Pandemic-era ECMO leads to paradigm shift

A perspective on extracorporeal membrane oxygenation (ECMO) services in Toronto during the pandemic was given on Tuesday morning by Niall Ferguson, head of critical care medicine at the University Health Network and Sinai Health System at Toronto General Hospital, ON, Canada. He runs the largest ECMO center in the province of Ontario, which provides all adult ECMO services for the greater Toronto area, serving a population of 5 million people.

In an interview with ISICEM News, Professor Ferguson said that although his department was not overwhelmed in the first wave, as other centers were, it did get extremely busy. For instance, one member of staff was tasked solely with answering the phone to ECMO referrals all day, every day, all pertaining to COVID-19 respiratory failure. And at its height, there were so many patients requiring ECMO that some adults even had to be treated at a children’s hospital.

“We were moving literally hundreds of ICU patients a week around the greater Toronto region.”

NIALL FERGUSON

In pre-COVID times two consultant intensivists were on call each week. We went to having five every day,” said Professor Ferguson.

The need for ECMO was so great that the mobile teams that existed before the first wave had to be abandoned. Teams of perfusionists, surgical fellows and consultant intensivists would otherwise be gone for many hours in a day – such are the distances clinicians normally have to travel – and this expertise was urgently required in the hospital. “In pre-COVID times two consultant intensivists are on call each week. We went to having five every day,” said Professor Ferguson.

Perfusionists, too, would ordinarily look after four to five patients on ECMO at a time. “But when we had upwards of 30 patients, perfusionists were in very short supply. So, we imported some...”
but we need to think about how different ECMO centers. We want the right volume–outcome relationship with preparedness approach should look like going forward. “There is a clear example, he now asks what a system should work, continued Professor Ferguson. “There is no shortage of discussions around the way ECMO other cardiac centers around the Toronto area, he said. “There has been very clear criteria and a strict process that we went through which each referral, with four or five or six clinicians who discussed every case and applied these criteria fairly and transparently,” he explained. “We have been thinking about which patients should receive ECMO, and who will benefit most. “It’s an ongoing question: how sick does somebody have to be in order to be too sick for ECMO? Often it is related to their underlying conditions,” stressed Professor Ferguson. “We are always thinking about what patients should receive ECMO, and who will benefit most. “This year, during our third wave … we had 32 patients on ECMO. That is more than our entire baseline ICU capacity.” NIALL FERGUSON

I’m sure that we might have given some people a shot in the past, but when we looked at all the data available we saw that their chance of doing well was low. Decisions were made, not just an individual patient level, but people were forced to look at it from the system-resource level.” Professor Ferguson and his team are in the process of carrying out several ECMO trials as a result of their experience. Historically, ECMO is thought of as rescue therapy for refractory hypoxemia, but his data – and that from the EOLIA (ECMO to Rescue Lung Injury in Severe ARDS [acute respiratory distress syndrome]) trial 1 – suggests its major benefit is not so much in reversing or stopping people from dying from low oxygen levels, rather that it may be helpful because it allows for reduction in the intensity of mechanical ventilation. “The pressures and the power we are exerting on the lung with a mechanical ventilator can be much lower when a patient is on ECMO,” he said. “If you can lower the intensity of the mechanical ventilation, the outcomes seem better.” To that end, Professor Ferguson and his team have initiated some studies to investigate further, and try and prove that use of ECMO to lower intensity of mechanical ventilation translates to better outcomes.

The concept behind platform trials – REMAP-CAP 2 and RECOVERY 3 – has also inspired Professor Ferguson and Canadian researchers. They are in the process of setting up their own platform trial that will have both local and national elements. “Our research focus at Toronto General is severe respiratory failure, so we’re going to look at various domains of treatment from when the patient is intubated, how best to use the ventilator, to which patients are going to be best suited to go on ECMO,” he explained. The trial is still in the protocol development stage, but Professor Ferguson hopes to start randomizing and enrolling patients later this year.

The ECMO portion of this trial will look specifically at the effect of ultra-protective ventilation facilitated by ECMO versus the best current conventional ventilation on all-cause hospital mortality among patients with early moderate-severe ARDS. This Ultra-Low Tidal Volume Mechanical Ventilation in ARDS Through ECMO (ULTIMATE) trial is led by Professor Ferguson and his colleague, Eddy Fan, an associate professor and director of research in critical care at Toronto General Hospital.

Platform trials such as this are probably the silver lining of COVID-19, Professor Ferguson said in his closing comments. For one, they signal a paradigm shift taking place within the ECMO community, one which increasingly recognizes the opportunity of embedding clinical research within clinical care. “It’s been happening in the cancer community for years – people look to be enrolled in trials for investigational drugs because they think it will improve their chances,” he said. “REMAP-CAP and RECOVERY have shown that this actually can be done in the intensive care sphere as well.”

References

On Monday, Brussels’ famous statue, Manneken Pis, was specially dressed in honor of the 40th ISICEM!
**Anti-IL-6 for all says REMAP-CAP UK chief**

The promising use of interleukin 6 (IL-6) receptor antagonists tocilizumab and sarilumab in the treatment of COVID-19 will be the focus of a talk by Anthony Gordon, the UK Chief Investigator for the international REMAP-CAP platform trial. Together with an international team, Professor Gordon has been evaluating treatments for COVID-19, and this afternoon he will talk about the domain of the platform focused on immunotherapies, of which IL-6 antagonists have emerged as the most exciting so far.

"I'll review the evidence of these IL-6 receptor antagonists," said Professor Gordon, who is also Chair in Anesthesia and Critical Care at Imperial College and a consultant in intensive care medicine based at St Mary's Hospital (London, UK). "We'll review the evidence from the REMAP-CAP trial which was the first trial to report positive effects of these drugs."

After publication, another platform trial, RECOVERY, also showed a beneficial effect in a wider group of patients. In addition, says Professor Gordon, it's also important to consider the evidence from all trials, including a recent WHO-led meta-analysis. "We'll consider the whole totality of the evidence. The meta-analysis showed that when you include all the trials — including some of the smaller ones where no clear effect was seen — there is a clear signal for benefit."

One reason why some of the trials may not have shown benefit was because they were not large enough, notes Professor Gordon. However, the effect of corticosteroids may be another reason. "These drugs seem to work best if they are also given in combination with corticosteroids," he added. "Maybe it is that combination of therapy which provides the real benefit."

Professor Gordon went on to explain that corticosteroids became a standard of care quite early on, so only a few patients were randomized to receive them separately. "Early on in the pandemic we were not giving corticosteroids," he said. "When assessing those few patients there was a suggestion that there was an effect of both drugs together, but it wasn't definitive. It was a weak association, but it did suggest there may be an important interaction."

But then RECOVERY saw something similar. "When you combine all of the trials together in the meta-analysis that signal comes out more clearly," he explained.

Importantly, however, the depth of the research leading to this result indicates that there has been a very important international collaboration in COVID-19. "All the academic investigators and all the industry investigators agreed to share their data," he explained. "And some of it was unpublished at the time."

The effect of such an enormous and rapid combined analysis has yielded very promising results. "The more data you have, the more precise your measurement of treatment effects can be, and it can provide more information to help guide physicians exactly who should, and who shouldn't, get IL-6 blockers," Professor Gordon explained.

The design of these adaptive platform trials, created specifically for use in pandemics, is crucial. "A multifactorial platform trial is important because it throws up the potential to look for interactions which, in modern medicine, is important," he explained. "We don't give drugs in isolation — we usually give them in combination, especially for the sickest patients in intensive care."

That's why Professor Gordon advocates the wider use of IL-6 receptor antagonists. "The evidence is now very clear that for the sickest patients with COVID-19 — those who are either receiving organ support in an ICU or perhaps in the ward, and receiving oxygen but with signs of severe inflammation — they should be given IL-6 receptor antagonists."

Several national and international guidelines now recommend these drugs. For example, the UK added its recommendation for IL-6 in January of this year, and so too has the National Institutes of Health (NIH) in the US, and most recently, the World Health Organization (WHO). "Unless they have any specific contraindications, patients who meet the criteria should be treated with these drugs in combination with corticosteroids," explained Professor Gordon.

He added that it's absolutely vital that research goes further to ascertain which patients benefit the most from the interventions going forward, given the possible side-effects: "There may be patients who are in our group at the moment who may not see as much benefit, but hopefully over time we can learn to refine the population who should be treated."

"I know that's where the intensive care world will go — to improve understanding as to which patients would benefit from these or other drugs."

What's also needed now, continued Professor Gordon, is to investigate further treatments within the immune modulation therapy domain, to which the tocilizumab and sarilumab belong. The platform has also been testing an IL-1 receptor antagonist, anakinra, and interferon beta-1a. "For those who don't respond to the IL-6 blockade, perhaps they could benefit from other inflammation-blocking pathways such as granulocyte-macrophage colony-stimulating factor," he explained. "Tumor necrosis factor is another pathway to investigate, if that isn't enough."

What's clear is that further research is required. "We've seen that at the beginning of COVID-19 there was a lot of opinion about what would work, and what wouldn't work," said Professor Gordon. "Now, we've been able to conduct randomized controlled trials which have provided clear evidence that corticosteroids work, and that IL-6 receptor antagonists work."

He concluded: "If you treat these COVID-19 patients, I encourage you to use these drugs to improve outcomes."

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**References**

The limitations of biomarkers in sepsis will be explored this afternoon by Jan De Waele, an intensivist at the surgical ICU of the Ghent University Hospital, Belgium. In what promises to be a thought-provoking talk, Professor De Waele will discuss the situations where biomarkers have value, and warn against their injudicious use.

Speaking to ISICEM News, Professor De Waele began by outlining how biomarkers should always be viewed in the light of a specific clinical aim.

"The first question one should ask is whether a biomarker is really useful," he said. "Usefulness primarily refers to the impact on patient care – for instance, improving outcomes, limiting harm, or shortening exposure to drugs or interventions. When looking critically at the available biomarkers, these goals are rarely met."

Professor De Waele's talk will review the use of biomarkers in relation to such goals, looking specifically at procalcitonin, one of the most widely researched biomarkers in sepsis. Procalcitonin has been examined in the context of prognostication, diagnosis, and monitoring of therapy, and Professor De Waele highlighted that evidence is strongest for the latter of these uses.

"When determining the duration of antimicrobial therapy, procalcitonin may be of value as it may help to reduce the number of days patients are receiving these drugs," he explained. "Given that antimicrobial exposure is one of the main drivers of multi-drug resistance, this is a very important consideration."

The use of procalcitonin for informing the decision to stop therapy has been well studied. Evidence from multiple randomized clinical trials indicates that stopping antibiotics on the day when procalcitonin levels reach less than 80% of baseline, or that stopping antibiotics on the day when procalcitonin levels are below 0.5 ng/ml, can help reduce the length of antimicrobial treatment, as well as decrease the likelihood of infections with multi-drug resistant organisms.

While this highlights how biomarkers can help curtail antibiotic therapy, the extent to which antimicrobial use can be reduced in this way is limited. "It should be acknowledged that, for many infections, antimicrobials can be discontinued after five to seven days," Professor De Waele added. "While biomarkers have helped us to steer away from prolonged courses such as 10 to 14 days, it is unclear if they will be of added value to push antimicrobial therapy below five to seven days."

From an antibiotic stewardship perspective, it would be of even greater value if procalcitonin – or any other biomarker – could be effectively used to determine whether to initiate therapy in patients with suspected sepsis. This could potentially have a marked impact on unnecessary antimicrobial use in the ICU as overdiagnosis of sepsis is a significant issue: a recent study found that approximately 60% of patients ultimately diagnosed with non-infectious systemic inflammatory response syndrome (SIRS) were initially given systemic antimicrobials.

However, while procalcitonin levels are typically higher in bacterial sepsis compared to SIRS and viral infections, evidence currently suggests this biomarker is not an adequate tool to determine whether to initiate empirical antibiotic therapy. Multiple systematic reviews and meta-analyses on the utility of procalcitonin for diagnosing sepsis have been conducted; the overall sensitivity for distinguishing bacterial infection from SIRS ranged from 0.72–0.93 and the specificity ranged from 0.64–0.84, suggesting only a modest discriminatory ability.

Professor De Waele commented that similar limitations apply to many other biomarkers as well as procalcitonin. A major reason for this, he said, is that many assess the host response rather than the presence of infection.

"This is probably a reason why many of them fail to adequately distinguish between infectious and non-infectious causes of organ dysfunction," he explained. "This makes it very challenging to use them to guide initiation of antimicrobial therapy in patients in the ICU."

Research into the use of biomarkers in this context is ongoing. However, the lack of a gold standard for the diagnosis of sepsis makes investigation in this area particularly challenging.

As well as these diagnostic limitations, Professor De Waele reported that there are multiple other reasons why biomarkers are difficult to study. One is that variation in a number of situational factors may potentially affect biomarker kinetics. "Such factors include different therapies or disease states, such as kidney failure or the use of renal replacement therapy," he observed.

A higher baseline procalcitonin level in people with renal impairment is thought to limit the diagnostic utility of this biomarker in these patients. Immune system capability may be another factor that affects the utility of procalcitonin, with a lower diagnostic sensitivity observed in immunocompromised than immunocompetent patients with bacteremia.

As well as the difficulties in generalizing between different patient groups, assuming parallels between different infections could also be an issue. Procalcitonin levels do not appear to increase appreciably in intracellular bacterial bloodstream infections, in contrast to bacteremia caused by extracellular pathogens.

"We often assume that procalcitonin behavior is similar in every type of infection, but this is highly questionable," stated Professor De Waele. "Fundamentally, when biomarkers are studied in specific populations or specific infections, extrapolating these findings to other settings may not be straightforward."

After outlining the many limitations of biomarkers in sepsis, Professor De Waele moved on to discuss how to employ them in a clinical context. "From a practical point of view, I think it is important never to use a single value of a biomarker as a standalone tool in medical decision-making," he advised. "Integrating biomarker results into the clinical evaluation and interpreting them in light of the clinical condition of the patient is essential."

Another key recommendation from Professor De Waele is to look at biomarker kinetics rather than relying on single value measurements. Evidence for the utility of serial measurements of procalcitonin is mounting, with studies now showing value in terms of predicting mortality as well as guiding therapy.

Moving on to give his perspective on the future of biomarker research, Professor De Waele drew attention to the promise of...

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**Know their limits: A critical look at sepsis biomarkers**

"When biomarkers are studied in specific populations or specific infections, extrapolating these findings to other settings may not be straightforward."

**JAN DE WAEL**
The combination of biomarkers is an interesting strategy, and also the use of artificial intelligence such as machine learning may help to identify biomarker- and clinical characteristics that will help us to refine patient therapy. As research progresses in this field, the number of sepsis biomarkers under investigation continues to increase, with over 250 identified in a 2020 review. While many of these may hold clinical promise, Professor De Waele believes the ‘perfect biomarker’ may remain elusive and we should not view the research landscape through this lens.

“The question remains whether one biomarker will be perfect for prognostication, diagnosing the presence of infection, identifying the need for specific sepsis therapies, and monitoring antimicrobial use,” he said. “So maybe we need to identify the goal first and then select the biomarker that is best suited for the job.”

Professor De Waele concluded the interview by emphasizing the importance of recognizing the current limitations of biomarkers while research develops. “Biomarkers are conceptually very attractive, but at this stage their impact on clinical management seems limited,” he summarized. “Our current tendency to oversimplify a complex disease such as sepsis or infection by reducing it to looking at the value of a single biomarker at a single point in time is potentially dangerous.”

“For now, biomarkers can never be the sole element in decision-making, and integrating them into a clinical evaluation into the clinical context is essential for proper patient care. Still, I think the future for biomarkers is bright, provided we understand their limitations, and refine the way we use them at the bedside.”

References

Important advances in the understanding of macrophage activation syndrome in sepsis were presented yesterday afternoon by Evangelos J. Giarmarlos-Bourboulis, Professor of Internal Medicine at the medical school of the National and Kapodistrian University of Athens (Greece).

Professor Giarmarlos-Bourboulis, who is the current President of the European Shock Society, and the current Chairman of the European Sepsis Alliance, presented his own research, alongside wider data from other centers.

One trial looked at the sudden clinical deterioration 7–8 days after initial symptom onset in COVID-19. Professor Giarmarlos-Bourboulis’ team studied immune responses of 54 COVID-19 patients, 28 of whom had severe respiratory failure (SRF). All patients with SRF displayed either macrophage activation syndrome (MAS) or very low human leukocyte antigen-D-related (HLA-DR) expression accompanied by profound depletion of CD4 lymphocytes, CD19 lymphocytes, and natural killer cells.

The group found a pattern distinct from bacterial sepsis or influenza. Importantly too, the interleukin (IL)-6 binding inhibitor tocilizumab stimulated an increase in circulating lymphocytes. This insight into a pattern of immune dysregulation in severe COVID-19 was very well received, continued Professor Giarmarlos-Bourboulis. “The paper has already been cited more than 1,000 times, and has generated insight about the role of this pattern to drive unfavorable outcomes in 25% of patients,” he said.

Similarly, Professor Giarmarlos-Bourboulis also talked about a study aimed at investigating the frequency of macrophage activation-like syndrome (MALS), as well as to develop a biomarker of diagnosis and prognosis. Importantly, the study found a correlation between levels of ferritin and mortality. “My group has developed the use of ferritin at concentrations 1,000 times, and has generated insight about the role of this pattern to drive unfavorable outcomes in 25% of patients,” he said.

That’s why Professor Giarmarlos-Bourboulis is participating in the pan-European ImmunoSep consortium. It was formed in February 2020 to run randomized clinical trials delivering immunotherapy tailored to the individual needs of patients. Coordinated by the Radboud University Medical Center (Professor Migai G. Netea, Nijmegen, the Netherlands), ImmunoSep will first create a proof-of-concept clinical trial of personalized immunotherapy in sepsis, identifying biomarkers, clinical endotypes, and therapeutic targets needed for future precision medicine approaches, followed by the development of a so-called ‘theranostics’ platform (combining specific targeted therapy based on specific targeted diagnostics) for the design of future personalized immunotherapy trials in sepsis.

“It is high time we changed our approach to the management of the critically ill.”

EVANGELOS J. GIAMARELLOS-BOURBOULIS

“Time to personalize treatment’ for sepsis patients

References
Lung recruitment, a quest for evidence

Despite its clinical use for almost 30 years, lung recruitment has still not reached the level required by modern evidence-based medicine standards, delegates will hear this afternoon in a session dedicated to acute respiratory distress syndrome (ARDS) management.

Speaking on lung recruitment will be Fernando Suarez Sipmann, an intensive care specialist based in the Hospital Universitario de La Princesa (Madrid, Spain), whose research focuses on respiratory physiology, mechanical ventilation and respiratory monitoring.

In conversation with ISICEM News, Dr. Suarez Sipmann said there are several reasons for the ongoing lack of evidence for lung recruitment. First, apart from the fact that it’s a very complex intervention, it is very heterogeneously described. “Everybody has their own understanding of ‘lung recruitment’, and if you look at the literature, there are many different types of maneuvers that are described,” he said. “That makes it difficult to gather all the studies together to make a specific recommendation on how, and in whom, lung recruitment should be performed.”

A crucial problem is that lung recruitment has typically been used as a rescue therapy for patients who are highly hypoxic, he explained. Rather, Dr. Suarez Sipmann believes oxygenation, while important, should not be the prime reason for using the maneuver. “Recruitment, if successful, and applied in the proper way, should promote a better lung protective environment for the ventilation of the lungs,” he explained.

Returning back to the essential issue of improved monitoring, he added: “We need a way to identify patients who will benefit from lung recruitment in order to implement it only in those that need it. And then we need to monitor to confirm that our PEEP setting afterwards, and we need to frequently assess the situation of this patient and reassess whether the chosen PEEP setting is the correct one or whether the situation has changed and to de-escalate the PEEP levels when necessary.”

The tool also allows to follow the changes in response and needs of PEEP in the same patient along the time. The process of mechanical ventilation support is very dynamic, and the patient changes over time, thus it is important to track how patients’ condition evolves. “This system allows us to better discriminate between these responses and to adapt to the changing conditions of the patient,” said Dr. Suarez Sipmann.

Although there is no formal study published on standardization or automation so far, some elements of the concept have been studied in randomized controlled trials. But evidence is critical, even if controversial. “We sometimes have to collect evidence for interventions that have been used on a daily basis for years,” he explained. “Lung recruitment is one of them.”

Importantly, it should not be forgotten that lung recruitment is a relatively complex strategy to apply, said Dr. Suarez Sipmann. “We need to move from only looking up one simple parameter, such as oxygenation, and understand this is a strategy that has a principal aim at improving lung-protective conditions.”

Dr. Suarez Sipmann underlined, there are clear benefits to having a tool that allows clinicians to better discriminate between which patients are responding to lung recruitment, as well as in improving repeatability. “We hope we can finally have a standardized way of doing it, and gather enough data to compare outcomes between hospitals and doctors,” he explained.

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FERNANDO SUAREZ SIPMANN

“Recruitment, if successful, and applied in the proper way, should promote a better lung protective environment for the ventilation of the lungs.”

FERNANDO SUAREZ SIPMANN

of PEEP is an essential component of a recruitment strategy as this is the pressure at which the patient will be ventilated for hours after recruitment,” he explained.

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Returning back to the essential issue of improved monitoring, he added: “We need a way to identify patients who will benefit from lung recruitment in order to implement it only in those that need it. And then we need to monitor to confirm that our aims – increased effective lung volume and improved lung mechanics – are achieved and maintained over time.”

Dr. Suarez Sipmann concluded: “Lung recruitment should be combined with a good and appropriate PEEP setting afterwards, and we need to frequently assess the situation of this patient and reassess whether the chosen PEEP setting is the correct one or whether the situation has changed and to de-escalate the PEEP levels when necessary.”

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Prediction of Hemodynamic Instability in the ICU

Edwards’ answer to hemodynamic instability buys time in the ICU

With a solid evidence base in arterial hypotension prediction, the Acumen Hypotension Prediction Index™ (HPI) software – the first fully approved foray into predictive analytics in anesthesia – is starting to show promising signs of having an impact on the management of hemodynamic instability in the ICU.

Such was the message yesterday at ISICEM during an Edwards Lifesciences Lunchtime Symposium dedicated to discussing this first-of-its-kind technology. Here, three experts in the fields of anesthetics and intensive care medicine addressed the performance of the Acumen HPI™ software in clinical practice, as well as the potential for its integration into the management of tissue oxygenation and hemodynamic instability in the ICU.

Moderator and presenter Thomas Scheeren, from the University of Groningen, in the Netherlands, told ISICEM News that he welcomed what the software could bring to the ICU. “This is all about pre-emptive treatment of a hypotensive event before it has become apparent,” he said, adding that, “It really is a paradigm shift.”

“I’d look forward to seeing the Acumen HPI™ software progress to something broader – a hemodynamic instability index, so it can predict other forms of instability earlier, and therefore prevent catastrophic events such as myocardial or kidney injury.”

Currently, in the ICU, hemodynamic instability is managed in real time, but as Professor Scheeren noted, predicting hypotension changes how we monitor the patient because it allows us to look into the near future, meaning we can predict hypotension while the patient is still normotensive.

Specifically, by being alerted to changes in the patient’s arterial waveform, clinicians can predict when a hypotensive event is due to occur in the next 10–15 minutes. This affords the time to consider the potential underlying mechanisms for the development of any hemodynamic instability, crucially, to identify the most appropriate course of action. It shifts hypotension care from a reactive to proactive position that may prevent damage.

Hemodynamic variables on the secondary screen, such as Eadyn, SVV, and dP/dt max help define the mechanism that will eventually lead to hemodynamic instability, and consequently determine the best pre-emptive treatment.

“If arterial blood pressure drops below 65 mmHg, there is risk of myocardial, kidney or cerebral damage. The longer the hypotension persists, the greater the harm,” Professor Scheeren cautioned.1,2

HPI™ – predicting the risk of hemodynamic instability

The HPI is a unitless number that ranges from 1 to 100. A high index means hemodynamic instability is shorter.

Developed using machine-learning methods, the HPI algorithm is based on data from a large database of patients from the ICU and operating room with various clinical conditions. The arterial waveform contains a wealth of information above and beyond the HPI alone, and this helps clinicians to determine the reasons underpinning an event.3

Expanding on this, Professor Scheeren explained: “There are three major reasons for such an event in an ICU patient: a decrease in preload, which precipitates hypovolemia, and is treated by increasing the patient’s intravascular volume; myocardial dysfunction (decreased myocardial contractility); and finally, decreased arterial tone (vasoplegia).”

“The Acumen HPI™ software looks at every single beat continuously, checking and monitoring changes over time. Take the upstroke, for example, which tells us about the myocardial contractility, or the diastolic decay, which is defined by the resistance and compliance on the large arteries. All of this is hidden within the arterial pressure waveform.”

Evidence in the peri-operative setting

Most evidence to support the use of the HPI algorithm is derived from the peri-operative setting, where MAP <65 mmHg is considered a reasonable physiological definition of arterial hypotension, as this threshold is associated with increased post-operative morbidity.4

Speaking on the performance of HPI in clinical practice was Denise Veelo from the University of Amsterdam, the Netherlands. She led a key study investigating the HPI early warning system for its ability to predict hypotension shortly before it occurs in the operating room.

Results of the single-center study in patients undergoing non-cardiac surgery showed a median time of hypotension per patient of eight minutes in the intervention group compared to 32.7 minutes in the control group, for a median difference of 16.7 minutes (95% CI, 7.7–31.0 minutes; p < .001).5

“There was good compliance with the study protocol, and we found that the HPI combined with a diagnostic guidance protocol was feasible,” said Dr. Veelo, adding that “the HPI can change practice in the treatment of hypotension in surgical patients.”

She continued: “I think it will be interesting to see how the HPI changes practice in the ICU. I think it will predict hypotension in the ICU patient as well as it does in the operating room, but the population and work setting are very different.”

She highlighted that, the full benefit of using the HPI algorithm depends not only on the prediction of arterial hypotension, but also on how it is treated. To this end, the prediction of HPI as an early alarm of hemodynamic instability needs to be combined with a therapeutic protocol based on information provided by the monitor and other hemodynamic parameters.

StO2: a complementary tool for checking resuscitation status

Jaume Mesquida, an intensivist at the Hospital de Sabadell, Barcelona, Spain, discussed a complementary technology, known as ForeSight, designed to measure tissue oxygenation.

To achieve this, a small optical sensor is placed on the tissue of interest to
provide information on oxygenation. Dr. Mesquida mainly uses the monitor to measure muscle oxygen saturation (StO2) on the forearm or thenar eminence during a vascular occlusion test (VOT).

“This sensor measures oxygenation in the organ directly, which depends on perfusion and local metabolic status,” he explained. “By conducting a three-minute VOT we can determine metabolic function, as well as information on endothelial functioning, observing the re-oxygenation rate (ReO2), which depends on microvascular reactivity.”

There are three important parameters in the monitoring of tissue oxygenation: baseline tissue oxygenation, which provides information on perfusion and metabolic rate; tissue de-oxygenation, which indicates metabolic rate; and microvascular reactivity, which indicates endothelial function. “All of these are a measure of the global status of the patient,” said Dr. Mesquida. The body shuts down the non-vital organs first, so by finding hypoperfusion here it can determine whether there might be a problem in the vital organs.

In a patient with shock, ensuring restoration of oxygen to the tissues is an essential component of the hemodynamic resuscitation, he pointed out. “While current, advanced hemodynamic monitoring will help us to achieve an adequate cardiac output and perfusion pressure, the StO2 monitoring will help us to determine when this resuscitation is truly achieved by improving the oxygenation of the tissues.”

“While current advanced hemodynamic monitoring will help us to achieve an adequate cardiac output and perfusion pressure, StO2 monitoring will help us to determine when this resuscitation is truly achieved.”

JAUME MESQUIDA

Thus far, StO2 monitoring has demonstrated value in monitoring tissue oxygenation in three patient groups: septic shock (for prognosis); trauma; and those being weaned off mechanical ventilation.

In fact, Dr. Mesquida noted that this third scenario was where tissue oxygenation monitoring was most likely to be used first. “Weaning off mechanical ventilation is a challenge because we need to ensure the patient has the cardiovascular and respiratory performance to breathe alone. During extubation, around 20% of patients fail and need reintubation. If they show failure in tissue oxygenation, this is associated with higher rates of mortality, pneumonia and other complications.”

Endothelial cells are often rendered dysfunctional as a result of infection – COVID-19 is a case in point. Alterations in vascular reactivity could be the first sign that the endothelial cell is failing, and the tissue oxygenation monitor used during a VOT can determine how the tissue reacts to ischemia, providing a direct correlation with endothelial function.

“If you stop blood flow entering a region, and the endothelial cells are working properly, then they’ll respond with microvascular reactivity by dilating the arteries in the low oxygen environment,” explained Dr. Mesquida. “In a septic patient, the endothelial reactivity is dysfunctional, and this is associated with mortality.”

In the future, microcirculation is likely to be a new target for monitoring in septic shock patients. “We’ve seen this in COVID-19 patients. Endothelial cells are a target of the virus and of the inflammatory activity seen in this disease. In our patients, we used the tissue oxygenation monitor and have observed the same effect on endothelial cells in COVID-19 as in patients with septic shock.”

In a patient with shock, ensuring restoration of oxygen to the tissues is an essential component of the hemodynamic resuscitation, he pointed out in conclusion: “While current advanced hemodynamic monitoring will help us to achieve an adequate cardiac output and perfusion pressure, StO2 monitoring will help us to determine when this resuscitation is truly achieved by improving the oxygenation of the tissues.”

For more information, please visit: https://www.edwards.com/gb/devices/hemodynamic-monitoring PP--EU-2727 v1.0

References
ROX index provides novel way to predict HFNC failure

Predicting high-flow nasal cannula (HFNC) failure was explored yesterday at ISICEM, with Oriol Roca (Vall d’Hebron University Hospital, Barcelona, Spain) discussing his insights surrounding the therapy.

Dr. Roca spoke to ISICEM News to offer a summary of his key messages, as well as sharing his latest research into respiratory indices1 that may help identify early signs of success, or failure, when using HFNC therapy.

By way of introduction, what are the core benefits of HFNC therapy, and where was (or still is) the unmet need in predicting its success?2

HFNC therapy has several physiological benefits. It decreases administered oxygen dilution with room air, increases airway pressure and end-expiratory lung volume, reduces dead space, and decreases inspiratory effort. Moreover, it is extremely comfortable.

It has been shown that, compared with conventional oxygen, it may decrease the need for intubation in patients with acute hypoxic respiratory failure. However, one of the main concerns with its use is that it may mask the signs of clinical deterioration in those patients who are going to fail, leading to the possibility of delaying intubation – which has been associated with worse outcomes.

Therefore, investigation into its early use (and ease of use) at the bedside, and the predictive factors which may identify, as early as possible, patients who are likely to fail with HFNC therapy is highly important.

Your team introduced the ROX (respiratory rate–oxygenation) predictive index.3 Could you briefly introduce the index, and its utility as a ‘best description’ of a respiratory status?

The ROX index is defined as the ratio between oxygenation (measured by SpO2/FiO2) and respiratory rate. It was based in the idea that a predictive index should reflect true pathophysiological determinants of HFNC-therapy failure. Thus, an index predicting the need for mechanical ventilation should be calculated from the measured respiratory variables assessing respiratory failure – i.e.

those that significantly differ in HFNC patients who fail, compared to those who succeed.

The aim was to obtain an additive effect of the different variables that composed the index, increasing its capacity to discriminate. With this approach, the diagnostic accuracy of the ROX index to identify the failure or success of HFNC therapy was better when compared to other previously described methods.

What were the take-home messages from the study you published in 2016?1

I think that the most important conclusion from the study was that the ROX index was a feasible and easy-to-use index that was a determinant of HFNC-therapy success in patients with pneumonia. Also, it could be easily applied at the bedside, helping in the day-to-day clinical decision-making process.

As the ROX index may help in the early identification of patients with low- vs. high risk of failure, it could have an important role to play in making sure there is no delay in the decision to intubate. In other words, intubate as early as possible when clinical deterioration starts to appear in patients who are going to fail HFNC therapy. This early decision is crucial as it minimizes the risk of delayed intubation, which has been associated with worse outcomes.

You mention your work was in pneumonia, specifically. Has the ROX index found a place outside non-COVID patients with pneumonia now? Or is work very much in progress?

It was described and validated in non-COVID patients with pneumonia. Now, we have data about its use in COVID-19 patients. Here, we saw that ROX also works – and does so with similar thresholds for prediction – as it did previously in non-COVID patients.

What about the role of HFNC in immunocompromised patients? Is it fair to say that as of yet there seems to be little or no effect on mortality? Immuno compromised patients are a very special population, and their outcome is highly influenced by the baseline disease. This may be an important reason to explain, at least partially, why HFNC therapy does not have an effect in preventing the need for intubation and mechanical ventilation in these patients.

But it should be also noted that the effect might not the same in a patient with leukemia who has received an allogeneic stem-cell transplant, and is presenting with graft vs. host disease, compared to, say, a lung transplant patient with a bilateral pneumonia or acute rejection.

What are the important next steps for HFNC therapy? Do you have new research in the pipeline which you can tell us about?

In terms of the therapy itself, I think that the next steps will be focused on personalizing and individualizing the treatment according to patient status. We are currently performing the ROX-1 trial,4 which is evaluating whether the use of an algorithm incorporating the ROX index, compared to standard-of-care, affects the time to intubation in patients with acute hypercapnic respiratory failure supported with nasal high-flow therapy.

The primary endpoint is the proportion of patients who will be intubated in the first 12 hours after inclusion, compared between the two groups.

References
Secondary infections must be prevented

Preventing secondary infections in COVID-19 patients will be addressed tomorrow by Massimo Giradis, a professor of anesthesia and intensive care medicine at Policlinico di Modena within the University of Modena and Reggio Emilia (Modena, Italy). In his talk, he will focus on the prophylaxis of secondary infections.

“The high prevalence of secondary infections in COVID-19 critically ill patients has been reported since the first wave in 2020,” said Professor Giradis. “As in other severe diseases, the impact of secondary infections on mortality is relevant, thus specific strategies should be put in action to prevent and treat these infections.”

Professor Giradis will focus on the potential benefits and risks of prophylaxis using published literature. In addition, he plans to preview some data (under evaluation for publication) on viral infections.

One paper, establishing the extent to which COVID-19 patients experienced secondary infections, was published this year. The research looked at adult patients with severe COVID-19 admitted to eight Italian hub hospitals between February and May 2020. Researchers found that critically ill patients with COVID-19 were at high risk for hospital-acquired infections (HAIs), especially ventilator-associated pneumonia (VAP) and bloodstream infections resulting from multidrug-resistant organisms.

Of the 774 included patients, 359 patients (46%) demonstrated 759 HAIs. Such HAIs prolonged mechanical ventilation and hospitalization, and HAIs complicated by septic shock almost doubled mortality (52% vs. 29%).

Likewise, another multicenter, observational, retrospective study assessed the incidence rate of VAP in 586 COVID-19 patients in the ICU between February to May 2020. It found that VAP is frequent in critically ill COVID-19 patients. Deep respiratory cultures were seen in 45% of patients. The most frequent organisms were Pseudomonas aeruginosa (35%) and Staphylococcus aureus (23%). Importantly, the related high fatality was likely the sum of the unfavorable prognostic impacts of the underlying viral and superimposed bacterial diseases according to the researchers (which included Professor Giradis).

Importantly, at ISICEM, Professor Giradis will present his research on bacterial and fungal infections. His team have reported on two fatal cases of acute liver failure secondary to herpes simplex virus 1 infection in COVID-19 patients, following a treatment of tocilizumab and corticosteroid therapy. If such patients had been screened, the outcomes may have been different, he notes: “Prompt recognition of herpes simplex virus 1 reactivation in patients undergoing immunomodulatory treatment, may have potentially relevant clinical consequences.”

Professor Giradis plans to talk about innovative ways to pre-empt such infections. “I will discuss the rationale for prophylaxis with selective digestive decontamination (SDD) in intubated patients for preventing VAP,” he explained. “I will also consider prophylaxis or pre-emptive therapy in patients at high risk for invasive Aspergillosis.”

However, more research should be conducted on SDD and fungal infections to ensure there are a wider range of appropriate prophylaxes available. “Real-world practice in prevention, identification and treatment of secondary infections is still quite heterogeneous,” he advised. “I guess that appropriate research will overcome the remaining doubts on the bacterial, fungal and viral infections in high-risk ICU patients as COVID-19.”

Professor Giradis relayed that the prevention of infections in critically ill patients has been discussed for many decades, and many different positions have been taken in terms of strategies. “For a better understanding of the problem and the potential role of prophylaxis in COVID-19 ICU patients, I usually compare the risk of infections in surgical patients with the risk in COVID-19,” he said. “And, as is also well known, in surgical patients we commonly use antibiotics for prophylaxis.”

But what is paramount, in his opinion, is better hand hygiene and the other infection-control strategies. “This is the cornerstone of infection prevention in hospital and particularly in the ICU.”

In closing, Professor Giradis asked that delegates be mindful of evidence-based strategies. “Please help prevent secondary infections in COVID-19 (and in other critically ill patients with high susceptibility for infections) by scrupulous infection-control strategies,” he said. “I’d urge you to use prophylaxis methods with good or reasonable evidence of benefit.”

References
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