Curr Pulmonol Rep (2017) 6:54–57
DOI 10.1007/s13665-017-0166-z

Persistent, Immunosuppression, Inflammation, Catabolism Syndrome and Diaphragmatic Dysfunction

Martin D. Rosenthal[1,2] · **Cameron M. Rosenthal**[3] · **Frederick A. Moore**[1] · **Robert G. Martindale**[4]

Published online: 24 January 2017

Abstract
Purpose of review The purpose of this review is to explore the relationship between ICU-acquired weakness, diaphragm dysfunction, and persistent immunosuppression, inflammation, catabolism syndrome (PICS), as well as if there are any therapies that can help rehabilitate these patients.
Recent findings Literature pertaining to PICS is scant, as it is a relatively new description of encompassing chronic multiorgan dysfunction and chronic critical illness. PICS patients invariably have persistent diaphragm dysfunction and ICU-acquired weakness. To better understand how severe each state is and how they are related, the literature was reviewed.
Summary Combating diaphragm dysfunction, ICU-acquired weakness, and PICS is a difficult task for intensivists. There are certain nutritional supplements that can help rehabilitate these patients, but there is no silver bullet right now. Helping these patients currently takes a multimodal approach.

Keywords PICS (persistent immunosuppression, inflammation, catabolism syndrome) · Diaphragm dysfunction · ICU-acquired weakness (ICUAW) · Arginine · Leucine · Specialized pro-resolving mediators

This article is part of the Topical Collection on *Nutrition and Clinical Care*

✉ Martin D. Rosenthal
martin.rosenthal@surgery.ufl.edu

[1] Department of Surgery, University of Florida, Gainesville, FL, USA

[2] College of Medicine, Department of Surgery, University of Florida, 1600 SW Archer Rd., Gainesville, FL 32608, USA

[3] Department of Pediatrics, University of Florida, Gainesville, FL, USA

[4] Department of Surgery, Oregon Health and Science, Portland, OR, USA

Introduction

Diaphragm dysfunction, atrophy, and weakness in the intensive care units (ICUs) have long plagued the immobile, chronically ill, catabolic patients who represent ICU-acquired weakness (ICUAW) [1•, 2, 3]. Severe sepsis stands as one of the main culprits for promoting ICUAW, which interestingly is also the main culprit of persistent immunosuppression, inflammation, catabolism syndrome (PICS) [4–7]. What is typically observed in patients with ICUAW as a response to illness is synonymous with the response PICS patients have to sustained catabolism. Using ICUAW as a surrogate for whole body muscle catabolism with wasting, especially in those patients with prolonged mechanical ventilation, we can see how this patient population ends up with diaphragm dysfunction, atrophy, and weakness leading to respiratory insufficiency.

Following severe sepsis, there are simultaneous pro-inflammation (called SIRS) and anti-inflammation (called CARS) systemic responses. In some cases, SIRS becomes overwhelming and can lead to early multiple organ failure (MOF) and even death. Fortunately, modern ICU care is directed at early detection and prevention of this trajectory's fatal expression. If severe sepsis patients do not die of early MOF, there are two alternatives: Either their aberrant immunology rapidly recovers (i.e., achieves homeostasis) or its dysfunction persists and they enter chronic critical illness (CCI) (defined as >14 days in ICU with organ dysfunction). These CCI patients experience ongoing immunosuppression (e.g., lymphopenia) and inflammation (e.g., neutrophilia) that is associated with a persistent acute-phase response (e.g., high CRPs) with ongoing protein catabolism (Fig. 1). It is within

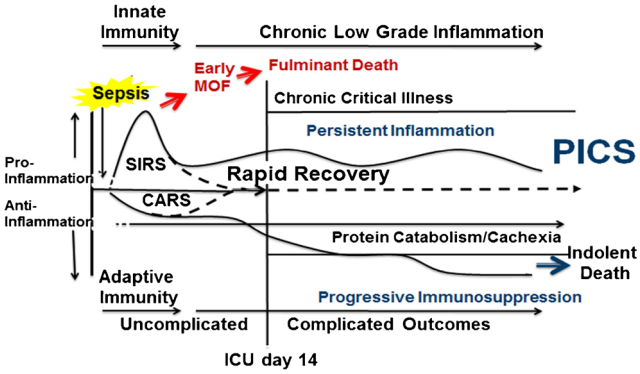

Fig. 1 Used with permission from the Wolters Kluwer Health

this arena that intensivists witness the significant lean muscle mass of ICUAW, diaphragm dysfunction, and ongoing catabolism [8••].

Even despite aggressive nutritional intervention, there is a tremendous loss of lean body mass and proportional decrease in functional status (including respiratory dysfunction from diaphragm atrophy) and poor wound healing. An estimated 30 to 50% of these CCI patients progress into PICS. Clinically, PICS patients suffer from recurrent nosocomial infections and poor wound healing, develop decubitus ulcers and ICUAW, and typically have prolonged mechanical ventilation leading to diaphragm atrophy. These patients typically undergo tracheostomy for respiratory insufficiency and are discharged to long-term acute care (LTAC) facilities where they experience sepsis recidivism requiring re-hospitalization, failure to rehabilitate, and an indolent death [9].

PICS and ICU-Acquired Weakness

The loss of lean body mass in patients with prolonged ICU stays is dramatic. In a classic study, Graham Hill and colleagues performed serial body composition by bioimpedance studies in critically injured patients over 25 days in the ICU. They demonstrated that despite optimal nutritional support, there was an obligatory 16% loss of lean body mass and that excessive administration of substrates was converted into fat. This tremendous loss of lean body mass was recently confirmed by Puthucheary et al. who performed serial ultrasound of the rectus femoris over the first 10 days of ICU stay and demonstrated a 20% decrease in cross-sectional area (CSA) and that a subset of MOF patients lost 30%. Interestingly, at 7 days, protein synthesis was variably increased, but continual breakdown led to negative protein balance despite all patients being fed. Muscle biopsies looking at intracellular regulators of protein homeostasis revealed decreased anabolic and increased catabolic signaling [10]. These studies indicate that simply giving macronutrients is not going to reverse the loss of lean body mass and that interventions are needed to promote anabolism.

Despite best efforts, persistent inflammation increasing metabolic demand, protein catabolism, and disuse atrophy (immobilization of ICU patients) promotes ICUAW. A better understanding of possible intervention could potentially help both patient populations: those with ICUAW and those with PICS. It should be made clear in this manuscript that the authors are not suggesting that all ICUAW patients have PICS, but it is certain that all PICS patients have some varying degree of ICUAW.

PICS and Diaphragm Dysfunction

It has long been accepted that prolonged mechanical ventilation causes diaphragm atrophy, weakness, and ventilator-induced diaphragm dysfunction (VIDD), which can lead to a multitude of poor outcomes including extubation failure, tracheostomy, and pneumonia and even increases mortality [11–13]. Irrespective of the etiology for prolonged mechanical ventilation, patients typically have varying degrees of ICUAW. In an elaborate study by Jung et al., diaphragm function was assessed in 185 patients mechanically ventilated for >48 h. Diaphragm function was assessed by magnetic stimulation of the phrenic nerve while observing change in endotracheal pressure. Of the 185 patients, 40 were diagnosed with ICUAW (based on a Medical Research Council Score <48) and 80% had diaphragm dysfunction defined by an endotracheal pressure change of less than 11 cmH_2O. They concluded that diaphragm dysfunction correlates with ICUAW [13].

This study demonstrates that as a muscle group, the diaphragm is certainly not spared when patients acquire muscle weakness in the ICU. Traditionally, many think of ICUAW afflicting voluntary muscles and the weakness associated with inability to ambulate, but ICUAW spares no muscle group and can have lasting implications on health care cost and recovery. In fact, Hermans et al. published that the cost for this patient population is typically 30.5% higher than a propensity-matched cohort [14]. Various hypotheses have been proposed to why ICUAW occurs: disuse atrophy, protein catabolism, cytokine milieu, decreased nerve stimulation, or a combination of these factors. It is not surprising that cross talk occurs between aggravating factors for ICUAW, VIDD, and PICS, including malnutrition, chronic electrolyte imbalance, hyperglycemia, corticosteroids, muscle relaxants, sepsis, and compromised cardiac function [15, 16].

The PICS patients represent an ongoing catabolic state with tremendous metabolic demand associated with inflammation; the observation seen by Jung et al. should be applied to PICS patients as they have all been critically ill with varying degrees of ICUAW. Despite best efforts in nutritional support, the PICS patient continues to have a net negative protein balance correlating with ICUAW and associated diaphragm dysfunction. De Jonghe demonstrated an association between

respiratory weakness and limb weakness [17]. ICU patients that have difficulty ambulating after critical illness would have ICUAW. If the same patient with ICUAW continues to be critically ill for 14 days, they would have CCI and may fall into the realm of a PICS patient if there is laboratory evidence of ongoing inflammation, immunosuppression, and catabolism (i.e., elevated CRP, low pre-albumin or visceral proteins, and reduced lymphocyte count). With the information provided by Jung and De Jonghe, intensivists should be more diligent towards rehabilitating the pulmonary muscle, as well. These patients should receive physical therapy directed at strengthening both limb muscles and pulmonary muscles and optimizing supplemental nutrition where appropriate, for example increasing protein calories (perhaps an argument for immunomodulatory, immune-enhancing formulas).

PICS and Nutritional Supplementation

After reviewing the literature, several possible therapies became apparent to overcome some of the immunosuppression, inflammation, and catabolism. For the sake of brevity, there are three supplements should be discussed to bring awareness to possible new practices. These supplements decrease the persistent inflammation (specialized pro-resolving mediators), restore immune competence (arginine), and help rebuild lean muscle and combat catabolism (leucine).

Specialized pro-resolving mediators (SPMs) are a purified fish oil that promote resolution of the aberrant inflammatory cascade and could potentially prevent patients with chronic critical illness from progressing to the chronic PICS phenotype [5, 18]. Serhan et al. discovered that SPMs have the ability to decrease inflammation by cessation of leukocyte infiltration and activation and "pro-resolve" inflammation through enhanced macrophage clearance of debris, bacteria, and apoptotic cells [18, 19].

Arginine is an interesting substrate that could help reverse some of the immunosuppression associated with sepsis. It is well established that arginine depletion occurs with increased states of stress [20]. Arginine is structurally part of the zeta chain on T cell receptor (TCR), and arginine deficiency has been shown to render T cells incompetent [21–28]. By supplementing arginine, studies have shown improved T cell function, proliferation, and maturation to better fight infections [28–34].

Leucine is an amino acid that can stimulate the mammalian target of rapamycin (mTOR) pathway to increase protein synthesis and inhibit proteosomal protein breakdown. Leucine stimulates multiple enzymes that ultimately increase either mRNA to produce anabolism (protein synthesis). Through leucine supplementation and mTOR signaling, a PICS patient ought to reduce catabolism and enter an anabolic state to regain muscle mass, increase the possibility of rehab, and regain baseline function/independence once discharged from the ICU.

These three supplements provide interesting possibilities in treating an ever-growing MOF phenotype: PICS. The implications may not be limited with PICS. Further research is warranted to determine whether these supplements have a therapeutic role in treating ICUAW and diaphragm dysfunction, atrophy, and weakness.

Conclusions

Patients with diaphragm dysfunction, ICUAW, and even PICS suffer poor, long-term consequences; typically use tremendous hospital resources; and can be a lofty burden on health care cost. By bringing awareness to an increasingly more prevalent phenotype, PICS, we see that ICUAW and diaphragm dysfunction lie along a spectrum. If the disability lasts long enough, these patients could progress to PICS, which ultimately has a worse prognosis. There is an overwhelming need for more concrete research to combat diaphragm dysfunction, ICUAW, and PICS. Future clinical trials will hopefully elucidate if the three supplements discussed above truly have a positive impact on patient care.

Acknowledgements The investigators acknowledge the contribution of the Sepsis and Critical Illness Research Center Award # P50 GM-111152 from the National Institute of General Medical Sciences.

Compliance with Ethical Standards

Conflict of Interest Martin Rosenthal, Frederick Moore, Cameron Rosenthal, and Robert Martindale declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Financial Disclosure Statement There were no funds provided for this manuscript.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014;370(17):1626–35. **Kress publication in NEJM is a complete review of ICUAW and what it means for critically ill patients' recovery/rehab potential**.
2. Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, et al. An official American Thoracic Society Clinical Practice guideline:

the diagnosis of intensive care unit-acquired weakness in adults. Am J Respir Crit Care Med. 2014;190(12):1437–46.
3. Eikermann M, Latronico N. What is new in prevention of muscle weakness in critically ill patients? Intensive Care Med. 2013;39(12):2200–3.
4. Rosenthal, M., A. Gabrielli, and F. Moore, The evolution of nutritional support in long term ICU patients: from multisystem organ failure to persistent inflammation immunosuppression catabolism syndrome. Minerva Anestesiol, 2015.
5. Rosenthal MD, Moore FA. Persistent inflammatory, immunosuppressed, catabolic syndrome (PICS): a new phenotype of multiple organ failure. J Adv Nutr Hum Metab, 2015;1(1).
6. De Jonghe B, Bastuji-Garin S, Sharshar T, Outin H, Brochard L. Does ICU-acquired paresis lengthen weaning from mechanical ventilation? Intensive Care Med. 2004;30(6):1117–21.
7. De Jonghe B, Sharshar T, Hopkinson N, Outin H. Paresis following mechanical ventilation. Curr Opin Crit Care. 2004;10(1):47–52.
8.•• Vanzant EL, Lopez CM, Ozrazgat-Baslanti T, Ungaro R, Davis R, Cuenca AG, Gentile LF, Nacionales DC, Cuenca AL, Bihorac A, Leeuwenburgh C, Lanz J, Baker HV, McKinley B, Moldawer LL, Moore FA, Efron PA. Persistent inflammation, immunosuppression, and catabolism syndrome after severe blunt trauma. J Trauma Acute Care Surg. 2014. 76(1): p. 21–9; discussion 29–30. **Moore et al. have a current P50 grant studying PICS. There are three specific aims of the P50 grant that allow them to better understand the epidemiology and pathophysiology that produce a PICS patient. Through innovative research, they hope to find potential therapeutic interventions for PICS patients**.
9. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501.
10. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013;310(15):1591–600.
11. Medrinal C, Prieur G, Frenoy E, Robledo Quesada A, Poncet A, Bonnevie T, et al. Respiratory weakness after mechanical ventilation is associated with one-year mortality—a prospective study. Crit Care. 2016;20(1):231.
12. Jung B, Gleeton D, Daurat A, Conseil M, Mahul M, Rao G, et al. Consequences of mechanical ventilation on diaphragmatic function. Rev Mal Respir. 2015;32(4):370–80.
13. Jung B, Moury PH, Mahul M, de Jong A, Galia F, Prades A, et al. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. Intensive Care Med. 2016;42(5):853–61.
14. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2014;190(4):410–20.
15. Martin AD, Smith BK, Davenport PD, Harman E, Gonzalez-Rothi RJ, Baz M, et al. Inspiratory muscle strength training improves weaning outcome in failure to wean patients: a randomized trial. Crit Care. 2011;15(2):R84.
16. Daniel Martin A, Smith BK, Gabrielli A. Mechanical ventilation, diaphragm weakness and weaning: a rehabilitation perspective. Respir Physiol Neurobiol. 2013;189(2):377–83.
17. De Jonghe B, Bastuji-Garin S, Durand MC, Malissin I, Rodrigues P, Cerf C, et al. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. Crit Care Med. 2007;35(9):2007–15.
18. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature. 2014;510(7503):92–101.
19. Serhan CN, Krishnamoorthy S, Recchiuti A, Chiang N. Novel anti-inflammatory—pro-resolving mediators and their receptors. Curr Top Med Chem. 2011;11(6):629–47.
20. Luiking YC, Poeze M, Dejong CH, Ramsay G, Deutz NE. Sepsis: an arginine deficiency state? Crit Care Med. 2004;32(10):2135–45.
21. Taheri F, Ochoa JB, Faghiri Z, Culotta K, Park HJ, Lan MS, et al. L-Arginine regulates the expression of the T-cell receptor zeta chain (CD3zeta) in Jurkat cells. Clin Cancer Res. 2001;7(3 Suppl):958s-965s.
22. Rodriguez PC, Zea AH, Culotta KS, Zabaleta J, Ochoa JB, Ochoa AC. Regulation of T cell receptor CD3zeta chain expression by L-arginine. J Biol Chem. 2002;277(24):21123–9.
23. Rodriguez PC, Zea AH, DeSalvo J, Culotta KS, Zabaleta J, Quiceno DG, et al. L-arginine consumption by macrophages modulates the expression of CD3 zeta chain in T lymphocytes. J Immunol. 2003;171(3):1232–9.
24. Zea AH, Rodriguez PC, Culotta KS, Hernandez CP, DeSalvo J, Ochoa JB, et al. L-Arginine modulates CD3zeta expression and T cell function in activated human T lymphocytes. Cell Immunol. 2004;232(1–2):21–31.
25. Makarenkova VP, Bansal V, Matta BM, Perez LA, Ochoa JB. CD11b+/Gr-1+ myeloid suppressor cells cause T cell dysfunction after traumatic stress. J Immunol. 2006;176(4):2085–94.
26. Scumpia PO, Delano MJ, Kelly-Scumpia KM, Weinstein JS, Wynn JL, Winfield RD, et al. Treatment with GITR agonistic antibody corrects adaptive immune dysfunction in sepsis. Blood. 2007;110(10):3673–81.
27. Popovic PJ, Zeh 3rd HJ, Ochoa JB. Arginine and immunity. J Nutr. 2007;137(6 Suppl 2):1681S–6S.
28. Zhu X, Pribis JP, Rodriguez PC, Morris Jr SM, Vodovotz Y, Billiar TR, et al. The central role of arginine catabolism in T-cell dysfunction and increased susceptibility to infection after physical injury. Ann Surg. 2014;259(1):171–8.
29. Bansal V, Ochoa JB. Arginine availability, arginase, and the immune response. Curr Opin Clin Nutr Metab Care. 2003;6(2):223–8.
30. Daly JM, Reynolds J, Thom A, Kinsley L, Dietrick-Gallagher M, Shou J, et al. Immune and metabolic effects of arginine in the surgical patient. Ann Surg. 1988;208(4):512–23.
31. Barbul A, Sisto DA, Wasserkrug HL, Efron G. Arginine stimulates lymphocyte immune response in healthy human beings. Surgery. 1981;90(2):244–51.
32. Morris Jr SM. Arginine: master and commander in innate immune responses. Sci Signal. 2010;3(135):pe27.
33. Barbul A, Rettura G, Levenson SM, Seifter E. Arginine: a thymotropic and wound-healing promoting agent. Surg Forum. 1977;28:101–3.
34. Barbul A, Wasserkrug HL, Sisto DA, Seifter E, Rettura G, Levenson SM, et al. Thymic stimulatory actions of arginine. JPEN J Parenter Enteral Nutr. 1980;4(5):446–9.