Predictors of mortality after extracorporeal cardiopulmonary resuscitation

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Despite advances in cardiopulmonary resuscitation (CPR), survival to hospital discharge after cardiac arrest (CA) remains poor,¹⁻³ with CPR duration greater than 20 minutes portending a rapid decline in rate of return of spontaneous circulation (ROSC) and subsequent survival to hospital discharge.⁴⁻⁶

By supplanting native heart function and restoring whole body and brain perfusion, extracorporeal membrane oxygenation (ECMO) can rapidly stabilise haemodynamics and restore end-organ function.^{7,8} With improvement in pump and circuit technology, and the ability to rapidly deploy support percutaneously at the bedside, ECMO has emerged as a promising adjunct to CPR. Several studies have shown the feasibility of extracorporeal CPR (ECPR) during refractory CA.⁹⁻¹²

The American Heart Association lists ECPR for refractory CA as a Class IIb recommendation, with consideration when "ROSC is not rapidly achieved after cardiac arrest".¹ The guidelines do not further define indications for ECPR deployment, reflecting an ongoing need to identify patients who could benefit from this resource-intensive technology.

Our centre reported a 54% neurologically favourable survival to hospital discharge in the CHEER trial¹³ — a pilot study of 26 patients with refractory CA treated with the bundle of mechanical CPR, hypothermia, ECMO and early coronary revascularisation. The current study reviews all ECPR cases at our centre to assess the impact of pre-ECMO variables on outcome to improve patient selection.

Materials

Design

This study is a retrospective analysis of a prospective cohort of patients initiated on ECPR for refractory CA.

Setting

All work was performed at the Alfred Hospital, an academic quaternary referral hospital in Melbourne, Vic, serving as the state referral centre for heart and lung transplantation, ventricular assist devices (VADs), and ECMO. The ECPR program started in January 2012, and is staffed 24 hours per day, 7 days per week.

ABSTRACT

Objective: Extracorporeal membrane oxygenation (ECMO) is a promising adjunct to cardiopulmonary resuscitation (CPR) in refractory cardiac arrest (CA). Factors associated with outcome are incompletely characterised. The aim of our study was to identify pre-ECMO factors associated with inhospital mortality after extracorporeal CPR (ECPR).

Design: Retrospective analysis of a prospective cohort of patients.

Setting: Academic quaternary referral hospital.

Participants: All patients who underwent ECPR from January 2012 through April 2017.

Interventions: A retrospective chart review was performed for CPR and ECMO. A multivariable logistic regression was performed to identify factors associated with mortality after ECPR.

Main outcome measures: Primary outcome was inhospital mortality. Secondary outcomes included survival with favourable neurologic outcome, days on ECMO, and intensive care unit (ICU) length of stay.

Results: During the study period, 75 patients received ECPR. Median age was 59 years, 81% were male, 51% had outof-hospital CA, and 57% had an initial shockable rhythm. Median time from arrest to ECMO was 91 minutes (IQR, 56–129) for non-survivors and 51 minutes (IQR, 37–84) for survivors (P = 0.02). Twenty-six patients (39%) were successfully separated from ECMO, with 31% surviving to hospital discharge and 29% with a cerebral performance category score of 1 or 2. In multivariable analysis, significant predictors of in-hospital mortality were ongoing CPR at the time of ECMO initiation (P < 0.01) and arrest to ECMO cannulation time (P = 0.02).

Conclusion: Following ECPR, the factors most strongly associated with mortality were ongoing CPR at the time of ECMO initiation and arrest to ECMO cannulation time. Interventions aimed at reducing time to ECMO initiation may lead to improved outcomes.



Patients

All patients who underwent ECPR from January 2012 through April 2017 were included. ECPR deployment was defined as a decision to initiate ECMO while a patient was receiving CPR. Institutional inclusion and exclusion criteria were previously published¹³ and are listed in Table 1.

Extracorporeal cardiopulmonary resuscitation

Members of the ECPR team include two critical care physicians for cannulation, a physician for ultrasound guidance, an ECMO specialist for circuit management, and a physician for coordination of resuscitation.

Once the decision for ECPR is made, a mechanical CPR device is applied. Percutaneous cannulation of femoral vessels is performed using the Seldinger technique under ultrasound guidance. The ECMO circuit consists of a Rotaflow pump (Maquet, Wayne, NJ, USA) and a Quadrox-iD oxygenator (Maquet, Wayne, NJ, USA). During cannulation, no defibrillation is performed and CPR is paused for vessel puncture and guidewire placement. 17Fr venous and 15Fr arterial cannulae (Medtronic, Minneapolis, MN, USA, or Maquet, Rastatt, Germany) are used. Anticoagulation is achieved with heparin bolus and infusion. Once ECMO is initiated, mechanical CPR is discontinued. Circuit blood flow is titrated to markers of perfusion, such as mean arterial pressure, venous saturation, lactate, and urine output. There is no targeted management of partial pressure of

Table 1. Extracorporeal cardiopulmonary resuscitationinclusion and exclusion criteria

Inclusion criteria	Exclusion criteria			
Age, 12–70 years (OHCA, IHCA)	Do not resuscitate order (OHCA, IHCA)			
Witnessed arrest (OHCA)	Pre-arrest neurologic status severely impaired (OHCA, IHCA)			
Shockable rhythm as initial rhythm (OHCA)	Chronic organ dysfunction limiting quality of life (OHCA, IHCA)			
CPR initiated within 10 min of collapse (OHCA)	Advanced malignancy with limited life expectancy (OHCA, IHCA)			
CPR > 10 min without ROSC, or with ROSC but inadequate circulation with persistently low cardiac output (OHCA, IHCA)	Arrest time > 60 min (OHCA, IHCA)			
Aetiology of arrest likely to be of reversible cardiac or respiratory aetiology (OHCA, IHCA)	Contraindication to anticoagulation (OHCA, IHCA)			
CPR = cardiopulmonary resuscitation. IHCA = in-hospital cardiac arrest. OHCA = out-of-hospital cardiac arrest. ROSC = return of				

oxygen or partial pressure of carbon dioxide and the circuit is run on unblended oxygen.

If a cardiac aetiology of arrest is suspected, coronary angiography and intervention are performed, as indicated. Upon arrival to the intensive care unit (ICU), a distal perfusion cannula is percutaneously placed in the superficial femoral artery of the limb with the arterial cannula under ultrasound guidance. Before publication of the TTM (Target Temperature Management after Cardiac Arrest) trial,¹⁴ all patients underwent mild therapeutic hypothermia at 33°C, but since December 2013, targeted temperature management at 36°C has been adopted. Patients are maintained on ECMO until weaning is possible due to cardiac recovery, VAD implantation, or support is withdrawn for futility.

Data collection

All patients receiving ECMO are prospectively entered into a database from which we identified patients who received ECPR and performed a retrospective chart review for data collection.

Demographic data included patient age, gender, arrest location, whether the patient was retrieved from another centre, and aetiology of cardiac arrest.

Cardiac arrest data included initial rhythm, whether arrest was witnessed, whether bystander CPR was performed, times from arrest to paramedics, defibrillation, emergency department (ED) arrival, time in ED, total CPR time, mechanical CPR device use and duration of use, and whether ROSC was obtained before ECMO initiation.

ECPR data included whether CPR was ongoing on ECMO initiation, time from arrest to ECMO initiation, time from last ROSC to ECMO, whether a perfusing rhythm (defined as the absence of asystole, ventricular tachycardia, or ventricular fibrillation) was present on ECMO initiation, whether pulsatility (defined as a pulse pressure of at least 10 mmHg) was present on ECMO initiation, ECMO blood flow at 4 hours, and maximum temperature in the first 24 hours after ECMO initiation.

The study was approved by the Alfred Human Research Ethics Committee (No. 80/16), which waived the need for informed consent.

Outcome measures

Primary outcome was in-hospital mortality. Secondary outcomes were survival with favourable neurologic outcome (defined as a Glasgow–Pittsburgh cerebral performance category [CPC] score of 1 or 2), number of patients successfully separated from ECMO, number of days on ECMO, ICU length of stay, number of patients transitioned to a VAD, cause-specific mortality, and number of organ donors.

spontaneous circulation.

ORIGINAL ARTICLES

Table 2. Patient and arrest characteristics				
	All patients	Survivors	Non-survivors	Р
Patient demographics				
Total number of patients	75	23	52	
Age (years), median (IQR)	50 (35–59)	53 (35–58)	49 (35–59)	0.88
Male	61 (81%)	20 (87%)	41 (79%)	0.53
Out-of-hospital cardiac arrest	38 (51%)	7 (30%)	31 (60%)	0.02
Retrieved from another centre on ECMO	21 (28%)	9 (39%)	12 (23%)	0.17
Cardiac arrest aetiology				
Acute MI	33 (44%)	7 (30%)	26 (50%)	
Non-ischaemic	8 (11%)	6 (26%)	2 (4%)	
Pulmonary embolus	10 (13%)	3 (13%)	7 (13%)	
Others	24 (32%)	7 (30%)	17 (33%)	0.04
Cardiac arrest details				
Shockable initial rhythm	43 (57%)	15 (65%)	28 (54%)	0.45
Witnessed arrest (OHCA)	31/38 (82%)	6/7 (86%)	25/31 (81%)	1.00
Bystander CPR, (OHCA)	36/38 (95%)	6/7 (86%)	30/31 (97%)	
Time (min) from arrest to paramedics (OHCA) [35 patients], median (IQR)	7 (0–11)	7 (0–10)	7 (1–11)	0.74
Time (min) from arrest to defibrillation (OHCA) [25 patients], median (IQR)	8 (2–11)	3.5 (2–8)	10 (2–14)	0.13
Time (min) from arrest to ED arrival (OHCA) [35 patients], median (IQR)	58 (44–75)	44 (23–53)	62 (47–80)	0.02
In-hospital time (min), median (IQR)	26 (20–39)	30 (15–45)	26 (20–39)	0.92
Total CPR time (min), median (IQR)	54 (36–88)	40 (20–50)	70 (42–95)	< 0.01
Mechanical CPR device use	49 (65%)	11 (48%)	38 (73%)	0.04
Mechanical CPR time (min), median (IQR)	42 (20–58)	30 (16–42)	48 (20–62)	0.09
Mechanical CPR of total CPR time (%) [41 patients], median (IQR)	56 (34–72)	44 (36–75)	61 (47–78)	0.36
ROSC at any time before ECMO initiation	33 (44%)	19 (83%)	14 (27%)	< 0.01
ECPR details				
CPR during ECMO initiation	56 (75%)	13 (57%)	43 (83%)	0.02
Time (min) from arrest to ECMO, median (IQR)	86 (46–121)	51 (37–84)	91 (56–129)	0.02
OHCA, median (IQR)	104 (84–137)	84 (40–122)	108 (88–137)	0.13
IHCA, median (IQR)	51 (30–87)	48 (35–60)	56 (30–90)	0.63
Time (min) from last ROSC to ECMO [19 patients], median (IQR)	37 (9–112)	19 (12–43)	72 (37–119)	< 0.01
Perfusing rhythm on ECMO initiation	48/68 (71%)	18/22 (82%)	30/46 (65%)	0.16
Pulsatility on ECMO initiation	34/70 (49%)	16/22 (73%)	18/48 (37%)	0.01
ECMO blood flow (L/min) at 4 h [73 patients], mean (SD)	3.4 ± 0.87	3.8 ± 0.66	3.2 ± 0.89	0.01
Maximum temperature in first 24 h (°C), median (IQR)	36.2 (35.0–36.8)	35.5 (35.0-36.8)	36.2 (35.0–36.8)	0.18

CPR = cardiopulmonary resuscitation. ECPR = extracorporeal cardiopulmonary resuscitation. ECMO = extracorporeal membrane oxygenation. ED = emergency department. IHCA = in-hospital cardiac arrest. IQR = interquartile range. MI = myocardial infarction. OHCA = out-of-hospital cardiac arrest. ROSC = return of spontaneous circulation. SD = standard deviation.

Statistical analyses

Continuous variables were expressed as mean with standard deviation or median with 25th and 75th quartiles,

and compared using Student *t* test or Mann–Whitney U test, as appropriate. Discrete variables were expressed as percentages and compared using Fisher exact test. A

P < 0.05 was taken as significant. We included pre-ECMO factors that were potentially associated with mortality in the logistic regression analysis. These variables were age, sex, diagnosis, location of CA, initial rhythm, ongoing CPR at the time of ECMO initiation, and time from arrest to cannulation. Univariable followed by multivariable logistic regression analyses were performed using these variables to determine their association with in-hospital mortality. The first category of each categorical variable included in the model provided the reference point. As arrest to ECMO duration was non-normally distributed, log-transformed values, which exhibited a normal distribution, were used in the model. The duration of arrest to ECMO cannulation was plotted against the predicted probability of in-hospital mortality obtained from the logistic regression model. Receiver operating characteristic (ROC) analysis was performed to obtain the optimal cut-off point to separate non-survivors from survivors. All statistical analyses were performed with STATA 11.2 (StataCorp, College Station, TX, USA) statistical package.

Results

Details regarding patient demographics, cardiac arrest and ECPR are listed in Table 2.

ROSC during resuscitation, and this was more common in survivors (83%) than in non-survivors (27%) (P < 0.01). For OHCA cases (n = 38), the majority were witnessed and had bystander CPR.

Extracorporeal cardiopulmonary resuscitation characteristics

All patients were cannulated via the femoral vessels. Fiftysix patients (75%) had ongoing CPR at the time of ECMO initiation. Median time from arrest to ECMO was 91 min (IQR, 56–129) for non-survivors and 51 min (IQR, 37– 84) for survivors (P = 0.02). On ECMO initiation, 65% of non-survivors and 82% of survivors (P = 0.16) exhibited a perfusing rhythm, while 37% of non-survivors and 73% of survivors (P = 0.01) had a pulsatile arterial tracing.

Outcomes

In-hospital mortality was 68% (Table 3). Twenty-six patients (35%) were successfully separated from ECMO and 23 (31%) survived to hospital discharge, of which 22 of 23 (96%) had a good neurological outcome with a CPC score of 1 or 2. Median times on ECMO support and ICU length of stay were shorter in non-survivors compared with survivors (median, 1 [IQR, 0–2] v 4 [IQR, 3–9] days and 1 [IQR, 1–3.5] v 12 [IQR, 9–18] days, respectively). Three patients were bridged to a VAD, with one subsequently receiving heart transplantation. Among patients who died, 7 (13%) became organ donors.

able 3. Patient outcomes				
	All patients	Survivors	Non-survivors	Р
Total number of patients	75	23	52	
Outcomes				
Survival to hospital discharge	23 (31%)			
► CPC 1-2	22 (29%)			
CPC 3	1 (1%)			
Separated from ECMO	26 (35%)	20 (87%)	6 (12%)	< 0.01
Transitioned to VAD	3 (4%)	3 (13%)	0 (0%)	< 0.01
ECMO duration (days), median (IQR)	2 (0–5)	4 (3–9)	1 (0–2)	< 0.01
ICU length of stay (days), median (IQR)	3 (1–10)	11.5 (9–18)	1 (1–3.5)	< 0.01
Cause-specific mortality				
Progressive multi-organ failure			23 (44%)	
Hypoxic brain injury			18 (35%)	
ECMO-related complication			6 (12%)	
Type A aortic dissection			3 (6%)	
Persistent left ventricular dysfunction			2 (4%)	
Organ donation			7 (13%)	

CPC = cerebral performance category. ECMO = extracorporeal membrane oxygenation. ICU = intensive care unit. IQR = interquartile range. ROSC = return of spontaneous circulation. VAD = ventricular assist device.

Patient demographics

During the study period, 319 patients received ECMO support, of which 75 received ECPR — all 75 patients are included. Median age was 50 years (interquartile range [IQR], 35–59) and 61 patients (81%) were male. There were similar numbers of out-of-hospital (OHCA) (n = 38) and in-hospital cardiac arrests (IHCA) (n = 37), and acute myocardial infarction was the most common aetiology (44%).

Arrest characteristics

Forty-three patients (57%) had an initial shockable rhythm. Nonsurvivors had a longer median CPR time compared with survivors (70 [IQR, 42–95] v 40 [IQR, 20–50] min; P < 0.01). Mechanical CPR use, as a proportion of total CPR time, was similar among nonsurvivors (61%) and survivors (44%) (P = 0.36). Thirty-three patients (44%) had intermittent

Table 4. Multivariate analysis of factors associated with mortality after
extracorporeal cardiopulmonary resuscitation

Factors	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Р
Age categories			
15–45*			
46–65	0.79 (0.28–2.19)	0.58 (0.11–2.94)	
≥ 66	2.05 (0.21–20.13)	6.03 (0.14– 251.78)	0.23
Sex			
Female*			
Male	0.56(0.14-2.23)	0.28 (0.04–2.13)	0.22
Diagnosis			
AMI*			
Cardiomyopathy and arrhythmias	0.09 (0.01–0.55)	0.20 (0.02–1.74)	
Pulmonary embolism	0.63 (0.13–3.08)	0.58 (0.05–7.57)	
Other	0.65 (0.19–2.20)	0.27 (0.03–2.27)	0.74
Location of cardiac arrest			
Out-of-hospital*			
In-hospital	0.30 (0.10–0.84)	0.64 (0.09–4.68)	0.66
Arrest rhythm			
Non-shockable*			
Shockable	0.58(0.21–1.59)	0.20 (0.03–1.48)	0.12
CPR at time of ECMO initiation			
No*			
		13.69 (2.09–	
Yes	3.68 (1.23–10.97)	89.66)	< 0.01
Total CPR time [†]	1.78 (1.05–3.02)	3.18 (1.19–8.53)	0.02

AMI = acute myocardial infarction. CPR = cardiopulmonary resuscitation. OR = odds ratio. ROSC = return of spontaneous circulation. * Reference categories. † CPR time is log-transformed in the model. The OR is interpreted as any twofold increase in CPR time is associated with odds of death equal to 3.18. This may be as low as 1.19 or as high as 8.53.

Cause of death

The most common causes of death were unsupportable circulation with progressive multi-organ failure (23 patients, 44%) followed by hypoxic brain injury (18 patients, 35%). Five patients (10%) progressed to brain death. Palliation was instituted in patients with hypoxic brain injury after prognosis was determined by a neurologist following neuroimaging, somatosensory evoked potential testing, and electroencephalogram. In the remaining patients, the cause of death was either an ECMO-related complication (6 patients, 12%), type A aortic dissection (3 patients, 6%), or persistent left ventricular dysfunction (2 patients, 3%). ECMO-related complications included haemorrhagic stroke, cannulation site bleeding, and left ventricular distension with pulmonary oedema.

Independent predictors associated with in-hospital mortality

In multivariable analysis including the pre-ECMO factors age, sex, CA aetiology, initial rhythm, ongoing CPR at the time of ECMO initiation, and arrest to ECMO duration (Table 4), significant predictors of in-hospital mortality were ongoing CPR at the time of ECMO initiation (adjusted odds ratio [OR], 13.7; 95% confidence interval [CI], 2.09-89.66; P < 0.01) and arrest to ECMO duration (adjusted OR, 3.2; 95% CI, 1.19-8.53; P = 0.02). Each doubling of interval in the duration from arrest to ECMO initiation was associated with a 3.2-fold increase in the odds of mortality. The explanatory model developed in logistic regression showed adequate discrimination and calibration (area under ROC curve = 0.87. Hosmer–Lemeshow goodness of fit test, $\chi^2_{(df = 8)} = 5.34; P = 0.72).$

Figure 1 shows the relationship between arrest to ECMO duration and probability of mortality derived from the logistic regression model. Using ROC analysis, 80 minutes were the optimal cut-off point discriminating non-survivors from survivors (sensitivity = 68.6%; specificity = 66.7%; area under the curve = 0.68; 95% CI, 0.55–0.82).

Discussion

In this observational study of all ECPR cases at a large academic centre, we found a 32% rate of survival to hospital discharge, with the majority of survivors having a favourable neurologic outcome. Primary factors associated with outcome were ongoing CPR at the time of ECMO initiation and arrest to ECMO duration, with each doubling of interval in the duration from arrest to ECMO initiation associated with a 3.2-fold increase in the odds of mortality.

Survival to hospital discharge in ECPR case series for OHCA is 15–33%, ^{11,15-24} and for IHCA 30–41%. ^{7,12,21,25-29} The largest study to date reviewed 1792 patients from the extracorporeal life support organisation registry and reported a survival to hospital discharge of 29%. ³⁰ Our results are consistent with these studies and add to the growing body of evidence supporting the role of ECPR in refractory CA.



Survival to hospital discharge in the current study is lower than previously reported for our centre in the CHEER trial.¹³ The CHEER trial included 26 patients, and survival to hospital discharge with favourable neurologic outcome was 54%. This difference may be due to several factors. First, 73% of patients in the CHEER study presented with an initial shockable rhythm compared with 57% in the current study. Second, median time from arrest to ECMO was longer in the current study than in the CHEER trial (86 [IQR, 46–121] v 56 [IQR, 40–85] min), likely reflecting the higher proportion of OHCA patients in this study (51% v 42%). Third, we noted that several patients in the OHCA group did not meet institutional selection criteria for ECPR: 8 (21%) had an initial non-shockable rhythm, 7 (18%) had unwitnessed CA, and 18 (51%) had more than 60 minutes of CPR before ECMO cannulation commencement. Finally, the CHEER study evaluated ECPR as part of a bundle of care, each of which may contribute additional survival benefit and requires further study.

We found ongoing CPR at the time of ECMO initiation to be strongly associated with in-hospital mortality. The incidence of ROSC during cannulation is variably reported to be between 10–60%,^{20,26,28,31-33} consistent with our finding of 44%. While several studies report no association between survival and ROSC before ECMO initiation, our findings agree with Ha and colleagues²⁰ and Jo and colleagues,²⁶ who report improved survival with ROSC prior to ECMO initiation. This discrepancy may relate to varying definitions of ROSC. We found that, in patients who had ROSC before ECMO initiation, some experienced sustained ROSC while others only short-lived or intermittent ROSC. It is likely that such differences account for the inconsistent correlations to survival and argue against a binary designation for ROSC in ECPR studies.

Several case series have suggested that duration of CPR before ECMO is a predictor of outcome.^{18,21,24,26,28,29,33} Lee and colleagues¹⁷ found that every 1-minute increase in CPR reduced the rate of survival to discharge by 4%, while Wang et al²¹ reported that every 1-minute increase in time to ECMO increased the hazard of mortality by 2%. We found that a doubling of CPR time was associated with increased odds of death of 3.2, with 80 minutes as a discriminatory point for predicting in-hospital survivors from non-survivors. Taken together, interventions aimed at reducing time to ECMO initiation may be associated with improved outcomes.

As ECPR use increases, concerns regarding providing a resource-intensive technology for prolonged duration to patients who are

neurologically compromised have been raised.³⁴⁻³⁶ Our results do not support these concerns. First, of the patients who survived, 22 of 23 were discharged with a favourable neurologic outcome, a finding that is in line with other studies.^{7,13,16,17,22,23,27,37} Moreover, in non-survivors, the median time on ECMO support and ICU length of stay were short, 1 day (IQR, 0-2) and 1 day (IQR, 1-3.5), respectively. This finding is notable in that it shows that patients who may not benefit from ECPR — a decision that can be challenging to discern during active resuscitation declare themselves early, as evidenced by an unsupportable circulation and progressive multi-organ failure. Other studies have also reported short ECMO runs in ECPR nonsurvivors.^{7,16,26,31,37} Finally, among non-survivors, 7 (13%) became organ donors, supporting the potential role for ECMO after CA in facilitating organ procurement in ECPR non-survivors.38,39

This study has several strengths. First, we included all patients who underwent ECPR during the study period. Second, our dataset included a large number of important pre-ECMO variables for evaluation as predictors of ECPR outcome. Finally, the inclusion of organ donation data is rarely reported but valuable as the use of ECMO in organ procurement becomes more commonplace.

The present study should be interpreted in the context of certain limitations. First, this is a single-centre study potentially limiting generalisability. Second, although the sample size is small, it is one of the largest ECPR studies. Third, while institutional ECPR guidelines were adopted, we noted deviations in selection criteria and in protocol implementation. Fourth, although we report discharge CPC score, longer term follow-up would be of additional value. Finally, while our results supporting the role of ECPR in refractory CA are encouraging, a randomised controlled trial comparing ECPR with conventional CPR is needed.

Conclusion

Following ECPR, the factors most strongly associated with mortality in our study are ongoing CPR at time of ECMO initiation and arrest to ECMO cannulation time. Interventions aimed at reducing time to ECMO initiation may lead to improved outcomes and require further study.

Competing interests

None declared.

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