[Original Research]

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Histopathologic Findings in Lungs of Patients Treated With Extracorporeal Membrane

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BACKGROUND: The outcome of extracorporeal membrane oxygenation (ECMO) might be influenced by its complications. Only limited information is available regarding the pathologic consequences of ECMO, especially in the era of modern ECMO technology.

METHODS: We studied the histopathologic findings in autopsy lungs of patients treated with ECMO compared with those without ECMO. Autopsy files were queried for cases with ECMO. An age- and sex-matched control group comprised of patients who died in the ICU without acute respiratory distress syndrome, pneumonia, or ECMO was compared with patients with ECMO for cardiac reason. Histopathology and medical records were reviewed.

RESULTS: Seventy-six patients treated with ECMO (38 men; median age, 40 years) and 47 control patients (23 men; median age, 45 years) were included. Common histologic pulmonary findings in the ECMO group were pulmonary hemorrhage (63.2%), acute lung injury (60.5%), thromboembolic disease (47.4%), calcifications (28.9%), vascular changes (21.1%), and hemorrhagic infarct (21.1%). Pulmonary hemorrhage was associated with longer ECMO duration (median, 7.0 vs 3.5 months; $P = .014$), acute lung injury with venovenous ECMO (91.7% vs 54.7%; $P = .039$) and longer ECMO (6.0 vs 4.0 months; $P = .044$), and pulmonary calcifications with infants (50.0% vs 22.4%; $P = .024$). Patients with ECMO for cardiac reasons (n = 60) more frequently showed pulmonary hemorrhage ($P < .001$), diffuse alveolar damage ($P = .044$), thromboembolic disease ($P = .004$), hemorrhagic infarct ($P = .002$), pulmonary calcifications ($P = .002$), and vascular changes ($P = .001$) than patients in the non-ECMO group.

CONCLUSIONS: Some findings are suspected to be associated with the patient's underlying disease, whereas others might be related to ECMO. Our results provide a better understanding of ECMO-related lung disease and might help to prevent it.

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KEY WORDS: acute lung injury; extracorporeal membrane oxygenation (ECMO); histopathology; lung; pulmonary hemorrhage; thromboembolic disease

ABBREVIATIONS: CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; IQR = interquartile range; VA = venoarterial; VV = venovenous

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Extracorporeal membrane oxygenation (ECMO) is increasingly used to treat patients with respiratory and/or cardiac failure, to bridge to lung and/or heart transplantation, or in posttransplantation primary graft dysfunction. Significant advances in ECMO technology have resulted in better clinical outcome in patients treated with ECMO and therefore have led to more widespread use of ECMO.[1-8] Outcome of ECMO is influenced by both the patient's underlying disease and ECMO-related complications.

ECMO-related complications are likely dependent on the type of ECMO, venovenous (VV) or venoarterial (VA), but in general include bleeding, thrombosis, infection, limb ischemia, compartment syndrome, hemolysis, thrombocytopenia, acquired von Willebrand syndrome, disseminated intravascular coagulopathy, and air embolism.[1,9] However, histopathologic findings in the lungs of patients treated with ECMO are not well known, especially in the era of modern ECMO technology. We aimed to identify ECMO-related histopathologic findings of the lung.

Methods

Patients

Autopsy files of Mayo Clinic Rochester (1995-2015) were queried for patients who underwent ECMO treatment shortly before or at the time of death. A total of 87 patients were identified. Histologic material of the lungs was available in 76 patients. For comparison of patients with ECMO for cardiac reasons, the largest group of patients on ECMO in our study, an age and sex-matched control group consisting of 47 patients who died in the ICU without a clinical history of ARDS or pneumonia before death and no ECMO treatment was recruited from the institutional file of the ICU (2012-2016). Medical records were reviewed. The study was approved by the Mayo Clinic Rochester Institutional Review Board (No. 14-0093).

Pathologic Examination

Hematoxylin and eosin-stained slides of the lungs of all cases were reviewed by a thoracic pathologist (A. C. R.) blinded to clinical information to characterize the histologic findings. Selected cases were stained with Verhoeff-van Gieson (n = 8) and/or Congo red (n = 1).

Statistical Analysis

Noncontinuous variables were compared using Pearson χ^2 test or Fisher exact (two-sided) test, and continuous variables were compared using the nonparametric Mann-Whitney *U* test. Continuous variables were presented as median values and interquartile ranges (IQRs) (25%-75%). Univariate and multivariate logistic regression models were used to identify predictive factors of each histopathologic finding. The covariates, which were statistically significant in the univariate analysis, were then included in the multivariate analysis; the OR with its 95% CI was assessed for each factor. All statistical analyses were conducted using SPSS 22.0 (IBM SPSS). *P* values of < .05 were considered statistically significant.

Results

Study Population

Seventy-six patients (38 men, 50%) with a median age of 40 years (range, 3 days-77 years) at time of death between 1998 and 2015 were included. Patient's major underlying diseases which were also the indications for ECMO and likely cause of death are presented in Table 1. Cardiac disease, pulmonary disease, and noncardiac, nonpulmonary disease comprised 77.6% (n = 59), 21.1% (n = 16), and 1.3% (n = 1) of all patients, respectively. We classified study cases into groups with ECMO for cardiac reasons (n = 60), which included patients with cardiac disease (n = 59) and hypothermia (n = 1), and ECMO for pulmonary reasons (n = 16). Sixty-four of 76 (84.2%) patients underwent VA ECMO, eight (10.5%) underwent VV ECMO, and four (5.3%) underwent both VA and VV ECMO. All 60 patients who underwent ECMO for cardiac reasons received VA ECMO. Median duration of ECMO treatment was 5.5 days (range, < 1-199 days; IQR, 2.3-11.0 days). Median time from weaning from ECMO to death was < 1 day (range, < 1-135 days; IQR, < 1-6.8 days).

General ECMO Management Practices

In general, the pediatric patients treated with ECMO in this study were managed with pediatric CentriMag centrifugal pumps (Thoratec) with polymethylpentene oxygenators, whereas the adult patients in this study were generally managed with a mix of CentriMag centrifugal pumps and CARDIOHELP centrifugal pumps (Maquet), both with polymethylpentene oxygenators. The general anticoagulation approach included predominantly heparin-based anticoagulation (and a minority of patients treated with direct thrombin inhibitors) with goal anticoagulation targets of aPTT of 60 to 80 seconds.

Histopathologic Findings in Patients Treated With ECMO

Pulmonary hemorrhage and acute lung injury were most commonly observed and occurred in more than one-half of the patients (63.2% and 60.5%, respectively).