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Original article

Caloric intake and the fat-to-carbohydrate ratio in hypercapnic acute respiratory failure: Post-hoc analysis of the PermiT trial

Hasan M. Al-Dorzi [a], Abdulaziz S. Aldawood [a], Hani Tamim [b, c], Samir H. Haddad [a], Gwynne Jones [d], Lauralyn McIntyre [d], Othman Solaiman [e], Maram Sakhija [a], Musharaf Sadat [a], Lara Afesh [b], Anand Kumar [f], Sean M. Bagshaw [g], Sangeeta Mehta [h], Yaseen M. Arabi [a, *]

[a] Intensive Care Department, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, King Abdulaziz Medical City, Riyadh, Saudi Arabia
[b] King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia
[c] Department of Internal Medicine, American University of Beirut- Medical Center, Beirut, Lebanon
[d] Department of Medicine, Division of Critical Care Medicine, University of Ottawa, Ottawa Hospital Research Institute, Ottawa, Canada
[e] Department of Adult Critical Care, King Faisal Specialist Hospital and Research Center, Riyadh 11426, Saudi Arabia
[f] Health Sciences Centre, Manitoba, Canada
[g] Department of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada
[h] Department of Medicine and Interdepartmental Division of Critical Care Medicine, Mount Sinai Hospital and University of Toronto, Toronto, Ontario, Canada

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SUMMARY

Background: The effect of moderate caloric enteral intake in critically ill patients with hypercapnic acute respiratory failure (HCARF) is unclear. We studied the impact of permissive underfeeding (PUF) compared with standard feeding (SF) on various HCARF outcomes.

Materials and methods: The PermiT trial randomized 894 patients to either PUF (40–60% caloric requirement) or SF (70–100% requirement) with similar protein intake and found no difference in mortality, mechanical ventilation (MV) duration and ventilator-free days. In this *post-hoc* study, we restricted analysis to mechanically-ventilated patients with HCARF ($PaCO_2$ >45 mmHg on the first two study days) and assessed the impact of trial interventions and fat-to-carbohydrate ratio on outcomes.

Results: One-hundred-twenty patients had HCARF (59 PUF and 61 SF, age 53.7 ± 17.8 years, body mass index 31.1 ± 11.2 kg/m^2, Acute Physiology and Chronic Health Evaluation II score 21.7 ± 7.1 and day-1 $PaCO_2$ 61 ± 16 mmHg). Caloric intake was 815 ± 270 kcal/day in PUF group and 1289 ± 407 kcal/day in SF group. The two groups had similar $PaCO_2$ levels during ICU stay. The 90-day mortality (33.9% versus 35.6%, p = 0.85), MV duration (10.7 ± 6.8 versus 11.1 ± 8.1 days, p = 0.56) and ventilator-free days (52.9 ± 38.6 versus 51.2 ± 38.0 days, p = 0.80) were also similar in PUF and SF groups, respectively. Ventilator-free days and 90-day mortality were similar when the fat-to-carbohydrate ratio was < or ≥ the median value (0.73) in all patients and in PUF and SF groups.

Conclusions: In patients with HCARF, SF and PUF were associated with similar $PaCO_2$, MV duration, ventilator-free days and mortality. Fat-to-carbohydrate ratio was not associated with mortality or ventilator-free days.

Trial registration: ISRCTN Registry: ISRCTN68144998.

Abbreviation list: APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; COPD, chronic obstructive pulmonary disease; VCO_2, carbon dioxide production; HCARF, hypercapnic acute respiratory failure; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; OR, odds ratio; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2:FiO_2, ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen; PUF, permissive underfeeding; SF, standard feeding; SOFA, Sequential Organ Failure Assessment; TPN, total parenteral nutrition.

* Corresponding author. Intensive Care Department, King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, King Abdulaziz Medical City, P.O. Box 22490 Riyadh, 11426, Riyadh, Saudi Arabia. Fax: +966 11 8011111 x18880.

E-mail addresses: aldorziha@NGHA.MED.SA (H.M. Al-Dorzi), dawooda@ngha.med.sa (A.S. Aldawood), hani_t@hotmail.com (H. Tamim), haddads55@yahoo.com (S.H. Haddad), GJones@ottawahospital.on.ca (G. Jones), lmcintyre@ottawahospital.on.ca (L. McIntyre), omsmd@yahoo.com (O. Solaiman), SakkijhaM@NGHA.MED.SA (M. Sakhija), sadatmu@ngha.med.sa (M. Sadat), Afeshla@ngha.med.sa (L. Afesh), akumar61@yahoo.com (A. Kumar), Sean.Bagshaw@albertahealthservices.ca (S.M. Bagshaw), SMehta@mtsinai.on.ca (S. Mehta), yaseenarabi@yahoo.com (Y. M. Arabi).

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Introduction

Hypercapnic acute respiratory failure (HCARF) is frequently observed in the intensive care unit (ICU), especially in patients with chronic obstructive pulmonary disease (COPD), persistent asthma, bronchiectasis, obesity-hypoventilation syndrome or chest wall deformity [1]. Higher caloric intake may have adverse effects. It may increase carbon dioxide production (VCO_2) [2] and its arterial partial pressure ($PaCO_2$) [3], which may negatively affect mechanical ventilation (MV) weaning [2,3]. It is also associated with higher feeding volume, which may cause gastrointestinal intolerance and aspiration [4,5], and lead to ventilator-associated pneumonia [6]. On the other hand, lower caloric intake may lead to or worsen malnutrition, which is commonly seen in COPD patients [7], and thus is potentially detrimental. In severe acute COPD exacerbation, weight loss and muscle wasting may be induced or accelerated [8–11], suggesting that adequate caloric intake may be important to attenuate such morbidity.

The studies on the impact of caloric intake on the outcomes of critically ill patients had mixed results. Lower caloric intake has been associated with reduced MV duration in unselected critically ill patients [12], and even in undernourished ICU patients [13]. One the other hand, high caloric and protein deficits have been associated with less survival in surgical ICU patients [14]. A systematic review of 21 trials found that lower compared with higher caloric intake was associated with similar hospital mortality (risk ratio 0.95; 95% CI 0.84–1.08), ICU mortality, total nosocomial infections, mechanical ventilation duration, and length of ICU or hospital stay [15]. Studies that assessed caloric intake in patients with HCARF are lacking. The feeding fat-to-carbohydrate ratio may also have an important impact in such patients. Intravenous fat emulsions have been associated with less VCO_2 than isocaloric amounts of glucose in acutely ill patients [2,16], which led clinicians to recommend higher fat-to-carbohydrate ratio feeding for the "respiratory patient". Such feeding has been associated with lower $PaCO_2$ and less MV duration in intubated patients [17]. However, these positive effects were not been observed in other studies [18]. Given the uncertainties about the optimal nutritional approach, the 2009 and 2016 Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition guidelines suggest against the routine use of specialty, high-lipid low-carbohydrate feeding formulae to reduce VCO_2 in ICU patients with ARF [19,20]. Such formulae have high omega-6 fatty acid content which may enhance inflammation and negatively affect outcomes [21].

The PermiT trial compared two feeding strategies in 894 ICU patients (96.8% were mechanically ventilated) and found no difference in multiple outcomes including $PaCO_2$, MV duration and MV free days [22]. However, these finding may not apply to patients with HCARF. The objectives of this study were to study the impact of permissive underfeeding compared with standard feeding on the outcomes of HCARF patients and evaluate the association between the fat-to-carbohydrate ratio and MV.

Table 1
Baseline characteristics of hypercapnic patients randomized to permissive underfeeding versus standard feeding.

Variables	All hypercapnic patients	Permissive underfeeding	Standard feeding	P-value
	N = 120	N = 59	N = 61	
Age – (year), mean ± SD	53.7 ± 17.8	52.6 ± 17	54.8 ± 18.6	0.51
Female sex – no. (%)	57 (47.5)	27 (45.8)	30 (49.2)	0.71
BMI – (kg/m^2), mean ± SD	31.1 ± 11.2	31.1 ± 11.8	31.1 ± 10.7	0.98
Admission category, no. (%)				
Medical	112 (93.3)	54 (91.5)	57 (93.4)	
Surgical	3 (2.5)	3 (5.1)	1 (1.6)	
Non-operative trauma	5 (4.2)	2 (3.4)	3 (4.9)	0.54
Sepsis on admission – no. (%)	48 (40.0)	26 (44.1)	22 (36.1)	0.37
Traumatic brain injury – no. (%)	1 (0.8)	0 (0)	1 (1.6)	0.32
APACHE II – mean ± SD	21.7 ± 7.1	22.4 ± 7.1	21.2 ± 7.1	0.34
Glasgow Coma Scale – mean ± SD	7.7 ± 4.7	7.1 ± 4.7	8.2 ± 4.7	0.22
SOFA Score Day 1 – mean ± SD	9.7 ± 3.8	9.9 ± 3.9	9.5 ± 3.6	0.59
Vasopressor use – no. (%)	62 (51.7)	35 (59.3)	27 (44.3)	0.99
Renal replacement therapy – no. (%)	12 (10)	6 (10.2)	6 (9.8)	0.95
Chronic illnesses – no. (%)				
Diabetes	39 (32.5)	22 (37.3)	17 (27.9)	0.27
Chronic respiratory disease	38 (31.7)	16 (27.1)	22 (36.1)	0.29
Chronic cardiac disease	11 (9.2)	4 (6.8)	7 (11.5)	0.37
Immunocompromised disorder	16 (13.3)	12 (20.34)	4 (6.6)	0.03
Chronic renal disease	6 (5)	4 (6.8)	2 (3.3)	0.38
Chronic liver disease	9 (7.5)	4 (6.8)	5 (8.2)	0.77
$PaCO_2$ on day 1 – (mmHg), mean ± SD	60.6 ± 16.3	61.2 ± 14.9	59.9 ± 17.7	0.69
PaO_2:FiO_2 ratio – (mmHg), mean ± SD	141.6 ± 91.0	149.6 ± 94.7	133.7 ± 87.1	0.34
Minute ventilation – (L/min), mean ± SD	8.6 ± 2.6	9.1 ± 2.7	8.2 ± 2.3	0.10
Inclusion blood glucose – (mmol/L), mean ± SD	10.5 ± 4.3	10.7 ± 4.3	10.3 ± 4.3	0.63
Hemoglobin – (g/L), mean ± SD	102.7 ± 21.4	102.2 ± 21.6	103.2 ± 21.4	0.80
Creatinine – (μmol/L), mean ± SD	114.7 ± 95.9	118.8 ± 112.5	110.8 ± 77.7	0.65
Bilirubin – (μmol/L), mean ± SD	25.9 ± 61.1	18.6 ± 24.6	32.7 ± 81.1	0.21
Platelets – (10^9/L), mean ± SD	232 ± 154	236 ± 163	227 ± 147	0.75
INR – mean ± SD	1.4 ± 0.9	1.3 ± 0.3	1.5 ± 1.2	0.11
Hemoglobin A1c – (%)	.78± 9.3	6.8 ± 1.6	9.2 ± 13.2	0.30
C-Reactive Protein – (mg/L), mean ± SD	100.8 ± 85.1	118 ± 90.5	82.9 ± 76.0	0.05
Albumin – (g/L), mean ± SD	28.1 ± 6.7	27.3 ± 7.0	28.8 ± 6.4	0.24
Pre-albumin – (g/L), mean ± SD	0.17 ± 0.17	0.15 ± 0.15	0.19 ± 0.19	0.44
Transferrin – (g/L), mean ± SD	1.6 ± 0.6	1.5 ± 0.6	1.7 ± 0.6	0.15
24-h urinary urea – (mmol/d), mean ± SD	381 ± 297	333 ± 226	426 ± 349	0.21

BMI: body mass index; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; INR: international normalized ratio; $PaCO_2$: arterial partial pressure of carbon dioxide, PaO_2:FIO_2 ratio: the ratio of partial pressure of oxygen to the fraction of inspired oxygen; GCS: Glasgow Coma Scale.

Table 2
Study interventions and co-interventions in hypercapnic patients randomized to permissive underfeeding versus standard feeding.

Variable	All hypercapnic patients	Permissive underfeeding	Standard feeding	P-value
	N = 120	N = 59	N = 61	
Study interventions				
Calculated caloric requirement – (kcal/day), mean ± SD	1785.4 ± 387.4	1831.2 ± 422.8	1742.6 ± 349.3	0.22
Calculated protein requirement – (g/day), mean ± SD	89.4 ± 25.2	89.6 ± 26	89.2 ± 24.7	0.94
Caloric source – (kcal), mean ± SD				
Enteral	951.8 ± 416.7	706.5 ± 212.7	1185 ± 409.7	<0.0001
Intravenous propofol	66.9 ± 93.5	70.0 ± 97.4	63.6 ± 90.2	0.71
Intravenous dextrose	41.5 ± 79.0	38.3 ± 84.6	44.7 ± 73.7	0.67
Parenteral nutrition	0.3 ± 3.5	0	0.65 ± 4.82	0.33
Daily caloric intake – (kcal), mean ± SD	1058.1 ± 419.9	814.8 ± 270.2	1289.4 ± 407.1	<0.0001
% of requirement – mean ± SD	60.6 ± 22.5	45.4 ± 10.5	74.7 ± 17.5	<0.0001
Daily protein intake – (g/day), mean ± SD	61.8 ± 26.4	62.1 ± 27.3	61.5 ± 25.7	0.91
% of requirement – mean ± SD	70.3 ± 24.7	70.5 ± 26.7	70.0 ± 22.8	0.92
Daily protein calories – (kcal), mean ± SD	200.8 ± 96.2	206.1 ± 85.3	195.7 ± 106.0	0.56
Daily carbohydrate intake – (kcal), mean ± SD	385.6 ± 241.5	309.8 ± 148.2	506.5 ± 254.8	<0.0001
Percentage from total calories (%)	42.0 ± 16.0	40.0 ± 15.0	44.0 ± 16.0	0.13
Daily fat intake – (kcal), mean ± SD	283.5 ± 219.9	264.3 ± 140.6	427.9 ± 232.2	<0.0001
Percentage from total calories (%)	33.5 ± 15.0	33.0 ± 14.0	34.0 ± 16.0	0.75
Total Fat-CHO ratio[a]	0.98 ± 0.73	1.07 ± 0.83	0.88 ± 0.61	0.15
Duration of intervention – (days), mean ± SD	9.0 ± 4.6	8.5 ± 4.7	9.5 ± 4.4	0.24
Study co-interventions				
Received insulin – no. (%)	60 (50.0)	29 (49.2)	31 (50.8)	0.86
Daily insulin dose – (unit), mean ± SD	24.2 ± 40.1	19.8 ± 36.0	28.4 ± 43.6	0.25
Blood glucose – (mmol/L), mean ± SD	9.9 ± 5.3	9.9 ± 4.8	9.8 ± 5.8	0.93
Formulae – no. (%)				
Disease non-specific	56 (47.5)	30 (50.9)	26 (42.6)	
Disease specific	63 (53.4)	28 (47.5)	35 (57.4)	0.36
Fluid intake – (ml/day), mean ± SD	3802 ± 2640	3704 ± 2598	3895 ± 2697	0.69
Fluid output – (ml/day), mean ± SD	3354 ± 2153	3287 ± 1735	3417 ± 2500	0.74

[a] Ratio of total fat calories over total carbohydrate calories macronutrients (enteral and nonenteral).

Methods

Study design

This was a post-hoc analysis of data from the PermiT trial (Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients; ISRCTN Registry: ISRCTN68144998) [22], which was an unblinded multicenter randomized controlled trial.

Setting

The original trial was conducted between November 2009 and September 2014 in 7 centers in Saudi Arabia and Canada.

Participants

The trial randomized 894 patients to either permissive underfeeding (caloric goal of 40–60% of caloric requirement) or standard feeding (caloric goal of 70–100% of caloric requirement) with similar amount of protein in the two groups and found no difference in the primary endpoint of 90-day mortality between the permissive and standard feeding groups (relative risk, 0.94; 95% confidence interval [CI], 0.76 to 1.16, p = 0.58) [22]. Also, there were no differences in MV duration and ventilator-free days between the two groups [22]. In this study, we restricted analysis to patients who were on invasive MV with hypercapnia defined as $PaCO_2$ > 45 mm Hg on the first two study days. This analysis was not planned a priori. Ventilator care of these patients was by the treating ICU teams.

Data collection

Collected data on admission included patient demographics, admission category (medical, surgical or trauma), Acute Physiology and Chronic Health Evaluation Scores (APACHE) II [23], Sequential Organ Failure Assessment (SOFA) score [24], presence of chronic illnesses, various tests ($PaCO_2$, the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen [PaO_2:FiO_2], blood glucose, creatinine, bilirubin, hemoglobin, platelets, international normalized ratio, C-reactive protein, albumin, pre-albumin, transferrin and 24-h urinary urea nitrogen). For the intervention period, which lasted for up to 14 days, we collected daily nutritional data (feeding formula and calories from enteral feeds, propofol, intravenous dextrose and parenteral nutrition), insulin dose, fluid intake and output and laboratory data ($PaCO_2$, blood glucose, and phosphate) and assessed the occurrence of various infections.

We calculated daily carbohydrate, fat and protein calories from enteral and parenteral sources. We then calculated the total fat-to-carbohydrate ratio by dividing fat calories by carbohydrate calories.

In this study, the 90-day all-cause mortality and ventilator-free days were the primary outcomes. We also studied ICU, 28-day, hospital, and 180-day all-cause mortality, daily $PaCO_2$, MV duration, ICU-free days, ICU and hospital length of stay (LOS), incident renal replacement therapy, ICU-associated infections [25], and hypophosphatemia.

Statistical analysis

In this study, we compared the characteristics and outcomes of hypercapnic patients in the permissive underfeeding and standard feeding groups. We also noted the patients who received respiratory-specialized formula (Pulmocare, Abbott Laboratories) on more than 50% of the intervention duration. Categorical variables were compared between the two groups using the Chi-square test or the Fisher's Exact test, as appropriate. Continuous variables were compared using the Student's t-test. For categorical outcomes, the odds ratio (OR) with 95% CI was reported. For serial measurements of daily $PaCO_2$, we tested change over time and the

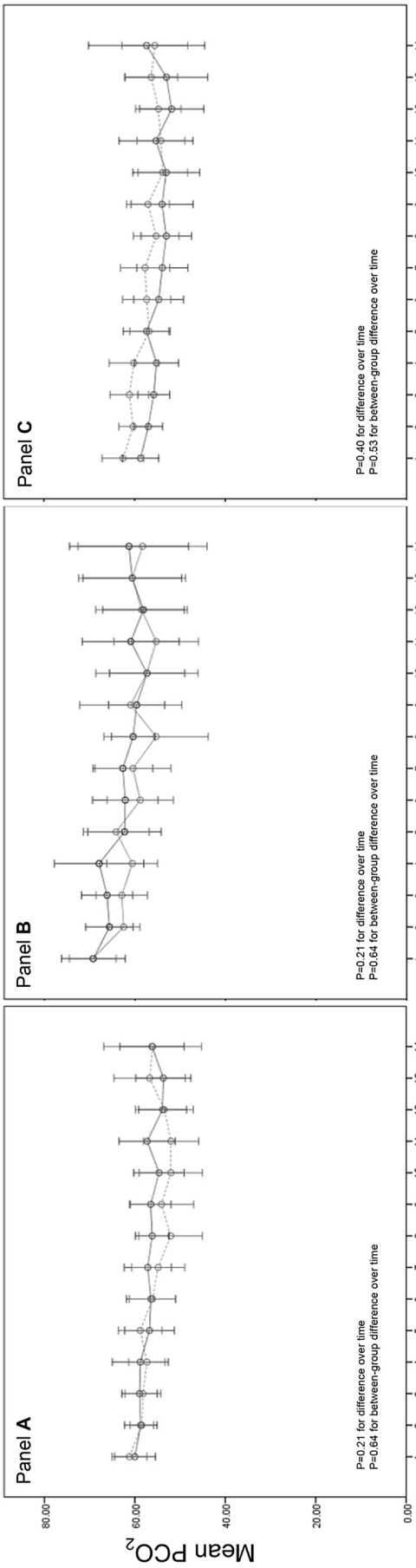

Fig. 1. Daily arterial partial pressure of carbon dioxide ($PaCO_2$)* of the permissive underfeeding and standard feeding groups in all hypercapnic patients (Panel A) and in patients with baseline $PCO_2 > 60$ mm Hg (Panel B) and of the groups with fat-to-carbohydrate ratio < 0.73 and ≥ 0.73** (Panel C). The error bars represent the 95% confidence interval of the mean. The difference between the groups at each time point was not significant by the t-test ($p > 0.05$). The change over time and the difference between the two groups over time was tested using repeated measures ANOVA. *For more than one value on the same day, the highest value was recorded. **0.73 was the median value of the fat-to-carbohydrate ratio. In Panel A and B, the broken and solid lines represent the permissive underfeeding and standard feeding groups, respectively. In Panel C, the broken and solid lines represent the group with fat-to-carbohydrate ratio ≥ 0.73 and < 0.73, respectively.

difference between the two groups over time using repeated measures ANOVA.

The primary outcomes were further compared by the study interventions in the following subgroups: age < the median age (58 years) and ≥ 58 years, body mass index < 30 and ≥ 30 Kg/m^2, APACHE II < the median value (18) and ≥18, presence of chronic respiratory disease and no respiratory disease, $PaCO_2$ < 55 and ≥ 55 mm Hg, received respiratory-specialized formula versus another formula and the fat-to-carbohydrate ratio < 0.73 (the median value) and ≥ 0.73 and. We also assessed outcomes in patients with high versus low cumulative calorie (< 6000 kcal versus ≥ 6000 kcal) and protein deficits (< 300 g versus ≥ 300 g) as per literature [14]. Cumulative calorie deficit was calculated by subtracting total caloric intake from calculated caloric requirement for up to14 days (5938.04 ± 4923.0 kcal). Cumulative protein deficit was calculated by subtracting total protein intake from calculated protein requirement for up to14 days (200.0 ± 168.57 g). Tests of interaction were also performed.

Multivariable analyses, mainly logistic and linear regression, were also done to determine the predictors of 90-day mortality and ventilator-free days, respectively, in hypercapnic patients. Clinically significant variables were entered in the model which were age, body mass index, APACHE II score, chronic illnesses (diabetes, chronic cardiac, respiratory, renal and hepatic disorders, PaO_2:FiO_2 ratio, fat-to-carbohydrate ratio, fluid intake and randomization. The results were presented as OR (90-day mortality) or parameter estimate (ventilator-free days) with 95% CI. All tests were two-sided and at the 5% significance level. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Characteristics of patients

Of the 894 patients enrolled in the PermiT trial, 120 (13.4%) had invasive mechanical ventilation and hypercapnia on the first two study days. The characteristics of these patients are shown in Table 1. The most common reasons for ICU admission were ARF from COPD (n = 18, 15.0%), respiratory tract infection (n = 18, 15.0%) and asthma (n = 7, 5.8%) and sepsis (n = 14, 11.7%). On the enrollment day, their $PaCO_2$ was 60.6 ± 16.3 mm Hg. $PaCO_2$ was 45–55 mm Hg in 44.2% of patients, 55–65 mm Hg in 38.3% and > 65 mm Hg in 27.5%. The PaO_2:FiO_2 ratio was > 300 mm Hg in 22 patients (18.3%), 200–300 mm Hg in 52 (43.3%) and < 100 mm Hg in 45 (37.5%). Among the 120 patients, 59 received permissive underfeeding and 61 standard feeding. The characteristics of patients in both groups were similar (Table 1). None of the patients received extracorporeal CO_2 removal therapy.

The details of feeding interventions are described in Table 2. The daily total, carbohydrate and fat calories were different between the permissive feeding and standard feeding groups. The fractions of carbohydrate and fat calories from total calories and protein intake were similar in both groups. The mean fat-to-carbohydrate calorie ratio was 0.98 (standard deviation = 0.73; median = 0.73; 25th percentile = 0.46, 75th percentile = 1.44) with no significant difference between permissive and standard feeding groups. The disease non-specific feeding formulae were used in 56 patients. Only 18 (15.0%; 8 in permissive underfeeding group and 10 in the standard group) patients received respiratory-specialized formula (Pulmocare).

Outcomes of hypercapnic patients

There was no significant difference in $PaCO_2$ during the 14-day study period between all hypercapnic patients in the permissive

Table 3
Outcome of hypercapnic patients randomized to permissive underfeeding versus standard feeding.

Outcomes	All hypercapnic patients	Permissive underfeeding	Target feeding	P-value	Odds ratio (95% confidence interval)
	N = 120	N = 59	N = 61		
28-day mortality – no. (%)	37 (30.8)	17 (28.8)	20 (32.8)	0.64	0.88 (0.51, 1.51)
90-day mortality – no. (%)	41 (34.2)	20 (33.9)	21 (35.6)	0.85	0.95 (0.58, 1.56)
180-day mortality – no. (%)	46 (38.3)	23 (39.7)	23 (39.0)	0.94	1.0 (0.65, 1.60)
ICU mortality – no. (%)	32 (26.7)	13 (22.0)	19 (31.2)	0.26	0.71 (0.39, 1.30)
Hospital mortality – no. (%)	39 (32.5)	18 (30.5)	21 (34.4)	0.65	0.89 (0.53, 1.49)
ICU LOS – (days) mean ± SD	17.8 ± 13.0	17 ± 12.8	18.6 ± 13.3	0.75	
ICU-free days– mean ± SD	48.3 ± 35.9	49.2 ± 36.4	47.4 ± 35.7	0.79	
Hospital LOS – (days), mean ± SD	39.4 ± 49.9	36.6 ± 36.4	42.1 ± 36.4	0.54	
Mechanical ventilation duration – (days), mean ± SD	12.8 ± 13.0	10.5 ± 7.1	15.0 ± 16.7	0.06	
Mechanical ventilation-free days– mean ± SD	52.1 ± 38.1	52.9 ± 38.6	51.2 ± 38.0	0.80	
New RRT – no. (%)	11 (9.2)	4 (7.6)	7 (12.7)	0.37	0.59 (0.18, 1.91)
RRT-free day– mean ± SD	9.6 ± 6.3	9.8 ± 6.3	9.4 ± 6.4	0.76	
Healthcare-associated infections – no. (%)	39 (32.5)	18 (30.5)	21 (34.4)	0.65	0.89 (0.53, 1.49)
Ventilator-associated pneumonia – no. (%)	18 (15.0)	5 (8.5)	13 (21.3)	0.49	0.40 (0.15, 1.04)
Hypophosphatemia – no. (%)	61 (50.8)	33 (55.9)	28 (45.9)	0.27	1.22 (0.86, 1.74)

ICU: intensive care unit; LOS: length of stay; RRT: renal replacement therapy.

underfeeding and standard feeding groups (Fig. 1, Panel A); nor in patients with higher baseline $PaCO_2$ (≥60 mm Hg) (Fig. 1, Panel B). $PaCO_2$ was similar in the patients who received lower versus higher fat-to-carbohydrate ratio (Fig. 1, Panel C).

Table 3 describes the outcomes of hypercapnic patients according to the feeding intervention. Mortality (28-day, 90-day, 180-day, ICU and hospital) rates were similar in permissive underfeeding and standard groups. Additionally, there were no difference in MV duration and ventilator-free days. In survivors, MV duration was also similar in the permissive underfeeding and standard group (10.7 ± 6.8 and 11.1 ± 8.1 days, respectively; p = 0.56).

The 90-day mortality was similar in the different studied subgroups as shown in Table 4. Notably, higher versus lower fat-to-carbohydrate ratio and the fraction of carbohydrate calories from total caloric intake were not associated with 90-day mortality. Also low versus high cumulative caloric and protein deficits were not associated with 90-day mortality and ventilation-free days.

On multivariable analysis, independent predictors of 90-day mortality were age (OR, 1.044 per year increment; 95% CI, 1.013–1.075), APACHE II score (OR, 1.070 per unit increment; 95% CI, 1.003 to 1.141) and chronic liver disease (OR, 8.715; 95% CI, 1.367 to 55.579). The fat-to-carbohydrate ratio was not associated with 90-day mortality (OR, 0.978 per 0.1 increment; 95% CI, 0.916 to 1.046). Independent predictors of ventilator free days were age (parameter estimate, −0.46 days; 95% CI, −0.85 to −0.07) and APACHE II score (parameter estimate, −1.02; 95% CI, −2.01 to −0.04). The fat-to-carbohydrate ratio was not associated with ventilator-free days (parameter estimate, 0.17 days; 95% CI, −0.76 to 1.10).

Discussion

This study evaluated the impact of permissive underfeeding versus standard feeding on the outcomes of patients with ARF and $PaCO_2$ > 45 mm Hg. We found no differences in $PaCO_2$ during the study period, MV duration, ventilator-free days or mortality in the two feeding groups. Additionally, higher versus lower fat-to-carbohydrate ratio did not affect $PaCO_2$ levels during the study period and had similar outcomes.

$PaCO_2$ is determined by alveolar ventilation and VCO_2 [26,27]. VCO_2 is influenced by the amount of caloric intake, type of foods (carbohydrates lead to higher VCO_2 compared with lipids) [16,28] and metabolic rate. Increases in VCO_2 may increase $PaCO_2$ only if the rise of VCO_2 is proportionately more than alveolar ventilation. Whether this is translated into worse MV outcomes is less clear. Several small studies evaluated the impact of high caloric intake and fat-to-carbohydrate composition on $PaCO_2$ in critically ill patients. In a small study, six mechanically ventilated patients with chronic respiratory failure were randomized to three nutritional regimens: control (255 kcal/day), glucose total parenteral nutrition (TPN) (2550 kcal/day), and lipid TPN (3000 kcal/day) [2]. TPN compared with control significantly increased VCO_2 and $PaCO_2$ and decreased pH [2]. The increase in VCO_2 and the hypercapnic acidosis were less with lipid than with glucose TPN [2]. In a report of two cases, two young patients recovering from adult respiratory distress syndrome experienced hypercapnia during weaning as a result of nutrition-related increased VCO_2 [3]. One was receiving 5400 kcal/day TPN (4284 carbohydrate kcal) to correct a severely depleted nutritional state and the other was receiving 3200 kcal/day TPN (2550 carbohydrate calories) [3]. As carbohydrate calories were decreased, VCO_2 diminished and hypercapnia resolved [3]. In a case report, excessive rates of carbohydrate infusion during TPN caused hypercapnia leading to inability to wean from a ventilator [29]. When the carbohydrate load was given over longer period, the patient tolerated unassisted ventilation [29].

But what about more “moderate” amounts of enteral calories? In a randomized controlled trial, 32 ventilator-dependent patients, who were candidates for weaning from MV, were randomized to high fat-to-carbohydrate enteral feeding and standard isocaloric enteral feeding, both in a dosage of 1.5 times basal metabolic rate [30]. High fat-to-carbohydrate feeding was associated with significantly lower respiratory quotient and reduced VCO_2 compared with standard feeding [30]. However, there were no significant differences in the $PaCO_2$ during weaning between the two feeding groups [30]. Lo et al. randomized 28 clinically stable patients on long-term MV and enteral feeding into hypercaloric (1.8-fold of resting energy expenditure) and control groups (1.2-fold of resting energy expenditure) for 4 weeks and found no significant changes in $PaCO_2$ between the two groups [31]. Barale et al. randomized patients with chronic pulmonary disease on MV to either enteral diet comprised of 55% of fats or control and showed a rapid decrease in VCO_2 from 243 to 215 ml/min in the high fat-to-carbohydrate diet compared with increase in VCO_2 in the control diet [32]. Nevertheless, there was no associated difference in $PaCO_2$ [32]. In a randomized crossover study of noncritically ill stable severe COPD patients, lower fat-to-carbohydrate diet was associated with higher VCO_2 and $PaCO_2$ and a greater fall in the six-minute walk distance compared with higher fat-to-carbohydrate diet [33].

Based on the above data, the effect of caloric dose and carbohydrate intake in ICU patients may be relevant only in patients who already have hypercapnia and chronic lung disease and in overfed

Table 4
Outcomes (90-day mortality and ventilator-free days) in subgroups of hypercapnic patients. Fifty-nine patients received permissive underfeeding and 62 received standard feeding.

Subgroups, N (%)	Permissive underfeeding	Standard feeding	P-value	Odds ratio (95% confidence interval)	Interaction p-value
	n/N (%)	n/N (%)			
90-day mortality					
Age < 58 years	8/30 (26.7)	5/29 (17.2)	0.38	1.74 (0.50, 6.14)	0.40
Age ≥ 58 years	12/29 (41.4)	16/30 (53.3)	0.36	0.62 (0.22, 1.73)	
Body mass index < 30 Kg/m^2	12/34 (35.3)	14/33 (42.4)	0.55	0.74 (0.28, 1.98)	0.23
Body mass index ≥ 30 Kg/m^2	8/25 (32.0)	7/26 (26.9)	0.69	1.28 (0.38, 4.27)	
APACHE II score < 18	3/19 (15.8)	6/23 (26.1)	0.42	0.53 (0.11, 2.5)	0.46
APACHE II score ≥ 18	16/39 (41.0)	14/35 (40.0)	0.93	1.01 (0.41, 2.60)	
Chronic respiratory disease	4/16 (25.0)	6/21 (28.6)	0.81	0.83 (0.19, 3.6)	0.92
No chronic respiratory disease	16/43 (37.2)	15/38 (39.5)	0.83	0.91 (0.37, 2.2)	
Baseline $PaCO_2$ < 55 mm Hg	7/18 (38.9)	11/26 (42.3)	0.82	0.87 (0.25, 2.96)	0.84
Baseline $PaCO_2$ ≥ 55 mm Hg	10/28 (35.7)	8/24 (33.3)	0.86	1.11 (0.35, 3.50)	
Received respiratory-specialized formula[a]	4/8 (50)	3/10 (30)	0.39	2.33 (0.34, 16.2)	0.33
Received another feeding formula	16/50 (32.0)	18/49 (36.7)	0.62	0.81 (0.35, 1.86)	
Total fat-to-carbohydrate ratio[b] < 0.73	9/29 (31.0)	10/29 (34.5)	0.78	0.86 (0.29, 2.56)	0.84
Total fat-to-carbohydrate ratio[b] ≥ 0.73	11/30 (36.7)	11/30 (36.7)	1.00	1.00 (0.35.2.86)	
Cumulative caloric deficit < 6000 kcal	7/25 (28.0)	16/49	0.68	0.80 (0.28, 2.30)	0.86
Cumulative caloric deficit ≥ 6000 kcal	13/32 (40.6)	5/10 (50.0)	0.60	0.68 (0.16, 2.85)	
Cumulative protein deficit < 300 g	15/45 (33.3)	14/45 (31.1)	0.82	1.11 (0.46, 2.68)	0.63
Cumulative protein deficit ≥ 300 g	5/12 (41.7)	7/14 (50.0)	0.67	0.71 (0.15, 3.38)	
Ventilator-free days					
Age < 58 years	58.0 ± 36.1	65.4 ± 30.6	0.40		0.20
Age ≥ 58 years	47.6 ± 41.0	37.5 ± 39.9	0.34		
Body mass index < 30 Kg/m^2	52.9 ± 39.9	47.8 ± 40.8	0.60		0.59
Body mass index ≥ 30 Kg/m^2	53.0 ± 37.6	55.6 ± 34.4	0.80		
APACHE II score < 18	67.6 ± 30.7	57.9 ± 35.9	0.36		0.45
APACHE II score ≥ 18	47.1 ± 40.1	48.4 ± 38.9	0.88		
Chronic respiratory disease	61.1 ± 36.8	26.0 ± 36.1	0.67		0.81
No chronic respiratory disease	49.9 ± 39.2	48.5 ± 39.2	0.87		
Baseline $PaCO_2$ < 55 mm Hg	51.5 ± 39.6	50.8 ± 39.1	0.95		0.91
Baseline $PaCO_2$ ≥ 55 mm Hg	53.9 ± 38.4	51.5 ± 37.6	0.80		
Received respiratory-specialized formula[a]	54.3 ± 38.1	50.6 ± 38.3	0.63		0.37
Received another feeding formula	40.0 ± 42.9	54.1 ± 38.0	0.47		
Total fat-to-carbohydrate ratio[b] < 0.73	55.7 ± 38.5	54.6 ± 38.7	0.92		0.91
Total fat-to-carbohydrate ratio[b] ≥ 0.73	50.3 ± 39.2	47.7 ± 37.6	0.79		
Cumulative caloric deficit < 6000 kcal	59.8 ± 38.3	53.8 ± 37.4	0.52		0.92
Cumulative caloric deficit ≥ 6000 kcal	45.4 ± 38.4	37.9 ± 40.4	0.60		
Cumulative protein deficit < 300 g	54.0 ± 39.0	54.7 ± 36.7	0.93		0.81
Cumulative protein deficit ≥ 300 g	43.2 ± 38.1	39.6 ± 41.5	0.82		

N: the number of patients in the subgroup; n: the number of patients who were dead at 90 days in the subgroup; %: the percentage of patients who died at 90 days.
APACHE: Acute Physiology and Chronic Health Evaluation, $PaCO_2$: arterial partial pressure of carbon dioxide.
[a] Pulmocare used on > 50% of the intervention days.
[b] Ratio of total fat calories over total carbohydrate calories macronutrients (enteral and nonenteral).

patients, especially with parenteral feeding. In the current substudy of the PermiT trial, the caloric difference between the permissive underfeeding and standard feeding groups was considerable (approximately 480 kcal, 30% of caloric requirement). With this difference in caloric intake, we observed no difference in $PaCO_2$ among hypercapnic intubated patients during the intervention period. Higher fat-to-carbohydrate ratio did not affect $PaCO_2$ either. In the early phase of critical illness, carbohydrate oxidation is increased more than that of fat [34]. Hence, providing high fat diet may lead to metabolic inefficiency. It is important to note that patients in this study were not overfed (mean daily caloric intake was 45 ± 11% of caloric requirement in the permissive underfeeding group and 75 ± 18% in the standard group. This supports the notion that macronutrient composition is unlikely to affect $PaCO_2$ when the provided calories do not exceed energy requirements [35].

The effect of caloric dose on MV duration in general is debatable, and when observed it is unclear if it was related to increased $PaCO_2$. Both the EPaNIC and PEPaNIC trials which randomized unselected adult and pediatric ICU patients to early versus late PN achieved significant differences in calories in the first week, and found lower MV duration with late PN, but it unclear if this was related to differences in $PaCO_2$ [36,37]. A recent meta-analysis of 8 randomized controlled trials of enteral feeding found no difference in MV duration between lower versus higher caloric intake (weighted mean difference, −1.12 days; 95% CI, −2.67 to 0.44 days) [15]. On the other hand, Al-Saady et al. found that higher fat-to-carbohydrate feeding was associated with lower $PaCO_2$ and less MV duration by a mean of 62 h [17]. In the current study, we found that permissive underfeeding versus standard feeding was associated with similar MV duration and ventilator-free days in patients with hypercapnia. We also found no impact on their mortality. The 2016 Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition guidelines did not directly address feeding in HCARF. The guidelines recommended, based on high-quality evidence, either full or trophic feeding to patients with ARF expected to require MV for $\geq$ 3 days and suggested, based on very low-quality evidence, against the use of high-fat/low-carbohydrate feeding formulae in ARF patients [20]. In the current study, only 15.0% of patients received respiratory-specialized formula. Our findings of no difference in $PaCO_2$ and MV outcomes are in line with these guidelines.

The study strengths include that data came from a multicenter randomized controlled trial; the sample size was relatively large compared with other studies; and the protein intake and fluid balance were similar and the was similar in both groups. The study limitations include the post-hoc analysis, the lack of indirect calorimetry, VCO_2 and dead space measurement data, and the inability to determine a priori the cause of hypercapnia. While there was a significant difference in caloric intake (~480 kcal) between the two groups, the higher (standard) feeding group received only ~ 75% of calculated caloric requirement. This may explain why the feeding composition was not associated with outcomes.

Conclusion

In conclusion, compared with standard feeding, permissive underfeeding was associated with similar mortality, MV duration and ventilator-free days in patients with HCARF. Higher fat-to-carbohydrate ratio was not associated with less MV duration and more ventilator-free days. Additional studies are needed to clarify the clinical significance of different levels of caloric intake on the outcomes of ICU patients with HCARF.

Declarations

Ethics approval and consent to participate

The Institutional Review Boards of the participating centers approved the original study, and informed consent was obtained from surrogate decision makers prior to enrollment.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Competing interest

The authors declare that they have no competing interests.

CRediT authorship contribution statement

Hasan M. Al-Dorzi: Data curation, Writing - original draft. **Abdulaziz S. Aldawood:** Data curation, Writing - review & editing. **Hani Tamim:** Data curation, Writing - review & editing. **Samir H. Haddad:** Data curation, Writing - review & editing. **Gwynne Jones:** Data curation, Writing - review & editing. **Lauralyn McIntyre:** Data curation, Writing - review & editing. **Othman Solaiman:** Data curation, Writing - review & editing. **Maram Sakhija:** Data curation, Writing - review & editing. **Musharaf Sadat:** Funding acquisition, Data curation. **Lara Afesh:** Funding acquisition, Data curation, Writing - review & editing. **Anand Kumar:** Data curation, Writing - review & editing. **Sean M. Bagshaw:** Data curation, Writing - review & editing. **Sangeeta Mehta:** Data curation, Writing - review & editing. **Yaseen M. Arabi:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing.

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Saudi Arabia:

King Saud bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center, Riyadh: Yaseen M Arabi, MD, Abdulaziz S Aldawood, MD, Samir H Haddad, MD, Hasan M Al-Dorzi, MD, Hani M Tamim, MPH, PhD, Maram H Sakkijha, RD, Musharaf Sadat, MBBS, Lara Afesh, MSN, Amorshiella Camba, Clinical Dietician, Eleonor Guevarra, Clinical Dietician, Joan Olivier, RN, Ahmed Deeb, RN, Shihab Mundekkadan, RN, Muhammad Rafique Sohail.

King Faisal Specialist Hospital and Research Centre, Riyadh: Othman Solaiman, MD, Reem Hawari, LD, Sawsan Albalawi, LD, Mini Joseph, RN, BSN.

Canada:

Ottawa General Hospital, Ottawa: Gwynne Jones, MD, Lauralyn McIntyre, MD, MSc, Shelley Acres, Allison Simpson Rebecca Porteous, Irene Watpool

Ottawa Civic Hospital, Ottawa: Gwynne Jones, MD, Lauralyn McIntyre, MD, MSc, Shawna Reddie, Tracy McArdle, Colleen Golka

Mount Sinai Hospital, Toronto: Sangeeta Mehta MD, Kristen MacEachern, Marnie Jakab, Sumesh Shah, Brittany Giacomino, Alan Kraguljac**.**

Health Sciences Centre, Manitoba: Anand Kumar, MD, Sevita Bector, Clinical Dietician, Wendy Janz, RN.

University of Alberta Hospital, Edmonton: Sean M. Bagshaw, MD, Sonya Hoag; Nadia Baig, Miranda Wong; Adele Delgado; Leanne Melusa

Appendix A. Supplementary data

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