



Clinical paper

Managing cardiac arrest with refractory ventricular fibrillation in the emergency department: Conventional cardiopulmonary resuscitation versus extracorporeal cardiopulmonary resuscitation[☆]



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ABSTRACT

Aim: Refractory ventricular fibrillation, resistant to conventional cardiopulmonary resuscitation (CPR), is a life threatening rhythm encountered in the emergency department. Although previous reports suggest the use of extracorporeal CPR can improve the clinical outcomes in patients with prolonged cardiac arrest, the effectiveness of this novel strategy for refractory ventricular fibrillation is not known. We aimed to compare the clinical outcomes of patients with refractory ventricular fibrillation managed with conventional CPR or extracorporeal CPR in our institution.

Method: This is a retrospective chart review study from an emergency department in a tertiary referral medical center. We identified 209 patients presenting with cardiac arrest due to ventricular fibrillation between September 2011 and September 2013. Of these, 60 patients were enrolled with ventricular fibrillation refractory to resuscitation for more than 10 min. The clinical outcome of patients with ventricular fibrillation received either conventional CPR, including defibrillation, chest compression, and resuscitative medication (C-CPR, $n=40$) or CPR plus extracorporeal CPR (E-CPR, $n=20$) were compared.

Results: The overall survival rate was 35%, and 18.3% of patients were discharged with good neurological function. The mean duration of CPR was longer in the E-CPR group than in the C-CPR group (69.90 ± 49.6 min vs 34.3 ± 17.7 min, $p=0.0001$). Patients receiving E-CPR had significantly higher rates of sustained return of spontaneous circulation (95.0% vs 47.5%, $p=0.0009$), and good neurological function at discharge (40.0% vs 7.5%, $p=0.0067$). The survival rate in the E-CPR group was higher (50% vs 27.5%, $p=0.1512$) at discharge and (50% vs 20%, $p=0.0998$) at 1 year after discharge.

Conclusions: The management of refractory ventricular fibrillation in the emergency department remains challenging, as evidenced by an overall survival rate of 35% in this study. Patients with refractory ventricular fibrillation receiving E-CPR had a trend toward higher survival rates and significantly improved neurological outcomes than those receiving C-CPR.

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Abbreviations: C-CPR, conventional cardiopulmonary resuscitation; E-CPR, extracorporeal cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; ROSC, return of spontaneous circulation; ROSB, return of spontaneous beating; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; AHA, American Heart Association.

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1. Introduction

Cardiac arrest that is refractory to cardiopulmonary resuscitation (CPR) carries a high mortality rate, especially when the duration of resuscitation persists beyond 10 min.¹ The effect of conventional CPR (C-CPR) falls rapidly, with decreased survival beyond the first 10–15 min and only 2% patients achieve a favorable neurological outcome.² Although patients with cardiac arrest due to ventricular fibrillation tend to respond more favorably to C-CPR compared with other etiologies of cardiac arrest,^{1,3} the clinical

outcome is poor if they fail to respond within the first 10 min.^{4,5} Indeed, the reported survival rate is 20.4% in this scenario, with only 5.6% of patients regaining good neurological outcomes in out of hospital arrest.⁶

A previous study suggests that using extracorporeal membrane oxygenation (ECMO) in extracorporeal CPR (E-CPR) can improve the clinical outcomes in patients with prolonged cardiac arrest beyond 10 min.⁴ However, the cost of ECMO is high and the patient characteristics that are likely to gain most from ECMO have not been established.^{7,8} Ventricular fibrillation is considered refractory if no return of spontaneous circulation (ROSC) occurs after C-CPR for more than 10 min. Few case reports describe the use of ECMO in patients with prolonged cardiac arrest due to refractory ventricular fibrillation, particularly with excellent clinical outcomes.^{9–13} Whether or not this unconventional strategy can be applied to the management of refractory ventricular fibrillation in the emergency department and improve patient outcomes is unclear.

In this study, we aimed to study the clinical outcomes of patients with refractory ventricular fibrillation. Specifically, we assessed the effects of C-CPR versus E-CPR in this patient group.

2. Patients and methods

A retrospective medical chart review at a medical center was performed between September 2011 and September 2013. The study was approved by our Institutional Review Board. We enrolled patients who fulfilled the following criteria: (1) age 18–75 years; (2) cardiac arrest with initial ventricular fibrillation and C-CPR initiated within 5 min (no flow duration <5 min); (3) refractory ventricular fibrillation defined as ventricular fibrillation resistant to at least three defibrillations, 3 mg of epinephrine, 300 mg of amiodarone, and no ROSC achieved after CPR for more than 10 min.¹⁴

Patients were excluded if they had (1) severe head trauma or severe acute active bleeding; (2) severe sepsis; (3) ventricular fibrillation that developed during resuscitation for initial asystole or pulseless electrical activity; (4) terminal stage of malignancy; and (5) any history of severe neurological deficits (including dementia, intracranial hemorrhage, or ischemic stroke and bedridden state).

2.1. Assessment of the resuscitation process and clinical outcome

We retrospectively reviewed the number of defibrillation attempts and drugs used, as well as the duration of resuscitation. Sustained ROSC was defined as more than 20 min of spontaneous circulation without recurrence of cardiac arrest. The CPR process was stopped when sustained ROSC was achieved. The decision to discontinue CPR was made if there was no ROSC after 30 min resuscitation. Neurological outcome was evaluated using the Glasgow–Pittsburgh cerebral performance category (CPC) scale. Good neurological outcome was defined as a CPC score of 1 or 2, poor cerebral function as a CPC score of 3 or 4, and brain death as a CPC of 5. Patients were followed to either discharge from the hospital or death.

2.2. The ECMO system and intervention

In our hospital, E-CPR was permitted as an option in prolonged CPR, according to the judgment of the attending physician. The ECMO system comprised a Bio-Pump® centrifugal blood pump (Medtronic Inc., Anaheim, CA), a Maxima Plus PRF hollow membrane oxygenator with an integral heat exchanger, and a heparin-bonded Carmeda Bioactive Surface circuit. The pump flow

was controlled to maintain a minimum flow of 2.0 L min⁻¹. The activated clotting time was maintained at 180–220 s with heparin.

We performed E-CPR via femoral cannulation in the emergency department. Once the patient achieved sustained ROSB (return of spontaneous beating) after ECMO, they were transferred to intensive care. Therapeutic hypothermia is considered when the patients remain comatose after ROSC (C-CPR group) or ROSB (E-CPR group) and decided by the attending physician of the intensive care unit. Therapeutic hypothermia was provided as follows: the patient was cooled to 33 °C for 24 h and rewarmed at 0.5 °C every 4 h till tympanic temperature reached 37 °C. Emergency coronary angiography was performed by cardiologist if acute myocardial infarction was suspected.

2.3. Statistical analyses

Continuous variables were compared using Student's *t*-test or Mann–Whitney *U*-test as appropriate. Categorical variables were evaluated using the χ^2 test. Logistic regression modeling was used to evaluate factors associated with clinical outcome. Differences between the two groups were considered significant when the *P*-value was <0.05. Statistical analyses were performed using MedCalc software version 11.5 (MedCalc Software bvba, Broekstraat 52, 9030 Mariakerke, Belgium).

3. Results

3.1. Patient characteristics of refractory ventricular fibrillation

During the study period, we identified 209 patients with cardiac arrest due to ventricular fibrillation. Of these, 60 patients who had initial ventricular fibrillation that fulfilled the inclusion and exclusion criteria were enrolled (Fig. 1). The mean age was 58.37 years, with male predominance. Forty-one of the cases had out of hospital cardiac arrest (OHCA). The leading cause of cardiac arrest was acute myocardial infarction (46.67%).

The resuscitation process was illustrated in Fig. 2. The mean duration of resuscitation was 46.22 min, with a mean of 7.65 defibrillations performed. ECMO support was provided for 20 (33.33%) patients and successful cannulation achieved in 19 patients. 18 (30%) patients received therapeutic hypothermia. In our study, 38 (63.33%) patients achieved sustained ROSC/ROSB and all were transferred to intensive care. In total, 21 (35%) patients survived to discharged; however, only 11 (18.33%) had good neurological function at discharge.

3.2. Comparison of the C-CPR and E-CPR groups

We divided patients into C-CPR and E-CPR groups for further comparison (Table 1). Age, sex, amiodarone dose, co-morbidity disease, cause of cardiac arrest, location of cardiac arrest, serum lactate levels, and therapeutic hypothermia were similar in both groups. In the E-CPR group, patients had longer duration of resuscitation (E-CPR vs C-CPR: 69.90 min vs 34.38 min, $p=0.0001$), more defibrillation attempts (E-CPR vs C-CPR: 9.72 vs 6.56, $p=0.0001$), and more doses of epinephrine (E-CPR vs C-CPR: 11.17 mg vs 8.29 mg, $p=0.032$). Patients in the E-CPR group also had significantly higher rates of sustained ROSC and survival to intensive care when compared with the C-CPR group (95% vs 47.5%, $p=0.0009$). The overall survival rate was also higher in the E-CPR group compared with the C-CPR group at discharge (50% vs 27.5%) and one year after discharge (50% vs 20%), although this was not statistically significant. However, the rate of good neurological function was significantly higher at discharge in the E-CPR group than in the C-CPR group (40% vs 7.5%, $p=0.0067$).

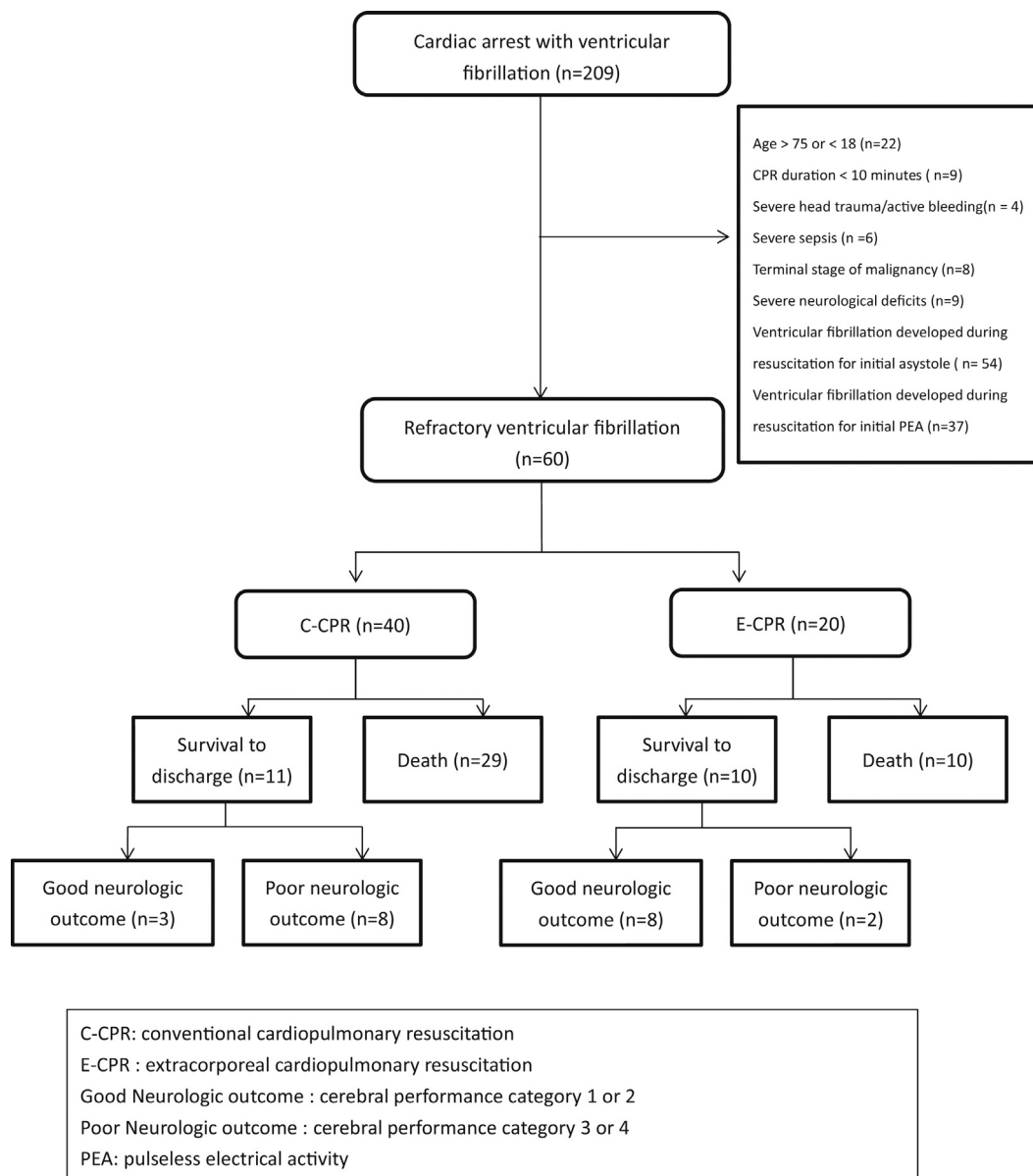


Fig. 1. Diagram for patient management and outcome.

3.3. Comparison of the E-CPR subgroup

We divided E-CPR patients into subgroups (survivor vs non-survivor) for further comparison with the time course of E-CPR were provided in Table 2. Age, sex, resuscitation drug dose, location of cardiac arrest, CPR to ECMO duration and ECMO set-up time were similar. In the survivor group, patients had shorter no-flow duration, lower lactate level and higher proportion of acute myocardial infarction (80%), although these were not statistically significant.

3.4. Factor analysis for clinical outcome

Clinical factors including age, sex, CPR duration, defibrillation episodes, ECMO use, and hypothermia use were further analyzed with logistic regression to determine the factors that predicted the two main clinical outcomes: survival to discharge (Table 3) and good neurological function at discharge (Table 4). No significant clinical factor was able to predict patient survival to discharge in refractory ventricular fibrillation. However, the ECMO support

(odds ratio: 25.44, 95% confidence interval: 2.6795–241.4981) significantly predicted good neurological function at discharge.

4. Discussion

Prolonged cardiac arrest due to refractory ventricular fibrillation represents an extremely critical status that can result in poor outcomes through C-CPR alone. Our results demonstrate that resuscitation with ECMO support (E-CPR) might produce outcomes that are more favorable for patients.

Overall, the survival rate was 35% in our study at discharge, with good neurological outcomes occurring in 18.3% of all patients resuscitated for refractory ventricular fibrillation at discharge. The results in our C-CPR group, with a survival rate of 27.5% and a good neurological outcome rate of 7.5%, were comparable to those in the existing literature.^{15–17} Although the survival rate of ventricular fibrillation following C-CPR improved from 15.4% in 1998 to 20.4% in 2006, neurological outcomes following refractory ventricular fibrillation have remained largely unchanged (from 7.7% to 5.6%) over the past decade.⁶ In contrast, we demonstrated particularly

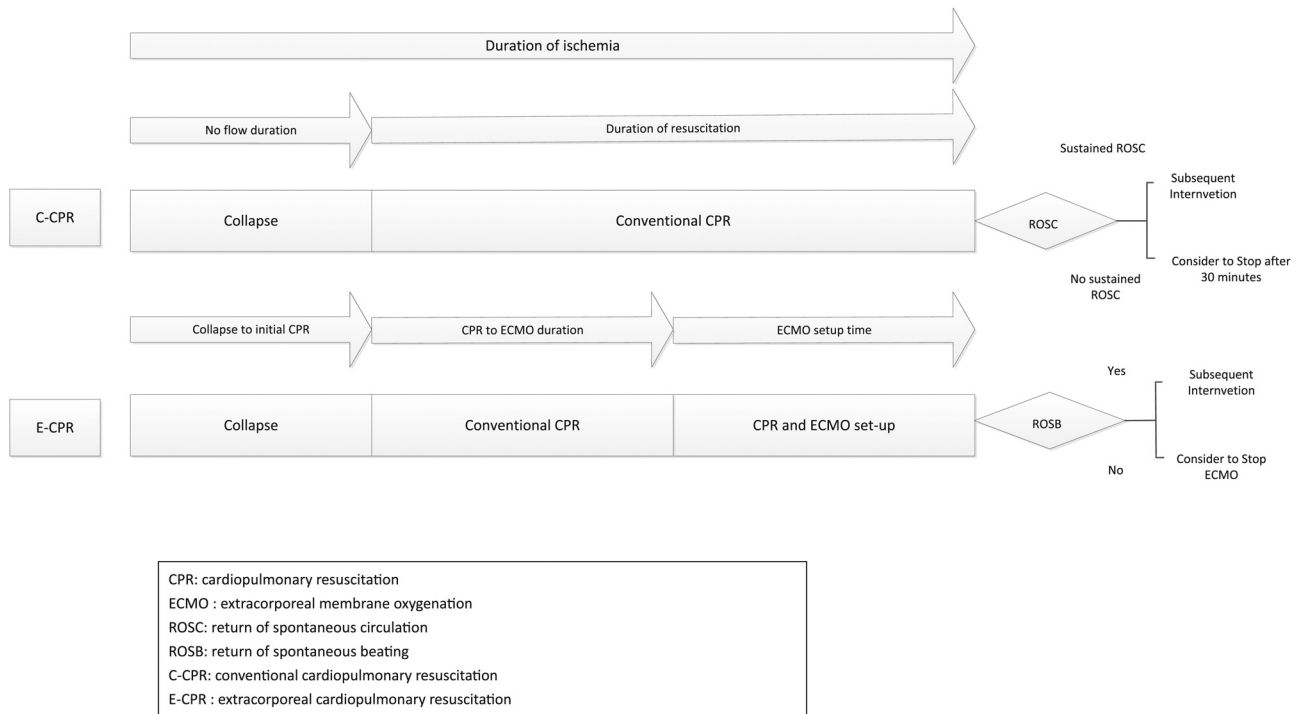


Fig. 2. Diagram for the resuscitation process.

Table 1
 Patient data and outcomes in conventional cardiopulmonary resuscitation and extracorporeal cardiopulmonary resuscitation subgroups.

| | C-CPR | E-CPR | All cases | <i>p</i> [*] |
|-----------------------------------------------------------------|-----------------|-----------------|-----------------|-----------------------|
| Case no (<i>n</i>) | 40 | 20 | 60 | |
| Age, year, mean (SD) | 60.28 (11.23) | 54.55 (11.94) | 58.37 (11.70) | 0.074 |
| Sex (M/F) | 28/12 | 18/2 | 36/14 | 0.178 |
| OHCA/IHCA | 30/10 | 11/9 | 41/19 | 0.2021 |
| Resuscitation drug usage | | | | |
| Amiodarone, mg, mean (SD) | 497.03 (205.23) | 583.33 (261.78) | 526.90 (227.63) | 0.1963 |
| Epinephrine, mg, mean (SD) | 8.29 (4.52) | 11.17 (4.37) | 9.29 (4.63) | 0.032 |
| Duration of resuscitation, min (SD) | 34.38 (17.71) | 69.90 (49.60) | 46.22 (35.84) | 0.0001 |
| Episodes of defibrillation, times, mean (SD) | 6.56 (3.66) | 9.72 (4.20) | 7.65 (4.12) | 0.0069 |
| Lactate level, IU/ml, mean (SD) | 8.25 (5.54) | 8.90 (2.29) | 8.63(3.92) | 0.6580 |
| Comorbidity disease | | | | |
| Coronary artery disease, <i>n</i> (%) | 18 (45%) | 13 (65%) | 31 (51.7%) | 0.2351 |
| Hypertension, <i>n</i> (%) | 17 (42.5%) | 13 (65%) | 30 (50%) | 0.1709 |
| Diabetes mellitus, <i>n</i> (%) | 17 (42.5%) | 8 (40%) | 25 (41.67%) | 0.9262 |
| Pulmonary disease, <i>n</i> (%) | 6 (15%) | 4 (20%) | 10 (16.67) | 0.9025 |
| Renal insufficiency, <i>n</i> (%) | 11 (27.5%) | 4 (20%) | 15 (25%) | 0.7518 |
| Chronic liver disease, <i>n</i> (%) | 6 (15.0%) | 2 (10.0%) | 8 (13.3%) | 0.8932 |
| Hyperlipidemia | 9 (22.5%) | 7 (35.0%) | 16 (26.67%) | 0.4700 |
| Cause of cardiac arrest | | | | 0.2084 |
| Acute myocardial infarction | 16 (40%) | 12 (60%) | 28 (46.67%) | |
| Cardiomyopathy | 4 (10%) | 2 (10%) | 6 (10%) | |
| Suspected myocarditis | 0 (0%) | 2 (10%) | 2 (3.3%) | |
| Valvular heart disease | 1 (2.5%) | 0 (0%) | 1 (1.7%) | |
| Respiratory disease | 6 (15%) | 2 (10%) | 8 (13.3%) | |
| Electrolyte/toxin | 6 (15%) | 1 (5%) | 7 (11.7%) | |
| Others | 7 (17.5%) | 1 (5%) | 8 (13.3%) | |
| Sustained ROSC/ROSB, <i>n</i> (%) | 19 (47.5%) | 19 (95.0%) | 38 (63.3%) | 0.0009 |
| Subsequent intervention | | | | |
| PCI | 16 (40%) | 12 (60%) | 28 (46.67%) | 0.2343 |
| IABP | 10 (25%) | 10 (50%) | 20 (33.3%) | 0.0998 |
| Therapeutic hypothermia, <i>n</i> (%) | 9 (22.5%) | 9 (45%) | 18 (30%) | 0.3136 |
| Survival to discharge, <i>n</i> (%) | 11 (27.5%) | 10 (50%) | 21 (35%) | 0.1512 |
| Good neurological function at discharge, <i>n</i> (%) | 3 (7.5%) | 8 (40%) | 11 (18.33%) | 0.0067 |
| 1 year survival, <i>n</i> (%) | 10 (25%) | 10 (50%) | 20 (33.3%) | 0.0998 |
| Good neurological function (CPC 1 or 2) at 1 year, <i>n</i> (%) | 3 (7.5%) | 8 (40%) | 11 (18.33%) | 0.0067 |

CPR, cardiopulmonary resuscitation (C-CPR = conventional CPR, E-CPR = CPR with ECMO support); ROSC, return of spontaneous circulation; ROSB, return of spontaneous beating; ECMO, extracorporeal membrane oxygenation; SD, standard deviation; ICU, intensive care unit; CPC, cerebral performance category; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest.

* Comparison between the C-CPR and E-CPR groups.

Table 2
Patient data and outcomes in extracorporeal cardiopulmonary resuscitation subgroups (survivor vs non-survivor).

| | Survivor | Non-survivor | <i>p</i> |
|-------------------------------------------------|-----------------|-----------------|----------|
| Case | 10 | 10 | |
| Sex (M/F) | 8/2 | 10/0 | 0.4561 |
| Age, year, mean (SD) | 55.9 (12.56) | 53.20 (11.80) | 0.626 |
| IHCA/OHCA | 6/4 | 3/7 | 0.3687 |
| Resuscitation drug usage | | | |
| Amiodarone, mg, mean (SD) | 583.33 (355.32) | 583.33 (139.19) | 1.0 |
| Ephiephrine, mg, mean (SD) | 10.89 (3.89) | 11.44 (5.03) | 0.796 |
| Cause of cardiac arrest | | | |
| Acute myocardial infarction (n, %) | 8 (80%) | 4 (40%) | 0.1709 |
| No-flow duration (min, collapse to initial CPR) | 1–4 | 1–5 | 0.07 |
| CPR to ECMO duration, min, mean (SD) | 56.5 (62.02) | 41.5 (25.73) | 0.489 |
| Median, min | 37.5 | 31 | 0.9698 |
| Range, min | 15–226 | 17–75 | |
| ECMO set-up time, min, mean (SD) | 18.80 (2.20) | 17.70 (3.95) | 0.451 |
| ECMO duration, h, mean (SD) | 77.90 (27.45) | 81.44 (42.81) | 0.207 |
| Lactate level, IU/ml, mean (SD) | 8.04 (1.97) | 9.97 (2.30) | 0.07 |

CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; SD, standard deviation; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest.

good neurological outcomes (40%) in those receiving E-CPR, which suggests that the addition of ECMO support may be a helpful tool in patients with refractory ventricular fibrillation.

The management of prolonged cardiac arrest due to refractory ventricular fibrillation is a clinical challenge. Among the various etiologies of cardiac arrest, when ventricular fibrillation is the initial rhythm, the outcome is relatively favorable. Following the increased use of automated external defibrillators in public, early defibrillation has improved the survival rate from this arrhythmia.¹⁸ However, management becomes challenging when the rhythm becomes “shock-resistant” in the emergency department, and there are no current guidelines for its management.¹⁴ A few case reports have illustrated successful beta-blocker use in patients with refractory ventricular fibrillation.¹⁹ Hassan et al.,²⁰ have tried magnesium sulfate, but showed similar survival rates of 4% compared to 2% for conventional therapy. Harayama et al.,²¹ reported 28% and 18% rates of survival to discharge with nifekalant and amiodarone, respectively. However, neither of these reports showed survival advantages or improved neurological outcomes over conventional therapy. Recently, case reports have indicated that ECMO, as an adjunct to cardiac resuscitation, can produce good outcomes for patients with refractory ventricular fibrillation.^{9–13} We previously reported a successful case of refractory ventricular fibrillation resuscitated with ECMO after 250 min of C-CPR.¹¹ However, the use of ECMO for prolonged cardiac arrest with refractory fibrillation in the emergency department is limited to case reports. The current study shows the favorable neurological outcomes in this setting and our finding is consistent with the recent published CHEER trial (Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion)²² with a protocol including E-CPR instituted by critical care physicians for refractory cardiac arrest (including mechanical CPR, therapeutic hypothermia and ECMO) showing a 54% survival rate with intact neurologic outcome.

Table 3
Logistic regression analysis of factors associated with survival to discharge.

| Variable | Odds ratio | 95% CI |
|--------------------------------|------------|----------------|
| Age (years) | 1.0224 | 0.9642–1.0841 |
| CPR duration (min) | 0.9658 | 0.9228–1.0108 |
| Use of ECMO | 4.1016 | 0.7914–21.2577 |
| Defibrillation (times) | 1.0105 | 0.7925–1.2884 |
| Female gender | 0.3738 | 0.0624–2.2410 |
| Use of therapeutic hypothermia | 3.3651 | 0.8936–12.6715 |

Results are odds ratios and 95% confidence intervals. ECMO, extracorporeal membrane oxygenation.

In the 2010 advanced cardiac life support (ACLS) guidelines, it is noted that there is insufficient evidence to recommend the routine use of E-CPR for patients in cardiac arrest.²³ A previous study from Taiwan found that E-CPR resulted in a higher survival rate compared with C-CPR (19.6% vs 13.0%), but that it had similar neurological outcomes following in-hospital cardiac arrest.¹⁵ A study of witnessed out-of-hospital cardiac arrest in Japan reported overall survival of 29.2% and 8.3% for E-CPR and C-CPR, respectively.²⁴ Although ECMO support could promote coronary blood flow and increase the rate of ROSC,²⁵ its use is restricted to the cost and the limited impact on neurological outcome. Therefore, the potential sub-group that can benefit from E-CPR is poorly characterized.^{7,8}

In this study, we aimed to target a specific group of patients with witnessed cardiac arrest due to refractory ventricular fibrillation. All patients received repeat defibrillation attempts and high doses of epinephrine and amiodarone, and the overall survival rate of 35% was higher than that previously reported.⁶ The study showed a trend toward a higher rate of survival in the E-CPR group compared with the C-CPR group (50% vs 27.5%, *p* = 0.1512). We also found a significantly higher rate of sustained ROSC/ROSB in the E-CPR group compared with that in the C-CPR group, despite the higher frequency of defibrillation and the higher doses of epinephrine in the E-CPR group. We believe that patients in the E-CPR group with a high rate of sustained ROSC/ROSB resulted from the use of ECMO support. During resuscitation, sustained ROSC/ROSB provides adequate time for subsequent intervention and contributes to survival to discharge and good neurological function. For example, in a case of acute coronary syndrome with refractory ventricular fibrillation,¹⁰ the achievement of sustained ROSC/ROSB allowed emergency coronary angiography and prompt percutaneous coronary intervention. In another case of hyperkalemia with refractory ventricular fibrillation,⁹ subsequent dialysis was not possible without ECMO support. Therefore, E-CPR

Table 4
Logistic regression analysis of factors associated with good neurological function at discharge.

| Variable | Odds ratio | 95% CI |
|--------------------------------|------------|-----------------|
| Age (years) | 1.0621 | 0.9757–1.1561 |
| CPR duration (min) | 0.9695 | 0.9194–1.0223 |
| Use of ECMO | 25.4382 | 2.6795–241.4981 |
| Defibrillation (times) | 0.9907 | 0.7366–1.3325 |
| Female gender | 1.2560 | 0.1190–13.2589 |
| Use of therapeutic hypothermia | 1.1057 | 0.1870–6.5362 |

Results are odds ratios and 95% confidence intervals. ECMO, extracorporeal membrane oxygenation.

appears suitable for the management of cardiac arrest due to refractory ventricular fibrillation.

Generally, the longer the duration of CPR, the more severe are the complications. These include gastrointestinal bleeding, acute renal injury, multiple organ failure, and brain death,²⁶ leading to greater mortality. Given that prolonged CPR results in a significant elevation in lactate levels, the high level of lactate may be a chemical marker of poor perfusion. For example, a previous report indicated that lactate levels were associated with neurological defects in patients resuscitated from ventricular fibrillation.²⁷ In addition, a recent animal study regarding ventricular fibrillation demonstrated a significant improvement in survival after 15 min of normothermic cardiac arrest with the use of an ECMO-based life support system to optimize blood pressure and flow.²⁸ These results support our hypothesis that using ECMO to control circulatory pressure and flow after arrest may be superior to C-CPR. Despite the longer resuscitation times for E-CPR (69.90 min vs 34.38 min for E-CPR vs C-CPR; $p = 0.0001$) in our patients, we found no differences in the blood lactate levels (8.90 vs 8.25 mmol L⁻¹ for E-CPR vs C-CPR, $p = 0.6580$) between the two groups, suggesting that ECMO may have helped to maintain tissue perfusion despite the prolonged resuscitation times.

In addition, a major complication of prolonged cardiac arrest is brain damage. Previous reports have indicated that therapeutic hypothermia with body temperature 32–34 °C for 12–24 h can improve neurological outcomes and decrease mortality in comatose patients following a cardiac arrest.²⁹ Although therapeutic hypothermia was considered when the patients remain comatose after ROSC in the 2010 AHA guideline, the use of therapeutic hypothermia was currently not covered by the health insurance in Taiwan.³⁰ Thus, this limits the universal use of such strategy in our intensive care unit. In our study, good neurological outcomes were more common in the E-CPR group compared with the C-CPR group (40% vs 7.5%, $p = 0.0067$). Despite the E-CPR group received more therapeutic hypothermia (45%) than the C-CPR group (22.5%), the use of ECMO was the only significant factor associated with good neurological function in this study. The recent Target Temperature Management trial (TTM-trial) randomized controlled trial involving 939 patients after cardiac arrest found therapeutic hypothermia with a targeted temperature of 33 °C did not confer benefit as compared with a targeted temperature of 36 °C.³¹ In fact, the body temperature usually fell below 36 °C after ROSC due to prolonged resuscitation in our observation. Only four patients (two in E-CPR group and two in C-CPR group) with a body temperature more than 36 °C did not receive therapeutic hypothermia in our study. This may explain why the benefit from therapeutic hypothermia is not found in this study. Our study suggests that the timely use of ECMO helped to maintain perfusion to vital organs such as the myocardium and the brain during the resuscitation process, which contributed to improved neurological outcomes.³²

This study has several limitations, notably that it was a retrospective observational study rather than a randomized controlled trial. It is not possible to randomize our patients to E-CPR or C-CPR in clinical practice. Indeed, although we provide informative data comparing E-CPR with C-CPR, the former is not a standard emergency department therapy. Because E-CPR is not routinely available, our findings cannot be generalized to emergency departments where ECMO is unavailable. Even in our department, clinicians may opt to use ECMO in younger patients with underlying coronary artery disease. While we concede that this may have led to selection bias and unduly favorable outcomes, we also observe that the E-CPR group had unfavorable features with prolonged CPR duration. A prolonged CPR times is known to decrease the survival and good neurological function rates. In addition, hypothermia is considered a useful therapeutic approach in unconscious patients

after ROSC but the optimal use (i.e. method, timing, target temperature, duration, indication) of therapeutic hypothermia is not standardized^{23,31} and is not routinely used in our daily practice. Our finding that ECMO rather than hypothermia contributed to intact neurological recovery is interesting and a large prospective study will be needed to explore their roles in refractory ventricular fibrillation. Finally, candidates who gain the most benefit from ECMO during cardiac arrest remain unclear, which is a critical issue given the cost of ECMO. Although our study is retrospective and limited the use of ECMO to specific cases, our finding suggest a favorable survival outcome using ECMO. Therefore, we believe that future studies on ECMO for this indication are warranted.

5. Conclusions

The management of refractory ventricular fibrillation in the emergency department is challenging, confirmed by an overall survival rate of 35% in this study. Patients with refractory ventricular fibrillation receiving E-CPR tended to have higher survival rates and significantly improved neurological outcomes when compared with those receiving C-CPR.

Conflict of interest statement

The authors declare that they have no competing interests.

Authors' contribution

FYS and HHY conceived and designed the study. Chun-Chieh Chiu and FYS contributed equally to draft the manuscript and approved of the manuscript. All authors read and approved the final manuscript. All authors contributed substantially to the revision of the manuscript. CWC, YCC, YLC, YKH, CHL, CTW, Chu-Chung Chou took care of the patients and also involved in final approval of the manuscript.

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References

- Shih CL, Lu TC, Jerng JS, et al. A web-based Utstein style registry system of in-hospital cardiopulmonary resuscitation in Taiwan. *Resuscitation* 2007;72:394–403.
- Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to novel therapies? *Circulation* 2013;128:2488–94.
- Chang MY, Lin M. Predictors of survival and hospital outcome of prehospital cardiac arrest in southern Taiwan. *J Formos Med Assoc* 2005;104:639–46.
- Chen YS, Yu HY, Huang SC, et al. Extracorporeal membrane oxygenation support can extend the duration of cardiopulmonary resuscitation. *Crit Care Med* 2008;36:2529–35.
- Enohumah KO, Moerer O, Kirmse C, Bahr J, Neumann P, Quintel M. Outcome of cardiopulmonary resuscitation in intensive care units in a university hospital. *Resuscitation* 2006;71:161–70.
- Sakai T, Iwami T, Tasaki O, et al. Incidence and outcomes of out-of-hospital cardiac arrest with shock-resistant ventricular fibrillation: data from a large population-based cohort. *Resuscitation* 2010;81:956–61.
- Thiagarajan RR. Extracorporeal membrane oxygenation to support cardiopulmonary resuscitation: useful, but for whom? *Crit Care Med* 2011;39:190–1.
- Teschendorf P, Bernhard M. A bridge to life: ECPR who, when, where and why? *Resuscitation* 2014;85:709–10.
- Chiu CC, Yen HH, Chen YL, Siao FY. Severe hyperkalemia with refractory ventricular fibrillation: successful resuscitation using extracorporeal membrane oxygenation. *Am J Emerg Med* 2014;32:943.e5–6.
- Chiu CC, Chiu CW, Chen YC, Siao FY. Cardiac arrest with refractory ventricular fibrillation: a successful resuscitation using extracorporeal membrane oxygenation. *Am J Emerg Med* 2013;31:264.e1–2.

11. Chiu CW, Yen HH, Chiu CC, Chen YC, Siao FY. Prolonged cardiac arrest: successful resuscitation with extracorporeal membrane oxygenation. *Am J Emerg Med* 2013;31:1627.e5–6.
12. Leung J, Finckh AS, Jansz P, Pye R, Nicholls M, Wilson SH. Extracorporeal membrane oxygenation as a resuscitation measure in the emergency department. *Emerg Med Australas* 2010;22:85–7.
13. Brown DF, Jaffer FA, Baker JN, Gurol ME. Case records of the Massachusetts General Hospital. Case 28-2013. A 52-year-old man with cardiac arrest after an acute myocardial infarction. *N Engl J Med* 2013;369:1047–54.
14. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999;341:871–8.
15. Chen YS, Lin JW, Yu HY, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet* 2008;372:554–61.
16. Sakamoto T, Morimura N, Nagao K, et al. SAVE-J Study Group. Extracorporeal cardiopulmonary resuscitation versus conventional cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: a prospective observational study. *Resuscitation* 2014;85:762–8.
17. Johnson NJ, Acker M, Hsu CH, et al. Extracorporeal life support as rescue strategy for out-of-hospital and emergency department cardiac arrest. *Resuscitation* 2014.
18. Weisfeldt ML, Everson-Stewart S, Sitlani C, et al. Resuscitation outcomes consortium investigators. Ventricular tachyarrhythmias after cardiac arrest in public versus at home. *N Engl J Med* 2011;364:313–21.
19. Driver BE, Debaty G, Plummer DW, Smith SW. Use of esmolol after failure of standard cardiopulmonary resuscitation to treat patients with refractory ventricular fibrillation. *Resuscitation* 2014;85:1337–41.
20. Hassan TB, Jagger C, Barnett DB. A randomised trial to investigate the efficacy of magnesium sulphate for refractory ventricular fibrillation. *Emerg Med J* 2002;19:57–62.
21. Harayama N, Nihei S, Nagata K, et al. Comparison of nifekalant and amiodarone for resuscitation of out-of-hospital cardiopulmonary arrest resulting from shock-resistant ventricular fibrillation. *J Anesth* 2014;28:587–92.
22. Stub D, Bernard S, Pellegrino V, et al. Refractory cardiac arrest treated with mechanical CPR, hypothermia, ECMO and early reperfusion (the CHEER trial). *Resuscitation* 2014. <http://dx.doi.org/10.1016/j.resuscitation.2014.09.010> [Epub ahead of print].
23. Cave DM, Gazmuri RJ, Otto CW, et al. Part 7: CPR techniques and devices: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010;122:S720–8.
24. Maekawa K, Tanno K, Hase M, Mori K, Asai Y. Extracorporeal cardiopulmonary resuscitation for patients with out-of-hospital cardiac arrest of cardiac origin: a propensity-matched study and predictor analysis. *Crit Care Med* 2013;41:1186–96.
25. Stub D, Byrne M, Pellegrino V, Kaye DM. Extracorporeal membrane oxygenation to support cardiopulmonary resuscitation in a sheep model of refractory ischaemic cardiac arrest. *Heart Lung Circ* 2013;22:421–7.
26. Massetti M, Tasle M, Le Page O, et al. Back from irreversibility: extracorporeal life support for prolonged cardiac arrest. *Ann Thorac Surg* 2005;79:178–83, discussion 183–4.
27. Mullner M, Sterz F, Domanovits H, Behringer W, Binder M, Laggner AN. The association between blood lactate concentration on admission, duration of cardiac arrest, and functional neurological recovery in patients resuscitated from ventricular fibrillation. *Intensive Care Med* 1997;23:1138–43.
28. Trummer G, Foerster K, Buckberg GD, et al. Superior neurologic recovery after 15 minutes of normothermic cardiac arrest using an extracorporeal life support system for optimized blood pressure and flow. *Perfusion* 2014;29:130–8.
29. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–56.
30. Wang CH, Chou NK, Becker LB, et al. Improved outcome of extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest – a comparison with that for extracorporeal rescue for in-hospital cardiac arrest. *Resuscitation* 2014;85:1219–24.
31. Nielsen N, Wetterslev J, Cronberg T, et al. TTM trial investigators. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med* 2013;369:2197–206.
32. Aoyama N, Imai H, Kurosawa T, et al. Therapeutic strategy using extracorporeal life support, including appropriate indication, management, limitation and timing of switch to ventricular assist device in patients with acute myocardial infarction. *J Artif Organs* 2014;17:33–41.