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Post-COVID changes in respiratory function in patients supported with veno-venous extracorporeal membrane oxygenation (V-V ECMO)

PhD Thesis Booklet

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I. BACKGROUND

Severe coronavirus disease 2019 (COVID-19) and associated pneumonia can seriously affect the gas exchange in the lungs. Acute respiratory distress syndrome (ARDS) caused by the viral infection can result in severe impairment of the lung function, leading to life-threatening hypoxemia. Mainly, the disease is characterized by hypoxemic respiratory failure, and it may necessitate invasive mechanical ventilation. Furthermore, in the most severe cases, veno-venous extracorporeal membrane oxygenation (V-V ECMO) support is required. In our Tertiary Centre we followed the recommendations of the European Extracorporeal Life Support Organization (EURO ELSO) guidelines for the management of severe respiratory failure caused by COVID-19 and ECMO support. The V-V ECMO as a rescue therapy provides an opportunity to ventilate the lungs on resting parameters and minimalize ventilator induced lung injury (VILI), providing time for lung recovery. On the other hand, the inflammation cascade is activated during ECMO support and as a consequence, endothelial and/or epithelial damage occurs in the pulmonary system leading to long-term gas exchange defect. During the COVID-19 pandemic, 18 patients were supported with V-V ECMO in our institution with nine patients surviving the hospitalization. Studies included in the present thesis gained information on this patient population in the acute phase, and extended assessments of the long-term consequences was also performed 6 months and 1 year after hospital discharge.

II. COVID-19 AND SEVERE RESPIRATORY FAILURE NECESSITATING V-V ECMO SUPPORT

II. 1. *SARS-CoV-2 infection*

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has widespread symptoms. Influenza-like manifestation with fever, cough, anosmia, in severe cases pneumonia and gas exchange defect occurs. In the most extreme cases, severe COVID-19 (coronavirus disease 2019) pneumonia and ARDS develops necessitating invasive mechanical ventilation.

II. 2. *ARDS and invasive mechanical ventilation*

As COVID-19 pneumonia progresses, severe gas exchange impairment develops with tachydyspnea, high respiratory drive and tidal volumes, referred as patient self-inflicted lung injury (P-SILI). P-SILI could further aggravate lung injury. Early invasive mechanical ventilation could prevent the development of P-SILI and has the potential to reverse hypoxemia. Nevertheless, it can also injure healthy and impaired lungs, and could even provoke newly onset lung injury. Ventilating the patients with high pressures, volumes lead to baro-, volu-, atelecto-

and biotrauma. These injuries are referred as ventilator-induced lung injury (VILI). Both P-SILI and VILI may converge to ARDS. ARDS is characterised by alveolar epithelial damage and vascular endothelial destruction, the release of inflammatory cytokins and the disruption of alveolo-epithelial barrier. The functional lung size is decreased as a consequence of interstitial and alveolar oedema (so-called „baby lung", demonstrating the size of the functional lung volume) and severe gas exchange impairment occurs.

II. 3. *Protective invasive mechanical ventilation*

Protective invasive mechanical ventilation is a pertinent aspect in diminishing the deleterious effects of VILI and P-SILI. The primary concern is to defend the baby lung from mechanical injuries associated with mechanical ventilation. During pressure-limited ventilation the main goal is to keep the plateau airway pressure <30 cmH_2O (minimizing barotrauma), and during volume-limited protective ventilation with tidal volumes 4-6 ml/kg ideal body weight (decreasing the odds of volutrauma). Administration of higher PEEP (positive end expiratory pressure) values (10-15 cmH_2O) prevents cyclic collapse and reopening of alveoli, i.e. atelectotrauma and plays a role in right ventricle protective ventilation. In addition, prone positioning can also be considered as a rescue maneuver to fragment large dorsal atelectatic lung regions allowing decreasing transpulmonary pressure and enhancing ventilation-perfusion matching and increase baby lung (functioning lung volume) size. If these interventions are unable to provide adequete gas exchange, or gas exchange optimization can only occur with high distending pressures, V-V ECMO offers pivotal opportunity to maintain systemic oxygenation while preventing further lung injury by using lung-protective ventilation settings.

II. 4. *ECMO in our tertiary centre*

V-V ECMO support is indicated in patients with preserved right heart function with severe respiratory failure. ELSO provided guidelines for the initialization of the ECMO support in COVID-19 pandemic and patient selection was based on individual decisions, taking into consideration the overall health data of the patients, and institutional availability of the resources, materials and equipments for the ECMO support.

As V-V ECMO support commence, lung-protective ventilation could take place in order to decrease the detrimental effects of high plateau pressure and to keep the lungs open with high PEEP and prevent atelectotruma. In our centre V-V ECMO setup and patient management took place in accordance with ELSO guidelines for COVID-19 ARDS. We supported 18 patients with V-V ECMO, 9 patients survived the hospitalization.

II. 5. *Population at risk*

The population at risk includes patients with obesity, elderly age and patients with cardiovasular comorbodities (i.e. hypertension). Obesity, hypertension and diabetes mellitus have a high impact on poor clinical outcome due to the fundamental changes in cardiovascular system. Another main risk factor is pregnancy associated altered immunological state. Pregnant women are naturally in a meticulously planned immunocompromised state to prevent the rejection of the fetus and they are at higher risk to develop serious coronavirus infection.

III. AIMS AND HYPOTHESIS

Treatment of severe respiratory dystress resulting from SARS-CoV-2 infection may comprise the application of V-V ECMO if the conventional ventilatory strategy involving protective lung ventilation and prone positioning is ineffective. However, patient outcomes following V-V ECMO support in these patients have not been chracterized in short and longer time window. Therefore, studies included in the present thesis aim at investigating the characteristics and outcomes of patients needing V-V ECMO in our ICU, whith specific focus on the

- survival rate;
- assessing the surviving patients' ability to perform activities of daily living in a follow-up manner;
- long-term (6 months) pulmonary effects;
- describing the clinical course of 3 postpartum women who required V-V ECMO support immediately after their urgent cesarean sections.

To address these aims, we collected data on the baseline demographics, patient history regarding COVID-19 infection and respiratory failure, including disease severity scores, and the specific challenges and time intervals of the invasive mechanical ventilation and V-V ECMO support. Regarding the respiratory and pulmonary effects of severe COVID-19 forced oscillation technique, spirometry, whole body pletysmography and alveolar gas diffusion measurement were used. Six-minute walk test (6MWT) and data from the 36 Item Short Form Survey (SF-36) were collected to measure physical and pschycological health and quality of life, social recovery.

Our hypothesis was that severe COVID-19 pneumonia requiring invasive mechanical ventilation and V-V ECMO is a highly valuable rescue treatment modality to facilitate patient survival, thereby allowing reintegration into the society, achieving independence and the ability to maintain self-sustaining life. However, long-term detrimental effect on the respiratory system

may be anticipated after hospital discharge, which may require a regular follow-up and treatment to maintain good general health and social embedding with active participation in the society.

IV. METHODS

IV. 1. *Patients*

We included all SARS-CoV-2 positive patients who received V-V ECMO support at our centre between March 2021 and May 2022 in our studies. 18 patients were eligible for the V-V ECMO support, we achieved ICU and inhospital survival rates of 56% and 50%, respectively. None of the patients had any serious comorbidity in their previous medical history, except one who had psoriasis.

IV.1.2. *Patients in the 6-month respiratory follow-up*

For the 6-month respiratory follow-up study, 55 subjects were assessed for eligibility and were divided into the two study groups. Nine post-ECMO patients were eligible for the follow-up measurements 6 and 12 months after hospital discharge (Group COVID). Control group of patients were recruited from an ongoing study applying the same methodology as for healthy adults (Group H). Exclusion criteria comprised a history of smoking, chronic respiratory disease, or COVID-19-induced pneumonia requiring hospitalization. We selected 9 control subjects using propensity score matching, based on demographic characteristics relevant to lung function outcomes such as sex, age, height, and weight.

At the 6-month assessments, results from the V-V ECMO patients were compared to those obtained in a control group of patients. They were recruited from an ongioing study that applied the same methodology used for healthy adults, with the exclusion criteria of history of smoking, chronic respiratory disease, or hospitalization for COVID-19 induced pneumonia. We used propensity score matching to select the healthy, matched control group. This selection was based on demographic characteristics relevant to lung function outcomes, such as sex, age, height and weight, from the control cohort.

IV. 1. 3. *Peripartum women with life-threatening COVID-19 with V-V ECMO support*

One noteworthy patient population is the peripartum women, who are particularly susceptible to severe respiratory symptoms. This complex pathophysiology involves mechanical and hormonal pathways, lung restriction and increased oxygen demand by pregnancy. We supported 3 postpartum patients in our ICU immediately after their urgent cesarean sections

due to severe hypoxemic respiratory failure and all of them survived the hospital discharge hence they were also included in the follow-up examinations.

Case 1 was a 26-year old pregnant woman who tested positive for COVID-19 at the 32nd week of gestation. She received oxygen supplementation for hypoxemia, but her condition worsened, necessitating an urgent cesarean section under regional anaesthesia. After delivery, she was admitted to the ICU, intubated and mechanically ventilated. Prone position was also performed for better oxygenation. Gas exchange worsened and she was referred to V-V ECMO support and was eligible for this life-saving intervention. Standard ECMO support continued for 25 days. An additional 10 days of mechanical ventilation was needed to wean from the ventilator. She left the ICU for a rehabilitation facility 38 days after ECMO initiation.

Case 2 was a 28-year old woman who tested positive for SARS-CoV-2 at the 26th gestational week of pregnancy. Urgent cesarean section was performed due to life-threatening hypoxemia under general anaesthesia and invasive ventilation. 2 days later V-V ECMO support started as her hypoxemia worsened. After 10 dyas on ECMO support, she was weaned from extracorporeal support. On the following day she was also weaned from invasive mechanical ventilation and extubated. Puerperal fever occurred and ultrasound examination confirmed the presence of a hematoma anterior to the uterus. Antibiotic treatment was started and the infection resolved. On day 29 she was discharged to a rehabilitation facility and 5 days later she was discharged home.

Case 3 was a 30-year old woman at the 38th week of her pregnancy. She was tested positive for COVID-19 with mild symptoms including fever and moderate dyspnea. She underwent secarean section under regional anaesthesia while receiving oxygen supplementation through a nasal cannula. Postpartum CT showed pneumonia, involving approximately 50% of the lungs. Her respiratory failure rapidly progressed and she was on NIV support for 8 days. Repeated chest CT scan showed progression to >75% of the lungs accompanied by pneumomediastinum. On postpartum day 10, her hypoxemic respiratory failure worsened, necessitating urgent endotracheal intubation and prone positioning. She was unresponsive to these interventions and V-V ECMO support was started. Her respiratory system compliance decreased day by day and she was completely ECMO-dependent. She was placed on prone position 2 times during ectracorporeal support. From day 9 on ECMO, bradycardic and asystolic periods occurred frequently necessitating chest compressions. No cardiac abnormalities were seen on echocardiography, leading to the assumption of vaso-vagal mechanism. On day 20, chest

radiography revealed complete left-sided pneumothorax, and after chest drain insertion, air leakage of 70-80% of inspiratory volume was observed and mechanical ventilation was ceased for the following 14 days. After 2 weeks, it became feasible to restart mechanical ventilation and lung compliance slowly increased, resulting in successful weaning from V-V ECMO on day 70 and on day 83 from invasive mechanical ventilation. She was discharged to a rehabilitation facility on day 91 and eventually discharged home.

IV. 2. *V-V ECMO and inflammatory cascade activation*

The management of patients on V-V ECMO support was based on the recommendations of the ELSO and EuroELSO guidelines.

One distinctive aspect of ECMO support is the activation of the clotting cascade on the large non-endothelial surfaces of the cannulas, pipes and inside the oxygenator. As the final result of the complex interaction between coagulation pathways and immune system, widespread acivation of the inflammatory cascade takes place. As a consequence, pro-inflammatory cytokine production leads to organ injury potentially further aggravating lung injury.

IV. 2. 2. *ECMO weaning and post-intensive care syndrome*

Weaning from V-V ECMO is a dynamic process and it takes several weeks. During this highly vulnerable period, several complications could occur, including bleeding, thrombosis and infections. As a consequence, the management of patients on V-V ECMO is a complex task for healthcare-providers. Patients are analgosedated and bed-ridden in the majority of the cases during the extracorporeal support, which results in immobility-associated muscle weakness, delirium, depression and cognitive impairment. These symptoms may persist even after discharge, called post-intensive care syndrome (PICS).

IV. 3. *Post-intensive care evaluation of quality of life*

To assess the physical consequences of PICS, we used 6MWT as simple and globally used method to assess activity limitation. Furthermore, health-related quality of life comprising to physical, mental, psychological and social well-being was measured by 36-Item Short-Form Health Survey referred as SF-36. The survey consists of 8 sections and each section transforms into 0-100 scale, and the lower the point the more decreased life quality. Furthermore, the Rankin score was used to measure disability scale, with scores ranging from 0 to 5. Score 0 means no impairment, whereas 5 denotes severe disability.

IV. 4. *Comprehensive respiratory function follow-up*

IV. 4. 1. *Measurement of airway and respiratory tissue mechanics*

Respiratory oscillometry was used to measure the mechanical properties of the airways and the respiratory tissues. The technique is based on the introduction of small-amplitude pressure oscillations into the airway opening by using an external pressure generator. Recording of the oscillatory pressure (Pao) and airflow (V') at various frequencies allows the calculation of the input impedance of the respiratory system, as Zrs = Pao/V'. Zrs data at each oscillatory frequencies can be expressed as a complex quantity represented by the respiratory resistance and reactance. Resistance expresses the oscillatory pressure in phase with the flow and reflects the resistive loss in the respiratory system. Reactance is defined as the oscillatory pressure component out of phase with oscillatory flow and demonstrates respiratory tissue elasticity at low oscillatory frequencies.

In the present study, Zrs was measured during spontaneous breathing with a pseudorandom forcing signal at a frequency range of 5–19 Hz. Measurements were performed in accordance with the European Respiratory Society (ERS) guidelines.

The resistance values of the whole breath at 5 Hz (R_5) and 19 Hz (R_{19}) were extracted from the Zrs data for further analyses. Large and small airways contribute to the parameter R_5, whereas R_{19} reflects mainly the airflow resistance of the central conducting airways with less influence from the smaller bronchi. Accordingly, subtracting R_{19} from R_5 (R_5–R_{19}) reveals the contribution of the small airways to the overall airway resistance, with providing information on the ventilation inhomogeneities. The area under the reactance curve from 5 Hz until the resonant frequency (AX_5) represented the respiratory tissue stiffness (elastance). The resonant frequency (f_{res}) at which Xrs crosses zero (where the elastic and inertial forces equilibrate with each other) was included in the data analyses.

IV. 4. 2 *Spirometry*

Spirometry was performed in accordance with the American Thoracic Society/ERS guidelines. Forced expiratory flow-volume curves were measured with a commercially available spirometer. The flow signal was integrated to identify changes in lung volume during the forced expiratory maneuvers. Data on forced expiratory volume in the first second of expiration (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, peak expiratory flow (PEF), and forced expiratory flow between 25 and 75% of the volume expired ($FEF_{25–75}$) were extracted from the recordings.

IV. 4. 3. *Whole body pletismography*

Functional residual capacity (FRC) and expiratory reserve volume (ERV) were measured via whole-body plethysmography using standard techniques established by the ERS/ATS Task Force.

IV. 4. 4. *Measurement of alveolar gas diffusion*

A single-breath method was used to evaluate the diffusing capacity of carbon monoxide (DLCO), carbon monoxide transfer coefficient (KCO), and alveolar volume (VA).

IV. 5. *Statisctical analyses*

The reference values for the oscillometry outcomes were based on earlier established equations. The reference values of the parameters obtained via spirometry and gas diffusion were established according to the Global Lung Function Initiative Network guidelines. The measured values were reported as absolute values with scatter expressed as standard deviations, percentage predicted, and Z-score if applicable. Data normality was tested with the Shapiro–Wilk test. The independent *t*-tests were used to compare the measured variables.

Sample sizes were estimated to detect a clinically relevant 25% difference in one of the primary outcome parameters (AX_5). This parameter was selected because restrictive dysfunction was mainly anticipated in patients with post-COVID-19 syndrome, and was best reflected by the oscillometric parameters reflecting respiratory tissue stiffness. Accordingly, nine patients in the control and diseased groups were sufficient for detecting a statistically significant difference, with a variability of 10%, power of 80%, and a significance level of 5%. Propensity score matching was performed using the *MatchIt* package. Statistical tests were performed with the SigmaPlot statistical software package, and a *p*-value of <0.05 was considered statistically significant.

V. RESULTS

V. 1. *Results in the patients with severe COVID-19 requiring V-V ECMO*

V. 1. 1. *Demographic data and clinical characteristics*

18 patients underwent V-V ECMO in our tertiary centre. Patients were middle-aged with male dominance and severe general and respiratory conditions. Our institute followed the ELSO recommendations to maintain relative short time intervals for starting extracorporeal support. Before initiating V-V ECMO support, repiratory parameters reflected the severe lung injury with a need for a 100% oxygen therapy supplemented with high PEEP, driving pressure and

tidal volume associated with low respiratory compliance. The blood gases show decompensated respiratory acidosis with low arterial oxygen partial pressure.

V. 1.2. *Clinical outcomes*

The duration of V-V ECMO support was prolonged, the longest run lasted 70 days. Eleven patients were successfully weaned from ECMO and decannulated. The patients were also mechanically ventilated for an extended period, in 15 cases we performed dilatational percutaneous tracheostomy. Average ICU and hospital length of stay were around 6–7 weeks. ICU and inhospital survival rates were 56% and 50%., respectively. The surviving patients were discharged to another acute care or rehabilitation facility.

V. 1. 3. *Outcomes at discharge*

Nine patients were discharged home after rehabilitation. At the follow-up that occurred between 150 to 489 days after ICU admission, we assessed their functional recovery and health-related quality of life. The results of 6-min walk tests showed that none of them was able to walk the distance expected for age, gender, height, and body weight; they reached 36–74% of predicted values. The Rankin score was 0 in three, 1 in three and 2 in three patients, corresponding with no symptoms at all; no significant disability despite symptoms; or slight disability. The SF-36 Survey showed that the mean scores in all eight categories were above 70, corresponding with good health related quality of life, except role limitation due to physical health, which received a slightly lower score.

V. 2. *Results in the ECMO-patients in the 6-month respiratory follow-up*

V. 2. 1. *Demographic data and clinical characteristics*

Regarding the clinical characteristics and anthropometric data of the COVID and healthy (H) matched control groups, no significant differences were observed between the groups COVID and H in terms of female/male ratio, height, age, and body mass index. Patients requiring V-V ECMO support received invasive ventilation for 0 to 10 days under pressure-controlled mode with specific ventilation parameters. None of the patients were smokers and none had chronic respiratory disease.

V. 2. 2. *Respiratory mechanics assessed by forced oscillations*

Significant differences were observed in some of the primary outcome variables reflecting the mechanical properties of the airways and the respiratory tissues between the two groups. No statistically significant difference was observed in terms of R_5 and R_{19} between the healthy matched control and COVID groups. Conversely, the COVID group had a significantly higher

R_5–R_{19} than in the control group. The difference in R_5 and R_{19} was associated with a significantly higher AX_5 and f_{res} in patients with COVID-19, with these differences remaining if these parameters are expressed as a percentage of predicted values or Z-scores.

V. 2. 3. ***Lung function measured by spirometry***

The COVID group exhibited a significantly lower FEV_1 and FVC than the healthy matched control group. Due to the more severe decrease in FVC compared to FEV_1, the COVID group showed a significantly higher FEV_1/FVC ratio, expressed as absolute values, percentage predicted, or Z-scores. Meanwhile, there were no significant differences in terms of $FEF_{25–75}$ or PEF between the healthy matched control and COVID groups.

V. 2. 4. ***Gas exchange assessments***

Regarding the diffusion capacity measurements, the COVID group had a significantly lower DLCO and VA, expressed as absolute or percentage predicted values than the healthy matched control group. However, there was no difference in terms of KCO between the COVID and healthy matched control groups.

V. 2. 5. ***Lung volumes measured by whole-body plethysmography***

As for the results using whole-body plethysmography, the significantly low FRC values obtained in the COVID group were associated with a remarkable decrease in ERV and its percentage predicted value.

V. 3. 1. ***Demography and clinical parameters of parturient patients***

All three women included in the study already had 2 older children, and their third child was delivered by cesarean section at the time of COVID infection. All parturient patients received the same management regarding COVID infection. All of the patients were otherwise healthy and young women, and V-V ECMO support started immediately after cesarean section. Patient number 3 had the longest run on ECMO and 4 oxygenators were used in the course of 70 days long ECLS. Pneumothorax occured in 1 patient and prone positioning was applied in 1 patient as rescue maneuver to refractory hypoxemia despite V-V ECMO support. All patients were successfully weaned from V-V ECMO and IMV and 1 patient was extubated after successful cessation of ECLS. Extracorporeal life support durations were 25 and 10 days for *Cases 1* and *2*, respectively; the third patient required an extended 70-day ECMO course, including an interim 2-week period without mechanical ventilation. Life support was successful for all 3 women regarding in regaining most of their physical and psychological health and performing

similar social tasks with some help from their family as before the COVID-19 ARDS. Their babies had normal physical and cognitive develpoment.

V. 3. 2. *Outcomes obtained in the parturient patients*

In *Case 1*, after 6 months, there were no signs of abnormalities in the central conductive airways as indicated by the spirometric (FEV_1, FEF_{25-75}, and PEF) and forced oscillometry (R_5 and R_{19}) outcomes. However, small airway dysfunction was detectable from the R_5-R_{19} data, which was associated with moderate lung restriction indicated by the diminished FVC, FRC, VA, and ERV. The decreased DLCO without alterations in the KCO suggests loss of alveolar surface, with maintained ventilation and perfusion in the working lung compartments. These mild respiratory symptoms allowed her to perform daily activities and care for her family without exhaustion. After 12 months, there was a mild improvement in the mechanical properties of the conducting airways in KCO. However, no improvement was observed in small airway function or lung volumes, which can be attributed to the opposing effect of respiratory regeneration and increase in body mass.

In *Case 2*, at the 6-month follow-up, this patient showed no evidence of airway abnormalities, either in the central conductive airways as indicated by the normal spirometric (FEV_1, $FEF_{25–75}$, and PEF) or forced oscillometry outcomes (R_5 and R_{19}, and R_5-R_{19}). The mild lung restriction affected the expiratory lung volumes only (FRC and ERV). The decreased DLCO was associated with diminished KCO, suggesting gas diffusion abnormalities through the alveolo-capillary barrier. However, the Rankin score demonstrated the maintenance of normal daily activities. After 12 months, the patient exhibited no obvious change in her lung function outcomes. The slight further decreases in FRC and ERV could be explained by the slight gain in body mass.

In *Case 3* lung function assessment 6 months after discharge showed marked lung restriction, as evidenced by markedly elevated AX_5 and deteriorated FVC, VA, FRC, and ERV. This resulted in a mild elevation in the tone of the central conducting airways. Persistent gas diffusion abnormalities through the alveolo-capillary barrier were indicated by the decreased DLCO and diminished KCO. This decrease in lung function was also reflected in her Rankin score. After 12 months, there was an improvement in lung restriction, as shown by improvements in AX_5, spirometric parameters, DLCO, and plethysmographic measures. Accordingly, the improved Rankin score parallelled these beneficial pulmonary changes.

VI. DISCUSSION

At our tertiary university center, we provided V-V ECMO support for 18 patients with severe ARDS caused by COVID-19 pneumonia. Of these, 9 patients survived to hospital discharge and were evaluated 6 to 12 months later. Among them, 3 subjects underwent V-V ECMO support immediately after cesarean section. V-V ECMO plays a crucial role in the management of these patients experiencing high and heterogeneous lung strain and stress. It enables lung-protective ventilation, allowing the lungs to rest and recover while minimizing ventilator-induced lung injury. This strategy forms a solid foundation for the regeneration of normal lung function. Our findings demonstrate that V-V ECMO is a vital and effective life-saving intervention in critical and even desperate clinical situations resulting in favorable long-term respiratory, physical and mental outcomes.

VI. 1. *Discussion of case series including all patients receiving V-V ECMO*

In this case series of SARS-CoV-2 positive patients receiving V-V ECMO support we achieved ICU and inhospital survival rates of 56% and 50%, respectively. However, most of these patients required very long ECMO runs, a long duration of IMV with extended ICU and hospital stay. Complications were frequent; the most common ones were nosocomial infections, clinically significant bleeding, and pneumothorax. At the 5–16 month follow-up assessment, all survivors reported good health-related quality of life.

VI. 2. *Discussion of results obtained in the 6-month respiratory follow-up*

The main findings of this study demonstrate long-term detrimental pulmonary changes six months after hospital discharge, with deteriorations in the respiratory oscillometric parameters reflecting the frequency dependence of resistance (R_5–R_{19}) and the respiratory tissue stiffness (AX_5). These adverse alterations in the oscillometric respiratory mechanical parameters were associated with reduced forced expiratory volumes (FEV_1, FVC) and static lung volumes (VA, FRC, and ERV) in patients with post-COVID-19 syndrome. The adverse changes in lung function were reflected in reduced lung diffusion capacity (DLCO) without alterations in the carbon monoxide transfer coefficient (KCO).

An important feature of the current study is the ability to individually characterize the long-term effects of severe COVID-19 on the airway and respiratory tissue compartments. Resistance parameters obtained via respiratory oscillometry have the ability to characterize both overall and peripheral airway function, taking advantage of the fact that low-frequency

oscillatory signals can reach even the small airways. Thus, this part of the oscillatory impedance reflects energy loss in the entire bronchial tree. Conversely, the proximal airways are mainly accessed by applying higher oscillatory frequencies. That is, these resistance components reflect central airway properties. Since R_{19} did not exhibit detrimental changes in patients with COVID-19, the mechanical properties of the large conducting airways were not affected by post-COVID-19 syndrome. On the contrary, the COVID group exhibited a significantly higher frequency dependence of respiratory resistance than the healthy matched control group, as evidenced by elevated R_5–R_{19} data. This indicates the presence of a distal airway dysfunction at >6 months after severe COVID-19 infection, which is a result of heterogeneous peripheral airway constriction and/or permanent closure of terminal airspaces. These oscillometric findings are also supported by the results obtained via spirometry, thereby demonstrating a significant decrease in FVC. This dominant change affects the changes in other forced expiratory volumes and flow parameters. The decrease in FEV_1 associated with a greater reduction in FVC results in an increased FEV_1/FVC ratio in patients with COVID-19. This finding also suggests that the central conducting airways have normal function. FEF_{25-75} reflects small airway function; however, this parameter did not differ between the healthy matched control and COVID groups. This apparent controversy regarding oscillometric findings can also be attributed to a significant decrease in FVC without changes in PEF, which results in a preserved mid-expiratory flow in patients with post-COVID-19 syndrome.

Another important finding of the current study is the presence of persistent deterioration in respiratory tissue elastance, as reflected by the sustained elevations in AX_5. No change in the resistive properties of the conducting large airways was detected, and the inertive forces remained unchanged. Therefore, the high f_{res} also reflects stiffer respiratory tissues in patients with post-COVID-19 syndrome compared to in healthy matched controls. This respiratory mechanical defect can be explained by two different mechanisms: a loss of lung volume leading to a stiffer working lung and intrinsic alteration in the respiratory tissues due to chronic remodeling. Our findings on the static lung volumes obtained via spirometry (FVC), plethysmography (FRC and ERV), and gas washout (VA) uniformly demonstrate the presence of persistent lung volume loss in patients with post-COVID-19 syndrome, thereby indicating the primary involvement of this mechanism in elevated respiratory tissue elastance. Regarding the potential additional effect of intrinsic changes in the respiratory tissues, our findings provide indirect evidence of the lack of tissue remodeling. Decreased DLCO, reflecting the overall gas-exchanging function of the whole lungs, was not associated with any change in KCO

representing gas exchange per unit of lung volume. Since the changes in KCO were not statistically significant, these findings indicate the dominance of lung volume loss over lung tissue remodeling.

V-V ECMO is an acute, life-saving extracorporeal gas exchange support modality. However, it has several direct and indirect pulmonary consequences. In terms of the direct effects of V-V ECMO, it can facilitate protective lung ventilation possibly, by applying low driving pressure and tidal volume (VT) with low FiO_2 and ventilation frequency. Conversely, the application of low VT may cause the development of persistent atelectasis, despite the maintenance of a relatively high positive end-expiratory pressure. In addition, the systemic inflammatory response induced by the pathogen may be further aggravated by indirect mechanisms related to the large artificial instrumental surface of the V-V ECMO. The resultant long-term effects of these pathophysiological processes are not completely understood. The respiratory outcomes of patients with severe COVID-19 requiring V-V ECMO support were comparable to those in earlier studies on patients with COVID-19 who presented with a more moderate disease severity, with or without the need for invasive ventilation. Hence, the long-term pulmonary protective features may outweigh the temporary negative effects of V-V ECMO, which is associated with good health-related quality of life.

VI. 3. *Discussion of results obtained in the postpartum patients*

In this thesis based on our case steries study three postpartum patients are presented who required V-V ECMO support due to life-threatening COVID-19 pneumonia. Extracorporeal life support durations were 25 and 10 days for *Cases 1* and *2*, respectively, while the third patient required an extended 70-day ECMO course, including an interim two-week-period without mechanical ventilation. Life support was successful for all three women. At the 6-month follow-up, the patients exhibited good general physical condition, characterized by Rankin scores of 0 to 1, and moderately impaired lung function, primarily restrictive in nature. At the 12-month follow-up, improvements in both physical condition and lung function were observed for all three patients, as evidenced by uniform Rankin scores of 0 and only mild restrictive lung function impairment.

VII. SUMMARY AND CONCLUSIONS

The studies presented in this thesis reveal that in patients with severe COVID-19 who required veno-venous extracorporeal membrane oxygenation (V-V ECMO) support for acute respiratory failure:

I. Hospital survival rates exceeded 50%, even when complex extracorporeal life support modalities were employed, including V-V ECMO and, in some cases, blood purification therapies such as continuous renal replacement therapy;
II. Survival outcomes were comparable to those reported by other centers treating similar critically ill patient populations;
III. Residual pulmonary dysfunction was frequently observed at the 6-month follow-up, most notably in the form of small airway impairment and loss of functional lung volume;
IV. Multidisciplinary long-term follow-up is essential to evaluate persistent effects on lung function and gas exchange;
V. Ongoing respiratory assessment is strongly recommended in patients who received V-V ECMO support during the acute phase of COVID-19, even six months post-discharge;
VI. Particular attention is warranted for postpartum patients, a subgroup that received ECMO for COVID-19-associated pneumonia and exhibited a distinct susceptibility to severe respiratory symptoms;
VII. Favorable long-term outcomes are achievable even in these high-risk individuals, as evidenced by preserved health-related quality of life during the 6–12 months follow-up period, despite undergoing prolonged, complex, and complicated life support therapy.

These findings underscore the potential benefits of early and optimal consideration of ECMO support. The complex and long intensive therapy require longitudinal perspectives to prove an optimal quality of life for the patients. A particularly compelling example is the successful delivery of a healthy "post-ECMO baby" by one of the postpartum patients in our cohort two years after hospital discharge.

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LIST OF SCIENTIFIC PUBLICATIONS INCLUDED IN THE PRESENT THESIS

I. Zöllei É, Rudas L, Hankovszky P, Korsós A, **Pálfi A**, Varga Z, Tomozi L, Hegedüs Z, Bari G, Lobozárné Szivós B, Kiszel A, Babik B. Venovenous extracorporeal membrane oxygenation for COVID-19 associated severe respiratory failure: Case series from a Hungarian tertiary centre. *Perfusion*. 2024; 39(4):790-796. doi: 10.1177/02676591231160272. [IF: 1.1, Q2]

II. **Pálfi A**, Balogh ÁL, Polónyi G, Schulcz D, Zöllei É, Bari G, Fodor GH, Baráth K, Somfay A, Peták F, Babik B. Post-COVID changes in lung function 6 months after veno-venous extracorporeal membrane oxygenation: a prospective observational clinical trial. *Front Med*. 2023; 10:1288679. doi: 10.3389/fmed.2023.1288679. [IF: 3.1, Q1]

III. **Pálfi A**, Zöllei É, Varga Z, Tomozi LB, Schulcz D, Bari G, Peták F, Kun-Szabó F, Baráth K, Rudas L, Balogh ÁL, Babik B. Venovenous Extracorporeal Membrane Oxygenation for COVID-19 in Postpartum Patients: 1-Year Outcome. *J Cardiothorac Vasc Anesth*. 2024 38(8): 1746-1752. doi: 10.1053/j.jvca.2024.04.027. [IF: 2.3, Q2]