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Seven unconfirmed ideas to improve future ICU practice

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Abstract

With imprecise definitions, inexact measurement tools, and flawed study execution, our clinical science often lags behind bedside experience and simply documents what appear to be the apparent faults or validity of ongoing practices. These impressions are later confirmed, modified, or overturned by the results of the next trial. On the other hand, insights that stem from the intuitions of experienced clinicians, scientists and educators—while often neglected—help place current thinking into proper perspective and occasionally point the way toward formulating novel hypotheses that direct future research. Both streams of information and opinion contribute to progress. In this paper we present a wide-ranging set of unproven 'out of the mainstream' ideas of our FCCM faculty, each with a defensible rationale and holding clear implications for altering bedside management. Each proposition was designed deliberately to be provocative so as to raise awareness, stimulate new thinking and initiate lively dialog.

Keywords: Microcirculation, Resuscitation, Shock, Sepsis, Ventilator-induced lung injury, Personalized medicine, Melatonin, Adaptive clinical trials, Metabolic monitoring

Background

In our current era of evidence based medicine, empirical results of clinical trials are most highly valued as the foundation of our knowledge, while experience-based and eminence-based opinions, often published as commentaries, editorials, essays and letters, take a 'back seat'. Yet, some insights that stem from the intuitions of experienced clinicians, scientists and educators help place current thinking into proper perspective and point the way toward formulating the novel hypotheses that direct future investigative scientific efforts. In fact, while technical innovations, experimental observations and statistical meta-analyses often lead clinical practice, at other times the opposite is true; conflicting data from imperfect studies generate lingering confusion and doubt. With imprecise definitions, study executions and measurements, our clinical science often lags behind practical experience and simply documents what appear to be the faults or validity of ongoing practice. As we have experienced in recent decades, progress made with these blunt tools for advancing the care of the individual can be vexingly slow and inexact. Better study designs, targeted biomarkers, integrative as opposed to reductionist thinking and 'big data' capabilities hold genuine promise to personalize critical care—but clearly, we are not there yet.

In most meeting formats, faculty presenters rely on established principles and an examination of what has recently been published or confirmed to present their ideas. Debates and panel discussions either help bring about consensus (always comforting and sometimes dangerous) and/or highlight genuine differences of opinion. As in the prior two Future of Critical Care Medicine (FCCM) meetings, one of our sessions took a radical departure from those traditional approaches. What follows is a wide-ranging set of unproven 'out of the mainstream' ideas of our faculty, each with a defensible rationale and holding clear implications for altering bedside management. The intent of this provocative format was to stimulate thinking and interchange, and perhaps to point toward new directions for productive research, concept development, and eventual application to improved care for the critically ill.

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Daniel De Backer: Release tissue nitric oxide for improving microvascular perfusion

Background

Tissue perfusion can be altered even when cardiac output and arterial pressure remain within reasonable goals. Alterations in microvascular perfusion have been shown to occur in sepsis and septic shock [1], as well as in a variety of other conditions (cardiogenic shock, trauma, ischemia reperfusion injury, etc.). These are characterized by the close proximity of non-perfused vessels to perfused vessels, leading to microvascular shunting and increased oxygen diffusion distances. The severity and the duration of such microcirculatory disturbances relate to mortality and development of organ dysfunction [2]. Several mechanisms have been implicated in the development of these alterations, including loss of communication between vascular segments, impaired endothelial reactivity, alterations in red and white blood cell rheologies, alteration in endothelial glycocalyx, platelet aggregation and microthrombosis.

Given the characteristics of microvascular alterations and the mechanisms potentially implicated, it seems logical to try to recruit the microcirculation more than to increase the flow within the already perfused vessels. In addition, an ideal intervention should help reverse the implicated pathological mechanisms, not only improve microvascular perfusion.

Among the suggested interventions, certain vasodilatory agents have been proposed. Nitroglycerin was the first to be introduced. After initial promising results of a pilot trial including eight patients [3], a confirmatory randomized trial found no difference in the changes in microvascular perfusion between patients receiving nitroglycerin and placebo. Several factors may explain this negative result, including a potential decrease in nitric oxide (NO) generation from nitroglycerin, as it requires efficient aldehyde dehydrogenase type 2 that may be inhibited in sepsis [4].

Another point of attack is to exploit local release of NO at the microcirculatory level to promote targeted vasodilation. There are two known ways to boost NO at the endothelial level, one through endothelial NO synthase and the other through nitrite reduction.

For the first reaction (Arginine + O_2 => Citrullin + NO], oxygen and an effective endothelial NO synthase are required. Interestingly, endothelial NO synthase may be dysfunctional in sepsis or in ischemia/reperfusion injury, due to a decrease in one of its mandatory cofactors, tetrahydrobiopterin. In an ovine model of septic shock, administration of tetrahydrobiopterin improved microvascular perfusion, vascular permeability, organ function and survival time [5]. Similarly, administration of vitamin C, which increases tetrahydrobiopterin availability, also improves microvascular perfusion in sepsis, in a pathway that depends on endothelial NO synthase [6].

The second reaction converts nitrite into NO ($Hb[Fe^{2+}] + NO_2^- + H^+ => NO + Hb[Fe^{3+}] + OH^-$). This reaction is accelerated in the presence of deoxyhemoglobin, as opposed to oxyhemoglobin [7]. As a result, it mostly occurs in the microcirculation in the hypoperfused capillaries of metabolically active areas where oxygen saturation is low.

Idea

Administer nitrites with the hope that they could be converted into NO in the most vulnerable parts of the microcirculation.

Can Ince: Better resuscitation fluids for shock can be devised that improve perfusion, boost oxygen delivery and reduce inflammation

Background

Resuscitation from cardiocirculatory compromise is aimed at correcting decreased microcirculatory perfusion by improving blood flow and consequently sustaining tissue oxygenation. Shock is associated with a compromise in oxygen transport to the tissues, resulting in organ dysfunction. If left uncorrected this condition results in organ injury and, ultimately, in organ failure. The current approach to resuscitation is to target systemic perfusion by administration of vasoactive compounds and non-oxygen carrying salty solutions with or without larger colloid molecules to ensure a longer presence in the circulation.

The primary challenge in fluid therapy is to ensure that sufficient oxygen gets transported to the microcirculation and ultimately to the tissue cells. Here conventional fluids fail on two counts: The first shortcoming of conventional fluids is their hemorheological effect. Lower viscosity reduces the ability of the diluted blood to recruit unfilled capillaries (for which the viscosity of hematocrit is needed). This reduces the functional capillary density, creating larger diffusion distances between oxygen-carrying red blood cell-filled capillaries and the respiring cells of organ tissue. The second potential shortcoming of resuscitation fluids is their poor oxygen solubility (less than 3% compared to hemoglobin (Hb)), which decreases the oxygen carrying capacity of blood. Indeed, several experimental studies directly measuring microcirculatory oxygen availability following fluid resuscitation in models of shock have shown repeatedly that although fluids are capable of correcting systemic hemodynamic variables such as blood pressure and cardiac output, they can be ineffective in improving microcirculatory perfusion and tissue oxygenation in vulnerable organs such as the kidney. The only therapeutic modality to improve oxygen levels in the microcirculation is provided by blood transfusions [8]. However, there is much clinical reluctance to administer blood due its potential harmful side effects, such as the rise in free Hb and

the potential immunological response of the host to homologous blood transfusions.

An alternative to homologous blood transfusion is offered by Hb-based oxygen carriers (HBOCs), and many such compounds have been developed over the past decades. Experimentally these compounds have been shown to improve microcirculatory oxygen availability in models of shock [9]. Although conceptually appealing, their clinical introduction has been mired by problems. These include the vasopressor effect caused by their high affinity for NO, causing vasoconstriction. Different types of HBOCs have been developed with the aim of reducing this vasopressor effect, but these compounds have not shown clinical efficacy. The reason for this lack of success are several; a) at the bedside, there is an inadequate monitoring methodology to assess the need for tissue oxygenation to indicate the need for HBOCs over simply giving fluids; b) the p50s of HBOCs ranges from 5 mmHg (where oxygen will stay stuck to the Hb) to p50s in the range of that of natural Hb where oxygen can be easily lost and not reach the parenchymal cells in need of oxygen; c) inadequately designed clinical trials have generated little knowledge about when, how much and to what target.

From a different perspective, HBOCs conventionally have been administered as stand-alone drugs, whereas they could potentially be used as an adjunct to conventional fluid therapy to increase the oxygen-carrying capacity of volume therapy. Besides improving perfusion and oxygenation, resuscitation fluids should also be effective in reducing and controlling inflammation. In pursuit of this idea, investigations have been conducted to examine the potential anti-inflammatory and antioxidant effects of infused fluids (e.g., starches) as well as attaching molecules such as CO and glutathione to HBOC to control inflammation and oxidative stress [10].

From a therapeutic hemodynamic point of view, therefore, resuscitation requires reversal of shock, sepsis and hypovolemia. The first objective is to ensure microcirculatory and tissue perfusion; second, to restore perfusion is accompanied by a restoration of adequate tissue oxygen availability; and finally, to ensure that the cellular constituents of the microcirculation and parenchymal cells are protected from injury associated with the inflammatory molecules and oxidative and nitrosative stress associated with shock and reperfusion.

The two categories of resuscitation fluid in current use are blood and non-oxygen carrying crystalloid or colloid solutions. Each of these has been shown to have adverse effects due to composition and uncertainty about how to titrate these solutions under different conditions of hypovolemia and shock, where too much and too little are both considered harmful. As already mentioned, the ultimate target for administering the optimal volume resides in the microcirculation for which handheld microscopy could be a potential tool to optimally administer resuscitation [11]. However, fluid content needs also to be more personalized, matching the specific needs of individual patients.

In doing so, a broth of molecules must be configured that addresses the specific type of fluid needed to target the specific physiological compartment of the individual patient in need of resuscitation. The compartments which can be identified include intracellular, interstitial and intravascular. Intracellular hydration requires a crystalloid solution with glucose, whereas interstitial hydration needs any physiologic crystalloid solution. Intravascular hypovolemia is best addressed by a colloid solution to ensure sustained filling of the vasculature. Resuscitation fluid should ideally also carry anti-inflammatory and oxygen carrying agents to completely meet the goals of resuscitation.

When considering the ultimate composition of such an ideal resuscitation fluid, one is reminded of the beneficial effects of the chicken soup cure for common inflammatory conditions [12]. It carries nutrients, provides hydration, is isotonic (if you don't add salt of course) and is anti-inflammatory. Looking at chicken soup as a pharmacological agent for resuscitation, therefore, it seems like an ideal candidate. What is missing in chicken soup, however, is an oxygen-carrying agent such as a HBOC. Such a 'pink chicken soup' would hydrate, fill the vasculature (colloid effect), offer anti-inflammatory properties and promote the transport of oxygen to the tissues (the pink stuff).

Idea

A 'pink chicken soup' that addresses the deficiencies of our current options may indeed be a candidate for the optimal shock resuscitation fluid of the future.

John J. Marini: We should address the forgotten but crucial vascular side of ventilator-induced lung injury

Background

Although ventilator-induced lung injury (VILI) is undoubtedly a complex process that is influenced by many factors, the great majority of investigative attention has been directed to airspace mechanics, as exemplified by tidal volume, plateau pressure, PEEP and driving pressure. Yet, because the fragile alveolus serves as the interface between gas and blood, and because the stresses applied to the airway epithelium also impact vascular endothelium, the potential for vascular pressures and flows to impact the development and/or evolution of VILI also deserves close consideration.

Mechanical forces that tear the delicate alveolar-capillary membrane can originate on either side of the boundary. Adverse ventilatory patterns applied to

previously healthy lungs not only cause proteinaceous edema, but also neutrophil aggregation and hemorrhage [13]. In the supine position, hemorrhagic edema forms preferentially in dependent areas [14, 15]. This proclivity is not subtle, and has been corroborated by the work of investigators using diverse injury models [16]. The tendency for hemorrhage to occur preferentially in the most dependent regions of the lung may have several explanations. One compelling reason to expect microvascular disruption to occur there is that the mechanical stresses applied by the tidal inflation cycle are greatly amplified at the interface of opened and closed lung tissues. An admittedly oversimplified geometrical argument indicates that strains at high airway pressure are several times as great as that experienced in the free walls of the open alveolus.

It is somewhat counter-intuitive that tissue disruption should occur in areas in which transmural stretching forces (as defined by plateau pressure minus pleural pressure) are weakest. That is to say, "alveolar stretch" is greatest in the non-dependent regions, which are relatively spared both the hemorrhagic infiltrate and most signs of inflammation. The tendency for hemorrhage to occur preferentially in the most dependent regions of the lung may have several explanations. The local mechanical driving power [17] may far exceed that experienced in non-dependent zones. Although understudied, surfactant depletion and inflammatory weakening of the interstitial structure could amplify the impact of such forces, whereas other changes of the microenvironment (e.g., flooding by edema) could abrogate the mechanical stresses experienced in distal lung units.

Interactions between vascular pressure and ventilation suggest strongly that closer attention should be paid to interventions that impact vascular pressures, flows, and resistances when high inflation pressures are in use. Because microvascular stresses appear to be a potent cofactor in the development of pulmonary edema as well as lung damage resulting from an injurious pattern of ventilation, the clinician managing acute lung injury must reconcile the competing objectives of ensuring adequate oxygen delivery and minimizing adverse effects. If increased pre-alveolar microvascular pressure accentuates a tendency for VILI, attempts to raise cardiac output may have unintended consequences. On the other hand, taking steps to reduce oxygen consumption demands could benefit the lung by reducing the pressure gradient developed across the microvasculature. Reduction in the demands for cardiac output and ventilation could dramatically reduce the tendency for VILI even when using patterns that generate similar values for peak, end-expiratory, and driving alveolar pressures.

Idea

Restrain pulmonary vascular flows and pressures by lowering oxygen demand to further reduce the incidence and severity of VILI.

Mervyn Singer: Outcomes and therapeutic responses to ICU care can be predicted for septic patients

Background

Septic critically ill patients may be predestined to survive or die, perhaps explaining the failure of the many trials testing interventions to interrupt the natural course of sepsis. Indeed, we have not shown yet that we can "beat nature"; most progress over the past 20 years relates to inflicting less iatrogenic harm to the patient, not improving response and accelerating natural healing. If this analysis is correct, we inadvertently may simply prolong the course to death among those destined not to survive, at high personal and economic costs.

Using modern bioanalytical techniques, numerous studies have demonstrated the predictive potential of biomarkers, metabolomes, and proteomes to differentiate among eventual survivors and non-survivors of sepsis, even at a very early stage. Three interesting studies conducted from blood samples taken upon presentation to the emergency room have demonstrated that inflammatory cytokines (IL-6, IL-10) [18], cardiac troponin-T [19], and metabolomes characterizing fatty acid transport, gluconeoenesis, and the citric acid cycle [20] can point the way to the outcome that time would eventually reveal.

Similar prognostication regarding the likely response to treatment is also possible using both inflammatory biomarkers or physiological indicators. For example, stratification on the basis of inflammatory biomarkers may help direct immune modulatory therapy. Steroids given to septic animals predicted to die proved beneficial; steroids given to those projected to survive did not [21]. Reflections of these experimental observations were observed retrospectively using physiological parameters in the CORTICUS hydrocortisone trial [22]. Despite the increased risks of superinfection that the corticosteroids imposed, those septic patients with systolic blood pressures persisting below 90 mmHg after one day of appropriate fluids and vasopressors experienced a significant reduction of mortality risk if given hydrocortisone.

Another important controversy regarding pharmacotherapy of sepsis concerns the wisdom of beta blockade. In a randomized clinical trial, esmolol showed the distinct potential to reduce mortality risk, but only for patients who were both tachycardic and receiving high-dose norepinephrine therapy at 24 hours, reflecting a similar result as obtained with experimental sepsis in rats [23]. In rats with septic physiology, esmolol treatment appeared to

benefit animals predicted not to survive and to harm the predicted survivors.

Such examples show that using both physiological and molecular indicators may allow us to predict the eventual outcome of life-threatening sepsis at an early time point and thereby select our treatments more effectively. Such predictive ability would not only improve the design of our clinical trials, but also help to select therapies for the individual that hold the most potential for effective and humane care.

Idea

Predict potential survivors and non-survivors of sepsis causing critical illness at an early stage and treat these patient categories differently.

Frank Van Heren: Novel adaptive designs of clinical trials improve their efficiency and value

Background

In clinical research, randomization among alternatives is central to progress because associations and inferences from observational studies may not prove causative. Unfortunately, as currently conducted, our large randomized trials often conflict and generally have proven disappointing in the critical care setting [24]. The most likely explanations include imprecise definitions, inexact or inappropriate controls, and an inability to control or account for all influential variables, as important synergistic interactions produce emergent phenomena that are not accounted for in the trial design. Inability to recruit sufficient numbers of appropriate candidate patients over a reasonable time drags out the data collection process (often attenuating relevance to current practices) or terminates many such investigative efforts.

One innovative approach to randomized trial design is to depart from rigid one-to-one randomization and into adaptive allocation to the study limbs in accordance with relative response as the study progresses. Under this paradigm, if a subgroup starts to do better with one treatment, more future patients are allocated to that limb to confirm or refute that trend and accelerate the pace of the investigation. Frequent looks at the developing data are implicit when taking this approach.

The platform trial, an efficient strategy for simultaneously and sequentially evaluating numerous treatments within the framework of a single study, has been proposed by Berry and colleagues [25] as a tool with which to determine their relative worth among a heterogeneous population. This approach recognizes the imprecision of our current definitions and classifications, as it explicitly recognizes that targeted populations and treatment responses may be heterogeneous, even when careful measures are taken to be appropriately selective. Such a strategy departs from that of the traditional trial, which assumes itself to be testing the efficacy of a single intervention in a generally homogeneous population. A unique aspect of this particular "adaptive" approach is that the platform trial can be carried out over the long-term—even perpetually, so long as there are suitable treatments requiring evaluation. The number of treated groups or specific treatments may change over time, with specific individual treatment groups removed for demonstrated efficacy or harm. Such capability departs from our current "fixed randomization" approach in which the entire trial is stopped for success, futility, or harm based on the effects of a single experimental treatment. We must change our clinical trial paradigm so that we recognize current limitations. Should we embrace the principle that most major public health problems should be the subject of perpetual global adaptive trials?

Idea

Continuous and adaptive clinical trials with interchangeable parts should be the research standard.

Martin Westphal: Disruption of sleep patterns and circadian rhythms is an important and addressable cause of varied ICU morbidities

Background

Melatonin, a hormone produced in the pineal gland, is well-known to influence the state of wakefulness. It is synthesized and released under the regulation of the clock genes concentrated and expressed in the suprachiasmatic nucleus of the brain. Promoted by darkness, release of melatonin peaks during health in the early morning hours and plummets just before awakening. In the ICU, that natural diurnal rhythm is seriously disrupted by internal factors related to the critical illness as well as by external factors such as light, noise, continuously infused sedatives, stress, and varied medical treatments [26]. Disrupted sleep architecture and cumulative sleep deficits are contributors to lingering delirium [27], now thought to be a major contributor to delays in extubation and rehabilitation. Selected clinical trials have shown the ability of exogenously administered melatonin to help address these issues [28]. In concept, better sleep should speed recovery and help prevent the post-ICU syndrome.

Less well appreciated by intensive care unit practitioners is the intriguing body of research evidence indicating that melatonin may have other important roles to play during serious illness and recovery. The spectrum of melatonin's effects unrelated to sleep ranges from antioxidant properties to antimicrobial activity and immunomodulation [29]. Neuroprotective [30], antioxidant, infection inhibiting, and anti-neoplastic actions have been reported [29]. Given melatonin's central importance as a regulatory hormone, restoring its normal daily influence and timing of its concentration could make a major contribution to ICU care.

Melatonin plays a pivotal role in the regulation of circadian rhythm, not only for the brain, but for the activities of other vital organs as well. Virtually free of deleterious side effects, melatonin is inexpensive to administer and offers a variety of potentially beneficial actions. It should therefore be routinely used in both the acute and chronic phases of serious illness.

Idea

Melatonin should be administered to all critically ill patients able to receive it.

Paul Wischmeyer: Non-invasive metabolism monitoring aids in personalizing critical illness interventions

Background

Prediction, early intervention, and monitoring of progress are essential to personalize critical care management. Treatments and doses applicable to one stage or severity of critical illness may be inappropriate to apply at a later one. An important challenge is to monitor the patient's pre-illness, acute, chronic, and recovery stage and status by noninvasive means. Metabolic changes reflect breakdown, rebuilding, and innate cellular functioning during the illness course. One currently available methodology determines the relationship of two carbon isotopes in exhaled gas to determine stage and status: the $^{13}CO_2/^{12}CO_2$ ratio [31]. C^{12}, the far more common form in the healthy individual, is easier to break down than C^{13} for energy production, and C^{12} is freely exhaled as $^{12}CO_2$. In contrast, C^{13} is incorporated into acute phase proteins and is not exhaled at usual concentrations during the inflammatory state. Consequently, at the very onset of an acute inflammatory illness, the ratio of $^{13}CO_2/^{12}CO_2$ decreases in the exhaled gas [32]. In fact, detectable changes in the ratio *precede* the clinically detectable signs of infection. While individual point determinations of breath analyses do not correlate well with the inflammatory status, *trends* in the $^{13}CO_2/^{12}CO_2$ ratio clearly do.

In clinical studies, down-trending of the $^{13}CO_2/^{12}CO_2$ ratio in exhaled gas significantly precedes alterations in leukocytes, body temperature, and clinical suspicion of such developing infections, such as pneumonia. Conversely, reversal of the trend in the ratio indicates that inflammation is receding and that a stage transition is underway, perhaps indicating the emergence of different nutritional requirements. Such trend analyses appear to be both sensitive and specific. Other potential applications of the $^{13}CO_2/^{12}CO_2$ ratio monitoring include determination of underfeeding or overfeeding status.

Metabolism monitoring may hold therapeutic potential not only for the acute state but also for the rehabilitation phase [33]. It is known that healthy mitochondria primarily utilize fatty acids to produce energy. In conjunction with the other standard physiological and biochemical indicators, monitoring of fat oxidation rate versus carbohydrate oxidation rate may help characterize tissue vitality and rehabilitation progress, and thereby help shape targeted exercise/nutritional/hormonal programs to aid faster recovery from critical illness.

Idea

Metabolism monitoring should be used to diagnose infection, determine the phase of critical illness, and guide post-ICU rehabilitation.

Conclusion

The seven ideas presented here are intended to be conceptually provocative and are not yet grounded in definitive scientific evidence. Nonetheless, the authors hope that they provide points of departure for thought, discussion and future investigation.

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Critical Care

REVIEW Open Access

Critical illness and flat batteries

Mervyn Singer

Abstract

An exaggerated, dysregulated host response to insults such as infection (i.e. sepsis), trauma and ischaemia-reperfusion injury can result in multiple organ dysfunction and death. While the focus of research in this area has largely centred on inflammation and immunity, a crucial missing link is the precise identification of mechanisms at the organ level that cause this physiological-biochemical failure. Any hypothesis must reconcile this functional organ failure with minimal signs of cell death, availability of oxygen, and (often) minimal early local inflammatory cell infiltrate. These failed organs also retain the capacity to usually recover, even those that are poorly regenerative. A metabolic-bioenergetic shutdown, akin to hibernation or aestivation, is the most plausible explanation currently advanced. This shutdown appears driven by a perfect storm of compromised mitochondrial oxidative phosphorylation related to inhibition by excessive inflammatory mediators, direct oxidant stress, a tissue oxygen deficit in the unresuscitated phase, altered hormonal drive, and downregulation of genes encoding mitochondrial proteins. In addition, the efficiency of oxidative phosphorylation may be affected by a substrate shift towards fat metabolism and increased uncoupling. A lack of sufficient ATP provision to fuel normal metabolic processes will drive downregulation of metabolism, and thus cellular functionality. In turn, a decrease in metabolism will provide negative feedback to the mitochondrion, inducing a bioenergetic shutdown. Arguably, these processes may offer protection against a prolonged inflammatory hit by sparing the cell from initiation of death pathways, thereby explaining the lack of significant morphological change. A narrow line may exist between adaptation and maladaptation. This places a considerable challenge on any therapeutic modulation to provide benefit rather than harm.

Background

A wide range of insults, including infection, trauma, pancreatitis and ischaemia-reperfusion injury, can trigger a dysregulated host response that can lead, via a (likely) common pathway, to multi-organ failure and death. The top end of the pathway is reasonably well characterized [1, 2]. Innate immune receptors known as pattern recognition receptors (PRRs; e.g. Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs)) are activated either by microbial PAMPs ('pathogen-associated molecular patterns') or host cellular components known collectively as DAMPs ('damage-associated molecular patterns'). Examples of PAMPs include endotoxin, lipoteichoic acid and bacterial or viral DNA or RNA, while DAMPs (released during cell damage or death) include DNA, mitochondria, uric acid and heat shock proteins. Activation of PRRs increases transcription of a wide range of both pro- and anti-inflammatory cytokines and production of multiple other mediators such as the eicosanoids and reactive oxygen species, including nitric oxide. Apart from activating the immune response, hormonal, metabolic, bioenergetic and other pathways are also modulated in either positive or negative directions [1, 2].

The innate immune response has been the primary focus of research, particularly in relation to infection. However, much less attention has been paid to identification of mechanisms that result in organ dysfunction/failure, especially affecting those organs removed from the site of the insult. A series of clinical observations in both patients and animal models add further intrigue and complexity. The histology of these failed organs show minimal, if any, cell death, even when examined soon after the patient's demise [3]. In survivors, the failed organs usually recover sufficient functionality within days to weeks such that a long-term requirement for organ support is rarely needed [4]. This occurs even in organs with poor regenerative capacity. Furthermore, after adequate resuscitation, levels of tissue oxygen tension in various organ beds are normal or even elevated [5–8], indicating an availability of oxygen that meets or even exceeds cellular metabolic demands. These findings

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are all incompatible with the concept of tissue hypoxia resulting in ischaemic injury and cell damage as the predominant pathophysiological mechanism.

A paradigm is thus needed that can embrace this seemingly paradoxical combination of organ dysfunction occurring in the absence of significant structural damage yet provision of adequate oxygen. Cellular metabolic shutdown is a concept that satisfies these above observations. This shutdown is analogous to hibernation or aestivation where the normal functioning of the organism is lost as part of a process that preserves cell integrity though at the expense of functionality. Oxygen consumption falls in such situations in conjunction with a fall in metabolic rate. Patients with sepsis and trauma are 'hypermetabolic' in the early stages of the insult as the body initially fights to defend itself. However, with a prolonged insult there is a progressive reduction in oxygen consumption which, in severely affected patients, can fall to near-baseline levels for a healthy person [9, 10]. A rebound increase in metabolism occurs in the recovery phase, with metabolic rate rising > 50% above normal [9, 11].

Several mechanisms can potentially induce this metabolic shutdown. These may relate to a direct effect on metabolism with repurposing of metabolic pathways, and/or to secondary effects related to a progressive decrease in energy substrate (ATP) availability and a consequent metabolic shutdown. If metabolic processes continue without sufficient ATP to fuel them, cellular ATP levels will fall and, beyond a certain threshold, can trigger activation of cell death pathways. To avoid suicide the cell can attempt to compensate by switching off metabolic processes unconnected with survival that can maintain ATP levels above the critical threshold [12]. There is significant control over the rates of individual ATP consumers by energy supply [13]. The hierarchy consists of protein and RNA/DNA synthesis being the most sensitive to energy supply, followed by sodium and then calcium cycling across the plasma membrane, and mitochondrial proton leak being the least sensitive. In consequence, processes relating to the usual functionality of the cell, such as protein synthesis, can be downregulated or even abandoned. Conversely, pathways needed to maintain cellular integrity are retained, such as Na^+K^+ATPase activity that preserves membrane potential, transports substrates and electrolytes into and out of the cell and prevents cell swelling and lysis.

As mitochondrial respiration is primarily responsible in most cell types for provision of ATP, this organelle is likely integral to the process of metabolic shutdown through a reduction in energy availability. Several factors associated with a prolonged and/or severe stressful insult can trigger this shutdown, and these may be synergistic (Fig. 1). Such factors include:

1. *Prolonged inflammation with excessive production of mediators such as nitric oxide and other reactive species.* Mitochondria are the predominant source of reactive oxygen species (ROS) production in the body and, in health, play an important role in signalling. In excess, however, ROS have a direct inhibitory effect on mitochondrial respiration, either through direct inhibition of the electron transport chain or damage to the organelle when mitochondrial antioxidant defences are overwhelmed [14–17]. Routinely used treatments in the critically ill, such as bacteriocidal antibiotics [18], catecholamines [19] and sedatives [20], may also inhibit mitochondrial respiration.
2. *Tissue hypoxia, especially before adequate resuscitation.* This hypoxia is of insufficient magnitude to trigger cell death pathways yet severe enough to compromise normal functioning of the cells. Consequential to the ongoing oxygen debt, the cell responds by an adaptive compensatory reduction in metabolism to balance supply and demand. There are further corollaries of tissue hypoxia. As oxygen and nitric oxide compete for the same binding site on complex IV (cytochrome oxidase), the last component of the electron transport chain, a decrease in local oxygen concentration will enhance the inhibitory effect of nitric oxide described above [21].
3. *Mitochondrial respiration, which is modulated by various hormones and transcription factors.* Thyroid hormone, for example, has profound effects on ATP synthesis and turnover [22, 23]. It can also activate uncoupling of oxidative phosphorylation (see below); this mechanism may be responsible for some of its hypermetabolic effects. Complex relationships are reported between mechanisms of mitochondrial proton leak, production of reactive oxygen species and thyroid status. However, with prolonged and severe illness, there is decreased availability of active thyroid hormone (low T3 syndrome, sick euthyroid syndrome, non-thyroidal illness syndrome), the degree of which is prognostic [24]. This may impact on mitochondrial function and ATP turnover during critical illness.
4. *Decreased turnover of healthy, functional mitochondria (biogenesis).* Mitochondrial biogenesis must keep pace with mitophagy (processes that eliminate dysfunctional mitochondria) to maintain mitochondrial density. Several mechanisms may all conspire to decrease mitochondrial biogenesis in sepsis. In a pioneering study, Calvano and colleagues administered endotoxin to healthy volunteers and noted a generalized downregulation of gene transcripts encoding mitochondrial proteins, including those within the electron transport chain

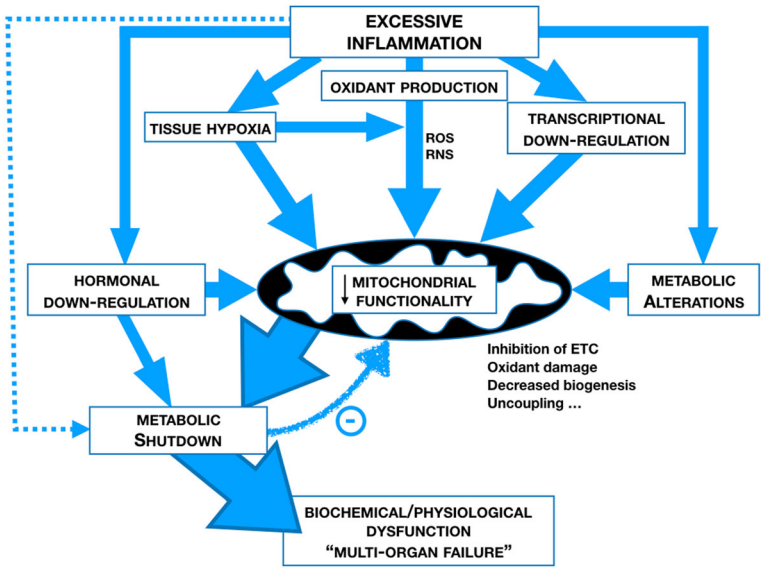

Fig. 1 Mechanisms of mitochondrial and metabolic shutdown. *ETC* electron transport chain, *RNS* reactive nitrogen species, *ROS* reactive oxygen species

[25]. Transcription factors such as PGC-1alpha, the 'master regulator' of biogenesis, is reduced in animal models of sepsis and in eventual human non-survivors [26, 27]. Of note, the reduction in mitochondrial turnover may be iatrogenically compounded by bacteriostatic antibiotic therapy that impacts negatively upon biogenesis through decreasing protein synthesis [28].

5. *Uncoupled respiration with production of heat rather than ATP.* Most of the oxygen used by the body is consumed by mitochondria, predominantly for generation of ATP—so-called 'coupled' respiration. A proportion is uncoupled, whereby the proton gradient created by electron transfer down the electron transport chain is dissipated, and the energy is 'lost' as heat [29]. The precise amount of oxygen utilised by uncoupled respiration is uncertain. Ex vivo studies in different rat tissues suggests this proton leak varies from 15% in heart to as high as 50% in skeletal muscle [29]. Whether this increases in sepsis and other critical illness is not yet established [30], although a recent study showed an increase in uncoupling protein-1 in white adipose tissue after human burn injury [31]. This may explain, at least in part, pyrexia, especially as other mechanisms of heat production, such as muscular activity and food breakdown, are reduced in a sick patient. However, two corollaries of increased uncoupling are a reduction in ATP for fuelling metabolism yet also a reduction in mitochondrial membrane potential that may decrease production of damaging ROS and thus offer protection [32, 33].

Circulating humoral factors likely play a role. Belikova et al. [34] studied the impact of peripheral blood mononuclear cells (PBMCs) incubated in healthy volunteer plasma or plasma pooled form septic patients. While overall oxygen consumption decreased by approximately a third, the proportion of respiration coupled to ATP production fell from 89 to 55%. Likewise, Boulos et al. found septic plasma had a depressant effect on endothelial cell oxygen consumption and ATP levels when incubated ex vivo, and this could be prevented by nitric oxide synthase inhibition [35].

The literature is, however, conflicted when analysing the presence of mitochondrial dysfunction in critical illness, especially with respect to animal models [36]. This disparity does not consider the impact of time or illness severity, nor inter-organ or inter-species differences. Short-term models often fail to show an effect, or even demonstrate increased activity, reflecting the need to use better representative models of the human condition [37].

It is feasible that the above changes represent an adaptive response to prolonged stress. The kidney is a useful exemplar organ to argue this case. Acute kidney injury and failure are commonplace in critical illness yet acute tubular necrosis is an unusual finding in both septic patients and animal models [38]. Indeed, awareness of this marked histological normality has been reported for critical illness in general for 60 years [39]. Forty years ago, Thurau and Boylan [40] argued that acute renal failure represented acute renal success; most of the workload of the kidney relates to reabsorption of approximately 98% of glomerular filtrate; sparing an ischaemic and/or stressed kidney with this heavily energy-dependent task of reabsorbing large volumes of salt and water is thus a

logical means of offering protection. Short-term shutdown translates into an ability to recover function in those who survive their critical illness.

There are many biological equivalents (torpor, dormancy, aestivation, hibernation) where metabolism switches off within hours in the face of an extreme and prolonged stress such as cold, heat, food shortage or drought. An approximate 40–70% of the decrease in metabolic rate is considered due to active metabolic suppression, with the remainder related to passive thermal effects as core temperature falls [41]. The dormouse can drop its core temperature to ambient and its metabolic rate by 90% within 3 h [42]. Mitochondrial respiration is suppressed and this occurs quickly during entrance into torpor when body temperature is still high. The rapidity of this response may reflect epigenetic modifications of mitochondrial electron transport chain complex activity, e.g. by phosphorylation or acetylation.

Another potential mechanism of metabolic suppression in sepsis may relate to inhibition of mitochondrial activity through increased production of the endogenous gases nitric oxide, carbon monoxide and hydrogen sulphide. This production can happen rapidly, within minutes to hours. We reported rapid falls in core temperature in septic mice given a faecal peritonitis insult, especially in eventual non-survivors [43]. Within 6 h the core temperature had fallen by 8 °C. Oxygen consumption fell by 38% within 2 h, and by 80% at 22 h. Conversely, in septic rats, temperature and oxygen consumption were initially maintained, although a pre-terminal fall in oxygen consumption was routinely seen commencing 6–8 h before death. It is conceivable that the maintained oxygen consumption in rats as well as humans is reprioritised towards heat production in sepsis, generating pyrexia but at the expense of fuelling normal processes. Of note, histological and biochemical changes analogous to those seen in hibernation have been described in septic mouse myocardium [44]. Myocardial hibernation is well recognized in humans in ischaemic hearts where persisting hypoperfusion results in decreased myocardial contractility to match substrate supply, but which recovers on reperfusion. The parallels between hibernation-like states in animals with critical illness in humans are striking and potentially translatable [45]. The underlying mechanisms are not necessarily duplicated as evolutionary pressures may have determined upregulation of different pathways. However, as Boutillier commented, "the key to (cell) survival (in hypoxia and hypothermia) lies in an inherent ability to downregulate cellular metabolic rate to new hypometabolic steady states in a way that balances the ATP demand and ATP supply pathways" [46]. A major challenge in patient management is to recognize when our efforts to intervene, which are often predicated on trying to achieve 'normality' of physiological and biochemical values, are counter-productive to the body's attempts to adapt and, ultimately, injurious.

Recovery from organ dysfunction is preceded by evidence of increased mitochondrial biogenesis in both long-term animal models [26] and patients [27]. This may simply be epiphenomenal; interventional studies demonstrating improved survival rates or faster resolution of organ failure through stimulation of biogenesis are still lacking. Nevertheless, recovery in human sepsis and trauma is associated with marked increases in metabolic rate as the body switches back to anabolism and repair processes [9, 11]. A failure to thrive—leading to a persistent inflammation, immunosuppression and catabolism syndrome (PICS) [47]—may potentially be caused by an ongoing failure of mitochondrial/metabolic recovery.

In conclusion, while pathways leading to inflammation and immune activation/suppression have been extensively studied in sepsis, the precise mechanisms underlying multi-organ failure remain unknown. Circumstantial evidence strongly points to a metabolic shutdown triggered by a failure of mitochondrial ATP generation and/or cellular reprioritisation of energy utilisation. Targeted modulation of these processes has yet to show improved outcomes but the concept is appealing [12, 45]. Nevertheless, timing is likely to be critical as the body may object to metabolism being driven up prematurely [48].

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Critical Care

REVIEW Open Access

The coming era of precision medicine for intensive care

Jean-Louis Vincent

Abstract

Recent advances in technology and better understanding of mechanisms underlying disease are beginning to enable us to better characterize critically ill patients. Instead of using nonspecific syndromic groupings, such as sepsis or acute respiratory distress syndrome, we can now classify individual patients according to various specific characteristics, such as immune status. This "personalized" medicine approach will enable us to distinguish patients who have similar clinical presentations but different cellular and molecular responses that will influence their need for and responses (both negative and positive) to specific treatments. Treatments will be able to be chosen more accurately for each patient, resulting in more rapid institution of appropriate, effective therapy. We will also increasingly be able to conduct trials in groups of patients specifically selected as being most likely to respond to the intervention in question. This has already begun with, for example, some new interventions being tested only in patients with coagulopathy or immunosuppressive patterns. Ultimately, as we embrace this era of precision medicine, we may be able to offer precision therapies specifically designed to target the molecular set-up of an individual patient, as has begun to be done in cancer therapeutics.

Background

Intensive care medicine is still a relatively young specialty but in its short lifetime has evolved rapidly with huge advances in technology and understanding of disease pathogenesis and processes. However, progress in therapeutics has been much less obvious. The fact that for decades we have enrolled heterogeneous, poorly characterized patient groups into our clinical trials goes a long way to explaining why we still have no new therapies, notably for sepsis; the sepsis response is so complex and personal that no single agent will be effective in all patients with sepsis. Now, as a result of advances in technology, greater comprehension of disease pathogenesis and pathophysiology, new understanding of biochemical and hematological data, novel genomic, proteomic, and metabolomic techniques, and improved data mining and computational modeling, we have begun to be able to characterize critically ill patients more precisely, moving beyond the global nonspecific syndromic groupings of the past (e.g., "systemic inflammatory response syndrome (SIRS)", "sepsis", "acute respiratory distress syndrome (ARDS)") to more detailed classification and characterization at an individual patient level. This approach will enable us to determine on a more personal level which treatments will be best adapted to each patient, thus maximizing his/her chances of survival.

From "poorly characterized" to "personalized" medicine

Although patients are individuals, traditionally we have tended to "label" them according to their disease or condition and often treated them accordingly, using similar interventions and therapies for all patients with the same "diagnosis". Indeed, this has been one of the key problems with randomized controlled trials in critically ill patients—particularly those with sepsis—in which interventions have been tested in poorly characterized groups of patients believed to be similar because they meet a specific definition or have a specific diagnosis, but in fact varying markedly at an individual level with different infecting organisms, durations of disease, degrees of immune response, comorbidities, and so forth [1–3]. The results of such trials have not surprisingly been mostly negative. However, for many of these studies that showed no overall efficacy on outcome, later analyses suggested that the intervention may have been effective

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in specific subgroups of patients. For example, Man et al. [4] used whole genome amplification on samples from patients in the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study [5] and identified genetic biomarkers that identified subgroups of patients with a greater response to drotrecogin alfa (activated). Similarly, Shakoory et al. [6] recently analyzed data from a randomized controlled trial of an interleukin (IL)-1 receptor antagonist that had shown no overall effect on outcome and identified a subgroup of patients with so-called macrophage activation syndrome (sepsis plus hepatobiliary dysfunction/disseminated intravascular coagulation) in which the mortality rate was significantly reduced with the intervention compared to placebo (hazard ratio for death 0.28 (95% confidence interval 0.11–0.71); $p = 0.0071$). Being able to better characterize patients will enable us to identify such subgroups, enabling interventions to be tested in more targeted populations and treatments to be personalized to a much greater extent than is currently possible.

Physicians have always characterized patients to some degree, using physical signs and physiological variables (e.g., blood pressure, heart rate, or blood glucose concentration) to diagnose and adjust aspects of management. However, these are very global measures and additional, more specific markers are needed to clearly distinguish one individual from another. Over the years, multiple biomarkers have been proposed for this purpose for various critical illness conditions, including sepsis [7], ARDS [8], and acute kidney injury [9]. However, no biomarker has been found to be adequate in terms of specificity. Indeed, individual biomarkers may be inadequate to represent these complex conditions and combinations or panels of biomarkers may be more effective. For example, Gibot et al. [10] reported that a combined score of procalcitonin (PCT), soluble triggering receptor expressed on myeloid cells (sTREM-1), and the polymorphonuclear CD64 index diagnosed sepsis better than did any of the individual biomarkers. Ware et al. [11] showed that a panel of five biomarkers for ARDS (surfactant protein-D (SP-D), receptor for advanced glycation end-products (RAGE), IL-8, club cell secretory protein (CC-16), and IL-6) could predict a diagnosis of ARDS in patients with sepsis with an AUC of 0.75. However, which biomarkers should be included in such panels remains unclear, especially as the inflammatory markers present likely vary at different time points during the disease; cost and availability are also important concerns.

Advances in genomic, proteomic, and metabolomic technology and application of these techniques to large datasets using sophisticated statistical modeling and analysis are facilitating the move toward more accurate and precise patient diagnosis and characterization. For example, Langley et al. [12] analyzed metabolomic and transcriptomic datasets from primates with *Escherichia coli* sepsis and identified a four-metabolite panel that was able to diagnose sepsis in two human cohorts with AUCs of 0.78 and 0.82, respectively. McHugh et al. [13] identified a microarray of four RNA biomarkers that predicted the presence of sepsis with an AUC of 0.88 and discriminated sepsis from infection-negative systemic inflammation better than all other tested clinical and laboratory parameters. Calfee et al. [14], using latent class data analysis, identified two subphenotypes of patients with ARDS, one of which was characterized by higher plasma concentrations of inflammatory biomarkers, greater vasopressor use, lower serum bicarbonate concentrations, and a higher prevalence of sepsis; these patients had worse outcomes and different responses to ventilator management strategies. Davenport et al. similarly identified two subphenotypes of patients with community-acquired pneumonia using a sophisticated genomic analysis. Patients with a type 1 sepsis response signature (SRS) profile had an immunosuppressed phenotype, with endotoxin tolerance, T-cell exhaustion, and HLA class II downregulation, and had higher 14-day mortality than patients with the type 2 SRS profile [15]. In children with septic shock, using whole-genome expression profiling, Wong et al. [16] identified two subphenotypes of septic shock based on a 100-gene expression signature; one of these subgroups was found to have increased mortality when prescribed corticosteroids, supporting the potential use of personalized medicine in guiding individual therapeutic decisions.

Challenges for the coming era

We are thus moving rapidly into an era where we will be able to "personalize" treatments for individual patients [17]. But the next step, to "precision" molecular-based targeting of treatments, is much further away. Indeed, critical illness is very different to the areas in which precision medicine has made a large impact, notably oncology in which therapies are now increasingly guided by the molecular and genomic features of a tumor in a specific patient. Most oncology patients will have one tumor that can be identified and clearly characterized, enabling the most appropriate treatment to be started. Most critically ill patients have more complex, heterogeneous disease with multiple comorbidities and conditions that can impact on outcomes and response to treatment, making it difficult to identify a single target. Moreover, although tumors progress and evolve over time and treatments may need to be adapted accordingly, in general such alterations are relatively slow compared to the very rapid changes that can occur in critically ill patients. Any tests to characterize or phenotype patients therefore need to be rapidly available and repeatable. This is just one of

the many challenges as we move toward personalized, and perhaps later "precision", medicine. Here I list just a few more that I see as of key importance—there are many others.

First, there is an urgent need for international collaboration among researchers and industry to ensure standardization of measurements and reporting so that the vast amounts of data that are being generated can be compared and used together for analysis. Ideally data should be input using similar structures and systems so that they can be combined easily into single datasets and shared among all players. Increasingly, in addition to physiological and other healthcare data, "omics" data need to be routinely monitored and recorded [18]. Problems of storage for the huge databases that will be generated will need to be overcome, as will ethical issues related to patient privacy and consent.

A second challenge will be to work out how exactly the ability to characterize and subphenotype patients at a research level can be moved into the clinical arena to improve patient outcomes. Being able to better characterize patients is already being used to more carefully select for clinical trials those patients who are most likely to respond to the treatment being studied. For example, a study comparing the immunostimulating drug granulocyte–macrophage colony-stimulating factor (GM-CSF) with placebo is currently ongoing, enrolling only patients know to be immunodepressed based on their human leukocyte antigen (HLA)-DR level (ClinicalTrials.gov NCT02361528). Pharmacogenomics is widely used in some cancer therapies, but has not yet been widely studied in the ICU, partly because genomic testing is not yet available sufficiently rapidly for use in the acute critical illness situation [19]. However, genetic variations and polymorphisms have been shown to influence the response and adverse effects of several drugs relevant to the critically ill population, including morphine, dexmedetomidine, vasopressin, and catecholamines [20]. Ultimately, it is hoped that the large databases of patient information currently being collected will be used to create so-called SuperModels [21]. By inputting the present patient's data and comparing them with the datasets already in the system, a simulated computational/mathematical model of the likely risks and therapeutic responses for that patient will be built, enabling precise preventive and/or therapeutic treatment to be given. Importantly, these complex models will need to be able to capture and predict the temporal and dynamic variability of critical illness [22]. Continuing data input into intelligent models will enable increasingly precise models to be developed, facilitating the translation to clinical reality.

The economic challenge of personalized medicine is unknown and impossible to predict. Although the costs of genomic analyses are currently high, prices will fall as these tests are more widely used and available. New drug development is expensive, but the improved knowledge of the underlying molecular mechanisms of disease provided by the advances discussed and the ability to more accurately target those patients most likely to respond to a new therapy may make drug development more efficient, thus potentially reducing costs. Precise knowledge of the most appropriate therapy for each patient and better preventive therapy will reduce unnecessary therapies and costly adverse drug reactions. Although costs are thus likely to be increased in the initial years, this is expected to be balanced by more accurate and efficient patient management.

Conclusion

The personalized medicine approach encourages us to develop a more singular approach to patients, treating each individual according to their specific history, characteristics, and ongoing needs. Treatment prescriptions will be (are already being) more accurately targeted at each individual's specific phenotype, resulting in more effective therapy and improved outcomes. Treating individuals rather than diseases will necessitate a paradigm change in our approach to diagnosis *and* management. Clinicians, researchers, and industry must all work ogether to embrace the promises and potential of this exciting new era.

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Critical Care

REVIEW Open Access

Tailoring nutrition therapy to illness and recovery

Paul E. Wischmeyer

Abstract

Without doubt, in medicine as in life, one size does not fit all. We do not administer the same drug or dose to every patient at all times, so why then would we live under the illusion that we should give the same nutrition at all times in the continuum of critical illness? We have long lived under the assumption that critical illness and trauma lead to a consistent early increase in metabolic/caloric need, the so-called "hypermetabolism" of critical illness. What if this is incorrect? Recent data indicate that early underfeeding of calories (trophic feeding) may have benefits and may require consideration in well-nourished patients. However, we must confront the reality that currently ICU nutrition delivery worldwide is actually leading to "starvation" of our patients and is likely a major contributor to poor long-term quality of life outcomes. To begin to ascertain the actual calorie and protein delivery required for optimal ICU recovery, an understanding of "starvation" and recovery from starvation and lean body mass (LBM) loss is needed. To begin to answer this question, we must look to the landmark Minnesota Starvation Study from 1945. This trial defines much of the world's knowledge about starvation, and most importantly what is required for recovery from starvation and massive LBM loss as occurs in the ICU. Recent and historic data indicate that critical illness is characterized by early massive catabolism, LBM loss, and escalating hypermetabolism that can persist for months or years. Early enteral nutrition during the acute phase should attempt to correct micronutrient/vitamin deficiencies, deliver adequate protein, and moderate nonprotein calories in well-nourished patients, as in the acute phase they are capable of generating significant endogenous energy. Post resuscitation, increasing protein (1.5–2.0 g/kg/day) and calories are needed to attenuate LBM loss and promote recovery. Malnutrition screening is essential and parenteral nutrition can be safely added following resuscitation when enteral nutrition is failing based on pre-illness malnutrition and LBM status. Following the ICU stay, significant protein/calorie delivery for months or years is required to facilitate functional and LBM recovery, with high-protein oral supplements being essential to achieve adequate nutrition.

Keywords: Protein, Lean body mass, Muscle, Calories, Critical care, ICU, Quality of life, Recovery, Malnutrition

Background

"One size does not fit all"

Without doubt, in medicine as in life, one size does not fit all. We do not administer the same drug or dose of drug to every patient at all times, so why would we live under the illusion that we should give the same nutrition or amount of nutrition at all times? We have long lived under the assumption that critical illness and trauma lead to a consistent early increase in metabolic/caloric need, the so-called early "hypermetabolism" of critical illness and injury. What if this is, and has always been, incorrect? Further, recent data have indicated that early hypocaloric feeding (so-called trophic feeding) may be superior [1, 2]. Could there be some truth to this? Or is the reality that our current ICU feeding practice around the world is actually leading to "starvation" of our patients and is a major contributor to poor long-term quality of life (QoL) outcomes [3]?

Before we can discuss the actual calorie and protein needs of ill and injured patients, what constitutes "starvation-level" nutrition delivery? The reality is, very limited data exist on what constitutes starvation and calorie/protein deprivation, even in healthy individuals. However, one landmark study that very few of us in medicine are ever taught (or even told about) defines much of the world's knowledge about starvation, and most importantly what is required for recovery from starvation and massive lean body mass (LBM) loss, as

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commonly occurs in the ICU. This is not a new study, the reality is it was completed > 70 years ago and will almost assuredly never be repeated.

"The Minnesota Starvation Study—The Most Important and Daring Nutrition Trial Ever Conducted?"

In 1944, as World War II began to draw to a close, many in the USA and around the world began to recognize that the greatest threat to the survival of the world's population, both for the remainder of the war and after, was not bombs and bullets, but hunger! The war had left hundreds of thousands starving in Europe and Asia, and rebuilding these nations would not be possible with much of the world suffering from a lack of basic nutrition. US soldiers entering liberated European cities found emaciated, cachectic, and starved civilians surviving on meager portions of potatoes, bread, and little more. At that time, very little knowledge existed about the fundamental nutritional needs in humans. Thus, the USA and other nations wishing to support relief efforts worldwide realized a greater understanding of how to deal with refeeding and the nutrition delivery required to recover from severe starvation was desperately needed. How else would nations supplying the life-saving food relief know how much was needed to ensure recovery?

As a result, Dr Ansel Keys, a young physiology professor at the University of Minnesota and a consultant to the War Department, set out to assess how civilians would be affected physiologically and psychologically by such a limited diet and what would be the most effective way to provide postwar "nutritional rehabilitation" [4]. As a result, he and a small group of scientists conceived one of the most ambitious and important human clinical trials in history— the "Minnesota Starvation Study" [5]. (For further details, see the excellent summary by Kalm and Semba [6]).

As the US involvement in World War II grew, many young men (and women) enlisted in the military. However, due to religious beliefs, morals, or conscience some chose not to fight. These individuals became known as conscientious objectors (COs)—COs were commonly sent to do menial jobs like building roads, forestry work, and other peaceful homeland contributions. However, in 1944 Keys gave a few heroic COs a chance to contribute in a legendary way. Keys obtained approval from the War Department to find healthy men from the 12,000 COs registered across the country. The men had responded to a recruitment brochure that asked: "Will You Starve That They Be Better Fed?" (Fig. 1). Within months Keys received > 400 positive responses and 100 men were brought in for interviews and screening physical examinations. After extensive screening and explanation of the trial, 36 subjects were selected for the study.

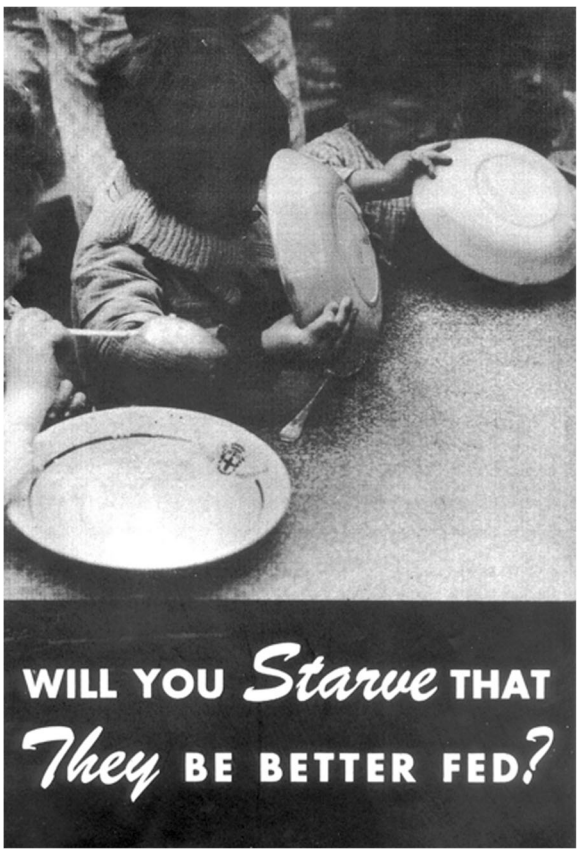

Fig. 1 Minnesota Starvation Study recruitment brochure from May 27, 1944. Adapted from [6]

As with most great scientific and medical endeavors, this experiment was jointly funded by the government (Office of the Surgeon General), foundational support (from religious groups including Mennonites, Brethren, Quakers, and Unitarians), and private industry funding. Thus, on November 19, 1944, 36 healthy young men entered the brick confines of the Laboratory of Physiological Hygiene, located in the South Tower of the football stadium at the University of Minnesota. The laboratory also served as their dormitory, and the windowless rooms of the laboratory were often referred to by Keys as "our cage" [5].

The "experiment" consisted of a 3-month baseline period in which subjects received 3200 kcal/day and participated in regular physical activity. Extensive physiologic, cognitive, intelligence, and laboratory testing was conducted throughout the experiment. A 6-month "semi-starvation" period, beginning on February 12, 1945, delivered a "starvation diet" of on average 1800 kcal of food/day with 0.7–0.9 g/kg/day of protein—considered a "low protein diet". During the semi-starvation period, subjects initially consumed an average of 23 kcal/kg/day with a protein intake of 0.7 g/kg/

day, with a plan for the subjects to lose ~ 25% of their body weight (~1.0 kg/week) by the end of the study period. Although the absolute amount of energy and protein consumption was fairly constant during the semi-starvation period, weight loss was occurring too rapidly in many subjects and by the end of the study the average intake per kilogram had increased to 30 kcal/kg/day and 0.9 g protein/kg/day, with significant starvation persisting at these energy delivery levels. The starvation diet was created to consist of foods reflecting the diet experienced in the war-torn areas of Europe (i.e., potatoes, turnips, rutabagas, bread, etc.).

The effects of the semi-starvation diet were quick and striking. Men in the study lost weight rapidly and all men developed significant edema from protein malnutrition. Subjects rapidly demonstrated a remarkable decline in strength and energy. Keys recorded a 21% reduction in their strength, as measured by performance on a back-lift dynamometer. All subjects complained that they felt old and constantly fatigued. Significant depression, anxiety, neurologic deficits, and loss of interest in sex occurred. Men become obsessed with food and cheating on the diet became an issue. Thus Keys began a buddy system to improve compliance in which no one was allowed out alone ("buddy system"). The stress proved too much for one of the men, 24-year-old subject Franklin Watkins (as described online: http://www.madsciencemuseum.com/msm/pl/great_starvation_experiment). He began having vivid, disturbing dreams of cannibalism in which he would consume the flesh of an old man. On trips into town, before the buddy system had been implemented, he was known to cheat extravagantly on the starvation diet, downing milkshakes and ice cream. Finally, Keys confronted him, and Watkins broke down crying. Watkins then became agitated and threatened to kill Keys and take his own life. Keys immediately dismissed Watkins from the study and had him admitted to the psychiatric ward of the university hospital. There, after a just a few days on a normal diet, Watkins' cognition and mood fully normalized, and he was released from the hospital. Strikingly, Watkins' breakdown occurred just a few weeks into the starvation phase of the experiment. This study received a great deal of national attention, including a prominent depiction in *Life* magazine in July 1945 (Fig. 2).

By the end of the 6-month starvation period, the men had lost almost a quarter of their weight, dropping from an average of 152.7 lb (70 kg) down to 115.6 lb (52 kg). The average heart rates of the subjects slowed dramatically, from an average of 55 to 35 beats per minute. Their blood volume dropped 10%, and their hearts shrank in size. The last day of the starvation period (July 28, 1945) was met with great enthusiasm and anticipation by the men.

However, July 29, 1945, did not prove to be the reprieve they had anticipated. The final 3 months of the

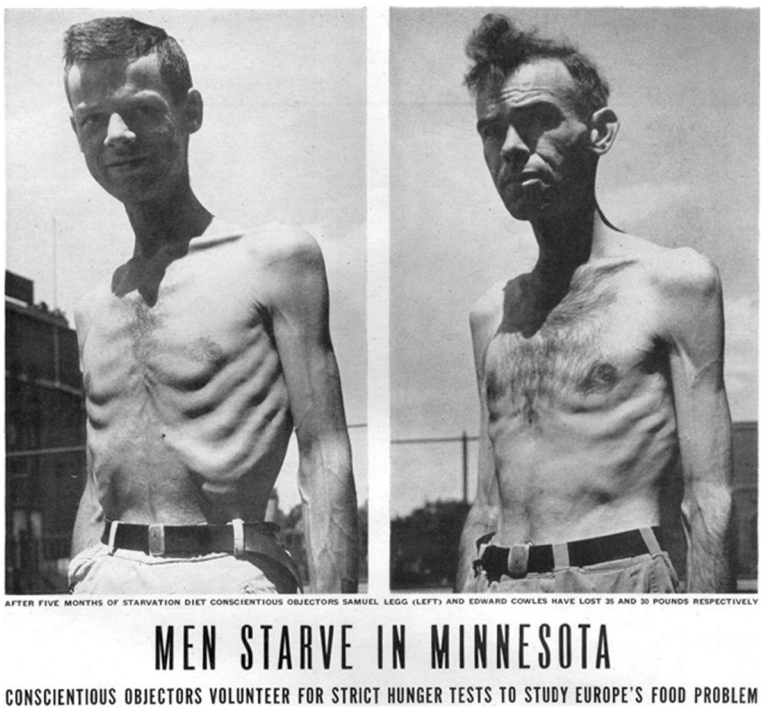

Fig. 2 Photograph from *Life* magazine on July 30, 1945 (volume 19, number 5, p. 43) showing men enrolled in the Minnesota Starvation Study during the semi-starvation diet. Adapted from [6]

study consisted of a structured "nutritional rehabilitation" period. Keys divided the men into four subgroups, with each receiving an additional 400, 800, 1200, or 1600 kcal/day respectively above the amount of food delivered in the starvation phase, leading to a total of 2200–3400 kcal/day. Unfortunately, this increase in caloric delivery did not improve the men's starvation state! Very little appreciable weight gain occurred in any of the groups and some men continued to lose weight on the increased calorie diets. This led Keys to further increase the men's caloric delivery by 800 kcal/day in each group. This led to a 1200–2400 kcal/day increase per group for a total of 3000–4200 kcal/day. This finally led to successful weight gain in the starving men. To attempt to assist post-war relief efforts, Keys released early results related to the most effective of the various rehabilitation diets before the experiment even ended [7, 8]. At a 1945 scientific meeting in Chicago, Keys noted:

> Enough food must be supplied to allow tissues destroyed during starvation to be rebuilt … our experiments have shown that in an adult man no appreciable rehabilitation can take place on a diet of 2000 calories [actually 2000 kcal] a day. The proper level is more like 4000 [4000 kcal] daily for some months.

The study officially ended on November 20, 1945. Keys convinced 12 of the men to stay on in the study for another 8 weeks so that he could monitor them during an "unrestricted nutritional rehabilitation" phase. Able to consume food at will, Keys observed that the men consumed an average of over 5000 calories/day. Some of the men were noted to take in as much as 11,500 calories in a single day! For many months, the men reported having a sensation of hunger they could not satisfy, no matter how much they ate. In these fully healthy, young men, recovery to a normal weight took an average of between 6 months and 2 years. No appreciable long-term or permanent adverse effects were noted in the subjects. This work led to the landmark two-volume, 1385-page publication *The Biology of Human Starvation* in 1950 [5].

Can we learn from the Minnesota Starvation Study how to provide "goal-directed" and targeted feeding in illness and recovery?

One of the first and most striking lessons from this study and others since is the amount of calories and protein a normal, healthy individual requires to maintain body weight and physical/mental function. Remember the initial caloric delivery in the control period of the Minnesota Study was 3200 kcal/day. This seems excessive as we think of the obesity epidemic and excess of caloric intake often present in the First World (clearly not true in many developing countries); however, based on the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations, this is not far from current WHO recommendations. Current data presented in Table 1 indicate that for a moderately active 70-kg individual (1.75 × BMR) between the ages of 30 and 60 the daily energy requirement (or approximate total energy expenditure (TEE)) is 3000 kcal/day (44 kcal/kg/day) for men and 2500 kcal/day (36 kcal/kg/day) for women (http://www.fao.org/docrep/007/y5686e/y5686e00.htm#Contents). The recommended WHO baseline protein delivery to avoid starvation in humans is ~ 0.75 g/kg/day. Interestingly, this calorie delivery is virtually identical to the control period of the Minnesota Study.

As we begin to examine how to deliver targeted calorie and protein delivery based on actual physiologically measured targets in critical illness, we must examine the existing data for caloric need in the different phases of critical illness. "Targeted" nutrition delivery emphasizes that we should take into account that long-standing basic metabolism data showing nutritional needs can change significantly over the course of critical illness. It is well described that the early or "acute phase" of critical illness is characterized by massive mobilization of the body's calorie reserves as muscle, glycogen, and lipid stores are broken down to drive glucose production [9, 10] (see Fig. 3). This evolutionarily conserved response allows the stressed or injured human to generate energy to escape its attacker and recover from initial injuries. This metabolic response to stress can generate 50–75% of glucose needs during illness [10], and this glucose generation is not suppressed by feeding or intravenous glucose infusion [11]. This is described in much greater detail by Oshima et al. [11] with recent data from our group. Further, we know that the early acute phase of sepsis and trauma are not hypermetabolic states, but rather the patients have a TEE to resting energy expenditure (REE) ratio of 1.0 and 1.1 for sepsis and trauma respectively [12]. Thus, caloric need does not increase in the early phases of injury (first few days post injury). In fact the more severe the septic shock, the lower the resting energy, as the body "hibernates" and shuts down metabolism in response to severe stress [13]. As presented in Table 1, data from Uehara et al. [12] show us that the REE in the first 2–5 days (acute phase) in elderly sepsis patients (mean age 67) is ~ 1850 kcal/day with a TEE of ~ 1920 kcal/day for a TEE of 25 kcal/kg. In the 2nd week following sepsis this increases to a TEE of ~ 3250 kcal/day or 47 kcal/kg/day—virtually identical to WHO requirements for normal, healthy humans. In younger trauma patients (mean age 34), Uehara et al. described an even greater increase in caloric need in the 2nd week post injury to an average of ~ 4120 kcal/day or 59 kcal/

Table 1 Summary of caloric needs of critically ill and healthy individuals in the context of the Minnesota Starvation Study and actual current ICU calorie delivery

	Mean REE (kcal/day)	TEE (kcal/day)	TEE/weight (kcal/kg/day)
Uehara et al., ICU study [12]			
Sepsis patients (mean age 67)			
Week 1	~ 1854	1927 ± 370	25 ± 5
Week 2		3257 ± 370	47 ± 6
Trauma patients (mean age 34)			
Week 1	~ 2122	2380 ± 422	31 ± 6
Week 2		4123 ± 518	59 ± 7
WHO calorie requirements, healthy subjects[a]			
Men		~ 3000	44 (range 35–53)
Women		~ 2500	36 (range 29–44)
Minnesota Starvation Study calorie delivery		Delivered energy (kcal/day)	Delivered energy/weight (kcal/kg/day)
Baseline period		3200	~ 50
Starvation period		~ 1800	23–30
Recovery period delivery (for recovery to occur)		~ 4000	~ 60

Actual average 1034 kcal/day delivered in critically ill patients over first 12 days of ICU stay [15]
REE resting energy expenditure, *TEE* total energy expenditure, *WHO* World Health Organization
[a]Data for a healthy 70-kg person with intermediate physical activity (1.75 physical activity level factor).
Reference: http://www.fao.org/docrep/007/y5686e/y5686e00.htm#Contents

kg/day, nearly identical to the 4000 kcal/day that Keys demonstrated was required to recover from starvation in the young subjects in Minnesota. This demonstrates that in the later recovery phase of critical illness, the body experiences a massive increase in metabolic needs, with TEE increasing as much as ~ 1.7-fold above REE [12]. With the onset of early ICU mobility programs, this may increase further as activity increases. Thus, as presented in Table 2, sources of energy supply transition in critical illness from largely endogenous supplies and release of energy early in illness to the need for primarily exogenous energy delivery in the late or recovery phase [11]. These data suggest we should consider feeding less nonprotein calories early in the acute phase (first 24–96 hours) of critical illness and markedly increase calorie delivery during recovery as illustrated in Fig. 4. Further,

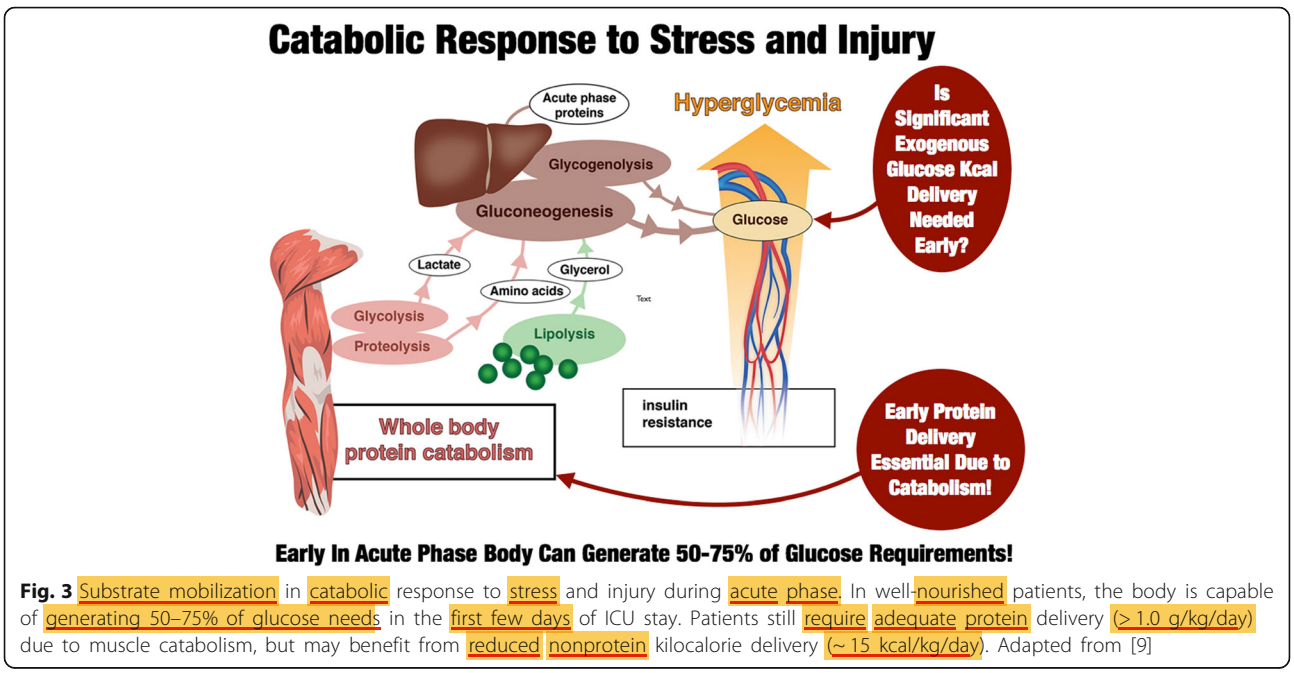

Fig. 3 Substrate mobilization in catabolic response to stress and injury during acute phase. In well-nourished patients, the body is capable of generating 50–75% of glucose needs in the first few days of ICU stay. Patients still require adequate protein delivery (> 1.0 g/kg/day) due to muscle catabolism, but may benefit from reduced nonprotein kilocalorie delivery (~ 15 kcal/kg/day). Adapted from [9]

Table 2 Conceptual transitions of utilization of energy supply in acute illness

Utilization of energy source	Phase of critical illness		
	Acute	Chronic	Post-acute
Endogenous	Maximal	Reduced	Marginal
Exogenous	Minimal	Increasing	Maximal

Adapted from [11]

new data indicate that thiamine deficiency occurs in up to 35% of septic shock patients [14]. A recent randomized, double-blind, controlled trial administered 200 mg thiamine to patients with septic shock and elevated lactate [14]. Administration of thiamine did not improve lactate levels or other outcomes in the overall group of patients with septic shock and elevated lactate. However, in thiamine-deficient patients, a statistically significant decrease in mortality over time in those receiving thiamine was observed ($p = 0.047$), as well as reduced lactate at 24 hours [14].

At the same time, it is also well known that protein losses increase 4-fold in the first 24 hours of critical illness [15] and we are exceedingly poor at meeting these needs [15]. Unfortunately, large, international surveys indicate that we as ICU practitioners deliver an average of 0.6 g/kg/day of protein for the first 2 weeks following ICU admission [16]. This is one-third to one-half of the latest ICU guideline-recommended protein delivery of 1.2–2.0 g/kg/day [17]. In contrast to what is often taught, the delivery of additional nonprotein calories does not significantly improve the nitrogen balance in illness beyond delivery of 50% of predicted REE. Thus, an ideal "targeted" feeding strategy is perhaps ~ 15–20 kcal/kg/day of total energy during the early ICU stay (acute phase), while ensuring patients receive adequate protein delivery (1.0–1.2 g/kg/day) as early as possible post ICU admission [18] (Fig. 4). Reduced calorie delivery during the acute phase is likely not applicable in malnourished patents (i.e., patients with significant pre-ICU weight loss or NUTRIC Score (w/o IL-6) > 5) who are unlikely to have the metabolic reserve to generate needed endogenous energy [17, 19]. Ironically, our most recent SCCM/ASPEN Guidelines emphasize these points in updates suggesting hypocaloric PN (≤ 20 kcal/kg/day or 80% of estimated energy needs) with adequate protein (≥ 1.2 g protein/kg/day) should be considered in patients requiring PN over the first week in the ICU [17]. Further, in early sepsis (or the acute phase of critical illness) the new SCCM/ASPEN Guidelines suggest provision of trophic feeds (defined as 10–20 kcal/hour up to 500 kcal/day) for the initial phase of sepsis, advancing as tolerated after 24–48 hours to > 80% of target energy with early delivery of 1.2–2 g protein/kg/day [17].

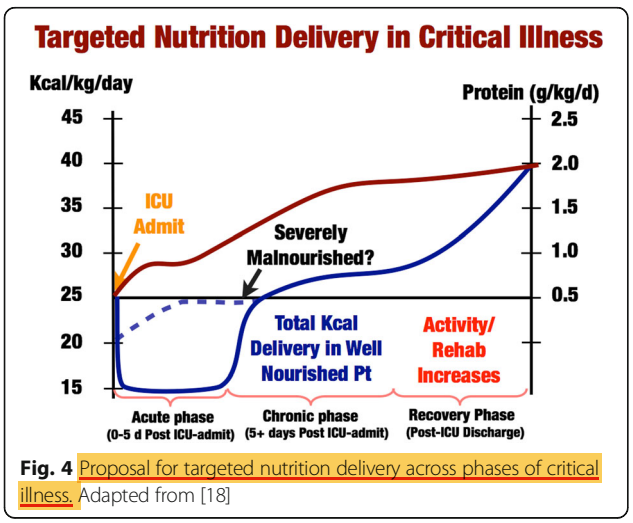

Fig. 4 Proposal for targeted nutrition delivery across phases of critical illness. Adapted from [18]

Is it possible we already "hypocalorically" feed our ICU patients far beyond the acute phase?

Extensive data for international ICU nutrition delivery currently exist from the International Nutrition Survey, which is conducted regularly by the Canadian Critical Care Nutrition Group (www.criticalcarenutrition.com). These data reveal that the average for calories delivered in the ICU over the first 12 days is 1034 kcal and 47 g of protein (Table 1) [16]. This period is far longer than the first 1–5 days of the acute phase where hypocaloric feeding (with adequate protein) may make physiologic sense. In fact, more troubling, this total is far lower than the 1800 kcal/day and ~ 0.8 g/kg/day which led to severe starvation in the Minnesota Starvation Study! Thus, in comparison, nutrition delivery in the ICU versus Key's Starvation Study is as follows: Minnesota Starvation Study (starvation period), 1800 kcal/day and 0.75–0.8 g/kg/protein; and ICU patients worldwide for the first 12 days in the ICU, 1034 kcal/day and 0.6 g/kg/protein.

These data confirm that ICU patients worldwide average far less energy and protein than in the legendary Minnesota Starvation Study, a study that would likely never be repeated today due to questions around the ethics of inducing potentially life-threatening starvation in a healthy volunteer. Yet it appears to be quite acceptable to actively starve ICU patients worldwide, and to a much more severe degree then the men in Minnesota suffered (which drove many of the men nearly to the point of insanity). Further, we know that starvation in humans leads to active slowing of metabolism and reduced catabolism of protein over time. Unfortunately, after the first week in the ICU we know that critical illness leads to significant hypermetabolism and severe ongoing protein losses. Moreover, we know that 30–50% of patients are malnourished at hospital admission (unlike the well-nourished men in Key's Starvation Study), greatly increasing the risk of ongoing inhospital starvation in our ICU patients. Thus, how can we justify the

magnitude of starvation we inflict upon our patients daily in our ICUs? Is this not some of the explanation for the increasing number of ICU survivors who ultimately become "victims" of post-ICU syndrome (PICS), never to walk again or return to a meaningful QoL post ICU discharge [20, 21]?

Again we must ask, are we creating survivors, or are we creating victims with the starvation we daily allow to occur in our ICUs?

How can we improve the worldwide epidemic of starvation in ICU patients?

The basic metabolism and physiology of human nutritional needs described indicate that early hypocaloric feeding in the first few days (acute phase) of critical illness would need to be accompanied by adequate protein delivery to help account for marked protein losses early in the ICU stay. Unfortunately, given the limited high-protein, lower-kilocalorie enteral feeding options available commercially, TPN or enteral protein supplements will currently be required to achieve this in most cases. TPN is now a significantly more viable option to achieve this as three recent large trials of both supplemental and full TPN support versus EN in the ICU setting have shown that TPN use in the ICU is no longer associated with increased infection risk [22–24]. This is likely due to improvements in glucose control, central line infection control measures, and potentially as a result of improved (nonpure soy-based) lipid formulations as described in detail in the recent review by Manzanares et al. [25]. In support of early TPN use, the new SCCM/ASPEN Guidelines indicate that for any patient at high nutrition risk (NRS 2002 $\geq$ 5 or NUTRIC Score (w/o IL-6 score) $\geq$ 5) or found to be severely malnourished when EN is not feasible, exclusive PN should be initiated as soon as possible following ICU admission [17].

A subsequent question that must continue to be addressed for the future of critical care is whether achieving goal energy delivery (kcal/day) or just achieving goal protein early during the ICU stay is more essential to outcome. Recent data from Nicolo et al. [26] examined this question and found that only achieving > 80% of protein goals by ICU day 4 or ICU day 12 improved 60-day mortality. Achieving energy goals at day 4 and day 12 was not associated with a statistically significant improvement in mortality outcomes. However, many experts are calling for post-ICU QoL, not survival, to be the most important outcome we should focus on in future ICU outcome trials [27]. When examining the effect of nutrition delivery on post-ICU QoL, Wei et al. [28] recently showed in patients requiring mechanical ventilation for > 8 days that for every additional 25% of goal calories/protein delivered over the first 8 days of the ICU stay, QoL was improved in a number of SF-36 physical function scores and this effect was most significant in the medical ICU patients studied. Thus, avoiding the frequent starvation that plagues our ICU patients in the first 1 or 2 weeks may markedly improve their QoL many months later. This is reinforced by data showing that delivery of greater than 1.0–1.2 g/kg/day of protein seems to be a minimum requirement for nutrition to show a benefit on outcome in the ICU setting [11, 29]. Finally, our recently published TOP-UP trial of supplemental parenteral nutrition in high malnutrition risk patients shows a promising trend in QoL measures for supplemental PN toward improved hospital discharge Barthel Functional Index ($p = 0.08$), handgrip strength ($p = 0.14$), and 6-minute walk test ($p = 0.2$) [30]. This requires further study and QoL measures need to be emphasized as future endpoints of ICU nutrition trials.

Should all patients receive hypocaloric high-protein feeding in the acute phase: role of pre-existing malnutrition?

Reduced calorie delivery during the acute phase is likely not applicable in malnourished patents (i.e., patients with significant pre-ICU weight loss or NUTRIC Score (w/o IL-6) > 5) who are unlikely to have the metabolic reserve to generate the needed endogenous energy [17, 19]. The NUTRIC Score may be the best and most useful marker to discern patients who are candidates for early high-protein, hypocaloric feeding in the acute phase and which patients are at great nutritional risk and should be started on ~ 25 kcal/kg/day shortly after admission. Patients with a NUTRIC Score (w/o IL-6) $\geq$ 5 have been shown in both the original trial and in a number of validation trials (i.e., [31]) to benefit most from early goal-oriented (> 80% energy goal) feeding. Thus, these data would suggest that these patients should not receive early hypocaloric feeding given their severe nutrition risk. As the new SCCM/ASPEN Guidelines indicate in patients found to be significantly malnourished (i.e., nutrition risk in critically ill patients with NUTRIC Score (w/o IL-6) > 5 or Nutrition Risk Score (NRS) > 5), when EN is not feasible a recommendation is made for initiating exclusive PN as soon as possible following ICU admission.

Targeted nutrition in the recovery phase? Significantly increased protein and calorie needs

As the patient enters the recovery phase, total protein and calorie delivery needs to increase significantly as suggested in Fig. 4. As data from the landmark Minnesota Starvation Study [5, 6] demonstrate, a healthy 70-kg human, following significant weight loss, requires an average of 4000–5000 kcal/day for between 6 months and 2 years to fully regain lost muscle mass and weight [5]. As many ICU patients suffer similar marked weight/LBM loss, we must consider that significant calorie/

protein delivery will be required to restore this lost LBM and QoL. This is supported by the aforementioned seminal metabolism studies showing that the average TEE in the second week of ICU stay was 47 kcal/kg/day in sepsis and 59 kcal/kg/day in trauma [12] (Table 1). This is well beyond what most units deliver to recovering ICU patients; however, these are actual measured metabolic requirements of patients as they recover, and with new early ICU mobility programs this delivery of increased energy in the recovery phase may be vital.

These data demand that we ask whether it is possible our patients have been unable to recover their QoL post ICU for months to years due to our lack of understanding of their fundamental metabolic needs in different phases of illness? For example, the need for additional protein intake has been well described by Hoffer and Bistrian [32–34] in a number of recent publications questioning whether it is actually "protein-deficit" and not calorie deficit that is important to improving outcome in critical illness.

Personalizing nutrition following discharge to optimize recovery

Finally, we must ask ourselves whether patients leaving our ICUs will be able to consume adequate calories and protein to optimally recover? I think experience has taught us in most cases that the answer is certainly not! Recovering patients, especially elderly individuals, are challenged by decreased appetites, persistent nausea, and constipation from opiates, and lack of education about how to optimize their diet [18]. In ICU patients in the week following extubation, an observational study demonstrated an average spontaneous calorie intake of 700 kcal/day and the entire population studied consumed < 50% of calorie/protein needs for 7 days [35]. It also emphasizes the importance of closely observing food intake in postoperative patients. To address this, a large body of data demonstrates that oral nutrition supplement (ONS) must become fundamental in our post-ICU and hospital discharge care plan. Meta-analysis in a range of hospitalized patients demonstrates that ONS reduces mortality, reduces hospital complications, reduces hospital readmissions, shortens the length of stay, and reduces hospital costs [36–39]. A large hospital database analysis of ONS use in 724,000 patients matched with controls not receiving ONS showed a 21% reduction in hospital LOS and that for every $1 (US) spent on ONS, $52.63 was saved in hospital costs [40]. Finally, a very recent large randomized trial of 652 patients and 78 centers studied the effect of high-protein ONS with β-hydroxy β-methylbutyrate (HP-HMB) versus placebo ONS in older (≥ 65 years), malnourished (Subjective Global Assessment (SGA) class B or C) adults hospitalized for congestive heart failure, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease over 90 days in the hospital and post-hospital period [41]. The data demonstrated that high-protein HP-HMB reduced 90-day mortality by ~ 50% relative to placebo (4.8% vs 9.7%; relative risk 0.49, 95% confidence interval (CI) 0.27 to 0.90; $p = 0.018$). The number needed to treat to prevent one death was 20.3 (95% CI 10.9 to 121.4) [41]. This trial was key as it was the first large multicenter randomized controlled trial to confirm the extensive data from smaller trials demonstrating a similar beneficial effect.

Role of specific anabolic/anti-catabolic agents, vitamin D, and microbiome/probiotics in recovery

The data from the large ONS trial using HMB [41] and recent data emphasize that anabolic/anti-catabolic interventions, such as propranolol, oxandrolone, and other agents targeted at restoring lean muscle mass (such as HMB), may be vital in optimal recovery and survival from critical illness [42]. As shown in Fig. 5, targeted nutrition with adequate protein delivery and "muscle-recovery targeted" agents when combined with exercise will likely play a vital role in improving survival and recovery of QoL post ICU [21]. Figure 5 also shows the emerging key role for vitamin D to reduce mortality in vitamin D-deficient ICU patients (as shown in the recent *JAMA* paper by Amrein et al. [43]), as was reviewed in expert detail recently by Christopher [44]. Further, new data indicate that thiamine deficiency occurs in up to 35% of septic shock patients [14]. This recent randomized, double-blind, controlled trial administered 200 mg thiamine to patients with septic shock and elevated lactate. Although administration of thiamine did not improve survival in the overall group of patients with septic shock, in thiamine-deficient patients a statistically significant decrease in mortality over time for those receiving thiamine was observed ($p = 0.047$), as well as reduced lactate at 24 hours [14]. Finally, new data expanding our understanding of the microbiome in the ICU and "dysbiosis" therapies including probiotics and fecal microbiota transplantation (FMT) have recently been reviewed by our group [45]. A summary of these interventions and their proposed timing is described in Fig. 5.

My personal experience with optimizing nutrition delivery during recovery following acute illness

As described previously [21], I have personally experienced critical illness and major surgical interventions throughout my life as a result of complications of ulcerative colitis and > 20 subsequent surgeries. Thus, recovery from ICU and surgery is a part of my daily life. I faced recovering from ICU and surgery once again in summer 2014, when I was in perhaps the best physical condition of my life, only to acutely suffer a major bowel obstruction leading to massive bowel edema and an operation

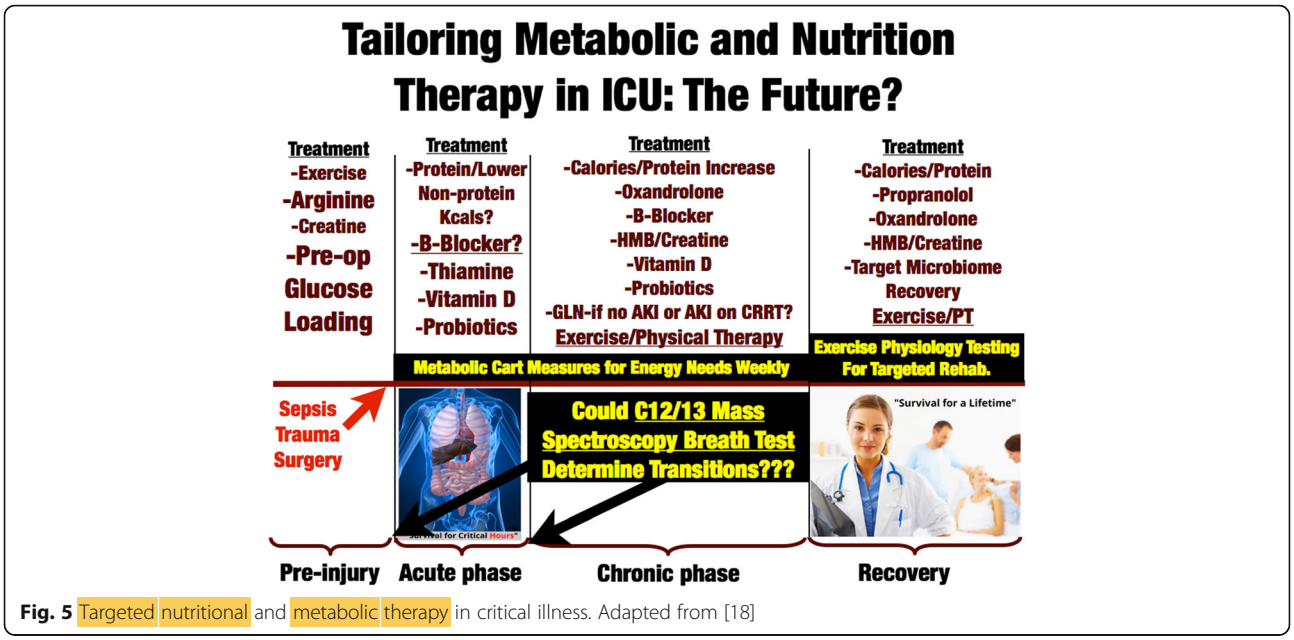

Fig. 5 Targeted nutritional and metabolic therapy in critical illness. Adapted from [18]

that led to a brief ICU stay and a prolonged hospital stay postoperatively. During this 23-day postoperative stay I lost 20 kg of body weight (quite similar to the total weight loss of the Minnesota Starvation Study—only over a much shorter time-frame). At discharge, I had lost significant LBM and was not able to walk down the hospital hallway without being short of breath. As I had found following previous major operations and subsequent weight loss episodes, I needed to consume 4000–5000 kcal/day for ~ 18 months, exercise 5 days/week, and take 2.0 g/kg/day of protein to regain the strength, QoL, function, and weight I had enjoyed prior to surgery. In addition, over 30 years of personal experience I have refined a daily regimen of anabolic and anti-catabolic supplements as presented in Table 3. Again, I personally was struck how accurate and vital the data from the Minnesota Starvation Study is today for both our patients and even myself to optimize recovery.

Table 3 Post-ICU/postoperative targeted rehabilitation nutrition program (PEW's daily program)

Exercise	Run and weight train 5 days/week
Nutrition	4000–5000 kcal/day
Calories	2 g/kg/day
Protein (whey, eggs)	(~ 2.0 g/kg body weight)
Supplements	
Branch chain amino acids	10 g/night
HMB	3 g/day
Vitamin D	2000 IU/day
Fish oil	2 g/day
L-Carnitine	Daily
Stress B multivitamin complex	Daily
Alpha lipoic acid	600 mg BID
DHEA	100 mg/BID
β-alanine	4–5 g/day
Creatine	5 g/day first 6–12 months post ICU (or longer for potential benefits on cognition and muscle strength)
Glutamine	10 g BID first 3–6 months post ICU

Note: This is the author's personal recovery program developed over 30 years of personal experience with illness, surgery, and ICU recovery. It is not suggested that this program is ideal for all recovering individuals. It is only meant as a suggestion to consider in recovery. Readers are encouraged to email the author (Paul.Wischmeyer@Duke.edu) with specific questions and evidence for particular elements of the program
BID twice daily, *HMB* β-hydroxy β-methylbutyrate

Conclusions

We need to consider basic metabolism and our historic understanding of starvation and recovery to employ targeted nutritional care for our critically ill patients. If we are to optimize patient outcomes and start creating "survivors and not victims" we must realize that one-size nutrition and one calorie delivery "does not fit all". It is clear our patients' nutritional needs change over the course of illness. Further, the presence of preexisting nutritional risk, such as that defined by the NUTRIC Score or sarcopenia (even low BMI < 25 as described by our recent published TOP-UP trial of supplemental PN [30]) should guide how we feed our patients, with high-risk malnourished patients getting more aggressive early calorie (~ 25 kcal/kg) and protein delivery via early EN and/or PN. Lower risk patients likely need lower early calories ~ 15 kcal/kg/day with adequate protein (~ 1.2 g/kg/day) as supported by the 2016 SCCM/ASPEN Guidelines. Early enteral nutrition during the acute phase should attempt to correct micronutrient/vitamin deficiencies, deliver adequate protein, and moderate nonprotein calories in well-nourished patients, as in the acute phase they are capable of generating significant endogenous energy. Post resuscitation, increasing protein (1.5–2.0 g/kg/day) and calories are needed to attenuate LBM loss and promote recovery. Malnutrition screening is essential and parenteral nutrition can be safely added following resuscitation when enteral nutrition is failing based on pre-illness malnutrition and LBM status. Following the ICU stay, significant protein/calorie delivery for months or years is required to facilitate functional and LBM recovery, with high-protein oral supplements being essential to achieve adequate nutrition. To better understand the nutrition delivery required in the post-ICU period, we must all take a moment to read and revel in the defining achievement that is the Minnesota Starvation Study and learn from its landmark lessons. Most important among these is that even healthy subjects require significant calories (typically > 3000-4000 kcal/day) to recover from massive weight and LBM loss, such as occurs following critical illness (or even major surgery). How will many of our care protocols, or our patients, acknowledge or achieve this well-described goal? Is it possible that this lack of understanding of caloric and protein need in recovery has led to the extremely poor long-term outcomes and QoL that follows ICU care? Only time and further research will tell for sure. But, as always, this increase in calorie delivery should be targeted with objective data when possible via use of improved metabolic cart technology. In the future, great promise seems to exist for bedside $^{13}C/^{12}C$ breath carbon ratio mass spectroscopy [46, 47] to assist in direct objective measurement of overfeeding and underfeeding. Finally, we must learn to target and incorporate nutritional therapies such as vitamin D, probiotics, and anabolic/anti-catabolic agents to optimize our patients' chance to survive and thrive against all evolutionary odds. We have long known Mother Nature does not want our ICU patients to win this war and become "survivors … and not victims". But to begin winning the war on long-term ICU outcomes and give our patients back the lives they came to us to restore, we must ensure our patients are getting the right nutrition, in the right patient, at the right time!

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Authors' contributions

PEW served as the only contributor in developing, writing, reviewing, and editing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This is a review and concept manuscript. No human subjects were enrolled or human data collected for this manuscript.

Consent for publication

Only individual descriptions from the author PEW is contained in these data, who gave permission to publish all included information.

Competing interests

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Critical Care

REVIEW Open Access

Regional physiology of ARDS

Luciano Gattinoni*, Tommaso Tonetti and Michael Quintel

Abstract

The acute respiratory distress (ARDS) lung is usually characterized by a high degree of inhomogeneity. Indeed, the same lung may show a wide spectrum of aeration alterations, ranging from completely gasless regions, up to hyperinflated areas. This inhomogeneity is normally caused by the presence of lung edema and/or anatomical variations, and is deeply influenced by the gravitational forces.

For any given airway pressure generated by the ventilator, the pressure acting directly on the lung (i.e., the transpulmonary pressure or lung stress) is determined by two main factors: 1) the ratio between lung elastance and the total elastance of the respiratory system (which has been shown to vary widely in ARDS patients, between 0.2 and 0.8); and 2) the lung size. In severe ARDS, the ventilatable parenchyma is strongly reduced in size ('baby lung'); its resting volume could be as low as 300 mL, and the total inspiratory capacity could be reached with a tidal volume of 750–900 mL, thus generating lethal stress and strain in the lung. Although this is possible in theory, it does not explain the occurrence of ventilator-induced lung injury (VILI) in lungs ventilated with much lower tidal volumes. In fact, the ARDS lung contains areas acting as local stress multipliers and they could multiply the stress by a factor ~ 2, meaning that in those regions the transpulmonary pressure could be double that present in other parts of the same lung. These 'stress raisers' widely correspond to the inhomogenous areas of the ARDS lung and can be present in up to 40% of the lung.

Although most of the literature on VILI concentrates on the possible dangers of tidal volume, mechanical ventilation in fact delivers mechanical power (i.e., energy per unit of time) to the lung parenchyma, which reacts to it according to its anatomical structure and pathophysiological status. The determinants of mechanical power are not only the tidal volume, but also respiratory rate, inspiratory flow, and positive end-expiratory pressure (PEEP). In the end, decreasing mechanical power, increasing lung homogeneity, and avoiding reaching the anatomical limits of the 'baby lung' should be the goals for safe ventilation in ARDS.

Background

During the acute respiratory failure caused by inflammatory edema—the condition to which we will limit our discussion—the lungs present a high degree of inhomogeneity [1]. Indeed aerated, poorly aerated, and consolidated/collapsed regions do coexist throughout the lung parenchyma.

From the sternum to the vertebrae and in the supine position, the lung with acute inflammatory edema (acute respiratory distress syndrome (ARDS)) presents as a rough simplification: 1) few regions of possible hyperinflation (difficult to define by computed tomography (CT) due to the increased lung mass); 2) regions with normal ratio between gas and tissue (usually defined as well aerated); 3) regions with gas-tissue ratios lower than normal (usually defined as the ones with a ratio between gas and tissue below 1); and 4) completely gasless areas in the most dependent lung regions (situated at different lung heights depending on the severity of the syndrome). It is important to realize that these gasless regions may be due either to a complete collapse of 'empty' pulmonary units (which can be possibly reopened and refilled with gas) or to a complete consolidation of the pulmonary units, in which the inner space is occupied by solid/liquid material [2]. Obviously, the differences in lung inflation are a signal of inhomogeneity and we may infer that the difference in gas-tissue ratio (i.e., in inflation) between different lung regions may be due either to anatomical variations in a given area of interest, or to the presence of different forces acting on contiguous structures of the lung parenchyma.

The interest for the pathophysiology of the ARDS lung derives from the need (in most of these patients) for

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mechanical ventilation. This technique substitutes the respiratory muscles, completely or in part, in the role of providing the energy needed to inflate the lung. Therefore, the possible harm of mechanical ventilation derives from the interaction between the anatomical-physiological characteristics of the lung parenchyma and the mechanical power delivered to it. Ideally, a proper setting of mechanical ventilation should find the best compromise between mechanical power and lung structure. In extreme synthesis, we should provide the lowest mechanical power in a parenchyma made as much homogeneous as possible. In this brief paper we will give our view on the interaction between mechanical power and regional lung physiology.

The lung parenchyma

Forces acting on the lung

It is worth remembering that the pressure (i.e., force per surface unit) distending the lung is the transpulmonary pressure, which equals the difference between the pressure at the airway and the pleural pressure. The appropriateness of this terminology has been recently questioned [3]. In fact, in pure physiology, the airway opening pressure is the airway pressure measured at the beginning of the endotracheal tube, which may be split into two components: the one used to move gas through the airways ('resistive' component), and the one used to distend the lung ('elastic' component). Accordingly, the transpulmonary pressure, in this purely physiological view, is the difference between the airway opening pressure and the corresponding pleural pressure. The terminology used by intensivists (and some physiologists) is different, as it refers to the conditions in which the pressure at the airway opening is measured as the peak pressure (which includes the resistive and elastic components), the plateau pressure (assumed to be equal to the alveolar pressure when the flow is zero), and the end-expiratory pressure. The changes in esophageal pressure at peak, plateau, and positive end-expiratory pressure (PEEP) or zero end-expiratory pressure (ZEEP) would reflect the corresponding changes in the pleural pressure. The esophageal pressure is used as a surrogate of the pleural pressure, as its changes are equal to the changes of the pleural pressure. It must be noted that trying to equate the absolute esophageal pressure to the pleural pressure is more a physiological dream than a reality. We never found any association between absolute esophageal pressure and the anatomical characteristics of the lung after examining hundreds of CT scans in ARDS. In this paper, according to our previous work [4] and other authors [5, 6], we define the transpulmonary pressure as the difference between the airway pressure measured in static conditions (plateau and PEEP/ZEEP) and the corresponding difference in esophageal pressure:

$$\Delta P_L = (Paw_{plat} - Paw_{end-exp}) - (Pes_{plat} - Pes_{end-exp})$$

where Paw_{plat} is the airway plateau pressure, $Paw_{end-exp}$ is the airway pressure at PEEP or ZEEP, Pes_{plat} is the esophageal pressure at plateau and $Pes_{end-exp}$ is the esophageal pressure at PEEP or ZEEP.

Accordingly, being:

$$\frac{\Delta P_L}{1\,L} = E_L \text{ and } \frac{\Delta P_{aw}}{1\,L} = E_{rs}$$

it derives that:

$$\Delta P_L = \Delta P_{aw} * \frac{E_L}{E_{rs}}$$

where ΔP_L is the driving transpulmonary pressure, ΔP_{aw} is the driving airway pressure, E_L is the lung elastance and E_{rs} is the total elastance of the respiratory system (i.e., $E_{rs} = E_L + E_w$, where E_w is the chest wall elastance).

In a series of studies we found that the average E_L/E_{rs} ratio in supine patients with ARDS was approximately 0.7 [7]. This indicates that at an airway plateau pressure of 30 cmH_2O, the plateau transpulmonary pressure is approximately 21 cmH_2O. However, we found that in single individuals the E_L/E_{rs} ratio may vary from 0.2 to 0.8 [7]. This indicates that, at the plateau pressure usually accepted as the threshold for a 'safe' mechanical ventilation, the transpulmonary pressure may be as low as 6 cmH_2O (with all the risks of hypoventilation and/or collapse) and as high as 24 cmH_2O, fully within the borders of the total lung capacity (TLC). In experimental models we found that lethal ventilation occurs when the total lung capacity region is reached [8]. In Fig. 1 we report the classical volume-transpulmonary pressure curve, readapted to the scenario of ventilator-induced lung injury (VILI). As shown, whatever the initial lung size (that we call 'baby lung' in ARDS), its inspiratory capacity is reached at 2.5–3 times the initial volume. Indeed, in a 'baby lung' of 300 mL, the TLC is reached at a volume of 750–900 mL. If the delivered tidal volume is in this order of magnitude, it would generate a transpulmonary pressure (also known as lung stress) of ~24 cmH_2O and a lung strain (i.e., the ratio of tidal volume to the functional residual capacity (FRC)) of 2.5–3.0, which have been shown to be lethal in animal models. Therefore, the lung size is the first factor to be considered for the development of VILI.

The stress raisers

Although in an extremely small 'baby lung' it is possible to reach the TLC with the tidal volume (TV), this mechanism cannot explain the harm observed in human ARDS with a tidal volume of 12 mL/kg [9, 10]. Indeed, reaching the TLC in most of the ARDS patients would require a tidal volume greater than 12 mL/kg. A possible

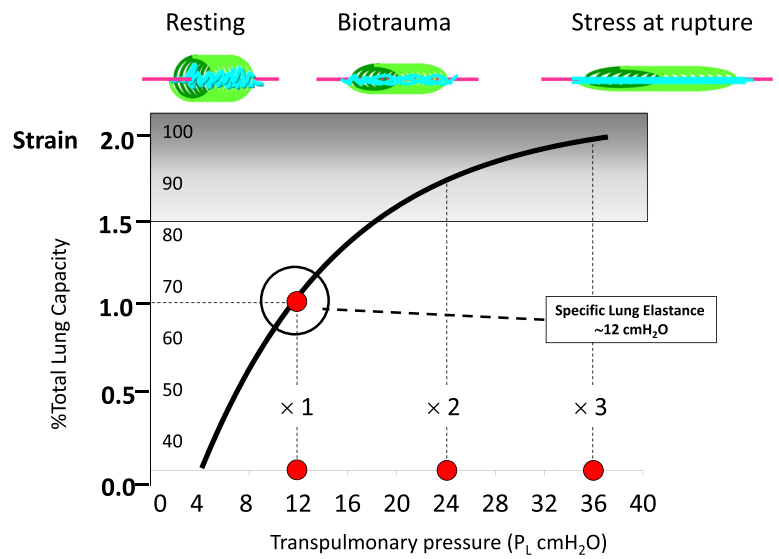

Fig. 1 Strain (tidal volume divided by the functional residual capacity) and total lung capacity (*y* axis) are represented as a function of the applied transpulmonary pressure (*x* axis) [22]. In the resting position, the collagen fibers are folded within the elastic spring [23]. Increasing the transpulmonary pressure, the excessive strain may lead firstly to an inflammatory reaction and, when the collagen is completely unfolded, to stress at rupture. At ~ 12 cmH_2O transpulmonary pressure (i.e., the specific elastance), the initial lung volume is doubled [7]

explanation of the damage observed in ARDS patients ventilated with 12 mL/kg tidal volume compared to 6 mL/kg is the presence of local factors which may locally multiply the applied pressures, with consequent increase in local stress and strain. This may occur to a greater extent with greater lung inhomogeneity, according to a theoretical model developed by Mead in the 1970s [11] and popularized by Lachmann in the 1990s [12]. Accordingly, if we imagine a given 10-kg load, hanging on 10 elastic fibers, each fiber will carry 1 kg. If for any reason (as an example, atelectasis) one fiber does not carry its own fraction of load anymore, the remaining fibers will carry ~ 1.11 kg each. If the inhomogeneity extends further to four fibers, the remaining six will carry ~ 1.67 kg each, and so on. The load in our case is represented by the transpulmonary pressure recorded at plateau. In a theoretical computation, and referring to a more complex geometrical model, Mead found that the multiplication factor for pressure at the interface between completely collapsed (volume = 1) and completely distended pulmonary units (volume = 10) would be equal to [11]:

$$\left(\frac{10}{1}\right)^{\frac{2}{3}} = 4.64$$

from which it has been often claimed that at 30 cmH_2O the local pressure could be as high as ~ 120 cmH_2O [12]. Actually, when we estimated the inhomogeneity by comparing the inflation ratio of neighboring lung regions [1], we found that the multiplication factor was ~ 2. According to the ARDS severity, the stress raisers were present in up to 40% of the lung parenchyma, suggesting that a given transpulmonary pressure is doubled in ~ 40% of the lung.

As a proof-of-concept of the presence of the stress raisers we hypothesized that the lesions during mechanical ventilation would firstly occur at the interfaces between regions of different elasticity, which, in healthy lungs, are mostly represented by the interfaces between the visceral pleura and the subpleural alveoli (see Fig. 2). Actually, we found that after an average of 8 h of mechanical ventilation small lesions start to occur at the pleuric-alveolar interfaces, and extend in about 20 h to the whole lung (see Fig. 3) [13]. Therefore, the bulk of

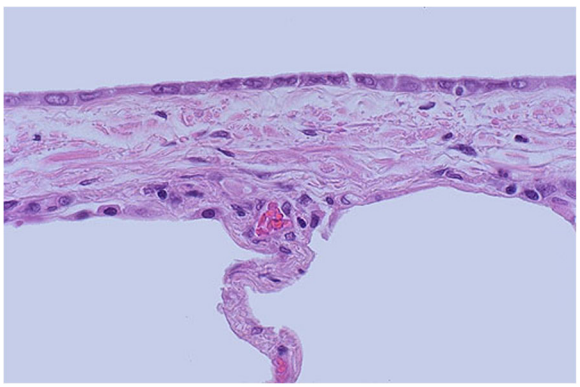

Fig. 2 Visceral pleura from which an alveolar wall departs. The interface between these two structures of different elasticity acts as a stress raiser with a possible local multiplication of stress and strain. Photograph courtesy of Dr. Edward C. Klatt, M.D., © WebPath

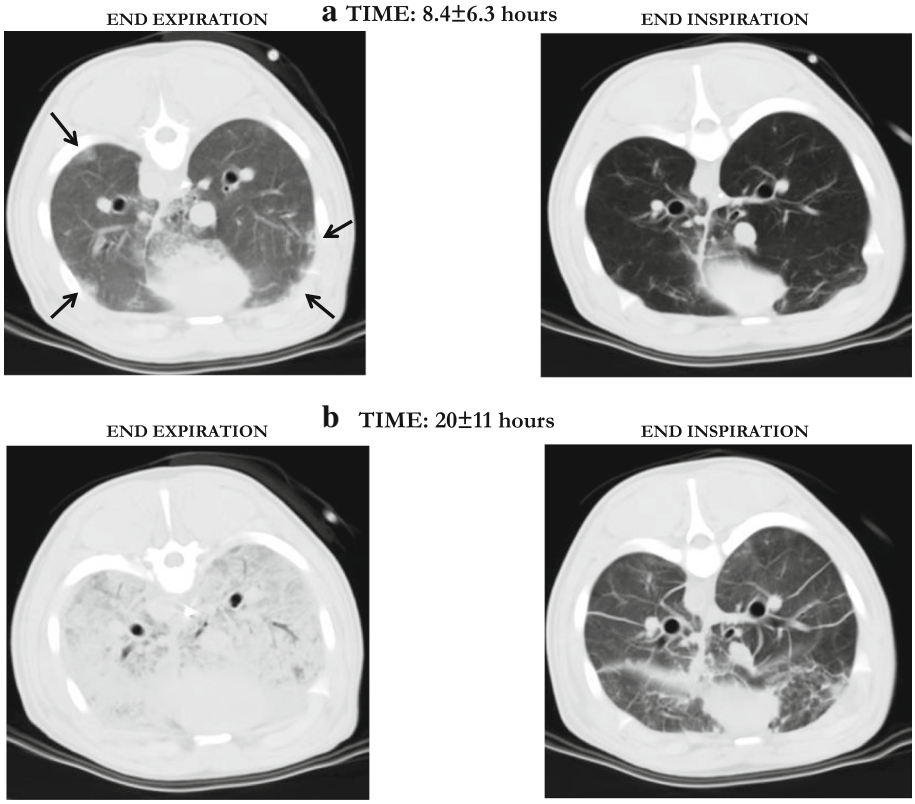

Fig. 3 a The first button-like densities (*arrows*) appear at the interface with the visceral pleura and, after 20 h of 2.5 strain ventilation (**b**), are extended to the whole parenchyma. Note that these VILI lesions are almost fully recruitable, suggesting that they develop primarily as interstitial edema

data available strongly suggest that there is an indication to reduce the lung inhomogeneity as much as possible in moderate-severe and severe ARDS patients through appropriate maneuvers (essentially prone positioning).

The mechanical power

The literature on VILI concentrates primarily on the possible danger of tidal volume. Recently the possible relevance of airway driving pressure (i.e., tidal volume normalized to the respiratory system compliance) has been emphasized [14]. Other possible causes of VILI have been identified in the respiratory rate [15] and in the inspiratory flow [16]. Additional factors, such as total/regional perfusion, local acidity, and temperature, may play a role in modulation of VILI but, for simplicity, will not be considered here.

In a series of experiments in pigs, aiming to identify a possible threshold for VILI, we found that the VILI was a function of how a harmful strain of 2.5 was reached, which is different to that observed by Dreyfuss et al. in rats [17]. In fact, while in the rats the VILI rapidly occurred at certain plateau pressures, independently of the way through which the plateau was reached (i.e., with or without PEEP), we found that ventilation at 15 bpm respiratory rate and strain equal to 2.5 (i.e., total volume close to 2.5 times the FRC) was lethal if provided totally as tidal volume and completely innocent (without any damage) if 75% of the added volume was provided as PEEP and 25% as tidal volume [18]. This led us to hypothesize that the damage was not due to the tidal volume per se, but to the product of tidal volume and pressure. This product (i.e., absolute pressure multiplied by the tidal volume) is the tidal energy delivered to the lung parenchyma. Actually, if a given amount of energy is given at a different rate, the mechanical power delivered per minute may be completely different. As a proof of concept, we ventilated pigs with a 2.5 strain (which is lethal when delivered 15 times per minute) at the rate of 3, 6, 9, 12, and 15 bpm and we found that below certain levels of mechanical power no VILI occurred after 54 h of mechanical ventilation [19]. Therefore, starting from the equation of motion of the respiratory system, we developed the power equation [20] simply by multiplying each component of the original equation by the change in volume and the respiratory rate. We found an impressive relationship in humans between computed and measured mechanical power, as well as in experimental animals (see Fig. 4). Considering the effects of the single

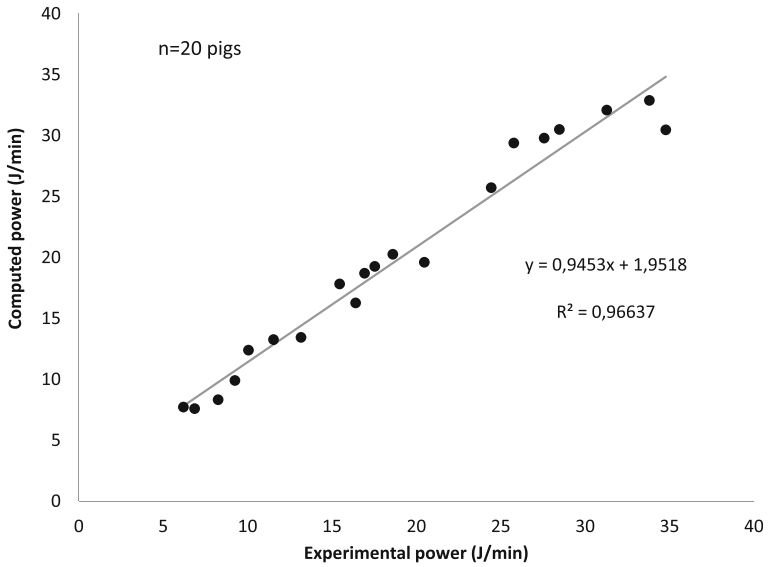

Fig. 4 Relationship between the power computed through the power equation and that measured through the graphic analysis of the pressure-volume loops. As shown, the relationship ($p < 0.001$) is close to the identity line

components of mechanical power, we found that doubling the tidal volume or the driving airway pressure (i.e., plateau minus PEEP) leads to a fourfold increase in mechanical power (exponent 2). In contrast, doubling the respiratory rate led to an increase in mechanical power of ~2.5 times (exponent 1.4) and of two times (exponent 1) if the PEEP is doubled [20].

This 'mechanical hypothesis' obviously needs further studies: 1) the mechanical power should be related to the transpulmonary pressure; and 2) it should be normalized for lung size and, likely, for specific lung elastance to allow comparison between different mammalian species. It is possible that in identifying an unsafe threshold for mechanical ventilation, based on 'lung-directed/normalized' mechanical power, a more rational approach to safe mechanical ventilation and indications for possible extracorporeal support may be established.

Conclusion

Mechanical ventilation is applied to the ventilatable fraction of the ARDS lung (the 'baby lung'). The anatomical threshold is likely represented by the total lung capacity which may be reached through local pressure rises depending on the lung inhomogeneity. Inside this framework, we can consider that:

- Whatever the decrease in mechanical power (due to the reduction of whichever of its components) should decrease the likelihood of ventilator-induced lung injury.
- The best available maneuver to increase lung homogeneity (without causing any increase in mechanical power) is prone positioning [21]. This is clearly indicated in patients with moderate-severe and severe ARDS, who present with the highest degree of lung inhomogeneity.
- PEEP has a dual effect: on one side, it may decrease lung inhomogeneity, at least in the patients in whom lung collapse can be substantially reduced. On the other hand, for a given tidal volume, PEEP increases the mechanical power and the likelihood of reaching the anatomical threshold for VILI, i.e., the total lung capacity.

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LG designed the paper and drafted the manuscript. TT helped draft the manuscript and revised it critically for important intellectual content. MQ helped draft the manuscript and revised it critically for important intellectual content. All authors approved the final manuscript.

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Critical Care

REVIEW Open Access

Personalized physiological medicine

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Abstract

This paper introduces the concept of personalized physiological medicine that is specifically directed at the needs of the critically ill patient. This differs from the conventional view of personalized medicine, characterized by biomarkers and gene profiling, instead focusing on time-variant changes in the pathophysiology and regulation of various organ systems and their cellular and subcellular constituents. I propose that personalized physiological medicine is composed of four pillars relevant to the critically ill patient. Pillar 1 is defined by the frailty and fitness of the patient and their physiological reserve to cope with the stress of critical illness and therapy. Pillar 2 involves monitoring of the key physiological variables of the different organ systems and their response to disease and therapy. Pillar 3 concerns the evaluation of the success of resuscitation by assessment of the hemodynamic coherence between the systemic and microcirculation and parenchyma of the organ systems. Finally, pillar 4 is defined by the integration of the physiological and clinical data into a time-learning adaptive model of the patient to provide feedback about the function of organ systems and to guide and assess the response to disease and therapy. I discuss each pillar and describe the challenges to research and development that will allow the realization of personalized physiological medicine to be practiced at the bedside for critically ill patients.

Background

Randomized controlled clinical trials (RCTs) have failed to provide needed direction for the diagnosis and treatment of the critically ill patient. Such trials, based on the idea that evidence for the treatment of individual patients can only be achieved by demonstrating efficacy of one treatment modality over another in large groups of patients, have not been able to demonstrate effective therapies; at best, the trials (e.g., TRIC, SPLIT, SAFE, PROCESS, ARISE, CHEST, PROWESS, SEPSISPAM, etc.) have shown no difference between groups. These results often lead, in practice, to the mistaken conclusion that there is no difference between the interventions. A more correct conclusion could be that such RCTs, by design, are unable to demonstrate differences in heterogeneous intensive care patients because the physiology of individual patients at the bedside indeed shows differences between various interventions. These shortcomings of RCTs have led to the suggestion that such trials should be abandoned to focus on a more personalized approach for identifying the optimal therapy for each individual patient [1]. This concept has been referred to as "personalized medicine" and has been mainly associated with the measurement of pharmacological biomarkers and genetic profiling with the goal of identifying personalized therapy to result in improved survival benefit (e.g., [2]). However, additional requirements and concepts may be needed for personalized medicine if this concept is to be applied to the critically ill patient. The time-variant changes in (patho)physiology in response to the wide range of disorders with complex interactions between failing organ systems being treated with a variety of drugs and organ-supporting devices distinguishes critically ill patients from other categories of patients (e.g., oncology and cardiology). These considerations lead to the idea that a new form of personalized medicine may need to be designed to meet the specific needs of the critically ill patient.

Personalized physiological medicine

Conventional personalized medicine based on genetic profiling and pharmacological biomarkers will need development if they are to be applied to the practical needs of the critically ill patient. The main challenges of this form of personalized medicine will be to obtain genetic and biomarkers in a semicontinuous manner and to link this information to specific organ function allowing targeted therapy to be realized. The genetic profile and

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transcription factors of the critically ill patient continuously change over time [3]. Levels of pharmacological biomarkers also change continuously over time [4], and the currently available biomarkers of sepsis have been found to lack specificity and sensitivity [5]. These aspects of conventional personalized medicine have prompted the idea that considering physiological variables as biomarkers may provide an essential addition to the needs of the critically ill patient because they relate more closely to the aims of intensive care medicine in terms of providing physiological recovery and organ support [6, 7]. Such a physiological approach to personalized medicine must be focused on the phenotype of the patient as well as on the functional properties of their organs and ultimately their cells as they change over time in response to disease and therapy. From this perspective, I propose here the concept of personalized physiological medicine as being more appropriate in achieving these aims. In doing so, I identify four pillars of personalized physiological medicine on which this concept is based (Fig. 1): 1) fitness and frailty; 2) organ function and response to therapy; 3) hemodynamic coherence; and 4) integration and feedback.

Pillar I: fitness and frailty

The first pillar of personalized physiological medicine is the assessment of fitness and frailty of the patient to determine their physiological reserve. Although obviously not applicable to critically ill patients, the gold standard for determining fitness is cardiopulmonary exercise testing (CPT), in which cardiovascular stress is imposed by incremental amounts of work and maximum oxygen consumption. Consequently the aerobic threshold is considered as the best index of cardiorespiratory fitness [8] but this has not been applied to critically ill patients. Inadequate exercise has been shown to be a risk factor for sepsis mortality, particularly in diabetics [9]. Exercising critically patients using a bedside cycle ergometer has been shown in survivors to result in improved 6-min walking distance, isometric quadriceps force, and the subjective feeling of well-being following discharge [10]. In experimental studies in septic rats, exercise protected organs from damage and lowered inflammatory mediators [11]. Increasingly, muscle is being recognized as a key hormone secreting organ where myokines, hormones secreted by the exercising muscle, are being shown to play a central role in resolving a host of disease states including cancer and diabetes [12]. Indeed, Montgomery and colleagues demonstrated that muscle wasting during critical illness is directly related to organ failure [13]. That is why developing objective measures of fitness in bed-ridden patients and maintenance of muscle mass by developing exercise modalities during critical illness must be recognized as an important aim in this pillar of personalized physiological medicine.

Extended lack of fitness can translate into frailty, a condition in which homeostatic mechanisms begin to fail, resulting in reductions in the physiological reserve of the neural, renal, skeletal, respiratory, cardiovascular, endocrine, immune, and coagulation systems when challenged by stress [14], such as in critical illness. Several studies have identified phenotypes associated with frailty, including measures related to physical activity, energy, nutritional status, strength, and cognition [15, 16]. The evaluation of frailty as a phenotype in the critically ill patient has been shown in several studies to be of special relevance in the prediction of intensive care unit (ICU) survival (e.g., [17]); frail survivors of critical illness have been shown to experience greater impairment in health-related quality of life and disability compared with those who are not frail [18]. Frailty, defined as a physiologic loss of reserve capacity and resistance to stressors [16, 19], has been quantified in several studies [15]. It is clear that continuous measures of fitness, frailty, and physiological reserve, along with coexisting comorbidity and primary disease, are key input variables defining the phenotype of the patient and therefore represent the first pillar of personalized physiological medicine.

Pillar II: organ function

The second pillar of personalized physiological medicine involves the function of the organ systems and their response to therapy. Evaluation of the regulatory capacity of the organ systems to stress factors is central because a loss of this regulatory capacity occurs in advance of physical injury to the parenchymal cells associated with upregulation of conventional pharmacological biomarkers. Loss of regulatory capacity represents a window of opportunity for treatment prior to the occurrence of irreversible injury requiring long-term regeneration [6]. Here, providing a physiological challenge to the patient and measuring organ response at the bedside is a central concept in evaluating physiological reserve. For instance, the dobutamine challenge test to evaluate the regulatory capacity of the β-adrenergic system in septic patients was introduced by Vallet and coworkers, who were able to predict survival in septic patients by measuring the response to oxygen delivery, consumption, and extraction [20]. A nonpharmacological version of the dobutamine stress test was explored by Kimmoun et al. to assess the efficiency of cardiac adaptation to septic shock by measuring cardiac contractility reserve-related parameters, including cardiac index, double product, and cardiac power index during the resuscitation procedure [21]. In this context, the heart rate response is also a promising methodology to assess the ability of the autonomic nervous system to

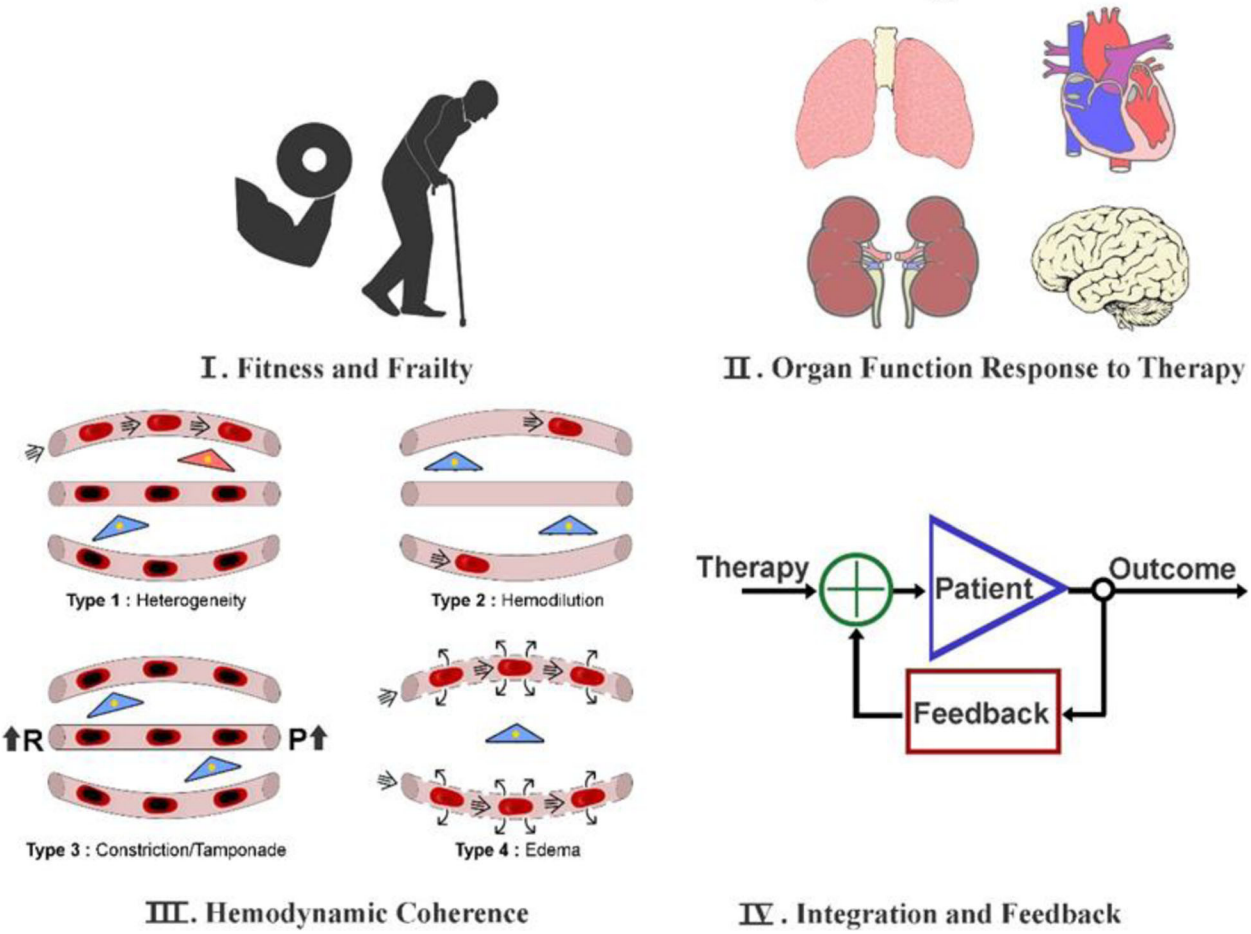

Fig. 1 The four pillars of personalized physiological medicine. Pillar I is measurement of the fitness and frailty of the patient and their physiological reserve and fitness to deal with the physiological stress of critical illness. Pillar II concerns measurement of the function of organ systems and their response to therapy as well as their functional capacity and reserve including the immunological, humoral and coagulatory systems. Pillar III concerns the measurement of the hemodynamic coherence between the macro- and microcirculation and parenchymal cells in response to resuscitation. The loss of hemodynamic coherence can be identified by observation of the microcirculation, where type 1 concerns inflammation and infection-induced heterogeneous obstructions of microcirculatory flow, type 2 concerns hemodilution-induced loss of red blood cell filled capillaries, type 3 concerns microcirculatory stasis induced by excessive vasopressor load or raised venous pressures, and type 4 concerns tissue edema (*red* cells are well oxygenated and *blue* cells are hypoxic cells; taken from [35] with permission). Pillar IV is the integration and feedback of the various elements of the personalized physiological medicine modules to provide input in an integrative and time variant holistic manner to identify and assess the success of therapy and severity of organ and cellular dysfunction, as well as identifying the essential parameters in need of correction

regulate cardiovascular responses and assess interorgan communication [22, 23]. The future challenge will be how to therapeutically treat the regulatory capacity of the β-adrenergic system to improve outcome.

Achieving optimal ventilation recruitment and avoiding ventilator-induced lung injury are arguably the main targets in achieving good ventilation-perfusion matching and gas exchange during mechanical ventilation. Adjustment of ventilator settings, assessing deleterious effects of often-used therapy, including fluid therapy and mechanical ventilation, and evaluating the direct effects of therapies directed at the lung itself, such as nebulization of antibiotics [24], anticoagulants [25], anti-inflammatory [26] and vasoactive compounds [27], truly requires a personalized approach in which bedside lung function evaluation is essential. Although several lung function parameters are available at the bedside (e.g., airway resistance, tidal volume, end-expiratory lung volume, intrinsic positive end-expiratory pressure (PEEP), compliance, dead space, and volumetric capnography) and novel clinical methodologies such as electric impedance tomography are being developed [28], essential lung function parameters directly related to the capacity of the lung to achieve gas exchange are lacking. A need

exists for the quantitative assessment of functional residual capacity (FRC), inhomogeneity of ventilation, and ventilation-perfusion matching. Indeed the importance of such measurements have been demonstrated in experimental models of acute lung injury (ALI) where the effects of respiratory movements could be directly observed in exposed mice lungs using dark-field intravital microscopy [29]. Measurement of these parameters has classically required the quantitative measurement of the washout of inert indicator gases requiring the use of complex mass spectrometry [30] at the bedside [31]. More practical measurement of these parameters at the bedside is currently under investigation (e.g., [32]). In addition to these volumetric measures, more comprehensive physical properties of the lung tissue itself are required beyond conventional dynamic compliance and airway resistance measures. Such information can be obtained, for example, by the forced oscillation technique in which the frequency-dependent impedance of the complete pulmonary system can be obtained, providing detailed information about the mechanical properties of the lung (e.g., [33]). It is clear from these considerations that there is a need to further develop techniques to measure these pulmonary parameters and to integrate them into a single monitoring platform to meet the requirements of this pillar of personalized physiological medicine.

Measuring kidney function is a specific challenge in intensive care management. This has typically been limited to the measurement of urine production and creatinine levels, both of which are considered inadequate indicators of kidney function. As a result, there has been a surge in renal pharmacological biomarker research. Although these biomarkers have been effective in identifying renal injury, they have not yet proven successful in guiding therapy. Their time-variant changes and their sensitivity only to advanced renal injury led us to develop the concept of physiological biomarkers of acute kidney injury (AKI) [6]. We proposed that such physiological biomarkers be related to renal hemodynamics and regulation, microcirculation and oxygenation, and tubular function because these are expected to be altered in advance of an injury, thereby identifying a window of therapeutic efficacy. Consistent with these concepts, Ronco and co-workers developed methodologies to measure renal physiological reserve, which was defined as the capacity of the kidney to increase the rate of glomerular filtration in response to a physiological stress; they proposed the administration of a fixed protein load for this purpose [34]. Using a similar concept to measure the functional capacity of the kidney, Chawla and co-workers administered furosemide to stimulate urine production and found that the furosemide stress test was much more sensitive in predicting stage 3 AKI than pharmacological biomarkers [35]. From these examples it is clear that there is a concerted effort to establish a functional platform to more comprehensively monitor organ function and assess the capacity to regulate functional reserve in real time as an essential goal for personalized physiological medicine. Recent advanced in ultrasound such as contrast-enhanced ultrasound may make such sensitive monitoring of the renal microcirculation feasible in patients [36].

Pillar III: hemodynamic coherence

Resuscitation aims at normalizing systemic hemodynamic variables, such as stroke volume or blood pressure, with the expectation that a parallel improvement will occur in the perfusion and oxygenation of the microcirculation feeding the tissue beds of the organ systems. Homeostatic coupling between the systemic circulation and the microcirculation is essential for such an expectation to be met; in addition to the primary disease, resuscitation fluids and medications themselves can adversely affect this regulation. We have termed the required coupling between the macro- and microcirculation essential for successful resuscitation based on the correction of systemic hemodynamic variables as "hemodynamic coherence" [37]. Loss of hemodynamic coherence can occur if the factors affecting the microcirculation are not corrected by the resuscitation procedure focused on correction of the macrocirculation by resuscitation following shock. Such factors affecting the microcirculation can include immunological and/or factors affecting endothelial, leucocyte, and red blood cell function. In this context, its manifestation should be regarded as a dynamic process depending on the interactions between disease, therapy, and time. Whether the correction of systemic hemodynamic variables achieves adequate microcirculatory and tissue perfusion is often unknown and may manifest at the bedside as the patient being unresponsive. Such a situation prompts the clinician to administer even more fluids and medications, potentially causing harm. Assessment of the presence or absence of hemodynamic coherence requires the simultaneous measurement of the response of the macro- and the microcirculation. The microcirculation can be effectively visualized in the sublingual area using hand-held vital microscopy (e.g., [38]), which allows the parallel improvement in the microcirculation to resuscitation efforts based on the response of systemic parameters to be verified [39]. Identification of the presence or absence of hemodynamic coherence and the response of the microcirculation to therapy forms the third pillar of personalized physiological medicine because it assesses the physiological coupling between the various compartments in the hierarchy of the circulation to achieve uniform resuscitation. Loss of hemodynamic coherence at

the level of the microcirculation can be divided into four types (Fig. 1). Type 1 loss of hemodynamic coherence is characteristic of states of sepsis, in which inflammatory mediators and oxidative and nitrosative stress factors cause endothelial and erythrocyte injury resulting in obstruction of the capillaries. This causes a heterogeneous microcirculatory flow and functional shunting in parts of the microcirculation, resulting in reduced oxygen extraction capacity characteristic of sepsis [40]. Type 2 loss of hemodynamic coherence occurs when an excessive volume of fluids is given in an attempt to correct systemic variables, such as stroke volume and blood pressure. While systemic variables may be normalized, hemodilution causes reduced viscosity and dilution of the blood, both of which cause a reduction in capillary filling. This increases the diffusion distances between oxygen-carrying erythrocytes and tissue cells, thereby reducing the oxygen delivery capacity of the microcirculation and its oxygen extraction capacity [39]. Type 3 loss of hemodynamic coherence is the condition where high levels of vasopressors intended to improve blood pressures can paradoxically cause constriction of microcirculatory blood flow [41]. Similarly, microcirculatory impediment of flow can occur when high venous pressures are targeted, resulting in microcirculatory flow restriction due to tamponade [42]. Type 4 loss of hemodynamic coherence occurs as a result of edema (e.g., in burns [43] and in malaria [44]) in which leaky vessels also cause increased diffusion distances and a reduction in oxygen extraction.

Pillar IV: feedback and integration

Personalized physiological medicine directly relates to the practice of intensive care in supporting organ function and restoring homeostasis. Concepts from systems and control engineering, in which integration and feedback are central for the control of complex systems [22], are important to consider. To this end, I define the fourth pillar of personalized physiological medicine as the integration of the modules in the aforementioned three pillars to provide feedback on the functional activity of different physiological compartments, to identify the functional state and stability of the system, and to provide practical feedback to guide therapy and ensure resolution of the unstable patient prior to the development of irreversible states of critical illness.

Intensivists are confronted with an overwhelming amount of patient data, including historical clinical information as well as continuous online data regarding the condition of the patient, which changes from moment to moment [45]. Decisions based on assessment of these data are based on clinical experience as well as evidence from trials and knowledge of the literature; however, this assessment relies more on the subjective judgment of the physician rather on a strict analysis of data. Various initiatives have been formulated to integrate and simplify the vast amount of data being generated from the patient, describing both the condition of the patient (e.g., APACHE, SAPS and SOFA) and that of specific organ systems (e.g., AKIN and KDIGO for AKI). Currently, more sophisticated predictive methodologies are being developed, making use of complex mathematics such as chaos and complexity theory [46]. Almost without exception, these methods are used to evaluate the severity of disease without providing any insight into the physiologic basis for the condition of the patient. These approaches neither identify a given physiological parameter in need of correction nor identify optimal therapy and provide feedback for a therapeutic maneuver in a goal-directed manner.

For these reasons, the fourth pillar of personalized physiological medicine requires not only a predictive environment to describe the condition of the patient, but a more comprehensive mathematical model directly related to the function of the organ systems from a systems engineering and integrative systems physiological perspective. Here, measuring the interactions between the various physiological compartments, including the immune and humoral systems as well as the cellular and ultimately even the genetic profile, stemming from the previous three pillars of personalized physiological medicine should provide a holistic description of the physiological state of the patient and, more importantly, provide practical feedback for identifying the need, response, and success of therapy. Such an approach requires adaptive modeling in which the model is continuously responding, considering time-variant changes and providing an optimal model for patient care (e.g., [47]). Central to the model should be the measures of organ function of pillar 2 to provide the needed feedback to evaluate organ and therapy support and interactions between the different physiological compartments. In this way, the model should be capable of assessing the stability of the system so that successful weaning from an assisted mode can be accomplished, in which therapy and organ-supporting devices are successful in achieving eventual independent organ function. It can even be conceived that such models can become closed loop control systems for control of specific parts of the support system (e.g., [48]).

Conclusion

Personalized medicine is a developing trend for the future of intensive care medicine. However, the practical implementation of this concept, if limited to the use of genetic screening and pharmacological biomarkers, however appealing, is still in need of considerable development. I therefore propose a personalized physiological

approach which I argue is much more suited to the requirements of critically ill patients. I have presented four pillars of personalized physiological medicine to address the full spectrum of this idea. This classification allows a modular approach, as its various aspects are under development in sometimes unrelated areas of critical care medicine. Integration of the concepts will provide a true challenge for the future, requiring collaboration between clinicians, physiologists, and engineers; the realization of bedside instruments to practice personalized physiological medicine remains a real challenge to industry. Nevertheless, I anticipate that the road map outlined in this paper may provide a conceptual framework within which critically ill patients will benefit from the promises of personalized medicine.

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Critical Care

REVIEW Open Access

Detailing the cardiovascular profile in shock patients

Daniel De Backer

Abstract

Evaluation of the cardiovascular profile of critically ill patients is one of the most important actions performed in critically ill patients. It allows recognition that the patient is in shock and characterization of the type of circulatory failure. This step is crucial to initiate supportive interventions and to cure the cause responsible for the development of shock. Evaluation of tissue perfusion allows identification of the patient insufficiently resuscitated and also to trigger therapeutic interventions. Monitoring tissue perfusion can be achieved by lactate, venoarterial gradients in PCO_2, and central venous or mixed venous oxygen saturation. Ultimately, monitoring the microcirculation may help not only to identify alterations in tissue perfusion but also to identify the type of alterations: diffuse decrease in microvascular perfusion versus heterogeneity in the alterations, as in sepsis, with well perfused areas in close vicinity to poorly perfused areas. Regarding supportive therapy, a step-by-step approach is suggested, with fluid optimization followed by vasoactive support to preserve perfusion pressure and global and regional blood flows. The different variables should be integrated into decision and management pathways, and therapies adapted accordingly.

Background

Evaluation of the cardiovascular profile of critically ill patients is one of the most common explorations performed in the ICU. Several tools can be used to evaluate the hemodynamic state of a patient but the interest of a given technique goes well beyond its invasiveness. Even though ideally less invasive methods should be preferred over more invasive methods, the reliability of cardiac output measurements with some of the noninvasive techniques is sometimes questioned in patients in shock states [1]. More importantly, the interest in hemodynamic monitoring in shock states goes beyond the simple measurement of cardiac output and the interest in the multiple derived variables often orients the choice for one technique over another.

In patients with shock, the decision to use a given hemodynamic technique should be based on what the physician expects from the measured variables. The following four important questions should be addressed: Is the patient in shock? What is the type of shock? Is tissue perfusion adequate, and if not how to improve it? Is cardiovascular function adequate?

Recognition of shock

In a recent consensus, shock was defined as "a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells". Shock is thus a state in which the circulation is unable to deliver sufficient oxygen to meet the demands of the tissues, resulting in cellular dysoxia. Hence, VO_2 by the tissues becomes limited by DO_2. In the past, VO_2/DO_2 relationships were evaluated at the bedside, but this was quite cumbersome and subject to errors in measurements. Accordingly, surrogate markers are often used to identify shock, among which are measurements of blood lactate levels as lactate levels rise sharply when DO_2 reaches the point at which VO_2 becomes dependent on DO_2. Shock is also associated with signs of impairment of tissue perfusion (skin vasoconstriction or mottling, acrocyanosis, impaired capillary refill time, impaired microcirculation, increased venoarterial PCO_2 gradient), but these may already be present before the onset of VO_2/DO_2 dependency.

Importantly, even though hypotension is often encountered in shock states, shock may sometimes develop

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without hypotension (especially in previously hypertensive patients). Accordingly, a patient who presents signs of impaired tissue perfusion and increased plasma lactate levels should be considered a patient in shock.

What is the type of shock?

The next important point would be to evaluate the type of shock that the patient presents, as it would orient not only supportive therapies but also causal management. There are four types of shock: hypovolemic, cardiogenic, obstructive, and distributive. Several hemodynamic tools can be used to determine the type of shock. However, echocardiography is the most convenient tool as it can rapidly lead to the diagnosis of the type of shock. In a study including 108 patients in shock, echocardiography diagnosed the type of shock within 4.9 ± 1.3 min [2]. There was also an excellent agreement between the various observers. Accordingly, echocardiography is now recognized as the preferred initial modality to evaluate the type of shock [3]. Accordingly, many patients can be monitored just with an arterial line and a central line, in addition to initial echocardiography (Fig. 1). When the patient does not respond to initial therapy, or in complex cases, additional hemodynamic monitoring is recommended. In these cases, the pulmonary artery catheter or transpulmonary thermodilution are the preferred methods [3].

The advantage of the pulmonary artery catheter and transpulmonary thermodilution over other less invasive techniques is that these provide not only reliable cardiac output measurements even in extreme conditions, but also additional variables that help to understand the cardiovascular profile. The pulmonary artery catheter allows the measurement of intravascular pressures while transpulmonary thermodilution estimates intravascular volumes. With the measurements of intravascular pressures and volumes it is feasible to identify the type of shock (Fig. 2).

Evaluation and therapeutic approach of tissue hypoperfusion

Lactate

Measurements of blood lactate levels can be useful to detect occult tissue hypoxia and also to monitor the effects of therapy.

Lactate is a byproduct of glycolysis. In the first phase, which is anaerobic and occurs in the cytoplasm, glucose is transformed into pyruvate. If oxygen is present, the pyruvate enters the mitochondria to participate in the second phase of reactions, generating ATP, H_2O, and CO_2, but can also be transformed into lactate if oxygen is lacking or in some cells that do not contain mitochondria. In normal conditions, most pyruvate enters the mitochondria, so that the normal lactate/pyruvate ratio is around 10. In anaerobic conditions, pyruvate cannot enter the mitochondria and massive amounts of lactate will be produced and the lactate/pyruvate ratio increases well above 20.

It is commonly accepted that hyperlactatemia is mostly of hypoxic origin in critically ill patients with circulatory failure. However, tissue hypoxia cannot be sustained for long periods of time without inducing cell death, as the energy produced by anaerobic metabolism is quite low compared to aerobic metabolism. Mild hyperlactatemia

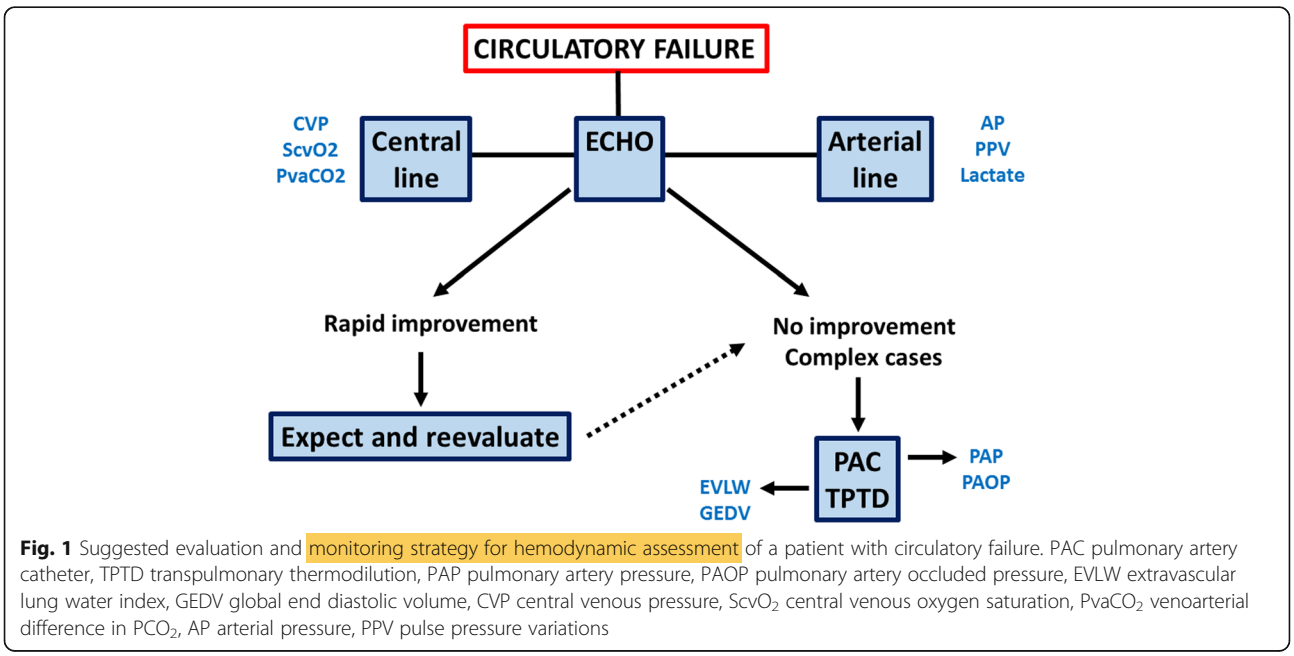

Fig. 1 Suggested evaluation and monitoring strategy for hemodynamic assessment of a patient with circulatory failure. PAC pulmonary artery catheter, TPTD transpulmonary thermodilution, PAP pulmonary artery pressure, PAOP pulmonary artery occluded pressure, EVLW extravascular lung water index, GEDV global end diastolic volume, CVP central venous pressure, $ScvO_2$ central venous oxygen saturation, $PvaCO_2$ venoarterial difference in PCO_2, AP arterial pressure, PPV pulse pressure variations

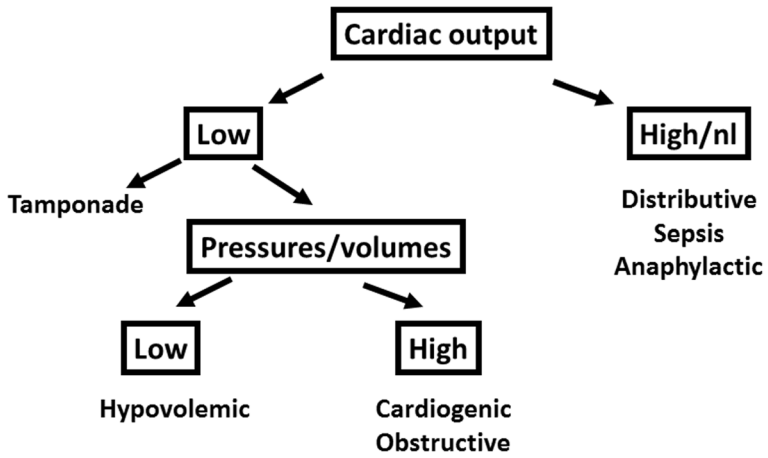

Fig. 2 Diagnostic algorithm for the characterization of different types of shock. nl normal

in hemodynamically stable septic patients is often not related to tissue hypoxia. Sepsis-induced inflammatory mediators accelerate aerobic glycolysis, increasing pyruvate availability. This increase in pyruvate availability can lead to increased lactate production, even in the presence of large amounts of oxygen. In addition to the increased lactate production, a decrease in lactate clearance can participate in hyperlactatemia. In patients with shock, hyperlactatemia is often of hypoxic origin shortly after admission, while hyperlactatemia persisting for more than 1 day is often of nonhypoxic origin [4].

Venoarterial PCO_2 gradients

According to the Fick equation, the difference between venous and arterial PCO_2 is inversely related to flow, provided CO_2 production remains constant. The normal $PvaCO_2$ gradient is lower than or equal to 6 mmHg. When $ScvO_2$ is abnormal, the increase in $PvaCO_2$ mostly reflects the decrease in cardiac output. When $ScvO_2$ is normal, an increase in $PvaCO_2$ reflects microcirculatory dysfunction [5, 6].

Interestingly, the increase in $PvaCO_2$ can also reflect occurrence of anaerobic metabolism. In anaerobic conditions, aerobic CO_2 production decreases but CO_2 is also generated by buffering the protons generated by ATP hydrolysis so that CO_2 production becomes higher than VO_2. Accordingly, the respiratory quotient becomes higher than 1. The respiratory quotient can be approximated by dividing $PvaCO_2$ by arteriovenous O_2 difference, and a ratio above 1.3 suggests anaerobic metabolism. In order to eliminate potential interference with the Haldane effect, the ratio between venoarterial CO_2 content/arteriovenous O_2 difference is computed, with a ratio above 1 reflecting anaerobic metabolism.

In patients with septic shock, Ospina-Tascon et al. [7] demonstrated that a venoarterial CO_2 content/arteriovenous O_2 difference ratio above 1 was associated with a poor outcome.

How to combine lactate, venoarterial PCO_2 gradients, and $ScvO_2$ measurements?

Combining lactate, CO_2 differences, and $ScvO_2$ can help to discriminate between normal and abnormal patterns, and to identify which part of the system is mostly contributing to these alterations. Of course, combination of several processes may occur (i.e., low cardiac output and microvascular alterations) but one often prevails over the other. The decision algorithm is shown in Fig. 3.

Microcirculation assessment

In patients with circulatory failure, organ perfusion is often decreased as a result of a low cardiac output or perfusion pressure. However, tissue perfusion can remain altered even after achievement of within-target cardiac output and arterial pressure. The microcirculation is the part of the circulation responsible for fine tuning the distribution of flow at the organ level. Alterations in microvascular perfusion occur in sepsis and septic shock [8], as well as in cardiogenic shock [9]. The severity and the duration of microcirculatory alterations are related to the occurrence of organ dysfunction and risk of death [10]. Different mechanisms have been implicated in the development of these alterations including loss of communication between vascular segments, impaired endothelial vasoreactivity, alterations in red and white blood cell rheology, alteration in endothelial glycocalyx, platelet aggregation, and microthrombosis. In addition to the alterations in microvascular perfusion, alteration in microvascular endothelium is associated with activation of coagulation and inflammation, reactive oxygen species generation, and permeability alterations [11].

Microvascular perfusion can be monitored by several techniques, but direct videomicroscopy is probably the

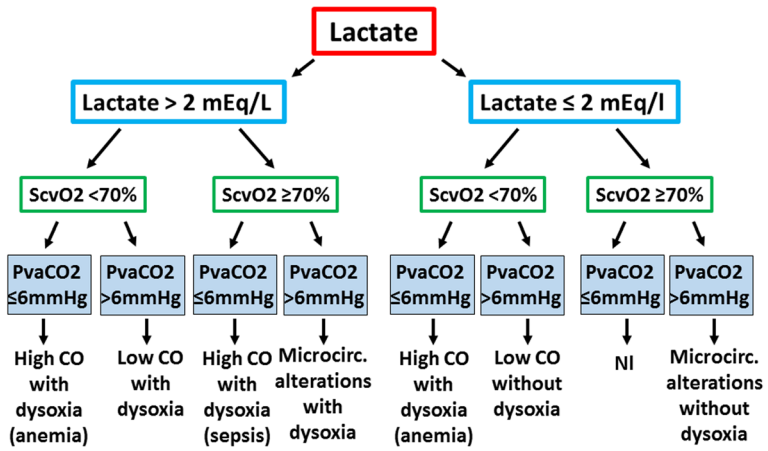

Fig. 3 Interpretation of measurements of lactate, central venous oxygen saturation, and venoarterial PCO_2 gradients. $PvaCO_2$ venoarterial difference in PCO_2, $ScvO_2$ central venous oxygen saturation, Microcirc. microcirculation, NI normal

most appropriate method as it allows one to detect heterogeneity of perfusion, which is the hallmark of these alterations [12]. In normal conditions, microvascular perfusion is quite homogeneous with a density of perfused vessels that increases or decreases in proportion to metabolic needs. In septic shock, microvascular perfusion is characterized not only by a decrease in vessel density but mostly by heterogeneity in perfusion, with nonperfused vessels in close vicinity to well perfused vessels [8–10]. The consequence is a decrease in perfused vascular density and microvascular shunting, resulting in hypoxic zones while venous saturation is increased.

Therapeutic approach

The therapeutic approach should be guided by the hemodynamic monitoring variables. An important question is whether therapy should be protocolized or individualized. Protocolized hemodynamic resuscitation is based on the concept that similar target values should be achieved in all patients, and these targets are determined on the basis that the majority of the patients reaching these goals would have a better outcome. However, some patients may be exposed to the side effects of the therapies applied to reach these goals when reaching lower goals was sufficient.

Fluid management

Fluid management is the cornerstone for the resuscitation of the septic patient, aiming at improved tissue perfusion through an increase in cardiac output. While most patients are usually fluid responsive in the initial stages, fluid resuscitation becomes more challenging at a later stage as many patients may no longer be fluid responsive. In addition, a positive fluid balance, especially at later stages, is associated with poor outcome. Hence, several approaches can be used to predict the response to fluids. Static measurements of preload such as CVP are only useful at their extreme values [13]. Targeting a specific CVP value is only valid at the population level, as close to two-thirds of the patients respond to fluids when baseline CVP is below 8 mmHg and two-thirds do not respond when CVP is higher than 12 mmHg [14]. Use of dynamic tests allows prediction of the response to fluids at the individual level. Among the most attractive tests, respiratory variations in stroke volume (directly measured by different pulse contour techniques or by Doppler ultrasounds) or its derivative variations in pulse pressure can reliably predict the response to fluids when several pre-requirements are met (absence of arrhythmias, tidal volume larger than 8 ml/kg, no respiratory movements, etc.). Passive leg raising is another reliable test, but this requires a fast-response cardiac output monitor and can be fastidious if it has to be repeated frequently. These dynamic tests are now recommended in recent guidelines [3].

An alternative is the so-called mini fluid challenge. It has been proposed that administration of a limited amount of fluids (~100 ml) in a short period of time may predict the administration of further fluids [15]. This concept is only partly valid: if a patient does not respond to the first bolus, there is very limited chance that they will respond to further fluid administration. However, a positive response to the first bolus does not imply a response to further fluid administration (and the trials were biased as the response to the first bolus was integrated in the assessment of the total amount of fluids). If anything it should be the contrary, as the likelihood of the response to fluids in preload responsive patients (and thus on the ascending part of the Starling relationship) is higher with the initial bolus than with later boluses. It is nevertheless safer to repeatedly

administer small boluses of fluids, evaluating their effects, and to predict the response to fluids before the next bolus, than to administer large boluses of fluids once patients are predicted to be fluid responsive. The decision algorithm is shown in Fig. 4.

Blood pressure

Blood pressure is a resuscitative target that has been investigated broadly. Guidelines recommend reaching a mean arterial pressure of 65 mmHg while recognizing that some patients may require higher values [3, 16]. This target is based on observational data reporting higher death rates when this target is not reached, while reaching higher values was not associated with a better outcome. Nevertheless, small-sized studies have shown a huge variability in the response to increasing mean arterial pressure to higher targets, suggesting that some patients may benefit from higher values [17, 18]. In a multicentric randomized trial including 776 patients in septic shock, no difference in 28-day mortality was observed between patients allocated to 65 or 85 mmHg. Interestingly, there was a lower incidence of acute kidney injury in the previously hypertensive patients allocated to the higher target [19]. As a result of the higher doses of norepinephrine that were required to reach the higher target, the incidence of atrial fibrillation was also significantly higher in that group. Hence, higher targets cannot be recommended in all patients. This study nicely illustrates that minimal targets should be reached in all patients and that, if needed, higher targets can be considered in some patients. If higher targets are considered, it is important to evaluate whether the patient responds adequately to the therapy, illustrating the need to measure the variable that is expected to be corrected.

Early goal directed therapy vs individualized approach

Early goal directed therapy (EGDT) is the second target that has been studied extensively in septic shock patients.

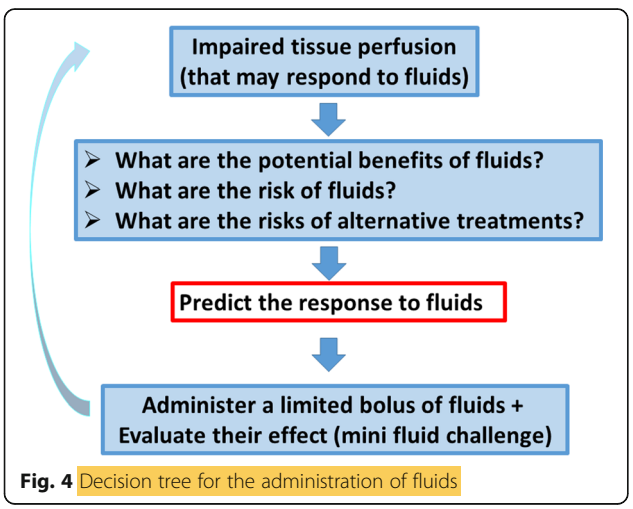

Fig. 4 Decision tree for the administration of fluids

Of note, the term EGDT has become evasive as it was interpreted in many directions, so its initial meaning is sometimes lost. For some, EGDT represents aggressive fluid resuscitation, sometimes based on CVP, for others it represents optimal early hemodynamic resuscitation, for others the prompt use of broad-spectrum antibiotics, and so forth. EGDT consists of the optimization of oxygen transport (DO_2) based on measurements of $ScvO_2$ and administration of fluids, red blood cell transfusions, and inotropes. The concept of EGDT was initially tested by Rivers et al. [20] who demonstrated in a randomized trial including 263 patients with septic shock that EGDT markedly decreased 28-day mortality from 49% in the control group to 33% in EGDT patients. Even though the results of this study created an inspiring wave for early resuscitation, they also generated some debate, especially as the concept was brought into a resuscitation package, the so-called bundles, that initially were suggested as a help to guide resuscitation of septic patients, especially in difficult environments (when critical care specialists are not available), and were then moved into a law-enforced mandatory bundle. This was of course highly criticized as some part of the bundles (i.e., CVP/MAP) used elements that were present in both trial arms and could not be responsible for the differences in outcome between the two arms.

Several large-scale randomized trials failed to reproduce these results [21]. Does this mean that the concept is dead? Probably not, as many factors differed between the different trials [22]. First, $ScvO_2$ at inclusion was already within target in more than 75% of the cases in the recent trials, while it was markedly abnormal in the Rivers et al. trial. Second, the patients included in the recent trials were much less severe, as reflected by their mortality rates but also by the fact that up to 20% of the patients were not admitted to the ICU, even though presenting the same inclusion criteria at baseline. As there was no harm objectivized in the new trials, a reasonable approach may be that EGDT should not be used in all patients with sepsis but can (should?) still be implemented in the most severe, especially if presenting with low $ScvO_2$ at baseline. It should nevertheless be noted that high $ScvO_2$, together with signs of tissue hypoperfusion and organ dysfunction, is not reassuring. High $ScvO_2$ is associated also with a poor outcome and may represent microvascular alterations as well as mitochondrial dysfunction.

The second aspect of the bundle that was criticized was the use of CVP to guide fluid resuscitation. Indeed, initial bundles recommended maintaining CVP between 8 and 12 mmHg. While this may be relatively satisfactory on a statistical basis, as many (2/3) of the patients with CVP values below 8 mmHg would respond to fluids and as most of the patients with CVP > 12 mmHg

will not respond to fluids [23], the use of CVP for the prediction of response to fluids is far from optimal even though used frequently [24]. The new version of the Surviving Sepsis Campaign Guidelines takes this aspect into account for the guidance of fluid resuscitation: "We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (Best Practice Statement)" [16]. The frequent reassessment is based on the use of clinically relevant variables, hemodynamic monitoring, and the use of dynamic over static variables to predict fluid responsiveness, where available [16]. This is a major advance toward individualization of EGDT procedures that is a further step forward in improving the care of septic patients [25].

Treatment of microvascular disorders

How to manipulate the microcirculation? Increasing flow without recruiting the microcirculation is ineffective. Fluids, at the early stages, improve the microcirculation but this effect is blunted at later stages [26, 27]. Interestingly, when fluids had positive effects on the microcirculation, this translated into an improvement in organ dysfunction score the next day [28]. Dobutamine may increase microvascular perfusion, but this effect is often limited [29, 30]. The use of vasodilatory agents has been proposed [31] but there is still insufficient evidence to support their use [32]. In particular, due to their absence of selectivity, these can also dilate already perfused vessels and lead to a steal phenomenon. Modulation of endothelial nitric oxide synthase appears promising [33]. More data are required before using the microcirculation as a direct therapeutic target, it is nevertheless important to understand what could be the potential impact of our interventions on the microcirculation.

Evaluation of and therapeutic approach for cardiovascular dysfunction

Cardiac output measurements provide only one part of the information. However, it is very important to evaluate whether or not cardiac output is adequate. Adequacy of cardiac output can be evaluated by $ScvO_2$ or SvO_2, in addition to signs of tissue perfusion.

In addition, measurements of filling pressures or volumes of cardiac chambers can be helpful to evaluate the cardiovascular performance [1].

When deciding to treat or not an alteration in myocardial contractility, it is important to evaluate the consequences of the impaired contractility: is cardiac output inadequate and is it associated with impaired tissue perfusion? Indeed, the relationship between contractility and cardiac output is relatively loose [34]. Some patients may have decreased contractility with preserved cardiac output, and these patients should not be treated with inotropic agents [34]. Other patients may have a low cardiac output and these patients should also not be treated with inotropic agents. Only patients with a low cardiac output related to an impaired contractility may benefit from inotropic agents.

A recent trial illustrated the need for individualizing therapy in this domain. In the trial administering levosimendan to patients with septic shock, the addition of levosimendan to standard treatment was not associated with a lower incidence of sepsis-induced organ dysfunction or lower mortality [35]. However, levosimendan was associated with higher risk of tachyarrhythmia. Admittedly, this trial was not optimally designed, as cardiac output and cardiac function were not evaluated so that patients with high cardiac output and/or high contractility may have received levosimendan even when not required or even when contraindicated. Indeed, one-fifth of the patients with septic shock may present left ventricular outflow tract or mid-ventricular obstruction [36], which contraindicates the use of inotropic stimulation. Hence, individualization of therapies, based on hemodynamic assessment, is the preferred approach in these patients.

Conclusion

Hemodynamic assessment remains an important aspect of the care of the critically ill patient. Several tools are available, and the selection of the different tools should be based on the potential interest in a given patient of the measured variables. More than the tools, the use of the measured variables is of critical relevance. The different variables should be integrated into decision and management pathways, and therapies adapted accordingly.

Abbreviations

CVP: Central venous pressure; DO_2: Oxygen delivery; EGDT: Early goal directed therapy; $ScvO_2$: Central venous oxygen saturation; VO_2: Oxygen consumption

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Critical Care

REVIEW Open Access

Time-sensitive therapeutics

John J. Marini

Abstract

Much of what we now do in Critical Care carries an air of urgency, a pressing need to discover and act, with priorities biased toward a reactive response. However, efficacy often depends not simply upon what we do, but rather on whether, when, and how persistently we intervene. The practice of medicine is based upon diagnosis, integration of multiple sources of information, keen judgment, and appropriate intervention. Timing may not be everything, as the well-known adage suggests, but in the intensive care unit (ICU) timing issues clearly deserve more attention than they are currently given. Successfully or not, the patient is continually attempting to adapt and re-adjust to acute illness, and this adaptive process takes time. Knowing that much of what we do carries potential for unintended harm as well as benefit, the trick is to decide whether the patient is winning or losing the adaptive struggle and whether we can help. Costs of modern ICU care is enormous and the trend line shows no encouraging sign of moderation. To sharpen our effectiveness, reduce hazard, and pare cost we must learn to time our interventions, help the patient adapt, and at times withhold treatment rather than jump in on the impulse to rescue and/or to alter the natural course of disease. Indeed, much of the progress made in our discipline has resulted both from timely intervention when called for and avoidance or moderation of hazardous treatments when not. Time-sensitive ICU therapeutics requires awareness of trends in key parameters, respect for adaptive chronobiology, level-headed evaluation of the need to intervene, and awareness of the costs of disrupting a potentially constructive natural response to illness.

Keywords: Adaptation, Timing, Homeostasis, Bio-rhythms, Circadian, Stages of illness

Background

Intensivists have become adept in caring for critically ill patients and now enable many to survive illnesses that in prior years would have proven fatal. Improved survival has resulted not only from better understanding of individual diseases and implementation of useful innovations, but also from optimizing intensive care unit (ICU) organization, standardizing best practices, and improving key processes of care delivery. This decline in short-term mortality is a major achievement, but there is increasing awareness that chronic critical illness often continues well beyond ICU discharge, often culminating in long-term morbidity and mortality [1]. Why does this happen? The traditional principles of applied physiology provide the foundation upon which personalization and optimization of critical care are currently based. While these serve well during the rescue phase of intensive care, it is the thesis of this paper that our current knowledge of the *physiology of critical illness* is at a rudimentary stage and that we know relatively little about the continuously interactive processes—both natural and iatrogenic—that determine either an ultimately catastrophic outcome or appropriately adaptive response to the challenges of critical illness (Table 1).

Almost all treatments that we provide to the critically ill patient hold potential for injury to both targeted and non-targeted organs. Ideally, selection of treatment, dose, and duration should be based on awareness of the underlying dynamics of the evolving pathophysiology. It can be reasonably argued that well-intentioned treatments often frustrate and delay an appropriate adaptive response. Moreover, innate responses of the body to critical illness may themselves be inappropriate. Whereas it is an unassailable fact that homeostatic regulation is indispensable during health and moderate illnesses, the same may not be true in the presence of overwhelming challenge.

In his famous book "The Wisdom of the Body", Walter B. Cannon outlined the intricate feedback mechanisms which allow and modulate appropriate responses to

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Table 1 Patho-physiology of critical illness continually evolves

- Almost all treatments hold potential for injury to both targeted and untargeted organs.
- Selection of treatment, dose, and duration should ideally be based on awareness of underlying dynamism of evolving pathophysiology.
- *Thesis:* Well-intentioned treatments often frustrate and delay an appropriate adaptive response.

challenges to homeostasis [2]. He and others called attention to the intricacies of innate biorhythms which during health maintain an exquisite balance. Critical illness and treatments disrupt normal physiology and adaptive mechanisms, and often ignore biorhythms, destabilizing and perhaps invalidating normal physiological controls. Increasing evidence indicates that the body does not remain invariably "wise" during catastrophic illness.

Evolution may not have provided for appropriate responses to severe acute injuries. Until recent decades, such illnesses were not survivable. Indeed, to strengthen the gene pool, evolutionary pressures may have been biased toward ensuring an adverse outcome for susceptible individuals. In other words, evolved responses to life-threatening stresses might not be on side. The exuberant "rogue inflammation" response to a septic challenge provides one good example of how an exaggerated, counterproductive reaction may provoke or promote organ damage [3].

Enumerating the key characteristics of health and disease underlines the importance of time-based physiology to the expression and resolution of critical illness (Table 2). Pattern variation, appropriate corrections in response to moderate stress (allostasis), and diurnal biorhythms are expressions of adequate strength and endurance potential. During life-threatening critical illness these are replaced by the pattern rigidity, disproportionate reactions, and monotony that indicate loss of compensatory reserve [4, 5]. In health and in response to tolerable illness, gradual transitions prevail and homeostatic adaptation is expressed in response to stressors, whether mechanical, environmental, or biochemical. In severe disease, transitions are abrupt and there is a failure to adapt appropriately to the imposed stressor. Such inflexibility is often coupled to dysfunctionally exuberant or inadequate responses.

Our medical job is to help the patient recover adaptive homeostatic control. In order to do this, the critical caregiver should aim to first attenuate dysfunctional early responses and then promote gradually adaptive homeostatic ones. To accomplish these goals, good intervention timing and dosing are essential (Table 3). Adaptive accommodation to a seriously stressful challenge often takes time to fully develop. A good example is provided by the dynamics of the heat shock response. After exposure to a brief but strong heating stress pulse, the synthesis of cell protective heat shock proteins is initiated quickly but only peaks many hours later [6]. Once fully developed, this protection mitigates the damage resulting from a potentially injurious pattern of mechanical ventilation [7]. On the other hand, heating encountered synchronously with a similar injury-provoking ventilation stimulus markedly accentuates the deterioration of lung mechanics, oxygen exchange, and tissue injury [8].

Although the underlying and continuously evolving patterns of injury and response usually take place below the threshold of our clinical recognition, our therapeutic interventions influence the eventual outcome due to poorly timed imposition, maintenance, or withdrawal of treatment. Foremost among those that have received recent attention are excessive sedation and enforced bed rest for prolonged periods [9]. Undoubtedly there are others; in fact, I strongly believe that many of our current practices that encourage monotony (e.g., volume controlled ventilation, sustained drug infusions and feedings) or squelch variation (e.g., unnecessarily rigid targeting of isolated hemodynamic variables such as blood pressure) are counterproductive to long-term adaptive response.

In critical care, imprecise definitions and the impersonal approaches of randomized trials threaten to oversimplify management and encourage neglect of personalized physiologic dynamics. Randomized clinical trials, though often instructive and useful for hypothesis generation, often guide decision-making with answers that are interpreted to be 'all or none' categorical directives suitable for encoding into care protocols. Although generally helpful for treating the targeted population at large, at times these approaches may conflict with optimized care for the individual. Following such population-based 'answers,' many critical care practitioners consider low tidal volumes to be appropriate for everyone [10], conservative fluid therapy invariably to be superior to liberal administration at all phases of acute respiratory distress syndrome (ARDS) [11], steroids to be inappropriate for all stages and forms of lung injury [12], etc. In reality, few practice-altering trials have been designed with deep and detailed

Table 2 Key characteristics of health and disease

Health	Critical illness
Variation	Rigidity
Homeostasis	Disproportionate reactions
Diurnal biorhythms	Monotony
Adaptability	Loss of adaptive reserve

Table 3 Timing issues in critical illness

- Stage of disease and recovery
- Intensity of management
- Length of application
- Adaptation
- Diurnal physiology

understanding of the underlying mechanisms or account for individual variation, complexity, biological variation, and the timing of pathophysiology and treatment effects. Our current management approaches can be viewed as rather inflexible and primarily reactive management when, in fact, improved patient health demands proactive, time sensitive, and flexible strategies. The four Ds of drug, dose, duration, and de-escalation are applicable to many ICU interventions, including fluid therapy, antibiotics, and ventilatory support [13]. When facing a complex and evolving problem, the clinician requires appropriate tools, functional probes, and careful reasoning. The need for midcourse corrections should be anticipated and frequently made in response to monitored observations or relevant variables. These decisions must be rooted in physiological understanding. Sadly, however, that educational foundation and skill set has been seriously eroded by the electronically aided, "look it up" medical management structures in which we now work [14].

Timing issues in critical illness

Precise and personalized critical care management requires awareness of certain timing issues that are often neglected. The critically ill patient passes through stages of disease and recovery which demand differing intensities of therapeutic intervention as well as keen awareness of when to withdraw external supports so as to allow adaptation and re-establishment of diurnal homeostatic physiology. The stages of critical illness can be viewed as progressing from rescue to stabilization, strengthening, and recovery. Wound healing progresses along such a timeline [15], and increasingly we are paying attention to the facts that pathologic expression varies widely among patients and that reactions to treatments continually evolve and change. We have been relatively slow to learn that responsiveness to many interventions depends on the stage of illness. In sepsis, immediate intervention with appropriate antibiotics is a key to survival, whereas prioritizing abrupt and aggressive fluid resuscitation may be somewhat less helpful [16]. Regarding ARDS, these stage-dependent interventions include positive end-expiratory pressure (PEEP) [17], prone positioning [18], recruitment maneuvers [19], neuromuscular blockade [20], corticosteroids [21], fluid management [22], and undoubtedly other common interventions that we have not yet seriously questioned (Table 4). For example, the internal endocrine environment continuously evolves as the acute inflammation of sepsis and ARDS progresses into the chronic and recovery phases [23]. Considerable experimental evidence indicates that the stages of illness should dictate metabolic therapy as well [24], with appropriate nutritional support and gut microbiome health depending on the composition and the timing of component feedings [25].

Table 4 Responsiveness to many interventions for ARDS depends on the stage of illness

- Positive end-expiratory pressure (PEEP)
- Prone positioning
- Recruitment
- Neuromuscular blockade
- Steroids
- Nutrition

The intensity issue is undoubtedly important but frequently ignored. For example, minute ventilation can be considered an intensity variable that determines whether an identical driving pressure for ventilation may cause injury or be well tolerated. The total power that lung tissue must endure is determined by the frequency of breathing as well as the conformation of the individual tidal cycle [26, 27]. The flow profile of each individual breath determines the rate at which alveolar pressure develops, and experimentally has been shown to be important in minimizing ventilator-induced lung injury [28, 29]. At the bedside, however, the inspiratory to expiratory ratio and inspiratory flow profile are given relatively little attention. Extending the duration of inspiration and 'squaring' the inspiratory flow profile have been shown in both small and large animal models to blunt the degree of injury inflicted by the same driving pressure. How fast strain is achieved is especially important when the lung is subjected to high stretching forces. In fact a recent experimental study suggests the driving airway or transpulmonary pressures—both based on static variables of plateau and PEEP—did not predict lung outcome when flow rate was altered through a wide range [30].

It is interesting to consider the question as to why early short-term muscle relaxants administered for a brief period early in ARDS demonstrated benefit which emerged much later with regard to mortality [20]. It is tempting to speculate that by attenuating the intensity of the initial native response we interrupt a catastrophic early feedback sequence which eventually would result in the patient's demise. Along a similar vein, early sepsis intervention, though obviously important, sometimes may carry unintended consequences in situations where sudden cell lysis under the influence of antibiotics provokes inflammation and threatens survival [31]. Again, the unchecked exuberance of the body's innate response may not always be helpful; this idea is given further support by demonstrations that early corticosteroids improve all-cause mortality in community-acquired pneumonia and blunt tendency for treatment failure [32]. In fact, early steroids appear to help stabilize severe pneumonia [33].

We have also learned harsh lessons regarding the appropriate length of application of our drugs and treatments. After the second phase of stabilization, decisions

must be made regarding duration of treatment and the program for weaning support. It has been suggested that the reasons why corticosteroids hastened liberation from mechanical ventilator but failed to improve survival in the ARDS Network trial [34] are linked to inadequate duration of their use; in other words, steroids were stopped too soon. Perhaps the more common problem, however, is that we apply aggressive treatments for too long. It is clear that sustained steroid and neuromuscular blocking agents will weaken or atrophy muscle, producing ventilator-induced diaphragmatic dysfunction and peripheral muscle weakness that delay recovery [35, 36]. Excessive and long-term use of sedation is strongly suspected of contributing to delirium and sustained cognitive impairment in all age groups after critical illness. A link has been established between duration of delirium and long-term impairment of cognition [37]. Perhaps by using less sedation and fewer opiates we may mitigate this process.

One of the most important timing issues of critical illness concerns our interference with the body's natural adaptive processes. The normal human body has an incredible capacity to adapt to stress. Endurance athletes have completed more than 50 marathons on consecutive days [38], high-altitude acclimatization has allowed multiple climbers to ascend Mount Everest without oxygen [39], and extraordinary adaptation to low temperature has been demonstrated by motivated and gradually trained individuals [40]. However, the capacity for the critically ill to adapt to the stresses of acute and subacute disease has not been extensively or systematically probed. Nevertheless, permissive hypercapnia [41] and more recently graded permissive hypoxemia [42] appear to offer well-tolerated alternatives to potentially noxious interventions such as high pressure ventilation and high inspired concentrations of oxygen. It has been argued that we should more aggressively encourage adaptation in the ICU by resetting our targets and gradually but methodically reloading the patient's systems by graded withdrawal of supports required to sustain life during the initial days [43]. Such retargeting might be directed toward goals for blood pressure, hemoglobin, muscular workloads, and position, as well as blood gases. We know little about the advisability of imposing stress for brief periods in a fashion parallel to that of heat shock exposure. It has been shown, however, that adaptive ischemic preconditioning (intentional "stunning") reduces infarct size in experimental coronary occlusion [44]. It is been suggested that inter-organ adaptive preconditioning (limb stress helping to condition other organs, for example) might also occur via hormonal or neural reflex pathways [45].

Were encouraging adaptation to critical illness a viable possibility, there would be a modified two-stage approach to management. The initial rescue phase would minimize demands, providing full support, encouraging gentle transitions and tolerance of monotonous supportive treatments such as continuous infusions and fully controlled mechanical ventilation. In the adaptation phase, there would be intermittent stresses in rest periods, with ongoing targeted reductions of vital supports to acclimatize the patient. These would include FiO_2, ventilating pressure, vasopressors, and body position. Variability—not monotony—would be encouraged. Although, "ICU conditioning" is attractive in concept, major questions remain unanswered before such an approach can be advocated. These include: Are injured tissues capable of stress conditioning? Or are they hibernating or to injured to respond? Which variables should we monitor to guide the rate of withdrawal of life-sustaining measures? Can we rely on bedside biomarkers of distress and reserve? Can we automatically program or protocolize the graded withdrawal of support? Which conditioning pattern is optimal?

An important but largely neglected aspect of our management of the critically ill relates to diurnal and circadian physiology [46] (Fig. 1). Although we are well aware of sleep-wake cycles, most practitioners are relatively oblivious to the brain organ crosstalk that may determine eventual outcome. Neural pathways and hormonal communications link many organs with the brain. Indeed, the potential for two-way neuroinflammatory linkage has been well described [47]. Recent reports regarding patient-ventilator asynchrony strongly suggest that important prognostic information may be gleaned from determining its incidence and clustering, and that ignoring the demands of the neural controller of the breathing pattern might even contribute to adverse outcomes through as yet undetermined pathways [48].

Most organ systems have some degree of brain-influenced circadian rhythm. The supra-chiasmatic nucleus (SCN), which itself is influenced by light exposure, motion, and other cues, is the master clock that regulates the peripheral clocks of other organ systems and sets the circadian

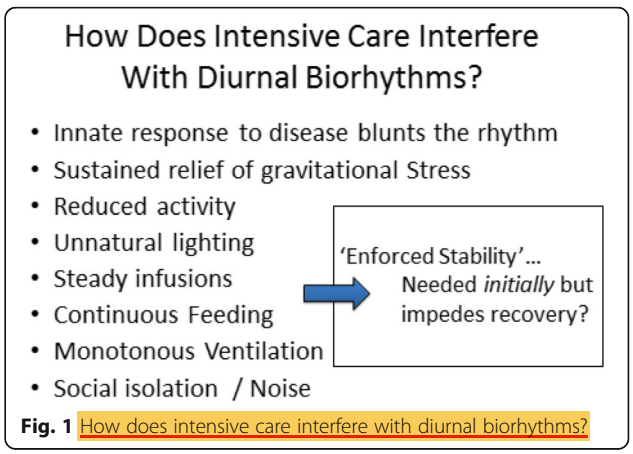

Fig. 1 How does intensive care interfere with diurnal biorhythms?

rhythms of temperature, sleep-wake cycles, and metabolic, neuroendocrine, and cardiovascular regulations [49]. Melatonin appears to be central to such connections; its activity affects not only wakefulness but also endocrine function such as growth hormone and cortisol regulation, cardiovascular function in terms of heart rate variability and vascular tone, and immune cell function [50]. Melatonin strongly influences the inflammatory response via the antioxidant cascade, reducing oxidative stress when levels are high. The complexity of such interactions will require considerable additional research in the intensive care setting to determine the importance of maintaining appropriate diurnal biorhythms. Whatever the explanation, however, diurnal variation of inflammatory and oxidative sensitivity to lipopolysaccharide (LPS) has been shown in humans as well as experimental animals [51]. Presentation of LPS to rats at the wrong time of their diurnal cycle predisposes to severe injury or death, whereas animals challenged at the opposite time in the diurnal pattern show much greater tolerance.

The therapies that we apply in the ICU cause circadian dysrhythmias [52, 53]. The deleterious effects of noise, artificial light, stress, medical interventions, sedatives, and anesthetics interact with genetic predisposition to cause asynchrony. Innate response to disease blunts normal biorhythms, but we accentuate these tendencies with sustained relief of gravitational stress-reduced activity, steady infusions of drugs, continuous feedings, monotonous ventilation, social isolation, excessive noise, etc. Although this enforced stability may be needed initially, it likely impedes recovery when sustained. There are likely to be multiple contributors to diurnal biorhythm asynchrony. Critical illness alters the amplitude and variability of neuroendocrine hormones, a phenomenon which may contribute to an observed circadian incidence of cardiac arrhythmia such as ventricular tachycardia in critically ill patients, with a greater incidence during the day and lesser incidence at night. Considerable experimental evidence indicates that circadian disruption predisposes to cardiac arrhythmia [52] and disorders inflammatory responses [53]. Sleep deprivation, a well-recognized problem in critical care units, may itself blunt immune competence [54]. The role of circadian disruption in the generation of delirium has been recently explored by attempting to intervene by imposing diurnal light amplification [55]. Failure of light therapy alone to influence the incidence of delirium simply underscores that many factors contribute to this problem [56] and, as has already been mentioned, multiple factors apart from light exposure contribute to diurnal biorhythm patterns. Physical activity, auditory cues, and gravitational stresses may help re-establish appropriate diurnal physiology.

New approaches to understanding dynamic physiology and time-based therapeutics will require better matching of patient to treatment, better tracking of the evolution of the underlying physiology, carefully modulated intensity and duration of therapeutic interventions, attention to re-establishing natural biorhythms, and perhaps deliberate stress conditioning (Table 5). Although we currently lack suitable biomarkers, certain dynamic functional probes of patient capability have already been implemented. One example is the awake and breathe (ABC) trial in which an awakening intervention, followed by spontaneous breathing, showed better results than the conventional approach lacking the awakening component [57]. Clinicians have become adept at using certain bedside biomarkers such as brain natriuretic peptide (BNP), C-reactive protein (CRP), and procalcitonin. Indeed BNP may provide a good weanability indicator in well selected patients [58]. These humoral bio-markers, however, are not well suited to the moment by moment tracking of the patient's underlying status with regard to the stabilization and recovery phases of illness. The bedside biomarkers of tomorrow, such as genomics, transcriptomics, proteomics, and metabolomics, offer both promise and limitation [59]. We currently lack suitable humoral biomarkers that pinpoint the stage of recovery. Associating detailed biochemical and physiologic information with newly developed technologies, however, may eventually disclose informative patterns of response. Certain physiological observations such as temperature pattern may eventually be integrated by "big data" analytics into important decision supports [60, 61]. Perhaps for the first time in history the complexity of continuously evolving molecular interactions may be monitored and trended to track the underlying dynamic physiology of critical illness. Such innovations point the way to time-sensitive individualized care throughout the continuum of life-threatening disease [62].

Summary

New approaches to time-sensitive dynamic physiology include better matching of patient to treatment, tracking the evolution of the underlying physiology with functional monitoring, following trends of integrated variables and selected biomarkers, and modulating the intensity and duration of our life supports. We need to

Table 5 New approaches to time sensitive dynamic physiology

- Precisely match patient to treatment
  - Gene arrays
  - Big data analytics
    - Selection
    - Trending of progress and response
- Track the evolution of the underlying physiology
  - Functional monitoring
  - Follow trends of integrated variables
  - Selective biomarkers
- Modulate intensity
- Optimize duration

Table 6 A two-stage approach to critical care

- Rescue phase
  - Minimize demand and establish stability
  - Full support/gentle transitions
  - Take control (monotony may be needed)
- Adaptation phase
  - Intermittent stresses and rest periods
  - Ongoing targeted reductions of vital supports (acclimatize)
    - FiO_2
    - Ventilating pressure
    - Vasopressors
    - Positioning
  - Encourage variability

restore circadian rhythms by providing the appropriate ambient environment, promoting activity and gravitational stress, and encouraging natural sleep-wake cycles by physical measures, perhaps aided by pharmacological adjuvants such as modafinil and melatonin. We require improved research methodologies that employ more biologically plausible disease models that allow study over extended periods so as to pursue our time-weighted research focus. We need to keep in mind a two-stage approach that stabilizes the early response and then encourages recovery of adaptive homeostasis. In doing so we may eventually flip the switch from reactive to better informed, time-sensitive, proactive therapeutics (Table 6).

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