CURRENT OPINION

Muscle mass and physical recovery in ICU: innovations for targeting of nutrition and exercise

Paul E. Wischmeyer[a,b], *Zudin Puthucheary*[c], *Iñigo San Millán*[d], *Daniel Butz*[e,f], and *Michael P.W. Grocott*[g,h,i]

Purpose of review

We have significantly improved hospital mortality from sepsis and critical illness in last 10 years; however, over this same period we have tripled the number of 'ICU survivors' going to rehabilitation. Furthermore, as up to half the deaths in the first year following ICU admission occur post-ICU discharge, it is unclear how many of these patients ever returned home or a meaningful quality of life. For those who do survive, recent data reveals many 'ICU survivors' will suffer significant functional impairment or post-ICU syndrome (PICS). Thus, new innovative metabolic and exercise interventions to address PICS are urgently needed. These should focus on optimal nutrition and lean body mass (LBM) assessment, targeted nutrition delivery, anabolic/anticatabolic strategies, and utilization of personalized exercise intervention techniques, such as utilized by elite athletes to optimize preparation and recovery from critical care.

Recent findings

New data for novel LBM analysis technique such as computerized tomography scan and ultrasound analysis of LBM are available showing objective measures of LBM now becoming more practical for predicting metabolic reserve and effectiveness of nutrition/exercise interventions. 13C-Breath testing is a novel technique under study to predict infection earlier and predict over-feeding and under-feeding to target nutrition delivery. New technologies utilized routinely by athletes such as muscle glycogen ultrasound also show promise. Finally, the role of personalized cardiopulmonary exercise testing to target preoperative exercise optimization and post-ICU recovery are becoming reality.

Summary

New innovative techniques are demonstrating promise to target recovery from PICS utilizing a combination of objective LBM and metabolic assessment, targeted nutrition interventions, personalized exercise interventions for prehabilitation and post-ICU recovery. These interventions should provide hope that we will soon begin to create more 'survivors' and fewer victim's post-ICU care.

Keywords

13C-breath testing, cardiopulmonary exercise testing, CT scan, lean body mass, muscle glycogen, post-intensive care syndrome, quality of life

INTRODUCTION

In-hospital mortality following severe sepsis has consistently declined in recent years [1]. However, the same data also reveal that many of these patients are not returning home to functional lives post-ICU, but instead to rehabilitation settings where it is unclear whether they ever returned to a meaningful quality of life (QoL). In fact, in the same period that in-hospital ICU mortality appears to be declining appears we have tripled the number of patients going to rehabilitation settings [1]. We also know that up to 40% of mortality within the first year of ICU stay occurs following ICU discharge [2]. Unfortunately for those who do survive, nearly half of the survivors will not return to work in the first

[a]Department of Anesthesiology and Surgery, Duke University School of Medicine, [b]Duke Clinical Research Institute, Durham, North Carolina, USA, [c]Centre for Human Health and Performance, University College London, London, UK, [d]Department of Physical Medicine and Rehabilitation, University of Colorado, Denver, Colorado, [e]Department of Animal Sciences, University of Wisconsin, [f]Isomark LLC, Madison, Wisconsin, [g]Respiratory and Critical Care Research Area, NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, [h]Integrative Physiology and Critical Illness Group, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK and [i]Morpheus Collaboration, Department of Anesthesiology Duke University School of Medicine, Durham, North Carolina, USA

Correspondence to Paul E. Wischmeyer, MD, EDIC, Professor of Anesthesiology and Surgery, Duke University School of Medicine, 2400 Pratt Street, NP 7060, Durham, NC 27705, USA. Tel: +1 919 668 3063; e-mail: Paul.Wischmeyer@Duke.edu

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KEY POINTS

- We have significantly improved in-hospital mortality from sepsis and critical illness in last 10 years; however, due to PICS over this same period we have tripled the number of 'ICU survivors' going to rehabilitation where it is unclear whether they ever return to a meaningful QoL.
- New innovative techniques are demonstrating promise to target recovery from PICS utilizing a combination of objective LBM and metabolic assessment, targeted nutrition interventions, personalized exercise interventions for prehabilitation, and post-ICU recovery.
- Admission skeletal muscle mass and quality via CT scan are predictive of mortality and complications following surgery and critical care and may prove useful to predict preillness metabolic reserve and patients in need of preillness nutritional optimization.
- Novel technique such as 13C-breath testing to assess over-feeding/under-feeding and muscle glycogen to evaluate muscle recovery and transition to 'recovery phase' are showing promise as objective methods to personalize nutrition and recovery interventions.
- CPET is being utilized to predict operative risk and personalize preoperative (prehabilitative) exercise interventions, with promise to guide post-ICU exercise interventions for PICS.

year postdischarge [3▪▪], often due to postintensive care syndrome (PICS) and weakness post-ICU [4▪]. As a result, many leading experts are calling for future ICU trials to not focus on mortality as the primary endpoint, but rather to focus on QoL [5▪▪], physical function, and addressing the epidemic of PICS [1,6].

Specific to lean body mass (LBM) in the ICU, we know a critically ill burn patient can lose as much as a kilogram of LBM a day [7▪]. Other critically ill patients also suffer significant LBM loss, much of it in the first 7–10 days of ICU stay [8▪▪]. Patients will gain weight back following ICU stay, but virtually all this weight is fat mass, not functional LBM [9]. This is not surprising, as data from the burn ICU demonstrates the catabolic/hypermetabolic state following injury can persist for up to 2 years following discharge from hospital, and this can markedly hinder recovery of patients LBM and function following injury [7▪]. As will be discussed in this review, we desperately need objective methods of screening and quantifying a patient's metabolic, exercise, and LBM reserve prior to anticipated injury/illness (such as surgery/cancer therapy). These should serve as key predictors of preoperative/preillness risk and screen for patients in need of 'prehabilitation' prior to a surgical intervention. As this review will describe, interventions such as computerized tomography (CT) scan LBM analysis and cardiopulmonary exercise testing (CPET) are already being utilized and studied around the world to assess preoperative 'metabolic reserve' and 'fitness for surgery'. These should be complemented by objective measures of patient's nutritional needs during illness and recovery. Further the effect of nutrition delivery on muscle uptake of nutrients and muscle 'fitness' for exercise interventions may be a reality in our ICU's soon [8▪▪,10▪]. Finally, we must improve our post-ICU care 'recovery' care and take responsibility for the deficits in strength, function, and cognition we create in our ICU care. We owe it to our ICU patients to continue to use new innovations in objective nutrition delivery to guide nutrition and personalized exercise interventions to guide functional recovery.

ANALYSIS OF LEAN BODY MASS AND RELATIONSHIP TO SURGICAL AND ICU OUTCOME

Baseline skeletal muscle mass [11] and quality [12▪▪] are demonstrated to be predictive of mortality in ICU patients. Muscle wasting and weakness are also major contributors to PICS [4▪,13▪]. This is not unsurprising, as these parameters reflect 'metabolic reserve', which is effected by physical activity, nutrition, chronic disease and is tightly linked to function [3▪▪]. In surgical patients, a rapidly growing body of literature demonstrates low baseline skeletal muscle mass may be an independent risk factor for surgical complications in patients undergoing hepatic [14▪] colorectal [15▪,16▪], diverticular [17▪], and pancreatic [18▪] oncological surgery. Muscle mass loss prepost oncological surgery (just as with ICU patients [19]) is an additional risk factor for complications [20▪] and mortality [21▪▪,22▪]. Low muscle contributes to increased length of stay in cardiac surgery [23▪] and in patients undergoing transcatheter aortic valve replacement (TAVR) [24▪].

A major limitation of these studies is their retrospective nature. First, we are unable to exclude type II errors: in contrast to the studies above no complications were seen in a patient cohort undergoing endometrial cancer resection [25] and ovarian surgery [26▪]. Although low muscle mass was associated with mortality in gastric cancer, no association was seen with complications [27▪]. Secondly, we are therefore unable to dissect differences between positive and negative studies, that is, in which surgical procedures does low skeletal muscle mass pose an additional risk for complications?

PROSPECTIVE TRIAL ASSESSMENT OF MUSCLE MASS

Although the evidence from observational studies of baseline muscle mass and quality continues to grow, sufficient data to justify intervention development exists. Primary outcomes should be focused on function and/or complications as opposed to mortality.

Performing a baseline muscle mass assessment in the acutely critically ill patient is challenging. Transfer for CT scans is not without risk and may be ethically difficult to justify and lead to selection bias. Muscle ultrasound is an attractive emerging technique and is also able to offer qualitative analysis [28▪]. Ultrasound is inexpensive and readily available. Bedside measurements of muscle mass are possible with existing routine ICU ultrasound equipment. Unlike CT however, international consensus does not exist on methodology, with significant differences between techniques [29▪▪].

To advance this science, studying the high-risk surgical patient has two major advantages. First, if the complication and return to work rates can be altered, there are significant gains to be attained for the patient, healthcare providers, and society. Secondly methodological difficulties are minimized regarding consent, obtaining muscle mass measurements preinsult and determining preexisting functional outcome. A recent prospective observational study demonstrated the ability of preoperative CT assessment of muscle quality in predicting surgical complications [21▪▪]. In designing interventional trials, caution will be needed with regard to data analysis planning and power calculations. Muscle mass must be considered one of a group of stratification variables in a multidimensional fashion [30▪], much like the ICU Nutritional Risk Score or (NUTRIC) score [30▪]. We have yet to understand how interdependent muscle mass, muscle quality, and functional disability are, and which and how we should either stratify or correct for baseline differences [31▪▪].

BEDSIDE ANALYSIS OF METABOLIC STATE AND OVER-FEEDING/UNDER-FEEDING: PROMISE OF NEW TECHNOLOGY

The accurate determination of caloric needs and objective measures of over-feeding/under-feeding over time in critical care has long been a challenge for ICU practitioners and a recent large observational cohort has been conducted on this topic [32▪]. Indirect calorimetry, despite its limitations in the hospital setting, has been traditionally utilized for estimating energy needs [32▪]. The next evolution of modern indirect calorimetry is described in this issue by De Waele *et al.* [33▪]. However, indirect calorimetry has traditionally proven expensive, has significant limitations in the ICU (i.e., cannot be used on CVVH or with $FiO_2 > 60\%$), and is not readily available.

To address this need for objective, bedside metabolic monitoring, new technologies to measure carbon-12 and carbon-13 ($^{13}CO_2/^{12}CO_2$) ratios in exhaled breath are showing promise to objectively indicate type of metabolic fuel use and over-feeding/under-feeding over time in an easy-to-use, noninvasive fashion. This technology is currently under study to for applications related to early infection detection and macronutrient use and caloric need Fig. 1a and b) [34,35].

Carbon-12 and carbon-13 (^{12}C, ^{13}C) are naturally occurring isotopes that are found in exhaled breath. Stable isotopes of carbon isotope exist naturally in the body; however, the isotopic distribution of is not uniform. Because of chemical and enzymatic discrimination against the heavier ^{13}C (i.e., fractionation) in various steps in lipid synthesis body fats are 3–10‰ depleted in ^{13}C compared with body proteins and carbohydrates (CHOs) [36,37▪]. Based on this isotopic difference between the primary metabolic fuel sources, it is possible to determine relative differences in metabolic fuel use at the macronutrient level by measuring the isotopic ratio of exhaled breath (Fig. 1a and b), which now is possible in small ICU-based or bedside devices. Similar to the respiratory exchange ratio that measures rate of oxygen consumption and CO_2 production in exhaled breath, the exhaled $^{13}CO_2/^{12}CO_2$ ratio is correlated to ratio of CHO/protein:lipid oxidation [37▪,38]. This technique has been used in wild life ecology studies to determine metabolic fuel usage in birds during different types of flight. For example, humming birds rely primarily on CHO source during hovering flight while migratory birds rely on stored lipids to power long range flights over may thousands of kilometers [39▪▪,40]. More recently, this technique has been applied in humans to understand metabolic fuel usage in health and disease. For example, exhaled $^{13}CO_2/^{12}CO_2$ was a biomarker for metabolic fuel usage in women with polycystic ovarian syndrome shown to have metabolic inflexibility in switching from CHO to lipids during an overnight fast [34]. Similarly, healthy adults during intense exercise ($>50\%VO_{2max}$) increased $^{13}CO_2/^{12}CO_2$ ratio post-exercise indicting increased reliance on CHO for energy [41]. In another study, adults on a healthy weight loss diet (40% energy restriction) demonstrated decreases in $^{13}CO_2/^{12}CO_2$ from prediet baseline, indicating increased reliance on body lipids [35]. Ongoing studies are examining the exhaled

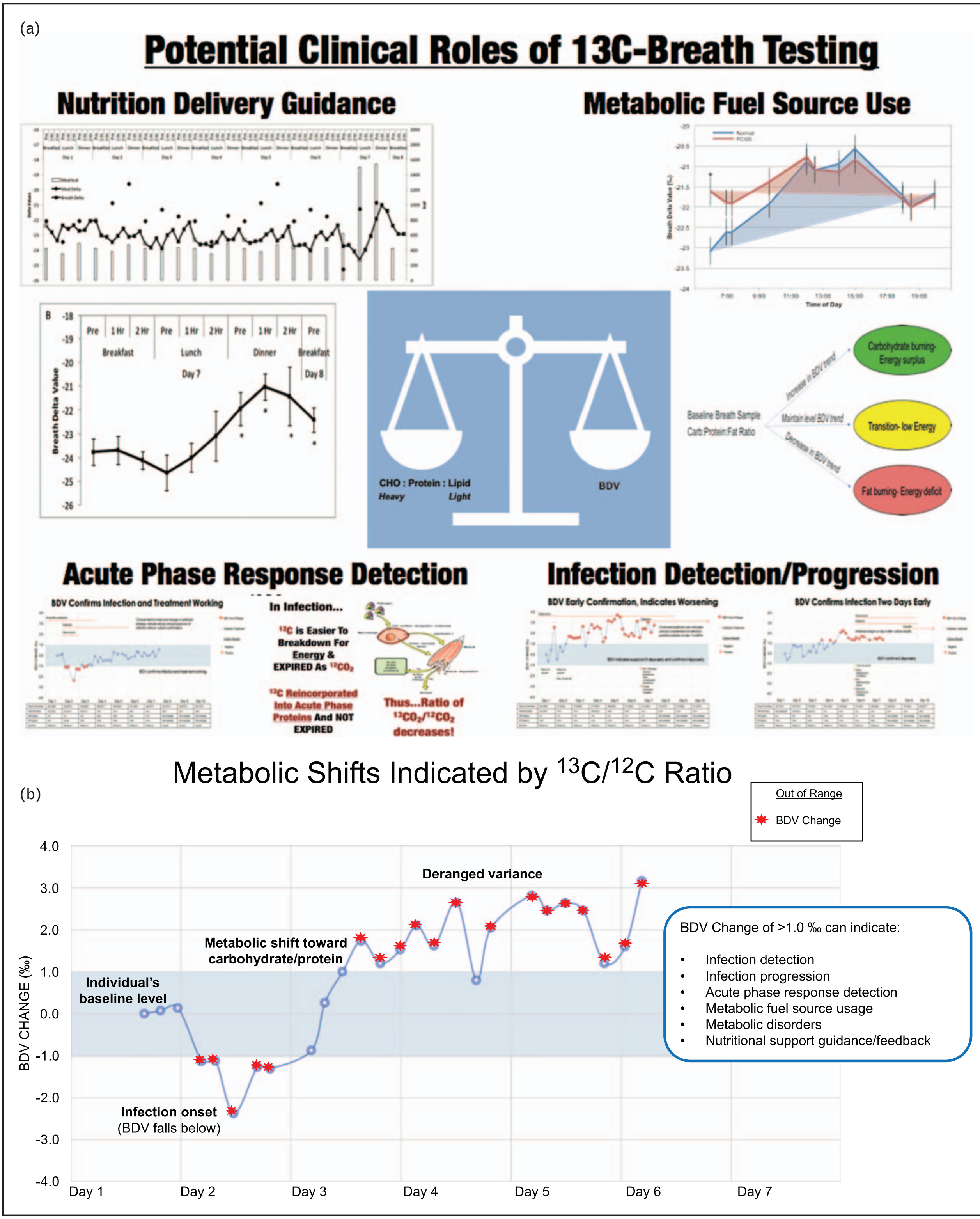

FIGURE 1. (a) Multiple potential roles of 13C-carbon breath testing in ICU and hospitalized patient. (b) Hypothetical example of readout from 13C-carbon breath testing and data that may be able to obtained by future clinicians in ICU. Adapted from refs. [34,35]).

$^{13}CO_2/^{12}CO_2$ ratio for metabolic fuel usage in our hospital/ICU setting at Duke University and at other US centers for patients requiring total parenteral nutrition (personal communication).

METABOLIC RESPONSE TO ICU: RELATIONSHIP TO EXERCISE STRESS AND MEASUREMENT

The hypermetabolic response to physiological stress weather at the ICU or running a marathon necessary for cellular energy requirements elicits major alterations in CHO metabolism, which in critically ill patients can have an important impact on muscle mass and survival. During exercise, CHOox increases due to the higher rate for ATP synthesis to satisfy muscle contractile demand [42] (Inigo San-Millan and George Brooks, 2017, personal communication) (Fig. 2) [42,43]. Surprisingly, a paucity of information on CHOox rates in ICU patients exists. It is believed though that CHOox can be 4–7 mg/kg/min [43], which is approximately two to three times that of resting levels.

During both exercise and critical illness, CHOs need to be mobilized in an orchestrated manner. During exercise, glycogenolysis for glycolysis is provided from both the liver and from skeletal muscle glycogen. Upon ceasing exercise, glycogen stores are repleted via proper nutrition. However, metabolic demand of ICU patients represents, overtime, the most extreme metabolic demand observed in humans. This demand is nonstopping, stretching the limits of 'human performance'. Humans are not 'trained' to be critically ill, which is challenging as the body attempts to mobilize energy stores, driven mainly by cortisol. Therefore, a second phase of CHO metabolism relies on gluconeogenic precursors from skeletal muscle proteolysis. Glycogen depletion can elicit a significant increase in muscle protein breakdown. During physiological stress situations such as exercise, protein breakdown accounts for ~4% of total exercise caloric expenditure under CHO loading. However, under glycogen depletion, protein breakdown is significantly elevated contributing to ~10% of total caloric expenditure [44]. During exercise post-CHO loading, protein breakdown during exercise accounted for 5.8 versus 13.7 g/h when muscle glycogen was depleted [44]. Undoubtedly, the repercussions of glycogen depletion on skeletal muscle protein breakdown and catabolism in ICU can be significant and devastating.

New cutting-edge ultrasound technology [45] is being utilized routinely by the world's most elite professional athletes (i.e., Tour de France) to directly measure muscle glycogen in a few minutes at the bedside [45]. This technology is utilized by athletes to predict and prevent overtraining and guide nutritional needs during training. Glycogen depletion leads to marked muscle damage and an inability for muscle to recover and become anabolic, as muscle protein must be broken down for energy when energy cannot be obtained from glycogen stores. This leads to ongoing catabolism and inability to recover muscle mass and function [45]. We have previously shown muscle glycogen stores are depleted in ICU patients [10▪], even within hours of admission (Figs 3 and 4) [10▪]. In contrast, even elite endurance athletes do not completely deplete their glycogen stores after a major competition, such as prolonged bike racing or a marathon (Figs 3 and 4). Thus, one might equate being in the ICU as similar to continuously running multiple marathons. It is hoped this ultrasound technique [45] can open new doors in monitoring nutritional and catabolic status in critically ill patients. This

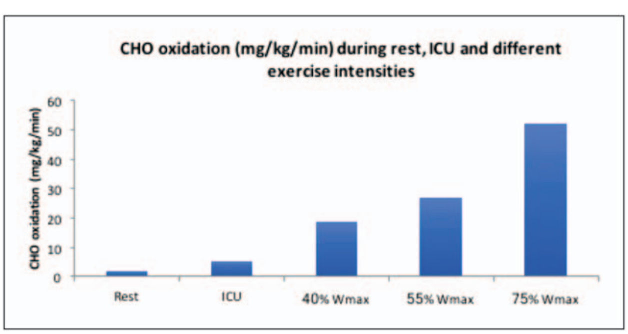

FIGURE 2. Carbohydrate (CHO) oxidation (mg/kg/min) during rest, ICU and different exercise intensities. Adapted from [42,43] and Inigo San-Millan and George Brooks, 2017, personal communication). Wmax, percentage of maximal exercise work.

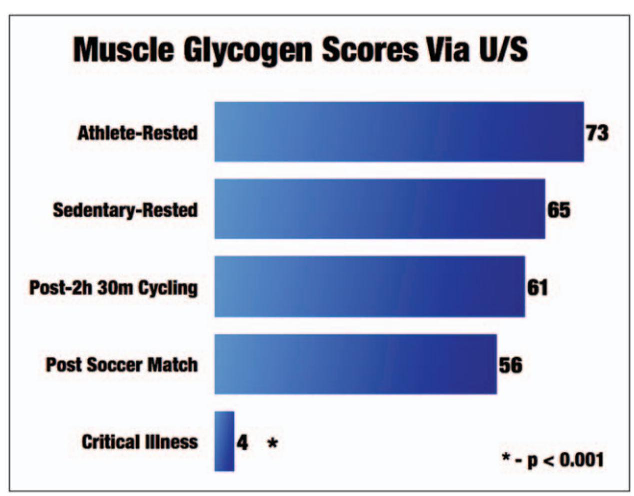

FIGURE 3. Muscle glycogen scores via ultrasound. Adapted from ref. [10▪].

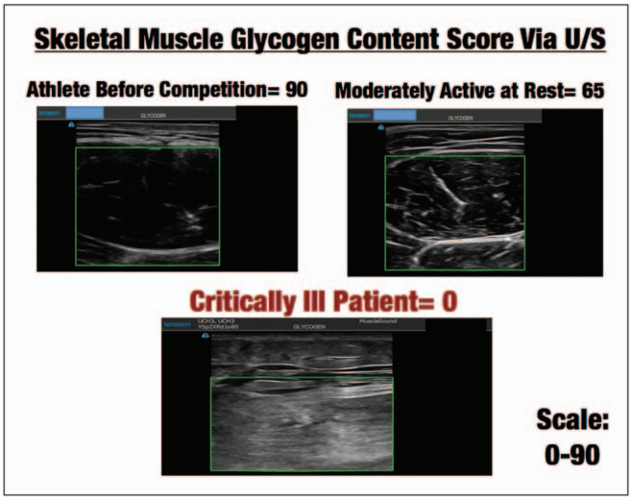

FIGURE 4. Skeletal muscle glycogen content score via ultrasound. Adapted from ref. [10▪].

technology we hope can guide when patients transition from the acute, catabolic phase of critical illness to a chronic or recovery phase, where increased nutrition delivery and potentially anabolic agents are warranted.

PERSONALIZING PREHABILITATIVE AND POST-ICU EXERCISE INTERVENTIONS

Although clearly distinct from critical care, the perioperative setting provides interesting data on the relationship between physical fitness and clinical outcomes, along with some intriguing mechanistic insights. This is relevant to critical care because many patients undergoing elective major surgery are subsequently admitted to ICU, electively or in response to postoperative complications. Furthermore, patients undergoing major surgery have long been considered a valuable model for critical illness: many of the same pathophysiological processes occur and reliable premorbid physiological data is available – a rare luxury in the ICU.

The relationship between physical fitness and clinical outcomes postoperatively has been known for more than 20 years. This relationship demonstrates a consistent association between higher levels of activity and/or physical fitness in almost every aspect of human health and disease. Much of the perioperative literature utilizes cardiopulmonary pulmonary exercise testing (CPET) to measure preoperative 'fitness'. The early seminal publications originated from Older *et al.* [46], but more recently work in the UK has illuminated the field. A recent systematic review [47▪▪] from 37 studies including 7852 patients concluded CPET was a useful preoperative risk-stratification tool able to predict postoperative outcome in patients across a range of surgical specialties, but further research was needed to justify ability of CPET to predict postoperative outcome. Following this review, the first multicenter perioperative CPET study [48▪▪] evaluated the relationship between CPET measurements and in-hospital morbidity in 703 patients undergoing major elective colorectal surgery in six centers. Consistent with previous studies, both anaerobic threshold and peak oxygen consumption (VO_2P) were predictive of postoperative morbidity with area under the receiver operating characteristic curve (AUROC) of 0.79 and 0.77, respectively. Multivariable logistic regression model showed low anaerobic threshold and VO_2P along with high BMI and nonlaparoscopic techniques to be associated with increased odds of in-hospital morbidity. A model comprising all these variables discriminated well between patients with, and without, in-hospital morbidity (AUROC 0.83).

Other approaches to evaluating physical fitness before surgery that have been less well evaluated including 6-min-walk tests and simple stair climbing. Although all the indices of physical fitness are correlated to each other, the strength of this relationship is often surprisingly weak [49▪] and it is unclear whether alternative approaches will be as effective at predicting adverse outcome as CPET, the technology with the vast majority of data. Data collection for the international multicenter measuring exercise tolerance after surgery (METS) study [50▪] recently completed (target sample size 1723 patients). METS will provide comparative data on CPET, questionnaire-based activity assessment (the Duke Activity Status Index), cardiac biomarkers (NT-pro-BNP), and clinician judgment for the prediction of perioperative risk and a comparison with 6-min walk testing in a substudy of patients.

A recent development has been the observation that presurgery cancer therapies, such as neoadjuvant chemoradiotherapy and chemoradiotherapy, may impact preoperative physical fitness and outcome following surgery. A UK study demonstrated a significant decrement in CPET-derived anaerobic threshold and peak oxygen consumption in neoadjuvant chemotherapy (NAC) patients before elective upper gastrointestinal surgery [51▪▪]. Lower baseline fitness associated with reduced 1-year-survival in patients completing NAC and surgery, but not in patients who did not complete NAC. A follow-up study in elective colorectal cancer surgery demonstrated a similar harmful effect on physical fitness that was in turn associated with increased morbidity in the least fit patients [52▪]. Larger studies are currently underway in this area.

The advent of the neoadjuvant therapies before surgery brought both the challenge of a reduction in physical fitness, but also an opportunity due to the period after therapy and before surgery typically allowed for patients to recover from these often-debilitating therapies. The result has been studies evaluating effect of exercise interventions preoperatively in these patients, many of which are currently ongoing. An early blinded, nonrandomized, trial [53] in elective colorectal surgery demonstrated a 6-week structured in-hospital aerobic training program could reverse the effect of neoadjuvant chemoradiotherapy and return patients to baseline fitness levels. A systematic review of prehabilitation for major intercavity surgery [54] concluded preoperative aerobic exercise training interventions were feasible, safe, and effective in improving physical fitness, but limited evidence for improved clinical outcomes.

At present, data are not available to provide strong recommendations about clinical outcome but several large (>1000 patients) studies are currently ongoing. Although improved cardiorespiratory fitness may be the most intuitively obvious benefit of such training, early mechanistic studies suggest that changes in mitochondrial physiology also occur [55], and it may be these will be more relevant if/when clinical outcome benefit. If this is true, it raises the concept of mimicking benefits of exercise by pharmacological means in patients who cannot or will not exercise. Finally, the potential for CPET techniques to be utilized in the ICU setting and in the post-ICU recovery needs to be explored.

CONCLUSION

The current call for personalizing ICU care is beginning to be addressed in the metabolism and nutrition delivery field [8▪▪] by early studies validating the role of the NUTRIC score in nutrition risk prediction [56▪]. This data shows high-malnutrition risk patients may benefit to a greater degree than those with lower risk. The novel assessments, as described in this review, may be key innovations preoperatively and in facilitating post-ICU recovery. Patients with low muscle quality and quantity via CT scan may have greater and different specific nutritional needs. Preoperative patients with low LBM or poor skeletal muscle quality could be enrolled in prehabilitative exercise/nutrition programs to improve skeletal muscle quality and quantity [57▪▪]. Interventional trials evaluating muscle quality and quantity measures via CT scan and/or ultrasound will also need to be performed to assess targeted methods to optimize patients. Furthermore, in ICU, these techniques need additional research to determine the muscle-level effects of individual nutrition (e.g., protein delivery, anabolic agents [10▪]) and specific ICU-rehabilitation (e.g., in-bed ergometry, functional electrical muscle stimulation [58]) interventions. Current functional testing (i.e., Medical Research Council sum score, hand-grip strength, walk-testing) are volitional and not muscle specific, and have significant implementation, interpretation, and compliance challenges [59]. Thus, the role of objective measures of LBM, muscle, nutrition need and exercise targeting measurement described here deserve additional study and validation to add an additional ‘dimension’ to our prediction of outcome and personalization of care in the ICU [30▪].

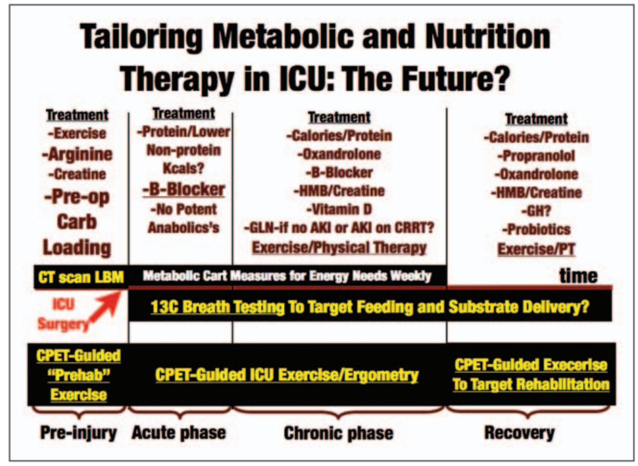

FIGURE 5. Future of targeted metabolic, lean body mass, exercise, and nutrition care in ICU. CPET, cardiopulmonary exercise testing; GH, growth hormone; GLN, glutamine; HMB, β-hydroxy β-methylbutyrate; LBM, lean body mass.

In conclusion, we must strive to not only continue to evolve technology and therapeutics targeted at improving survival in the ICU, but at the same time focus on innovations to improve our delivery of nutrition, metabolic support, and exercise interventions. These interventions should be implemented throughout the continuity of care – beginning in the ‘prehabilitation’ period (i.e., preoperatively or precancer therapy period), continue in the hospital and ICU setting, and then intensify in the post-ICU ‘recovery’ phase (Fig. 5).

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Conflicts of interest

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- ▪ of special interest
- ▪▪ of outstanding interest

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Retrospective computer tomography scan analysis assessing surgical outcomes. Low muscle density is associated with major postoperative complications in older patients who undergo surgery for colorectal cancer.

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