Volume Based Feeding Versus Rate Based Feeding in the Critically Ill: A UK Study

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Introduction

Nutrition support is an essential part of treatment in patients requiring intensive care. Timely provision of greater energy and protein intake is associated with lower mortality and a faster time to discharge alive [1, 2]. However, underfeeding in intensive care patients is commonplace and multi-factorial [3]. In response to stress, underfeeding can lead to malnutrition and poor clinical outcomes, including increased mechanical ventilation days, infectious complications, length of stay (LOS) in the Intensive Care Unit (ICU) and in hospital, with an increase in associated healthcare costs [4-8].

Enteral nutrition (EN) remains the preferred route of feeding in ICUs, providing both nutritional and non-nutritional benefits [9-12]. However, there is currently insufficient evidence for the optimal EN delivery method in the literature for intensive care patients, with options including Rate Based Feeding (RBF) or bolus feeding [13, 14]. Frequent interruptions to EN including routine fasting for procedures and investigations exacerbate underfeeding in ICU patients [15, 16] and recent studies have demonstrated that RBF is ineffective in addressing this issue [17-20]. Despite this, RBF remains the most common method of EN delivery throughout ICUs in Europe. The recent International Nutrition Survey (INS, 2014/15), demonstrated that adequacy of energy and protein in enterally fed ICU patients in Europe was 58% and 54% respectively (unpublished data; Darren Heyland, personal communication, 2017).

A Volume Based Feeding (VBF) approach has been recommended to address the challenges of frequent interruptions and optimise the delivery of EN [12,14]; designed to adjust the infusion rate to make up for daily interruptions in delivery, enabling a greater volume of EN to be delivered compared to a fixed hourly RBF [18]. This recommendation for VBF is based on studies in North America [18-21]. To date there are no studies evaluating VBF alone and its effect on EN delivery or clinical outcomes outside of North American healthcare institutes. Although the practice of intensive care medicine is universal in most countries, there can be significant differences in healthcare and populations in this already heterogeneous patient group; these previous VBF studies may not be generalisable to other intensive care populations where differing health systems, barriers, patient characteristics and priorities towards nutrition might present [22].

So far there has been no study in the United Kingdom (UK) that addresses whether VBF is a safe and more effective method than RBF in improving energy and protein delivery in mechanically ventilated ICU patients. We hypothesised that VBF would improve energy and protein delivery without deleterious effects on glycaemic control or gastrointestinal tolerance and subsequently, may improve clinical outcome.

Methodology

Study Design and Setting

We conducted a single centre study in an adult, mixed medical and surgical ICU in England, UK between January 2015 and March 2017. This is a cohort study, comparing the usual RBF protocol (cohort 1) to a newly implemented VBF Protocol (cohort 2). Retrospective data were used for RBF participants and prospective data were collected for VBF participants, before and after VBF was introduced. An application to both City, University of London's Senate Research Ethics Committee (Reference number MRes/15-16/40) and UK's Health Research Authority advised that ethical approval was not required for this service evaluation, in that these patients would not undergo any additional intrusive procedure to their normal attention, the data collected was part of their routine care and further patient consent was not required.

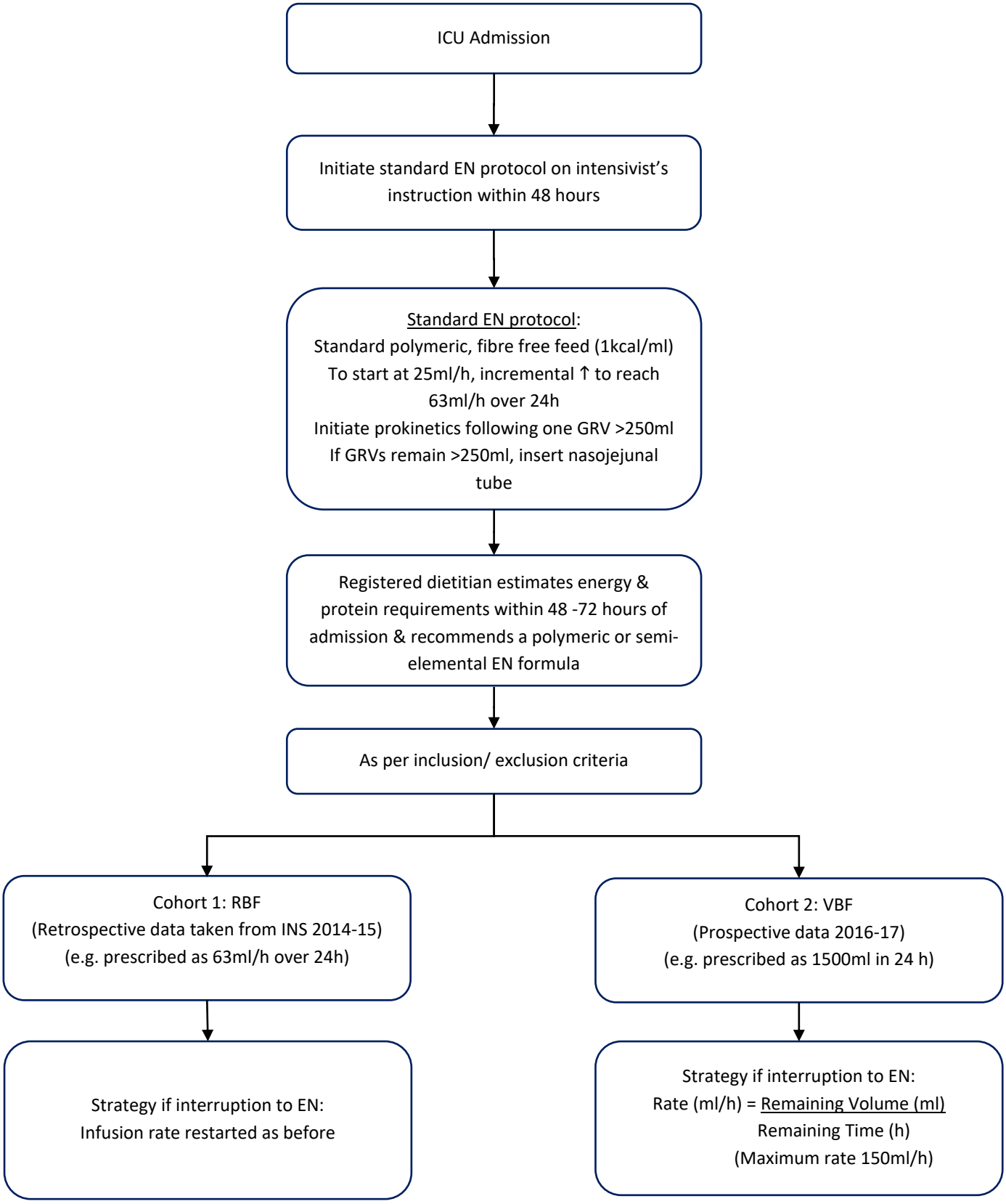
Participants

Eligible patients were mechanically ventilated adults (>18 years), requiring EN for >48 hours at any point during their first 12 days of stay. Consecutive patients were assessed and selected by a registered dietitian for both cohorts. Patients were excluded for the following reasons: contraindications to EN including bowel obstruction, complex bowel surgery (not including post-operative, uncomplicated colonic resections), proximal enterocutaneous fistula, short bowel, bowel ischaemia or paralytic ileus; pre-existing or onset of GI intolerance including profuse diarrhoea (5 stools or >750ml/ 24 hours), nausea, vomiting, abdominal distension (based on nursing assessment), one episode or more of GRV >250ml; receiving parenteral nutrition; aspiration of feed within 48 hours; pregnancy.

Figure 1 outlines the feeding protocol for our study. Gastric residual volumes were monitored every four to six hours and in the absence of a GRV > 250ml, feed rates were advanced every four to six hours. If there was one

or more GRV > 250ml, feeds were initially reduced to a previously tolerated rate or subsequently reduced to 10-25ml/hour and prokinetic agents were prescribed. EN was stopped if GRVs were excessive (>500ml).

Figure 1: Feeding Protocol



Recruitment of Rate Based Feeding Patients (Cohort 1)

Data for RBF patients was collected retrospectively between January and April 2015 as part of an International Nutrition Survey (Critical Care Nutrition, INS Study Protocol, 2014/15). Of the 48 participants recruited for the INS, 27 met the inclusion criteria for this study.

Recruitment of Volume Based Feeding Patients (Cohort 2)

Consecutive patient data was collected prospectively between March 2016 and March 2017. Patients that were established on the standard EN protocol or RBF regimen were assessed by the dietitian for VBF.

A previously reported VBF protocol [18] was modified and adopted for this study, including using a maximum rate of 150ml/hour [17] and the pre-calculated algorithm in which the remaining volume has been rounded to one hundred millilitres volumes (instead of 50 millilitres) to simplify calculations (figure 2). Education before, during and after the implementation of VBF protocol was provided for ICU staff by the unit dietitian.

If patients subsequently developed a poor tolerance to EN, presenting with a single GRV > 250ml, vomiting, blood glucose concentration (>18mmol/l) or profuse diarrhoea (defined as 5 stools or 750 mL per 24h period), the nurses were permitted to reduce the rate back to a previously tolerated rate or to 25ml/hour, after the accepted treatments such as prokinetics for high GRV, change of enteral formula for diarrhoea or insulin treatment were unsuccessful.

Data Collection

Patient characteristics, demographics, anthropometry, Acute Physiology and Chronic Health Evaluation II (APACHE II) [23] score and admission details (date and type of admission, i.e. medical/ surgical and aetiology) were recorded on ICU admission. The goals for requirements were determined by the unit dietitian using predictive formulas such as 25kcal/kg and 1.2-1.5g/kg for protein [10] or Penn State equation [24].

The primary outcome measures were the percentage of energy and protein requirements delivered over the patients' ICU stay and included non-nutritious energy from medications such as Propofol. Data were collected until ICU discharge, death, or for a maximum of 12 days; whichever came first.

Secondary outcome measures included the number of vomiting episodes, GRV >250ml, prokinetic use, morning and highest daily blood glucose concentrations in addition to insulin usage. Mechanical ventilation days, ICU and hospital length of stay, ICU and hospital mortality were also collected for 60 days during and post ICU admission or until discharge/ death.

Statistical Analysis

Statistical analysis was completed using IBM SPSS version 22.0 (U.K version). The power calculation was based on a similar study [18] which demonstrated improvement in the delivery of EN calories on percentage means of energy delivered for RBF (n=20) at 80.9% (SD = 18.9%) and VBF (n=37) 92.9% (SD = 16.8%) of goal energy requirements ($P < 0.01$), with a medium to high effect size of 0.67. A priori analysis with G*Power for a 2-tailed t test of the difference between these independent means (RBF vs VBF), using this effect size, and α error level of 0.05 with 80% power resulted in a sample size of 36 patients per group (total 72). The tests used to compare cohort 1 (RBF) and cohort 2 (VBF) were Mann-Whitney U for continuous variables with skewed distributions and independent t tests for normally distributed variables. Chi Square test or Fischer's Exact test were used for the categorical data as appropriate. Some differences in patient characteristics between groups were adjusted for using regression methods. Continuous outcomes were analysed using linear regression, with a log transformation performed before analysis for those outcomes with positively skewed distributions. Logistic regression was used to analyse binary outcomes. Subsequently, multiple regression was used to adjust for factors found to vary between the two groups from the initial analyses.

Figure 2: Volume Based Feeding Schedule

Goal total mL formula per 24h	Hours remaining in the day to feed 24h volume																							
	24	**23**	**22**	**21**	**20**	**19**	**18**	**17**	**16**	**15**	**14**	**13**	**12**	**11**	**10**	**9**	**8**	**7**	**6**	**5**	**4**	**3**	**2**	**1**
2400	100	104	109	114	120	126	133	141	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
2300	96	100	105	110	115	121	128	135	144	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
2200	92	96	100	105	110	116	122	129	138	147	150	150	150	150	150	150	150	150	150	150	150	150	150	150
2100	88	91	95	100	105	111	117	124	131	140	150	150	150	150	150	150	150	150	150	150	150	150	150	150
2000	83	87	91	95	100	105	111	118	125	133	143	150	150	150	150	150	150	150	150	150	150	150	150	150
1900	79	83	86	90	95	100	106	112	119	127	136	146	150	150	150	150	150	150	150	150	150	150	150	150
1800	75	78	82	86	90	95	100	106	113	120	129	138	150	150	150	150	150	150	150	150	150	150	150	150
1700	71	74	77	81	85	89	94	100	106	113	121	131	142	150	150	150	150	150	150	150	150	150	150	150
1600	67	70	73	76	80	84	89	94	100	107	114	123	133	145	150	150	150	150	150	150	150	150	150	150
1500	63	65	68	71	75	79	83	88	94	100	107	115	125	136	150	150	150	150	150	150	150	150	150	150
1400	58	61	64	67	70	74	78	82	88	93	100	108	117	127	140	150	150	150	150	150	150	150	150	150
1300	54	57	59	62	65	68	72	76	81	87	93	100	108	118	130	144	150	150	150	150	150	150	150	150
1200	50	52	55	57	60	63	67	71	75	80	86	92	100	109	120	133	150	150	150	150	150	150	150	150
1100	46	48	50	52	55	58	61	65	69	73	79	85	92	100	110	122	138	150	150	150	150	150	150	150
1000	42	43	45	48	50	53	56	59	63	67	71	77	83	91	100	111	125	143	150	150	150	150	150	150
900	38	39	41	43	45	47	50	53	56	60	64	69	75	82	90	100	113	129	150	150	150	150	150	150
800	33	35	36	38	40	42	44	47	50	53	57	62	67	73	80	89	100	114	133	150	150	150	150	150
700	29	30	32	33	35	37	39	41	44	47	50	54	58	64	70	78	88	100	117	140	150	150	150	150
600	25	26	27	29	30	32	33	35	38	40	43	46	50	55	60	67	75	86	100	120	150	150	150	150
500	21	22	23	24	25	26	28	29	31	33	36	38	42	45	50	56	63	71	83	100	125	150	150	150

Results

Recruitment and Demographics

A total of 82 patients met the eligibility criteria and were enrolled into the study. Twenty-seven from 48 patients were enrolled pre-VBF implementation from the INS study for the RBF group and 55 out of 56 patients were enrolled for the VBF group. One patient was excluded from the VBF group after enrolment due to the development of a gastrointestinal disorder which required parenteral nutrition.

There was a significant difference in APACHE II score (RBF 23.4 vs VBF 19.4; p=0.02), type of admission (p=0.02) and reason for admission diagnoses (p=0.04) between the groups (see Table 1). Surgical admissions were less common in the VBF group (9% vs 30%; p=0.02). The majority of patients were admitted for respiratory conditions in both RBF (22.2%) and VBF (59.3%) groups. The VBF group (n=31, 56%) had a higher number of patients with a medical respiratory diagnosis than the RBF group (p=0.004).

Gastric feeding occurred in most patients; only two patients had post pyloric feeding, both in the VBF group. Enteral feeding was interrupted at least once in 96% of patients for both cohorts. The primary reason for these interruptions was fasting for endotracheal intubation or extubation. The mean hours of all daily interruptions between the RBF and VBF was 2.7 vs 2.2 hours per day respectively (p=0.233). The average time to start EN was significantly different with a median of 2 days (IQR 1, 2) for RBF and 1 day (IQR 1, 2) for VBF (p=0.01). The number of days in which patients started VBF from date of admission was 4.5 ± 2.5 days.

Table 1. Demographics and Other Baseline Characteristics

Characteristics	Rate Based Feeding (n=27)	Volume Based Feeding (n=55)	*P*-value
Male sex, No. (%)	15 (56%)	31 (56%)	0.95
Age, median [IQR], years	63 [51,75]	63 [43,75]	0.57
APACHE II score, mean ±SD	23.4 ± 6.4	19.4 ± 6.7	0.02
Weight, median [IQR], kg	76 [57, 90]	68 [58, 85]	0.37
BMI, median [IQR], kg/m^2	26.2 [24.0, 28.4]	25.0 [21.3, 29.1]	0.34
Type of admission			
Medical, No. (%)	19 (70%)	50 (91%)	0.02
Surgical, No. (%)	8 (30%)	5 (9%)	
Admission diagnosis			0.04
Medical, No (%)			
• Cardiovascular /vascular	5 (19%)	7 (13%)	0.48
• Respiratory	6 (22%)	31 (56%)	0.004
• Neurological	5 (19%)	8 (15%)	0.65
• Sepsis	0 (0%)	2 (4%)	N/A
• Other	3 (11%)	2 (4%)	0.22
Surgical			
• Respiratory	1 (4%)	1 (2%)	0.59
• Gastrointestinal	1 (4%)	1 (2%)	0.59
• Head & Neck	4 (15%)	2 (4%)	0.79
• Other	2 (7%)	1 (2%)	0.26
Estimated energy **requirements** mean ± SD, kcal	1645 ± 255	1702 ± 279	0.38
Estimated protein requirements median [IQR], g	90 [76, 97]	90 [73, 104]	0.66
Start of EN median [IQR], days	2 [1, 2]	1 [1, 2]	0.01
Start of VBF mean ±SD, days		4.5 ± 2.5	
Patients with interruptions to feed, No. (%)	26 (96%)	53 (96%)	1.00
Interruptions to feed (hours/day)	2.7	2.2	0.77

APACHE II, Acute Physiology and Chronic Health Evaluation II, BMI, Body Mass Index; ICU, Intensive Care Unit; EN, enteral nutrition; VBF, volume based feeding.; GRV, Gastric Residual Volume.
kg, kilograms; m, metres; kcal, kilocalories; g, grams;
Data are reported as mean ± standard deviation (SD), or median and interquartile range (IQR); No, number; N/A, Not Applicable

Table 2. Mean Daily Delivery of Energy and Protein from Rate Based and Volume Based Feeding

Outcome	Analysis	Rate Based Feeding (n=27)	Volume Based feeding (n=55)	Difference Mean (95% CI)	P value
Energy (kcal) received	Unadjusted	737 ± 282	1308 ± 239	570 (452, 689)	<0.001
	Adjusted (*)	-	-	488 (318, 629)	<0.001
% Energy requirements	Unadjusted	46.1 ± 19.7	77.8 ± 13.4	31.7 (24.4, 39.1)	<0.001
	Adjusted (*)	-	-	25.2 (15.0, 35.5)	<0.001
Energy (kcal) received (+)	Unadjusted	826 ± 256	1383 ± 245	557 (441, 674)	<0.001
	Adjusted (*)	-	-	492 (327, 666)	<0.001
% Energy requirements (+)	Unadjusted	51.6 ± 18.6	82.2 ± 13.8	30.6 (23.3, 37.9)	<0.001
	Adjusted (*)	-	-	26.2 (16.1, 36.2)	<0.001
Protein (g) received	Unadjusted	33.4 ± 14.1	64.7 ± 15.0	31.2 (24.4, 38.1)	<0.001
	Adjusted (*)	-	-	25.3 (15.7, 34.9)	<0.001
% Protein requirements	Unadjusted	40.1 ± 18.9	72.9 ± 15.0	32.8 (25.2, 40.5)	<0.001
	Adjusted (*)	-	-	25.2 (14.5, 35.9)	<0.001
Energy delivered (kcal / kg)		10.8	20.3		
Protein delivered (g/kg)		0.44	0.95		

Kcal, kilocalories; kg, kilograms; g, grams
Summary statistics are mean ± standard deviation or number (percentage) in each category
(*) Adjusted for: APACHE II score, admission type, method of estimated energy requirement, time to start enteral nutrition
(+) Including energy from Propofol

Primary Outcome

Delivery of Energy and Protein

Table 2 reports the difference in energy and protein delivered between the groups. The VBF patients received a significantly greater percentage of prescribed energy, including non-nutritious energy from Propofol (82% versus 52%, p<0.001) and protein (73% versus 40%, p<0.001) compared to RBF patients. There was also a significant difference in percentage energy delivery from EN alone (78% versus 46%, p<0.001). The daily mean energy and protein calculated over ≤12days indicated that the RBF group received 11kcal/kg and 0.4g protein/kg in contrast to 20kcal/kg and 1.0g protein/kg for the VBF group.

Secondary Outcomes

Safety Outcomes

After adjusting for the differences in patient characteristics, there was no significant difference in glycaemic control, units of insulin administered, episodes of GRV >250mls and prokinetic use between the two groups (Table 3). Vomiting was higher in the RBF group, but this difference was non-significant after adjusting for confounding factors, such as APACHE II score, admission type, time to start EN and method of estimated energy requirements (p=0.08).

Patient Outcomes

The results demonstrated a significant difference between groups in the number of days of mechanical ventilation in the unadjusted analysis (p=0.002), which was no longer statistically significant (p= 0.12) after controlling for APACHE II score, type of admission and time to start EN. There was no significant difference in both ICU and hospital length of stay or ICU and hospital mortality.

Rates of Enteral Nutrition Infusion During VBF

The mean 'average' rate of infusion for VBF was 54ml/h ± 9.0 and the mean 'maximum' rate was 85ml/h ± 32.6. However, in six cases, rates were increased up to a maximum 150ml/hour with no complications observed.

Table 3: Safety and Patient Outcomes

Outcome	Analysis	Rate Based Feeding (n=27)	Volume Based Feeding (n=55)	Difference (+) (95% CI)	P value
Glycaemic control					
Hypoglycaemic event	Unadjusted	1 (4%)	3 (5%)	-	1.00
Highest blood glucose concentrations (mmol/l)	Unadjusted	11.7 ± 3.2	11.6 ± 2.8	-0.2 (-1.5, 1.2)	0.80
	Adjusted (*)	-	-	0.1 (-1.9, 2.0)	0.94
Morning blood glucose concentrations (mmol/l)	Unadjusted	8.4 ± 1.9	8.6 ± 1.3	0.2 (-0.5, 0.9)	0.57
	Adjusted (*)	-	-	0.5 (-0.5, 1.6)	0.33
Insulin (daily units)	Unadjusted	4 [0, 52]	18 [0, 53]	1.83 (0.78, 4.34)	0.17
	Adjusted (*)	-	-	1.21 (0.36, 4.10)	0.75
Gastrointestinal tolerance					
Vomiting	Unadjusted	7 (26%)	5 (9%)	0.29 (0.08, 1.01)	0.05
	Adjusted (*)	-	-	0.21 (0.04, 1.21)	0.08
≥1 GRVs > 250ml	Unadjusted	2 (7%)	7 (13%)	1.82 (0.35, 9.44)	0.47
	Adjusted (*)	-	-	1.82 (0.18, 18.7)	0.62
Prokinetic use	Unadjusted	5 (19%)	5 (9%)	0.44 (0.12, 1.67)	0.23
	Adjusted (*)			0.39 (0.05, 3.04)	0.37
Mechanical ventilation days	Unadjusted	6 [4, 10]	9 [6, 15]	1.76 (1.23, 2.51)	0.002
	Adjusted (*)			1.46 (0.91, 2.35)	0.12
Length of ICU stay (days)	Unadjusted	10 [6, 15]	11 [7, 19]	1.24 (0.88, 1.75)	0.22
	Adjusted (*)	-	-	1.02 (0.63, 1.66)	0.93
Length of hospital stay (days)	Unadjusted	13 [10, 44]	23 [11, 48]	1.14 (0.75, 1.73)	0.52
	Adjusted (*)	-	-	0.90 (0.49, 1.64)	0.72
Mortality					
ICU mortality	Unadjusted	3 (11%)	10 (18%)	1.78 (0.45, 7.08)	0.42
	Adjusted (*)	-	-	8.67 (0.95, 79.4)	0.06
Hospital mortality	Unadjusted	6 (22%)	12 (22%)	0.98 (0.32, 2.96)	0.97
	Adjusted (*)	-	-	3.64 (0.66, 20.1)	0.14

GRV Gastric Residual Volumes ICU Intensive Care Unit
Summary statistics are mean ± standard deviation, median [inter-quartile range] or number (%) in each category
(*) Adjusted for: APACHE II score, admission type, method of estimated energy requirement, time to start enteral nutrition (EN)
(+) Difference between groups reported as mean difference (normally distributed continuous variables), ratios (skewed continuous variables) or odds ratios (binary variables)

Discussion

This study established that VBF can significantly increase energy and protein delivery in the first 12 days of intensive care admission. These findings offer further evidence that VBF is a safe, alternative strategy in achieving target energy and protein goals in both clinical and research settings in spite of frequent interruptions to EN; intending to minimise nutritional deficits which have been associated with improving clinical outcomes [1, 4, 6, 7]. Volume based feeding has previously been used as part of a multi strategy protocol [17, 20, 21] and has shown to increase energy and protein delivery but it is difficult to determine if this increase was attributed entirely to VBF. Other contributing components from these studies include the routine use of protein supplementation (≥24g protein) at initiation of EN; use of a semi-elemental or peptide feed (1.0-1.5kcal/ml); initiation of EN at target rate; use of prophylactic prokinetics on initiation of EN and higher GRV threshold [17, 20, 21]. Whilst other VBF studies have also successfully improved the delivery of percentage goal energy [18, 19], this is the first study to demonstrate an increase in protein delivery from VBF alone.

Previous work has demonstrated that during interrupted EN days, there was a statistically significant difference in goal energy delivered between VBF (78%) and RBF (62%) [18]. Our study epitomises the perpetual interruptions to EN, where 96% (n=79) of patients experienced routine interruptions of 2.7 hours per day (RBF) and 2.2 hours per day (VBF), with no significant difference between the two groups. We identified various reasons for interruptions to EN during our study, primarily fasting for endotracheal intubation or extubation; in addition to medical investigations or procedures, drug administration, an inaccessible gastrointestinal tract or enteral tube displacement. The delays in extubation or possible re-intubation, resulted in EN being held for long periods and on consecutive days, leading to difficulties making up for the entirety of EN hours missed.

Observational studies on mechanically ventilated patients have demonstrated that providing at least 80% of energy [27] and protein [28] target was associated with improved clinical outcomes, in particular patients with a higher nutritional risk [2]. However, there is currently debate on the most efficacious dose of energy and protein to optimise patient outcomes, especially in the early phase of critical illness. Current guidelines recommend 20-25kcal/kg and 1.2-2.0g protein per day [10, 12]. Although our VBF group succeeded in meeting 80% of goal energy, this did not translate into improved clinical outcomes, with the study insufficiently powered for such aspects. In addition, despite a significant increase in protein delivery, it fell short at 73%. The barriers in providing adequate protein can be related to the additional provision of energy from non-nutritious sources such as Propofol, glucose containing infusions and citrate anticoagulation used in continuous venovenous haemofiltration [29]; which often requires a reduction in energy from EN, subsequently reducing protein provision. Patients will benefit from EN formulas modified to avoid overfeeding exogenous energy and using higher protein formulas or protein supplementation together with VBF [17].

This is a study exploring the delivery of energy and protein, safety and clinical outcomes of VBF, which is a relatively novel approach to EN delivery in the UK. It measures the impact of VBF on both gastrointestinal tolerance and glycaemic control. Our results suggest that VBF was delivered safely, with no significant difference in gastrointestinal tolerance, including GRV, vomiting, prokinetic use, glycaemic control and insulin use compared to RBF. The intensive monitoring of GRVs for EN tolerance is currently under question but was included as another measure of safety for this study. Holding or reducing EN is common after a GRV >250ml, contributing to further interruptions and resulting in a reduction in the volume of EN received and an energy deficit [5]. Recent research findings [25,26] of patients predominantly with medical diagnoses indicate that monitoring GRVs may be unnecessary and that this, in turn, may assist in further reducing EN interruptions. This study found that GRVs were unaffected by VBF despite being perceived as more aggressive and less likely to be tolerated with potentially faster rates than RBF. Similar studies comparing VBF with RBF, demonstrated no difference in gastrointestinal tolerance and pulmonary aspiration [18], ventilator acquired pneumonia (VAP) and urinary tract infections [19]. The anticipated concerns relating to the implementation of VBF in ICUs are the higher rates of hourly EN delivery, leading to vomiting and aspiration of EN resulting in an increase in mechanical ventilation days. Our study demonstrated that irrespective of higher respiratory diagnoses in our VBF group (n=31, 56%) than the RBF group (n=6, 22.2%) which also might account for the higher number of

mechanically ventilated days, VBF strategy had no significant effect (p= 0.12). Our findings together with several studies [17-21] suggest vomiting was also not increased (p= 0.08). This is presumably related to VBF patients in this study being selected based on having good gastrointestinal function and previously tolerating EN.

Data relating to nutritional intake and tolerance was collected from day 1 of admission up to day 12 or until discharge from ICU. We recognise that EN delivery in the early acute phase is often difficult and it remains uncertain whether VBF is a suitable strategy at admission [13]. However, it is conceivable that VBF may be beneficial when patients are established on EN post-acute phase and in their recovery phase, over a longer ICU stay. The average number of days from admission to start of VBF in this study was 4.5 ± 2.5.

Our study was conducted in a mixed medical and surgical adult ICU in England, UK. The characteristics of patients were broadly representative and, as a pragmatic effectiveness study, probably represent the reality of current nutritional practice in critical care in the UK. It is notable that the mean APACHE II score for VBF and RBF patients recruited to this study was 23.4 ± 6.4 and 19.4 ± 6.7 respectively, similar to the mean APACHE II (20.5 ± 8.5) of intensive care patients in the UK [22]. A similar study by Haskins et al investigated VBF on intensive care patients in United States America (USA) with median APACHE II scores of 10 (8, 16) and 17 (12, 19) for RBF and VBF groups respectively [19]. The original single centre (USA) VBF study by McClave et al [18] confirmed safe and improved energy delivery in patients with a mean Simplified Acute Physiology Score (SAPS) score of 21.7 ± 9.0 19.5 ± 9.3. Our UK study demonstrated that VBF can be tolerated in patients with a higher disease severity. Although the practice of critical care medicine is universal in most countries, there can be differences in disease severity and populations in this already heterogeneous patient group [22] and these previous VBF studies [18,19] might not be generalisable to critical care populations outside North America.

Strengths of this study include a heterogeneous, adult population in a UK single centre ICU that had pre-existing, established protocols and guidelines for managing nutritional support, raised GRVs and glycaemic control, reflecting good mainstream practice [9, 10, 12]. Despite using a convenience sample from the INS data for cohort 1, the same inclusion and exclusion criteria was used for selection for both cohorts.

The non-randomised controlled design, single centre population that had a greater representation of medical rather than surgical patients may limit generalisability. Recent studies using a multi-strategy EN protocol

including VBF have demonstrated an improvement of nutrition delivery in medical patients [3, 17, 21] but did not have the same effect in surgical patients [30]. The low frequency of gastrointestinal complications for our VBF group could be due to the selection of patients that were already established on EN. Comorbidities and Nutrition Risk in Critically ill (NUTRIC) or other nutrition screening scores were not collected but might have influenced secondary outcomes such as lower mortality and faster time to discharge alive, in that patients with higher nutritional risk may benefit more from optimal provision of energy and protein compared with those with lower risk [2, 31, 32,].

Other limitations include, the small sample size and therefore, underpowered to determine statistical significance for secondary outcomes. The regular education sessions held on VBF for ICU nurses and doctors possibly heightened awareness of nutrition on the unit, contributing to better EN delivery in the VBF cohort. The patients for the two cohorts were recruited over a year apart. During that time the ICU updated its' GRV threshold to 350ml (from 250ml) before VBF was implemented, therefore, to avoid bias, GRVs recorded by nurses at 250ml or above were considered as 'high' for both groups. Protein supplementation was also introduced during this period however, it was not routine practice. When protein supplementation was prescribed in 19% of the intervention group, nurses did not routinely administer it, having little effect on total protein intake. Finally, indirect calorimetry was not available and predictive equations were used which are less reliable [33, 34].

In future, a more robust, adequately powered randomised controlled trial, including more surgical patients is recommended to investigate the impact of the VBF protocol on nutrition delivery. The use of body composition analysis, functional or health related quality of life (HRQOL) measures as primary outcomes to evaluate nutrition intervention may be more suitable than mortality and infectious complications [35].

In conclusion, this study described an alternative strategy to the RBF protocol. It confirmed that compared to RBF, VBF protocol can be successfully implemented to significantly enhance the delivery of EN safely, with no adverse effect on glycaemic control and gastrointestinal tolerance. However, despite this improvement, there was no beneficial effect observed on clinical outcomes, as it was underpowered to do so. This study's findings should encourage the development of a robust, adequately powered randomised controlled trial to investigate the impact of this safe VBF protocol on nutrition delivery and appropriate clinical outcomes.

List of Abbreviations

APACHE II: Acute Physiology and Chronic Health Evaluation

ASPEN: American Society of Parenteral and Enteral Nutrition

BAPEN: British Association of Parenteral and Enteral Nutrition

BMI: Body Mass Index

CCPG: Canadian Clinical Practice Guidelines for nutrition

EN: Enteral Nutrition

ESPEN: European Society of Parenteral and Enteral Nutrition

GRV: Gastric Residual Volumes

ICU: Intensive Care Unit

INS: International Nutrition Survey

IQR: Inter Quartile Range

LOS: Length of Stay

RBF: Rate Based Feeding

SD: Standard Deviation

VBF: Volume Based Feeding

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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