Pathology findings in nonsurvivors of veno-venous extracorporeal membrane oxygenation treatment

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Abbreviations:

ECMO – Extracorporeal membrane oxygenation

CPB – Cardiopulmonary bypass

VV – Veno-venous

VA – Veno-arterial

ELSO – Extracorporeal life support organization

ARDS – Acute respiratory distress syndrome

VAD – Ventricular assist device

ICU – Intensive care unit

PEEP – Positive end expiratory pressure

SIRS – Systemic inflammatory response syndrome

ICH – Intracranial hemorrhage

VAP – Ventilator associated pneumonia

CBC – Complete blood count

PT – Prothrombin time

INR – International normalized ratio

ACT – Activated clotting time

APTT – Activated partial thromboplastin time

AT - Antithrombin

TEG - Thromboelastography

ROTEM – Rotational thromboelastometry

FFP – Fresh frozen plasma

VWF – von Willebrand factor

UFH – Unfractionated heparin

HIT – Heparin induced thrombocytopenia

Contents

1. Summary

Pathology findings in nonsurvivors of veno-venous extracorporeal membrane oxygenation treatment

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ECMO is a life-support intervention allowing for oxygenation of blood independent of the function of lungs and/or heart. Developed and enhanced for decades, its use has peaked in the previous decade, particularly with the 2009 H1N1 pandemics. Invasive procedures involving severely ill patients carry a large risk of complications, which have to be weighed when choosing to perform the procedure. Majority of complications are related to the delicate coagulation status, with procoagulant and anticoagulant effects in interplay at the same time. Monitoring of anticoagulation during ECMO is difficult, and many different tests are required to paint the full coagulation status picture. Despite the array of tests available, no test is available to predict bleeding complications and adequately guide anticoagulation therapy during treatment. Hemorrhagic complications ranging in severity are the most common, and they greatly influence treatment length and mortality in VV ECMO patients. Case series presented in this thesis depicts patients in which hemorrhage was only diagnosed at autopsy, and serves as a reminder to include severe hemorrhage in the differential diagnosis in deteriorating patients on VV ECMO support.

Key words: ECMO; ARDS; pulmonary hemorrhage; anticoagulation

2. Sažetak

Patohistološki nalazi u pacijenata umrlih tijekom liječenja veno-venskom ekstrakorporealnom membranskom oksigenacijom

Armin Atić

ECMO je intervencija koja omogućuje oksigenaciju krvi neovisno o funkciji pluća i/ili srca. Razvijana i poboljšavana desetljećima, uporaba ECMO tehnologije je dosegla svoj vrhunac u prethodnom desetljeću, naročito tijekom H1N1 pandemije. Invazivne procedure, naročito u teško bolesnih pacijenata, nose visok rizik komplikacija na koje treba misliti tijekom donošenja odluke za vršenje procedure. Većina komplikacija je vezana za delikatni koagulacijski status jer su zbog naravi bolesti i procedure prokoagulantni i antikoagulantni učinci u stalnom međudjelovanju. Praćenje stanja koagulacije tijekom ECMO-a je komplicirano i potrebni su brojni testovi kako bi se prikazala cijela slika koagulacijskog stanja. Unatoč širokom izboru testova, niti jedan test se nije pokazao savršenim za predviđanje i procjenu krvarenja te precizno navođenje antikoagulacijske terapije. Komplikacije u vidu krvarenja svih stupnjeva su najčešće, a značajne su jer znatno utječu na duljinu liječenja i stopu smrtnih ishoda. Prikaz serije u ovom radu sadrži pacijente kod kojih je krvarenje dijagnosticirano tek na autopsiji i služi kao podsjetnik da se ozbiljno krvarenje uvijek treba naći u diferencijalnoj dijagnozi kod naglog pogoršanja stanja u pacijenata na VV ECMO potpori.

3. Preface

Extracorporeal membrane oxygenation is a rescue life-support intervention which enables oxygenation of blood independent of the function of lungs and/or heart. First used during the seventies as a long-term variant of cardiopulmonary bypass used in cardiac surgery, ECMO use peaked in the previous decade after the publication of the CESAR trial (1,2) and increased rates of ARDS due to H1N1 pandemics. In United States of America alone, ECMO use has increased by 433% from 2006-2011 (3). Two types of ECMO circuits exist, veno-venous (VV) and veno-arterial (VA) ECMO. VV ECMO provides only respiratory support, while VA ECMO additionally enables circulatory support, bypassing both the heart and the lungs. This paper will only discuss VV ECMO, and the case series presented involves exclusively patients treated by VV ECMO. University Hospital for Infectious Diseases "Dr. Fran Mihaljević" is a high volume adult ECMO center, first established in 2009 and progressed to become the Croatian National Referral ECMO center in 2013. Procedure survival and hospital mortality rates in the center are comparable to an average ELSO center (4). This thesis will outline the basic principles of VV ECMO use, complications which arise during treatment and with a case series accentuate a potentially foreseeable clinical complication.

3.1 VV ECMO circuit

VV ECMO is the preferred treatment modality for severe respiratory failure when cardiac output is preserved. It does improve cardiac function as mechanical ventilation is reduced and oxygenation of the myocardium is improved. ECMO works by draining blood from the venous circulation which then flows through a pump, an artificial oxygenator and heat exchanger and then back to the patient. The ECMO circuit is composed of the drainage and return cannulae, tubing, pump, oxygenator and a heat exchanger. Both cannulation sites are in the systemic venous circulation, with cannulation sites depending on patient size. In older children and adults, the drainage of oxygen-depleted blood is from one or both femoral vessels, and the re-infusion of oxygenated blood is through the right-internal jugular vein (5). There are several working options, including two single lumen cannulas draining in the IVC and reinfusing in the SVC, draining in the SVC and reinfusing in the IVC (6). Recently bi-caval venous-venous dual lumen cannulas appropriate for older children and adults were developed, simplifying the ECMO cannulation process and avoiding the complications associated with femoral cannulation (5). Most ECMO circuits use two-types of pumps: roller and centrifugal. Roller pumps move blood forward by compressing the tubing and thus propelling the blood. They are cheaper, have low

priming volumes but can produce high negative pressures and micro-particles shed from compressed tubing (5,7). Centrifugal pumps were first used as ventricular assist devices, and they work by smooth plastic cones or an impeller rotating rapidly and moving blood using centrifugal force. Centrifugal pumps generate lower negative pressure, and therefore create less cavitation and fewer gaseous micro emboli. Blood flow is preload and afterload dependent, meaning that there is no fixed relationship between pump speed and blood flow, which requires addition of a flowmeter within the circuit. Because of constant driving force, centrifugal pumps produce pulseless blood flow while roller pumps produce a sine wave pulse of around 5 mm Hg (7). Oxygenators have greatly developed over time, and current ECMO oxygenators use either non-microporous hollow-fiber membranes or microporous polypropylene hollow fiber membranes (7–9). Heat exchanger controls the body temperature and most are incorporated with the membrane oxygenators. Hemo- and histocompatibility have been issues tackled over time, with efforts pushed towards creating more efficient oxygenation membranes, decreased contact of blood with non-endothelial surfaces, gas emboli reduction, decreased hemostatic complication rates and mimicry of normal lung physiology, reduction of priming volume and resulting pressure drops on connection to the circuit.

3.2 Indications and contraindications for VV ECMO

VV ECMO is a salvage option for severe respiratory failure and allows buying time while awaiting improvement of the underlying disorder. Generally VV ECMO is indicated for potentially reversible severe respiratory failure refractory to conventional intensive care management (10). According to ELSO, initiation of ECMO for severe hypoxic respiratory failure should be considered when the risk of mortality is 50% or greater, which is defined by a PaO2/FiO2 < 150 mm Hg on FiO2 > 90% and/or a Murray score of 2 to 3, uncompensated hypercapnia with acidemia (pH <7.15) despite the best accepted standard of care for management with a ventilator, and excessively high end-inspiratory plateau pressure (11,12). Furthermore, ELSO suggests the use of ECMO when the risk of mortality exceeds 80%, which is defined by a PaO2/FiO2 < 80 on FiO2 > 80% and/or a Murray score of 3 to 4 (13,14).

Most frequent etiology of respiratory failure on ECMO includes isolated pulmonary diseases such as pneumonia and ARDS of any etiology, status asthmaticus, air leak syndromes, mediastinal mass, aspiration syndromes and multisystem disorders including: posttraumatic acute respiratory distress syndrome, pulmonary contusion, congenital diaphragmatic hernia, alveolar proteinosis, pulmonary infiltration as a metastatic process from cancer or lymphoma

and other causes (11,15,16). Additionally, an evolving indication for ECMO is use as bridge to lung transplantation (15,17).

General contraindications for ECMO are futile treatment without exit strategies for: known severe brain injury, unwitnessed cardiac arrest, prolonged CPR without adequate tissue perfusion, severe chronic organ dysfunction, disseminated malignancy, unrecoverable heart and not a candidate for transplantation or VAD support, unrepaired aortic dissection, severe aortic regurgitation and poor compliance in sense of financial, cognitive or social limitations. VV ECMO is specifically contraindicated in cardiogenic failure and severe chronic pulmonary hypertension (mean pulmonary artery pressure >50 mmHg). Relative contraindications are contraindication to anticoagulation, advanced age and obesity (11).

3.3 Acute respiratory distress syndrome (ARDS)

First described in 1967 in a case series of 12 patients by Ashbaugh and his colleagues (18), ARDS represents a life-threatening condition which can arise from different etiologies, including sepsis, pneumonia, trauma and pancreatitis (19). Most common histopathologic correlate of ARDS is diffuse alveolar damage (20), accompanied with intense lung inflammation, progressive microatelectasis, increased pulmonary vascular permeability, increased lung weight, and loss of aerated tissue (19,21). Currently valid is the Berlin definition developed by an international panel of experts in 2012. Criteria for ARDS are presented in table 1. In the development of these criteria empirical data on clinical outcome, radiographic features and physiologic measures were all taken into consideration. The Berlin definition removed inter-observer bias for radiographic interpretation by providing clear criteria with provided radiographs. Further value was given by subcategorization of ARDS by severity based on patient-level meta-analyses (20,22).

ARDS is underdiagnosed and undertreated worldwide, in both high and low income countries (23). Known risk factors for ARDS are active or passive cigarette smoke, chronic alcohol abuse and long-term ozone exposure. No other environmental or ecological hazards or pollutants have been established as risk factors. Interestingly, the levels of ozone that were established as a risk factor for ARDS were within the levels allowed by United States Environmental Protection Agency (24). Further preventable risk factors for ARDS include gastric aspiration, influenza and pneumococcal vaccination and preventative strategies for these conditions should reduce the incidence of ARDS (25). A large armory of treatment options exists for ARDS, including: lung protective mechanical ventilation and PEEP, recruitment maneuvers, prone positioning, steroid use, fluid restriction, neuromuscular blockade, selective pulmonary vasodilation, high frequency

oscillatory ventilators and extracorporeal membrane oxygenation (19,25). Years of trials have identified ineffective treatment and plenty of interventions should not be used anymore, including: vasodilators, N-acetyl-cysteine, β2 agonists, antioxidants, lisophylline, prostaglandin E1, neutrophil elastase inhibitors, activated protein C, ketoconazole (21, 22), surfactant and statins (25). Recently the focus started shifting towards prevention of ARDS, ranging from primary prevention of risk factors mentioned above, secondary prevention by good ICU practices including early detection, risk identification, low tidal volumes for all patients, early antibiotic treatment and (not excessive) volume resuscitation for sepsis, male plasma donors and restrictive transfusion all reduce the incidence of ARDS (20,25).

Table 1 - Berlin criteria for ARDS

Criterion	Definition
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Radiographic appearance on chest X-ray/CT scan	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present
ARDS severity categorization	Oxygenation status
Mild	200 mm Hg < PaO2/FIO2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5cmH2O
Moderate	100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg with PEEP ≥ 5cmH2O
Severe	PaO2/FIO2 ≤ 100 mm Hg with PEEP ≥ 5cmH2O
Adapted from: The ARDS Definition Task Force. Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA. 2012;307(23):606–614.e3.	

3.4 VV ECMO Complications

VV ECMO is an invasive procedure and it is important to weigh the possible complications which arise from the catheterization procedure itself, extravasation of blood, contact with non-endothelial surfaces and turbulent flow all combined with the severe underlying pathology which

necessitated the ECMO intervention. The complex pathophysiology of the organism's response to the intervention in interplay with the response to the pathology and to already attempted treatment all created a distorted image of complications. Decades of experience have elucidated the perplexing range of complication which can arise during treatment, and in this paper both machine- and patient-related complications will be discussed together.

Systemic response

ECMO initiation is associated with an inflammatory response similar to that of systemic inflammatory response syndrome (SIRS), and as such plays a role in pathophysiology of all other complications. Contact of blood with non-endothelial surface rapidly activates coagulation and pro-inflammatory cascades, resulting in rapid rise of pro-inflammatory cytokines and leukocyte activation. This can all present as vasodilation with pleural effusion, ascites, anasarca and worsening of pulmonary failure (26,27).

Technical and mechanical failure

When positioning the cannulas vessel dissection or bleeding may occur, however this is readily diagnosed on the bedside or via ultrasound. Approximation of the two cannula tips may result in recirculation of blood through the extracorporeal circuit, resulting in insufficiently oxygenated blood in the systemic circulation (6,26). Advances in cannulation technology (6) and radiological confirmation of positioning reduce the incidence of this complication. In rare cases malfunction of the oxygenator can occur and necessitates emergent replacement of the device. Most frequent mechanical complications are thrombus formation in the pump, oxygenator or the hose connection points. This can lead to malfunction of the oxygenator or shed off to the systemic circulation (26). Shedding from the circuit and embolization is a larger problem in VA ECMO, as in VV ECMO the pulmonary circulation serves as a filter for clots, protecting from embolization in cerebral and systemic circulation (28).

Neurological Complications

Neurological complications occur frequently during ECMO procedures, and most commonly reported are intracranial hemorrhage (ICH), stroke, seizures, ischemic encephalopathy and brain death (28). Studies analyzing the Extracorporeal Life Support Organization registries for VV ECMO show rates of 7% (29), with in-hospital mortality of around 25%. Same studies showed higher risk for brain hemorrhage in VV ECMO than VA ECMO patients, displaying that ICH is not a single-factor event. This was demonstrated in another study linking the underlying

disease to ICH rather than only to VV ECMO. Same study showed that early ICH is associated with early mortality (30). Taking into account that the primary indication for VV ECMO is respiratory failure, rapid correction of hypercarbia has been implicated as a cause of neurological injury (31). Furthermore, use of sedation and/or neuromuscular blockade may reduce mean arterial pressure and result in cerebral hypoperfusion which can clinically mask neurological deficits (28).

Infection

ELSO registry reviews have shown rates of hospital-acquired infections during ECMO (32,33) to be around 10–12%, but also that their occurrence is likely to be more frequent compared with other critically ill patients. High rates of ventilation-associated pneumonia (VAP) were reported, most commonly caused by *Enterobacteriaceae* (34). Infectious complications of ECMO have been associated with increased mortality and morbidity, and predisposing factors include long ECMO runs, severity of illness, ECMO immune impairment and bacterial translocation from the gut (34).

Thromboembolism

Thrombosis is common during ECMO, both within the circuit and patient's circulation. Clinical data for thromboembolism in patients is scarce. Easily observable are small thromboemboli in the skin, while embolization within the pulmonary system would not be readily seen and/or suspected (16). Central nervous system infarction was reported to occur in up to 3.5% of patients (35). A retrospective study by Trudzinski et al (36) used different imaging modalities together with autopsy studies and has found a total rate of venous thromboembolism of 46,1%, despite adequate anticoagulation. Larger studies should be performed to fully illustrate the rates of thromboembolus formation during ECMO treatment.

Bleeding

Labeled the Achilles' heel of ECMO, bleeding is the most frequent complication and is one of the leading causes of mortality during ECMO, studied by and confirmed in a number of studies (35,37,38). Multilevel pathophysiology is discussed in the following paragraph. Bleeding during ECMO, unlike thromboembolism, is usually clinically obvious, ranging from epistaxis, wound and puncture site bleeds to internal bleeding in the bladder, GI tract, intracerebral (ICH) and pulmonary hemorrhage, with the latter pair associated with significantly higher mortality (31,37).

Management of bleeding is mainly by withholding anticoagulation, while prevention by adequate monitoring and safe anticoagulation practices should be stressed throughout treatment course.

3.5 Anticoagulation during VV ECMO

Before initiation of VV ECMO, for every candidate patient, if time allows, baseline test values should be obtained, including complete blood count (CBC), prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, D-dimers, activated clotting time (ACT), antithrombin activity (AT) and thromboelastography (TEG) or rotational thromboelastometry (ROTEM)(39,40). Any preexisting coagulopathy should be corrected with fresh frozen plasma (FFP), platelets, cryoprecipitate and vitamin K (39). The coagulation alterations upon ECMO intervention are complex, and are a result of several pathophysiological mechanisms activating in parallel, notably the complement and contact system (factor XII) activation as result of contact with the biomaterial surface, and the products released directly interact with neutrophils, leukocytes and the vascular endothelium (27). This eventually leads to thrombus formation, which has been partially dealt with by heparin-coated tubing, however no completely adequate solution has been found. Thrombin generation response of platelets and their adherence to fibrinogen result in a consumptive coagulopathy, and aforementioned factor activation leads to dilution of coagulation factors (27,41). The reported thrombocytopenia ranges from 25-40% without signs of heparin induced thrombocytopenia (HIT)(42). Furthermore, increased shear stress results in breakage of von Willebrand factor (vWf) multimers, causing decreased binding to collagen, clinically seen as acquired von Willebrand syndrome (42,43). There is a wide requirement for tight follow up of coagulation parameters during entire ECMO treatment, and hemostatic balance is usually monitored by ACT, aPTT, PT/INR, fibrinogen, anti-factor Xa and thrombocyte count. Reference ranges and a short overview is presented in Table 2. A study from 2013 among ELSO centers showed that 43% of centers regularly employ TEG and ROTEM, while ACT was used in 97% of cases (44). ACT is used most widely at the bedside to direct UFH dosage, however due to its shortcomings and non-specificity to heparin, current opinion places anti-factor Xa on a superior position (39,40). Unlike ACT, anti-FXa levels are not influenced by coagulopathy, thrombocytopenia or dilution, and in some centers this is the golden standard method. APTT is more useful as it is more sensitive to low UFH levels frequently used for ECMO than ACT (39,42). TEG/ROTEM complete the hemostatic mosaic, giving information on viscoelastic properties of clot formation for multiple phases of the process, which is relevant for ECMO patients as they may have more than one reason for coagulation abnormalities. Most widely

used anticoagulant is unfractionated heparin (UFH) (16,39,40,44), however if heparin-induced thrombocytopenia (HIT) occurs, a direct thrombin inhibitor may be used.

Table 2 – Commonly monitored coagulation parameters

Test	Reference value	Comment
Thrombocytes	>80 x10^9/L	Does not reflect thrombocyte function
ACT	180-220 s	Insensitive to low UFH levels; Affected by many factors; Nonspecific
aPTT	1,5-2,5 (ratio)	Sensitivity to UFH is decreased in inflammatory, hyperfibrinolytic, pregnancy and increased FVIII states. Affected by antipholipid antibodies, FXII deficiency,
AT	>70%	Guides AT replacement for heparin resistance; Not all heparin resistance is because of AT deficiency
D-dimers	Rise from baseline	Increase indicates need for oxygenator replacement
Fibrinogen	>100 g/dl	Increased in inflammatory conditions; Time consuming
TEG/ROTEM		Lack of standardization; Expensive
Anti-factor Xa assays	0,3-0,7 IU/mL	Most reliable; Lack of standardization;
ACT – activated clotting time; aPTT – activate partial thromboplastin time; AT – anti thrombin; TEG – thromboelastography; ROTEM – rotational thromboelastometry		
Adapted from: Mulder, M.M.G. & Hassan, Ibrahim & Lancé, Marcus. (2018). ECMO and anticoagulation: A comprehensive review. Netherlands Journal of Critical Care. 26. 6-13. Doymaz S. Anticoagulation during ECMO: The Past, Present and Future. J Intensive & Crit Care Vol.4 No.2:12 The Extracorporeal Life Support Organization. ELSO Anticoagulation Guideline. Ann Arbor, MI; 2014.		

4. Hypothesis

This case series hypothesized that over-heparinization of patients estimated by the highest single aPTT measurement during VV ECMO treatment serves as a risk factor for severe bleeding complications.

5. Objective

Primary goal of this study was to determine the relationship of the highest aPTT measurement with bleeding complications. Our focus was on pulmonary hemorrhage, as it prolongs duration of ECMO treatment and contributes to increased mortality (45).

6. Material and methods

Patient data for this case-series was retrospectively collected from hospital archives. Data used were patients' biochemistry, anticoagulation and other laboratory parameters and autopsy findings. Patients selected were ones with a lethal outcome during VV ECMO treatment with an unexpected pathology finding of severe hemorrhage. From the period 2013-2018, 16 patients were selected. Records were not available for one patient, and for two patients we did not have access to pathology findings. Therefore, thirteen patients were eligible for the case series. For one transfer patient all laboratory results before VV ECMO implantation were inaccessible, as the patient was an ECMO transfer from another hospital, and pre-ECMO findings were not included in the available records. As our research objective did not depend on pre-ECMO patient status, this patient was included in the study. Pulmonary hemorrhage was defined as pathology reports of: pulmonary hematoma, pulmonary hemorrhage, hemothorax or intraalveolar hemorrhage.

7. Results

Patients hospitalized in the period 2013-2018 with a lethal outcome on VV ECMO with unexpected hemorrhage reports on autopsy were all hospitalized at University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Department for Intensive Medicine and Neuroinfectology. Ten patients (77%) were male, and the median age was 57 (± 11). Five patients (38%) were transferred on mobile ECMO from other hospitals. All patients had ARDS as a result of pneumonia, demographic data, etiology and intervention number and duration are displayed in Table 2. One patient was in post-partum state. On average patients spent 14 (range 1-42) days on VV ECMO, while 4 (31%) patients have underwent two or more ECMO interventions. On analysis of autopsy findings, all patients had the typical histopathological feature of diffuse alveolar injury, confirming the diagnosis of ARDS. Pulmonary hemorrhage as defined earlier was described in 8 (62%) of all included patients. Other sources of bleeding and coexisting histopathological findings will not be discussed in this paper. Comparison of age, sex, pre-ECMO coagulation parameters, and peak aPTT during ECMO treatment between pulmonary hemorrhage and non-pulmonary hemorrhage groups is displayed in Table 3. No significant correlation was observed.

Table 3 – Patient characteristics

Case no.	Age	Sex	Etiology	Transport (yes/no)	Multiple ECMO procedures (Yes/No)	ECMO days	Pre-ECMO findings Thrombocytes (x10^9/L)	aPTT (s)	Highest aPTT	Pulmonary hemorrhage
1	58	M	Bacterial pneumonia; Sepsis	No	No	8	593	50	66.9	Yes
2	57	M	Influenza A pneumonia	No	No	18	248	31.4	94.1	Yes
3	40	M	Pneumonia nonspec.; Septic shock	Yes	No	14	306	-	76	Yes
4	65	M	Influenza A pneumonia; Bacterial pneumonia	No	Yes	6	230	25.8	69.5	No
5	52	M	Bacterial pneumonia	Yes	No	1	253	77	77	No
6	68	M	Pneumonia nonspec.	No	Yes	22	90	-	66.1	Yes
7	65	M	Bacterial pneumonia	No	Yes	17	177	26.8	41.7	Yes
8	29	F	Influenza A H1N1 pneumonia	No	No	42	266	38.2	52.6	Yes
9	60	M	Interstitial pneumonia; Septic shock	No	No	32	287	-	56	No
10	57	F	Pneumonia nonspec.	Yes	No	10	457	22.7	120.6	No
11	53	M	Influenza H1N1 pneumonia; *P. Aeruginosa* sepsis	Yes	No	2	-	-	50.2	No
12	52	M	VAP, ARDS	No	No	10	238	36	49.1	Yes
13	48	F	Bacterial pneumonia; Nosocomial pneumonia	Yes	Yes	18	124	22.7	87.8	Yes
Overall median	57					14	250.5	31.4	66.9	

Table 4 – Comparison of characteristics between patients with and without pulmonary hemorrhage defined on pathology reports

Characteristics	With pulmonary hemorrhage (n=8)	Without pulmonary hemorrhage (n=5)
Age (years) (mean ± SD [range])	51.3 ± 13.8 (29-68)	57.4 ± 5.3 (52-65)
Sex		
Male (n)	6	4
Female (n)	2	1
VALUES BEFORE VV ECMO IMPLANTATION		
pO2 (mmHg) (mean [SD])	61.6 (± 15.5)*	60.6 (± 21.5)*
pCO2 (mmHg) (mean [SD])	72.8 (±14.2)	71.8 (± 31.0)*
Thrombocytes (x10^9/l) (median [IQR])	243 (164-276)	270 (247-330)*
pH (mean [SD])	7.27 (± 0.12)*	7.22 (± 0.17)*
PT (mean [SD])	0.89 (± 0.23)*	0.66 (±0.25)**
INR (mean [SD])	1.16 (± 0.34)**	1.27 (± 0.22)**
aPTT (s) (median [range])	33.7 (22.7-50.0)**	37.9 (22.7-77.0)**
CRP (mg/l) (median [IQR])	206.0 (140.0-331.6)	247.5 (216.6-289.9)*
VALUES AFTER VV ECMO IMPLANTATION		
Highest aPTT (s) (median [range])	66.5 (41.7-94.1)	69.5 (50.2-120.6)

*missing measurement for 1 patient
**missing measurements for 2 patients

8. Discussion

In our case series we did not observe any association between peak aPTT and pulmonary hemorrhage in patients with lethal outcome during VV ECMO treatment for ARDS. Pre-ECMO intervention coagulation and inflammatory parameters were similar between the two groups, however in the whole study the population is predominantly male, and in the group of bleeding patients there is larger age variation. Average aPTT levels are associated with a higher need for RBC transfusions and bleeding (46,47). The latter study, however, analyzed mainly patients on VV ECMO and had a significantly higher aPTT than recorded in our patients (bleeding group mean aPTT=86s). At aPTT levels similar to ours (mean 35-40s), Kreyer et al. (37) did not find an association and excluded an effect of heparin on the bleeding results, a trend fortified by our case series. Levels of aPTT have been shown to be beneficial when predicting complication on the other pole of the coagulation compass, as Trudzinski et al. (36) have shown that aPTT and run-time predict venous thrombosis or venous thromboembolism. Constraining studies on this topic are difficulties in exclusion of disease factors and/or etiology of ARDS on the bleeding complications, inclusion of various interpatient variations in coagulation, ranging from inherent

coagulopathies, acquired pathologies and medication taken. Strengths of this case series are that all included patients had a primary pulmonary source of ARDS, and all of the involved patients were on VV ECMO. Furthermore, all patients were treated at the same ICU and had similar pre-ECMO coagulation and biochemistry parameters. Limitations to this study include a small number of included patients and a small number of included test results. None of the patients had TEG or ROTEM performed as it is not performed at our center.

Sudden, non-otherwise explained, deterioration of patients warrants exclusion of hemorrhagic complications, and the first steps include immediate laboratory workup and use of imaging methods of source identification, primarily CT or bronchoscopy. CT has the advantage of visualizing bleeding in several possible locations, and the use of contrast may aid in differentiating active bleeding from other pathological processes, particularly in the lungs. Discerning an active hemorrhage from some other type of fluid accumulation may be challenging, and bronchoscopy readily visualizes active bleeding and includes the possibility of direct balloon tamponade (48). Confirmed hemorrhage, its profuseness and new coagulation parameters direct further management. Approaches to bleeding include: withholding/decreasing heparin, platelet infusion, vWF concentrate infusion, administration of tranexamic or aminocaproic acid and factor XIII or recombinant factor VIIa (16). Addressing new-onset bleeding in a timely fashion will additionally direct regular anticoagulation management of the patient, and treatment of bleeding episodes will likely decrease mortality.

9. Conclusion

Leading objective of this study was to remind physicians to include occult yet severe bleeding in the differential diagnosis of sudden deterioration of patients undergoing VV ECMO treatment. Especially if respiratory function deteriorates, pulmonary hemorrhage should be considered and not mistaken for a ventilator associated pneumonia. High rates of bleeding complications have been demonstrated in a number of studies, and diagnostic measures towards exclusion of an active bleeding should be undertaken in such clinical scenarios. Prudent approach should include temporary withholding heparin infusion, especially if patient requires concomitant RBC transfusion, and treatment to ameliorate coagulation factor deficits if present. This and previous studies have failed to demonstrate any benefit of using aPTT in prediction of bleeding at currently recommended aPTT levels. Further obscuring a uniform answer or tool is the complex range of coagulation profiles in patients undergoing ECMO procedures. Studies should be directed towards elucidating predictors of bleeding which would allow undertaking prophylactic measures and possibly lead to lower complication and mortality rates in ECMO patients.

10. Acknowledgements

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12. Biography

I was born in Nuremberg, Germany in 1995. but have spent my entire childhood in my native Bosnia and Herzegovina. After proudly graduating from "Sjenjak" elementary school, I have enrolled in the "Meša Selimović" gymnasium in Tuzla. During high school, I have actively pursued my interests in film and photography and have participated in several exhibitions, the most notable being the 50 best photographs of Bosnia and Herzegovina for 2011 in Sarajevo. After graduating gymnasium with excellent marks, I enrolled at the University of Zagreb Medical School in English. Throughout my studies I was actively involved in teaching as student assistant in Anatomy and History taking and Physical Examination. I have actively participated in the DiaTransplant 2018 Congress of Nephrology with a paper titled "Community acquired Legionnaire's disease in a renal transplant recipient". Furthermore, I have received the City of Tuzla award for outstanding students on two occasions and was awarded the Dean's commendation for the academic year 2017/2018. My skills in photography created the opportunity for me to work as the official sports photographer for FC "Rudeš" during a part of my studies. With a desire to learn more, besides my native language(s) and English, I speak German with good proficiency (B2).