Using Physiology to Personalize Mechanical Ventilation

A summary report from MeetingPoint Nijmegen 2015
Over 200 intensive care clinicians and scientists from 23 different countries around the world gathered at the Radboud University Medical Centre in Nijmegen, Netherlands for a two-day meeting, following the popular success of the first MeetingPoint program in 2012.

The scientific program for this year’s meeting focused on the physiological concepts related to mechanical ventilation, and personalization of respiratory support for intensive care patients of all ages. The distinguished faculty included well-known profiles in intensive care from Belgium, Canada, France, Germany, Greece, Italy, the Netherlands, Switzerland, United Kingdom and the United States.

Recorded lectures from the meeting will be published on www.ventquest.ca in the near future, with a link from the Critical Care News website. In the meantime, here is a summary report of some of the highlights of MeetingPoint 2015.
Respiratory muscle monitoring and decision support

Ventilated patients have a right to breathe

Jennifer Beck, PhD, Toronto posed the question “What can we learn from the electrical activity of the diaphragm (Edi)?” and quoted a study by Doorduin et al (2014) establishing dysynchrony 30-60% in NIV-Pres- sure Support compared to only 3% in NIV NAVA. She showed an example of a patient with synchronized pressure-flow waveforms, with an Edi tracing indicating no diaphragm activity. She also presented an analysis of 272 studies where asynchrony index was reported, with 4.57% in NAVA compared to 26.17% in conventional ventilation modes.

She ended her presentation with a quote from a study by M Picard from 1985: “The diaphragm is a unique skeletal muscle designed to be rhythmically active throughout life. Within a short period after initiating mechanical ventilation, the diaphragm develops muscle atrophy, damage and diminished strength”.

Why measure respiratory muscle function in critically ill patients?

Ewan Goligher, MD, Toronto reviewed different methods of measuring respiratory muscle function. He cited a prospective follow-up study of patients after ICU discharge and readmissions due to respiratory causes by Adler et al in AJRCCM 2014. Patients discharged with a reduced inspiratory muscle function ran higher risks of ICU readmission.

Edi indices during different physiological conditions

Lise Piquilloud, MD, Lausanne reviewed a number of Edi studies in intubated and healthy or non-intu- bated subjects, and a comparison of healthy versus COPD patients at rest and at max voluntary ventilation by Jolley et al (2009). She briefly reviewed current ongoing research to explore quantitative Edi monitoring in healthy volunteers.

She concluded that Edi can be used to monitor respiratory drive in physiological and physiopathologi- cal situations, where Edi interest for qualitative monitoring of respiratory drive is demonstrated, and that Edi is promising for quantitative monitoring of neural inspiratory drive.

Value of oesogastric pressure recording in children

In her presentation, Brigitte Fauroux, MD, PhD, Paris reviewed the importance of understanding the patho-physiology of respiratory failure and evaluation of respiratory muscle per- formance, and adaptation of non-invasive ventilation.

Her conclusion was that oesogastric pressure recording is extremely valuable to understand not only respiratory failure and to assess respiratory muscle performance, but also to optimize mechanical ventilation. She stated that this technique is underused in pediatrics and should be developed and extended.

Edi during peri-extubation period

Tomasso Maraffi, MD, Milan presented his prospective observational study to explore behavior of Edi and its association with other clinical val- ues, before and 48 hours post-extu- bation. He summarized that different profiles of Edi may characterize differ- ent etiologies of extubation failure, and that during a successful weaning trial, Edi is significantly increased in patients later requiring reintubation.

He stated that in successfully extu- bated difficult to wean patients, the Edi increases significantly between the weaning trial and the post-ex- tubation period, and is maintained for up to 24 hours, suggesting an increased effort to wean.

Mechanical ventilation during sleep and sedation

Physiology of sleep during mechanical ventilation

Dimitris Georgopoulos, MD, Crete, Greece cited a number of studies showing that unstable breath- ing during sleep is associated with decreased sleep efficiency, increased sleep fragmentation and reduced REM and SWS (Meza et al, Alexo- pouloou et al, Parthasarothy et al). It is also associated with cognitive dysfunction, delirium and post-trau- matic stress disorders (Weinhouse et al and Sanders and Maze).

He referred to studies by Delisle S et al and Brander L et al stating that compared to Pressure Sup- port, NAVA is associated with better sleep architecture. He summarized that during mechanical ventilation, sleep quality largely depends on ventilation mode and settings (both are main determinants of breathing stability), and that patients with increased risk of periodic breathing (heart failure, CNS damage, meta- bolic alkalosis, high CO2 sensitivity) are likely to suffer from poor sleep during mechanical ventilation. He stated that proportional modes such as PAV and NAVA promote stable breathing and may have beneficial effects on sleep quality.

Sleep and mechanical ventilation in children with neuromuscular disease (NMD)

Brigitte Fauroux MD, PhD presented examples of studies of children with NMD and how sleep is affected. She stated that sleep is an “at risk” period where ventilatory drive, respira- tory muscles and mechanics are potentially affected by physiological decrease of SpO2 and increase of PCO2. She concluded that children with NMD should be systematically screened for sleep disordered breathing (SDB) in terms of dia- phragm paralysis and rigid spine, and that NIV can correct SDB and improve sleep quality and structure. NIV should be initiated on an indi- vidual basis when SDB is present and before daytime hypercapnia, according to Dr Fauroux.

Fighting the ventilator: Should I sedate or synchronize?

Alexandre Demoule MD, Paris started his presentation by defining asynchrony as a mismatch between patient spontaneous breathing cycle and ventilator cycle delivered by the ventilator, and patient breathing demand and level of assistance provided by the ventilator. He cited a study by Thille et al (2006) where patient ventilator asynchrony has an impact on need for tracheoto- my as well as on patient mortality. Dr Demoule showed examples of ineffective triggering as shown by Edi signals, and described the risk...
of over-assistance on thoracic dis- tention and diaphragm flattening. He presented a study by Terzi et al (2010) showing that NAVA reduces ineffective triggering. To synchronize is easy with proportional modes and reduces resistance, and sedation worsens ineffective triggering according to Dr Demoule. However sedation should be considered if the patient is at risk of VILI, i.e. ARD, in his opinion.

Effects of Midazolam and Flumazenil on Edi during weaning after respiratory failure
Hadrien Rozé, MD, Bordeaux presented from his previous research of daily titration of neurally adjusted ventilatory assist using the diaphragm electrical activity, and neuro-ventila- tory efficiency during weaning from mechanical ventilation using neurally adjusted ventilatory assist. The medi- an duration of controlled ventilation in both studies was 10 days. In the most recent study by Dr Roze et al (2015), 13 ARDS patients were studied. He summarized that Midazolam was known to reduce TV around 40%, increase respiratory rate and reduce minute ventilation, with increased work of breathing. The study results found a direct inhibitory effect of Midazolam on Edi and the reversal of this effect with Flumazenil. Patients had no sign of distress and no accessory muscle activation. Initial low Edi was associated with a higher reversal effect.

How to manage intrinsic PEEP

Overview of intrinsic PEEP
Laurent Brochard MD, Toronto reviewed a number of issues related to intrinsic PEEP: time constant, resistance and compliance, as well as dynamic compliance. He described inverse ratio ventilation to increase oxygenation, that generated intrinsic PEEP that could be managed with extrinsic PEEP. He suggested that inspiratory effort can be offloaded with extrinsic PEEP during spontaneous breathing until PEEPi is reduced to 80%. Techniques to measure intrinsic PEEP were reviewed, including ultrasound, but Edi is a diagnostic support tool, according to Dr L Brochard. He concluded that high intrinsic PEEP matters and can result in weaning failure.

Patient-ventilator asynchrony in COPD
Lise Piquilloud, MD referred to a recently published observational study by L Blanch et al (2015) of 50 asynchronies in ICU patients on conventional mechanical ventilation. Asynchronies were detected in intubated patients (25%) as well as non-invasive ventilated patients (43%). She shared her experiences with the crossover study comparing PS with NAVA in 19 children conducted by herself and L Vignaux et al (2013). NAVA resulted in an almost ten-fold reduction in asynchrony, compared to PS. She also referred to her study (2012) of NIV NAVA in 13 patients, several with COPD. Compared to PS, NAVA improved patient ventilator synchrony during non-invasive ventilation by reducing T(d) and AI (asynchrony index). Moreover with NAVA, ineffective efforts and late and premature cycling were absent. She also referred to the study by Doorduin et al (2014) of NIV NAVA in 12 COPD patients. In COPD patients, non-invasive NAVA improved patient-ventilator interaction compared to PSV. The study also identified that progressive mismatch between neural effort and pneumatic timing is associated with wasted efforts.

Patient-controlled PEEP
Christer Sinderby, PhD, Toronto started his lecture by stating that NAVA is the only ventilation mode integrating the central nervous system. He reviewed a number of studies related to the Hering-Breuer reflex; strong physiological reflexes to prevent hurt and harm to humans when breathing. He cited a study by L Brander et al (2009) in regard to
vagal feedback and a CO₂ response model. Monitoring of Edi illustrates how sighing may open the lungs, which consequently will reflect less drive in the Edi curve, according to Dr Sinderby.

**Neural triggering of PSV**

Ling Liu, MD, Nanjing outlined the problems inherent with intrinsic PEEP; increased respiratory effort and time constant. She referred to her previous studies of NAVA in ARF patients (2015) and presented data from her most recent physiological study of neural vs pneumatic control of PS in 12 patients with COPD at different levels of PEEP (June 2015). The study conclusion was that neutrally triggered Pressure Support (PSn) abolishes the need for PEEPe in COPD patients, improves patient-ventilator interaction and reduces the inspiratory mechanical effort to breathe.

**NAVA in Bronchiolitis**

Guillaume Emeriaud, MD, Montreal referred to the frequency of infant bronchiolitis and intensive care and CPAP as first choice for ventilation (Essouri 2014). He presented his latest research with Ducharme-Crevier et al (2015) regarding a crossover physiological study of conventional NIV and NIV NAVA in 13 PICU patients, with improved synchrony and fewer wasted efforts in NIV NAVA compared to conventional NIV. He also cited a study by F Baudin et al (2014) of 11 children with severe bronchiolitis comparing non-invasive ventilation in pressure assist/control modes and NAVA, resulting in dramatically lower levels of asynchronies and trigger delay in NAVA.

**Non-invasive ventilation**

**Physiology of upper airways in relation to NIV**

In presenting his recent randomized interventional study together with Carrière et al (2015), Jean-Paul Praud, MD, Quebec, reported that inspiratory laryngeal narrowing during nasal PS was not altered by inspiratory rise times 0.05-0.4 s or moderate hypoxia.

**NAVA and upper airways**

Lisanne Roesthuis, MSc, Nijmegen referenced the study by Doorduin et al (2014) regarding analysis of 12 COPD patients with a dedicated NIV ventilator, NIV in Pressure Support and NIV NAVA, and calculation of NeuroSync index. NIV NAVA improved patient-ventilator interaction. She showed patient examples from the study of a male COPD and exacerbation with restored synchrony in NIV NAVA as shown on Edi tracings.

She also presented the glottal view during NIV with camera documentation, with opening of glottis before maximum of Edi = inspiration. She stated that high Pressure Support levels affect upper airway patency.

**NAVA in the neonate**

Howard Stein, MD, Toledo shared his experience in treating over 800 neonatal patients with NAVA. In his opinion, endotracheal tube placement is to be avoided in neonates whenever possible. He addressed a number of issues: how to set NAVA level, if the neonate can regulate his own ventilation. Dr Stein suggested titrating NAVA in steps of 0.5 up to 4 in the neonate, and to look at the traditional curves and the Edi to determine the optimal level: avoiding overassist and under-support.

He recommended to start with NIV NAVA, or if necessary, extubate to NIV NAVA as early as possible when at a NAVA level of 1-2µV/cm H₂O. In his experience of over 800 babies on NAVA, most have been able to self-limit their peak inspiratory pressures. He stated that NAVA and NIV NAVA were safe and more synchronous modes in neonatal patients.

**NIV NAVA in pediatrics**

Jennifer Beck, PhD stated that in many hospitals up to 17-29% of children are ventilated with NIV as primary ventilator mode in bronchiolitis, and nasogastric tubes are routinely used there for feeding patients. In pediatric ARDS, many factors can affect success with NIV according to Jennifer Beck, including leakage, auto triggering and ventilator hang-ups. The challenges of leakage in NIV have been described in studies by Vignaux et al.

The recent feasibility study on NIV NAVA in infants after cardiac surgery was presented (L Houtekie et al 2015). NIV NAVA allowed for good synchronization and decreased work of breathing more effectively than nasal CPAP in these patients.

The study by Emeriaud with Baudin F et al (2014) was also reviewed, where impact of ventilation mode on breathing variability was studied in 10 infants.

**Respiratory muscle weakness**

**Respiratory muscle activity and protection from VIDD**

In defining ventilator induced diaphragm dysfunction, Alexandre
Demoule, MD referred to a study by Powers et al in controlled MV comparing specific force to stimulation frequency. He described the pathway of VIDD from mechanical ventilation to diaphragm unloading, oxidative stress leading to myofiber injury and resulting in diaphragm dysfunction. A study by Hudson et al (2012) establishes that both high level Pressure Support ventilation and controlled mechanical ventilation induces diaphragm dysfunction and atrophy. Dr Demoule summarized that respiratory muscle activity is needed to prevent VIDD, and that promotion of spontaneous ventilation through Pressure Support and proportional modes such as NAVA and PAV is valuable, and that daily monitoring of Edi is needed.

**Daily monitoring of Edi throughout PICU stay**

Guillaume Emeriaud, MD shared his experience of how Edi as a new vital sign leads to a change in practice and provides new knowledge, such as detecting respiratory distress after extubation by means of the Edi curve. He reviewed his study from 2014 of 55 PICU patients from 1-35 months old, with Edi measurements and diaphragm activity at different parts of their stay. Driving pressure as seen by Edi is very variable, and diaphragm activity is not stable depending on the activity of the PICU patients. This variability is difficult to address with conventional ventilation. He presented two patient cases with Steinert disease and tetraplegia, where Edi monitoring helped to titrate the ventilation necessary to activate the diaphragm and patient breathing. His take home message was that Edi monitoring provides for detection of extubation readiness, Edi overassist, asynchrony, adaptive support reflection of patient efforts and follow-up of the diaphragm.

**Myotrauma**

Ewan Goligher, MD presented various studies of diaphragm thickness, including his recent study from 2015, investigating how diaphragm disuse and overload can lead to dysfunction. As disuse is very common during mechanical ventilation, severe thickening fraction may indicate severe dysfunction in terms of overassist and under-assist injuring the diaphragm.

**ICU acquired muscle weakness**

Greet Hermans, MD from Loevens, Belgium reviewed research on the subject, a case by Germans G et al of pronounced muscle wasting in a pancreatitis patient after 2 months, and the study that Dr Hermans and colleagues published in 2014: to determine acute outcomes, 1-year mortality and costs of ICU-acquired weakness among long-stay (>8 d) ICU patients, and impact of recovery of weakness at discharge. 122 weak patients were carefully matched to 122 not-weak patients.

The data suggests that ICU acquired weakness worsens acute morbidity and increases healthcare-related costs and 1-year mortality.

**Impact of mechanical ventilation on diaphragm muscle fibers**

Coen Ottenheijm, MD, PhD, Amsterdam presented recently published research by himself and PE Hooijman et al based on the findings that diaphragm muscles of mechanically ventilated patients display atrophy and contractile weakness, and that the ubiquitin-proteasome pathway (mechanism for protein catabolism) is activated in the diaphragm.

**VILI: State of the art**

Art Slutsky, MD, PhD Toronto, reviewed a number of studies on atelectrauma, volutrauma leading to epithelial cells transforming into pulmonary fibrosis with 57% patient mortality (Cabrera-Benitz et al, Ichikado et al). He also reviewed systemic effects and multi-organ dysfunction affecting kidney, liver and the brain (Quiles et al, Gonzalez-Lopez et al). Although cause and effect may be difficult to determine, effects on the brain are dependent on how we ventilate, according to Dr Slutsky. He also reviewed his own study with consideration to stiff chest wall and driving pressure (2013) and the recent study (2015) by Amato et al, where it is indicated that normalizing tidal volume to body weight is not sufficient in terms of VILI. He summarized by stating that driving pressure is a key number, and that ARDSNet is perhaps not the right approach.

**NAVA during ARDS**

Leo Heunks, MD, PhD, Nijmegen presented a study by Doorduin et al (2015) examining 12 patients in assisted ventilation in ARDS with 30 minutes per mode: PCV – PSV – NAVA. There was no significant difference in peak airway pressures, however there were lower mean airway pressures with NAVA. Delta mean esophageal pressure was lower with NAVA, as well as delta mean transpulmonary pressures.

The coefficient of variation between the modes showed increased variability in Pressure Support but highest
variability with NAVA. Patient-ventilator interaction improved with NAVA compared to the other modes.

**EIT during PSV and NAVA**
Diederik Gommers, MD, Rotterdam presented his study with P Blankman et al of 10 mechanically ventilated patients comparing effect of varying levels of assist during Pressure Support and NAVA on aeration of dependent and non-dependent lung regions with electrical impedance tomography. Tidal impedance variation significantly decreased during descending levels of PSV but not during NAVA. The investigators found that NAVA had a beneficial effect on ventilation of dependent lung region and showed less over-assistance compared to PSV in ALI patients.

**Bronchopulmonary Dysplasia (BPD): State of the art**
Anne Greenough, MD, London referred to a Cochrane review by Cools et al (2010) with reference to 17 prophylactic HFO trials in 3652 infant patients and frequency of death or BPD. She also presented a long term follow-up study of these children and respiratory health at ages 11-14 (UKOS study, Johnson et al 2002).

According to a study by Doyle et al (2006) in infants with BPD, the natural decline in lung function starts at a lower baseline, and airflow reduction worsened in BPD children between ages 8 and 18 years. Dr Greenough summarized that very premature birth results in chronic respiratory morbidity regardless of BPD, and that ventilatory interventions which may influence chronic respiratory morbidity from BPD include increased use of NIV and CPAP and prophylactic HFO.

**NAVA in the preterm: how early can we start?**
Howard Stein, MD presented his experience of more than 800 neonatal patients treated with NAVA and NIV NAVA, including a number of specific patient cases, including infants born at gestational age 23 weeks. He has been using NAVA in preterm babies since 2008. In terms of continuum of care for the premature neonate, Dr Stein recommends that if the baby is intubated, treat with surfactant and caffeine, place the preterm baby on NAVA and there after wean to a NAVA level of 1, with FiO2 < 30%. The neonate may then be extubated to NIV NAVA level of 2 (within 48 hours if possible) according to Dr Stein, and weaned to a NIV NAVA level of 1 and placed on CPAP.

**Controlling respiratory drive through CO₂**

**Ventilatory response to CO₂**
Anne Greenough, MD reviewed earlier studies related to the topic (Björklund et al, Keszler et al) and a recently published crossover study of PAV versus assist control ventilation by herself and P Bhat et al (2015) in 12 neonatal infants. The results suggested that PAV compared to ACV may have physiological advantages for prematurely born infants remaining ventilated after first week of birth.

**ECMO during NAVA**
Giacomo Grasselli, MD stated that there are no randomized controlled trials in general with regard to how to ventilate during ECMO. He stated that in high blood flow, it is important to maintain viable oxygenation and that CO₂ is nearly never a problem. He presented that in his experience NAVA was a protective mode in ECMO, providing tidal volume control and improving synchrony, as reported in the study by Mauri T et al (2013) about patient-ventilator interaction in 10 ARDS patients with low compliance undergoing ECMO as a novel approach based on Edi. Their conclusion was that Edi allows accurate analysis of asynchrony patterns and magnitude in ARDS patients undergoing ECMO. In these patients, NAVA was associated with reduced asynchrony.

**Extracorporeal CO₂ removal in COPD (NIV)**
Christian Karagiannidis, MD, Cologne presented his earlier study (2010) of autoregulation of ventilation with NAVA on extracorporeal lung support, and another study by Chandra et al (2012). He stated that NIV early in the course of respiratory failure reduces intubation and mortality.

**Tidal volume under Neurally Adjusted Ventilatory Assist after double lung transplantation**
Hadrien Rozé, MD referred to the interest of tidal volumes in maintaining a lung protective strategy in transplant patients, and considerations of chest wall size. He presented some data from his former study (2011) and then posed the question: what is the right level of assist in these patients and if adaptive tidal volume in NAVA is possible? Other aspects to be considered are the effect of cutting the vagal nerve during transplantation. Dr Rozé showed some preliminary results of his current study related to the topic which is in revision with AJRCCM.

**Debate: Are we protected with synchrony?**
A lively debate was initiated by Laurent Brochard, MD on the topic of “Asynchrony and controlled ventilation protects the lungs and dia-
phragm”. He began with a review of the literature on whether or not spontaneous breathing is positive. Based on physiology, he stated that spontaneous breathing is good because it promotes lung aeration and maintains muscle activity. He quoted a paper by Papazian which showed lower mortality in patients with ARDS who received neuromuscular blockade, hence adding to the controversy about paralyzing vs. spontaneous breathing. One rationale he proposed for the “no spontaneous breathing” side is that if a patient breathes in synchrony while the ventilator delivers assist, the transpulmonary pressure (PL) will be bigger than anticipated, and may be injurious. He referred to his paper with Richard et al showing different degrees of synchrony on PL with different modes. He concluded that in patients with ARDS who are at risk for VILI, “Asynchronous” ventilation could be an interesting compromise and help to achieve two important goals, namely: protective lung ventilation and maintained respiratory muscle activity.

Dimitris Georgopoulos took the opposing viewpoint with “Synchrony and proportionality protect the lungs and diaphragm”. He began with a physiological description of the control of breathing, and explained how there are two “Guards”, chemo responses and reflexes (mainly Hering-Breuer) from the lung stretch. He presented the basic concepts of NAVA and PAV, two modes of synchrony and proportionality. He quoted a number of papers showing improved synchrony with these modes, the lack of overassist with these modes, and the improved variability. He also talked about the potential diaphragm damage that can occur when there are “wasted efforts”, and suggested that the muscle undergoes lengthening during contraction, which can cause damage during asynchrony.

MeetingPoint Nijmegen 2015 summary

In summarizing lessons learned during the meeting, Art Slutsky MD, PhD listed the following items:

- A strong recommendation to include respiratory muscle monitoring (Edi/Peso) in complicated patients (neonates, pediatrics and adults)
- There is a high incidence of asynchronies and overassist (Myotrauma/VIDD – ICUAW much more complicated)
- There is a decrease in asynchronies with proportional/neural assist modes
- There is uncertainty about the clinical consequences of asynchrony (double triggering vs missed breaths)
- Upper airway dyssynchrony exists during NIV in animal models and in COPD patients
- (NIV) NAVA is applicable in neonates and children with bronchiolitis and in adults with COPD and ARDS and on ECMO with disturbed sleep
- According to Dr Stein, NAVA and NIV NAVA may be associated with improved outcomes in neonates.

Editorial note: The term “Edi” is also known in research as “EAdi”. They both describe the electrical activity of the diaphragm.

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