

Brain natriuretic peptide levels predict 6-month mortality in patients with cardiogenic shock who were weaned off extracorporeal membrane oxygenation

Hyoung Soo Kim, MD, PhD^a, Kyu Jin Lee, MD^b, Sang Ook Ha, MD^c, Sang Jin Han, MD, PhD^d, Kyoung-Ha Park, MD, PhD^{d,*}, Sun Hee Lee, RN^a, Yong Il Hwang, MD, PhD^b, Seung Hun Jang, MD, PhD^b, Sunghoon Park, MD, PhD^{b,*}

Abstract

There are limited data regarding the association between brain natriuretic peptide (BNP) levels obtained after weaning from extracorporeal membrane oxygenation (ECMO) and the outcomes of patients with acute coronary syndrome (ACS)-associated cardiogenic shock.

We prospectively obtained data regarding patients (aged ≥ 19 years) with ACS-associated cardiogenic shock who received ECMO and were subsequently weaned off the treatment. BNP levels were collected at 5 time points: pre-ECMO implantation, post-ECMO implantation, pre-ECMO weaning, day 1 after ECMO weaning, and day 5 after ECMO weaning.

Of 48 patients with ACS-related cardiogenic shock, 33 were included in this analysis. Mean patient age was 59.0 (50.0–66.5) years, and 5 patients (15.2%) were women. Eight patients had asystole/pulseless electrical activity before ECMO and 14 (42.4%) had 3-vessel disease on coronary angiography. During the 6-month follow up, 12 (36.4%) patients died. BNP levels after ECMO weaning were significantly different between 6-month survivors and non-survivors. Cox proportional hazards model revealed that BNP levels (tertiles) on days 1 and 5 after ECMO weaning were significantly associated with 6-month mortality (hazard ratio, 7.872; 95% confidence interval, 1.870–32.756; 8.658 and 1.904–39.365, respectively). According to the Kaplan–Meier curves, the first tertile had significantly longer survival compared to the third tertile for both days 1 and 5 after ECMO weaning.

Post-ECMO weaning BNP levels (days 1 and 5) were significantly associated with increased 6-month mortality in patients with ACS complicated by refractory cardiogenic shock who were weaned off ECMO.

Abbreviations: AMI = acute myocardial infarction, ACS = acute coronary syndrome, BNP = brain natriuretic peptide, CRRT = continuous renal replacement therapy, ECMO = extracorporeal membrane oxygenation, ELSO = extracorporeal life support organization, LCX = left circumflex artery, MV = mechanical ventilation, SAVE = survival after veno-arterial ECMO, SOFA = sequential organ failure assessment, Tn-I = troponin I, VA = venoarterial.

Keywords: acute coronary syndrome, brain natriuretic hormone, cardiogenic shock, extracorporeal membrane oxygenation

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HSK, KJL are contributed to this study equally.

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

^a Department of Cardiothoracic surgery, ^b Department of Pulmonary, Allergy and Critical Care Medicine, ^c Department of Emergency Medicine, ^d Department of Cardiology, Hallym University Sacred Heart Hospital, Anyang, South Korea.

* Correspondence: Sunghoon Park, Department of Pulmonary, Allergy and Critical Care Medicine Hallym University Sacred Heart Hospital, 22 Gwanpyeong-ro, Anyang, 14068, South Korea (e-mail: f2000tj@gmail.com).

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1. Introduction

Although the development of pharmacological agents and mechanical revascularization has reduced mortality in patients with acute coronary syndrome (ACS),^[1,2] outcomes remain unsatisfactory when they are complicated by cardiogenic shock or cardiac arrest.^[1,2] Cardiogenic shock is a life-threatening condition that occurs when the heart cannot pump sufficient blood to vital organs, and is a primary cause of early death in patients with acute myocardial infarction (AMI).^[3] Therefore, early intervention during cardiogenic shock is important for protection of vital organs through restoration of blood flow.^[4]

A recent meta-analysis showed no effect of routine intra-aortic balloon pump support in patients with AMI-related cardiogenic shock.^[5] However, several medical devices with different features are currently available for cardiogenic shock, and extracorporeal membrane oxygenation (ECMO), with its technical advancements, has been widely used as salvage therapy (or a bridge-to-recovery approach) in experienced centers.^[6–8] ECMO is known to stabilize systemic circulation, ensure end-organ perfusion, and reduce preload in patients with cardiogenic shock.^[9]

Brain natriuretic peptide (BNP) is a cardiac neurohormone secreted from the ventricular myocardium in response to myocardial stretching and volume overload.^[10] Although this hormone has diagnostic and prognostic utility for heart failure,^[10,11] data regarding the role of BNP in patients with cardiogenic shock receiving ECMO are very limited. However, many studies have emphasized the importance of fluid balance in critically ill patients.^[12–15] We hypothesized that fluid balance might also be important for patients receiving ECMO for cardiogenic shock, and that BNP levels might play a role in those patients.

Therefore, in the present study, we investigated the association between BNP levels obtained after weaning from ECMO and outcomes of patients with ACS-associated cardiogenic shock.

2. Methods

2.1. Study population

We prospectively screened patients (aged ≥ 19 years) with ACS-associated cardiogenic shock who received ECMO as salvage treatment at Hallym University Sacred Heart Hospital from May 2018 to December 2019. Among these patients, those who were successfully weaned off ECMO treatment were enrolled in the study. The ethics committees of the Hallym University Institutional Review Board (approval no. 2018-05-033) approved this study. Informed consent was obtained from patients or their legal surrogates.

In accordance with current guidelines, ACS was diagnosed in patients with serum cardiac markers elevated to at least twice the upper reference limit plus the presence of ischemia-related symptoms lasting > 30 minutes or ischemic changes in ≥ 2 contiguous leads on 12-lead electrocardiogram (i.e., AMI); or in patients with ischemia-related symptoms, which were characterized by at least one of the following (i.e., unstable angina): occurrence at rest or during minimal exertion and typically lasting > 20 minutes, severe presentation (at least Canadian Cardiovascular Society Classification 3^[16]) and new-onset status (within the past 1 month), or occurrence with a crescendo pattern without increases in cardiac markers.^[17,18]

ECMO was indicated for patients with the following conditions:

- 1) refractory cardiogenic shock unresponsive to inotropes or a high-dose vasopressor infusion (norepinephrine $> 0.5 \mu\text{g}/\text{kg}/\text{minutes}$)
- 2) witnessed in-hospital or out-of-hospital cardiac arrest, unresponsive to standard advanced cardiac life support with CPR duration (defined as the interval from beginning CPR to return of spontaneous circulation) of > 10 minutes^[19,20]

Cardiogenic shock was defined as persistent hypotension (systolic blood pressure < 90 mm Hg) with a clinical manifestation of hypoperfusion. Patients with a do-not-resuscitate order, severe irreversible brain damage, or terminal malignancy were not indicated for ECMO. At our hospital, 1 interventional cardiologist, 1 cardiac surgeon, and 1 perfusionist remained in the hospital 24 hours per day; they were able to initiate ECMO immediately in the emergency department, cardiac catheterization laboratory, or coronary care unit.

Patients with the following conditions were excluded from the analysis: circulatory shock unrelated to ACS; other ECMO configurations, such as veno-arteriovenous (VAV) ECMO; and transfer to another hospital during treatment. Intra-aortic balloon pump placement was not routinely performed during the study period at our hospital.

2.2. EMCO implantation and management

We used Capiiox EBS (Terumo, Tokyo, Japan) or PLS (MAQUET, Hirrlingen, Germany) equipment. One femoral vein and 1 femoral artery (VA ECMO) were percutaneously cannulated using the Seldinger technique under fluoroscopic guidance. 17- to 19-Fr (for artery) and 21-Fr (for vein) cannulas were placed (DLP and Bio-Medicus, Medtronic, Minneapolis, MN; RMI, Edward's Life sciences LLC, Irvine, CA). Circulation through ECMO system was established with venous blood drainage from the right atrium and arterial blood return to the femoral artery. During ECMO support, mean arterial pressure was maintained at > 60 mm Hg and the target activated partial thromboplastin time (aPTT) was 60 to 80 s; heparin or nafamostat mesilate (SK Chemicals Life Science Biz., Seoul, Korea; licensed by Torii Pharmaceutical, Tokyo, Japan) was used for anticoagulation. The target hematocrit and platelet counts were $> 35\%$ and $> 50,000$ to $80,000/\text{mm}^3$, respectively. Patients received antithrombin III when the initial antithrombin III level was $< 70\%$, with a loading dose of 2,000 IU followed by a maintenance dose of 500 IU every 6 hours for 3 days. Continuous renal replacement therapy (CRRT) was commenced if a patient exhibited progressive oliguria (i.e., urine output $< 0.5 \text{cc}/\text{kg}/\text{h}$ for > 6 hours).

2.3. Weaning from EMCO

The criteria for ECMO weaning included hemodynamic stability, improvement of cardiac function on echocardiography (ejection fraction $> 30\%$), and normalized lactate levels. Pump flow was gradually tapered to 2 L/min, and sweep gas to 0 L/min; decannulation was indicated if the patient tolerated these settings for at least 2 hours.^[21] ECMO weaning was considered successful when the patient remained stable for 24 hours without ECMO support. Patients who succeeded in a second weaning although the first weaning attempt failed were also considered to be successfully weaned from ECMO. Weaning from mechanical ventilation (MV) was undertaken in accordance with the general recommendations.^[22]

2.4. Coronary interventions

After initiation of ECMO, diagnostic angiography was conducted by an interventional cardiologist unless asystole or pulseless electrical activity (PEA) persisted. Significant coronary artery disease was defined as a lumen diameter stenosis > 70% in a major coronary artery. Percutaneous coronary intervention was performed when thrombolysis in myocardial infarction (TIMI) flow of the ACS-related artery was < 3 or the diseased coronary artery was considered the culprit lesion. Successful angioplasty was defined as achievement of < 20% diameter stenosis with TIMI 3 flow.

2.5. Data collection and outcomes

The following data were obtained: demographic characteristics (age, sex, and body mass index); comorbidities; causes of cardiogenic shock; clinical situation before ECMO implantation (e.g., cardiogenic shock, ventricular fibrillation/ventricular tachycardia, and asystole/PEA); cardiopulmonary resuscitation before or during ECMO; severity-of-illness scores (Sequential Organ Failure Assessment [SOFA]^[23] and Survival After Venous-arterial ECMO [SAVE] scores^[24]) before ECMO implantation; BNP and troponin I (Tn-I) levels; and hospital outcomes. BNP and Tn-I levels were collected at 5 time points:

- 1) pre-ECMO implantation
- 2) post-ECMO implantation (i.e., day 1 after ECMO implantation)
- 3) pre-ECMO weaning
- 4) day 1 after ECMO weaning
- 5) day 5 after ECMO weaning

BNP levels were transformed into tertile variables for multivariate analysis. Serum BNP levels were measured using the microparticle enzyme immunoassay test (Abbott, Chicago, IL).

The primary outcome constituted the relationship between BNP level and 6-month mortality among patients who were weaned off ECMO. The secondary outcome comprised other risk factors for 6-month mortality in those patients.

2.6. Statistical analysis

All results are presented as numbers with percentages for categorical variables, and as medians with interquartile ranges for continuous variables. The Mann–Whitney *U* test or a repeated measure analysis of variance (ANOVA) was used to compare continuous variables, and the Chi-squared or Fisher exact test was employed to compare categorical variables. Cox proportional hazard method was performed using covariates significant (*P* < .10) in the univariable analysis to identify independent risk factors for hospital mortality; a stepwise backward method based on the likelihood ratio was used. Kaplan–Meier method with a log rank test was also used to estimate survival function. All probability values were 2-sided and a *P* value < .05 was considered statistically significant. IBM SPSS version 24.0 software for Windows (IBM Corp., Armonk, NY) was used for all statistical analyses.

3. Results

3.1. Study population

During the study period, 72 patients received VA-ECMO in our institute; among them, 48 patients had cardiogenic shock due to ACS. After exclusion of those who failed to wean from ECMO and those who were transferred to other hospitals, 33 patients were included in the analysis (Fig. 1). Mean patient age was 59.0 years (50.0–66.5 years), and 5 (15.2%) patients were women (Table 1). AMI constituted 90.9% of the causes of cardiogenic shock, and 12 (36.4%) patients developed cardiogenic shock during or immediately after angioplasty. Twenty-eight (84.8%) patients experienced cardiac arrest and 17 received extracorporeal cardiopulmonary resuscitation. The SAVE and SOFA scores before initiating ECMO were –4.0 (–6.0 to –3.0) and 5.0 (5.0–6.0), respectively (Table 2).

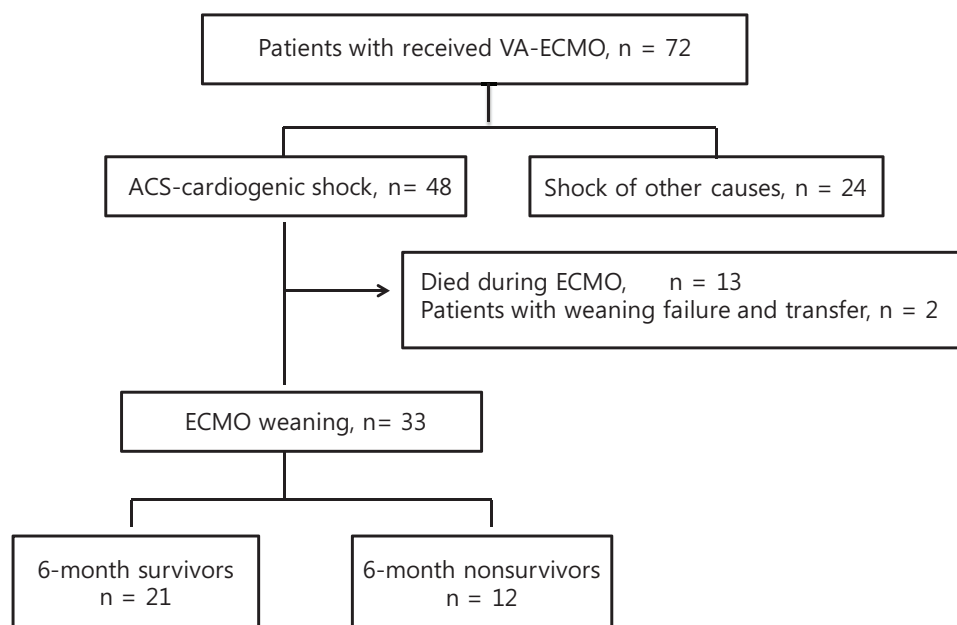


Figure 1. Flowchart of patient enrolment.

Table 1
Baseline characteristics of enrolled patients.

	6-month survivors* (n=21)	6-month nonsurvivors (n=12)	P value
Age, yr	54.0 (48.0–63.0)	64.0 (52.8–69.8)	.103
Gender, M/F	17/4	11/1	.630
Body mass index, kg/m ²	23.9 (22.8–26.8)	24.9 (23.4–27.6)	.432
Diabetes, n (%)	9 (42.9)	6 (50.0)	.692
Hypertension, n (%)	9 (42.9)	6 (50.0)	.692
COPD, n (%)	1 (4.8)	0 (0)	1.000
Chronic kidney disease, n (%)	1 (4.8)	2 (16.7)	.538
Cerebrovascular disease, n (%)	0 (0)	3 (25.0)	.040
Connective tissue disease, n (%)	1 (4.8)	0 (0)	1.000
Laboratory parameters			
WBC, ×10 ³ /μL	13.0 (11.3–18.2)	18.7 (8.5–15.4)	.153
Hemoglobin, g/dL	13.9 (12.5–15.2)	12.8 (9.9–14.9)	.432
Platelet, ×10 ³ /μL	21.4 (154.5–263.5)	223.5 (92.0–270.0)	.852
Blood urea nitrogen, mg/dL	19.3 (15.6–33.7)	14.7 (13.7–24.1)	.349
Creatinine, mg/dL	1.3 (1.0–1.8)	1.4 (1.1–1.7)	.447
Bilirubin, mg/dL	0.5 (0.3–0.8)	0.5 (0.4–0.8)	.410
Cause of cardiogenic shock, n (%)			
Acute myocardial infarct	20	10	.538
Unstable angina	1	2	
Cardiogenic shock on arrival, n (%)	16 (76.2)	9 (75.0)	1.000
Cardiac arrest			
IHCA/OHCA	12/6	5/5	.678
ECPR, n (%)	11 (52.4)	6 (50.0)	1.000

COPD=chronic obstructive pulmonary disease, ECPR=extracorporeal cardiopulmonary resuscitation, IHCA=intrahospital cardiac arrest, OHCA=out of hospital cardiac arrest, WBC=white blood cell.

* 3 patients were censored at 51, 118, and 121 days.

Table 2
Data associated with ECMO treatments.

	6-month survivors* (n=21)	6-month nonsurvivors (n=12)	P value
SOFA score before ECMO	5.0 (4.0–5.5)	5.5 (5.0–6.8)	.115
SAVE score before ECMO	−4.0 (−5.5–2.0)	−5.0 (−7.8–4.3)	.017
Circulatory status before ECMO			
Cardiogenic shock	10	6	.489
VF/VT	7	2	
Asystole (PEA)	4	4	
Time from collapse to ECMO	27.0 (15.0–34.0) [†]	28.5 (21.5–42.8) [‡]	.546
Culprit lesions, n (%)			
Left main artery	1 (4.8%)	3 (2.5%)	.125
Left anterior descending artery	18 (85.7%)	7 (58.3%)	.106
Left circumflex artery	11 (52.4%)	11 (91.7%)	.027
Right coronary artery	11 (52.4%)	9 (75.0%)	.278
3-vessel diseases	7 (33.3%)	7 (58.3%)	.162
Successful PCI, n (%)	20 (95.2%)	9 (75.0%)	.125
Echocardiography			
Initial EF, %	12.0 (10.0–23.5)	10.0 (9.3–16.5)	.246
RV dysfunction, n (%)	11 (52.4%)	3 (25.0)	.126
Pre-weaning EF, %	36.0 (30.0–40.0)	30.0 (30.0–40.0)	.187
Hypothermia treatment, n (%)	2 (9.5%)	1 (8.3%)	.252
SOFA score before ECMO weaning	4.0 (3.0–6.5)	9.0 (7.3–10.0)	<.001
ECMO duration, days	10.0 (7.0–11.5)	13.0 (8.3–15.8)	.029
MV weaning, n (%)	21 (100.0%)	2 (16.7%)	<.001
CRRT, n (%)	16 (76.2%)	12 (100.0%)	.133

CRRT=continuous renal replacement therapy, ECMO=extracorporeal membrane oxygenation, EF=ejection fraction, MV=mechanical ventilation, PEA=pulseless electrical activity, RV=right ventricle, SAVE=survival after veno-arterial ECMO, SOFA=sequential organ failure assessment, VT=ventricular tachycardia, VF=ventricular fibrillation.

* Three patients were censored at 51, 118, and 121 days.

[†] Eleven patients.

[‡] Six patients.

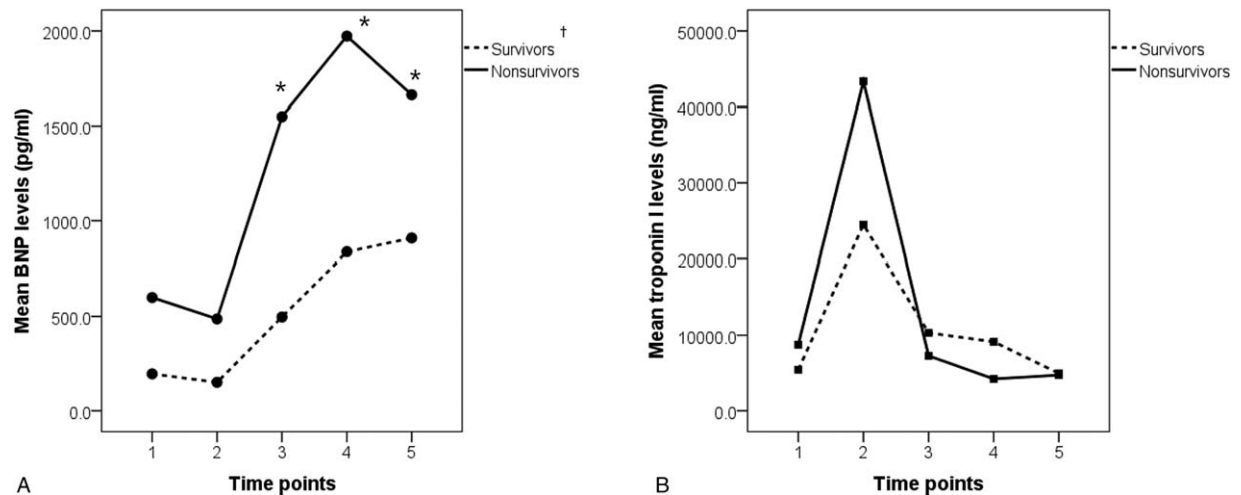


Figure 2. Changes in BNP and Tn-I levels among the 5 time points. a Comparison of BNP levels between survivors and non-survivors. b Comparison of Tn-I levels between survivors and non-survivors. *All $P < .05$ after correction for multiple comparisons. † $P < .05$ by repeated-measures analysis of variance. Time points 1, 2, 3, 4, and 5 indicate pre-ECMO implementation, post-ECMO implementation (day 1), pre-ECMO weaning, day 1 after ECMO weaning, and day 5 after ECMO weaning, respectively. BNP = brain natriuretic peptide, Tn I = troponin I.

3.2. Cardiac evaluations

Coronary angiography was undertaken for all 33 patients during their hospital stays (Table 2). Three-vessel disease was found in 14 (42.3%) patients, and successful angioplasty was achieved in 29 (87.9%) patients. Echocardiography performed before or during ECMO revealed an ejection fraction of 10.0% (10.0%–20.0%).

3.3. Treatment and outcomes

Both MV and VA-ECMO were undertaken for all 33 patients. Therapeutic hypothermia (i.e., body temperature target, 32°C–34°C) was performed in 3 (9.1%) patients and continuous renal replacement therapy was performed in 28 (84.8%) patients. Median durations of MV and ECMO were 17.0 days (12.0–23.0 days) and 11.0 days (7.0–13.0 days), respectively. Successful weaning from MV was achieved in 23 patients (69.7%). Eleven patients (33.3%) died at intensive care unit discharge and 12 (36.4%) died at hospital discharge (heart failure in 7, sepsis in 4, and post-operative complication in 1). Six-month mortality was 36.4%; among all patients who received ECMO for ACS-associated cardiogenic shock ($n=46$), except for the 2 patients who were transferred to other hospitals, a total of 25 (54.3%) died during the 6-month period. The lengths of the intensive care unit and hospital stays were 20.0 days (15.5–27.5 days) and 30.0 days (20.0–44.5 days), respectively. Ejection fractions were not different at the ECMO weaning between survivors and non-survivors (Table 2). Regarding the ECMO-related complications, a higher number of packed red blood cells were transfused in non-survivors (Supplemental digital content, Table S1, <http://links.lww.com/MD/E564>).

3.4. BNP and Tn-I levels in 6-month survivors and non-survivors

Tn-I levels did not differ between survivors and non-survivors at each of the 5 time points. However, BNP levels were significantly higher in non-survivors than in survivors at 3 time points (i.e.,

pre-ECMO weaning [$P=.036$], day 1 after ECMO weaning [$P=.013$], and day 5 after ECMO weaning [$P=.013$] (Fig. 2 and Supplemental digital content, Table S2, <http://links.lww.com/MD/E564>).

3.5. Risk factors for 6-month mortality

Ten variables, including 3 BNP variables, had P values $< .10$ in univariate analyses and were included in the multivariate analysis (Table 3). No significant association was observed between the pre-ECMO weaning BNP tertile and 6-month mortality (Model I). However, the BNP tertiles on days 1 and 5 after ECMO weaning (Models II and III, respectively) were significantly associated with 6-month mortality (hazard ratio, 7.872 and 95% confidence interval, 1.870–32.756; 8.658 and 1.904–39.365, respectively). The Kaplan–Meier curves revealed that patients in the first tertile had significantly longer survival, compared to those in the third tertile, for both days 1 and 5 BNP levels after ECMO weaning (Fig. 3). The SAVE (before ECMO initiation) and SOFA (pre-ECMO weaning) as well as MV weaning, were significantly associated with 6-month mortality.

4. Discussion

This study revealed that post-ECMO weaning BNP levels (days 1 and 5) were associated with increased mortality during the 6-month follow-up period in patients with ACS complicated by refractory cardiogenic shock who were weaned off ECMO.

Based on international registry data (i.e., Extracorporeal Life Support Organization [ELSO]),^[25] the survival rate of patients who receive ECMO for cardiac failure remains unsatisfactory. However, ECMO has been indicated in patients with circulatory shock associated with various conditions,^[7,26,27] and several non-randomized studies have shown that early use of ECMO may offer a survival advantage for these patients.^[28,29] Previously, the percentage of patients with refractory cardiogenic shock who were successfully weaned from ECMO varied (i.e., 31%–76%) depending on underlying causes and weaning

Table 3
Cox proportional analysis for 6-month mortality.

	Univariable analysis		Multivariable analysis	
	ORs	95% CIs	ORs	95% CIs
Model I				
Age	1.035	0.984–1.088	1.011	0.954–1.082
Cerebrovascular disease	8.552	1.978–36.979	4.884	0.723–33.008
MV weaning	0.036	0.008–0.173	0.043	0.008–0.218
BNP tertiles (before weaning)*	2.008	0.954–4.227	1.219	0.557–2.666
Model II				
Age	1.035	0.984–1.088	1.158	1.022–1.312
Cerebrovascular disease	8.552	1.978–36.979	1.256	0.141–11.198
MV weaning	0.036	0.008–0.173	0.150	0.026–0.869
SOFA score†	1.154	1.206–1.901	2.213	1.264–3.875
BNP tertiles (day 1)*	3.121	1.335–7.292	7.872	1.870–32.756
Model III				
Age	1.035	0.984–1.088	1.001	0.938–1.069
SAVE‡	0.810	0.678–0.966	0.557	0.371–0.834
MV weaning	0.036	0.008–0.173	0.019	0.003–0.148
BNP tertiles (day 5)*	2.404	1.085–5.324	8.658	1.904–39.365

BNP = brain natriuretic peptide, CI = confidence interval, MV = mechanical ventilation, OR = odds ratio, SAVE = survival after veno-arterial ECMO, SOFA = sequential organ failure assessment.

* The ranges of BNP tertiles are presented in the Supplemental digital content.

† Before ECMO initiation.

‡ Before ECMO weaning.

definitions.^[30,31] However, several patients did not survive to discharge, despite successful ECMO weaning.^[30,31] Thus far, various risk factors have been investigated in terms of successful weaning or hospital outcomes. Lactate levels, echocardiographic variables (e.g., aortic velocity-time integral and left or right ventricular function), and pulse pressure have been associated with successful weaning from ECMO.^[31–34] However, asystole (or PEA) and ECMO-related complications have been associated with in-hospital mortality.^[7] Cardiac markers, such as NT-pro-BNP, BNP, and Tn-I, which were typically checked during the early period of ECMO treatment, showed no differences between patients with successful weaning and those without.^[35]

A distinctive feature of our study, compared to previous studies, is that we only enrolled patients who were successfully

weaned from ECMO, and investigated the association between BNP levels at various time points and long-term outcomes. The finding that BNP levels before and after ECMO implantation were not associated with 6-month survival was similar to the findings of previous studies^[35]; however, we found that BNP levels on days 1 and 5 after weaning from ECMO were significantly associated with 6-month mortality.

BNP levels have long been known to exhibit diagnostic and prognostic value in patients with heart failure.^[11] Although the half-life of BNP is short and its plasma level can be affected by various factors,^[36] this hormone is associated with the occurrence of new cardiac events, even in patients with concomitant chronic kidney disease.^[10] A randomized controlled trial of patients using MV showed a positive effect of a BNP-driven fluid management

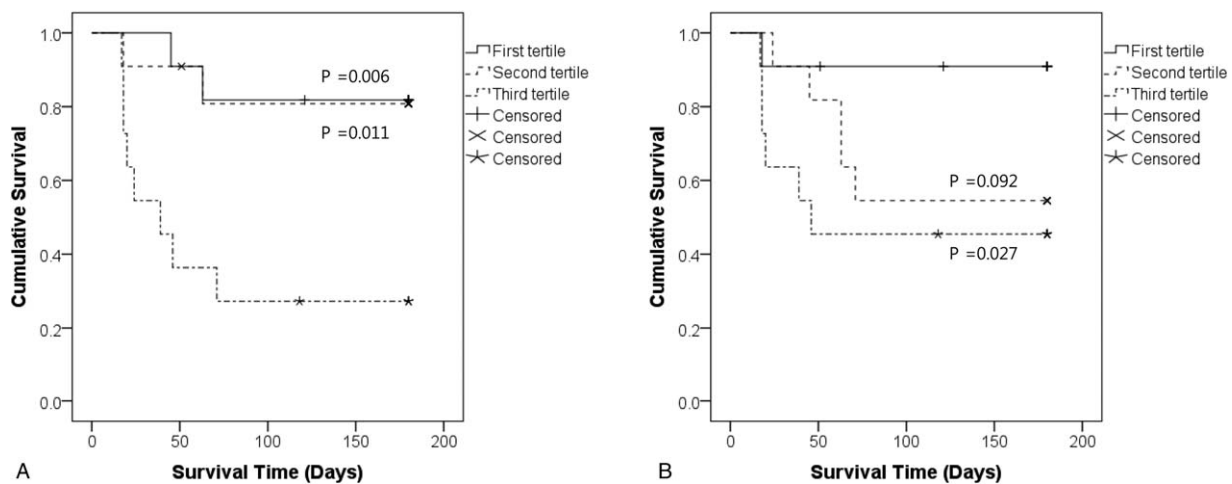


Figure 3. Kaplan–Meier survival curves by BNP level (tertile) obtained after ECMO weaning. a Survival curves for the day 1 BNP tertile groups (the first tertile vs the third tertile, $P = .006$; the second tertile vs the third tertile, $P = .011$). b Survival curves for the day 5 BNP tertile groups (the first tertile vs the second tertile, $P = .092$; the first tertile vs the third tertile, $P = .027$). BNP = brain natriuretic peptide.

strategy in decreasing weaning time, which was strongest in patients with left ventricular systolic dysfunction.^[13] These results indicate that BNP levels can be a valuable outcome predictor for patients with various conditions where left ventricular systolic dysfunction is involved. Our study is clinically relevant in this context.

The role of BNP has rarely been investigated in patients receiving ECMO – only case reports or studies of children were found in a literature search.^[30,37,38] In 2006, Huang et al reported that BNP levels of children on the fourth day after removal from ECMO were significantly lower in survivors than non-survivors, which was consistent with our findings.^[30] They suggested that serial BNP levels can be a valuable parameter for monitoring patients on ECMO. Besides, fluid balance seems important in patients receiving ECMO. Schmidt et al demonstrated that a positive fluid balance on ECMO day 3 is an independent factor for 90-day mortality.^[39] Although data regarding fluid balance were not available in our cohort, these results suggest an important role for BNP in patients receiving ECMO.

It is reasonable that severity-of-illness scores and MV weaning were risk factors for 6-month mortality in our cohort. However, patients with left circumflex (LCX) arterial lesions had higher 6-month mortality, compared to other patients, in the univariate analysis (Table 2). The LCX artery is the least frequent culprit lesion, and patients with an LCX lesion are less likely to present with ST-segment elevation AMI and undergo emergency percutaneous coronary intervention.^[40] In another study, the frequency of LCX lesions was found to be lower than that of right coronary artery lesions, but patients with LCX lesions had higher cTn-I levels and a lower left ventricular ejection fraction.^[41] In our study, stents were less frequently inserted in culprit arteries (68.2% vs 90.0%), and BNP levels tended to be higher in patients with LCX lesions, compared to those without LCX lesions (data not shown). These results should be clarified in future studies.

Notably, the outcomes of our cohort seem better than those from international registry data (i.e., survival to discharge rate for patients VA-ECMO [43%] or extracorporeal cardiopulmonary resuscitation [29%]).^[25] There could be several explanations for this difference in outcomes. First, in our cohort, we only included patients who were successfully weaned from ECMO. Hence, the survival rate was higher than that from other VA-ECMO studies. Second, successful angioplasty was achieved in 87.9% of our patients. Third, although we included 17 patients with extracorporeal cardiopulmonary resuscitation, the median interval between collapse and ECMO was shorter than 30 minutes, leading to low mortality (35.3%). Fourth, for 12 patients who developed cardiogenic shock during or right after coronary angiography, it is highly likely that the time interval between the development of cardiogenic shock and ECMO was very short, which may have positively influenced patient outcome.

The Kaplan–Meier survival curves (Fig. 3A and 3B) revealed that the result of the second BNP tertiles was inconsistent between days 1 and 5 after ECMO weaning. This was partially due to the small number of patients. However, our data clearly showed that patients in the first BNP tertile (i.e., the lowest level) had longer survival than those in the third BNP tertile. Although cost-effectiveness could be a problem in some areas,^[37,38] BNP is a simple and objective parameter, compared to echocardiographic data, which is rather user-dependent. It remains unclear whether this hormone can be used as a therapeutic target. However, there

is evidence to suggest that BNP levels are useful in various clinical situations.^[10,11,36] Taken together, the findings suggest that BNP level might be a useful parameter for monitoring patients with ACS-associated cardiogenic shock who were weaned off VA-ECMO.

This study had several limitations. First, there may have been unintended bias in the results due to the small sample size. Second, this was a single-center study that could limit the generalizability of the results. Third, although we followed the ELSO guidelines, the ECMO management practices (including weaning from ECMO) have not been standardized. Fourth, although we collected data on ejection fractions during ECMO weaning, other echocardiographic parameters, such as cardiac output or right ventricular function, would have strengthened our results. Fifth, percutaneous left ventricular assist devices could have benefited the patients who failed to be weaned off ECMO. However, unfortunately, the devices are not currently available in our country. Finally, patient quality of life after weaning from ECMO was not evaluated in our study. However, this is the first study to show the usefulness of BNP levels obtained after ECMO weaning for predicting outcomes in patients with ACS-related refractory cardiogenic shock. Therefore, despite these limitations, our results merit consideration.

5. Conclusions

In conclusion, post-ECMO weaning BNP levels (days 1 and 5) were associated with increased mortality during 6-month follow-up of patients with ACS complicated by refractory cardiogenic shock who were successfully weaned from ECMO. Further large-scale prospective studies are needed to confirm these findings.

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Author contributions

Conceptualization: Hyoung Soo Kim, Kyu Jin Lee, Sun Hee Lee, Sunghoon Park

Data collection and analysis: Sang Ook Ha, Sang Jin Han, Kyoung-Ha Park

Methodology: Sang Ook Ha, Yong Il Hwang, Seung Hun Jang

Project administration: Sun Hee Lee, Yong Il Hwang, Seung Hun Jang

Writing – original draft: Hyoung Soo Kim, Kyu Jin Lee, Sunghoon Park

Writing – review & editing: Hyoung Soo Kim, Kyu Jin Lee, Sang Ook Ha, Sang Jin Han, Kyoung-Ha Park, Sun Hee Lee, Yong Il Hwang, Seung Hun Jang, Sunghoon Park

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