Importance of Pulse Pressure after Extracorporeal Cardiopulmonary Resuscitation

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Abstract

Background: Recent reports have revealed better clinical outcomes for extracorporeal cardiopulmonary resuscitation (ECPR) than conventional cardiopulmonary resuscitation (CPR).

In this retrospective study, we attempted to identify predictors associated with successful weaning off extracorporeal membrane oxygenation (ECMO) support after ECPR.

Methods: The demographic and clinical data of 30 ECPR patients aged over 18 years treated between August 2016 and January 2019 were analyzed. All clinical data were retrospectively collected. The primary endpoint was successful weaning from ECMO support after ECPR. Patients were divided into two groups based on successful or unsuccessful weaning off ECMO support (Weaned (n=14) vs. Failed (n=16)).

Results: Univariate logistic regression analysis showed that age, CPR duration, ECMO complications, and loss of pulse pressure significantly predicted the results of weaning off ECMO support. However, multivariate logistic regression analysis showed that only CPR duration and loss of pulse pressure independently predicted unsuccessful weaning from ECMO support.

Conclusion: We conclude that long CPR duration and loss of pulse pressure after ECPR predict unsuccessful weaning from ECMO. However, unlike CPR duration, loss of pulse pressure during post-ECPR was related to subsequent management. In patients with reduced pulse pressure after ECPR, careful management is warranted because this reduction is closely associated with unsuccessful weaning off ECMO support after ECPR.

Introduction

The benefits of extracorporeal cardiopulmonary resuscitation (ECPR) remain an area of debate. Furthermore, studies on optimal patient selection and timing of extracorporeal membrane oxygenation (ECMO) application for patients with cardiac arrest are lacking. Nevertheless, ECMO has recently emerged as a major treatment modality for patients with refractory cardiac arrest.[1-4] A small number of researches have reported favorable predictors for successful ECPR,[5-8] but their results were based on comparisons of variables before and when ECMO was applied.

Post-ECPR care factors, for example, ECMO maintenance, left heart decompression, and hypothermia, are equally important.[9, 10] The pulse pressure on arterial waveform after ECMO initiation decreases because preload decreases while the afterload increases.[11] Furthermore, post-cardiac arrest myocardial dysfunction affects pulse pressure after ECPR.[12] Lack of pulse pressure can lead to left ventricle (LV) dilation, myocardial injury, pulmonary edema, and development of LV thrombosis and systemic embolization. Previous reports suggested that pulsatile ECMO, which may provide physiologic pulsatile pressure, is more beneficial than non-pulsatile ECMO in terms of clinical outcomes.[13-15] Sustained pulse pressure after ECPR may better maintain physiologic hemodynamic status like as pulsatile ECMO.

The purpose of this study was to identify predictors associated with successful weaning off ECMO support after ECPR, that involve post-ECPR care as well as pre- and intra-ECPR variables. We hypothesized that some post-ECPR variables would be associated with clinical outcomes.

Materials and Methods

Patients and definitions

Initially, we enrolled 32 patients (aged > 18 years) that underwent ECPR at our institute between August 2016 and January 2019. However, two patients were excluded due to failure of return to spontaneous circulation. The demographic and clinical data of the 30 patients were retrospectively collected from our institutional computerized clinical database. This study was approved by the institutional ethics committee/review board of Gil Medical Center (Institutional Review Board No. GAIRB2019-209).

The primary endpoint was successful weaning from ECMO after ECPR. Procedure duration was defined as time between heparin administration and start of ECMO perfusion. Procedure complications included those related to peripheral cannulation and chest compression, such as bleeding, hemothorax, and pneumothorax. ECMO complications included leg ischemia, gastrointestinal bleeding, pulmonary edema, and abrupt ECMO flow disturbance. Loss of pulse pressure was defined as a pulse wave of arterial monitoring that persists less than 15mmHg for over 6 hours within 24 hours after ECPR. Given that no consensus for definition of pulse pressure (pulsatility), we decided pulsatility by referring to "Extracorporeal Life Support: The ELSO Red Book 5th edition" and a previous report.[16,17] Arterial monitoring was performed using a radial or brachial artery. Mortality was defined as in-hospital death. Therapeutic hypothermia was induced using Arctic Sun® (Bard Medical, Covington, USA) at a core body temperature target of 33 within 6-8 hours after the return of spontaneous circulation (pulse). Core temperature was monitored using a rectal probe and hypothermia maintained for 12-24 hours. Subsequently, rewarming was performed at 0.3 per hour to 36.5, and then normothermia was maintained at this temperature for three days. Neurologic sequelae were defined as the absence of recovery of cognitive function and neurologic status to those before CPR.

ECMO procedure

Two operators performed ECMO insertion to patients during CPR in our institute. Arterial (15 and 17Fr, Bio-medicus, Medtronic Inc. MN, USA) and venous (20, 22, and 24Fr Edwards Lifescience Inc., Irvine, CA, USA) cannula were inserted through a femoral artery and vein by the percutaneous Seldinger technique without ultrasonographic or fluoroscopic guidance. Heparin was administered immediately before cannulation at 50 IU/kg and continuously infused after ECPR, and activated prothrombin time was maintained between 1.3-1.8 times normal range. Two types of ECMO consoles were used (Capiox Emergency bypass system; Terumo Inc., Tokyo, Japan, and Permanent Life Support; Maquet Cardiopulmonary AG, Rastatt, Germany). Left heart decompression was achieved using a left atrial catheter (22, and 24Fr Edwards Lifescience Inc., Irvine, CA, USA) via percutaneous atrial septostomy through a femoral vein. When leg ischemia was confirmed, distal perfusion was achieved by inserting a 16 gauge central venous catheter (ARROW/Teleflex, Wayne, USA) into a superficial femoral artery; the catheter was then attached to the side port of the return cannula. "Awake ECMO" was attempted without mechanical ventilation support when a patient could spontaneously maintain breathing. In some patients, where the mean arterial blood pressure (MAP) or pulse pressure could not be maintained during ECMO support, inotropes such as dobutamine, and isoproterenol were administered. MAP was controlled according to patient perfusion status after checking lactate level – usually, target MAP ranged from 60-80 mmHg. When MAP could not be maintained in the target range despite full ECMO support, inotrope infusion was initiated. At this time, either isoproterenol or dobutamine was chosen if pulse pressure had disappeared along with decline in MAP. On the other hand, if pulse pressure was maintained, vasopressors such as norepinephrine or vasopressin were initiated. Weaning off ECMO was commenced when cardiac function improvement was confirmed by transthoracic echocardiography. A reduction in ECMO flow by 50 % was attempted for more than 30 minutes if hemodynamic stability was maintained. Optimized inotropic support was considered for patients exhibiting a fall in MAP of more than 10 mmHg during the 50% ECMO support period. Because the blood in the ECMO circuit was discarded, two units of packed red blood cells were transfused into all patients when ECMO was weaned.

Statistical analysis

Patients were divided into two groups based on the success of weaning off ECMO support (Weaned vs.

Failed). Non-normally distributed continuous variables were compared using the Mann-Whitney U test, and categorical variables using the Chi-square and Fisher's exact tests. Continuous data are presented as medians (interquartile ranges 25%-75%), and categorical data as numbers and fractions (%). Potential risk factors of the primary endpoint were identified by multivariate logistic regression analysis. One multivariate logistic regression analysis model was constructed using variables found to be associated with successful weaning by univariate logistic regression analysis, and the other model included variables affected to clinical outcomes in addition to these factors of univariate logistic regression (Table 3, figure 1). All p-values given are two-sided and p-values of < 0.05 were considered to indicate significance. SPSS version 22.0 (Korean version; IBM Corporation, USA) was used for the analysis.

Results

Baseline characteristics

Patient characteristics related to ECPR are summarized in table 1. Patients in the weaned group were significantly younger than those in the failed group ($p = 0.03$) and had a shorter CPR duration ($p < 0.01$). Arterial blood gas analysis showed that pH and lactate levels at pre-ECPR were no different in the two groups, but that these levels of post-ECPR and on hospital day 1 improved more in the weaned group. Etiologies are described in table 1. The most common cause of cardiac arrest was acute myocardial infarction (AMI). Revascularization with percutaneous coronary intervention (PCI) was performed in 14 of the 18 AMI patients. Three patients received ECPR after PCI due to cardiac arrest within an hour of the procedure, and eleven AMI patients were treated by PCI after ECPR. Median time between ECMO initiation and PCI was one hour (interquartile range -0.5 – 2.0). Other etiologies included cardiac arrest from cardiac tamponade after cardiac surgery, dilated cardiomyopathy, tricyclic antidepressant intoxication, aluminum phosphide intoxication and severe aortic stenosis. Six AMI patients suffered cardiac arrest with ventricular tachycardia (VT).

Clinical outcomes

ECMO associated factors, such as procedure duration, type of ECMO, size of cannula, left heart decompression, and distal perfusion, were not significantly different in the two groups (Table 2). Awake ECMO was applied to seven of the 14 patients in the weaned group. Loss of pulse pressure was more common in the failed group ($p < 0.01$).

Three patients in the weaned group died due to recurrent AMI, biliary sepsis from cholecystitis, or pneumonia after heart transplantation. Left heart decompression was performed for two patients with loss of pulse pressure in the weaned group because of pulmonary edema aggravation. Pulse pressure in these two patients recovered at 24 and 48 hours post-ECPR, respectively.

Predictors of successful weaning off ECMO support after ECPR

Univariate logistic regression was used to detect variables that affect successful weaning off ECMO support (Table 3). Age, CPR duration, ECMO complications, and loss of pulse pressure were identified as risk factors. Two models were designed for multivariate logistic regression analysis (Figure 1). One model consisted of only four variables, which were significantly identified by univariate logistic regression analysis. The other model included variables of out-of-hospital cardiac arrest (OHCA), left heart decompression, and procedure complications in addition to these four variables. Loss of pulse pressure and long CPR duration remained independent predictive factors of unsuccessfully weaning from ECMO after ECPR according to both models (Figure 1).

Subgroup analysis

Subgroup analysis between the two groups with respect to loss of pulse pressure and left heart decompression was performed because pulse pressure plays an important role in LV decompression (Table 4). Left heart decompression did not benefit weaning off ECMO support by subgroup analysis in patients with loss of pulse

pressure (28.6% vs. 16.7%, p = 0.46). Nevertheless, pulse pressure importantly affected successful weaning off ECMO support in patients that did not undergo left heart decompression (16.7% vs. 100%, p < 0.01).

A comparison of patients with or without pulse pressure showed only four of 19 patients with loss of pulse pressure were successfully weaned off ECMO support, whereas weaning was successful in ten of eleven patients with pulse pressure (21.0% vs. 90.9, p < 0.01, Figure 2). The most common cause of death among those that could not be weaned off ECMO support was multiple organ failure. Of the 19 patients with loss of pulse pressure, six lost the pulse pressure immediately after ECMO initiation, and only one of these six was successfully weaned off ECMO support. The reason for cardiac arrest in this one survivor was fulminant myocarditis, and in this patient, left heart decompression by left atrial venting was performed. Three of the remaining 13 patients that lost pulse pressure could wean off ECMO support. Cardiac arrest in these three patients was caused by variant angina, respiratory cardiac arrest, and VT from Brugada syndrome, respectively.

Eighteen patients suffered AMI and 14 of these were offered revascularization. Of these 14 patients, seven lost pulse pressure and could not be weaned off ECMO support. Six of the seven that maintained pulse pressure could be successfully weaned. The four patients that did not undergo revascularization lost pulse pressure and one of these patients was successfully weaned off ECMO.

Discussion

Extracorporeal life support has been proposed as an emerging rescue therapy in cases of refractory cardiac arrest. The Extracorporeal Life Support Organization (ELSO, Ann Arbor, MI, USA) and the American Heart Association (AHA, Dallas, TX, USA) also recommend that ECPR should be considered in selected patients.[18-21] Previous studies have reported that in-hospital cardiac arrest (IHCA), duration of pre-ECPR resuscitation, and etiology of cardiac arrest are prognostic factors.[22] Several studies related to post-ECPR care focused on improving neurologic outcomes.[8-10, 23] This present study was the first study that investigated predictive factors for successful weaning off ECMO support by analyzing parameters of pre-, intra-, and post-ECPR.

Long CPR duration and loss of pulse pressure were identified as independent risk factors of unsuccessful weaning off ECMO support after ECPR. Previous studies have demonstrated that shorter low-flow time increases survival rate after ECPR in both IHCA and OHCA,[5, 6] and our results confirmed the risk of unsuccessful weaning off ECMO support after ECPR.[5-10, 22]

We consider that loss of pulse pressure after ECPR is a risk factor worth emphasizing. In patients that lost pulse pressure after ECPR, the probability of successful weaning off ECMO support was reduced. In fact, loss of pulse pressure was the only prognostic factor related to post-ECPR management. Although pulse pressure may disappear due to severe impairment of the LV after ECPR, and a non-contractile LV can dilate and lead to pulmonary edema or LV thrombosis. Even when full support of ECMO is provided, blood supplied from the bronchial artery, pulmonary and coronary circulations can cause left heart dilation leading to left ventricular myocardium injury. LV dilation also increases myocardial oxygen consumption and delays cardiac restoration particularly in the setting of AMI,[24] and this might form a vicious cycle due to aggravation of loss of pulse pressure by LV injury.

Furthermore, substantial enhancement of intravenous volume is required to maintain full ECMO support as pulmonary edema and hemorrhage could reduce intravascular volume. In addition, systemic ischemia and reperfusion response after resumption of spontaneous circulation from cardiac arrest cause systemic inflammatory response of the immune system and coagulation.[25] Clinical manifestations of this include intravascular volume depletion, impaired vasoregulation and impaired oxygen delivery. The first priority for hemodynamic stabilization after CPR is the optimization of right-heart filling pressures using intravenous fluids.[23, 25] Furthermore, intravenous volume replacement after ECPR may greater than that required after CPR because extracorporeal circulation could exacerbate systemic inflammatory responses and intravascular volume depletion. Also, loss of pulse pressure might lead to excessive volume replacement to maintain ECMO

flow, which aggravates the systemic inflammatory responses. Our findings indicate that loss of pulse pressure after ECPR might trigger this vicious cycle. This hypothesis might explain that loss of pulse pressure is an unfavorable factor for weaning off ECMO support after ECPR.

Post-cardiac arrest myocardial dysfunction also contributes to loss of pulse pressure. Due to the small sample size, this study could not distinguish a bias that weaning off ECMO support was unsuccessful, because myocardial dysfunction of patients with loss of pulse pressure was more severe. Nevertheless, the study does demonstrate that patients with loss of pulse pressure after ECPR should receive more careful monitoring and management to facilitate successfully weaning off ECMO support. Although our subgroup analysis did not show left heart decompression had a significant effect, left heart decompression, such as LA venting and Impella (Abiomed, Danvers, MA), might help reduce injury caused by LV dilation and pulmonary edema.[23, 26-28] At our center, left heart decompression is performed when pulmonary edema was aggravated after ECPR regardless of pulse pressure. Furthermore, we infuse inotropes related to heart rate, such as isoproterenol and dobutamine, to patients with reduced pulse pressure to help maintain pulse pressure. Temporary pacing might help maintain pulse pressure as well. Reducing the afterload burden of ECMO may also have an important contributory effect to maintain pulse pressure. When pulse pressure is lost, full ECMO support may be necessary to maintain organ perfusion, and when satisfactory, probably increases the likelihood of patient recovery.

According to several studies conducted on pulsatile ECMO model, pulsatile ECMO generates more hemodynamic energy than nonpulsatile ECMO and improves clinical outcomes.[13, 14] Previous reports have demonstrated that pulsatile flow reduces systemic vascular resistance and hypothyroidism and improves catecholamine response, gastrointestinal perfusion, myocardial blood flow, and clinical outcomes.[29-34] Although physiologies associated with pulsatile extracorporeal circulation and the maintenance of pulse pressure cannot be directly compared, conceptually maintaining pulse pressure would appear to have a positive effect on successfully weaning off ECMO support after ECPR. Although continuous-flow left ventricular assist devices (CFVAD) are now the most widely used because they are smaller, more reliable, and more durable than pulsatile-flow left ventricular assist devices (PFVAD), there is research that PFVAD might have potential advantages due to natural physiology.[35] Maintenance of pulse pressure after ECPR should be considered for successful weaning off ECMO after ECPR like as the physiology of pulsatile ECMO or PFVAD.

Limitations

Several limitations of the present study warrant mention. First, the study was inherently limited by its observational retrospective design. Second, the number of cases analyzed was small, and this may have introduced bias. Third, unsuccessful weaning off ECMO support in patient without pulse pressure could not be clearly explained because pulse pressure may have been influenced by degree of remaining myocardial function after CPR. Furthermore, successful revascularization of AMI may have affected cardiac function recovery and be related to pulse pressure and successful weaning off ECMO support. We attempted subgroup analysis to minimize bias, but the small sample size prevented meaningful analysis. Nevertheless, our finding indicate that patients with the loss of pulse pressure immediately after ECPR are unlikely to be successfully weaned off ECMO support, and thus, we recommend that such patients require more careful management after ECPR. Forth, no clear definition of pulse pressure is avalable, and thus we defined it by adopting the definition provided in "Extracorporeal Life Support: The ELSO Red Book 5th edition" and used in previous report.[16,17] In future, consensus should be determined for pulse pressure. Finally, because high dose vasopressor induced peripheral artery spasms, pulse pressure measurements at peripheral arteries, such as radial artery, may have an error.

Conclusion

Long CPR duration and loss of pulse pressure after ECPR predict failure to wean successfully off ECMO support. Patients that lose pulse pressure after ECPR require more careful monitoring and management because loss of pulse pressure may be modifiable in some patients. Large-scale randomized studies are needed to confirm that pulse pressure after ECPR importantly predicts successful weaning off ECMO support.

Conflict of interest

The authors have no conflicts of interest to declare.

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Figure 1. Multivariate analysis results for variables associated with successful weaning off extracorporeal membrane oxygenation (ECMO) support after extracorporeal cardiopulmonary resuscitation. Loss of pulse pressure and longer cardiopulmonary resuscitation duration were identified as significant risk factors of unsuccessful weaning off ECMO support using both models.

CI; confidence interval, CPR; cardiopulmonary resuscitation, ECMO; extracorporeal membrane oxygenation

Figure 2. Subgroup analysis of the effect of loss of pulse pressure on successful weaning off extracorporeal membrane oxygenation (ECMO) support. More patients in failed group than in weaned group exhibited loss of pulse pressure (n= 15 vs. 4, $p < 0.01$).

CI; confidence interval, ECMO; extracorporeal membrane oxygenation

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