Satisfactory outcome with activated clotting time <160 seconds in extracorporeal cardiopulmonary resuscitation

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Abstract

Patients undergoing cardiopulmonary resuscitation (CPR) prior to extracorporeal membrane oxygenation (ECMO) can have severely altered physiology, including that of the coagulation pathway. This could complicate the extracorporeal cardiopulmonary resuscitation (ECPR) management. We aimed to show that targeting an activated clotting time (ACT) < 160 seconds does not affect the complication rates in these patients. In this single-centered retrospective study, the medical records of 81 adult patients who were on ECMO support from March 2017 to March 2020 were reviewed. We compared the low ACT and conventional ACT groups, which were defined on the basis of the median of the ACT values of the included patients (160 seconds). The primary outcomes included bleeding or thromboembolic events. This study included 32 patients, who were divided into the low (n = 14) and conventional (n = 18) ACT groups. There were 2 cases of gastrointestinal bleeding (P = .183), one of intracranial hemorrhage (P = .437), and one of peripheral skin color change (P = .437) in the low ACT group. There was one case of prolonged bleeding at the cannulation site (P = 1.000) reported in the conventional ACT group. The successful weaning rate differed significantly between the low and conventional ACT groups (92.9% vs 50.0%; P = .019). Maintaining the ACT lower than the conventional ACT in patients requiring ECPR did not show a significant increase in the thromboembolic risk. Therefore, targeting a low ACT should be considered for this particular group of patients.

Abbreviations: ACT = activated clotting time, A-ECMO = venoarterial-extracorporeal membrane oxygenation, aPTT = activated partial thromboplastin time, CKD = chronic kidney disease, CPR = cardiopulmonary resuscitation, CVA = cerebrovascular accident, ECMO = extracorporeal membrane oxygenation, ECPR = extracorporeal cardiopulmonary resuscitation, ELSO = Extracorporeal Life Support Organization, FH = unfractionated heparin, GI = gastrointestinal, ICH = intracranial hemorrhage, PCI = percutaneous coronary intervention, VV-ECMO = veno-venous extracorporeal membrane oxygenation.

Keywords: activated clotting time, anticoagulation, complication, extracorporeal cardiopulmonary resuscitation, extracorporeal circulation, outcome

1. Introduction

Extracorporeal membrane oxygenation (ECMO) serves as a supportive treatment that is increasingly being used for patients with critical respiratory and circulatory failure. The indications for this treatment are also expanding; ECMO is used to aid in resuscitating patients with refractory cardiac arrest and referred to as extracorporeal cardiopulmonary resuscitation (ECPR). This type of support incorporates venoarterial-extracorporeal membrane oxygenation (VA-ECMO) during CPR. As the rate of utilization is increasing, the Extracorporeal Life Support Organization (ELSO) has proposed an ECPR addendum form for additional data collection.\textsuperscript{1,2}

Although many studies have reported improved survival rate and good neurological outcomes, whether ECPR is superior to conventional CPR remains controversial.\textsuperscript{1,3–5} The ELSO registry international report showed a survival to discharge rate of 29% in the adult ECPR group.\textsuperscript{2} Among the common adverse events occurring during ECMO support, bleeding and thrombosis are the most common and are associated with a significant increase in mortality.\textsuperscript{1,6} Anticoagulation is a crucial part of ECMO management that prevents the occurrence of thrombosis in the circuit, pulmonary vessels, and heart chambers, and microthrombi and fibrin deposition in the end organs.\textsuperscript{7,8} In the context of ECPR, the physiology of patients is severely deranged prior to ECMO support, which makes it difficult to maintain the fine balance between bleeding and thrombosis.

Unfractionated heparin (UFH) remains the mainstay of continuous anticoagulation therapy despite its drawbacks. The activated clotting time (ACT) and activated partial thromboplastin
time (aPTT) are the most commonly used measures to monitor heparin activity. Although therapeutic anticoagulation during ECMO is defined as an ACT of 180 to 220 seconds, the guidelines vary across different centers. Many studies have reported heparin dose titration outside the target range in cases of major bleeding or thromboembolism, resulting in favorable outcomes. Additionally, a satisfactory outcome with low ACT was reported. Therefore, we hypothesized that low ACT would show satisfactory results with fewer side effects than conventional ACT, and the purpose of this study is to investigate the safety and outcomes of maintaining an ACT target (<160 seconds) lower than the conventional ACT target (180–200 seconds) during ECPR support.

2. Methods

The data were retrospectively collected from electronic medical records. Patients aged > 18 years who received ECMO support from March 2017 to March 2020 were initially included. Out of 81 patients, 51 underwent ECPR. Nineteen patients were excluded for the following reasons: veno-venous ECMO (VV-ECMO) support (n = 4), pulmonary embolism as the cause of arrest (n = 2), ECMO support duration < 24 h (n = 9), and non-availability of ACT data (only aPTT was monitored; n = 4) (Fig. 1). Finally, the data of 32 patients were analyzed in this study.

Cannula size was chosen according to the weight of the patient and diameter of the vessels as identified using ultrasound. The venous cannula was inserted into the common femoral vein, and the arterial cannula was inserted into the common femoral artery due to limited vascular access during manual chest compression. The 19–23 Fr venous (draining) and femoral vein, and the arterial cannula was inserted into the common femoral artery due to limited vascular access during manual chest compression. The 19–23 Fr venous (draining) and 17–19 Fr perfusion (outflow) cannulas were used. The percutaneous Seldinger technique, with or without ultrasound guidance, was the preferred method. Lower leg perfusion through a distal-perfusion catheter was performed after the return of spontaneous circulation.

We used 2 different sets of ECMO circuits. One circuit comprised a poly-methyl-pentene membrane oxygenator (PLS Quadrox, Maquet Cardiopulmonary, Hirrlingen, Germany), a centrifugal pump (Rotaflow, Maquet Cardiopulmonary, Hirrlingen, Germany), and recombinant human albumin and heparin-coated tubes (Bioline, Maquet Cardiopulmonary, Hirrlingen, Germany). The other circuit comprised a poly-methyl-pentene membrane oxygenator (Terumo CAPIOX EBS, Japan), a centrifugal pump (SL 45, Terumo CAPIOX EBS, Japan), and biocompatible hydrophilic polymer surface-coated tubes (Xcoating, Terumo, Japan).

During cannulation, a heparin bolus (30–50 units/kg body weight) was administered at the discretion of the attending surgeon. The ACT was measured at the bedside using the portable Hemochron 401 device (Hemochron, ITC Medical, Edison, NJ) with HRFTCA510 tubes. The circuit was then managed either with or without continuous intravenous UFH administration to maintain the target ACT according to the individual physiological status. If the initial ACT was >200 seconds due to CPR-related hypothermia, deteriorating coagulopathy, or previous intake of antiplatelet medications, such as ticagrelor, and there was development of cannulation site bleeding, mucosal bleeding, or bloody nasogastric tube drains, the UFH infusion was not initiated until the resolution of these conditions. A low ACT (<160 seconds) was maintained unless the oxygenator showed a visible clot or if left ventricular thrombus or spontaneous echo contrast was observed on echocardiography. An ACT point-of-care test was performed every hour until stabilization, followed by testing every 2 to 4 hours. In addition to ACT, laboratory measures, such as aPTT (measured every 6 hours), fibrinogen, d-dimer, and antithrombin III levels, were also monitored on a daily basis. We did not routinely perform thromboelastography or antifactor Xa assay. The circuit was routinely checked for any visible clot formation. Plasma-free hemoglobin levels were monitored, and postoxygenator blood gas analysis was performed to assess the efficacy of the oxygenator. The oxygenator was changed if the postoxygenator blood gas results were inadequate or if gross hematuria or a clot > 5 mm in size on the infusion side of the circuit was detected in the oxygenator. The target ACT range varied according to the patient’s condition and the physician’s preference (target ACT: 130–200 seconds). The patients were divided into 2 groups for comparison, a low ACT group and a conventional ACT group, based on a cutoff ACT of 160 seconds. We used the median ACT observed on day 2 of ECMO when the intravenous UFH dose had been titrated and the ACT had stabilized within the desired range. The blood products were transfused to reach a target hemoglobin concentration > 9.0 g/dL, platelet count > 50,000/mm³, international normalized ratio < 1.5, and fibrinogen concentration > 200 mg/dL. The primary outcomes were thromboembolism and bleeding, and the secondary outcomes were the rates of successful weaning from ECMO support and survival to discharge. This study was approved by the Korea University Ansan Hospital Institutional Review Board (IRB 2020AS0094). The requirement for patient consent was waived owing to the retrospective design of the study.

3. Statistical analysis

Continuous variables are expressed as medians and interquartile ranges or means and standard deviations. The descriptive statistics are expressed as numbers and percentages. The categorical variables were compared using the chi-square test or Fisher exact test and continuous variables using student t-test or the Mann-Whitney U-test. The results were considered statistically significant for P-values < 0.05. Statistical Product and Service Solutions, version 18.0 (SPSS Inc., Chicago, IL), was used for data analysis.
4. Results

This study included 32 patients. There were 14 patients in the low ACT group and 18 patients in the conventional ACT group. The median ACT of all patients was 164 seconds (131–221 seconds). The median ACT was 155 seconds (131–159 seconds) in the low ACT group and 171.5 seconds (163–221 seconds) in the conventional group ($P < .001$) (Fig. 2).

There were no significant differences in the baseline characteristics of the 2 groups before ECPR (Table 1). Male patients were predominant in both groups. Comorbidities reported in the study sample included dyslipidemia (most common), hypertension, diabetes mellitus, chronic kidney disease (CKD), history of percutaneous coronary intervention (PCI), and history of cerebrovascular accident (CVA). The major cause of cardiac arrests was acute myocardial infarction (84.4%). Other causes included septic shock, exacerbation of heart failure, myocarditis, and electrolyte imbalance in a patient with CKD.

Table 2 shows the ECPR-related parameters in each group. The median duration of ECPR support in the low and conventional ACT groups was 7.6 days (1.0 to 22.9 days) and 7.8 days (1.2 to 39.6 days), respectively ($P = .779$). The ratio of the use of PLS and EBS company machines was similar between the low ACT and conventional ACT groups (5:9 vs 7:11; $P = 1.000$). Additionally, the average flow rates were similar between the low ACT and conventional ACT groups (2.95 ± 0.86 L/min vs 3.09 ± 0.92 L/min; $P = .670$).

Regarding ECMO-related bleeding and thromboembolic complications, the oxygenator exchange, peripheral color change, cannulation site bleeding or hematoma formation, gastrointestinal (GI) bleeding, and CVA (either ischemic or hemorrhagic) were assessed. Oxygenator exchange occurred in 3 and 6 patients of the low ACT and conventional ACT groups, respectively ($P = .760$). All oxygenators were electively replaced due to decreased oxygen exchange capability. A visible clot inside the circuit was not confirmed during daily observation in any patient. Bleeding or thromboembolic complications occurred in 4 patients in the low ACT group (peripheral skin color change, n = 1; GI bleeding, n = 2; and intracranial hemorrhage [ICH], n = 1) and in one patient in the conventional ACT group (femoral artery cannulation site) who was permitted voluntary movements before heart transplantation 19 days after ECMO.

Of the 14 patients in the low ACT group, 13 (92.9%) were weaned-off ECMO support, while 9 (64.3%) survived to discharge without further complications. Of the 18 patients in the conventional ACT group, 9 (50.0%) were successfully weaned-off from ECMO support and 7 (38.9%) survived to discharge. The weaning rate was significantly better in the low ACT group than in the conventional ACT group ($P = .019$), but the survival to discharge rate did not differ significantly between the 2 groups ($P = .285$).

Among the patients suspected with acute myocardial infarction and requiring coronary angiogram, 7 were treated with ticagrelor before or after the ECMO cannulation. Of these 7 patients, 3 belonged to the low ACT group and 4 to the conventional ACT group. One patient in the conventional ACT group did not require any anticoagulation therapy, but their ACT was maintained > 160 seconds.

5. Discussion

Optimal anticoagulation is critical for successful ECMO support as bleeding and thromboembolic complications are associated with increased mortality. Patients receiving ECPR support present with even more challenging conditions that affect the coagulation pathway, such as hypothermia, hypoxemia, acidosis, coagulation factor dysfunction, and cardiovascular instability.[16] Furthermore, the ECMO circuit itself may cause complications. An inflammatory cascade occurring during VA-ECMO could lead to thrombosis. The adverse effects of thrombosis include oxygenator failure, pump malfunction, hemolysis, and thromboembolic events (e.g., limb ischemia or stroke).

Table 1

| Baseline preextracorporeal cardiopulmonary resuscitation characteristics in the 2 groups. |
|----------------------------------|----------------------------------|------------------|
|                                   | Low ACT (n = 14)                 | Conventional ACT (n = 18) |
| Age (yr)                         | 55.4 ± 14.0                     | 59.1 ± 10.0       | 0.399 |
| Male (n, %)                      | 10 (71.4)                       | 13 (72.2)         | 1.000 |
| Comorbidities (n, %)             |                                 |                   |      |
| Hypertension                     | 8 (57.1)                        | 9 (50.0)          | 0.964 |
| DM                               | 7 (50.0)                        | 6 (33.3)          | 0.556 |
| CKD                              | 2 (14.3)                        | 2 (11.1)          | 1.000 |
| Dyslipidemia                     | 10 (71.4)                       | 11 (61.1)         | 0.712 |
| h/o PCI                          | 4 (28.6)                        | 6 (33.3)          | 1.000 |
| h/o CVA                          | 2 (14.3)                        | 2 (22.2)          | 0.672 |

ACT = activated clotting time, CKD = chronic kidney disease, CVA = cerebral vascular accident, DM = diabetes mellitus, PCI = percutaneous coronary intervention.
Improvements in the ECMO equipment, such as poly-methylpentene oxygenators, centrifugal pumps, and heparin coating, aid in reducing the incidence of thrombosis during and after heparin discontinuation. Heparin is extensively utilized because it is easily titratable and readily metabolized and has a relatively short half-life. Moreover, its effect can be reversed immediately using protamine. [15] With these improvements, systemic heparinization during ECMO can be reduced or stopped, and the use of subcutaneous low-molecular weight heparin (enoxaparin 40–80 mg/day) may be feasible. [10–14]

According to the ELSO guidelines, the therapeutic anticoagulation range is defined as an ACT of 180 to 220 seconds; however, there is no consensus on this. Technical improvements to reduce blood–biomaterial interaction have rapidly evolved, further contributing to heterogeneity in the protocols of different centers. [17] To the best of our knowledge, there are no randomized controlled studies of anticoagulation strategies in patients at a high risk of bleeding during ECMO. The guidelines suggest decreasing the anticoagulant infusion rate until the ACT is 1.4–1.5 times the normal range while managing bleeding during ECMO support. [9] The lack of clarity in the guidelines leads to surgeons refraining from maintaining relatively high ACT in patients with minor or major bleeding. According to a recent international survey, the target ACT for VA- and VV-ECMO ranged from 140 to 220 seconds. The majority of institutions used an ACT of 160–200 seconds. [9]

In this study, we report the safety and efficacy of lower than conventional ACT in patients receiving ECPR support. Although there were no significant differences regarding bleeding and thromboembolic complications between the 2 groups, it is worth noting that a patient in the low ACT group developed ICH during ECPR support, which is considered a major bleeding event. Furthermore, 2 patients developed GI bleeding (spontaneous oral and rectal bleeding and bleeding through the Levin tube). In all 3 cases, early development of such complications led to a target of low ACT or even normalization of the coagulation status by transfusing blood components. Even though the ACTs were maintained on the lower side, coagulopathy persisted in one of the 2 patients with GI bleeding, who even developed peripheral skin color change. No other major thromboembolic events, such as ischemic stroke, pulmonary thromboembolism, or mesenteric ischemia, were observed.

The oxygenator exchange rate was not significantly different between the 2 groups. Decreased oxygenation capability was inspected on a daily basis by postoxygenator blood gas analysis, and all exchange procedures were performed electively.

The rate of weaning from ECPR support was higher in the low ACT group than in the conventional ACT group, but the survival to discharge rate did not differ significantly between them. The majority of the patients who did not survive after weaning died from septic shock following multi-organ failure.

As mentioned above, heparin-coated circuits allow for the reduction or discontinuation of the anticoagulation infusion for some time, as long as the blood flow is maintained at a high rate (>3.0 L/min). [19] We believe that ECMO flow is also important in preventing thrombus formation in the oxygenator. In our study, the average flow rates were 3.0 ± 0.9 L/min and 3.1 ± 0.9 L/min in the low ACT and conventional ACT groups, respectively, without a significant difference (P = .670). If the ECMO flow decreases for even < 15 min, extensive thrombosis may develop in the 4 heart chambers, despite a high ACT (>170 seconds). [19]

At our center, we try to maintain adequate left ventricular contraction and a wide pulse pressure range to prevent intracardiac stagnation of blood and formation of thrombi. When the pulse pressure range is small and there is echocardiographic evidence of severe left ventricular dysfunction without opening of the aortic valve or spontaneous echogenic contrast in the left ventricle, we routinely perform left atrial venting using an 8-Fr Mullins sheath via the femoral vein. [19] [20–22]

The concept of maintaining ECMO in cases of multiple trauma with severe bleeding and ICH with a heparin-free or heparin-sparing strategy is evolving. [10,11,22,23] Currently, this concept has been accepted by most intensivists. However, there are only a few reports on the feasibility of low ACT during VA-ECMO. [13,15] ECPR is usually associated with hypothermia, metabolic acidosis-induced coagulopathy, antiplatelet medication (e.g., clopidogrel- or ticagrelor-induced platelet dysfunction) before PCI, and mechanical chest wall massage-induced bleeding (e.g., sternal or rib fracture or intrapericardial bleeding). Sometimes, it is accompanied by cannulation site bleeding, mucosal bleeding, and bloody nasogastric tube drains.

The strength of our study is that we showed that ECMO can be safely applied even in high-risk situations such as ECPR by applying low ACT. ECPR causes a variety of coagulation disorders, which poses many challenges to the use of anticoagulants. Although there are still no clear guidelines for this situation, our findings will help determine treatment options in the future.

This study has several limitations. First, it was a retrospective analysis of a relatively small sample at a single center. Second, because the oxygenator and cannula thrombus formation were assessed by gross inspection of the oxygenator from the outside, and microthrombi that did not influence oxygenator function

| Variables | Low ACT (n = 14) | Conventional ACT (n = 18) | P-value |
|-----------|----------------|--------------------------|---------|
| ECPR duration (d) | 7.6 (1.0–22.9) | 7.8 (1.2–29.6) | 0.779 |
| ECPR machine (PLS/EBS) (%) | 5 (35.7) | 9 (64.3) | 1.000 |
| Average flow rate (L/min) | 3.0 ± 0.9 | 3.1 ± 0.9 | 0.670 |
| Initial ACT (s) | 168 (123–315) | 212 (156–428) | 0.018 |
| Median ACT (s) | 155 (131–159) | 171.5 (163–221) | 0.001 |
| Successful weaning (%) | 13 (92.9) | 9 (50.0) | 0.019 |
| Survival to discharge (%) | 9 (64.3) | 7 (38.9) | 0.285 |
| ECPR-related complications | | | |
| Oxygenator exchange | 3 | 6 | 0.760 |
| Peripheral color change | 1 | 0 | 0.437 |
| Cannulation site bleeding | 0 | 1 | 1.000 |
| Gastrointestinal bleeding | 2 | 0 | 0.185 |
| CVA | 1 | 0 | 0.437 |
| Blood product transfusion (units) | | | |
| RBC | 14.50 ± 9.92 | 10.22 ± 7.06 | 0.164 |
| FFP | 5.5 (0–29) | 7.5 (2–21) | 0.587 |
| Platelets | 49.00 ± 48.08 | 41.06 ± 36.96 | 0.601 |

ACT = activated clotting time, CVA = cerebral vascular accident, ECPR = extracorporeal cardiopulmonary resuscitation, FFP = fresh frozen plasma, RBC = red blood cells.
may have gone unnoticed. Third, we did not compare other anticoagulation monitoring methods, such as aPTT analysis, thromboelastography, or antifactor Xa assay.

In conclusion, maintaining the ACT lower than the conventional ACT (<160 seconds) did not significantly increase the risk of thromboembolism, weaning failure, or mortality during ECPR management. A low ACT target should be considered for patients with ECPR support who are at a high risk of hemorrhagic complications. Further randomized controlled and multicenter studies are warranted to validate our study results.

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