# Mechanical ventilation in brain injured patients: seeing the forest for the trees

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The birth of intensive care medicine, as generally acknowledged today, took place in Denmark, during the dramatic poliomyelitis epidemic in 1952. As conventional treatments resulted to be totally ineffective, Dr. Lassen, Chief Physician at the hospital in charge of poliomyelitis in Copenhagen, asked the help of an anesthesiologist, Dr. Björn Ibsen. On August 27th 1952, Dr. Ibsen used his skills on a 12-year-old polio patient with severe respiratory failure. The girl was tracheostomized, sedated, manually ventilated and suctioned. She survived and one week later every patient with respiratory failure from poliomyelitis received manual ventilation via tracheostomy. The mortality rate of the severely affected polio patients dropped, approximately, from 80% to 40%. Thereafter, the Danish doctors assembled the patients requiring complex treatments, including mechanical ventilation (MV), in special units for intensive care of critically ill patients (1).

Therefore, the first patient treated by positive pressure through a tracheal tube suffered of a neurologic disease, and the first intensive care unit (ICU) was instituted for managing neurologic patients requiring MV. From the principles of intensive care established during the poliomyelitis epidemics, neurological intensive care then progressed into a specific field covering all aspects of neurological and neurosurgical critically ill patients. Clinical pathophysiology of intracranial pressure and cerebral blood flow, monitoring of brain function, postoperative care of neurosurgical patients, treatment of severe head injury, stroke and cerebral hemorrhage, prevention of secondary brain injuries, and management of brain death became over a few decades the central matters of knowledge and practice of neurological intensive care, making neurocritical care a discipline predominantly concentrated on the neurologic findings and diseases (2). Correspondingly, research mainly focused on specific neurological diagnostic, monitoring and management perspectives.

The advances reached in the field of neurocritical care field have increased the potentiality of the treatment of such patients and some studies suggest the outcomes of traumatic and hemorrhagic brain injured patients to be improved when treated in dedicated Neuro-ICUs, as opposed to general ICUs (3). Nonetheless, neurointensivists should in principle consider the interplay between the brain and other systems by integrating the aspects of neurological and medical management into a unique care plan, while an approach considering exclusively the specific aspects of the discipline may lead to disregard the general principles valid for any critically ill patient (3).

Indeed, irrespective of the subspecialty, any intensivist should master, to some extent, hemodynamics, sedation, infections, nutrition, renal care and, above all, MV, the most common procedure in ICU. Ensuring airway protection,

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improving tissue oxygenation and modulating cerebral vascular reactivity are the primary reasons why brain injured patients are intubated and mechanically ventilated (4). The damaged brain, nonetheless, induces changes in respiratory system mechanics, such as increased of elastance and airway resistance (5). Furthermore, patients with severe traumatic brain injury (6,7) and cerebral hemorrhage (8) are at increased risk to develop acute respiratory distress syndrome (ARDS) and ventilator-induced lung injury (VILI), which prolong ICU and hospital length of stay (9). After brain injury, a systemic inflammatory state develops, with inflammatory cells also migrating to airways and alveolar spaces (10). Neurogenic pulmonary edema, neurotransmitter-related engagement, or adverse effects of neuroprotective therapies are additional potential mechanisms of lung damage (5). Indeed, irrespective of the underlying mechanisms, in the presence of an inflammatory state an injurious ventilatory strategy may significantly add to worsening lung damage (5).

The manner in which MV is delivered in ARDS patients has remarkably changed in recent years, primarily because of recognition of VILI. The use of lung protective MV (LPMV) has been repeatedly proved effective in reducing complications and side effects, and overall improving the outcomes of ARDS patients (9). LPMV is based on application of low tidal volumes (VTs) and contained plateau airway pressure on the one hand, which avoid alveolar rupture and the generation of forces determining the release of inflammatory mediators, and PEEP levels such to recruit collapsed parenchyma on the other hand, which prevent injuries consequent to repetitive opening and closing of collapsed alveoli (9). However, this approach may lead to increasing arterial partial pressure of carbon dioxide ($PaCO_2$), which negatively affects intracranial pressure. In a retrospective study from a cohort of 620 ICU patients with subarachnoid hemorrhage, 170 individuals, having mean ± SD intracranial pressure of 48±26 $cmH_2O$, were complicated by acute lung injury (11). Noteworthy, $PaCO_2$ and pH values of 51 of these patients, who underwent LPMV with VT of 7 mL/kg of predicted body weight (PBW) and PEEP up to 10.5 $cmH_2O$, were not significantly different from those observed in the 119 patients who received conventional MV (11), suggesting that brain injury and intracranial hypertension are not per se impeding LPMV.

LPMV is advisable also for brain injured patients with healthy lungs. If on the one hand increasing minute ventilation may help containing $PaCO_2$ and avoid worsening of cerebral edema, on the other hand high VTs and respiratory rates are independent predictors of acute lung injury in patients with severe brain injury (7). In neurological patients without ARDS, applying LPMV reduces lung inflammation, resulting in a lower rate of development of lung injury (12). A meta-analysis including 20 trials comparing LPMV with conventional MV in patients without ARDS, shows that the latter, as opposed to the former, significantly increases the risk of developing lung injury, the incidence of pulmonary infection and atelectasis, and the rate of death (13). In a study including 697 patients admitted for cerebral hemorrhage, 70% of the time on MV was spent with VT >8 mL/kg PBW (8). The use of high VTs was a significant risk factor for development of ARDS, the magnitude of this association being greater at higher VTs, with a sort of dose-response relationship (8). Furthermore, a significant increased risk of ARDS was associated with every 10% increase in time ventilated with VT >8 mL/kg of PBW (8). It looks then crucial preserving the balance between the needs of brain and lungs in brain injured patients.

Though a life-saving intervention, MV is associated with side effects and life-threatening complications and should be then discontinued as soon as possible, regardless of the underlying disease. The process of discontinuing MV is referred to as weaning, which is initiated when the patient is clinically stable and has adequately recovered from the acute disorder that indicated instituting MV. Weaning is considered successful when the patient can sustain a spontaneous breathing trial (SBT), during which the patient's spontaneous breathing is completely unassisted or supported by low levels of ventilator assistance. Both weaning delay and failure are major clinical problems. In fact, undue delays in withdrawing ventilator support and extubating the patient increase the risk of complications, prolong the stay in the ICU, and significantly add to costs, while premature attempts of withdrawing MV lead to development of severe distress, hamper the process of recovery and further delay the process of weaning (14).

When the SBT is successful, the patient is considered ready for extubation. Premature attempts of extubation are complicated by post-extubation respiratory failure and reintubation, which is associated with higher mortality, increased rate of tracheotomy and longer duration of MV and ICU stay (15). Rates of extubation failure and reintubation ranging from 5% to 35% have been reported for patients with neurologic disorders (14). In these patients, the altered mental status is the primary cause of extubation failure, but signs of disrupted ventilation, decreased minute

ventilation and atelectasis are frequently observed in patients who fail extubation (16). Coplin *et al.*, however, in a prospective cohort of 136 consecutive, intubated brain-injured patients, reported that in many instances patients meeting predefined readiness criteria could be successfully extubated even with a Glasgow Coma Scale (GCS) ≤8. Patients with delayed extubation had higher rates of pneumonia and longer ICU and hospital stays. There was no significant difference in the rate of reintubation between patients who underwent extubation with (17.2%) or without (18.9%) delay (17). In a randomized controlled trial (RCT) including, overall, 100 neurosurgical patients, a ventilator management protocol, not incorporating assessment of the GCS, did not reduce either duration of MV and length of ICU stay (primary endpoints), or rate of reintubation and mortality (secondary endpoints). Worth remarking, the adherence to the protocol by the attending physicians was low and decreased from 50% to 13% on the first and sixth (and last) two-month period (18). Later on, another single center RCT including 318 neurologic or neurosurgical patients found that, compared to the sole physician's judgment, a systematic approach to weaning and extubation, consisting of daily screening of meaningful physiologic and clinical variables followed by SBT, reduced the rate of reintubation secondary to extubation failure occurring within 48 hours (primary endpoint), without affecting any of the additional outcomes considered as secondary endpoints, such as duration of MV and ICU stay, mortality and rate of tracheotomy (19). In contrast to the previous study (18) the protocol adherence in this study was high, achieving overall 97% (19). Interestingly, a recent RCT evaluating the same systematic approach for the purpose of weaning tracheostomized brain injured patients off the ventilator was prematurely interrupted after inclusion of 168 patients as the rate of failure (29%) was much higher than previously reported in intubated individuals (20).

Consequent to the abovementioned studies, there is enough information to consider that a wise approach to MV, such as the use of LPMV, and a thorough management of weaning and extubation might play a role in order to improve the outcome of severely brain injured patients requiring ICU admission and MV. Recent work has attempted to reconcile the specific aspects of neurological and neurosurgical critically ill patients with the general principles of critical care medicine. In a before-after study conducted in two ICUs of one university hospital, a multifaceted bundle was implemented in patients with brain injury to assess the efficacy in reducing the duration of MV (21). This 3-phase study enrolled 499 patients receiving MV for more than 24 hours. The first phase consisted of a 3-year control period, during which treatment was at the discretion of the attending physician (299 patients). During the second 1-year phase, the ICU staff was trained to perform a four-point bundle including the following components: (I) LPMV, consisting of VTs ranging from 6 to 8 mL/kg of PBW, coupled with PEEP >3 cmH$_2$O and respiratory rate set to achieve normocapnia or moderate hypocapnia; (II) early enteral nutrition; (III) standardized antibiotic therapy; and iv) a systematic approach to extubation, as defined by GCS ≥10, effective cough, and a successful 30-minute SBT performed either by means of a T-tube or applying minimal ventilator assistance (<10 cmH$_2$O trial). This second part of the study was followed by a final 22-month intervention phase (200 patients). Adherence to the whole set of best practices increased from 6.0% in the control phase to 21.1% in the intervention phase. Compared to controls, patients in the intervention group had a shorter duration of MV. The implementation of the bundle also diminished the rate of hospital-acquired pneumonia, and increased the ventilator-free days and ICU-free days at day 90. No mortality differences were observed. The number of extubation-related complications was also not different between the two groups, but the rate of unplanned extubation was significantly lower in the intervention group (21).

Following these encouraging findings (21), Asehnoune *et al.* recently carried out a multicenter before-after trial to assess the impact on brain-injured patient outcomes of a quality improvement project, consisting in a protective ventilation strategy associated with a systematic approach to early extubation (22). All patients with brain injuries, as defined by GCS ≤12 combined with one or more acute processes visualized on brain computed tomography scan, were included in the study protocol. Likewise the previous study (21), during the pre-intervention phase the control group underwent treatment at the discretion of the attending physician (22). The staff of each ICU was then trained through a standardized educational program to implement a protocol consisting of LPMV with VT ≤7 mL/kg of PBW and PEEP ranging between 6 and 8 cmH$_2$O. Also, patients were indicated for immediate extubation when the all following criteria were satisfied: (I) successful 30-minute SBT, through a T-tube or with pressure support <10 cmH$_2$O; (II) effective cough and (III) GCS ≥10 (22). A total of 744 patients were recruited, 391 in the control group and 353 in the intervention group. Controls received on average significantly higher VT and PEEP, compared to patients enrolled in the intervention group, whereas the rate of early extubation was not different between the two groups.

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The overall compliance with the full set of evidence-based recommendations was only 2% in the control group, and rose up to just 15% in the interventional group. No significant difference was detected in invasive ventilation free days at day 90 (primary endpoint) between the two groups. Also, none of the secondary endpoints was significantly different, which included 90-day mortality, neurological outcomes and respiratory complications, although a trend toward a reduction of the occurrence of hospital-acquired pneumonia and unplanned extubation was observed in the intervention group, as opposed to controls (22).

Clearly, this study fails to prove that a strategy of MV combining LMPV and early extubation improves the outcome of brain injured ICU patients. Considering the scanty adherence to the protocol during the intervention phase, however, the study does not prove the opposite too. A post-hoc analysis indicated that 60 patients for whom the protocol was fully applied had significant improvements in invasive ventilation-free days at day 90, mortality and the probability of breathing without invasive ventilation, compared to 684 patients whose care involved deviations from the protocol (22). While the reasons of such a low protocol adherence are not reported, the authors, among other hypothesis, propose that clinicians may have been concerned of possible detrimental effects on cerebral function of LPMV and early extubation, which is not entirely surprising also considering the lack of recommendations regarding LPMV and early extubation in the most recent guidelines for management of severely brain-injured patients (22). Noteworthy, the average VT of the patients with full protocol adherence was 6.4 mL/kg of PBW, compared to 7.3 mL/kg of PBW in the patients whose care involved deviations from the protocol, which did not affect the values of $PaCO_2$ observed in the two groups (22).

As a matter of fact, it seems there is still a long way for bringing together the various aspects of critical care medicine. Should we consider that there is a specific resistance of neurointensivists in considering aspects of care other than those related to the nervous system, neglecting the results of studies outside their specific field? Not indeed, as recently indicated by a large international survey describing the actual practice for ARDS patients (23). Is it a peculiarity of ours, ICU physicians, being reluctant to applying the evidence produced by our studies? Surely not; if on the one hand there is an intrinsic inertia of physicians to introduce in their practice the novelties produced by researchers, on the other hand patient selection of RCTs may limit applicability in the routine clinical practice. All

that said, we should not forget the lesson of Dr. Ibsen who understood the potentials of a therapeutic technique used in a different field of application, and the Danish doctors who immediately accepted the novelty and accordingly changed their practice. They saved many human lives, seeing the forest rather than the trees.

## Acknowledgements

## Footnote

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