Stroke During Extracorporeal Membrane Oxygenation: Timing, Risk Factors and Clinical Outcomes

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Research

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Abstract

Background Among various complications of extracorporeal membrane oxygenation (ECMO), stroke continues to be a major factor that worsens the clinical outcome because it is associated with mortality and adverse neurologic outcomes. Appropriate risk evaluation, screening, and management of neurologic injury under ECMO support has not yet been established and requires further investigation. Thus, this study analyzes the stroke related risk factors and outcomes in order to determine the appropriate intervention to minimize neurologic sequalae while on ECMO.

Method Total 1039 patients who underwent ECMO from January 2012 to September 2019 at the Samsung Medical Center were reviewed and 759 subjects were selected for the analysis. The exclusion criteria were age < 18y, failure of successful ECMO initiation, multiple ECMO runs, underlying severe brain injury, and incomplete medical records. Multivariate analysis was performed to identify the risk factors of strokes on ECMO support using cox proportional hazard regression. In order to analyze the timing of stroke after ECMO initiation, the Mann–Whitney U test and Kruskal–Wallis rank sum test were performed.

Results Among The overall incidence of stroke was 5.1% (n = 39) without a significant difference between venoarterial (VA) and venovenous(VV) ECMO (5.3% and 4.8%, respectively, $p = 0.480$). Independent risk factors for stroke were intraaortic balloon pump (IABP, $p = 0.0008$) and a history of stroke ($p = 0.0354$). Most hypoxic brain injuries were found in the VA ECMO (93.3%), and 54.5% of intracranial hemorrhage were in the VV ECMO. Most patients with strokes (61.5%) were diagnosed within 72hours after ECMO initiation. The time taken for stroke event from the time of ECMO insertion was shorter in the VA ECMO than in the VV ECMO (median 1.5 vs. 3 days). The stroke group had a higher mortality rate than the non-stroke group (64.1% and 44.7%, respectively, $p = 0.014$).

Conclusion Concurrent ECMO and IABP use may increase the incidence of stroke during ECMO support. Evaluation for stroke that includes CT within 72 hours of ECMO insertion may enable early diagnosis, allowing timely intervention.

Background

Extracorporeal membrane oxygenation (ECMO) is widely accepted as a rescue therapy for failing heart or lung function in cases where the patient is unresponsive to conventional treatment methods. Even with its efficacy and advanced technology, the reported mortality rate in patients receiving ECMO is reported up to 75% [1] and > 10% of these patients develop neurologic complications [2]. Among the various complications of ECMO, stroke is a major factor that worsens the clinical outcome as it is related with mortality [3, 4] and adverse neurologic performance.

Stroke in ECMO can be classified into the following three subtypes: ischemic stroke (**Additional file 1**: Fig. 1**)**, hemorrhagic stroke (**Additional file 1**: Fig. 2**)**, and hypoxic brain injury (**Additional file 1**: Fig. 3**)**. Each type of stroke differs in pathophysiology; however, few studies have conducted a comprehensive analysis of the types of stroke and their predictor. Moreover, the timing of stroke after ECMO initiation is not well established and requires further investigation. In this regard, this manuscript documents the incidence of each type of stroke and explores the possible contributing factors, with a review of the previously known risk factors. Instead of a specific or stratified population, all ECMO patients were reviewed in order to compare the incidence and presentation of stroke as per the cannulation type. Using the above-mentioned analysis, our findings suggest the optimal strategy for prevention and early detection of stroke during ECMO.

Methods

Study Population and Definitions

The medical records of all 1039 patients who underwent ECMO insertion from January 2012 to September 2019 at the Samsung Medical center were analyzed. Patients aged < 18y or those who underwent multiple ECMO sessions were excluded from the study. Moreover, patients with failure of ECMO insertion were excluded.

Stroke was identified using image finding corresponding to stroke (either hemorrhagic or ischemic) or an assessment by the neurologists at the time. Hypoxic brain injury (HBI), either found on radiologic findings or EEG, was also categorized as stroke. In the case of brain death, the preceding event was reviewed and considered as stroke if the stroke was the triggering factor or the main contributor to brain death.

The study planned to analyze the strokes resulting from ECMO insertion; therefore, stroke caused by distinct underlying mechanisms were excluded, such as rupture of a known aneurysm. Patients with underlying brain lesions were excluded (e.g., brain abscess or meningioma). In a similar manner, stroke that occurred before ECMO insertion were not considered as stroke unless there was further aggravation of neurologic complications or abnormal neurologic signs were noted after ECMO insertion. Strokes occurring after ECMO removal were recorded as strokes only if they were found within 48 hours and if the stroke was diagnosed 2 days after ECMO removal, and the patient was classified into the non-stroke group. This is because patients undergoing ECMO are mostly sedated and diagnosis may be delayed. After applying medical reasons for exclusion, for statistical perfection, 30 patients with incomplete data were intentionally excluded and 759 patients were analyzed.

Stroke was classified into the following three categories: HBI, ischemic stroke, and hemorrhagic stroke. If ischemic stroke showed hemorrhagic transformation, it was categorized as an ischemic stroke only. Several patients could be classified into > 2 categories; therefore, a comparison could be made only between the VA and VV ECMO groups. Brain hemorrhage due to trauma was not included in the hemorrhagic stroke category.

Statistical Analyses

In the primary analysis, the stroke (n = 39) and non-stroke groups (n = 720). For the univariate analysis, categorical variables were analyzed using the chi-square and continuous variables were assessed with the Student T-test, Mann–Whitney U test, or ANOVA. Variables with a p value < 0.1 were included in the multivariate analysis. Multivariate analysis was performed to identify the risk factors of strokes on ECMO support using cox proportional hazard regression. Here, death was set as a competing risk. For stroke subtype, other stroke subtypes were set as the competing risk. In order to analyze the timing of stroke after ECMO initiation, the Mann–Whitney U test and Kruskal–Wallis rank sum test were performed. All the statistical analyses were executed using either SAS version 9.4 or R 3.6.3.

Results

Patient Characteristics and Stroke Incidence

Of the 1039 patients who received ECMO, 759 met the inclusion criteria (**Additional file 1: Fig. 4)**. The clinical characteristics of the 759 patients have been shown in **Additional file 2: eTable 1)**. The average patient age was 56.57 ± 15.74 y, 34% (n = 258) of study population comprised of women. Baseline lactic acid and creatinine levels before ECMO insertion were high (6.36 ± 5.21, and 1.62 ± 1.66, respectively). The average platelet count was within the normal range but showed considerable variation (260.1 k ± 168.74). The main reasons for ECMO initiation were cardiopulmonary arrest (47.8%, n = 363), followed by cardiogenic shock (22.8%, n = 173), and respiratory failure (22.4%, n = 170). Of these 759 patients, 570 (75.1%) underwent VA ECMO, and 189 (24.9%) received VV ECMO insertion. There were 303 extracorporeal cardiopulmonary resuscitation (ECPR) cases (39.9%) and the stroke incidence in ECPR group was 6%. The overall incidence of stroke was 5.1% (n = 39) and there was no significant difference between the VA and VV ECMO groups (5.3% and 4.8%, p = 0.480).

Outcomes of ECMO and timing of the stroke

The ECMO-related complications in our institution have been detailed in **Additional file 2: eTable 2**. Bleeding from the ECMO site or the gastrointestinal tract were found in approximately 10% of the patients (11.2% and 10.1%) and there was no significant difference between the stroke and non-stroke groups. Culture-proven infection after ECMO initiation was reported by 10.1% of all the patients. Stroke group showed a higher prevalence of infection (17.9%, $p = 0.089$); however, the difference was not statistically significant. The overall in-hospital mortality of ECMO at our institution was 45.7% ($n = 347$) and the stroke group had a higher mortality rate than the non-stroke group (64.1% vs. 44.7%, $p = 0.014$). The mortality rate as per stroke subtype was 73.33% for HBI, 52.63% for ischemic stroke, and 63.64% for hemorrhagic stroke (**Additional file 2: eTable 3)**. The mortality in the non-stroke group (44.72%) was lower than that in all the stroke groups.

Of the total stroke cases, 61.5% strokes occurred within 72 hours of ECMO insertion (Fig. 1). The median day of the stroke was the second day following ECMO initiation (interquartile range, 1.0–10.0) in total stoke patients. The median days for each ECMO type were 1.0 day in ECPR, 3.0 days in non-ECPR VA ECMO, and 3.0 days in VV ECMO. ECMO support days were longer in the VV ECMO ($p = 0.000$) (**Additional file 1: Fig. 5)** and the average time taken for the stroke event from the time of ECMO insertion was shorter in VA ECMO ($p = 0.1425$) (Fig. 2).

Predictors of stroke

Multivariate analysis revealed that the risk factor for stroke was IABP (hazard ratio, 4.36 [95% CI, 1.84–10.35]; $p = 0.0008$) and history of cerebrovascular accident (hazard ratio, 2.736 [95% CI, 1.07–6.99]; $p = 0.0354$) (Table 1). Moreover, IABP was associated with HBI (hazard ratio, 5.146 [95% CI, 1.65–16.10]; $p = 0.0048$), while ECPR itself was not a significant contributing factor ($p = 0.3326$) (**Additional file 2: eTable 4)**. The incidence of stroke was 15% in IABP and VA ECMO, while it was 4.5% and 4.76% for VA ECMO without IABP and VV ECMO group, respectively ($p = 0.0147$) (Fig. 3). In cases of intracranial hemorrhage, IABP [hazard ratio, 7.144 (95% CI, 2.06–24.79); $p = 0.0019$] and female sex[hazard ratio, 5.04 (95% CI, 1.39–18.27); $p = 0.0138$] was suggested as independent risk factors (**Additional file 2: eTable 5)**. Univariate analysis was performed in order to identify the differences in the stroke incidence by subtype. Most cases of hypoxic brain injury developed in the VA ECMO group(93.3%, $p = 0.058$) and 54.5% of the intracranial hemorrhage cases in the VV ECMO ($p = 0.008$).

Table 1
Predictors of Stroke While on Extracorporeal Membrane Oxygenation

Variables	Univariable Competing risk Analysis					Multivariable Competing risk Analysis ($p < 0.1$ from univariate analysis)				
	Chi-Square	p-value	Hazard Ratio			Chi-Square	p-value	Hazard Ratio		
Age	0.0058	0.9391	0.999	[0.981	1.018]					
Platelet(k/ul)	0.5465	0.4598	0.999	[0.997	1.001]					
VV ECMO	1.4042	0.2360	0.64	[0.306	1.339]					
IABP	10.3489	**0.0013**	4.079	[1.732	9.606]	11.155	**0.0008**	4.361	[1.838	10.348]
ECPR	2.2961	0.1297	1.614	[0.869	2.998]					
Female Sex	0.5582	0.4550	1.277	[0.672	2.426]					
Malignancy	0.9212	0.3372	0.653	[0.274	1.558]					
Diabetes	0.0708	0.7901	1.096	[0.557	2.157]					
Hypertension	0.1719	0.6785	0.869	[0.449	1.684]					
Dyslipidemia	2.496	0.1141	1.989	[0.848	4.667]					
Smoking	2.0669	0.1505	0.61	[0.31	1.197]					
CKD	0.2067	0.6493	1.268	[0.455	3.533]					
PAOD	0.0333	0.8552	0.829	[0.111	6.205]					
CVA History	3.5603	**0.0592**	2.484	[0.965	6.394]	4.4278	**0.0354**	2.736	[1.071	6.987]
MI history	0.0677	0.7948	0.883	[0.346	2.253]					
PCI history	2.0293	0.1543	1.678	[0.823	3.42]					
CRRT	1.1227	0.2893	1.421	[0.742	2.719]					
Mechanical Ventilation	0.5981	0.4393	0.738	[0.342	1.594]					

VV = venovenous, *IABP* intraaortic balloon pump, *ECPR* extracorporeal cardiopulmonary resuscitation, *CKD* chronic kidney disease, *PAOD* peripheral artery occlusive disease, *CVA* cerebrovascular accident, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CRRT* continuous renal replacement therapy

Discussion

IABP and ECMO

The combined use of IABP and ECMO is suggested to help by decompressing the left ventricle; however, the clinical outcome of IABP with ECMO remains unclear. Some studies report decreased mortality with the concomitant use of ECMO and IABP [5–7]; however, conflicting views are constantly being raised [8, 9]. A meta-analysis by Vallabhajosyula et al. and Cheng et al. reported no significant difference in the mortality when IABP was used with

ECMO. In Vallabhajosyula's study, subgroup analysis showed that acute myocardial infarction (AMI) group showed improved survival rate than the non-IABP ECMO group. However, Park et al. reported contradictory results as per which the combined use of ECLS and IABP did not improve survival in AMI patients [10]. In the current study population, the mortality in the IABP and non-IABP group was similar (45.0% vs. 45.8%, $p = 0.529$). We found a significantly increased risk of stroke in patients with ECMO and IABP.

When heart is unable to maintain optimal systemic circulation, VA ECMO replaces its role via retrograde flow. However, when the balloon is dilated in the diastole of the cardiac cycle, the retrograde flow of the oxygenated blood from the ECMO to the ascending aorta and the brain would be reduced by the inflated balloon in the descending thoracic aorta, potentially causing comparative hypoperfusion in the brain [11]. An animal experiment with pig model supports this idea in that the femoro-femoral VA ECMO combined with IABP showed significant decrease in both the coronary and carotid flow by IABP [12]. Our study result is in agreement with these studies in that IABP is related to a higher incidence of stroke and was a risk factor of HBI in subgroup analysis. Furthermore, as suggested by Tay et al. [11], retrograde flow of ECMO passing around the catheter of IABP may cause thromboembolism and embolic stroke. Although there is no established evidence for adverse outcomes of IABP use, the risks and benefits of IABP use should be considered carefully. The effect of an IABP on the macrocirculation and microcirculation remains debatable [13–15]. Therefore, actual measurement in a human model in future studies would enable a better understand of the hemodynamics and the clinical benefit of ECMO with IABP.

Stroke in VV and VA ECMO

One important variable that is often neglected in ECMO study is ECMO time until stroke occurrence. Based on our study findings, the time until stroke from the time of ECMO insertion was significantly different between the ECMO types: the median days for stroke accident were 1.5 days for VA ECMO (interquartile range, 1, 5.75) and 3.0 days for VV ECMO (interquartile range, 2, 20). When compared among the three groups, ECPR, non-ECPR VA, and VV ECMO, the duration was much shorter for ECPR : median 1 day for ECPR (interquartile range 0.5, 4.5, 3 days for non-ECPR VA(interquartile range 1, 9.5), and 3 days for VV(interquartile range 2, 20). Considering that 48.3% of stroke cases in VA ECMO patient were owing to HBI, prolonged CPR, or pre-ECMO hypoxic condition may have contributed to early manifestation of stroke. For VV ECMO, > 50% of the stroke cases were associated to intracranial hemorrhage and took longer time for diagnosis. This suggests that predicting stroke time and specific stroke type in certain types of ECMO may help medical practitioners be ready for possible upcoming complications and if possible, prevent, or attenuate adverse outcome. Lockie et al. demonstrated that early detection of intracranial hemorrhage with initial brain CT screening results in the prompt modification of anticoagulation and improved survival rate [16, 17]. In this study, the brain image was taken within 6 hours of ECMO insertion and anticoagulation was withheld until image interpretation. However, this approach may not be feasible in patients owing to unstable patient condition. Moreover, the benefit of withholding anticoagulation until image confirmation should be weighed cautiously, considering the risk of circuit thrombosis. Based on our study data, the median days of stroke accident was the second day after ECMO initiation, and 61.5% of the strokes occurred within 72 hours of ECMO insertion. Thus, CT scanning of the brain after 3 days of ECMO insertion can detect > 50% of stroke cases. Considering that many patients undergoing ECMO are sedated and stroke diagnosis is delayed, adoption of brain CT screening at a designated date after ECMO initiation may help early detection of stroke.

Neurologic complication rates and outcomes can vary substantially, depending on the etiology, subtype, and clinical management; however, studies mention the overall incidence without mentioning the subtypes. Ischemic stroke and intracranial hemorrhage have been relatively well documented in ECMO patients; however, HBI remains poorly understood in the adult population. Recent studies by Sutter et al. and Migdady et al. [18] mention the subtypes of

stroke, including HBI; however, they only mention the incidence. In this regard, our study intended to investigate each type of stroke, documenting the risk factors and mortality data. Based on the present results, ischemic stroke and HBI were dominant types of stroke in the VA ECMO group, and intracranial hemorrhage in the VV ECMO group. In-hospital mortality was highest for HBI, reaching 73.33% at discharge. Considering that ECPR was not associated with the occurrence of HBI in the multivariate analysis, the underlying physical condition or clinical intervention, especially IABP, may be more closely associated with HBI. Previous studies have shown that stroke while on ECMO is associated with a higher mortality rate [2, 19]. Data from our institution corresponds with previous results, with the mortality in the stroke group being 64.1% and that in the non-stroke group being 44.7% ($p = 0.014$). As shown in our data, stroke in ECMO is variable and may be affected by various clinical conditions. In order to improve the clinical outcome of ECMO, further studies are needed to identify high-risk patients and establish sophisticated treatment guidelines.

Strengths and limitations

Our study is valuable in the following aspects. Although several studies have mentioned ECMO support time or the factors associated risk factors and time to stroke from ECMO insertion are rarely mentioned. Furthermore, very few trials have performed comprehensive subtype analysis of stroke, including HBI in the adult population with all ECMO types. Many studies with a large database or meta-analysis include data from the 1900s; however, our data are from 2012 to 2019, reflecting recent advancement and experience in ECMO treatment. In addition, to our knowledge, this is the first and only study to perform a comprehensive comparison of the ECMO patients as per the cannulation type and stroke types at a single center. However, the following limitations of our study should be considered. As a single center study, the sample size was relatively small and was exposed to selection bias. Owing to the smaller number of cases, statistical analysis with subtypes and multivariate analysis for ischemic stroke may not be accurate or meaningful. Strict categorization could have led to an underestimation of the stroke incidence; treatment was discontinued in several patients, and no further diagnostic test was performed. Our study is also limited by its retrospective nature in terms of bias and causality. Future studies with a prospective design and larger sample may overcome these limitations.

Conclusion

Concurrent ECMO and IABP use may contribute to a higher incidence of stroke during ECMO support. For hemodynamic support, the use of other cardiac devices or the development of new mechanical circulatory support devices may improve the clinical outcome. Most strokes occur within 72 hours of ECMO initiation; therefore, any concerns regarding the neurologic status should be thoroughly investigated, using a brain CT scan. Further studies are necessary to define the associated risk factors of stroke and contribute toward the development of the ideal treatment protocol.

Abbreviations

VA
venoarterial
VV
venovenous
ECMO
Extracorporeal Membrane Oxygenation
ECPR
Extracorporeal Cardiopulmonary Resuscitation

IABP
intraaortic balloon pump
HBI
hypoxic brain injury
AMI
acute myocardial infarction

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Samsung Medical Center (approval number: SMC 2020-07-074). Patients' records were reviewed and published according to the Declaration of Helsinki. Informed consent was waived because of the retrospective nature of this study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

No individual participant data is reported that would require consent to publish from the participant (or legal parent or guardian for children).

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' Contributions

H Kim contributed to writing the manuscript. JH Yang and CR Chung helped compile clinical data and analyze cases appropriate for studies. K Jeon helped with analysis and interpretation of data. GY Suh provided critical feedback and helped with literature review. S Chung and K Sung helped devise study design and construct supporting details. YH Cho supervised the project and took lead in developing main ideas and thoroughly reviewing the main manuscript.

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Figures

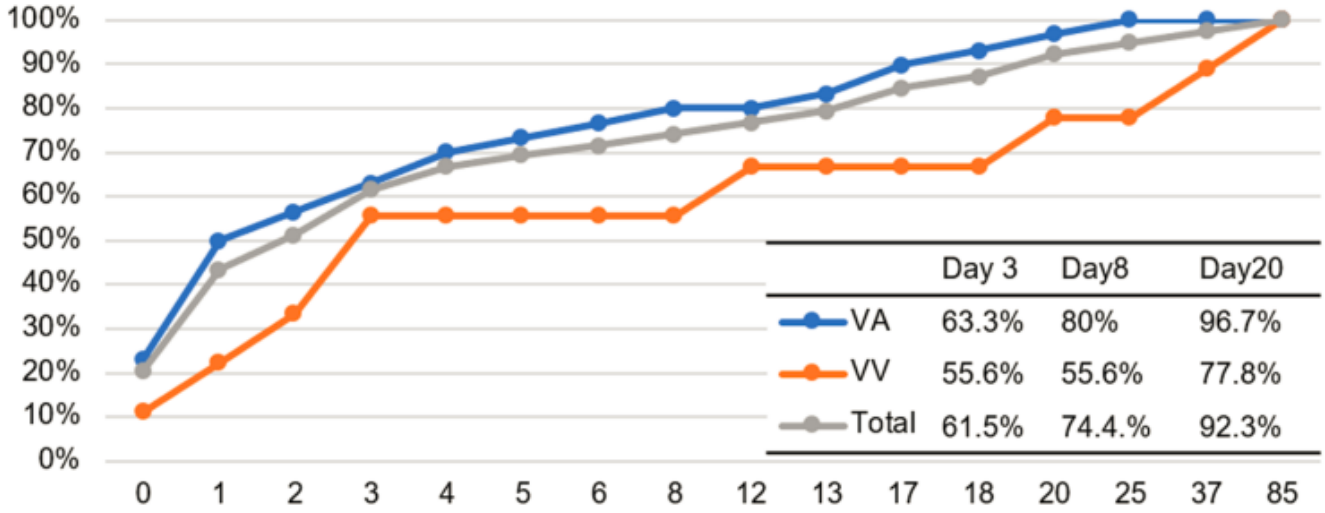

Figure 1

Cumulative Stroke Incidence from Extracorporeal Membrane Oxygenation insertion Of the total stroke cases, 61.5% strokes occurred within 72 hours of ECMO insertion. It took comparatively shorter time from ECMO insertion to stroke in VA ECMO, 80% being diagnosed within 8 days after ECMO initiation. For VV ECMO, it took more than 20 days until 80% of stroke was diagnosed. VA venoarterial, VV venovenous

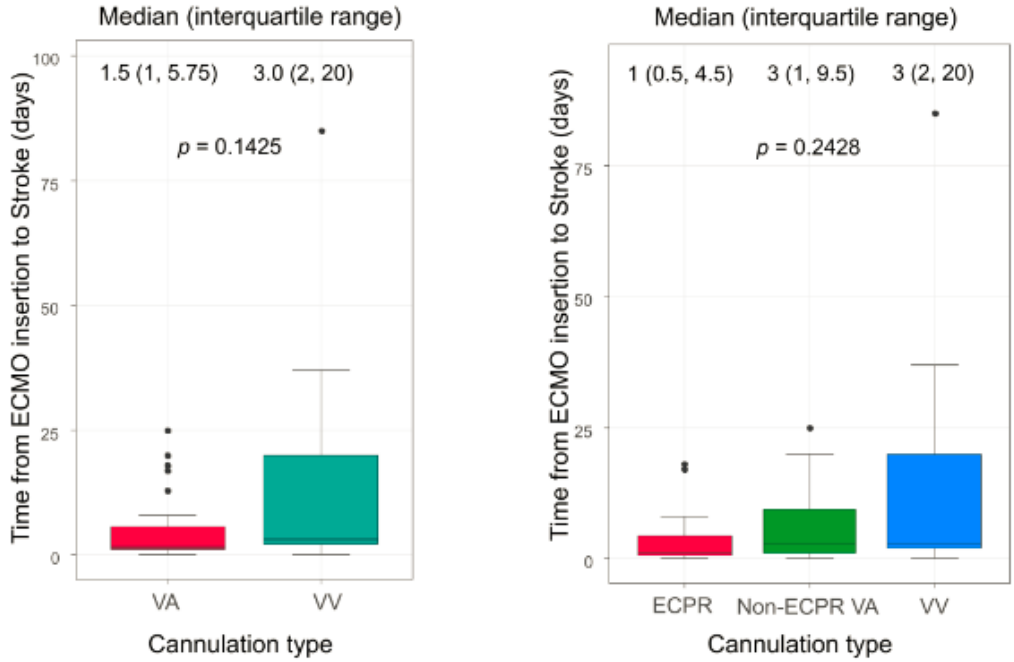

Figure 2

ECMO insertion to stroke time by cannulation type The time until stroke from the time of ECMO insertion was significantly different between the ECMO types: the median days for stroke accident were 1.5 days for VA ECMO (interquartile range, 1, 5.75) and 3.0 days for VV ECMO (interquartile range, 2, 20). When compared among the three groups, ECPR, non-ECPR VA, and VV ECMO, the duration was much shorter for ECPR : median 1 day for ECPR (interquartile range 0.5, 4.5, 3 days for non-ECPR VA(interquartile range 1, 9.5), and 3 days for VV(interquartile range 2, 20). VA venoarterial, VV venovenous, ECMO Extracorporeal Membrane Oxygenation, ECPR Extracorporeal Cardiopulmonary Resuscitation

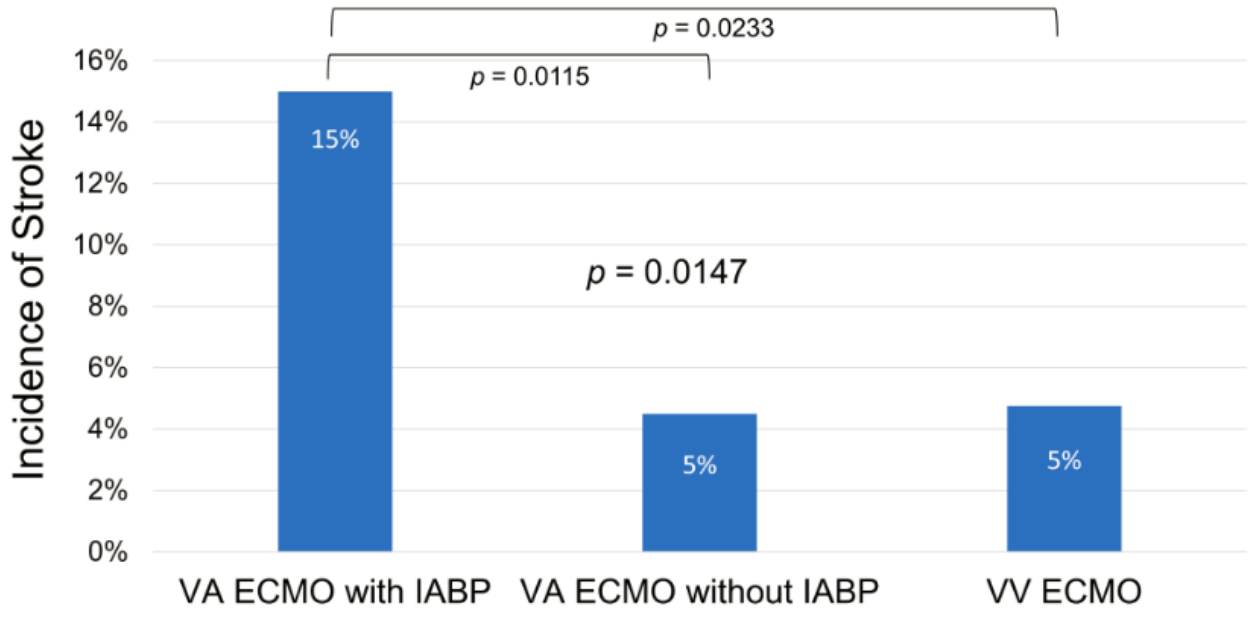

Figure 3

Incidence of Stroke depending on intraaortic balloon pump use The incidence of stroke was 15% in IABP and VA ECMO, while it was 4.5% and 4.76% for VA ECMO without IABP and VV ECMO group, respectively (p = 0.0147). VA venoarterial, VV venovenous, ECMO Extracorporeal Membrane Oxygenation, IABP intraaortic balloon pump

Supplementary Files

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