Ventilatory Management of the Noninjured Lung

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INTRODUCTION

The concept that mechanical ventilation (MV) could produce lung injury was advanced during the polio epidemic of the 1950s when it was noted that patients dying after prolonged mechanical ventilatory support had considerable lung structural damage. Most reports focused on pneumothorax and other manifestations of barotrauma. In their seminal article of 1974, Webb and Tierney eloquently describe the rapid development of pulmonary edema in the lungs of rats ventilated with high inflation pressures and the protective effect of positive end-expiratory pressure (PEEP). The concept of ventilator-induced lung injury other than barotrauma was extended by others, in a variety of animal models, supporting the concepts that lung injury can be caused by overdistension of the lungs (as with high tidal volumes) and that preexisting lung injury could sensitize the lungs to overdistension injury (henceforth called volutrauma). Volutrauma is associated with high permeability pulmonary edema, ultrastructural changes in both the lung epithelium and endothelium, alteration of surfactant structure and function, and the generation of inflammatory cytokines that can extend injury beyond the lungs themselves. Clinically, the lung injury caused by volutrauma is indistinguishable from other causes of the acute respiratory distress syndrome (ARDS). The clinical relevance of these concepts has now been well characterized, and the use of low tidal volumes in patients with acute respiratory distress syndrome is a cornerstone of management. However, in animal models, the lung volumes required to generate lung injury in previously normal lungs are large, typically approaching total lung capacity (TLC), and the relevance of tidal volume limitation to the mechanical ventilatory support of patients without lung injury has often been questioned. However, over the last decade, the accumulated evidence suggests that volutrauma can occur when patients are ventilated with tidal volumes long considered acceptable. Recommendations regarding mechanical ventilatory support of patients without lung injury who require mechanical ventilation should adhere to a schema of lung protective ventilation. Lung protective ventilation in the perioperative period, using low tidal volumes and positive end-expiratory pressure, is associated with reduced postoperative pulmonary complications. The exception may be the patient with high cervical spinal cord injuries who depends on mechanical ventilation. There is no consensus on timing of tracheostomy in patients with neurologic diseases.

KEY POINTS

- Patients without lung injury who require mechanical ventilation should adhere to a schema of lung protective ventilation.
- Lung protective ventilation in the perioperative period, using low tidal volumes and positive end-expiratory pressure, is associated with reduced postoperative pulmonary complications.
- The exception may be the patient with high cervical spinal cord injuries who depends on mechanical ventilation.
- There is no consensus on timing of tracheostomy in patients with neurologic diseases.

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injury must take into account the underlying diseases or injuries of the patient. This discussion begins with generally applicable discussions of tidal volume followed by specific considerations for patients: (1) in the perioperative period, (2) undergoing lung resection, (3) organ donors, and then (4) a more expansive discussion of patients with neurologic disorders including spinal cord injury (SCI), traumatic brain injury, stroke, and neuromuscular diseases.

**TIDAL VOLUME**

Until the last decade, MV of patients undergoing endotracheal intubation and general anesthesia commonly used tidal volumes of 10 mL/kg or greater. The use of high tidal volume ventilation (10 mL/kg predicted body weight and greater) was supported by studies in the 1960s and 1970s showing that the hypoxemia, airway closure, and reduced functional residual capacity seen during the mechanical ventilatory support of patients undergoing general anesthesia could be mitigated by the use of large tidal volumes (15 mL/kg) or the application of PEEP.\(^{13,14}\) These concepts were then applied more generally to mechanically ventilated critically ill patients in intensive care units (ICUs). Once it was found that limiting tidal volume in patients with ARDS could reduce mortality,\(^{15}\) it was speculated that smaller tidal volumes might be appropriate for most patients requiring mechanical ventilatory support. Gajic and colleagues,\(^{16}\) in an observational study of 332 patients (mixed medical and surgical) without ARDS at the onset of ventilatory support, found that ARDS developed in 24% and there was a strong link between the development of ARDS and the use of tidal volumes in excess of 6 mL/kg of predicted body weight (odds ratio, 1.3 for each 1 mL >6 mL/kg; \(P<.001\)). In a randomized trial of 150 patients (mixed medical and surgical) comparing ventilation with conventional tidal volumes of 10 mL/kg predicted body weight with low tidal volumes of 6 mL/kg in patients without ARDS at the onset of ventilatory support, Determann and colleagues\(^{17}\) found that 13.5% of the conventional group developed ARDS as opposed to only 2.6% of those in the low tidal volume group \(P = .01\). A recent systematic review supported these conclusions.\(^{18}\) Although no controlled trial has translated this reduced development of ARDS to a reduction in mortality,\(^{19}\) given the impact of smaller tidal volumes on the development of ARDS, it is reasonable to target tidal volumes of 6 mL/kg of predicted body weight in unselected patients without lung injury.

**INTRAOPERATIVE AND PERIOPERATIVE PATIENTS**

The use of high tidal volumes has been a common practice in the perioperative period to reduce the incidence of hypoxemia and atelectasis. However, this practice can no longer be recommended. In a multicenter trial in 400 patients undergoing abdominal surgery under general anesthesia, Futtier and colleagues\(^{20}\) compared the incidence of postoperative pulmonary and extrapulmonary complications in patients ventilated with high tidal volumes (10–12 mL/kg) and zero PEEP (ZEEP) and those ventilated with low tidal volumes (6–8 mL/kg) and 6 to 8 cm H\(_2\)O PEEP. The incidence of perioperative complications was significantly higher in the high tidal volume zero PEEP group. Similar findings have been noted in small observational and randomized trials in patients undergoing cardiac surgery.\(^{21,22}\)

Patients undergoing lung resectional surgery usually require 1-lung ventilation for at least a portion of their operative course. Without a marked reduction in tidal volume with initiation of 1-lung ventilation, the potential for volutrauma in this patient population seems real, despite the often short duration of one lung ventilation. Observational studies suggest a link between tidal volume, peak inspiratory pressure, or duration of 1-lung ventilation in patients undergoing pneumonectomy and the subsequent development of ARDS.\(^{23,24}\) Further, a recent small randomized trial of ventilation with higher tidal volumes (10 mL/kg) and zero PEEP versus low tidal volume (6 mL/kg) and 5 cm H\(_2\)O PEEP in patients undergoing lung cancer resectional surgery found an increased incidence of the composite endpoint of decreased PaO\(_2\)/fraction of inspired oxygen (FiO\(_2\)) ratio, atelectasis, or lung infiltrates in the group receiving high tidal volumes and zero PEEP.\(^{25}\)

**POTENTIAL ORGAN DONORS**

Volutrauma may also be observed in those individuals who are potential organ donors after declaration of death by neurologic criteria (brain death). Mascia and colleagues\(^{26}\) randomly assigned 118 potential organ donors to a conventional MV strategy using tidal volumes of 10 to 12 mL/kg and 3 to 5 cm H\(_2\)O PEEP or to a lung protective ventilation strategy using tidal volumes of 6 to 8 mL/kg and 8 to 10 cm H\(_2\)O PEEP during a 6-hour observation period before determining suitability for organ donation. The percentage of patients who met lung donor eligibility criteria were 54% in the conventional strategy group and 95% in the lung protective strategy group \(P<.001\). Lungs were
harvested from 27% of the conventional group and 54% of lung protective group (\(P = .004\)), and the 6 month survival rate did not differ between patients receiving lungs from the conventional or lung-protective groups.

**MODE OF MECHANICAL VENTILATION**

Volume-targeted or volume-controlled ventilatory modes (henceforth termed volume controlled) are most commonly used at the initiation of mechanical ventilatory support, but the use of pressure-targeted or pressure-controlled (henceforth termed pressure controlled) modes have seen increasing use in the last decade and are now more commonly used after 2 or 3 days of mechanical ventilatory support.\(^{27}\) Pressure-controlled modes typically use higher flow rates at the beginning of inspiration and are thus less susceptible to the production of patient-ventilator dyssynchrony caused by inadequate flow rates in spontaneously breathing patients with vigorous inspiratory efforts.\(^{27,28}\) However, pressure-controlled modes may permit the generation of excessive tidal volumes, as transpleural pressure is increased because of the decrease in pleural pressure with spontaneous ventilatory efforts.\(^{27,28}\) The former can be corrected by increasing the flow rate to match the needs of the patient when using volume-controlled ventilation and the latter by careful monitoring of delivered tidal volumes and adjusting inspiratory pressures accordingly (either manually or through automated feedback systems such as pressure-regulated volume control). Understanding the limitations of both volume-controlled and pressure-controlled modes and the characteristics of the mechanical ventilator being used should mitigate each of these concerns. To date, there is little evidence that a particular mode of ventilation is superior to another with respect to its propensity for lung injury.\(^{27}\)

**POSITIVE END-EXPIRATORY PRESSURE**

Low levels of PEEP (5–8 cm of H\(_2\)O) are commonly used in patients receiving mechanical ventilatory support. These levels are largely a holdover from anesthesia practices noted above, as few clinical studies have actually studied this. In one small series, these low levels were found to reduce the incidence of ventilator-associated pneumonia and the development of hypoxemia during ventilatory support.\(^{28}\) No adverse effects were noted. Despite the paucity of evidence, it is reasonable to use 5 cm H\(_2\)O PEEP routinely.

**BLOOD GAS TARGETS**

Although hypercarbia results in a respiratory acidosis and increases respiratory drive, in the absence of intracranial pathology (see later discussion) or myocardial dysfunction, modest hypercarbia is usually well tolerated in the absence of significant pulmonary hypertension or right ventricular dysfunction.\(^{30–32}\) Targeting tidal volumes of 6 mL/kg predicted body weight can result in mild hypercarbia even in patients with relatively normal lungs and gas exchange. This hypercarbia is usually more problematic in patients with severe lung injury resulting in increased physiologic dead space. Maintaining alveolar ventilation at levels resulting in normocarbia or mild hypercarbia is a reasonable strategy.

High inspired oxygen concentrations are toxic to the lung. Healthy volunteers experience chest discomfort and cough when exposed to F\(_{\text{IO}}\)\(_2\) greater than 0.75 for 24 hours.\(^{33}\) Manifestations of oxygen toxicity include disruption of the epithelial-endothelial barrier function, increased vascular permeability, and increased lung inflammation. However, the concentrations required and the duration of exposure to manifest these changes is highly variable.\(^{34–37}\) Because hemoglobin is nearly fully saturated at Pa\(_{\text{O}}\)\(_2\) levels greater than 70 mm Hg, oxygen delivery is not markedly improved by driving Pa\(_{\text{O}}\)\(_2\) higher than 70 mm Hg. Therefore, using the lowest F\(_{\text{IO}}\)\(_2\) consistent with maintaining Pa\(_{\text{O}}\)\(_2\) near 70 mm Hg or oxygen saturations greater than 92% is appropriate in most patients.

**MECHANICAL VENTILATION AFTER NEUROLOGIC INSULT**

Patients with a neurologic insult or injury that requires mechanical ventilatory support offer unique challenges. The pathologic conditions of this cohort range from SCI with tetraplegia, to traumatic brain injury (TBI) with elevated intracranial pressure (ICP), to neuromuscular syndromes. This is not a small problem. In a review of 350 ICUs in 23 different countries, 1 in 5 mechanically ventilated patients had a neurologic diagnosis as the reason for initiation of MV.\(^{38}\)

Although many patients with neurologic injury have some pulmonary insult, such as aspiration or contusion, most do not have an underlying pulmonary condition. MV for the most part is required because of hypoventilation consequent to unreliable respiratory drives or muscle weakness or for airway protection.

Different neurologic disease states often mandate different approaches to respiratory support.
Therefore, the discussion is divided into 4 disease groups: (1) SCI, (2) TBI, (3) stroke, and (4) neuromuscular diseases.

**SPINAL CORD INJURY**

Patients with SCI, particularly cervical, often require MV. Fortunately, most can be successfully weaned and do not require long-term ventilatory support or even tracheostomy.\(^{39}\) Atelectasis (36.4%), pneumonia (31.4%), and respiratory failure (22.6%) are the most common complications within the first few days after injury. Atelectasis can occur in over one third of patients with SCI thereby increasing the risk of pneumonia and developing worsening respiratory failure.\(^{40}\) It therefore becomes paramount to prevent atelectasis.

Strategies to prevent atelectasis are mostly dependent on whether the patient is dependent on MV. Patients not requiring long-term MV but who have some respiratory compromise can be treated with noninvasive ventilation along with other modalities such as chest physiotherapy and mechanically assisted coughing.\(^{41}\) After an SCI, weak or paralyzed abdominal muscles reduce or eliminate an effective cough leading to impaired secretion clearance. Several techniques of mechanically and manually assisted coughing have been described.\(^{42}\) Although both manually assisted cough and mechanically assisted cough (insufflation-exsufflation) are reported to increase peak cough flow, increased peak cough flow with mechanical assistance may be restricted to patients with very low baseline peak cough flow (<5 L/s). Further, data from controlled trials regarding clinical outcomes are not available, and a recent Cochrane review concluded that there was insufficient evidence for or against mechanical cough assist devices.\(^{43}-^{45}\)

How best to manage a patient with SCI that requires MV is controversial. In part because of poor airway secretion clearance and the propensity for atelectasis, it has been recommended to use much higher tidal volumes than what is considered standard of care.\(^{46}\) Although the risk of barotrauma is present, data in patients with SCI failed to showed barotrauma with tidal volumes as high as 20 mL/kg.\(^{47}\) Although this finding is completely antithetical to lung protective strategies, SCI patients have not been included in the ARDSNet trials, and the loss of chest wall compliance may be a protective factor against high airway pressures.

There may be risks to maintaining higher-than-acceptable tidal volumes in individuals with SCI. However, low tidal volumes can lead to atelectasis, mucous plugging, and decreased production of surfactant, thus, increasing the work to expand the lungs. Peterson and colleagues\(^{48}\) found that 60% of patients with SCI on low tidal volume ventilation had atelectasis. However, it was not clear that this led to increased length of stay or other morbidities. The role of PEEP in preventing atelectasis has not been well studied, and its use is based mostly on anecdotal experiences. It makes intuitive sense, however, that some degree of PEEP would increase the residual functional capacity and may prevent the collapse and cyclic closure of alveoli.

The role and timing of tracheostomy in SCI patients requiring prolonged MV is also an area of considerable debate. Ganuza and colleagues\(^{49}\) retrospectively reviewed patients with SCI that received either early tracheostomy (defined as less than 7 days) or late tracheostomy (greater than 7 days). The authors found no appreciable differences and that complication rates were low whether using open surgical or percutaneous technique.

Efforts to show advantages to early tracheostomy versus delayed tracheostomy have been elusive. Some centers have, therefore, looked at coexisting injuries, injury severity scoring, or facial fractures to guide the decision.\(^{50}\) For example, Branco and colleagues\(^{51}\) found that 20% of SCI patients will require tracheostomy and identified several factors that were independently associated with the need for tracheostomy; intubation on scene or in the emergency department, complete SCI at C1 to C4 or C5 to C7 levels, injury severity score greater than 16, facial fracture, and thoracic trauma were independently associated with the need for tracheostomy.

**TRAUMATIC BRAIN INJURY**

Patients that have suffered a TBI often require intubation and MV. It has been suggested that both hypoxemia and hyperventilation be vigorously avoided.\(^{52}\) Hyperventilation, even for brief periods can lead to cerebral vasoconstriction and cerebral-ischemia. Routine hyperventilation in patients with TBI is associated with worse outcomes.\(^{53}\) Thus, hyperventilation is recommended only as a temporizing measure to reduce an elevated ICP. A brief period (15–30 minutes) of hyperventilation, to a PaCO\(_2\) of 30 to 35 mm Hg, is recommended only to treat acute neurologic deterioration related to increased ICP.\(^{54}\)

Intubated patients with moderate to severe head injury that present with PaCO\(_2\) either above 49 or less than 30 mm Hg demonstrated a worse outcome. If however, the patient is spontaneously...
breathing, the PaCO₂ did not correlate to outcome.\textsuperscript{55} This observation reinforces the axiom that we cannot outsmart the brainstem and the regulatory effects of the Cushing response.

Timing of tracheostomy is another area that is unsettled in patients with TBI. One study comparing early versus late tracheostomy found no significant differences between the groups in overall mortality or incidence of pneumonia. The median hospital length of stay and discharge to a rehabilitation center were also not significantly different between the groups.\textsuperscript{56} However, in another observational study, early tracheostomy (<8 days) was associated with a shorter duration of MV and ICU length of stay but did not affect mortality.\textsuperscript{57} The debate regarding early versus late tracheostomy in patients with moderate-to-severe TBI remains unsettled.

There are no guidelines for mode of ventilation or target tidal volume. It would make sense to use lung protective strategies (low tidal volumes, modest levels of PEEP). However, maintaining tight PaCO₂ control is crucial with a target of 35 to 45 mm Hg.

TBI patients often have additional injuries that may increase risk of ARDS. ARDS has been reported in 20\% to 25\% of patients with TBI.\textsuperscript{58} Ventilation with higher tidal volumes has been associated with an increased risk for ARDS development in patients with TBI.\textsuperscript{59} However, using low tidal volumes can create a clinical conundrum, balancing the desire for lung protective strategies yet maintaining PaCO₂ goals. In patients with TBI and ARDS who do not respond to lung protective maneuvers or who can oxygenate but not maintain acceptable PaCO₂ levels, extracorporeal membrane oxygenation is an option. There are numerous case reports and case series describing the safe use of extracorporeal membrane oxygenation in this population and for CO₂ control; a pumpless extracorporeal CO₂ removal device was also found to be useful in controlling PaCO₂.\textsuperscript{60}

PEEP increases intrathoracic pressure and thus impedes central nervous system venous return potentially elevating ICP and reducing cerebral perfusion pressure (CPP). In animal models, the use of high PEEP levels has been reported to be safe, but in humans with brain injury, the impact of PEEP on cerebral oxygenation and CPP is highly variable.\textsuperscript{61} It is uncommon to see changes in CPP or cerebral blood flow at PEEP levels less than 10 but it provides a rationale for recommending that monitoring of the CPP or central nervous system oxygen kinetics should be used in brain-injured patients requiring PEEP levels higher than 8 or 10 cm H₂O.\textsuperscript{62,63}

**STROKE**

There are no specific guidelines for MV management in patients with severe stroke, whether ischemic or hemorrhagic. Similar to TBI patients, the risk of ARDS seems higher in stroke patients ventilated at higher tidal volumes.\textsuperscript{64} However, evidence is currently lacking to guide clinicians striving to optimize the balance between the potentially adverse neurologic impact of higher levels of PaCO₂, higher PEEP, and potentially lower oxygenation consequent to lung protective strategies against the risks of excess risk of lung injury. What is clear is that the mortality rate for patients with either ischemic or hemorrhagic stroke requiring mechanical ventilation approaches 50\% and is higher than that of patients requiring mechanical ventilatory support who do not have neurologic injury. The mortality rate for patients with hemorrhagic stroke is likely higher than those with ischemic strokes.\textsuperscript{65}

Stroke-related Early Tracheostomy versus Prolonged Orotracheal Intubation in Neurocritical care Trial (SETPOINT) is a pilot trial to investigate the safety, feasibility, and potential benefits of early tracheostomy versus prolonged intubation in patients with severe ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage.\textsuperscript{66} The primary outcome is to compare early tracheostomy and prolonged intubation with respect to ICU length of stay and the time until the start of rehabilitation. Secondary endpoints are functional outcome and mortality, duration of ventilation, duration and quality of weaning from MV, need of analgesia and sedation, procedure-related complications, frequency of pneumonia and sepsis, and costs. Until the results of this trial are known, no recommendations can be made as to timing of tracheostomy in the stroke patient.

**NEUROMUSCULAR DISEASES**

Important issues in this population are when to initiate noninvasive versus invasive ventilatory strategies and, as with the other neurologic processes, when to proceed to tracheostomy. Farrero and colleagues\textsuperscript{67} outlined 10 basic steps in respiratory management of the patient with neuromuscular disease:

1. Assessment of lung function should be made in all neuromuscular patients, even in the absence of symptoms, and should be subsequently monitored.
2. For the choice of future treatments, it is important to distinguish rapidly and slowly progressive diseases.
3. It is advisable to evaluate the possible existence of cardiovascular diseases and associated aspiration conditions.

4. Difficulty in draining respiratory secretions requires specific respiratory physiotherapy and occasionally mechanical assistance to achieve effective cough.

5. Ventilatory assistance is indicated when there is severe ventilatory impairment (forced vital capacity <50%), symptoms of diaphragmatic dysfunction (orthopnea), or hypoventilation (hypercapnia).

6. The correct choice of equipment and ventilation mode is fundamental. Portable respirators designed for life support are recommended.

7. The indication for treatment with invasive MV by tracheostomy should be individualized and requires adequate care infrastructure.

8. Early, continuous communication with the patient and their family and advance decision making are essential for choosing the best therapeutic measures, especially invasive MV.

9. Palliative treatment should not be delayed when indicated.

10. Multidisciplinary, coordinated care by all professionals involved in the management of these patients is desirable.

Assessing the need for MV in patients with neuromuscular disease requires the analysis of many parameters and physical examination findings. What is reassuring is that with early treatment, the long-term outcome and quality of life are fairly good, and the need for long-term MV is minimal in both Guillain-Barre syndrome and myasthenia gravis.68,69

Vital capacity (VC) and maximum inspiratory pressure are most frequently used in the ongoing assessment of the respiratory status of patients with neuromuscular disease. What single measurement is best is unresolved. A recent study by Prigent and colleagues70 found VC to have a better predictive value that maximum inspiratory pressure. However, Serrano and colleagues71 found that a maximal expiratory pressure

<table>
<thead>
<tr>
<th>Study</th>
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<th>Outcome (Protective vs Control)</th>
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</tr>
<tr>
<td>Mascia et al,83 2010</td>
<td>Donors</td>
<td>118</td>
<td>Low TV, PEEP</td>
<td>More lung donors eligible</td>
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</table>

**Abbreviations:** Abd surg, abdominal surgery; ALI, acute lung injury; BALF, bronchoalveolar lavage fluid; Card Surg, cardiac surgery; Donors, organ donors; FRC, functional residual capacity; IL, interleukin; LOS, length of stay; Low TV, low tidal volume; press index, ventilatory pressure index; Retro, retrospective; RM, recruitment maneuver; SP-A, surfactant protein A; SP-D, surfactant protein D; Thor surg, thoracic surgery; TNF, tumor necrosis factor.
of $\leq 30 \text{ cm H}_2\text{O}$ and maximal inspiratory pressure lower (closer to zero) than $-28 \text{ cm H}_2\text{O}$ were associated with need for prolonged MV. In patients with progressive neuromuscular disorders, nocturnal hypoventilation may be one of the early signs of respiratory failure and of the need for mechanical ventilatory support.72

In Guillain-Barre syndrome specific neurologic findings may better predict those patients who will deteriorate to the point of requiring MV. The presence of upper extremity weakness less than grade 3/5 and the presence of neck and bulbar weakness along with bilateral facial involvement were more frequently associated with the need for MV. Neck weakness along with a weak VC is also a strong predictor for the need for MV.73 Those that retain upper extremity reflexes, on the other hand, rarely progress to need MV.74

In patients with amyotrophic lateral sclerosis, no single pulmonary function measurement has shown superiority in predicting the need for initiation of MV. VC is less likely to be predictive for various reasons, one of which is the core muscle strength required to perform the task. The sniff nasal inspiratory pressure test correlated best with transdiaphragmatic strength. An effort less than $-18 \text{ cm H}_2\text{O}$ identified patients at highest risk of respiratory failure and need for tracheostomy.75

**SUMMARY**

With respect to mechanical ventilatory support in patients with normal lungs, the nature of most of the above-cited studies do not permit separating injury consequent to the use of high tidal volumes from that caused by the absence of PEEP or their interaction. However, given the consistency of findings across animal models and humans, the use of low levels of PEEP and low tidal volumes should be used in the absence of a compelling contradictory rationale in patients without lung injury requiring mechanical ventilatory support. Within these constraints, there is little evidence that a particular mode of ventilation is preferable over another. The evidence for the timing of tracheostomy remains contradictory, although consideration for tracheostomy before day 8 in patients likely to require long-term ventilatory support may reduce the duration of ICU stay (Table 1).

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