10. Streszczenie w języku angielskim

Abstract

Introduction

ECMO (Extracorporeal Membrane Oxygenation) is a technique of extracorporeal blood oxygenation, which employs an extracorporeal system comprising a pump and an oxygenator, allowing for the temporary replacement of lung and/or heart functions. Although the use of ECMO does not directly treat the failing organ, it provides valuable time necessary for its regeneration. ECMO is increasingly used as an additional treatment method for patients in cardiogenic shock, with severe heart failure, or pulmonary dysfunction, when standard therapy proves insufficient. Due to the specific nature of the therapy, it may be associated with the risk of severe and potentially life-threatening complications. Proper patient selection is crucial for treatment success. It is essential to consider the initial clinical condition, the likelihood of regeneration of the damaged organ (heart or lungs), the possibility of transplantation, or transition to another method of long-term support. According to the current guidelines of the European Society of Cardiology on the treatment of acute and chronic heart failure, ECMO therapy should be considered (recommendation class IIa) for patients in cardiogenic shock, at the lowest level of evidence (C), which means consensus of experts. This indicates the need for further research on the efficacy and potential complications of ECMO therapy. Scientific evidence on the use of VA ECMO is limited and mainly based on retrospective studies, making the optimal timing of mechanical circulatory support, including ECMO, in patients with cardiogenic shock a subject of expert discussion.

Most information on ECMO therapy comes from population studies conducted in Western European and North American countries. The differences in healthcare organization and budgets are undeniable, necessitating a separate verification of the epidemiology and treatment outcomes of patients in cardiogenic shock, especially in the context of such costly and advanced therapy as VA-ECMO, for the populations of Central and Eastern Europe. The use of ECMO therapy should be considered in several aspects:

- Evaluating treatment outcomes within the Polish population and comparing these results with those from institutions in Western Europe and the United States.

- Identification of risk factors for in-hospital and long-term mortality.
- Evaluation of the optimal timing for the application of VA-ECMO during the therapeutic management of cardiogenic shock.

Objectives

The objectives of the doctoral thesis align with the aims of three publications forming a series of studies focused on the application of VA-ECMO therapy in patients with cardiogenic shock. They include:

- Evaluating the indications for VA-ECMO therapy, identifying risk factors for in-hospital and long-term mortality, and outcomes of VA-ECMO therapy in patients with cardiogenic shock based on the experiences of the National Institute of Cardiology from 2013-2018 (publication number 1,2,3).
- Assessing organ complications and their impact on the treatment outcomes of patients undergoing VA-ECMO therapy (publication number 1,2,3).
- Evaluating the outcomes of VA-ECMO application in specific patient groups:
    1. Patients after cardiac surgery (publication number 1,2,3)
    2. Patients with cardiogenic shock not undergoing surgical treatment (publication number 1,2)
    3. Patients post-heart transplantation with acute graftt failure (publication number 1).
- Assessing the risk factors of VA-ECMO therapy, including the analysis of the impact of arterial oxygenation during VA-ECMO support on patient mortality (publication number 2).
- Evaluating the possibilities of early risk stratification in patients supported by VA-ECMO, including the assessment of the prognostic value of postoperative troponin T concentration in patients supported by veno-arterial ECMO due to post-cardiotomy cardiogenic shock (publication number 3).
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Methodology

This is a single-center retrospective analysis conducted as a clinical study at the National Institute of Cardiology (number 2.33/VI/18) carried out in the years 2018-2021. The study population included all patients treated with ECMO at the National Institute of Cardiology between 2013-2018. Inclusion criteria were: veno-arterial ECMO support for cardiorespiratory failure during cardiogenic shock, age over 18 years, and availability of complete medical documentation. The research material consisted of clinical data, laboratory parameters, echocardiographic findings, descriptions of surgical procedures performed, pharmacotherapy applied, and data regarding the course of support and complications during treatment. The data were collected into a database, which was subjected to statistical analysis.

In publication number 1, the application of veno-arterial ECMO therapy in 198 patients of the National Institute of Cardiology between 2013-2018 was analyzed. Risk factors for in-hospital and distant mortality (12 months after VA-ECMO implantation) were assessed. The outcomes of VA-ECMO application in specific patient groups were evaluated, distinguishing patients after cardiac surgery, those with decompensated circulation not undergoing surgical treatment, and patients after heart transplantation with acute graft failure.

Various risk factors for mortality in patients supported by ECMO were assessed among organ complications (publication 1) and by evaluating therapy side effects, such as arterial hyperoxia (publication number 2). In publication number 2, patients were divided into tertiles (T) based on the median value of arterial blood partial oxygen pressure (PaO2) during VA-ECMO support.

The search for prognostic survival factors was also conducted through the evaluation of the biomarker, troponin T, in patients with post-cardiotomy cardiogenic shock supported by VA-ECMO. A detailed analysis of troponin T concentrations within 24–48 hours post-surgery, 24–48 hours after VA-ECMO implantation, and peak troponin T values was presented in publication number 3. The relationship of Troponin values measured at specific time intervals was analyzed in the context of the possibility of ECMO weaning, as well as mortality after 90 days and one year post ECMO implantation.

Statistical analysis

The analysis of variables was conducted using IBM SPSS Statistics 27 software. Depending on the topic of the issue being developed, analyses were performed:

- In groups across three stages: before ECMO, during ECMO support, and after ECMO (publication 1).
- Based on the etiology of heart failure (post-cardiotomy shock or cardiogenic shock without prior surgical intervention) (Publication 1,2,3).
- After dividing into tertiles (T) based on the median value of arterial blood partial oxygen pressure (PaO2) during ECMO support (Publication 2).

Categorical variables were presented as numbers and percentages and analyzed using Pearson's chi-square test for binary comparisons, Cochran-Mantel-Haenszel test for categorical variables not related to time-to-event, and Cochran-Armitage test for trend analysis across three levels of PaO2. Continuous variables were expressed as median and interquartile range (IQR) according to their distribution and analyzed using Mann-Whitney U test or Wilcoxon rank sum test (for two-level classification) and Kruskal-Wallis test or one-way ANOVA (for three-level classification) with Bonferroni correction for multiple comparisons. To assess the impact of specific variables on in-hospital and long-term mortality, univariate and multivariate logistic regression analysis was conducted. The fit of multivariate models was assessed using the C-Harrell index. Cumulative survival curves for the one-year observation were created using the Kaplan-Meier method. Surgical and non-surgical groups were compared using the log-rank test. Statistical significance was set at a level of 0.05 for the hypotheses tested.

Results

In the conducted study, detailed information on the application of VA-ECMO therapy in 198 patients at the National Institute of Cardiology was collected, as thoroughly described in publication number 1. Data concerning 179 patients were presented in publication number 2, while the analysis included in publication number 3 covered 102 patients. At the time of publication, publication number 1 constituted the most extensive single-center retrospective analysis documenting the use of VA-ECMO in the therapy of cardiogenic shock in the Central and Eastern European region.

As described in publication number 1, the median duration of VA ECMO support was 207 (IQR 91-339) hours, with no significant difference between patients who survived hospital treatment and those who died in the hospital (P = 0.09). 40.4% died during VA-ECMO support, while in-hospital and six-month mortality increased to 65.2%, and annual mortality to 67.2%. Nearly every tenth patient supported by VA ECMO (9%) underwent heart transplantation afterwards. The main adverse events that occurred were bleeding (76%), infections (56%), acute neurological episodes (15%), and lower limb ischemia (15%). Multiorgan failure was the most decisive risk factor for in-hospital mortality (OR 4.45, P<0.001). Patients with post-cardiotomy cardiogenic shock had a significantly lower rate of post-hospital survival than the non-surgical group (32.3% vs. 45%, log rank P = 0.037).

Publication number 2 demonstrated a possible association between arterial hyperoxygenation and increased total mortality in the population of patients treated with VA-ECMO. The median PaO2 during VA-ECMO was 122 mmHg (Q1–Q3: 111–158) and was significantly higher in patients who died within the 90-day observation compared to those who survived (134 (Q1–Q3: 114–175) vs. 114 (Q1–Q3: 109–136); P<0.001. At all analyzed time points after VA-ECMO implantation (in-hospital mortality, 90-day, and one-year), mortality increased with the rise in PaO2 tertile. The lowest mortality rates were observed in patients with a median PaO2 value ≤114 mmHg (T1), while patients with a median PaO2 ≥145 mmHg (T3) had the highest mortality rates. Multivariable analysis showed that T3 PaO2 is an independent predictor of reduced 90-day survival compared to T1 (p<0.001) and T2 (p = 0.002). Multivariate Cox regression analyses for in-hospital, 90-day, and annual mortality showed a significant association of T3 compared to T2 and T1 with mortality at all endpoints.

Publication number 3 presented the results of an analysis exploring the relationship between troponin T levels post-VA-ECMO implantation and short-term and long-term (up to 1 year post-VA-ECMO implantation) mortality in a subgroup of patients with post-cardiotomy cardiogenic shock after cardiac surgery (N=102). Troponin T levels measured between 24 to 48 hours post-cardiac surgery, 24 to 48 hours post-VA-ECMO implantation, and the peak troponin T value during ECMO support were analyzed. No statistically significant association was found between the examined troponin T values and mortality during VA-ECMO support, after 90 days, and one year post-VA-ECMO support. Multivariate

analysis models did not reveal any correlation between troponin levels and studied demographic and clinical features, such as age, urgency of the procedure, pre-operative left ventricular ejection fraction, or the duration of VA-ECMO, among others. Acute kidney failure requiring hemodiafiltration was identified as the strongest risk factor for mortality [HR 2.4].

Conclusions:

Based on the series of three studies, the following coherent conclusions can be drawn for the analyzed group:

1. The mortality rate of patients in cardiogenic shock supported by VA-ECMO remains high during support (40.4%), after 6 months (65.2%), and after one year (67.2%). This indicates the critical condition of patients qualified for VA-ECMO therapy and the therapy's limitations in improving long-term survival.

2. Patients with post-cardiotomy shock supported by VA-ECMO had a significantly lower rate of post-hospital survival compared to the non-surgical group (32.3% vs. 45%, log rank P = 0.037).

3. The median duration of VA-ECMO did not significantly differ between patients who survived hospital treatment and those who died, suggesting that the length of therapy was not directly related to treatment outcomes.

4. VA-ECMO plays a significant role as a bridge therapy – nearly one in ten patients from the studied group (9%) underwent heart transplantation after the period of circulatory support using VA-ECMO.

5. VA-ECMO therapy is associated with a high frequency of serious adverse events: bleeding and infections.

6. Multiorgan failure is a significant risk factor for in-hospital mortality, suggesting the search for the optimal timing for ECMO support implantation before the occurrence of organ complications in cardiogenic shock.

7. Arterial hyperoxygenation during VA-ECMO therapy is associated with significantly higher short-term and long-term mortality, emphasizing the need for precise monitoring

of oxygen supplementation and control of partial oxygen pressure levels in patients in this group.

8. Isolated early release of Troponin T and peak Troponin T levels had limited early prognostic value in the context of VA-ECMO therapy outcomes in patients with post-cardiotomy shock.

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