

Article

Early Enteral Nutrition Does Not Cause Excessive Inflammatory Response in Venous-Arterial Extracorporeal Membrane Oxygenation Patients

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Abstract

Background: To evaluate the safety between early enteral nutrition (EN) and parenteral nutrition (PN) by observing changes in inflammatory cytokines and gastrointestinal hormones in venous-arterial extracorporeal membrane oxygenation (VA ECMO) patients. **Methods:** This study was a prospective, observational study that enrolled patients receiving VA ECMO treatment from 1 January 2020 to 31 December 2023. Patients were enrolled in an EN group or a PN group according to the inclusion criteria. The concentration of interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor α (TNF- α) on the first five days of VA ECMO treatment were tested in both groups. Serum concentrations of Motilin (MOT), Gastrin (GAS), Cholecystokinin (CCK), and Calcitonin gene-related peptide (CGRP) were measured for the EN group. Student *t* test or Fisher test was used to compare the difference between the two groups. **Results:** 28 patients were enrolled in this study; 16 in the EN group and 12 in the PN group. The baseline characteristics were comparable between the two groups. The concentration of IL-1 β in the EN group was significantly lower than that of the PN group on day 3 and day 4 (day 3: 0.65 ± 0.17 pg/mL vs. 0.93 ± 0.09 pg/mL, $p < 0.01$, day 4: 0.52 ± 0.16 pg/mL vs. 0.74 ± 0.12 pg/mL, $p < 0.01$). The concentration of IL-6 and TNF- α in the EN group were also significantly lower than in the PN group on day 3 and day 4. There was no statistical difference in IL-10 serum concentration between the EN group and the PN group from day 1 to day 5. On day 3, the concentration of MOT, GAS and CCK reached the highest level and then gradually decreased. **Conclusions:** Implementation of early EN in patients receiving VA ECMO does not cause significant elevation of pro-inflammatory cytokines with an excessive inflammatory response.

Keywords

veno-arterial extracorporeal membrane oxygenation; enteral nutrition; inflammatory cytokine; gastrointestinal hormone

Introduction

Patients undergoing venous-arterial extracorporeal membrane oxygenation (VA ECMO) are often in critical condition, facing hemodynamic instability and insufficient organ perfusion. The profound stress and systemic inflammatory response syndrome (SIRS) triggered by artificial materials and organ ischemia can result in varying degrees of gastrointestinal damage, leading to gastrointestinal dysfunction [1,2]. Circulatory instability may result in intestinal ischemia. Premature restoration of enteral nutrition (EN) may cause intestinal reperfusion injury, release inflammatory mediators, and further exacerbate the inflammatory response, delaying recovery of gastrointestinal function [2]. Therefore, parenteral nutrition (PN) has traditionally been the mainstay of therapy for ECMO patients in the intensive care unit (ICU). However, for critically ill patients, according to the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines, if nutritional support therapy is required, EN is preferred over PN [3]. It has been shown that properly administered early EN has the potential to alleviate or prevent SIRS and improve gastrointestinal function [4]. In VA ECMO patients, the primary disease and VA ECMO device have a special and serious impact on the internal environment. With the development of VA ECMO, it is necessary to further optimize the nutritional support for VA ECMO patients. Therefore, this study aimed to evaluate the safety of early EN by observing changes in inflammatory cytokines and gastrointestinal hormones in VA ECMO patients.

Materials and Methods

Study Design

This study was a prospective, observational study that enrolled patients receiving veno-arterial ECMO (VA ECMO) treatment from 1 January 2020 to 31 December 2023. The study protocol was approved by the Institutional Ethics Committee. The study consisted of two groups: the EN group and the PN group. The inclusion criteria for the EN group were: (1) patients ≥ 18 years old, (2) receiving VA ECMO support, (3) receiving early EN treatment. The inclusion criteria for the PN group were: (1) patients ≥ 18 years old, (2) receiving VA ECMO support, (3) first five days of ECMO receiving only PN. Exclusion criteria for both groups were: (1) duration of mechanical ventilation exceeding 7 days, (2) patients with gastrointestinal functional impairment before VA ECMO, (3) irreversible neurological dysfunction, (4) contraindications to anticoagulation therapy, (5) uncorrected anatomical abnormalities in cardiac surgery, and (6) irreversible damage to the central nervous system.

ECMO Indications

Patients with cardiac or circulatory failure, patients with refractory shock due to other conditions, and those receiving support during cardiopulmonary resuscitation.

VA ECMO Management

Anticoagulation

The dosage of heparin sodium (H31022053, Shangyao First Biochemical Pharmaceutical Co., Ltd, Shanghai, China) was determined by the activated clotting time (ACT). The dosage of heparin was 4–20 IU/kg/h to maintain an ACT at approximately 180 s. Both ACT and activated partial thromboplastin time (aPTT) were tested every 3 hours.

Vasoactive Medications

During the initiation phase of ECMO, the doses of vasoactive agents were as follows: dopamine (H31021174, Hefeng Pharmaceutical Co., Ltd, Shanghai, China) 8–10 $\mu\text{g}/\text{kg}/\text{min}$, dobutamine (H31021904, Shangyao First Biochemical Pharmaceutical Co., Ltd, Shanghai, China) 8–10 $\mu\text{g}/\text{kg}/\text{min}$, epinephrine (H31021062, Hefeng Pharmaceutical Co., Ltd, Shanghai, China) 0.2–0.36 $\mu\text{g}/\text{kg}/\text{min}$. The dose was adjusted according to the patient's condition to maintain a mean arterial pressure (MAP) at approximately 50 mmHg during ECMO. During the weaning phase, the vasoactive drugs were: dopamine 2–5 $\mu\text{g}/\text{kg}/\text{min}$; dobutamine 2–6 $\mu\text{g}/\text{kg}/\text{min}$; epinephrine 0–0.01 $\mu\text{g}/\text{kg}/\text{min}$; and nitroglycerin (H11020289, Yimin Pharmaceutical Co., Ltd, Beijing, China) 0.3–0.6 $\mu\text{g}/\text{kg}/\text{min}$.

Flow Rate

According to the patient's hemodynamic conditions, lactate level and arterial oxygen saturation, the flow rate fluctuated within the range of 40–60 mL/kg/min, the venous oxygen saturation was maintained at more than 70%, and the oxygen concentration of the membranous lung was between 40% and 70%. This ensures that the arterial partial pressure of oxygen at the exit of the membranous lung was about 150 mmHg, and the arterial oxygen saturation was not less than 95% during the period of ECMO support.

Respiratory Parameters

The respiratory synchronized intermittent command ventilation mode parameters were as follows: FiO_2 30%–60%, respiratory rate 12–18 breaths/min, tidal volume 8–10 mL/kg, positive end expiratory pressure (PEEP) 4–6 cm H_2O , and peak airway pressure 15–25 cm H_2O .

Fluid Management

Diuretics were used to maintain the patient's urine output of at least 2–3 mL/kg/h; if persistent oliguria or anuria occurred, peritoneal dialysis, continuous renal replacement therapy (CRRT), or artificial renal ultrafiltration were instituted.

EN Management

All patients received total PN before starting EN. The target energy requirement was determined according to the Harris-Benedict (HB) formula, the type of disease, and stress factors. In the PN group, patients received only PN for the first five days of ECMO with glucose 250 mL, fat-soluble and water-soluble vitamins, trace elements, sodium glycerophosphate and amino acids. Calories and dosages were calculated using the HB formula. For the EN group, the initiation of EN followed the principles of low dose, low concentration and low calories, and the infusion was delivered at a steady rate by an infusion pump. In the initial period, EN may not fulfill of the total caloric requirement, necessitating the supplementation of PN. PN could be discontinued once EN reached 80% of the target amount.

After 24–48 h of ECMO support, as hemodynamics and the internal environment showed signs of recovery and gradually stabilized, EN was attempted and gradually increased according to the patient's tolerance until the expected nutritional goal was reached. Nutritional regimen: EN via nasogastric tube was started in all patients when the circulatory system was stabilized and the amount of gastric retention was < 100 mL. The EN solution was Jevity (con-

Table 1. Clinical characteristics.

	EN group	PN group	t value	p value
Gender (male/female)	11/5	10/2	/	0.66
Age (years)	49.13 ± 12.72	56.33 ± 10.26	-1.61	0.12
Weight (kg)	61.53 ± 13.51	66.00 ± 13.97	-0.85	0.40
Diagnosis (CAD/VD/AC/PE/CMP)	5/5/2/1/3	7/3/1/0/1	/	0.73
Weaning	12/4	11/1	/	0.36
Discharge situation (discharge/death)	12/4	11/1	/	0.36
ECMO time (hours)	178.25 ± 41.95	166.33 ± 36.37	0.79	0.44

EN, Enteral nutrition; PN, parenteral nutrition; CAD, Coronary artery disease; VD, Valvular disease; AC, Aortic coarctation; PE, Pulmonary embolism; CMP, Cardiomyopathy.

sisting of water, maltodextrin, casein, vegetable oil, fiber, minerals and vitamins, and other essential nutrients, and containing 418 kJ calories, 4 g protein, 3.74 g fat, and 14.05 g carbohydrates per 100 mL). According to the 2016 American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines, the target amount was calculated as 125 kJ/kg/d, and the feeding amount was 1/4 of the target amount (approximately 400 mL) on the first day, with the amount increasing by 1/4 each day to the target amount as tolerated by the patients. The temperature was 37–42 °C, the feeding rate was started at 20–30 mL/h and gradually increased by 10–25 mL every 4–24 h according to the gastrointestinal response, and then increased to 80–100 mL/h after 3–5 d.

Observation Indicators

①Serum concentrations of interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor α (TNF- α) on the first day of ECMO (day 1), the second day (day 2), the third day (day 3), the fourth day (day 4), and the fifth day (day 5), respectively for the EN and PN groups. ②Serum concentrations of Motilin (MOT), Gastrin (GAS), Cholecystokinin (CCK), and Calcitonin gene-related peptide (CGRP) were measured at the beginning of ECMO (day 0), the first day (day 1), the third day (day 3), the fourth day (day 4), and the fifth day (day 5) for the EN group.

Statistical Methods

The quantitative data were normally distributed and expressed as mean \pm standard deviation (Mean \pm SD), comparisons about cytokines between two groups were performed by *t* test, and comparisons about gastrointestinal hormones of EN group at different time points were Paired Samples *t* test. The qualitative data were expressed as constituent ratio, and comparisons between groups were performed by the Fisher test. Graph Pad Prism 9.0 (GraphPad Software Inc., San Diego, CA, USA) was used to analyze the data, and a *p* < 0.05 was regarded as a statistically significant difference.

Results

The Clinical Characteristics of the Patients

There were 16 patients in the EN group, 11 of whom were male. The details are summarized in Table 1. The age of the patients ranged from 32 to 71 years (49.13 \pm 12.72 years); and weight from 35.5 to 90 kg (61.53 \pm 13.51 kg). The duration of ECMO support ranged from 112 to 242 hours (178.25 \pm 41.95 hours). There were 4 deaths and 12 survivors before discharge, with a survival rate to discharge of 75%. There were 12 patients in the PN group. The age of the patients ranged from 38 to 70 years (56.33 \pm 10.26 years); and weight from 45 to 87 kg (66.00 \pm 13.97 kg). The duration of ECMO support ranged from 123 to 233 hours (166.33 \pm 36.37 hours). There were 1 death and 11 survivors before discharge, with a survival rate to discharge of 91.7%. The baseline characteristics were comparable between the two groups.

Serum Concentration of Pro-Inflammatory Factors during ECMO

Changes in IL-1 β

There was no statistical difference in IL-1 β serum concentration between the EN group and the PN group on day 1, day 2 and day 5; the concentration of IL-1 β of the EN group (0.65 \pm 0.17 pg/mL) was significantly lower than that of the PN group (0.93 \pm 0.09 pg/mL) on day 3 (*p* < 0.01); it was also significantly lower than that of the PN group on day 4 (0.52 \pm 0.16 pg/mL vs. 0.74 \pm 0.12 pg/mL, *p* < 0.01) (Table 2).

Changes in TNF- α

There was no statistical difference in TNF- α serum concentration between the EN group and the PN group on day 1, day 2 and day 5; the concentration of TNF- α of the EN group (2.08 \pm 0.31 pg/mL) was significantly lower than that of the PN group (2.99 \pm 0.56 pg/mL) on day 3 (*p* <

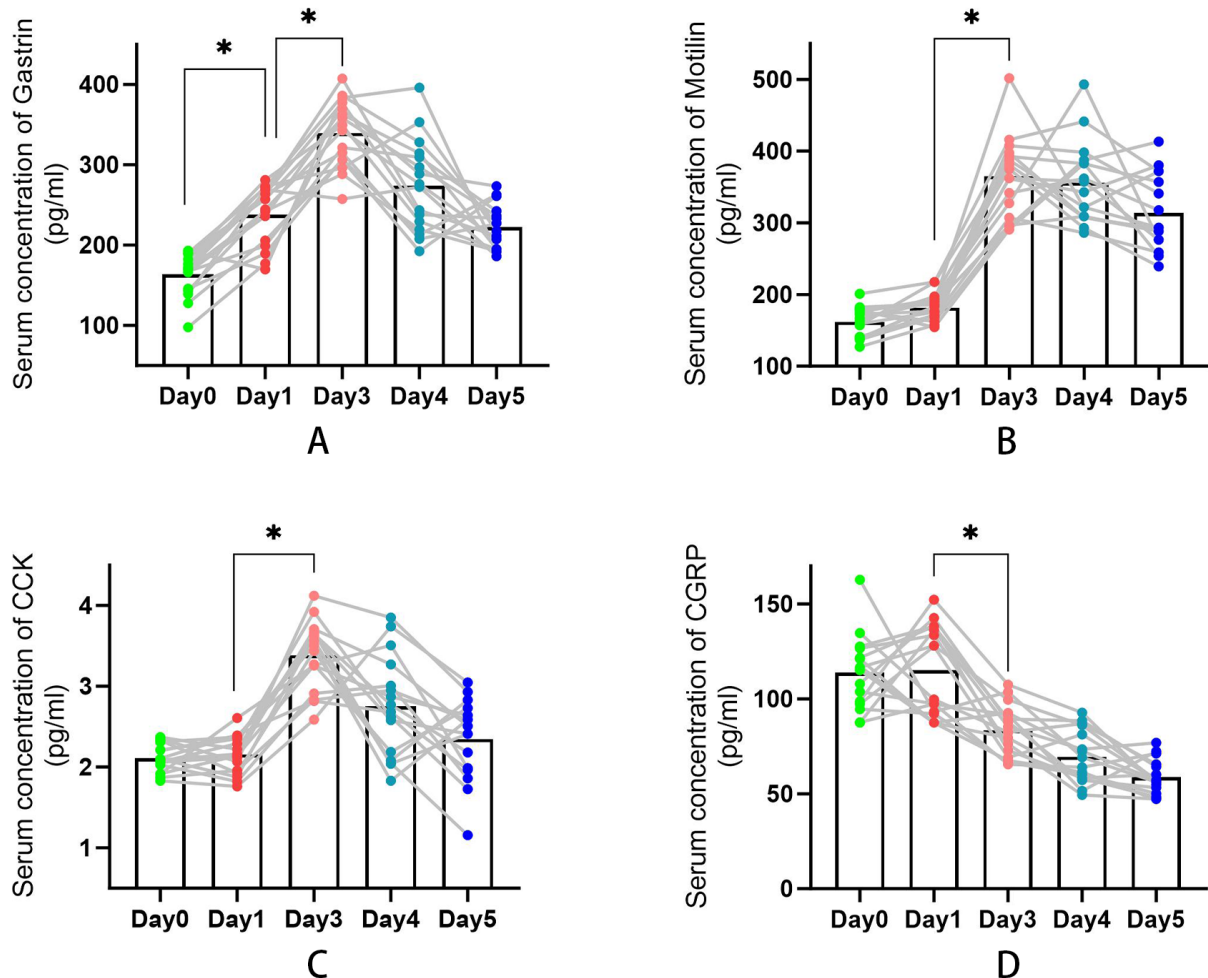


Fig. 1. Changes of Gastrointestinal Hormones. (A) illustrates changes of gastrin. (B) illustrates changes of motilin. (C) illustrates changes of CCK. (D) illustrates changes of CGRP. CCK, Cholecystokinin; CGRP, Calcitonin gene-related peptide. * $p < 0.05$.

0.01); the concentration of TNF- α of the EN group (1.86 ± 0.10 pg/mL) was significantly lower than that of the PN group (2.00 ± 0.16 pg/mL) on day 4 ($p = 0.01$) (Table 2).

Changes in IL-6

There was no statistical difference in IL-6 serum concentration between the EN group and the PN group on day 1, day 2 and day 5; the concentration of IL-6 of the EN group (159.08 ± 14.01 pg/mL) was significantly lower than that of the PN group (171.96 ± 10.24 pg/mL) on day 3 ($p = 0.01$); the concentration of IL-6 of the EN group (144.32 ± 15.57 pg/mL) was significantly lower than that of the PN group (158.14 ± 8.30 pg/mL) on day 4 ($p = 0.01$) (Table 2).

Anti-Inflammation Cytokine IL-10 Concentration Changes

There was no statistical difference in IL-10 serum concentration between the EN group and the PN group from day 1 to day 5 (Table 2).

Changes in Gastrointestinal Hormones of the EN Group

Changes in Gastrin

Gastrin had the highest level on day 3, which was 339.37 ± 41.95 pg/mL; the lowest level on day 0 was 163.39 ± 26.14 pg/mL. Gastrin concentration was significantly higher at day 1, day 3, day 4, day 5 of ECMO than at day 0, and peaked at day 3 (Fig. 1A).

Changes in Motilin

Motilin had the highest level of 365.15 ± 55.50 pg/mL on day 3; the lowest level of 162.17 ± 20.71 pg/mL on day 0. Compared to the serum concentration of motilin on day 0 and day 1, the concentration on day 3, day 4, day 5 was significantly higher (Fig. 1B).

Table 2. Serum concentration of proinflammation and anti-inflammation cytokines during ECMO.

Time	Cytokines	Mean \pm SD (pg/mL)		t value	p value
		EN group	PN group		
Day 1	IL-1 β	0.65 \pm 0.19	0.73 \pm 0.15	-1.22	0.23
	TNF- α	2.18 \pm 0.43	2.23 \pm 0.48	-0.24	0.81
	IL-6	134.34 \pm 8.02	130.84 \pm 13.57	0.85	0.40
	IL-10	63.07 \pm 19.68	70.19 \pm 15.06	-1.04	0.31
Day 2	IL-1 β	0.94 \pm 0.30	1.04 \pm 0.15	-1.00	0.33
	TNF- α	3.16 \pm 1.11	2.98 \pm 1.07	0.44	0.66
	IL-6	184.61 \pm 19.65	193.81 \pm 19.98	-1.22	0.24
	IL-10	69.17 \pm 21.42	64.73 \pm 13.62	0.63	0.54
Day 3	IL-1 β	0.65 \pm 0.17	0.93 \pm 0.09	-5.19	<0.01
	TNF- α	2.08 \pm 0.31	2.99 \pm 0.56	-5.51	<0.01
	IL-6	159.08 \pm 14.01	171.96 \pm 10.24	-2.69	0.01
	IL-10	85.02 \pm 24.80	86.69 \pm 11.73	-0.22	0.83
Day 4	IL-1 β	0.52 \pm 0.16	0.74 \pm 0.12	-4.02	<0.01
	TNF- α	1.86 \pm 0.10	2.00 \pm 0.16	-2.83	0.01
	IL-6	144.32 \pm 15.57	158.14 \pm 8.30	-3.02	0.01
	IL-10	70.40 \pm 18.99	73.71 \pm 10.87	-0.54	0.60
Day 5	IL-1 β	0.49 \pm 0.14	0.55 \pm 0.10	-1.28	0.21
	TNF- α	1.76 \pm 0.11	1.79 \pm 0.16	-0.71	0.48
	IL-6	119.11 \pm 19.84	129.29 \pm 13.56	-1.53	0.14
	IL-10	65.36 \pm 13.28	70.30 \pm 8.55	-1.12	0.27

IL-1 β , interleukin-1 β ; TNF- α , tumor necrosis factor α ; IL-6, interleukin-6; IL-10, interleukin-10.

Changes in Cholecystokinin

The serum concentration of CCK was highest on day 3 with 3.39 ± 0.43 pg/mL and lowest on day 0 with 2.11 ± 0.17 pg/mL. The concentration of CCK was significantly higher on day 3 of ECMO than on day 0 and day 1 (Fig. 1C).

Changes in Calcitonin Gene-Related Peptide

The serum concentration of CGRP was highest on day 2 with 114.89 ± 23.81 pg/mL and lowest on day 5 with 58.69 ± 9.18 pg/mL. CGRP levels were significantly lower on day 3, day 4, day 5 of ECMO compared to day 0 and day 1 (Fig. 1D).

Discussion

SIRS manifests as an imbalance between systemic inflammatory and anti-inflammatory responses induced by severe physiological injury [1]. Patients receiving VA ECMO may suffer from SIRS due to the primary pathological trauma and the inflammatory response triggered by the VA ECMO device material, leading to cytokine release [2,5]. EN has been widely employed in critically ill patients. Some patients experience SIRS-related symptoms,

such as tachypnea, tachycardia, fever, leukocytosis, and C-reactive protein (CRP) elevation in the initial stage of EN resumption. This phenomenon is particularly evident in critically ill patients with long-term intestinal apraxia and may even be associated with serious complications such as leukocytosis and cholestasis, termed “intestinal reperfusion syndrome” [6]. This study observed the changes in serum concentrations of inflammatory cytokines and gastrointestinal hormones in patients receiving VA ECMO support during the implementation of early EN and explored the effects of early EN on the inflammatory response in these patients. Our results showed that the concentration of cytokines increased on the second day after VA ECMO and then decreased. The anti-inflammatory cytokine increased on the third day. Compared with the PN group, EN does not cause an excessive inflammatory response in VA ECMO patients. The gastrointestinal hormones increased on the third day. These results will provide more information for future clinical management in gastrointestinal nutrition during ECMO support.

TNF- α is a critical pro-inflammatory factor in the inflammatory response, playing a crucial role in regulating the body’s immune function and mediating the inflammatory response, tissue damage, shock and other pathophysiological processes [7–9]. Excessive production and release of TNF- α can contribute to the development of SIRS, exacerbate tissue and organ damage, and increase mortality and morbidity in VA ECMO patients. In this study, we observed the changes of TNF- α during the early implementation of EN in VA ECMO patients. This research revealed a significant increase in the serum concentration of TNF- α within the first 48 hours of VA ECMO and then gradually decreased. Compared with the PN group, serum concentration of TNF- α of the EN group decreased significantly ($p < 0.05$) on day 3 and day 4. There were no statistical differences of TNF- α levels between the two groups on day 1, day 2 and day 5. Gastrointestinal nutrition was effectively implemented in all patients between 24 and 48 hours after initiation of VA ECMO, suggesting that early EN did not increase, but decreased the serum concentration of TNF- α in VA ECMO patients and reduced the inflammatory response. It has been shown that a significant reduction in TNF- α concentration upon the initiation of EN, indicates an improvement in the immune function of the gastrointestinal system in patients who received early EN compared to those who received PN [10,11]. IL-1 β , TNF- α , and IL-6 not only play crucial roles in mediating immune and inflammatory responses but also are associated with the disruption of the body’s nutritional homeostasis [12,13]. Increasing evidence suggests that elevated serum levels of IL-1 β , TNF- α , and IL-6, observed in critically ill patients, contribute to a variety of mechanisms that increase the risk of cachexia [14]. Patients receiving VA ECMO are often associated with hypoxemia due to the primary disease and surgery, resulting in elevated serum IL-1 β levels, combined

with fasting, which may further exacerbate the nutritional imbalance of patients and increase the risk of cachexia during VA ECMO. In our study, we observed a statistically significant decrease in IL-1 β levels following early EN implementation in the EN group compared with the PN group on day 3 and day 4. There were no statistical differences of IL-1 β levels between the two groups on day 1, day 2 and day 5. Yang *et al.* [4] observed similar conclusions in patients with SIRS after burn injuries. We observed a statistically significant decrease in IL-6 levels following early EN implementation in the EN group compared with the PN group on day 3 and day 4. There were no statistical differences in IL-6 levels between the two groups on day 1, day 2 and day 5. This suggests that early EN does not increase the production and release of IL-6, which can increase the inflammatory response and promote the occurrence of SIRS. EN may help to reduce the production and release of pro-inflammatory cytokines, thus alleviating the inflammatory response.

IL-10 inhibits the inflammatory response, maintains the balance between pro-inflammatory and anti-inflammatory responses, and prevents tissue destruction caused by excessive inflammation [15]. Elevated circulating levels of IL-10 are considered to be an important protective mechanism for balancing pro- and anti-inflammatory responses during inflammation and acute infection [16,17]. This study observed that IL-10 levels gradually increased from day 1 to day 3 in VA ECMO-supported patients and peaked on day 3, reflecting a gradually increasing inflammatory response during this period. With the initiation of EN approximately 24–48 hours after the implementation of VA ECMO, pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6 decreased, while IL-10 reached the highest level about 24 hours after the peak of pro-inflammatory cytokines, followed by a gradual decrease. This indicates that early gastrointestinal nutrition does not exacerbate the inflammatory response but also promotes and facilitates recovery from the disease. There were no statistical differences of IL-10 levels between the two groups. This indicates that early EN does not suppress the release of anti-inflammatory cytokine IL-10, maintains the balance between pro-inflammatory and anti-inflammatory responses, and protects gastrointestinal function.

Gastrin stimulates mucosal growth, promotes digestion and absorption of stored nutrients, and also activates gastrin receptors on mural cells to promote hydrochloric acid secretion from the fundic glands and glucose-induced insulin release [18]. The results of this study showed that gastrin concentrations were elevated on day 1, day 3, day 4, day 5 of VA ECMO compared with day 0, peaking on day 3 and then gradually decreasing. This suggests that with the initiation of VA ECMO, the patient is exposed to progressively more stressful stimuli, with increased gastrin secretion. When enteral feeding is initiated between 24 and 48 hours of VA ECMO, the gastric contents increase in-

tragastric pressure, which, coupled with the stimulation of the gastric feed, stimulates gastrin release, which further increases gastrin release, causing its levels to reach their peak [3]. Subsequently, as the body gradually adapted to VA ECMO and EN, the stressful stimuli diminished and gastrin levels gradually decreased, and on the fifth day of VA ECMO, gastrin levels were still significantly higher than at the beginning of VA ECMO. Some studies on extracorporeal circulation suggest the intense stress response can exacerbate gastrin production and release in patients [19]. Some studies also found that early EN could lead to an increase in blood gastrin concentration in infants compared with neonates with only PN [20]. Moderately elevated gastrin levels can stimulate growth of the stomach lining, promote digestion and absorption, and improve the nutritional status of patients.

Motilin is a polypeptide molecule consisting of 22 amino acids with a molecular mass of approximately 2700, discovered in 1973 by Brown *et al.* [21] and isolated and purified in 1972, and named gastric motility hormone because of its ability to stimulate gastric motility. Motilin exerts its physiological effects by binding to the gastrin receptor, and its physiological effects are mainly to promote gastrointestinal motility, stimulate pepsin secretion, and release growth inhibitors. The results of this study showed that the levels of gastric motility hormone concentrations were significantly higher on the third, fourth, and fifth days of VA ECMO compared with those at the beginning of VA ECMO and on the first day of VA ECMO, and decreased slowly, suggesting that stress hormones do not have a significant effect on the changes in motilin; whereas, the initiation of EN markedly promotes motilin secretion.

In the gastrointestinal tract, CCK promotes the digestion and absorption of food. It stimulates gallbladder contraction, dilates the sphincter of Oddi, stimulates the release of growth-inhibiting hormone, and promotes pancreatic growth and development and the release of pancreatic enzymes [22]. The results of this study showed that CCK concentrations on the third and fourth days of VA ECMO were significantly higher than those at the beginning of VA ECMO and on the first day of VA ECMO. Possible reasons for this include: ①strong stress stimulation of the organism promotes the secretion of CCK. ②VA ECMO non-pulsatile blood flow affects renal perfusion, which in turn affects the renal function, resulting in a decrease in the clearance of CCK. ③After the initiation of enteral nutrition, stimulated by proteins and their catabolic products, fats, and other nutrients, CCK synthesis and release are increased. Similar findings have been reported showing an increase in serum CCK concentrations in patients during VA ECMO support [23]. The results of this study suggest that the administration of gastrointestinal nutrition may induce CCK secretion, which in turn may affect the gastric emptying status of the patient, especially in VA ECMO patients, so that care should be taken to closely monitor the patient's gastroin-

testinal tolerance when giving gastrointestinal nutrition in the early stages and to adjust the appropriate rate and dosage of EN.

The release of CGRP is innervated by capsaicin-sensitive afferent nerves that influence gastrointestinal tract function by inhibiting gastric acid secretion, increasing gastric mucosal blood flow, slowing gastrointestinal motility, modulating the inflammatory response, decreasing free radical damage, and regulating the secretion of gastrointestinal hormones [24]. This study found significantly lower levels of CGRP on days 3, 4, and 5 of VA ECMO compared to VA ECMO at baseline and on day 1 of VA ECMO. In the early stage of VA ECMO support, changes in CGRP levels were not observed. With the introduction of enteral nutrition, CGRP levels gradually decreased, suggesting progressively enhanced gastrointestinal vasoconstriction and increased risk of gastrointestinal ischemia, leading to impaired gastrointestinal function. Although early EN is beneficial for restoring the patient's gastrointestinal function and providing nutritional support, the patient's tolerance for early EN should also be considered in selecting the appropriate enteral nutrition support regimen to promote the patient's recovery.

Limitation

This study is subject to the inherent limitations of observational data, and the sample size is small, we need to further observe and include a larger number of patients in our study to strengthen the validity of our findings in the future.

Conclusions

Implementation of early EN in patients receiving VA ECMO does not cause significant elevation of pro-inflammatory cytokines with excessive inflammatory response. Although the implementation of early EN is beneficial for restoring patients' gastrointestinal function and providing nutritional support, the patient's tolerance of early EN should also be considered in selecting the appropriate mode and timing of enteral nutritional support.

Availability of Data and Materials

The original data of this article can be requested from the corresponding author on reasonable grounds.

Author Contributions

SY, FH, AW designed the research study. SY performed the research. SY, AW analyzed the data and SY

wrote the manuscript. CW provided help and advice on data collection and analysis. SY, CW, FH and AW revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This prospective observational cohort study was conducted in Fuwai hospital from January 2020 to December 2023 and was approved by our Institutional Ethics Committee (record number: Z131100006813006). The informed consent was waived because of its observational nature. The patients participating in this study were from Fuwai Hospital, where both the data collection and analysis took place, leading to the involvement of the Ethics Committee of Fuwai Hospital in the review process. However, a discrepancy between the author's affiliation and the ethics committee arose as a result of a change in workplace.

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Conflict of Interest

The authors declare no conflict of interest.

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