Neurally Adjusted Ventilatory Assist: Insufficient Evidence of Broad Clinical Outcomes

To the Editor:

This is a reply to the editorial by Moss[1] on the study by Delisle et al,[2] entitled "Effect of Ventilatory Variability on Occurrence of Central Apneas." In their prospective crossover study, Delisle et al[2] compared neurally adjusted ventilatory assist (NAVA) and pressure support ventilation in intubated adult patients during sleep and wakefulness. The results showed increased variability in tidal volume and elimination of central apneas (> 10 s duration) during non-rapid-eye-movement sleep during NAVA. Delisle et al stated that their findings were due to over-assistance during pressure support ventilation, and that this was avoided during NAVA due to adaptation of the assist. This study carries several important and novel findings of physiological interest.

Physiology is one of the pillars of medicine, especially in mechanical ventilation, where the knowledge gained in respiratory and circulatory physiology has formed the clinical standards of today. A question to Ms Moss is why she summarizes the outcome of the well performed physiological study by Delisle et al[2] by the statement "What is the clinical importance of the study; the 'So what?' if you will."

There is clear evidence that conventional modes frequently fail to assist inspiration during both invasive[3–5] and noninvasive ventilation.[6,7] Opposite to traditional views, increased sedation seems to worsen asynchrony.[8] Though it is debatable whether adverse effects such as prolonged time of ventilation and ventilator-induced diaphragm dysfunction are directly related to patient-ventilator asynchrony, it is clear that the search for methods to monitor and prevent the patient from fighting the ventilator has been a key issue of mechanical ventilation in spontaneously breathing patients for at least 5 decades.[9]

Thus, is it not in the best interest of respiratory therapists to reduce this problem? NAVA is a scientifically documented mode of mechanical ventilation; it has regulatory approval by the United States Food and Drug Administration. Since NAVA allows monitoring of diaphragm electrical activity, you can—for the first time—reliably detect patient-ventilator asynchrony at the bedside.[10] Twenty studies (involving a total of 280 patients) have compared conventional modes to NAVA and showed improved patient-ventilator interaction during both invasive and noninvasive ventilation, in patients of all ages. Nineteen studies (involving a total of 291 patients) have reported that physiological parameters are equivalent or improved during NAVA, compared to conventional modes. For a recent review and book chapter see Sinderby and Beck.[11,12]

Thus, I am not sure that Ms Moss's statement, "I believe the use of NAVA has not yet been adequately justified in the literature" is fully justifiable.

Finally, I agree in principle with Ms Moss that evidence-based medicine and "well designed" randomized controlled trials are important. However, the approach of the randomized controlled trial in the critical care setting is very "young"[13,14] and is still encountering major methodological challenges in both design and outcome.[15] For example, meta-analyses of PEEP trials have shown beneficial outcome only in patients with ARDS.[16] Yet physiology can teach us that applying external PEEP overcomes intrinsic PEEP and improves patient triggering and synchronizes ventilator assist to inspiratory effort. Should we apply PEEP or not in COPD?

Is it not that, despite decades of research, we have no universally accepted clinical evidence that any mode of ventilation is superior to any other mode? To suggest that only outcome data from randomized controlled trials are required before new modes can be used simply perpetuates a myth and blinds us to other approaches to rationally selecting the best treatment options.[17]

Until having reached the point (if ever) where both new and conventional modes of mechanical ventilation have been sufficiently validated, it is the skills of the practitioner that ensure the safety of the patient. If treatments are based on adequate information, innovations that improve monitoring and delivery of ventilatory assist could strengthen personalized care, without affecting protocolized care. Is it now that evidence-based medicine has become an excuse to avoid the disruption of "normal" clinical activities that follow the introduction of medical innovations?

"Anyone who has never made a mistake has never tried anything new." — Albert Einstein

I welcome further productive discussions on the topic of how best to integrate new technologies of mechanical ventilation into the clinical arena.

Christer Sinderby PhD
Keenan Research Centre
Li Ka Shing Knowledge Institute
Department of Critical Care
St Michael's Hospital
and
Interdivisional Department of
Critical Care
Department of Medicine
University of Toronto
Toronto, Ontario, Canada

Dr Sinderby has disclosed relationships with Neurovent Research and Maquet Critical Care.

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Table 1. Variables Demonstrating a Statistically Significant Difference in Primary Research Comparing NAVA to an Alternative Ventilation Strategy

First Author	Year	Outcome Variables With Statistically Significant Differences
Alander[3]	2012	Asynchrony time, peak inspiratory pressure, breathing frequency
Beck[4]	2009	Neural expiratory time, breathing frequency
Bengtsson[5]	2010	Peak airway pressure, breathing frequency, trigger synchrony, cycle synchrony
Bertrand[6]	2013	EAdi, trigger delay, asynchrony index
Bordessoule[7]	2012	Trigger delay, cycle asynchrony, asynchrony index, coefficient of variation
Brander[8]	2009	Mean airway pressure, tidal volume, breathing frequency
Breatnach[9]	2010	Trigger synchrony, cycle synchrony, peak airway pressure
Cammarota[10]	2011	Mechanical expiratory time, inspiratory time, duty cycle, time synchrony, asynchrony index
Clement[11]	2011	Trigger delay, ventilator response time, pressure-time product
Coisel[12]	2010	P_{aO_2}/F_{IO_2}; tidal volume; variability of airway pressure, tidal volume, and minute ventilation; EAdi
Colombo[13]	2008	Tidal volume, breathing frequency, asynchrony index
Lee[14]	2012	Peak inspiratory pressure, work of breathing
Moerer[15]	2008	Patient-ventilator synchrony, trigger effort, breathing comfort
de la Oliva[16]	2012	Asynchrony index, EAdi, tidal volume, COMFORT score
Piquilloud[17]	2012	Trigger delay, asynchrony index
Piquilloud[18]	2011	Trigger delay, inspiratory time in excess, total asynchrony events, number of patients with asynchrony index > 10%, ineffective trigger effort events, late cycling events, premature cycling events, double triggering
Schmidt[19]	2012	Trigger delay, inspiratory time in excess, asynchrony index, asynchrony index influenced by leaks
Schmidt[20]	2010	Variability of flow, variability of breathing pattern
Spahija[21]	2010	Trigger delay, cycle delay
Terzi[22]	2010	Tidal volume, asynchrony index

EAdi = electrical activity of the diaphragm

Neurally Adjusted Ventilatory Assist: Insufficient Evidence of Broad Clinical Outcomes—Reply

In reply:

Responding to my editorial[1] that accompanied the research by Delisle et al,[2] Sinderby raises 3 main questions. First, Sinderby asks why I summarize the outcome of the study with: "What is the clinical importance of this study; the 'So what?' if you will." A well designed physiological study such as that by Delisle et al[2] provides essential evidence of a treatment's functional effects. Table 1 identifies other primary research that has identified statistically significant changes relevant to the implementation of neurally adjusted ventilatory assist (NAVA) and to the care of critically ill patients.

As the body of the physiological evidence relating to NAVA has grown, authors and researchers have hypothesized expected clinical outcomes, such as a decreased number of ventilator days[16] and decreased ICU stay and hospital stay.[23] A smaller number of studies have investigated any association between patient-ventilator synchrony and clinical outcomes. Two projects have identified an association between patient-ventilator trigger asynchrony and longer duration of mechanical ventilation.[24,25] De Wit et al demonstrated an association between ineffective triggering and longer duration of mechanical ventilation, longer ICU and hospital stay, and a reduced likelihood of discharge to home.[26] De Wit et al have also identified a statistically significant relationship between ineffective triggering index and deeper sedation level: a finding that may result in false conclusions of weaning intolerance and longer duration of mechanical ventilation.[27] A recent study including adult trauma subjects identified no association between patient-ventilator synchrony and ventilator days, ICU and hospital stay, proportion of subjects who were discharged to home, or mortality.[28]

I certainly acknowledge that consistently demonstrated outcomes of NAVA (such as enhanced patient-ventilator synchrony) also happen to be those factors identified with desired clinical outcomes (such as a reduced number of ventilator days), though I have identified no studies to date that have investigated a direct link between the two. Though preliminary research outcomes related to NAVA are promising, well designed studies are needed to directly measure clinical outcomes.[3,6,7,10,12,13,17-20,22,25,29-31]

Referring to the failure of conventional ventilators to provide ventilation synchronous with patient efforts, Sinderby asks, "is it not in the best interest of respiratory therapists to reduce this problem?" I would respond with a resounding Yes! Respiratory