CHEST

Intermittent Enteral Nutrition as a Sole Intervention Has No Impact on Muscle Wasting in Critical Illness

Emma J. Ridley, BNutriDiet, MPH, PhD
Sandra L. Peake, MD, PhD
Melbourne, VIC, Australia

In this issue of *CHEST*, McNelly et al[1] report the findings from a phase II randomized controlled trial investigating the impact of intermittent enteral nutrition (EN) on muscle wasting compared with continuous EN in mechanically ventilated adults with multiorgan failure and predicted to stay in ICU for ≥ 7 days.

A number of high-quality randomized trials have addressed optimal nutrition in the critically ill, including early parenteral nutrition (PN), PN vs EN, trophic and permissive EN, and the delivery of international guideline-recommended energy delivery using an energy-dense enteral formulation.[2-5] Perhaps unsurprisingly, a benefit on clinically important outcomes has not been observed.[2-5] Moreover, clinicians have not been informed as to the mechanism(s) whereby nutrition may play a role in improving patient-centered outcomes including survival and functional status.

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AFFILIATIONS: From the Australian and New Zealand Intensive Care Research Centre (Drs Ridley and Peake), School of Public Health and Preventive Medicine, Monash University; the Nutrition Department (Dr Ridley), Alfred Hospital; the Department of Intensive Care Medicine (Dr Peake), The Queen Elizabeth Hospital, Woodville South, SA, Australia; and the Faculty of Health and Medical Sciences (Dr Peake), University of Adelaide, Adelaide, SA, Australia.

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CORRESPONDENCE TO: Emma J. Ridley, BNutriDiet, MPH, PhD, Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Level 3, 553 St Kilda Rd, Melbourne, 3004, VIC, Australia; e-mail: emma.ridley@monash.edu

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The rapid and significant muscle wasting associated with critical illness was first characterized in a seminal paper by members of this authorship team who reported that muscle loss was greatest in those with multiple organ failure, independent of nutrition load.[6] Protein synthesis was also found to be impaired on day 1.[6] The implications of marked muscle wasting for functional recovery from critical illness call for the evaluation of mitigating interventions.

McNelly et al[1] hypothesized that intermittent vs continuous EN would reduce skeletal muscle wasting; the rationale being that the usual continuous delivery of EN may be associated with muscle loss because of ongoing raised amino acid concentrations and suppression of muscle protein synthesis (the muscle full effect), thereby leading to muscle wasting. They further suggested that a temporal variation in amino acid concentration associated with intermittent feeding may promote an anabolic process. Accordingly, in this unblinded, clinical trial conducted in eight mixed UK ICUs, 3,487 patients were screened, and 127 patients were randomized: 62 patients to six 4-hourly feeds delivered over 3 to 5 min (intermittent EN) and 59 patients to continuous EN (usual care). The primary outcome was 10-day loss of rectus femoris muscle cross area (RF_{CSA}), measured by ultrasound. Several secondary outcomes were assessed including nutrition adequacy, glycemic control, and physical function. The study was designed with 80% power to detect a 10% difference between groups at a 5% significance level, assuming a baseline reduction in day 10 RF_{CSA} of 21.5%. Accounting for a possible interaction with chronic disease, 29 patients per group were required. The total sample size was inflated to at least 116 to account for anticipated dropout because of early death or recovery or protocol violation.

Sixty-three patients (49%) were available for assessment at day 10. No difference in RF_{CSA} between the intermittent and continuous groups was demonstrated (−1.1%; 95% CI, −6.1 to −4.0; $P = .676$), even after adjustment for important confounders (age, chronic

disease, admission bicarbonate, and Pao_2/Fio_2 ratio). Although delivery of the intervention was not blinded, the assessment of RF_{CSA} was assessed by an investigator blinded to the treatment allocation. Importantly, the median duration of EN delivery was only 4 days (range, 0-10 days) in both groups; therefore, a clinically important difference in muscle wasting is perhaps unlikely. Although the inclusion criteria were designed to select a group of patients most likely to benefit from a feeding intervention (ie, those with prolonged ICU stay), other studies have reported similar difficulties in identifying this at-risk population.[5]

Nutrition targets were more likely to be achieved with the intermittent vs continuous regimen; the chance of achieving ≥ 80% of target energy and protein prescription was approximately 1.5 times greater with intermittent EN. Interestingly, the intermittent group did not achieve higher concentrations of plasma amino acids before and after EN on days 1 and 10, and there was no impact on any physical function or health-related quality of life outcomes. The intermittent regimen was deemed safe, with no clinically important differences in GI side effects and glycemic control; however, more glycemic variability was observed in the intermittent group.

Strengths of the study include the randomized and multicenter design, the pragmatic nature of the intervention, and the careful consideration of the sample size to allow for an interaction with chronic illness and likely high dropout rate. Regardless, the trial did not result in the finding hypothesized by the authors, and possible explanations should be considered. Although careful attention was given by the authors to predict the magnitude of the treatment effect, the use of a relatively new outcome potentially hampers reliable sample size calculations. Despite rigorous training and pretrial assessment of interassessor RF_{CSA} measurement variability in healthy individuals, RF_{CSA} measurement in critically ill patients by multiple trial personnel across multiple sites may also have been unreliable.

The investigation team should be congratulated for doing something many of us in the nutrition field have long considered, namely, the use of an outcome that is more intuitive to a nutrition intervention than traditional outcome measures such as mortality. The trial marks a welcome shift in nutrition research, addressing both the nutrition process and the physiological rationale underpinning how nutrition may benefit critically ill patients. Nutrition and metabolism in the critically ill are complex, and we now have several examples that simply providing more is not the answer for improving patient-centered outcomes such as mortality and functional outcomes. This group has made a positive contribution toward understanding the mechanistic issues surrounding the effects of nutrition in critical illness.

There are also several important practical implications of this trial. First, intermittent feeding as a sole intervention is unlikely to significantly impact muscle wasting; albeit, it can safely result in improved nutrition targets. Furthermore, although the impact of intermittent feeding on satiety was not addressed, it could be hypothesized that in the chronically critically ill, this feeding strategy may deliver target nutrition in a more physiological way as a transition from EN to oral diet. However, the effect of intermittent feeding on glucose variability should be considered and may not be appropriate in critically ill patients with unstable blood glucose management.

In summary, this thoughtful investigation comparing the effect of intermittent vs continuous EN on skeletal muscle wasting provides a template for further research into understanding the mechanistic issues whereby supplemental nutrition can improve recovery after critical illness. Focusing simply on dose and/or timing, while important, is not the whole story and we need to understand why.

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CHEST

Effect of Intermittent or Continuous Feed on Muscle Wasting in Critical Illness

A Phase 2 Clinical Trial

Angela S. McNelly, PhD; Danielle E. Bear, MRes; Bronwen A. Connolly, PhD; Gill Arbane, BSc; Laura Allum, BSc; Azhar Tarbhai, BSc; Jackie A. Cooper, MSc; Philip A. Hopkins, PhD; Matthew P. Wise, MBBS; David Brealey, PhD; Kieron Rooney, MBBS; Jason Cupitt, MBBS; Bryan Carr, MBBS; Kiran Koelfat, MD; Steven Olde Damink, PhD; Philip J. Atherton, PhD; Nicholas Hart, PhD; Hugh E. Montgomery, MD; and Zudin A. Puthucheary, PhD

BACKGROUND: Acute skeletal muscle wasting in critical illness is associated with excess morbidity and mortality. Continuous feeding may suppress muscle protein synthesis as a result of the muscle-full effect, unlike intermittent feeding, which may ameliorate it.

RESEARCH QUESTION: Does intermittent enteral feed decrease muscle wasting compared with continuous feed in critically ill patients?

STUDY DESIGN AND METHODS: In a phase 2 interventional single-blinded randomized controlled trial, 121 mechanically ventilated adult patients with multiorgan failure were recruited following prospective informed consultee assent. They were randomized to the intervention group (intermittent enteral feeding from six 4-hourly feeds per 24 h, n = 62) or control group (standard continuous enteral feeding, n = 59). The primary outcome was 10-day loss of rectus femoris muscle cross-sectional area determined by ultrasound. Secondary outcomes included nutritional target achievements, plasma amino acid concentrations, glycemic control, and physical function milestones.

RESULTS: Muscle loss was similar between arms (–1.1% [95% CI, –6.1% to –4.0%]; $P = .676$). More intermittently fed patients received 80% or more of target protein (OR, 1.52 [1.16-1.99]; $P < .001$) and energy (OR, 1.59 [1.21-2.08]; $P = .001$). Plasma branched-chain amino acid concentrations before and after feeds were similar between arms on trial day 1 (71 μM [44-98 μM]; $P = .547$) and trial day 10 (239 μM [33-444 μM]; $P = .178$). During the 10-day intervention period the coefficient of variation for glucose concentrations was higher with intermittent feed (17.84 [18.6-20.4]) vs continuous feed (12.98 [14.0-15.7]; $P < .001$). However, days with reported hypoglycemia and insulin usage were similar in both groups. Safety profiles, gastric intolerance, physical function milestones, and discharge destinations did not differ between groups.

INTERPRETATION: Intermittent feeding in early critical illness is not shown to preserve muscle mass in this trial despite resulting in a greater achievement of nutritional targets than continuous feeding. However, it is feasible and safe.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT02358512; URL: www.clinicaltrials.gov

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KEY WORDS: critical care; energy delivery; muscle wasting; nutrition; protein delivery

FOR EDITORIAL COMMENT, SEE PAGE 15

ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; CF = continuous feeding; GRV = gastric residual volume; IF = intermittent feeding; RF_{CSA} = rectus femoris cross-sectional area; SOFA = Sequential Organ Failure Assessment

AFFILIATIONS: From the William Harvey Research Institute (Drs McNelly and Puthucheary), Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; University College London (UCL) (Dr McNelly,

Acute skeletal muscle wasting occurs rapidly in critical illness, and contributes to increases in length of stay, mortality, and functional disability.[1-4] This in turn has significant detrimental impacts on patients, carers, and health service use postdischarge. This disability has proven resistant to exercise rehabilitation[5-8] or goal-directed nutrition[9] interventions, highlighting the need for primary prevention.

Decreased muscle protein synthesis is a major pathophysiologic component of muscle wasting,[1,10] and continuous feeding (CF) may contribute to this. Continuous provision (and continuously raised concentrations) of amino acids suppresses myofibrillar protein synthesis (the muscle-full effect[11]), demonstrated in both enteral[12] and parenteral amino acid delivery.[13]

Conversely, peaks in amino acid concentration (leucine in particular[14]) promote anabolism,[15] and intermittent feeding of critically ill patients might therefore be advantageous.

Intermittent feeding (IF) increases splanchnic blood flow and results in pulsatile changes in ghrelin, insulin, and peptide YY concentrations,[16] which may increase amino acid availability, further stimulating muscle protein synthesis.

For these reasons, studying the benefits of IF in the critically ill has been strongly advocated[17] as this may offer a more efficacious form of acute nutrition support[18] and decrease the development of disability.[19]

We hypothesized that IF would abolish the muscle-full effect, and therefore ameliorate acute skeletal muscle wasting. This in turn may influence length of ICU/hospital stays, time on mechanical ventilation, Health-Related Quality of Life scores, functional ability, and gut-to-plasma amino acid transfer. The study was performed specifically in patients at risk of persistent critical illness, as these patients experience significant muscle wasting,[1] are at greatest risk of subsequent functional disability, and are less likely to return home.[20,21]

Methods

This was a multicenter, single-blinded randomized controlled phase 2 trial conducted in eight mixed UK ICUs, with an allocation ratio of 1:1. Basic characteristics of the ICUs are shown in e-Table 1.

Participants

Participants qualified for enrollment up to 24 h after ICU admission.

Inclusion Criteria: Adult (> 18 years), expected to be intubated and ventilated for ≥ 48 h; requiring enteral nutrition via nasogastric tube; multiorgan failure (Sequential Organ Failure Assessment [SOFA] score[22] > 2 in ≥ 2 domains at admission); likely ICU stay ≥ 7 days and likely survival ≥ 10 days (assessed as previously by senior ICU clinicians[1]).

Exclusion Criteria: Prerandomization enteral feeding on the ward or > 12 h on ICU; unlikely to meet nutritional requirements by 72 h, using a standard feeding schedule (based on predicted clinical trajectory); need for sole/supplemental parenteral nutrition or postpyloric feeding on ICU admission. The full list of exclusions is available in e-Appendix 1.

Prospective informed assent was obtained in writing from a nominated personal consultee or professional consultee. Retrospective participant consent was obtained on return of participant's mental capacity. Permission to use participants' data if capacity did not return or they did not survive was included in the assent process.

The study received ethics committee approval (National Research Ethics Service Committee London-Queens Square; REC reference 14/LO/1792; IRAS project ID 160281) and was publicly registered before the first patient was randomized (ClinicalTrials.gov, NCT02358512). We used the CONSORT (Consolidated Standards of Reporting Trials) statement when reporting this trial.[23]

Prof Montgomery, Mr Tarbhai, and Ms Cooper); the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC), UCL Hospitals NHS Foundation Trust (Drs McNelly and Brealey, and Prof Montgomery), London, United Kingdom; the Department of Nutrition and Dietetics (Ms Bear) and the Department of Critical Care (Ms Bear), Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; the NIHR BRC, King's College London (Ms Bear and Dr Connolly), London, United Kingdom; the Lane Fox Clinical Respiratory Physiology Research Centre (Dr Connolly and Prof Hart; and Mss Arbane and Allum), Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; Kings College Hospital (Dr Hopkins), London, United Kingdom; the University Hospital of Wales (Dr Wise), Cardiff, Wales, United Kingdom; the Bristol Royal Infirmary (Dr Rooney), Bristol, United Kingdom; the Blackpool Victoria Hospital (Dr Cupitt), Blackpool, United Kingdom; the University Hospitals of North Midlands (Dr Carr), Stoke-on-Trent, United Kingdom; the Department of Surgery and School of Nutrition and Translational Research in Metabolism (NUTRIM) (Dr Koelfat and Prof Olde Damink), University of Maastricht, Maastricht, The Netherlands; the Department of General, Visceral and Transplantation Surgery (Prof Olde Damink), RWTH University Hospital Aachen, Aachen, Germany; the Medical Research Council/Arthritis Research UK Centre for Musculoskeletal Aging (Prof Atherton), University of Nottingham, Nottingham, United Kingdom; and the Adult Critical Care Unit (Dr Puthucheary), Royal London Hospital, London, United Kingdom.

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CORRESPONDENCE TO: Angela McNelly, PhD, Critical Care and Perioperative Medicine Research Group, Adult Critical Care Unit, Royal London Hospital, London, E1 1BB, United Kingdom; e-mail: angela.mcnelly@qmul.ac.uk

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Feeding Regimens

Enteral feeding was allowed for up to 6 h prerandomization. The same IF regimen (intervention) was used at every site, consisting of six 4-hourly feeds during 24 h,[24] administered via nasogastric tube using a syringe over 3 to 5 min. Depending on each Trust's approved supplier, either Ensure Compact (energy content, 2.4 kcal/mL; protein content, 0.104 g/mL; Abbott Nutrition) or Fortisip Compact Protein (energy content, 2.4 kcal/mL; protein content, 0.144 g/mL; Nutricia) was used, with a range of starter bolus sizes of 60 to 80 mL according to the participants' initial individual nutritional targets. The CF regimen (control) consisted of the total volume of feed administered over 24 h, as per local feeding protocols.

The specific feed used for each patient in either arm of the trial was prescribed by each ICU's dietitian at a dose calculated to meet that patient's nutritional needs. Further details of the feeds and feeding protocols are described in the online article and in e-Table 2, and e-Figs 1 and 2.

Nutrition targets were individualized by each unit's dietitian within 72 h of randomization. The modified Penn State equation or a weight-based equation (eg, 25 kcal/kg) was used to estimate energy targets. Protein targets were individualized with a minimum of 1.2 g/kg being used (actual body weight if BMI $<$ 30 and ideal body weight if BMI $>$ 30). After the intervention period, participants reverted to continuous feeding if enteral feed was required. Deviations from prescribed nutritional delivery (and their rationale) were recorded. The adequate nutritional threshold was set at $>$ 80% of prescribed targets.[25] Analysis was further performed on those achieving $>$ 60%, in keeping with international practice.[26]

End Points

The primary end point was change in rectus femoris cross-sectional area (RF_{CSA}) on trial day 10.[1] This method is fully validated for use in the critically ill,[1] and was chosen as an outcome given the difficulties with volitional measures of physical function in acute critical illness.[27] Using B-mode ultrasound,[1] RF_{CSA} was measured on trial days 1, 7, and 10 after randomization and at ICU and hospital discharge. Members of the research team were trained to perform RF_{CSA} measurements, and scan quality at each site was deemed adequate with an intraclass correlation coefficient $>$ 0.9. Full details are provided in the online article.

Secondary end points and their method of assessment are listed in Table 1. Blood samples were taken on trial days 1, 7, and 10. Plasma concentrations of 21 amino acids (including branched chain and nonbranched chain) were determined immediately before and 30 min after intermittent feeds at 9:00 and 13:00 in the intervention arm and at equivalent time points in the control arm. Plasma concentrations of citrulline (a marker of gut integrity[28]) were additionally measured.

Measures of adverse safety impacts included proven or suspected aspiration, increased daily rates of vomiting or diarrhea (Bristol Stool Chart score $\geq$ 5[29]), gastric residual volume (GRV) $\geq$ 300 mL, or impaired glycemic control from 4-hourly glucose measurements. Normoglycemia was defined as a blood glucose concentration of 4 to 10 mM, and thus concentrations of $\geq$ 10.1 or $\leq$ 3.9 mM were defined as hyperglycemia or hypoglycemia, respectively. Daily variation in blood glucose concentration was assessed by the coefficient of variation (SD/mean x 100).[30]

Sample Size

Patients with multiorgan failure suffer a 21.5% (SD, 10.6) reduction of RF_{CSA} in 10 days.[1] A sample of 26 per group would give 90% power to detect a 10% difference between groups, at the 1% significance level. We performed a stratified analysis to allow for the different response of patients with preexisting chronic disease (defined as a stable chronic health condition requiring primary or secondary care follow-up),[31,32] estimating the proportion of chronic disease-to-nonchronic disease participants in the study cohort to be 2:1. A sample size of

TABLE 1] Secondary End Points and Methods of Assessment

Secondary End Point	Method of Assessment	Personnel
Change in muscle mass between trial day 7 and trial day 1	Ultrasound-derived rectus femoris cross-sectional area	Investigator
Length of ICU stay	Electronic/paper clinical records	Investigator
Length of hospital stay	Electronic/paper clinical records	Investigator
Days of mechanical ventilation	Electronic/paper clinical records	Investigator
Amino acid concentrations (including citrulline)	Biochemical analysis plasma samples	Investigator
Gastric residual volume ($>$ 300 mL)	Electronic/paper clinical records	Investigator
Diarrhea	Electronic/paper clinical records	Investigator
Vomiting	Electronic/paper clinical records	Investigator
Prokinetic use	Electronic/paper clinical records	Investigator
Discharge location	Electronic/paper clinical records	Investigator
Sit-to-stand test post-ICU	Bedside assessment	ICU nurse
Bed-to-chair transfer post-ICU	Bedside assessment	ICU nurse
6-Minute Walk Test	Ward assessment	Physiotherapist
Short Physical Performance Battery	Ward assessment	Physiotherapist
Health-Related Quality of Life	Ward assessment/SF-36 questionnaire (telephone)	Investigator
Primary health care usage/costs	Electronic medical records	Investigator

SF-36 = 36-Item Short Form Health Survey.

29 per group would detect a large interaction effect ($f = 0.4$) for a factor with a 2:1 ratio of subgroups with 80% power at the 5% level.[33] Identifying those patients at risk of persistent critical illness is challenging, and a high dropout rate was expected from both early death and early recovery. We aimed to recruit at least 116 patients to allow for a dropout rate and protocol violations (common in many critical care trials) of up to 50%, with increased recruitment allowed to ensure equal numbers per arm.

Randomization and Blinding

Randomization was stratified for recruitment site (1:1 basis), and for the presence of chronic disease, and occurred once assent was obtained. Treatment group allocation used an independent remote electronic web-based random allocation service to generate an unpredictable allocation outcome, and to conceal that outcome from research staff until assignment occurred. Z. A. P. (who assessed all ultrasound scans for the primary outcome) and the data analysts were blinded to allocation until data analysis was complete (see the online article).

Statistical Analyses

The statistical plan was designed by a statistician (J. A. C.), and approved a priori as part of the process of obtaining ethical approval. Further details are available in the online article.

Both the intention-to-treat cohort and the per-protocol cohort (those that spent 10 days in ICU and had their muscle mass measured) were analyzed. We compared results between groups by analysis of variance with subgroup analysis by presence of chronic disease states. An adjustment for a small number of prespecified prognostic covariates (admission bicarbonate [HCO_3^-] and ratios of Pao_2/Fio_2[1]) was made by analysis of covariance.

A change in RF_{CSA} of –21.5% (as per power calculation) was assigned to those patients who were lost to follow-up or had their intervention discontinued[9] in the intention-to-treat analysis. Sensitivity analyses were performed with (1) a score assignment of –0% at 10 days, (2) multiple imputation, and (3) the per-protocol subgroup.

All data were assessed for normality, using D'Agostino and Pearson omnibus normality tests. Data were then analyzed by Student t test, Pearson coefficient, Mann-Whitney U test, and Wilcoxon signed rank test as appropriate. The area under the curve was used as a measure of amino acid concentration.[34] Glucose variability was described using the coefficient of variation.[30] Differences in nutritional delivery were assessed by Fisher exact test. Fragility indexes, describing the robustness or its lack ("fragility") of a clinical trial's results, were calculated. These indicate how many additional patients would be required in order for statistically significant results from a trial to be rendered nonsignificant.[35] Two-tailed t tests were used, and statistical significance was indicated by $P \leq .05$.

Results

Between February 9, 2015 and September 12, 2017, 3,487 patients were screened, of whom 2,926 were ineligible. Of these, 998 patients (29.7%) were not expected to be intubated for 24 h or more, 305 (9.1%) had single organ failure (SOFA score < 2 in two or more domains), and 307 (9.1%) were not expected to survive for 10 days. Of the 561 patients meeting inclusion criteria, 127 patients were randomized; 394 patients were unable to be recruited because of shortage of research staff, primarily outside the weekday recruitment period. Five were withdrawn before feed commenced and one was randomized in error, leaving 121 randomized: 62 in the intervention group and 59 in the control group. Ethical approval was given to increase recruitment so that randomization could continue until the minimum number per arm (determined a priori) was met (see the online article).

A total of 63 patients completed the 10-day trial period (Fig 1); reasons for premature withdrawal are shown in e-Table 3. Participants' demographics were not different between trial arms (Table 2).

Change in Muscle Mass

No difference in loss of RF_{CSA} was seen between intermittent and continuous arms at 10 days (–1.1% [95% CI, –6.1% to –4.0%]; $P = .676$) (Fig 2, e-Fig 3, e-Tables 4, 5). This lack of difference between groups persisted after adjustment for age, Pao_2/Fio_2 ratio, HCO_3^-, and chronic disease at trial day 10 (–1.8% [95% CI, –6.3% to 2.7%]; $P = .429$). Chronic disease states were not associated with any difference in muscle wasting (effect size, –3.2 [95% CI, –12.6 to 5.5]; $P = .505$) (e-Tables 6 and 7). These results did not differ with any of the three sensitivity analyses (e-Table 8).

Nutritional Delivery

Data were available for 441 days of enteral feeding received by participants in the IF arm and for 413 days received by those in the CF arm. Patients received a similar number of days of nasogastric feeding in both arms (4 days [range, 0-10 days] vs 4 days [range, 0-10 days]; $P = .576$) (not necessarily contiguous, because of various clinical and logistical reasons for disruption of nutritional delivery) (see e-Table 9). The IF regimen resulted in greater nutritional delivery for both protein (80.3% [95% CI, 77.3%-83.4%] vs 69.9% [95% CI, 66.6%-73.1%]; $P < .001$) and energy (82.4% [95% CI, 79.2%-85.6%] vs 72.5% [95% CI, 69.3%-75.7%]; $P < .001$) relative to nutritional targets. More patients met the 80% protein threshold with IF (57.0% vs 46.5%; OR, 1.52 [95% CI, 1.16-1.99]; $P < .001$; fragility index, 15) and the 60% threshold (78.6% vs 65.9%; OR, 1.89 [95% CI, 1.4-2.6]; $P < .001$; fragility index, 28). Energy thresholds were similarly affected at 80% (63.0% vs 51.6%; OR, 1.59 [95% CI, 1.21-2.08]; $P = .001$; fragility index, 19) and 60% (80.5% vs 69.0%; OR, 1.83 [95% CI, 1.34-3.50]; $P < .001$; fragility index,

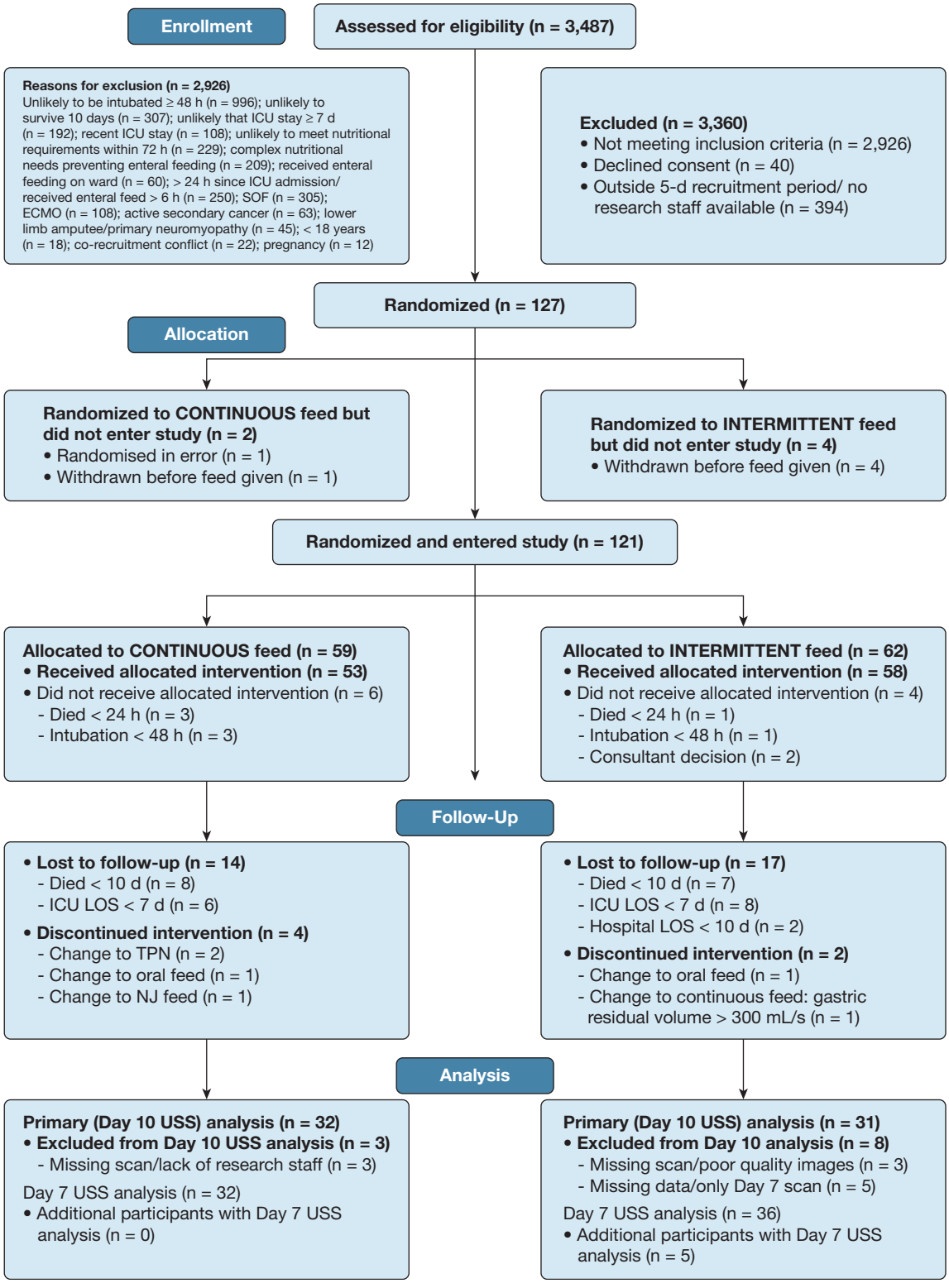

Figure 1 – *CONSORT flowchart. CONSORT = Consolidated Standards of Reporting Trials; ECMO = extracorporeal membrane oxygenation; LOS = length of stay; NJ = nasojejunal; SOF = single organ failure; TPN = total parenteral nutrition; USS = ultrasound scan.*

24) thresholds (Figs 3A and 3B, e-Table 10). Between-group differences were similar or greater in the per-protocol analysis (e-Tables 11 and 12).

No difference was seen in days of adequate nutrition prescribed and delivered between arms (n = 111; 86.6% vs 85.4%; P = .681). Feeding interruptions and/

or missed feeds occurred 157 times in the IF arm and 156 times in the CF arm. IF was less disrupted by airway management (12 [7.6%] vs 27 [17.3%]; $P = .017$), or intolerance secondary to vomiting (5 [3.2%] vs 16 [10.3%]; $P = .019$) or diarrhea (0 [0.0%] vs 4 [2.6%]; $P = .050$). IF was more likely to be disrupted for abdominal distension (5 [3.2%] vs 0 [0.0%]; $P = .021$) and was more likely to have feed prescription or delivery errors (14 [8.9%] vs 2 [1.3%]; $P = .001$) (e-Table 9).

TABLE 2] Patient Characteristics and Demographics

Characteristic	All (N = 121)	Intermittent Feeding (n = 62)	Continuous Feeding (n = 59)	*P* Value
Age, y	57.7 (54.7-60.6)	55.2 (51.0-59.3)	60.3 (56.0-64.1)	.086
Male, No. (%)[a]	81 (66.9)	41 (66.1)	40 (67.8)	.997
LOS before ICU admission, d[b]	0.0 (0-15)	0.0 (0-15)	0.0 (0-15)	.259
Period ventilated, d[b]	7.3 (0.5-48)	9.5 (0.5-48)	6.0 (0.63-43)	.249
ICU LOS, d[b]	13.0 (0.7-93)	13.0 (0.7-93)	12.0 (1.5-52)	.626
Hospital LOS, d[b]	22.8 (1.5-183)	22.0 (1.7-183)	26.0 (1.5-102)	.907
APACHE II score	21.8 (19.9-23.6)	23.1 (19.9-26.2)	20.2 (18.2-22.3)	.134
SOFA score on admission	10.4 (9.7-11.0)	10.3 (9.4-11.2)	10.6 (9.6-11.5)	.709
ICU survival, No. (%)[a]	87.0 (71.9)	44.0 (71.0)	43.0 (72.9)	.173
Hospital survival, No. (%)[a]	79.0 (66.4)	39.0 (63.9)	40.0 (69.0)	.571
RRT, No. (%)	43.0 (36.8)	25.0 (41.7)	18.0 (31.6)	.338
NMBA use, d[b]	0.0 (0-9)	1.0 (0-9)	0.0 (0-7)	.109
Hydrocortisone dose, mg,[b,c] day 1	0.0 (0-800)	0.0 (0-800)	0.0 (0-800)	.240
Hydrocortisone dose, mg, total by day 10	0.0 (0-25,000)	0.0 (0-8,120)	0.0 (0-25,000)	.149
Statin use, No. (%)	1 (0.01)	0.0 (0)	1.0 (0.02)	.495
Gastroprotection, d[b]	9.5 (0-11)	10.0 (1-11)	8.0 (0-11)	.569
Vasopressor support, d[b]	4.0 (0-22)	4.0 (0-11)	4.0 (0-22)	.962
Sedation use, d[b]	6.0 (0-11)	7.0 (0-11)	5.0 (0-11)	.279
Total propofol dose, g, by day 10	10.6 (3.9-10.6)	11.3 (3.8-14.2)	9.9 (3.6-9.9)	.377
Admission diagnosis, No. (%)				
Sepsis	47 (38.8)	21 (33.9)	26 (44.1)	
Cardiogenic shock	27 (22.3)	16 (25.8)	11 (18.6)	
Trauma	14 (11.6)	6 (9.7)	8 (13.6)	
Respiratory failure	9 (7.4)	6 (9.7)	3 (5.1)	
Intracranial hemorrhage	6 (5.0)	3 (4.8)	3 (5.1)	
Acute liver failure	5 (4.1)	2 (3.2)	3 (5.1)	
Acute kidney Injury	4 (3.3)	3 (4.8)	1 (1.7)	
Drug overdose	4 (3.3)	3 (4.8)	1 (1.7)	
Emergency surgery	3 (2.5)	1 (1.6)	2 (3.4)	
Cerebrovascular accident	2 (1.7)	1 (1.6)	1 (1.7)	
Comorbidities, No. (%)				
Hypertension	44 (36.4)	24 (38.7)	20 (33.9)	
Chronic respiratory diseases	39 (32.2)	23 (37.1)	16 (27.1)	
Diabetes mellitus	32 (26.4)	20 (32.2)	12 (20.3)	
Ischemic heart disease	18 (14.9)	11 (17.7)	7 (11.9)	
Psychiatric diseases	23 (19.0)	12 (19.4)	11 (18.6)	
Renal impairment	8 (6.6)	2 (3.2)	6 (10.2)	

(Continued)

TABLE 2] *(Continued)*

Characteristic	All (N = 121)	Intermittent Feeding (n = 62)	Continuous Feeding (n = 59)	*P* Value
Obesity	10 (8.3)	6 (9.7)	4 (6.8)	
Liver cirrhosis	9 (7.4)	3 (4.8)	6 (10.2)	
Haem-oncologic disease	9 (7.4)	6 (9.7)	3 (5.1)	
Thyroid disease	5 (4.1)	3 (4.8)	2 (3.4)	
Crohn's disease	3 (2.5)	2 (3.2)	1 (1.7)	
Previous CVA	2 (1.7)	1 (1.6)	1 (1.7)	
Chronic pancreatitis	1 (0.8)	1 (1.6)	0 (0.0)	

Data represent mean (95% CI), unless indicated otherwise. The Student t test was used unless indicated otherwise. APACHE II = Acute Physiology and Chronic Health Evaluation; CVA = cerebrovascular accident; LOS = length of stay; NMBA = neuromuscular blockade agent; RRT = renal replacement therapy; SOFA = Sequential Organ Failure Assessment.
[a]χ^2 test was used.
[b]Data represent median with range. Mann-Whitney U test was used.
[c]Corticosteroid dosing as hydrocortisone equivalents.

Plasma Amino Acid Concentrations

Amino acid profiling was performed for 329 time points. Change in plasma concentrations of branched-chain amino acids before and after feeds did not differ between arms on trial day 1 (71 μM [95% CI, 44-98 μM]; P = .547), 7 (90 μM [95% CI, 57-122 μM]; P = .587), or 10 (239 μM [95% CI, 33-444 μM]; P = .178) (e-Fig 4), nor did nonbranched chain amino acid or citrulline concentrations differ at any time point ($P > .05$ in both cases; e-Fig 5).

Plasma concentrations of leucine (the major stimulant of muscle protein synthesis) over time exhibited a sinusoid waveform in the IF arm (Figs 4A-4C) sufficient to stimulate protein synthesis.[14]

Safety

The coefficient of variation for plasma glucose concentrations was higher in the intermittent arm than in the control arm (17.84 [95% CI, 18.6-20.37] vs 12.98 [95% CI, 14.0-15.7]; $P < .001$) (Fig 4D). There was no difference in the number of days in which hypoglycemic (≤ 3.9 mM) episodes occurred (0.0% [95% CI, 0.0%-0.0%] vs 0.0% [95% CI, 0.0%-0.0%]; P = 1.00) between groups. More days with a reported hyperglycemic (≥ 10.1 mM) episode were seen with IF compared with CF (50.0% [95% CI, 33.3%-72.7%] vs 33.3% [95% CI, 18.2%-50.0%]; $P < .001$). Differences in the total number of episodes of hyperglycemia (280 vs 192 in the IF group vs CF group, respectively) appear to have been driven by a few individuals (Fig 4E). While cumulative insulin use was no different between groups (0.0 IU [range, 0-1,582 IU] vs 0.0 IU [range, 0-1,403 IU]; P = .697), IF patients received less exogenous insulin on trial days 8 to 10 than did patients with CF (Fig 4F).

There were no differences between IF and CF arms in trial days with diarrhea (35.9% [95% CI, 27.95%-43.9%] vs 28.1% [95% CI, 20.9%-35.3%]; P = .198), vomiting (0.8% [95% CI, 0.2%-1.8%] vs 3.7% [95% CI, 0.8%-6.6%]; P = .104), or use of prokinetics (13.8% [95% CI, 6.3%-21.3%] vs 20.8% [95% CI, 13.0%-28.7%]; P = .115). There was no difference in trial days with reported GRVs > 300 mL (16.1% [95% CI, 10.0%-22.2%] vs 21.3 [95% CI, 14.6%-28.0%]; P = .230). Seven adverse events (e-Tables 13 and 14) were reported in the intermittent arm and three in the continuous arm. Two from the former group (erratic glucose levels in patients with diabetes mellitus) were considered probably or possibly secondary to the intervention.

One patient was transferred from the intermittent to the continuous arm for no clear reason, after consultant physician review. Three were transferred from the continuous arm to either parenteral nutrition or nasojejunal feed for GRVs > 300 mL (e-Table 3).

Physical Function Milestones and Health-Related Quality of Life

Of the 87 patients who survived to ICU discharge, 39 (44.8%) had a first sit-to-stand time recorded and 38 (43.7%) had a first transfer from bed-to-chair time recorded. There was no difference in sit-to-stand time (1 day [95% CI, −4 to +6] vs 2 days [95% CI, −5 to +1]; P = .324) or first transfer (2 days [95% CI, −4 to +3] vs 1 day [95% CI, −5 to +2]; P = .868) before ICU discharge between arms. Data for 6-min walking distance, Short Physical Performance Battery, and

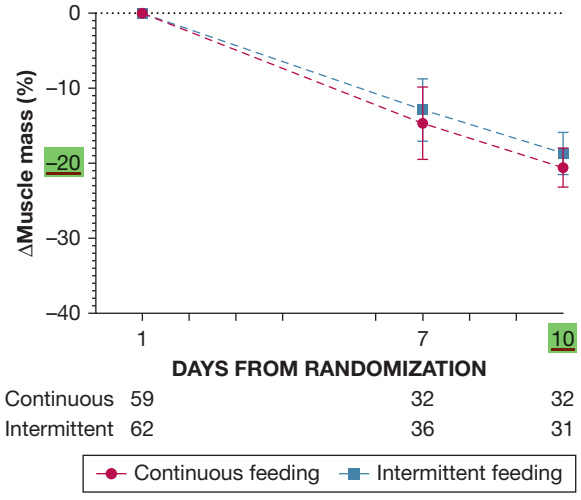

Figure 2 – *Loss of muscle mass over 10 trial days in patients randomized to continuous or intermittent feeding. Data represent mean with 95% CIs. Patient numbers are shown for trial days 1, 7, and 10 post-randomization. Patient numbers on specific trial days are shown below the figure.*

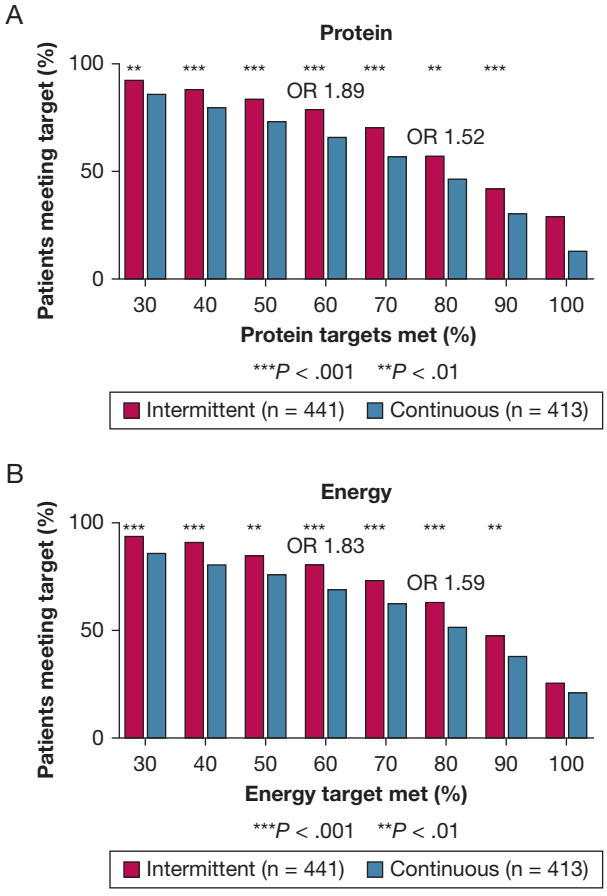

Figure 3 – *Cumulative nutritional delivery. A, Cumulative protein delivery in intermittent (n = 441 days of feeding prescribed) and continuous (n = 413 days of feeding prescribed) feeding arms. B, Cumulative energy delivery in the same cohort. OR = odds ratio of achieving nutritional target. Red bars represent intermittent feeding regimen, Blue bars represent continuous feeding regimen. ***P < .001; **P < .01.*

Health-Related Quality of Life (pre- and post-ICU) were collected from only 11 participants (9.1%) for each of the first two outcomes, and from 56 participants (46.3%) and three participants (2.5%) for the last two outcomes, because of an unexpected lack of staff resources; these data were not included in the analysis. Primary care cost data proved not feasible to collect because of research staff shortage and are not reported.

Discharge Destination

No difference was seen in rates of discharge to home as opposed to rehabilitation or nursing facilities between arms (24 [39.3%] vs 32 [54.2%], respectively; $P = .123$). Further data are available in the online article.

Discussion and Interpretation

We performed a multicenter, assessor-blinded randomized trial comparing intermittent with continuous enteral feeding in critically ill patients with multiorgan failure and at risk of prolonged intensive care stay. IF increased nutritional target achievement; was safe, tolerated, and feasible; but did not result in amelioration of acute skeletal muscle wasting. As a likely consequence, no differences were seen in either physical function milestones or in discharge destination between groups. Plasma concentration of amino acids and markers of intestinal function and absorption did not differ between groups, although the IF regimen resulted in peak leucine concentrations sufficient to stimulate protein synthesis, unlike CF.[14,36]

These data demonstrate that IF over the first 10 days of ICU admission, as a sole intervention in critically ill patients with multiorgan failure, does not prevent muscle wasting or improve time to achieving physical function milestones. This is in keeping with new data suggesting that the success of any intervention might depend on the contemporaneous suppression of IM inflammation[37,38] and on addressing bioenergetic failure,[37] both of which hinder muscle anabolism.

Better nutritional delivery from IF has been hypothesized[39] and observed in small studies.[40] These data demonstrate, in > 800 feeding days of critically ill patients, that IF allows nutritional targets to be met more effectively. The fragility index was higher than those reported for other critical care trials,[35,41] allowing confidence in these data.

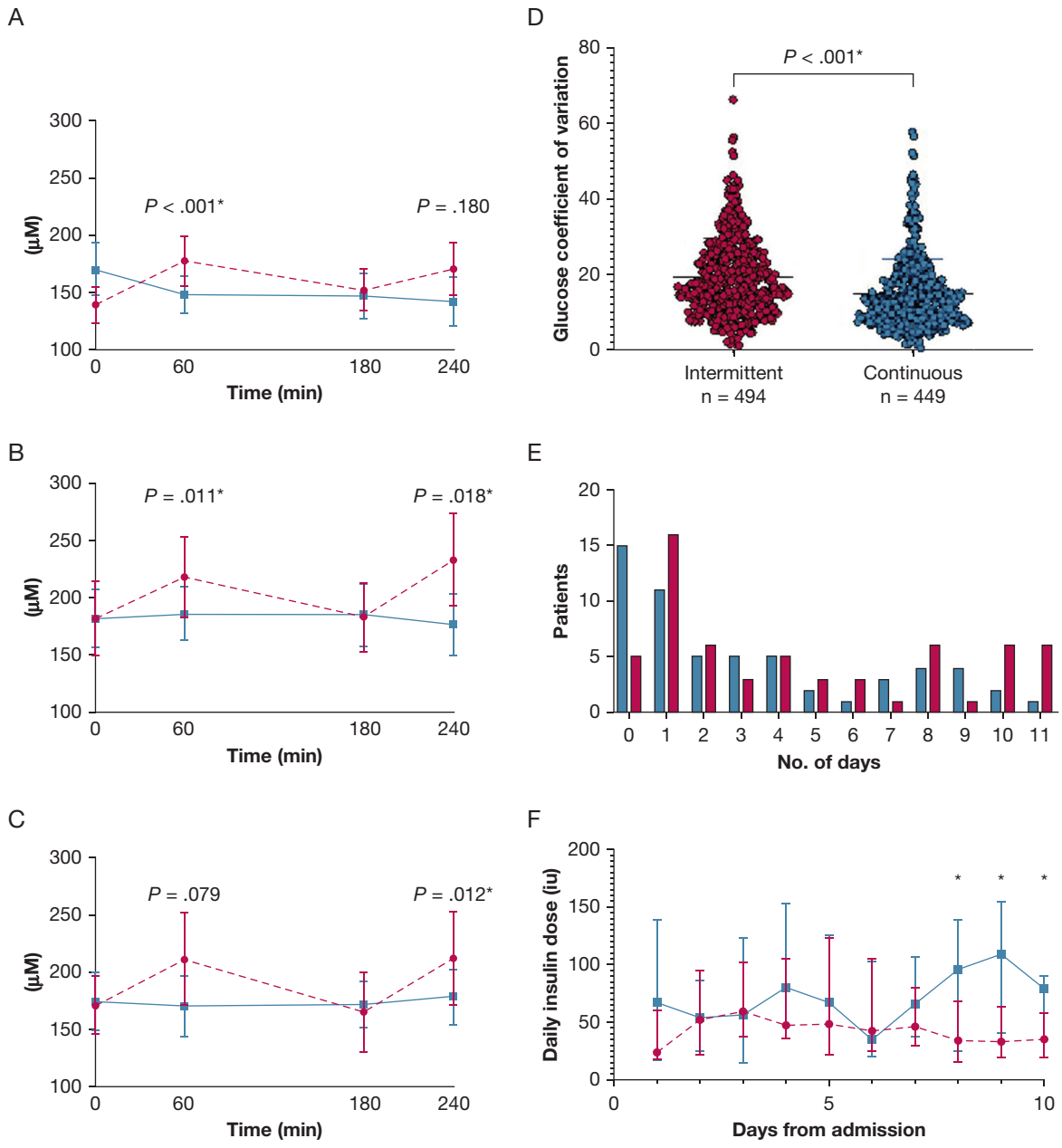

Figure 4 – *A-C, Leucine concentration curve over the 4-h sampling period on trial day 1 (A), day 7 (B), and day 10 (C). D, Glucose variability over the 10-day time frame. E, Number of hyperglycemic days. F, Daily insulin doses. Dashed lines represent intermittent feeding cohort, and full lines continuous feeding cohort. *P < .05.*

In keeping with previous studies,[42,43] the IF regimen was feasible and safe. Although no disparities in hypoglycemia incidence were seen, the increased variability of blood glucose levels with IF may require more bespoke insulin protocols for those patients with greater insulin resistance. The corollary of this is that a decrease in insulin use on trial days 8 to 10 with IF was observed, likely reflecting the increase in insulin resistance associated with continuous amino acid availability.[44]

Our study has several strengths including that of the randomized multicenter design and blinding of primary outcome by separating data acquisition (at site) from data analysis (blinded, centrally performed). Standardized teaching of RF_{CSA} data collection and independent assessment of data quality allow us to be confident in the results of our trial. We further adjusted for known risk factors of muscle wasting (age, Pa_{O_2}/F_{IO_2} ratio, HCO_3^-, and chronic

disease), increasing the validity and generalizability of our data.

We studied those at risk of a prolonged intensive care stay,[45] who face a greater risk of death, prolonged hospital stay, and disproportionate use of health resources compared with patients without persistent critical illness.[21] Studying this population allowed more effective intervention delivery in those patients in whom the primary outcome was measured. Despite this being a particularly challenging group to study, a per-protocol analysis was achieved in 50% of patients randomized over eight sites, a similar proportion to another nutritional interventional trial[9] and sufficient for our a priori power calculation.

The presence of a chronic disease can affect response to interventions[31] and can alter metabolism differentially.[37] No interaction was seen between the presence of a chronic disease and intervention response. The role of chronic disease status and response to nutritional interventions remains unclear.

Data are conflicting regarding protein adequacy affecting muscle mass and physical function positively[46] or negatively.[1,47,48] Similarly, differential energy intake has yet to be proven to affect muscle mass or physical function.[49] Hence it remains unclear as to whether the difference in nutritional delivery would affect the primary outcome. Nutritional delivery was not an a priori factor for adjustment, for the reasons detailed above, unlike those chosen that have supportive data.[1]

Our study does have several limitations. For logistic reasons, we could not blind staff at local sites to the allocated nutritional protocol, but this would not result in systematic bias. However, the single central scan assessor was blinded to treatment allocation. Each site used their local CF protocol as per Trusts' nutritional guidelines, although protocols are highly comparable and a level of careful pragmatism was accepted, to allow generalizability. The weakness of predictive equations for deriving energy expenditure has been recognized,[50] and indirect calorimetry will be considered in future studies as available and appropriate. Recording of physical function and health-related quality of life data was inconsistent. The use of functional outcomes in nutritional research remains novel,[51] and the process of data collection will inform future trials. Funding was not available for recruitment and nutritional assessment over weekends. Although the emergency admission case-mix in the United Kingdom does not differ between weekdays and weekends,[52] future pragmatic trials might seek to make daily recruitment possible.

Finally, while we studied a mix of different disease states, current evidence suggests muscle wasting is determined by severity of organ failure, not admission diagnosis, with similar rates seen in unselected populations[1,53] and in selected populations such as trauma,[54] extracorporeal membrane oxygenation support,[55] or tetanus.[56] The patients we chose to study (likely to have a length of stay $>$ 10 days) constitute only approximately 16% of the critically ill population[21]: It is possible that such a group has the greatest resistance to any mitigating intervention. The temporal relationship of interventions with muscle mass preservation remains relatively unknown in the critically ill patient.[57] Further, longer periods of nutritional interventions are likely needed for differences in muscle mass to become apparent.

In future trials IF may still have a role as a cointervention with others intended to increase muscle protein synthesis (such as metabolic modulators or antiinflammatory interventions), as the observed branched-chain amino acid concentration peaks are sufficient to stimulate protein homeostasis in healthy individuals.[14] Specifically, IF may lower the amount of resistance exercise necessary to induce an anabolic effect, and therefore combined interventions might be studied.[58,59] IF may also help establish a normal circadian rhythm for these patients, and may be included in trials of interventions intended to have this effect.[60]

Second, a role for IF in the optimization of nutritional delivery needs to be explored, as this may be a pragmatic, inexpensive, safe, and easily implemented method by which to ensure patients receive the nutrition they require.

To conclude, in this trial intermittent enteral feeding in early critical illness does not preserve muscle mass as a sole intervention. However, it is feasible and safe, and results in a greater achievement of nutritional targets than a continuous feeding regimen.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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