Aus dem Fachbereich Medizin
der Johann Wolfgang Goethe-Universität
Frankfurt am Main

aus der
Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie
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betreut an der
Asklepios Klinik Langen
Abteilung für Anästhesie, perioperative Medizin
und interdisziplinäre Intensivmedizin

Ischemic Complications In Patients With Extracorporeal Membrane Oxygenation

Dissertation
zur Erlangung des Doktorgrades der Medizin
des Fachbereichs Medizin
der Johann Wolfgang Goethe-Universität
Frankfurt am Main

vorgelegt von
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aus Würzburg

Frankfurt am Main, 2021

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Tag der mündlichen Prüfung:	09.12.2022

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List of abbreviations

ARDS	acute respiratory distress syndrome
CI	confidence interval
CK	creatine kinase
COVID-19	coronavirus disease 2019
CPR	cardiopulmonary resuscitation
CT	computed tomography
DIC	disseminated intravascular coagulation
ECG	electrocardiogram
ECLS	extracorporeal life support
ECMO	extracorporeal membrane oxygenation
FiO_2	fraction of inspired oxygen
HIT	heparin-induced thrombocytopenia
ICU	intensive care unit
IQR	interquartile ranges
lactate	serum lactate level
LDH	lactate dehydrogenase
NSTEMI	non ST-elevation myocardial infarction
OR	Odds Ratio
PaO_2	arterial oxygen partial pressure
SAPS II	Simplified Acute Physiology Score II
SLEDD	sustained low-efficiency daily dialysis
SOFA	Sequential Organ Failure Assessment Score
STEMI	ST-elevation myocardial infarction
V-A	veno-arterial
V-V	veno-venous
V-V-A	veno-venous-arterial

1. Introduction

1.1. Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is an established therapy which became popular over the last decades, especially during the influenza H1N1 pandemic 2009 and the ongoing coronavirus disease 2019 (COVID-19) pandemic.[1,2,3]

There are three different kinds of ECMO modes with different therapeutical indications depending on the type of support.[4–9] Veno-venous (V-V) ECMO is used as a sole lung support for patients suffering from acute respiratory distress syndrome (ARDS) for example caused by pneumonia.[4,5] Veno-arterial (V-A) or veno-venous-arterial (V-V-A) modes can be used as extracorporeal life support (ECLS) to assist or replace both cardiac output and pulmonary gas exchange in patients with cardiogenic shock.[6,7] In addition, for patients with septic shock refractory to vasopressors attempts are being made to reduce the high mortality of this patient group by using V-A or V-V-A ECMO.[8,9] Regardless of the ECMO mode, all consist of the same components: a blood drawing venous and a back leading venous and/or arterial cannula that are placed transcutaneous in the patient's jugular and/or femoral vessels, a centrifugal or roller pump to secure a continuous blood flow and an oxygenator which is connected to a gas blender.[10] This blender allows to regulate the FiO_2 and the gas flow and by this the oxygenation and decarboxylation of the patient's blood.[10] To prevent the blood and thereby the patient from cooling, a heat exchanger is also integrated in the extracorporeal circulation.[11] In order to prevent the formations of blood clots an adequate anticoagulation is needed, for example with low molecular heparin or argatroban.[12,13]

In patients with V-V ECMO mode both cannulas are placed in two different venous vessels, usually the right internal jugular vein and one femoral vein. [10,14,15] For V-A mode one femoral vein and one femoral artery are punctured. [10,14,15] In case of V-V-A mode, an additional venous cannula is placed in the right internal jugular vein.[10,14,15] Meanwhile, special cannulas have been developed which can be advanced directly through the right heart into the pulmonary artery.[10,16]

The venous, oxygen-deficient blood, containing a higher amount of carbon dioxide is drawn via the venous cannula and passes the oxygenator.[10] Here the removal of carbon dioxide and the oxygen enrichment take place.[10] Afterwards the blood is lead back to the patient, depending on the mode, into the venous (V-V mode) arterial (V-A mode) or both systems (V-V-A mode).[14] Thereby it is possible to support or completely replace the patient's heart and/or lung function.[4,7] In addition, ECMO can also be used as a bridge to either heart or lung transplant or bridge to implantation of persistent left ventricular assist device.[10,14]

1.2. Ischemia during ECMO therapy

In addition to complications during ECMO implantation, for example failed punction, many different complications can occur, especially during ECMO therapy.[17–19] Bleeding at the cannulation side or ischemia of the cannulated limbs or other organs systems such as the small bowel or the colon are potential lethal complications.[17,18] Since ECMO always leads to an activation of both the pro- and anticoagulatory cascade by contact of the blood with non-endothelial surfaces, it is important to identify those complications in time.[20,21] Adequate anticoagulation is needed to prevent ischemia but may lead to an increased risk of bleeding.[17,20,21]

1.3. Question

To act early and purposeful, both the type of ischemic complication as well as the frequency of their occurrence and their impact should be known. Accordingly, this study evaluated the occurrence of ischemic complications during ECMO therapy in a retrospective analysis of all patients treated at the ECLS/ECMO center of Asklepios Klinik Langen between April 2011 until March 2020. Aim of this study was to answer the following questions:

- How frequent did ischemic complications occur in different locations during ECMO therapy?
- Did ischemic complications affect patients' survival?
- What were the risk factors and predictors of those ischemic complications?

2. Patients and Methods

2.1. Study design

The study was approved by the Ethics Committee of the Medical Association of Hessen (file number 2020-1977-evBO). The records from 348 patients who underwent V-V, V-A or V-V-A ECMO therapy at the Asklepios Klinik Langen between April 1st 2011 and March 31st 2020 were retrospectively reviewed.

The data of all patients with the diagnosis of either ARDS, cardiogenic or septic shock were retrieved. Diagnosis of ARDS, cardiogenic or septic shock were defined as follows:

1) ARDS was diagnosed in the presence of refractory acute respiratory failure with a ratio of PaO_2 to FiO_2 (Horowitz index) of <100 on mechanical ventilation with a positive end-expiratory pressure >5 mmHg.[22]
2) Cardiogenic shock was diagnosed in the presence of a critical reduction of cardiac output e.g., by myocardial infarction or pulmonary embolism with a systolic blood pressure <90 mmHg despite appropriate fluid resuscitation with the need of vasopressor therapy and clinical and laboratory evidence of end-organ damage.[23]
3) Septic shock was diagnosed according to the current definition as acute life-threatening organ dysfunction due to an inadequate host response to infection with concomitant persistent arterial hypotension with a serum lactate level of >2 mmol/l despite adequate volume therapy with the need for vasopressor therapy to achieve a mean arterial pressure of ≥65 mmHg.[24]

The patients were then divided into two groups:

Group 1 without ischemic complications and group 2 with ischemic complications.

Documented ischemic complications were differentiated by organ system and classified into limbs, mesenteric, cardiac and neurological and diagnosed as follows:

1) Limb ischemia was diagnosed based on clinical signs (pallor, absent capillary pulse, pulselessness), absent flow signal on Doppler sonography and if performed, CT angiography. In addition, repetitive measurements of blood samples including creatine kinase (CK), lactate dehydrogenase (LDH) and

arterial blood gas analysis including serum lactate level (lactate) were performed.

2) Mesenteric ischemia was diagnosed based on diminished or absent perfusion of any intrabdominal organ as shown by an angiographic CT scan. In addition, repetitive measurements of CK, LDH and arterial blood gas analysis including lactate were performed.
3) Cardiac ischemia was diagnosed by 12-lead ECG (STEMI or NSTEMI), wall motion abnormalities on echocardiography and/or coronary angiography. In addition, repetitive measurements of CK and troponin-T and arterial blood gas analysis including lactate were performed.
4) Neurological ischemia was diagnosed after starting ECLS/ECMO support during the course of the ICU treatment based on new occurring focal neurological symptoms in the clinical examination with corresponding changes in a cerebral CT-scan. In addition, somatosensory evoked potentials, if performed, were also recorded.

2.2. Setting

The interdisciplinary intensive care unit (ICU) of the Asklepios Klinik Langen, managed by the department of anesthesiology, provides 14 places with ventilators and the possibility of sustained-low-efficiency daily dialysis (SLEDD). ECMO therapy is provided since 2011, the ICU has been certified in 2019 by the Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin as ECMO and weaning center.

ECMO cannulation sites were the right internal jugular vein and the femoral vessels on both sides. All cannulations were performed under ultrasound guidance. V-V ECMO was performed via the right internal jugular vein with a 15 F or 19 F cannula in combination with a 23 F or 25 F cannula in one femoral vein. In case of an Avalon double lumen cannula, only the right internal jugular vein (27 F or 31 F) was cannulated. For V-A ECMO, one femoral artery and one femoral vein on the same or the contralateral side had been selected (15 F or 17 F arterial and 23 F or 25 F venous cannula). In case of V-V-A ECMO, the right internal jugular vein (15 F or 19 F) was also cannulated. To prevent leg ischemia

in V-A mode, a 6 F bypass cannula was placed into the superficial or profunda femoral artery on the side of the arterial cannula.
From 2011 to 2015 unfractionated heparin, thereafter solely intravenous argatroban has been used for continuous intravenous anticoagulation, to achieve a partial thromboplastin time of around 40 seconds.

2.3. Study population

Of the 348 patients treated with ECMO between 2011 to 2020, 321 met the prespecified criteria and could be assigned to one of the three diagnostic groups. 16 patients died during cannulation, 11 patients were transferred to other hospitals to receive cardiac artery bypass with ongoing ECMO therapy.
54 patients were transported to the ICU by the mobile ECMO team from an external hospital after implantation of V-V or V-A ECMO on site. In 11 patients, clinical characteristics could not be fully ascertained. The minimum age was 18 years, no patient was diagnosed with COVID-19.

2.4. Data acquisition

Primary outcome variable was the type of ischemic complication. Secondary outcome variables were serum lactate levels 24h before and immediately after diagnosis of the ischemic complication, arterial blood gas analysis on day of admission to the ICU, duration of ICU and hospital stay, ECMO therapy and duration of invasive ventilation. In addition, age, sex, ECMO mode, diagnosis, Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment Score (SOFA), hospital mortality, the use of renal replacement therapy and tracheotomy, the occurrence of infections during the ICU stay (diagnosed by microbiological findings in blood or endotracheal aspirate) and the need for cardiopulmonary resuscitation (CPR) before ECMO implantation were recorded. Data acquisition took place from December 2020 to February 2021. All data were transferred to a Microsoft Excel spreadsheet.

2.5. Statistics

Statistical analysis was performed using SPSS 25.0 (IBM). The null hypothesis was that there was no difference in the incidence of ischemic complications during ECMO therapy between the three modes, V-V, V-A and V-V-A.

The descriptive statistics were performed with medians and interquartile ranges (IQR; 25^{th}-75^{th} percentiles). After checking for normal distribution using Shapiro-Wilk test, univariate tests were performed using the chi-square test, Mann-Whitney U test, Kruskal-Wallis test, Fisher's exact test and Friedman's test. The data were processed within a multivariate logistic regression to the primary outcome variable to identify possible predictors, by using odds ratio and confidence intervals. The regression was carried out stepwise backwards. All tests were two-sided and with a significance level of $p < 0.05$.

The statistical evaluation was carried out under the advice and supervision of members of the Institute for Biostatistics and Mathematical Modelling at the Department of Medicine of the Goethe University Frankfurt (Prof. Dr. Eva Herrmann and Dr. Natalie Filmann).

3. Results

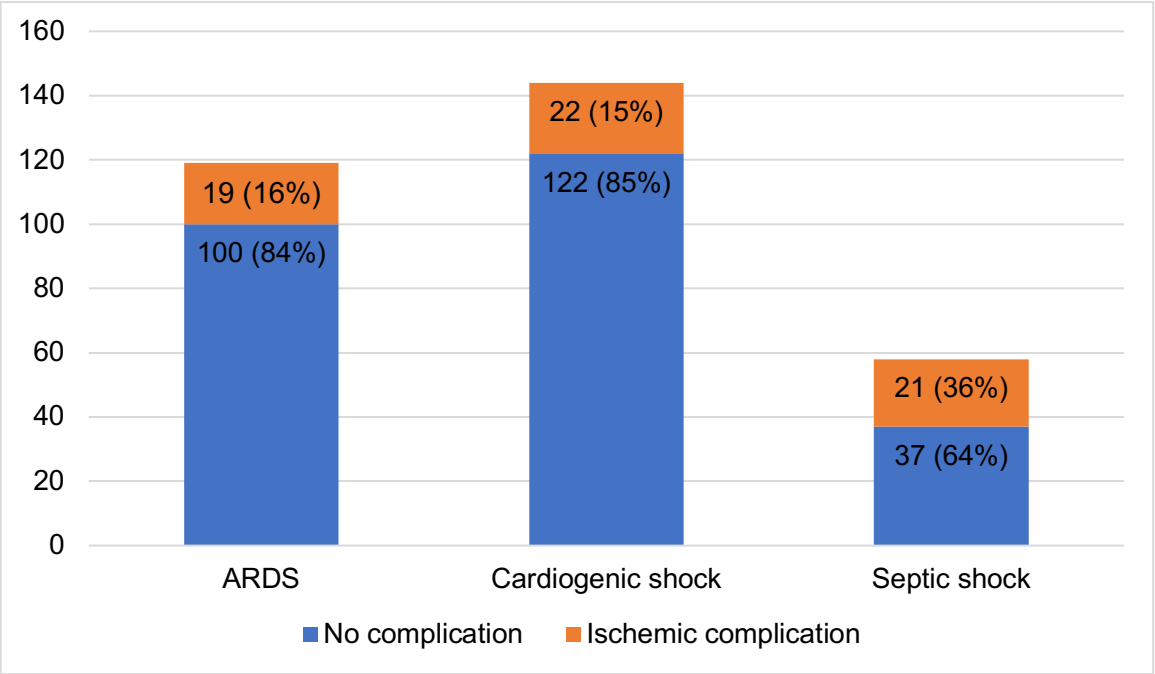
Data from 321 patients who had undergone ECMO therapy for ARDS, cardiogenic or septic shock at the Asklepios Klinik Langen between April 1st 2011 and March 31st 2020 were analyzed.

3.1. Ischemic complications in the study population

Table 1 shows the demographic and clinical characteristics. Group 1 (n=259; 80.7%) consisted of all patients without and group 2 (n=62; 19.3%) of all patients with ischemic complications.

204 out of 259 (78.8%) patients without ischemic complication (group 1) were ≥50 years old compared to 56 out of 62 patients (90.3%) with ischemic complication (group 2; p=0.046). The median length of hospital stay was 19 days in group 1 and 29 days in group 2 (p=0.015). Patients without ischemic complication (group 1) remained 13 days on ICU, those with complications (group 2) 24 days (p=0.002). Patients in group 2 received invasive ventilation significantly longer than patients in group 1 (19.1 days vs. 7.7 days; p<0.001). Compared to patients in group 1, those in group 2 received significantly longer ECMO therapy (7 vs. 10d; p=0.010). With respect to ischemic complications there was no difference between the V-V, V-A or the V-V-A ECMO mode (p=0.063). Compared to patients of group 1, at least one infection was detected in significantly more patients in group 2 (59.8% vs. 74.2%; p=0.041). Significant more patients in group 2 required hemodialysis compared to patients in group 1 (85.5% vs. 59.8%, p<0.001). 19 patients (16.0%) with ARDS, 22 (15.3%) with cardiogenic shock and 21 patients (36.2%) with a diagnosis of septic shock suffered an ischemic complication during ECMO therapy (p=0.002) as shown in figure 1.

Figure 1: Ischemic complications by diagnosis



No difference was found in hospital mortality: 118 patients survived in group 1 and 28 in group 2 (45.6% vs. 45.2%; p=1.0). With respect to the three a priori defined diagnostic groups 76 out of 119 (63.9%) patients with ARDS, 52 out of 144 (36.2%) patients with cardiogenic shock and 18 out of 58 (31.0%) with septic shock survived their critical illness (ARDS vs. cardiogenic vs. septic shock; p<0.001).

Table 1: Clinical and demographic characteristics of the study population

Characteristic	**Total** n=321	**No complication** n=259	**Ischemic complication** n=62	**p-value**
Age (y)	64 (54 – 72)	64 (53 – 72)	65 (57 – 72)	0.211
Age ≥50 y	260 (81.0)	204 (78.8)	56 (90.3)	0.046
Sex (m)	206 (64.2)	169 (65.3)	37 (59.7)	0.462
ECMO mode				0.063
V-V	107 (33.3)	91 (35.1)	16 (25.8)	
V-A	95 (29.6)	80 (30.9)	15 (24.2)	
V-V-A	119 (37.1)	88 (34.9)	31 (50.0)	
Diagnosis				0.002
ARDS	119 (37.1)	100 (38.6)	19 (30.6)	
Cardiogenic Shock	144 (44.9)	122 (47.1)	22 (35.5)	
Septic Shock	58 (18.1)	37 (14.3)	21 (33.9)	
Survival	146 (45.5)	118 (45.6)	28 (45.2)	1.0
Palliation	131 (40.8)	104 (40.2)	27 (43.5)	0.667
Duration ICU (d)	15 (4 – 28)	13 (4 – 25)	24 (7.75 – 49.75)	0.002
Duration hospital stay (d)	20 (6 – 38)	19 (6 – 36)	29 (9.25 – 63.5)	0.015
Duration ECMO therapy (d)[a]	8 (3 – 16)	7 (2.75 – 15)	10 (4 – 25.25)	0.010
Duration invasive ventilation (d)[b]	10.1 (1.6 – 23.6)	7.7 (1.1 – 20.4)	19.1 (4 – 43.8)	<0.001
CPR	143 (44.5)	112 (43.2)	31 (50.0)	0.394
Infections[c]	198 (62.7)	152 (59.8)	46 (74.2)	0.041
Tracheotomy[c]	177 (56.0)	137 (53.9)	40 (64.5)	0.154
Hemodialysis[c]	205 (64.9)	152 (59.8)	53 (85.5)	<0.001
SAPS II[d]	56 (40 – 75)	56 (40 – 78)	53.5 (37.75 – 70)	0.283
SOFA[d]	8 (5 – 10)	8 (5 – 10)	8 (6 – 10)	0.806

Data are median (IQR) or n (%)

[a] (total n=320; no complication n=258)

[b] (total n=315; no complication n=253)

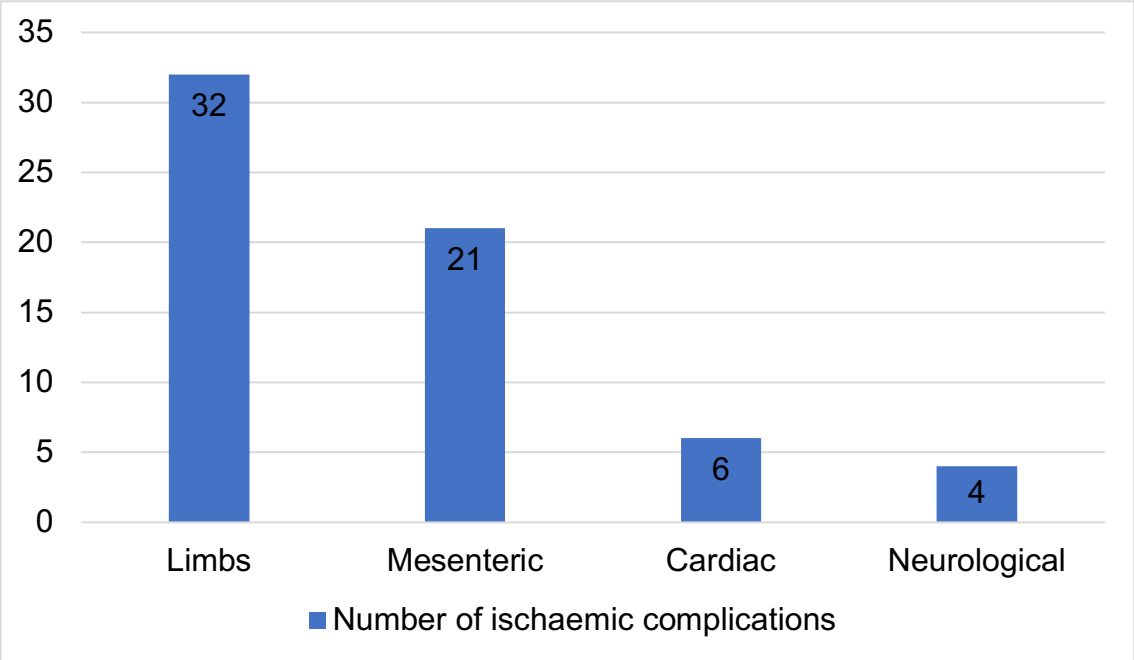
[c] (total n=316; no complication n=254)

[d] (total n=313; no complication n=251)

3.2. Ischemic complications differentiated by locations

Table 2 and figure 2 show a differentiation according to the type of ischemia. Most ischemic events (51.6%) occurred in the extremities, followed by mesenteric (33.9%), cardiac (9.7%) and neurological (4.8%) ischemia. Patients with septic shock were particularly frequently affected by ischemia in the extremities (n=12) and mesenteric vessels (n=7). 8 patients with ARDS suffered limb ischemia, 7 patients had mesenteric ischemia. 12 patients with cardiogenic shock suffered limb ischemia, 7 patients had mesenteric ischemia (ARDS vs. cardiogenic vs. septic shock; p=0.033).

Figure 2: Ischemic complications differentiated by affected locations



A difference between the ischemic localizations was found with respect to the duration of ICU stay, as well as the duration of invasive ventilation. Here, patients with neurological ischemias had the longest stays (p=0.008) and the longest duration of ventilation (p=0.004; Table 2). For all types of ischemia, a significant association with the use of hemodialysis could be demonstrated (p=0.004; Table 2).

Table 2: Differentiation of clinical and demographic characteristics by type of ischemia

Characteristic	**Limbs** n=32	**Mesenteric** n=21	**Cardiac** n=6	**Neurological** n=3	**p-value**
Age (y)	62 (54.75 – 70.75)	69 (60 – 75)	68 (53.75 – 71.25)	72 (56 – 72)	0.309
Age ≥50 y	26 (81.3)	21 (100.0)	6 (100.0)	3 (100.0)	0.096
Sex (m)	15 (46.9)	16 (76.2)	3 (50.0)	3 (100.0)	0.099
ECMO mode					0.118
V-V	4 (12.5)	8 (38.1)	2 (33.3)	2 (66.7)	
V-A	10 (31.3)	3 (14.3)	2 (33.3)	0 (0.0)	
V-V-A	18 (56.3)	10 (47.6)	2 (33.3)	1 (33.3)	
Diagnosis					0.033
ARDS	8 (25.0)	7 (33.3)	2 (33.3)	2 (66.7)	
Cardiogenic Shock	12 (37.5)	7 (33.3)	3 (50.0)	0 (0.0)	
Septic Shock	12 (37.5)	7 (33.3)	1 (16.7)	1 (33.3)	
Survival	20 (62.5)	5 (23.8)	2 (33.3)	1 (33.3)	0.083
Palliation	10 (31.3)	13 (61.9)	3 (50.0)	1 (33.3)	0.248
Duration ICU (d)	28 (9 – 61.75)	11 (5 – 45)	26 (1 – 50.25)	33 (19 – 33)	0.008
Duration hospital stay (d)	34.5 (14 – 80.75)	15 (5 – 54.5)	33 (1 – 54)	33 (25 – 33)	0.530
Duration ECMO therapy (d)	9.5 (5 – 25)	10 (3 – 24.5)	22.5 (1 – 31)	9 (8 – 9)	0.130
Duration invasive ventilation (d)	19.4 (4.0 – 53.1)	10.2 (3.0 – 50.5)	24.3 (0.3 – 49.3)	29.7 (12.8 – 29.7)	0.004
CPR	15 (46.9)	10 (47.6)	5 (83.3)	1 (33.3)	0.388
Infections	25 (78.1)	14 (66.7)	4 (66.7)	3 (100.0)	0.191
Tracheotomy	23 (71.9)	11 (52.4)	3 (50.0)	3 (100.0)	0.180
Hemodialysis	26 (81.3)	19 (90.5)	5 (83.3)	3 (100.0)	0.004
SAPS II	63.5 (41.25 – 71)	48 (37 – 64.5)	38 (24 – 56.75)	50 (49 – 50)	0.363
SOFA	8 (6 – 10)	8 (7 – 12)	3.5 (2.25 – 6.75)	9 (4 – 9)	0.160

Data are median (IQR) or n (%)

3.3. Ischemic complications by ECMO mode

Table 3, 4 and 5 show the demographic and clinical data of the study population depending on ECMO mode. Patients with V-V mode (Table 3), who developed ischemic complications were significantly older than those without ischemic complications (p=0.003) and remained longer on ventilation (p=0.016). Also, there was a difference in survival (with vs. without ischemic complication; 63.7% vs. 31.3%; p=0.025).

In those patients who were treated with V-A (Table 5) and V-V-A (Table 6) mode, significantly more with ischemic complication received dialysis than those patients without ischemia (p=0.020 for V-A; p=0.049 for V-V-A). In V-A mode patients with ischemia were more likely to stay longer in hospital than those without (p=0.049). Patients with V-V-A ECMO and ischemic complication remained longer on ICU (p=0.048), received longer invasive ventilation (p=0.029) and ECMO therapy itself (p=0.005) than those patients with V-V-A mode without ischemic complication.

Table 3: Clinical and demographic characteristics of patients with V-V mode

Characteristic	**Total** n=107	**No complication** n=91	**Ischemic complication** n=16	**p-value**
Age (y)	62.0 (48.25 – 70)	62 (45 – 68)	71 (60 – 74.75)	0.003
Age ≥50 y	80 (74.8)	64 (70.3)	16 (100.0)	0.010
Sex (m)	60 (56.1)	48 (52.7)	12 (75.0)	0.111
Survival	63 (58.9)	58 (63.7)	5 (31.3)	0.025
Palliation	37 (34.6)	30 (33.0)	7 (43.8)	0.408
Duration ICU (d)	20 (10 – 34.5)	19 (10 – 28.75)	34 (13 – 43.25)	0.111
Duration hospital stay (d)	27 (16.25 – 45.75)	26.5 (16.25 – 43.25)	42.5 (13.0 – 81.5)	0.313
Duration ECMO therapy (d)	12.5 (6 – 22)	12 (6 – 12.75)	15.5. (6 – 36)	0.298
Duration invasive ventilation (d)[a]	16.6 (4.7 – 29.8)	15 (4.1 – 24.8)	30.6 (12.8 – 55.8)	0.016
CPR	14 (13.1)	10 (11.0)	4 (25.0)	0.219
Infections	92 (86.0)	77 (84.6)	15 (93.8)	0.461
Tracheotomy	67 (62.6)	57 (62.6)	10 (62.5)	1.0
Hemodialysis	62 (57.9)	50 (54.9)	12 (75.0)	0.174
SAPS II[b]	45.5 (32.3 – 61.5)	44.5 (32 – 63.8)	45.5 (37.3 – 49.8)	0.717
SOFA[b]	7 (3 – 9)	6.5 (3 – 9)	7 (4 – 8.8)	0.430
Double lumen cannula	64 (59.8)	52 (57.1)	12 (75.0)	0.269

Data are median (IQR) or n (%)

[a] (total n=105; no complication n=89)

[b] (total n=106; no complication n=90)

Table 4: Clinical and demographic characteristics of patients with V-A mode

Characteristic	**Total** n=95	**No complication** n=80	**Ischemic complication** n=15	**p-value**
Age (y)	67.5 (56.25 – 75)	67 (56 – 75)	68 (57 – 76)	0.907
Age ≥50 y	85 (89.5)	70 (87.5)	15 (100.0)	0.355
Sex (m)	65 (68.4)	58 (72.5)	7 (46.7)	0.069
Survival	24 (25.3)	18 (22.5)	6 (40.0)	0.196
Palliation	54 (56.8)	44 (55.0)	10 (66.7)	0.571
Duration ICU (d)	5 (1 – 17.75)	5 (1 – 17)	11 (4 – 34)	0.063
Duration hospital stay (d)	6 (1 – 20)	6 (2 – 20)	15 (4 – 52)	0.049
Duration ECMO therapy (d)[a]	3 (1 – 6)	4 (1 – 7)	4 (2 – 9)	0.351
Duration invasive ventilation (d)[b]	1.4 (0.4 – 12.8)	1.6 (0.5 – 12)	5.2 (1 – 31)	0.071
CPR	68 (71.6)	60 (75.0)	8 (53.3)	0.119
Infections[c]	28 (30.8)	21 (27.6)	7 (46.7)	0.219
Tracheotomy[c]	36 (39.6)	28 (36.8)	8 (53.3)	0.259
Hemodialysis[c]	52 (57.3)	39 (51.3)	13 (86.7)	0.020
SAPS II[d]	65.5 (41 – 82.3)	70 (41 – 84)	61 (31 -70)	0.145
SOFA[d]	9 (6 – 11)	9 (6 – 11)	9 (6 – 11)	0.886
Cardiogenic shock	74 (77.9)	65 (81.3)	9 (60)	0.091
Septic shock	16 (16.8)	11 (13.8)	5 (33.5)	0.124

Data are median (IQR) or n (%)

[a] (total n=94; no complication n=79)

[b] (total n=93; no complication n=78)

[c] (total n=90; no complication n=75)

[d] (total n=89; no complication n=74)

Table 5: Clinical and demographic characteristics of patients with V-V-A mode

Characteristic	**Total** n=119	**No complication** n=88	**Ischemic complication** n=31	**p-value**
Age (y)	63.5 (54.25 – 71)	64 (53.5 – 72)	62 (55 – 69)	0.641
Age ≥50 y	95 (79.8)	70 (79.5)	25 (80.6)	1.0
Sex (m)	81 (68.1)	63 (71.6)	18 (58.1)	0.184
Survival	59 (49.6)	42 (47.7)	17 (54.8)	0.536
Palliation	40 (33.6)	30 (34.1)	10 (32.3)	1.0
Duration ICU (d)	17 (5 – 29.75)	16 (4 – 26)	26 (9 – 55)	0.048
Duration hospital stay (d)	21 (7.25 – 38)	6.5 (2 – 20)	10 (3 – 26)	0.234
Duration ECMO therapy (d)	8 (3 – 16.75)	7 (3 – 13)	12 (8 – 26)	0.005
Duration invasive ventilation (d)[a]	12.7 (3 – 26.5)	10.7 (2 – 21.9)	17.9 (4 – 42.4)	0.029
CPR	61 (51.3)	42 (47.7)	19 (61.3)	0.216
Infections[b]	78 (66.1)	54 (62.1)	24 (77.4)	0.184
Tracheotomy[b]	74 (62.7)	52 (59.8)	22 (71.0)	0.290
Hemodialysis[b]	91 (77.1)	63 (72.4)	28 (90.3)	0.048
SAPS II[b]	61.5 (46.3 – 76.8)	60 (48 – 81)	64 (44 – 73)	0.497
SOFA[b]	9 (7 – 11)	9 (7 – 11.5)	8 (6 – 10)	0.368
Cardiogenic shock	61 (51.3)	49 (55.7)	12 (38.7)	0.143
Septic shock	31 (26.1)	18 (20.5)	13 (41.9)	0.031

Data are median (IQR) or n (%)

[a] (total n=117; no complication n=86)

[b] (total n=118; no complication n=87)

3.4. Arterial blood gas analysis

Arterial blood gas analysis variables at ICU admission did not differ between group 1 and group 2 (table 6). The median serum lactate levels of the patients with ischemic complication increased significantly during the ICU stay from 21.3

mg/dl to 38.0 mg/dl (24h before complication vs. diagnosis of complication; p<0.001; table 7).

Table 6: Arterial blood gas analysis on admission

	No complications n=251	**Ischemic complications** n=62	**p-value**
pH	7,29 (7,15 – 7,39)	7,34 (7,20 – 7,43)	0,063
pO_2 (mmHg)	76,2 (60,6 – 111,0)	78,3 (59,0 – 131,8)	0,755
pCO_2 (mmHg)	46,0 (35,8 – 59,8)	42,5 (33,9 – 61,0)	0,465
BE	-3,7 (-9,7 – 0,8)	-1,9 (-10,1 – 2,9)	0,116
Lactate (mg/dl)	23,0 (11,0 – 49,0)	20,5 (11,0 – 53,5)	0,892

Data are median (IQR)

Table 7: Progression of serum lactate concentration in patients with ischemic complications

	Admission n=62	**24h before complication** n=62	**Diagnosis of complication** n=62	**p-value**
Lactate (mg/dl)	20,5 (11,0 – 53,5)	21,3 (16,0 – 38,3)	38,0 (22,0 – 128,4)	<0,001
Admission to 24h before complication				0,003
24h before complication to diagnosis of complication				<0,001
Admission to diagnosis of complication				0,001

Data are median (IQR)

3.5. Multivariate logistic regression

Using the results of the univariate analyses, a multivariate logistic regression was performed on the occurrence of ischemic complications (Table 8). The diagnosis of ARDS was selected as reference category to compare the different types of diagnoses. The duration of ICU stay, ECMO therapy, invasive ventilation and the occurrence of infections were removed by stepwise elimination. Overall, an age ≥50 years (p=0.029; OR=2.793; CI 1.109 – 7.033), the use of hemodialysis (p=0.003; OR=3.283; CI=1.513 – 7.124) and a diagnosis of septic shock

(p=0.049; OR=2.144; CI=1.003 – 4.583) correlated positively with the occurrence of ischemic complications.

Table 8: Multivariate logistic regression on the occurrence of ischemic complications

Characteristic	**p-value**	**Odds Ratio (OR)**	**95% confidence interval (CI)**
ARDS	0.046		
Cardiogenic Shock	0.718	0.880	0.439 – 1.763
Septic Shock	0.049	2.144	1.003 – 4.583
Age ≥50 y	0.029	2.793	1.109 – 7.033
Hemodialysis	0.003	3.283	1.513 – 7.124

n=310

4. Discussion

Three predictors for the occurrence of ischemic complications during ECMO therapy were identified: an age ≥50 years, the use of hemodialysis and diagnosis of septic shock. The mode of ECMO therapy had no influence on the occurrence of ischemic complications.

19.3% (n=62) of patients suffered an ischemic complication, most of which were limb ischemias (n=32). The second most common region was mesenteric ischemia (n=21), followed by cardiac (n=6) and neurological ischemia (n=3; Table 2). In patients with VV mode and ischemic complications there was a significant lower survival (p=0.025; table 4). In the whole cohort, compared to patients with ARDS, those with cardiogenic or septic shock had a significantly lower survival rate (p<0.001; table 1).

4.1. Location of ischemias

Overall, ischemia in the extremities is described with a frequency of 13-20% with most studies referring to patients with ARDS and/or cardiogenic shock.[18,19,25,26] Zangrillo et al. describe in their meta-analysis the occurrence of complications and mortality during and shortly after ECMO therapy, predominantly in the V-A mode.[19] No differentiation was made according to the leading cause for ECMO.[19] Leg ischemia occurred in 10%.[19] Heparin was used for anticoagulation in eight of twelve studies reviewed, and no information was given in four.[19] Survival was 46% after 30 days.[19] In this study, 32 out of 321 patients suffered limb ischemia (10%) with the most cases occurring in patients with septic shock. Survival in patients with ischemic complications was 45.2%.

Cheng et al. report a limb ischemia rate of 16.9% in their meta-analysis of patients on ECMO for cardiogenic shock and cardiac arrest, but only refer to the lower limbs.[27] A possible explanation for the higher numbers in the other trials is that not all patients received a distal limb bypass on the arterial cannula side.[27]

The second most common ischemic complication was mesenteric ischemia with 21 (6.5%) cases. Renaudier et al. described a rate of mesenteric ischemia of 9% in 150 patients treated with V-A ECMO for cardiogenic shock or cardiac arrest.[28] Overall survival was 44%, while all patients diagnosed with mesenteric ischemia

died.[28] They identified the use of renal replacement therapy as independent risk factor.[28] The patients diagnosed with mesenteric ischemia had the lowest survival rate compared to the other ischemic locations and the second highest rate of dialysis use (Table 2). Furthermore, the study showed that hemodialysis per se correlated positively with the occurrence of ischemic complications (Table 8).
6 (1.9%) patients were diagnosed with cardiac ischemia during ECMO therapy. They had the longest duration of ECMO therapy and the highest rate of pre-ECMO CPR compared to the other ischemic locations (Table 2). Thus, in all likelyhood cardiac ischemia seems to be related to the pre-ECMO condition of the patient rather than the ECMO therapy per se.

4.2. Neurological ischemias

3 out of 321 (1%) patients studied suffered neurological ischemia during ECMO therapy of whom 1 survived. Patients with neurological ischemia had the highest age and the longest stay on ICU (Table 2). The results are in sharp contrast to those of Sutter et al.[29] They reviewed 44 studies with a median frequency of neurologic complications of 13% (range 1-78%) during V-V and V-A ECMO therapy, with intracranial hemorrhages (5%; 2-21%) and ischemic stroke (5%; 1-33%) as the two most frequent complications.[29] Patients with ischemic stroke had a mortality rate of 84% (25-100%).[29] They note that these large ranges might be explained by variations of screening methods and awareness, since in the papers reviewed by Sutter et at. all patients were sedated and to some extent neuromuscular blockers have been used.[29]
Since in the ICU of Asklepios Klinik Langen analgesia was provided by continuous infusion of a short acting opioid and none of the patients received neuromuscular blockers, repeated neurological assessments were feasible compared to sedated patients and those treated with neuromuscular blockers. Nevertheless, this does not explain the very low incidence of neurological ischemic complications in the patients.

4.3. Influence of age

In the multivariate regression, an age ≥50 years was identified as one of three predictors for an ischemic complication during ECMO therapy. 90.3% of the

patients with ischemic complications in this study were 50 years or older. The findings may also have clinical implications since the number and severity of ischemic complications seemed to increase rather than to decrease with advancing age and there is currently no de facto age limit for ECMO/ECLS therapy.[30,31]

4.4. Influence of ECMO mode

No relationship could be shown between the occurrence of ischemic complications and the ECMO mode (Table 1). Nevertheless, a significant lower survival rate in patients with VV mode and ischemic complications compared to those without ischemia in VV mode (p=0.025; Table 4), but not in VA and VVA mode was identified. This could be due to the circumstances that patients with VA and VVA ECMO are often more seriously ill than those with VV mode resulting in higher mortality rate of these two groups per se. [4,7,15]

The initial diagnosis was significantly associated with ischemic complications (Table 1). Thus, the indication for ECMO therapy seems to be more decisive for the outcome than the choice of mode. Patients with a diagnosis of septic shock had the highest rate of ischemic complications (n=21; 36.2%), with the extremities being particularly affected (n=12). In fact, this increased risk of ischemic complications was confirmed in the multivariate analysis (OR 2.144, CI 1.003 – 4.583, p=0,049). This high rate of ischemic complications might be responsible for the low survival rate compared to patients with ARDS and cardiogenic shock. However, disseminated intravascular coagulation (DIC) is a feared complication of severe sepsis and septic shock, with a high rate of ischemic complications and mortality.[32,33] The activation of pro- and anticoagulatory cascades in DIC leading to micro- and macroangiopathy, as well as bleedings, might also be responsible for the high incidence of ischemia in this patient group unrelated to the use of ECMO therapy.[32,34] The results also show that the diagnosis of "septic shock" and not the ECMO/ECLS mode per se is associated with ischemic complications. Finally, the benefit of ECMO therapy in the case of septic shock has not yet been prospectively evaluated, with mortalities ranging from 10-90%.[9,35,36]

4.5. Renal replacement therapy during ECMO therapy

Patients with ischemic complications were significantly more likely to receive hemodialysis (85.5%) compared to those without complications (59.8%; $p<0.001$). The overall dialysis rate (64.9%) is comparable to other studies in which renal replacement therapies in patients with ECMO therapy were used.[19,27,37]

In their systematic review Chen et al. report a longer ECMO duration, and a higher mortality in patients with renal replacement therapies during ECMO therapy.[38] In addition, Schmidt et al. showed that a positive fluid balance on the third day and the use of a renal replacement therapy in the first three days of ECMO therapy are independent predictors for 90-day mortality.[37]

Overall, patients on renal replacement therapy are often more severely ill than those who do not require such therapy, probably leading to an increased incidence of ischemic complications.[39]

4.6. Anticoagulation in patients with ECMO

Activation of coagulation is a well-known side effect of ECMO therapy.[12,17,20,40] Therefore, appropriate anticoagulation is needed.

In this study a detailed evaluation of each patients' anticoagulation was limited due to the retrospective nature. However, from 2015 onwards, solely argatroban was administered for systemic anticoagulation since heparin-induced thrombocytopenia (HIT) had occurred frequently before. Especially in patients with septic shock thrombocytopenia could also be induced by DIC, making it difficult to distinguish the reason of thrombocytopenia.[32,33] Argatroban, a direct thrombin inhibitor, is easy to dose and not associated with HIT.[41] So far, clear recommendations regarding an appropriate anticoagulation strategy in patients with ECMO therapy are still lacking.[40–43]

4.7. Limitations

The study is limited by several factors:

1) It is a monocentric retrospective analysis.
2) The indication and therapy were at the discretion of the responsible ICU team, which may lead to sample bias.

3) The same applies to the start time and mode of ECMO therapy, which may also lead to a selection bias due to a too early or too late start of therapy or a change of ECMO mode.
4) It is a heterogeneous study population with different pre-existing conditions and a limited number of cases.
5) There was no long-term follow-up of the patients.

5. Conclusions

In summary, an age of D50 years, the use of hemodialysis and a diagnosis of septic shock were identified as predictors for the occurrence of ischemic complications during ECMO therapy with the multivariate logistic regression. The extremities were most frequently affected, followed by mesenteric, cardiac and neurological ischemia. An influence of ischemic complications on survival could be determined in VV mode. Finally, the mode of ECMO therapy – V-V, V-A, or V-V-A – was not associated with ischemic complications.

6. Summary

Background:

During ECMO therapy ischemia of the limbs or internal organs are potential lethal complications. This study analyzed incidence and type of ischemic complications during ECMO therapy, divided in limb, mesenteric, cardiac and neurological ischemia.

Methods:

In this single-center retrospective observational study data from 348 patients treated with veno-venous, veno-arterial or veno-venous-arterial ECMO at the Asklepios Klinik Langen between April 1st 2011 and March 31st 2020 was screened. 321 patients with diagnosis of acute respiratory distress syndrome, cardiogenic or septic shock were included.

Primary outcome variable was type of ischemic complication. Further variables were serum lactate levels 24h before and immediately after diagnosis of the ischemic complication, duration of ICU and hospital stay, ECMO therapy and duration of invasive ventilation and arterial blood gas analysis on day of admission to the ICU. Age, sex, ECMO mode, diagnosis, SAPS II, SOFA score, hospital mortality, the use of renal replacement therapy and tracheotomy, the occurrence of infections during the ICU stay and the need of CPR before ECMO implantation were recorded as well.

Results:

62/321 patients (19.3%) were diagnosed with an ischemic complication. Most common areas were limbs (n=32) and mesenteric ischemia (n=21). Patients who were diagnosed with a septic shock had the highest rate of ischemic complications (36.2%). In VV mode there was a difference in survival between patients with and without ischemic complication (p=0.025). Using multivariate logistic regression, age ≥50 years (p=0.029; OR=2.793; CI 1.109 – 7.033), use of hemodialysis (p=0.003; OR=3.283; CI=1.513 – 7.124) and initial diagnosis of a septic shock (p=0.049; OR=2.144; CI=1.003 – 4.583) could be identified as predictors for ischemic complications.

Conclusions:

Ischemic complications are frequent during ECMO therapy. An age of at least 50 years, the use of hemodialysis and diagnosis of a septic shock were predictors of ischemic complications. No correlation between ECMO mode and ischemic complications was found. An influence of ischemic complications on survival could be found only in patients treated with VV mode.

7. Zusammenfassung

Hintergrund:
Während einer Therapie mittels extrakorporaler Membranoxygenierung (ECMO) treten häufig Komplikationen auf, die potenziell tödlich sind, insbesondere Ischämien im Bereich der Extremitäten oder inneren Organen. In dieser Studie wurden Häufigkeit und Art der ischämischen Komplikationen während ECMOTherapie analysiert, unterteilt in Extremitäten-, Mesenterial-, kardiale und neurologische Ischämien.
Methoden:
Es wurden die Daten von 348 Patienten ausgewertet, die vom 1. April 2011 bis 31. März 2020 mit venös-venöser, venös-arterieller oder venös-venös-arterieller ECMO auf der Intensivstation der Asklepios Klinik Langen behandelt wurden. 321 Patienten mit der Diagnose eines akuten Lungenversagens, eines kardiogenen oder eines septischen Schocks wurden in die Auswertung eingeschlossen.
Primäre Zielvariable war die Art der ischämischen Komplikation. Weitere Variablen waren Serumlaktatspiegel 24h vor und unmittelbar nach Diagnose der Ischämie, Dauer des intensiv- und normalstationären Krankenhausaufenthalts, Dauer der ECMO Therapie und invasiven Beatmung. Des weiteren Alter, Geschlecht, ECMO Modus, Diagnose, SAPS II, SOFA score, Krankenhaussterblichkeit, Einsatz von Nierenersatzverfahren und Tracheotomie, Auftreten von Infektionen während des intensivstationären Aufenthalts, sowie die Notwendigkeit einer kardiopulmonalen Reanimation vor ECMO Implantation und arterielle Blutgasanalysen zum Zeitpunkt der intensivstationären Aufnahme.
Ergebnisse:
Bei 62 von 321 Patienten (19,3 %) wurde eine ischämische Komplikation diagnostiziert. Am häufigsten traten Ischämien im Bereich der Extremitäten (n=32) und Mesenterialregion (n=21) auf. Patienten, bei denen ein septischer Schock diagnostiziert wurde, hatten die höchste Rate an ischämischen Komplikationen (36,2 %). Im VV-Modus konnte ein Unterschied im Überleben zwischen Patienten mit und ohne ischämische Komplikation gezeigt werden (p=0.025). Mittels multivariater logistischer Regression konnten ein Alter von mindestens 50 Jahren (p=0.029; OR=2.793; CI 1.109 – 7.033), der Einsatz der

Hämodialyse (p=0.003; OR=3.283; CI=1.513 – 7.124) und die Diagnose eines septischen Schocks (p=0.049; OR=2.144; CI=1.003 – 4.583) als Prädiktoren für ischämische Komplikationen identifiziert werden.

Schlussfolgerungen:

Ischämische Komplikationen sind häufig während einer ECMO Therapie. Ein Alter von mindestens 50 Jahren, der Einsatz der Hämodialyse und die Diagnose eines septischen Schocks waren Prädiktoren für ischämische Komplikationen. Es wurde kein Zusammenhang zwischen dem ECMO Modus und ischämischen Komplikationen festgestellt. Ein Einfluss der ischämischen Komplikationen auf das Überleben konnte nur für den veno-venösen ECMO Modus festgestellt werden.

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Appendix

Ethik-Kommission bei der Landesärztekammer Hessen

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PERSÖNLICH

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vorab via ethikPool

Ihr Zeichen

(bitte immer angeben)
Unser Zeichen:
V/1/sja/gas
2020-1977-evBO

Datum
5 Januar 2021

Ischämische Komplikationen bei extrakorporaler Membranoxygenierung

Vorgangsnummer: 2020-1977-evBO (stets anzugeben)

Nachgereichte Unterlagen
Ihre Nachricht über ethikPool vom 6. November 2020

Sehr geehrter Herr Professor Hopf,

wir bestätigen den Eingang der oben aufgeführten Nachricht vom 6 November 2020 Damit sind die Forderungen der Ethik-Kommission aus dem Schreiben vom 3 November 2020 umgesetzt worden

Gegen die Durchfuhrung der Studie

Ischämische Komplikationen bei extrakorporaler Membranoxygenierung

bestehen nunmehr weder berufsethische noch berufsrechtliche Bedenken

Dieses Vorhaben wurde gemäß § 8 Abs. 6 der Satzung der Ethik-Kommission bei der Landesarztekammer Hessen außerhalb einer Sitzung beraten

Es wird darauf hingewiesen, dass datenschutzrechtliche Aspekte von Forschungsvorhaben durch die Ethik-Kommission grundsatzlich nur kursorisch gepruft werden und dieses Schreiben nicht die Konsultation des zuständigen behördlichen Datenschutzbeauftragten ersetzt.

Die Ethik-Kommission geht davon aus, dass bei der vorliegenden retrospektiven Studie eine klinikinterne Auswertung vorgesehen ist, bei der die eigentlichen Akten in der Klinik

...

verbleiben, die Datensicherheitsmaßnahmen gewahrleistet, die datenschutzrechtlichen Vorschriften - insbesondere § 27 BDSG und § 24 HDISG einschließlich der Bereithaltung eines Datenschutzkonzeptes – beachtet und die nach EU-DSGVO sowie HDISG bzw. BDSG erforderlichen technischen und organisatorischen Maßnahmen eingehalten werden

Es wird darauf hingewiesen, dass Anderungen oder Erweiterungen des Versuchsplanes der Ethik-Kommission anzuzeigen sind und gegebenenfalls eine erneute Beratung erforderlich wird In den einzureichenden Studienunterlagen sind die Änderungen und/oder Erweiterungen deutlich zu kennzeichnen; es müssen alle Änderungen nachvollziehbar aus den Unterlagen hervorgehen (insbesondere Streichungen).

Die Ethik-Kommission bittet außerdem nach Abschluss des Forschungsvorhabens um einen Bericht mit der Mitteilung der bei der Studie gewonnenen Ergebnisse.

Die ärztliche und juristische Verantwortung des Studienleiters und der an der Prufung teilnehmenden Ärzte bleibt entsprechend der Beratungsfunktion der Ethik-Kommission durch unsere Stellungnahme unberuhrt

Der Beratung lagen die in der Anlage aufgefuhrten Unterlagen zugrunde, es haben die in der Anlage aufgefuhrten Mitglieder der Ethik-Kommission mitgewirkt

Mit freundlichen Grüßen
i.A.

Prof. Dr. med. S. Harder
Vorsitzender der Ethik-Kommission

cc Herrn Matthias Gartner, Asklepios Klinik Langen

Hinweis

Falls noch nicht geschehen, reichen Sie die Unterlagen noch einfach in Papierform ein

Anlagen

Zur Beratung vorgelegte Unterlagen

Dokument	Version	Datum
Deckblatt für die Antragstellung fur Studien außerhalb des AMG/MPG	/	24 08 2020
Prufplan für eine retrospektive Beobachtungsstudie	2 0	06 11.2020
Literatur		24 08.2020

Ihr Schreiben vom 24 August 2020, hier eingegangen am 24 August 2020

An der Beratung teilnehmende Mitglieder:

Prof Dr med Sebastian Harder, Vorsitzender, Klinischer Pharmakologe
Prof Dr med. Michael Weber, Internist /Kardiologe

Die Ethik-Kommission bei der Landesarztekammer Hessen verarbeitet Ihre personenbezogenen Daten im Einklang mit den jeweils anzuwendenden gesetzlichen Datenschutzanforderungen Die Informationspflichten nach Art 13 und Art 14 DSGVO im Rahmen unserer Tatigkeit haben wir fur Sie auf unserer Homepage unter https //www laekh de/fileadmin/user_upload/Aerzte/Rund_ums_Recht/Ethikkommission/DSGVO_Informationspflichten_Ethikkommission pdf zusammengefasst

Curriculum vitae

Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann Wolfgang Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

Ischemic Complications In Patients With Extracorporeal Membrane Oxygenation

in der Asklepios Klink Langen, Abteilung für Anästhesie, perioperative Medizin und interdisziplinäre Intensivmedizin unter Betreuung und Anleitung von Prof. Dr. med. Hans-Bernd Hopf mit Unterstützung durch Dr. med. Julia Fichte ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

_____ _____

(Ort, Datum) (Unterschrift)