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Pathophysiological changes related to Sars-CoV-2 infection and advanced methods of treatment

Natalia Popłonyk[1], Łukasz Mazurkiewicz[1], Wojciech Lizurej[1], Filip Lorek[1], Michał Mazurkiewicz[1], Anna Kluzik[2,3], Małgorzata Grześkowiak[2]

[1] Studenckie Koło Naukowe Anestezjologii I Intensywnej Terapii, Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu
[2] Zakład Dydaktyki Anestezjologii i Intensywnej Terapii, Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu
[3] Klinika Anestezjologii, Intensywnej Terapii i Leczenia Bólu, Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu

Streszczenie

Niedawno odkryta i opisana choroba COVID-19, wywołana przez koronawirusa Sars-Cov-2 jest poważnym problemem dla opieki zdrowotnej z powodu wysokiej zachorowalności i śmiertelności. Do ciężkiego przebiegu choroby i zgonu pacjenta przyczyniają się głównie hipoksja i tworzące się mikro zakrzepy. Zakrzepica powstaje w wyniku reakcji czynników zapalnych, jak i w wyniku zniszczenia nabłonka naczyń przez wirusa. Mechanizmy hipoksji są skomplikowane, a jej powikłania poważne. Stan znany jako „silent hypoxemia" – cicha hipoksemia – jest do tej pory nieodkrytym zagadnieniem, a jego rozpoznawanie jest kluczowe. Istotne jest stosowanie pulsoksymetrii. Pozaustrojowe utlenowanie krwi (ECMO - Extracorporeal Membrane Oxygenation) jest metodą pozwalającą na czasowe zastąpienie u pacjenta funkcji układu krążenia oraz układu oddechowego. Dwa najczęściej stosowane typy to ECMO żylno-żylne oraz ECMO żylno-tętnicze. W przypadku pacjentów z COVID-19 w przebiegu ostrej niewydolności oddechowej, ECMO żylno-żylne, które wspomaga głównie funkcje układu oddechowego jest stosowane jako terapia ostatniej szansy. Ważnym elementem ochrony przed niepowodzeniem terapii jest monitorowanie jakości ECMO w celu przede wszystkim wykluczenia formowania się skrzepów, mogących skutecznie blokować pracę urządzenia. Powikłania stosowania ECMO dotyczą także między innymi zwiększonego ryzyka zakażeń. Istnieje wiele przeciwskazań do stosowania ECMO. Zdecydowana większość z nich jest względna, jednak zdarzają się te bezwzględne, uniemożliwiające wdrożenie wspominanej techniki. Mimo, że temat resuscytacji pacjenta znajdującego się w pozycji na brzuchu wciąż oczekuje wiarygodnych badań klinicznych, najnowsze wytyczne międzynarodowych towarzystw do spraw resuscytacji sugerują jej zasadność w sytuacji, kiedy przełożenie pacjenta na plecy nie jest natychmiastowo możliwe bądź stwarzałoby dla niego znaczące ryzyko. *Anestezjologia i Ratownictwo 2022; 16: 135-145. doi: 10.53139/AIR.20221616*

Słowa kluczowe: COVID-19, Sars-Cov-2, ECMO, hipoksja, mikrozakrzepica, pozycja leżąca na brzuchu, resuscytacja krążeniowo-oddechowa

Abstract

The recently described COVID-19 disease caused by severe acute respiratory syndrome coronavirus 2 (Sars-Cov-2), has emerged as a serious health issue with its global pandemic burden characterized by high morbidity and

mortality. Severe course and patient's death are caused mainly by hypoxia and microthrombosis. Thrombosis arise as a result of hyperinflammatory state and endothelial damage caused by virus. Mechanisms leading to hypoxia are complex. Silent hypoxemia is undiscovered phenomenon which can lead to serious consequences. Pulse oximetry plays a crucial role in diagnosing these patients. Extracorporeal Membrane Oxygenation (ECMO) allows to temporary replace functions of cardiopulmonary system. Generally veno-venous and veno-arterial ECMO are used. For COVID-19 patients in case of acute respiratory syndrome ECMO veno-venous is a last chance therapy. It is necessary to control D-dimer levels to avoid clot formation which can blockade ECMO device. Complications of ECMO also concern infections. Before implementation of ECMO therapy it is indispensable to analyze balance between benefits and risk and to strain to optimize patient's treatment. While prone resuscitation still awaits for scientific evidences, current recommendations of the international societies suggest its legitimacy in those cases when standard supine patient's position is not immediately possible or poses a significant risk. *Anestezjologia i Ratownictwo 2022; 16: 135-145. doi: 10.53139/AIR.20221616*

Keywords: COVID-19, Sars-Cov-2, ECMO, hypoxia, micro thrombosis, prone position, cardiopulmonary resuscitation

Introduction

The recently described COVID-19 disease caused by severe acute respiratory syndrome coronavirus 2 (Sars-Cov-2), has emerged as a serious health issue with its global pandemic burden characterized by high morbidity and mortality. The outbreak of COVID-19 has become threat to the medical care worldwide, overwhelming hospitals, and interrupting social relations [1].

The pathophysiology underpinning the Sars-Cov-2-related disease is associated with binding the virus to the cell by angiotensin converting enzyme-2 (ACE-2) receptor which is expressed on the surface of endothelial cells in the lungs, heart, kidneys, brain and all the blood vessels. The disruption of the ACE-2 receptor and impairment of normal ACE-2 functions induces the immune response with overproduction of inflammatory mediators, known as cytokine storm [2]. The symptoms are most frequently similar to common cold like fever, coughing, and shortness of breath, however, infection can lead to serious and life-threatening sequelae such as pneumonia, respiratory distress syndrome, multiorgan failure, and eventually death [1]. COVID-19 patients may require hospitalization in intensive care unit to implement invasive or non-invasive ventilation, extracorporeal membrane oxygenation (ECMO), traditional and optional prone cardiopulmonary resuscitation methods, and pharmacotherapy implementing antiviral and anticoagulation drugs [3].

Some patients experience symptoms in the aftermath of suffering COVID-19, known as long-covid. Shortness of breath, myalgia, anxiety, fatigue and sleep disturbance appear without elevated inflammatory markers or radiographic findings in the lungs [4].

COVID-19 induces hypoxia

Oxygen is essential for humans to produce energy, which is necessary for survival [5]. Mean arterial partial pressure of oxygen (PaO_2), and the oxygen saturation are dependent on many factors. Probably the lowest PaO_2 in a human-being was noted during a Mount Everest climb in 2007 [6,7]. Every fetus matures in an oxygen-deprived environment [7]. Hypoxia happens, when the oxygen content in cells is being lower than the cells oxygen request, which leads to reduced partial oxygen pressure in the cell [5]. Hypoxia during coronavirus disease 2019 (COVID-19) may by triggered by various mechanisms. During infection, ventilation/perfusion (V/Q) mismatch can occur due to blood delivery to unventilated alveoli. Lung edema may be developed, which, together with superimposed pressure, alveolar collapse, and perfusing non-aerated lung tissue can result in intrapulmonary shunting [8]. Furthermore, loss of lung perfusion regulation due to inappropriate functioning of hypoxic pulmonary vasoconstriction mechanism has impact on maintenance of high pulmonary blood flow through non-ventilated alveoli [9]. Sars-CoV-2 can also lead to injury of endothelium of pulmonary vessels presenting angiotensin converting enzyme-2 (ACE-2) [10]. This phenomenon may lead to imbalance between procoagulant and fibrinolytic activity and result in intravascular micro thrombi [11]. Autopsy of lungs of patient's who suffered from severe course of COVID-19 revealed large fibrino-

gen deposit, diffuse alveolar damage, complement-rich micro thrombi plugging lung capillaries and bigger thrombi leading to pulmonary artery thrombosis [12].

To the statement that hypoxia is a serious condition, Alhusain et al. carried out a study on 195 patients admitted to the hospital with oxygen saturation lower than 90%, 116 of them (60%) required Intensive Care Unit admission, 66 (34%) needed intubation, 13% of these patients were described as 'silent hypoxia' patients, and 26% died [13].

Sars-CoV-2 infection might be asymptomatic, mild with symptoms such as fever, fatigue and dry cough, and may lead to severe conditions including respiratory system failure [14]. In Sars-CoV-2 infected patients, the blood vessels and tissues are being damaged, which entail improper heart and lung function [15]. One hypothesis mentions myocardium to be damaged by the entrance of Sars-CoV-2 virus to human cells by the ACE-2, and the alteration of the signaling pathway leading to direct myocardial damage [16].

Severe lung injury due to high ACE-2 expression in the respiratory tract is said to be one of the COVID-19 clinical characteristics. Lung edema, loss of surfactant and finally, alveolar collapse makes a huge part of cardiac output fraction not possible to properly carry oxygen [17]. Consequently, the heart of patients with respiratory system failure will be insufficiently supplied with oxygen [18]. Greater impairment of the respiratory system will affect the oxygen supply to the heart, with the result that heart failure will occur earlier [19]. That is why lots of COVID-19 patients require various oxygen support [16]. Dyspnea may be the best 'marker' for COVID-19 hypoxemia, but this is not a determinant, because some patients experience so-called 'happy hypoxia' or 'silent hypoxemia' [20]. During this condition, saturation decreases and reaches 50-80%, whereas the expected value is >95% [21]. Crucial fact is, that patients do not have to complain of dyspnea or shortness of breath [20,22]. The patients do not need to suffer from tachypnea what is observed in typical hypoxic patient. Silent hypoxemia affects 20-40% of patients struggling with Sars-CoV-2 and it is still unknown, why it is so common [23]. The mechanism leading to silent hypoxemia is not discovered yet, one hypothesis presents the cause in a slight preservation of the ability of the lungs to excrete carbon dioxide even in hypoxia, so that symptoms of dyspnea are not experienced [24]. Silent hypoxemia is not recognized as something good – contrary – this may cause the impression of no need for help. This is often accompanied with low peripheral oxygen saturation readings and may be a prediction of state deterioration [22]. Unrecognized or untreated hypoxia leads to the damage of several organs and plays a crucial role [23].

Acute cardiac injury may be one of the hypoxia--consequences. Bavishi et al. revealed in their systematic review including 11625 patients, that overall incidence of acute cardiac injury in patients with COVID-19 was 21.4% [25]. Furthermore around 5-25% of patients hospitalized due to COVID-19 had elevated cardiac troponins [26,27]. The mechanism leading to myocardial injury during COVID-19 is not yet fully understood. The possible mechanisms leading to this phenomenon are for example: hyper inflammation and cytokine storm mediated through pathologic T-cells and monocytes leading to myocarditis; respiratory failure and hypoxemia resulting in damage to cardiac myocytes; down regulation of ACE2 receptors and signaling pathways which have protective impact on heart's cells; increased coagulation resulting in thrombosis in coronary vessels; endothelium injury and endothelitis in many organs, also in the heart. [25]. Myocardial damage in COVID-19 may be asymptomatic and characterized only by an elevation of markers of myocardial damage, and may also progress to more severe form leading to fulminant myocarditis [25,28]. The incidence of myocardial damage is associated with a poorer prognosis. Cardiac injury is independent risk factor for in-hospital mortality in COVID-19 patients [29]. Also hypoxemia is associated with in-hospital mortality [30,31]. The 'silent hypoxemia' mystery forces the importance of pulse-oximeter use in COVID-19 patients, and the use of other methods just to prevent or to detect 'silent hypoxia' [23]. Blood gas levels and performing 6-minute walking test may be also helpful in diagnosing silent hypoxemia [23]. The presence of metabolic or cardiovascular diseases among patients may be significant, because it puts at risk of COVID-19 associated pneumonia [32], and further – hypoxia. Patients who suffer from respiratory system diseases, diabetes, cardiovascular system diseases are also exposed to greater risk of adverse outcomes and death due to COVID-19 [33]. Hypoxia was present in 57% of COVID-19-positive patients who experienced cardiac arrest, making it the most common factor preceding cardiac arrest [34]. Furthermore, hypoxia is considered as a risk factor of survival in COVID-19 patients [35]. Hypoxia also influences the immune system through

change of immune cells response in abnormal hypoxic environment, resulting in tissue damage [19]. Moreover hypoxia may drive on immune reaction of innate immune cells such as eosinophils, basophils, mast cells which are the major part of cytokine storm leading to airway remodeling and inflammation [36].

Micro thrombosis and endothelial dysfunction in COVID-19

The COVID-19 is a systemic disorder that provokes an immune dysregulation as the predominating pathomechanism contributing to its unfavorable cause. The disease is characterized by the proinflammatory state due to the hyper activation of T lymphocytes and aberrant cytokine release. During Sars-CoV-2 infection, remarkably increased secretion of interleukin (IL)-6, IL-2, IL-10, as well as tumor necrosis factor (TNF)-α, complement components, elevated d-dimers, C-reactive protein (CRP), and neutrophil extracellular traps (NET-osis) contribute to the procoagulable state. As a result, endothelial injury, and leucocyte-mediated platelet activation contribute to immunologically--mediated micro-and macro thrombosis [37,38]. Hypercoagulability may also be promoted by hypoxia during COVID-19 which leads to endothelial injury [38,39]. The causative hyper activation of the immune response leading to cytokine release syndrome or a related hemophagocytic syndrome is a major risk factor for multiorgan failure and mortality [38]. Furthermore, microvascular endothelial dysfunction is exacerbated by preexisting chronic diseases associated with endothelial damage, such as hypertension, obesity, diabetes, dyslipidemia, and chronic kidney disease [40]. These incriminatory factors were confirmed in large cohort studies on hospitalized COVID-19 patients who underwent cardiopulmonary resuscitation (CPR) with poor outcomes [41,42].

The hyper inflammatory state in COVID-19 leading to epithelial damage in microvasculature results in impaired vital organ perfusion thereby contributing to the risk of thromboembolic episodes. Micro thrombi are a major cause of cardiac injury with acute myocyte necrosis and intramyocardial thromboembolic associated with an increased risk of death. Epicardial coronary artery thrombi, micro thrombi in myocardial capillaries, arterioles, and small muscular arteries were found in autopsies of fatal COVID-19 cases [43]. Likewise, hypertension, obesity, and dyslipidemia-related microvascular dysfunction was major risk factor for mortality due to respiratory failure in COVID-19. In postmortem examination, exudative diffuse alveolar damage and massive capillary congestion accompanied by micro thrombi reflecting pulmonary thrombotic microangiopathy were assessed [44].

The immune response to Sars-Cov-2 is also characterized by the local central nervous system cytokine storm and hyper activation of microglia. This, in turn, triggers neuroinflammatory events with the increased risk of acute cerebrovascular disease, ischemic brain injury, and cerebral hemorrhage potentially contributing to the COVID-19-related burden of cardiac arrest [45]. Furthermore, while Sars-CoV-2 infection leads to an acute tubular kidney injury, it also results in microvascular dysfunction due to endothelial damage. Alike in other organs, microangiopathy disturbs the hemostatic balance and triggers renal micro thrombosis. Acute COVID-19-related kidney injury manifests clinically as metabolic and electrolyte disturbances, in particular hyperkalemia, and hematuria, which remarkably increase the mortality rate [46].

It needs therefore to be highlighted that in COVID-19, the use of anticoagulation therapy improves the outcome and reduces the risk of disturbed microvascular homeostasis and thrombosis-related multiorgan failure and mortality. Further studies are needed to delineate precisely preventive and therapeutic anticoagulation therapy protocols based on clinical scoring systems and biomarker approach [47].

Advanced methods of COVID-19 treatment - Extracorporeal membrane oxygenation (ECMO)

Extracorporeal membrane oxygenation (ECMO) allows to temporary support gas exchange during organs failure. The technique involves draining the blood outside the body, oxygenating and removing carbon dioxide, then reintroducing blood to vessels. Depending on the type of vessel into which the blood returns to the body, we distinguish veno-venous (VV) ECMO and veno-arterial (VA) ECMO. In addition, there is an another special type of ECMO – venous to arterial and venous (VAV) [48].

Veno-venous-ECMO is a variant, which supports only the respiratory system, therefore, it is used in the treatment of acute respiratory distress syndrome (ARDS) in COVID-19 [49] and reversible lung diseases

when traditional methods are not sufficient [48]. The requirement for VV-ECMO connection is hemodynamic stability [50]. The most commonly used technique for applying VV-ECMO is the double venous cannula system. The blood is collected through inflow cannula from femoral vein and returns to the internal jugular vein [48]. Inflow cannula must be inserted not deeper Th10-Th11, because this will impair hepatic venous outflow. The second technique involves the use of a single cannula inserted through the internal jugular vein, which draws blood from the superior and inferior vena cava and returns oxygenated blood to the right atrium at the level of the tricuspid valve. The advantage of this technique is that the patient can be rehabilitated while connected to the ECMO [51].

Compared to veno-venous-ECMO, VA and VAV type of ECMO provides support for both the circulatory and respiratory systems [52]. Peripherally VA-ECMO technique involves drawing blood from femoral vein and reinfusion to the femoral artery. Ultrasonography significantly facilitates correct placement of the catheter, nevertheless profound hypotension or hemodynamic instability may impede proper insertion. The veno-arterial-ECMO can also be applied centrally. This technique requires a surgery procedure, which is associated with a risk of mediastinal bleeding. Venous cannula is placed in the left atrium and the arterial cannula in the ascending aorta [53]. Basing on population level, there is no difference in the superiority of any of the techniques of VA-ECMO in hemodynamic stability or outcomes [54].

Besides the obvious advantages of using ECMO, the system itself has - as it seems – a great deal of downsides. A dozen of them concerns the technical aspects, as ECMO is a complicated mechanical device, but a part of them concern patient-related factors [55]. Avoiding technical failures is necessary. The oxygenation membrane and the whole ECMO-circuit should be monitored extra-stringently, as it is a crucial place for clot formation, which can definitely block the correct ECMO function – for example the gas transfer [56–58]. The main thing is to inspect the system visually, but some laboratory-tools can be useful [56,57,59]. Daily analysis of hemostatic parameters, especially D-dimers may be indicated and the elevation may foreshadow the need to replace the oxygenation membrane, which should not be done needlessly, because it is a high-risk procedure. D-dimers are used in diagnostic issues and their elevation should not be linked directly to the membrane failure due to clot formation. The conditions accompanying elevated D-dimers, are – among others – thrombosis, disseminated intravascular coagulation (DIC), pulmonary embolism, sepsis and more [56,59]. Both the clotting complications and bleeding episodes are a headache of medical practitioners [57].

Potential danger in continuing ECMO-treatment is a rupture in ECMO-circuit [55]. This includes quick exsanguination and gas embolism, depending on the exact placement of the rupture or disconnection of the system [55,56].

Heparin induced thrombocytopenia may occur, when a patient's ECMO therapy extends, due to the presence of heparin on ECMO-circuit elements [57,60]. This leads to a massive pro-thrombotic state and thromboembolic complications [60]. In this condition heparin should be replaced with other drugs [57,60]. Looking further – the necessary anticoagulation therapy leads to bleeding consequences – ECMO-patients are at risk of – among others - intracranial hemorrhages, insertion site bleedings, intraabdominal hemorrhages[55]. Thrombocytopenia occurs normally, when clotting factors and platelets are getting used up due to massive contact with foreign material [55]. If we sum it up with multiple factors resulting from the general condition of an ECMO-requiring patient - multiorgan failure, sepsis, DIC – we get a chaotic list of factors affecting hemostasis – thrombosis or bleeding events [55,57].

Neurological complications of ECMO include intracranial hemorrhages (mentioned above), cerebral infarcts caused by thrombi and seizures [55,61]. ECMO is obviously an invasive tool for treatment of critically ill patients. As blood contacts foreign surfaces – an inflammatory reaction begins [57,61,62]. A complex immune response is activated and may lead to serious complications, including disrupted microcirculation and end-organ dysfunction [62]. It is not obvious if the organism derive any advantages of this state, except for downsides [62]. Another point of this invasive procedure is high infection risk associated with the presence of non-physiological tools. The diagnosis may be difficult to make though specific symptoms often accompany the infections. In the case of ECMO-patients, the symptoms do not need to be incidental [56]. In combination with the previously mentioned immune response activation, the infection-diagnosis is very hard to make [56]. The pathogens often associated with bloodstream infections are Candida, Pseudomonas aeruginosa and Staphylococcus aureus [63].

Acute renal injury (AKI) is common in ECMO-patients [55,56,64]. The ethology of this state is still very complicated, but many ECMO-patients require renal support therapy, due to uremia, acidosis, electrolyte abnormalities and fluid overload [64,65]. These patients are set at high risk of fatal outcome [65].

The list of contraindications for ECMO in COVID-19 patients is long. These criteria are not varying much from patients without COVID-19. Some of them can even disqualify the patient from this sort of treatment. There are many research papers that describe contraindications in patients without COVID-19, but a few that put emphasis on patients with Sars-CoV-2 virus infection. Harnish et al. [66] write that there are more relative contraindications than the absolute ones. Therefore it is necessary to find accurate balance between possible losses and gains before starting ECMO. Absolute contraindications, which disqualify every patient from ECMO, according to Harnish et al. [66] include refusal by the patient, advanced stage of cancer, fatal intracerebral hemorrhage, cerebral herniation, intractable intracranial hypertension. Relative contraindications according to Harnish et al. [66] include age over 70 years, immunocompromised patients or patients with pharmacological immunosuppression, over 7 days on injurious ventilator settings, right-heart failure, hematologic malignancies, especially bone marrow transplantation and graft-versus-host disease. They describe that interpreting of some existing score scales such as Simplified Acute Physiology Score (SAPS II), Sepsis-Related/Sequential Organ Failure Assessment Score (SOFA) or Predicting Death of Severe ARDS on VV-ECMO can determine if ECMO can be beneficial to the patient. Brandi et al. [67] classify contraindications into two main groups – cardiac and pulmonary contraindications. Brandi et al. [67] collects some absolute contraindications from studied documents such as moderate to severe aortic valve insufficiency and vascular diseases such as aortic dissection, severe arteriosclerosis or peripheral artery disease. Some contraindications were classified depending on document to absolute or relative - unobserved circulatory arrest and/or prolonged resuscitation (>20min) or fresh intracranial-intracerebral hemorrhage. The most of pulmonary contraindications according to Brandi et al. [67] are relative: duration of medical ventilation over days or severe immunosuppression. Riera et al. [68] in their research emphasize that ECMO contraindications in COVID-19 patients appeared in 46.3% of patients. The most frequent was advanced age, long time on mechanical ventilation, immunosuppression and morbid obesity. Hermann et al. [69] also highlighted that long time duration of mechanical ventilation is a relative contraindication, but it was accepted when patients were otherwise eligible for ECMO. Badulak et al. [70] agreed with the foregoing contraindications and noticed that the criteria may be changing according to the system capacity in the pandemic times.

Contraindications for ECMO play a significant role in planning treatment in patients with COVID-19. Every possible contraindication has to be considered individually to optimize the treatment. It also depends on the potential of the unit and where we are in the pandemic.

New methods - Prone resuscitation

Although whole concept of prone cardiopulmonary resuscitation (prone CPR or reverse CPR) was suggested much earlier for such events as out-of-hospital arrest patients found face down or arrested during prone surgeries such as spine and neurosurgery [71,72], it was mechanical ventilation in prone position, which escalated burning need of investigating prone resuscitation. Its effectiveness is being emphasized in patients where predefined ventilation parameters were not met and those with refractory hypoxemia [73]. Changing position from supine to prone increases oxygenation and reduces mortality in ARDS patients. This is due to more even distribution of the gas-tissue rations along the dependent-nondependent axis and more homogeneous distribution of lung stress and strain [74]. The most common complications include pressure sores and facial edema. Changing position requires a skilled team of 4-5 caregivers [74], thus leaving patients vulnerable to emergency situations, like cardiac arrest or arrhythmias (especially those induced by hydroxychloroquine and azithromycin, which predisposed to QT interval elongation, being widely used as treatment for COVID-19 [75]). The main reason for implying prone CPR was to save time consumed by turning prone patients to supine position and thus reducing no-flow time. As we all know the most crucial factors, which may eventually save patient's live are high quality chest compressions and defibrillation – both of them initiated as soon as possible after cardiac arrest [76]. There was hope that during pandemic, scientists will find the answer whether potentially time-consuming

standard supine resuscitation is still relevant when the patient experiences cardiac arrest in prone position. Soon after COVID-19 pandemic escalated, in July 2020, Douma et al. searched grey literature to find out if prone resuscitation may help manage their intensive care patients' infected with Sars-CoV 2. Eventually they did not identify sufficient evidence to justify conducting a systematic review or modify resuscitation guidelines, however they suggested initiating resuscitation in prone position if turning patient supine would lead to delays or risk to providers or patients [77].

Moscarelli et al. prompted conducting further studies on this topic, meanwhile illustrating how the procedure should look like based on case reports and small sized nonrandomized studies [78]. Compressions should be delivered either by placing one hand with sternal counter pressure (Figure 1A), both hands laterally (Figure 1B) or both hands in midline (Figure 1C). The pads should be placed either antero-posteriorly, bi-axillary or postero-laterally. Respirations should be continued using tracheal tube as patient with ARDS was already intubated [79].

A systematic review conducted by Hsu et al. in September 2021 warned that besides handful of case reports, there were only two prospective nonrandomized studies on implying prone CPR, both of them deemed at critical risk of bias [80]. Despite that it is worth to mention the researchers reported significantly higher systolic blood pressure during compressions in the prone position (all enrolled patients were declared dead after conventional supine CPR) [79,81]. Simulation studies gave two important answers on the time it takes to change position from prone to supine: the delay for chest compressions was 50+/-34 seconds to 110 seconds [82,83]. Delivering a defibrillation in prone position took 22 seconds compared with an average time of 108+/-61 seconds when the patients was turned supine [82]. Despite low scientific evidence mentioned above, American Heart Association in their interim 2020 guidelines suggested performing prone CPR if transitioning a patient with an advanced airway into supine position was not safely manageable. To provide defibrillation when defibrillator's pads are in the anterior-posterior position and apply compressions with hands in the standard position over the thoracic (Th) 7/10 vertebral bodies [84]. The European Resuscitation Council (ERC) guidelines confirmed this standpoint adding the expected depth of 5-6 cm with frequency of two compressions per second [85]. The 2021 International Consensus on CPR concluded

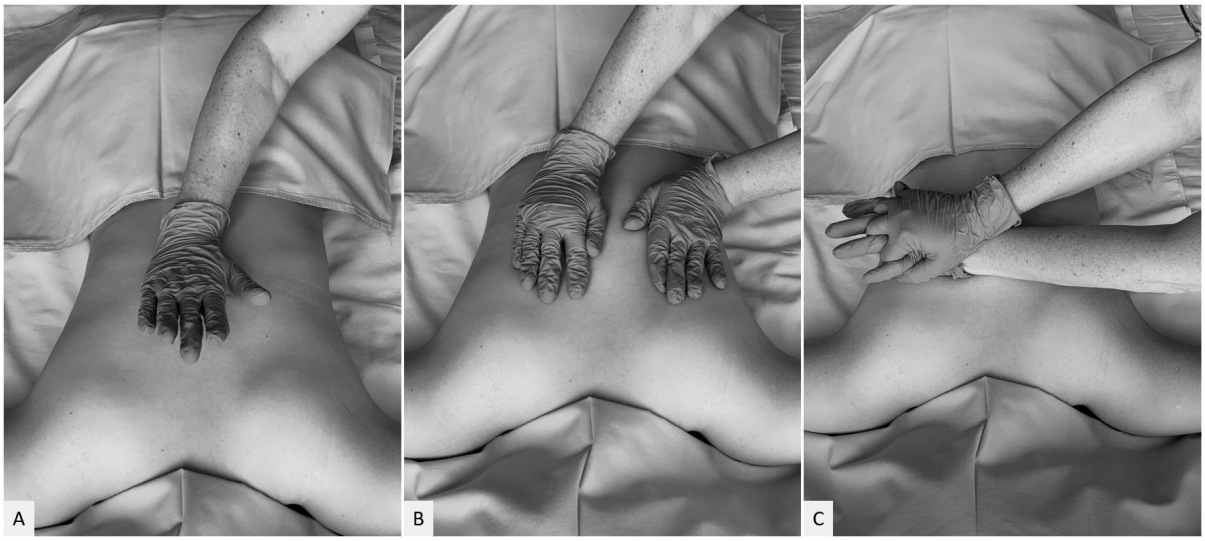

Figure 1. Hand position during prone CPR (authors' own modification of techniques illustrated by Moscarelli A, et al. [78]). 1A- one hand with sternal counterpressure, 1B- both hands laterally, 1C- both hands in midline.

Rycina 1. Pozycja rąk podczas resuscytacji w ułożeniu na brzuchu (własna modyfikacja autora techniki zilustrowanej przez Moscarelli A, et al. [78]). 1A - jedna ręka z przeciwciśnieniem mostka, 1B- obie ręce bocznie, 1C - obie ręce w linii środkowej

recommendations mentioned above as a good practice statement, emphasizing that the CPR should be provided supine, whenever it's immediately feasible and does not pose significant risk to the patient [86].

Having in mind latest recommendations of these societies (for sedated prone patients on mechanical ventilator with a tracheal tube), Car and Becker [87] as well as Soar et al. [88] recommend starting prone CPR while preparing patient for rolling supine, and when changing position is possible, continuing standard supine CPR. Transition to mechanical chest compression should be introduced right away [87]. Lastly, the newest available ERC review by Nolan et al. [89] featured simulation study showing that it is feasible to provide mechanical chest compressions in prone position with only minor modifications to mechanical device [90], which may eventually result in introducing procedures with measurable and comparable outcomes that might be considered as significant scientific evidence, which in case of prone CPR are still lacking.

Conclusions

Hypoxia, procoagulation and hyper inflammation play a crucial role in triggering multiorgan failure during the Sars-Cov-2 infection. In the most severe cases extracorporeal membrane oxygenation may be required. Intensive care unit staff may encounter performing prone CPR in face down laying intubated patients as a new resuscitation method.

Konflikt interesów / Conflict of interest
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Adres do korespondencji / Correspondence address
Natalia Popłonyk
Zakład Dydaktyki Anestezjologii i Intensywnej Terapii, Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu, ul. św. Marii Magdaleny 14, 61-861 Poznań
☎ (+48 61) 668-78-36
mgrzesko@ump.edu.pl

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