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Understanding of Pathophysiological Basis of Feeding Intolerance in Critically ill Children

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ABSTRACT

Children with critical illnesses are at increased risk for intestinal injury, gastrointestinal dysfunction, and feeding intolerance, which are associated with delayed recovery and increased morbidity and mortality during their course in the pediatric intensive care unit (PICU). Optimizing energy and protein delivery significantly reduces the incidence of infectious complications and multiorgan failure in critical illness. Enteral nutrition (EN) is the preferred mode of nutrient intake in patients with critical illnesses. Despite the growing awareness of the benefits of EN in patients with critical illnesses, subsequent maintenance of EN delivery in PICUs remains suboptimal. In children with critical illnesses, little data are reported on the factors that influenced EN. Feeding intolerance in children with critical illnesses may be due to alterations in gastrointestinal motility secondary to underlying disease or medication administration. This study aimed to summarize recent insights into the role of hyperglycemia, EN caloric density, and gastrointestinal feedback mechanism, and routine intensive care management, such as sedation, analgesia, and catecholamine on feeding intolerance in children with critical illnesses.

Keywords: Feeding intolerance, gastric emptying, opioid, catecholamine, children

Introduction

Children with a critical illness are at increased risk for intestinal injury, gastrointestinal dysfunction, and feeding intolerance, which are associated with delayed recovery and increased morbidity and mortality during their course in the pediatric intensive care unit (PICU). Moreover, malnutrition is a frequent finding in children with a critical illness (1,2). The prevalence of severe malnutrition in PICU admission of children with a critical illness is reported to be over 30%, as it was 30 years ago (1,2). Optimizing energy and protein delivery significantly reduces the incidence of infectious complications and multiorgan failure in critical illness (3,4,5). Therefore, the provision of optimal nutritional therapy is a fundamental goal of critical care.

Enteral nutrition (EN) is the preferred mode of nutrient intake in patients with critical illness with a functional gastrointestinal system because studies have shown multiple beneficial effects of EN compared with parenteral nutrition (PN). EN allows the use of the nutrients better than PN, and maintains gastrointestinal integrity, and

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improves gastrointestinal barrier dysfunction by its trophic effect, stimulates the immune system, and reduces intestinal bacterial translocation (3,4,5). The Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition promoted early EN of patients in the PICU (6).

Despite the growing awareness of the benefits of EN in patients with critical illness, subsequent maintenance of EN delivery in PICUs remains suboptimal (2). On average, nearly 50% of children with critical illness in most reports fail to reach nutrition goals, with 37-70% of prescribed energy delivery before discharge from the PICU (7,8). EN is frequently impeded or interrupted in the PICU for a variety of reasons, failing to achieve nutrition goals (2,7). An important factor contributing to inadequate provision of EN is feeding intolerance, which occurs frequently due to delayed gastric emptying and gut dysmotility in critical illness. The reported prevalence of feeding intolerance in a recent systematic review ranged from 0.0% to 57.1% with a median prevalence of 20.0% (Interquartile range 7.4-33.0) (9). This wide range is due to the confusion in feeding intolerance definition, which often results in unnecessary feeding interruptions in children with a critical illness (9,10).

Generally, feeding intolerance means the presence of high gastric residual volume, vomiting, diarrhea, and abdominal distention (9,10). However, compared to adults, signs of feeding intolerance in children are difficult to quantify and can be easily confused with gastrointestinal symptoms associated with a patient's medications or underlying illness.

In children with critical illness, little data is reported on the factors that influenced EN. Feeding intolerance in children with critical illness may be due to alterations in gastrointestinal motility secondary to the underlying disease or medication administration. This study aimed to summarize recent insights into the role of hyperglycemia, the caloric density of EN, and gastrointestinal feedback mechanism, and routine intensive care management, such as sedation, analgesia, and catecholamine, on the feeding intolerance in children with a critical illness.

Pathophysiological Basis of Feeding Intolerance

Control of Gastric Emptying

The main function of the stomach is to act as a reservoir of ingested food and perform a mechanical and chemical breakdown of the contents to a fluid chyme that is delivered to the duodenum at a controlled rate. The regulation of gastric emptying is a complex process, which allows optimal intestinal digestion and absorption of foodstuffs. The rate of gastric emptying is determined by the integrated activity of the proximal stomach, antrum, pylorus, and proximal small intestine (11).

The proximal fundus of the stomach functions as a reservoir, and the muscles are adapted to maintain a continuous contractile tone, whereas the antro pyloro duodenal region exhibits phasic and peristaltic contractile activity and functions both as a pump and a grinding mill. The pyloric sphincter tone regulates the outflow to the small intestine. The interaction of nutrients with the small intestine plays a major role in gastric emptying regulation; small-intestinal nutrients slow gastric emptying, which is associated with proximal stomach relaxation, antral contraction suppression, and pyloric motility stimulation (12). Moreover, other factors, including the systemic hormonal environment, enteric nerve activity, central nervous system drive, and ingested meal properties, appear to regulate gastric emptying. Consequently, changes in any of these factors will affect the rate of gastric emptying (13).

Delayed Gastric Emptying in Critical Illness

In patients with critical illness, a marked reduction in antral motility and poor coordination of antroduodenal contractions has been reported during fasting. In addition, proximal and distal gastric motor responses to small-intestinal nutrient stimulation are abnormal in critical illnesses. Moreover, proximal gastric relaxation and the recovery of proximal gastric volumes to pre-stimulation levels are delayed and fundic wave activity and antral motility are reduced (14,15). Failure of the relaxed proximal stomach to return to baseline volume after nutrient stimulation in these patients provides a reservoir for gastric residue retention in the fundus.

Factors Contributing to Gastric Emptying Delay in Children with Critical Illness

The pathophysiology of delayed gastric emptying in children with critical illness is multifactorial. Delayed gastric emptying was reported to be due to impaired gastroduodenal motility related to patients' clinical severity, premorbid conditions, and pharmacological and surgical treatments. Only a few studies specifically focus on delayed gastric emptying in children with critical illnesses. Thus, this study reviewed the outstanding animal and observational adult studies that clarify the factors that contribute to a gastric emptying delay in children with critical illnesses.

Food Composition Effects

In healthy subjects, a relaxed proximal stomach, reduced antro-duodenal motility, and increased isolated pyloric

pressure waves were found in response to small-intestinal feedback (12). Lin et al. (16) demonstrated that the proximal, as well as the distal small intestine, are capable of participating in negative feedback control.

Gastric emptying appears to be regulated by factors, such as the systemic hormonal environment, enteric nerve activities, central nervous system drive, and ingested meal properties. The relative importance of these factors has not been exactly established; however, some evidence presented that the rate of emptying of both solids and liquids depends on their chemical compositions. Several studies have identified different meal properties, which influence the rate of gastric emptying. Low pH and temperature, as well as high osmolality, viscosity, fiber content, and caloric density, delay gastric emptying (17,18). However, Calbet and MacLean (19) reported that the rate of gastric emptying is mainly a function of the caloric density of the ingested meal and that a linear relationship exists between these variables when solutions of similar volumes and osmolalities are administered at the same temperature and pH in healthy humans. For example, an increasing caloric density of 6-fold resulted in a 3-fold decreased rate of gastric emptying (19). Moreover, the rates of gastric emptying for isocaloric amounts of fat, protein, and carbohydrates were reported to be similar, suggesting that the delaying effect of caloric density on gastric emptying seems to be independent of the nature of the solutes (20,21). In addition, the energy properties of the meal are detected by duodenal receptors, which regulate the rate of gastric emptying (17).

Caloric content plays a crucial role in gastric emptying; however, differences in solution osmolality may also change the rate of gastric emptying. A hyperosmolar solution is thought to slow gastric emptying by triggering duodenal osmoreceptor feedback on the stomach (22,23), which may be especially important in patients who receive post-pyloric feeding. Nevertheless, the influence of osmolality on the rate of gastric emptying may be of physiological relevance only at high tonicity levels (1,200 mosmol/kg H_2O) (23).

Enterogastric Feedback Hormones Effects

Cholecystokinin (CCK) and peptide YY (PYY) are important enterogastric feedback hormones, which regulate gastric emptying. In response to the presence of fat and protein in the small intestine, CCK and PYY are released in a dose-dependent fashion from the enteroendocrine cells, which are predominantly located in the proximal small intestine for CCK and the distal small intestine for PYY (24,25). The initial release of PYY after food intake is likely to be mediated by CCK (26). Endogenous CCK has been demonstrated as an important regulator of gastric emptying of both the solid and liquid meal phases and thus a major determinant of gastric emptying of a physiological meal in humans (27). An exogenous administration of CCK and PYY is associated with proximal stomach relaxation, antral motor activity inhibition, isolated pyloric contraction stimulation, and gastric emptying slowing (27,28).

Proximal and distal gastric motor responses to small-intestinal nutrient stimulation are demonstrated to be abnormal in critical illness. In addition, proximal gastric relaxation and proximal gastric volumes recovery to pre-stimulation levels are delayed and fundic wave activity and antral motility are reduced (14). Failure of the relaxed proximal stomach to return to baseline volume after nutrient stimulation in these patients provides a reservoir for gastric residue retention in the fundus. Nguyen et al. (29,30) demonstrated in their studies that both fasting and nutrient-stimulated plasma CCK and PYY concentrations are increased in patients with critical illnesses, particularly in those with feeding intolerance, suggesting a contribution of this hormone in delayed gastric emptying. Moreover, a close relationship has been reported between nutrient-stimulated plasma PYY and CCK concentrations in these patients (29). As gastric emptying was inversely related to postprandial plasma CCK and PYY concentrations in patients with critical illnesses, these studies suggested that hypersensitivity to a small-intestinal nutrient leads to motility changes, which result in reduced gastric emptying, is found in critical illness (29,30).

Blood Glucose Concentration Effects

Changes in blood glucose concentration are among the most frequently encountered components of disturbed homeostasis in children with critical illnesses. Hyperglycemia is a risk factor for poor outcomes in patients with critical illness, and tight glycemic control improves clinical outcomes, including survival (31). Mechanical ventilation, vasopressor/inotropic infusion, continuous renal replacement therapy, and high illness severity scores were known to be associated with hyperglycemia in these patients (32). No definite criteria for hyperglycemia diagnosis among patients without diabetes mellitus, thus the authors used more than two cut-off values to present the hyperglycemic status of children with critical illness in their studies. Through the use of cut-off values of blood glucose level >110 mg/dL, 120 or 126 mg/dL, 150 mg/dL, and 200 mg/dL, the reported incidence of hyperglycemia in children with critical illness ranged from 85% to 95%, 70-86%, 61-72%, and 16.7-35.2%, respectively (33,34,35).

Acute changes in the blood glucose concentration were well recognized to have a major reversible effect on gastrointestinal motility and rate of gastric emptying in both healthy participants and those with diabetes. Acute hyperglycemia that is induced by intravenous glucose infusion was shown to slow the emptying of nutrient-containing liquid and solid meals in patients with and those without diabetes (36), whereas hypoglycemia has the opposite effect and increases the gastric emptying rate for both liquid and solid meals in healthy volunteers and patients with insulin-dependent diabetes mellitus (37). In healthy volunteers and patients with type 1 diabetes, hyperglycemia stimulates phasic pressure waves that are localized to the pylorus, reduces the frequency and propagation of antral pressure waves under fasting and postprandial conditions, and increases proximal gastric compliance, which reflects a gastric tone reduction (38,39). Furthermore, marked hyperglycemia (blood glucose 210-270 mg/dL) showed to decrease in the motility index and propagation of duodenal and jejunal waves and slow small-intestinal transit in healthy volunteers (38,40).

Recent observations indicate that not only pathological but also physiological changes in the blood glucose concentration within the normal postprandial range (140-180 mg/dL) act synergistically with stimuli that arise from the small intestine to slow gastric emptying of solid and liquid meals. For example, at a blood glucose concentration of 180 mg/dL (10 mmol/L), the phasic and tonic pyloric responses to duodenal distension are greater than during euglycemia (41). Antral motility index was noted to be significantly reduced when intravenous glucose infusions raised serum glucose levels to approximately 120 mg/dL (6.6 mmol/L) in fasting humans (42). Moreover, the stimulation of pyloric tone by exogenous CCK was demonstrated to be greater and gastric emptying is slower at a blood glucose level of 144 mg/dL (8 mmol/L) compared with 72 mg/dL (4 mmol/L) in both healthy participants and patients with diabetes (43,44). Furthermore, the evidence presented that hyperglycemia attenuates the prokinetic effect of intravenous erythromycin on gastric emptying in both healthy participants and patients with diabetes (45).

Contrarily, patients with type 1 diabetes without complications had markedly accelerated gastric emptying during hypoglycemia compared with euglycemia, as in healthy participants (37). The finding that cholinergic muscarinic blockade with atropine inhibited the hypoglycemia-induced acceleration of gastric emptying indicates that vagal stimulation plays an important role in this mechanism (46,47).

Sedation and Analgesic Effects

Many sedative and analgesic agents that are commonly administered in the PICU are known to have negative effects on the digestive system with gastric emptying inhibition and small-bowel transit prolongation (48,49,50).

Propulsive gut motility inhibition is especially marked after an opioid-based technique. The inhibitory effect of opioids on gastrointestinal motility has been extensively studied, but the mechanism and understanding are complex. Opioid receptors are known to be present in the gastrointestinal tract. Gut motility inhibition is mainly mediated via opioid receptors because recently developed opioid antagonists reverse opioid-induced gastrointestinal motility inhibition (51,52). Another effect of opioid analgesics is the inhibition of the release of acetylcholine from the mesenteric plexus, thereby increasing colonic muscle tone and reducing propulsive activity in the gastrointestinal tract (53,54). Moreover, the pylorus has been clearly shown to have rich enkephalinergic innervation, and opioids may therefore increase pyloric tone (55).

Morphine, even at a low dose, markedly inhibits gastric emptying due to enhanced proximal gastric relaxation, increased pyloric tone, and increased retrograde duodenal contractions in healthy humans (48,49,50). Remifentanil, an ultra-short-acting opioid, increases pyloric tone and thereby delays gastric emptying (56). Using a guinea-pig small-bowel model, Fruhwald et al. (57) demonstrated that sufentanil, an ultra-short-acting opioid and μ-receptor agonist, had a very strong inhibitory effect on small-bowel motility at moderate concentrations. The most striking finding of this study was that the antiperistaltic effect of epinephrine on intestinal motility is intensified by the combination of sufentanil, especially if the opioid is given at moderate and higher concentrations. Contrary to epinephrine, dobutamine seems to be less capable of depressing peristalsis even when combined with higher sufentanil concentrations (57). Therefore, the physician in the ICU should be alert to possible negative interactions during the long-term combination of opioids and catecholamines, such as epinephrine, norepinephrine, dopamine, and vasopressin combinations, in patients with critical illnesses.

In a laboratory setting, propofol exhibits an inhibitory effect on spontaneous contractile activity and concentration-dependent depression of acetylcholine-induced contraction on human gastric and colonic smooth muscles at clinically relevant concentrations (58). Clinical studies involving human volunteers who are lightly sedated with propofol demonstrated a significantly increased orocecal transit time

(59,60). Contrarily, propofol at low doses (up to 5 mg/kg/h over 1-3 h) has been reported to not affect gastric emptying in healthy humans or in patients who have undergone minor surgery (60,61). In addition, Nguyen et al. (62) recently demonstrated that 56% of patients with critical illness who are sedated with propofol in their study at a mean rate of ~2 mg/kg/h had delayed gastric emptying. However, the incidence of delayed gastric emptying in patients who received propofol was significantly lower than in patients who are sedated with morphine and midazolam. Moreover, whether the delayed gastric emptying is an effect of propofol or critical illness remains unclear (62). An animal study reported that midazolam slows gastric emptying in mice (63). The inhibitory effects of morphine and midazolam on gastric motility are also observed in patients with critical illnesses (64,65).

Ketamine is a unique drug because it is a powerful analgesic in addition to its dissociative anesthetic property. Ketamine was previously demonstrated to suppress endotoxin-induced production of proinflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6 production in the intestine (66,67). Recently, Suliburk and Mercer (68) demonstrated that ketamine attenuates lipopolysaccharides that induced increases in gastric volume and gastric pH in rats.

Clonidine and dexmedetomidine are potent and selective α2-adrenoceptor agonists with sedative and analgesic properties, which are used for perioperative and intensive care sedation. Moreover, clonidine and dexmedetomidine have been reported to facilitate some signs and symptoms of opioid and benzodiazepine withdrawal. Therefore, they are preferred as a non-opioid alternative for managing opiate withdrawal syndrome, not only in adults but also in infants and children with a critical illness (69,70,71). The physiological role of α2-adrenoceptors in the regulation of gastrointestinal function has been documented (72,73). Activation of α2-adrenoceptors has been reported to mediate several responses in the gastrointestinal tract (72,73). Clonidine and dexmedetomidine were shown to inhibit gastric acid secretion, gastric emptying, and gastrointestinal transit in animal and human studies (73,74,75). Recently, Iirola et al. (76) demonstrated that dexmedetomidine markedly inhibited gastric emptying and orocecal transit compared with placebo and morphine in healthy volunteers.

In conclusion, patients who are sedated with opioids and midazolam are more likely to have slow gastric emptying, and proximal meal retention and may be at higher risk of feeding intolerance, gastroesophageal reflux, and aspiration pneumonia than those receiving propofol or ketamine. Ketamine may be preferred as the analgesic drug of choice, combined with propofol rather than a high-dose barbiturate, midazolam, or opioids in patients with critical illness, especially with sepsis or septic shock.

Catecholamine Effects

In the 1970s, catecholamines, which are frequently used in patients with critical illness because of their cardiovascular effects, were described to significantly alter the rate of gastric emptying (77). The role of alfa- and beta-adrenoceptors and dopamine receptors in the regulation of gastrointestinal motility were well documented (78,79,80). Catecholamines can affect gastric and intestinal motility through direct activation of smooth muscle adrenoceptors, which may belong to the alfa-1, alfa-2, beta-1, beta-2, and beta-3-class (74,81,82). In general, both alfa- and beta-adrenoceptor agonists inhibit gastric or intestinal motility in experimental animals by a direct effect on the smooth muscle or by neural inhibition (83). However, the inhibitory effect of catecholamines on gastric emptying and intestinal motility are dominantly due to the activation of alfa-2 and dopamine-2 receptors. The alpha receptors are found not only in the smooth muscle, such as beta-adrenoceptors, but also on the nerves that modify the release of neurotransmitters, such as acetylcholine, which is an excitatory neurotransmitter in the intestine, and its release increases smooth muscle contraction. The inhibition of acetylcholine release is mediated by alpha-adrenoceptors. Moreover, the activation of DA-2 neural receptors appears to depress digestive motility via an inhibition of acetylcholine that is a release from cholinergic motor neurons that innervate gastrointestinal smooth muscle (84).

Dopamine receptors (DA-2) are known to be present in the human enteric nervous system (85). In mechanically ventilated patients with critical illness, Dive et al. (86) demonstrated that continuous intravenous administration of dopamine at a low dose (4 µg/kg per min) decreased the number of contractions in the gastric antrum and induced phase III motor activity in the duodenum both during fasting and during continuous nasogastric feeding. Similar results were observed by Levein et al. (87) in healthy male participants. They reported that a continuous infusion of dopamine at 5 micrograms kg^{-1} min^{-1} slows gastric emptying and prolongs orocecal transit time (87). In addition to its depressing effect on the antrum, Hartley et al. (88) have shown that dopamine that is infused at a rate of 2 µg/kg per min is normally used to promote renal function and produced a profound relaxation of the corpus fundus of the stomach in healthy volunteers. The authors concluded that giving dopamine at that dose to patients who are receiving nasogastric feeding may put them at risk of vomiting, regurgitation, and gastric content aspiration.

Recently, an experimental study of pharmacologic effects of catecholamines on intestinal motility demonstrated that catecholamines markedly differ in their inhibitory and stimulatory actions on the peristaltic motility of guinea-pig ileum (79). Dobutamine and dopexamine are ~500 times less potent in inhibiting peristalsis than epinephrine, which shows the most inhibitory potency among the catecholamines (79). The authors concluded that the low inhibitory potency of dobutamine (beta 1-adrenoceptor agonist) and dopexamine (beta 2-adrenoceptor agonist and dopamine receptor agonist) are consistent with the finding that alpha-adrenoceptor agonists are more active in inhibiting acetylcholine release from the enteric neurons and suppressing peristalsis than beta-adrenoceptor agonists (79,81). The α2-adrenoceptor agonists clonidine and dexmedetomidine are used as additive analgesic drugs that inhibit gastric, small bowel, and colonic motility in animal and human studies (74,75,78).

Fruhwald et al. (79) ranked inhibitory potency of catecholamines on the peristaltic motility of guinea-pig ileum *in vitro* as follows: Epinephrine > norepinephrine > dopamine > dobutamine ~ dopexamine (Table 1 summarizes the effects of different catecholamines on different receptors). The use of dobutamine and dopexamine may be preferred in patients with critical illness because of their low potency in suppressing intestinal propulsion, but this recommendation is only based on their effects on intestinal motility and does not take their effects on gut perfusion into account (79). Inadequate splanchnic perfusion in the critically ill is known to compromise the gut barrier that leads to bacterial translocation, which may ultimately lead to multiple organ dysfunction. The evidence demonstrates that dopexamine, dobutamine, and dopamine increase splanchnic perfusion, thereby protecting the gut from further injury.

The effect of vasopressin on the GI tract is only rudimentary examined. Using a dog model, Xu et al. (89) showed that that vasopressin significantly delayed gastric emptying and induced gastric and intestinal dysrhythmia. Compared with the gastric slow wave, the inhibitory effect of vasopressin on the intestinal slow wave was relatively mild. Similar results were reported by Langhans et al. (90) in rats, which demonstrated that intraperitoneally injected vasopressin inhibits gastric emptying and reduces food intake in rats. This effect was mediated by an alpha-adrenergic mechanism (91).

Caras et al. (92) studied the effects of vasopressin on gastric myoelectrical activity in healthy women. They demonstrated that intravenous vasopressin influences gastric motility and result in gastric arrhythmia, predominantly bradyarrhythmias, and caused significant nausea and abdominal cramping compared with baseline and controls in dose-dependent fashions (92).

In conclusion, several studies support that the use of dobutamine and dopexamine in critical illness may be more protective on the gastrointestinal system than other catecholamines, including preservation of gut mucosal integrity and lower risk of delayed gastric emptying.

CONCLUSION

Causes for feeding intolerance remain unclear and are probably multifactorial during critical illness. A better understanding of its pathophysiology in children with critical illness may allow an optimized strategy to avoid motility disorders. Therapeutic options, however, are still limited. Current recommendations mostly focused on optimizing all factors that contribute to delayed gastric emptying, early initiation of EN, and individual use of prokinetic agents. Insufficient studies preclude the routine use of newer therapeutic approaches, such as μ-opioid and CCK receptor agonists in children with critical illness and the further investigation appears warranted based on their risk/benefit ratios.

Table 1. Effects of different catecholamines on different receptors

	Receptor				
Catecholamine	α	β1	β2	DA1	DA2
Dopamine (μg/kg/min)					
0-3	0/+	+	+	++	++
3-10	+	++	+	++	++
>10	++	++	+	++	++
Dopexamine	0	+	+++	++	+
Dobutamine	+	+++	++	0	0
Epinephrine	+++	++	+++	0	0
Norepinephrine	+++	++	+	0	0

DA: Dopamine

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

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