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Original Article

Autopsy and clinical discrepancies in patients undergoing extracorporeal membrane oxygenation: a case series☆,☆☆

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ABSTRACT

Background: Extracorporeal life support is used as a salvage procedure to treat refractory cardiopulmonary failure. There are limited data addressing discrepancies between pre- and postmortem findings in patients undergoing extracorporeal membrane oxygenation (ECMO). We investigated discrepancies between clinical and autopsy findings in patients placed on ECMO to assess in what proportion of patients were there significant cardiovascular or other pathologies present that were not clinically apparent prior to death.
Methodology: After institutional review board approval, a list of deceased ECMO patients who underwent autopsy examination from 2004 through 2015 was obtained from our institutional database. Retrospective analyses of findings on clinical investigations done while patients were on ECMO and findings on autopsy examination were compared and stratified according to modified Goldman Criteria, which classify discrepancies into four grades depending on their impact on patient's management and mortality.
Results: Of 19 patients, 18 patients had venoarterial ECMO (9 central + 5 peripheral + 4 conversions of ECMO type) and 1 patient received venovenous ECMO. Clinically unrecognized findings were found on autopsy in all patients. 56.6% of total discrepancies found were major [class I/II; e.g., myocardial infarction (MI), intracranial bleeding]. All patients had major discrepancies (class I/II) with an average of 4.21 class I discrepancies per patient. Class I discrepancies are findings which could have altered the course of treatment and survival of the patient if recognized premortem. The most common discrepancies were cardiovascular (MI 63.2%, marked cardiac remodeling 42.1%, severe coronary disease 31.6%) in nature across four classes of discrepancies.
Conclusions: We found major discrepancies between premortem and postmortem diagnoses in patients who underwent ECMO. Our findings underscore difficulties in clinically diagnosing events on ECMO as well as the need for enhanced surveillance and better diagnostic techniques in ECMO patients. Further prospective studies are necessary to understand effects of ECMO on major organs.

1. Introduction

Extracorporeal membrane oxygenation (ECMO, also known as extracorporeal life support) is a form of advanced life support in which venous blood is taken from the patient and pumped through an external artificial circuit to a membrane lung (or oxygenator), where carbon dioxide is removed and oxygen is added to the blood. The blood is then returned to the patient's venous or arterial circulation. Venovenous (VV) ECMO is used to provide gas exchange support for patients with severe respiratory failure refractory to conventional ventilatory support. Venoarterial (VA) ECMO is used to provide both circulatory and gas exchange support for patients with severe cardiac failure refractory to inotropic support. Venous blood from the patient is accessed from the large central veins and returned to the arterial system in the ascending aorta (central VA ECMO) or a peripheral artery (femoral, carotid, or axillary artery, referred to as peripheral VA ECMO). Patients who need salvage ECMO therapy are often very unstable and are generally managed under heavy sedation, at least initially. Developments in cardiopulmonary bypass machinery with newer pump technologies, better cannulation techniques, and improvised management guidelines have resulted in better survival of ECMO patients in recent years [1]. However, there are limited data addressing discrepancies between pre- and postmortem findings in patients undergoing ECMO.

Autopsy remains an important tool for assuring and improving the quality of medical care by monitoring the diagnostic accuracy and treatment of patients. Although the possibility that a given autopsy will reveal important unsuspected diagnoses has decreased over time, it

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remains sufficiently high that some of the reversible clinical conditions remain undiagnosed when the patient is critically ill and heavily sedated [2]. Early detection and active treatment for these previously missed diagnoses and complications may have a significant impact on the patients' mortality and morbidity. Despite the presence of publications reporting the discrepancies between clinical findings and autopsy reports [2,3], autopsy rates have been declining worldwide over the past few decades [4,5].

Previous studies reporting the discrepancy between clinical findings and autopsy reports in pediatric ECMO patients have been published in the literature, while analytical studies in adult ECMO patients were rarely found. The aims of this study were to investigate discrepancies between clinical and autopsy findings in patients placed on ECMO at our institution and to assess the value of autopsy in these patients.

2. Material and methods

2.1. Study design and patient population

This retrospective single-center observational study was conducted on deceased ECMO patients who underwent autopsy examination from 2004 through 2015 in our institution. After institutional review board approval, clinical and autopsy details of these patients were obtained from our institutional ECMO database and the hospital medical records. All adult patients who were admitted on ECMO to the intensive care unit were included in the study. In accordance with local laws, we referred all patients who die on ECMO to the coroner, who finally decided on whether an autopsy is warranted. Patients without autopsy reports were excluded from our study.

2.2. Data variables

From the medical records, we extracted patient demographics, past medical history, clinical, laboratory, and radiological/echocardiography findings in addition to details on indication, course, type, and duration of ECMO. From their detailed autopsy reports, we collected their autopsy findings corresponding to each organ. Three different investigators (D.J., R.N., E.L.) reviewed the medical records to establish the principal diagnoses and cause of death for each patient and the autopsy findings. Disagreements in either clinical or autopsy findings were resolved by further discussion with senior investigators (R.K. and G.M.). Retrospective analyses of clinical findings and investigations done while patients were on ECMO and findings on autopsy examination were compared and stratified according to modified Goldman criteria [6] (Table 1), which classify discrepancies into four grades depending on their impact on patient's management and mortality.

Table 1
Modified Goldman criteria

Major discrepancies	Class I	Undiagnosed major unexpected findings before death that probably would have changed the therapy or improved survival E.g., Myocardial infarction
	Class II	Undiagnosed major unexpected findings before death that would not have changed the treatment or the patient's survival because: - Of ineffective therapy - The patient received the indicated treatment even though the diagnosis was unknown The patient refused evaluation or therapy E.g., Moderate cardiomegaly
Minor discrepancies	Class III	Unexpected findings that were not immediate or primary causes of death but could have influenced the prognosis or the process leading to death in a terminally ill patient E.g., Mild coronary atherosclerosis
	Class IV	Unexpected findings (nondiagnosable) of possible epidemiological or genetic importance E.g., Fatty liver

2.3. Calculations

Categorical variables were described using frequencies and percentages, whereas continuous variables were represented using median and range. Associations between types of discrepancies and ECMO cannulation strategies were compared using Poisson's regression model. One patient on VV ECMO was excluded from the Poisson's regression model analysis as he was considered an outlier based on his VV status. The R statistical software was used to perform the analysis, and P value of less than .05 was considered to be statistically significant.

3. Results

Of the 122 patients who received ECMO between 2004 and 2015, 53 (43.4%) adult patients died on ECMO; all of them were referred for autopsy. Nineteen adult patients had autopsy performed. There were 19 patients included in our analysis; 13 of them were males. The mean age of the patients was 47.1 years, and the mean duration of ECMO was 12.5 days. The demographics of our patients are shown in Table 2. Eighteen patients received VA ECMO for a primary cardiac cause, while one received VV ECMO for respiratory failure. Nine patients had central venoarterial (VA-c) ECMO, five patients had peripheral venoarterial (VA-p) ECMO, four patients had conversion of VA ECMO from peripheral to central or vice versa, and one patient received VV ECMO. Among the four patients with conversions, three were converted from VA-p ECMO to VA-c ECMO, while one patient was converted from VA-c ECMO to VA-p ECMO. The indications for VA ECMO included myocarditis, myocardial infarction (MI), post cardiopulmonary bypass, and traumatic myocardial injury, while one patient needed VV ECMO for community-acquired pneumonia (Table 2).

Our patients had discrepancies between clinical and autopsy findings. There were no discrepancies on the indication for ECMO. Clinically unrecognized findings were found on autopsy in all patients. A total of 56.6% of the total discrepancies found were major

Table 2
Demographic and ECMO indication by patient

Patient no.	Gender	Age (years)	ECMO type	ECMO indication	ECMO duration (days)
1	M	59	V-A central	PCB	5
2	M	52	V-A central	Acute MI	1
3	M	44	V-A central	CABG	5
4	M	73	V-A central	CABG	13
5	F	60	V-A central	PCB	5
6	F	23	V-A central	PCB	5
7	F	66	V-A central	PCB	5
8	M	46	V-A central	PCB	2
9	M	62	V-A central	PCB	2
10	M	41	V-A peripheral	Inferior wall MI	4
11	M	34	V-A peripheral	Traumatic myocardial injury	4
12	F	42	V-A peripheral	PCB	2
13	F	48	V-A peripheral	Myocarditis	25
14	M	47	V-A peripheral	PCB	2
15	F	22	V-A peripheral, then V-A central	Myocarditis	49
16	M	65	V-A central, then V-A peripheral	PCB	4
17	M	56	V-A peripheral, then V-A central	PCB	6
18	M	19	V-A peripheral, then V-A central	PCB	11
19	M	42	V-V	CAP	88

M, male; F, female; V-A, venoarterial; VV, venovenous; PCB, post cardiopulmonary bypass; MI, myocardial Infarction; CABG, coronary artery bypass graft; CAP, community-acquired pneumonia.

Table 3
Total number of discrepancies for all ECMO patients — by class

Class	Found in autopsy report but not in clinical findings	Found in clinical findings but not in autopsy report
Class I	80	13
Class II	74	14
Class III	97	1
Class IV	21	2

Table 4
Number of discrepancies for all patients by system

Class	System	Total number of discrepancies (in autopsy report but not in clinical findings)		Average number of discrepancy per patient	
Class I	Cardiovascular	33	80	1.74	4.21
	Endocrine	3		0.16	
	Gastrointestinal	3		0.16	
	Neurologic	23		1.21	
	Pulmonary	18		0.95	
Class II	Cardiovascular	39	74	2.05	3.89
	Gastrointestinal	8		0.42	
	Hepatobiliary	2		0.11	
	Pulmonary	25		1.32	
Class III	Cardiovascular	38	97	2.00	5.11
	Gastrointestinal	12		0.63	
	Hepatobiliary	12		0.63	
	Neurologic	3		0.16	
	Pulmonary	1		0.05	
	Reticuloendothelial	13		0.68	
	Urinary	18		0.95	
Class IV	Gastrointestinal	8	21	0.42	1.11
	Hepatobiliary	9		0.47	
	Musculoskeletal	3		0.16	
	Reproductive	1		0.05	

(class I/II; e.g., MI, intracranial bleeding) (Table 3). All patients had major discrepancies (class I/II), with an average of 4.21 class I discrepancies and 3.89 class II discrepancies per patient (Table 4). Class I discrepancies are serious critical incidences missed on clinical diagnosis but found on autopsy. These included 12 patients with undiagnosed myocardial infarction and 1 patient with dissection of right coronary artery. Autopsy also identified 3 patients with adrenal hemorrhage, 2 patient with retroperitoneal hemorrhage, 1 patient with diffuse bowel ischemic infarction, and 13 patients with lung lesions that were not detected clinically. Class I neurological discrepancies including intracranial hemorrhage/ hemorrhagic infarction (seven patients), subarachnoid hemorrhage (six patients), subdural hemorrhage (two patients), and thrombus in the ventricular system (one patient) could not be detected clinically.

The most common discrepancies were cardiovascular (proportion of patients: class I MI — 63.2%, class II epicardial/pericardial lesions — 47.4%, class III epicardial/pericardial lesions — 47.4%, class II marked cardiac remodeling — 42.1%) in nature across four classes of discrepancies. Our analysis also revealed clinical discrepancies where clinical signs recorded were not appropriately revealed during the autopsy. Clinically suspected pathologies including myocarditis, endocarditis, cardiac thrombus on echocardiography, brainstem herniation, ischemic colitis, pleural lesions, and splenic infarction were absent on autopsy. However, there were more autopsy discrepancies than clinical discrepancies in our patients (Fig. 1).

There was no association between number of discrepancies and sex, gender, or race of patients. There is also no association between class of discrepancy and type of ECMO used. Patients with conversion (Conv) from VA-c or VA-p ECMO had significantly more discrepancies than either of them alone (Fig. 1). We identified that the median of total discrepancies, defined as the sum of autopsy and clinical differences, was significant across the central, peripheral, and conversion ECMO runs. (VA-c vs. VA-p vs. Conv: 10.1 vs. 14.5 vs. 15, P value = .014) (Table 5). Central ECMO was associated with significantly fewer discrepancies compared to peripheral and conversion ECMO runs. Median autopsy discrepancies were significantly more with peripheral compared to central ECMO runs; however, the differences were not significant when they were compared with discrepancies in patients who needed ECMO conversion (VA-c vs. VA-p vs. Conv: 9 vs. 14 vs. 11.5, P value = .07) (Table 5). An analysis comparing only the major discrepancies (class I and class II) between the three groups of ECMO patients revealed that clinical inconsistencies were significant between patients on central, peripheral, and converted ECMO groups. Minor discrepancies remained insignificant between the groups (Table 6).

4. Discussion

Our results demonstrate that autopsies are valuable in patients who underwent ECMO as all the patients in our analysis had at least one major discrepancy between the clinical findings and autopsy reports. The major clinical discrepancies were significant, implying that fatal near misses are common and recognition of clinical signs could be challenging in patients who are deeply sedated during ECMO. Patients also had an average of more than seven major critical events (class I or class II discrepancies) that were not detected clinically but on autopsy. Clinical recognition of these major discrepancies could have had significant effects on patients' diagnoses, treatment, or prognoses.

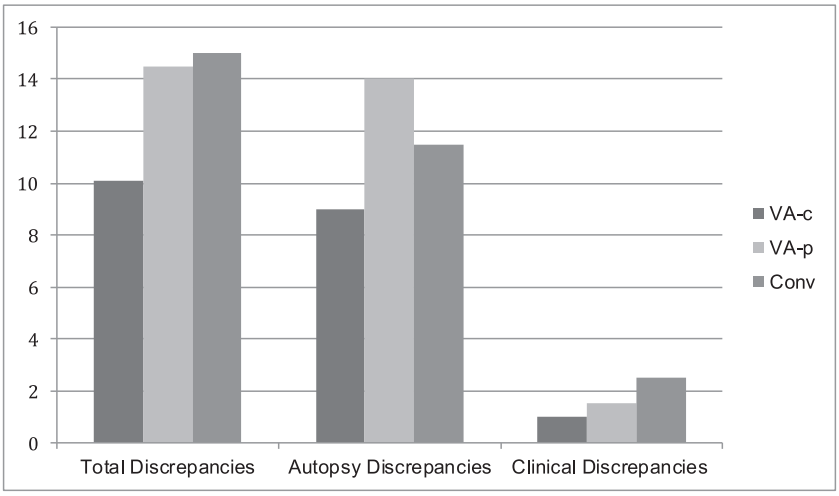

Fig. 1. Median discrepancies for different types of ECMO.

Table 5
Median discrepancies and *P* value for different types of ECMO

	VA (c)	VA (p)	Converted	Comparison	*P* value
Total	10.1	14.5	15	VA(c) VS VA(p)	.02
				VA(c) VS Conv	.02
				VA(p) VS Conv	.671
				Total	.014
Autopsy discrepancies: findings found in autopsy but not clinically	9	14	11.5	VA(c) VS VA(p)	.04
				VA(c) VS Conv	.06
				VA(p) VS Conv	.97
				Overall	.07
Clinical discrepancies: findings found clinically but not in autopsy	1	1.5	2.5	VA(c) VS VA(p)	.21
				VA(c) VS Conv	.02
				VA(p) VS Conv	.32
				Total	.08

Blanco et al. conducted a similar study in pediatric patients and found that nearly half of the patients who underwent ECMO had at least one major discrepancy between autopsy and clinical diagnosis [7]. Comparatively, in our series, at least one major discrepancy between the clinical findings and autopsy reports was found in all patients, with an average of 4.21 class I discrepancies and 3.89 class II discrepancies per patient.

A systematic review on the changes in autopsy rates not only detected diagnostic errors over time but also showed a significant amount of major and class I errors detected in the autopsy series [2]. Diagnostic error rates have shown a relative decrease of 19.4% for major errors and 33.4% for class I errors per decade [2]. However, the authors concluded that it still remains sufficiently high enough to warrant autopsies. ICU studies that focused on heterogeneous, non-ECMO adult populations found much lower discrepancy rates between autopsy and clinical findings (19.8%–27.9% major discrepancy rate/4.1%–12% class I error rate) compared to our study [2]. Major error rates and class I error rates were 23% and 11% in surgical ICU patients [8], while the major error rate was 27% in medical coronary ICU patients [9]. This may be due to the fact that patients who are receiving ECMO are often deeply sedated and thus may not present with typical signs of the underlying pathology. This also makes it difficult to detect neurological events such as intracranial hemorrhage. Concurrent pathologies that patients have while on ECMO or as a result of ECMO can also be easily missed. Beyond simply recommending autopsies to be done more frequently in future ECMO patients, it is also more important for us to recognize the value of autopsy findings and learn from autopsies already conducted. Our findings also highlight the need for enhanced surveillance and better diagnostic techniques in ECMO patients.

It can be argued that ECMO patients should undergo more thorough and aggressive investigations such as computed tomographic scans to look for underlying pathologies so as to reduce discrepancies. However, transport of patients on ECMO can be cumbersome with additional risks and needs multidisciplinary team involvement. It has been noted that the hazard of critical incidents remains high during intrahospital transport of ICU patients [10]. Although it is often difficult for patients on ECMO to undergo excessive investigations while being sedated, clinicians should have a low threshold to investigate ECMO patients to actively look for common pathologies. The most common discrepancies were cardiovascular in nature across four classes of discrepancies, and MI was the commonest discrepancy found in our patients. Given that most of the patients needed VA ECMO support, it is not surprising that nonsurvivors had a tendency to have coronary ischemia. Also, the high incidence of hemodynamic instability before and on ECMO such as episodes of hypotension can add on to the risk of myocardial ischemia [11,12].

Blanco et al. conducted a study on patients who underwent ECMO support in the pediatric and cardiac ICU, and they found a higher rate of class I and II discrepancies in patients with cardiac diagnosis than those without [7]. However, we found that patients who converted from central or peripheral ECMO had significantly more discrepancies than those who were on central VA ECMO. One possible reason is that central VA ECMO is usually done in a controlled environment such as the operating theater, while conversions are usually done in the ICU when patients are more hemodynamically unstable, resulting in more discrepancies. Interestingly, we also found discrepancies that were diagnosed clinically but were not found in the autopsy report. Clinically suspected pathologies like myocarditis, endocarditis, cardiac thrombus, brainstem herniation, and ischemic colitis in some of the ECMO patients were absent on autopsy.

Our study is limited by the fact that it is a single-center retrospective analysis. It is also limited by the probable presence of selection bias since only 19 out of the 53 referred patients eventually had autopsy. Coroner's decision to conduct the autopsies may be based on the inconsistency between clinical findings and cause of death, and thus, patients who underwent autopsies may have a higher incidence of both clinical and autopsy discrepancies. Also, clinicians may have diagnosed findings clinically but might have failed to document them. Some of the discrepancies such as myocarditis and endocarditis could not be found in the autopsy reports as detailed histological biopsy findings were not available postmortem. Autopsy reports were descriptive, and hence, specific diagnoses could have been missed. It was also difficult to differentiate terminal occurrences from missed events completely; however, we did attempt to look at the corroborative clinical, biochemical, and radiological evidences to rule out terminal events.

However, the presence of significant major discrepancies emphasizes the importance of closer surveillance, thorough documentation, and better diagnostic techniques in ECMO patients. Further prospective studies would be necessary to understand the effects of ECMO on major organs. Further research into the pathophysiology of the diseases that develop in patients while on ECMO and the effect that existing

Table 6
Table comparing the major (class I and II) discrepancies and minor discrepancies (class III and IV) across the three subgroups of ECMO*[a]

		Major discrepancies (class I and II)			Minor discrepancies (class III and IV)		
	Type	Median (min– max)	*P* value	Adjusted *P* value[a]	Median (min– max)	*P* value	Adjusted *P* value[a]
Total	VA(c) VS VA(p)	7 (1–9) vs. 8 (6–12)	**.056**	.168	5 (2–8) vs. 6.5 (4–8)	.328	.984
	VA(c) VS Conv	7 (1–9) vs. 10.5 (6–12)	**.026**	.078	5 (2–8) vs. 7 (3–9)	.327	.981
	VA(p) VS Conv	8 (6–12) vs. 10.5 (6–12)	.640	1	6.5(4–8) vs. 7 (3–9)	.919	1
	Overall		.464			.502	
Autopsy discrepancies	VA(c) VS VA(p)	6 (1–8) vs. 7.5 (3–10)	.232	.696	5 (2–8) vs. 6.5 (3–8)	.345	1
	VA(c) VS Conv	6 (1–8) vs. 7 (4–11)	.222	.666	5 (2–8) vs. 6 (3–9)	.471	1
	VA(p) VS Conv	7.5 (3–10) vs. 7 (4–11)	.884	1	6.5 (3–8) vs. 6 (3–9)	.917	1
	Overall		.351			.594	
Clinical discrepancies	VA(c) VS VA(p)	1 (0–2) vs. 1.5 (0–4)	**.046**	.138	0 (0–1) vs. 0 (0–1)	.774	1
	VA(c) VS Conv	1 (0–2) vs. 2.5 (1–4)	**.004**	**.012**	0 (0–1) vs. 0 (0–2)	.219	.657
	VA(p) VS Conv	1.5 (0–4) vs. 2.5 (1–4)	**.010**	**.03**	0 (0–1) vs. 0 (0–2)	.370	1
	Overall		**.020**			.424	

P<.05 is considered significant. VA(c), central ECMO; VA(p), peripheral VA ECMO; Conv ECMO, needing conversion.
[a] Adjusting for multiple testing.

comorbid diseases have on determining the risk of patients developing these pathologies while on ECMO needs to be carried out as well.

5. Conclusions

In conclusion, we found major discrepancies between premortem and postmortem diagnoses in patients who underwent ECMO. Our findings highlight the possible difficulties in clinically diagnosing events on ECMO. Low threshold for investigations coupled with improved scrutiny and better diagnostic techniques in ECMO patients might enhance lesser discrepancies and better outcomes in ECMO patients. The use of newer advanced beside investigations and monitoring modalities may help to detect the underlying pathologies early so that prompt treatment can be carried out. Autopsy remains an important tool for ECMO program evaluation and better understanding of complex medical problems in patients needing salvage support for cardiopulmonary failure.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carpath.2019.03.001.

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