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Chapter

Introductory Chapter: Shock is a Physiological State of War

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1. Introduction

Among specialists in critical care medicine, emergency medicine, infectious diseases, and trauma surgery, shock elicits a sense of impending immediacy and sets off a cascade of clinical interventions designed to support systemic circulation. This includes urgent focus on ensuring end-organ perfusion, definitive treatment of the underlying cause (from anaphylaxis to sepsis), and providing subsequent physiological restoration. Despite the apparent heterogeneity of "shock" as a clinico-pathological entity, there are some common threads that permeate all forms and manifestations of shock, with apparent increase in observed commonalities in the more advanced (and often irreversible) stages of the systemic syndrome [1–7].

Let us take a closer look at septic shock as an excellent example of the above concepts. More than 19 million people annually develop sepsis, which is defined as a "life-threatening acute organ dysfunction secondary to infection [8]." Approximately 14 million survive to hospital discharge, 50% recover, 33% die in the following year, and about 15% experience continuing problems and ailments [8]. Patients who survive hospitalization develop, on average, one to two new functional problems (such as challenges with simple tasks like dressing or other daily functions one may otherwise take for granted); a significant increase in cognitive difficulties; as well as various behavioral sequelae such as anxiety, depression, and post-traumatic stress disorder (PTSD) [8]. Survival of sepsis, septic shock, and other forms of shock (e.g., hemorrhagic, anaphylactic, cardiogenic, neurogenic) has improved in recent years [9–13]. Yet our understanding of the war-like ravages the state of shock creates remains limited, especially in the context of the cumulative impact of the initial physiologic insult, its duration and severity and the subsequent recovery. This book aims to highlight commonly encountered forms of shock by focusing on contemporary diagnostic and treatment approaches. For the purposes of this introductory chapter, the authors will focus on one of the best understood models of shock—the septic shock. References to other types of shock will also be made when appropriate.

2. Gearing for wartime

In the acute setting, it is easy to become mesmerized by the superficial manifestations of the physiological devastation inflicted by shock as it affects the human body—elevated (or depressed) temperature, low blood pressure, diaphoresis,

tachycardia, etc. [14–16]. For most providers, these signs, combined with laboratory markers, such as leukocytosis, specifically bandemia [17–19], an elevated C-reactive protein [19, 20], or perhaps alterations in procalcitonin [20], send out an alert, prompting aggressive and largely protocolized clinical management. Yet, an in-depth understanding of what is mechanistically occurring throughout the body, as well as the magnitude and scale of the events that are taking place, tends to be lacking.

When examining the hematologic system during sepsis and septic shock, the body undergoes a shift, readily comparable to a transition to a *war economy* [21]. In effect, the contingencies in time of war require that a "system of producing, mobilizing and allocating resources to defend and sustain" is put in place to ensure the means necessary for survival [22]. This rapid, often "violent" change is bidirectional; the host's invader attacks the patient physiologically, and the host, in return, mounts a vigorous defense. The sudden physiological retooling, including massive changes in resource allocation are difficult to grasp. Consider the effect of sepsis and the associated doubling of the white blood cell (WBC) count. More specifically, it has been estimated that approximately 4.4% of the entire body mass of a healthy, 70 kg man is allocated to blood cells [23]. This translates to approximately 3.1 kg! Assuming about 2.2 kg of the totality of all blood cells are erythrocytes or red blood cells (RBCs), it is reasonable to also assume the approximate normal WBC mass would be in the range of 0.9–1.0 kg [24]. It has also been estimated that the human body produces, on average, approximately 100 Watts (Joules/sec) of energy [25, 26]. Consequently, the hypothetical doubling of the WBC count within a 24–48-hour period during sepsis is thus representative of a net gain of approximately 0.9–1.0 kg of new WBCs—an amazing feat of energy and power, in that it takes anywhere between 5 and 50 Joules/sec to form these new cells [27–29] and about 0.9–1.0 Joules/sec/kg to effectively power this freshly conceived army of defenders [26].

Similar to the preparation for and the conduct of war, the body experiences an acute and massive elevation in its baseline metabolic needs as it is actively fighting for its survival. Vast energetic surge is allocated to sustaining various forms of synthetic activity and enabling multiple, synergistic defense mechanisms, including immune cell metabolism, the production and release of innumerable cytokines, hormones, and the on-demand creation of other complex molecules and processes [30–36]. While we discuss these microbiological, immunological, and energetic "frontlines," we must not forget the active resistance that our pathologic foes are putting up. The medical community must apply proper stewardship of its antibiotic assets, only using our limited resources (e.g., "therapeutic bullets") when needed and only rarely resorting to the "nuclear option" of widest available spectrum of agents in our antibiotic armamentarium [37]. In fact, the emergence of antibiotic resistance is a worldwide concern, and it is highly reflective and typical of warfare-like conflict and combat. Effects of this phenomenon are far-reaching, including patients, physicians, pharmacists, administrative actions, and broadly understood public health infrastructure. Antibiotic resistance adds $1383 to the cost of caring for a patient with a bacterial infection. Using the estimates of Thorpe et al. [37], the number of such resistant infections in 2014 alone amounted to a national cost of $2.2 billion annually [37].

It is important to note that other forms of shock, such as hemorrhagic shock, also trigger a variety of similarly extensive metabolic responses [38]. Although the inciting mechanism may be different, there are certain "end pathway" similarities and parallelisms. For example, the post-hemorrhage state can be characterized as having the following stages: "ischemia-reperfusion," "leukocytic," and "angiogenic" [39]. Likewise, new erythrocytes must be produced in large quantities to replace those lost during the hemorrhagic injury. Not unexpectedly, energy depletion is one of the key determinants of tissue (and systemic) recovery following shock [38].

From more philosophical (and also structural) perspective, when the human body is exposed to near-lethal state of shock, a large number of individual cells will die, regardless of whether the organism survives or not. Perhaps one might call this "compensated" versus "uncompensated" shock, depending on the extent of damage that is difficult to "see or quantify." Thus, the question arises—at any particular organ system or tissue level—"how many cells can die before the organ (or the entire organism) can no longer function, cope, and/or survive?"

3. Finding new equilibrium

As the body gains the upper hand over the tectonic shifts brought upon it by this state of shock, a temporary new equilibrium is achieved, whereby the state of heightened physiologic alert continues, but some signs of normalization and stabilization return. The so-called systemic inflammatory response syndrome (SIRS) starts to resolve [40]. For example, the WBC count begins to trend back toward normal (or baseline) range, constant fevers are interrupted by increasingly frequent afebrile periods, and the patient's intravenous fluid and vasopressor requirement begins to decrease [40, 41]. In more sophisticated terms, objectified measurement of this re-equilibration and normalization process can be seen by down-trending of various physiologic acuity indices, such as the sepsis-related organ failure assessment (SOFA) score [42]; different iterations of the acute physiology and chronic health evaluation (APACHE) score [43, 44]; as well as the simplified acute physiology (SAPS) score [45].

Although this particular state does not yet represent a "truce," because such an ebb and flow of physiological parameters is not conducive to the well-being of the host, it is a general signal that "hostilities" are subsiding. From the perspective of medical care, there has to be an end to hostilities, with the pendulum shifting in favor of the host. Sometimes it is an outright win, but most times the successes of care are negotiated with the "invaders" over time. Importantly, the quicker the end of hostilities, the better it is for the patient. Nonetheless, as the new equilibrium is reached, there is a price to pay for fighting off an invader. Usually, it is the use and liquidation of valuable assets (e.g., muscle wasting, cellular death). In financial terms, there is a large "physiologic" loan with a lot of interest to be paid on the way to recovery. Achieving equilibrium requires a strategy that incorporates effective interventions, in addition to quality care in early shock, such as the management of delirium, pain, and agitation, as well as early mobilization to attenuate atrophy of the patient's musculature and nervous system [8, 46]. The next step in the patient's recovery, as outlined in the subsequent section, is the re-tooling of the "war economy" back into "peacetime economy" of everyday functioning.

4. Return to peace

As discussed and logically outlined in previous sections of this chapter, the all-out effort of the human body to initially react, then more formally respond to the shock state, eventually leads to a binary outcome. For the most acutely ill patients, it is mortality versus survival. Once the probability of mortality decreases and the likelihood of survival rises sufficiently, the human physiological machine must at some point transition out of *war economy* mode and return to the baseline *peace economy* [47]. In economic terms, this translates into a gradual metamorphosis from war-related activities, or catabolism, into peace-related ones, or anabolism, whereby factories producing armored vehicles, machine guns, bombs and missiles in wartime, now

re-tool to make civilian vehicles, refrigerators, or perhaps personal computers [47, 48]. Essentially, this is a fairly well-structured "recovery plan." It is very much akin to the Marshall Plan (a 1948 American initiative to aid post-World War II Europe) [49]. Wherein, not only physiological and psychological assistance and recovery are necessary, but also an expenditure of resources to help one overcome any morbidities in order to restore function and enable the patient to become a contributing member of the society. This process occurs both on the short-term and long-term scales. Acute physiological problems are solved early, the solutions providing for life, i.e., survival. Nonetheless, there are long-term problems also, such as PTSD, and the "aftershocks" of functional and cognitive decline which create high costs to the patient and society [50, 51]. The recovery costs are not only biological and psychological, but also financial. For example, hospital-associated cost of sepsis increased from $58,000 USD per patient in 2015 to $70,000 USD per patient in 2018 with patients who developed sepsis being 10% more likely to have septic shock on hospital admission. This represents an estimated increase of $1.5 billion USD over a 3-year period [52].

The processes and difficulties involved in the physiological transition from *war economy* to *peace economy* are exceedingly complex and poorly understood. The ravages of the war, no matter the final victory, leave the patient with long-term disability, cognitive decline, pressure-related wounds, end-organ damage and dysfunction, and signs of accelerated physiological aging [53–63]. A patient suffering from chronic post-sepsis state should receive ample support, including close medical follow-up, physical therapy, occupational therapy, and speech therapy. Previously compared to the "Marshall Plan," such post-sepsis intensive recovery should focus on restoring the patient to optimal functioning, including activities of daily living (ADL); good exercise capacity; rebuilding of muscle strength (skeletal, respiratory and otherwise); and other key areas of independent living [64, 65]. In a more philosophical way, the "price of survival" (and recovery to the point of fully resuming ADLs) is measured through some form of a complex mathematical relationship where chronological age becomes modified (e.g., advanced) according to the totality of physiological stress, the total amount of energy expended, as well as the rate of that energetic expenditure while fighting to survive the shock state. Similar observations can be made about post-traumatic and other forms of shock discussed in this book, as evidenced by the increasing amount of literature documenting post-critical care disability and complications [66–70]. Finally, there seems to be a relationship between the "time to treatment" and patient outcomes across all types of shock, including short-, mid-, and long-term considerations.

In essentially all forms of shock (septic, cardiogenic, hypovolemic, anaphylactic, and neurogenic), there are highly impactful transformations of energy, or bioenergetics. Such alterations in the production and utilization occur through cellular and metabolic processes and result in mitochondrial dysfunction and oxidative stress that influence patient outcomes [71]. In shock states, despite hemodynamic recovery and recovery of oxygen-related variables, there seems to be a persistent oxygen extraction deficit. Dysfunction of oxygen transport pathways during the critical illness of the patient underlies the events resulting in organ failure. We have a limited technical ability to measure tissue oxygenation bioenergetics. Consequently, it is imperative that we develop effective, easily applied, novel techniques that allow a quantitative approach into the determinants of microcirculatory and mitochondrial oxygenation [72, 73].

5. Conclusions

This book is a collection of unique chapters, each dedicated to a different area within the expansive and heterogeneous subject of shock. As the reader progresses

through the book, we hope to help stimulate further discourse and innovative thinking about the topic and to shed light on a clinical problem that all too often becomes reduced to protocolized management approaches without much reflection into its true mechanistic and energetic implications and impact. While the authors hope that this textbook will enlighten practitioners as to diagnosis and treatment of shock, it must be acknowledged that the current sepsis guidelines regarding the treatment of this malady do not provide sufficient guidance on post-hospital care or recovery. It is also critical that basic, translational, and clinical research on shock is well balanced between different types of shock to improve our understanding of all pertinent pathophysiologic states. In this way, scientific progress will help improve outcomes for patients with both rare and common forms of shock.

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