GE SYMPOSIUM

Tuesday, October 4th

12:30-14:00

Room Glasgow

Advanced Tools for Lung Protection and Nutrition

More Complexity or Less Complication?

Supplement from GE Healthcare in collaboration with ICU Management & Practice

ADVANCED TOOLS FOR LUNG PROTECTION AND NUTRITION

MORE COMPLEXITY OR LESS COMPLICATION?

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Introduction

The intensive care unit (ICU) is a complex environment, due to the surroundings, the heterogeneity of patients, caregiver turnover and the at times lengthy patient stays, which lead to increased complexity. The multiple technologies available add another layer of intricacy. However, with the modern tools available to the intensivist, it is now possible to personalize care to meet the heterogeneous needs of our patients. "One size fits all" is not possible or advisable any more, and the technology is crucial to enable intensivists to personalize therapy, whether that is lung protective ventilation or a nutritional plan.

I am delighted to introduce this supplement, based on presentations at a workshop at the European Society of Intensive Care Medicine LIVES 2016 in Milan.

PROTECTIVE VENTILATION

WHEN AND WHY TO INDIVIDUALIZE

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ARDS is Heterogeneous

Acute respiratory distress syndrome (ARDS) is a heterogeneous entity. Calfee and colleagues' analysis of the ARMA and ALVEOLI trials (Calfee et al. 2015) differentiated two ARDS subphenotypes, one of which was categorized by more severe inflammation and worse clinical outcomes. Response to positive end-expiratory pressure (PEEP) was different in the two subphenotypes. High PEEP showed more ventilator-free days and organ failure-free days and increased survival only in the subphenotype characterized by a greater inflammation. ARDS severity also affects the response to treatment. In a meta-analysis on studies of high vs. low PEEP in ARDS, Briel and colleagues showed that higher PEEP reduced the risk of death and shortened the time to unassisted breathing only in moderate-to-severe ARDS cases (Briel et al. 2010). In mild ARDS the opposite may be true. So, the same treatment may change the outcome according to the phenotype and to severity. This concept has been incorporated in current

recommendations (Ferguson et al. 2012), stating that higher PEEP should be reserved to moderate-to-severe ARDS cases (**Figure 1**).

Why and How to Individualize Ventilation

Individualized treatment has the potential to improve patient outcome and reduce side effects of treatment in patients who do not respond, thus allowing better use of resources. Protective ventilation is currently used in ARDS and it is based on the application of low tidal volume (Vt) and moderate-to-high PEEP with the aim of avoiding overdistension and optimizing recruitment. Individualising protective ventilation in ARDS means selecting the right tidal volume and the right level of PEEP for each individual patient.

ARDS is a restrictive disease and this is well reflected in the concept of the "baby lung" (the size of the aerated lung still accessible to ventilation is reduced to the size of the lung of a baby). The obvious implication is that the size of the "baby" lung should determine the ventilator settings. Decreasing Vt from 12 ml/kg of predicted body weight (PBW) to 6 ml/kg PBW was shown to improve survival, likely because of the decrease in lung overdistention (Acute Respiratory Distress Syndrome Network 2000). A Vt of 6 ml/kg PBW does not assure that lung overdistension is always avoided in every patient. A smaller "baby" lung can in fact be hyperinflated even using a Vt of 6 ml/kg PBW (Terragni et al. 2007), suggesting that Vt should be better tailored on the size of the baby lung than on the body weight (Gattinoni et al. 2016). Modern ventilators have the technology to measure directly the aerated lung volume thus allowing to normalize tidal volume on the size of the baby lung.

Another way to try to normalize the tidal volume to the size of the baby lung is to use the compliance of the respiratory system (Crs). Compliance in ARDS is not low because the lung is stiff, it is low because the aerated lung is small. Thus, compliance is a good index of normally aerated lung tissue and can give an estimation of the baby lung size.

Normalising tidal volume to the compliance of the respiratory system gives the driving pressure (Vt/Crs). The driving pressure (ΔP) can be calculated at the bedside as plateau pressure minus PEEP (Pplat – PEEP), and it can be considered as an estimate of the lung strain. Lung strain is the lung deformation imposed by tidal ventilation, and it is equal to the ratio of tidal volume divided by the functional residual capacity, that is the size of the aerated baby lung at end-expiration.

$$\text{Lung Strain } (\Delta P) = \frac{\text{Tidal volume } (Vt)}{\text{Size of the baby lung } (Crs)}$$

An analysis of data on 3562 ARDS patients examined the relationship between driving pressure and survival (Amato et al. 2015), and found that driving pressure was the ventilation variable most strongly associated with survival. Their analysis demonstrated that the mortality rate paralleled changes in tidal volume only when it is expressed as a function of compliance, which is an estimation of the baby lung, that is the driving pressure (Vt/Crs). On the contrary, mortality rate was not correlated with tidal volume when it is expressed as a function of body weight (Vt/PBW). This shows clearly that the tidal volume should not be sized on patient' predicted body weight but on the size of the baby lung.

There is a relationship between the size of the baby lung, recruitability, recruitment, tidal volume and PEEP. Richard and colleagues demonstrated that low tidal volume promotes alveolar derecruitment that can be prevented by an increase in PEEP (Richard et al. 2003). This study found that, for a given plateau pressure (i.e., similar end-inspiratory distension), a high

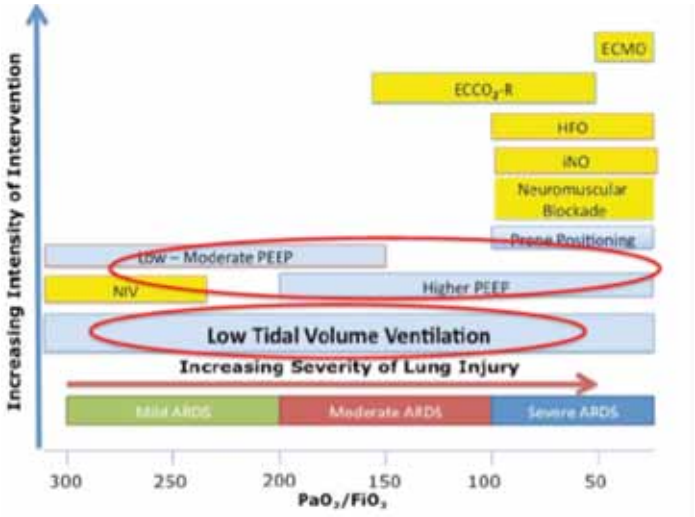

Figure 1. Aligning Therapeutic Options with the Berlin Definition
Source: Ferguson et al. (2012) With permission of Springer

PEEP-low Vt strategy increased recruitment and PaO_2 as compared to a low PEEP-high Vt strategy, suggesting that the effect of PEEP on recruitment is greater than that of Vt. By promoting alveolar recruitment, PEEP may increase the size of the baby lung, allowing a better accommodation of tidal volume, which is reflected by a decrease in the driving pressure. Thus, PEEP is a measure that can increase the size of the baby lung.

High PEEP is not recommended for all ARDS patients. Two trials comparing high vs. low PEEP failed to show any advantages of an indiscriminate use of high PEEP in all ARDS patients (Brower et al. 2004; Meade et al. 2008). In fact, it is logical to use higher PEEP only in patients who have some parts of the lungs that can be recruited. Recruitability (lung that can be recruited) is clearly correlated with recruitment (lung that is actually recruited) (Gattinoni et al. 2006), suggesting that PEEP should only be applied when there is a potential for recruitment. Gattinoni showed that patients with highly recruitable lung have more severe and more diffuse injury, i.e., they have a smaller baby lung at low PEEP (Gattinoni et al. 2006).

Caironi and colleagues (2015) further elucidated this concept. These authors differentiated patients according to the amount of cyclic lung opening (during inflation) and closing (during deflation), which is a measure of recruitability (the higher the cyclic opening-closing, the higher the recruitability). They demonstrated that increasing PEEP decreases the cyclic opening and closing (i.e., increases lung recruitment) only in patients with higher recruitability. In addition, the increased recruitment obtained with PEEP in these patients was correlated with an increased survival. Thus, using high PEEP increases recruitment when there is a high potential for recruitment and this may improve outcome. Increasing PEEP has no effect and may even be detrimental in patients with a lower potential for recruitment.

How to Assess Recruitment to Set PEEP at the Bedside

PEEP is used to recruit the lung. Measuring or estimating lung recruitment is therefore important for optimizing the PEEP setting.

A simple way to assess recruitment induced by PEEP is to measure the lung volume. Dellamonica and colleagues (2011) compared a method to estimate alveolar recruitment derived from bedside measurement of end-expiratory lung volume (nitrogen washout/washin technique) with the measurement of recruitment obtained on the pressure volume curves

(standard technique). Estimated recruitment with increasing PEEP was expressed by: ΔPEEP (ΔEELV x Crs at low PEEP). They showed that the two methods yielded similar results, thus demonstrating that the nitrogen washout/washin technique can be used for bedside assessment of PEEP-induced recruitment.

Changes in oxygenation can be used to estimate recruitment. Maggiore and coworkers reported that a significant correlation exists between recruitment and oxygenation (Maggiore et al. 2001). This correlation, however, is too weak to allow, in an individual patient, to assess PEEP-induced recruitment by its effect on oxygenation.

Maggiore and colleagues also found a very tight correlation between compliance at zero or low PEEP and recruitment obtained with PEEP 15 cm H_2O (Maggiore 2001). In other words, compliance is an estimate of recruitability—the higher the compliance, the higher the recruitment with PEEP.

It is possible to use compliance to individualize the PEEP setting according to recruitability. Let's imagine to ventilate an ARDS patient with a Vt 6mL/kg PBW and to keep the plateau pressure at the safe limit of 28-30 cmH_2O. If the compliance at low PEEP (e.g., 5 cm H_2O) is high, the pressure oscillation due to tidal ventilation (i.e., the driving pressure) will be small. So the maximum PEEP that can be applied to reach a plateau pressure of 28-30 cm H_2O will be high. The opposite will occur if the compliance at low PEEP is low. In this case, tidal volume will produce a higher driving pressure, so that the maximum PEEP that you can use to reach the target plateau pressure is low, because much of the pressure is already taken by the driving pressure. This is a way to individualize the PEEP setting in order to maximize recruitment in a safe way and it was used in the EXPRESS trial.

The EXPRESS trial compared a moderate PEEP strategy (5-9 cm H_2O), to minimize overdistension, to a PEEP setting to safely maximize recruitment, as described above. In this study, there was no difference in mortality, but there were more patients breathing without ventilator assistance when PEEP was individually set to maximize recruitment. In more severe patients, there was a clear trend to a lower mortality and a significantly higher number of patients breathing without ventilator assistance when PEEP was set to maximize recruitment. On the contrary, higher PEEP had no effect in patients with mild ARDS (Mercat et al. 2008). We also need to consider cases where mechanical ventilation fails, i.e., patients with a too small baby lung to allow for a safe conventional mechanical ventilation. In these patients, Terragni and colleagues (2009) showed that use of extracorporeal carbon dioxide removal ($ECCO_2R$) allowed to provide ultraprotective ventilation with a reduction of tidal volume below 6 ml/kg PBW (up to 4 ml/kg).

Conclusion

The future of mechanical ventilation in ARDS is an individualized approach. First of all, intensivists need to become better at recognising ARDS. As shown by the LUNG-SAFE study (Bellani et al. 2016), ARDS is in fact still under-recognised, undertreated and, probably for these reasons, still associated with high mortality. We should also understand that ARDS is a heterogeneous syndrome, comprised of distinct phenotypes, different severity and different response to treatments. We need to recognise this and to adapt mechanical ventilation to individual patient conditions, particularly when there is a clear failure of the standard lung protective ventilation strategy. This means knowing the size of the lung that should be ventilated, to select the optimal tidal volume, and knowing if the lung is recruitable and how much can be recruited, to optimize the level of PEEP. Modern technology allows us to have this information at the bedside.

As Timothy G. Buchman wrote: "Precision medicine for critical illness and injury is desirable and achievable. Part of precision lies in standardization of practice. Part of the precision lies in individualization of care" (Buchman 2016). These all come together as the right care for the right patient, every time. ■

Conflict of Interest

Prof. Maggiore is principal investigator of the RINO trial (NCT02107183), sponsored by Fisher & Paykel. He has received research grants from Fisher & Paykel and lecture fees from Draeger and GE Healthcare.

Take Home Points

- Individualized ventilation in ARDS can potentially improve outcome, reduce treatment side effects and use resources better
- Recognition and diagnosis of ARDS needs to improve
- Differentiating and recognising the ARDS phenotypes is important for treatment and outcome
- Protective ventilation is mandatory to reduce ventilator-induced lung injury (VILI) and improve survival in ARDS patients
- Individualized ventilation should be based on: 1) recognising ARDS 2) assessing features of lung injury and its severity 3) individually titrating tidal volume and PEEP, according to the lung volume 4) most importantly, understanding the physiology behind mechanical ventilation

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INDIRECT CALORIMETRY TO MEASURE ENERGY REQUIREMENTS

FROM CONSENSUS TO DAILY PRACTICE

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Why Personalize Nutrition Therapy?

The need for personalized nutrition therapy for ICU patients is shown by several observational studies that measured the energy needs of critically ill patients. The 2005 study by Villet and colleagues found that patients with an energy deficit had an increased number of complications, especially infections (Villet et al. 2005). Weijs and colleagues (2014) showed in a cohort of 843 patients that survival varied according to the energy deficit; with no energy deficit there was a high rate of survival, but with a certain energy deficit a low rate of survival. In non-septic critically ill patients, early high protein intake was associated with lower mortality and early energy overfeeding with higher mortality. In septic patients early high protein intake had no beneficial effect on mortality. The study by Krishnan and colleagues showed that a moderate caloric intake of approximately 9 to 18 kcal/kg per day was associated with better outcomes than higher levels of caloric intake, and yet this was below the American College of Chest Physicians' recommendations (Krishnan et al. 2003).

The hypothesis that hypocaloric feeding is beneficial is summarized in a recent review of randomized controlled trials comparing standard amounts of enteral nutrition with lesser amounts (Koretz 2016), with varied outcomes. The study by Petros and colleagues is a small study (n=100) that showed hypocaloric feeding to be associated with more nosocomial infections but with more glucose control and less gastrointestinal intolerance. We are still waiting for conclusive data on hypocaloric feeding, however.

Surveys show that there is a difference between what nutrition is prescribed and what the patient actually receives (for example, Alberda et al. (2009) showed that patients received approximately half of what was prescribed). It seems that we do practise hypocaloric nutrition.

In the ICU there will be a proportion of patients with a high risk of mortality, in whom nutrition is not likely to change the course of the illness. At the other extreme are the patients who will do well, who have a short stay in the ICU (**Figure 1**). Then are the others for whom nutrition is very important. But if we included all these groups of patients in a nutrition study, the results would be distorted. That is why many studies are inconclusive, as they do not have clearly defined inclusion criteria.

In ICU patients who receive nutrition there is basal energy expenditure, diet-induced energy expenditure, as we feed the patient, and activity-induced energy expenditure, as we try to mobilise patients. There is exogenous energy intake and the question is if this exogenous energy intake can completely eliminate mobilisation from endogenous stores. Very little is known about this, and there are good examples that it is the case that we cannot completely counteract mobilisation of energy inside the body. It is an important research question, as it relates to whether the energy expenditure we measure is always synonymous with caloric need. We know that we lose muscle regardless of what we do, because of inactivity and allergic reactions. There is much evidence that if you overfeed ICU patients, they are quite capable of having their body fat stores expanded by nutrition. There is a consensus not to overfeed patients, but not on how to define this, and whether energy expenditure is the correct parameter or not.

Guidelines Recommend Indirect Calorimetry

The European and North American nutrition guidelines both recommend the use of indirect calorimetry to measure energy expenditures (Singer et al. 2009; McClave et al. 2016). The European guidelines state that during acute illness, the aim should be to provide energy as close as possible to the measured energy expenditure in order to decrease

Figure 1. A schematic cartoon illustrating the heterogeneity of critically ill patients. Outcome is most often related to acute pathology and co-morbidities not related to nutrition. Therefore it is necessary to define which patients may benefit from the nutrition intervention, which are the patients in the yellow zone. This concern applies both to bedside prescription and to elucidation of the external validity of published evidence.

Source: Wernerman and Rooyackers (2015)

Arguments for Indirect Calorimetry
• Promotes individualized nutrition
• Prevents ovefeeding
• Easy to do
• Puts focus on nutrition
• Best in show

negative energy balance, and there is a recommendation for parenteral nutrition if indirect calorimetry is not used (Singer et al. 2009). The North American guidelines suggest use of indirect calorimetry (IC) to measure energy requirements, in the absence of variables that affect the accuracy of measurement (McClave et al. 2009).

There are arguments heard against indirect calorimetry—that it is expensive, inexact, technically difficult and time-consuming. It is not easy to interpret the data you get in all cases, but measurement is better than guesswork, and nothing is easy in the ICU. To sustain a correct nutrition plan we need the correct data. When continuous indirect calorimetry measurements were compared with formulas used to predict energy expenditure, they were better (Reid et al. 2007). It can be difficult to interpret, depending on the conditions. However, for patients at either extreme of body mass index (BMI), estimation with formulas is very difficult, and indirect calorimetry is the best tool. Indirect calorimetry should be used regularly because there is a learning curve and if it is not used regularly readings may be less reliable (Wernerman and Rooyackers 2015). The greatest difficulty in my view is to have a fair estimate of endogonous energy production that we cannot eliminate by exogonous energy production. And this is not a constant measurement and should therefore be repeated later in the ICU stay.

Indirect calorimetry is not time-consuming. Taking indirect calorimetry measurements for 15 minutes under standardised conditions is usually sufficient to measure energy expenditure. Zijlstra et al. (2007) showed that in their study that took measurements over 24 hours. If the patient has a long stay in the ICU, their energy expenditure will vary a lot, so measurements have to be taken on different days.

Most instruments for indirect calorimetry have sampling close to the patient and they have a flow meter that measures breath by breath. The International Multicentric Study Group for Indirect Calorimetry explored the issues with measurement for patients on mechanical ventilation; there are some technical difficulties in this as temperature and humidity must be measured (Oshima et al. 2016). Our ICU Metabolism and Nutrition research group at Karolinska Institute has published studies that compared indirect calorimetry instruments, and they compare quite well, with a scatter that, though not ideal, is better than using a formula or some other method of estimating energy expenditure (Sundström et al. 2013; Sundström Rehal et al. 2016).

Indirect calorimetry is integrated on a monitor or on a ventilator, and it does not need to be purchased separately. You should measure the cost of the device against the number of measurements it will take. Indirect calorimetry is not expensive when you consider that most of the ICU costs are staffing costs.

The most compelling argument for indirect calorimetry is that if you want to individualize nutrition for your patients, then you have to measure energy expenditure. Use of indirect calorimetry means there is a large scatter in relation to body size that clinicians need to be aware of. However, indirect calorimetry is an instrument to prevent overfeeding, it is easy to use, and it puts the right focus on nutrition. It is the "best in show". ■

Conflict of Interest

Jan Wernerman declares that he is a member of Medical Advisory Boards and also an invited speaker for Baxter, Danone, Fresenius-Kabi, GE Healthcare, Grifols, and Nestlé.

Take Home Points

- Indirect calorimetry (IC) is the gold standard to assess the energy requirements of patients
- 15 minutes of indirect calorimetry under standardised conditions is sufficient time to measure energy expenditure
- IC is available integrated into monitors or ventilators so technically easy to measure and not an expensive add-on
- The best measurement we have right now
- No more difficult to interpret than many other measures

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OPTIMIZING NUTRITION WITH AN INTEGRATED NUTRITION MODULE

MYTH OR REALITY?

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As a neurointensivist with a strong interest in nutritional support, I was delighted to trial a new integrated nutritional module. We know that nutrition really matters to our ICU patients in the context of first indicators. For example, our research group recently published a paper about two patients with viral meningoencephalitis. Invasive neuromonitoring of brain metabolism showed episodes of severe neuroglycopenia (brain glucose <0.7 mM/l) in both patients that were not attributable to decreased cerebral perfusion or hypoglycaemia. CMD-glucose levels changed depending on variations in insulin therapy, nutrition, and systemic glucose administration. The metabolic profile showed a pattern of non-ischaemic metabolic distress suggestive for mitochondrial dysfunction (Kofler et al. 2016).

Our ICU has 10 beds equipped with mechanical ventilation. At the time of the presentation, we had tested this system for 6 weeks.

IT Solution

The Nutrition Module tested at Innsbruck was created by GE and Nestlé to integrate the hardware (pumps, monitor, ventilator) with the patient data management system software (Centricity). tirolkliniken University Hospital Innsbruck IT supported the installation and implementation. The module is installed on a PC and connected to the nutrition pump and to the monitor (**Figure 1**).

Nutritional Needs in a Single View

After using indirect calorimetry to assess the energy requirements of the patient, the doctor prescribes the nutrition. Using the new Nutrition Module we can also easily input body weight and check the calorie amount the patient needs. The nutrition is delivered through a pump, provided by Nestlé, and at a glance the doctor can see how much has been administered, compared to the patient's energy needs. The system makes the calculation and shows how many calories and how much protein has been administered. This information can be displayed as a data spreadsheet and we plan to provide this also visually, to show trends. So, in one page view the doctor can see what has been delivered and what the metabolic, caloric and protein needs of the patient are, and can immediately understand and optimize the prescription to achieve those needs and see if this leads to improved patient outcomes.

With the new Nutrition Module our intention was to keep it simple. While the prescription of energy and protein relies on calculations, we are doing it now in a structured way. The module integrates six numbers and we can see the middle or late phase of the treatment period of the patient. The initial system does not have indirect calorimetry attached yet. This will improve it even more. We are also working with our pharmacists to attach other infusion pumps. There are many nutrition products available and we will liaise with our hospital pharmacy so that we can implement the key components of the nutrition formulas so these will be included in the caloric and protein calculations for macro- and micronutrients.

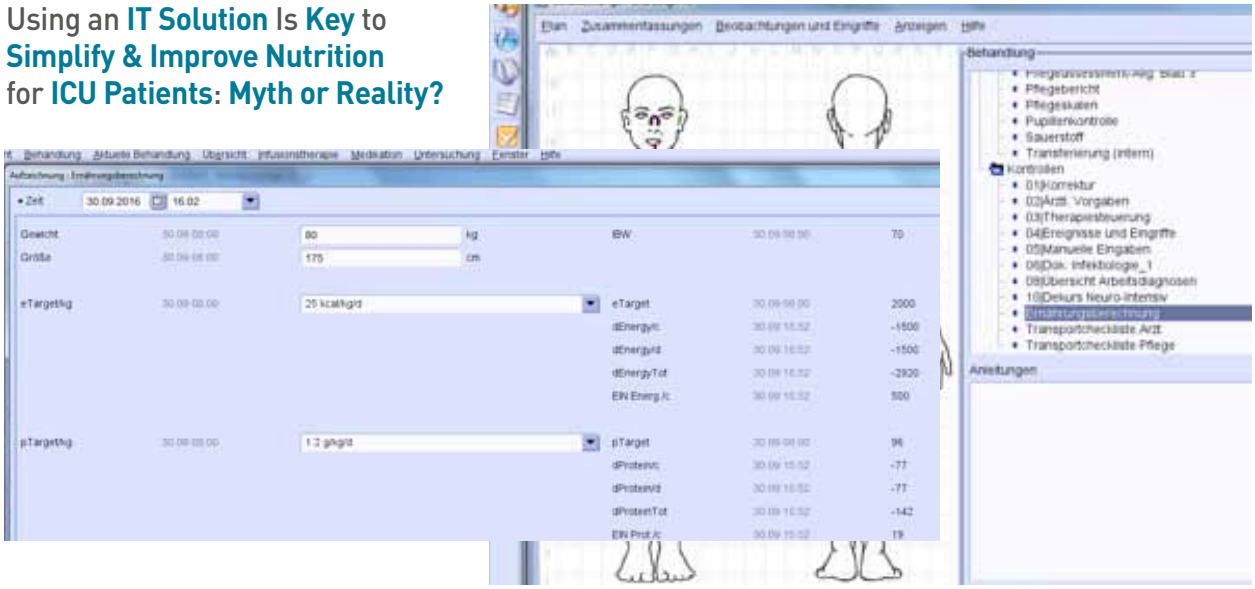
We use blind formulations for ongoing clinical trials on nutrition, and at the moment we cannot account for these in the system. Some medications need to be accommodated in future, for example propofol and those that use glucose as a carrier solution for other medications and contribute non-nutritional calories (Bousie et al. 2016).

Figure 1. Nutrition Module

«*Critical Care Nutrition Therapy*» – Synopsis (My Personal View)

© PDMS Neurological Intensive Care Unit, Innsbruck General Hospital – Medical University of Innsbruck Hospital

→ Using an **IT Solution** Is **Key** to **Simplify & Improve Nutrition** for **ICU Patients**: **Myth or Reality?**



- **No** more **myth** (*Busted!*), it has become **real**
- However, there is always **space for improvement** (e. g., **visualization**, **integration** of **indirect calorimetry** tools, **non-nutritional calories** etc.)
- Let's make the next step towards **improving** the **quality of treatment/care**

Conclusion

Using the Nutrition Module will enable us to overcome variability in nutritional support, and use the data provided to plan for the future by analysing process and outcome indicators. Using this system is much simpler than our previous method, which involved complex and time-consuming calculations, and switching between screens.

There is room for improvement in this system, including some issues with visualisation, integration of indirect calorimetry tools, non-nutritional calories etc. We have used the system for a few months only and we are working together to improve this tool to provide even better quality of patient care. However, by using an IT solution, we can combine all the different measurements, and optimize and improve the quality of treatment of the patient. ■

Conflict of Interest

Ronny Beer has received meeting attendance compensation from Baxter, research support and meeting attendance compensation from Bayer HealthCare, speakers' fees from Boehringer Ingelheim and GE, research support and meeting attendance compensation from Pfizer, contract research, speaker's fees and meeting attendance compensation from Fresenius Kabi, contract research from vasopharm, a research grant from Austrian Science Fund (FWF). He is a member of the European Stroke Organisation's ICH Guidelines Working Group.

Take Home Points

- A new tool integrates hardware and software to provide doctors with the full picture of the patient's nutritional requirements and intake
- A single view replaces switching between screens
- Data is provided in a spreadsheet and will in future be provided visually, to show trends
- Future development will integrate indirect calorimetry and infusion pumps to account for non-nutritional calories
- We should use these tools to improve further the quality of patient treatment and care

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Chair's Concluding Remarks

Partnership with companies is essential for technological development in our ICUs. We have to face complexity every day, and if we have the help of an advanced technology in better targeting our therapies, we can better identify the most serious and severe patients. This technology greatly assists intensivists in their everyday clinical practice.