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## Point-counterpoint: Indirect calorimetry Is essential for optimal nutrition therapy in the intensive care unit

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### Abstract

Iatrogenic malnutrition and underfeeding are ubiquitous in intensive care units (ICUs) worldwide for prolonged periods after ICU admission. A major driver leading to the lack of emphasis on timely ICU nutrition delivery is lack of objective data to guide nutrition care. If we are to ultimately overcome current fundamental challenges to effective ICU nutrition delivery, we must all adopt routine objective, longitudinal measurement of energy targets via indirect calorimetry (IC). Key evidence supporting the routine use of IC in the ICU includes (1) universal societal ICU nutrition guidelines recommending IC to determine energy requirements; (2) data showing predictive equations or body weight calculations that are consistently inaccurate and correlate poorly with measured energy expenditure, ultimately leading to routine overfeeding and underfeeding, which are both associated with poor ICU outcomes; (3) recent development and worldwide availability of a new validated, accurate, easy-to-use IC device; and (4) recent data in ICU patients with coronavirus disease 2019 (COVID-19) showing progressive hypermetabolism throughout ICU stay, emphasizing the inaccuracy of predictive equations and marked day-to-day variability in nutrition needs. Thus, given the availability of a new validated IC device, these findings emphasize that routine longitudinal IC measures should be considered the new standard of care for ICU and post-ICU nutrition delivery. As we would not deliver vasopressors without accurate blood pressure measurements, the ICU community is only likely to embrace an increased focus on the importance of early nutrition delivery when we can consistently provide objective IC measures to ensure personalized nutrition care delivers the right nutrition dose, in the right patient, at the right time to optimize clinical outcomes.

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#### AUTHOR CONTRIBUTION

P. E. Wischmeyer, J. Molinger, and K. Haines contributed to the conception and design of the research; P. E. Wischmeyer, J. Molinger, and K. Haines contributed to the acquisition and analysis of the data; P. E. Wischmeyer, J. Molinger, and K. Haines contributed to the interpretation of the data; and P. E. Wischmeyer drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

#### FINANCIAL DISCLOSURE

None.

## Keywords

critical illness; energy expenditure; indirect calorimetry; intensive care unit; malnutrition; nutrition support

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## INTRODUCTION

All existing intensive care unit (ICU) nutrition guidelines<sup>1,2</sup> emphasize early nutrition delivery via enteral nutrition (EN) and/or parenteral nutrition (PN) as a key primary therapy leading to both nutrition and nonnutrition clinical outcome benefits. Unfortunately, iatrogenic malnutrition and underfeeding are virtually ubiquitous in ICUs worldwide for prolonged periods after ICU admission.<sup>3–5</sup> A major driver leading to the lack of emphasis on nutrition therapy in the ICU is lack of objective data to guide nutrition care. As energy requirements are known to change throughout the course of critical illness, and given the recent availability of a new generation of indirect calorimeters,<sup>6</sup> it is essential that we move to a culture of personalized, targeted nutrition delivery. ICU physicians would not deliver vasopressors without accurate blood pressure measurements from an arterial line or blood pressure cuff; thus, the ICU community has not embraced a focus on nutrition delivery being equally important to other care areas (ie, cardiovascular, respiratory, renal systems), owing to a lack of objective data to guide nutrition care. ICU nutrition care will not gain the respect it deserves until we are able to provide objective data to guide nutrition delivery. This is essential to address if we hope to bring nutrition care in line with other aspects of ICU care on ICU ward rounds. This is now more urgent than ever, as critical illness—and recently, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection that leads to the need for ICU care—is posing an ever-growing major healthcare challenge worldwide.<sup>7</sup> The longitudinal metabolic phenotype and the measured resting energy expenditure (mREE) requirements of the critical care patients receiving current standards of ICU care are poorly understood, as very few recent longitudinal studies of IC exist. Further, the metabolic challenges that modern ICU care poses—and especially coronavirus disease 2019 (COVID-19) now poses as a new threat to human health—are poorly understood.

It is a critical research and clinical imperative to understand the metabolic consequences and nutrition needs of modern critically ill patients, including in severe COVID-19. This is essential to assist in improving the clinical and functional outcomes for the rapidly growing number of critically ill and COVID-19–related ICU survivors. To improve clinical and quality-of-life (QoL) outcomes in ICU survivors, an obvious therapeutic strategy is objective, targeted nutrition therapy to address preexisting and subsequent iatrogenic malnutrition, which commonly occurs in ICU patients. Preexisting malnutrition is highly prevalent in ICU patients, with up to 1 in 2 (30%–50%) patients with malnutrition at ICU admission.<sup>8</sup> Unfortunately, clinical outcomes in patients with preexisting malnutrition are further complicated by the acute catabolic response that occurs in critical illness, leading to rapid loss of muscle mass and thus muscle weakness and functional disability.<sup>9–11</sup>

Unfortunately, as mentioned, iatrogenic malnutrition and underfeeding continue to be ubiquitous in ICUs worldwide for prolonged periods following ICU admission.<sup>3–5</sup> Despite

extensive efforts to improve ICU nutrition delivery, studies of current practice reveal that actual nutrition delivery in ICU patients is <50% of prescribed targets, even in the most malnourished patients.<sup>3</sup> Alarming, US ICUs have the poorest track record of nutrition delivery compared with other world regions.<sup>3</sup> In the present era of focus on medical error and patient safety, we and others have consistently document ICU patients only receive, on average, 40%–50% of their nutrition targets for prolonged periods (often >7–10 days) following ICU admission<sup>5,12–16</sup>. Further, it takes over 60 hours on average for any nutrition to be started in US ICUs.<sup>3</sup> This is particularly concerning given that the average protein delivery (believed to be essential for muscle and functional QoL recovery) over the initial 12 days following ICU admission is only 0.6 g/kg/d,<sup>12</sup> which is approximately one-third of current nutrition guidelines recommending 1.2–2.0 g/kg/d in the ICU.<sup>2</sup> We believe a major barrier to overcoming this long-standing lack of emphasis on nutrition delivery is due to a lack of objective energy targets and other objective, measurable data to guide nutrition delivery as is present in virtually every other area of ICU management discussed on rounds. This presents an urgent patient safety crisis we must address in critical care.

### **The challenge of determining objective nutrition targets: We must do better!**

Defining an ICU patient's nutrition target is the essential first task of an ICU clinician prior to prescribing nutrition therapy. As stated, we believe a major driver of the lack of emphasis on improved nutrition therapy in the ICU and post-ICU period is the lack of objective energy target data. Our research group and many others have hypothesized that energy needs and targets change frequently throughout the course of critical illness and post-ICU recovery.<sup>11,17,18</sup> However, this has not been validated with actual, measured, longitudinal REE measures. EE in critically ill patients is believed to be highly variable and dependent on a range of key features including initial illness/injury, illness severity, initial nutrition status, and current therapies.<sup>11</sup> For example, older adult patients with reduced lean body mass (and/or sarcopenia) and increased fat mass have a reduced EE, which is difficult to accurately predict by using traditional equations for energy need. Similarly, patients with weight loss and cachexia related to surgery, cancer, anorexia nervosa, chronic obstructive pulmonary disease, chronic infections, or prolonged ICU stay or those with impaired muscle mass and function (ie, extensive muscle paralysis or muscle wasting, ICU-acquired weakness, sarcopenia) often have reduced EE, which is difficult to estimate. By contrast, younger ICU patients and those with acute infection, severe trauma, or obesity can have increases in EE that are quite difficult to accurately estimate.<sup>19,20</sup> As stated, a range of published studies demonstrate that predictive equations developed to estimate EE in such patients are largely inaccurate at almost all time points in the course of critical illness and are commonly not clinically relevant,<sup>21–23</sup> owing to the complex and dynamic metabolic alterations observed in critical illness.<sup>24,25</sup> Given this, clinicians must regularly measure their patients' EE to optimize the prescription of nutrition support and clinical outcomes,<sup>1,2</sup> and IC is considered to be the gold standard for determination of EE in the ICU setting. Further emphasizing the need for routine, longitudinal IC measures, it has recently become clear that both overfeeding and underfeeding are associated with increased ICU mortality.<sup>1,2,26</sup> To address accurate determination of EE and to optimize clinical outcomes, the most recent international ICU nutrition guidelines recommend routine use of IC to measure the EE in ICU patients to provide accurate determination of caloric needs.<sup>1,2</sup> This is supported

by data showing the use of metabolic cart (IC) data to optimize nutrition support has been associated with improved clinical outcomes from nutrition therapy.<sup>19,20</sup>

Unfortunately, recent studies demonstrate that current commercially available IC devices are often inaccurate<sup>27,28</sup> and the inconvenience and challenge of IC measurements (ie, long warm-up duration and challenging calibration, complex maintenance, large device size, etc) have significantly limited IC use in clinical practice.<sup>29,30</sup> These comparative studies raising concern for the accuracy of currently available IC technology include a study by Sundstrom et al in which 3 currently available IC devices were compared and conflicting estimates of REE, respiratory quotient, and expiratory minute volume were observed between devices in mechanically ventilated patients.<sup>27</sup> A second study by Graf et al compared 3 currently available IC devices, and differences in REE between devices were observed, which authors concluded were not acceptable for clinical practice. The authors indicate new indirect IC technology was in need of development.<sup>28</sup> Further, a comprehensive study of a large number of recent existing IC devices showed quite variable validation, accuracy, and reliability by device.<sup>31</sup> Specifically, via testing of 12 current IC devices, accuracy was shown at only 1 of the 2 study sites for each of the devices tested and not for all variables tested.<sup>31</sup> Most clinical studies using IC utilize a device developed ~35 years ago (Deltatrac Metabolic Monitor, Datex). The production of this device was discontinued 10 years ago, and very few working units remain in use. Difficulties in IC conduct, calibration, and interpretation of results have also continued to limit the use of IC in ICU patients.<sup>29,30</sup> Further limitations of existing IC technology in the ICU are also discussed in the accompanying point-counterpoint paper (*Reference per NCP publisher when available*) in this issue. Given the consistent inaccuracy of the estimation of caloric need by equations and the unreliable results from the calorimeters on the market, the development of an accurate and reliable calorimeter has been urgently needed. The ideal new IC device must be convenient and simple to use, require minimal calibration and maintenance, and have a reasonable cost to allow for the routine, longitudinal IC measurements that are needed in ICU patients.

## **A NEW-GENERATION INDIRECT CALORIMETER: AN OPPORTUNITY FOR OBJECTIVE, LONGITUDINAL NUTRITION TARGET ASSESSMENT**

To address the urgent need for a new-generation metabolic cart (IC), an ambitious endeavor was recently undertaken, uniting leaders in the critical care nutrition field with industry leadership to address this essential deficiency in ICU nutrition care. The group, the International Multicentric Study Group for Indirect Calorimetry (ICALIC), championed a project to develop an accurate, cost-affordable, reliable, and user-friendly indirect calorimeter to measure EE in the ICU and other patients. The result of this project was the development of the next-generation Q-NRG indirect calorimeter device, which is now US Food and Drug Administration (FDA) approved and available worldwide.<sup>32</sup>

The new Q-NRG (Baxter and COSMED, Inc) device was extensively validated vs mass spectroscopy (gold standard) to assure accuracy and evaluate analytical performance. This new IC device was found to be accurate at FIO<sub>2</sub> ranges up to 70%, extending the traditional range of IC Fraction of Inspired Oxygen (FiOs) measurements beyond 60%.<sup>33</sup> The

performance of the new-generation IC device in clinical practice and vs existing IC devices was recently published in the new ICALIC project paper.<sup>34</sup> This multicenter study evaluated the ease of clinical use of the new IC device in critical care patients in a wide range of ICU settings. The study examined real-world device performance in 6 international academic ICU centers on 3 continents. The results of the study demonstrate the Q-NRG IC required a much shorter time (with reliable, steady-state measurements in ~10 minutes) to determine EE in mechanically ventilated ICU patients vs other existing IC devices. A summary of critical differences between the new-generation Q-NRG IC device and previous IC devices is shown in Table 1. This new IC device allows accurate measurements in a much broader range of patients, including FIO<sub>2</sub> up to 70% and higher positive end-expiratory pressure (PEEP) settings, and as described in recent publications on extracorporeal membrane oxygenation<sup>35</sup> and potentially during continuous renal replacement therapy (CRRT).<sup>36</sup> We as the authors concluded the new Q-NRG provides accurate EE and IC measures in an efficient and timely fashion. It fills a long-standing void in ICU and clinical nutrition care as the only commercially available IC device tested against mass spectrometry to ensure gas accuracy while being easy to use for longitudinal IC measures in a range of settings in and out of the ICU. These characteristics should allow for a much broader use of IC to optimize the prescription of nutrition support by objectively determining energy targets to limit poor clinical outcomes due to the risk of underfeeding or overfeeding.

## USE OF IC IN COVID-19 ICU PATIENTS

In response to the recent worldwide COVID-19 pandemic,<sup>7</sup> the new-generation Q-NRG IC device was utilized to conduct the first longitudinal study of the metabolic phenotype and mREE in this novel pandemic illness. To address defining the metabolic phenotype of COVID-19, the LEEP-COVID study group recently published data<sup>37</sup> demonstrating first that longitudinal IC measures can be efficiently and routinely obtained in mechanically ventilated COVID-19 ICU patients. The LEEP-COVID results show that during the first ICU week in intubated COVID-19 patients, mREE fell between 15 and 20 kcal/kg (for actual body weight in BMI < 30 and adjusted body weight in obese patients).<sup>1</sup> Markedly increased hypermetabolism and wider variability in mREE values were observed following the first ICU week. Unlike data from smaller studies in other ICU populations,<sup>38</sup> the hypermetabolism observed in COVID-19 patients persisted and, in fact, increased during the second and third ICU week (mean mREE = 150%, predicted REE [pREE] in third ICU week). In fact, some patients exhibited resting metabolic rates >2 times that predicted by the Harris-Benedict equation (HBE). Consistent with previous studies showing the inaccuracy of predictive equations throughout ICU stay,<sup>23</sup> the HBE significantly underpredicted mREE consistently following the first ICU week and, in fact, often overpredicted need in the first ICU week in COVID-19 patients. This further emphasizes that current predictive equations do not appear to accurately predict energy targets and that currently utilized predictive equations likely lead to significant overfeeding and underfeeding. We found observed changes in mREE do not demonstrate a significant relationship to organ failure severity and are only minorly affected by prone positioning/paralysis, as over the study period the use of these therapies was not significantly different. This is consistent with previously published data showing that paralysis appears to have only a minor effect on mREE.<sup>39</sup> Our data

strongly suggest that personalization of nutrition delivery via routine, longitudinal IC use<sup>1,34</sup> should be considered as the new standard of care to accurately assess EE, help guide nutrition therapy in COVID-19 (and, likely, other ICU patients), and improve patient care overall.

## **SUMMARY: KEY EVIDENCE SUPPORTING ROUTINE USE OF IC IN THE ICU AND CLINICAL IC PROTOCOL RECOMMENDATIONS**

If we are to ultimately overcome the fundamental challenges and perceptions in delivering nutrition in the ICU, we must all adopt routine objective, longitudinal measurement of energy targets and nutrition requirements.

### **KEY EVIDENCE SUPPORTING ROUTINE IC USE IN THE ICU**

The following list highlights key evidence for supporting routine IC use in the ICU:

1. Universal guideline recommendations calling for use of IC to determine energy requirements in ICU<sup>1,2</sup>
2. Data showing that pREE from predictive equations or body weight calculations is consistently inaccurate and correlates poorly with mREE, ultimately leading to routine overfeeding and/or underfeeding, which are both associated with poor ICU outcomes<sup>1</sup>
3. The development and worldwide availability of IC devices that are validated, accurate, and easy to use, maintain, and interpret<sup>32-34</sup>
4. Recent data in COVID-19 ICU patients from LEEP-COVID study showing progressive hypermetabolism throughout ICU stay and the variability in metabolic responses in different forms of critical illness and emphasizing inaccuracy of predictive equations with marked day-to-day variability in nutrition needs<sup>37</sup>
5. New metabolic cart technology (Q-NRG device) that is simple to use and maintain allows for a range of disciplines and healthcare professionals to perform IC testing (ie, registered dietitians [RDs]) and develop IC teams

Thus, given these key findings, the use of this new-generation metabolic cart device provides an opportunity for IC to be the new standard of care for objective delivery of all nutrition, including EN, PN, and oral nutrition in the ICU and post-ICU patient.

A structured approach to the use of routine, longitudinal IC measurements to guide evidence-based ICU nutrition delivery is essential, as it is utilized in other areas of critical care. Key recommendations for guidelines for patient use of the new IC are summarized in Table 2. Additionally, a suggested personalized IC-guided ICU nutrition algorithm derived from a range of recent evidenced-based ICU nutrition reviews is presented in Figure 1.<sup>11,17</sup> Another excellent algorithm is described in a recently published landmark paper (the Effect of early nutritional support on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial [EFFORT] trial), supporting the essential role of an RD-driven

nutrition pathway. This large, multicenter randomized trial in acutely ill hospitalized patients at high malnutrition risk<sup>40</sup> found that a structured nutrition pathway led to significant reductions in complications at 30 days and in mortality and significantly improved recovery of functional independence and QoL as measured by EQ-5D at 30 days after hospitalization. Importantly, this nutrition pathway can easily be adapted for both care of the ICU patient and post-ICU care.

In conclusion, it is essential that longitudinal IC measures before, during, and after ICU care become the new worldwide standard of care to guide nutrition care and become as ubiquitous in their reporting on rounds as blood pressure values and heart rates are reported to guide vasopressor and other ICU care. It is only with continued implementation of objective nutrition data, such as longitudinal IC measures and ultrasound-derived muscle mass measures,<sup>41</sup> that we will ensure each ICU patient receives personalized nutrition care that delivers the right nutrition, in the right patient, at the right time to optimize clinical outcomes.

## CONFLICT OF INTEREST

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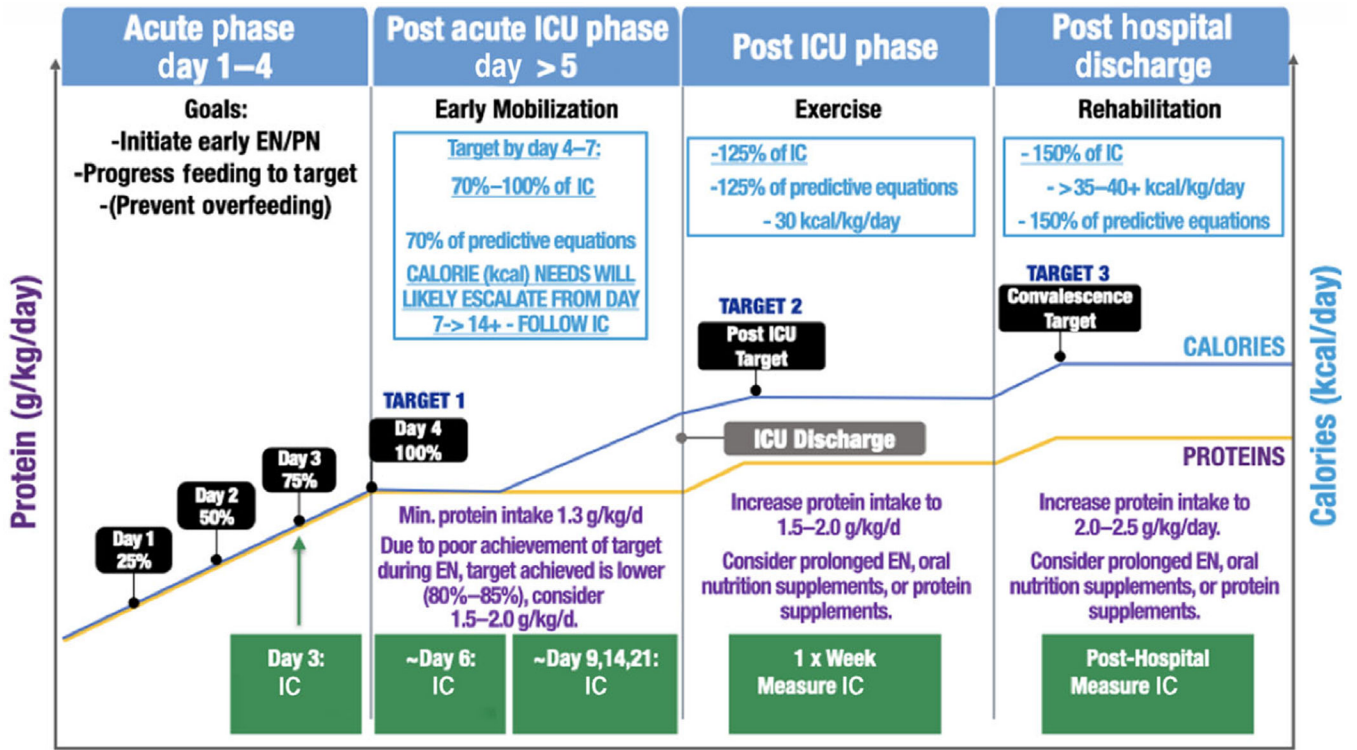
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**FIGURE 1.** Personalized IC-guided ICU nutrition algorithm (derived from recent evidenced-based ICU nutrition reviews<sup>11,17</sup>). Please note that suggested IC measurement days are meant as general guidelines to create consistency in measurement throughout patient stay. IC should ideally be performed 2–3 times per week or when there is a significant clinical change in patient status. EN, enteral nutrition; IC, indirect calorimetry; ICU, intensive care unit; PN, parenteral nutrition

**TABLE 1**

Comparison of barriers to use in existing IC vs new-generation IC device

Barriers	Past/existing IC technology <sup>a</sup>	New-generation IC device <sup>b</sup>
Setup and measurement time	45→60 minutes	~10–15 minutes
Calibration time	Extensive calibration time required	Minimal calibration time Self-calibrating
Size	Bulky, large device	Lightweight, portable, easy to transport
-	Variable validation, accuracy, and reliability by device <sup>27,28,31</sup>	Accuracy validated via mass spectrometry <sup>33,34</sup>
Patient-use flexibility	Typically limited to ventilated patients in ICU only	Use in ventilated and spontaneously breathing patients in and out of ICU
FIO <sub>2</sub> limits of accuracy	60% FIO <sub>2</sub>	70% FIO <sub>2</sub>
Potential PEEP limits	Suggested: <10–12	<16 (per Longitudinal Energy Expenditure and Metabolic Effects in Patients With COVID-19 [LEEP-COVID] data) <sup>37</sup>

FIO<sub>2</sub>, fraction of inspired oxygen; FiOs, xxxxx; IC, indirect calorimetry; ICU, intensive care unit; LEEP-COVID, xxxxx; PEEP, positive end-expiratory pressure.

<sup>a</sup>Some data from Graf et al.<sup>28</sup> De Waele et al.<sup>29</sup> Kaviani et al.<sup>31</sup> and Oshima et al.<sup>32</sup>

<sup>b</sup>Some data from QNRG+ Technical Brochure- (COSMED, Inc), (website: [https://www.cosmed.com/hires/Q-NRG+\\_brochure\\_A3\\_C04672-22-93\\_EN\\_web.pdf](https://www.cosmed.com/hires/Q-NRG+_brochure_A3_C04672-22-93_EN_web.pdf)) Accessed 03/04/2021

**TABLE 2**

## New-Generation (Q-NRG) IC measurement guidelines

- ✓ Patient not agitated and sedation and analgesia drug doses stable, neuromuscular blockade are acceptable for measures and has minimal effect on REE measure
  - ✓ Ideally, for best measures:
    - Patient temperature should not change by  $>1^{\circ}\text{C}$
    - Patient ABG should not change by  $\text{pH} >0.1$ , hour before IC
  - ✓ Establish  $\text{FIO}_2$  of  $<70\%$ , the maximum expected for clinical accuracy for new QNRG Device accuracy
  - ✓ Preferred PEEP: 16 cm  $\text{H}_2\text{O}$ , and peak airway pressure: 30 cm  $\text{H}_2\text{O}$
  - ✓ No air leaks (ie, no chest tubes) and patient has stable ventilator settings for 30 minutes
  - ✓ Perform IC 4 hours before/after CRRT use. Perform IC before or  $>4$  hours after intermittent hemodialysis
  - ✓ Ideally, wait 60 minutes after painful procedure or changes in catecholamine, sedative, or analgesic dose
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Recommendations taken from Oshima et al,<sup>6</sup> Kaviani et al,<sup>31</sup> and Uehara et al<sup>38</sup> and QNRG operating manual (COSMED, Inc).

ABG, arterial blood gas; CRRT, continuous renal replacement therapy; IC, indirect calorimetry;  $\text{FIO}_2$ , fraction of inspired oxygen; PEEP, positive end-expiratory pressure; REE, resting energy expenditure.