ECMO Used in a Refractory Ventricular Tachycardia and Ventricular Fibrillation Patient

A National Case–Control Study

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Abstract: Refractory cardiac arrhythmia, which has a poor response to defibrillation and antiarrhythmia medication, is a complicated problem for clinical physicians during resuscitation. Extracorporeal membrane oxygenation (ECMO) may be used to sustain life in this situation. ECMO is useful for cardiopulmonary resuscitation among patients suffering from cardiac arrest; the use of ECMO in this context is called E-cardiopulmonary resuscitation. However, a large-scale and nationwide survey of ECMO usage in cases involving refractory cardiac arrhythmia during resuscitation is lacking. We aimed to clarify the characteristics and efficacy of the application of ECMO in cases involving refractory cardiac arrhythmia during resuscitation by conducting a nationwide study.

Using national insurance data from 1996 to 2011, 2702 patients who experienced cardiac arrest and refractory VT and VF. We excluded trauma patients (n = 316) and those aged <20 years (n = 24). A total of 2362 patients were included, 376 of whom had ECMO support, and 1986 of whom had no ECMO support. After propensity score matching, 320 patients had ECMO support and 640 patients without ECMO support. Conditional logistic regression was used to estimate the risk of death in ECMO users compared to non-EMCO users. ECMO used in refractory cardiac arrhythmia with high propensity score patients had lower risk of death (odds ratio [OR] = 0.59, 95% confidence interval [CI] = 0.36–0.98). However, prolonged ECMO used >1 day was higher risk of death (OR = 2.88, 95% CI = 1.27–6.53).

In our retrospective case control study in refractory cardiac arrhythmia patients, ECMO supportive in high propensity score patients showed improving the overall survival rate but ECMO support for >1 day would be harmful. The evidence derived from this retrospective study using data from the national insurance system is generally of lower methodological evidence than that from randomized controlled trials because a retrospective study is subject to many biases due to lack of the necessary adjustments for possible confounding factors. Therefore, further investigation with a randomized clinical trial is needed to recommend ECMO as a routine in this specific population of patients experiencing cardiac arrest and refractory VT and VF.

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Pulseless ventricular tachycardia (VT) and ventricular fibrillation (VF) is a life-threatening form of ventricular arrhythmia but has the highest survival rate in cardiac arrest patients if proper and timely treatment is provided. VF is the most common initial rhythm of sudden cardiac arrest, and the treatment of VF is defibrillation.1 Early defibrillation can reverse arrhythmia and increase the survival rate, which decreases every minute without defibrillation and cardiopulmonary resuscitation (CPR).2 Early defibrillation is crucial to restoring cardiac output. If ventricular arrhythmia persists, then antiarrhythmia medication, such as amiodarone, should be prescribed to correct the rhythm. Amiodarone affects sodium, potassium, and calcium channels and has α- and β-adrenergic blocking properties, which can be considered for treatment of VF or pulseless VT that are unresponsive to shock delivery.3 It is a tough situation, if ventricular arrhythmia were refractory to
defibrillation and antiarrhythmia agents. No evidence or guidelines have been produced to solve this problem.

Extracorporeal membrane oxygenation (ECMO) is a proven rescue strategy for patients with cardiac arrest that are unresponsive to conventional cardiopulmonary resuscitation; this is called E-cardiopulmonary resuscitation (E-CPR). Patients with witnessed in-hospital cardiac arrest of cardiac origin treated with E-CPR have higher survival rates than those treated with conventional CPR do.5 Despite the previously mentioned advances, this therapy still creates complications such as bleeding and infection.3 Because of its potential benefits, gradually increasing ECMO use was mentioned and became a complex ethical, financial, and health care problem. Increasing ECMO may be used for situations in which it provides no benefits. Refining the indicators of when to use ECMO is suggested.6 Because of its uncertain risks and benefits, ECMO should be used more carefully in cardiac arrest patients. More evidence is required to determine appropriate criteria for ECMO intervention.7 We hypothesized that the survival of the refractory VT/VF group, which needed defibrillation and amiodarone injection, could be increased through ECMO support. ECMO supports patient with VT refractory to antiarrhythmic agents and cardiovascular attempts. One case report showed ECMO provide patient adequate perfusion to survival without neurologic deficiency in recurrent ventricular fibrillation refractory standard cardiopulmonary resuscitation.8 The Extracorporeal Life Support Organization and Department of Intensive Care at Alfred Hospital, Melbourne calculated SAVE scores to predict the survival rate for venoarterial (VA) mode ECMO users and patients diagnosed with refractory VT/VF for determining whether treatment with VA mode ECMO increased survival.9 We used data collected by the Bureau of National Health Insurance in Taiwan to ascertain the effect of ECMO used in refractory VT/VF patients.

MATERIALS AND METHODS

Data Source
A total of 99.9% of Taiwan’s population is enrolled in the National Health Insurance (NHI) program, which was launched in 1995. The electronic database of this program, the National Health Insurance Research Database (NHIRD), is maintained by the National Health Research Institutes and contains registration files as well as inpatient, outpatient, and pharmacy claims data (http://www.nhi.gov.tw/english/index.aspx). All datasets of the NHIRD can be linked using scrambled personal identifications. The data used in this study were a subset of the NHIRD consisting of the registration files and longitudinal medical records of 1 million beneficiaries randomly selected from the NHI program. Disease diagnoses were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved by the institutional review board of China Medical University Hospital (CMUH104-REC2-115).

Study Participants
Patients who were hospitalized and received defibrillation and amiodarone injection between 1996 and 2011 were included in our study and divided into 2 groups: patients with and without ECMO treatment during hospitalization. Those with trauma or <20 years of age were excluded (Figure 1). For the baseline characteristics between ECMO and non-ECMO users was similar, we used propensity score mating to select study subjects at a ratio 2:1. The propensity score was counted according to demographics, comorbidity, and academic medical center care for each patient. Based on the propensity score matching method, we selected 320 patients with ECMO treatment and 640 patients without ECMO treatment. A total of 640 patients died during hospitalization. Comorbidities including congestive heart failure (CHF) (ICD-9-CM 428), chronic obstructive pulmonary disease (COPD) (ICD-9-CM 496), chronic kidney disease (CKD) (ICD-9-CM 585), liver disease (ICD-9-CM 571, 572.2, 572.3, 572.8, 573.1–573.3, 573.8, and 573.9), diabetes mellitus (DM) (ICD-9-CM 250), malignancy (ICD-9-CM 140–208), CNS problems [included stroke (ICD-9-CM 430–438), dementia (ICD-9-CM 290, 291.4, and 331.0–331.2) and hemiplegia (ICD-9-CM 342)], hypertension (ICD-9-CM 401–405), and ischemic heart disease (ICD-9-CM 410–414) were defined before the index date.

Statistical Analysis
The baseline characteristics of ECMO and non-ECMO patients were compared using the chi-square test and the t test to estimate the difference of categorical and continuous variables. The odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of death in ECMO users compared to non-ECMO users using conditional logistic regression. We also assessed the death risk stratified by propensity score based on tertile. In future analysis, the association between death risk and the duration of ECMO used was estimated. All statistical analyses were performed using SAS software (Version 9.3 for Windows; SAS Institute, Cary, NC). The statistical significant level was set at P < 0.05 under 2-tailed testing.

RESULTS
Based on propensity score matching, 320 patients had ECMO support and 640 patients without ECMO support were selected in this study. There were no significantly different of demographic characteristics, comorbidities, and medical care between 2 groups (Table 1). In ECMO users, the mean age was 65.6 years old (standard deviation = 12.0) and more men (68.7% vs 31.3%). More ECMO users were living in urban areas, white collar, and with academic medical center care. The top 3 prevalent comorbidities were hypertension (75.0%), ischemic heart disease (70.0%), and CHF (33.4%) in ECMO users.

The associations between death and ECMO stratified by the propensity score in conditional logistic regression are listed in Table 2. There were 128 (40.0%) and 277 (43.3%) patients died in ECMO and non-ECMO groups. Overall death risk in ECMO user was lower than non-ECMO users, but it did not attach the statistical different (OR = 0.87, 95% CI = 0.66–1.15). We divided patients into 3 portions according to the propensity score. The high propensity score (≥T2) patient with ECMO used had lower risk of death than non-ECMO patient did (OR = 0.59, 95% CI = 0.36–0.98).

Table 3 demonstrates the association between death and duration of ECMO. Compared to non-ECMO users, patients on ECMO for 1 day had a lower death risk (OR = 0.72, 95% CI = 0.54–0.98). But patients on ECMO for >1 day had a markedly higher risk of death than non-ECMO patients did (OR = 2.88, 95% CI = 1.27–6.53).

DISCUSSION
In the national cohort of 2362 refractory VT/VF patients in Taiwan, propensity score matching was used to estimate the
effect of ECMO used. Lower risk of death in the high propensity score with ECMO used patient. However prolonged ECMO used >1 day would increase risk of death.

This retrospective cohort study used the Taiwan NHIRD to analyze the effect of ECMO. A total of 99.9% of Taiwan’s population is enrolled in the NHI program, which was launched in 1995.

The initial treatment of VF or VT in unstable patients is defibrillation. If cardiac arrhythmia persists despite defibrillated and CPR, then amiodarone should be administered. Ventricular arrhythmia that does not respond to defibrillation and requires antiarrhythmic drugs, such as amiodarone, is rare but life-threatening. The most plausible reason of cardiac arrhythmia is severe underlying structural heart disease, such as myocardial infarction or dilated cardiomyopathy, but few cases of VT/VF are reported in patients with structurally normal hearts (e.g., Brugada syndrome or long QT syndrome). Among of patients with post-infarction cardiomyopathy, myocardial scar might cause ventricular tachycardia and could be terminated byfocal radiofrequency ablation. However, no patient received radiofrequency ablation in our study. A case series study in 2007 found that ECMO for refractory VT patients had a high survival rate. Eleven patients were included, 8 of whom had acute myocarditis, one of whom had coronary artery spasm, and 2 of whom had hypoxemia secondary to acute respiratory distress syndrome. Nine (82%) patients received VA mode support, and the remaining 2 (18%) were supported with venovenous mode to correct hypoxemia. Additionally, a retrospective cohort study included 98 acute coronary syndrome patients who received ECMO to reverse hemodynamic collapse refractory to conventional treatment. A total of 23 patients had VF or pulseless VT, 34 had cardiogenic shock, and 41 had asystole or pulseless electrical activity. Patients with acute coronary syndrome (ACS) complicated by cardiogenic shock or cardiac arrest refractory to conventional treatment had high mortality. However, ECMO use produced favorable outcomes for patients with ACS with refractory VF or pulseless VT. Furthermore, a retrospective study found that acute myocardial infarction patients who required ECMO support and suddenly developed refractory pulseless VT or VF without

![Flowchart](image_url)
deteriorating low output syndrome had a high probability of recovering with ECMO use. Moreover, an international study (SAVE-score) predicted the survival rate before ECMO use in refractory cardiogenic shock patients and determined that refractory VT/VF were protective factors. In addition, an observational study in a medical center included patients who had refractory ventricular arrhythmia because of acute myocardial infarction and found that ECMO is a feasible rescue

### TABLE 1. Demographic and Medical Characteristics Between Patients With and Without ECMO Treatment

|                | ECMO N = 320 | Non-ECMO N = 640 | P Value |
|----------------|--------------|-----------------|---------|
| Age, y         |              |                 |         |
| 20–44          | 23           | 58              | 0.60    |
| 45–64          | 101          | 203             |         |
| 65+            | 196          | 379             |         |
| Mean (SD)      | 65.6 (12.0)  | 66.1 (14.8)     | 0.56    |
| Gender         |              |                 |         |
| Women          | 100          | 198             |         |
| Men            | 220          | 442             |         |
| Urbanization   |              |                 | 0.93    |
| 1              | 118          | 231             |         |
| 2              | 92           | 197             |         |
| 3              | 40           | 77              |         |
| 4              | 70           | 135             |         |
| Occupation     |              |                 | 0.94    |
| White collar   | 130          | 261             |         |
| Blue collar    | 115          | 235             |         |
| Other          | 75           | 144             |         |
| Medical center |              |                 | 0.65    |
| Yes            | 175          | 360             |         |
| No             | 145          | 280             |         |
| Comorbidity    |              |                 |         |
| CHF            | 107          | 208             | 0.77    |
| COPD           | 40           | 81              |         |
| CKD            | 28           | 62              | 0.64    |
| Liver disease  | 67           | 142             | 0.66    |
| DM             | 101          | 205             | 0.88    |
| Malignancy     | 10           | 12              | 0.22    |
| CNS problems   | 62           | 127             | 0.86    |
| Ischemic heart disease | 224 | 446 | 0.92 |
| Hypertension   | 240          | 477             | 0.87    |
| Mean propensity score (SD) | 0.21 (0.10) | 0.21 (0.10) | 0.90 |

CNS problems included stroke, dementia, and hemiplegia.
CHF = congestive heart failure; CKD = chronic kidney disease; CNS = central nervous system disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; SD = standard deviation.

### TABLE 2. Associations Between Death and ECMO Stratified by Propensity Score Based on Tertile in Conditional Logistic Regression

|                | ECMO N = 320 | Non-ECMO N = 640 | Odds ratio (95% CI) |
|----------------|--------------|-----------------|----------------------|
| Overall        | 320          | 640             | 0.87 (0.66–1.15)     |
| Propensity score |              |                 |                      |
| T1             | 212          | 106             | 0.84 (0.53–1.35)     |
| T2             | 206          | 103             | 1.33 (0.80–2.19)     |
| T3             | 222          | 111             | 0.59 (0.36–0.98)*    |

CI = confidence interval; ECMO = extracorporeal membrane oxygenation.
T1 the first tertile (< = 0.14); T2 the second tertile (0.15–0.26); and T3 the last tertile (>0.26).
* P < 0.05.
therapy that can lead to further therapy. This study included patients with clinical diagnoses of acute myocardial infarction and excluded those who did not receive coronary catheterization or received ECMO implantation during or after revascularization therapy.

Comorbidities are risk factors for mortality. Life-threatening ventricular arrhythmia generally suggests the presence of heart disease caused by myocardial infarction, cardiomyopathy, or genetic arrhythmia. Genetic syndromes, such as long QT syndrome, Brugada syndrome, catecholaminergic-related polymorphic VT, and short QT syndrome, typically occur in young people without comorbidities. ECMO had the most therapeutic benefit in myocardial in-hospital cardiac arrest (IHCA) patients. Myocardial infarction is multifactorial and often has risk factors such as diabetes, dyslipidemia, smoking, and hypertension. These risk factors influenced with the aforementioned comorbidities. One observation study for cardiovascular compromise patients found that combined ECMO and intra-aortic balloon pumps (IABPs) also found that the dyslipidemia group had a lower risk of mortality. Patients with more comorbidities had a higher risk of myocardial infarction. If myocardial infarction is the cause of refractory VT/VF, then ECMO support has a therapeutic benefit. The SAVE scores reflected that chronic kidney injury increased mortality, but the validation cohort showed no difference. Our observation study showed no therapeutic benefits of ECMO for patients with chronic kidney disease in the ECMO cohort.

Taiwan has a strong general insurance program that imposes little financial burden for patients. The financial burden of ECMO patients in Taiwan could be minimized due to well insurance system. No national data have been recorded to compare the effect of ECMO in refractory VT/VF patients.

Taiwan has 19 academic medical centers and 74 regional hospitals that can provide ECMO, and some district hospitals also have the equipment necessary for ECMO treatment. The poor outcome of ECMO group in academic medical centers may be attributable to tertiary bias; however, 1 prospective study on cardiac arrest also showed worse neurologic outcomes in medical centers. Academic medical centers in Taiwan are generally located in cities, and the incidences and outcomes of VF in different regions were mentioned in a retrospective review. Nonmedical centers can dedicate more time, resources, and personnel to deliver high-quality care. This observation requires further explanation.

Prolonged ECMO use seems to not yield a superior outcome of survival rate. The mortality rate increased among patients >1 day of ECMO used. One observation study on 135 cardiovascular compromise patients who were treated with ECMO and IABP showed that the length of ECMO support did not predict in-hospital mortality. The mean duration of ECMO support in the aforementioned study was 8.5 ± 7.1 days (range 1–40 d). Another observational study examined 98 patients with ECMO support because of acute coronary syndrome. The mean duration of ECMO support was 68.9 ± 62.7 hours. The duration of ECMO support was related to mortality by excluded multivariate analysis because patients who could not wean from ECMO inevitably required ECMO support until death. Most of these patients had a longer duration of ECMO support than the patients who survived did. ECMO was eventually used as bridge therapy, and prolonged ECMO use showed no survival benefits.

When ECMO is used as a supportive measure during or immediately after CPR in adults, this is also called E-CPR. A meta-analysis of observational studies in 2009 showed that the overall survival rate of patients with ECMO support was 40% (54 of 135 patients) and the protective effect is greater for younger patient groups (17–41 years). A prospective observational study that compared E-CPR and conventional CPR for patients aged 18 to 75 years with witnessed IHCA of cardiac origin undergoing CPR for >10 minutes showed the survival benefit of E-CPR. Recent studies have also proven that ECMO increases the survival of IHCA patients. A study on IHCA resulting from myocardial infarction showed that E-CPR improved survival in patients with ST segment elevation or initial VT/VF rhythm. However, a reference showed no survival difference between patients who had a relapse of spontaneous breathing after ECMO use and those who had a relapse of spontaneous circulation after conventional CPR. But these 2 groups were not comparable due to basic selection difference. According to above reference, ECMO might increase the survival rate in INCA patient with cardiac origin and support our conclusion.

A 2011 study showed that using ECMO for out-of-hospital cardiac arrest (OHCA) patients produced a poor outcome. Only 2 patients (4%) (95% CI, 1–13%) were alive in day 28 with a favorable neurologic outcome. However, a recent retrospective study in 2 urban academic medical centers discussed ECMO used for OHCA patients and showed a survival rate of 15% (4 of 26 patients), 3 of whom were neurologically intact at 6 months. Another retrospective study in a rural tertiary care center showed that 5 of the 32 patients (16%) with OHCA of cardiac origin had favorable neurologic outcomes. For OHCA patients with VT/VF on the initial ECG, the Cerebral Performance and Overall Performance Category 1 or 2 was 13.7% (32 of 234 patients) in the E-CPR group and 1.9% (3 of 159 patients) in the non-E-CPR group at 1 month. E-CPR may enhance cerebral blood flow and the recovery of neurologic function; the most significant advantage of E-CPR was observed in patients with VT/VF.

Limitations

Because this is a retrospective study, the physician selection bias in initiating the ECMO support is the first problem.
although statistical correction were attempted to decrease assessable confounders. Besides, hospital with ECMO available may be better equipped than other hospital to treat patients but also may attract sicker patients. There are 2 confounders between ECMO and survival. Additionally, we could not estimate the period before ECMO was performed. Moreover, we were unaware of the ECMO complications and disease severity of each patient.

CONCLUSION

In our retrospective case control study in refractory cardiac arrhythmia patients, ECMO supportive in high propensity score patients showed improving the overall survival rate but ECMO support for >1 day would be harmful. The evidence derived from this retrospective study using data from the national insurance system is generally of lower methodological evidence than that from randomized controlled trials because a retrospective study is subject to many biases due to lack of the necessary adjustments for possible confounding factors. Therefore, further investigation with a randomized clinical trial is needed to recommend ECMO as a routine in this specific population of patients experiencing cardiac arrest and refractory VT and VF.

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