Targeted interventions in mechanically ventilated patients

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General introduction and thesis outline

In the Intensive Care Unit (ICU), it is imperative to provide optimal care to improve patients' pathophysiological conditions. This is particularly true for patients requiring mechanical ventilation, as they are in a fragile state and have a limited ability for physiological compensation. Through various treatments and supportive measures, clinicians aim to support the patient in order to improve their health. The use of target ranges during these treatments may offer helpful guidance, helping clinicians to provide the intervention in the most effective way and reduce the risk of complications by staying within specific target ranges. However, finding optimal target ranges for each therapy can be a complex task, since different pathologies, different severeness of pathologies, and use of target ranges in different individuals can all affect what the best target range might be.

In this thesis we aimed to enhance the use of targeted interventions in mechanically ventilated ICU patients in three key areas, namely, oxygenation, anticoagulant treatment, and pain management.

OXYGEN

Oxygen has played an important role in acute care settings for over hundreds of years and has proven to be a lifesaver for critically ill patients at risk for hypoxemia (1). A hypoxic condition, characterized by low levels of oxygen in the blood, can lead to severe tissue damage, organ failure, and even death if not timely assessed. Health care professionals have traditionally responded to this risk by administering supplemental oxygen, at times even aiming for supranormal arterial oxygen levels (2, 3). While this approach has been effective in treating hypoxemic patients, the growing recognition of the potential deleterious effects of oxygen has caused a shift in practice. Adverse outcomes of hyperoxia can include cerebral and coronary vasoconstriction, reduced cardiac output, and various forms of lung and central nervous system damage (4). Confronted with these uncertainties and the potential risks of both hypoxia and hyperoxia, researchers have attempted to establish an oxygen target for safe oxygen administration, however, identifying a safe range has proven to be a challenge.

The initial publication that revealed a link between elevated PaO2 levels and increased mortality rates among ICU patients was published in 2008 (5). Subsequent to this publication, a variety of observational studies were conducted. A meta-analysis aggregating these studies indicated a correlation between hyperoxia and a higher risk of mortality, although the different patient populations and the observational design of the studies necessitated a careful interpretation of these results (6). The first randomized controlled trial (RCT) specifically examining oxygenation strategies in the

ICU was published in 2016, and showed a higher mortality for the higher oxygenation group, seemingly confirming the results found in previous observational studies (7). In 2020, however, a contradictory study was published, demonstrating a higher 90-day mortality in the lower oxygenation group (8). Four RCTs that followed, also comparing low and high oxygenation targets in the ICU, found no differences in patient outcomes (9-12). So far, analyses of both single and combined datasets have been inconclusive, potentially due to different subgroups, utilization of different targets (either SpO2 or PaO2), an absence of statistical power, or insufficient contrast between the achieved oxygenation targets of the two groups (13, 14). In order to provide an overview of the results, we systematically reviewed evidence from all most recent RCT's comparing higher and lower oxygenation strategies in mechanically ventilated ICU patients in chapter 2. In chapter 3, we describe the methodology of our multicenter RCT, the ICONIC trial, where we compare conservative and liberal oxygenation targets in ICU patients. Following this, in chapter 4, we discuss the findings of the ICONIC trial.

Achieving optimal oxygenation in mechanically ventilated patients is a complex process that can be influenced by many factors, such as, ventilator settings, lung function, and the amount of oxygen administered. Research pointing to the potential detrimental effects of oxygen therapy has predominantly relied on indirect markers of oxygen exposure, such as PaO_2 and SpO_2. While these markers are routinely used in clinical settings and hold relevance, they serve as an indirect indicator of the exposure to the potentially toxic effects of oxygen and do not provide a direct reflection of oxygen exposure. Therefore, in chapter 5, we investigate a novel parameter to measure oxygen exposure, examining the volume of oxygen administered during mechanical ventilation as a direct parameter to assess oxygen exposure.

Informed consent is a fundamental ethical principle in medical research (15). However, obtaining informed consent from patients in the ICU proves to be a challenge. Patients in the ICU are often unable to provide informed consent due to their condition and seeking consent from a representative before starting the trial is often not an option due to the time-sensitive nature of initiating trial treatment and the overwhelming impact of the critical situation (16). In the ICONIC trial, an emergency trial requiring to start the intervention within 2 hours after intubation, we used the deferred consent procedure. Despite being an effective strategy that is generally accepted by most patients, this approach continues to generate ethical debates, weighing the necessity of conducting emergency research against the potential violation of patient autonomy. In chapter 6, we explore the retrospective views of ICONIC trial participants on their enrollment prior to giving consent, evaluating how their quality of life post-ICU admission might have influenced their opinions on the consent process.

ANTICOAGULANT TREATMENT

Since its emergence in December 2019, Corona Virus Disease 2019 (COVID-19) has profoundly impacted global public health, resulting in over 750 million infections and almost 7 million deaths (17). Patients with severe progression of the disease often experience intense pulmonary inflammation, necessitating mechanical ventilation and extended ICU stays. A frequently seen complication in these patients is the development of a prothrombotic state, leading to thrombotic complications, predominantly pulmonary embolism, despite the administration of adequate thromboprophylaxis (18).

The distinct pathogenesis of coagulation activation in COVID-19 differs from that seen in disseminated intravascular coagulation (DIC) associated with sepsis, presenting a unique challenge in understanding and managing the disease. Contrary to DIC, COVID-19 patients tend to have high d-dimer levels, normal platelet counts, and coagulation tests, pointing towards a different mechanism of coagulation activation (19). Furthermore, the phenotype of COVID-19 associated pulmonary embolism (PE) appears to differ from non-COVID-19 PE, often manifesting in the peripheral lung segments and being less extensive (20).

Due to the different pathophysiology of coagulation in COVID-19 patients, question were raised whether unfractionated heparin (UFH), or anticoagulation in general, were effective in the attenuation of the procoagulant state. Therefore, we evaluated the effectiveness of UFH treatment in COVID-19 patients in chapter 7. In addition, COVID-19 patients appeared to require higher UFH doses compared to control ICU patients. To verify whether these doses were indeed higher, we compared UFH doses in COVID-19 patients and a historical ICU cohort in chapter 8, and explored factors that could potentially have influenced the UFH dose in COVID-19 patients.

PAIN MANAGEMENT

Ensuring optimal pain management is crucial for mechanically ventilated patients, as inadequate pain management can lead to a cascade of negative physiological responses, such as elevated stress hormones, hypercoagulability and immune system dysfunction (21, 22). The interaction between pain and physiological processes in mechanically ventilated patients necessitates an increased emphasis on pain management. However, assessing pain in sedated mechanically ventilated patients presents significant challenges, as they cannot self-report on their pain levels.

Pain assessment in sedated patients often relies on vital signs. In the ICU additional pain assessment tools incorporating behavioral variables are used (23). Vital signs, however, can be influenced by various physiological conditions, and while tools like the Behavioral Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT) are considered valid and reliable, they are subjective and may vary between healthcare professionals. Therefore, there is need for more objective tools that can quantify pain in sedated patients.

In the last few years, the medical field has seen the development of various monitors that objectively measure nociception in sedated patients. Nociception refers to the neural processes involved in identifying, transforming, and transmitting signals of harmful stimuli (24). The Nociception Level (NOL) monitor, produced by Medasense Biometrics Ltd. in Ramat Gan, Israel, is one of these tools. It evaluates pain by integrating various physiological parameters, including heart rate, heart rate variability, photo-plethysmographic amplitude, and skin conductance, and their time derivates. These parameters are aggregating into a single index, ranging from 0 (no nociception) to 100 (maximal nociception) (25). The monitor has been approved for use in the operating room based on multiple studies, and showed a reduction in stress hormones, postoperative pain, and improved hemodynamics (25-32). In chapter 9 we aggregated data from two of these studies in order to verify if the use of NOL reduced pain scores in the post-anesthesia care unit (PACU).

Studies demonstrating the use of NOL within an ICU setting are limited, but have shown that NOL is capable to detect nociceptive stimuli in patients able to self-report. However, further research is needed to assess efficacy of NOL in anesthetized ICU patients. During the COVID-19 pandemic, opioid dosing in ICU patients notably increased, and sometimes tripled compared to historical ICU data (33), raising questions about whether this was due to a genuine need for higher pain relief or if clinicians aimed at a higher level of analgesia. Therefore in chapter 10, we conducted an explorative observational study aiming to evaluate opioid dosing in sedated COVID-19 and control patients, by comparing subjective (CPOT, BPS) and objective measure (NOL) to assess pain in both groups.

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