Nutrition in the intensive care unit — you must breathe what you eat

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Nutrition is required not only for the survival but also the wellbeing of all living organisms. For patients in the intensive care unit, the concept of optimal nutrition has become incorporated into guidelines, standards, performance indicators and educational programs. However, what defines optimal nutrition in the seriously ill remains controversial and difficult to define, because such patients have lost their normal self-regulatory signals of appetite, satiety and motivation.

In the absence of the normal signals which regulate intake, it is assumed that energy intake should match expenditure. The formal measurement of energy expenditure is technically complex and not widely available, so energy delivery is based on predictive equations, which have been repeatedly shown to be inaccurate.[1] Such imprecise targeting is unique in critical care, a specialty in which physiological measurements guide most treatment modalities. It is therefore perhaps not surprising that authors of clinical trials of nutrition in the seriously ill have had difficulty showing unequivocal outcome benefits.[2] On the other hand, it is surprising that some additional aspects of nutrition and its consequences are not more widely considered, such as those related to overfeeding.

There is a paucity of literature reporting the incidence, features and consequences of overfeeding. It is therefore possible that the risks of overfeeding seriously ill patients are widespread and not well appreciated. More may not be better with nutrition, nor with fluids, oxygen, ventilatory support and many other therapies used in the ICU. Problems of hyperglycaemia and liver dysfunction generally come first to mind with overfeeding (especially parenteral overfeeding), and it is also possible that increased CO_2 generation might result in increased work of breathing and more prolonged ventilator dependence.

The purpose of our article is an armchair evaluation of this possibility, initially referring to the available literature and then by mathematical analysis of the data in The Augmented versus Routine Approach to Giving Energy Trial (TARGET) feasibility study and the information in the protocol of the main TARGET study.

ABSTRACT

- The imprecision in prescribing of enteral nutrition in critically ill patients must result in occasions of overfeeding as well as underfeeding.
- Overfeeding could cause increased CO_2 production and thus increased work of breathing and prolonged ventilator dependence. This possibility is supported by the limited relevant literature.
- We examined this possibility mathematically using the data in The Augmented versus Routine Approach to Giving Energy Trial (TARGET) feasibility study and in its main study protocol.
- Patients in the energy-dense feeding arm will receive 50% more calories and produce 52% more CO_2 than patients in the standard feeding arm.
- The full TARGET study is ideally positioned to answer the practical clinical question of whether increased feeding in critically ill patients can be delivered without prolonging ventilator dependence.

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Association between calorie input and work of breathing

Although recent literature on feeding ventilated patients is largely silent on the issue of CO_2 production, low-level evidence of an association between increased calorie input and ventilator dependence can be found in a few case studies. Covelli and colleagues described three patients in whom respiratory failure was precipitated by high carbohydrate loads with a combination of enteral nutrition (EN) and parenteral nutrition (PN).[3] Sullivan and colleagues reported a patient with acute respiratory distress syndrome (ARDS) who was fed predominantly by PN.[4] All four patients showed evidence of an elevated Pa_{CO_2} level and/or minute ventilation, which decreased on reduction of the calorific intake.

Higher-level, but indirect, evidence of a relationship between feeding and ventilation in critically ill adults comes from randomised controlled trials (RCTs). In the Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) trial, Vanderheyden and colleagues randomised 2312 patients to receive PN within 48 hours of ICU admission and compared their outcomes with 2328 patients for whom PN was not initiated for 8 days.[5] The authors reported that patients commenced on early PN were more likely to be ventilated for an extra 2 days (40.2% v 36.3%; $P = 0.006$). Singer and colleagues conducted an RCT in 130 mechanically ventilated patients receiving EN with or without PN, in which patients received 25 kcal/kg/day or a calorie input guided by repeat indirect calorimetry.[6] Patients in the study group had a higher mean energy intake (2086 kcal/day [SD, 460 kcal/day] v 1480 kcal/day [SD, 356 kcal/day]) and this was associated with a longer length of mechanical ventilation in the study group (16.1 days [SD, 14.7 days] v 10.5 days [SD, 8.3 days]; $P = 0.03$). Arabi and colleagues showed that increasing calorie intake towards target in critically ill patients was associated with several adverse outcomes, including an increased duration of mechanical ventilation.[7]

On the other hand, the benchmark Early Versus Delayed Enteral Feeding (EDEN) study of trophic feeding versus full enteral feeding in 1000 patients with ARDS, by the ARDS Clinical Trials Network, showed no difference in ventilator-free days between the two groups.[8] However, Doig and colleagues found, in 1372 patients unable to receive early EN who were randomised to early PN or standard care, that patients who received early PN and thus more calories required fewer ventilator days.[9] Subsequently, Elke and colleagues, in a secondary analysis of a large nutrition database, also reported that critically ill patients with sepsis receiving the closest-to-recommended calorie and protein intake had more favourable outcomes, including more ventilator-free days.[10]

The available literature thus provides limited and conflicting evidence on the relationship, if any, between calorie intake and ventilator dependence in critically ill patients. On balance, an adverse effect of increasing calorie intake appears more likely. This dilemma is perhaps not surprising, given the difficulty (despite many articles on the topic) in showing a consistent relationship between nutritional intake and any major outcome measure in the critically ill. Thus, a mathematical dissection of this issue could provide some insight and could stimulate specific analysis in future clinical trials.

Examination of real-life data

To examine this question, we have analysed the information presented in the protocol for the large forthcoming Australasian TARGET study. This randomised, double-blind, controlled, multicentre study is designed to recruit 4000 mechanically ventilated patients, who will receive either standard enteral feeding (1 kcal/mL) or energy-dense enteral feeding (1.5 kcal/mL) at the rate of 1 mL/kg ideal bodyweight (IBW)/hour. This study has been preceded by a feasibility study of 112 patients in whom the protocol was tested satisfactorily.[11] We have used the data from the feasibility study and the information from the proposed main study to illustrate the concepts related to nutrition-driven CO_2 production.

If we assume that an average IBW, or perhaps preferably an adjusted IBW, is 70 kg, the target nutritional intake would be 1680 mL/day of a 1 kcal/mL solution. This would deliver 1680 kcal/day in the standard feeding group and 2420 kcal/day in the energy-dense feeding group in the TARGET trial.

However, in the feasibility study, the actual amounts received per day were 19 kcal/kg/day of standard feed and 27 kcal/kg/day of energy-dense feed (75%–80% of target amounts). This actual delivery is consistent with achievable targets reported in the literature. Thus, the two groups may be expected to actually receive 1330 kcal/day and 1890 kcal/day, respectively. These data allow calculations and estimations of CO_2 generation.

Metabolic calculations

First, the specific compositions of the two nutritional preparations (feeds) need to be identified (Table 1). Second, the CO_2 production and O_2 consumption associated with the relevant substrates need to be known (Table 2). Third, given the known composition of the two feeds and the known metabolism of their individual substrates, it is possible to calculate the CO_2 production and O_2 consumption when 1 L of either feed is metabolised (Table 3).

Finally, the estimated volumes of feeds to be received daily (1.33 L of standard feed or 1.26 L of energy-dense feed) are based on the amounts actually received in the TARGET feasibility study (19 kcal/kg/day of standard feed or 27 kcal/kg/day of energy-dense feed). Thus, the CO_2 production ($\dot{V}CO_2$) in the two groups may be calculated as 172 mL/min and 248 mL/min, respectively.

Table 1. Composition of feeds used in TARGET

Content	Standard feed	Energy-dense feed
Carbohydrate	125 g/L	188 g/L
Fat	27 g/L	58 g/L
Protein	55 g/L	56 g/L
Estimated volume per day	1330 mL	1260 mL

TARGET = The Augmented versus Routine Approach to Giving Energy Trial.

Table 2. Substrate metabolism

Substrate	CO_2 production (L/g)	O_2 consumption (L/g)
Carbohydrate	0.829	0.829
Fat	1.427	2.019
Protein	0.782	0.966

Table 3. Metabolism of feeds

Metabolism	Standard feed	Energy-dense feed
CO_2 production (L/L feed)	186	283
O_2 consumption (L/L feed)	212	327
Respiratory quotient	0.88	0.87

Respiratory calculations

The alveolar ventilation equation relates CO_2 production to alveolar ventilation (VA) and arterial Pco_2:

$$V_A = V_{CO_2} \times 0.863 \div Pa_{CO_2}$$

where VA is in L/min, Vco_2 is in mL/min and $Paco_2$ is in mmHg. If $Paco_2$ = 40 mmHg, VA for the two feeding groups should therefore be 3.71 L/min and 5.35 L/min, respectively.

Next, alveolar ventilation equals tidal volume (VT) minus physiological dead-space volume (VD) multiplied by respiratory rate (f):

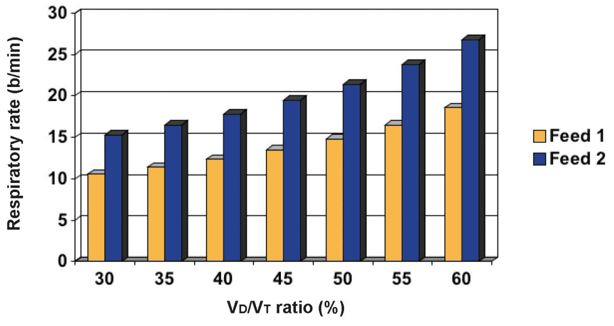
$$V_A = (V_T - V_D) \times f$$

If VT is 500 mL and VD/VT = 50% (ie, average figures), then the required respiratory rate in the two feeding groups will be 15 breaths/min and 21 breaths/min, respectively. Alternatively, if the respiratory rate in the energy-dense feed group is also set with the ventilator at 15 breaths/min, the $Paco_2$ would be 58 mmHg.

As the patient's lung function improves before weaning from mechanical ventilation, the VD/VT ratio will be expected to become more normal; say, 30%. At this time, the required respiratory rate in the two feeding groups will be 11 breaths/min and 15 breaths/min, respectively. However, if the respiratory rate in the energy-dense feed group is also set at 11 breaths/min, the $Paco_2$ would still be 58 mmHg.

The range of respiratory rates for different VD/VT ratios, ranging from normal (30%) to grossly abnormal (60%), while maintaining a $Paco_2$ of 40 mmHg, is shown in Figure 1 for each feeding group. In the first group, the required respiratory rate is 11–18 breaths/min, but in the second group it needs to be 15–27 breaths/min.

Figure 1. Respiratory rates, by VD/VT ratio*



VD = physiological dead-space volume. VT = tidal volume.
* $Paco_2$ = 40 mmHg.

Examined another way, the range of respiratory rates for $Paco_2$ levels ranging from 40 mmHg to 50 mmHg, at different VD/VT ratios, is shown for each feed in Table 4. The elevated $Paco_2$ levels are included to accommodate the practice of permissive hypercapnia, if required. This table shows the dependence of the required respiratory rate on the desired $Paco_2$ level and on the degree of respiratory dysfunction.

Given the current practice of setting a tidal volume based on IBW, it follows that ventilator dependence is then best reflected in the respiratory rate required to achieve an acceptable $Paco_2$. The range of the required respiratory rate, and thus indirectly the degree of ventilator dependence, has been shown above for different feeding regimens, different levels of lung dysfunction and different ventilatory goals.

Respiratory changes

The Vco_2 changes primarily affect ventilation requirements (mechanics). The effect on oxygenation (gas exchange) is seen only if there is permissive hypercapnia and, even then, it is a minor effect. In the present example, if the $Paco_2$ level is allowed to be 58 mmHg, the Pao_2/Fio_2 ratio will decrease by only about 30.

Respiratory implications

In accord with the aim of the TARGET study, patients receiving the energy-dense feed will, necessarily, receive 50% more calories. As a consequence, they will have a 52% greater CO_2 production, as calculated above. The much greater CO_2 production in these patients may have

Table 4. Respiratory rates, by $Paco_2$ level and VD/VT ratio

		Respiratory rate (breaths/min)	
VD/VT ratio (%)	$Paco_2$ (mmHg)	Feed 1	Feed 2
30	40	10.6	15.3
	45	9.4	13.6
	50	8.5	12.2
40	40	12.4	17.8
	45	11.0	15.9
	50	9.9	14.3
50	40	14.8	21.4
	45	13.2	19.2
	50	11.9	17.1

VD = physiological dead-space volume. VT = tidal volume.

an adverse effect on their respiratory course, given that all patients will be mechanically ventilated, so any general benefit of greater feeding could be potentially offset by a respiratory detriment.

Conclusions

Nutrition trials in sick ICU patients may have failed to show an overall benefit because of competing beneficial and adverse effects in patient subgroups. Perhaps sick ICU patients should not be forced to be normal with feeding, any more than they are with other therapeutic interventions. Thus, the current ICU mantra that less may be more could also apply to feeding.[12]

The concept that an increased CO_2 level could be bad for patients with damaged lungs has not received attention in the recent large volume of literature on nutrition in the critically ill. Specifically, it is possible that a high calorie intake may increase the work of breathing, minute ventilation and duration of mechanical ventilation by increasing CO_2 production. To discover whether the implications of our mathematical exercise can be seen in practice will require specific examination in an appropriate clinical trial. Although there was no signal reporting ventilator-related problems in the TARGET pilot study,[11] the full TARGET study is ideally positioned to examine this question.

Competing interests

None declared.

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