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Clinical paper

Outcomes associated with delayed enteral feeding after cardiac arrest treated with veno-arterial extracorporeal membrane oxygenation and targeted temperature management

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Abstract

Introduction: While early enteral nutrition is generally preferred in critically ill patients, the optimal timing of feeding among refractory cardiac arrest patients is unknown. We examined the association between timing of enteral nutrition and patient survival and safety outcomes in patients with refractory out-of-hospital cardiac arrest (OHCA) who were treated with extracorporeal cardiopulmonary resuscitation (ECPR).

Methods: We performed a retrospective analysis of 142 consecutive patients presenting with OHCA due to ventricular fibrillation or ventricular tachycardia treated with ECPR and targeted temperature management (TTM). Neurologically favorable survival and clinical outcomes were compared between patients who received early enteral nutrition (<48 h after admission to the intensive care unit) and patients receiving delayed enteral nutrition (initiated >48 h after admission).

Results: Enteral nutrition was initiated in 90/142 (63%) patients. Early enteral nutrition was provided in 34/90 (38%) while delayed nutrition occurred in 56/90 (62%). In adjusted analysis including patients who received nutrition, delayed enteral feeding was associated with increased odds of neurologically favorable survival (29 vs 54%, CI 1.04−7.25, p = 0.04). There were no significant differences in the incidence of pneumonia (18 vs 27%, p = 0.16), gastrointestinal bleeding (5.9 vs 3.6%, p = 0.42), intestinal ischemia (5.9 vs 5.4%, p = 0.90), ileus (12 vs 11%, p = 0.98), or need for tracheostomy (15 vs 20%, p = 0.81) between early and late feeding groups.

Conclusion: In patients with refractory OHCA treated with ECPR and TTM, delayed enteral nutrition was associated with improved neurologically favorable survival. Adverse events related to enteral feeding were not associated with timing of feeding initiation.

Keywords: Nutrition, Cardiac arrest, Extracorporeal cardiopulmonary resuscitation, Targeted temperature management

Introduction

Approximately 360,000 people suffer out-of-hospital cardiac arrest (OHCA) in the United States each year.[1] Of these, one-third present to emergency medical services (EMS) with a shockable rhythm including ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT).[2,3] While presenting to EMS with a shockable rhythm is a favorable prognostic marker for survival,[4] approximately 50% of these patients are refractory to medical therapy and defibrillations, decreasing their survival to 6−15% with use of standard ACLS therapies.[5–7] Extracorporeal cardiopulmonary resuscitation (ECPR) utilizing

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veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has improved survival for these refractory patients to >40%.[6–10] However, this new patient population presents challenges with severe multi-system organ failure, cardiopulmonary resuscitation (CPR)-related trauma, and prolonged recovery times adding to the complexity of the post-arrest critical care.[11]

The optimal timing of nutrition support therapy for cardiac arrest patients remains unknown. Cardiac arrest and its associated treatments, such as vasopressors, may cause systemic ischemia and reperfusion injury. Further, patients who survive refractory cardiac arrest are subjected to prolonged CPR, VA-ECMO, and targeted temperature management (TTM). Consequently, they may be at increased risk for intestinal injury due to longer duration of hypoperfusion in addition to reduced intestinal blood flow during TTM.[12,13] Hypothermia and critical illness are also thought to cause delayed gastric emptying, decrease peristalsis, and perpetuate poor absorption which may limit the efficacy of enteral nutrition support[14] and may increase the risk of aspiration pneumonia.[15]

In contrast, early initiation of enteral nutrition has been associated with improved mortality and reduced ICU length of stay in critically ill patients leading to guidelines recommending that nutritional support be provided within 24–48 h of admission to the intensive care unit.[14,16–22] However, it is generally accepted that hypotension and vasopressor use in hemodynamically unstable patients may lead to subclinical intestinal ischemia. Thus, guidelines recommend caution when initiating enteral nutrition in patients requiring stable vasopressors while also suggesting that enteral nutrition be withheld from patients who are hypotensive or requiring escalating vasopressor doses.[22]

This study aims to examine the association between timing of initiation of enteral nutrition and neurologically favorable survival in patients suffering refractory VF/VT OHCA treated with prolonged CPR, ECPR, and TTM. In addition, feeding-associated safety outcomes are reported in relation to timing of feeding initiation.

Methods

Study population

All patients suffering refractory VF/VT OHCA presenting to the University of Minnesota refractory cardiac arrest ECPR program from December 2015 through January 2020 who met criteria for VA-ECMO cannulation and survived to ICU admission were included in the study. The study was approved by the University of Minnesota Institutional Review Board (#1703M11301).

Minnesota resuscitation consortium extracorporeal cardiopulmonary resuscitation protocol

Details of the UMN-ECPR protocol have been published previously.[8,23] Briefly, patients were screened in the pre-hospital setting by paramedics using the following criteria: 1) age 18–75 years, 2) OHCA of presumed cardiac etiology, 3) initial rhythm VF/VT, 4) received 3 direct current shocks for VF/VT without return of spontaneous circulation (ROSC) or shock resulting in conversion to ongoing pulseless electrical activity or asystole, 5) received amiodarone 300 mg, 6) body habitus accommodating a Lund University Cardiac Arrest System (LUCAS) automated CPR device, 7) estimated transfer time from scene to cardiac catheterization lab (CCL) <30 min. If appropriate, patients were rapidly transported from the pre-hospital setting directly to the University of Minnesota Cardiac Catheterization laboratory (CCL) with ongoing CPR where arterial blood gases were collected and assessed for physiologic inclusion criteria including the following: 1) $PaO_2 \geq 50$ mmHg or O_2 Sat $\geq 85\%$ and 2) lactic acid ≤ 18 mmol/L and 3) end-tidal $CO_2 > 10$ mmHg. Patients with ROSC prior to VA-ECMO initiation were not included in this analysis.

Patients with ongoing CPR who met at least two of the physiologic inclusion criteria were cannulated for VA-ECMO. Coronary angiography was performed in all patients and percutaneous coronary intervention undertaken as indicated. If a patient did not achieve an organized rhythm despite reversal of all potential etiologies and 90 min of stabilized hemodynamics with ongoing anti-arrhythmic therapy, they were declared dead in the CCL, and they were excluded from this study. All patients with an organized rhythm were admitted to the cardiovascular ICU (CVICU) on VA-ECMO.

All patients received TTM with goal temperature 32–34 °C for 24 h unless life threatening bleeding occurred necessitating a modified target of 36 °C. Anticoagulation was maintained while on VA-ECMO using heparin with an activated clotting time (ACT) goal of 180–200 s. The ACT goal was reduced for any serious bleeding, as determined by the treating physician. Sedation administration was targeted to achieve deep sedation (Richmond Agitation-Sedation Scale −5 to −4) during TTM. Neuromuscular blockade was used at the discretion of the treating physician to minimize shivering and improve time at goal temperature. Vasopressors were utilized as needed to maintain mean arterial blood pressure >65 mmHg. Feeding was initiated at the discretion of the treating physician as ordered by registered dietitians following the medical nutrition therapy protocol. Enteral nutrition was provided by gastric or post-pyloric tube as available and confirmed by X-ray. Once initiated, the feeding rate was increased to goal at the discretion of the physician in consultation with the dietician. The goal rate was calculated to provide a total average nutritional intake of 25–30 kcal/kg and 1.5–2 g of protein/kg. Standard free water flushes of 30 ml of water every 4 h were included for tube patency and adjusted per the provider based on fluid status and sodium levels.

Data collection

All patient data was gathered by retrospective review of the medical records. Patients were divided into three groups: 1) those who did not receive enteral nutritional support, 2) those who received enteral nutritional support within 48 h of CVICU admission (early), 3) and those who received enteral nutritional support more than 48 h after CVICU admission (delayed). The duration of CPR was defined as the time of CPR prior to establishing VA-ECMO. The SOFA,[24] APACHE II,[25] and NUTRIC[26] scores were calculated, as previously described, using the first vital signs and laboratory values recorded on admission to the CVICU. The vasoactive score was calculated using the highest dose of each vasopressor required each day: dobutamine (μg/kg/min) + dopamine dose (μg/kg/min) + milrinone (mcg/kg/min) + 100 × epinephrine (μg/kg/min) + 100 × norepinephrine (μg/kg/min) + 10,000 × vasopressin (units/kg/min).[27–29]

Study outcomes

The primary outcome was neurologically favorable survival to discharge from the index admission. Neurologically favorable survival was defined as Cerebral Performance Category (CPC) score of 1–2. Secondary outcomes included feeding-related safety outcomes

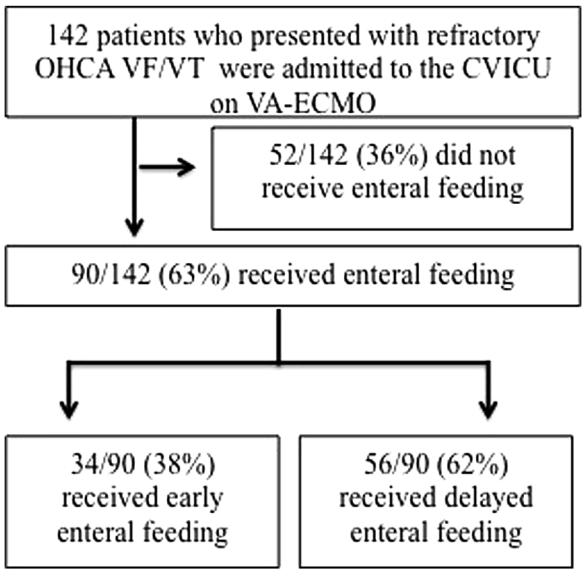

Fig. 1 – Patient flow diagram.

including ileus, gastrointestinal bleeding, intestinal ischemia, aspiration pneumonia, and the need for tracheostomy. The diagnosis of gastrointestinal bleeding was based on the judgement of the treating physician. Intestinal ischemia was diagnosed by imaging. All patients in this cohort were treated for aspiration pneumonia for five days upon admission to the CVICU in response to the high rate of intra-arrest aspiration in this patient population.[11] Therefore, pneumonia was defined as a positive sputum culture associated with clinical signs of infection including a new consolidation on chest X-ray, fever, worsening leukocytosis and/or new hemodynamic instability that prompted initiation of antibiotics at least five days after admission to the CVICU. Ability, and time, to achieve goal feeding rate and the need to suspend enteral nutritional support for >2 h were also secondary outcomes.

Statistical analysis

Clinical data were placed in a REDCap database hosted at the University of Minnesota. Data analysis was performed using IBM SPSS Statistics 22 (Armonk, NY, IBM Corporation). Frequencies and percentages were determined for categorical variables and means with standard deviations or median with interquartile range for continuous variables based on whether they were normally distributed. Categorical variables were compared with Chi-square and Fisher's exact test as required. Continuous variables were compared with independent sample t-tests or ANOVA. Associations between timing of nutrition initiation and outcomes were assessed by multiple logistic regression and were adjusted for APACHE II score and CPR duration. All hypothesis testing was done with an α level of 0.05.

Results

Baseline characteristics

Overall, 142 consecutive refractory VF/VT OHCA patients were admitted to the CVICU with VA-ECMO and TTM during the time

Table 1 – Baseline characteristics.

	Overall cohort (N = 142)	No enteral feeding (N = 52)	Early enteral feeding (N = 34)	Delayed enteral feeding (N = 56)
Demographics				
Age, years, mean (SD)	57.2 (11.8)	55.5 (11.9)	58.0 (11.7)	58.2 (11.7)
Sex, male, N(%)	117 (82.4)	44 (84.6)	24 (70.6)	49 (87.5)
Comorbidities				
BMI, mean (SD)	31.8 (9.6)	32.9 (10.6)	32.1 (12.9)	30.6 (5.2)
CHF, N(%)	20 (14.1)	5 (9.6)	9 (26.5)	6 (10.7)
Hypertension, N(%)	55 (38.7)	16 (30.8)	13 (38.2)	26 (46.4)
CAD, N(%)	38 (26.8)	10 (19.2)	9 (26.5)	19 (33.9)
Diabetes, N(%)	36 (25.4)	12 (23.0)	8 (23.5)	16 (28.6)
Hyperlipidemia, N(%)	44 (31.0)	10 (19.2)	14 (41.2)	20 (35.7)
COPD N(%)	5 (3.5)	3 (5.7)	1 (2.9)	1 (1.8)
ESRD N(%)	4 (2.8)	0 (0.0)*	4 (11.8)[a] *	0 (0.0)[a]
Characteristics of cardiac arrest				
APACHE II, mean (SD)	32.8 (4.7)	34.3 (4.2)[b]	32.4 (5.3)	31.8 (4.6)[b]
SOFA, mean (SD)	8.7 (2.0)	9.4 (1.9)[b] *	8.2 (1.8)*	8.3 (2.0)[b]
NUTRIC, mean (SD)	5.0 (0.08)	5.3 (1.1)	5.0 (1.1)	4.9 (1.3)
CPR duration, min, mean (SD)	64.2 (15.6)	69.7 (13.7)[b] *	60.6 (17.3)*	61.1 (15.0)[b]
ECMO duration, days, median, (IQR)	3.0 (2.0,5.0)	2.0 (2.0,4.0)[b] *	4.0 (3.0,5.3)*	4.0 (3.0,5.0)[b]
Neuromuscular blockade, N(%)	122 (85.9)	41 (78.8)	33 (97.1)	48 (85.7)

Abbreviations: APACHE II, acute physiology and chronic health evaluation; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; NUTRIC, nutrition risk in critically ill; SOFA, sequential organ failure assessment.

* Denotes a significant difference between no enteral feeding and early enteral feeding.

[a] Denotes a difference between early enteral feeding and delayed enteral feeding.

[b] Denotes a difference between delayed enteral feeding and no enteral feeding.

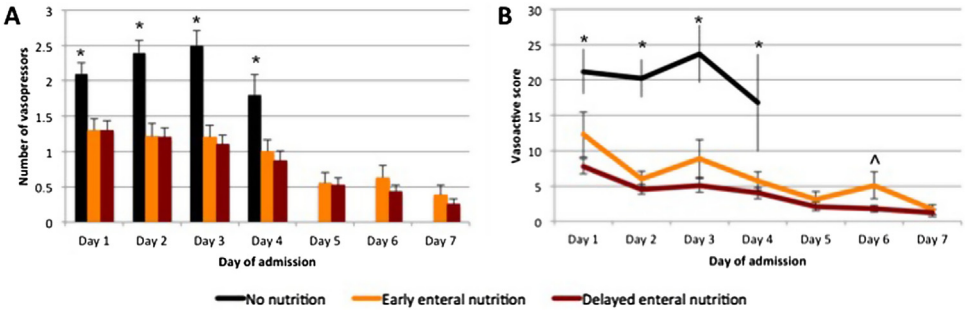

Fig. 2 – Use of vasoactive medications. A. Mean number of vasopressor medications administered per hospital day of admission. B. Vasoactive scores in patients with no enteral feeding, early feeding, and delayed enteral feeding. * Denotes a significant difference between patients who did not receive enteral nutrition and patients who were fed. + Denotes a significant difference between patients who received early enteral nutrition and those who received delayed enteral nutrition.

period studied (Fig. 1). Baseline characteristics are shown in Table 1. In the overall cohort, the majority of patients were male (82%) with a mean age of 57 ± 12 years. Pre-arrest comorbidities included diabetes mellitus in 25.4% (36/142), hypertension in 38.7% (55/142), coronary artery disease (CAD) in 26.8% (38/142), chronic renal failure requiring outpatient dialysis in 2.8% (4/142), and COPD in 3.5% (5/142) (Table 1). The mean duration of cardiopulmonary resuscitation (CPR) was 64.2 ± 15.6 min. Neuromuscular blockade was used in 85.9% (122/142) of patients. All patients underwent TTM with a mean temperature nadir of 33.5 ± 1.3 °C. Enteral feeding was started in 63% (90/142) of patients while the remaining 36% (52/142) did not receive enteral feeding during their hospital course (Fig. 1).

Characteristics of patients who received enteral feeding

Of those patients receiving enteral feeding, early feeding occurred in 34/90 (38%) and delayed feeding occurred in 56/90 (62%). There were no other differences in pre-arrest comorbidities, CPR duration, or severity of illness scores including the NUTRIC score between patients who received early enteral feeding and those who received delayed nutrition (Table 1). The never fed group had longer CPR duration, higher illness severity scores including SOFA and APACHE II (Table 1), more vasopressors used per day and a higher mean vasoactive score compared to patients that did receive enteral feeding (Fig. 2). The NUTRIC score, which predicts individuals that may benefit from early nutrition, was not significantly different between any of the groups. All of the patients who did not receive enteral nutrition died.

The time-to-initiation of enteral feeding ranged from 1 to 11 days post-admission with a mean of 3.2 ± 1.6 days. The early feeding group initiated feeding in an average of 1.3 ± 0.6 days after admission, while the delayed feeding group began feeding in 3.3 ± 1.7 days ($p < 0.001$; Table 2). Enteral feeding began upon completion of rewarming in most cases though 37 degrees was not yet achieved in all patients at the time of feeding initiation. All patients were rewarmed prior to initiation of feeding in the delayed feeding group. Most patients (64.4%) received Impact Peptide 1.5 as their initial formula. A renal formula was used if hyperkalemia occurred. Two patients in the delayed enteral feeding group recovered rapidly, were decannulated from VA-ECMO, extubated, and had conventional oral intake. The mean goal caloric intake was 27.5 ± 2.8 Kcal/kg/d with a mean time from initiation of nutrition to goal of 75.6 ± 45.8 h. Age, gender, and pre-arrest comorbidities were not associated with likelihood of receiving enteral feeding.

Neurologically favorable survival and timing of enteral feeding

In patients who received nutrition, neurologically favorable survival was more common in patients who had delayed enteral feeding (29.4% versus 53.6%, p = 0.03). This remained significant in multivariable analysis including APACHE II score and CPR duration (OR 2.74; CI 1.04–7.25, p = 0.04). Length of hospital stay was similar

Table 2 – Feeding characteristics.

	Early enteral feeding (N = 34)	Delayed enteral feeding (N = 56)	p Value
Time to TF initiation (hours)	31.2 (14.4)	79.2 (40.8)	<0.001
Goal reached	26 (76.4)	44 (78.6)	1.00
Time to goal (hours)	75.8 (52.3)	75.4 (43.2)	0.97
Goal caloric intake (Kcal/kg/d)	27.4 (3.3)	27.7 (2.6)	0.66
Feeding interruption	14 (41.2)	26 (47.3)	0.73

Abbreviation: TF, tube feed.
Proportions are stated as number (percentage), continuous variables are represented as mean (standard deviation).

Table 3 – Comparison of study outcomes by feeding group.

	Early enteral feeding (N = 34) (count, percentage)	Delayed enteral feeding (N = 56) (count, percentage)	Adjusted OR	95% CI	p Value
Primary outcome					
Neurologically favorable survival, N(%)	10 (29.4)	30 (53.6)	2.75	1.04–7.25	0.04
Secondary outcomes					
Pneumonia, N(%)	6 (17.6)	15 (26.8)	2.29	0.73–7.22	0.16
Tracheostomy N(%)	5 (14.7)	11 (19.6)	1.16	0.34–3.93	0.81
Ileus, N(%)	4 (11.8)	6 (10.7)	0.98	0.25–3.86	0.98
Intestinal ischemia, N(%)	2 (5.9)	3 (5.4)	1.13	0.16–7.87	0.90
GIB N(%)	2 (5.9)	2 (3.6)	0.31	0.02–5.34	0.42

Abbreviations: CI, confidence interval; N, number; OR, odds ratio.
All analyses were performed with multivariate logistic regression and included adjustment for CPR duration and APACHE II scores.

in both groups (18.2 ± 11.3 days in early feeding group versus 22.6 ± 20.5 days in the delayed feeding group, p = 0.26). There was no significant difference in the number of vasopressors used per day according to timing of initiation of feeding (Fig. 2A). Vasoactive scores, representing total vasopressor dose, tended to be higher in those who had early enteral feeding but was only statistically significant on day 6 (Fig. 2B).

Secondary outcomes

Nutrition was well-tolerated regardless of timing of initiation. There were no differences in the proportion of patients achieving the goal rate of enteral feeding (76.4% versus 78.6%, p = 1.00), and the time required to reach the goal rate (75.8 ± 52.3 h versus 75.4 ± 43.2 h, p = 0.97) was similar between groups (Table 2). Interruption of enteral feeding occurred in 44.4% (40/90) of patients and was not associated with timing of enteral feeding initiation. The most common reasons for interruption of feeding were need for surgical intervention in 23.3% (21/90) and ileus in 11.1% (10/90) of patients.

Overall the rate of pneumonia was 21/90 (23.3%), ileus was diagnosed in 10/90 (11%), intestinal ischemia in 5/90 (5.5%), gastrointestinal bleeding in 4/90 (4.4%), and tracheostomy in 16/90 (17.8%) (Table 3). The odds of these outcomes were similar between early and delayed feeding groups.

Discussion

This is the first study describing patterns of nutrition support and outcomes in a cohort of refractory cardiac arrest patients treated with VA-ECMO and TTM. In this study, delayed enteral nutritional support initiated >48 h after CVICU admission with a mean of 79.2 h, was associated with improved neurologically favorable survival at discharge when compared to early feeding (<48 h after CVICU admission). There were no significant differences in baseline characteristics of patients who had early versus delayed enteral feeding and the association persisted in multivariable analysis. Importantly, patients who were never fed during their index hospitalization were excluded from the analysis. Safety outcomes including intestinal ischemia, gastrointestinal bleeding, ileus, and pneumonia, were not associated with timing of initiation of enteral nutrition.

There are several potential mechanistic explanations for the improved neurological outcomes in the delayed nutrition group. First, the presence of nutrients in the small intestine leads to secretion of vasoactive hormones and a 2-fold increase in the blood flow through the superior mesenteric artery. This may lead to redistribution of the cardiac output and potentially decrease brain perfusion.[30,31] This physiology may provide one mechanism for the improved neurologically favorable survival observed in patients receiving delayed enteral nutrition. Metabolic effects such as increased serum glucose may also be considered; however, all patients in the studied cohort received an insulin drip with goal blood glucose levels of ≤150 mg/dl as previously published.[11] The potential effects of increased insulin requirements are not known. The pre-hospitalization nutritional status of the patients may also play a role in the observed outcome. The largest benefit of early enteral nutrition is expected in patients who are malnourished at presentation.[32,33] In contrast, the patients in this study were ambulatory and living independently prior to admission, which may limit the benefits of early feeding. Finally, critically ill patients have delayed gastric emptying while TTM may further potentiate gut dysmotility. This has been postulated to increase the risk of gut ischemia, aspiration, and pneumonia in post-arrest patients. Therefore, outcomes may improve if feeding begins after the patient is euthermic.[34,35] Collectively, these mechanisms inform current guidelines that advise caution when starting enteral nutrition in hemodynamically unstable patients.[22,36] The findings in this study support the application of this caution to the ECPR population.

Contrary to the results of the present study, early enteral feeding is generally considered safe in critically ill patients and has been associated with a mortality benefit.[16,17,19,20,32,37–39] Enteral nutritional support is thought to prevent malnutrition, improve wound healing, maintain intestinal integrity, and modulate stress and systemic immune responses.[17,19,40] However, given concerns for bowel ischemia and increased risk of pneumonia, feeding initiation is frequently delayed in critically ill patients.[18,20,32]

Multiple studies have examined the effects of early nutrition in cardiac arrest populations. In a retrospective analysis Joo et al. looked at more than 400 propensity score matched patients with out-of-hospital cardiac arrest receiving TTM including 13% who were also supported with ECMO. They compared patients with early enteral feeding (initiated within 48 h of admission) to all others and found no difference in 30 day mortality.[32] In another retrospective study of adults admitted for TTM after cardiac arrest, early initiation of nutrition (initiated within 48 h of admission) was associated with improved mortality (OR 0.35; CI 0.2–0.5) and better 3-month neurologic outcomes as assessed by CPC 1–2 (OR 3.47; CI 1.48–8.14) compared to late enteral feeding.[20] Importantly, in both of these studies, patients who did not receive enteral feeding were included in the delayed feeding group.

There are two important differences between the above studies and our present results. First, the refractory cardiac arrest population in our study is likely to have sustained a more severe injury related to the refractory nature of their cardiac arrest with prolonged CPR requiring VA-ECMO. Second, we excluded patients who never received enteral feeding from our analysis, as this represents a distinct treatment strategy likely chosen in response to severe illness and death. Combining the group who is never fed with the delayed nutrition cohort is likely to decrease the latter group's apparent survival.[20,32] When we included patients who were not fed at any time in the delayed feeding group, the significant difference in mortality (55.9% versus 69.4%, OR 0.56; 95% CI 0.25, 1.23; p = 0.15) and neurologically favorable survival (55.9% vs 49.1%; OR 0.92; 95% CI 0.39,2.16; p = 0.85) was negated.

Nutrition support was well tolerated in our refractory cardiac arrest population with low rates of feeding-related adverse events, regardless of timing of feeding initiation. Despite this, rates of potentially life threatening events such as intestinal ischemia and gastrointestinal bleeding, ranging between 5.5% and 4.4%, warrant consideration. Joo et al. report a much lower incidence of intestinal ischemia (0.4% based on hospital coding).[32] Our rate of intestinal ischemia was much higher (5.5%) perhaps due to the refractory arrest population with longer ischemic times and need for mechanical hemodynamic support and higher vasoactive medication requirements. Use of hospital coding data in the Joo et al. study may also underreport cases of intestinal ischemia while our study may demonstrate a higher rate of complications due to the detailed chart review and uniform use of computed tomography scanning in all patients. Rates of gastrointestinal bleeding after cardiac arrest are not widely reported. However, the rate of gastrointestinal bleeding for patients in a large VA-ECMO registry was 4.3%,[41] which is consistent with our findings. Finally, the rate of pneumonia differs widely in the literature ranging from 65% when initial aspiration pneumonia is included to 10–22% later in hospitalization.[20,32] We found that the occurrence of pneumonia after 5 days of admission was 23.3%, which is within the reported range. Timing of feeding initiation did not change the rate of pneumonia. Overall, our results are consistent with other data in cardiac arrest populations suggesting that adverse events are independent of timing of initiation of enteral nutrition. [32,42]

Our study has multiple limitations due to its retrospective and non-randomized design. Although consecutive cases spanning the entire duration of the Minnesota Resuscitation Consortium refractory cardiac arrest ECPR program were included, selection bias cannot be excluded. The decision to start enteral nutrition support and the timing of initiation was determined at the discretion of the treating physician and was not controlled. The lack of randomization may have led to selection bias that would influence the timing of initiation of nutrition. Although adjustment was performed for possible confounding, it is possible that some covariates were not addressed. Lastly, the limited size of the patient population reduces the statistical power and may underestimate some differences between the study subpopulations. Future prospective studies should focus on refining the ideal timing for nutrition initiation in this ultra-sick population and, in particular, evaluating the association of timing of feeding initiation with neurologically favorable survival.

Conclusion

In refractory VF/VT OHCA patients treated with prolonged CPR, VA-ECMO, and TTM who received nutrition, delayed enteral feeding (>48 h after admission to the CVICU) was associated with improved neurologically favorable survival compared to early feeding. Enteral nutrition was well-tolerated overall with few safety events. There were no significant associations between timing of feeding and safety events.

Authorship statement

All authors meet ICMJE recommendations for authorship as they have made substantial contributions to the design of the study, acquisition of data, interpretation of the data, drafting and revision of the article, and final approval of the manuscript.

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Conflicts of interest

None of the authors have any financial or personal relationships with people or organizations that could have inappropriately influenced this work.

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