Handbook of Shock and Trauma

Volume 1
Basic Science

Editors

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Preface

The dramatic development of the multidisciplinary field of shock in the past 75 years has attracted many investigators to this area. However, despite their significant and productive contributions, to date there has been no single source of information in the field. The *Handbook of Shock and Trauma* presents to the investigator, student, and clinician an incisively comprehensive analysis of the state-of-the-art in shock research and management.

This handbook has benefitted from the collaboration of basic and clinical scientists who have been selected because of their recognized expertise in the latest advances in the field of shock. Included are internists, surgeons, anesthesiologists, physiologists, biochemists, pharmacologists, anatomists, and critical care medicine specialists. Their contributions cover a broad spectrum of material, from the total organism through individual organ systems, and down to the cellular, subcellular, and molecular levels. Volume 1 of this handbook is an authoritative, current, and easily accessible source of basic scientific information which will be applied in the development of therapeutic principles of shock management in Volume 2.

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Contents

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Historical Perspective of Shock

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The term *choc* was coined in 1743 by the French physician Le Dran to indicate a sudden collapse in the clinical status of a patient after a serious traumatic episode (2). In 1867 the English physician E. A. Morris used the word *shock* for the first time in the monograph *A Practical Treatise on Shock After Operations and Injuries* (4). By the end of the nineteenth century, knowledge of the nature of this lethal disorder and its treatment was minimal. The experimental era in shock began in 1899 when the pioneering investigator George W. Crile published *An Experimental Research into Surgical Shock* (1). Investigation of the pathophysiology of shock was initiated early in the twentieth century by V. H. Moon and associates, who published their findings in the 1938 compendium *Shock and Related Capillary Phenomena* (3). Carl J. Wiggers, the noted cardiovascular physiologist, was actually the first investigator to attempt to quantify the research field of shock by establishing standardized models. His techniques for the study of the various components of the circulatory system are the foundation for our current knowledge of hemorrhagic shock. The modern era of shock research had finally arrived with Wiggers' publication in 1950 of his classic treatise *The Physiology of Shock* (5).

This brief historical sketch highlights only the most significant events in shock research, as it is beyond the scope of this book to present a detailed history of the investigations performed in the last 30 years, which is to be found in Wiggers' classic monograph.

DEFINITION OF SHOCK

Shock is a significant and sustained loss of effective circulating blood volume. It eventuates in the hypoperfusion of peripheral tissues, and leads to a deficit in transcapillary exchange function.

CLASSIFICATION OF SHOCK

The classification of shock is based on etiology. Those shock syndromes caused by inadequate cardiac function are termed cardiogenic shock. Those shock syndromes caused by a true loss of blood volume, whether endogenous or exogenous, are known as hypovolemic shock. Those shock syndromes that are due to the transudation of volume secondary to sepsis are known as septic shock. Furthermore, traumatic shock is a combination of the cardiogenic, hypovolemic, and septic shock syndromes produced by tissue injury. The common denominator of all these diverse forms of shock is microcirculatory hypoperfusion.

STATE OF THE ART

The biomedical sciences, which have dramatically evolved over the last 30 years, offer

a wide diversity of concepts and techniques in the fields of cell biology, biochemistry, physiology, and pharmacology. In the study of cell biology, the electron microscope with its scanning and transmission modalities, supported by quantitative histochemical techniques, has been invaluable in the exploration of basic cellular alterations. In biochemistry, high-pressure liquid chromatography, radioimmunoassay, dual-beam spectroscopy, and newer immunochemical techniques define more clearly the changes in the fluxes of energy pathways and protein and fat metabolism in the shock state. In physiology, new advances in quantitative microcirculatory techniques have revealed new information about the peripheral circulatory system. For example, radioactively labeled microspheres to measure blood flow give new insights into organ perfusion in circulatory shock; electronic probes measure pH and oxygen changes secondary to decreased peripheral perfusion. The development of newer shock models, specifically those related to sepsis, has been a significant contribution. Previously, injection of endotoxin was used to simulate clinical septic shock. Today, the infusion of whole bacteria into the circulation, or the production of peritonitis septic shock through a perforated cecum or a resection of the appendix, is a significant development in the study of the effects of septic shock. In pharmacology, the development of receptor binding techniques and the measurement of components of the cyclic nucleotide system have aided in exploring the mechanisms by which pathological effectors produce the shock state.

Probably the most important development over the last 30 years of shock research has been the bridging of the informational gap between the basic scientist and the clinician. Organizations such as the Shock Society and The American Physiological Society have fostered this interrelationship to encourage the practical application of basic concepts and techniques to the treatment of the shock patient. One of the goals of this handbook is to promote this beneficial trend.

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Section One

The Cardiovascular System in Shock

Historically, shock arose as a term denoting severe homeostatic perturbations of the circulatory system. Indeed, the modern terminology uses "circulatory shock" as a key phrase in this area. It is therefore clear that a thorough understanding of the major components of the circulatory system is essential in order to appreciate shock. Although one can divide the study of the circulatory system into a score of important topics (e.g., heart, veins, lymphatics, conduit arteries, true arterioles, etc.), we have elected to simplify our consideration of the circulatory system into its three essential features: the pump, the system of distributing and collecting vessels, and the exchange vessels (i.e., the microcirculation). All four chapters are written by basic scientists who have had long experience in the area of shock research in addition to being leaders in their own cardiovascular discipline.

To do a proper and thorough review of these extensive areas, these chapters are somewhat lengthier than many of the others. We feel that this expresses the wealth of historical, physiological, and pathophysiological findings that constitute much of the shock literature over the last three decades.

This section should form the basis for determining much of the pathophysiology of shock that follows in the next section dealing with organ systems. A thorough understanding of the circulation is vital for application of these principles to important organs and organ systems, particularly the lungs, kidneys, and gastrointestinal tract.

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The Heart in Shock

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> On the basis of changes in effective atrial pressures, ventricular volume changes, intraventricular pressures, and electrocardiograms, the conclusions appear warranted (1) that deterioration of myocardial expulsive power contributes to the progressive circulatory failure of oligemic shock, (2) that the various compensating mechanisms which tend to maintain an adequate coronary circulation are not sufficient to spare the myocardium, and (3) that myocardial depression contributes to the redevelopment of circulatory failure when transfusions are given after the development of an irreversible state.
>
> Carl J. Wiggers, 1950 (177)

Shock is probably best viewed as a process potentially or actually associated with disordered function of virtually every organ system in the body, including the heart. The final pathway may reasonably be assumed to involve injury and ultimate destruction of cell membranes and their vital synthetic and energetic functions. The conceptual framework becomes excessively complex, however, if one attempts to encompass the vast array of feedback loops, modulators, and cascades that participate in the process. Hence, it is necessary to isolate fragments of the total problem for detailed analysis. But while doing so, it should be remembered that important links in the complete chain of events may be severed. Time-intensity factors and the widely varying sensitivity of different tissue components to the same injurious stimulus must be considered. Specific host factors may also assume major importance. Examples particularly pertinent to the human heart include obstructive coronary vascular disease, systemic hypertension, and diabetes mellitus associated with altered autonomic reflex function. Species differences and the broad range of experimental models employed to study shock require careful evaluation for pertinence to the clinical setting and implications for therapy.

The goal of this chapter is to describe and analyze changes that occur in the heart during circulatory shock. A key question to be addressed with each form of shock is if the heart is a significant target organ in the process, thereby contributing to progressive loss of circulatory function, ultimate irreversibility, and death of the organism. A second objective will be to define pathophysiological mechanisms that are common to the several forms of shock, regardless of the initiating events. These common mechanisms can best be elucidated by

models of hemorrhagic hypotension. Specific effects introduced by endotoxins or cardiac factors can be added to this framework.

HEMORRHAGIC SHOCK

Functional and Structural Evidence for Cardiac Involvement in Hemorrhagic Shock

Blood loss of sufficient magnitude to override autonomic, hormonal, and other compensatory mechanisms and result in a lowering of the arterial pressure will eventually lead to irreversible circulatory failure. This immediately introduces two key interrelated variables—severity of the hypotension and time. Identification of the target organ or tissues responsible for initiation of the descending cascade and factors that may trigger these changes are under intense investigation. However, the weight of evidence supports the view that cardiac performance deteriorates with time during prolonged hypotension. This does not necessarily mean that cardiac failure is the earliest or sole reason for irreversible collapse of the circulation. Nor does it mean that if cardiac function were preserved, the organism would necessarily survive a similar insult.

The first clear suggestion that cardiac failure could be a significant factor in the hemorrhagic shock syndrome is generally ascribed to Wiggers and Werle (178). Their conclusions, which appeared in 1942, gained support from the studies of Sarnoff and associates (151) published some 12 years later. The hemodynamic measurements available at that time for estimation of cardiac function were indirect and relatively insensitive. Nevertheless, these workers demonstrated in the dog that after 90 min of hemorrhagic shock, left atrial (LA) pressure rapidly increased. This was interpreted as evidence for heart failure, and considered "a complicating factor in late hemorrhagic shock." This early work was supported by a series of studies from Guyton's laboratory (27,28,30) that showed that some 4 hr after hemorrhaging dogs to mean arterial pressure levels of 30 mm Hg, LA pressure began to rise. Transfusion of the animals back to normal arterial pressure did not prevent progressive heart failure and death. This group provided further evidence for cardiac failure by obtaining serial cardiac output curves during the course of shock (28). They were plotted in relation to both right and left atrial pressures and demonstrated a progressive reduction in output for a given atrial pressure. These data are strongly suggestive of declining pump function of both ventricular chambers as the duration of shock continues. Digitalization with ouabain improved pump performance substantially, although the effect was transitory. The importance of this latter observation is presumably reflected in the survival of animals subjected to a duration of shock that is otherwise lethal (30).

These early physiological observations have been supported by findings of metabolic, enzymatic, and morphological alterations that reflect progressive myofiber injury during shock. Thus, Hackel and Goodale (77) showed in 1956 that dogs bled to arterial pressure levels of 45 to 55 mm Hg for 3 hr developed important changes in cardiac metabolism. These included increased oxygen extraction and reduction of pyruvate uptake. Regan et al. (147) found a close association between progressive myocardial failure following hemorrhage, and rising concentrations of serum glutamic-oxaloacetic transaminase in coronary sinus blood. This change appeared in animals with irreversible shock but not in those that recovered following retransfusion, and was interpreted as evidence for ischemic myofiber necrosis. Direct morphological confirmation of myofiber injury by light microscopy was not considered feasible because survival for 24 hr or more is generally necessary for full anatomical expression of ischemic lesions. However, 2 of the 9 dogs studied by Hackel and Goodale survived for 2 weeks, and these manifested foci of myofiber necrosis. Similar findings had been reported earlier after less severe shock (128). A more detailed study was provided by Henson et al. (81) who used dogs subjected to usually lethal episodes

of hemorrhagic shock. These investigators took advantage of previous observations that pretreatment with certain drugs, including allopurinol, resulted in a 60% survival rate from a shock insult that was uniformly fatal in untreated dogs (29). No cardiac lesions could be identified by light or electron microscopy in animals sacrificed 5 hr after bleeding to an arterial pressure of 30 mm Hg. However, in 12 survivors sacrificed at intervals of 3 to 7 days, significant myocardial damage was identified, and the morphological changes increased in frequency and severity with time. Intramyocardial hemorrhage with focal necrosis was present at 3 days after recovery from shock, and fiber hyalinization, myocytolysis, and heavy leukocytic infiltrates were present in the later stages. The ultrastructural findings included loss of myofibrils with translocation and swelling of mitochondria and sarcomeric disorganization. Thus, given the necessary time for histological markers to appear, changes in myofibers consistent with ischemic damage can be anticipated in hearts from animals with "irreversible" hemorrhage shock. The frequent finding of subendocardial and interstitial hemorrhage suggests significant vascular damage as well.

A distinctive lesion has been recognized by electron microscopy that appears to be uniquely associated with hypovolemic shock. This has been termed the zonal lesion (78,126). Its features include hypercontraction with marked sarcomeric shortening occurring adjacent to an intercalated disc. There is also Z band fragmentation, distortion of myofilaments, and displacement of mitochondria away from the disc. These lesions appear separable from those associated with catecholamine injury by the absence of contraction bands and mitochondrial damage and by their specific location at the ends of the cardiac cells. Moreover, in contrast with the myofibrillar degeneration lesion (148), which represents irreversible injury, the zonal lesions are thought to be reversible. Separation of actin filaments from the intercalated disc provides a potential morphological correlate of cardiac failure in shock (146,171). In contrast with the changes of myocardial hemorrhage and necrosis seen in late irreversible shock, the zonal lesions appear early. They increase with the duration of shock and are probably independent of tissue hypoxia (145). Whether or not these structural changes can explain the progressive decline in cardiac performance before the stage of irreversible failure is reached is uncertain, but this provides tempting speculation.

Changes in Cardiac Function During Hemorrhagic Shock

The several hemodynamic studies already cited suggest that the heart is an important target organ in hemorrhagic shock. However, the hemodynamic parameters used to assess cardiac performance in that era were often indirect, and frequently were obtained in preparations in which several variables were changing simultaneously. The methods were expected to detect only major changes in cardiac function, as might be anticipated in the late stages of irreversible shock. Moreover, studies from respected laboratories had concluded that cardiac performance is well maintained far beyond the point of irreversibility as previously defined (22,71,180). This raised considerable doubt that failure of the heart contributes importantly to the sequence of circulatory collapse and death of the organism.

Contraction of the heart is a complex process involving tension development, fiber shortening, specific loading conditions, and many more mechanical factors. Accurate translation of these events to hemodynamic measurements that can be made in the intact circulation is essential for an adequate analysis of cardiac performance. This requirement for a conceptual linkage between intrinsic mechanical properties of cardiac muscle and hemodynamic events associated with ventricular contraction was met in large measure by the studies of Sonnenblick in the early 1960s (159,160). Moreover, these and succeeding

studies focused on those mechanical determinants that could be used to define and measure myocardial contractility. Important for our discussion is that descriptions of cardiac performance often include evaluation of both force and time (velocity) parameters (49). It is necessary to distinguish these variables because they may change simultaneously in the same direction, or independently, or even in opposite directions. Many laboratories presently employ velocity measurements and define contractility in terms of V_{max}. Measurements related to force and shortening are often referred to as pump function. The relevance of these considerations is perhaps best exemplified by the report of Forrester et al. (62). They showed in both dogs and cats a dissociation between changes in myocardial contractility and pump performance during hemorrhagic shock. Contractility, assessed by estimating V_{max} from the isovolumic force–velocity relationship, remained unchanged. But pump function progressively declined. Maintenance of V_{max} was heavily dependent on adrenergic stimulation. It also declined in animals with beta-blockade. Evaluation of pump performance may be more pertinent, however (38). Clearly, if the heart is too weak to support an adequate circulation, speed of contraction is of limited importance. Tachycardia, which usually accompanies the early hypovolemic stage, is adrenergically mediated and matched by increased velocity of contraction (V_{max}). In the later stages of shock, the tachycardia usually disappears and speed of contraction becomes a less significant issue.

The force characteristics (or pump function) of the intact left ventricle (LV) can be assessed from measurements of stroke volume (SV) ejected from a given end-diastolic pressure (LVEDP) against a constant mean arterial pressure (afterload). A rise in LVEDP for a given SV indicates reduced performance. This might be reflected by an elevated LA pressure, as was observed by Sarnoff et al. (151). However, a more comprehensive approach is to utilize ventricular function curves. These are obtained by progressively increasing venous return to the heart in a stepwise manner, providing the equivalent of a calibration curve for the ventricle (Fig. 1). Data that relate SV to LVEDP may be obtained at intervals during the course of shock without elevating arterial pressure (34). This latter point is important because methods for assessing ventricular function that repeatedly reelevate arterial pressure to or above control values (71), even if for brief periods, may prevent or greatly retard the decline in performance observed with sustained hypotension (156).

A preparation that meets the criteria for control and measurement of the essential hemodynamic variables reflecting force characteristics of the LV has been described in detail (106,155,156), and can be briefly summarized. After anesthesia and thoracotomy, the thoracic aorta is cannulated to introduce an extracorporeal loop of plastic tubing. In this loop is incorporated a flow probe, to measure LV output, a heat exchanger, and a temperature probe. The loop is connected to a

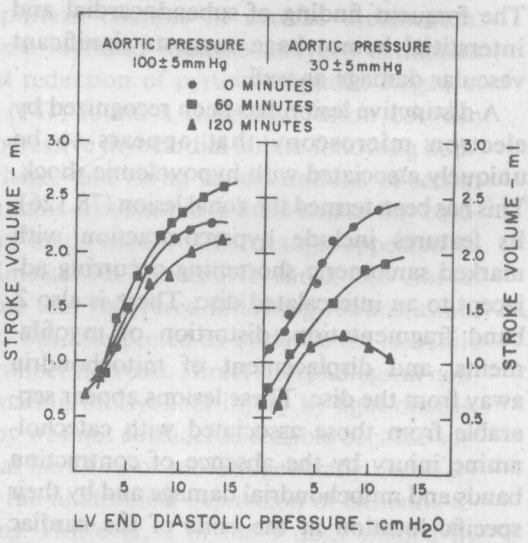

FIG. 1. Ventricular function curves from normotensive (**left**) and shock (**right**) preparations. The latter exhibits a progressive decline in left heart performance. (Modified from Siegel and Downing, ref. 156, with permission of the *American Journal of Physiology*.)