CURRENT OPINION

Novel approaches to metabolic assessment and structured exercise to promote recovery in ICU survivors

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Purpose of review

Survivorship or addressing impaired quality of life (QoL) in ICU survivors has been named 'the defining challenge of critical care' for this century to address this challenge; in addition to optimal nutrition, we must learn to employ targeted metabolic/muscle assessment techniques and utilize structured, progressive ICU rehabilitative strategies.

Recent findings

Objective measurement tools such as ccardiopulmonary exercise testing (CPET) and muscle-specific ultrasound show great promise to assess/treat post-ICU physical dysfunction. CPET is showing that systemic mitochondrial dysfunction may underlie development and persistence of poor post-ICU functional recovery. Finally, recent data indicate that we are poor at delivering effective, early ICU rehabilitation and that there is limited benefit of currently employed later ICU rehabilitation on ICU-acquired weakness and QoL outcomes.

Summary

The combination of nutrition with effective, early rehabilitation is highly likely to be essential to optimize muscle mass/strength and physical function in ICU survivors. Currently, technologies such as muscle-specific ultrasound and CPET testing show great promise to guide ICU muscle/functional recovery. Further, we must evolve improved ICU-rehabilitation strategies, as current methods are not consistently improving outcomes. In conclusion, we must continue to look to other areas of medicine and to athletes if we hope to ultimately improve 'ICU Survivorship'.

Keywords

cardiopulmonary exercise testing, critical illness, muscle, rehabilitation, ultrasound

INTRODUCTION

Modern ICU care now allows prolonged survival from Critical Illness by providing life-sustaining support for extended periods of time, making previously nonsurvivable ICU insults, survivable. In fact, innovations in ICU care have resulted in yearly reductions in hospital mortality from sepsis and critical care [1–3]. However, these same data reveal many ICU 'survivors' are not returning home to functional lives post-ICU; but, instead to postacute care facilities for prolonged periods wherein they incur substantial costs of nearly $3.5 million/functioning survivor [4,5]. Tragically, ICU survivors experience a high burden of muscle weakness, functional impairment and activity limitation [5,6]. ICU follow-up data consistently show persistent functional limitation resulting in only 50% of patients returning to employment at 1 year post-ICU [7], difficulty performing activities of daily living and only reaching 60–65% of functional exercise capacity at 12 months [8]. Survivors report that prolonged weakness and loss of function associated with ICU are the most concerning disabilities they experience [8]. Unfortunately, post-ICU functional disability or ICU-acquired weakness (ICU-AW) is most common and most severe in ICU survivors,

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KEY POINTS

- ICU survivors experience a high burden of muscle weakness, functional impairment and activity limitation; to address this challenge, in addition to optimal nutrition, we must learn to employ targeted metabolic/muscle assessment techniques and utilize structured, progressive ICU rehabilitative strategies.
- Severe muscle wasting, a hallmark of the development of ICU-acquired weakness and post-ICU functional disability, is a common complication of critical illness and is caused by impaired muscle protein homeostasis that ultimately results in reduced muscle mass and muscle strength, which are both independent predictors of survival.
- New hand-held muscle-specific ultrasound technology allows for measurement of muscle mass, muscle quality and muscle glycogen that will allow for objective evaluation of muscle changes during ICU and analysis of the effect of nutrition and exercise on muscle through hospital course.
- Cardiopulmonary exercise testing (CPET) needs to become the standard for evaluation of metabolic/exercise physiology and exercise prescription in patients, as new studes of CPET evaluation in acutely/chronically ill patients are showing that exercise intolerance is largely due to persistent mitochondrial dysfunction and this is responsive to CPET-prescribed exercise training.
- Recent data indicate that we are poor at delivering effective, early ICU rehabilitation and that there is limited benefit of currently employed later ICU rehabilitation on ICU-acquired weakness and QoL outcomes; thus, we must evolve improved ICU-rehabilitation strategies to include progressive multidisciplinarexercise that is carried out through entire ICU patient journey.

wherein recent data show that two out of three ICU survivors with lung injury (65%) suffer significant functional limitations [5]. It must be asked in modern ICU care: ‘are we creating survivors…or victims?’. ‘Survivorship’, or addressing impaired quality of life (QoL) in ICU survivors has been named ‘the defining challenge of critical care’ for this century [9]. In his landmark paper, Iwashyna states:

’The emerging picture of ICU survivorship is deeply disturbing. In year after discharge, patients are ravaged. They cannot walk . . . their bodies refuse to function as they did before. Many intensivists have a file of heartbreaking letters from patients, grateful to be alive but desperate for help in getting their lives back’.

Major national ICU trials groups emphasize with recent declining mortality rates in ICU patients that future trials need to focus on functional QoL as a primary endpoint, rather than mortality [1]. Finally, in a recent survey of ICU survivors and family members, physical function was rated as most important outcome future ICU studies could address (over mortality) by both patients and family members [10▪▪]. Thus, there remains a significant unmet need to develop new therapies to address the devastating impairments ICU survivors face and improve functional outcomes for the rapidly growing number of ICU survivors.

Severe muscle wasting, a hallmark of the development of ICU-acquired weakness and post-ICU functional disability ,is a common complication of critical illness [11▪,12]. Impaired muscle protein homeostasis ultimately results in reduced muscle mass and muscle strength, which are both independent predictors of survival [13▪▪,14▪]. As many as 80% critical illness survivors will continue to exhibit exercise limitations, decreased physical QoL, increased overall healthcare costs and higher utilization of healthcare services, after 12 months to even 5 years after ICU discharge [15,16▪▪]. Effective interventions to address ICU-acquired weakness, or post-ICU syndrome (PICS), during and after ICU stay continue to be elusive [17▪▪]. The development of metabolically targeted interventions to ICU-AW has been challenging, as there is significant heterogeneity in metabolic demands and energy requirements between ICU patients that are still poorly understood [17▪▪]. Thus, we believe it is imperative that targeted nutritional and metabolic interventions personalized to the highest risk metabolically challenged and malnourished patients continue to be studied and developed. Undoubtedly, these nutritional and metabolic interventions need to be targeted to preserve and rebuild muscle mass to allow for functional recovery. Inevitably, these nutritional and metabolic interventions must be teamed with structured, progressive and objectively prescribed and measured exercise and physical therapy. This manuscript will discuss the latest innovations in

(1) Muscle mass evaluation;
(2) Structured, progressive exercise and physical therapy;
(3) Specific objective measurement technique to target and personalize these exercise interventions.

Effect of critical illness on muscle mass/quality and objective evaluation of muscle in ICU

A growing body of evidence suggests that the decline in muscle function and physical fitness both before, during and after critical illness is the result of not only a reduction in skeletal muscle mass but also a result of changes in muscle quality such as muscle composition and morphology [18,19,20▪]. Skeletal muscle quality is recognized as a marker of function in healthy individuals and critically ill patients. It is also an emerging descriptor of prognosis and is characterized by the accumulation of intra and intermyocellular lipids, which are associated with altered muscle function, insulin resistance, diabetes type 2 and obesity, as well as survival in critical illness [13▪▪,21,22,23▪]. Qualifying lean tissue or muscle mass in clinical populations is of increasing importance due to the emerging associations between low muscle quality with low muscle mass/size and poor functional status after discharge ICU [16▪▪]. In regard to nutritional support and early mobilization, research to date has shown inconsistent results in terms of muscle wasting and functional outcome [13▪▪]. Therefore, there is a need for valid and reliable measures of skeletal muscle mass, quality and metabolic phenotype. This is important because distinguishing true muscle weakness from poor motivation or inability to complete the task is challenging and use of manual muscle testing in the early stages of critical illness is limited [24]. Alterations in muscle composition, defined by a loss of muscle density and surface area measured by computed tomography (CT) in mechanically ventilated patients are independently associated with higher 6-month mortality in several different critically ill populations [19,25▪▪,26▪]. Intramuscular adipose tissue (IMAT) can also be derived from CT and MRI images and has been shown to correlate well with functional outcomes, physical fitness and mortality in the elderly population and patients undergoing major abdominal surgery [20▪,23▪,27▪,28▪]. Muscle protein breakdown measured from biopsies of the vastus lateralis muscle, and by reduction in rectus femoris muscle cross-sectional area and compromised skeletal muscle bioenergetic status have been observed during the first week of critical illness [13▪▪]. This breakdown is more severe in patients with multiorgan failure [13▪▪]. With the advent of high-resolution nuclear magnetic resonance spectroscopy and MRI, muscle quality can be assessed by quantification of lipid components (IMAT) in the muscle tissue [27▪]. These techniques have been extensively reported but are complicated and not without risk to the critically ill patient [29].

Ultrasound has also been used to assess muscle composition during health and disease [30]. It is cost-effective, noninvasive and sensitive to changes over time when compared with the other assessments such as muscle biopsy, CT or nuclear magnetic resonance/MRI [31▪–33▪].

Muscle wasting results in an increase of IMAT, fibrosis, myonecrosis and even effusion surrounding the fascicles [13▪▪]. Muscle with a high amount of intramuscular fat infiltration (IMAT) has a predominantly hyperechoic appearance, with only minor hypoechoic regions [34▪].

Equations intended to quantify and translate muscle echo intensity into percentage IMAT (%IMAT) of the rectus femoris muscle were introduced by Young *et al.* [35] through comparison of IMAT determined from T_1-weighted MRI image with ultrasound images of the rectus femoris muscle. More recently, these equations have been incorporated into an automated image analysis algorithm as part of MuscleSound (Denver, Colorado, USA) Technology. MuscleSound image analysis uses proprietary software to identify muscle and fat boundaries, and analyze muscle composition using the principles and calibration equations and algorithms outlined above [35]. The technology has been extensively used in healthy individuals, elite athletes and critically ill patients (see Fig. 1), in whom temporal changes in muscle composition, including intramuscular glycogen content, have been described and validated by muscle biopsies [36,37].

Increased IMAT combined with a decrease in muscle CSA (M_{CSA}) has been described previously during critical care admission [13▪▪]. Puthucheary *et al.* [13▪▪] found that intramuscular lipid accumulation, assessed by muscle biopsies, results in dysregulated lipid oxidation and reduced ATP bioavailability, which contributes to a compromised skeletal muscle bioenergetic status. Thus, the accumulation of intramuscular lipids (IMAT) during ICU stay combined with the decrease of M_{CSA} indicates a compromised skeletal muscle metabolic status and is synonymous with acute mitochondrial dysfunction and even perturbed regeneration [13▪▪,38]. Figure 2 shows the comparison between a CT scan at the level of L3 (with segmentation analyses) and the MuscleSound heatmap assessed from the rectus femoris muscle. IMAT derived from the MuscleSound IMAT algorithm compared with IMAT forms segmented CT analyses, correlated well. Intramuscular fat infiltration (IMAT) is therefore not an ad-hoc process but shows the systemic nature of muscle metabolic dysfunction.

Hypoxic and/or inflammatory stimuli, associated with critical illness, impairs muscle protein synthesis and replacement of the functional muscle tissue with IMAT due to reduced mitochondrial biogenesis [39▪]. The systemic inflammatory response gives rise to skeletal muscle wasting within 24 h upon admission ICU. Acute skeletal muscle wasting occurs early and rapidly defined as the reduction in mitochondrial beta-oxidation, mitochondrial biogenesis markers and intramuscular ATP content [13▪▪].

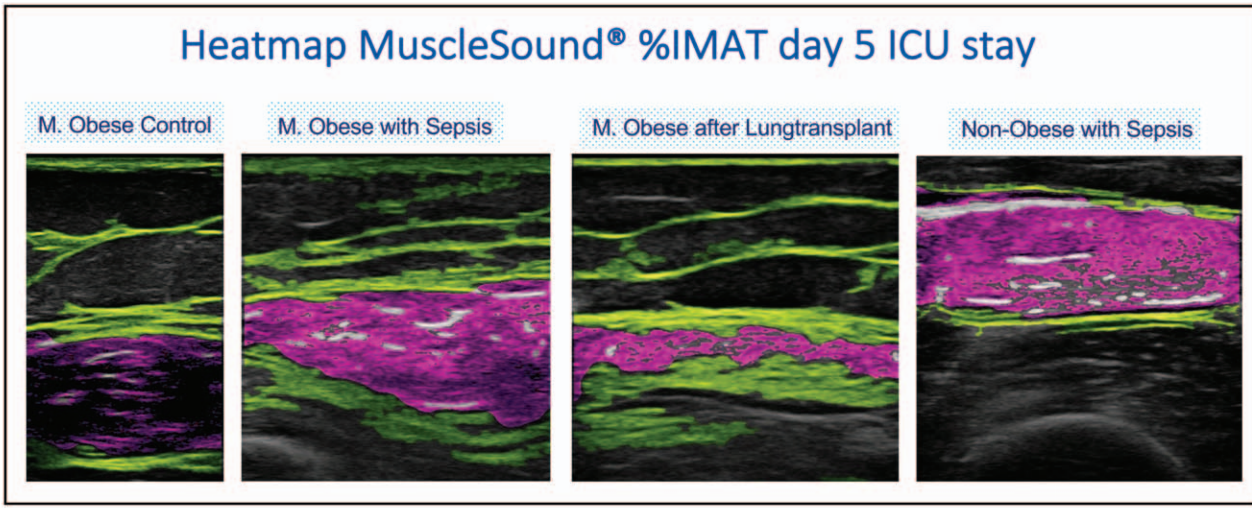

FIGURE 1. MuscleSound echo-intensity heatmap of the rectus femoris muscle, showing different stage of muscle wasting in a clinical population.

EXERCISE CAPACITY IN ICU PATIENTS AND SURVIVORS

The underlying mechanisms of ICU-AW are key to understanding the role for formal measurement of exercise capacity in ICU patients and survivors, as well as the prescription of nutritional and exercise support both in and out of the intensive care environment. A significant component of the observed reduced exercise tolerance after critical illness is likely to arise from acquired systemic mitochondrial dysfunction (the degree of and recovery of which appears to predict survival from multiorgan dysfunction) consequent to critical illness [40] (Fig. 3) . This acquired mitochondrial dysfunction urgently requires better description in translational and clinical models as a potential target for assessment and intervention.

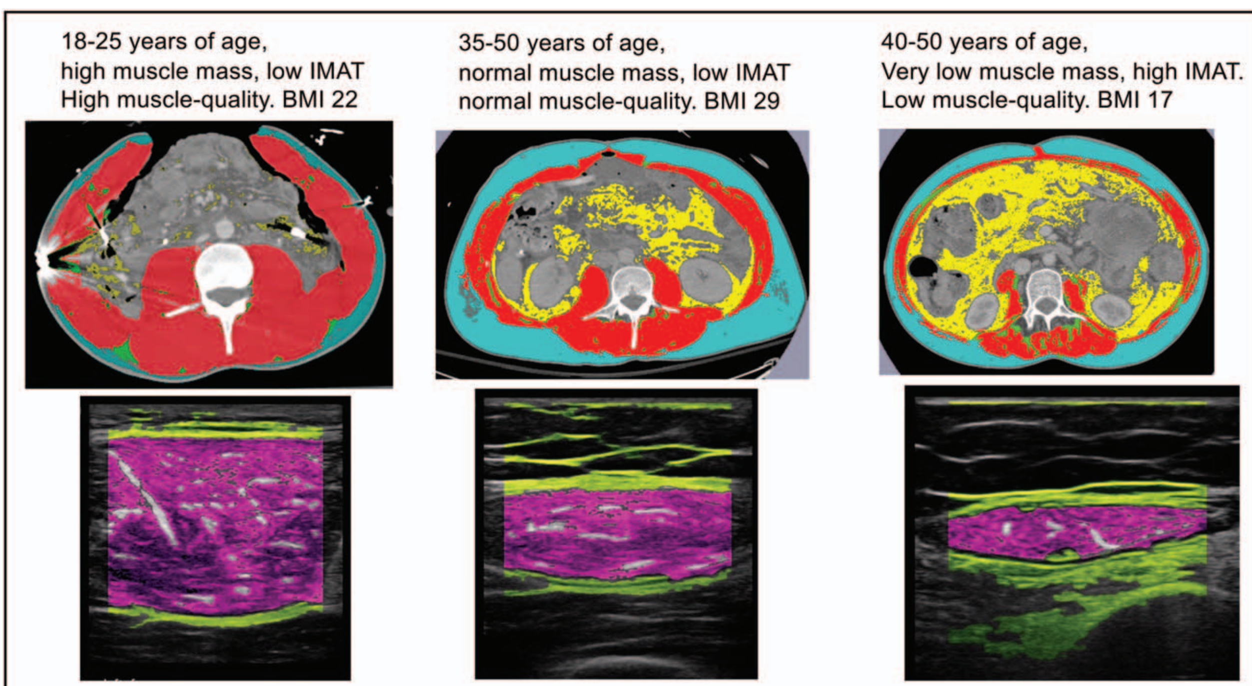

FIGURE 2. Segmented computed tomographic analysis at the level of L3; blue is the subcutaneous adipose tissue (SAT) layer, red is muscle, green is intramuscular adipose tissue (IMAT) and yellow is visceral adipose tissue (VAT). MuscleSound echo-intensity heatmap of the rectus femoris muscle. Reprinted from Wischmeyer, PE (2019) Objective Malnutrition Diagnosis and Personalised Nutrition Delivery in the ICU. ICU Management & Practice, 19(3):167:172.

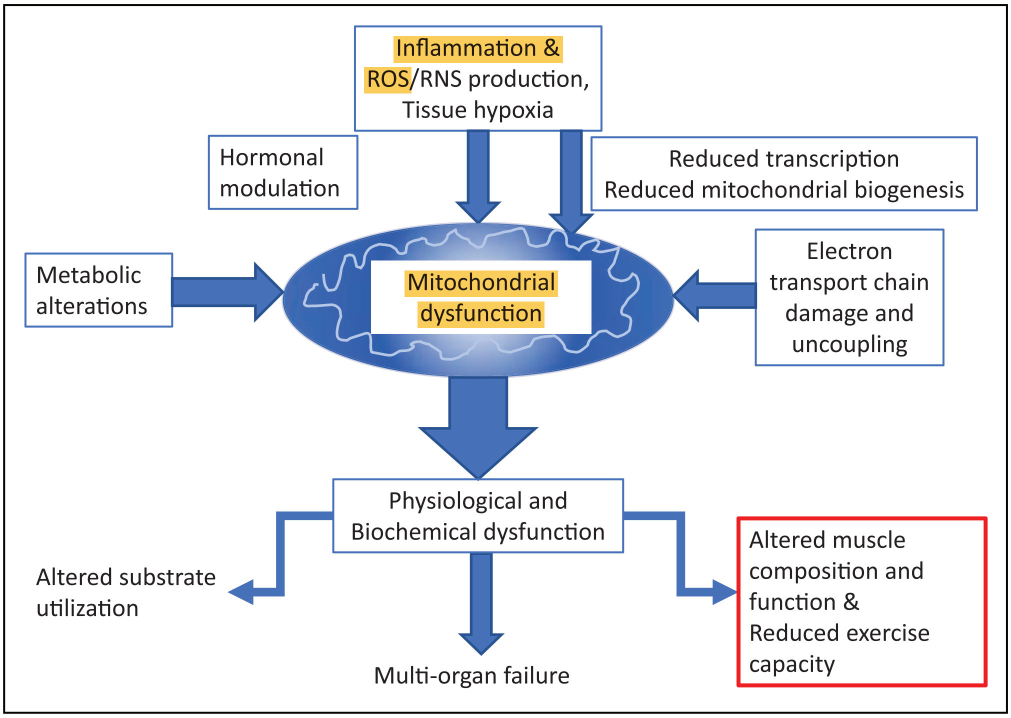

FIGURE 3. Central role of mitochondrial dysfunction in impaired physical and muscle recovery in critical illness.

In the majority of individuals, aerobic deconditioning, especially at its most severe, is consequent to reduced mitochondrial capacity rather than a failure of oxygen delivery [40,41]. This is in contrast to the limitation seen in athletes (and the established dogma), in whom oxygen delivery is the limiting factor. This reduced mitochondrial capacity (coupled with dysfunctional responses to stressors such as infection or surgery consequent to established comorbidity) has important implications for individuals, predominant amongst these being altered metabolic fuel usage in response to exercise.

Cardiopulmonary exercise testing as a tool to assess and guide intensive care rehabilitation

Cardiopulmonary exercise testing (CPET) is commonly used with established utility in the perioperative context to assess individual aerobic exercise capacity and increasingly as a tool to prescribe structured exercise prehabilitation with the goal of improving outcomes after major surgery [42]. Above and beyond other measures of physical capacity, such as the 6-min walk test, or questionnaires such as the Duke Activity Status Index, CPET provides multichannel, objective, rich cardiopulmonary and metabolic data that both allows the calculation of peak oxygen uptake, and also the causes, including the underlying pathophysiology, of decreased exercise capacity.

Taking into account the increasing body of literature that supports the concept that multimorbid deconditioned individuals are 'primed' to develop multiorgan pathophysiology, it is conceivable that CPET is in fact more of a test of mitochondrial function under physiological stress than of cardiopulmonary oxygen delivery capacity in most preoperative patients. This is the subject of ongoing research at Duke University in our ongoing and beyond.

Given the utility of CPET in preoperative assessment, especially in objective assessment of metabolic capacity and the consequent prescription of exercise training protocols 'matched' to known exercise physiology, and also the potential utility of CPET, coupled with muscle quality and resting metabolic assessments, in the assessment of metabolic capacity for the guidance of nutritional support in the perioperative period, it is highly likely that CPET will become a useful tool for the assessment of the critical illness survivor, providing invaluable data to help guide nutritional and exercise interventions in the post-intensive care rehabilitative period [43▪▪].

To date, few studies have been undertaken wherein formal exercise testing has been used during or after critical illness. Early work in the Netherlands has confirmed apparent safety and feasibility of CPET on bed-based cycle ergometer in critically ill patients [43▪▪]. Similarly, there is a paucity of data available for formal CPET assessment in the postintensive care period. In survivors of acute respiratory syndrome, the majority of patients assessed 3 months after hospital discharge display reduced exercise capacity, which cannot be explained by persistent impairment of pulmonary function [44]. Similarly, at around 1 month after discharge from hospital, general adult critical illness survivors demonstrate significant multifactorial exercise limitation, the underlying cause being described as general deconditioning (i.e. not ascribed to one organ system). In all studies, no significant adverse events were reported, despite the severe deconditioning of the patients assessed.

Cardiopulmonary exercise testing as part of an integrated pathway for metabolism support in intensive care

Critical illness is part of a health continuum. The physical condition of an individual, including their metabolic health (comprising aerobic fitness, metabolic fuel usage efficiency, body composition and nutritional status) and impacted/influenced by presence/absence of named comorbidity prior to the development of critical illness predicts the likelihood of development of critical illness, the likely course of said illness and the chances of death or delayed/impaired recovery including ongoing health needs.

In major surgery, wherein rich preoperative assessment is feasible, it is recommended that thorough physiological and nutritional assessment guide preoperative optimization efforts. This is conceived of as being only part of the patient's health journey through the perioperative period, wherein prehabilitation aims to improve functional resilience to the stress of surgical trauma, reducing the risk of functional decline below the threshold for dependence. Combined with muscle health and nutritional assessments, including metabolic cart measurements of caloric and metabolic substrate usage, an integrated optimization plan can be conceived of and initiated.

In general adult intensive care, the same approach can be taken with our critically ill patients in whom metabolic, nutritional and formal exercise capacity assessments can, and should form the cornerstone for ongoing objective assessment of and intervention in critical illness. These data will help assess stage of critical illness, recovery from illness and prescription of exercise intensity for effective training. Furthermore, the same assessments in the postintensive care period, just as conceived of in major surgery, can help guide ongoing interventions to create survivors and not victims from intensive care. Our proposed novel metabolic assessment and intervention pathways across all phases of critical illness to promote survivorship and optimal post-ICU muscle and physical recovery are summarized in Fig. 4.

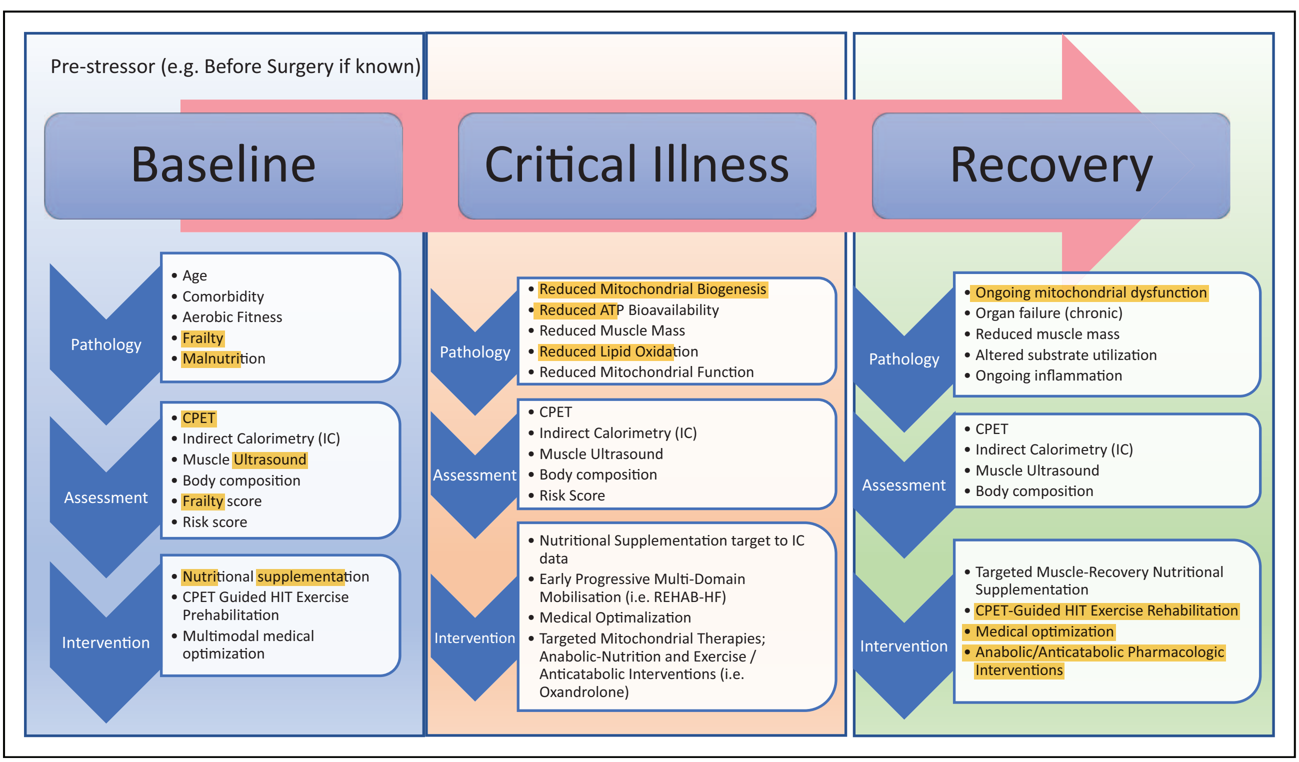

FIGURE 4. Proposed novel metabolic assessment and intervention pathways across all phases of critical illness to promote survivorship and optimal post-ICU muscle and physical recovery. (CPET, cardiopulmonary exercise testing; HIT, high-intensity training targeted to patients' abilities by CPET testing results.

Key role of early structured and progressive physical therapy

Patients surviving critical illness are at risk for persistent functional mobility impairments that significantly impact their QoL. Physical activity interventions that begin in the ICU are purported to mitigate the negative sequela of critical illness. For instance, the most recent systematic review with meta-analysis of 23 RCTs comprising 2308 patients concluded that early intervention may be associated with decreased incidence of ICU-acquired muscle weakness, improved functional mobility capacity and increased number of ventilator-free days and discharged-to-home rates. Unfortunately, rehabilitation did not significantly decrease ICU mortality, ICU length of stay and hospital length of stay and muscle strength were not significantly improved. The certainty of the evidence for these outcomes was 'very low'. Data on activities of daily living, return to work and delirium were not available in any of the trials. Rehabilitation of patients with sepsis might not decrease ICU mortality, but might improve QOL [45■■]. Unfortunately, most recent studies are demonstrating that current ICU rehabilitative strategies are failing to consistently improve outcomes [46■■]. Further, a majority of ICU patients are not being mobilized until day 9 or later and [8,47,48]. A large multisite point prevalence study showed that less than 20% of ICU patients were mobilized out of bed [49]. More troubling, the current standard of practice of delayed ICU rehabilitation has shown limited benefit on ICU-AW and QoL outcomes. Thus, the success of current ICU rehabilitation practice is tempered by the significant variations in frequency, duration, intensity and volume of intervention and heterogeneity in outcome assessments and timing of those assessments across the RCTs [45■■,50■■]. To address the latter limitation, the Physical Rehabilitation Core Outcomes In Critical illness (PRACTICE) study is using a modified Delphi consensus process with researcher, clinician and patient/caregiver stakeholders to develop a core outcome set for trials of physical rehabilitation interventions delivered across the continuum of a patient's recovery from the ICU until reintegration in the community following hospital discharge [51■■]. At the present time though, implementation of standardized interventions in the ICU or that span ICU to hospital floor remains low in clinical practice [51■■].

An intervention design that addresses multiple domains necessary for independent functional mobility, that is individually tailored with targeted milestones for progression, and that extends through the hospital stay has yet to be fully explored. A potential model of interest is that used in the REHAB-HF trial (clinicaltrails.gov NCT02196038), which implemented exercise across domains of strength, balance, mobility and endurance for heart failure patients with profound physical deficits paralleling those associated with critically illness [52■■]. Another design option includes incorporation of assistive rehabilitation technology. Some of these technologies can be used to complement functional mobility interventions, especially during periods wherein full voluntary and active participation is not possible, as occurs with sedation or profound weakness. For instance, cycle ergometry is gaining more attention given its capacity to provide passive or active movement with or without functional electrical stimulation (FES). Currently, three major funded trials of cycle ergometry are of high interest. eStimCycle, conducted in Australia and the USA across five centres, compares cycle ergometry with FES and routine rehabilitation to routine rehabilitation alone; recruitment is complete and results are pending (clinicaltrials.gov NCT02214823) [53]. Nutrition and Exercise in Critical Illness (NEXIS), conducted across four centres in the USA, compares cycle ergometry and amino acid supplementation with usual care; recruitment is in process (clinicaltrials.gov NCT03021902) [54■]. CYCLE: A Randomized Clinical Trial of Early In-bed Cycling for Mechanically Ventilated Patients, conducted in Canada, USA and Australia across 17 centres, compares cycle ergometry and routine rehabilitation care with routine rehabilitation care alone; recruitment is in process (clinicaltrials.gov NCT03471247) [55■]. Valuable lessons will be learned from these multicentre and international trials.

DISCUSSION

In short, as others have described in a recent elegant review of combining nutrition and exercise to optimize ICU recovery [56], the combination of nutrition and exercise is highly likely to be essential to optimize maintenance and recovery of muscle mass, strength and physical function in critical illness survivors. Currently, there are rapidly evolving technologies, many adapted from the domains of elite athletic performance and recovery that we believe provide unique opportunities for research and clinical programmes in the ICU of tomorrow's include techniques in common use by professional sports teams such as muscle-specific ultrasound for muscle mass/quality/glycogen measurement and CPET (CPET testing) that is routine now to guide training ability and goals even in amateur athletes. Why would the ICU patients we have invested so much of our time and energy as ICU providers (and a substantial fraction of many countries Gross Domestic Product) not deserve benefit from the study and use of these fundamental technologies? These technologies and exercise programmes will allow optimal evaluation of muscle mass/quality; muscle function; aerobic and mitochondrial function; and optimal structured multidomain progressive rehabilitative therapy to promote recovery of physical function in the ICU survivor. It is also essential we continue to evolve structure, multidomain ICU rehabilitation and exercise programmes that span the entire hospital stay of the ICU patient (such as that being studied in the REHAB-HF strategy described above). This is urgently needed for as stated in the recent key review of interventions for PICS article (Approaches to Addressing Post–Intensive Care Syndrome among Intensive Care Unit Survivors by the Addressing Post Intensive Care Syndrome (APICS-01) study team) 'Randomized controlled trials of physical rehabilitation interventions initiated several days after ICU admission have generally yielded no consistent evidence of benefit [46▪▪]'.

CONCLUSION

Thus, in conclusion, we must continue to look to other areas of medicine (i.e. heart failure, cancer) and to strategies employed by elite athletes for metabolic evaluation and rehabilitation if we hope to ultimately improve 'ICU Survivorship', address the impaired QoL in ICU survivors and overcome 'the defining challenge of critical care' for this century [9].

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Conflicts of interest

PEW serves as a consultant to Abbott, Fresenius, Baxter, Nutricia and Takeda for research related to nutrition in surgery and ICU care; received unrestricted gift donation for surgical and critical care nutrition research from Musclesound and Cosmed; received honoraria or travel expenses for CME lectures on improving nutrition care in surgery and critical care from Abbott, Baxter, Nutricia and Fresenius.

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