primary neurologic diseases leading to acute neuromuscular respiratory failure are acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome [GBS]) and myasthenia gravis (MG) crisis. Other causes of neuromuscular respiratory failure, such as botulism, tick paralysis, porphyria, and critical exacerbations of chronic inflammatory demyelinating polyradiculoneuropathy, are fortunately rare, and little research has been published in regard to their specific ventilatory management. In all of these conditions, timely recognition of ventilatory insufficiency is essential. The reader should refer to a recent manuscript that reviews the typical symptoms and signs of impending neuromuscular respiratory failure [1].

Critically ill patients may also develop persistent respiratory failure due to neuromuscular weakness caused by metabolic disorders (such as hypophosphatemia induced by hyperalimentation), persistent effect of paralytic agents, or myopathy and polyneuropathy associated with sepsis and multiorgan dysfunction syndrome [2]. These conditions should be considered in the differential diagnosis of any patient in whom attempts to wean mechanical ventilatory support fail repeatedly.

Guillain-Barré syndrome

Nearly one third of patients with GBS require mechanical ventilation during the course of their disease. Severe generalized weakness, rapid disease progression, and bulbar involvement are known to be associated with the need for ventilatory support. Traditional guidelines for intubation, based on a small observational series (19 patients) published by Ropper and Kehne [3], include a vital capacity of less than 12 to 15 mL/kg or a PO_2 less than 70 mm Hg breathing room air, or clinical signs of respiratory fatigue. Although widely applied and useful in practice, these guidelines lacked formal scientific validation. Meanwhile, timely intubation in patients with GBS is important because emergency intubation due to critical respiratory distress or respiratory arrest may result in anoxic brain damage [4]. Therein lies the importance of the study reported by Lawn *et al.* [5••] assessing the value of bedside respiratory measurements for predicting what patients with GBS will require mechanical ventilation. The authors reviewed 114 consecutive patients with GBS admitted to the ICU, including 60 who had been mechanically ventilated. Patients requiring ventilatory support exhibited faster disease progression and had greater rates of bulbar signs, autonomic dysfunction, and bilateral facial palsy.

Vital capacity less than 20 mL/kg, maximal inspiratory pressure worse than -30 cm H_2O, maximal expiratory pressure less than 40 H_2O, and a reduction of more than 30% in vital capacity, maximal inspiratory pressure, or maximal expiratory pressure were predictive of requiring mechanical ventilation. Bulbar dysfunction and low vital capacity (< 20 mL/kg) were the strongest indicators of impending respiratory failure. Another study singled out the presence of IgG anti-GQ1b antibodies as a possible predictive factor for respiratory failure in patients with GBS [6].

Bedside respiratory tests are also valuable to monitor clinical course after intubation. This value was demonstrated by comparison of patients with GBS ventilated for longer than 3 weeks with those that required shorter times of ventilation [7]. A drop in vital capacity, maximal inspiratory pressure, and maximal expiratory pressure between measures at baseline and day 12 predicted the need for prolonged intubation. The authors proposed the use of an integrated measurement, the pulmonary function (PF) score, calculated by adding the values of vital capacity, maximal inspiratory pressure, and maximal expiratory pressure. A PF ratio was obtained by dividing the PF scores from days 1 and 12 after intubation. A PF ratio of less than 1 (indicating worsening strength of inspiratory and expiratory muscles compared with the time of intubation) was uniformly associated with ventilatory requirement longer than 3 weeks (Fig. 1). Thus, this simple measurement may be used to predict before the end of the second week of ventilation which patients will necessitate prolonged mechanical assistance and consequently tracheostomy. Performance of tracheostomy has also been associated with advanced age and pre-existing pulmonary disease [8].

Apart from persistent or worsening respiratory muscle weakness, prolonged ventilation may result from the development of medical complications during the critical phase of the illness. In a cohort of 114 patients with GBS admitted to the ICU, pulmonary complications (particularly tracheobronchitis and pneumonia) affected over half of the patients who received mechanical ventilation [9•]. The occurrence of major complications was associated with the requirement for prolonged mechanical ventilation (> 14 days). Bacteriemia was documented in one fifth of the patients but severe sepsis was uncommon. Infectious complications were more frequent in patients treated with steroids, and their incidence correlated positively with the duration of stay in the ICU. Other potentially life-threatening conditions, such as gastrointestinal hemorrhage and pulmonary embolism, were seen rarely. Contrary to common fears, no major complications related to dysautonomia were noticed in this population. The practical message of these findings is that aggressive respiratory therapy (frequent suctioning of bronchial secretions, use of ventilatory strategies aimed at minimizing atelectasis, performance of surveillance cultures in units with outbreaks of specific microorganisms), early extubation in patients who tolerate weaning, and timely tracheostomy in patients who will require prolonged ventilatory support (as predicted by lack of improvement or worsening of bedside respiratory tests) should be emphasized to avoid preventable respiratory complications.

The long-term functional outcome of patients with GBS was assessed in the same cohort of patients (n = 114; 60 mechanically ventilated) [10]. Good recovery (defined by the ability to ambulate independently) was observed in 75% of patients. Requirement for mechanical ventilation was significantly associated with poor outcome; 21 of 26 patients (81%) who remained unable to walk without assistance had necessitated ventilatory support. Mortality occurred in 20% of ventilated patients. However, ventilated patients who survived often reached meaningful recovery, with 79% of them regaining independent ambulation. Age and delayed transfer from the referring hospital (after more than 2 days of hospital stay) were the only variables independently associated with poor outcome at the time of maximal recovery in patients who required mechanical ventilation. Therefore, early referral to a specialized neurologic ICU with extensive experience in the management of critical cases of GBS must be advocated to minimize preventable deaths and enhance the chances of functional recovery.

A retrospective analysis of a series of 77 adults with GBS from Taiwan found that 32% of patients required ventilatory support [11]. After 1 year of follow-up, three of the 25 ventilated patients had died (due to septic shock in all cases), six were wheelchair-bound or bed-bound, three needed assistance for ambulation, six had moderate functional impairment but were capable of unassisted gait, and seven were normal or had mild signs and symptoms. Worse maximal inspiratory and expiratory pressures at the time of intubation and occurrence of medical complications during mechanical ventilation were associated with poor long-term functional recovery. This study also highlights the importance of avoiding delays in intubation and optimizing respiratory management to improve the outcome of patients with GBS and ventilatory failure.

Myasthenia gravis crisis

Myasthenia gravis often follows an unpredictable course. Hence, there is considerable interest in establishing what factors may predict a more aggressive course and a greater tendency to develop respiratory compromise. The presence of anti–muscle-specific kinase (MuSK) antibodies may be one such factor. In a study evaluating 78 patients with seronegative MG, the subgroup of patients with positive serology for anti-MuSK antibodies (n = 37) differed by their greater rate of bulbar weakness (100% vs 58%) and higher frequency of respiratory crisis (46% vs 7%) [12]. Preferential involvement of respiratory muscles was also noted in another smaller series of patients with anti-MuSK antibodies [13]. Exacerbation of myasthenic symptoms resulting in respiratory compromise is not infrequent after thymectomy. In a series of 122 patients who underwent

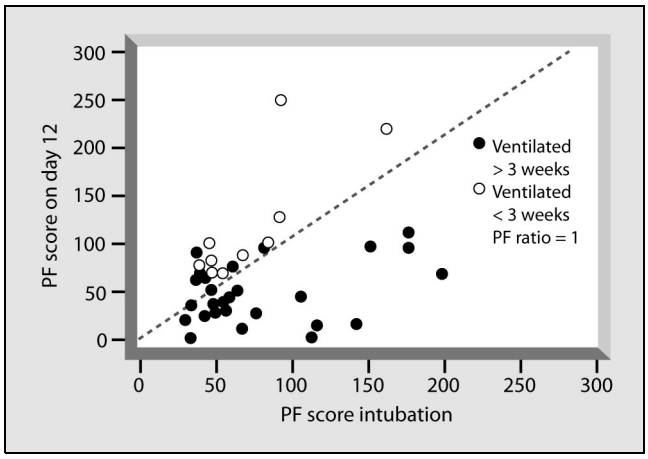

Figure 1. Illustration of how pulmonary function (PF) ratios reliably discriminate Guillain-Barré syndrome patients who could be successfully weaned within the first 3 weeks of ventilation from those requiring more prolonged ventilatory support. (*Adapted from* Lawn and Wijdicks [7].)

trans-sternal thymectomy, Watanabe *et al.* [14] identified 14 cases requiring prolonged postoperative ventilatory support (> 48 hours) due to worsened weakness. Multivariate logistic regression analysis singled out preoperative bulbar symptoms, higher preoperative serum levels of anti-acetylcholine receptor antibodies (> 100 nmol/L), and larger intraoperative blood loss (> 1 L) as independent predictors of postoperative myasthenic crisis.

The value of respiratory function tests in the monitoring of MG and diagnosis of early involvement of respiratory muscles was evaluated in two recent studies. The first study tested the usefulness of measuring maximal voluntary ventilation, defined as the largest volume of air that can be inhaled and exhaled with voluntary effort during 10 to 15 seconds (measured volumes are then extrapolated to 1 minute and results are expressed as flow rate in liters per minute) [15]. Maximal voluntary ventilation correlated well with clinical severity of MG, and patients with compromise of respiratory muscles presented a pattern of progressive reduction in inspiratory and expiratory volumes throughout the course of the test. The second study evaluated the more traditional maximal inspiratory and expiratory pressures, which are measures of muscle strength against a continuous resistance [16]. The investigators found a correlation between reduction in these pressures and clinical worsening. However, these two studies were performed in relatively stable outpatients. The application of these respiratory function tests to the management of patients with acute MG exacerbations remains empirical. In fact, serial measurements of vital capacity were found to be poor predictors of the need for intubation and mechanical ventilation in patients with myasthenic exacerbations [17].

The indications of noninvasive ventilation to treat acute respiratory failure are expanding [18] and may represent a useful alternative to traditional mechanical ventilation for some patients with myasthenic crisis. In a small series from the Mayo Clinic, noninvasive ventilation with a bilevel positive airway pressure (BiPAP) mask averted endotracheal intubation in seven of 11 cases of severe MG exacerbation in which this intervention was tried [19••]. Bulbar weakness was present in seven of these episodes, including four cases in which ventilation with BiPAP was successful. BiPAP ventilation was well tolerated and excessive respiratory secretions never led to discontinuation of the trial in this series. Hypercapnia (PCO_2 > 50 mm Hg) at the time of initiation of the noninvasive ventilation trial predicted the need for endotracheal intubation. My subsequent experience using a BiPAP mask to ventilate patients with MG exacerbation has been similarly successful.

The disadvantages of noninvasive ventilation for myasthenic patients are the lack of airway protection against sudden obstruction or aspiration and the possibility that it might result in hazardous delays in intubating patients with fulminant forms of crisis who fail to respond to BiPAP support. These potential drawbacks must be weighed against the probable reduction in the risk of ventilator-associated pneumonia that may be afforded by noninvasive ventilation. It is also quite likely that avoiding intubation may shorten lengths of stay in the ICU. I strongly believe that a trial of noninvasive respiratory support should be considered in most MG patients with incipient respiratory failure without established hypercapnia. This approach deserves to be formally compared with the traditional protocol of early intubation in a randomized trial.

Patients intubated for myasthenic crisis often develop pneumonia and atelectasis during the course of their mechanical ventilation [20–22]. A retrospective study from the Neurosciences critical care group at Johns Hopkins Hospital analyzed the impact of implementing an intensive respiratory care program in preventing these complications [23•]. The respiratory management protocol included the use of sighs, positive end expiratory pressure, frequent bronchial suctioning, chest physiotherapy, bronchodilator nebulizer treatments, turning of the patient every 2 hours, and administration of antibiotics in cases of documented infection. Because not every component of this protocol was applied to every case, the authors of the manuscript designed a respiratory intervention index to categorize the level of aggressiveness of the respiratory treatment offered to each patient (the higher the index, the more aggressive the treatment). Not surprisingly, the respiratory intervention index was positively correlated with the severity of pulmonary disease (as defined by the lung injury score). More interestingly, this index had an inverse correlation with forced vital capacities, indicating that aggressive respiratory care promoted an improvement in ventilatory function. In this series, the rates of atelectasis and pneumonia were 29% and 17%, respectively. These rates are remarkably low compared with other reports in the literature [20–22], but comparing the observations among these retrospective studies has limited scientific validity. Nonetheless, this

study provides evidence to strongly support intensive respiratory care in patients with myasthenic crisis. Future studies should aim at defining more precisely what ventilatory strategies and what specific components of respiratory therapy have the greatest impact in improving the outcome of myasthenic patients on mechanical ventilation.

Weaning mechanical ventilation in MG patients is often challenging because of the erratic nature of the disease. Reintubation rates in these patients may be more substantial than commonly thought. In a review of 26 episodes of myasthenic crisis, the rate of extubation failure was 27% (median time to re-intubation was 36 hours) [21]. Older age, atelectasis, and pneumonia were significantly associated with this complication. Patients with an episode of failed extubation had considerably longer ICU stays (median of 28 days vs 7 days; $P < 0.01$) and hospital stays (median of 40 days vs 12 days; $P < 0.01$). BiPAP ventilation may be useful to prevent reintubation in selected patients with persistent or recurrent respiratory failure after extubation in patients with MG [24]. Pressure-controlled ventilation via a mini-trachostomy tube has been proposed for MG patients requiring prolonged ventilatory assistance as a means of safely achieving effective ventilation while preserving phonation [25]. The value of this alternative requires validation in larger series.

Respiratory Failure after Stroke

Although in relative numbers respiratory failure is not common after a stroke, cerebrovascular disease is so prevalent that this problem is often encountered in practice. In addition, pneumonia is a frequent complication during the clinical course of patients with acute stroke, and upper airway dysfunction is an increasingly recognized sequela of brain infarctions that may lead to disordered breathing and oxygen desaturations during sleep. Hence, respiratory care of stroke patients involves mechanical ventilation in the most severe cases but should also include preventive measures to avoid pneumonia, timely treatment of established infections, and early diagnosis and treatment upper airway dysfunction and obstructive sleep apnea.

Several studies have evaluated the prognosis of patients with stroke who require endotracheal intubation and mechanical ventilation [26–30]. Reported mortality rates have ranged between 50% and 90%. Depressed level of consciousness at presentation or at the time of intubation, loss of brainstem reflexes, and evidence of neurologic decline have been identified as predictors of fatal outcome. Information on the long-term functional outcome in survivors was more scant until recently.

In a review of 101 consecutive patients with acute ischemic stroke who required mechanical ventilation for longer than 24 hours, Schielke *et al.* [31] observed a mortality rate of 44% within 60 days. Survival rates were 40% at 1 year and 33% at 2 years. Age older than 60 years and Glasgow Coma Scale sum score less than 10 on admission were significantly associated with early (at 2 months) and late (at 2 years) mortality. History of myocardial infarction was predictive of late mortality. Survivors were interviewed to assess functional outcome, and the evaluation included the use of measures to gauge cognitive impairment, presence of depression, and quality of life. Functional independence was achieved by 27% of the survivors and the great majority of those patients had limited cognitive and emotional impairments. Quality of life was strongly related to the degree of functional recovery.

Another study assessed the outcome of patients with acute stroke who required prolonged mechanical ventilation (mean time of 11 days) and tracheostomy [32]. Poor outcome (death or severe disability) occurred in 74% of patients at 1 year (with 30% mortality) and was associated with history of previous brain damage and neurologic worsening after intubation. One quarter of the patients achieved good functional recovery; these patients were younger and more likely to have strokes involving the posterior circulation. Pulmonary complications during mechanical ventilation were quite prevalent (pneumonia was documented in 57% of cases) but they did not determine worse outcome. Earlier tracheostomy correlated with shorter ICU and hospital stays.

Foerch *et al.* [33••] reported a prospective cohort study of 65 stroke patients older than 65 years of age (mean age of 75 years) who had required mechanical ventilatory assistance during the acute hospitalization. Sixty percent of patients expired within the first 6 months after the stroke, with three quarters of these fatalities occurring during the first month. Multivariate logistic regression analysis indicated that age older than 77 years and presence of leukocytosis on admission predicted fatal outcome whereas elective intubation was associated with survival. A cross-sectional survey conducted after a mean follow-up time of nearly 16 months revealed that 36% of surviving patients had achieved good to moderate functional outcome (Barthel index score ≥ 60) and 27% had moderate to good quality of life ratings. No patients close to or older than 80 years of age reached meaningful recovery.

In conjunction, these studies indicate that treatment with mechanical ventilation after an acute stroke is compatible with adequate functional recovery. Even prolonged ventilation is justified in younger patients. Some elderly stroke patients requiring respiratory support may achieve functional independence, particularly when intubation is performed electively, but mechanical ventilation appears to be futile in patients older than 80 years of age. Respiratory complications are common during the course of mechanical ventilation but they are treatable; thus, aggressive care should be continued in patients deemed to be capable of neurologic recovery.

Pneumonia can still represent a formidable foe to patients with acute stroke. The predictors and clinical impact of pneumonia in stroke patients were analyzed in a population of 55 patients with acute stroke admitted to an

ICU [34]. The incidence of pneumonia was 47%, including 16% of patients with early pneumonia (criteria met within 48 hours of hospital admission) and 31% of patients with nosocomial pneumonia. Brainstem involvement was associated with early cases, and endotracheal intubation and failed swallowing evaluation were associated with nosocomial infections. Patients with nosocomial pneumonia tended to have longer durations of mechanical ventilation (15 vs 5 days in patients without pneumonia) and more prolonged hospital stays (31 vs 8 days). Nosocomial pneumonia was not associated with increased mortality but the study did not include any measure of functional outcome in survivors. In fact, pneumonias may have a detrimental impact on outcome according to other studies. In their analysis of 124 critical stroke patients, Hilker *et al*. [35•] found that the diagnosis of pneumonia (present in 21% of patients) was associated with greater mortality rates and poorer long-term clinical outcomes. Mechanical ventilation, abnormal chest radiograph on admission, multiple stroke locations, involvement of posterior circulation territories, and dysphagia were independent risk factors for pneumonia. In a series of 100 patients with swallowing dysfunction after acute stroke, early pneumonia was very prevalent (44%) despite the use of nasogastric tubes, and it was significantly associated with poorer functional outcomes [36]. Decreased level of consciousness and severe facial palsy also predicted the occurrence of early pneumonia [36]. Therefore, the prevention and early recognition and treatment of pneumonias related to aspiration or mechanical ventilation must be a priority when caring for patients with severe strokes. Performing early swallowing testing, having low thresholds to initiate empirical antibiotic coverage (after obtaining adequate samples for culture) in suspected cases, and following an aggressive protocol of respiratory care in intubated patients are reasonable practical advices to minimize the negative impact of pneumonia on stroke outcome.

Upper airway obstruction occurs commonly after a stroke but it may remain unrecognized unless patients undergo sleep studies. Among 120 patients tested with sleep study within 24 hours of stroke onset, Turkington *et al*. [37] found that nearly 80% of the patients had some degree of sleep apnea, including 61% who had a respiratory disturbance index greater than 10. Obstructive apneas clearly predominated (median of 37 per study) over central apneas or Cheyne-Stokes breathing pattern, and obstruction worsened when the patient was in supine position. Higher body mass index, larger neck circumference, and limb weakness were independently associated with the presence of upper airway obstruction, but, somewhat surprisingly, stroke severity and pharyngeal dysfunction (defined by documented unsafe swallowing) were not. Perhaps these findings can be explained by the pre-existence of obstructive apneas in many patients who suffer strokes [38]. The same group of researchers reported data on the functional outcome of this cohort after 6 months [39]. Patients with more severe upper airway obstruction were more likely to be dead or dependent, especially when long apneas had been documented. Sleep-related breathing disorders have also been found to be associated with increased mortality after a stroke by others [40]. These data argue in favor of early treatment of obstructive sleep apneas after an acute stroke.

Treatment with nasal continuous positive airway pressure (CPAP) is highly effective in reducing upper airway obstruction, thus preventing apneas. Poor compliance with this treatment by acute stroke patients has been found by some researchers [41,42] but not others [43]. However, the benefits of this intervention in stroke patients are multiple, including decreased nocturnal blood pressure, less symptoms of depression, and improved overall sense of well-being [42,43]. It remains to be established if use of nasal CPAP after an acute stroke may actually improve neurologic outcome and reduce mortality.

Withdrawal of Mechanical Ventilation

Withholding or withdrawing life-sustaining treatments is undoubtedly one of the most difficult decisions to be made by any physician. Yet, it is the most compassionate course of action once it becomes clear that recovery is no longer possible despite maximally aggressive care. The challenge is to correctly identify those hopelessly ill patients in whom further treatment is futile. Predictors for fatal outcome or permanent disability are rarely infallible but some have been reported in the literature for the most common neurologic catastrophes. The evidence supporting the value of these prognostic indicators was the topic of a recent systematic review [44•].

The factors associated with withdrawal of mechanical ventilation in the neurologic/neurosurgical ICU were analyzed in a cohort of over 2000 patients [45••]. Mechanical ventilation was withdrawn from 13.5% of all patients. Variables independently associated with withdrawal of mechanical ventilation included greater severity of the primary acute neurologic disease and older age. Both Glasgow Coma Scale sum scores and Acute Physiology and Chronic Health Evaluation (APACHE) II scores were significantly lower in patients who had ventilation withdrawn. The diagnoses that most frequently resulted in withdrawal (proportionally to all patients admitted with the diagnosis) were brainstem hemorrhage, cerebellar lesions, intracerebral hemorrhage, subarachnoid hemorrhage, and large ischemic strokes. Neither the type or presence of insurance coverage nor the type of physician (private versus academic) in charge of the patient's care influenced the likelihood of withdrawal. However, ventilatory assistance was less likely to be removed from African American patients and those who had undergone surgery. Notably, 81% of patients in whom ventilatory support was withdrawn had normal premorbid status. Among patients who died, 35% had withdrawal of mechanical ventilation.

A previous study on withdrawal of life-sustaining treatments in critical neurologic patients had also found a high frequency of terminal intubation (43% of patients in that series had their ventilatory support removed before their demise) [46]. This insightful study showed that although some patients may continue to breathe for many hours after removal of ventilatory assistance, the great majority of the surrogate decision-makers were satisfied with the process of withdrawal and would repeat their decision to withdraw life support.

Conclusions

Appropriate respiratory care is essential to achieve good recovery in patients with critical neurologic conditions that compromise ventilatory function. Mechanical ventilation is often needed in patients with GBS, and clinical variables and bedside respiratory function tests can be reliably used to identify those patients who will require ventilatory support. These tests are also valuable to monitor ventilated patients with GBS and predict the need for prolonged ventilatory requirement. In patients with myasthenic crisis, noninvasive ventilation via BiPAP mask may avert intubation before hypercapnia ensues. Respiratory function tests may be useful but are less dependable than in GBS. Intensive respiratory care protocols aimed at reducing the risk of pneumonia and atelectasis must be instituted as soon as a myasthenic patient is intubated. Extubation of these patients may be associated with considerable risks of need for reintubation. Use of BiPAP ventilation after extubation may be a useful strategy to prevent this complication.

Mechanical ventilation is consistent with meaningful functional recovery in patients with severe strokes. Although even prolonged ventilation is justified in younger patients, the decision to ventilate elderly stroke patients must be individualized and may not be justified in those older than 80 years of age. Pneumonia is a frequent complication after stroke and may result from aspiration or be related to mechanical ventilation. The occurrence of sleep apneas from upper airway obstruction may have a detrimental impact on recovery from an acute stroke. Because most patients who develop this complication have pre-existing risk factors for the disorder, stroke patients should be screened to assess their risk for sleep apnea and high-risk patients should undergo early sleep study. Nasal CPAP is a successful treatment for sleep-related breathing disorders in stroke patients and must be prescribed in patients with documented obstructive apneas.

Withdrawal of mechanical ventilation is a very appropriate medical decision in patients with massive brain damage who have no chances of meaningful recovery. It is, therefore, greatly relevant to learn how to recognize validated prognosticators of death or permanent dependency in specific acute neurologic diseases.

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