

Sequential use of hemadsorption using Cytosorb® and Biosky® filter- technology in a COVID-19 patient suffering from severe ARDS

Matthias Mezger (✉ Matthias.Mezger@UKSH.de)

Department of Cardiology, Angiology and Intensive Care Medicine, University Heart Center Lübeck, Lübeck, Germany

Ingo Eitel

Department of Cardiology, Angiology and Intensive Care Medicine, University Heart Center Lübeck, Lübeck, Germany

Stephan Ensminger

Department of Cardiac and Thoracic Vascular Surgery, University Heart Center Lübeck, Germany

Dirk Pogorzalek

Life Systems, Germany

Zhipan Huang

Foshan Biosun Medical Technology Co., Ltd, China

Tobias Graf

Department of Cardiology, Angiology and Intensive Care Medicine, University Heart Center Lübeck, Lübeck, Germany

Case Report

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Abstract

In March 2020, the World Health Organization (WHO) declared the novel coronavirus disease (COVID- 19) pandemic. Here, we present the case of a patient who was admitted to our hospital with acute respiratory distress syndrome (ARDS) following infection with COVID-19. After initial stabilization through restrictive fluid management, hemadsorption using Cytosorb® was performed and finally temporary extubation of the patient was possible. However, the patient again clinically deteriorated and needed ventilation and finally ECMO-support and high catecholamine application. Whilst being on VV- ECMO, hemadsorption using Biosky® MG 350 filter was performed. In this manuscript, after a brief overview of the role of hemadsorption in ARDS, a detailed case presentation is followed by a critical discussion of the current literature.

Background

Novel SARS- Coronavirus 2 (SARS CoV-2) associated disease (COVID- 19) developed into a pandemic health problem during the first quarter of the year 2020. Recommendations for treatment are derived from insights during ARDS treatment or expert opinions [1]. Ongoing inflammation is a major contributing factor to SARS CoV-2 morbidity and mortality and immunomodulation is one promising approach for treatment of COVID-19 [2]. Besides immune modulating agents that are systemically administered and currently applied in clinical studies, another possible way of modulating the immune response, - especially if renal replacement therapy or ECMO therapy is necessary -, is hemadsorption. During this therapy, blood is perfused through a special filter system that is inserted into an extracorporeal circuit. Within the filter, membranes, creating a large surface area, adsorb immune modulating agents that might fuel the vicious circle of inflammation by contributing to vascular leakage and organ failure. Currently there is only limited evidence for filter technology available mostly from small observational studies or case reports in non-COVID-19 patients [3-5]. One available system for hemadsorption is the Cytosorb® system. So far, beneficial effects of Cytosorb® treatment have been described with respect to sepsis [5], ARDS [6, 7] and endocarditis [8], respectively. Besides Cytosorb®, Biosky® is another commercially available filter for hemadsorption. So far, results from studies investigating the use of hemadsorption with respect to COVID- 19 disease are scarce. We applied Cytosorb® as well as Biosky® filters to treat a patient suffering from severe ARDS due to COVID-19 pneumonia.

Case Presentation

The 56 year- old male patient was administered to our tertiary care hospital due to severe ARDS following infection with COVID-19. Previously, he had been treated in another hospital. At the time point of arrival, he was under controlled ventilation. The pre- existing conditions documented for the patient were asthma and obesity. On admission, he was under controlled ventilation with an FiO₂ of 1,0. PEEP was 16 mbar.

Chest x- ray at admission showed bilateral infiltrates. Blood sampling was done immediately after arrival. In addition, urine was checked for infection with legionella, pneumococcus and chlamydia, too. Also,

tracheal suctioning was performed to look for bacterial superinfection.

Blood count at administration showed leukocytosis (12.700/ μ l) and anemia (Hb 13,1 g/dl). D- dimers were highly increased (> 33 mg/l). Na⁺ was slightly reduced (133 mmol/l). Chloride and Calcium were also reduced (95 mmol/l and 1,99 mmol/l, respectively). Phosphate was increased (1,53 mmol/l). Renal function appeared normal (creatinine 94 μ mol/l). Creatinine- kinase was not elevated (163 U/l), LDH was highly increased (636 U/l). GOT and GPT both were slightly increased (92 U/l and 90 U/l, respectively) as was GGT (88 U/l). CHE was decreased (3,4 kU/l). Troponin levels were slightly increased (16 ng/l). CRP was highly increased (319 mg/l). Protein and albumin levels were decreased (56 g/l and 26 g/l, respectively).

Adequate blood pressure could be achieved through administration of norepinephrine (0,48 μ g/h). Initially, MAP was 72 mmHg. Heart rate was 103/min. SpO₂ was 94%, Horowitz- index was 76 mmHg. Body temperature, which was measured via the transurethral catheter was 37°C, but increased in the following hours, finally reaching 38,8°C. Fever could be controlled via administration of acetaminophen and metamizole. At the ventilator, pressure-controlled ventilation was performed. PEEP was set to 14 mbar, initially, but had to be increased to 16 mbar the following hours due to inadequate oxygenation. Peak pressure was set to 30 mbar, breathing rate 30/min and inspiration time was 1,1 sec. Tidal voluminal were between 425 ml and 550 ml. Since FiO₂ could not be reduced the following hours below 0,9 despite repeated relaxation through administration of rocuronium, we decided to begin prone positioning. In addition, sedation that was initially performed with propofol and remifentanil was switched to sevoflurane and sufentanil. Prone positioning was done for 16 hours daily followed by supine positioning for additional 8 hours. With prone positioning, slowly, improvement of respiratory function was visible and FiO₂ could be gradually decreased to 0,4. After 7 days, prone positioning could be stopped after we observed sustained improvement of respiratory function also in supine position.

The next days, the patient developed progressive renal failure. Creatinine level increased to 423 μ mol/l and urine output almost completely suspended. Therefore, we started continuous renal replacement therapy (CRRT). Here, GeniusÒ 90 system (Fresenius Medical Care, Bad Homburg Germany), was used. Both PCT and IL-6 level shortly after administration were elevated to 3,7 μ g/l and 800 ng/l, respectively. Therefore, a CytosorbÒ filter was added to CRRT (Fig. 2). Treatment with a CytosorbÒ filter was performed for a total of three days. After that, blood sampling revealed a significant drop of IL-6, from 800 ng/l to 113 ng/l (Fig 1). Before admission to our university hospital, the colleagues had already started an antibiotic therapy with Ampicillin/Sulbactam and Clarithromycin. We went on with this antibiotic therapy for further 12 days (Ampicillin/Sulbactam) and 8 days (Clarithromycin). Circulation continuously improved, reflected through decreasing doses of Norepinephrine, necessary. We started another antibiotic treatment with Piperacillin/Tazobactam when inflammatory markers, again, began to increase. Diagnostics could exclude infection with legionella and pneumococcus. We could only find staphylococcus epidermidis in one blood culture drawn from the arterial catheter line, which we considered contamination.

Disease course was complicated by pneumothorax that was successfully treated with drainage, which we could remove later on. We finally tried extubation after a total of 23 days of ventilator support. However, intubation became necessary again after three days, due to progressive respiratory failure. After intubation, severe respiratory acidosis was seen in blood gas sampling, despite FiO_2 of 1,0. Tidal volume was 280 ml only, although inspiratory pressure was as high as 40 mbar and PEEP was 14 mbar, too. Both, incorrect position of the endotracheal tube and de novo pneumothorax were excluded. We quickly decided to implant VV- ECMO (Maquet Cardiohelp, Rastatt, Germany). Implantation was done through the right internal jugular vein and right femoral vein. Blood was drawn from the right femoral vein and returned after oxygenation to the right internal jugular vein (Fig. 3). After implantation, respiratory acidosis slowly improved. Both, high norepinephrine support (4,8 $\mu\text{g}/\text{h}$) and intensive fluid therapy were necessary, to achieve sufficient mean arterial pressure. Since blood sampling showed high levels of the inflammatory cytokines IL-6 and soluble IL-2 receptor, we decided to integrate Biosky® filter into the ECMO circuit for cytokine removal (Fig. 3). In addition, antibiotic therapy was first escalated to Vancomycin and Meropenem, finally changed to Caspofungin, Linezolid and Meropenem. With the combination of a changed antibiotic regimen and Biosky® filter all markers of inflammation, e.g. leukocytes, CRP, PCT, IL-6, soluble interleukin 2- receptor started to decrease (Fig. 1). Interestingly, neither blood and urine cultures nor tracheal suctioning could reveal microbial infection. Finally, weaning from VV- ECMO was possible. However, after weaning from VV- ECMO had been done, the patient again deteriorated and unfortunately, finally died.

Discussion

With this case we want to present our experience using Cytosorb® and Biosky® filter in a case of severe ARDS due to infection with COVID-19. ARDS might follow infection with SARS- CoV 2, as has been published previously [9]. However, the time point of hemadsorption might be critical and a treatment late in a disease course, despite improving inflammatory markers, could be unable to prevent a fatal course. There exist several filter systems on the global market (Tab. 1). Initially, our attempts were to stabilize pulmonary function through adjusting parameters of ventilation, according to current recommendations [1, 10, 11]. In addition, a restrictive fluid management strategy was chosen since this is currently recommended in ARDS [11-14] and beneficial effects have been described with respect to COVID-19 [15]. We also did relaxation although there is conflicting evidence regarding relaxation of patients with severe ARDS [16].

Initially, creatinine kinase level was not elevated suggesting preserved renal function. Only a few days later, however, creatinine levels markedly increased, suggesting acute kidney injury. Therefore, we started CRRT. To our knowledge, renal disease following infection of COVID-19 is a rare phenomenon [17], which might be associated with cytokine release syndrome [18]. Since markers of inflammation, e.g. CRP, PCT, IL-6 all were increased in our patient, too, we decided together with the consulting nephrologist to add Cytosorb® filter to CRRT (Fig. 2) in order to combat ongoing inflammatory response. IL-6 is known to be increased early after inflammation starts since it is produced directly at the site where inflammation

occurs [19]. Further inflammatory responses are exerted through the effect IL-6 has, for example on liver biosynthesis, e.g. leading to CRP release [19]. In COVID-19, IL-6, together with CRP, has been shown to correlate with disease severity [20]. Therefore, modulation of immune responses through targeting IL-6 has been suggested [21, 22], e.g. through administration of the anti-IL-6 antibody tocilizumab [23]. Of note, albumin levels were dramatically reduced in our patient (26 g/l), as well, which might be associated with the highly increased levels of IL-6 (Fig.1) and CRP, since IL-6 has been described to have inhibitory effects on albumin synthesis in the liver [19].

As already mentioned, we continued the antibiotic regimen consisting of Ampicillin/Sulbactam and Clarithromycin. Indeed, regarding treatment of COVID-19, beneficial effects after receiving macrolide antibiotics have been reported [24, 25]. Both bacterial superinfection e.g. with PVL- positive staphylococcus aureus [26] and fungal superinfection with aspergillus have been shown to complicate infection with COVID-19 [27].

After the patient, again, needed invasive ventilation, respiratory function was severely compromised, which was reflected through severe respiratory acidosis despite high peak pressure chosen on the ventilator. To solve that problem VV- ECMO therapy was commenced. ECMO therapy has been suggested for severe ARDS following COVID-19 [28]. Indeed, successful use of VV- ECMO in COVID-19 disease has been reported [29]. Since inflammatory markers again, were dramatically increased in our patient, we decided to integrate Biosky® filter into the ECMO circuit (Fig. 3). We chose the Biosky® system because we were more familiar with its implantation into the ECMO circuit. With the combination of both, antibiotic and fungal treatment and the Biosky® filter system, all inflammatory markers were falling (Fig. 1). Since soluble IL-2 receptor was suggested to be a useful marker in inflammation, e.g. soluble IL- 2 receptor- concentrations have been associated with disease activity in inflammatory bowel disease [30], sarcoidosis [31] and hemophagocytic syndrome [32], this parameter was added to our routine diagnostic panel.

Despite the fact that we could not detect bacteria or fungal infection when progressive respiratory failure happened, we think, that the observed aggravation was most likely due to superinfection as a consequence of prolonged time on ventilator. Sequential PCR for coronavirus that we performed from respiratory specimen, repeatedly acquired from lower respiratory tract, remained negative. Nosocomial pneumonia, especially in mechanically ventilated patients is a major issue in intensive care medicine worldwide [33]. However, in ventilator associated pneumonia, blood cultures quite often remain negative [34].

To our knowledge this is the first case reported so far, where hemadsorption on CRRT and ECMO was performed in a COVID-19 patient. We believe, that hemadsorption might be a helpful tool in patients suffering from severe disease course of COVID-19, however, timing is crucial, and more data are needed to conclusively ascertain the use of hemadsorption in severe ARDS following infection with COVID-19

Conclusion

Hemadsorption, in combination with adequate antimicrobial therapy, seems to be effective in the treatment of patients suffering from severe infection with COVID-19. The only prerequisite for this therapy is, that an extracorporeal circuit needs to be established for renal- replacement therapy or ECMO.

Declarations

Ethics

We got in contact with the wife who is the legal representative of the patient since the patient was permanently sedated on our ICU ward and, finally, died. She agreed to the publication of the case report.

Disclosures

The authors declare that they have no conflict of interest.

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Figures

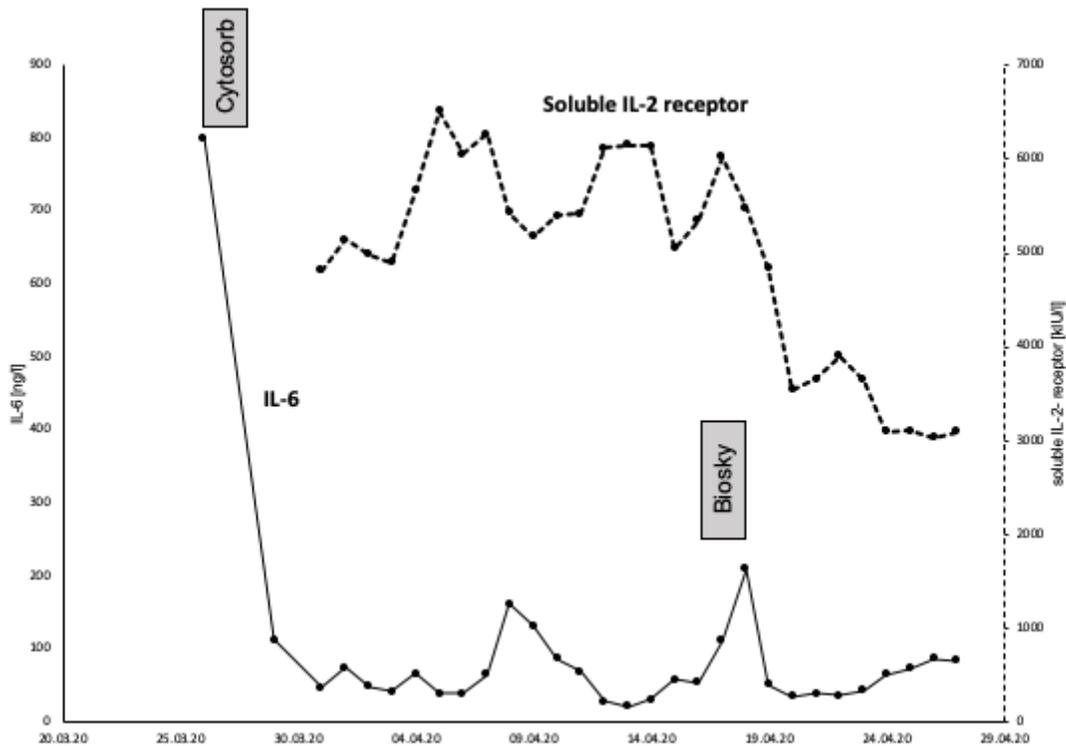


Figure 1

Inflammatory markers Initially, the levels of all inflammatory markers were highly increased. Here, the time course of IL-6 and soluble IL-2 receptor concentration is illustrated. Soon, after admission, the IL-6 concentration was highly increased at 800 ng/l. After three days of CRRT with Cytosorb®, IL-6 had fallen to 113 ng/l. With ongoing disease course, IL-6 again increased. After change of the antibiotic regimen, finally Caspofungin/Meronem/Linezolid were applied, and after completion of Biosky® filter- treatment for additional three days whilst being on VV- ECMO support, IL-6 was as low as 51,9 ng/l. In addition, soluble IL-2- receptor concentration, we measured as well, also decreased tremendously.

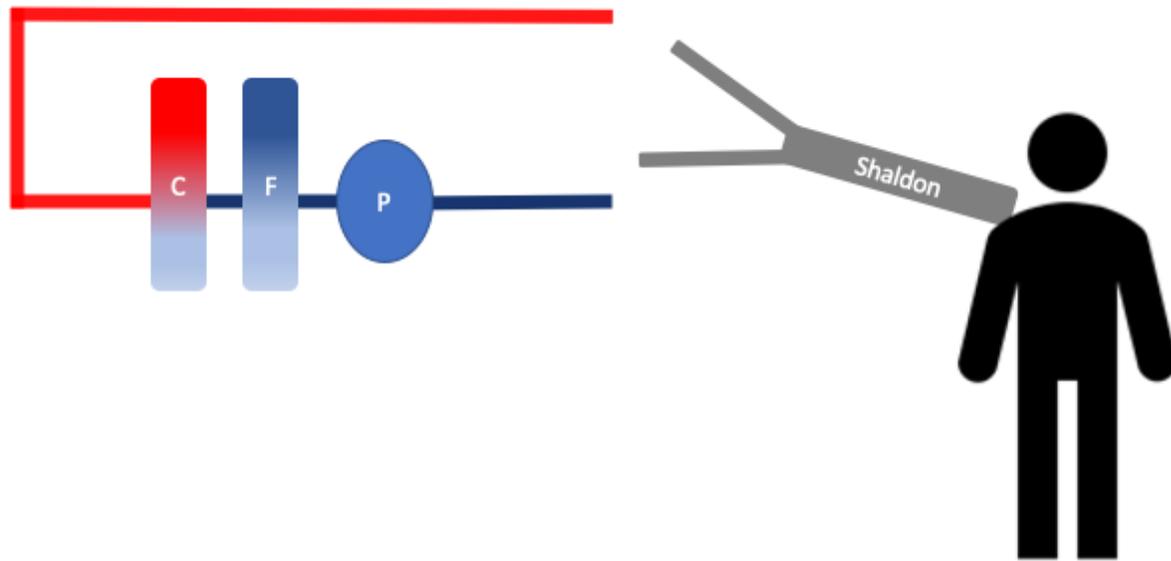


Figure 2

Cytosorb circuit We applied the Cytosorb® system for three days while CRRT (Genius® 90 system, Fresenius Medical Care, Bad Homburg Germany) was performed. Shaldon's catheter was inserted into the jugular vein. The blood, taken from jugular vein, first was perfused through a pump (P), then through a standard filter (F) for renal replacement. Finally, the blood passed another filter, the Cytosorb® filter (C), before returning to systemic circulation. The Cytosorb® filter was applied in series to the extracorporeal circuit.

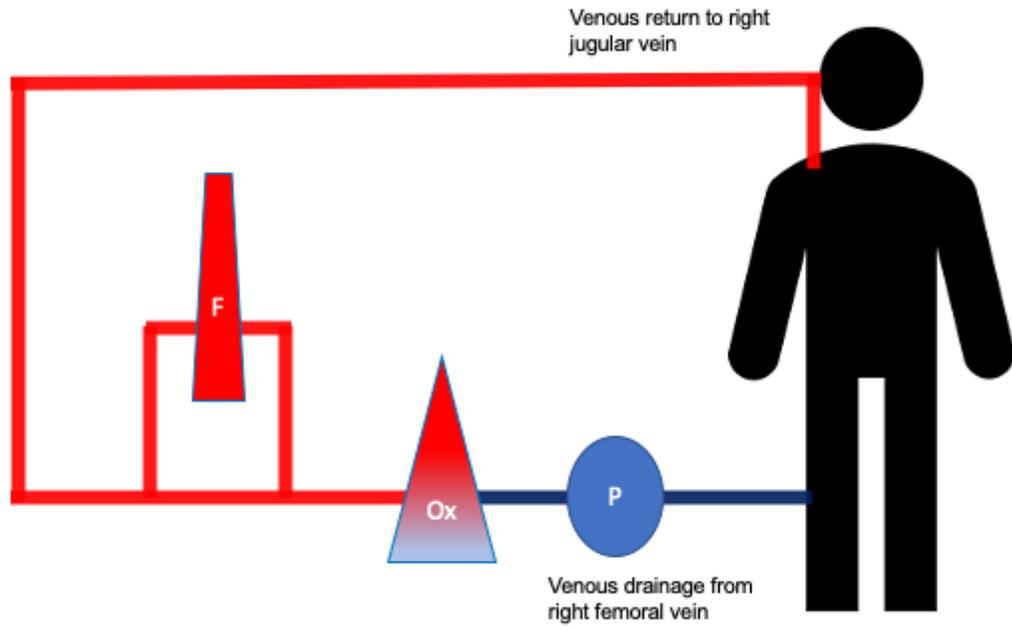


Figure 3

Biosky circuit