CRITICAL CARE

Chapter 13

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Table of Contents

Introduction

The provision of critical care in the combat environment is never a passive process. There is always an opportunity to affect great change that can alter the course of a patient's recovery. A command of several core concepts is vital for those who practice in the combat intensive care unit (ICU). This chapter will review basic mechanical ventilation, pulmonary contusion management, acute respiratory distress syndrome management, endpoints of resuscitation, sepsis, several basic ICU care considerations for the combat casualty care (CCC) patient, and the critical care air transportation system. In a given day at a wartime trauma resuscitation hospital, a clinician will encounter every one of these issues. They are fundamental, common, and important to master.

Mechanical Ventilation

The birth of the intensive care unit can be traced back to the application of invasive positive-pressure mechanical ventilation during the polio epidemic of 1952 in Denmark.[1] Prior to that time, positive-pressure ventilation (PPV) had been used only sparingly for a few decades by anesthesiologists in the operating room. Most of the mechanical ventilation provided to patients with neurologic disorders or respiratory failure prior to 1952 was done with negative-pressure ventilation (NPV) devices such as the cuirass respirator or the iron lung (tank respirator). While negative-pressure ventilation more accurately simulates normal physiologic breathing, positive-pressure ventilation is used almost exclusively in modern critical care, mainly due to improved access to the patient.

Mechanical ventilation has evolved as a discipline quite rapidly over the last few decades, and lessons learned are now paying substantial dividends with respect to morbidity and mortality. This section will focus primarily on the use of invasive mechanical ventilation to support the trauma patient encountered in the combat critical care setting. The use of noninvasive mechanical ventilation will be discussed in certain settings below where it may have a role, such as mild pulmonary contusion. The most important aspect of mechanical ventilation is defining the goals associated with its use in a given setting. A clear understanding of the clinical endpoint for this therapy will allow earlier liberation and improved outcomes.

Key Concepts

Many trauma patients are placed on invasive mechanical ventilation primarily for airway protection early in a resuscitation or during perioperative periods. The method used to secure an airway depends upon the nature of the injury and the expected clinical course. Options include endotracheal intubation, nasotracheal intubation, cricothyroidotomy, and formal operative tracheotomy. Ensuring a stable, secure airway is always the first priority of any resuscitation. As vital as this step is, it is only the beginning. Mechanical ventilation is primarily a supportive therapy that buys time for an injury to heal, but it also has the ability to cause great harm if not used appropriately. A basic understanding of pulmonary system compliance, gas exchange, and ventilator-induced lung injury (VILI) is vital for its rational use.

A clear understanding of the goals and clinical endpoint of mechanical ventilation will allow for earlier weaning and improved outcomes.

Compliance is defined as a change in volume divided by a change in pressure. In a given system, it may describe the change in volume expected if a given pressure is applied or vice versa. A system is said to be highly compliant when a large change in volume is associated with a small change in pressure.

With respect to invasive mechanical ventilation, pulmonary system compliance is assessed by the machine at bedside. This measurement is made at some distance from the patient, and its significance depends upon the clinical setting. Pulmonary system compliance is a combination of the pulmonary compliance and that of the chest wall. The lungs have a tendency to pull the chest wall centrally while the chest wall is inclined to pull the lungs outward. The balance of these two forces defines the pulmonary system compliance in a given patient. A lung that is stiff due to pulmonary edema surrounded by a normal chest wall may generate a similarly decreased pulmonary system compliance as a normal lung enclosed within a chest whose motion is restricted by a circumferential burn eschar. While esophageal manometry can be used to distinguish chest wall versus pulmonary contributions to the overall system compliance, bedside clinical assessment will need to be relied upon during CCC.

When a compliance abnormality is identified, it is helpful to classify it as a static or dynamic defect. If using a conventional volume-control mode, as described later in this chapter, a compliance defect will result in an elevated peak pressure. The peak pressure is the highest pressure generated as the machine pushes a given volume of gas into a patient's lungs. Once the initial portion of the breath is introduced, a more stable plateau pressure is reached until the end of inhalation.

A static compliance abnormality is one in which there is an elevated peak pressure as well as a similarly elevated plateau pressure. No matter how long the inspiration period lasts, an elevated pressure will continue to be noted that is similar to the peak pressure. Conditions causing stiff lungs such as pulmonary edema or a stiff chest wall will result in a static compliance abnormality. A dynamic compliance abnormality is characterized by an elevated peak pressure that is significantly higher than the plateau pressure, the breath has difficulty getting into the lungs initially, but then is able to overcome the obstruction. A common example of this is mucus or other secretions in the airways that is significant enough to hamper, but does not completely obstruct airflow.

Gas exchange in the lungs is accomplished at the level of the alveolar capillary interface. Ideally, flow of air into an alveolus and flow of blood into a surrounding capillary vessel bed should be matched. Areas of ventilation (V) should generally correspond to areas of perfusion (Q); V/Q = 1. When ventilation is present in the absence of blood flow (V/Q = infinity), this is known as dead-space ventilation.[2] The dead-space fraction is the ratio of dead-space (Vd) to tidal volume (Vt). The dead-space fraction is the portion of each breath that is unavailable for gas exchange. A normal person has a dead-space fraction of approximately 30 percent at rest that decreases to 18 percent at maximal exercise.[3] A higher dead-space fraction results in difficulty eliminating carbon dioxide.

Perfusion in the absence of ventilation makes it impossible for oxygen to diffuse from the airways into the blood and bind hemoglobin. Areas with preserved blood flow but an absence of ventilation (V/Q = 0) cause a right-to-left shunt.[2] The proportion of blood that passes from the right side of the heart to the left without being exposed to adequately ventilated alveoli is called the shunt fraction.

In the normal lung, there are three physiologically distinct zones with respect to gas exchange as described

by West.[4] From the top to the bottom of the lungs, there is an increase in alveolar ventilation as well as an even greater relative increase in blood flow. The uppermost portions of the lung are characterized by West Zone 1 physiology and are defined by an alveolar pressure (Palv) that is greater than the pulmonary artery systolic (PAs) and pulmonary artery diastolic (PAd) pressures. In West Zone 1 conditions, dead-space ventilation always exists since V/Q is by definition infinite. In West Zone 2 sections, PAs pressure is greater than Palv, which is greater than PAd pressure. Finally, in West Zone 3 sections, PAs pressure is greater than PAd pressure, which is greater than Palv. The majority of gas exchange happens in West Zone 3 conditions in the spontaneously breathing adult in the mid and basilar portions of the lungs.[4]

Positive-pressure invasive mechanical ventilation is often used to support patients who have inadequate oxygenation (respiration). Options available to improve respiration include increasing the fraction of inspired oxygen (FiO_2) or increasing the mean airway pressure. There are several ways to increase the mean airway pressure including inverse ratio ventilation, application of positive end-expiratory pressure (PEEP), and purposefully allowing the development of intrinsic PEEP. Treatment of hypoxemic respiratory failure will be covered in more detail later in this chapter when pulmonary contusion and acute respiratory distress syndrome are addressed.

Augmentation of oxygenation and elimination of carbon dioxide may be achieved though invasive mechanical ventilation.

Augmentation of carbon dioxide elimination (ventilation) is often facilitated with invasive mechanical ventilation. Each breath that is provided for the patient (Vt) can be thought of as a combination of a portion used for gas exchange (effective alveolar ventilation [Va]) and that lost to dead-space ventilation (Vd). Thus, Vt = Va + Vd. If one considers these components over the course of a minute (by multiplying each by the respiratory rate per minute), minute ventilation (Ve) = Va + Vd. Rearranging the equation for effective alveolar ventilation (Va) yields: Va = Ve – Vd = Ve (1 – Vd/Vt).

The actual partial pressure of carbon dioxide in arterial blood ($PaCO_2$) is a function of how much CO_2 is generated by the body (VCO_2) and how much is eliminated (largely dependent upon Va):

$$PaCO_2 = k(VCO_2)/Va = k(VCO_2)/Ve(1 - Vd/Vt).$$

The CO_2 production is generally proportional to the basal metabolic rate, and increases in times of physiologic stress and with temperature elevation. The respiratory quotient ($R_Q = VCO_2/VO_2$) of enteral and parenteral feeds may also impact CO_2 production in some critical care patients. Other than manipulating the R_Q of feeds or controlling temperature, effective control of the $PaCO_2$ is largely a function of mechanical ventilation and the ability to control the minute ventilation (Ve), which is equal to the respiratory rate (f) multiplied times tidal volume ($Ve = f \times Vt$). It should be noted that overdistension of alveoli with excessive ventilator pressures or intravascular volume depletion can both lead to an increase in West Zone 1 conditions by increasing the dead-space fraction. This can happen in an unpredictable manner at times, but should be considered when carbon dioxide elimination is proving difficult with positive-pressure ventilation.

Ventilator-Induced Lung Injury

One of the unfortunate lessons of critical care has been the realization that positive-pressure mechanical ventilation has the capacity to cause significant harm. Injury caused to the lung as a direct result of the use of a ventilator is called ventilator-induced lung injury (VILI). The pathophysiology of VILI is complex, but includes the effects of extrapulmonic air trapping (see barotrauma below) as well as the development of diffuse alveolar damage that is indistinguishable from that seen in acute respiratory distress syndrome (ARDS). As our understanding of VILI increases, so does the nosology to classify it. At present, it is helpful to think of four distinct subsets: barotrauma, volutrauma, atelectotrauma, and biotrauma.

Morbidity associated with positive-pressure mechanical ventilation is termed ventilator-induced lung injury (VILI). It may be broadly classified into barotrauma, volutrauma, atelectotrauma, and biotrauma.

Barotrauma

Barotrauma describes the most commonly appreciated adverse effects, such as the development of air collections outside of the lung, due to the use of inappropriately high pressure levels for a given clinical condition. While it is possible for a pneumothorax to develop directly at the periphery of the lung as a direct result of pressure changes, it is more frequently observed that air ruptures into the bronchovascular bundles first and dissects proximally resulting in a pneumomediastinum. Since the pleural space and the mediastinal space are separated by a pleural reflection on each side, a pneumothorax may or may not develop. Any subsequent pneumothorax will not necessarily form on the side of the initial airway defect. Finally, air may dissect in a cephalad or caudal direction, resulting in palpable air collections in the skin of the face, neck and chest, or intestinal wall (pneumatosis intestinalis) (Fig. 1).

Volutrauma

Volutrauma describes a physical overdistension of alveolar lung units that leads to pulmonary inflammation and can trigger the development of diffuse alveolar damage. It may occur in association with barotrauma, especially when excessive ventilatory pressures are used. Volutrauma is most likely to be a problem in conditions characterized by uneven ventilation such as pulmonary contusion or ARDS. Air becomes preferentially diverted to alveolar units with preserved compliance, leading to their overdistention. Animal models demonstrate that alveolar overdistention is likely a larger contributor to the development of VILI than elevated intraalveolar pressures.[5] From a pressure standpoint, it is the transalveolar pressure that is most dangerous, rather than the absolute pressure applied by the ventilator. The transalveolar pressure is directly correlated with the subsequent volume of expansion and therefore the potential development of volutrauma.

Atelectotrauma

Atelectotrauma refers to the repetitive opening and closing of alveolar lung units, which can lead to the development of local inflammation and diffuse alveolar damage. This occurs because opening and closing of alveoli that are adjacent to alveoli that are incapable of opening contribute to a shearing stress at their interface. Cytokines are released that perpetuate the local inflammatory response and may serve as a catalyst for injury in other parts of the body. This is one hypothesized mechanism for the development of multiple organ dysfunction syndrome and is more likely to be a major player in VILI associated with asymmetric lung injury.[5]

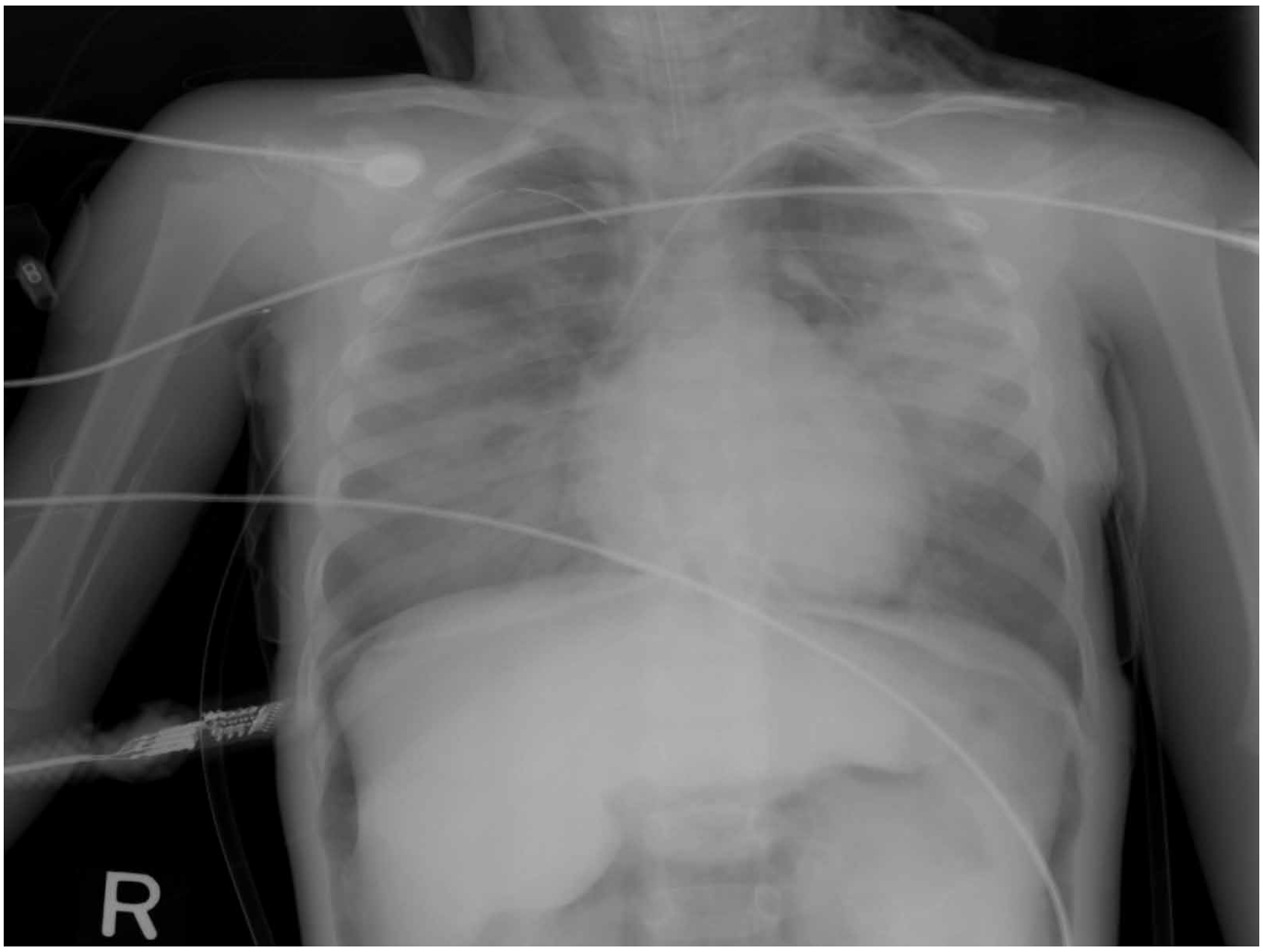

Figure 1. *Four-year-old child with severe ARDS at a Level III facility. Very high mean airway pressure requirements to maintain minimal oxygenation resulted in severe barotrauma.*

Biotrauma

An emerging concept that links the three aforementioned mechanisms of VILI is that of biotrauma. Biotrauma describes the impact on the lungs and body of biologically active molecules such as inflammatory mediators that are released as a direct result of positive-pressure ventilation. Alveolar volume, pressure, and cyclical opening have all been associated with the development of biotrauma.[6,7] It is likely that biotrauma is a final common pathway resulting in lung injury for many otherwise seemingly disparate mechanisms. Use of antiinflammatory agents to prevent or mitigate the impact of VILI has thus far been unsuccessful, further underlining the importance of prevention.[8]

Oxygen toxicity primarily leads to the development of pulmonary fibrosis. Efforts to limit the FiO_2 should be made whenever possible (FiO_2 less than 50 percent) to minimize this complication.

Oxygen toxicity should also be considered a local form of biotrauma. There is no "safe" level of oxygen supplementation since its presence in any concentration will be associated with some degree of oxidation and damage to tissues. Animal models have convincingly demonstrated that higher levels

of oxygen supplementation lead to the development of a form of VILI that is independent of the effects of pressure, volume, and cyclical changes.[9] Oxygen toxicity leads primarily to the development of pulmonary fibrosis and efforts to limit the FiO_2 should be made whenever possible. While no completely safe threshold has been demonstrated convincingly in clinical trials, most advocate decreasing the FiO_2 to less than 50 percent as soon as possible.[10]

Basic Modes of Positive-Pressure Ventilation

Overview

The provision of positive-pressure ventilation can be accomplished in an ever-increasing variety of ways. The increasing complexity of computer-driven algorithms can be confusing, but focusing on the fundamentals can help the clinician choose an appropriate mode for a given clinical situation. This section reviews some basic concepts applicable to all methods of providing positive-pressure ventilation and how they apply to more common modes of ventilation in clinical use. At the heart of understanding the different modes of ventilation is appreciating the impact of compliance and how the ventilator and patient communicate with each other. As discussed previously, compliance is the change in volume over the change in pressure. At any given point in time, the pulmonary system has a given overall compliance that will dictate the pressure change expected if a volume is provided by the ventilator. Conversely, if a pressure is provided by the ventilator, the compliance will determine the volume that is generated. Generally, a positive-pressure breath provides a volume or a pressure as an independent variable to the patient, and the compliance of the pulmonary system determines the value of the dependent variable.

Communication between the ventilator and the patient is what defines the actual mode of ventilation. When a given mode of ventilation is chosen, a set of rules for communication between the patient and ventilator is established. At a basic level, the defining questions are as follows: (1) how does the machine know when to start a breath?; (2) how does the machine provide the breath?; and (3) how does the machine know when to stop giving the breath? The combination of answers to these three questions defines the basic rules of communication and, therefore, the ventilator mode.

The trigger is the signal to the ventilator that it is time to provide a positive-pressure breath. For the common modes of ventilation, the trigger for a given breath is time (a breath is delivered at a set rate regardless of patient effort) or patient-driven. A patient-triggered breath is provided when the patient initiates a predetermined negative inspiratory pressure or a change in flow in the ventilator circuitry. This is interpreted by the machine as a desire on behalf of the patient to receive a breath. Some modes have both time and patient triggers (assist-control), as will be discussed later.

Provision of a breath to the patient depends on whether the machine or the patient initiated the breath. When the breath is given to the patient in accordance with a predetermined rate, it is said to be a control breath. A breath that is given by the machine in response to initiation by the patient is said to be an assist breath. Occasionally, the patient may initiate a breath that is in close proximity to when a control breath was going to be given by the machine. Most current ventilators recognize this and provide the planned control breath rather than an assist one in order to maintain minimum minute ventilation and avoid patient-ventilator synchrony problems.

Modes of ventilation are generally referred to as volume-control or pressure-control modes. Volume control is unfortunately a misnomer. A volume-control breath delivers a set volume to the patient; however, flow is actually the controlled variable. A specific flow is given by the machine until a predetermined volume is achieved. It is more accurate to think of volume control as volume set and flow control. A pressure-control mode of ventilation does deliver a set pressure using a pressure control and is therefore an accurate description. The cycle defines how the machine knows to stop giving a breath to the patient and allow exhalation to begin. Available cycle mechanisms commonly used include time, volume, pressure, and flow. Time cycles are often used in both pressure- and volume-control modes where a set inspiratory to expiratory (I:E) ratio is important to maintain. Flow cycles are frequently applied to pressure-supported assist breaths in modes such as pressure-support ventilation, as will be described below.

With this brief background, it is now time to consider how trigger, control, and assist breath delivery and cycle define the modes that are commonly used for positive-pressure ventilation. A few less conventional modes will also be described that may be of use in the combat casualty critical care setting today or in the near future.

Assist-Control (A/C)

Trigger: Time (controlled breaths), Patient (assisted breaths)
Breath Delivery: Control (volume set and flow controlled)
Assist (volume set and flow controlled)
Cycle: Time or Volume

In A/C mode, a respiratory rate, tidal volume, and inspiratory flow rate are set by the operator. The combination of these three variables will define the I:E ratio. The patient can trigger an assist breath that is recognized by the machine as either a negative pressure or change in flow in a closed circuit. The assist breath given has an identical tidal volume to the control breaths. Cycling depends on the ventilator manufacturer. In the past, a volume cycle was used for both the controlled and assisted breaths, and an operator set flow rate would determine the I:E ratio. Most current ventilators provide a mechanism for setting an I:E ratio, and the machine will automatically determine a time cycle based on the average number of total breaths the patient is breathing per minute. To achieve the desired I:E ratio, the machine may vary the flow and/or have a built-in inspiratory hold after the set volume is applied in order to achieve the desired I:E ratio.

Synchronized Intermittent Mandatory Ventilation (SIMV)

Trigger: Time (controlled breaths), Patient (assisted breaths)
Breath Delivery: Control (volume set and flow controlled)
Assist – none (SIMV) versus pressure-support (SIMV/PSV)
Cycle: Time or Volume (controlled breaths), Flow (assisted breaths)

With SIMV mode ventilation, the operator determines a set respiratory rate and tidal volume, and cycling of controlled breaths is identical to that described in the A/C section. In fact, in a patient who takes no spontaneous breaths, SIMV mode is identical to A/C mode. Assisted breaths that are initiated by the patient have a trigger that can be either a change in flow or the generation of a predefined negative

inspiratory pressure. When SIMV is used alone, there is no support given by the ventilator during an assist breath. The machine recognizes that a spontaneous breath has been initiated and responds by opening a valve that allows the patient to take as deep a breath without support as the patient can. Frequently, SIMV is combined with pressure-support ventilation (PSV). The combined SIMV/PSV mode allows an operator determined pressure-support to be applied by the ventilator through the inspiratory phase of an assist breath. The resulting tidal volume will be determined by the pulmonary system compliance at the time the breath is delivered and may or may not be similar to the set tidal volume delivered on controlled breaths. A flow cycle is used to terminate assist breaths in both SIMV and SIMV/PSV. The machine determines the maximal inspiratory flow at breath initiation and cycles the breath off when the inspiratory flow generated by the patient declines to a predetermined point, such as 20 to 25 percent of the maximal value.

Although SIMV is frequently used in critical care units today, it cannot be recommended as a weaning mode of ventilation. The rationale for its use as a maintenance mode of ventilation, above other modes, has little support in the literature.

Synchronized intermittent mandatory ventilation was initially designed as a weaning mode where an operator could transition a patient to a completely spontaneous mode of ventilation from a completely controlled mode simply by decreasing respiratory rate over time. Unfortunately, SIMV performed inferiorly to PSV and T-piece trials in two major prospective, randomized weaning studies and delayed overall extubation time.[11,12] Several hypotheses have been proposed to explain these findings, many relating to the way in which SIMV was applied. Of note, research indicates that as the set respiratory rate declines as a percentage of the overall respiratory rate, the work of breathing goes up substantially.[13] Assisted breaths in the SIMV mode can be quite variable and may not be adequate. Proponents of SIMV argue that combining SIMV with PSV allows assist breaths that have less variability relative to the control breaths and therefore decreased work of breathing. Others argue that titrating PSV to achieve assist breaths that are similar to control breaths in SIMV/PSV is no different from what can more easily be accomplished with A/C. Although SIMV is frequently used in critical care units today, it cannot be recommended as a weaning mode, and the rationale for its use as a maintenance mode of ventilation above other modes has little support in the literature.[11,12,14]

Pressure-Control Ventilation (PCV)

Trigger: Time (controlled breaths), Patient (assisted breaths)
Breath Delivery: Control (pressure controlled)
Assist (pressure controlled)
Cycle: Time or Pressure

Pressure-control-ventilation mode is identical to A/C mode with the exception that the breath delivered in the control or assist setting is a pressure breath set by the operator. This mode is frequently utilized in disease states where pulmonary system compliance is limited, and it is perceived by the clinician that using a predefined pressure control will decrease the likelihood of barotrauma. It is also used in situations where manipulation of the I:E ratio to greater than or equal to 1:1 (inverse ratio ventilation) is felt to be advantageous. When volume control A/C is set appropriately, there is little advantage to the use of PCV even in disease states where both such concerns manifest, such as ARDS. Pressure-control ventilation and volume-control A/C are in actuality very similar modes of ventilation, and either can be used in most cases, the choice being largely related to operator comfort.

Pressure-control ventilation mode is frequently utilized in disease states where pulmonary system compliance is limited and where pressure control will decrease the likelihood of barotrauma.

Understanding the concept of compliance is key. A given volume can be given that will generate a certain pressure. Conversely, a pressure can be given that will generate a certain volume. The relationship between the volume and pressure is defined by the system compliance, and whether the breath is given as a volume or a pressure is largely irrelevant in most circumstances. When pressure-controlled breaths are used in conditions characterized by reduced pulmonary system compliance, inadequate tidal volumes are possible and should be watched for closely. Occult air trapping with significant intrinsic PEEP that is unrecognized will also result in a lower than expected tidal volume when using pressure-controlled breath delivery.

Pressure-Support Ventilation (PSV)

Trigger: Patient
Breath Delivery: Pressure support
Cycle: Flow

Pressure-support ventilation is a mode of ventilation that is strictly an assist mode. The patient triggers the ventilator by generating a change in flow or a negative inspiratory pressure that is recognized by the ventilator. The machine then provides an operator defined pressure support throughout the inhalation portion of the breath until a flow cycle is reached. The breath cycles off typically when inspiratory flow drops below 20 to 25 percent of the maximal inspiratory flow. One concern related to PSV is the potential for its application in patients who have an inadequate respiratory drive or respiratory muscle strength. In either case, an inadequate minute ventilation may result. Most modern ventilators that have PSV as an option also allow a predefined backup control mode such as A/C that is automatically initiated when the minute ventilation is below a certain threshold. Some proprietary programs will only augment the number of breaths needed at a given time to achieve the minimum minute ventilation and will continue to allow the patient to otherwise remain in PSV. Pressure-support ventilation is commonly used as a weaning mode in the ICU, although with enough pressure support this mode can also be used quite effectively as a fully supportive mode, as long as the patient is able to generate an adequate respiratory effort.

Pressure-support ventilation is an assist mode commonly used to wean patients in the ICU.

Patients with significant air trapping may become dysynchronous with PSV. Prolonged exhalation times due to increased airway resistance (inflammation, secretions, etc.,) or increased compliance (emphysema) may result in incomplete alveolar emptying and the development of air trapping. Patients who have significant air trapping will be noted at end-exhalation to have a pressure within the lungs that is above atmospheric pressure (Patm). This is referred to as intrinsic positive-end expiratory pressure (iPEEP) or autoPEEP. The pressure difference between the intrinsic PEEP and atmospheric pressure can establish a significant expiratory flow between the gas exchanging units and the mouth, even when the patient considers the breath complete. This flow can be recognized by the ventilator and complicate the ability of the machine to accurately determine the proper time to end the inhalation portion of a breath that is flow cycled as in PSV. The machine may terminate the breath at a different time than the patient would prefer, creating the potential for significant dysynchrony. While use of PSV in patients with the potential for air trapping is not absolutely contraindicated, close attention should be paid to patient ventilator interaction.

The basic modes of ventilation, as presented here, represent the most commonly utilized methods of delivering positive-pressure breaths today. They are, however, very rudimentary modes with respect to their ability to accommodate the underlying neuromuscular processes involved in producing a patient breath. Several newer modes of ventilation are currently being evaluated and can be expected to be seen shortly in modern critical care units. Three of these modes are discussed below as they are used from time to time in the current combat casualty critical care environment.

Advanced Modes of Positive-Pressure Ventilation

Airway Pressure Release Ventilation (APRV)

Airway pressure release ventilation (APRV) is a time-triggered, pressure-controlled, time-cycled mode used in conditions where limiting airway pressure and manipulating the I:E ratio are both desirable, such as ARDS. High PEEP (PEEPh) and low PEEP (PEEPl) levels are set, as are the amount of time to be spent at the high PEEP level (Th) and the time to be spent at the low PEEP level (Tl). The patient spends at least 60 percent of the respiratory cycle at PEEPh, typically closer to 80 to 90 percent. If the patient attempts to take a spontaneous breath, the trigger can be either flow or a negative inspiratory pressure. Generally, spontaneous breaths in APRV are unassisted when taken while at PEEPh. They may be assisted by preset pressure support when taken during PEEPl; however, often they are not when the Tl is of a very short duration. When pressure support is used to assist a spontaneous breath taken at PEEPl, it is often set to be equal to the difference between PEEPh and PEEPl.

Airway pressure release ventilation (APRV) is a time-triggered, pressure-controlled, and time-cycled mode used in conditions where limiting airway pressure and manipulating the I:E ratio are both desirable (e.g., ARDS).

The advantage of APRV is the ability to control mean airway pressure by varying the I:E ratio without having to force the patient to complete an entire respiratory cycle with each spontaneous breath. For instance, if a patient were undergoing inverse ratio ventilation using either A/C or PCV, each spontaneous breath would force an entire iteration of the breathing cycle. This can be extremely uncomfortable to a patient and frequently mandates very high levels of sedation or even chemical paralysis. With APRV, a spontaneous breath does not change where the patient is in the time-triggered, pressure-controlled, time-cycled breath. If a breath is taken, the patient takes what he can and returns immediately to the PEEPh or PEEPl plateau that he was previously on. This is more comfortable for the patient, in spite of the maintenance of a significantly inversed I:E ratio. As the lung injury improves, the Th and Tl can be manipulated to a more normal I:E ratio over time, allowing an easy transition to more traditional modes of ventilation, particularly PSV.

Pressure-Regulated Volume Control (PRVC)

Pressure-regulated volume control (PRVC) is a time- and patient-triggered, volume set/pressure-supported, time-cycled (set inspiratory time, Ti) mode of ventilation that adjusts the pressure support over the course of several breaths to achieve a preset tidal volume. This ensures adequate minute ventilation while augmenting patient efforts to the minimal extent necessary. PRVC use can be difficult in patients with significant variability in spontaneous respiratory breath generation. The ventilator looks at the

tidal volume achieved with a given pressure support during the set inspiratory time over the last several breaths and compares the average tidal volume achieved to the desired tidal volume. By calculating a compliance using the average tidal volume and the difference between the pressure support and the PEEP, the ventilator determines what increase in pressure support is necessary to achieve a target tidal volume. Unfortunately, variable pressure swings on a breath to breath basis can cause the ventilator to over or underestimate the optimal pressure support. Cough, significant patient movement, or tachypnea may all render PRVC a difficult mode to use and result in extreme patient work of breathing variability.

High-Frequency Ventilation (HFV)

High-frequency ventilation (HFV) has several variants that are all based on the idea of providing very low tidal volumes at very high respiratory rates. The most commonly studied of the HFV modes are high-frequency jet ventilation (HFJV) and high-frequency oscillatory ventilation (HFOV). High-frequency jet ventilation uses pulses of gas to generate very small tidal volumes at frequencies of one to 10 hertz (Hz). The mode was used initially for thoracic surgery involving the major airways, but today is generally limited to the pediatric critical care population. High-frequency oscillatory ventilation uses even higher frequencies of five to 50 Hz along with exceptionally small tidal volumes to maintain a predefined mean airway pressure in lung conditions with extremely limited pulmonary system compliance such as ARDS. Because of the extremely small tidal volumes being used, the method of gas exchange is fundamentally different when HFV is used relative to more conventional modes of ventilation. Chan et al. provided an excellent review of HFOV in the treatment of ARDS.[15] The use of HFOV in ARDS will be discussed in further detail below.

Basic Ventilator Settings When Lungs Are Normal

When mechanical ventilation is used for patients with normal lungs, it is being done for airway protection during the initial resuscitative period (Fig. 2). When employing mechanical ventilation, careproviders must avoid VILI. Finally, some lung conditions not appreciated initially may evolve or develop over time, such as pulmonary contusions, tracheal injury, or acute lung injury. The initial ventilator settings considered here assume normal pulmonary system compliance and an absence of identifiable lung injury.[16,17,18]

It is recommended that most be placed on traditional A/C ventilation as follows: FiO_2 = 100 percent, *f* = 16 to 20, Vt = 5 to 8 milliliters (ml) per kilogram (predicted body weight), PEEP = 5 centimeters (cm) H_2O and flow = 60 liters per minute.[19]

The FiO_2 can be turned down quickly after intubation to the lowest amount necessary to keep pulse oximeter oxygen saturation (SpO_2) greater than 92 to 94 percent (a higher SpO_2 may be desired when shock states are present). In cases of hypoperfusion where the SpO_2 cannot be measured accurately, serial arterial blood gas assessments may need to be obtained to appropriately titrate the FiO_2.

The FiO_2 should be titrated downward after intubation to the lowest amount necessary to keep SpO_2 greater than 92 to 94 percent.

The minute ventilation (Ve = *f* x Vt) adequacy is determined primarily by the pH. Whatever minute ventilation is necessary to achieve an adequate pH is the goal of mechanical ventilation. Efforts to achieve a normal partial pressure of carbon dioxide in arterial blood ($PaCO_2$) are not generally productive. Partial

Figure 2. *Intubation of a patient with blast injury to the head and neck is performed during primary trauma survey to protect his airway.*

pressure of carbon dioxide in arterial blood manipulation should be more appropriately considered as a way of achieving a desired pH. In most patients, a pH above 7.25 is adequate, although 7.35 to 7.40 is ideal in most settings. In some conditions, such as those associated with significant cerebral edema, low pH should be rigorously avoided.[20,21] The tidal volume described here of 5 to 8 ml per kilogram is lower than the 8 to 12 ml per kilogram classically described for initial settings in a patient with normal lungs and more closely resembles recommendations for ventilation of ARDS patients. This is because a significant body of data is beginning to emerge that VILI also develops in normal lungs at volumes that were previously considered safe.[22,23] It is important to note that the weight used in these formulas is the predicted (ideal) body weight (PBW) as used in the ARDSnet trials (see section on ARDS):

PBW in kilograms (male) = 50 + 2.3 x (height in inches – 60)
PBW in kilograms (female) = 45.5 + 2.3 x (height in inches – 60)

To compensate for the lower tidal volume recommended here, a higher respiratory rate will also be necessary. Adjustments in the respiratory rate should be made as necessary to achieve the pH goals outlined previously, as long as the patient's spontaneous rate does not already exceed the machine set rate. If the

spontaneous rate does already exceed the set rate, the set rate should be established as approximately 80 percent of the total rate, and further changes in the pH can be achieved with tidal volume manipulation. As the patient rate decreases, a decrease can be made in the set rate while attempting to keep the ratio of machine breaths to total breaths constant at about 80 percent. If the total rate does not exceed the set rate, then the set rate can be manipulated as necessary to achieve the pH goals described.

In the absence of any lung injury, PEEP greater than 5 cm H_2O is generally not initially necessary. As the amount of time spent on the ventilator increases, dependent atelectasis frequently develops and can create a very significant shunt leading to hypoxemia. Increased levels of PEEP may need to be applied in order to combat the development of atelectasis or to counteract the effects of lung injury in evolution. The manipulation of PEEP will be discussed in more detail below as it pertains to pulmonary contusion and ARDS.

In the absence of lung injury, PEEP greater than 5 cm H_2O is generally not initially necessary. Increased levels of PEEP may be needed in order to prevent the development of atelectasis or to counteract the effects of lung injury in evolution.

There is rarely a significant benefit to the manipulation of flow. In patients with prolonged exhalation times, such as asthma and chronic obstructive pulmonary disease (COPD), flow is frequently increased in an attempt to decrease the I:E ratio and allow more time for exhalation. However, at a standard flow of 60 liters per minute, a tidal volume of 500 ml is supplied in 0.5 seconds (60 liters per minute = 1000 ml per second). Therefore, doubling the flow rate to 120 liters per minute will decrease the inspiratory time to 0.25 seconds, extending the exhalation time by only 0.25 seconds. Simply decreasing the respiratory rate from 20 to 12 will increase the expiratory time by two seconds without having to manipulate the flow at all.

Pulmonary Contusion

Basic Concepts

Pulmonary contusion represents a heterogeneous, generally asymmetric, lung injury that is associated with blunt trauma or blast injury (Fig. 3).[24,25] It frequently evolves over hours to days and can result in significant right-to-left shunt as well as impaired ventilation. Associated injuries may include injury to the pulmonary vasculature and the airways. If a major airway injury occurs in association with blunt trauma, it frequently will appear within 2.5 cm of the carina and may not be appreciated during the initial resuscitation.[26] Blast injury to the lungs can result from primary blast effects, penetrating trauma (projectiles), or blunt trauma that results in pulmonary contusion. The blunt trauma that is applied to the chest in the case of blast injury may be either from physical contact (being thrown against an object) or from air pressure waves. The development of pulmonary contusion in the setting of blast injury was said to be unlikely in the absence of tympanic membrane perforation.[27] Recent reports dispute the reliability of tympanic membrane rupture as a sensitive screening tool for primary blast injury detection.[28,29]

Blast injury to the lungs can result from primary blast effects, penetrating trauma (projectiles), or blunt trauma that results in pulmonary contusion. The blunt trauma that is applied to the chest in the case of blast injury may be either from physical contact (being thrown against an object) or from air pressure waves.

Contusion in the pulmonary parenchyma is characterized by collections of blood and exudative fluid in alveoli in response to destruction of the alveolar capillary interface by transmitted pressure. As the pressure waves propagate through the lung tissue, they transmit less energy per unit of lung tissue so the destruction is greatest closer to the point of impact. This is the primary reason for the asymmetric nature of the injury. Lobar collapse and focal atelectasis may also occur due to the collection of blood, blood clots, reactive airway secretions, mucus plugging, and occasionally aspirated secretions or foreign bodies such as teeth or food particles. All of these factors create significant regions of lung that have minimal ventilation but relatively preserved blood flow, resulting in right-to-left shunt development. The resulting hypoxemia may present fairly abruptly many hours after the initial injury.

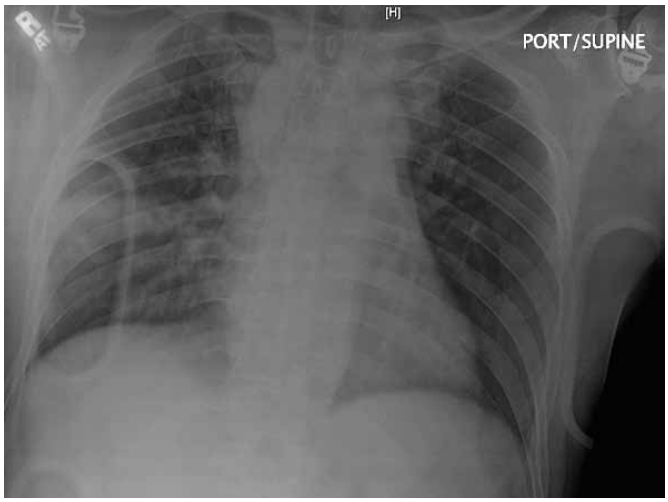

Figure 3. *Pulmonary contusion represents a heterogeneous, generally asymmetric, lung injury that is associated with blunt trauma or blast injury.*

Pulmonary system compliance decreases significantly with blunt trauma that is substantial enough to result in pulmonary contusion. Fractured ribs may limit the efficiency of rib cage movement, as may resultant pain. The particular condition of flail chest is characterized by the presence of two or more adjacent ribs that each have at least two sites of fracture (Fig. 4). Inspiration in the spontaneously breathing patient normally results from chest wall expansion and diaphragm contraction that generates a negative intrathoracic pressure relative to atmospheric pressure. This serves to draw the flail segment inward during inspiration and contributes to respiratory compromise. It also may not be recognized when a person is on positive-pressure mechanical ventilation because there is no mechanism for the flail chest to develop. The presence of significant chest wall injury of any kind can be expected to decrease the chest wall compliance.

The alveolar injury pattern described previously creates a decrease in lung compliance. The compliance is further decreased by any postobstructive atelectasis associated with airway occlusion by blood or other secretions. Inability to take deep breaths due to pain will contribute to the development of dependent atelectasis as well as make postobstructive atelectasis more likely. Decreased chest wall compliance and lung compliance both contribute to a limited total pulmonary system compliance. The limited compliance decreases the tidal volume that a patient is able to generate. In addition, given that a normal pair of lungs has a given amount of dead-space, a decreased tidal volume by necessity implies a greater dead-space fraction. A larger dead-space fraction means that there will be increased difficulty getting rid of carbon dioxide, so the body must compensate by increasing the minute ventilation ($Ve = f \times Vt$). Since tidal volume is limited, patients with significant pulmonary contusions are often noted to breath shallowly

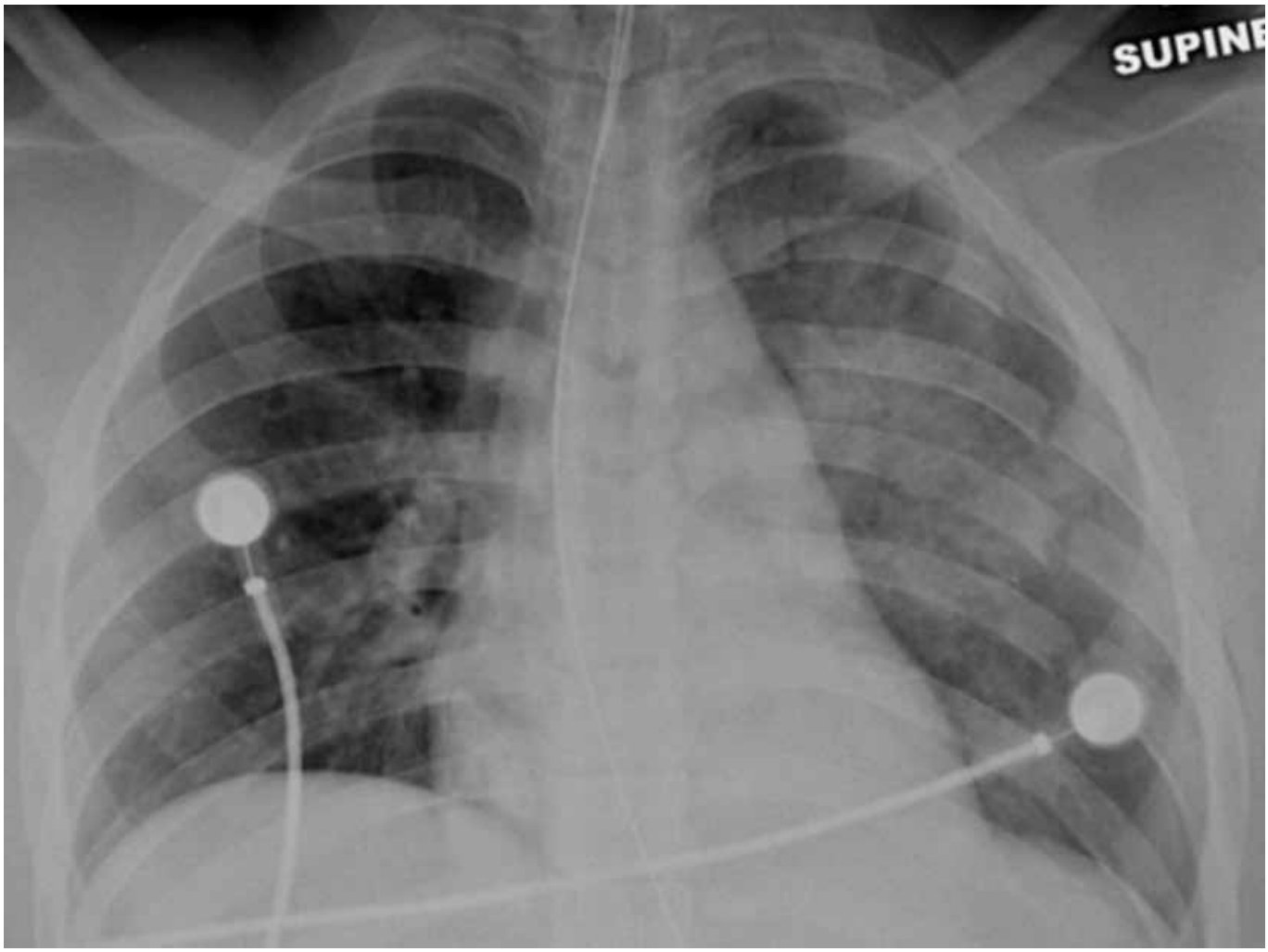

Figure 4. *Flail chest is described as the paradoxical movement of a segment of chest wall due to fractures of two or more ribs in at least two different sites. Here, multiple left-sided posterior rib fractures are noted.*

and rapidly as they try to increase respiratory rate. However, once tidal volume becomes sufficiently shallow and dead-space fraction significantly large, the patient is at great risk for the development of hypercarbic respiratory failure.

Management

Airway Protection and Pulmonary Toilet

Airway protection and ventilator support are extremely important facets of pulmonary contusion management. Upper airway control with endotracheal intubation or tracheostomy is generally accomplished early in the resuscitation of severely injured patients. Due to the progressive nature of pulmonary contusion symptomatology, careproviders should obtain early airway control and provide ventilator support for all moderate to severely symptomatic pulmonary contusion patients. Mildly symptomatic cases may be managed with supplemental oxygen, serial observation, and pulse oximetry.[30] Occasionally, patients may benefit from the use of noninvasive positive-pressure ventilation (NIPPV) if they are alert.[31]

Due to the progressive nature of pulmonary contusion symptomatology, early airway control and ventilator support should be provided to all moderate to severely symptomatic patients. Mildly symptomatic cases may be managed with supplemental oxygen, serial observation, and pulse oximetry.

The concept of airway protection in the case of pulmonary contusion also extends to airways that can be reached by flexible fiberoptic bronchoscopy easily, such as those serving the major pulmonary segments (Fig. 5). Bronchoscopy allows removal of clots and secretions, thereby decreasing the percentage of lung that may have been prone to postobstructive atelectasis.[32] A survey can be performed with flexible fiberoptic bronchoscopy to rule out any evidence of major airway injury and localize any major bleeding that may be present from vessel injury. Serial flexible fiberoptic bronchoscopy as the contusion progresses may be necessary to maintain adequate pulmonary toilet by clearing mucus plugging or inspissated secretions that may contribute to the late development of atelectasis. It should be noted that flexible fiberoptic bronchoscopy does not have the ability to clear blood or exudative secretions at the level of the alveoli.

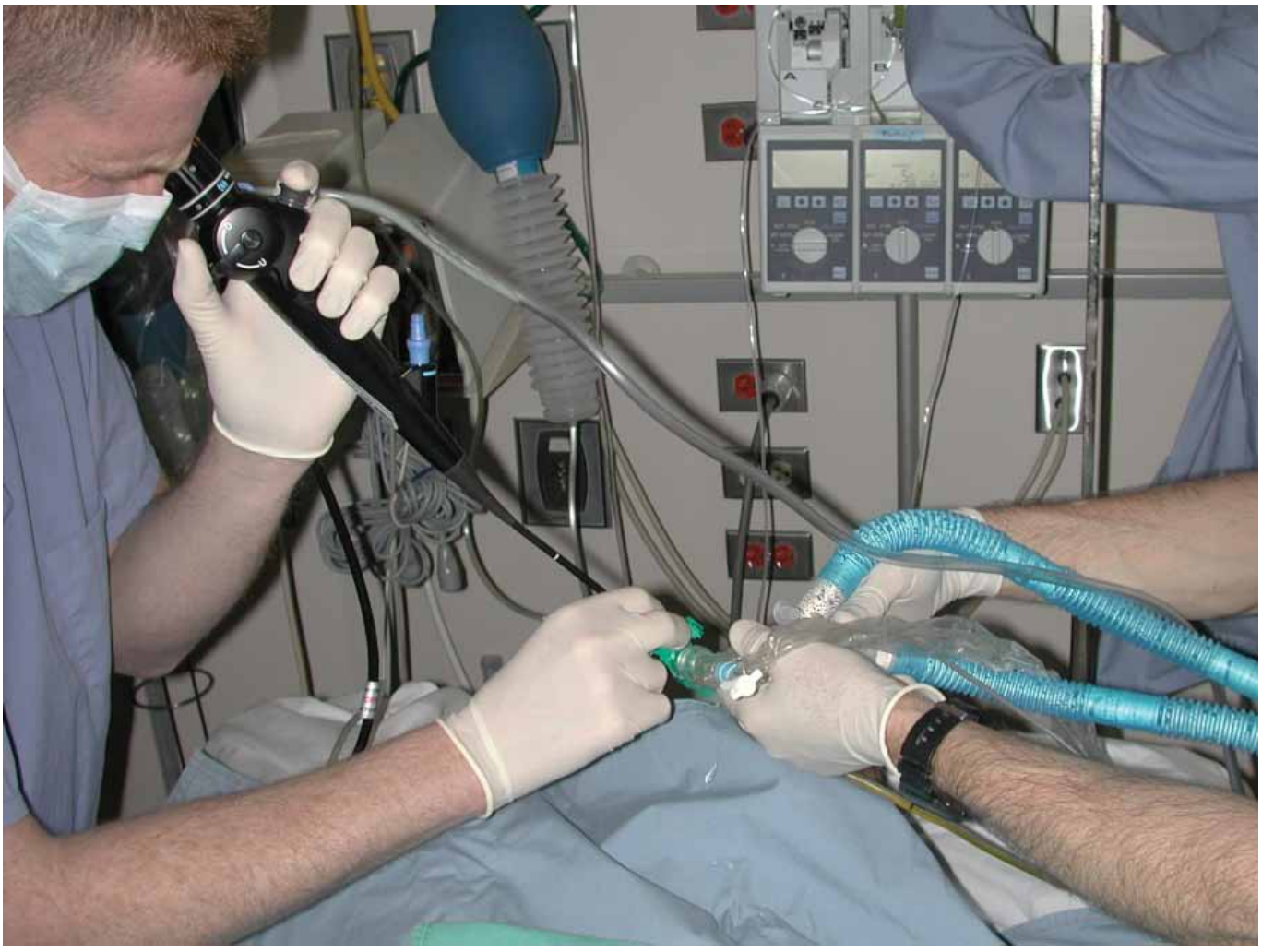

Figure 5. *Flexible fiberoptic bronchoscopy allows removal of blood clots and secretions, thereby decreasing the likelihood of postobstructive atelectasis.*

Positive-Pressure Ventilation

Positive-pressure ventilation has a key role in the care of pulmonary contusions by supporting adequate gas exchange.[24] The application of a positive-pressure breath can augment the tidal volume enough to allow an adequate minute ventilation. The minute ventilation necessary may also be decreased by the use of positive-pressure ventilation since a more effective tidal volume will lead to a decreased dead-space fraction. Remembering that the $PaCO_2$ is inversely related to Ve (1–Vd/Vt), it is easy to see that an augmented tidal volume will significantly improve ventilation in the setting of pulmonary compliance limitations.

As discussed earlier, positive-pressure ventilation can augment respiration (oxygenation) in two ways: increasing the FiO_2 and increasing the mean airway pressure. Increasing the mean airway pressure can be accomplished in several ways, but is easiest to do in the setting of pulmonary contusion by increasing the PEEP. Positive end-expiratory pressure results in an increased functional residual capacity (FRC), which is the volume of the lung at end-tidal exhalation. The increased functional residual capacity helps to maintain the patency of alveoli and counteract the tendency towards atelectasis and shunt development. The application of PEEP may also open some previously closed alveoli, further improving the shunt fraction.

Positive-pressure ventilation is instrumental in the care of pulmonary contusions by supporting adequate gas exchange.

One potential complication of excessive PEEP application results from the asymmetric nature of the lung injury.[24] Any pressure applied by the ventilator will preferentially go first to portions of the lung with relatively normal compliance such as those that are not affected by the contusion. Serial increases in PEEP may paradoxically result in decreasing oxygenation if overdistension of normal lung becomes severe enough to decrease blood flow by the creation of West Zone 1 conditions. West Zone 1 conditions comprise alveolar pressures greater than pulmonary artery systolic pressures greater than pulmonary artery diastolic pressures. Blood will then preferentially flow to the contused lung units where ventilation is poor, increasing the shunt fraction and worsening hypoxemia. Increasing areas of West Zone 1 conditions by definition imply larger areas of dead-space ventilation, and the dead-space fraction is therefore increased leading to less effective ventilation. It is difficult to know in a given patient what level of PEEP may prove to be too much, but progressively worsening hypoxemia and hypercapnea in the setting of increasing levels of PEEP may imply that the level of PEEP being applied is excessive.

It is important to remember that positive pressure can be applied noninvasively (NIPPV). This is an excellent option for patients with mild pulmonary contusions, who otherwise are not in need of invasive mechanical ventilatory support. The appropriate use of NIPPV can be expected to result in decreased ventilator-associated pneumonia.[31] However, as contusions may heal slowly and may progress over several days, the decision to use NIPPV should be accompanied by aggressive serial clinical evaluations. Use of NIPPV also makes the use of flexible fiberoptic bronchoscopy for airway survey and serial pulmonary toilet difficult.

Adjunctive Strategies

For patients with isolated pulmonary contusion, intravascular volume should be minimized to that necessary to ensure adequate systemic perfusion.[31] This will minimize the adverse effects on pulmonary physiology. When pulmonary contusion is encountered in the multisystem trauma patient, it may not be the dominant or most life-threatening injury. In such cases, intravascular volume should be maintained as

dictated by the overall injury pattern, but fluid minimization should be accomplished when possible. Even in the setting of isolated pulmonary contusion, forced diuresis does not have a role except in patients who are otherwise intravascularly volume overloaded, as in the case of a congestive heart failure patient who may have sustained blunt thoracic trauma.[31]

In patients with isolated pulmonary contusion, intravascular volume administration should be kept to the minimum amount necessary to maintain adequate systemic perfusion.

Pain control is vital, as is stabilization of the chest wall. In the case of rib fractures, the application of positive-pressure ventilation may be all that is necessary for chest wall stabilization.[33] Direct fixation of rib fractures may be necessary in some cases, particularly when large areas of flail chest are involved.[33] Adequate pain control may be aided greatly by the use of epidural anesthesia and paravertebral blocks.[34] Such techniques may be especially effective in the marginal, unintubated patient. Most deployed medical facilities that have anesthesia support should be facile in these methods of achieving pain control.

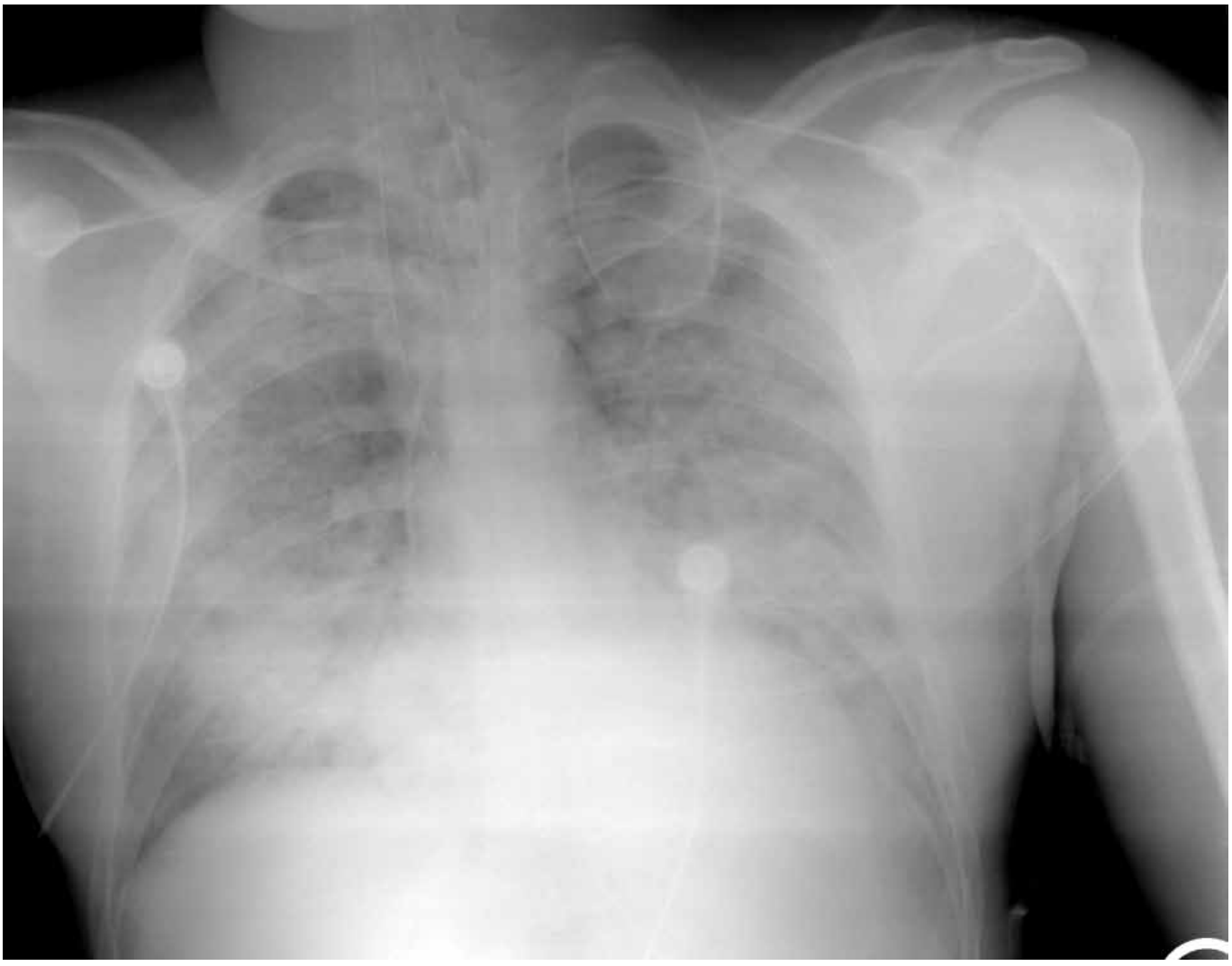

Figure 6. *Patient with severe ARDS following trauma. ARDS is a clinical syndrome characterized by noncardiogenic pulmonary edema in response to lung injury.*

Control of cough is debatable, and it is difficult to offer guidance that applies to all cases.[35] Cough is beneficial in that it may allow improved pulmonary toilet by dislodging clot and secretions in the airway, thereby decreasing postobstructive atelectasis. On the other hand, cough that is associated with significant chest wall pain may prolong the period where patients feel incapable of taking adequate deep breaths. This may contribute to hypercarbic respiratory failure as well as the development of more atelectasis. Cough in general should probably be encouraged, but any associated pain should be treated aggressively. Cough should only be suppressed when the pulmonary contusion is accompanied by active, uncontrolled pulmonary hemorrhage and intractable pain.

Cough should only be suppressed when a pulmonary contusion is accompanied by active, uncontrolled pulmonary hemorrhage, or intractable pain. Otherwise, coughing should probably be encouraged, and any associated pain should be treated aggressively.

Chest physical therapy is often prescribed for patients in the ICU, but there is almost no literature supporting its use in any setting outside of that associated with bronchiectasis.[36,37] Some describe benefits in cases where postobstructive focal atelectasis is present, such as that associated with a maturing pulmonary contusion. If chest physical therapy is used for a pulmonary contusion patient, pain control is vital for the same reasons as outlined above with respect to cough.

The significant shunt associated with pulmonary contusion is due to a heterogenous, largely asymmetric process.[24,31] The injury process and resultant shunting associated with acute lung injury and the acute respiratory distress syndrome are also heterogenous but more likely to be symmetric (Fig. 6). There are significant differences in the management of these conditions as will be outlined in the next section.

Acute Respiratory Distress Syndrome (ARDS)

Basic Concepts

Acute lung injury (ALI) and ARDS both describe a common clinical syndrome characterized by the development of noncardiogenic pulmonary edema in response to a direct or indirect lung injury.[38] Both processes have an identical pathophysiologic origin and management is the same.[39] The difference between ALI and ARDS is one of severity with respect to the partial pressure of oxygen in arterial blood (PaO_2)/FiO_2 ratio and is therefore somewhat arbitrary. For this reason, ARDS will be used exclusively in this review to describe any patient with a clinical syndrome compatible with either ALI or ARDS. The American-European Consensus Criteria for ALI and ARDS both include the following characteristics: acute onset (less than seven days), diffuse bilateral patchy infiltrates seen on standard chest radiography, and an absence of left atrial hypertension clinically (or with a pulmonary capillary wedge pressure [PCWP] less than 18 mm Hg if a pulmonary artery catheter is already in place). As noted previously, ALI and ARDS differ only in the PaO_2/FiO_2 used for their definition. Acute respiratory distress syndrome is notable for a PaO_2/FiO_2 less than 200, while that of ALI is between 200 and 300.[39]

Acute respiratory distress syndrome can be caused by both direct and indirect injuries.[40] Direct causes include aspiration, pneumonia, blunt trauma to the chest, and other pulmonary processes that may trigger a significant inflammatory response. Indirect injury may cause ARDS by triggering systemic inflammation through the release of cytokines. Examples of indirect injury relevant to the critical care

ICU environment include multisystem trauma, shock, blood product transfusion, and sepsis. The common pathway for both direct and indirect causes is inflammation. When ARDS presents clinically, it usually develops several hours to days after the initial precipitating injury.[40,41]

Acute lung injury and ARDS both describe a common clinical syndrome characterized by the development of noncardiogenic pulmonary edema in response to a direct or indirect lung injury.

The likelihood of ARDS development secondary to an underlying insult rises with the age of the patient. The mortality attributable to ARDS is approximately 40 percent but increases with the number of concomitant organ system failures.[40] The development of renal failure in the setting of ARDS denotes a particularly poor prognosis. A recent study demonstrated that the likelihood of eventual death due to ARDS is related to dead-space fraction on presentation.[42] Those with a higher dead-space fraction had a higher mortality. The mortality due to ARDS is improving with aggressive supportive therapy and an increasing appreciation of the role that mechanical ventilation can play in both recovery and injury propagation.[10]

The pathology associated with ARDS is that of diffuse alveolar damage, regardless of the inciting injury, which may represent a stereotypic lung injury and healing response.[40] There are two distinct clinical phases in the evolution of the lung injury: an exudative phase that predominates in the first five to seven days, followed by a proliferative phase after this point.[40] Cytokines and other inflammatory mediators initiate changes that lead to disruption of the normal alveolar-capillary interface and the introduction of exudative fluid into the alveolus. This causes two major changes: the first is inactivation of surfactant, and the second is sloughing of the alveolar and bronchial epithelial cells. Loss of surfactant function makes alveolar collapse more likely, and the loss of epithelial cells leads to hyaline membrane formation on the denuded basement membrane. The injury leads to attraction of neutrophils as well as stimulation of alveolar macrophages. These cells release several cytokines, proinflammatory agents as well as some antiinflammatory mediators. On balance, there is a net effect to perpetuate the inflammatory process and to recruit other neutrophils. It is not clear to what extent local release of these agents impacts other organ systems.

The late phase of ARDS evolution, the proliferative phase, is notable for the development of fibrotic changes in the interstitium and alveolar spaces.[40] There may be significant architectural distortion, and it is common to see an increase in dead-space fraction that may manifest as an increased $PaCO_2$ or a suddenly increased spontaneous minute ventilation. While it is convenient to think of ARDS pathophysiology as having two distinct phases, there is evidence of abnormal fibroproliferation early in the syndrome, and fibroblast mitogenic activity on bronchoalveolar lavage specimens has been correlated with mortality.[43] Most patients who die as a direct result of ARDS will do so during the exudative phase of the syndrome, but there is still a significant mortality risk for those in the fibroproliferative stage who require prolonged ventilation.[40] Their mortality is increasingly likely to be related to nosocomial complications as well as failure of other organ systems.

In a clinical sense, there are three distinct lung zones created in patients with ARDS. There are significant portions of the lung that are dominated by shunt physiology secondary to alveolar filling and atelectasis, associated both with the loss of surfactant and dependent collapse. Most of these areas will either heal or they will not irrespective of interventions. Vigorous efforts to open involved alveoli are unlikely to be of benefit and may be harmful to more compliant areas of the lungs. A second important lung zone is

characterized by significant atelectasis or alveolar-capillary barrier damage that may be reversible. Some areas in this region may even open with the introduction of a positive-pressure breath but close as the breath is allowed to exit the lung. The cycle then repeats with each subsequent breath. This area is the battleground for ARDS supportive management. The goal is to utilize this region for gas exchange as much as possible while simultaneously protecting it from further injury evolution. The third lung zone is a relatively normal one. It is likely that there are significant inflammatory changes taking place in these regions as well, but from a gross macroscopic standpoint, this zone appears to behave in a normal physiologic manner. As described for the second region, one of the fundamental goals of ARDS care is to protect this normal lung zone from injury. Gattinoni et al. have used the term "baby lungs" when thinking about mechanical ventilation of ARDS patients, since a smaller than normal lung volume is actually available to perform the necessary physiologic function normally accomplished by the uninjured pulmonary system.[44]

The edema and atelectasis create a significant amount of physiologic right-to-left shunt that generally leads to progressive, severe hypoxemia. These changes also cause a significant reduction in lung compliance. Efforts to provide "normal" tidal volume breaths using a traditional volume-control mode will result in the development of very high peak and plateau pressures.[40,45] Use of a pressure-control mode with the intent of limiting these high pressures will often lead to very low tidal volumes.[46,47] Strategies for addressing both the shunt and compliance abnormalities will be discussed in further detail below.

Ventilator-induced lung injury is one of the significant dangers associated with the care of the ARDS patient.[7] Volutrauma in ARDS has been noted with excessive tidal volumes in both retrospective and prospective human trials and demonstrated convincingly in animal studies.[10] Volutrauma is felt to be one of the primary mediators of VILI in ARDS patients and has been the impetus for the low-tidal-volume strategies described below. Barotrauma was seen frequently in the past when overaggressive positive-pressure ventilation was applied to ARDS patients with severely limited lung compliance, resulting in very high transalveolar pressures. Atelectotrauma due to cyclic opening and closing of alveoli is of greatest concern at the edges of portions of the lung that are densely consolidated. Alveoli that open and close adjacent to those that are incapable of opening create a shearing force with each cycle. This shearing force may disrupt the alveolar-capillary interface and perpetuate the lung injury. Finally, biotrauma associated with mechanical ventilation use will exacerbate the underlying inflammatory milieu already present in the ARDS patient and may serve to encourage further lung injury. With this as a background, attention now turns to the complex task of ARDS management. Goals for management of ARDS include: (1) eliminate the source of the ARDS; (2) provide aggressive supportive care to allow time for healing to take place; and (3) do not cause further harm with iatrogenic interventions.

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Mechanical Ventilation

Tidal Volume

Volutrauma has long been noted in animal models to both perpetuate existing ARDS and to cause a lung injury de novo with pathology consistent with diffuse alveolar damage. It was therefore hypothesized

that using a lower tidal volume with mechanical ventilation may result in improved outcomes. Four randomized controlled trials conducted using so-called lung protective strategies were published in the late 1990's.[48,49,50,51] Only one of the four was able to demonstrate a statistically significant improvement in mortality.[48] A consortium of institutions known as the Acute Respiratory Distress Syndrome Clinical Trials Network (ARDSnet) led by the National Heart Lung and Blood Institute was formed in the mid 1990's to coordinate ARDS research efforts. They conducted a large phase III randomized controlled trial comparing a low tidal volume (4 to 6 ml per kilogram) versus high (conventional) tidal volume (12 ml per kilogram) that was published in 2000.[52] The low-tidal-volume intervention resulted in statistically significant improvements in mortality, ventilator-free days and organ-failure-free days. It should be noted that the weight used for the tidal volume calculation is the predicted body weight. This same low-tidal-volume strategy was used in subsequent ARDSnet studies described later that addressed issues such as optimal PEEP settings, fluid strategy and corticosteroid use in ARDS. A reproduction of the ARDSnet low-tidal-volume strategy is included in the Appendix.

An early criticism of the low-tidal-volume ARDSnet trial was that it is unclear from the design of the study that a low tidal volume of 4 to 6 ml per kilogram is optimal. Another explanation of the study findings perhaps is that a tidal volume of 12 ml per kilogram may be excessive and did not represent the common standard of care at the time the study was done.[53] The criticism has been countered by survey data from the mid 1990s demonstrating that average tidal volumes in use at the time of the study design were in fact similar to those produced in the ARDSnet study control group. At this point in time, the ARDSnet low-tidal-volume strategy is considered the standard of care for initial ventilator management of ARDS, and deviations from this basic protocol should only be made when it has failed in a given clinical setting.

Low-tidal-volume strategy is considered the standard of care for initial ventilator management of ARDS.

Based on the ARDSnet study findings, initial ventilator settings for a patient with ARDS are illustrated below.[52] For patients who were previously receiving invasive mechanical ventilation prior to the diagnosis of ARDS, adjust the FiO_2 and PEEP as indicated in the Appendix. For patients who were intubated at the same time that the initial diagnosis of ARDS was made, begin with an FiO_2 of 100 percent, a PEEP of 10 cm H_2O and titrate both according to the Appendix.

1. Assist-Control (A/C) Mode (volume set/flow controlled for assist and control breaths)
2. Initial Vt = 8 ml per kilogram (PBW)
   PBW in kg (male) = 50 + 2.3 x (height in inches – 60)
   PBW in kg (female) = 45.5 + 2.3 x (height in inches – 60)
3. Reduce Vt by 1 ml per kilogram until Vt = 6 ml per kilogram
4. Adjust *f* (up to 35) and Vt (4 to 6 ml per kilogram) to achieve peak plateau pressure (Pplat) less than 30 cm H_2O and pH 7.3 to 7.45
5. Bicarbonate can be added if pH is less than 7.3 and if *f* is maximal at 35.
6. Initial FiO_2 and PEEP levels were not predefined in the ARDSnet low-tidal-volume study.

An important concern related to the use of low tidal volumes to limit plateau pressures in ARDS patients is the development of clinically significant respiratory acidosis. Previous research has demonstrated that

moderate degrees of respiratory acidosis are well tolerated in most instances and therefore represent a small price to pay relative to the benefits of decreasing volutrauma and barotrauma.[54] This trade-off of ventilation for lung function preservation became known as permissive hypercapnia. The ARDSnet protocol allowed for the use of bicarbonate to help counteract the effects of hypercapnia and normalize the pH.[52] There was little difference in pH between intervention and control groups after the initial 72 hours. Other options in clinical practice include the use of proton scavengers such as tromethamine and less commonly limiting CO_2 production by manipulating the respiratory quotient of feeds, decreasing body temperature, or minimizing metabolic rate through deep sedation or paralysis. The use of permissive hypercapnia in the setting of a severe elevation in intracranial pressure should be avoided due to associated worsening elevations in intracranial pressure.[20,21,55,56]

The use of low tidal volumes to limit plateau pressures in ARDS patients can lead to clinically significant respiratory acidosis. When permissive hypercapnia is practiced, the resultant acidemia can be mitigated by use of bicarbonate or other interventions.

Positive End-Expiratory Pressure (PEEP)

The optimal PEEP to be used for mechanical ventilation of the ARDS patient is an area of great interest and few definite answers.[57] The maintenance of pressure in the airways at end-exhalation should help to prevent collapse of alveoli and preserve the current functional residual capacity, which is the volume in the lungs at the end of tidal exhalation. In ARDS, progressive atelectasis is a problem due to progression of the injury itself, as well as the effects of compression by a heavy, edematous lung on more dependent portions. The use of PEEP can counteract this trend.

An intuitive approach to the application of PEEP would involve the examination of a static pressure-volume curve as represented in Figure 7. Pressure is applied initially to the lung in an effort to cause inflation. The initial portion of the curve is characterized by little change in volume in spite of pressure application, which represents alveoli that are closed and will not open without a significant amount of energy. Once a critical opening pressure is reached, the compliance of the system improves markedly, and the lung opens quickly with relatively little subsequent pressure application. This critical opening pressure is referred to as the lower inflection point. At some point, the lung cannot expand further and compliance again drops drastically yielding no significant gain in volume regardless of the further application of pressure. This point of sudden decrease in compliance is called the upper inflection point.

Many experts have argued that the optimal PEEP should be one that is just above the lower inflection point, since the fundamental goal of PEEP is to prevent collapse of alveoli and loss of functional residual capacity. Others argue that it is more effective to use a higher level of PEEP just below the upper inflection point in order to maximize the ability to keep the lungs open. A third opinion relates to the fact that a static pressure-volume curve in ARDS often demonstrates a degree of hysteresis. The sigmoidal shape curve seen as air is pushed into the lungs is not identical to that seen when air is allowed to passively leave on exhalation. The exhalation curve is typically shifted slightly to the left, implying a higher lung volume at any given transpulmonary pressure relative to that seen on inhalation. Some advocate using the exhalation curve to determine the optimal PEEP rather than any point on the inhalation curve, since the goal is to help alveoli remain open as air leaves the lungs.

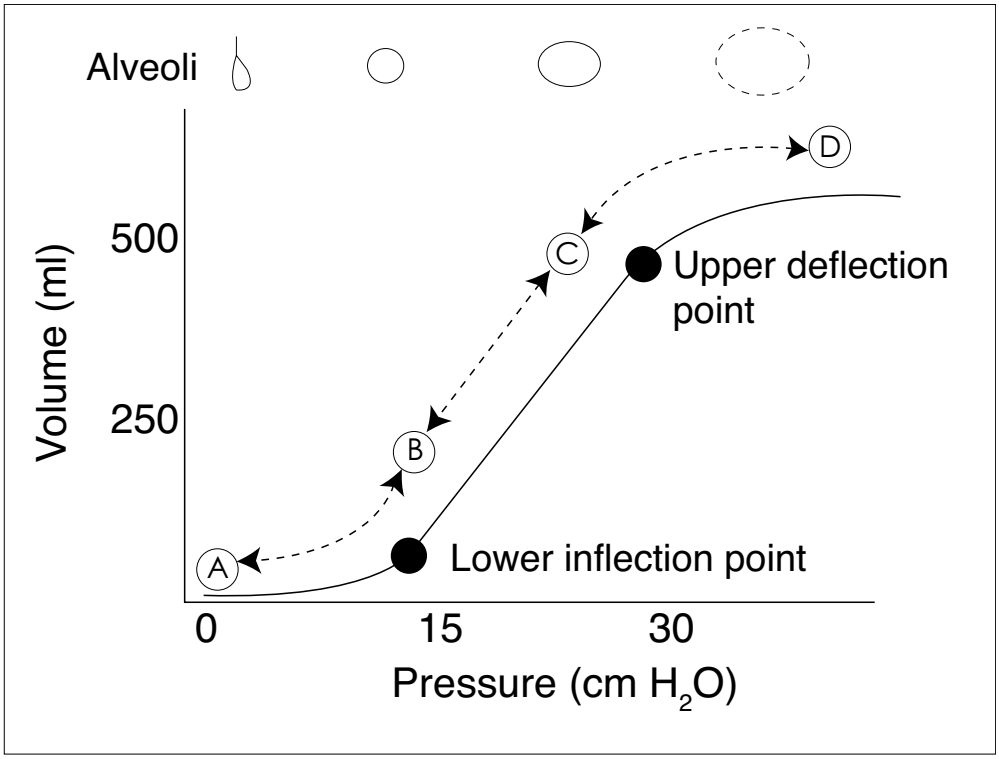

Figure 7. *An ARDS static compliance curve. Once a critical opening pressure is reached (B), the compliance of the system improves markedly and the lung opens quickly with relatively little subsequent pressure application.*

Several ventilator packages have sophisticated software algorithms available that can project a pressure-volume curve. However, measurement of a true static pressure-volume curve involves paralyzing the patient and serially measuring pressures after different volumes are introduced into the patient. In the day-to-day clinical management of an ARDS patient, this process is time consuming, risky for the patient, and not practical to consider several times a day when compliance may be expected to change rapidly.

Attempts to define the optimal use of PEEP have resulted in the evolution of two schools of thought, one advocating more moderate levels of PEEP and one favoring a high level of PEEP.[58,59]

Potential problems may be envisioned with both approaches. If a low-PEEP strategy is used, it may not be adequate enough to maximally prevent alveolar collapse. Additionally, worsening compliance due to evolution of the lung injury may lead to the emergence of an inadequate level of PEEP within hours or days that may have been adequate at the time it was set. If a low-PEEP strategy is used, close attention must be paid to the development of worsening compliance and shunt. The use of very high levels of PEEP may result in overdistension of relatively normal lung tissue. Excessive alveolar distending pressures may cause diversion of blood to less ventilated sections of the lung. This creates increased dead-space in the more compliant areas of lung and increased shunt in the more consolidated areas. Other complications to consider in the scenario would be atelectotrauma exacerbation at the interfaces between more and less compliant areas of lung, as well as volutrauma and possibly barotrauma in the overdistended lung regions. All of these effects would perpetuate biotrauma and add the effects of VILI to those already ongoing due to the ARDS.

In 2004, the ARDSnet published the results of a multicenter randomized controlled trial comparing a low-PEEP/high FiO_2 strategy to a high-PEEP/low FiO_2 strategy known as the Assessment of Low Tidal Volume and Elevated End-Expiratory Lung Volume to Obviate Lung Injury (ALVEOLI) trial.[59] The study enrolled 549 patients to completion and did not show a significant difference in terms of hospital mortality or ventilator-free days. The average PEEP in the low-PEEP group was 8.3 cm H_2O compared to 13.2 cm H_2O in the high-PEEP group. A subgroup analysis of the ALVEOLI trial compared the effects of recruitment maneuvers in ARDS patients who were ventilated in the high-PEEP group. Recruitment maneuvers were performed by transitioning the patient from A/C to continuous positive airway pressure (CPAP) with a pressure of 35 cm H_2O and maintaining this pressure for 30 seconds before transitioning back to A/C. There were some transient improvements in SpO_2 in some patients, but no sustained improvements after an hour were noted. Some patients experienced desaturation and hypotension as complications. A recent study compared the use of a moderate level of PEEP (5 to 9 cm H_2O; the minimal distension group) to an increased recruitment approach (increasing the PEEP to reach a plateau pressure of 28 to 30 cm H_2O).[60] All patients received a low-tidal-volume (6 ml per kilogram) strategy with volume set/flow controlled, A/C as the mode of mechanical ventilation. There was no significant difference in mortality, but the increased recruitment strategy led to a statistically significant improvement in the number of ventilator-free days and organ failure-free days. It should also be noted that adjunctive therapies such as prone positioning and inhaled nitric oxide were used more frequently in the minimal distension group. Meade et al. compared an "open-lung" strategy of ventilation versus the now standard ARDSnet low-tidal-volume algorithm in a multicenter randomized controlled trial published in 2008 involving 983 patients with ARDS.[61] The intervention group received a plateau pressure limit of 40 cm H_2O, pressure-control ventilation, and a significantly higher PEEP than that seen in the 2000 ARDSnet low-tidal-volume trial. There was no difference in mortality, but there was a statistically significant decrease in refractory hypoxemia and the use of rescue therapy (inhaled nitric oxide, prone positioning, high frequency oscillatory ventilation and extracorporeal membrane oxygenation) in the intervention group.

In most cases of ARDS, the optimal PEEP is likely at least 10 to 12 cm H_2O. Higher levels should be attempted in patients with more severe ARDS manifestations, while close attention is paid to the development of iatrogenic complications.

Conclusions regarding PEEP remain a source of great debate. The data appears to favor a higher PEEP with respect to oxygenation, but there does not appear to be a mortality benefit to this approach.[59,61] Concern exists that excessively high levels of PEEP may perpetuate VILI, exacerbate hypoxemia and hypercapnia, and may cause hypotension.[62] The optimal PEEP is likely at least 10 to 12 cm H_2O in most cases, and higher levels should probably be attempted in patients with more severe ARDS manifestations while close attention is paid to the development of iatrogenic complications.[59,61]

Airway Pressure Release Ventilation (APRV)

Airway pressure release ventilation (APRV) has been used as an alternative mode of mechanical ventilation in the ARDS patient.[63,64] As discussed earlier, it involves controlling the mean airway pressure by cycling between two different levels of PEEP. The ability to generate a high mean airway pressure augments oxygenation, while the upper PEEP level serves to limit the plateau pressure generated by driving air into a noncompliant lung. The ability to limit the plateau pressure is an attractive feature of this mode of ventilation in ARDS, as is such a precise ability to control the mean airway pressure. The

fact that the ventilator does not have to change its controlled pressure release cycle based upon patient effort is also very helpful and allows the use of very aggressive inverse ratio ventilation with less patient discomfort.[63] This allows a decreased requirement for sedation and chemical paralysis.[65]

One drawback of APRV mode is that the tidal volume generated by the controlled breaths is determined by the difference between the high PEEP and low PEEP levels. Most who use APRV tend to use relatively aggressive PEEPh levels but PEEPl levels of 0 to 5 cm H_2O. This large difference creates the potential for excessive tidal volume generation greater than 6 ml per kilogram and therefore may perpetuate VILI. The development of intrinsic PEEP may mitigate this concern somewhat since the time spent at the PEEPl is frequently very short. The time at the PEEPl is often set so that the expiratory flow versus time curve is only 80 to 90 percent of the way back to a baseline of zero flow when the machine cycles back to the PEEPh level. Significant intrinsic PEEP will cause the tidal volume to be proportional to the difference between the PEEPh and intrinsic PEEP rather than the larger difference between PEEPh and PEEPl.

There is no data to support the use of APRV over other modes of ventilation in the setting of ARDS. It should be thought of as a potentially useful salvage therapy in the critical care setting for patients who have failed a traditional ARDSnet low-tidal-volume strategy.

At this time, there are no data to support a benefit of this mode of ventilation versus any other mode in the setting of ARDS. There are studies that describe the successful application of APRV for ARDS patients, and some major medical centers have a great deal of experience with the mode.[66] A randomized, open labeled, parallel assignment study comparing APRV to the ARDSnet low-tidal-volume standard of care for ALI/ARDS is currently enrolling patients.[67] At this time, APRV should be thought of as a potentially useful salvage therapy in the CCC setting for patients who have failed the traditional ARDSnet low-tidal-volume strategy.

Adjunctive Strategies

Inhaled nitric oxide (iNO) has been used to cause selective pulmonary artery vasodilation in several conditions, including primary pulmonary hypertension, pulmonary reperfusion lung injury after pulmonary thromboendarterectomy, and ARDS in both adults in infants.[68,69,70] Inhaled nitric oxide is very short-acting and does not enter the systemic circulation to an appreciable extent. Its effects are therefore locally confined to well-ventilated alveoli, serving to improve ventilation-perfusion matching. Importantly, perfusion is diverted away from poorly ventilated regions, which has the effect of decreasing the shunt fraction and therefore improving hypoxemia. Several clinical trials have evaluated the use of iNO in ARDS with variable designs and outcomes. A recent meta-analysis concluded that there is a small but significant improvement in PaO_2/FiO_2 at 24 hours but no improvement in mortality and potential harm (renal dysfunction). Thus it cannot routinely recommended at this time.[69]

Although there is a small but significant improvement in PaO_2/FiO_2 at 24 hours, inhaled nitric oxide fails to improve mortality, and cannot be routinely recommended for treatment of ARDS.

High-frequency oscillatory ventilation is the intellectually extreme manifestation of the low-tidal-volume approach. The majority of clinical experience with this mode of ventilation and its application in ARDS is confined to a few major academic medical centers. A study published by Derdak et al. in 2002 compared

the use of HFOV versus a more conventional mode of ventilation.[71] There was no mortality benefit noted in that study, although there was a trend towards improved survival noted as many as 90 days after randomization (p = 0.1, 148 patients enrolled in the study). The average tidal volume in the conventional ventilation group was 10 ml per kilogram. There has not been a prospective randomized controlled trial comparing HFOV to the ARDSnet low-tidal-volume strategy. High-frequency oscillatory ventilation should be thought of as a rescue therapy only in centers with significant experience in its use. It may find wider application in the future as further prospective studies are conducted.

Extracorporeal membrane oxygenation (ECMO) has been used in neonatal intensive care for ARDS for several decades with success.[72] The therapy involves diverting blood through a filter outside of the body to allow gas exchange and then reintroducing the treated blood into the vasculature. A large prospective study evaluating the use of ECMO in adults with severe acute respiratory failure during the 1970's failed to show a significant benefit to the therapy.[73] Extracorporeal membrane oxygenation is used as therapy for ARDS in a few large medical centers today with relatively stringent criteria used for selection of patients believed to derive benefit. A portable extracorporeal carbon dioxide removal ($ECCO_2R$) device called the NovaLung® has been used in the ICU as rescue therapy for United States (US) service members wounded in Iraq with severe ARDS and for their critical care air transport out-of-theater. Rationale for this approach stems from allowing the use of very low minute ventilation in an effort to minimize ventilator induced lung injury.[74] Experience is limited, but anecdotal success has been encouraging.[75] Randomized controlled trials further evaluating ECMO and $ECCO_2R$ technology relative to ARDSnet low-tidal-volume standards are needed.

Fluid Management

A recent study compared a conservative versus liberal fluid management strategy in ARDS.[76] The study also compared the use of a central venous catheter in the internal jugular or subclavian position versus a pulmonary artery catheter to guide assessment of intravascular volume status. The conservative fluid strategy limited fluid infusion and encouraged early diuresis. There was a profound difference in cumulative fluid balance between the liberal and conservative fluid groups by day seven after randomization. Of note, the cumulative fluid balance curves for the initial ARDSnet low-tidal-volume and ALVEOLI studies were almost identical to the liberal fluid curve in the Wiedeman et al. study.[52,59,76] With respect to fluid balance approaches, there was no significant difference in mortality; however, an improvement was noted in both ventilator-free days and ICU-free days in the conservative fluid group. There was no difference in any major outcome when comparing the use of a standard central venous catheter versus a pulmonary artery catheter. It is recommended that outside of the initial resuscitation for hypovolemic shock, intravascular volume be minimized to the extent possible. There does not appear to be a significant role for the routine use of a pulmonary artery catheter for the management of ARDS.

Apart from the initial resuscitation for hypovolemic shock, intravascular fluid administration should be minimized during management of ARDS.

Role of Corticosteroid Therapy

Corticosteroids have been evaluated in both the early and late phases of ARDS in several well-designed randomized controlled trials over the last fifteen years. An ARDSnet trial published in 2006 evaluating the efficacy and safety of corticosteroid use for persistent ARDS did not demonstrate a mortality benefit

to their use.[77] In fact, corticosteroids started more that two weeks after onset of ARDS were associated with an increased mortality. There was a statistically significant improvement in ventilator-free days in the treatment group through 28 days after randomization. Two meta-analyses published recently arrived at conflicting conclusions.[78,79] Agarwal et al. were unable to find any benefit in mortality with the use of corticosteroids for ARDS in either the early or late phase.[78] Meduri et al. found a statistically significant improvement with the use of corticosteroids with respect to ventilator-free days as well as mortality.[79]

The routine use of corticosteroids in either the early or late phase of ARDS is not recommended at this time.

Currently evidence suggests there may be some physiologic improvement with the use of corticosteroids for ARDS, particularly when started before the development of a significant amount of fibrosis.[80] There does not appear to be a consensus that mortality is improved with the therapy, and the potential for complications directly related to the therapy is significant. The routine use of corticosteroids in either the early or late phase of ARDS is not recommended at this time.

Role of Prone Positioning

Prone positioning has been advocated as an adjunctive therapy for ARDS to improve oxygenation and has been studied prospectively in several trials.[81,82,83,84,85,86] The physiologic basis for improvements in oxygenation is not entirely clear, but is hypothesized to involve improved ventilation perfusion matching, regional changes in ventilation, and decreased compression of the dependent portions of the left lower lobe by the heart. Proning a patient with ARDS can be a difficult undertaking and requires a special bed that can assist in the position change and several personnel. In the CCC environment, a frame made by the Stryker company is available that can be used in the ICU and during critical care air transportation (Fig. 8). The potential for dislodgement of endotracheal tubes and lines is significant and may be life threatening for a patient with marginal oxygenation at baseline.

Figure 8. *A Stryker frame allows a patient to be turned to the prone position as a single unit without individually moving parts of the body.*

Gattinoni et al. were unable to demonstrate a mortality benefit to prone positioning for 304 ARDS patients enrolled in a randomized controlled trial, but a significant improvement in PaO_2 was noted in 70 percent of patients in the experimental group.[83] A post-hoc analysis was able to demonstrate an improvement in mortality in the quartile of patients with the lowest PaO_2/FiO_2 on enrollment as well as in the quartile of patients with the highest simplified acute physiology score (SAPS) II at enrollment. One criticism of the study was the relatively short duration of prone positioning. Of note, there was no difference in the number of endotracheal tubes that were dislodged between the experimental and control groups.

A 2002 review of the literature for the use of prone positioning with ARDS concluded that improvement in oxygenation can be expected in 70 to 80 percent of early ARDS patients undergoing prone positioning, but the effects of this improvement are not seen after seven days.[82] There does not appear to be a substantial mortality benefit and significant care must be taken during patient position changes. Finally, the incidence of pressure sores was increased in patients who were proned and related directly to the duration of time in the prone position. A recent prospective randomized trial evaluated the use of prone positioning for periods of at least 20 hours at a time for the treatment of moderate and severe ARDS.[86] The primary endpoint of all-cause mortality at 28 days was equivalent for both the supine and prone patient groups, as was a secondary endpoint of mortality at six months. In the severe ARDS patient group, there was a slight trend towards benefit with respect to mortality at both time points, but the difference did not reach statistical significance.[86]

Prone positioning is not recommended for routine therapy of ARDS patients at this time.

Prone positioning is not recommended for routine therapy of ARDS patients at this time. It is recommended as an adjunctive therapy in patients with severe hypoxemia. Care should be taken to closely coordinate the efforts of those involved in proning the patient, and dislodgement of the endotracheal tube should be prevented at all costs.

Nutritional Goals

Nutrition in the ICU is increasingly being appreciated as an active therapy with the potential for a significant impact on patient outcomes.[87] The patient with ARDS has an injury that is driven to a great extent by inflammatory mediators. Using any therapy, including nutrition, to help modulate the pathologic response is desirable. Several small studies suggest a possible benefit to the use of omega-3 fatty acids in ARDS as a mechanism for reducing inflammation.[88,89,90] The balance of fat versus carbohydrate in enteral feeds also significantly impacts the respiratory quotient and therefore the carbon dioxide production. An increased CO_2 production may complicate efforts to use permissive hypercapnia as a strategy in the management of ARDS.

A recent study evaluated the effect of a specific enteral feed on patients with sepsis and respiratory failure.[90] The experimental group was given a feed with significant amounts of omega-3 fatty acids (replacing omega-6 fatty acids which are metabolized to inflammatory mediators) as well as borage oil. They noted a statistically significant improvement in mortality and PaO_2/FiO_2 (at days four and seven) as well as an increase in ICU-free days and ventilator-free days. A major prospective randomized controlled trial that will address nutrition specifically in ARDS patients is currently underway in the ARDSnet consortium of research centers.

While definitive data supporting the use of specific enteral feeds in ARDS are still lacking, the preponderance of available data at this time supports the use of feeds high in omega-3 fatty acids.

Summary

Acute respiratory distress syndrome (ARDS) is a diffuse, heterogenous disorder resulting in significant shunt physiology and pulmonary compliance limitations that are seen commonly in the CCC ICU. The

use of a low-tidal-volume, open-lung strategy can improve mortality by limiting the propagation of the lung injury and possibly decreasing the incidence of multisystem organ failure.

Endpoints of Resuscitation

Basic Concepts

At the most basic level, shock is defined as a state where there is inadequate oxygen available relative to the metabolic needs of the intracellular processes.[91] This may be a result of decreased oxygen delivery, increased oxygen requirement in the setting of fixed delivery, or an inability to utilize oxygen at the cellular level. It is important for the clinician to have a solid appreciation of oxygen delivery (DO_2), aerobic metabolic demand, oxygen uptake (VO_2), the oxygen extraction ratio (ER), and their interrelationships. In the normal healthy state, the oxygen uptake correlates directly with aerobic metabolic demand. As will be discussed shortly, conditions that affect the mitochondrial electron transport chain will influence the relationship between aerobic metabolic demand and oxygen uptake. Failure of appropriate aerobic metabolism defines the presence of shock, and resultant adverse outcomes are related both to the severity of the failure as well as its duration.[92]

Ensuring adequate resuscitation and early recognition of hypoperfusion is critical in the treatment of shock.

Oxygen delivery is directly proportional to the oxygen content of the blood as well as the volume of blood transmitted to the body per-unit-time. The most important components of oxygen delivery are therefore hemoglobin (Hgb), oxygen saturation of hemoglobin (SaO_2), and the cardiac output (Q). The amount of oxygen dissolved in the blood is very small relative to that bound to hemoglobin. While the PaO_2 is included in the definition of oxygen delivery, it is physiologically of little importance.

Q = Stroke Volume x Heart Rate
$DO_2 = Q \times [1.39 \times Hgb \times SaO_2 + 0.0031 \times PaO_2]$

The interrelationship of oxygen uptake and oxygen delivery in the normal state is affected greatly by the integrity of the mitochondrial electron transport chain. Generally, there is an abundance of oxygen delivery relative to oxygen uptake. Efforts to increase oxygen delivery will not result in increased oxygen uptake. Below a critical oxygen delivery, the oxygen uptake is said to be supply dependent as the reduction-oxidation (redox) state of the mitochondrial electron transport chain changes towards a more reduced state in response to the oxygen delivery. The amount of oxygen utilized will mirror that which is provided, and the relationship is defined by the oxygen extraction ratio ($ER = VO_2/DO_2$). In a non-supply-dependent state where there is an abundance of oxygen delivery relative to oxygen uptake, the redox state of the electron transport chain adjusts towards increased oxidation to yield a progressively lower oxygen extraction ratio as oxygen delivery increases. A normal oxygen extraction ratio in this setting is approximately 15 to 30 percent. When oxygen delivery is limited enough to become supply dependent, a maximum oxygen extraction ratio is established by a maximally reduced electron transport chain. A normal global oxygen extraction ratio in the supply dependent setting is in the range of 60 to 70 percent; however, it should be recognized that each tissue has its own oxygen extraction ratio that may play a large role in determining its risk of injury in a given low oxygen supply state.

In patients who have sustained prolonged or severe decreases in oxygen delivery, expected redox changes may fail, leading to inefficient activity of the electron transport chain. The result is a lower than expected oxygen extraction ratio and the development of an oxygen uptake that becomes supply dependent across all levels of oxygen delivery. The inability to move away from supply dependence, even with supranormal oxygen delivery, signifies a failure of the expected change towards oxidation of the electron transport chain. Decoupling of the electron transport chain redox state from the oxygen delivery can result in the production of free radical mediated damage as well as the generation of reactive oxygen species. This decoupling is a commonly described phenomenon in patients who eventually develop progressive organ dysfunction as the trauma resuscitation evolves. Inefficient oxygen utilization can be difficult to detect at bedside, but inadequate oxygen availability at the cellular level will lead to increased rates of anaerobic metabolism that can be detected in a variety of different ways. Most methods investigated to detect the presence of anaerobic metabolism rely on secondary acid-base physiology changes reflecting the increased production of lactate and the increased consumption of bicarbonate.

In the CCC setting, hypovolemic shock is seen most frequently initially, and many patients may go on to develop distributive shock secondary to the systemic inflammatory response syndrome. Rapid resolution of the etiology is the most critical aspect of the management of either, but aggressive supportive care directed at normalization of oxygen delivery is vital.

Hypovolemic shock is seen in the immediate phase of resuscitation, but distributive shock may follow, secondary to the systemic inflammatory response syndrome.

Markers of global perfusion adequacy do not necessarily mean that regional perfusion is intact. Inadequate regional perfusion that is clinically unrecognized is common and may be seen in as many as 85 percent of patients with normal bedside hemodynamics early in a major trauma resuscitation.[93,94] Uncompensated shock is generally easy to diagnose at bedside, as it is heralded by decreased urine output, tachycardia, and hypotension. Compensated shock is a condition characterized by normal bedside markers of resuscitation with underlying evidence of regional oxygen delivery inadequacy such as a progressive metabolic acidosis. It is clear that traditional bedside parameters available to the clinician are inadequate to establish an effective resuscitation endpoint. Available options for defining such an endpoint follow.

Clinical markers such as decreased urine output, tachycardia, and hypotension may herald uncompensated shock. Conversely, clinical markers may be normal in compensated shock, and additional biochemical markers may be necessary to establish an effective resuscitation endpoint.

Lactate

The use of lactate to assess resuscitation adequacy follows logically from the recognition that anaerobic metabolism leads to increased production. Understanding its strengths and weaknesses in this regard follow from an appreciation of how it is formed and subsequently cleared. Glycolysis, whether anaerobic in the cytoplasm or aerobic in the mitochondria, results in the production of a small amount of adenosine triphosphate (ATP) and pyruvate. Any stress state will increase the rate of glycolysis and result in increased pyruvate production. In an anaerobic environment, pyruvate is converted almost exclusively to lactate. In an aerobic environment, the majority of pyruvate is consumed by the tricarboxylic acid (TCA) cycle resulting in efficient production of ATP. However, even in an aerobic environment, there is a fixed ratio

of lactate to pyruvate (a normal lactate to pyruvate ratio [L:P] is 10:1). Any increase in pyruvate production will also result in increased lactate production regardless of the availability of oxygen, but the percentage of pyruvate used to create lactate increases in the anaerobic environment (L:P greater than 30:1). Lactate is cleared from the body by actions of the liver (60 percent), kidney (30 percent), and muscle (10 percent).

Lactate should not be used as a sole marker for adequacy of resuscitation in the CCC environment.

Lactate is increased in trauma resuscitation patients who are nonsurvivors relative to those who survive.[95] Time to resolution of lactic acidosis appears to be predictive of survival in the setting of trauma resuscitation as well as postoperative surgical patients being cared for in the ICU.[96,97] Use of lactate as an endpoint for resuscitation is appealing given its ease of measurement. However, its use is complicated by the fact that its generation is not completely related to the presence of anaerobic conditions, and its clearance may be delayed when liver or kidney damage is present. As a real-time marker of perfusion, both of these are important considerations. An elevated lactate level can serve as a useful prognostic marker.

In summary, an elevated lactate level has prognostic value, but a normal level is not helpful. Lactate should not be used as a sole marker for adequacy of resuscitation in the CCC environment.

Base Deficit

The base deficit is a theoretical construct designed to simplify acid-base interpretation and has no true physiologic basis. It is the amount of bicarbonate in millimoles (mmol) per liter required to titrate one liter of whole blood to achieve a pH of 7.4, assuming the $PaCO_2$ of the patient is 40 mm Hg. The base deficit does not have any relationship to the cause of the acidemia, and the amount of base predicted assumes a stable acid-base system at the time of measurement.

One of the few areas in the critical care literature where base deficits have been shown to be of clinical benefit is in the setting of early trauma resuscitation.[98,99,100] This is a reflection of the fact that most cases of acidemia seen in this setting result from hypovolemic shock leading to inadequate oxygen delivery and the subsequent development of lactic acidosis. A progressively worsening base deficit argues that the resuscitative efforts are not adequate and should prompt the clinician to ensure adequate hemostasis, intravascular volume repletion, and replacement of hemoglobin.

Base deficit has been shown to be of clinical benefit in guiding the management of hypovolemic patients during early trauma resuscitation. The base deficit should not be used to guide therapy after the initial resuscitative period, as too many variables affecting acid-base physiology are likely to exist.

Scenarios that will complicate the use of base deficit as an endpoint of resuscitation include any condition that impacts the acid-base status other than lactic acidosis.[95,101] A non-anion gap metabolic acidosis is frequently seen after aggressive crystalloid resuscitation, particularly if saline is used. This will worsen the base deficit and may not reflect inadequate resuscitation at all. Respiratory acidosis will worsen a base deficit, and a respiratory alkalosis will improve it. Exogenous bicarbonate therapy or buffers used in total parenteral nutrition (TPN) may also complicate the use of the base deficit as a marker of resuscitation adequacy. A final problem with the base deficit is that it is a more appropriate marker of global resuscitation than regional resuscitation.

An increased base deficit in the trauma resuscitation period has been correlated with increased resuscitation requirements in terms of fluid and blood as well as increased mortality.[99,102,103] The progression of the base deficit during resuscitation has also been correlated with worsened outcomes.[104] Serum bicarbonate levels correlate well with base deficit in trauma patients, but the serum lactate level is not well-predicted by the base deficit.[95,105]

Base deficit has value in predicting prognosis and guiding resuscitation in the hypovolemic patient. It is easy to measure at the bedside in austere environments and can be calculated with reasonable accuracy during critical care air transport using portable handheld arterial blood gas analyzers based upon measured pH and $PaCO_2$ values. It is not recommended for use as a resuscitation endpoint in patients who have other sources of acid-base physiology derangement, such as those who have received a significant amount of crystalloid fluid therapy. The base deficit should not be used to guide therapy after the initial resuscitative period, as too many variables affecting acid-base physiology are likely to exist other than lactic acidosis related to inadequate intravascular volume. Finally, the base deficit may be insensitive to the existence of regional hypoperfusion, and a normal base deficit should be therefore greeted with guarded optimism.

Supraphysiologic Oxygen Delivery Attainment

The development of supply dependence of oxygen uptake on oxygen delivery has long been recognized in shock resuscitation as a marker of suboptimal oxygen utilization at the cellular level. Patients demonstrating decoupling of the electron transport chain demonstrate supply dependence across all levels of oxygen delivery and a lower maximal oxygen extraction ratio. It has been hypothesized that: (1) patients who are unable to generate an adequate oxygen delivery to meet the basic oxygen uptake needs of the body will do poorly; (2) increased aerobic metabolic needs in a time of stress will necessitate the generation of a higher than normal oxygen delivery, particularly when supply dependent physiology is present; and (3) the presence of a lower than normal maximal oxygen extraction ratio will also necessitate the generation of a supraphysiologic oxygen delivery.

Groundbreaking work by Shoemaker and colleagues found that high-risk surgical patients who survived were able to generate significantly higher cardiac indices and oxygen delivery values than nonsurvivors.[106,107] Early efforts to incorporate supraphysiologic oxygen delivery as a goal of resuscitation resulted in improved outcomes.[108,109] Subsequent studies using cardiac index and oxygen delivery goals defined by the experience of Shoemaker et al. were not successful in improving outcomes.[110,111] A study comparing clinical resuscitation using an oxygen delivery goal of 500 ml/min/m^2 versus the value of 600 ml/min/m^2 found no significant difference in outcomes.[112] There is difficulty in interpreting these studies because of significant variations in study design and patient population. A recent meta-analysis failed to show an overall benefit to the use of supraphysiologic oxygen delivery in surgical patient resuscitation.[113] However, a subset analysis of patients who had the intervention initiated before the onset of organ dysfunction did show a significant benefit.

Supraphysiologic oxygen delivery achievement is not recommended as a resuscitation endpoint for trauma patients encountered in the combat environment. Measurement is difficult to perform, and the data does not support a specific oxygen delivery goal that is absolutely better than any other in all patient populations. While it is true that severely ill patients are more likely to need a supraphysiologic oxygen delivery to meet oxygen uptake goals, the necessary oxygen delivery should be determined by targeting other endpoints of resuscitation.

Mixed Venous Oxygen Saturation / Central Venous Oxygen Saturation

In a stressed patient with an intact ability to appropriately adjust the redox state of the mitochondrial electron transport chain toward reduction, supply dependence will develop below a critical oxygen delivery, and a maximal global oxygen extraction ratio of 65 to 70 percent can be expected. Measurement of the mixed venous oxygen saturation (SvO_2) in this case will yield a value of 30 to 35 percent, if one assumes that the SaO_2 is 100 percent. In the nonstressed state, the redox state of the electron transport chain favors oxidation, and the global oxygen extraction ratio is much lower than in the stressed state (typically less than 30 percent). Measurement of the mixed venous oxygen saturation in this setting, again assuming a SaO_2 of 100 percent, will be greater than 70 percent.

Measurement of mixed venous oxygen saturation has been hypothesized to be a useful endpoint of resuscitation because changes in its value theoretically reflect the balance between oxygen utilization and oxygen demand. A lower value, particularly less than 60 to 70 percent, indicates a relative inadequacy of oxygen delivery and a trend towards increased electron transport chain reduction in order to maintain adequate oxygen uptake relative to intracellular oxygen demand. A problem with this concept is commonly seen in the resuscitation of septic patients where decoupling is commonly seen, and oxygen uptake demonstrates supply dependence across a very broad range of oxygen delivery values, and a lower maximal oxygen extraction ratio is also seen. This reflects a significant inefficiency in oxygen utilization at the cellular level; however, the lower than expected oxygen extraction ratio may mask the inefficiency. A very low oxygen extraction ratio will result in a normalization of the mixed venous oxygen saturation that does not draw attention to the dysfunctional oxygen utilization at the cellular level. This scenario may also be observed in severely injured trauma patients who develop the systemic inflammatory response syndrome.

The measurement of mixed venous oxygen saturation is made using blood drawn from the distal tip of a pulmonary artery catheter. Efforts have been made to correlate the value of mixed venous oxygen saturation and the central venous oxygen saturation ($ScvO_2$) obtained from the distal tip of a central venous catheter positioned in the superior vena cava. It is normally expected that the two values will be slightly different owing to the contribution of blood from the coronary sinus as well as variable extraction of blood returning to the heart from the inferior vena cava relative to the superior vena cava. Several studies have noted a tight correlation between mixed venous oxygen saturation and central venous oxygen saturation, even if the actual values varied by a few percentage points.[114,115,116]

The mixed venous oxygen saturation was used as one of three goals for resuscitation in a prospective study of critically ill patients.[117] Patients were either resuscitated to a normal cardiac index, a supranormal cardiac index, or a mixed venous oxygen saturation of 70 percent. There were no differences in mortality or the development of multiple organ dysfunction syndrome.[117] Rivers et al. used a central venous oxygen saturation of 70 percent as one endpoint in their groundbreaking study of early goal-directed therapy in the treatment of severe sepsis and septic shock and demonstrated improved mortality.[118]

Central venous oxygen saturation is recommended as one easily measured endpoint for resuscitation in the combat care environment. Central venous oxygen saturation less than 60 to 65 percent signifies inadequate resuscitation.

Central venous oxygen saturation is recommended as one easily measured endpoint for resuscitation in the

combat care environment. A frankly low central venous oxygen saturation that is less than 60 to 65 percent should be taken as a marker of inadequate resuscitation.[119] Efforts should be made to ensure hemostasis, adequate intravascular volume, optimization of hemoglobin concentration, and oxygen saturation. Inotropic therapy can be considered if these parameters are all adequate but the central venous oxygen saturation remains low. There is no benefit to be gained from the placement of a pulmonary artery catheter specifically to measure the mixed venous oxygen saturation.

A normal central venous oxygen saturation should not be interpreted as confirming adequate resuscitation. Poor oxygen utilization at the cellular level may lead to a normalized central venous oxygen saturation while significant intracellular hypoxia continues. Efforts to confirm adequacy of regional oxygenation should continue if the central venous oxygen saturation is normal.

Gastric Intramucosal pH (pHi)

Blood flow is not uniform across the tissues of the body, and decreased systemic perfusion pressures cause redistribution away from tissues that are not immediately necessary for survival. In hypovolemic shock, blood flow redistributes away from the gut mucosa early on and does not return until relatively late in the recovery process. Gut mucosa is one of the regions that is most sensitive to decreased perfusion pressure and therefore represents an excellent location to assess the adequacy of regional oxygen delivery.

Anaerobic metabolism in the gut mucosa leads to the increased production of tissue pressure of carbon dioxide (PCO_2), which rapidly equilibrates with the gastric secretions and lowers the gastric intramucosal pH (pHi). The gastric intramucosal pH can be measured using a gastric tonometry balloon or a continuous monitoring CO_2 electrode. A normal gastric intramucosal pH suggests adequate regional oxygen delivery, while an abnormally low gastric intramucosal pH suggests inadequate resuscitation in spite of possibly normal vital signs or markers of global oxygenation.

If available, gastric intramucosal pH is recommended for the assessment of the adequacy of regional oxygen delivery in trauma patients in the combat care environment.

Several studies have noted a statistically significant correlation between a low gastric intramucosal pH and mortality.[120,121,122,123] When used as a prospective endpoint for a protocol driven resuscitation, a delay in achieving the gastric intramucosal pH goal was associated with increased mortality and the development of organ system failure.[124,125]

Gastric intramucosal pH is recommended for the assessment of the adequacy of regional oxygen delivery in trauma patients in the combat care environment if available. Gastric tonometry performed using saline filled probes with semipermeable membranes is unlikely to be widely used in most wartime critical care units, but continuous gastric CO_2 monitoring capability may be available in the near future as validation of increasingly portable technology continues. Such a capability would also be extremely useful in the critical care air transport setting.

Sublingual PCO_2 ($PslCO_2$)

The measurement of sublingual PCO_2 ($PslCO_2$) concentrations is easy to do at the bedside and correlates well with gastric intramucosal pH.[126,127] A handheld monitor is used in much the same way as an oral

temperature probe. The implications of an elevated sublingual PCO_2 are identical to those of a low gastric intramucosal pH, and a normal value is felt to represent normal regional oxygen delivery.

The measurement of sublingual PCO_2 concentrations may be useful in assessing adequacy of resuscitation of trauma patients.

The use of sublingual PCO_2 as a noninvasive surrogate marker of gut mucosa perfusion has been described in two studies.[129,128] The sublingual PCO_2 has also been used in a prospective fashion to identify hemorrhage in penetrating trauma patients.[129] The degree of sublingual PCO_2 elevation correlated with the volume of blood loss.

The technology surrounding sublingual PCO_2 may be a very useful adjunct to the care of the combat trauma patient and represents a cheap, easily transportable method of assessing adequacy of resuscitation in austere environments. It is likely to offer the same benefits as gastric intramucosal pH assessment but will be much easier to perform.

Tissue Carbon Dioxide and Oxygen Assessment

Transcutaneous oxygen content (PO_2) is expected to decrease when oxygen delivery is inadequate to meet demand. The development of anaerobic metabolism leads to the elevation of tissue PCO_2 in a fashion that is analogous to that described in the gut mucosa. Electrodes have been used to assess transcutaneous PO_2 and PCO_2 in critically ill trauma patients. Lower PO_2 values and higher PCO_2 values were associated with increased mortality.[130] One problem with older methods of assessing transcutaneous PO_2 and PCO_2 is that they were invasive. Near infrared spectroscopy (NIRS) offers a noninvasive method of assessing skeletal muscle oxyhemoglobin levels, which have been hypothesized to correlate with adequate regional oxygenation. Oxygen saturation of hemoglobin in tissue (StO_2) is the percentage of oxygenated hemoglobin relative to total hemoglobin. The oxygen saturation of hemoglobin in tissue was studied during the resuscitation of trauma patients and found to correlate well with oxygen delivery, lactate, and base deficit and less so with gastric intramucosal pH.[131] A prospective randomized observational study found that oxygen saturation of hemoglobin in tissue using NIRS technology was able to reliably identify severe shock but may not be able to reliably identify mild shock states.[132]

Tissue assessment of oxygenation may be useful as a resuscitation endpoint for trauma patients in the future, and NIRS technology may ensure ease of its application in the combat setting. At this time, it cannot be recommended as an endpoint of resuscitation due to its lack of demonstrated ability to identify early shock.

Summary

Several of the commonly used endpoints of resuscitation such as mixed venous oxygen saturation, lactate concentration, and base deficit are useful in identifying global deficiencies in oxygen delivery. Increased sensitivity is required to identify patients with regional oxygen delivery abnormalities, and this capability is becoming available in the form of gastric intramucosal pH monitoring, sublingual PCO_2 assessment, and oxygen saturation of hemoglobin in tissue analysis. Markers of regional perfusion adequacy will likely largely replace global perfusion assessment in the future. Technological advancements will allow these more sensitive endpoints to be assessed in austere combat environments and during critical care air

transport. A future frontier will involve the sensitive detection of oxygen utilization abnormalities at the cellular level. However, this capability will only be useful if therapies can be developed in the future that can act upon the information in a beneficial manner.

Sepsis

Definition of Sepsis

Sepsis is a clinical syndrome that is extremely common in the multisystem trauma patient and associated with great morbidity, mortality, and cost of care.[133,134] The presence of sepsis can be a challenge to identify in the combat casualty population since there are frequently numerous reasons for the presence of a systemic inflammatory state. However, early recognition and aggressive management of sepsis are necessary to maximize the chance of patient survival. Severe organ dysfunction associated with untreated infection has been recognized for over a millennium. Attempts to define the syndrome of sepsis did not become formalized in a largely agreed upon manner until 1991.[135] This consensus definition described the systemic inflammatory response syndrome (SIRS) as a condition that may result from either an infectious or noninfectious etiology. Sepsis was defined as the presence of SIRS most likely due to infection.

The traditional SIRS criteria are as follows:

- Temperature greater than 38°C or less than 36°C
- Heart rate greater than 90 beats per minute
- Respiratory rate greater than 20 breaths per minute or $PaCO_2$ less than 32 mm Hg
- White blood cells (WBCs) greater than 12,000 cells per cubic millimeter; less than 4,000 cells per cubic millimeter; or with greater than 10 percent band forms

SIRS and Sepsis Definition	
SIRS (Systemic Inflammatory Response Syndrome)	Two or more of the following criteria: • Temperature > 38°C or <36°C • Heart rate > 90 beats per minute • Respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mm Hg • WBCs > 12,000 cells per cubic millimeter or < 4,000 cells per cubic millimeter or > 10 percent immature (band) forms
Sepsis	Documented infection together with two or more SIRS criteria
Severe Sepsis	Sepsis associated with organ dysfunction, including, but not limited to, lactic acidosis, oliguria, hypoxemia, coagulation disorders, or an acute alteration in mental status
Septic Shock	Sepsis with hypotension, despite adequate fluid resuscitation, along with the presense of perfusion abnormalities. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time when perfusion abnormalities are detected.

Table 1. *Definition of SIRS and sepsis syndromes.*

Severe sepsis was defined as sepsis associated with evidence of organ dysfunction, hypoperfusion, or hypotension. Septic shock was defined as the persistence of organ dysfunction, hypoperfusion, or hypotension in spite of adequate fluid resuscitation. The diagnostic criteria for sepsis were revised in 2001 in an effort to incorporate new biomarkers of inflammation and offer an improved system for staging sepsis.[136] The PIRO staging system takes into account predisposition toward sepsis, the infectious insult likely to have caused the condition, the response of the body (SIRS), and evidence of organ dysfunction (Table 1). From a clinical standpoint, the initial consensus definitions offered in 1991 are most useful and worth committing to memory for every physician in the combat environment. The revised guidelines from 2001 are most useful for research protocol development, but the definitions of organ dysfunction can serve to remind the trauma critical care clinician of relevant physiologic variables to trend.

Pathophysiology

Sepsis is characterized by four basic clinical defects: vasodilation, leaky endothelial membranes, disseminated intravascular coagulation, and cellular oxygen utilization inefficiency.[137] In a given patient, some of these defects may be more relevant than others. A distributive shock pattern with relative intravascular volume depletion is frequently seen, leading to organ hypoperfusion. Disseminated intravascular coagulation contributes significantly to ineffective end-organ oxygen delivery and can induce a systemic hypocoagulable state. The inefficient utilization of oxygen at the cellular level is a result of decoupling at the level of the mitochondrial electron transport chain as described in the previous section on endpoints of resuscitation. Mitigating the adverse impact of each of the aforementioned defects defines the goals of sepsis management.

Prognosis

Severe sepsis and septic shock are associated with mortality rates of 30 to 60 percent.[133,134,138,139] In spite of improvements in critical care and the development of several broad-spectrum, highly active antibiotics, the mortality associated with sepsis has not improved greatly in the last several decades.[133,134] This is likely due to several factors, among them being a larger number of immunosuppressed patients, a higher proportion of elderly patients, and the emergence of several virulent pathogens with challenging patterns of antimicrobial drug resistance.

The expected mortality associated with infection is directly related to the development of severe sepsis or septic shock.[140] Multiple organ dysfunction syndrome as a result of inadequate oxygen delivery and ineffective oxygen utilization at the cellular level is a poor prognostic marker, and the mortality is related to the number of organ system failures present.[141] In the setting of sepsis some specific organ system dysfunctions are associated with higher odds of subsequent death, with hematologic and neurologic failure both being particularly concerning.[142]

Management

Critical care is a process rather than the definition of a form of medicine that happens only in an ICU. Over the last two decades, the importance of an institutional approach to several complex care issues has been demonstrated. The management of sepsis involves the coordinated efforts of numerous healthcare providers and the synthesis of a large body of clinical data. It is vital that each institution adopt an aggressive, protocolized approach to the resuscitation of the septic patient.

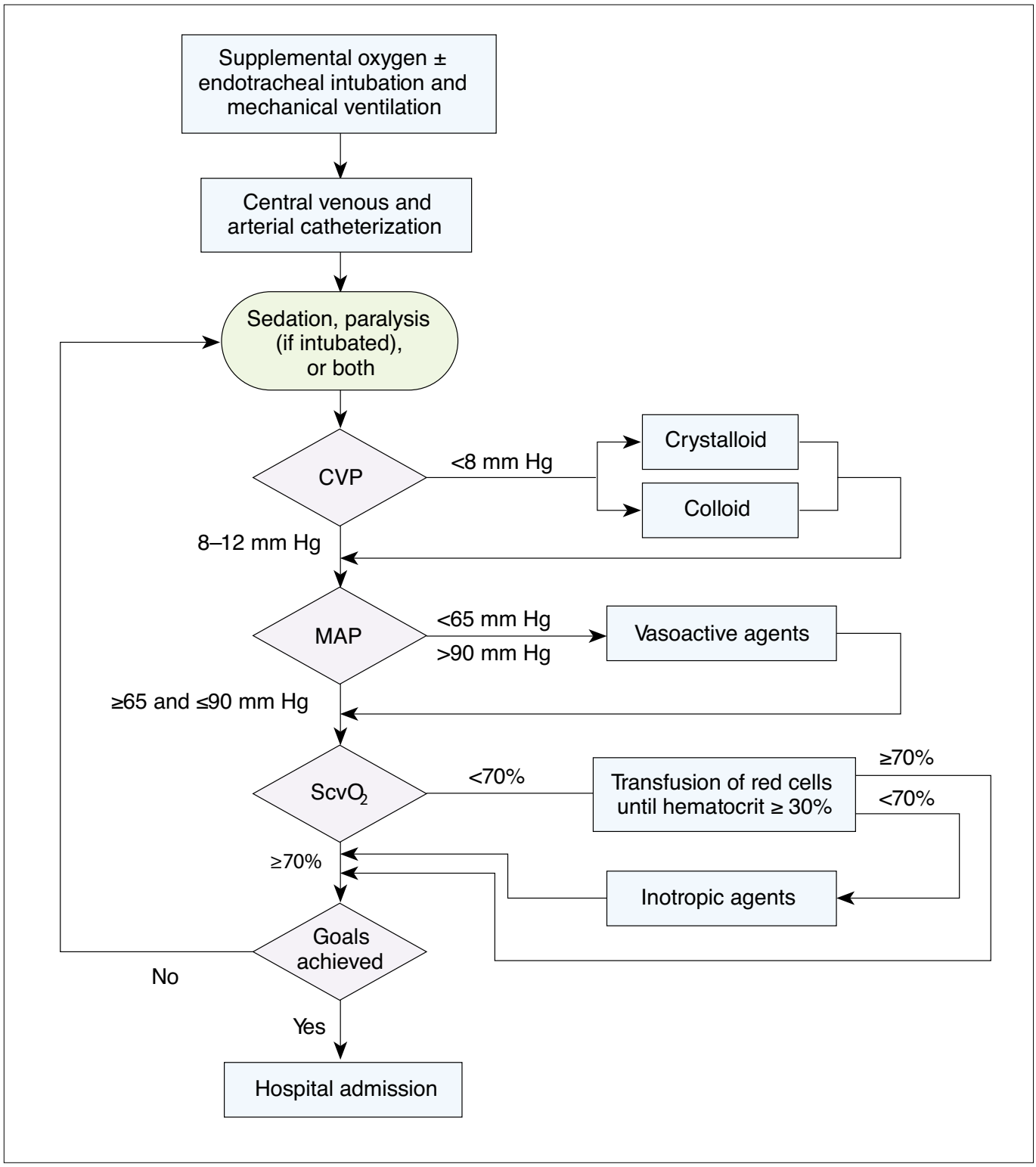

Figure 9. *Early goal-directed therapy protocol used by Rivers et al. in the management of severe sepsis. Image courtesy of Massachusetts Medical Society.*[118]

The use of an early goal-directed therapy protocol for the management of severe sepsis has been shown to significantly improve mortality.

The use of an early goal-directed therapy protocol for the management of severe sepsis has been shown to significantly improve mortality (Fig. 9).[118] One of the most important aspects of this study was that resuscitations were initiated early in the emergency room setting and continued in the ICU.[118] Waiting for transfer to the ICU to begin aggressive resuscitation should never be considered an appropriate strategy. Several subsequent studies have described morbidity, mortality, and economic benefits associated with a protocolized, institutional approach to sepsis resuscitation.[143,144,145,146] Rivers et al. published an excellent review of one approach to implementation of an institutional commitment to sepsis resuscitation.[147]

Infection Source Control

Perhaps the most important aspect of the management of the septic patient involves identification of the etiology of infection and ensuring adequate infection source control. While this seems intuitive, it is often forgotten as a fundamental priority during the initial activity surrounding other aspects of the resuscitation. Source identification and efforts to control the infection should be considered part of the initial resuscitation.[147,148,149] Timing of transport for radiologic studies or operative intervention will need to be individualized based on patient stability.

The most important aspect of the management of the septic patient involves identification of the source of infection and achieving infection source control.

When drawing blood cultures, two or more cultures should be obtained.[150,151,152] Patients with indwelling catheters that have been in place for greater than 48 hours should have blood drawn through each lumen of each catheter.[148] The vascular device is more likely to be the source of the infection if cultures drawn through the line become positive more than two hours prior to cultures simultaneously drawn peripherally.[153,154] In the CCC setting, the use of empiric antibiotics is necessary while attempting to achieve successful source control. This involves the early identification of the etiology of infection as well as an understanding of the most likely associated microorganisms and any common antimicrobial resistance patterns. A recent series of articles regarding combat related infections and the experience in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) is helpful for physicians taking care of patients in these settings.[155,156]

Resuscitation Goals

The Surviving Sepsis Campaign 2008 guidelines recommend the following initial resuscitation goals:[148]

1. Central venous pressure (CVP) 8 to 12 mm Hg
   8 mm Hg for unintubated patients
   12 mm Hg for intubated patients
2. Mean arterial pressure (MAP) greater than or equal to 65 mm Hg
3. Urine output greater than 0.5 ml per kilogram per hour
4. Central venous oxygen saturation ($ScvO_2$) greater than or equal to 70 percent or mixed venous oxygen saturation (SvO_2) greater than or equal to 65 percent.

The resuscitation goals offered here are similar to those used in the early goal-directed therapy study by Rivers et al.[118] They do not offer a mechanism for evaluating regional oxygen delivery adequacy and should be supplemented at a given institution with intramucosal gastric pH, sublingual PCO_2, or oxygen saturation of hemoglobin in tissue assessment if available. In the typical CCC scenario, however, the resuscitation goals above are likely to be the best available.

Intravascular Volume

Relative intravascular volume depletion is seen in sepsis as a result of vasodilation and endothelial leak. Hemorrhage in the trauma patient may also be a complicating factor. Maintaining an adequate intravascular volume is necessary to ensure adequate cardiac preload and therefore cardiac output. Decreased cardiac output will, by necessity, lead to a decrease in oxygen delivery which can be particularly important in sepsis where oxygen consumption may be supply-dependent.

Static measures are most often used in the ICU setting to estimate intravascular volume. The CVP is most often used at the bedside due to its ease of measurement, and there is no advantage to obtaining a pulmonary capillary wedge pressure over the CVP. Unfortunately, CVP is a very poor predictor of the intravascular volume status in the septic patient.[157] As an example, a CVP less than 5 mm Hg in sepsis has only a 47 percent positive predictive value for the presence of intravascular volume depletion.[158] Changes in intrathoracic pressure due to any cause may cause CVP to be an inaccurate representation of intravascular volume status. In the trauma ICU, mechanical ventilation and abdominal compartment syndrome are common complicating factors.[159,160]

Dynamic measures such as pulse pressure variation are better predictors of intravascular volume status in sepsis than CVP.[161,162] As technology evolves, it is likely pulse pressure variation measurement capability will be available in the CCC setting. Transthoracic and transesophageal echocardiography have both been shown to be excellent markers of intravascular volume status as well.[163] Small portable ultrasound machines are commonly available at Level III facilities and may be useful when CVP and the clinical exam do not correlate (Fig. 10).

Figure 10. *Portable ultrasound machines, available at Level III facilities, may be used for hemodynamic assessment.*

Bedside ultrasonography available in Level III facilities has been shown to be an excellent marker of intravascular volume status.

The type of fluid used for resuscitation may depend on associated injuries, such as traumatic brain injury accompanied by intracranial pressure elevation, where hypertonic saline may be a preferred resuscitation fluid.[164,165] A recent large trial failed to show a benefit to the use of albumin or normal saline during the resuscitation of patients in the ICU.[166] However, the same outcomes were obtained using smaller resuscitation volumes in the colloid group. Two reviews of the topic also failed to show a significant outcome benefit using one or the other approach.[167]

Figure 11. *Intravenous fluid administration should be performed aggressively during sepsis resuscitation.*

Fluid should be given in an aggressive manner early in sepsis resuscitation using boluses of greater than 1,000 ml crystalloid or greater than 300 to 500 ml colloid at a time until adequate cardiac filling pressures are obtained (Fig. 11).[148] After this point, intravascular volume supplementation should be eliminated until evidence of intravascular hypovolemia is once again demonstrated. Fluid balance is directly proportional to mortality. To some extent, this may reflect the severity of the underlying disease, but even when this is controlled for, there appears to be a benefit to minimizing intravascular volume overload after the initial resuscitation period.[168]

Role of Vasopressors

The use of a vasopressor may be beneficial in the management of sepsis and should be thought of as a temporizing measure that is only used as long and as much as necessary.[148,169] A mean arterial pressure goal of 65 mm Hg is sufficient for most, but higher goals may be necessary as a way of preserving cerebral perfusion pressure in those with an elevated intracranial pressure. The human body tightly autoregulates blood flow to a given organ or tissue. This means that over a large range of blood pressure variation, the actual blood flow is controlled fairly precisely. In very low-pressure states, the blood pressure may fall below the pressure necessary for autoregulation, and the blood flow becomes linearly related to the pressure. In this setting, immediate improvement of the blood pressure will improve blood flow and oxygen delivery.[170,171] Patients with a history of essential hypertension may benefit from a higher mean arterial pressure due to a rightward shift in their normal autoregulatory range. Myocardial perfusion is a function of the difference between the diastolic blood pressure and the ventricular end-diastolic pressure. While the end-diastolic pressure is typically low early in the resuscitation of severe sepsis, it will normalize with resuscitation. Ensuring an adequate diastolic blood pressure can prevent myocardial ischemia or infarction.

The optimal vasopressor in sepsis depends upon the individual patient scenario.[169] The Surviving Sepsis Campaign 2008 guidelines suggest that either norepinephrine or dopamine be used as a first-line agent.[148] Patients who fail to respond should have epinephrine added to the vasopressor regimen. Vasopressin or phenylephrine can be considered for patients who are still hypotensive in spite of the above measures and who have been adequately volume resuscitated. Some studies have suggested that norepinephrine is a better first line choice of vasopressor in severe sepsis than dopamine. These studies evaluated the hemodynamic effects of norepinephrine versus dopamine in septic patients and demonstrated improved clinical outcomes and improved splanchnic circulation in patients treated with norepinephrine.[172,173,174] Recent studies analyzing the use of norepinephrine in septic shock have come to opposite conclusions, linking the use of norepinephrine to worse or equivalent outcomes relative to alternative vasoactive agents.[175] Epinephrine is an alternative vasopressor. It has been associated with elevation of lactic acid levels in the serum independent of oxygenation or blood flow. This is likely secondary to increased glycolysis and production of higher amounts of pyruvate with a normal L:P ratio of 10:1.[176]

Vasopressin levels are decreased in patients with severe sepsis and those who die from sepsis, when compared to those with mild sepsis and those who survive.[177] Two clinical studies have demonstrated a hemodynamic and vasopressor sparing benefit to the addition of a low-dose vasopressin infusion in patients with septic shock.[178,179] No mortality benefit was identified in either study. The recently completed Vasopressin and Septic Shock Trial (VASST) trial did not demonstrate a mortality benefit by adding vasopressin to a patient already being managed with norepinephrine.[180]

Dopamine is not recommended specifically for the prevention or management of acute renal failure in the septic patient. Several trials have failed to demonstrate benefit, while noting a decrease in splanchnic perfusion, associated with the use of dopamine (versus norepinephrine) in patients with severe sepsis.[181,182,183,184] Consensus opinion currently is that there is potential harm that may be expected when low-dose dopamine is used for renal failure prevention or management in the critically ill patient.[148,185]

Vasopressors may be of benefit in the management of sepsis, but they should be viewed as a temporizing measure.

Role of Corticosteroids

Corticosteroids should be added in total daily dose equivalents of hydrocortisone less than or equal to 300 milligrams (mg) intravenously daily in patients with hypotension associated with septic shock that is unresponsive to vasopressors or is of prolonged duration.[148,186] If a steroid is used with less mineralocorticoid activity than hydrocortisone, fludrocortisone can be added in a dose of 50 mcg per day. Three randomized controlled studies have shown clinical benefit to the use of corticosteroids in the setting of septic shock.[187,188,189] The first of these three studies was able to demonstrate a mortality reduction for patients who failed to increase their cortisol level more than 9 mcg per deciliter after an adrenocorticotropic hormone (ACTH) stimulation test.[187] The recently completed Corticosteroid Therapy of Septic Shock (CORTICUS) trial failed to show a mortality benefit to the use of corticosteroids in the setting of septic shock but did demonstrate faster resolution of shock in patients who were given steroids.[190] The response to an ACTH stimulation test did not predict those who responded to steroid therapy and those who did not. It is not clear from the study why improved resolution of the shock state with corticosteroids did not translate into a meaningful outcome advantage.

The use of steroids in the management of refractory septic shock should be limited to patients who have failed at least two vasopressor agents.

The shock state associated with sepsis is frequently complicated by absolute or relative adrenal insufficiency. Unfortunately, the data supporting a benefit to the use of corticosteroids is minimal. Corticosteroids should be used in those with a previous condition requiring replacement and should be considered early in those who are likely to have secondary adrenal insufficiency due to chronic steroid therapy prior to the sepsis interval. The use of steroids strictly for the management of refractory septic shock should be limited to patients who have failed vasopressor therapy with at least two agents.

Assessing Adequacy of Oxygen Delivery

An assessment of the adequacy of oxygen delivery with central venous oxygen saturation was part of the Rivers et al. early-goal directed therapy strategy for severe sepsis management and is recommended by the most recent Surviving Sepsis Campaign 2008 guidelines.[118,148] The goals are a central venous oxygen saturation greater than or equal to 70 percent or a mixed venous oxygen saturation greater than or equal to 65 percent depending on which is being followed in a given patient.

The topic of assessing adequacy of resuscitation was discussed in more detail previously, but a few concepts should be emphasized for the patient with severe sepsis. First, both central venous oxygen saturation and mixed venous oxygen saturation are markers of global oxygen delivery and may not be sensitive to regional inadequacy.[191] Where possible, technology to assess regional perfusion should be employed to supplement the data gained from the central venous oxygen saturation or mixed venous oxygen saturation. Just as a normal blood pressure does not mean that a patient is necessarily adequately resuscitated, neither does a normal central venous oxygen saturation.

A second important point regarding mixed venous oxygen saturation assessment is that a high value is commonly seen in very advanced septic shock. Because patients with septic shock frequently have decoupling of the mitochondrial electron transport chain, their oxygen consumption is supply dependent across most values of oxygen delivery, and the maximal oxygen extraction ratio may be profoundly decreased. A normal mixed venous oxygen value may be measured in spite of significant intracellular hypoxemia.[191] This perpetuates a shock state that may lead to death through the development of progressive multiple organ dysfunction.

The central venous oxygen saturation or mixed venous oxygen saturation is useful in identifying those with a need for further resuscitation when the values are low, but they are of little use when normal.[191] When low, the defective component of oxygen delivery must be identified, remembering that oxygen delivery is a function of cardiac output and oxygen content of the blood. If the central venous oxygen saturation or mixed venous oxygen saturation is low, efforts to ensure adequate hemoglobin oxygen saturation should be made first. Second, transfusion to a hemoglobin value of at least 10 g per deciliter should be considered.[148] Finally, if the mixed venous saturation remains low, an inotrope can be added with the intent of increasing cardiac output. The necessity of maintaining adequate intravascular volume during this process should be emphasized since an inadequate cardiac output can result from inadequate preload, direct myocardial suppression by cytokines in sepsis, or from myocardial infarction.

Central venous oxygen saturation or mixed venous oxygen saturation is useful in identifying patients needing further resuscitation when the values are low, but are of little use when normal.

Blood Product Transfusion

The transfusion of blood products carries the potential for great benefit but also great harm to the patient and cost to society. In the CCC setting, it may be a very limited resource that must be used judiciously. Massive transfusion during a trauma resuscitation or transfusion goals associated with inadequately controlled hemorrhage are separate topics than the use of blood products strictly for the management of sepsis. Sepsis frequently develops during the course of care of the trauma patient rather than being present during the initial patient resuscitation. For the management of sepsis, component therapy is recommended rather than the use of whole blood.[148] Component therapy allows correction of identifiable defects (Fig. 12). Specific goals for the transfusion should be defined and effects of the therapy subsequently assessed.[192]

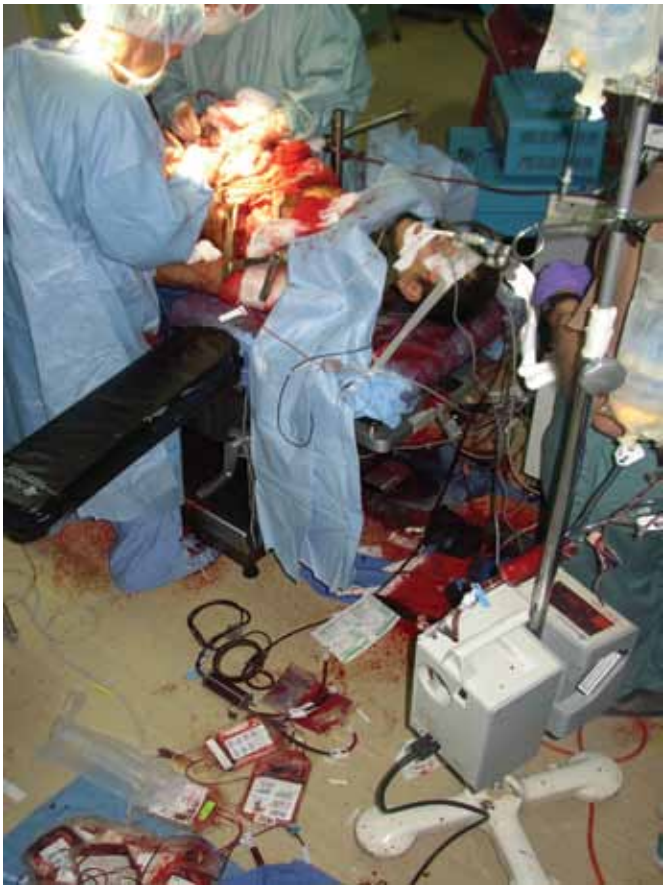

Figure 12. *Selective blood component therapy is recommended in the setting of sepsis complicated by coagulopathic bleeding.*

The most likely component to be considered for transfusion is packed red blood cells. The Transfusion Requirements in Critical Care (TRICC) trial demonstrated the adequacy of a conservative transfusion strategy in critically ill patients.[193] In spite of the linear relationship between oxygen uptake and oxygen delivery over a broad range of oxygen delivery, ineffective oxygen utilization precludes a significant oxygen uptake benefit from very aggressive red blood cell (RBC) transfusion in the setting of severe sepsis.[194] It is recommended that packed red blood cell therapy only be used when hemoglobin concentrations are less than 7 g per deciliter unless evidence of ongoing oxygen delivery inadequacy (e.g., low central venous oxygen saturation, myocardial ischemia, cerebral hypoperfusion) exists or active hemorrhage is present.[148] In that case, a hemoglobin goal of at least 10 g per deciliter is prudent, although overaggressive transfusion may be potentially harmful in the multisystem trauma patient, and these competing goals must be balanced carefully.[195] Once adequate oxygen delivery is felt to be present based upon available assessment tools, efforts to minimize red blood cell transfusion should be made.

It is recommended that packed red blood cell therapy only be used when the hemoglobin value is less than 7 g per deciliter, unless evidence of ongoing oxygen delivery inadequacy exists, or active hemorrhage is present.

Erythropoietin should not be used to improve hemoglobin or prevent future potential blood transfusions in the setting of sepsis. Two prospective clinical trials failed to demonstrate a significant benefit to the use of erythropoietin supplementation in critically ill patients.[196,197] Both of these studies show erythropoietin results in increased hemoglobin concentrations and decreased need for blood transfusion, but there is no data showing improved survival or clinical outcomes. Thus, it is not recommended in surviving sepsis guidelines.[148]

Correction of coagulopathy due to factor depletion or thrombocytopenia is not recommended strictly for the management of sepsis.[148,198] There may be settings where correction is desirable, as in the case of early trauma resuscitation, uncontrolled intracranial hemorrhage, or spinal surgery. Strict goals for resuscitation that are well-validated remain elusive and largely a matter of opinion. In the setting of sepsis, a platelet count of less than 5,000 per cubic millimeter should prompt transfusion, as should values of 5,000 per cubic millimeter to 30,000 per cubic millimeter when active bleeding is present.[148] Some procedures may require higher transfusion goals. There is no absolute international normalized ratio (INR) that should prompt transfusion of fresh frozen plasma in the absence of active bleeding or an anticipated procedure, but the risk of spontaneous intracranial hemorrhage correlates directly with anticoagulation intensity.[199,200]

Disseminated intravascular coagulation (DIC) results from an abnormal balance of procoagulant and anticoagulant factors in the blood that ultimately results in excessive accumulation of fibrin in the microvasculature. This contributes to organ dysfunction and may eventually lead to a generalized inability to form clot due to excessive consumption of coagulation factors. In the setting of active bleeding due to DIC, fresh frozen plasma may be considered in an attempt to improve the overall coagulopathy, platelet transfusion may be of benefit, and cryoprecipitate can be used to correct the fibrinogen deficiency. It is important to emphasize that all of these therapies are likely to be ineffective unless the source of the DIC is corrected. Specific goals for the supportive management of DIC will depend upon a bedside clinical assessment of any resulting hemorrhage.

Role of Inotropic Therapy

The necessity of inotropic therapy may be suggested by the presence of a decreased central venous oxygen saturation in the setting of adequate intravascular volume repletion, hemoglobin oxygen saturation, and hemoglobin content.[170] If a pulmonary artery catheter is in place, a decreased cardiac output in the setting of normal or high cardiac filling pressures suggests a role for inotropic therapy. A pulmonary artery catheter is not necessary for the identification of the need for inotropic therapy or the utilization of an inotrope but may allow more accurate dose titration.

Dobutamine is the inotrope of choice in septic patients.[148,170,201] Dobutamine increases oxygen utilization, and care must therefore be exercised in states where cardiac oxygen delivery is marginal. When started, it is started at 5 micrograms (mcg) per kilogram per minute and titrated to a maximum dose of 20 mcg per kilogram per minute. If using a central venous catheter with the tip in the superior vena cava, the central venous oxygen saturation can be used to guide therapy. The dose is increased until the central venous oxygen saturation normalizes or the maximum dose is reached. Arrhythmias may complicate the ability to titrate dobutamine. If a pulmonary artery catheter is in place, the cardiac index can be trended, as can the mixed venous oxygen saturation.

A large part of the blood pressure improvement seen when dopamine is used as a vasopressor at moderate doses may be due to increased stroke volume; therefore, it can be considered an inotrope as well.[169] Norepinephrine has some inotropic properties, but its major mode of improving blood pressure is through peripheral vasoconstriction.[169]

Role of Recombinant Human Activated Protein C (rhAPC)

The Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial was the first to demonstrate a mortality benefit with the use of an agent (recombinant human activated protein C [rhAPC]) designed to prevent abnormal clotting in severe sepsis.[202] Subset analysis of the PROWESS trial found the greatest benefit in patients with more severe manifestations of sepsis. The process by which the PROWESS study was conducted and its conclusions (i.e., based on subgroup analysis) have generated controversy.[203] The limitations of rhAPC were delineated by the Administration of Drotrecogin Alfa (activated) in Early Stage Severe Sepsis (ADDRESS) trial, which was designed to evaluate the use of rhAPC in patients with severe sepsis but a low risk of death.[204] It was stopped early due to futility, and a subset analysis of patients with recent surgery and only a single-organ dysfunction had a significantly higher 28-day mortality if they received rhAPC. The study concluded that rhAPC (drotrecogin alfa or Xigris®) "should not be used in patients with severe sepsis who are at low risk for death, such as those with single-organ failure or an APACHE II score less than 25."

Recombinant human activated protein C has been recommended by some for patients with severe sepsis and either multiple organ failures or an APACHE II score greater than 25.[148] Use of rhAPC, specifically in the combat trauma population, needs to be tempered by a higher risk of bleeding noted in national surveys relative to that reported in the initial PROWESS trial.[205,206] Risks and benefits must be carefully assessed, and adequate hemostasis must be ensured. When used, it is best to initiate therapy with rhAPC as soon as the need is identified, since outcomes appear to be best when the therapy is introduced early.[207,208,209] The cost-effectiveness of administering rhAPC in all severe sepsis patients has been questioned, and calls for more selective use in this subset of high-risk patients have been made.[203]

Management of Hyperglycemia

The publication in 2001 of a significant mortality benefit in critical care patients treated with an intensive insulin therapy protocol with resultant glucose values of 80 to 120 mg per deciliter was met with great enthusiasm.[210] Because this initial experience was primarily with surgical ICU patients, a subsequent study by the same author was conducted in the medical ICU population.[211] The medical ICU study was able to demonstrate a mortality benefit only in those patients with a length of stay greater than three days, which cannot be predicted when patients are admitted. It is important to note as well that the rate of significant hypoglycemia was 18 percent, relative to the 6.2 percent seen in the 2001 surgical ICU study. Both of these studies were performed at a single institution. While tight glucose control was adopted quickly by several major clinical organizations, the results of other studies have failed to demonstrate similar outcomes, and in fact, not only show no benefit, but provide evidence of harm.[212,213]

The recently completed Normoglycemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study randomized 6,104 critical care patients into intensive glucose control (81 to 108 mg per deciliter) versus conventional glucose control (180 mg per deciliter or less) groups and followed a number of variables over 90 days from enrollment.[214] The results are striking in their demonstration of a 2.6 percent mortality increase at 90 days in those treated with an intensive approach,

although there was no significant difference in mortality at 28 days. Subgroup analysis in the NICE-SUGAR study noted a trend toward improved outcomes with conventional control in patients with severe sepsis, as well as those with an APACHE II score greater than 25 on admission.

Moderate glucose control (less than 150 mg per deciliter) should be achieved using insulin infusion protocols in patients with sepsis.

Of particular relevance to the trauma critical care population was a trend toward improved outcomes in trauma patients with intensive insulin control. Excitement over this result should be tempered by the wide confidence intervals (0.50 to 1.18) and the fact that there was a statistically significant improvement in operative admission patients who were treated with conventional control. Hyperglycemia has been associated with worsened outcomes following traumatic brain injury and sepsis. At this time, it is recommended that moderate glucose control (less than 150 mg per deciliter) be achieved using insulin infusion protocols in patients with sepsis.[148] Future studies are needed to help clarify what degree of glucose control is most beneficial for the critically ill patient.

Role of Bicarbonate Therapy

Bicarbonate therapy has been used in clinical practice for years in an attempt to mitigate the effects of acidemia caused by numerous metabolic and respiratory challenges. In the setting of sepsis-induced lactic acidosis, there does not appear to be any benefit to the routine use of bicarbonate therapy.[215,216]

It is hypothesized that conformational changes at the level of the sympathetic receptor occur at very low pH values that may lead to unresponsiveness to vasopressor therapy. There is no firm clinical data supporting an absolute pH where such an effect may occur. In the aforementioned studies, the number of patients enrolled with pH less than 7.15 was small.[215,216] The use of bicarbonate is associated with volume overload that may complicate other goals of sepsis therapy, particularly after the initial resuscitation phase. It is recommended in the Surviving Sepsis Campaign 2008 guidelines that bicarbonate not be used for the sole purpose of raising pH greater than 7.15 in an effort to improve hemodynamics.[148]

In the setting of sepsis-induced lactic acidosis, there does not appear to be any benefit to the routine use of bicarbonate therapy.

For patients with profound acidemia, raising the pH may be an immediate lifesaving maneuver.[217] Manipulation of mechanical ventilation may allow a sufficient respiratory alkalosis to improve the overall pH adequately, or bicarbonate therapy may be utilized. In a theoretical sense, bicarbonate combines with hydrogen ions and eventually creates water and carbon dioxide via the action of carbonic anhydrase. Carbon dioxide readily crosses cell membranes and may therefore contribute to intracellular pH reduction in spite of improved pH in the blood. This might be more significant when sepsis is associated with ARDS or other conditions where ventilation is limited and carbon dioxide elimination is suboptimal. The potential for poor outcomes due to intracellular pH decrease associated with bicarbonate therapy has not been demonstrated conclusively in a prospective clinical fashion.

Other options for raising the pH include the use of tromethamine, which is a proton scavenger that is eliminated renally.[218] The tromethamine solution is hypertonic and has a pH of 8.6. The hypertonic nature

of the solution can induce a mild osmotic diuresis and will result in improved urine output, but it should not be used as an agent to prevent or treat acute renal failure. For those with established renal failure, tromethamine is not appropriate given the necessity of renal clearance. Bicarbonate therapy is associated with a significant sodium load and increased generation of carbon dioxide; therefore, tromethamine may be preferred in patients with hypernatremia or a limited minute ventilation.[218] There is no evidence that outcomes are better with tromethamine versus bicarbonate therapy versus no therapy at all in the setting of lactic acidosis associated with severe sepsis.

Unfortunately, there is no clear guidance than can be offered for pH values less than 7.15. Until better data emerges, the decision to correct the pH and the best way to accomplish this goal are both up to the bedside clinician.

Nutritional Goals

The literature regarding optimal nutrition for the septic patient continues to evolve, but few firm recommendations can be made at this time. It appears that septic patients have a higher basal energy expenditure than nonstressed patients.[219,220] Glutamine and arginine supplementation may be of benefit.[221,222] The method by which critical care patients are fed has generally received as much attention as what is fed (Fig. 13). Enteral nutrition is preferred over total parenteral nutrition when possible.[223,224] Enteral feeding is cheaper, preserves the integrity of the gut mucosa (possibly decreasing the incidence of multiple organ dysfunction syndrome), and has a lower rate of secondary infection. The exact timing of feed initiation is unclear. It seems intuitive that earlier achievement of adequate caloric intake would be beneficial. This has been demonstrated in the hypercatabolic adult burn patient population.[225] However, in the sepsis population undergoing initial resuscitation, it is unclear whether the body is able to use the nutrients provided to it. Decreased gut perfusion may also make the use of enteral nutrition risky, and total parenteral nutrition may be favored earlier if feeds are started during the periresusciation period.

It is probably best to achieve adequate caloric intake as early as possible after the initial resuscitation period with enteral nutrition being favored over total parenteral nutrition unless there are significant contraindications (severe ileus, recent gastrointestinal surgery, etc.). The choice of feeds remains an unsettled matter with many favoring antioxidant formulas, although there is little outcome data at this point to argue for or against such recommendations.

Enteral nutrition is preferred over total parenteral nutrition when possible and should be started as early as possible after the initial resuscitation period.

Summary

The sepsis syndrome is characterized by vasodilation, leaky endothelial membranes, DIC, and ineffective oxygen utilization at the cellular level. It is associated with a high mortality. Early syndrome recognition, infection source control, and a protocolized approach to resuscitation are key factors for ensuring patient survival. Components of supportive therapy include maintenance of adequate intravascular volume, vasopressor support, inotropic support, moderate glucose control, rhAPC in select patients with severe sepsis, and the rational use of blood products. There may be a role for the use of corticosteroids in some patients, and the optimal nutrition strategy continues to emerge.

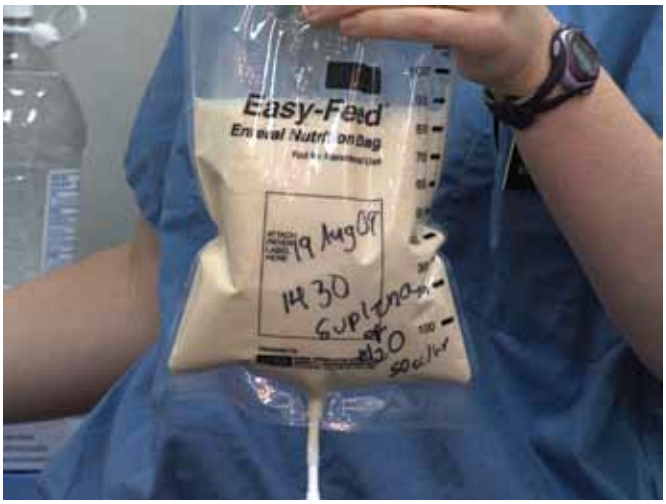

Figure 13. *Enteral nutrition is preferred over total parenteral nutrition.*

Figure 14. *Ventilator-associated pneumonia is defined as a pneumonia that arises after 48 to 72 hours of endotracheal intubation.*

Basic Care Considerations in the Combat Casualty Care ICU

Combat-Associated Pneumonia Prevention

Ventilator-associated pneumonia (VAP) is a frequent complication of prolonged mechanical ventilation that leads to increased duration of mechanical ventilation, prolongation of ICU care, and, most importantly, an increase in mortality.[226] Ventilator-associated pneumonia is defined as a pneumonia that arises after 48 to 72 hours of endotracheal intubation (Fig. 14).[227] Multidrug-resistant bacteria of nosocomial origin are more likely to be associated with ventilator-associated pneumonia after the first four to five days of hospitalization as the patient becomes colonized with organisms that live in an environment characterized by extraordinary antibiotic selection pressure. Organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant gram-negative organisms such as *Pseudomonas aeruginosa* and *Acinetobacter baumanii* are commonly encountered.[227]

Ventilator-associated pneumonia is a frequent complication of prolonged mechanical ventilation that leads to increased duration of mechanical ventilation, prolongation of ICU care, and increased mortality.

The flow of combat casualties out-of-theater in OEF and OIF for the vast majority of critically ill patients involves a handful of medical centers (Fig. 15). This is done to consolidate medical resources in a few locations and because patient flow via the air evacuation system uses aircraft of opportunity that are flying regularly established mission routes. Multidrug-resistant organisms are extremely common in these node locations, and patients who become colonized tend to carry such organisms to each successive node.[228] Of particular concern has been the emergence of extremely virulent multidrug-resistant acinetobacter and pseudomonas strains that have been associated with ventilator-associated pneumonia. The concept of "combat-associated pneumonia" as a variant of ventilator-associated pneumonia has emerged to accentuate the importance of these extremely difficult to treat, multidrug-resistant organisms as a cause of nosocomial pneumonia.[229] Combat-associated pneumonia also highlights the role that the nodal structure of patient flow plays in the emergence of multidrug-resistant organisms at each successive military treatment facility.[228]

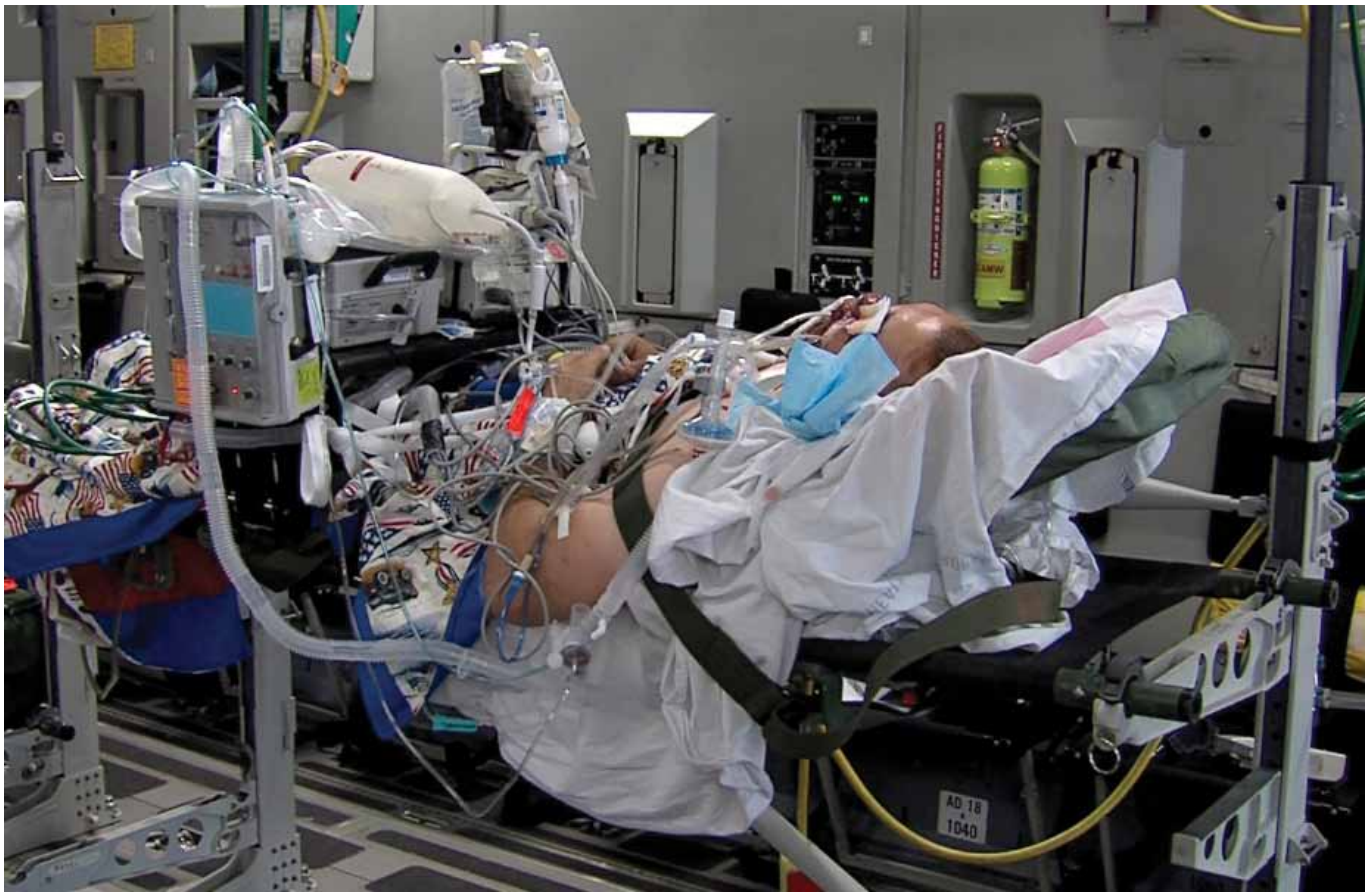

Figure 15. *Multidrug-resistant organisms are common in the evacuation chain, and patients who become colonized tend to carry such organisms to each successive facility.*

Combat-Associated Pneumonia Prevention Bundle
1. Keep head of bed elevated greater than 30 to 45 degrees at all times, unless contraindicated
2. Daily sedation interruption
3. Gastrointestinal bleeding prophylaxis
4. Deep venous thrombosis (DVT) prophylaxis
5. Heat and moisture exchanger (HME) use unless otherwise specified; no daily changes of HMEs
6. Oral care every two hours, with chlorhexidine every 12 hours
7. Consider vaccination with PNEUMOVAX® and influenza vaccine
8. Continuous subglottic suctioning endotracheal tube if duration of intubation expected to be greater than or equal to four days
9. No routine ventilator circuit changes

Table 2. *Combat-associated pneumonia prevention interventions.*

Prevention of combat-associated pneumonia in ventilated patients is vital since treatment is extremely difficult. The development of ventilator-associated pneumonia prevention bundles is now common practice in critical care units. A suggested combat-associated pneumonia bundle is depicted in Table 2. Posting these recommendations at bedside can serve as a helpful reminder for clinicians, nurses, and respiratory therapists. Such recommendations should also be included in standard ICU admission order

sets. Critical care air transport teams can continue all of these recommendations during flight and should be encouraged to do so prior to each movement of an intubated patient.

In combat critical care units, consideration should be given to relatively liberal use of an invasive diagnostic strategy to confirm suspected cases of combat-associated pneumonia. Options include flexible fiberoptic bronchoscopy (with or without protected specimen brush) and blind bronchoalveolar lavage (BAL) using specially designed catheters. This will decrease the use of broad-spectrum antibiotics and hopefully decrease some of the selection pressure that exists in downrange ICUs.

Deep Venous Thrombosis Prophylaxis

Multisystem trauma patients have numerous risk factors for the development of venous thromboembolic disease. In the combat environment, there is a higher likelihood of intravascular dehydration prior to injury that may contribute to an increased risk over that seen in the civilian trauma population in the US.[230] A more important distinction between the two populations is the periods of prolonged immobilization that will necessarily accompany air evacuation out of the combat theater.

Representatives from the American College of Chest Physicians recently reviewed the literature regarding a number of common patient populations encountered in the combat environment such as those with head and spine injuries, orthopedic injuries, and multisystem trauma.[231] Several insightful recommendations for each population are made and levels of evidence are reviewed.

When possible, trauma patients should receive either graded compression stockings or intermittent pneumatic compression devices, given the higher than normal risk for venous thromboembolism in the combat environment.

Given the higher than normal risk for venous thromboembolism in the combat environment, it is recommended that each patient receive either graded compression stockings or intermittent pneumatic compression devices unless injury severity does not allow the placement of such devices on any extremity (Fig. 16). In addition, low-molecular-weight heparin dosed as 30 mg injected subcutaneously twice daily should be used unless contraindicated by active uncontrolled hemorrhage or recent intracranial bleeding.[231,232] An aggressive approach to venous thromboembolism prophylaxis in the combat trauma environment is wise since treatment with full-dose anticoagulation for DVT or pulmonary embolism (PE) may be problematic in patients with ongoing hemostasis inadequacy or who may need repeated trips to the operating room.

Figure 16. *Intermittent pneumatic compression devices are used for venous thromboembolism prophylaxis. Image courtesy of DJO, LLC.*

Gastrointestinal Bleeding Prophylaxis

Stress gastritis is a common complication in critical care patients.[233] Significant risk factors for gastrointestinal bleeding due to stress gastritis include mechanical ventilation greater than 48 hours, coagulopathies, shock, sepsis, hepatic failure, renal failure, multiple trauma, greater than 35 percent total body surface area burn, head/spinal cord trauma, and a prior history of upper gastrointestinal hemorrhage.[234]

All patients admitted to a combat ICU should be treated with an intravenous proton-pump inhibitor or H_2-receptor antagonist due to risk of stress gastritis.

All patients admitted to a combat ICU should be treated with an intravenous proton-pump inhibitor or H_2-receptor antagonist. This is generally continued even when the patient is tolerating enteral feeds, although some experts would consider discontinuation of prophylaxis at that point.[233]

Preventive Care and Infection Control

Exposure keratopathy is common in the critical care setting when the eye is left exposed to dry air in patients who are not capable of spontaneously blinking (e.g., chemical sedation or central nervous system injury).[235] Efforts to protect the eyes with the regular application of lubrication is a basic necessity of care that can be overlooked during combat critical care with devastating consequences. Exposure keratopathy may lead to the development of infections that are extremely difficult to eradicate and frequently result in permanent loss of vision.[235]

Aggressive skin care is extremely important in the multisystem trauma patient due to the prolonged periods of immobility that often accompany convalescence.[236] Decubitus ulcers can develop quickly in dependent regions where weight is focused on a single point and allowed to compress the soft-tissue underneath. Common ulcer locations include the sacral region, heels, and portions of the body that are left pressed up against solid objects such as a bedrail. What appear at first to be small areas of redness can evolve over hours to days into large, poorly healing regions of necrotic soft-tissue that may require extensive debridement and occasional skin grafting.[237] There is also a risk for the development of osteomyelitis in exposed bone. Prevention involves frequent turning in an effort to continually redistribute pressure points as well as the use of foam blocks under the feet and legs.

Aggressive skin care is extremely important in the multisystem trauma patient in order to prevent decubitus ulcers. Efforts to protect the eyes with regular application of lubrication are necessary to prevent exposure keratopathy.

Intensive care unit infection control measures are extremely important in the current mature theaters of combat in Afghanistan and Iraq. The spread of multidrug-resistant pathogens needs to be limited as much as possible in an effort to improve outcomes. The epidemiology, history, prevention, and treatment of combat-related infections were outlined in a recent series of articles.[155,228,238,239,240] Basic recommendations for preventing the spread of nosocomial multidrug-resistant pathogens include universal standard precautions, contact precautions with all direct patient care, consideration of cohorting patients who are likely to be in the ICU less than 72 hours, and antibiotic control. Antibiotic control recommendations include avoiding unnecessary use of broad-spectrum empiric antibiotics, establishment of a local antibiogram that can be used to guide initial therapy, and limiting antibiotic therapy duration as much as possible.[156]

Structure of the Combat Casualty Care ICU

Critical care is a process that begins at the point of injury and continues until resolution of the physiologic insult. Care that is provided in the ICU is one piece of a larger systemic effort to provide care. The ICU is a complicated environment charged with the coordination of the efforts of many as a wealth of data is prioritized and acted upon. Traditionally, physicians have practiced in a relatively independent manner, and several different approaches to a given disease process may be expected at a given institution. Numerous studies in the last two decades have demonstrated that protocolized approaches to complex disease processes can result in better patient outcomes.[120,241,242,243] In many instances, the improved outcomes are as likely to be due to the development of an institutional approach to a given problem rather than the intervention per se. An institutional approach allows multiple services to prepare for involvement in a predictable fashion and improve efficiency. Additionally, a protocol allows more frequent adjustment of therapies in response to real-time data collection than is possible when decisions are deferred to once or twice daily physician rounds.

Figure 17. *The ability to adapt available resources to the needs of many will dictate the success or failure of a combat ICU. Image courtesy of Harold Bohman, MD, CAPT, MC, US Navy.*

The importance of multidisciplinary rounds cannot be overemphasized. While it has been demonstrated during the current OEF and OIF conflicts that an intensivist-directed ICU team improves outcomes in the combat theater, every member of the critical care team has a role to play and an expertise to bring to the bedside.[244] Simply adding a clinical pharmacist to daily rounds in the ICU improves mortality.[245] Multidisciplinary rounds offer both a chance to share ideas and impressions about a patient's care as well as a method of communicating a plan simultaneously to all of the care team members.

Telemedicine is in its infancy as a specialty but will be seen with increasing frequency in the combat environment in the next decade. The technology behind telemedicine is evolving rapidly and allows a limited resource to be in many places at once. It is a medicine force-multiplier that has the potential to help minimize the forward-positioned medical logistical footprint.

A final key concept regarding the structure of the combat casualty care ICU is the need for flexibility. The combat care environment is fluid and frequently unpredictable. Large numbers of patients may appear suddenly at anytime (Fig. 17). The ability to adapt the available, sometimes limited, resources to the needs of many will in large part dictate the success or failure of a combat ICU.[246] Deviations from optimum care are to be expected, but a firm understanding of the relevant medical concepts will help prioritize efforts and maximize the chances for a successful patient outcome.

Critical Care Air Transport Team (CCATT)

Historical Background and System Basics

All coalition patients with critical care requirements in the current conflicts in Afghanistan (OEF) and Iraq (OIF) are flown out-of-theater to Germany with the assistance of a Critical Care Air Transport Team (CCATT) (Fig. 18). A CCATT is composed of a physician with some critical care training, a critical care nurse, and a respiratory therapist. They are prepositioned in the area of operation to facilitate transport to Landstuhl Regional Medical Center (LRMC) in Germany, and more teams are prepositioned in Germany for transport back to the continental US.[247,248] Each team has a specified equipment allowance standard that is designed to support between three and six patients, with the number on a given mission being determined in part by the severity of illness. A CCATT represents an additional critical care capability that augments the capabilities of an air evacuation team. Air evacuation teams are composed of two to three nurses and four to seven technicians that provide care to non-critically injured patients and act as the liason between the CCATT and the aircraft crew members.[248,249]

All coalition patients with critical care requirements in the current conflicts in Afghanistan (OEF) and Iraq (OIF) are flown out-of-theater to Germany with the assistance of a CCATT. Critical Care Air Transport Teams facilitate the rapid evacuation of severely ill patients, which translates both into better patient care as well as a significantly decreased forward medical footprint.

The birth of the CCATT asset can be traced back to 1988, when the program was first proposed by then Col PK Carlton, USAF, MC. Subsequent experiences in the Gulf War and Somalia highlighted a need for a coordinated approach to augmenting the in-flight critical care capability of standard air evacuation teams. A pilot program was formed in 1994 and the program was later formally adopted in 1996. The role of CCATT in patient movement has matured in the OEF and OIF areas of operation since 2001 and 2003, respectively.[250] Critical Care Air Transport Teams facilitate the rapid evacuation of severely ill patients, which translates both into better patient care as well as a significantly decreased forward medical footprint. The evolution of this unique capability has been one of the great success stories of military medicine during the current conflicts.

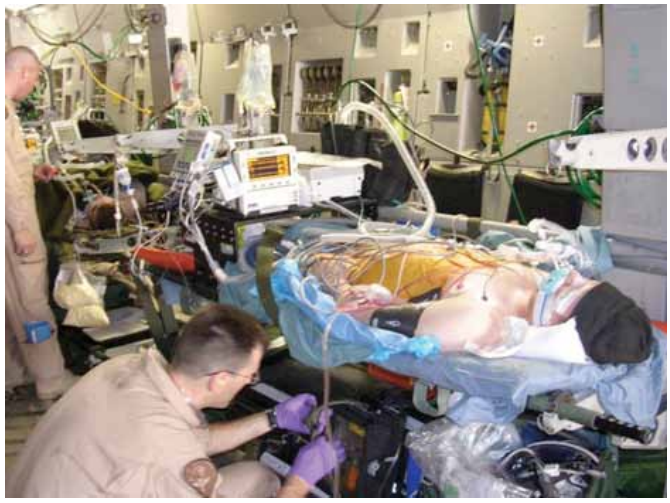

Figure 18. *A CCATT transports critically injured soldiers out-of-theater.*

The overall approach to care of the severely injured trauma patient has evolved in parallel with the CCATT system. The concept of damage control resuscitation emphasizes a first surgery to control immediately life-threatening hemorrhage while delaying more definitive surgical therapy until after a period of resuscitation that may take several hours to days.[251] In practice in OEF and OIF, patients will often have a first damage control surgery at a forward surgical location and are transported to a larger military trauma center in-theater by helicopter that is colocated with a CCATT. A second washout surgery

may be performed at the trauma center and then the patient is flown with a CCATT to Germany.[252] During the five to nine hours in the air, the CCATT is able to continue an aggressive resuscitation and deliver a patient to Landstuhl that is better prepared for more definitive surgical therapy. The success of damage control resuscitation in civilian trauma settings and in other military conflicts has lent itself well to the CCATT concept, and the presence of this new capability allows damage control to be pursued without delaying patient transport.

The US Air Force used to have a fleet of dedicated air evacuation aircraft, the majority of which were C-9 aircraft based on the DC-9 airliner airframe (Fig. 19). A set fleet of aircraft was found to be expensive and inflexible since all of the aircraft had identical capabilities in terms of range and logistics footprint and were located in only a few locations worldwide. Today, the air evacuation system uses "aircraft of opportunity." Air evacuation and CCATT teams are designed to be modular and have been trained to use the unique capabilities of numerous aircraft to allow patient transport. Today, the majority of CCATT missions are flown on C-17 and C-130 aircraft. Refueling aircraft such as the KC-135 and KC-10 have been used, as has the largest aircraft in the US inventory, the C-5. CCATT missions in-theater are occasionally flown on HH-60 Black Hawk helicopters, and some missions in the continental US and Europe are conducted with the C-21, which is the military version of a standard Learjet.

When the critical care team downrange identifies the need for CCATT transport, an air evacuation liason officer is contacted. The air evacuation liaison officer notifies a local flight surgeon who can evaluate the patient and identify any special needs the patient may have in flight. The request is then forwarded to a Joint Patient Movement Requirement Center (JPMRC) in-theater. The request is cleared, and an effort is coordinated with the Tanker Airlift Control Center (TACC) to find an aircraft in the theater that can be made available for patient movement. The patient, an air evacuation team, and a CCATT are then assigned

Figure 19. *C-17 aircraft is commonly used for CCATT missions.*

to that aircraft and preparations are made in the critical care unit for flight. While the system seems at first glance to be complex, it has become relatively efficient and results in much faster patient evacuation than in any prior conflict as well as a significantly decreased need for forward medical resources.[253]

Challenges Associated with Critical Care in the Air

Critical care in the back of an aircraft can be challenging and represents a significant physiologic stressor for the patient. Older aircraft may have poor temperature control and are typically very cold in flight. While flying in-theater below a certain threshold altitude, aircraft are kept dark inside to minimize the chances of being shot down. Vibration and noise are common factors that make patient monitoring more difficult than on the ground. Aircraft cabins are typically pressurized to 6,000 to 8,000 feet leading to lower oxygen content in the air as well as a tendency for any gas contained within an enclosed space to expand. This can complicate the care of patients with closed eye injuries associated with air pockets in the vitreous or patients with unrecognized pneumothoraces. Finally, acceleration changes associated with steep combat takeoffs and landings may contribute to the development of increased intracranial pressures in patients with traumatic brain injury.[254,255]

Physiologic stressors associated with cabin temperature, vibration and noise, air pressure, and steep combat takeoffs and landings may compound patient morbidity.

Perhaps the biggest challenge facing the CCATT when caring for a patient is the reality that there are limited options for assistance. The medical equipment that accompanies a CCATT is designed to support numerous interventions such as endotracheal intubation, central venous catheter insertion, arterial line placement, emergent tracheostomy, and chest tube thoracostomy. However, there are occasions when it is necessary to divert an aircraft to allow urgent transport of a patient to a ground based medical facility. Luckily, this has been a rare occurrence. A specialized Acute Lung Rescue Team (ALRT) is positioned at Landstuhl Regional Medical Center to assist in the evacuation of OEF/OIF patients with profound respiratory failure that may exceed basic CCATT capabilities.[76]

The relatively austere, resource-limited environment that a CCATT practices within demands that every effort be made prior to the flight to anticipate complications that may arise. With experience during a deployed rotation, the sending ICU teams and CCATTs become very adept at anticipating the needs of a patient. Those with marginal oxygenation on the ground should be intubated prior to flight.[256] Developing extremity compartment syndromes should be addressed with fasciotomies, and abdominal compartment syndromes should lead to laparotomy and the placement of an adjustable temporary abdominal closure.[250,257] Patients with suspected intracranial pressure elevations should be considered for early placement of intracranial pressure monitoring capability.[255] Blood products that may be needed for resuscitation and medications such as antibiotics and vasopressors should be identified prior to the mission.

The biggest challenge facing the CCATT when caring for a patient is that there are limited options for assistance, and every effort must be made prior to the flight to anticipate complications that may arise.

The use of the air evacuation system with CCATT augmentation has resulted in excellent patient outcomes, increased speed of evacuation, and a decreased downrange medical footprint. Even in its

relative infancy, the CCATT capability is demonstrating a new way to allocate medical resources in the combat care environment. The successful evolution of the system has created a new paradigm for how major industrialized countries involved in protracted wartime operations will address the care of their wounded warriors.

Summary

Aggressive, attentive, evidence-based critical care is a key component of recovery for the multisystem trauma patient. The ability to adapt the lessons of the medical literature to the challenges of the combat environment often determines the difference between a successful or poor patient outcome. Those who have the privilege of caring for our nation's heroes will always look back on the experience as one of the defining moments of their lives. Even in the most austere settings, there is no limit to the good that can be done.

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Appendix

Summary of Ventilator Procedures*

Variable	Group Receiving Traditional Tidal Volumes	Group Receiving Lower Tidal Volumes
Ventilator mode	Volume assist-control	Volume assist-control
Initial tidal volume (ml/kg of predicated body weight) †	12	6
Plateau pressure (cm of water)	≤ 50	≤ 30
Ventilator rate setting needed to achieve a pH goal of 7.3 to 7.45 (breaths/min)	6-35	6-35
Ratio of the duration of inspiration to the duration of expiration	1:1 - 1:3	1:1 - 1:3
Oxygenation goal	PaO_2, 55-80 mm Hg, or SpO_2, 88-95%	PaO_2, 55-80 mm Hg, or SpO_2, 88-95%
Allowable combinations of FiO_2 and PEEP (cm of water)‡	0.3 and 5	0.3 and 5
	0.4 and 5	0.4 and 5
	0.4 and 8	0.4 and 8
	0.5 and 8	0.5 and 8
	0.5 and 10	0.5 and 10
	0.6 and 10	0.6 and 10
	0.7 and 10	0.7 and 10
	0.7 and 12	0.7 and 12
	0.7 and 14	0.7 and 14
	0.8 and 14	0.8 and 14
	0.9 and 16	0.9 and 16
	0.9 and 18	0.9 and 18
	1.0 and 18	1.0 and 18
	1.0 and 20	1.0 and 20
	1.0 and 22	1.0 and 22
	1.0 and 24	1.0 and 24
Weaning	By pressure support; required by protocol when $FiO_2 \leq 0.4$	By pressure support; required by protocol when $FiO_2 \leq 0.4$

* PaO_2 denotes partial pressure of arterial oxygen, SpO_2 oxyhemoglobin saturation measured by pulse oximetry, FiO_2 fraction of inspired oxygen, and PEEP positive end-expiratory pressure.

† Subsequent adjustments in tidal volumes were made to maintain a plateau pressure of 50 cm of water in the group receiving traditional tidal volumes and 30 cm of water in the group receiving lower tidal volumes.

‡ Further increases in PEEP, to 34 cm of water, were allowed but were not required.

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