Journal of Veterinary Emergency and Critical Care

Clinical Practice Review

Journal of Veterinary Emergency and Critical Care **22**(2) 2012, pp 179–186
doi: 10.1111/j.1476-4431.2012.00727.x

Severe burn injury, burn shock, and smoke inhalation injury in small animals. Part 1: Burn classification and pathophysiology

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Abstract

Objective – To review the literature related to severe burn injury (SBI), burn shock, and smoke inhalation injury in domestic animals. Current animal- and human-based research and literature were evaluated to provide an overview of thermal burn classification and the pathophysiology of burn shock and smoke inhalation injury.
Etiology – Severe burn injury, burn shock, and smoke inhalation injury may be encountered as a result of thermal injury, radiation injury, chemical injury, or electrical injury.
Diagnosis – Burns can be subdivided based on the amount of total body surface area (TBSA) involved and the depth of the burn. Local burn injuries involve <20% of the TBSA whereas SBI involves >20–30% of the TBSA. The modern burn classification system classifies burns by increasing depth: superficial, superficial partial-thickness, deep partial-thickness, and full-thickness.
Summary – Local burn injury rarely leads to systemic illness whereas SBI leads to significant metabolic derangements that require immediate and intensive management. SBI results in a unique derangement of cardiovascular dysfunction known as "burn shock." The physiologic changes that occur with SBI can be divided into 2 distinct phases; the resuscitation phase and the hyperdynamic hypermetabolic phase. The resuscitation phase occurs immediately following SBI and lasts for approximately 24–72 hours. This period of hemodynamic instability is characterized by the release of inflammatory mediators, increased vascular permeability, reduced cardiac output, and edema formation. The hyperdynamic hypermetabolic phase begins approximately 3–5 days after injury. This phase is characterized by hyperdynamic circulation and an increased metabolic rate that can persist up to 24 months post burn injury in people.

(J Vet Emerg Crit Care 2012; 22(2): 179–186) doi: 10.1111/j.1476-4431.2012.00727.x

Keywords: canine and feline, carbon monoxide, hyperdynamic, hypermetabolic, resuscitation, thermal injury

Introduction

Burn injury in animals can lead to severe metabolic, cardiovascular, and pulmonary derangements. Patients with severe burn injury (SBI) require intensive management, and therefore, a thorough understanding of burn pathophysiology is recommended. The 4 main types of burn injuries in small animals include thermal injury, radiation injury, chemical injury, and electrical injury.[1,2] Most burn injury knowledge in veterinary medicine is based on advances in human medicine and research performed on experimental animals. Within the last 10 years, numerous experimental studies have been performed providing information that can be extrapolated for use in veterinary patients. The purpose of this review is to discuss thermal burn injury classification including etiology, the pathophysiology of SBI, burn shock, and smoke inhalation injury. A companion article will review patient evaluation, treatment recommendations, complications, and prognosis of patients with SBI and smoke inhalation injury.

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The authors declare no conflicts of interest.

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Submitted October 22, 2010; Accepted February 7, 2012.

Burn Classification

Burns are classified both according to burn depth and the amount of total body surface area (TBSA) involved.[2–5] Previously, burn wounds were classified by degree, first through fourth, but these terms do not accurately reflect depth.[2,5,6] The modern burn classification system classifies burns by increasing depth: superficial, superficial partial-thickness, deep partial-thickness, and

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Table 1: Classification of burn wounds

Classification of burn wound	Dermal layers involved	Wound characteristics	Healing
Superficial	Epidermis only	Erythematous desquamation Dry, flaky appearance	Heals in 3–5 days via re-epitheliazation Minimal scar formation
Superficial partial-thickness	Epidermis	Erythematous, moist blanches	Heals in 1–2 weeks via re-epithelialization
	Upper 1/3 of dermis (papillary layer)	Painful blisters may be present Edema may be present Eschar formation	Minimal scar formation
Deep partial-thickness	Epidermis All dermis	Red-waxy white Reduced pain sensation Blisters absent Eschar formation	Heals in 2–3 weeks Recommend surgical intervention to prevent significant scar formation
Full-thickness	Epidermis dermis Subcutaneous tissue	Bloodless pearl-white Eschar formation Hair easily plucked	Requires surgical intervention

full-thickness.[2,3,5–7] (Table 1) The percent TBSA is also used to classify burns. Burn injuries that encompass <20% of the TBSA are referred to as local burns whereas those that encompass >20–30% of the body are classified as SBI.[1,3,8–10] SBI lead to systemic derangements that require intensive management.

The current conceptual understanding of burn wounds includes 3 zones of injury: zone of coagulation, zone of stasis, and zone of hyperemia.[1,5,6] Burns have a necrotic center secondary to ischemia that becomes progressively less severe at the periphery. This central portion of the wound, the *zone of coagulation*, correlates with the initial area of thermal injury. It is therefore the deepest and has the greatest amount of cellular damage.[5] The irreversible tissue loss is secondary to coagulation of the constituent proteins and it is the primary location of eschar formation.[1] The surrounding *zone of stasis* is defined by capillary vasoconstriction, decreased tissue perfusion, and ischemia. There is also a mixture of viable and nonviable cells in this region.[1] Tissue damage in the zone of stasis is potentially reversible with appropriate fluid therapy that promotes blood flow to the region. Without appropriate treatment, progressive ischemia and cellular death ensues and the zone of stasis becomes a portion of the zone of coagulation.[5] The outermost zone, the *zone of hyperemia*, has significantly less cellular damage than the innermost zones.[5] The zone of hyperemia is characterized by viable cells and local inflammatory mediated vasodilation and is very similar to superficial burns.[1,5]

Local burn injury

Local burn injury in small animals is typically caused by heat from fires, boiling liquids, electrical heating pads, animal dryers, hot metals (e.g., mufflers and wood stoves), hot water bottles, and improperly grounded electrocautery units.[2,8,11–13] The extent of the local burn injury depends on the temperature of the burn object and the duration of contact.[5,7,8] Most burns evaluated by veterinarians are local burn injuries and do not involve more than 20–30% of the TBSA.[3] The percentage of involvement has a great impact on survival.[8] Local burn injury, unlike SBI, does not result in metabolic derangements, and therefore, aggressive systemic therapy is typically not required. Local burn injuries may take approximately 24–48 hours to become readily apparent to owners and veterinarians.[3,4,8] Prior to visible alterations to the epidermal surface, the affected area may be hypersensitive or painful.

The clinical appearance of the wound will vary with the severity of the burn. (Table 1). Unlike superficial burns, partial-thickness and full-thickness burns will be readily apparent immediately after the injury.[2–4,8] They will both develop a thick leathery surface of dead tissue, an eschar, which encourages bacterial growth.[5,7] With eschar development, the protective mechanisms of the skin are lost predisposing the burn wound to infection.[5] Until the eschar is removed or naturally separates from the healthy skin, it may be difficult to fully classify the depth of the burn injury.[3]

Superficial burns typically heal without scarring in 3–5 days.[3] Partial-thickness burns can heal rapidly over 1–2 weeks with little or no scarring due to re-epithelialization from hair follicles and sebaceous glands.[7,8] Full-thickness burns result in complete destruction of all cutaneous structures making surgical intervention necessary. Without surgical intervention, these burns heal via contraction and epithelialization resulting in hypertrophic scarring and possible deformation.[2,3,5,7,8]

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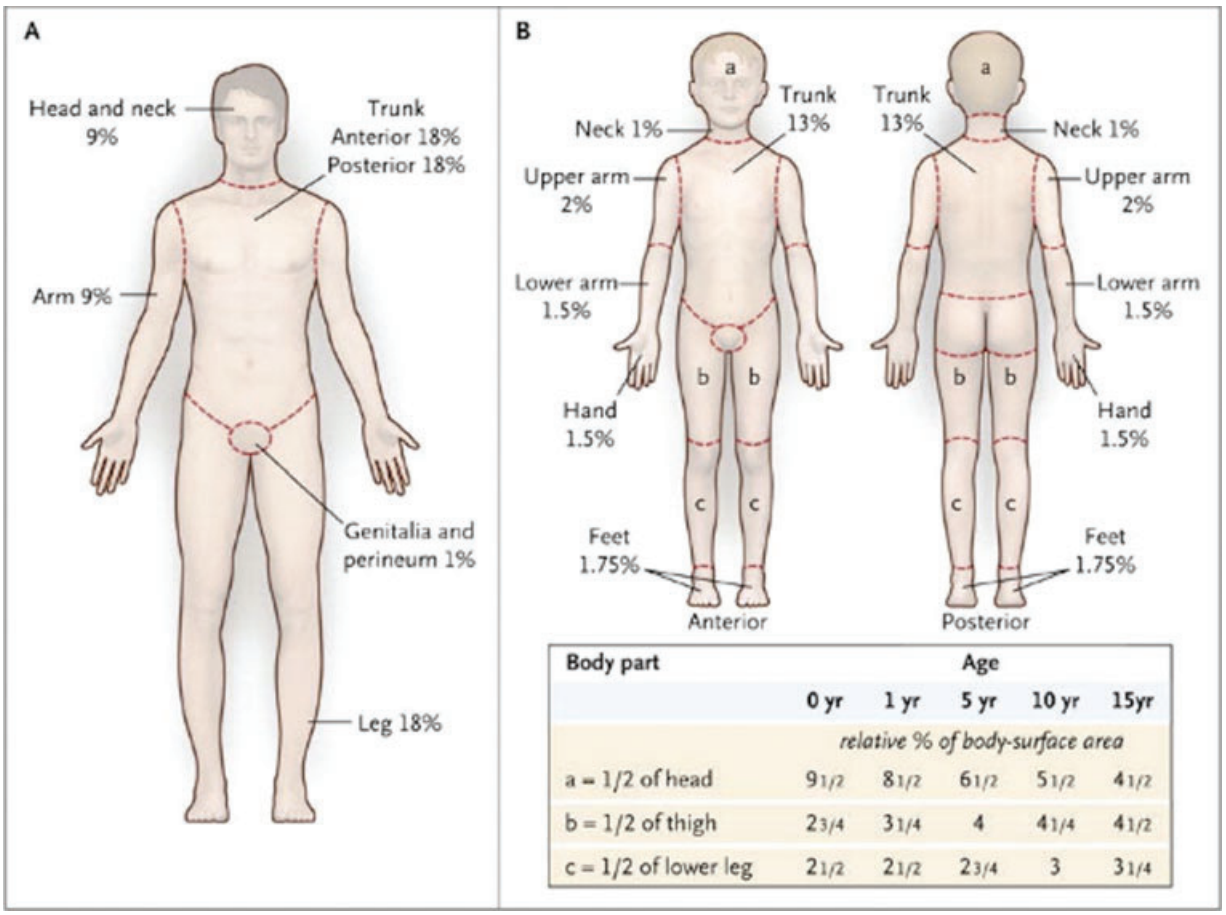
Severe burn injury

Determination of the TBSA involvement of burn patients is crucial because patients with SBI (>20–30% of TBSA) will have significant systemic derangements that require intensive medical and surgical management. In human medicine, the TBSA involved can be predicted by utilizing the "Rule of Nines" for adults and the Lund–Browder chart for children (Figure 1).[2,6,14,15]

The "Rule of Nines" divides the surface area of the body into areas of "9%" or "multiples of 9%" equal to 18%. The head and neck account for 9% of the TBSA, each arm is 9%, each leg is 18%, the thorax and abdomen are 18%, and the back is 18%.[2,3,15] The Lund–Browder chart subdivides body areas into segments and accounts for changes in body proportion that occur with growth.[2,6] This method may be more useful in small animal patients, since like children, they also have a larger body surface area–mass ratio compared to adults.[6] The fact that children have proportionally larger heads and smaller lower extremities is accounted for when utilizing the Lund–Browder chart.[14] The "Rule of Nines" is a more rapid method for TBSA estimation but is considered less accurate than the Lund–Browder chart.[2,15] Inaccurate estimation may result in excessive fluid administration leading to exacerbation of edema formation and potential complications. Currently, there is no schematic to estimate TBSA in veterinary medicine and therefore caution should be used when these systems are extrapolated for use in small animals.

SBI results in a unique derangement of cardiovascular dysfunction known as "burn shock."[1] Burn shock is characterized by intravascular volume depletion, reduced cardiac output (CO), and increased systemic vascular resistance (SVR) with resulting decreased peripheral blood flow.[1,9,16,17] The physiologic changes that occur with SBI can be divided into 2 distinct phases; the resuscitation phase and the hyperdynamic hypermetabolic phase.[4,17]



Body part	Age				
	0 yr	1 yr	5 yr	10 yr	15yr
	relative % of body-surface area				
a = 1/2 of head	9 1/2	8 1/2	6 1/2	5 1/2	4 1/2
b = 1/2 of thigh	2 3/4	3 1/4	4	4 1/4	4 1/2
c = 1/2 of lower leg	2 1/2	2 1/2	2 3/4	3	3 1/4

Figure 1: The Rule of Nines and Lund–Browder charts. The Rule of Nines (Panel A) is often used to estimate the surface area of a burn in adults. However, this approach is less accurate in children. Lund–Browder (Panel B) uses values for the legs and head that vary according to a patient's age. Taken in entirety from Orgill D. Excision and skin grafting of thermal burns. N Eng J Med 2009;360(9):893–901. Reprinted with permission.

Resuscitation phase

The resuscitation phase, also known as the "hypodynamic" or "ebb phase," occurs immediately following SBI and lasts for approximately 24–72 hours.[4,17,18] This period of hemodynamic instability is characterized by increased vascular permeability, fluid shifts resulting in intravascular volume depletion, and edema formation in burned and nonburned tissues.[4] In addition, this phase is characterized by reduced CO which is poorly responsive to therapeutic efforts. The primary goal during this phase involves restoring and preserving tissue perfusion in order to avoid ischemia from hypovolemic and cellular shock.[16] Burn shock results from a combination of both hypovolemia and the effects of inflammatory mediators.[1] In severe burn patients, almost all components that control fluid and protein loss from the vascular space are altered.[19] An imbalance between oncotic and hydrostatic forces develop. A marked increase in microvascular permeability occurs secondary to direct vascular thermal injury and to the release of inflammatory mediators.[4,10,17] Increased vascular permeability leads to a shift of intravascular fluid and plasma proteins into the interstitial space resulting in decreased capillary oncotic pressure.[19] The new interstitial particles create an osmotic gradient that pulls additional fluid into the interstitium resulting in edema formation.[9,19] Hypoproteinemia occurs from loss of proteins into the edema fluid and from the injured skin surface. Edema is most prominent within or directly surrounding the burned tissue; however, edema can also develop in nonburned tissues, including soft tissue, muscles, intestines, and lungs.[19]

Major burn injuries can lead to decreased cellular transmembrane potential in injured and noninjured cells.[16] The disruption of the sodium-ATPase pump leads to an increase in the intracellular sodium concentration which results in an osmotic shift, cellular swelling, and worsened hypovolemia.[10,20] As much as 50% of the total plasma water can be lost from the vascular compartment within 2–3 hours after a 40% TBSA burn.[4] In major thermal injuries, maximal edema formation, intravascular hypovolemia, and hemoconcentration occur 12–24 hours post injury.[10,16]

Many biochemical factors released after thermal injury contribute to edema formation and lead to systemic derangements associated with SBI.[1,19] Reactive oxygen species (ROS) and many mediators, including histamine, prostaglandins, thromboxane, serotonin, kinins, hormones, and leukotrienes have been implicated in the pathophysiology of burn shock.[1,4,10,16,19,21]

Patients with SBI are in a state of oxidative stress, characterized by an imbalance between cytotoxic ROS and the antioxidative defense systems. There is an overproduction of ROS which exceeds the neutralizing capacity of antioxidants, therefore oxidative injury to tissues and organs occurs.[22,23] Neutrophils, the primary source of ROS, have been demonstrated in various tissues such as gastric mucosa, liver, and lung in the early phases of burn injury.[24] Inflammatory cells (mainly neutrophils) will infiltrate the tissue within minutes of the insult persisting for approximately 72 h post burn injury[19] and gradually decreasing thereafter. Additionally, activated macrophages produce nitric oxide which can exacerbate oxidative injury.[24] The production of ROS in the injured tissue and distant noninjured tissue is hypothesized to be the pathogenesis of organ damage in SBI.[24] Production of ROS leads to lipid peroxidation of cell membranes resulting in an osmotic shift and death of the affected cell.[22]

Histamine is released via mast cells within minutes following tissue damage but its effects are transient.[1,16,19] Histamine causes contraction of the venular endothelial cells leading to the formation of intracellular junctional gaps which results in an increase in vascular permeability.[1] In addition, by causing arteriolar dilation and venular contraction, histamine acts as a vasoactive agent that increases capillary hydrostatic pressure, exacerbating burn-associated edema.[1,16,19] The significance of histamine-induced alterations on vascular permeability is questionable due to the lack of a significant reduction in edema formation with the administration of histamine receptor antagonists.[25]

Potent vasoactive products from the arachidonic cascade, including prostaglandins, prostacyclins, and thromboxanes are released from burn tissue and are a key mediator in inflammation, fever, and pain.[16,21,26–28] Prostaglandin (PGE_2) and prostacyclin (PGI_2) are potent systemic vasodilators that are released after thermal injury. Vasodilation causes an increase in intravascular hydrostatic pressure in the face of altered capillary permeability resulting in exacerbation of edema formation.[1,19] Thromboxane (TXA_2), a potent vasoconstrictor, is produced by platelets after burn injury in people.[27] TXA_2 may be responsible for the persistent decrease in blood flow and may contribute to the zone of ischemia.[1,21,27] In addition, TXA_2 results in irreversible platelet aggregation; therefore, increased concentrations may predispose burn patients to thrombus formation.[27]

Kinins, specifically bradykinin, are produced at the burn injury site and exert their effects locally and distantly.[1,16,19,21] The inflammatory process associated with SBI favors activation of the kallikrein–kinin system, resulting in systemic release of bradykinin.[16,19] Bradykinin is a powerful vasoactive mediator that causes venular dilation, increased microvascular permeability, smooth muscle contraction, and pain.[21]

Reduced CO is the hallmark of the early post burn period.[10] A significant decrease in CO occurs as early as 2 hours after burn injury and gradually resolves in

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48–72 hours.[20,29] Reduction in CO is a combined result of a decrease in plasma volume, an increase in afterload, and a decrease in myocardial contractility.[1,4,9,10] Depression of CO occurs before there is a notable decrease in plasma volume.[1,20] Immediately following injury, heart rate and systolic blood pressure are preserved, while SVR increases 2–3 fold.[20] Sympathetic stimulation and hypovolemia result in the release of catecholamines, vasopressin, angiotensin II, and TXA_2, which are all potent vasoconstrictors that contribute to increased afterload and SVR.[1,4,20] The massive fluid shift from the intravascular space to the interstitial space reduces cardiac preload and therefore CO.[20] In both dogs and people, despite aggressive fluid therapy and correction of hypovolemia, preload and CO are unable to be restored until 24 hours post injury.[30,31] The persistent decreased CO was at one time thought to be secondary to circulating myocardial depressant factor.[1,4,20] Recently, it has been determined that burn-associated decreases in cardiac contractility are likely multifactorial. Research in rats reveals that decreased contractility is a result of the production of an inflammatory cascade, caspases activation, and cardiomyocyte apoptosis.[32–37]

Nuclear factor κB (NF-κB), a transcription activator protein, is activated immediately following SBI and is thought to regulate the induction of several inflammatory mediators.[33] Following the activation of NF-κB, tumor necrosis factor (TNF-α) is released from the cardiac myocytes.[33] TNF-α results in the release of numerous other cytokines including interleukin (IL)-6 and IL-1β.[29] In rats that suffered SBI, the progressive secretion of TNF-α, IL-6, and IL-1β concentrations were paralleled by a progressive decrease in myocardial contractility.[32] The synergistic action of these cytokines produced significant cardiomyocyte injury and contractile deficits as early as 2 hours post burn injury compared to the effects of each cytokine alone.[32] The percentage of TBSA involvement in human burn patients is associated with the degree of cardiac depression, likely correlating to increased production of inflammatory mediators.[38]

Cardiomyocyte apoptosis is thought to contribute to cardiac dysfunction in the early stages of burn injury.[29,36,37] Caspases, a family of cysteine proteases, play an essential role in cardiomyoctye apoptosis, necrosis, and inflammation.[29] Evaluation of rat hearts reveals that myocardial caspase activation occurs within 2–4 hours after SBI.[36,37] Various stimuli such as the generation of ROS, an increase in intracellular calcium, or inflammatory cytokine production can trigger the activation of caspases.[37] Experimentally, inhibition of caspase production in rats improves cardiac contractile function after SBI.[37] Caspase activation not only causes myocardial apotosis but also contributes to the production of many inflammatory mediators.[37]

Although NF-κB, TNF-α, IL-1β, IL-6, and caspases-associated cardiomyocyte apoptosis play a significant role in early cardiac dysfunction in post burn injury, it is hypothesized that cardiac dysfunction is also related to macrophage migration inhibitor factor (MIF).[29,34,35] MIF, a constitutively expressed protein found in many cells throughout the body, has been found to play a role in adaptive and innate immunity, as an inflammatory cytokine, a neuroendocrine hormone, and catalytic enzyme.[35] MIF is released in response to burn injury by the skin and cardiomyocytes. Direct thermal injury leads to release of MIF from the basal layer of the epidermis whereas oxidative stress associated with burn injury leads to the release of MIF from cardiomyocytes.[34] Willis et al.[34] evaluated mice that were subjected to 40% TBSA burn injury and MIF was a critical mediator of late and prolonged (12 hours post burn injury) cardiac dysfunction.

Hyperdynamic hypermetabolic phase

After successful resuscitation, a "hyperdynamic and hypermetabolic phase" (also known as "flow phase") begins approximately 3–5 days after injury.[4,6,18,38] This phase is characterized by hyperdynamic circulation and an increased metabolic rate that can persist for up to 24 months post burn injury in people.[39,40] The hyperdynamic phase is characterized by decreased vascular permeability, increased heart rate, and decreased peripheral vascular resistance resulting in an increase in CO.[3,4,6,17,20,40] Approximately 24–48 hours after SBI, the microvascular integrity begins to restore and peripheral blood flow is augmented by a reduction in SVR with preferential redistribution to the area of the burn wounds.[3,4,17,17] Cardiac output is >1.5 times that of a nonburned, healthy patient approximately 3–4 days post burn injury.[40] During this time period, patients require significantly less fluid volume administration compared to the resuscitation phase. In addition to having persistent hyperdynamic circulation, people with SBI have an increased metabolic rate approximately 3× that of their basal metabolic rate.[4] Hypermetabolism in burn patients is characterized by protein catabolism, gluconeogenesis, glycogenolysis, lipolysis, hepatic insulin resistance, increased glucose and oxygen consumption, decreased lean body mass, and a fever.[4,6,17,39,40]

Augmented release of counter-regulatory hormones, cortisol, glucagon, and catecholamines drive the hypermetabolic response.[6,17,39,40] The extent of TBSA affected by burn wounds is directly related to the severity and duration of the hypermetabolic resonse in human burn patients secondary to an increased production of counter-regulatory hormones.[38] The increased metabolic demand is met by mobilization of proteins and amino

acids resulting in protein catabolism and a decrease in lean body mass.[40] Burn patients have a negative energy balance until at least 9–12 months post burn injury.[41] At this time, patients begin to build lean muscle due to an improvement in the net balance of protein synthesis and breakdown.[41] In people, the metabolic rate exceeds 140% of normal at admission, reduces to 130% once wounds are fully healed, then to 120% at 6 months postinjury, and 110% at 12 months postburn.[40,41] Overproduction of catecholamines and stress hormones in SBI not only affects lean body mass, but also produces derangements in glucose production, uptake, and utilization and leads to insulin resistance.

Increased concentrations of the counter-regulatory hormones stimulate hepatic gluconeogenesis, glycogenolysis, and lipolysis.[6,39,40] SBI patients have increased gluconeogenesis to support the relatively inefficient anaerobic metabolism of fibroblasts, endothelial cells, and inflammatory cells associated with the burn wound.[18,39,40] The utilization of glucose in burn patients is through inefficient anaerobic metabolism with resultant lactate production.[39] Lactate is then recycled through the liver to produce additional glucose.[18,42] Utilization of amino acids in hepatic gluconeogenesis makes them unavailable for reincorporation into body protein.[38,40] Burn patients are typically hyperglycemic and can have significantly increased insulin concentrations for up to 4–5 weeks post burn injury.[40,40] The characteristic hyperglycemia with concurrent hyperinsulinemia indicates that post burn injury patients have hepatic and skeletal insulin resistance and a decrease in peripheral glucose uptake.[38–40,43] The degree of insulin resistance is directly correlated with the severity of the burn injury.[38] Hyperglycemia is an important risk factor that can adversely affect survival in severely burned patients.[43] Hyperglycemia in burn patients is associated with an increased incidence of bacteremia and fungemia, decreased wound healing, and significantly increased mortality, when compared to burn patients with normoglycemia.[43]

The hypermetabolic phase is also characterized by fatty infiltration of the liver and an increase in the patient's temperature setpoint.[39,40] The counter-regulatory hormones promote lipolysis leading to increases in serum triglycerides and free fatty acids.[40] Hepatomegaly occurs in patients with SBI and is thought to be secondary to fatty infiltration of the liver. Jeschke et al.[40] evaluated pediatric patients with SBI and noted marked hepatomegaly, which increased by 225% of normal by 2 weeks, which, in turn, is associated with an increased incidence of sepsis and mortality. The inefficient substrate cycling (e.g., gluconeogenesis, glycogenolysis, and lipolysis) contributes to an increase in body temperature.[4,18,39,40,44] Severely burned adult and pediatric patients' core temperatures are reset 2°C (3.6°F) greater than normal nonburned patients on average.[44]

Inhalation injury

Patients with SBI often have associated smoke inhalation injury. Five common clinical consequences in patients with smoke inhalation injury include acute upper airway obstruction, bronchospasm, small airway occlusion, pulmonary infection, and respiratory failure.[16] Damage to the upper respiratory tract is secondary to direct thermal injury and chemical irritation whereas damage to the lower respiratory tract is secondary to distal migration of upper airway material and the effects of systemic inflammatory mediators.[4,17,45,46]

The effects of smoke inhalation injury on the upper respiratory tract are seen within the first 24 hours.[4,17,45,46] Soot, the principal product of most fires, adheres to the respiratory mucosa allowing other irritants to bind to the mucosa.[45] Direct thermal injury and adherence of irritants to the upper respiratory tract results in the release of inflammatory mediators and ROS, increased vascular permeability, and edema formation as previously described in burned tissue.[4,45–47] The formation of edema in the upper respiratory tract can progress to airway obstruction and bronchospasm that peaks at 24 hours and subsequently resolves over a few days.[4,48] Hemorrhage, mucosal congestion, ulceration, and laryngospasm may also occur within the first 24 hours.[4] The damaged mucosal cells produce copious exudates rich in protein, inflammatory cells, and necrotic debris.[45] Neutrophils begin to migrate through the glandular epithelium and into the airway lumen. This chemotactic response occurs within 4 hours after injury in response to the release of inflammatory mediators such as IL-1α, Il-8, IL-6, and TNFα.[49] The resultant damage to the columnar epithelia inhibits the mucociliary apparatus of the trachea allowing distal migration of upper airway material and bacteria.[50] The distal migration of upper airway material such as mucus, cellular debris, neutrophils, and fibrin leads to obstruction of the bronchi, bronchioles, and terminal bronchioles.[46,48–50]

Exfoliation of the epithelial lining of the trachea and mainstem bronchi occur between 3 and 5 days post smoke inhalation.[4,17,45,46] The distal movement of this material creates pseudomembrane casts that block lower airways, inactivates the surfactant, and results in segmental atelectasis.[4,45,46] Evaluation of experimentally induced smoke inhalation injury in sheep reveals that bronchiolar obstruction peaks at 72 hours.[50] The casts noted in the sheep were composed of mucus, inflammatory cells, and fibrin that had originated in the upper airway and migrated distally over time. Sheep that had smoke inhalation in conjunction with SBI had more

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obstructed bronchi than those with SBI or smoke inhalation alone.

Migration of particulate matter and bacteria trapped in the sloughing epithelial cells and mucus predisposes smoke inhalation patients to pneumonia.[4,17,45] Several other factors that increase burn patients' susceptibility to pneumonia include dysfunction of the mucociliary apparatus resulting in decreased clearance, pulmonary inflammatory activation, increased leakage of nutrient-rich plasma into lung parenchyma, denuded mucosal surfaces, and endotracheal intubation.[4,51] Approximately 50% of human patients with smoke inhalation injury will develop a pulmonary infection.[17]

Carbon Monoxide Toxicity

Carbon monoxide (CM) is the most common inhaled agent producting complications in smoke inhalation victims.[45] The extent of injury secondary to CM toxicity is directly dependent on the concentration of inhaled CM, the duration of exposure, and the underlying health status of the patient.[52] Carbon monoxide, the product of combustion of organic material in the presence of insufficient oxygen, is rapidly absorbed across the alveolar membrane.[53] Carbon monoxide binds hemoglobin with an affinity 200–250 × that of oxygen.[53–55] Binding of CM prevents binding of oxygen to hemoglobin molecules producing a 'functional anemia'.[6,45,52–54] Carbon monoxide inhibits the release of oxygen and produces cellular hypoxia and thus shifts the oxygen–hemoglobin dissociation curve to the left.[46,53–56] Additional detrimental effects of CM toxicity include induction of lipid peroxidation, direct cellular damage, reperfusion injury, and central nervous system demyelination.[45,53]

Delayed neurologic sequelae (DNS) occurs in approximately 10–30% of people following CM toxicity.[17,55] Delayed neurological sequelae is more common in people that are initially more symptomatic or present comatose after CM toxicity.[54] Delayed neurological sequelae is characterized by a relapse in neurologic dysfunction after a transient period of improvement.[52,54] Patients typically re-present 2–40 days after initial improvement.[54] People with DNS experience memory loss, personality changes, confusion, ataxia, and seizures.[52–54] Delayed neurological sequelae after CM toxicity has been described in veterinary medicine.[53,55] One case report described a dog that was found comatose secondary to CM toxicity with apparent recovery.[53] The dog re-presented 5 days later for progressive neurologic signs including tetraparesis and dementia. With intensive supportive care, the dog recovered completely with no evidence of neurologic dysfunction at a 34-month follow up. Another case series evaluated multiple animals from the same household that had evidence of CM toxicity.[55] All but 1 animal had apparent recovery from CM toxicity but were subsequently diagnosed with total deafness 2 weeks after exposure. Approximately 6 weeks after initial presentation, all animals had subjectively normal hearing and no residual neurologic sequelae. There is limited information available regarding DNS in veterinary patients but complete recovery is possible.

Cyanide Toxicity

In addition to CM toxicity, cyanide toxicity should also be suspected in animals with inhalation injury or with burns from a structural fire.[57] Hydrogen cyanide forms from the combustion of nitrogen-containing products.[45] Cyanide binds to cytochrome oxidase and impairs tissue oxygenation by converting intracellular aerobic metabolism to anaerobic metabolism.[57] In human burn victims, fatal exposure to cyanide is uncommon.[58] To the authors' knowledge, there are no reports of cyanide toxicity secondary to structural fires in veterinary medicine. The diagnosis and treatment of both CM and cyanide toxicity are discussed in the companion article.

Conclusion

Severe burn injury and burn shock pose a significant challenge for patient management. The 2 phases described in this review are unique to patients with SBI and burn shock. The resuscitative or hypodynamic phase begins immediately after SBI and requires aggressive management for survival. With appropriate therapy, the resuscitative phase subsides giving rise to a hyperdynamic hypermetabolic phase that can persist for 2 years post burn injury. Patients that suffer from SBI are likely to have concomitant smoke inhalation injury and potentially CM and cyanide toxicity. An understanding of the pathophysiology associated with these conditions is necessary to provide appropriate therapy to veterinary patients presenting as emergencies.

Acknowledgments

The authors would like to thank Dr. Patricia Walters and Dr. Alan Glazer for their critical review of this manuscript.

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