ICU

MANAGEMENT & PRACTICE

INTENSIVE CARE - EMERGENCY MEDICINE - ANAESTHESIOLOGY

VOLUME 21 - ISSUE 3 - 2021

Oxygen Therapy

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Oxygen Therapy

Supplemental oxygen is an essential component of intensive care and is a commonly used therapy worldwide. The primary goal of oxygen therapy is to prevent hypoxaemia. Since oxygen is usually widely available (except in special circumstances such as during the COVID-19 pandemic) and is relatively inexpensive, it is frequently used in patients with declining oxygen saturation.

However, while oxygen therapy may be critical for some patients, it is important to ensure it is not used unnecessarily or administered longer than required. Most of the time, it is better to adopt a less is more strategy because there is now sufficient evidence to show that excessive oxygen therapy may, in fact, be harmful to some patients. Management of hypoxaemia can be a challenge, but while interventions for mitigating hypoxaemia may be necessary, the possibility of harm from excess oxygen administration cannot be overlooked. In critical care, the appropriate dose of oxygen, duration of oxygen therapy and specific use and application in different patient populations remain vague. Therefore, it is important to establish realistic and rational oxygen therapeutic goals for individual patients and ensure a balance between oxygenation targets so that they are neither too conservative nor too liberal.

In this issue, our contributors discuss **Oxygen Therapy** in the ICU. Jörn Grensemann and Samir Sakka provide an overview of current recommendations for oxygen administration in different patient populations and discuss optimal oxygen target values, while Bruno Pastene and Marc Leone discuss the benefits and harms of supplemental oxygen administration in the intensive care unit.

Samuele Ferrari, Alessandro Isirdi, Erika Taddei and co-authors talk about oxygen therapy and mechanical ventilation in patients with COVID-19 and discuss steps to choose the right therapeutic strategy. Audrey De Jong, Clément Monet and Samir Jaber discuss apnoeic oxygenation and how it can be used in critically ill patients without replacing preoxygenation.

Vincenzo Russotto, Sheila Myatra and co-authors provide an update on the findings of the INTUBE study, a large international prospective observational study on peri-intubation adverse events in critically ill patients. Frederic Michard discusses the clinical applications of pulse oximetry and how it can help improve the quality of care in patients with respiratory and circulatory disorders, particularly those with COVID-19.

Orlando R. Pérez-Nieto, Eder I. Zamarron-Lopez, José Antonio Meade-Aguilar and co-authors talk about the challenges of respiratory therapy in patients with COVID-19 and highlight the importance of evidence-guided protective mechanical ventilation to reduce mortality while Kunal Karamchandani, Ashish Khanna and co-authors discuss tracheal intubation in critically ill patients and the steps that can reduce the antecedent morbidity and mortality.

Joanna Poole provides an overview of hyperoxia, the effect of reactive oxygen species on biological processes and tissues and effective strategies for oxygen therapy. Yassir Aarab and co-authors discuss diaphragm ultrasound and how it can be used for easier assessment of diaphragmatic function and a better understanding of pathophysiological processes afflicting the diaphragm.

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IN EVERY ISSUE

COVER STORY

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Oxygen Therapy in Intensive Care Medicine

An overview of current recommendations for oxygen administration in different patient populations and a discussion on optimal oxygen target values.

Oxygen is the most commonly used substance in hospitals today. After its discovery around 1771 by the German-Swedish pharmacist Carl Wilhelm Scheele and the English chemist Joseph Priestley, oxygen underwent rapid adoption as a drug in medicine and was already used in 1783 for the treatment of tuberculosis patients and in newborn asphyxia. However, oxygen synthesis remained problematic and sufficient amounts of oxygen only became available after the development of an air separation process by C. von Linde in 1902 that is still in use today. The Lubeca valve patented in 1889 by J. H. Draeger and his son B. Draeger was originally intended for the dosage of carbon dioxide in draught beer dispensers but served equally well as a pressure regulator for the dosage of medically indicated oxygen from compressed gas cylinders (Koehler et al. 2011). But soon, the first reports of oxygen toxicity surfaced. Laboratory mammals were exposed to different oxygen atmospheres over varying periods of time and e.g. suffered from seizures, pulmonary oedema or perished. Along with the spirit in these times, researchers verified the results on themselves, although these experiments were usually aborted before serious harm was done (Bornstein 1912).

Today, our understanding of oxygen has grown significantly and is not limited to the observation of its toxic effects. We know that in the blood, oxygen is predominantly transported by haemoglobin and that due to the sigmoidal binding curve, only little of oxygen is transported above a partial pressure of approximately 80 mmHg while the overall physically dissolved oxygen remains negligible under normobaric conditions. In the respiratory chain, oxygen is reduced by cytochrome c oxidase, contributing to the formation of a mitochondrial transmembrane gradient for protons, which is required for the synthesis of adenosine triphosphate. If sufficient oxygen is not available, the respiratory chain is interrupted, and energy production is limited to anaerobic glycolysis. Clinically, hypoxia results in lactic acidosis and necrosis of hypoxia-sensitive tissues such as central nervous system cells. Therefore, oxygen is vital for primates and its application life-saving in emergency situations when hypoxaemia is present (Grensemann et al. 2021).

However, sometimes we seem to have forgotten the results of early medical research that has pointed out adverse effects in terms of oxygen toxicity. Often enough, we see blood gas analyses in critically ill patients with partial pressures of oxygen far above the physiological range, despite our understanding that hyperoxia leads to an increase of free oxygen radicals (reactive oxygen species, ROS) that leads to cell damage resulting in apoptosis or necrosis. Additional factors such as an infection, in which pathogen associated molecular patterns (PAMPs) are released, further promote cell damage. Both apoptosis and necrosis lead to the release of further mediators and danger associated molecular patterns (DAMPs), which in turn, together with oxygen free radicals, cause further cell damage and thus maintain a vicious circle (Helmerhorst et al. 2015). The formation of ROS is favoured by a high oxygen partial pressure.

But is this clinically relevant as well? Looking at diseases in which a vascular occlusion is causative as in myocardial infarction or ischaemic stroke, at first sight it seems logical to increase oxygen tension in an attempt to improve oxygenation of the ischaemic tissue. However, this conversely might lead to the demise of tissue at risk by the vicious cycle explained above. With respect to the currently available data, this second mechanism seems to be in the lead.

In the prospective randomised AVOID trial in patients with ST-segment elevation myocardial infarction, one group received oxygen when oxygen saturation as measured peripherally by pulse oximetry was < 94%, whereas the other group received a fixed dose of 8 L/min (Stub et al. 2015). After six months, the fixed-dose oxygen group had a higher serum creatine kinase, a higher re-infarction rate as well as arrhythmias, and larger infarct size on magnetic resonance imaging.

In the DETO2X-AMI study, the oxygen group received a fixed dose of 6 L/min of oxygen, and the other group received oxygen only when peripherally measured oxygen saturation was < 90% (Hofmann et al. 2017). Patients with non-ST-segment elevation myocardial infarction (NSTEMI) were also included. Mortality did not differ, nor did the rate of reinfarction, atrial fibrillation, or cardiogenic shock.

In summary of these two studies, it must be postulated that hyperoxia may be harmful in myocardial infarction, but at least it has no benefit. Therefore, supplemental oxygen should not be given as long as peripheral oxygen saturation is ≥ 90%, as is now recommended by the European and American guidelines.

Furthermore, oxygen has a vaso-constrictive effect not only on the coronary system, presumably by antagonising nitric oxide (NO), which acts as a vasodilator. It could be shown that in patients without coronary artery disease, an acetylcholine provocation test induces coronary spasm in conjunction with breathing pure oxygen but not with breathing ambient air (McNulty et al. 2005).

Concerning ischaemic stroke, several prospective randomised trials with a combined total of over 8,300 patients investigated conventional oxygen administration in non-hypoxaemic patients with ischaemic stroke. The largest study of these was the SO2S trial with over 8,000 patients alone, in which one group received oxygen only at night, one group received oxygen continuously, and one group received no oxygen. However, a minimum oxygen saturation of 94% was maintained in all groups. There was no difference in outcome measured according to the modified Rankin scale (Roffe et al. 2017). This approach has also found its way into the guidelines, which recommend maintaining a target oxygen saturation between 94% and 98% in ischaemic stroke.

What are the actual data when focusing on patients without underlying ischaemia? For mechanically ventilated intensive care patients, a retrospective analysis over ten years ago identified a U-shaped relation between oxygen partial pressure and mortality with the highest survival between partial pressures of approximately 65 and 80 mmHg (de Jonge et al. 2008). Interestingly, these limits are close to the values one would expect from a strictly theoretical point of view: below 60 mmHg, oxygen saturation drops below 90% with an increasing risk for hypoxia and above 80 mmHg only little additional oxygen may be transported while the formation of ROS increases. Several randomised controlled trials have been conducted in this patient population since then trying to identify the optimal range for the oxygen partial pressure and to prove superiority for this target range.

The OXYGEN-ICU study with 434 patients demonstrated that ICU and in-hospital mortality were lower when treated with a median partial pressure of oxygen of 87 mmHg vs. 102 mmHg [ICU mortality 11.6% vs. 20.2%, relative risk 0.57, p=0.01] (Girardis et al. 2016). It must be noted though that this study was terminated prematurely due to an earthquake, as no further patients could be included due to the degradation of the necessary infrastructure. Furthermore, although randomised, patients differed in baseline characteristics with a slightly higher predicted mortality in the liberal oxygen group.

The HYPER2S trial in ICU patients with sepsis was stopped for safety reasons after 442 patients due to a significantly higher rate of severe adverse events in the hyperoxia group [85% vs. 76%, p=0.02, including muscle weakness, atelectasis] (Asfar et al. 2017).

> **“even a relatively short exposure to hyperoxia over a few hours could have negative effects on outcome”**

In the ICU-ROX study, no difference in mortality was found between the groups in 965 patients. However, one might argue that this study compared like with like as virtually no difference existed between the two groups: one group aimed at an oxygen saturation of 90-97% which resulted in a mean partial pressure of approximately 80 mmHg, while the other group targeting an oxygen saturation of > 90% reached a partial pressure of approximately 90 mmHg (Mackle et al. 2020).

Very recently, the LOCO2 study comparing groups with an arterial oxygen partial pressure of 55-70 and 90-105 mmHg was terminated after the enrollment of 205 of 850 originally planned patients, because it did not appear likely that a difference in the primary outcome measure, the mortality at day 28, could be reached (Barrot et al. 2020). Furthermore, safety reasons were brought up. A slight difference in one of the secondary endpoints, the mortality at day 90 was higher in the lower oxygen group (44.4% vs. 30.4, difference: 14% with 95% confidence interval 0.7 to 27.2). For the interpretation of the results, it is noteworthy that this study included ARDS (acute respiratory distress syndrome) patients with a p/F-ratio of around 120 ± 50 mmHg and an inspiratory fraction of oxygen of 0.8 ± 0.2 in both groups. No other study had included patients with such severe disturbances in pulmonary gas exchange, so far. For interventions as e. g. suctioning, no preoxygenation was performed and this presumably induced hypoxia on several occasions that should be avoided.

The O2-ICU study from The Netherlands (clinicaltrials.gov NCT02321072), comparing 60-90 with 105-135 mmHg is currently still recruiting patients.

The question of the optimal oxygen partial pressure for ventilated intensive care patients currently remains unanswered, but it is undisputed that hyperoxia certainly offers no benefit for this group of patients.

For acute exacerbated chronic obstructive pulmonary disease (COPD), the main focus of treatment undoubtedly lies on the relief of the fatigued respiratory musculature, preferably by non-invasive ventilation. However, special attention should be given to therapy with oxygen as a too liberal application has been shown to have adverse consequences. Oxygen application can result in a further increase in arterial partial pressure of carbon dioxide with subsequent CO2 narcosis. For a long time, the mechanism was thought to be due to desensitisation of the peripheral chemoreceptors in the glomus caroticum involved in respiratory control, caused by the chronic hypercapnia that occurs in COPD. In this case, much of the respiratory drive would be triggered by hypoxaemia, which is reduced by oxygen administration; this would result in a decrease in respiratory minute volume with consecutive hypercapnia. According to experimental studies, this mechanism may only be responsible for a fraction of the observed hypercapnia, with a reduction in respiratory minute volume of approximately 15% and may for example, mathematically account for only 5 mmHg of an increase in carbon dioxide partial pressure of 23 mmHg. Most of the hypercapnia is due to changes of the ventilation/perfusion ratio in the lungs. Oxygen application suppresses hypoxic vasoconstriction, which is important for maintaining an optimal ventilation/perfusion ratio, and results in perfusion of sub-optimally ventilated alveoli and an increase in alveolar dead space. Furthermore, the Haldane effect is

Patient Population	Recommendation	Medical Society
ICU patients on mechanical ventilation	O_2 administration as restrictive as possible, target: SpO_2 90-94% or paO_2 60-80 mmHg	AWMF/German Society of Anesthesiology and Intensive Care Medicine (DGAI)
Acute exacerbated COPD	Target: SpO_2 88-92%	British Thoracic Society
Myocardial infarction	STEMI: O_2 administration if SpO_2 < 90%	European Society of Cardiology (ESC) and American Heart Association (AHA)
	NSTEMI: O_2 administration if SpO_2 < 90%	European Society of Cardiology (ESC) and American Heart Association (AHA)
Cardiogenic shock	Target: SpO_2 94-98%	German Society of Cardiology (DGK)
Post-resuscitation	O_2 administration if SpO_2 < 94%, target: SpO_2 94-98%	European Resuscitation Council (ERC)
	Administration as restrictive as possible to establish SpO_2 ≥ 94%	American Heart Association (AHA)
Stroke	No routine administration of O_2, target: SpO_2 > 94%	American Stroke Association
Carbon monoxide (CO) poisoning	Administration of 100% of oxygen until COHb < 3% Administration of 100% of oxygen until patient free of symptoms, hyperbaric oxygen treatment should be considered for COHb 25-30%	AWMF (awmf.org/leitlinien/detail/anmeldung/1/ll/040-012.html) Centers for Disease Control and Prevention (CDC)

Table 1. Recommendations for adjusting oxygen administration. Adapted from Grensemann et al. 2021
ICU= intensive care unit, COPD= chronic obstructive pulmonary disease, SpO_2= oxygen saturation as obtained by pulse oximetry, paO_2= arterial oxygen partial pressure, STEMI= ST elevation myocardial infarction, NSTEMI= non-ST elevation myocardial infarction, AWMF= The Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften)

involved, which describes that deoxygenated haemoglobin is able binding carbon dioxide in form of carbamino compounds via amino groups and release it after oxygenation in the lungs. In hypercapnia as present in acute exacerbated COPD, the ability of haemoglobin to bind further carbon dioxide is reduced. Normally, the carbon dioxide would be released in the lungs and exhaled, but this is no longer possible in these patients due to the already maximal respiratory effort. Oxygen administration results in a reduction in the binding capacity of haemoglobin for carbon dioxide with additional release of already bound carbon dioxide, which then also increases hypercapnia (Abdo and Heunks 2012).

That this is clinically relevant could be shown in a randomised trial: 405 patients were treated prehospitally with titration of oxygen to an oxygen saturation between 88-92% or with a fixed oxygen therapy of 8-10 L/min (Austin et al. 2010). In the group treated with titrated oxygen, mortality was significantly lower (2% vs. 9%), likewise acidosis was higher for liberal oxygen administration, and mean pH was 0.12 lower than in the group receiving titrated oxygen. This trial resulted in recommendations to titrate oxygen in acute exacerbated COPD to achieve a target range for the oxygen saturation between 88%-92% [UK recommendation as well as international recommendation of GOLD (Global Initiative for Chronic Obstructive Lung Disease)].

Although these examples show that oxygen should be applied cautiously, every coin has two sides. In cases of carbon monoxide intoxication, the pathophysiological quandary of a 200-fold affinity of carbon monoxide to haemoglobin as compared to oxygen must be solved to preserve oxygen transport and prevent from tissue hypoxaemia. As carbon monoxide competitively displaces oxygen from haemoglobin the solution is to increase oxygen tension and thus shift the chemical flow equilibrium to the oxygen side. The half-life of the carboxyhaemoglobin is decreased from 320 min in breathing ambient air to 74 min when breathing pure oxygen. The half-life may be further decreased under hyperbaric conditions [e. g. 20 min at 2.5 bar] (Rose et al. 2017; cdc.gov/disasters/co_guidance.html). However, transport of a critically ill patient to a hyperbaric chamber may be a cumbersome challenge and as no consensus could be reached so far, is regarded as optional.

Besides carbon monoxide intoxication, patients with cardiac arrest should be ventilated with pure oxygen as this increases the chances for a return of spontaneous circulation. However, after successful resuscitation, it is recommended to lower oxygen partial pressures to a physiological range to prevent from ROS mediated cell damage.

One question that has received limited attention so far is if oxygen could exhibit a dose-effect relationship. We often create a short-term hyperoxia in the context of preoxygenation before medical procedures as e.g. endotracheal suctioning or endotracheal intubation. This leads to a denitrogenisation of the pulmonary functional residual capacity, creating an "oxygen reserve" to prolong apnoea tolerance and thus prevent hypoxaemia. Currently, it is not known whether this short-term hyperoxia may already have negative effects on the outcome of these patients, but should, on the other hand, be balanced against the deleterious effects of hypoxia.

Regarding this question, one retrospective study analysed approximately 700 patients in an emergency department that were ventilated for a median of approximately 5.5 hours before being transferred to an intensive care unit (Page et al. 2018). Patients were categorised based on partial pressures of oxygen. The highest mortality of approximately 30% was found in the hyperoxia group (pO2 > 120 mmHg); in contrast, mortality in the normoxia group (pO2 60-120 mmHg) was only approximately 20%. The result was statistically significant. Although this is a retrospective evaluation, these data may provide a first indication that even a relatively short exposure to hyperoxia over a few hours could have negative effects on outcome. However, a change in clinical practice is not warranted from these data; presumably, the benefit of preoxygenation on the avoidance of hypoxia outweighs the disadvantage of oxygen toxicity. Most recently, the randomised, prospective HOT-ICU study having enrolled 2928 patients from 35 ICUs in Denmark, Switzerland, Finland, the Netherlands, Norway, UK and Iceland between 2017 and 2020 has been published. Control group (targeted PaO2 of 90 mmHg) and intervention group (targeted PaO2 of 60mmHg) were similar, i.e., pneumonia was the main acute illness: 57.7% vs 57.4%. As main result, 90-day all-cause mortality was not significantly different (42.9% vs 42.4%, p = 0.64). Furthermore, secondary outcomes (alive without life support, alive after hospital discharge) and serious adverse events (shock, myocardial ischaemia, ischaemic stroke and intestinal ischaemia) were comparably often. For illustration, current recommendations for adjusting oxygen administration in different patient populations are summarised in Table 1.

Although the quest for optimal oxygen target values is still ongoing and a possible dose-effect relationship should be elucidated in the future, it is essential to implement oxygen targets in clinical practice as hyperoxia may be harmful or at least, have no benefit (Grensemann et al. 2018). The implementation may prove difficult due to long-time engraved mental models that only hypoxia increases mortality. On the other hand, a step-by-step implementation strategy accompanied by appropriate interprofessional training has been proven safe and feasible (Helmerhorst et al. 2016).

Conflict of Interest

None. ■

References

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For full references, please email editorial@icu-management.org or visit https://iii.hm/1a0f

Vasopressor Management in Septic Shock: General Overview and Personalised Approaches

This article summarises the proceedings of an ESICM webinar in which two experts discuss vasopressor therapy and its fundamental role in the treatment of septic shock-induced hypotension. They provide an overview of severe septic shock, the benefits of second-line vasopressors and their use in COVID-19 patients.

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Vasopressors in Severe Septic Shock - An Overview

(Jacob C. Jentzer)

Vasopressors are classified as drugs that are designed to increase arterial pressure by peripheral vasoconstriction. There are two types of vasopressors: pure vasoconstrictors and catecholamines. Pure vasoconstrictors only affect the peripheral vessels and do not have direct cardiac inotropic effects. Examples include phenylephrine which is a pure alpha-1 agonist, as well as vasopressin and angiotensin-II. These drugs have an important advantage as they have no direct cardiac toxicity (Jentzer 2015).

Catecholamines are more commonly used as inoconstrictors since, in addition to causing peripheral vasoconstriction, they exert inotropic effects by activating beta receptors. These beta ionotropic effects increase cardiac output and heart rate, which might be beneficial but also increase the risk of cardiac toxicity, especially at higher doses. Drugs such as epinephrine and dopamine have much stronger beta inotropic effects than norepinephrine, which predominantly has beta inotropic effects at higher doses (Jentzer 2015).

In patients who do not respond adequately to vasopressors, two dominant mechanisms may be involved. The first is related to metabolic abnormalities that can interact to cause alpha one receptor desensitisation through a number of mechanisms. Examples include the systemic inflammatory response, acidaemia or lactic acidosis. These can cause dysregulation of nitric oxide metabolism and accumulation of reactive oxygen species, both of which can act through a number of mechanisms to impair the vascular responsiveness to catecholamines. The other mechanism is related to absolute or relative deficiencies in vasopressin, angiotensin-II and corticosteroids. It is important to remember these different mechanisms, since potential treatments are available for patients with refractory shock (Jentzer 2018).

Vasopressors have a better safety profile at lower doses. As higher doses are given, the potential for toxicity increases. In patients who require high doses of catecholamines, there is a risk of off-target cardiac toxicity due to beta receptor activation. Therefore, the best approach would be to use drugs with different mechanisms at lower doses to maximise both safety and efficacy. This approach is often referred to as the vasopressor toolbox approach. In patients who do not respond well to or do not tolerate an initial catecholamine, it is recommended that a second agent should be added - predominantly a catecholamine-sparing drug - to improve the clinical status (Levy 2010).

Vasopressor requirements are used as a simple metric of shock severity. Burstein et al. (2021) show that patients requiring more than 0.3 µg/kg/min of norepinephrine are at a very high risk of death. Once a level of 0.5 µg/kg/min or above is reached, the outcome will be fatal in the majority of patients. Therefore, this has been used as a threshold to define refractory shock (Burstein 2021).

Norepinephrine is the first-line vasopres-sor drug not only for septic shock but for most forms of shock, including cardiogenic shock. The Surviving Sepsis Campaign guidelines recommend norepinephrine as the first-line vasopressor for septic shock, and there is sufficient evidence to support this recommendation (SSC Guidelines; Rhodes ICM 2017).

In a secondary analysis of the VASST study (Russell et al. 2008), it was observed that adding on vasopressin to reduce norepinephrine requirements was associated with lower mortality in patients who had less severe shock at baseline and those who also received corticosteroids. Vasopressin was also associated with a lower risk of acute kidney injury (AKI). Vasopressin may be a better choice when given as a second vasopressor to reduce catecholamine doses.

When using vasopressors in septic shock, severity should be the deciding factor. For patients with mild septic shock, defined as a norepinephrine requirement <0.1 µg/kg/min, norepinephrine is sufficient, and there is no need for secondary vasopressors in these patients as long as they are managed with adequate antibiotic source control and fluid resuscitation.

In patients not responding to low doses of norepinephrine and who may need higher doses up to 0.2 µg/kg/min, it is important to determine why they are not responding. It must be ensured that the patients do not have concomitant cardiac dysfunction, which could possibly result in a mixed cardiogenic septic shock state. It is also important to address reversible metabolic abnormalities before starting a second vasopressor. In patients with a more severe septic shock where they require a dose of 0.2 µg/kg/min of norepinephrine or higher, it might be beneficial to add a second vasopressor. A second vasopressor should be added before patients develop resistant or refractory septic shock, defined as a norepinephrine requirement of >0.3 µg/kg/min or >0.5 µg/kg/min.

Adding dopamine or phenylephrine when a patient is refractory despite significant doses of norepinephrine is not a recommended strategy as the response is often poor. Because of its strong beta inotropic effects, epinephrine can increase cardiac output, which can be advantageous for patients with low heart rate, cardiac output or venous oxygen saturation. However, it is associated with significant cardiac toxicity with myocardial ischaemia, arrhythmias, and tachycardia. It can also cause increases in lactate and glucose levels. In contrast, vasopressin and angiotensin-II have similar haemodynamic effects and are free from major cardiac toxicity. They do not cause off-target metabolic abnormalities and may be associated with better outcomes when added on to catecholamines. Vasopressin can be useful when the arterial pH is low, and catecholamine receptors are not effective.

In another analysis, researchers investigated the cost-effectiveness of second-line vasopressors. They compared escalating norepinephrine doses with the use of norepinephrine plus adjunctive vasopressin or angiotensin II for septic shock. Adjunctive vasopressin demonstrated to be the most cost-effective therapy and resulted in a higher ICU survival rate at less cost (Lam 2020).

When individualising second-line therapies, it is recommended to use epinephrine in patients with inappropriately low cardiac output, a low SvO_2 or inappropriately low heart rate. Many patients with sepsis either have pre-existing cardiomyopathy, septic cardiomyopathy or cor pulmonale lung disease and may require inotropic support. In these cases, dobutamine can be used, but can cause excessive vasodilation, aggravating the problem. Still, in patients with severe lactic acidosis or uncontrolled hyperglycaemia with diabetic ketoacidosis, epinephrine is not recommended, and the default drug should be vasopressin.

If catecholamine doses are rising rapidly, it is important to confirm that the patient is suffering from septic shock and to ensure source control and appropriate antibiotics. It is also important to identify treatable and reversible metabolic abnormalities. Rapidly rising catecholamine doses suggest that catecholamines are not effective. This should prompt consideration of an additional catecholamine-sparing vasopressor and a corticosteroid. It is important to note that catecholamine sparing vasopressors may not be effective if the patient is not deficient in these signalling molecules.

> **“the Surviving Sepsis Campaign guidelines recommend norepinephrine as the first-line vasopressor for septic shock”**

Overall, with early septic shock, it is important to identify and treat the underlying aetiology. Appropriate fluid resuscitation guided by optimal measures of fluid responsiveness should be used. Norepinephrine should be the drug of choice as long as high doses are not needed (<0.2 µg/kg/min). In patients with severe septic shock requiring > 0.2 µg/kg/min of norepinephrine, secondary contributing factors must be identified to ensure the patient is not hypovolaemic, acidaemic or hypocalcaemic. Vasopressin should be added to norepinephrine. If a patient has borderline or low cardiac output, epinephrine is a reasonable alternative. If one or both of those drugs do not work, angiotensin-II can be used, especially if the patient requires >0.3 µg/kg/min of norepinephrine after vasopressin has been added.

Second-line Vasopressor: Benefits and COVID-19 Cases

(Arthur R.H. van Zanten)

Patients on high levels of vasopressors have high mortality rates. This is primarily due to the severity of illness. However, there is sufficient clinical evidence on the harmful effects of catecholamines. They can be injurious to the myocardial cells, induce oxidative stress and have immunomodulating effects. Recent studies show that high-dose norepinephrine may dysregulate the innate immune system. In late phase recovery of sepsis, sepsis-induced immunoparalysis may occur, which can further induce secondary infections. All these factors can have a significant impact on clinical outcomes (Stolk 2016).

However, vasopressin does not have this effect. In the late phase of septic shock, there may be vasopressin deficiency. Vasopressin not only has an effect on vasoconstriction but can also address vasopressin deficiency (Landry et al. 2017). Vasopressin is a vasoconstrictor hormone that is naturally produced for raising blood pressure and inducing water retention. There are three receptors involved. The v1 receptor induces vasoconstriction; the v2 receptor induces water retention in the kidney, and the v3 or v1b receptor leads to the release of ACTH from endocrine cells, which stimulate cortisol release from the adrenal gland. This is very important during septic shock. At higher levels, v1 activation and the vasoconstrictive properties of vasopressin are predominant, but at low plasma levels of vasopressin (10 pmol/l), arginine vasopressin's v2 receptors anti-diuretic actions predominate.

While definitions for refractory shock, septic shock, or vasodilatory shock are lacking, a threshold of 0.5 µg/kg/min is generally accepted. However, at Gelderse Valley Hospital, 0.25 µg/kg/min is considered to indicate refractory shock because, after that point, mortality increases rapidly. Adding a second vasopressor may be helpful in these patients, along with optimal fluid resuscitation, and cardiac output should also be closely monitored.

The VAAST trial compared norepinephrine with norepinephrine plus vasopressin. While the study did not show a significant reduction in mortality rates with the vasopressin group (baseline mean arterial pressure (MAP) of patients were NE. Group 73±10 and Vaso. group 72±9), the effect of adding vasopressin had a

marked norepinephrine sparing effect (Russell et al. 2008).

In a post-hoc analysis of the VAAST trial, patients were separated into groups according to APACHE-II scores. In patients with lower APACHE-II scores (and NE ≤15µg/min) there was a significant reduction in mortality when vasopressin was added to the catecholamines. These findings suggest that in patients with refractory shock, it might be a good idea to add vasopressin earlier (Russell et al. 2011; Wacharasint 2012).

Findings from McIntyre et al. (2018) show that the incidence of new-onset atrial fibrillation distributive shock is about 23% less when catecholamines are combined with vasopressin. An 11% lower mortality was observed when the drugs were combined. There was also a trend towards less use of renal replacement therapy (RRT) in septic shock. More ischaemia was observed in patients treated with vasopressin, especially digital ischaemia. The risk is higher when the use of vasopressin is increased without optimal fluid status and optimal cardiac output (McIntyre 2018).

In another recent meta-analysis that compared vasopressin with catecholamines versus catecholamines alone and with a focus on renal outcomes, the incidence of AKI and renal failure and the need for RRT was lower with the use of the combination with vasopressin (Nedel 2019). The Surviving Sepsis Campaign Guidelines also recommend adding vasopressin up to a dose of 0.03 IU/min if there is a need to raise the mean arterial pressure and reduce the dose of norepinephrine (Martin et al. 2015).

In a patient with refractory shock, where MAP is still insufficient, despite norepinephrine 0.25 µg/kg/min, adequate fluid resuscitation, and adequate to high cardiac output, vasopressin can be started with 0.01IU/min and gradually increased to 0.03IU/min in steps of 20 minutes. When the desired blood pressure level is achieved and maintained sufficiently, norepinephrine should be gradually decreased to 0.1 µg/kg/min, after which vasopressin should be tapered to 0.01IU/min every 60 minutes, providing that MAP is stable. Once vasopressin infusion stops, then noradrenaline should be tapered. Tapering norepinephrine first, then vasopressin has less risk of rebound hypotension (Duclos et al 2019). This is the tapering protocol being used in the vasopressin registry in the Netherlands (Netherlands ICU Sepsis Protocol).

Overall, high-dose norepinephrine or noradrenaline monotherapy may not be the best approach. Catecholamine sparing effects can be achieved by treating the patient with vasopressin. This also helps vasopressin deficiency in sepsis and may reduce atrial fibrillation, AKI incidence and the need for RRT. ■

This article is based on a webinar on vasopressor therapy streamed by ESICM and sponsored by AOP Orphan. To watch the complete webinar please visit: https://youtu.be/BQbSYHSK4VAx

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Oxygen: Too Much is Bad

Benefits and harms of supplemental oxygen administration in ICU for critically ill patients

Supplemental oxygen administration is a routine treatment administered to a wide majority of critically ill patients. Nevertheless, evidence suggest that exposure to hyperoxia is associated with impaired outcomes. We discuss here the benefits and harms of supplemental oxygen administration in the intensive care unit.

Introduction

In the intensive care unit (ICU), supplemental oxygen administration is a routine treatment administrated to a large number of patients. The rationale for this oxygen administration is the prevention and the treatment of hypoxia, which has deleterious effects and ultimately leads to cell death (O'Driscoll et al. 2017). As a reminder, hypoxia is a condition in which there is not enough oxygen available to the blood and body tissues while hypoxaemia is an abnormally low concentration of oxygen in the blood. The formula to calculate the arterial content of oxygen in blood is:

(*arterial oxygen saturation.haemoglobin*.1.34) + (*arterial oxygen tension*.0.003)

suggesting that oxygen saturation is the main determinant of oxygen content in blood. For this reason, excessive values of arterial oxygen tension (PaO_2) are often tolerated and perceived by physicians as a safety net against hypoxaemia and its consequences (Suzuki et al. 2013; Young et al. 2015).

Increasing evidence suggests that exposure to hyperoxia during critical illness is associated with impaired outcome and conservative oxygen therapy should be a future recommendation in most guidelines (Barbateskovic et al. 2019; Chu et al. 2018). Nevertheless, inconsistent findings are reported with no deleterious effect or even a protective effect of hyperoxia in ICU patients (Duclos et al. 2021; Mackle et al. 2020).

We briefly reviewed the current literature on the topic to discuss the benefits and harms of supplemental oxygen administration in ICU for critically ill patients.

Definitions

The term "hyperoxia" generically refers to an excess oxygen supply (administration of any inspired oxygen fraction (FiO_2) higher than 0.21) leading to a raise of PaO_2 above normal values.

Normoxaemia is often defined as a PaO_2 between 80 and 100 mmHg in a subject breathing room air at sea level. Unfortunately, clinical studies used a wide variety of definition for hyperoxia, explaining partly the inconsistency of findings (Barbateskovic et al. 2019; Damiani et al. 2014). A linear relationship was found between elevated PaO_2 and mortality when PaO_2 is analysed as a continuous variable, but without a strong threshold for harm (Janz et al. 2012). In a cohort study, ICU mortality appeared to increase linearly with exposure time even with mild hyperoxia [120-200 mmHg] (Helmerhorst et al. 2017a).

Hyperoxia Effects

Aerobic metabolism generates reactive oxygen species (ROS). Those are responsible for oxidative stress, which leads to cell death if not counterbalanced (Davies 1995). Thus, antioxidant systems are available in eucaryotic cells to eliminate ROS and maintain cell life. Situations of imbalance between oxidative stress and antioxidant defenses aggravate oxidative stress, cause damage to the cells with potential cell death and exacerbate the inflammatory response (Helmerhorst et al. 2015). In mouse lungs, hyperoxia caused oxidative stress, increased inflammatory pulmonary response, increased pro-inflammatory cytokines and macrophages rates and created histological pulmonary damage (Helmerhorst et al. 2017b). Denitrogenation after high oxygen concentration breathing leads to alveolar collapse and lung atelectasis (Aboab et al. 2006).

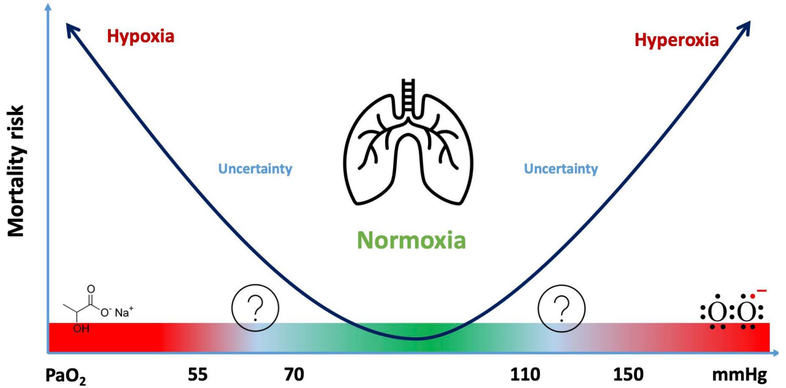
Hyperoxia has also well-described systemic effects. Animal studies found greater spread of infection as well as altered organ perfusion and haemodynamics in models of septic and haemorrhagic shock occurring during hyperoxia (Dyson et al. 2009; Rodríguez-González et al. 2014). Whereas hypoxia may be viewed as a natural response to injury, hyperoxia is never found except in conditions generated by human interventions. In this sense, oxygen should be assessed as a drug with possible side effects in case of overdosage.

Hyperoxia is Certainly Deleterious

Hyperoxia is a frequent event in critically ill patients. In a multicentre retrospective cohort study, Douin et al. (2021) showed that among 3,464 injured patients, 46% of ICU time was spent in hyperoxia defined by an arterial oxygen saturation (SaO_2) above 96%. Hyperoxia was associated with a greater risk of in-hospital mortality.

Several randomised controlled trials reported deleterious effects of prolonged hyperoxia. Girardis et al. (2016) found an increased ICU mortality in 218 patients treated with a liberal oxygen therapy compared with 216 patients treated with a conservative strategy, defined by a PaO_2 between 70 and 100 mmHg (20.2% vs. 11.6%, absolute risk reduction at 0.086 [95% confidence interval (CI) from 0.017 to 0.150], p = 0.01). Of note, in this study, the patients were hospitalised in the ICU for at least three days and received mechanical ventilation. Those findings were confirmed in a meta-analysis reporting a deleterious effect of prolonged hyperoxia exposure over time in a heterogeneous patient population (Chu et al. 2018).

Sepsis is associated with excessive radical oxygen species (ROS) formation from the nitric oxide (NO) pathway (Rodríguez-González et al. 2014). Additional ROS formation from hyperoxia could further worsen organ dysfunction. The HYPERS2S randomised controlled trial showed that hyperoxia, defined by a group treated with FiO_2 at 1, increased the risk of 28-day mortality in patients with septic shock: 93 (43%) of 217 patients were non-survivors in the hyperoxia group versus 77 (35%) of 217 patients in the normoxia group [hazard ratio 1.27, 95% CI 0.94-1.72; p = 0.12] (Asfar et al. 2017). The authors reported a significant difference in the overall incidence of serious adverse events between the hyperoxia (185 [85%]) and normoxia groups (165 [76%]; p = 0.02), with a clinically relevant doubling in the hyperoxia group of the number of patients with ICU-acquired weakness (24 [11%] vs. 13 [6%]; p = 0·06) and atelectasis (26 [12%] vs 13 [6%]; p=0·04) compared with the normoxia group. This higher rate of complications resulted in the premature interruption of this trial.



> **oxygen should be assessed as a drug with possible side effects in case of overdosage**

A meta-analysis of the Cochrane group assessed the supplemental use of oxygen in patients with acute myocardial infarction. The authors concluded that randomised controlled trials did not support the routine use of inhaled oxygen in patients with acute myocardial injury, and a harmful effect of hyperoxia cannot be ruled out (Cabello et al. 2013). In cardiac arrest, high concentration of inhaled oxygen is routinely used during the resuscitation phases to increase presumably the tissular oxygen availability. Nevertheless, a randomised controlled trial showed an increase at 24 hours of neuronal injury markers in post-cardiac arrest patients ventilated with a FiO_2 at 1 rather than those ventilated with a FiO_2 at 0.3. (Kuisma et al. 2006). The 2021 European Resuscitation Council guidelines on post-resuscitation care recommend normoxia to improve recovery after cardiac arrest (Nolan et al. 2021).

Limitations and Questions

Despite this body of evidence, several studies did not confirm the deleterious effects of hyperoxia. In 205 patients with acute respiratory distress syndrome, a randomised controlled trial found that early exposure to a conservative oxygen therapy defined by a target arterial oxygen tension from 55 to 80 mmHg did not increase survival at day 28 (Barrot et al. 2020). Same findings were reported in another multicentre randomised controlled trial including 2928 patients with acute hypoxaemic respiratory failure (Schjørring et al. 2021). The ICU-ROX investigators randomised 1000 patients undergoing mechanical ventilation to receive conservative or usual oxygen therapy. The primary endpoint was the number of ventilator free-days, which was not significantly different between the two groups (Mackle et al. 2020). In a post-hoc analysis including 251 patients with sepsis, although the difference of 90-day mortality did not reach a significant level, the trend was in favour of the usual group, i.e. that with high target of PaO_2 [36.2% vs. 29.2%, p = 0.24] (Young et al. 2020).

In brain injured patients, observational studies suggest a beneficial effect of early hyperoxia (Crawford et al. 2017; Jeon et al. 2014). However, high quality studies found no effect or even deleterious effects in the hyperoxia groups (Damiani et al.

2014; Roffe et al. 2017). In severe blunt chest trauma patients, a cohort study with a propensity score-based analysis found that early hyperoxia was not associated with more complications, including death and/or hospital-acquired pneumonia and/or acute respiratory distress syndrome. Hyperoxia was also associated with an increase in hospital-acquired pneumonia-free, mechanical ventilation-free, and ICU-free days (Duclos et al. 2021).

Several reasons may explain these conflicting findings. First, in observational studies, the most severe patients often develop hypoxia due to shock and acute respiratory failure. Then, the effects of oxygen threshold setting can be misleading by the weight of covariates. Second, it was now well-recognised that administration of high concentration oxygen is deleterious. Hence, the recent randomised controlled trials set the level of PaO_2 in their control group around 90 mmHg (Barrot et al., 2020; Mackle et al. 2020; Schjørring et al. 2021). Even if this variable is not reported in the protocol, the medical teams in charge of patients pay attention to avoid hyperoxia. In the ICU-ROX, in both groups, the patients had a PaO_2 below 100 mmHg from day 2 (Mackle et al. 2020). Actually, the control groups received a normoxic ventilation. The third explanation is the duration and timing of intervention. The studies in which hyperoxia was associated with improved outcome used high concentration of oxygen for a short duration at an early time-point after the injury (Duclos et al. 2021; Rockswold et al. 2013). In patients with traumatic brain injury, the administration of oxygen at a FiO_2 set at 1 was performed only for three hours (Rockswold et al. 2013), while those with chest trauma were assessed for their oxygenation levels only during the first 24 hours (Duclos et al. 2021). Fourth, oxygen toxicity is probably increased among the patients receiving invasive mechanical ventilation (Girardis et al. 2016). Fifth, factors not related to oxygen administration can interfere with the oxygen metabolism. The effects of bringing more oxygen to tissue has been challenged during the nineties by increasing the cardiac index. A seminal randomised controlled trial showed an increased in mortality among patients receiving supra-therapeutic goals of oxygen delivery, as compared with those receiving standard of care (Hayes et al. 1994).

Conclusion

In critically ill patients, the risks associated with hypoxaemia have led to the administration of high quantity of oxygen (Suzuki et al. 2013; Young et al. 2015). Results from the more recent studies suggest that hyperoxia was associated with poor outcomes. The actual trend is to navigate towards a more conservative approach of oxygen administration. Nevertheless, even if a definitive threshold has not been discovered yet, a target of PaO_2 ranging from 70 to 90 mmHg seems safe. However, the best timing of interventions on oxygen and the best monitoring of oxygen metabolism remains to be determined to develop personalised approaches within the next years in order to maintain critically ill patients within the safe zone of the U-shaped curve of hypoxaemia and hyperoxia (**Figure 1**).

Conflict of Interest

Pr. Leone reports personal fees from MSD, Pfizer, Octopharma, Aspen, Orion, Amomed, Aguettant outside the submitted work. Dr Pastene has nothing to disclose. ■

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Oxygen Therapy in COVID-19 Patients: The Role of HFNC and CPAP

Oxygen therapy and mechanical ventilation in patients with COVID-19 and steps to choose the right therapeutic strategy for each patient.

Introduction

Severe acute respiratory syndrome coronavirus CoV-2 is the highly contagious viral agent responsible for the ongoing COVID-19 pandemic. COVID-19 is the name of the syndrome caused by SARS-CoV-2 infection. Common signs of infection include upper respiratory tract symptoms as well as more severe symptoms: thromboembolic events, pneumonia, ARDS and respiratory failure eventually leading to multi-organ failure (Allado et al. 2021). Acute hypoxic respiratory failure (AHRF) is the most dreaded COVID-19 complication commonly resulting in ICU admission. During the pandemic, the abrupt and increasingly high demand for intensive care was unmatched by struggling healthcare systems throughout the world. Fortunately, several patients with AHRF could also be treated with great results using non-invasive ventilation and conventional oxygen therapy in general wards or specifically created wards. Currently, thanks to massive worldwide vaccination campaigns, infections rates are decreasing, reducing pressure on ICUs and hospitals.

Clinical & Pathological Findings

Usual diagnostic criteria for severe SARS-CoV-2 infection include positive molecular swab, compatible symptoms, and imaging studies. CT scans of COVID-19 induced lung injury are mostly described as ground glass opacities and variable degree of honeycombing with areas of lung consolidation that do not always correlate with gas exchanges variations (Ball et al. 2021). Pathology reports describe congested lungs with focal fibrosis and interstitial oedema along with capillary congestion and thrombi in small arterial vessels plus dilated alveolar ducts spaces filled with hyaline membranes (Carsana et al. 2020). In advanced stages of the disease, fibrosis progresses resulting in airspace obliteration, lung fibrosis and remodelling (Grillo et al. 2021). Clinically, this translates to AHRF with patients experiencing tachypnoea, dyspnoea and eventually increased work of breathing (WOB) often requiring conventional oxygen therapy or more advanced forms of ventilatory support.

Monitoring: Understanding FiO_2 SpO_2 SaO_2 PaO_2

Supplemental oxygen is typically started for hypoxic patients with oxygen saturation <92% as measured by pulse-oximetry. However, SpO_2 does not always correlate well with SaO_2 nor with PaO_2 values. In fact, given the sigmoid shape of the oxygen dissociation curve, SpO_2 higher than 90% may correspond to a large range of PaO_2 values (Tobin 2020). The mean difference and limits of agreement between SpO_2 and true SaO_2 were 25.8 + 16% with SpO_2 readings in critically ill patients being less reliable, and reproducible than in healthy volunteers (Ottestad et al. 2018; Tobin et al. 2020). Arterial blood samples offer reliable measurements of gas exchanges that should be used to set a suitable course of treatment. Another factor that contributes to change in the oxygen dissociation curve is represented by an increase in body temperature that generates a right shift in the curve: for a given PaO_2 value, SaO_2 will be lower (Tobin et al. 2020). Although these changes produce significant variation in SaO_2 and PaO_2, values remain constant as tissues in the body respond only to PaO_2 and not SaO_2 (Tobin et al. 2020).

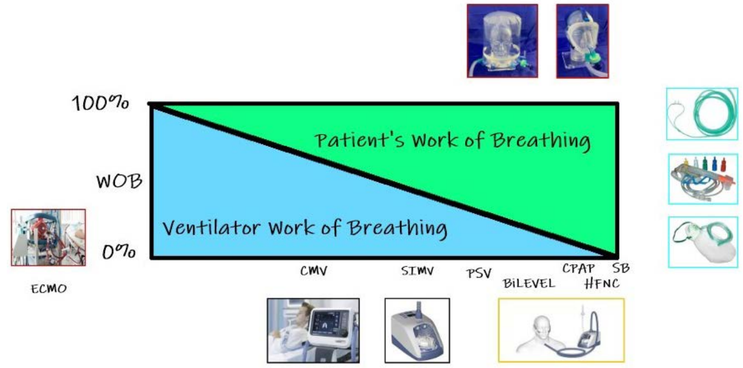

Figure 1. Work of breathing (WOB) variations from spontaneous breathing (SB) to invasive mechanical ventilation and ECMO

Respiratory Management and Considerations

When the pandemic started, knowledge of the disease was scarce and indications for non-invasive ventilation (NIV) limited, resulting in relatively high intubation rates (Grasselli et al. 2020). As knowledge of the disease progressed and treatment options improved, we became aware that tachypnoea alone is not a justification for intubation because increased respiratory rate in COVID-19 patients represents a physiological response to lung inflammation (Tobin 2020), whereas work of breathing (WOB) is determined by the magnitude of swings in pleural pressure and tidal volume (Grieco et al. 2019). Evaluation of pulmonary infiltrates as a criterion for intubation is only valid when severely abnormal gas exchanges are present (Alhazzani et al. 2021). Furthermore, physiological response to values of PaO_2 of around 60 mmHg is minimal dyspnoea and values higher than 40 mmHg have difficultly been associated with organ damage (Tobin 2020). Thus, hypoxaemia without dyspnoea or respiratory distress is not an indication for intubation without a prior attempt of non-invasive forms of oxygen therapy (Tobin 2020).

Oxygen therapy is suggested for values of SpO_2 < 92% and is recommended if SpO_2 <90%, but should be maintained no higher than 96% (Alhazzani et al. 2021). These targets can be reached by increasing oxygen delivery, the product of arterial oxygen content and cardiac output (Tobin 2020). Lower oxygen delivery is initially counterbalanced by higher oxygen extraction and normal consumption until reaching a critical threshold – decrease to less than 25% normal value – then total oxygen consumption decreases and metabolism shifts to anaerobiosis leading to vital organ dysfunction (Tobin 2020).

Oxygen Delivery Systems

Venturi masks

Venturi masks (VM) are frequently used when nasal cannulas are not providing adequate FiO_2 control in hypoxic patients. Venturi's effect is used to provide supplemental oxygen, but this setup is limited to flow rates of 15 litres/minute, offering only a fraction of the needed flow in dyspnoeic patients. An increase in respiratory rate and/or tidal volume generates high minute volume ventilation and the FiO_2 will be diluted in a larger volume of air decreasing the actual inspiratory FiO_2. When 15 litres/minute flows are insufficient to satisfy respiratory needs, a step up is required to increase inspiratory flows.

High flow nasal cannulas

High flow nasal cannulas (HFNC) is an oxygen delivery system capable of providing 30-60 litres/minute of heated and humidified gas meeting the demands of tachypnoeic patients providing high minute ventilation while ensuring constant FiO_2 (Rochwerg et al. 2020). High flows have a double effect on upper airways: enhancing anatomical dead space washout and CO_2 clearance thus reducing respiratory rate and effort, resulting in an increased lung homogeneity and end expiratory lung volume (Basile et al. 2020). Thus, given our experience in Pisa, the main indications for HFNC are represented by 1) patients that do not tolerate CPAP/NIV in the absence of increased work of breathing; 2) early stages of the disease to prevent therapeutic escalation - if PEEP is not required as inferred by chest CT and/or lung echo; 3) alternation to CPAP especially in weaning contexts. When compared to conventional oxygen therapy HFNC decreased the need for intubation as well as respiratory support escalation though there is no clear evidence on its effects on mortality and hospital or ICU stay (Rochwerg et al. 2020).

Continuous positive airway pressure

Continuous positive airway pressure (CPAP) and non-invasive ventilation are first line treatments for respiratory failure with concomitant clinical signs of increased WOB or fatigue, inside and outside the ICU (Gattinoni et al. 2020). Advantages include possible application in early pre-hospital and hospital settings resulting in lower intubation and infection rates, decreasing morbidity and mortality and providing more favourable outcomes (Brusasco et al. 2015). CPAP system consists of an interface delivering an inspiratory flow with an adjustable FiO_2 and constant end-expiratory positive pressure (PEEP) at the patients mouth adjustable via a PEEP valve (Grieco et al. 2021). CPAP interfaces are either a helmet or a facial mask with the latter generally being less tolerated by patients if treated for long periods of time. During respiratory distress, patients can generate extremely high inspiratory flows - in some cases exceeding 60 litres/minute - hence, it is mandatory to use systems capable of providing high flows that match patients' peak inspiratory flow in order to be able to revert increased work of breathing and to prevent respiratory muscle exhaustion (Brusasco et al. 2015; Grieco et al. 2021). Its use in acute lung injury decreases arteriovenous shunting improving oxygenation and dyspnoea while decreasing WOB (L'Her et al. 2005). Efficient CPAP must not only provide appropriate inspiratory airflow but also guarantee minimal CO_2 rebreathing (Patroniti et al. 2003). A simple way to ensure proper inspiratory flow to patients during CPAP is to match their inspiratory demands. This can be achieved by measuring the temperature inside the helmet: an early sign of CO_2 rebreathing and expression of unmatched inspiratory airflow demands. Concerning PEEP titration, CT studies have shown that PEEP induced alveolar recruitment using PEEP of 8-16 cmH_2O resulted in minimal recruitment of lung parenchyma independently of respiratory system mechanics and compliance as well as modifications in gas exchange (Ball et al. 2021). This is easily explained by autopsy findings which reported injury in the alveolar epithelial cells, hyaline membrane formation, hyperplasia of type II pneumocytes, diffuse alveolar damage with consolidation due to fibroblastic proliferation with extracellular matrix and fibrin forming clusters in air-spaces and capillary vessel finally leading to alveolar spaces substituted by fibrosis (Ball et al. 2021; Grillo et al. 2021). Thus, high PEEP levels are not routinely recommended but rather PEEP titration should be individualised case by case.

> "increased respiratory rate in COVID-19 patients represents a physiological response to lung inflammation"

Pressure support ventilation

Physiological effects of pressure support ventilation (PSV) during acute lung injury include increments in tidal volume (L'Her et al. 2005), but we have to be aware that increased tidal volumes inferred by the absolute changes in transpulmonary pressure (Pl) are considered to be associated with dynamic lung stress and NIV failure for de novo AHRF (Carteaux et al. 2016). Only one study reports physiological measurements during NIV (L'Her et al. 2005). It showed that non-invasive pressure support of 10-15 cmH_2O above a PEEP of 5-10 cm H_2O was the best combination to reduce inspiratory effort, dyspnoea and ameliorate oxygenation but inspiratory effort and WOB, estimated by Pes pressure-time product, are highly inter-individually variable among patients. Hence, this could imply that not all the patients are exposed to the same risk of self-induced lung injury. Moreover, ventilator settings during PSV have been shown to influence patient-ventilator synchrony and asynchronies which are associated with prolonged mechanical ventilation (Chao et al. 1997) and mortality (Blanch et al. 2015).

Helmet-NIV in pressure support mode, compared to HFNC, has shown lower incidence of intubation though there was not a significant difference of in-hospital mortality (Grieco et al. 2021). Despite that, the reported overall in-hospital mortality for Helmet-PSV was quite high (24%) if compared with another retrospective study on Helmet-CPAP in-hospital mortality which was 14% (Brusasco et al. 2021) and was additionally confirmed by other reports (Oranger et al. 2020; Tobin et al. 2021). This difference in in-hospital mortality can be explained by the fact that during PSV, but not during CPAP nor during HFNC, oesophageal pressure (Pes) swings, sum up with positive airway pressure to determine transpulmonary pressure (Pl) possibly leading to SILI if the treatment is not individualised by assessing early inspiratory efforts through oesophageal manometry (Tonelli et al. 2020).

Treatment Failure and Indications for Invasive Mechanical Ventilation

HFNC and CPAP/NIV should be the first line of treatment in acute hypoxic respiratory failure and a transition to invasive ventilation should be made when they are no longer effective as described by an increased WOB at risk of SILI (Cabrini et al. 2020). Non-invasive treatment failure is more likely in patients with more severe clinical conditions: higher SAPSII and lower PaO_2/FiO_2 ratio (Carteaux et al. 2016). Predicted treatment success and failure of HFNC therapy can be calculated using ROX index (SpO_2/FiO_2 to respiratory rate): values >4.88 are likely to avoid intubation whereas lower values are at high risk of treatment failure (Roca et al. 2016). Detection of CPAP/NIV failure can be estimated by using the HACOR score (HR, pH, GCS, PaO_2/FiO_2, RR) after one hour of treatment: scores >5 represent high risk for NIV failure (Duan et al. 2017). Also expired tidal volumes greater than 9.5 ml/kg of predicted body weight during NIV for moderate-severe hypoxaemia in AHRF are independently associated with non-invasive ventilation failure (Carteaux et al. 2016). Diaphragmatic ultrasonography has been suggested as a potential useful tool to predict adverse outcomes (Corradi, et al. 2021) and to predict response to CPAP in hospitalised patients for COVID-19 pneumonia (Corradi et al. 2021). Respiratory muscle ultrasonography, represents a quick method to evaluate other factors indicative of treatment failure such as respiratory muscle dysfunction during dyspnoea, increased WOB and patient-ventilator asynchronies (Tuinman et al. 2020).

In light of high mortality rates, up to 90% in COVID-19 patients submitted to invasive mechanical ventilation. The appropriate time for tracheal intubation is when signs and symptoms of significant respiratory distress or tissue hypoxia are present despite maximal non-invasive support (Pisano et al. 2021; Tobin et al. 2021). In those cases progression to invasive mechanical ventilation should be carried out without delay, especially in case of persisting dyspnoea and/or vigorous respiratory efforts despite 4-6 hours of CPAP (COVID-19 Lombardy ICU Network et al. 2020; Gattinoni et al. 2020). However, no significant difference of in-hospital mortality rate, between early versus late intubation policy has been described (Lee et al. 2020) and there is no prospective study that evaluates whether a comprehensive strategy of intubation, according to predefined criteria, could affect outcomes.

Conclusions

Oxygen therapy and non-invasive ventilation in COVID-19 should be based on pathophysiological changes and a step-by-step approach should be adopted in choosing the right therapeutic strategy for each patient. CPAP has been demonstrated to be an effective alternative to invasive mechanical ventilation even for severe acute hypoxic respiratory failure in COVID-19 patients. Hence, the choice to treat a patient with non-invasive supports should not be viewed as a second choice due to lack of ICU availability, but rather as the best early therapeutic approach in the initial phase of the disease (Pisano et al. 2021).

Conflict of Interest

None. ■

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Apnoeic Oxygenation for Intubation - Where is the Evidence?

Apnoeic oxygenation for critically ill patients

Apnoeic oxygenation can be used in critically ill patients, without replacing preoxygenation.

Introduction

Hypoxaemia is one of the most common complications during tracheal intubation of critically ill patients (Jaber et al. 2006; Russotto et al. 2021) with an incidence of severe hypoxaemia reaching up to 50% (De Jong et al. 2013; Jaber et al. 2006). Severe hypoxaemia can lead to cardiac arrest, neurologic damage, or multiple organ failure (De Jong et al. 2013; De Jong et al. 2018) and anticipating and avoiding such episodes is of critical importance to prevent the development of subsequent complications.

In order to reduce the occurrence of hypoxaemia, preoxygenation is mandatory before tracheal intubation, increasing the duration of apnoea before desaturation. Preoxygenation consists of increasing the pulmonary oxygen reserve, and thus the functional residual capacity (FRC), in order to prevent hypoxaemia that could occur during the intubation attempt. Obese patients, ICU patients and pregnant women are particularly at risk of reduced efficiency of preoxygenation due to certain pathophysiological changes: decreased FRC, increased risk of atelectasis, shunt.

However, the most common device used, a face mask, has to be taken off after preoxygenation in order to allow the passage of the orotracheal tube through the mouth. Furthermore, positioning the orotracheal tube in the trachea takes time, varying from a few seconds to several minutes in case of difficult intubation (De Jong et al. 2013).

High-flow nasal cannula oxygen therapy (HFNO) can be continued during the passage of the orotracheal tube through the mouth, and as a consequence may be used to continue blood oxygenation during the apnoea period of intubation, especially when the facial mask used for preoxygenation is removed (Papazian et al. 2016). All the same, the possible role of apnoeic oxygenation during intubation procedures in critically ill patients remains debated. When and how could it be used?

What is the Physiological Basis of Apnoeic Oxygenation?

In 1959, a study reported eight patients scheduled for minor operations who were intubated and paralysed to prevent breathing (Frumin et al. 1959) but not ventilated. Pure oxygen was administered in the endotracheal tube. The patients drastically increased their carbon dioxide tension (up to 250 mm Hg) and developed respiratory acidosis (up to a pH of 6.72) while maintaining 100% oxygen saturation. Indeed, whereas carbon dioxide tension depends on minute ventilation, oxygenation depends on positive end-expiratory pressure (PEEP) and FIO_2. **Figure 1** summarises the course of oxygen from the atmosphere to the blood vessel during apnoea. Apnoeic oxygenation is a physiological phenomenon in which the difference between the alveolar rates of oxygen removal and carbon dioxide excretion generates a negative pressure gradient of up to 20 cmH_2O. This negative pressure gradient can allow a flow of oxygen into the lungs, as long as airway permeability between the lungs and the atmosphere, open alveoli and high alveolar oxygen pressure are maintained (**Figure 1**).

What are the Most Recent Data Published?

Interpretation of the many existing trials in the field remains difficult because preoxygenation and apnoeic oxygenation are often evaluated concomitantly.

Guitton et al. (2019) included non-severely hypoxaemic patients, and found no significant difference between the median lowest SpO_2 during intubation in the HFNO group compared with the standard bag valve mask group. However, there was less severe desaturation (<90%) in the HFNO group compared with the standard bag valve mask group. These results confirm the encouraging results of an observational study (Miguel-Montanes et al. 2015) performed, also in mildly hypoxaemic patients.

However, in severely hypoxaemic patients intubated in the intensive care unit (ICU), HFNO has never proved its efficiency, compared to absence of apnoeic oxygenation. Vourc'h et al. (2015) found no difference on the minimal SpO_2 values during intubation in hypoxaemic patients between 60L/min of HFNO and oxygen facial mask (92% vs 90%, p=0.44). Semler et al. (2016) found that the administration of 15L/min nasal cannula oxygen in the apnoeic oxygenation group was not associated with significantly increased minimal SpO_2 values during intubation procedures (from 92% in the apnoeic oxygenation group to 90% in the usual care group [p=0.16]).

The discrepancies between the results of these studies (Semler et al. 2016; Miguel-Montanes et al. 2015; Vourc'h et al. 2015; Sakles et al. 2016) could mainly be explained by the oxygen flow used for the apnoeic oxygenation group (from 15 to 60 L/min) and the different studied populations in term of hypoxaemia (severe vs mild to moderate). Moreover, if the efficiency of using HFNO for preoxygenation and apnoeic oxygenation is still a matter of debate (Chanques and Jaber 2019; Ricard and Gregoretti 2019; Hanouz et al. 2019a), it is mostly because preoxygenation (before induction of apnoea, when the patient is still breathing) is not separated from apnoeic oxygenation (after induction of apnoea, when the patient is not breathing anymore).

Preoxygenation using a tightly applied facial mask remains the method of choice. In a physiologic study (Hanouz et al. 2019b) comparing the ETO_2 following preoxygenation, 96% and 46% (P<0.001) of volunteers had an ETO_2 of at least 90% in the face-mask and HFNO groups, respectively. In the face mask group, the hazard ratio to achieve an ETO_2 of 90% was 5.3 (95% CI: 3.2 to 8.9; P<0.001).

Noninvasive ventilation (NIV) preoxygenation of patients with severe hypoxaemic acute respiratory failure is associated with less hypoxaemia than preoxygenation with oxygen facial mask during intubation procedures (Baillard et al. 2006). Indeed, associating pressure support (PS) with positive end expiratory pressure (PEEP) limits alveolar collapse and atelectasis formation (Pepin et al. 2016; Hemmes et al. 2014), responsible for hypoventilation and low perfusion ventilation ratio (De Jong et al. 2014). Incidence of severe hypoxaemia defined by a pulse oximetry (SpO_2) of less than 80% can be decreased by applying NIV preoxygenation, a method which is now used by many teams for preoxygenation of patients with severe hypoxaemic acute respiratory failure.

In a randomised controlled trial including 313 patients, NIV was recently compared to HFNO for preoxygenation of critically ill patients with acute hypoxaemic respiratory failure (Frat et al. 2019). Severe hypoxaemia (pulse oximetry < 80%) occurred in 33 (23%) of 142 patients after preoxygenation with NIV and 47 (27%) of 171 with HFNO (absolute difference −4.2%, 95% CI −13.7 to 5.5; p=0.39). In the subgroup of patients with PaO_2/FiO_2 lower than 200 mmHg, severe hypoxaemia occurred less frequently after preoxygenation with NIV than with HFNO (28 (24%) of 117 patients vs 44 (35%) of 125; adjusted odds ratio 0.56, 0.32 to 0.99, p=0.0459). Preoxygenation using NIV remains the most efficient way to decrease oxygen desaturation

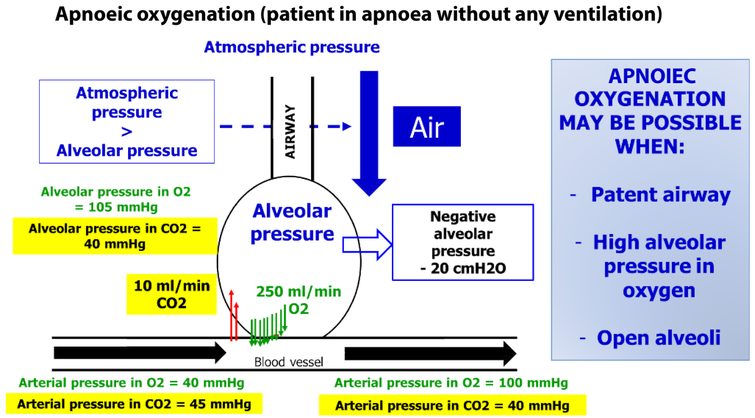

Figure 1. Mechanisms of apnoeic oxygenation

Figure 2. OPTINIV method

in critically ill patients, and furthermore in the obese patient (Schetz et al. 2019).

Using HFNC combined with NIV may have potential advantages over conventional NIV alone for preoxygenation before intubation procedures in hypoxaemic ICU patients.The OPTINIV method (**Figure 2**) (Jaber et al. 2016), associating preoxygenation with pressure support and PEEP (NIV) and HFNO for both preoxygenation and apnoeic oxygenation, allowed a significantly higher oxygen saturation during the intubation procedure, when compared to preoxygenation with NIV alone.

What To Do in Practice?

Several preoxygenation methods are available in practice: bag valve mask, HFNO, pressure support associated with PEP (NIV), OPTINIV method (NIV combined to HFNO).

Three methods provide sufficient reserves in oxygen: bag valve mask oxygenation, NIV, OPTINIV method, the latter permitting higher oxygen saturation during intubation procedures in severely hypoxaemic patients. HFNO can be added for apnoeic oxygenation in case of high risk of desaturation, ensuring good mandible subluxation, after an attempt to open alveoli using NIV (**Figure 1**).

One very efficient way to oxygenate during the apnoea period remains to ventilate the patient.The efficiency of ventilation during apnoea after rapid sequence induction was recently assessed (Casey et al. 2019). Among critically ill adults undergoing tracheal intubation, patients receiving bag valve mask ventilation had higher oxygen saturations and a lower incidence of severe hypoxaemia than those receiving no ventilation. In very hypoxaemic critically ill patients, without high risk of aspiration, considering bag valve mask ventilation may help to limit the rapid drop in oxygen saturation.

Conclusion

To date, the evidence for apnoeic oxygenation being beneficial during ICU intubation is conflicting, most likely because its success depends on upper airway patency during laryngoscopy and intubation, as well as the FiO_2, oxygen flow rate, patient position and the extent and cause of any pre-existing hypoxaemia.There is little or no evidence of harm. However, the clinician must avoid confusion between preoxygenation and apnoeic oxygenation. Whereas NIV is the method of preference for preoxygenation of critically ill hypoxaemic patients, HFNO can be used for apnoeic oxygenation, and might limit the occurrence of desaturation especially in mild to moderately hypoxaemic patients. The OPTNIV method, combining NIV and HFNO, is the method of choice to increase the lowest oxygen saturation reached during the intubation procedure. In patients at high risk of desaturation and without high risk of aspiration, preventive ventilation during apnoea should be considered.

Conflict of interest

Dr De Jong reports receiving consulting fees from Medtronic. Pr. Jaber reports receiving consulting fees from Drager, Medtronic, Baxter, Fresenius-Xenios, and Fisher & Paykel. Dr Monet has no conflict of interest. ■

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Major Adverse Peri-intubation Events in Critically Ill Patients – Update on the INTUBE Study

A third anniversary update on the findings of the INTUBE study, a large international prospective observational study aiming at collecting data on peri-intubation adverse events in critically ill patients.

Introduction

Tracheal intubation in critically ill patients is among the most commonly performed and high-risk procedures (Russotto et al. 2019). Until now, information on peri-intubation adverse events was limited to data from single-centre, national level or retrospective studies.

In 2018 we launched the INTUBE study, a large international prospective observational study aiming at collecting data on peri-intubation adverse events in critically ill patients. In this third anniversary update we are pleased to describe our journey and our findings from the primary analysis recently published in JAMA (Russotto et al. 2021).

In INTUBE study, we enrolled critically ill patients undergoing in-hospital tracheal intubation. Each site collected data on a series of consecutive intubations in critically ill patients performed in ICU, emergency department and wards. In this regard, INTUBE study is unique in focusing on critical illness rather than on the procedure location.

We excluded patients undergoing intubation to receive general anaesthesia, patients intubated during cardiopulmonary resuscitation for cardiac arrest and out-of-hospital intubation. One hundred ninety-seven centres from 29 countries across five continents joined the INTUBE family, making this the first study providing data not only from Europe, US and Australia but also from Asia, South America and Africa. A total of 2964 patients were finally enrolled. The primary reason for intubation was respiratory failure in 52.3% of patients, followed by neurological impairment in 30.5% and cardiovascular instability in 9.4%. The primary outcome of the study was the composite of cardiovascular instability, severe hypoxaemia and cardiac arrest. Secondary outcomes included incidence of aspiration of gastric contents, difficult intubation, airway injuries and ICU mortality.

Key Findings and Discussion

Among the study patients, 45.2% experienced at least one major adverse peri-intubation event. The predominant event was cardiovascular instability, observed in 42.6% of patients. Severe hypoxaemia and cardiac arrest were observed in 9.3% and 3.1% of patients respectively. First-pass intubation success was achieved in approximately 80% of patients, a second attempted intubation was necessary for 16%, while 4% of patients required more than two attempts. First pass intubation failure was associated with an increased risk of adverse events.

Patients experiencing major adverse events were at higher risk of both ICU (adjusted OR 1.52, 95% CI 1.26 – 1.83) and 28-day mortality (adjusted OR 1.44, 95% CI 1.19 – 1.74) after adjustment for underlying disease severity.

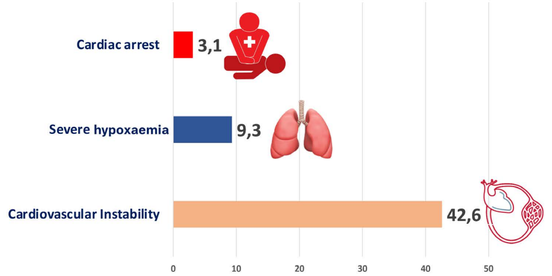
Important information has emerged from the description of the intubation procedure. The leading preoxygenation method was bag-valve mask, used in approximately 60% of patients, while noninvasive ventilation was used in only 12% of patients and continuous positive airway pressure in approximately 2% of patients. High-flow nasal cannula were used in approximately 5% of patients. Moreover, apnoeic oxygenation was seldom used (10% of patients).

The "haemodynamically friendly" agents ketamine and etomidate were used in 14% and 18% of patients respectively, while propofol, used in 40% of patients, represented the most frequently used induction agent. When administered to patients with underlying haemodynamic instability, propofol was associated with a significantly higher incidence of cardiovascular collapse compared to etomidate.

Videolaryngoscopy has been used as a first-choice method in 17% of patients, in most cases when an anticipated difficult airway was detected.

Another striking observation was the use of waveform capnography as elective method to confirm successful intubation in only 25.6% of overall patients. In 70% patients who had undergone oesophageal intubation, capnography was not used. Although the study was not able to detect a direct association between the waveform capnography underuse and patients' related outcomes, this observation is of concern. Indeed, it came after 10 years from the publication of the National Audit Project 4 in UK which reported how the majority of catastrophic airway adverse events were associated with either an underuse or misinterpretation of capnography (Cook et al. 2011). The INTUBE study highlights how many recently investigated interventions (e.g., noninvasive ventilation for preoxygenation, apnoeic oxygenation, videolaryngoscopy), are poorly applied in daily clinical practice.

INTUBE Study: major adverse peri-intubation events



Conclusion

The INTUBE study highlights the high number of major adverse events associated with intubation of critically ill patients. The finding that cardiovascular instability constitutes the leading adverse event underlines the need for future research to optimise peri-intubation haemodynamics to make tracheal intubation in the critically ill a safer procedure.

Conflict of Interest

None. ■

Key Points

- Tracheal intubation in critically ill patients is among the most commonly performed and high-risk procedures.
- The INTUBE study enrolled critically ill patients undergoing in-hospital tracheal intubation.
- INTUBE study is unique in focusing on critical illness rather than on the procedure location.
- The INTUBE study highlights the high number of major adverse events associated with intubation of critically ill patients.
- Cardiovascular instability constitutes the leading adverse event.

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New Applications of Pulse Oximetry

During and beyond the COVID-19 pandemic

The clinical applications of pulse oximetry go far beyond the mere monitoring of SpO_2. From home to ICUs, pulse oximeters may help to improve quality of care in patients with respiratory and circulatory disorders, in particular those with the coronavirus disease 2019 (COVID-19).

Pulse oximetry was developed in the 1970's to monitor oxygen saturation (SpO_2) during anaesthesia. It is today a mainstay of perioperative and intensive care unit (ICU) monitoring, and is also widely used in ambulances, emergency and respiratory departments. In this article, new applications of pulse oximetry are described, with a focus on patients with coronavirus disease 2019 (COVID-19). Pulse oximetry is increasingly used for remote and self-monitoring of SpO_2 from home, for continuous wireless monitoring on hospital wards, and for controlling closed-loop oxygen administration systems. In addition, tracking changes in the peripheral perfusion index (PI), a variable derived from the pulse oximetry waveform, may help to detect tissue hypo-perfusion, as well as guide fluid management. In the future, pulse oximetry may also be useful to quantify respiratory efforts and to detect changes in blood pressure.

Remote and Self-Monitoring of SpO_2 From Home

Over the last decade, pulse oximeters have been miniaturised and have become wireless. They also became affordable, and several medical grade products can now be ordered online for less than €100. As a result, pulse oximeters are more often part of our home medicine cabinet and the COVID-19 pandemic definitely boosted their adoption. Home monitoring enables the early detection of patients requiring oxygen and hospitalisation, or the surveillance of patients after early discharge from the hospital (Shah et al. 2020). For patients unable to monitor themselves, several remote monitoring programmes have been created. They usually combine the use of a finger wireless sensor by the patient and a supervision by a dedicated and remote command centre receiving SpO_2 and pulse rate measurements via the patient's smartphone. In case of abnormalities detected by the pulse oximeter, a dedicated staff is available to advise the patient on a 24/7 basis. In addition to classical finger sensors using transmittance photoplethysmography, reflective sensors part of adhesive patches, wrist devices or watches are now available (**Figure 1**). In theory, these tools have potential to expand the use of pulse oximetry. However, their accuracy remains to be established by well-designed clinical studies and most have not been approved for medical use.

Continuous Monitoring on Hospital Wards

The recent surge of hospitalised COVID-19 patients created both ICU bed and healthcare worker shortages, raising concerns regarding patient safety. Therefore, the adoption of remote monitoring systems, specifically designed for hospital wards, dramatically increased. These systems enable the continuous monitoring of vital signs, including SpO_2, in a large number of ward patients at the same time, display the information on a central station, and, in case of clinical deterioration, immediately alert nurses directly on their pager or cellphone (Michard et al. 2019). During epidemics, remote monitoring also has the advantage of decreasing the number of physical interactions and thereby the risk of virus transmission.

In a large study done in the medico-surgical wards of 360 US hospitals (Lyons et al. 2020) before the pandemic, over 20% of rapid response interventions were triggered by a decrease in SpO_2. On the wards, vital sign spot-checks are usually done every 4-8h and another study showed that because of the intermittent nature of SpO_2 measurements, nurses may miss up to 90% of hypoxaemic events (Sun et al. 2015). In this context, continuous pulse oximetry systems, able to inform nurses directly on their pager in case of clinical deterioration, have been shown to be useful to decrease the number of rescue interventions and ICU transfers. Continuous monitoring of SpO_2 and other vital signs was already on the rise before the pandemic, and is today, more than ever, considered as a major opportunity to improve patient safety (Vincent et al. 2018).

Automated oxygen administration

In patients hospitalised for respiratory failure who require supplemental oxygen, precise manual oxygen titration is difficult to achieve and is time-consuming. Automated oxygen titration devices have been developed to avoid periods of hypoxaemia and hyperoxaemia (L'her et al. 2017). These systems are based on a closed-loop circuit that enables oxygen flow titration (the output variable) according to the patient's real-time SpO_2 (the input value). It intends to reverse the paradigm from a constant oxygen flow with a variable SpO_2 value, to a constant target SpO_2 set by the physician with continuous oxygen flow variations (**Figure 2**). The implementation of these closed-loop devices has been associated with a greater percentage of time spent within the SpO_2 target range, as well as shorter duration of oxygen administration and hospital length-of-stay (Denault et al. 2019).

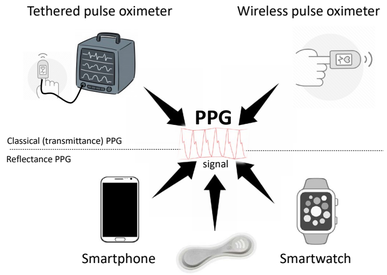


Figure 1. How to record a photoplethysmographic (PPG) waveform

Assessment of tissue perfusion

The PI is the pulsatile component of the photoplethysmographic wave form. In healthy volunteers, it represents between 0.5 and 5% of the non-pulsatile signal. The PI is calculated and displayed by many pulse oximeters and, until recently, was mainly used as a quality indicator for pulse oximetry. Monitoring PI has been proposed to assess the peripheral tissue perfusion. It is often low (<0.5%) in patients with shock or receiving vasopressors, has been shown to correlate with lactate and venous oxygen saturation and to be an independent risk factor for 30-day mortality (He et al. 2015).

Pulse oximeters are typically positioned on fingers or ears so that the PI provides information about the local perfusion. Sometimes, pulse oximeters are used on toes to monitor limb perfusion after vascular surgery or during veno-arterial extra-corporeal membrane oxygenation. A new Foley catheter, incorporating a photoplethysmographic sensor, was recently developed to continuously monitor the urethral PI (Dépret et al. 2020). By detecting early changes in pelvic perfusion, it may help to optimise haemodynamics during high-risk abdominal surgery and in shock states (**Figure 2**).

Other methods have been proposed to assess peripheral tissue perfusion or muscle oxygenation. They include the clinical evaluation of the capillary refill time and the assessment of tissue oxygenation by non-infrared spectroscopic (NIRS) sensors. The evaluation of the capillary refill time is intermittent and NIRS sensors are expensive. Whether they have any advantages to guide haemodynamic therapy over the mere and continuous monitoring of PI with a pulse oximeter remains to be demonstrated.

Fluid Management

During general anaesthesia

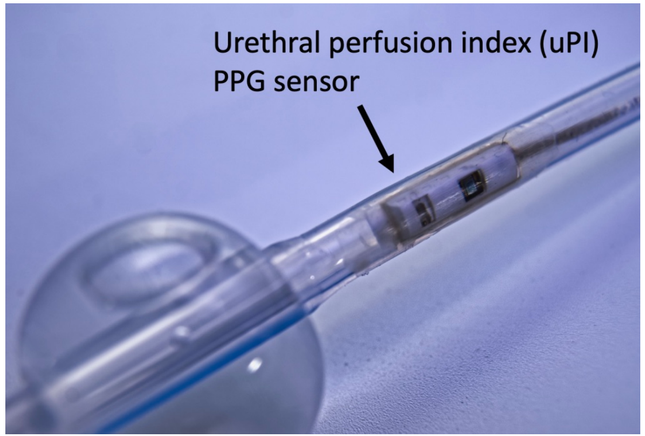
In anaesthetised and mechanically ventilated patients, the respiratory changes in left ventricular stroke volume induce proportional changes in arterial pulse pressure (PPV) and in PI, known as the pleth variability index (PVI). PVI has been shown to be a good predictor of fluid responsiveness in the operating room, but not in the ICU where motion artifacts are frequent, and the pulse oximetry signal is sometimes far to be optimal (as often evidenced by a low PI).

Because intra-operative PPV-guided fluid therapy has been shown to decrease postoperative morbidity, a recent study (Fischer et al. 2020a) investigated the value of PVI to guide fluid therapy during surgery. This randomised controlled trial assessed the postoperative outcome impact of maintaining PVI <13% during surgery. The study did not show any outcome benefits but the percentage of time within target (PVI < 13%) was low (< 40% of the surgery time) and did not differ between groups. Further studies are therefore needed to clarify the possible impact of PVI-guided fluid strategies on postoperative outcome. However, it is important to bear in mind that all non-invasive attempts made so far to rationalise fluid therapy during surgery, either with PVI or cardiac output monitoring systems, failed to impact postoperative outcome (Fischer et al. 2020b). These findings may simply reflect the fact that because postoperative complications are uncommon in low-risk surgical patients, there is not much room for improvement. In other words, if goal directed fluid therapy with PPV or invasive pulse contour methods has been shown to be useful to improve postoperative outcome in high-risk surgical patients (who usually have a radial catheter in place), it is unlikely that goal directed fluid therapy with non-invasive methods may be cost-effective in low-risk patients.

In patients with acute respiratory failure

In patients with acute respiratory failure, individualised fluid therapy is desirable to balance the risks of fluid overload (increase in pulmonary oedema) with the risks of fluid restriction (decrease in cardiac output and oxygen delivery to the tissues). Predicting preload responsiveness is a way to identify patients who may benefit from fluid administration and, maybe more importantly, to prevent unjustified fluid boluses in preload non-responders. Predicting preload responsiveness was recently recommended by WHO, the Surviving Sepsis Campaign guidelines and the NIH for the fluid management of COVID-19 patients.

In spontaneously breathing patients and during protective mechanical ventilation, it is well established that both PPV and PVI have a poor predictive value, which is mainly related to a low sensitivity. In contrast, the assessment of changes in cardiac output during a passive leg raising (PLR) manoeuvre has been shown to accurately predict preload responsiveness. This approach requires the use of cardiac output monitoring systems which are not always readily available or used, particularly in spontaneously breathing patients. Interestingly, the two main determinants of the pulse oximetry-derived PI are vascular tone and cardiac output. Assuming no significant changes in vascular tone, one may therefore assume that changes in PI may reflect changes in cardiac output. A recent study done in critically ill patients showed that a relative increase in PI >9% during a PLR manoeuvre predicts an increase in cardiac output >10% with a sensitivity of 91% and a specificity of 79% (Beurton et al. 2019). In summary,



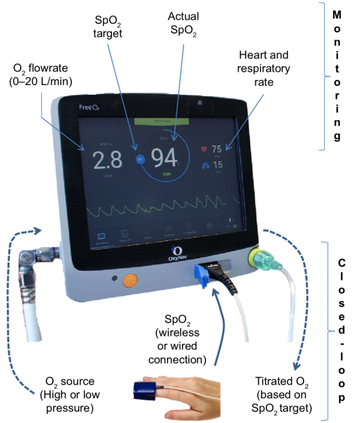


Figure 2. Examples of new medical devices using photoplethysmography (PPG). Left: modified Foley catheter with a PPG sensor enabling the continuous recording of the urethral mucosal perfusion (from Vygon, with permission). Right: closed loop system adapting automatically oxygen flow to individual needs (from Oxynov, with permission).

when cardiac output is not monitored, PLR-induced changes in PI may help to predict fluid responsiveness

What's Next?

Quantifying respiratory efforts

The physiologic response to hypoxaemia is an increase in respiratory frequency and tidal volume. Work of breathing increases, resulting in large changes in pleural pressure which may be responsible for self-inflicted acute lung injury. This phenomenon has been advocated to explain, at least in part, the rapid deterioration of lung function in severe COVID-19 patients. A recent study (Tonelli et al. 2020) suggests that patients with acute respiratory failure in whom respiratory efforts do not quickly decrease after initiating non-invasive ventilation, ultimately require tracheal intubation. In research studies, respiratory efforts are quantified by monitoring the respiratory swings in oesophageal pressure. But in clinical practice, oesophageal probes are not used. In spontaneously breathing patients, PVI depends mainly on the magnitude of changes in pleural pressure and could therefore be used to approximate respiratory efforts (Michard and Shelley 2020). Thus, when initiating oxygen therapy or non-invasive ventilation, monitoring changes in PVI may help to assess the impact on respiratory efforts and has potential to prevent intubation delays. Clinical studies are currently ongoing to confirm these hypotheses.

Tracking changes in blood pressure

Pulse oximeters can be used to calculate the pulse wave transit time (PWTT), which is the time difference between cardiac contraction and the peripheral pulse arrival. The PWTT depends on blood flow and the mechanical properties of the arterial bed. Both a decrease in cardiac output and in vascular tone (the two determinants

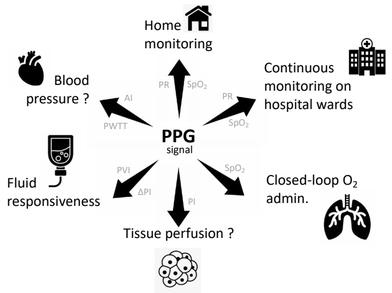


Figure 3. New and future applications of photoplethysmography (PPG)
PR, pulse rate; SpO_2, oxygen saturation; PI, perfusion index; PVI, pleth variability index; PWTT, pulse wave transit time; AI, artificial intelligence; admin., administration.

of blood pressure) induce an increase in PWTT. Thus, tracking changes in PWTT has been proposed to predict changes in blood pressure. For instance, continuous monitoring of PWTT has been shown to be useful to detect beat-to-beat changes in systolic arterial pressure during anaesthesia induction (Kim et al. 2013). It could therefore be used to predict hypotension and automatically trigger oscillometric brachial cuff measurements. In ward patients wearing wireless electrodes (to detect cardiac contraction) and a finger pulse oximeter, tracking changes in PWTT has been used to unmask hypotensive events that, otherwise, would have been missed by nurses who were spot-checking blood pressure only every 4h (Turan et al. 2019).

More recently, a machine learning algorithm has been developed to predict blood pressure from photoplethysmographic waveforms (Ghamri et al. 2020). A large number of pulse oximetry waveforms and corresponding invasive blood pressure numbers were used to "teach" the algorithm how to recognise specific patterns or signatures of blood pressure changes (learning phase). During the validation phase, the algorithm demonstrated an excellent performance to detect changes in arterial pressure during anaesthesia induction.

Conclusion

The surge of patients with COVID-19 has been a catalyst for the adoption of SpO_2 monitoring from home, remote and continuous monitoring of vital signs on hospital wards and closed-loop administration of oxygen (**Figure 3**). In patients with acute respiratory failure, tracking changes in PI during a PLR manoeuvre may help to identify fluid non-responders and hence prevent unjustified fluid administration. In spontaneously breathing patients, a decrease in PVI may reflect a decrease in respiratory efforts. Therefore, monitoring PVI may help to assess the efficacy of oxygen therapy, CPAP or non-invasive ventilation. Changes in PWTT predict changes in blood pressure and could be used to trigger upper-arm cuff measurements (automatic smart triggering). Machine learning systems have potential to extract more information from pulse oximetry waveforms, and such waveforms can now be recorded by smartwatches or adhesive patches. These innovations should further push the envelope of photoplethysmography and create new opportunities for physiologic monitoring beyond the operating room and the ICU.

Conflict of Interest

FM is the founder and managing director of MiCo (michardconsulting.com), a Swiss consulting and research firm. MiCo does not sell any medical device and FM does not receive royalties from any medical device company. ■

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Practical Strategies in Mechanical Ventilation for Patients With Acute Respiratory Failure Due to COVID-19

The clinical applications of pulse oximetry go far beyond the mere monitoring of SpO_2. From home to ICUs, pulse oximeters may help to improve quality of care in patients with respiratory and circulatory disorders, in particular those with the coronavirus disease 2019 (COVID-19).

Introduction

The SARS-CoV-2 virus responsible for the COVID-19 pandemic has a wide variety of clinical presentations. Age is the most important risk factor for critical illness and a poor prognosis, typically beginning on the seventh day after the onset of symptoms. In a large cohort of symptomatic patients who were followed early during the pandemic, 81% presented with mild disease, 14% had severe disease and 5% became critically ill (Berlin 2020). The most important variables associated with high mortality were age, presence of diabetes, obesity, and severe acute respiratory distress syndrome [ARDS] (Schimdt 2021). Regarding the high mortality associated with ARDS, it is known that adequate programming and manoeuvres to maintain an effective invasive ventilation strategy are significantly associated with a reduction in mortality.

Protective Mechanical Ventilation

In the setting of care of a patient with severe and critical COVID-19, a lung support strategy with invasive mechanical ventilation reaching alveolar protection targets is a priority, currently remaining the most impactful target measure on survival.

The goals of protective ventilation are decisive in the prognosis and evolution of patients with ARDS, therefore patient care should always be individualised based on their clinical presentation, haemodynamics and other conditions like availability of resources. The WHO proposes to perform protective ventilation in patients with ARDS due to COVID-19. It is critical to maintain a tidal volume (Vt) between 4-8 ml/kg adjusted to predicted weight (Brower 2000), establish a positive pressure at the end of expiration (PEEP), perform plateau pressure (Pp) and drive pressure measurements and keep them under their respective goal, as well as maintain normocapnia and normoxaemia (**Figure 1**).

The LOV-ED study proposes to perform protective ventilation in the emergency department since results showed a decrease in mortality, shorter stay in the ICU, and days off of mechanical ventilation in the group that was provided with a liberal strategy of ventilatory support. The ARMA study demonstrated that low Vt ventilation in patients with ARDS led to a significant decrease in in-hospital mortality. LUNG SAFE, an observational multicentre study demonstrated that mortality of severe ARDS in the intensive care unit is 46.1%, which is why it emphasises protective ventilation strategies. The ARDS Clinical Trials Network ALVEOLI study included 549 patients, the Lung Open Ventilation Study (LOVS) 983 patients, and the ExPress trial almost 1000 patients. The results of the three studies consistently showed that an indiscriminate increase in PEEP strategy does not change survival in ARDS.

Amato (2015) conducted a retrospective analysis and coined the term driving pressure (Dp) or distending pressure (Pp - PEEP). Decreases in Dp due to changes in ventilator settings were strongly associated with an increase in survival establishing as cut point less than 13 cm H_2O. Villar (2017) evaluated the risk of hospital death based on Vt, PEEP, Pp, and Dp for 24 hours under protective ventilation to predict hospital mortality, reproducing what was reported by Amato.

Pelosi (2018) proposes to maintain a strategy with closed lungs and at rest, thus minimising ventilator-induced lung injury (VILI). High PEEP is associated with alveolar overdistension, oedema formation, decrease in lymphatic drainage, and deterioration of right ventricular function, as well as the impact on systemic haemodynamics. Also, a

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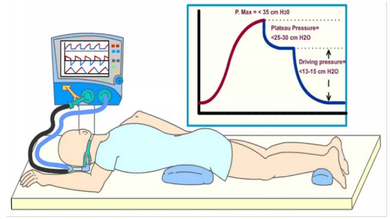

Figure 1. Goals of protective mechanical ventilation and prone position

Pp <25-30 cm H_2O is associated with a decrease in the proportion of hospital mortality.

It is recommended to start with a Vt of 6 ml/kg and do an inspiratory pause to measure the Pp. If it exceeds 30 cm H_2O, the Vt should be decreased until it is 30 cm H_2O. It is not recommended to lower the Vt less than 4 ml/kg because of the risk of severe hypercapnia and atelectasis. Dp in numbers greater than 13 to 15 cm H_2O have been associated with higher mortality (Amato 2015; LUNGSAFE, 2016); however, there are currently no prospective studies supporting Dp as a target of alveolar protection in patients with COVID-19 (despite this lack of evidence, there is a strong recommendation by international guidelines in ARDS produced by SARS-CoV-2 sustained by remaining evidence in all-cause ARDS).

Positive end-expiratory pressure (PEEP) in patients with severe ARDS is recommended at high levels, up to 15 cm H_2O of PEEP based on the low $PEEP/FiO_2$ table of the ARDSnet group. Despite the arbitrary method it generated, it has been validated in several ways, remaining as the best supportable way of setting the PEEP. That is why we strongly suggest its use (**Table 1**).

PaO_2 and $PaCO_2$ goals in ARDS must be maintained. These goals have been associated with survival within an O_2 range by pulse oximetry between 88 to 92-95% (Brower 2000; Papazian 2019). But in severe COVID-19, a target of SpO_2 between 92 to 96% is recommended. It is also recommended to keep PaO_2 between 60 to 100 mm Hg, as well as maintain strict supervision of $PaCO_2$ levels in order to keep less than 60-80 mm Hg as a secondary target.

Protective ventilation (and thus virtually every patient under mechanical ventilation) should avoid mechanical ventilation-induced injury (VILI). Close monitoring of respiratory system pressures should be performed to avoid barotrauma, with peak pressure (Pmax) less than 35 cm H_2O, Pp less than 25 cm H_2O, Dp less than 13 cm H_2O. With these interventions we can limit the damage and improve the prognosis and survival of patients with ARDS (**Figure 1**).

Prone Positioning

The first report on prone position (PP) in patients with acute respiratory distress syndrome (ARDS) appeared in 1976 and described a marked improvement in oxygenation. It is now clearly recognised that PP is associated with a significant improvement in oxygenation rates. In various studies in both animals and humans, it has been found that PP can reduce lung injury associated with mechanical ventilation (**Figure 1**).

ARDS is characterised by disruption of the alveolar-capillary barrier, with an increase in its permeability, alveolar oedema, also associated with depletion of lung surfactant, leading to alveolar instability and alveolar collapse. Lung involvement is heterogeneous, with well-ventilated lung regions, which participate in gas exchange, and in other areas that are collapsed by pressure superimposed by interstitial and alveolar oedema, mechanisms that explain the decrease in lung volume in these patients, thus lower Vt requirements. PP allows these alveolar areas to be recruited, redistributing and homogenising ventilation, decreasing the intrapulmonary shunt, improving oxygenation, ventilation, and lung mechanics. However, the degree of recruitment depends on factors such as the severity of the lung involvement, the pronation time, and the time elapsed from the lung injury to the pronation of the patient.

Patients with COVID-19 with moderate to severe ARDS seem to respond well to invasive ventilation in PP, which makes PP ventilation recommended in international guidelines for the treatment of COVID-19. This is corroborated in two meta-analyses and later in the PROSEVA trial, which showed a beneficial effect of PP in moderate to severe ARDS with an improvement in oxygenation and a reduction in mortality compared to the conventional supine position. PP is therefore one of three therapies that show a positive effect on ARDS mortality, with current volume reduction, and early use of neuromuscular blocking agents (NMBA). Its use in mild to moderate ARDS continues to be discussed, as well as the optimal duration of PP sessions. In the PROSEVA trial, they remained on average 17 hours in PP. A study conducted by Jochmans et al. (2020) showed that the beneficial physiological effects continued with even

Goal SpO_2: 92–96% (PaO_2 60–80 mm Hg) - Wait 5–10 mins before making modifications to the programmed PEEP regarding SpO_2.												
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	1
PEEP	5	5	8	8	10	10	10	12	14	14	15	15

Table 1. Positive end-expiratory pressure (PEEP) in patients with severe ARDS

Contraindications	
Absolute contraindications	**Relative contraindications**
Intracranial hypertension	Vertebral instability Shock Burns Recent tracheal surgery
Complications	
Transient desaturation, catheter removal, iatrogenic extubation, vomiting, facial and eye oedema, ischaemic neuropathy and ulcers on the face, knees and shoulders.	

Table 2. Contraindications and complications of the prone position

16 hours of PP and 24 hours in some patients.

The guide for the treatment of ARDS recommended the use of PP for at least 16 hours a day in patients with moderate-severe ARDS with a PaO_2/FiO_2 ratio <150. The criteria for responding to mechanical ventilation in PP are an increase of 20% in PaO_2/FiO_2, 10 mm Hg in PaO_2, and 1 mm Hg decrease in $PaCO_2$ at 4 hours after the manoeuvre.

Trained personnel are required to perform the PP of a patient under mechanical ventilation as they can identify its risks and complications. A delay greater than three days to the pronation of a patient with ARDS does not confer any benefit, so this technique should be used before 12 to 72 h of IMV, always based on its indications and contraindications (**Table 2**). It is suggested to keep patients in the supine position who, after having been pronated, can maintain a PaO_2/FiO_2 >150 after 4 hours in this position.

Recruitment Manoeuvres

WHO strongly recommends not to routinely perform recruitment manoeuvres. They can be considered in case of hypoxaemia refractory to the previous strategies. To date, there is no described ideal form of alveolar recruitment. A strategy using a lung recruitment manoeuvre and titrated PEEP increased mortality of patients with moderate to severe ARDS (Biasi 2017).

Conclusion

Low Vt with prone ventilation is associated with the greatest reduction in mortality for critically ill adults with moderate to severe ARDS. Reproducible protective ventilation strategies must be carried out to obtain better outcomes (Sud and Mathews 2021).

Conflict of Interest

None ■

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Airway Management in Critically Ill Patients – Striving to Improve Outcomes

Tracheal intubation in critically ill patients requires planning, preparation and optimisation of patient's physiology prior to the procedure. Reducing repeated attempts at tracheal intubation, improving peri-intubation oxygenation, and haemodynamic optimisation, are some of the steps that can reduce the antecedent morbidity and mortality.

Introduction

Airway management including tracheal intubation (TI) is a common and integral part of the care provided to critically ill patients. Critically ill patients have minimal physiological reserves, leading to a physiologically difficult airway and predisposing them to an increased risk of complications. Furthermore, anatomic and logistical difficulties with airway management are also very common in these situations. In a recent prospective observational study evaluating intubation practices in critically ill patients across 29 countries, adverse events occurred after intubation in 45.2% of patients, including cardiovascular instability in 42.6%, severe hypoxaemia in 9.3%, and cardiac arrest in 3.1% (Russotto et al. 2021). This baseline physiologic risk is often further exaggerated when more than one attempt at tracheal intubation is required (De Jong et al. 2020a). Therefore, the goal of tracheal intubation in the critically ill patients is to have a first pass success without adverse events. A recent prospective observational study in 1513 emergency tracheal intubations showed that first pass success without adverse events was reduced to a similar extent in patients with anatomically and physiologically difficult airways, highlighting the importance of physiological optimisation along with the use of strategies and tools to overcome anatomical difficulty (Pacheco et al. 2021).

Challenges Associated with Airway Management in Critically Ill Patients

Anatomic challenges

The incidence of an anatomically difficult airway in ICU patients has been estimated to be around 10% (Griesdale et al. 2008; Jaber et al. 2006; Schwartz et al. 1995). Patients who might have been intubated with ease in the operating rooms (ORs) tend to be harder to intubate in the ICU with antecedent complications (Taboada et al. 2018). Furthermore, airway assessment in such scenarios can be sub-optimal; there may not be enough time to perform an airway assessment, or the patient may not cooperate for an airway exam.

Physiologic challenges

An airway is considered physiologically difficult when the physiologic derangements place the patient at a higher risk of cardiovascular collapse with intubation and conversion to positive pressure ventilation (Mosier et al. 2015). Critically ill patients often have conditions such as hypoxaemia, hypotension, severe metabolic acidosis and right ventricular dysfunction, that predispose them to a physiologically difficult airway. **Table 1** lists some of the causes of physiologic challenges that providers might face in these circumstances as well as strategies to prevent associated complications.

Logistical challenges

Along with the anatomic and physiologic challenges, it is also important to take into account the situational or logistical challenges that accompany airway management in the ICU. These situationally difficult airways can arise due to infrastructure, personnel and/or equipment related concerns. Space and lighting limitations and poor access to the patient's head are some of the infrastructure related issues that exist. Personnel related limitations pose significant challenges as the airway team may be working at the bedside with members that are inexperienced and often times, expert help may not be readily available. Similarly, appropriate airway equipment and drugs may not be available in all situations and circumstances. W

Condition	Strategies to prevent complications
Hypoxia	• Preoxygenation with HFNO or NIV • Apnoeic oxygenation with HFNO
Hypotension	• Pre-procedure POCUS exam to assess cardiac and volume status • Prophylactic use of fluids and/or vasopressors/inotropes • Avoid propofol for induction
Severe metabolic acidosis	• Consider awake intubation • Optimise minute ventilation
Right ventricular dysfunction	• Use POCUS to evaluate for RV systolic function • Evaluate for fluid and vasopressor tolerance • Reduce RV afterload in fluid-intolerant patients • Consider pre-intubation diuresis in patients with RV volume overload
Full stomach/significant GERD	• Awake intubation or RSI • Consider sitting up position
Neurologic injury/raised ICP	• Avoid blood pressure fluctuations • Avoid hypercarbia
Anterior mediastinal mass	• Preserve spontaneous ventilation • Consider awake intubation

Table 1. Physiologic challenges associated with emergency tracheal intubation in critically ill patients

Planning and Preparation

Considering the high rates of complications associated with tracheal intubation in critically ill patients, adequate preparation during the peri-intubation period is essential. After assessing for potential anatomic, physiologic, or situational challenges that may be present, preparation and optimisation of the patient as well as the team is important. Ensuring availability of necessary equipment and personnel, maximising preoxygenation, and haemodynamic optimisation can prevent complications. Whenever feasible, a thorough discussion with the patient (or their surrogate) on the acceptance of intubation and mechanical ventilation should be held.

Clinical history and examination

A thorough review of the patient's medical record for clinical history, relevant laboratory investigations and imaging reports along with a focused physical exam is vital in tailoring the approach to airway management including the choice of drugs, to avoid associated complications. Bedside point of care ultrasound (POCUS) exam may be very helpful, not only to help assess the haemodynamic status of the patient, but also to assess for increased aspiration risk. The protocolised use of a handheld POCUS device can improve the accuracy of diagnosis and outcomes in patients with acute respiratory or circulatory failure (Zieleskiewicz et al. 2021), and its utility in ICU airway management needs further evaluation.

Airway assessment

Identifying a potentially difficult airway is crucial; however, current bedside screening tests are limited by their poor sensitivity and specificity (Shiga et al. 2005). A history of difficulty with airway management described by the patient or documented in the patients' medical record is important. Similarly, the time of last oral intake, contraindications to use succinylcholine or other drugs, drug allergies, history of sleep apnoea, presence of dentures, etc. is important to assess. Amongst the bedside airway assessment tests, the upper lip bite test has the highest sensitivity (Roth et al. 2018), and the combination of mallampati (MP) score and thyromental distance (TMD) provides the most accuracy at predicting difficult intubation (Shiga et al. 2005). Many of these methods are often not feasible in this setting where the patient may be uncoopera-

tive, sedated, agitated, unstable or delirious (Levitan et al. 2004). Automated face-analysis approach to predict a difficult airway may help overcome some of these limitations, though further studies are needed to validate this approach before it becomes part of routine assessment (Cuendet et al. 2016).

While recognising the anatomically difficult airway is one part of the pre-intubation assessment, the anticipation of physiologic challenges prior to airway management is equally important. The MACOCHA score (**M**allampati score III or IV, sleep **A**pnoea syndrome, decreased **C**ervical mobility, mouth **O**pening <3cm, **C**oma defined by a Glasgow score <8, severe **H**ypoxaemia, and if the practitioner is not an **A**naesthetist) that combines anatomic, physiologic, and operator characteristics is simple to perform, may be more suitable for use in critically ill patients and was recently validated in a multicentre study (De Jong et al. 2013).

Equipment and personnel

Considering the unpredictability associated with these situations, we suggest preparing for airway management in a way that assumes that every step might fail. The patient should be appropriately monitored and continuous $EtCO_2$ monitoring should be utilised. It is reasonable to make the monitors, especially pulse-oximetry loud and audible to everyone in the room. Next, it is important to ensure that necessary equipment is on hand and functional. A cart with all of the necessary supplies to facilitate tracheal intubation, rescue oxygenation and haemodynamic support is essential to avoid the need for securing essential equipment at the last minute. If deemed necessary and time permitting, a flexible intubation scope should be brought to the bedside to assist in intubation. Considering that blood and vomitus in the airway are common in this situation and may predict a difficult airway (Gaither et al. 2014), availability of functioning high-efficiency suction devices should be ensured.

Tracheal intubation is an aerosol generating procedure and can impact the transmission of respiratory virus illnesses such as COVID-19 (Brown et al. 2020). Hence, as recommended by national organisations, providers involved with TI in patients with or suspected to have a respiratory viral illness should adhere to full contact and airborne personal protective equipment (Cook et al. 2020). Also, in such circumstances, intubation should be performed in an airborne infection isolation room by an experienced provider, with additional help available outside the room.

Elucidating the skill level of available staff and establishing clear roles and responsibilities of the team members before proceeding for TI is essential. Closed-loop and clear communication among the team members about the airway concerns, airway plan, backup plan etc. is essential in such stressful situations and can help prevent medical errors, as well as increase speed and efficiency. The presence of two airway operators, with at least one being experienced has shown to reduce complications during tracheal intubation (Jaber et al. 2010).

> “the goal of tracheal intubation in the critically ill patients is to have a first pass success without adverse events”

Checklists

Instituting a checklist for non-OR airways may help ensure the necessary preparations and precautions have been taken. Pre-intubation checklist is especially effective in less experienced hands, and it was found that the implementation of an intubation bundle can reduce life-threatening complications associated with emergency airway management (Jaber et al. 2010). The key is to keep the checklist simple and succinct, thus improving compliance and acceptance. A randomised trial evaluating the use of a written checklist prior to tracheal intubation in ICU compared with usual care found no difference in lowest oxygen saturation and lowest systolic blood pressure (SBP) from induction up to two minutes after TI between the groups (Janz et al. 2018). However, the checklist did not include interventions aimed at physiological optimisation [e.g. non-invasive ventilation (NIV), fluid load, early use of vasopressors], thus explaining why the selected outcomes did not improve with the use of checklist. A pre-intubation checklist, which includes interventions to enhance oxygenation and haemodynamic optimisation, may be effective in less experienced hands, as observed by reduction in peri-intubation complications following the implementation of an ICU intubation bundle (Jaber et al. 2010).

Tracheal Intubation Procedure

Patient positioning

Optimal patient positioning during TI should strive to optimise both anatomic and physiological parameters and is essential to increase the success of intubation and avoid complications. The ramped position reduces the risk of pulmonary aspiration of gastric contents and of desaturation by maintaining the patient’s functional residual capacity. The debate about whether the sniffing or ramped position may be more appropriate still persists. Pulmonary fellows experienced increased intubation difficulty with intubations performed in the ramped position compared with the sniffing position (Semier et al. 2017), whereas patients intubated by emergency department residents showed improved first-attempt success with ramping compared with supine (Turner et al. 2017). Also while an obese patient would significantly benefit from a ramped position, a frail patient with limited neck range of motion may not. Thus, in the absence of clear cut evidence favouring one versus the other, it is suggested that positioning should be individually tailored to patient characteristics, as well as the skillset of the intubating provider (Myatra 2019).

Preoxygenation and apnoeic oxygenation

For majority of patients that require airway management in the ICU, life-threatening hypoxaemia during the procedure is a major concern. Adequate preoxygenation is essential to better prepare such patients for intubation and should be an integral component of all emergent airway interventions. It is important that oxygen therapy be initiated immediately on arrival while preparations are underway to maximise the duration of preoxygenation. Oxygen delivery can be achieved using a simple face mask, standard or high flow nasal oxygen (HFNO), NIV mask or a combination of these devices. NIV or HFNO should be considered over conventional oxygen therapy for preoxygenation for TI in critically ill patients (Baillard et al. 2006; Frat et al. 2019; Guitton et al. 2019).

In patients with moderate to severe hypoxaemia, NIV may be superior to HFNO. Apnoeic oxygenation should be continued during attempts at TI and gentle mask ventilation should be considered during rapid sequence intubation (RSI) to prevent or treat hypoxaemia (De Jong et al. 2020b).

Rapid sequence intubation

Critically ill patients may have gastroparesis associated with critical illness or may not be fasted at the time of TI and hence, an RSI technique is often used in this setting. The main objective of the technique is to minimise the time interval between loss of protective airway reflexes and TI. Despite the technique’s widespread use, there is still no agreement on how it should best be performed especially with regards to manual ventilation and application of cricoid pressure (CP) or Sellick’s manoeuvre. Avoidance of manual ventilation before TI was traditionally recommended to avoid gastric insufflation, but recent evidence suggests that bag mask ventilation between induction and endotracheal tube placement may be well tolerated (Casey et al. 2019). In patients with physiologically difficult airway, mask ventilation may be lifesaving, and providers should balance the perceived risk of aspiration versus life threatening complications related to desaturation. The Sellick’s manoeuvre has been shown to have a questionable benefit. While there is evidence that gastric insufflation can be prevented by this manoeuvre (Rice et al. 2009), there are concerns that application of CP can result in an increased risk of aspiration by decreasing the lower oesophageal sphincter tone (Tournadre et al. 1997) and may impair the laryngeal view and thereby delay intubation and increase the potential for aspiration (Haslam et al. 2005).

Neuromuscular blockade versus maintenance of spontaneous ventilation

Neuromuscular blockade can improve mask ventilation, improve intubating conditions, abolish upper airway muscle tone including laryngospasm, optimise chest wall compliance and overall improve the first-attempt success with tracheal intubation in the ICU (Mosier et al. 2015). Also, the avoidance of paralytics during TI in the ICU has been found to be associated with difficult facemask ventilation and severe oxygen desaturation (Heuer et al. 2012). As a result, the use of paralytics as part of TI is recommended in critically ill patients by various national guidelines (Higgs et al. 2018; Quintard et al. 2019). However, apnoea after institution of muscle paralysis, may result in rapid desaturation, thus emphasising the importance of preoxygenation and apnoeic oxygenation. The fear of inability to mask ventilate after giving neuromuscular blockade is also one of the reasons providers are reluctant in using these agents.

Device selection

Intubation in critically ill patients is technically more challenging than elective intubation performed in the OR with worse glottic visualisation, increase in moderate or difficult intubation, lower first-attempt success, and a higher rate of complications (Taboada et al. 2018). Video laryngoscopy (VL) improves visualisation of the glottic opening; however, difficulty with navigating the endotracheal tube to and beyond the larynx is a concern and requires

> “adequate preoxygenation is essential to prepare for intubation and should be an integral component of all emergent airway interventions”

training. A recent meta-analysis that included nine randomised controlled trials with over 2000 critically ill patients, found that the use of a video-laryngoscope (VL) did not improve first-pass success, even when evaluating the studies according to the experience of the operator (Cabrini et al. 2018). Thus, the routine use of a VL for tracheal intubation in ICU remains controversial, but it clearly improves glottic visualisation as compared with direct laryngoscopy making it an important tool for difficult airway management (Jaber et al. 2019). Future trials will better define the role of a VL in ICU. Nonetheless, a video-laryngoscope should always be available as a backup tool to rescue difficult intubation and/or unsuccessful first attempt at DL in all ICU TIs.

Supraglottic airways (SGAs) can be utilised for establishing an airway in critically ill patients and are usually used after failed intubation as a rescue device in these situations (Shavit et al. 2018). They are relatively easy to insert and provide some protection against aspiration. If successful oxygenation can be achieved with a SGA, then this can be maintained until expert help arrives. An SGA may be used as a primary airway device and an intubation conduit in situations where an anatomically difficult airway is predicted. The endotracheal tube introducer (Bougie) is also a useful tool when the epiglottis is visible but vocal cords cannot be seen with a significantly higher first attempt intubation success reported in emergency situations (Driver et al. 2018). Hence, a bougie may be used for TI in the ICU by providers who have experience with its use.

Haemodynamic optimisation and pharmacologic management

Hypotension or cardiovascular collapse is common during and following TI in critically ill patients. In fact, cardiovascular instability was observed in 42.6% of all patients undergoing emergency intubation in a large multinational observational study and was found to be associated with significant morbidity and mortality (Russotto et al. 2021). This haemodynamic instability possibly results from a combination of pharmacologically induced sympatholytic action, conversion from negative-pressure to positive-pressure ventilation as well as the amelioration of the hypoxia and hypercarbia associated sympathetic drive. There is limited prospective data on optimal strategies for haemodynamic support during emergency airway management. Administration of a fluid bolus prior to intubation has been shown to be of minimal benefit (Smischney et al. 2020) and may actually cause harm and lead to postintubation hypoxaemia in non-volume responsive patients (Janz et al. 2019). It could be helpful in patients that are hypovolaemic and assessment of fluid responsiveness by a quick passive leg raising test or bedside point of care ultrasound (POCUS) exam may help identify the suitable candidates for a fluid bolus. Another widely used intervention to avoid peri-intubation hypotension is the use of bolus or push-dose vasopressors and/or continuous infusion of vasopressor agents either during or immediately after intubation (Jaber et al. 2010; Weingart 2015).

This prophylactic use of vasopressors may be an alternative and needs further investigation.

Amongst the induction agents, ketamine preserves the patient's respiratory drive, and can be used for delayed sequence intubation (optimising airway preparation and preoxygenation in an otherwise uncooperative or agitated patient). Caution should be exercised with its use in patients in whom excessive sympathetic stimulation could be detrimental, such as those with acute myocardial infarction or acute cerebrovascular event. The combination of ketamine and propofol (ketofol) may offer an acceptable haemodynamic profile when used for intubation in critically ill patients (Smischney et al. 2019). Etomidate is frequently used in emergent intubations in critically ill patients, as it tends not to cause hypotension on induction. However, it is a selective adrenocortical 11 beta-hydroxylase inhibitor and causes transient adrenal insufficiency, the clinical implications of which are debatable. No difference in morbidity has been observed with the use of ketamine or etomidate for emergency endotracheal intubation of critically ill patients (Jabre et al. 2009). Propofol can have a profound effect on the haemodynamics, especially in patients with hypovolaemia and/or impaired cardiac function and is rarely used for TI in critically ill patients. Titrating the dose, using smaller doses, pre-emptive or concomitant administration of vasopressor agents and judicious fluid administration may avoid significant haemodynamic perturbations. With a lack of consensus on an ideal induction agent, either etomidate or ketamine could be used as the first choice induction agent based on specific scenarios. The use of propofol should be limited to situations where TI is required for airway protection in the absence of cardiopulmonary compromise.

Succinylcholine, which is a depolarising neuromuscular blocker, provides a rapid onset and short duration of action. Its major side effects include malignant hyperthermia and acute hyperkalaemia in susceptible patients. Rocuronium does not carry the same risk of malignant hyperthermia or acute hyperkalaemia, but the onset and duration of action is highly dependent on the doses used for intubation. While meta-analyses have reported that the intubating conditions are better with succinylcholine (Perry et al. 2003; Tran et al. 2017), a recent study showed that clinician grading of intubating conditions was similar with both these drugs, and intubation-related complications occurred more often in the succinylcholine group (Guihard et al. 2019).

Future Directions

Future research is required to find interventions to reduce the high incidence of cardiorespiratory complications associated with TI in critically ill patients. These interventions should be aimed at improving first-pass tracheal intubation success while optimising the patient's cardiorespiratory status. Although significant work has been done to enhance the actual process of TI in critically ill patients, there is still limited knowledge on appropriate management of a physiologically difficult airway. The use of POCUS prior to TI can help assess the patient's cardiovascular status, facilitate rapid screening for difficult laryngoscopy, and assess for increased aspiration risk. Its routine use and its impact on outcomes needs validation. Studies investigating patient positioning, techniques for preoxygenation and the role of RSI/Sellick's manoeuvre based on patients' physiologic derangements would be beneficial. Future work should also address device development, including different blade shapes, angles, lengths and cameras as well as stylet modifications. The optimum choice of drugs for induction of anaesthesia as well as muscle relaxation based on patients' physiological alterations also needs further evaluation.

Conflict of Interest

AKK is funded with a Clinical and Translational Science Institute (CTSI) NIH/NCTAS KL2 TR001421 award for a trial on continuous postoperative haemodynamic and saturation monitoring. ■

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Hyperoxia – A Journey to the Centre of the Cell

An overview of hyperoxia, effect of reactive oxygen species on biological processes and tissues and effective strategies for oxygen therapy.

The reliance of life on oxygen is a modern and terra-centric view. Oxygen only appeared on the scene about 450 million years ago – wiping out many life forms or forcing them to trap oxygen with porphyrin rings – the ancestor of our own haemoglobin.

Therefore strategies to cope with low oxygen are numerous – from the bar headed goose at altitude over the Himalayas, to the naked mole rat shrouded in subterranean earth, to the deep diving turtle, which can withstand anoxia for 15 minutes.

Strategies for excess oxygen have had little selection pressure – or have they? Reactive oxygen species (ROS) are the main by-product that draw attention. How does inspired oxygen affect this? What do they do to cells, and to organisms? What protection do we have from them? What does the evidence say for our patients?

Current RCTs

Evidence at present tends towards increased harm from hyperoxaemia, particularly in respiratory patients. However one trial suggested increased rates of ischaemic gut in a conservative oxygen arm and was stopped early due to unlikelihood of finding a significant primary endpoint difference (mortality) (Barrot et al. 2020).

HYPERS2S (oxygen in septic shock), and OXYGEN-ICU suggest increased mortality in hyperoxia. SO2S (oxygen in stroke), ICU-ROX (oxygen in ICU), and AVOID (oxygen in MI requiring PCI) found no benefit of hyperoxia. The IOTA 2018 metanalysis suggested a trend towards mortality in hyperoxia- albeit weighted heavily in OXYGEN-ICU which had some methodological flaws

Effect of FiO_2 on ROS Generation

Many of us will be familiar with the oxygen cascade – the journey from atmospheric concentration, to dilution with water vapour, respiratory tract mixing, diffusion across the lung surface, capture in blood, and delivery to the mitochondria. It is not clear how much inspired oxygen eventually reaches the mitochondrial electron transport chain (ETC), nor, how much of this is coupled to ATP production or, is leaked as ROS. The proportion varies by disease state and prior level of fitness.

For example, HIIT induces mitochondrial biogenesis genes that enable prompt repair and recovery from ROS-damage; furthermore it also induces the electron transport chain complexes to super-assemble into a formation that reduces ROS leak from the guilty party, which is often complex I. Thus, altitude trained athletes could use 60% oxygen with no measurable oxidative stress in blood or urinary measures of ROS production (Wilbur et al. 2004). However, the effect of cell stress/pathogen exposure/hypoxia on the mitochondrial ETC is often to break it between complex I. and II, reverse shunting oxygen back the way it has come and releasing it as a free radical (Liu et al. 2002). This is an alarmin signal that helps stabilise cell siege responses (for example an active subunit of HIFa, which transcribes an array of heat shock proteins, antioxidants and metabolic enzymes like pyruvate dehydrogenase, turning away from the Kreb's cycle). In this setting, ROS is enhanced by elevated FiO_2 (Yang et al. 2016).

Effect of ROS on Biological Processes Pertinent to Critical Care

ROS and other agents such as cyanide and hydrogen sulphide are actually used in health as short distance, rapid cell mediators, and are a completely normal and necessary part of cell function – coupling ATP production to consumption. However like all poisons, it is the dose that is important. Mismatch between ROS and antioxidant defence has become a focus of organ damage – see vitamin C advocation. However when a cell is stressed, iatrogenic intervention can confuse the cell siege strategy developed by pathogen exposure. In the setting of infection, giving a conflicting signal in the form of over-adequate oxygen, can generate ROS and further alarmins.

Effects of ROS on Tissues

Immune

The reverse electron transport mentioned above in the context of infection, is weaponised by neutrophils and other cells, to destroy invaders. Eukaryotic cells have better resistance to ROS than many invaders for a number of reasons, so ROS are a useful frenemy. One, DNA is inherently more stable than RNA in terms of oxidisation, inevitably why it arose, moreover keeping DNA tightly sealed in a lipid membrane means it is the nuclear envelope, ahead of the genetic material, that gets oxidised. Burst killing by neutrophils is infamous – visible as pus. In fact, increasing FiO_2 enhances burst killing as one might expect (Tantingco and Ryou 2020), and was an historic argument for the use of supplementary oxygen in reducing wound infection.

However ROS and their oxidisation of anything within reach – especially membrane lipids, are prone to activating both apoptosis via mitochondrial damage, as well as pyroptosis via activation of innate immune components, such as the inflammasome.

One group actually found that repeated (but not sustained) cycles of hypoxia reduced ROS generation and the inflammatory phenotype of microglia (Tantingco and Ryou 2020). This is similar to the concept of remote ischaemic conditioning – a distal distress signal that prepares other tissues for siege. Repeated hypoxic exposure also appears to have beneficial effects on mitochondrial and skeletal metabolism – and is under investigation in sport performance fields. The key is that it is never sustained to the point of apoptosis. Cyclical permissive hypoxia is a novel concept. Similarly it was noted that in presence of lactate, oxidative phosphorylation increased with increasing oxygen, maintaining VO_2max, whilst in presence of glucose, VO_2 was static. Cells require the correct substrate to utilise oxygen and limit ROS (Levasseur et al. 2006), and this is dynamic in stress.

Lung

FiO_2 is known to cause diffuse alveolar damage alone and in conjunction with mechanical ventilation (VILI); the two are synergistic. However hypoxia is of course, deleterious to the rest of the body, and as such, the lungs are often over-oxygenated to bypass an AA gradient or mismatch to improve blood oxygen content. The lungs are therefore a special focus of ROS interest. ROS are indicated in the mechanism of VILI (Zhu et al. 2018). Intriguingly, another source of oxidative stress in critical illness, is free heme. As a transition metal, its ability to flip between ferric and ferrous give it a unique tendency to oxidise its surroundings. It is therefore unsurprising heme stabilises siege players like HIFa, and also unsurprising that three of the proteins raised in inflammation are ferritin (binds heme), hepcidin, and heme oxygenase. The process by which heme causes cell death is called ferroptosis – mitochondria are especially susceptible, and they are also the site of its production. Chelation with deferoxamine (pre exposure rather during the insult) was able to markedly reduce VALI in mouse models (Zhu et al. 2018). This is tricky in a critical care setting, where we receive the insulted physiology after the event, however it could be a strategy before high risk anaesthetics and surgeries which are likely to require prolonged ventilation post operatively. As ICU patients are often also anaemic (although not pathologically so…), the body may already have chelated what it can.

> "mismatch between ROS and antioxidant defence has become a focus of organ damage"

Heart

Cardiac mitochondria are unique in that they use special peroxisomes to ship out ROS and manage the peroxide consequences of their hard work.

Brain

ROS are naturally an obvious problem with respect to hypoxia, ischaemia-reperfusion and sub arachnoid haemorrhage, the scope of which is extensive. Given the highly limited regeneration of neural tissue in the adult, attention has been given to keeping patients sedated with neuroprotective adjuncts, such as Xenon, whose neuroprotective properties seem to stem from repelling the excitotoxic effects of NMDA receptor stimulation.

Kidney

Acute Kidney Injury (AKI) has proved a valuable model in all the ways ROS cause renal dysfunction and various strategies have been used to try and reduce the issue (Tomsa et al. 2019).

Gut

As a highly metabolic tissue, prone to ischaemia, and also prone to resistant post-operative ileus, ROS are an important issue for the gut. Hypoxia here makes mucosal surfaces susceptible to erosion and invasion, the consequences of which bear hefty lethality and was a clinical concern in RCTs of conservative oxygen use in ICU. It is also in fly gut, that the ROS generation of sleep deprivation was proven to be fatal (Hindson 2020). A balancing act is plainly needed. Of note, ileus seems to be particularly related to NO more than mitochondrial ROS, as exogenously applied nitrite proved to be exceptional in a model of murine ileus (Cosyns et al. 2015), via inhibition of guanyl cyclase.

Defences Against ROS

ROS are an ancient foe and strategies are conserved across phyla, normally pertaining to antioxidant enzymes and free radical sinks. Classics are gluthionine, thioredoxin, superoxide dismutase, and manganese. Defects in all these systems tend to be associated with cardiac and CNS developmental issues/degeneration. They are the range of antioxidants switched on in arousal from hibernation (Yin et al. 2016), where metabolism climbs ten-to-hundred fold within hours.

Intriguingly, of the mammals, primates lost the ability to synthesise their own vitamin C and require it via diet. It is unclear then, if it is superfluous, or actively selected against. Numerous advantages for acquiring orally exist (Hornung and Biesalski 2019). Ascorbic acid levels are frequently quoted as reduced in sepsis (most antioxidants are consumed) and has wide controversy in terms of improving outcome in any kind of inflammatory setting, with most large RCTs failing to show a mortality benefit. For example, ascorbic acid transporters are downregulated in disease (Hornung and Biesalski 2019), and for another, ROS are highly reactive and disappear in a very short distance – almost all intracellularly. The utility of enteral and IV antioxidants when ROS speciation occurs inside cells, could be viewed with cynicism. Mitochondrially-targeted antioxidants, however, may be another avenue. ROS-independent benefits of vitamin C may be circulatory and also related to vasopressor synthesis.

ROS tend to evoke an inflammatory reaction but also invoke

stabilising intracellular networks – be it HIFa, heme oxygenase, heatshock proteins and mitochondrial proteins. As a dynamic illness, critical care admissions are likely in different seasons of wax and wane at any given time point.

Medical Interventions

Vitamin C remains controversial – the VITAMINS trial found no benefit, CITRUS-ALI found some survival benefit in a secondary endpoint, although there are some statistical flaws regarding survivor bias.

Novel interventions such as MitoQ (mitochondrial free radical scavenger) show promise in preventing organ damage in septic mice (Lowes et al. 2008). It is rarely as simple as ROS alone, as they are inextractably linked to metabolism, glycolysis and central mediators of them all, like mTOR (famous for improving animal survival when given the red grape extract resveratrol).

Additionally, paying attention to the beneficial effects of ROS (e.g. regulation of genes downstream from HIFa) has prompted development of both HIFa agonists, and antagonists to its oxygen sensitive component prolyl dehydroxylase (PHD). These are exceptional anti-inflammatory drugs (PHD inhibitors) – they show efficacy in protection from AKI in caecal ligation puncture models if delivered pre puncture, and reduce mortality from LPS-induced endotoxaemia, however, they increase mortality from polymicrobial sepsis because of a lack of inflammatory response (Vanderhaeghen et al. 2020). ROS are PHD inhibitors.

Other agents in development target the molecular clock – BMAL-1 and its nuclear transcription factor Rev-erb – be it plant or animal, UV light exposure and feeding has meant circadian enrichment of antioxidant genes, stress proteins, mitochondrial regulators and protectors.

Conclusion

Given that sepsis is a disease of exacerbated inflammation followed by inappropriate immune tolerance, timing is clearly everything with such drugs, and likely, also with oxygen. According to Vonnegut "science is magic that works".

Conflict of Interest

None. ■

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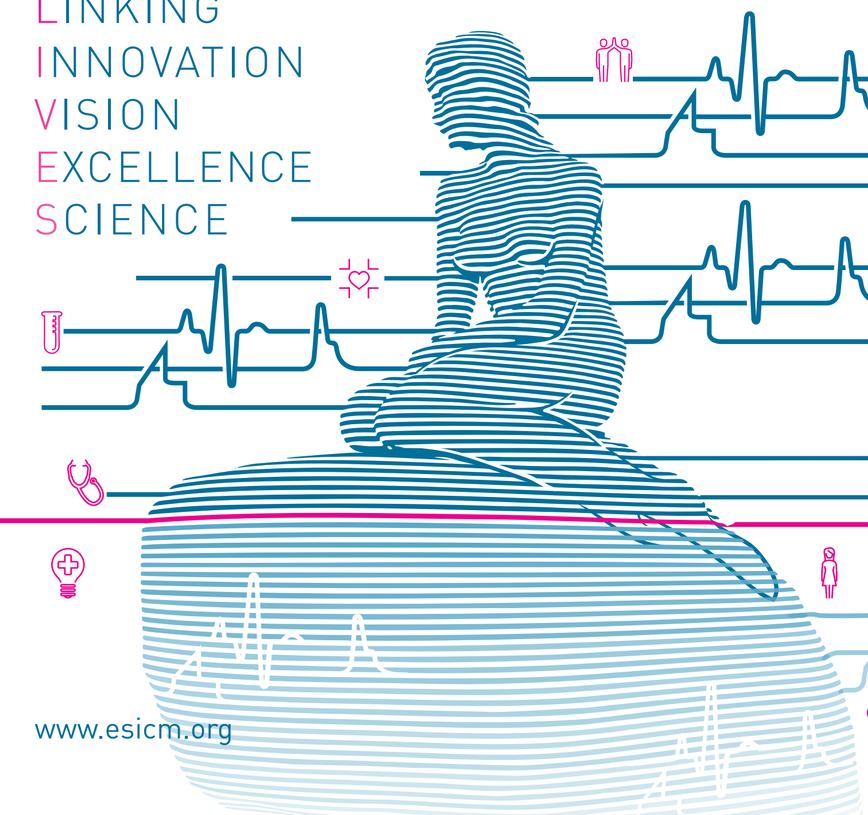

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Diaphragm Ultrasonography in ICU: Why, How, and When to Use It?

Diaphragm ultrasound for critically ill patients

An overview of the principles and current applications of diaphragm ultrasound and innovative ultrasound-based techniques.

Introduction

In the intensive care unit (ICU), ultrasound imaging has become increasingly popular for the diagnosis and to guide treatment in critically ill patients (Volpicelli et al. 2020). The use of ultrasound to evaluate the respiratory muscle function (especially the diaphragm) is relatively new, and remains infrequent due to the supposed difficulty in obtaining adequate ultrasound windows, and the common assumption that ultrasound evaluation of the diaphragm would not alter patient management. However, the ultrasound learning curve focused on this muscle is fast, requiring just a short course (Khurana et al. 2018). Diaphragm ultrasound is able to provide serial, non-invasive data at the bedside of critically ill patients (Grosu et al. 2012; Schepens et al. 2015). Various sources of injury (sepsis, mechanical ventilation, myotoxic drugs…) may alter the contractile function of the diaphragm in critically ill patients (Dres et al. 2017a). The prevalence of diaphragmatic dysfunction in intubated patients can exceed 60% on admission, reaching more than 80% in patients requiring prolonged mechanical ventilation with short and long term consequences (Jung et al. 2016; Dres et al. 2017b). The assessment of diaphragm function with ultrasound provides a first step towards improving the detection of diaphragm dysfunction as well as allowing protective and supportive strategies for its management (Supinski et al. 2018). Different ultrasound methods can be used to monitor diaphragm function, and some new interesting approaches have recently been described. The aim of this review is to provide an overview of the principles and current applications of diaphragm ultrasound and to describe innovative ultrasound-based techniques.

Why Use Diaphragm Ultrasound in Intensive Care?

The main goals of diaphragm ultrasound in critically ill patients are:

- Assessment of diaphragm function over time: normal, reduced (weakness), loss (paralysis) = diagnosis of diaphragmatic weakness.
- Assessment of the risk of successful/failed mechanical ventilation weaning.
- Guidance for management of ventilatory assistance settings.
- Monitoring diaphragm thickness over time for prognostic purposes.

The diaphragm is a fundamental muscle of the respiratory system. In physiological condition during spontaneous breathing, the diaphragm contracts and flattens for the inspiratory phase, decreasing thoracic pressure and causing air to flow into the lungs. This active movement called diaphragm excursion (DE), is possible thanks to the three-dimensional anatomy of the diaphragm with a non-contractile centre and muscular fibres departing from this apical centre and attaching to the ribs from T5 to T12. This area of attachment is referred to as the zone of apposition (ZOA). During contraction, the change in muscle fibres length leads to a thickening in diaphragm wall dimension in the ZOA, making the diaphragm move caudally during inspiration. The expiration phase is a passive relaxation of muscle fibres which returns to initial conformation causing air to flow out of the lungs. In case of increased work of breathing (bronchospasm, respiratory distress…) or in case of diaphragm dysfunction, the force generated by the diaphragm may become insufficient. Therefore, accessory muscles may intervene to allow inspiration, compensating for insufficient diaphragm strength. This can result in a paradoxical movement of the diaphragm (inverse to its physiological action: cranial inspiratory excursion). Exhalation can also become active with the abdominal muscles (McCool and Tzelepis 2012).

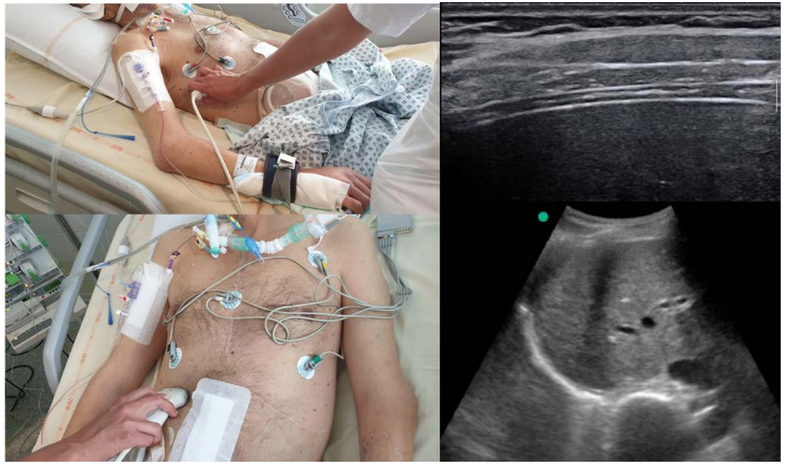

Figure 1. Left: position of the probe for the intercostal approach (up) and the subcostal approach (down). Right: Ultrasound images of the diaphragm using the intercostal approach (up) and the subcostal approach (down).

Diaphragm dysfunction is an under-estimated phenomenon that can pre-exist upon ICU admission, or develop early during the first 24 hours of ICU course (Jung et al. 2016). Sepsis and mechanical ventilation are the main risk factors (Vassilakopoulos and Petrof 2004; Jung et al. 2014). Prolonged mechanical ventilation (MV) duration, increased incidence of weaning failure, prolonged ICU stay, and long term mortality are associated with diaphragmatic weakness (Dres and Demoule 2018).

Ultrasonography has mainly been used to explore diaphragmatic contractile activity by measuring its excursion (DE), thickening fraction (TFdi) ((end-inspiratory thickness - end-expiratory thickness)/end-expiratory thickness), the velocity of diaphragmatic muscle motion (Tissue Doppler Imaging) and diaphragm mass using its thickness as a surrogate (Schepens et al. 2015; Kim et al. 2011; Dres et al. 2018; Umbrello et al. 2015; Soilmezi et al. 2020).

Usually used surrogates for diaphragm weakness are:

- DE of < 10–15 mm during tidal breathing
- (TFdi) < 20% during tidal breathing

The imbalance between load and force-generating capacity of the diaphragm is a main contributor of weaning failure. However, it is important to underline that some patients can be successfully weaned from the ventilator despite having diaphragm weakness. Anyway, diaphragm ultrasound may play an important role to predict weaning success (DiNio et al. 2014). Different parameters under different conditions were associated with weaning success or failure. The more relevant for a clinical perspective are as follows (all reported values are measured under standardised conditions: half-seated position, after 30 minutes of spontaneous breathing trial [SBT] (Tuinman and Jonkman 2020).

- DE: >10-12 mm during a T-piece SBT.
- DE: > 25 mm during a maximal inspiratory effort under T-piece.
- TFdi: > 20-35% during a T-piece SBT or under a pressure support ventilation (PSV) SBT with zero end-expiratory pressure and 7 mmHg PSV.
- Diaphragmatic-rapid shallow breathing index (= respiratory rate/DE): > 1.3 during a T-piece SBT or under a PSV 5 cmH_2O and PEEP 5 cmH20 SBT.
- Diaphragmatic time-excursion index (= DE x inspiratory time): An increase in this index between a PSV ventilation and T-piece SBT having a better prognosis than a decrease.

Recently, the diaphragmatic myotrauma concept in which abnormal diaphragm function is associated with either over-assistance (disuse atrophy) or under-assistance myotrauma (muscle overuse leading to inflammation, oedema, and injury) have been developed (Goligher et al. 2019). The authors hypothesised that both ventilator over-assist and ventilator under-assist play an important role in critical illness-associated diaphragm weakness pathophysiology (Goligher et al. 2017). Thus, it may be reasonable to titrate ventilator support for physiological diaphragm, in order to allow a diaphragm protective mechanical ventilation (Goligher et al. 2020). Diaphragm electrical activity and oesophageal pressure swings are often not available and difficult to use in daily practice. Even not specifically studied, TFdi between 15 and 30% during mechanical ventilation has been associated with stable diaphragm muscle thickness and shorter duration of MV (Goligher et al. 2015). Therefore, low TFdi (< 15%) under PSV mode may indicate ventilator over-

Parameter	General population	ICU patients	Abnormal values
End-expiratory thickness	2,8 +/- 0,4mm	2 +/- 0,4mm	<1,5mm
End-inspiratory thickness	-	4 +/- 0,9mm	-
TFdi at tidal breathing	-	25 +/- 5 %	<20-30%
TFdi at maximal breath	60 +/- 20%	40 +/- 10%	<35%
DE at tidal breathing	18 +/- 3mm	14 +/- 2mm	<10-12 mm
DE at maximal breath	60 +/- 10mm	27 +/- 5mm	<22-25 mm

Table 1. Reference values in ultrasound assessment of diaphragm function

assist, when high TFdi (> 30-40%) may indicate ventilator under-assist. Clinicians may personalise the level of pressure assist while monitoring other parameters (e.g., respiratory rate and tidal volume).

Diaphragm ultrasound allow prospective monitoring of end-expiratory diaphragm thickness. Although not correlated with diaphragmatic function, this parameter is an easy to obtain marker of severity of critical illness-associated diaphragm weakness (Schepens et al. 2015; Vivier et al. 2019; Sklar et al. 2020). Low baseline diaphragm thickness and significant changes in diaphragm thickness are defined by a change of > 10% over the baseline value. Both decrease and increase of > 10% of thickness are associated with poor outcomes [e.g., longer duration of MV] (Goligher et al. 2017; Goligher et al. 2020; Goligher et al. 2015).

How to Use Diaphragm Ultrasound in Intensive Care?

1) Technical approach

Patient set-up: supine position, half-seated position with a bed inclination at 30-45°.

a) Intercostal approach through the ZOA

- A linear array transducer (10-15 MHz) is positioned perpendicular to the skin between the 8th and 11th intercostal space and between the medial and anterior axillary lines, in the cranio-caudal direction.
- The diaphragm appears at a depth of 2 cm between the shadow cones of the upper and lower ribs.
- Three layered structure: a hypoechoic (dark) central layer corresponding to the diaphragm between 2 hyperechoic (white) lines corresponding to the pleural and peritoneal membrane.
- A hyperechoic (white) line can be visualised within the diaphragmatic muscle corresponding to the aponeurosis between the 2 heads of the diaphragm. It guarantees a reliable cross section of the muscle, and good intra and inter-operator reproducibility.

b) Subcostal approach.

- A phased-array or curved-array transducer (2-5 MHz) is positioned below the costal arch at the mid-clavicular line. The probe is angled cranially so as to target a perpendicular cross section of the dome with the ultrasound beam. Liver or spleen can be used as an acoustic window. The liver window is easier to obtain.
- The diaphragm appears as a hyperechoic convex line at 10 to 15 cm depth covering the liver and the spleen that moves toward the probe during inspiration.

2) Measured parameters

a) Diaphragm thickness

- Intercostal approach.
- Measurement in B-mode or in time-motion mode (M-mode).
- Measurement between the internal faces of the pleural and peritoneal membranes, perpendicular to the direction of the muscle fibres.
- Standardised measurement at the end of expiration.
- Reflects the muscular trophicity of the diaphragm.

b) Thickening fraction of the diaphragm (TFdi)

- Intercostal approach.
- Measurement on B-mode or in M-mode.
- Percentage inspiratory increase of diaphragm thickness compared to end-expiratory diaphragm thickness: ([End-inspiratory thickness - End-expiratory thickness]/End-expiratory thickness) x 100.
- Measured during calm (tidal) breathing, or during a maximal inspiratory effort.
- Reflects the contractile activity (function) of the diaphragm. Provides an index of diaphragmatic effort during mechanical ventilation (tidal TFdi) or an index of diaphragmatic function (maximal TFdi).

c) Diaphragm excursion (DE):

- Subcostal approach.
- Measurement in M-mode.
- Activation of the M-mode after visualisation of the hyperechoic diaphragmatic line, M-line placed perpendicular to the direction of the diaphragm movement.
- Measurement of the amplitude of the cranio-caudal movement of the diaphragm during inspiration (towards the probe).
- Measured during calm (tidal) breathing, or during a maximal inspiratory effort.
- Reflects the contractile activity (function) of the diaphragm, in spontaneous ventilation without artificial assistance.
- The excursion of both hemi diaphragms can be compared to identify unilateral weakness or paralysis).
- A negative inspiratory excursion indicates paradoxical diaphragmatic movement and is associated with diaphragmatic paralysis and use of accessory muscles.

When to Use Diaphragm Ultrasound in Intensive Care?

Diaphragm excursion and TFdi are useful to detect diaphragm weakness. One measure alone helps the clinician to easily diagnose the impairment in diaphragm contraction when below known cut-off values. This value at admission is associated with longer duration of MV and poor outcomes (Zamban et al. 2017). There are specific situations where the monitoring with repeated measurements of DE and TFdi as an estimate of the force generated by the diaphragm can be useful.

In patients admitted to emergency department acute exacerbation of chronic obstructive pulmonary disease, severe diaphragm weakness (defined as TFdi <20%) is highly sensitive (85%) and specific (92%) in predicting NIV failure were found to be associated (Kocyigit et al. 2020). In patients admitted to ICU for AECOPD, the same cut-off of TFdi<20% was found in almost 25% of patients. Diaphragm weakness at admission was associated with NIV failure, longer MV, and higher short-term and 90-day mortality (Marchioni et al. 2018). DE can also be used, as a predictor of NIV success in case of improvement (>18mm vs <12mm) after 2 hours of NIV (Cammarota et al. 2019).

> **the assessment of diaphragm function with ultrasound provides a first step towards improving the detection of diaphragm dysfunction as well as allowing protective and supportive strategies for its management**

Recently, in COVID-19 patients admitted to ICU for acute respiratory failure, a reduced TFdi (<21%) measured during spontaneous breathing with conventional oxygen therapy, was associated with CPAP failure and requirement of invasive ventilation (Corradi et al. 2021). Patients with COVID-19 often present with a silent hypoxaemia which may be especially bewildering to physicians. The lack of dyspnoea in the early stages of the disease is likely related to the absence of increased inspiratory drive due to compensatory mechanisms of hypoxaemia. It seems that COVID-19 patients can then develop patient self-inflicted lung injury even when there are still spontaneously breathing and without any sign of major struggle (Cruces et al. 2020). Assessment of inspiratory effort in spontaneously breathing patients may be difficult without complex monitoring such as oesophageal pressure. TFdi may help by detecting an increase in the generated effort (increase in TFdi) or even by detecting the beginning of exhaustion (decrease in TFdi). Finally TFdi may help to titrate bilevel positive airway pressure support in patients with acute respiratory failure (Laverdure et al. 2019).

In invasively ventilated patients, TFdi can be used to titrate the ventilatory support. It has been postulated that both ventilator over-assist and ventilator under-assist resulting in muscle atrophy and muscle injury, respectively, play an important role in critical illness-associated diaphragm weakness pathophysiology (Goligher et al. 2019). To limit these detrimental consequences, it seems reasonable to titrate ventilator support such that diaphragm effort is within physiological limits. Ultrasound can thus help us to combine the principles of lung protective ventilation (with tidal volume target) and diaphragm protective ventilation (with a TFdi target, as a proxy for effort) (Goligher et al. 2020). Data from Goligher and colleagues demonstrate that a TFdi between 15 and 30% during the first days of mechanical ventilation is associated with stable muscle thickness (Goligher et al. 2015). Accordingly, a low TFdi (< 15%) in a patient on a partially supported ventilatory mode raises the possibility of ventilator over-assist; a high TFdi (>30-40%) may indicate ventilator under-assist. Therefore, pressure support may be titrated targeting physiological levels of TFdi. Diaphragm ultrasound may also help to detect patient ventilator asynchrony which may be associated with worse outcome (Soilemezi et al. 2019).

Another important aspect of diaphragm ultrasound in the ICU is weaning time in which both excursion and thickness provide useful measures for assessing patient effort. TFdi was

shown to be strongly correlated with diaphragm strength and support level, while excursion during spontaneous breathing was found to be a reliable measure of an unsuccessful breathing trial (Dubé et al. 2017).

What's New in Diaphragm Ultrasound in Intensive Care?

Tissue Doppler imaging (TDI) quantifies the velocity of moving structures. Potential applications include assessment of regional diaphragm contractile function at rest and with loading, and measurement of diaphragm relaxation velocity. Diaphragm relaxation abnormalities have been described as a marker of impaired contractility in patients who failed weaning (Soilmezi et al. 2020).

Strain imaging is based on the ability to track ultrasound speckles over time and an excellent feature to quantify motion and deformation of anatomical structures. It was reported that strain and strain rate were highly correlated with transdiaphragmatic pressure (Oppersma et al. 1985).

Shear wave elastography is a technique that allows quantification of the elastic modulus of tissues (Creze et al. 2018). Application of this technique on the diaphragm could be of clinical importance since changes in muscle stiffness may reflect alterations in muscle physiology (e.g., injury, fibrosis). Recently, two studies have evaluated SWE during diaphragmatic contraction and have suggested that SM can be a surrogate for diaphragm contractile activity in healthy volunteers (Chino et al. 2018; Bachasson et al. 2019). Diaphragmatic SWE exploration is feasible in the critically ill population (Flatres et al. 2020). Fossé et al. (2020) investigated changes in SM during diaphragm contraction in mechanically ventilated patients as a potential surrogate to transdiaphragmatic pressure. Therefore, it might offer a new non-invasive method for gauging diaphragm effort.

Conclusion

In the ICU, ultrasound is starting to be acknowledged as a useful tool for studying the diaphragm. Until recently, the monitoring of diaphragmatic function could only be performed with specialised invasive instruments. We are now able to non-invasively assess diaphragmatic function at the bedside and on a daily basis, from ICU admission to discharge. That will surely allow physicians to better understand pathophysiological processes involved in diaphragm injuries in critically ill patients and will lead to improvements in patient outcome.

Conflict of Interest

Dr Aarab has no conflict of interest. Dr De Jong reports receiving consulting fees from Medtronic. Pr. Jaber reports receiving consulting fees from Drager, Medtronic, Baxter, Fresenius-Xenios, and Fisher & Paykel. ■

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AGENDA

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JULY

9-12 ECCMID 2021
Virtual event
https://iii.hm/1aai

17-21 International Society on Thrombosis and Haemostasis (ISTH) 2021
Virtual event
https://iii.hm/1aaj

AUGUST

31 AUG - 3 SEPT 40th ISICEM
Brussels, Belgium
https://iii.hm/1aal

SEPTEMBER

1-5 17th World Congress of Anaesthesiologists
Virtual event
https://iii.hm/1ae9

5-8 ERS International Congress 2021 - European Respiratory Society
Virtual event
https://iii.hm/1aam

8-10 European Society of Regional Anaesthesia (ESRA) Congress 2021
Virtual event
https://iii.hm/1aan

9-14 ESPEN 2021
Virtual event
https://iii.hm/1aao

13-14 British Association of Critical Care Nurses (BACCN) Conference 2021
Virtual event
https://iii.hm/1aap

20-22 Pediatric Cardiac Intensive Care Society (PCICS)
Annual International Meeting 2021
Virtual event
https://iii.hm/1aaq

23-24 Association of Anaesthetists Annual Congress 2021
Hybrid event, Liverpool, UK
https://iii.hm/1aar

23-25 SFAR Annual Congress 2021
Paris, France
https://iii.hm/1aas

OCTOBER

3-6 ESICM 34th Annual Congress, LIVES 2021
Virtual event
https://iii.hm/1aat

7-9 10th Europaediatrics 2021
Hybrid event, Zagreb, Croatia
https://iii.hm/1aau

8-12 ANESTHESIOLOGY 2021
Annual Meeting
San Diego, USA
https://iii.hm/1aav

12-15 44th Annual Conference on Shock 2021
Portland, USA
https://iii.hm/1aaw

25-28 ACEP 2021 - American College of Emergency Physicians
Boston, USA
https://iii.hm/1aax

26-29 39th Vicenza Course on AKI & CRRT
Virtual event
https://iii.hm/1aay

27-31 EUSEM 2021
Lisbon, Portugal
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ICU
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ICU MANAGEMENT AND PRACTICE IS PUBLISHED BY
MindByte Communications Ltd
Kosta Ourani, 5 Petoussis Court, 5th floor, CY-3085 Limassol Cyprus
Email — office@icu-management.org
Website — icu-management.org

PRODUCTION, FULFILMENT AND DISTRIBUTION
Total distribution: 21,500
ISSN = 1377-7564

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