ABSTRACT

Patients with terminal brain stem herniation experience global physiological consequences and represent a challenging population in critical care practice as a result of multiple factors. The first factor is severe depression of consciousness, with resulting compromise in airway stability and lung ventilation. Second, with increasing severity of brain trauma, progressive brain edema, mass effect, herniation syndromes, and subsequent distortion/displacement of the brain stem follow. Third, with progression of intracranial pathophysiology to terminal brain stem herniation, multisystem consequences occur, including dysfunction of the hypothalamic-pituitary axis, depletion of stress hormones, and decreased thyroid hormone bioavailability as well as biphasic cardiovascular state. Cardiovascular dysfunction in phase 1 is a hyperdynamic and hypertensive state characterized by elevated systemic vascular resistance and cardiac contractility. Cardiovascular dysfunction in phase 2 is a hypotensive state characterized by decreased systemic vascular resistance and tissue perfusion. Rapid changes along the continuum of hyperperfusion versus hypoperfusion increase risk of end-organ damage, specifically pulmonary dysfunction from hemodynamic stress and high-flow states as well as ischemic changes consequent to low-flow states. A pronounced inflammatory state occurs, affecting pulmonary function and gas exchange and contributing to hemodynamic instability as a result of additional vasodilatation. Coagulopathy also occurs as a result of consumption of clotting factors as well as dilution of clotting factors and platelets consequent to aggressive crystalloid administration. Each consequence of terminal brain stem injury complicates clinical management within this patient demographic. In general, these multisystem consequences are managed with mechanism-based interventions within the context of caring for the donor’s organs (liver, kidneys, heart, etc.) after death by neurological criteria. These processes begin far earlier in the continuum of injury, at the moment of terminal brain stem herniation. As such, aggressive, mechanism-based care, including hormonal replacement therapy, becomes clinically appropriate before formal brain death declaration to support cardiopulmonary stability following terminal brain stem herniation.

Keywords: brain death, brain stem herniation, endocrine dysfunction, hormonal replacement therapy, hyperdynamic cardiovascular state, multisystem resuscitation

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Traumatic brain injury (TBI) is among the leading causes of death in patients younger than 45 years. Approximately 1.4 million patients experience TBI annually. Of this subset, approximately 50,000 patients die, and between 70,000 and 90,000 are left with permanent disability. Note that 50% of patients dying from TBI may do so within the first 2 hours following injury.

Terminal brain stem herniation consequent to fatal TBI is associated with multiple and profound global physiological consequences affecting all body systems originating from the same final common pathway. Hemodynamic and pulmonary instability is common following TBI with terminal brain stem herniation. In patients with severe TBI, a low Glasgow Coma Scale (GCS) score such as a GCS of 3, and clinical findings of brain herniation such as bilateral fixed, nonreactive pupils, the prognosis is abysmal. With the incidence of severe TBI and rapid physiological instability, multiple decisions involving resuscitation and potential for organ donation and aggressive and early mechanism-based therapies specific to the causes of physiological instability are appropriate. A significant issue in rapid delivery of clinically appropriate care is prompt recognition of physiological events associated with progression of TBI to terminal brain stem herniation. Delays are possible at each step in the process of injury progression, clinical recognition, clinically appropriate care, brain death determination, and organ recovery. Early recognition and intervention are optimal for aggressive resuscitation and for preserving organ perfusion and function in the event the intracranial injury progresses to death by neurological criteria.

Intracranial pathophysiology following massive TBI generally follows the same final common pathway toward terminal brain herniation syndromes and final loss of brain stem function. The trajectory of neurological dysfunction generally follows a rostral to caudal pattern that may progress more rapidly in the event of a TBI such as a gunshot wound to the brain or massive intracranial hemorrhage. Severe, refractory intracranial pressure (ICP) elevations generally occur as a result of onset and evolution of severe primary and secondary brain injury.

Emergent management of impending and actual brain stem herniation includes prioritizing airway, breathing, and circulation. Decreased level of consciousness occurring as a result of progressive brain injury will compromise a patient’s ability to maintain an intact airway and lung ventilation. More direct interference with respiratory drive as a result of distortion within the posterior fossa and brain stem herniation mandates endotracheal intubation and controlled ventilation. Cardiovascular instability will require aggressive management to preserve cardiac output and blood pressure (BP) and stabilize organ perfusion, all of which is part of best practice in delivery of optimal intensive care unit (ICU) care. This article reviews the pathophysiology of catastrophic brain injury, consequences of terminal brain stem herniation, and related global clinical effects. Differential diagnosis of factors contributing to severe cardiopulmonary instability in a patient with clinically evident terminal brain stem herniation is reviewed. These factors include diabetes insipidus (DI), poor thyroid hormone bioavailability, and inflammatory state/stress hormone depletion, and they are correlated with mechanism-specific care, including hormonal/metabolic resuscitation.

**Pathophysiology and Trajectory of Severe TBI**

Traumatic brain injury, classified as closed head injury or penetrating brain trauma, may be categorized into 2 stages. The first stage, primary brain trauma, begins at the moment of injury and may be caused by a depressed skull fracture, subdural/epidural hematoma, and/or traumatic intracerebral hemorrhage as well as brain contusion or laceration. Diffuse brain injury may occur from rapid acceleration/deceleration and cause diffuse axonal injury and/or brain edema. The second stage, secondary brain injury, begins following the immediate trauma and includes brain ischemia, autoregulatory failure, anaerobic metabolism, increased tissue lactate, cellular energy failure, release of excitatory amino acids, and loss of cell membrane integrity. This loss of membrane integrity allows sodium and calcium influx into the cells, lipid peroxidation, and ultimately loss of structural integrity. This loss of structural integrity allows influx of water into the cell, with resulting progressive brain edema. Salient events in refractory ICP elevation and rostral to caudal progression of injury are alterations in the relative volume of 3 components contained within the intracranial vault. These 3 components are brain volume, blood volume within the arterial and venous systems, and cerebrospinal fluid volume.
One component of intracranial hypertension is increased brain bulk from brain edema as a result of tissue water influx and inflammatory response. Increased brain-blood volume in the arterial and/or venous systems also can occur from autoregulatory failure, hyperemia, and/or compromised venous drainage from the brain. The third component is increased (cerebrospinal fluid) volume consequent to communicating and/or obstructive hydrocephalus. Each component of intracranial hypertension is part of the continuum of secondary brain injury. During aggressive management of ICP elevations, several mechanism-based interventions are used to modulate 1 or more components of intracranial pathophysiology. For example, osmotic diuresis with mannitol and/or hypertonic saline creates an osmotic gradient between edematous brain tissue and circulating blood volume. This gradient facilitates water movement out of swollen brain tissue, treating brain edema. Managing increased brain-blood volume includes titration of controlled ventilation and facilitation of venous drainage from the head and neck. Optimal care for hydrocephalus includes ventricular drainage managed by vigilant ICP monitoring. Metabolic suppression therapies such as barbiturates or propofol decrease metabolic rate of brain tissue, decrease cerebral blood flow, and manage intracranial hypertension. In select cases, therapeutic hypothermia, though controversial, may be used for cerebral metabolic suppression and to modulate cerebral blood flow. Decompressive hemicraniectomy, also somewhat controversial, may be used on a case-by-case basis to treat refractory ICP elevations, pending resolution of severe brain edema.

Sedation may be part of the plan of care to decrease anxiety and brain arousal. Analgesic agents may be used to decrease response to noxious stimuli and blunt brain arousal. Neuromuscular blockade may be used to eliminate patient-ventilator dyssynchrony and coughing, both of which may raise intrathoracic pressure and, consequently, ICP. Neuromuscular blockade may also be used to decrease metabolic load by paralyzing skeletal muscles. Patients with malignant intracranial hypertension refractory to all aggressive, mechanism-based therapies progress to herniation syndromes, culminating in terminal brain stem herniation.

This refractory progression of injury following nonsurvivable TBI generally follows a rostral to caudal trajectory that may take varying amounts of time with a pattern as follows. In the setting of a rapidly expanding supratentorial lesion or rapid progression of brain edema, the higher brain centers typically experience dysfunction first, as evidenced by progressive loss of consciousness. Further progression of injury may lead to pathological posturing and/or seizure activity. Continued increases in pressure then may lead to transtentorial (central) herniation with distortion of the posterior fossa and brain stem. Ultimately, terminal brain stem distortion/herniation results in loss of autonomic control and unregulated mobilization of endogenous catecholamines. This sympathetic dysfunction occurs in 2 phases, each with risks to end-organ function and each having specific management priorities.

Progressive Intracranial Injury and Clinical Consequences

With this catastrophic progression of intracranial hypertension to the posterior fossa, a cascade of events occurs. One event is compression of the brain stem, as it is displaced toward the foramen magnum. Cushings triad may occur from pressure or ischemia on the pons, with resulting hypertension, bradycardia, and wide pulse pressure, a reflex response in an attempt to maintain brain perfusion. During early brain stem pressure and distortion, progression of ischemia and distortion to the medulla oblongata and hypothalamus results in additional sympathetic outflow as endogenous catecholamine stores are mobilized in an effort to maintain cerebral perfusion pressure.

Continued ICP elevations and resulting tissue displacement within the posterior fossa cause terminal brain stem herniation. Circulating epinephrine and norepinephrine levels increase significantly over baseline levels within a narrow time frame, leading to significant increases in sympathetic outflow. The sudden injury, rapid ICP elevation, and rapidly progressing herniation syndromes contribute to the speed of catecholamine mobilization and subsequent spike in BP and heart rate (phase 1). Following the unregulated catecholamine surge, time-specific catecholamine depletion occurs and heart rate and BP decline, concurrently with vascular tone. This declination of catecholamine levels results in a time-sensitive decrease in BP as a result of decreased inotropic state and vascular tone (phase 2).
Each extreme change in cardiopulmonary status following terminal brain stem herniation has specific and time-sensitive management priorities to optimize cardiac output and tissue perfusion.\textsuperscript{14} With the impending hypotensive state and compromised end-organ perfusion, aggressive surveillance of vital sign patterns following catastrophic brain injury effectively becomes part of the neurological assessment. In impending brain herniation, this surveillance can establish onset of terminal brain stem herniation and is vital in determining timing of mechanism-based therapeutics to address the multisystem consequences.

Clinical management priorities are always appropriately and ethically focused on preservation of the patient’s brain function and promotion of optimal neurological recovery until terminal brain stem herniation is clinically evident. In the event terminal brain stem herniation becomes evident despite the use of aggressive, mechanism-based therapeutics to manage intracranial pathophysiology, consideration may appropriately be given to clinical management directed toward optimal extracranial (systemic) organ function, which would potentially preserve the option of organ donation for the family. Evidence of terminal brain stem herniation includes development of a flaccid, areflexic neurological examination; pupils fixed, dilated, and midpoint; and characteristic sudden, massive cardiovascular hyperdynamic state in the face of all other confounding factors having been ruled out. Figure 1 illustrates terminal loss of brain/brain-stem function concurrent with trajectory of biphasic cardiovascular response.

**Brain Stem Herniation Effects on Cardiovascular Function: Phase 1**

The initial hypertensive and hyperdynamic phase is a result of catecholamine surges and includes massive increases in systemic vascular resistance (SVR).\textsuperscript{7,13,15-17} Massive sympathetic outflow can produce calcium influx into myocardial cells, electrocardiographic changes, release of free radicals, and direct myocardial necrosis.\textsuperscript{18} Increases in SVR, preload, and BP significantly increase cardiac work and myocardial oxygen consumption.\textsuperscript{15-17} Cardiac function is directly decreased as a result of both direct catecholamine toxicity and myocardial ischemia.\textsuperscript{7,9,13} Cardiac dysrhythmias occur consequent to ischemia as well as myocardial irritability and direct cellular damage\textsuperscript{10,13} in this phase following brain stem herniation.\textsuperscript{7,12} A significant risk of end-organ damage resulting from the profound vasoconstriction and dramatic increase in global perfusion pressure exists. These massive hyperperfusion state(s) and vasoconstriction may develop within minutes and subject the cardiovascular system and end organs, such as the liver, kidneys, and lungs, to severe hemodynamic stress and localized ischemia, which may cause significant volume shifts into the central circulation, impairing gas exchange and pulmonary function.\textsuperscript{7,12,13,17}

Given the rapid development of a hypertensive and hyperdynamic state, effective clinical management is facilitated by rapid recognition of final brain stem herniation and preparation to administer rapid-acting and short-acting agents, given the uncertain duration of phase 1.\textsuperscript{7,13} Appropriate management of this stage of cardiovascular instability depends on identifying the sequence of cardiovascular changes within the trajectory of management and following terminal brain stem herniation.

**Cardiovascular Clinical Management: Phase 1**

Rapidly acting agents such as nitroprusside (0.5-10.0 mcg/kg per minute), nicardipine (2.5-5 mg per hour and titrated),\textsuperscript{16} or esmolol (with a loading dose of 500 mcg/kg per minute for 1 minute and then 50 mcg/kg per minute for 4 hours and titrated) are appropriate drug therapies to address the initial hypertension and tachycardia associated with a phase 1 hyperdynamic state. Anticipating severe hypotension following catecholamine depletion, clinicians should use agents with short durations of action to potentially minimize the initial degree and duration of hypotension due to minimal systemic drug accumulation.\textsuperscript{13} Aggressive management during phase 1 can result in improved myocardial function and preservation of cardiac output in addition to improved heart recipient outcomes\textsuperscript{7} and may also modulate volume shifts from peripheral to central circulation and attenuate neurogenic pulmonary edema. Variability in heart rate can give an early indication of impending terminal events, providing an opportunity to preserve organ function and optimal cardiac output.\textsuperscript{20} Following catecholamine depletion and marked decline of excessive sympathetic outflow as well as marked vasodilatation, BP may drop precipitously,\textsuperscript{21} a state known as phase 2 cardiovascular instability following brain stem herniation.
metabolism with increased serum lactate, ultimately causing significant, multifactorial hypotension. One factor is that loss of vascular tone causes decreased SVR and increased venous capacitance. Increased venous capacitance results in decreased preload and cardiac output. Significant decrease in SVR also results in increased vessel capacitance on the arterial side. The end result of both arterial and venous dilatation is significant relative herniation. An overview of pharmacological therapies used in clinical management of patients during and after terminal brain stem herniation is given in Table 1.

Brain Stem Herniation Effects on Cardiovascular Function: Phase 2

The hypotensive stage is characterized by marked reduction in vascular tone in both arterial and venous systems, as well as anaerobic metabolism with increased serum lactate, ultimately causing significant, multifactorial hypotension. One factor is that loss of vascular tone causes decreased SVR and increased venous capacitance. Increased venous capacitance results in decreased preload and cardiac output. Significant decrease in SVR also results in increased vessel capacitance on the arterial side. The end result of both arterial and venous dilatation is significant relative...
<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Dosing</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Esmolol</td>
<td>500 mcg/kg per minute for 1 min</td>
<td>Rapid onset, ease of titration</td>
<td>Potential for heart blocks, decreased cardiac output at high doses or with poor titration</td>
</tr>
<tr>
<td></td>
<td>50 mcg/kg per minute for 4 h and titrated</td>
<td>Short acting, well tolerated</td>
<td></td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>0.5-10.0 mcg/kg per minute</td>
<td>Rapid onset, ease of titration</td>
<td>Potent antihypertensive</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>2.5-5.0 mg/h, titrated to maximum dose 15 mg/h</td>
<td>Rapid onset, ease of titration</td>
<td>Calcium channel blocker, negative inotropic effect at higher doses, Risk of chemical phlebitis if administered long term through peripheral IV</td>
</tr>
<tr>
<td>Crystalloid/volume resuscitation 0.9% saline</td>
<td>Volume titrated on the basis of actual and relative volume deficit May be as much as 3-4 L initially</td>
<td>Rapid administration and correction of circulating volume deficit Ease of access/administration</td>
<td>Risk of pulmonary edema, Dilution of clotting factors, Dilution of platelets/cellular components, Hypothermia</td>
</tr>
<tr>
<td>Dopamine</td>
<td>1-10 mcg/kg per minute or higher</td>
<td>Ease of administration, Rapid acting</td>
<td>Tachycardia, increased myocardial oxygen demand, Dysrhythmias, Vasoconstriction risk at higher doses, Tissue necrosis if through a peripheral access</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>1-10 mcg/kg per minute, titrated</td>
<td>Ease of administration, Rapid acting</td>
<td>Hypotension possible with initial dosing, Dysrhythmias, tachycardia, Increased myocardial oxygen demand</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.5-20 mcg per minute, higher doses possible</td>
<td>Rapid acting, Treats loss of vasomotor tone Augments coronary, tissue perfusion</td>
<td>Risk of severe vasoconstriction, tissue ischemia, Less-favorable heart recipient outcomes</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>20-300 mcg per minute</td>
<td>Rapid acting, Treats loss of vasomotor tone Augments coronary, tissue perfusion</td>
<td>Risk of severe vasoconstriction, tissue ischemia, Less-favorable heart recipient outcomes</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.01-0.04 U/min initially</td>
<td>May decrease vasopressor dosing requirements Control urine output in DI, Preserve circulating volume</td>
<td>Excessive vasoconstriction, risk of ischemia at high doses</td>
</tr>
</tbody>
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(continues)
hypovolemia. Fluid volume deficits caused by net volume loss can further compound hypotension. Loss of fluid can result from the use of diuretics such as mannitol or furosemide, blood loss from traumatic injury, urine volume losses due to DI, and insensible fluid losses. Residual effects of CNS depressants to treat the brain injury, such as barbiturates, opioids, and benzodiazepines, cause vasodilatation and myocardial depression in a dose-related manner. Inflammatory mediators are released from necrotic brain tissue through breakdown of the blood-brain barrier, resulting in systemic inflammation, additional vasodilatation, and increased vessel capacitance. Another factor is increased lactate production from anaerobic metabolism consequent to global hypoperfusion. A sixth factor is decreased coronary perfusion from afterload reduction and increased risk of ischemia and cardiac dysfunction. Finally, the patient is at risk for bradydysrhythmias following terminal brain stem herniation. At this stage, the heart is effectively denervated and atropine resistant. Effective, mechanism-based care for phase 2 (hypotensive) is aimed toward augmenting intravascular volume, using vasoactive agents, and controlling volume loss. Cardiovascular Clinical Management: Phase 2

Crystalloids such as 0.9% sodium chloride as well as colloid fluids and blood products are
appropriate for intravascular volume expansion. Volume replacement must account for actual volume losses due to therapeutic diuresis as well as DL. Rapid volume resuscitation may be accomplished with multiple large-bore peripheral intravenous (IV) catheters (16 g or 14 g) that may provide flow rates exceeding those of central venous catheters. Therapeutic goals for volume replacement are a central venous pressure (CVP) approximately 8 to 12 mm Hg or pulmonary artery occlusion pressure (PAOP) approximately 6 to 10 mm Hg as well as clinical findings of increased cardiac output and tissue perfusion, such as improved skin/nail bed color and improved capillary refill. Central venous pressure is considered less sensitive an indicator than PAOP in determining volume status. Central venous pressure can, however, be useful in determining trends over time in volume status in response to therapy such as volume resuscitation. Systemic BP targets include a mean arterial pressure of 60 to 70 mm Hg or greater or systolic BP of 100 mm Hg or greater. Treatment options with vasoactive and inotropic agents include initiating dopamine (1-10 mcg/kg per minute) and dobutamine (1-10 mcg/kg per minute) infusions titrated to clinical goals. Tachycardia may be a potential dose-limiting side effect with these agents. Norepinephrine (0.5-20 mcg per minute) or phenylephrine (20-300 mcg per minute) may be used to raise BP, augment tissue perfusion, and support coronary blood flow through direct treatment of loss of vasomotor tone and critically low SVR. Excessive catecholamine dosing, if possible, should be avoided because of risk of direct myocardial damage and potential for graft failure in the potential heart recipient if the patient progresses to organ donation. In addition, excessive catecholamine dosing risks end-organ ischemia and less-favorable recipient outcomes as a result of severe vasocostriction.

Options to limit catecholamine dosing include the addition of low-dose vasopressin (0.01-0.04 U per minute as a starting dose), acting synergistically with catecholamines. Vasopressin will also control urine output in DI and preserve circulating fluid volume. In addition to the obvious direct effects on cardiac stability, massive cardiovascular dysfunction between phases 1 and 2 has far-reaching and multifactorial effects on pulmonary function.

**Brain Stem Herniation Effects on Pulmonary Function**

Pulmonary dysfunction can be a result of multiple factors. Neurogenic changes can result in pulmonary edema. During vasoconstriction of the phase 1 cardiovascular response, a net fluid volume shift occurs from the periphery to the central circulation, acutely elevating atrial, pulmonary capillary, and hydrostatic pressures, causing pulmonary edema. Alteration of pulmonary capillary permeability due to α-adrenergic stimulation also allows fluid passage into alveoli. During pronounced vasodilatation of the phase 2 cardiovascular instability, ventilated lung areas may be inadequately perfused, limiting gas exchange and oxygenation, causing shunt physiology and ventilation/perfusion mismatch. In addition, the significant inflammatory state characterized by mobilization of immune system cells, proteases, cytokines, leukotrienes, and chemotactants following terminal brain stem herniation can have severe consequences. Inflammatory injury (biotrauma) at the level of the alveolus interface may directly inhibit gas exchange, causing refractory hypoxemia. This longer exposure of potential donor lungs to high levels of circulating cytokines and other inflammatory mediators increases risk of rejection in a potential lung recipient. The inflammatory state can be modulated with aggressive administration of glucocorticoids, decreasing plasma levels of cytokines and downregulating recipient immune response to transplanted organs.

In addition to direct effects of terminal brain stem herniation on pulmonary function, concurrent factors related to mechanism of injury may exist if catastrophic TBI is concurrent with blunt or penetrating chest trauma or other complications. These factors include aspiration, lung contusion, pneumonia, emboli, mucous plugs, volutrauma, and barotraumas as well as hemothorax and pneumothorax. Because the mechanism of pulmonary dysfunction is multifactorial, aggressive clinical management must also be multifactorial.

**Pulmonary-Specific Clinical Management**

One approach to aggressive pulmonary care includes measures to prevent ventilator-associated pneumonia. Such measures include gastrointestinal...
prophylaxis, deep vein thrombosis prophylaxis, turning and repositioning, and head-of-bed elevation at least 30°. Use of aggressive suctioning, chest physiotherapy, and oral hygiene with oropharyngeal suctioning removes secretions and microorganisms that can play a role in development of ventilator-associated pneumonia. Nebulizer therapy using β-agonists may also decrease alveolar fluid. Careful titration of ventilator flow rates, positive end-expiratory pressure, and tidal volumes, such as using 6 to 8 mL/kg, are considered lung-protective ventilation techniques. Alveolar recruitment strategies, including pressure control ventilation and higher levels of positive end-expiratory pressure at intervals, have also been used. Protocol-directed management strategies have been successful in significantly improving pulmonary function. Recruitment strategies, including controlled, short-term hyperinflation, may improve oxygenation and increase lung availability for transplantation. High-dose glucocorticoids (eg, methylprednisolone) have been used to modulate pronounced inflammation, improving oxygenation and reducing rejection risk in the recipient. Finally, close titration of intravascular volume can modulate the risk of pulmonary edema, especially during evaluation of a patient as a potential lung donor. As mentioned previously, volume status endpoints of CVP 6 to 10 mm Hg and/or, when used, PAOP of 8 to 12 mm Hg are appropriate. If the patient is considered a potential lung donor, conservative management of intravascular volume is indicated to minimize risk of pulmonary edema and optimize gas exchange, which may involve volume titration in some instances to lower CVP/PAOP ranges than those mentioned.

Other possible monitoring options include using oximetric catheters (Vigileo catheter, Edwards Lifesciences, Irvine, California) to monitor oxygen saturation in the central circulation. This monitoring can provide real-time feedback on tissue perfusion and be used to guide resuscitation and volume management. Using arterial catheter-based waveform analysis in real time is an additional option. Stroke volume can be determined by analysis of the arterial pressure waveform (FloTrac catheter, Edwards Lifesciences). From these data sources, additional parameters such as cardiac output, stroke volume, and SVR can be determined and used to guide therapy. Aggressive clinical management strategies, initiated early following terminal brain stem herniation, can improve pulmonary function, oxygenation, and increase lung availability for transplantation with better recipient outcomes.

**Brain Stem Herniation Effects on Thermoregulation**

Brain stem herniation adversely affects thermoregulation, and body temperature can become very unstable. Under most circumstances, the hypothalamus regulates body temperature. In response to elevated body temperature, neurons in the anterior hypothalamus activate sweating and vasodilatation of blood vessels in the skin to dissipate body heat. Conversely, in response to decreased body temperature, neurons in the posterior hypothalamus increase heat production by activating shivering and decrease heat loss by vasoconstriction in the periphery and decreasing peripheral vascular resistance. With total hypothalamic failure, endogenous thermoregulation is lost, causing significant extremes in body temperature. These temperature extremes depend on catecholamine surges and vasoconstriction (phase 1 cardiovascular instability), increasing body temperature initially. Vasoconstriction inhibits heat loss by limiting blood flow to peripheral body areas. Hyperthermia then develops as a result of decreased catecholamine levels (phase 2 cardiovascular instability), significant vasodilatation, and increased heat loss to the environment. Hypothalamic failure, loss of thermoregulation, and extremes in vascular tone lead to risk of biphasic temperature alterations. Hyperthermia may also occur as a result of pronounced inflammation or following multisystem trauma. Hyperthermia can lead to coagulopathies, tachycardia, increased oxygen consumption/carbon dioxide production, and further worsening of the inflammatory state as well as increased insensible fluid losses and increased hemodynamic instability. Potential consequences of hypothermia include refractory hypotension, increased volume loss through the kidneys, bradycardias, cardiac dysrhythmias, and impaired tissue oxygen delivery. Given the significant, global consequences of hypothermia and hyperthermia, aggressive surveillance, prevention, and clinical management are vital.

**Clinical Management of Hypothermia and Hyperthermia**

Hyperthermia and hypothermia are optimally treated by early recognition. Body
temperature should be monitored frequently as clinically appropriate and as determined by unit protocols. Temperature elevations should be addressed before they reach critical levels. Management options for hyperthermia include gastric lavage with ice water, cooling blankets, and applications of cool water to enhance heat loss by evaporation. Hypothermia is optimally managed with heat lamps, warming blankets, and convective warming devices using forced delivery of warm air to body surface areas. Measures for heat conservation include using warm blankets and using head coverings to minimize heat loss through the scalp. Either temperature extreme may be treated using surface cooling devices that circulate water through surface cooling/warming pads in contact with the patient’s skin. Intravascular cooling devices may also be used. Use of these devices entails placement of a percutaneous vascular catheter to allow an external heat exchange device to circulate chilled saline through the vascular catheter. Blood circulating around the catheter is cooled as is core body temperature.  

Endocrine Dysfunction Following Terminal Brain Stem Herniation

The effects of terminal brain stem herniation are not limited to thermoregulatory dysfunction. In most instances, massive ICP elevations and distortion in the posterior fossa eliminate communication among the pituitary gland, hypothalamus, and neuroendocrine axis, which causes total loss of hypothalamic and anterior and posterior pituitary function. This loss results in marked decreases in circulating adrenocorticotropic hormone (ACTH), insulin, vasopressin, cortisol, triiodothyronine (T-3), l-thyroxine (T-4), and thyroid-stimulating hormone. Significant thyroid hormone level reduction results in a hypometabolic state, bradycardia, hypotension, and increased dosing requirements for vasoactive and inotropic agents. In addition, direct mitochondrial dysfunction with decreased availability of myocardial phosphate energy stores results in transition from aerobic to anaerobic metabolism as evidenced by increases in lactate and pyruvic acid levels and hemodynamic instability.  

Clinical Management of Endocrine Dysfunction

Endocrine dysfunction affects the global neurohumoral environment and all body systems. Optimal clinical management for refractory cardiopulmonary instability and endocrine dysfunction is best described as mechanism-based care. Mechanism-based care for endocrine dysfunction includes replacement therapies for absolute and/or relative deficiencies in hormonal levels, including cortisol, insulin, T-3/T-4, and antidiuretic hormone (ADH). With pituitary dysfunction due to terminal brain stem herniation, thyroid-stimulating hormone levels fall, which prevents endogenous T-3 and T-4 release from the thyroid. Exogenous T-3/T-4 may be administered using IV forms of these agents and coordinating bolus administration with infusion dosing. T-3 administration includes an initial bolus dose of 4 mcg, followed by an infusion at 3 mcg per hour. T-4 may be administered with an initial bolus dose of 20 mcg followed by an infusion at 10 to 20 mcg per hour. T-3 may be more effective as the active form of thyroid hormone. With peripheral hypoperfusion and decreased cardiac output states, T-4 may not be as readily converted to active T-3. Thyroid hormone replacement increases mitochondrial function and energy production at the cellular level with a subsequent change from anaerobic to aerobic metabolism. On a global scale, effective cellular-level resuscitation is reflected by lower dosing requirements for vasoactive and inotropic agents, improved cardiac output, BP, and clinical findings of tissue perfusion. Anaerobic metabolism will convert to aerobic metabolism as evidenced by decreased serum lactate and pyruvate levels and increased BP. Hormonal/metabolic resuscitation may be appropriate for a patient who progresses to clinically evident terminal brain stem herniation despite aggressive clinical management of TBI. Blood glucose levels may be elevated following brain stem herniation as a result of preexisting diabetes, physiological stress, insulin resistance, decreased insulin levels, and the use of liver glycogen stores, which increases risk for severe hyperglycemia, osmotic diuresis, volume depletion, and electrolyte imbalances. Hyperglycemia is effectively treated.
by continuous IV administration of insulin, titrated in a protocol-directed approach to control elevated blood glucose levels.\textsuperscript{7,10} General starting points for insulin infusion may be 1 U per hour, titrated by protocol to clinical goals for blood glucose levels such as 120 to 180 mg/dL.\textsuperscript{7,10,17}

Cortisol and ACTH secretion are governed by interaction between the pituitary, hypothalamus, and an intact neuroendocrine axis. As such, terminal brain stem herniation can result in decreased ACTH and cortisol levels and impaired ability to respond to physiological stress, which may be evidenced by hypertension refractory to volume resuscitation and high doses of multiple vasoactive and inotropic agents.\textsuperscript{7} Following catastrophic brain injury and terminal brain stem herniation, a pronounced inflammatory state generally occurs in addition to neuroendocrine dysfunction. This inflammatory state is consequent to mobilization of cytokines and inflammatory mediators from massively injured and necrotic brain tissue. The resulting inflammatory state has consequences, including increased vasodilatation and refractory hypotension.\textsuperscript{7} “Tagging” of potentially transplantable organs with cytokines may also occur and increases risk of rejection in the organ recipient.\textsuperscript{7,8,12,13,15,17} In addition, decreased gas exchange at the alveolar-capillary interface may occur and result in increased needs for oxygenation and ventilation.\textsuperscript{7,8,12,15,17} Endocrine dysfunction, stress hormone depletion, and inflammatory state may be managed by high-dose steroid administration\textsuperscript{12,13,17,22} with agents such as methylprednisolone 15 mg/kg as an effective therapy.\textsuperscript{7,8,10,13} By treating cortisol/ stress hormone depletion consequence to endocrine dysfunction and a global inflammatory state, high-dose steroid therapy may improve oxygenation, hemodynamic stability, and downregulate recipient immune response to transplanted organs.\textsuperscript{7,8,12,13,15,17,22}

Steroid administration in this context is intended to manage an inflammatory state and stress hormone depletion following the terminal event of brain stem herniation consequent to clinically evident catastrophic progression of brain injury. Goals of care include optimizing cardiopulmonary and end-organ function to preserve the option of donation for the family and optimal organ function. As part of the plan of care in managing TBI, brain edema and elevated ICP prior to clinically evident terminal brain stem herniation steroid administration are contraindicated.\textsuperscript{39}

In addition, the pronounced inflammatory state and mobilization of cytokines and inflammatory mediators from massively injured and necrotic brain tissue has consequences that are 3-fold.\textsuperscript{8,13} One consequence is increased vasodilatation and refractory hypotension. A second consequence is “tagging” of potentially transplantable organs with cytokines and additional risk of rejection in the organ recipient.\textsuperscript{7,8,12,13,15,17} A third consequence is decreased pulmonary gas exchange at the alveolar-capillary interface, increasing oxygenation and ventilation needs.\textsuperscript{7,8,12,13,15,17} High-dose steroid administration\textsuperscript{12,13,17,22} with agents such as methylprednisolone 15 mg/kg is an effective therapy.\textsuperscript{7,8,10,15} High-dose steroid therapy may improve oxygenation, hemodynamic stability, and downregulate immune response in an organ recipient.\textsuperscript{7,8,12,13,15,17,22}

Antidiuretic hormone secretion requires intact pituitary function as well as communication between the pituitary and cardiovascular system for ADH delivery to target organs. In most patients, terminal brain stem herniation results in DI as a result of marked decreases in ADH within the circulating blood volume.\textsuperscript{6,10,17} With the dramatic decline in ADH bioavailability, a significant decrease in water reabsorption occurs in the collecting tubules within the kidney, resulting in significant volume loss through increased urine output.\textsuperscript{10,13,17} This fluid loss can cause significant hypotension from loss of circulating volume as well as significant electrolyte imbalances such as hypernatremia.\textsuperscript{7} Loss of potassium, magnesium, and calcium can cause dysrhythmias.\textsuperscript{7} Clinical management of DI includes volume replacement with colloid or crystalloid solution in addition to hormonal replacement therapy (HRT).\textsuperscript{7,8,12,13,15,17} One option for HRT is desmopressin (DDAVP [1-deamino-8-D-arginine vasopressin, a synthetic analog of vasopressin]).\textsuperscript{10,12,13,15,17,22} A loading dose of 8 ng/kg followed by an infusion of 4 ng/kg per hour may be used.\textsuperscript{7,10,17} A second option is vasopressin.\textsuperscript{4,10,12,13,15,17,22} An initial bolus dose of 1 U can be administered followed by infusion dosing between 0.5 and 4.0 U per hour, which may be titrated to clinical effect.\textsuperscript{7,10,13,17} Vasopressin may also be used for BP support as a result of the synergistic effect with other vasoactive agents.\textsuperscript{7,12,15,17}

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Coagulopathy Following Catastrophic Brain Injury

Coagulopathy is another significant complication of massive brain injury. Release of thromboplastin, fibrinogen, and tissue plasminogen from necrotic brain tissue can result in a consumptive coagulopathy. Dilutional coagulopathy occurs when circulating clotting factors and platelets are diluted by large crystalloid and colloid fluid volumes used during resuscitation, which results in decreased platelets and serum clotting factors per unit volume of circulating blood. Hypothermia and hyperthermia can interfere with platelet function, increasing risk of disseminated intravascular coagulation. Optimal management starts with monitoring for clinical findings of bleeding and following clotting times and fibrinogen levels. Fresh-frozen plasma, cryoprecipitate, factor VII, and pooled platelets may be administered as clinically appropriate.

Timing of Therapeutic Interventions Along the Continuum of TBI Care

Clinical management of the patient following TBI prior to terminal brain stem herniation is focused on stabilizing brain perfusion, managing ICP elevations, and preventing secondary brain injury to maximize neurological recovery. Clinical management of a patient following severe TBI progressing to terminal brain stem herniation despite aggressive management of ICP may be managed differently as a potential organ donor. Following clinically evident terminal brain stem herniation management, priorities change to optimize organ perfusion, volume status, and oxygenation. Close surveillance and attention to even subtle changes in neurological and cardiopulmonary assessment are vital for 2 reasons. One reason is to identify opportunity for interventions to maximize neurological recovery. A second reason is to identify the point at which terminal brain stem herniation becomes clinically evident and initiate mechanism-based interventions to aggressively treat multifactorial physiological instability, which requires close surveillance and aggressive management of injury using the concept of a continuum of care.

All events in the evolution of massive TBI, catastrophic ICP elevation, and terminal brain stem herniation occur along a continuum. Frequently, terminal brain stem herniation occurs before it is documented clinically and before starting most brain death protocols, which leaves potential for significant time intervals between the terminal event, recognizing loss of brain stem function as such, initiation/completion of a brain death protocol, and recovery of transplantable organs. Virtually all events causing BP extremes, inflammatory state, decreased ADH/T-3/T-4/stress hormone bioavailability, and cardiopulmonary dysfunction as well as immune upregulation in potential donor organs start at the moment of the terminal event. As such, mechanism-based management of these physiological consequences can become clinically appropriate ICU care before initiation or completion of formal brain death protocols and/or consent for organ donation. Figure 2 illustrates a timeline/continuum of care following catastrophic brain injury showcasing intervals/potential for delay between salient events following injury. What becomes more significant within this context is the role of all team members in recognition and rapid intervention for these physiological consequences as soon as possible and appropriate in the continuum of care, which enables faster and more streamlined delivery of appropriate ICU care and decreases risk of missed opportunities for donation and potentially improved recipient outcome with earlier delivery of optimal cardiopulmonary support and measures to downregulate immune response to possible transplanted organs. Earlier, mechanism-based therapeutics for cardiopulmonary dysfunction may be clinically appropriate with or without organ donation as a consideration in aggressive cardiopulmonary support.

Systems Approach to Care Following Massive Brain Injury

Optimal and rapid delivery of clinically appropriate care requires rapid recognition of physiological events associated with progression of catastrophic TBI. Nurses are integral in early recognition and aggressive advocacy for clinically appropriate care at each point in the patient’s trajectory following injury. The concepts of risk management and adverse events may be applicable in this context. An adverse event such as unrecognized or “silent” brain death can result in a delay in donor recognition, inadequate or delayed aggressive physiological management following herniation, and a delay between events such as terminal brain
stem herniation and initiation of a brain death protocol. Focused education and quality management initiatives can enhance early recognition of injury progression and potentially decrease the incidence of silent brain deaths, which can improve appropriate donor recognition, optimize ICU resource use, and increase availability of potentially transplantable organs. Early recognition of terminal brain stem herniation is an opportunity for aggressive, mechanism-based care, including metabolic/cellular-level resuscitation as part of goal-directed therapy to significantly improve physiological stability and organ availability. Goal-directed therapy may include goals for mean arterial pressure, CVP, pH, PaO₂, sodium, glucose, single vasopressor use, and urine output. Of these goals, optimizing PaO₂ and minimizing vasopressor use have been most associated with improved physiological stability and increased organ availability. Clinically appropriate pivoting in ICU care from management of ICP to aggressive, standardized, mechanism-based care can and does improve organ availability and can be advocated even before a brain death protocol is initiated or completed.

The following 2 cases illustrate appropriate and timely metabolic/cellular-level resuscitation prior to completion of brain-death protocols. Both patients had clinically evident terminal brain stem herniation following severe TBI and required high vasopressor dosing after aggressive volume resuscitation. In each instance, vasopressor dosing needs became markedly decreased, and the patients were optimally supported through conclusion of brain death determination and organ recovery for transplantation.

Case Study 1
D.F. is a 38-year-old man transported to the emergency department (ED) by emergency medical services personnel. He was unconscious following a deep, penetrating stab wound to his left eye. He was brought to the trauma resuscitation bay with a GCS score of 3. Following severe head trauma with cardiopulmonary instability, the priorities of airway, breathing, and circulation were followed. After ventilation with a bag-valve-mask system, his trachea was intubated and controlled ventilation was initiated. Multiple IV accesses were inserted for volume resuscitation and drug administration. His vital signs and cardiovascular status were closely monitored. He had no cough or gag reflexes. Evident head trauma included fracture in the globe of his left eye, significant periorbital ecchymoses, and blood evident within the nares, airway, and mouth. A pupillary examination was unobtainable on the left eye and his right pupil was fixed and dilated at 5 mm. D.F. had no spontaneous movements, had palpable...
pulses, and was aggressively resuscitated. Urgent head computed tomography (CT) was significant for a large left frontal-temporal-parietal subdural hematoma and bilateral intraventricular hemorrhage with dilatation of the right ventricle. Mass effect and significant midline shift were present with effacement of sulci. Bone fragments from the left orbital fracture were present.

Following head CT, D.F. was immediately transferred to the operating room (OR). Operative management included placement of a right-side ventriculostomy and decompressive craniectomy on the left side. On gross examination, the brain was noted to be tense and poorly compliant, and the dura was unable to be closed. Cardiovascular instability with significant hypotension necessitated BP support with continued aggressive volume resuscitation, vasopressin, norepinephrine, and phenylephrine. Following operative management, he was transferred to the surgical ICU. Critical care management included neuromuscular blockade, vasopressor support for BP, and ICP monitoring as well as titration of controlled ventilation. Despite an aggressive trauma resuscitation and ICP management, his neurological status remained remarkable for an unconscious, flaccid, areflexic, neurological examination, and he was totally unresponsive to noxious stimulation. During the evening and night of ICU day 1, he required high-dose norepinephrine (30 mcg per minute). This drug therapy was transitioned to phenylephrine with a dosing range from 150 to 300 mcg per minute. Vasopressin was administered at 0.035 U per hour. On ICU day 2, D.F. was still requiring phenylephrine at 150 mcg per minute for BP support.

The plan of care at this time included initiation of a formal brain death protocol. For optimal management of hypotension, additional evaluation was undertaken to assess potential causes. Reviewing his trajectory following injury, timing with neurological findings, and absent brain stem function, terminal brain stem herniation likely occurred within hours following injury (at 3:30 PM on ICU day 1) and would have placed D.F. clearly within the hypertensive cardiovascular phase at that time following brain stem herniation. Time in ICU day 2 (8:30 AM) would place him 16 to 17 hours following injury. This placed him within the time interval for depletion of cortisol/stress hormones and thyroid hormones as well as a significant mobilization of the inflammatory response consequent to cytokines/inflammatory mediator release from damaged and necrotic brain tissue.

As such, appropriate, mechanism-based management for hypotension in this setting, even before brain death declaration and consent for organ donation, legitimately included high-dose steroids, insulin, thyroid hormone replacement, and vasopressin. Vasopressin (0.035 U per hour) was already being administered. At 10:00 AM, an L-thyroxine (T-4) 20-mcg bolus was administered, followed by infusion dosing at 20 mcg per hour in addition to methylprednisolone 2-g IV bolus and IV insulin. Within 1 hour following these interventions, dramatic improvement in BP and cardiovascular stability was evident, enabling downward titration of phenylephrine, which was titrated to off by 5:00 PM on ICU day 2. D.F. was stabilized and underwent a formal brain death protocol, including radionuclide flow study, which showed no isotope uptake to the brain. Radionuclide flow study was performed, rather than clinical brain death testing, to decrease the interval between initiation and completion of the formal brain death protocol and, if needed, to provide visual assistance to the family in demonstrating absence of blood flow to the brain. He was pronounced dead by neurological criteria at 4:50 PM on ICU day 2. His family ultimately consented to organ donation, and his organs were recovered for transplant on ICU day 3. Figure 3 illustrates the timeline and trajectory of care and timing of metabolic/cellular-level resuscitation.

Case Study 2
M.H. was a 54-year-old man who was transported to the ED of a level 1 trauma center. He had fallen down a flight of stairs, and the initial ED evaluation revealed total loss of consciousness. His GCS score was 3. He was tachycardic and hypertensive with a heart rate of 192/min and BP of 184/120 mm Hg (mean BP 141 mm Hg). Oxygen saturation was 54%.

His hypertensive and tachycardic state on admission following severe TBI suggests phase 1 (hypertensive) cardiovascular instability following terminal brain stem injury/catecholamine surge. He was endotracheally intubated immediately in the trauma bay. Following airway management and initiating controlled ventilation as well as suturing a large left temporal/occipital laceration in the trauma bay, he

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had multiple IV accesses placed. M.H. was then immediately transported for head CT. Results from the head CT scan revealed a right-side subarachnoid hemorrhage and right-side subdural hematoma. Significant mass effect and midline shift were present, as was right-side skull fracture. Immediately following completion of the head CT, M.H.’s systolic BP precipitously decreased to 80 to 90 mm Hg and he became bradycardic with a heart rate of 40 to 50 beats per minute. Blood pressure and heart rate responded to a bolus dose of 0.5-mg IV epinephrine. M.H. was transported immediately to the OR in anticipation of emergent operative management.

Upon arrival in the OR holding area, the patient immediately underwent additional neurological evaluation. Neurological findings were pupils fixed, dilated, and midpoint; absent cough, gag and corneal reflexes; and negative oculocephalic reflexes as well as a completely unconscious and unresponsive state. These findings strongly suggested that the terminal event of brain stem herniation had occurred and the patient would not benefit from operative intervention. He was transferred to the surgical ICU for medical management and cardiopulmonary support. His BP level was supported with phenylephrine dosing between 250 and 300 mcg per minute and vasopressin dosing between 0.03 and 0.04 U per minute. For treatment of intravascular volume deficits, aggressive volume resuscitation with 3 L of sodium chloride was administered. The initial formal brain death examination was completed at 5:00 AM, approximately 6 hours postinjury. A total of 2 formal neurological examinations as part of a brain death protocol were planned. In the absence of confirmatory testing, the interval between neurological examinations was 12 hours, as per institutional protocol.

Timing of marked BP instability places M.H. well within the window of phase 2 (hypotensive) cardiovascular instability following terminal brain stem herniation. On review of M.H.’s pattern of vital signs through his hospital stay, it was evident that he was in phase 1 cardiovascular state (hyperdynamic) on admission. Noting his hypotensive state several hours after ICU admission and the temporal relationship with his severe TBI, he was appropriately considered in phase 2 cardiovascular instability. He progressed from phase 1 through phase 2 instability during the time between OR

Figure 3: Timeline and trajectory of care from surgical intensive care unit (SICU) admission through completion of brain death protocol including timing of metabolic/cellular-level resuscitations. Significant improvement in cardiovascular stability is evident consequent to mechanism-based interventions (hormonal replacement therapy protocol, initiated at approximately hour 20) for causes of hypotension. Abbreviations: FFP, fresh frozen plasma; HRT, hormonal replacement therapy; IV, intravenous; MAP, mean arterial pressure; OR, operating room.
evaluation to ICU admission, which was the rationale for instituting mechanism-based care for optimizing cardiopulmonary and organ function in the ICU.

Critical care management included pharmacological support of BP with norepinephrine dosing between 25 and 30 mcg per minute and phenylephrine dosing at 300 mcg per minute. Vasopressin was administered at 0.04 U per minute for BP support as well as control of DI and high urine output. Blood pressure and oxygenation remained unstable, with a mean arterial pressure of 50 to 60 mm Hg and oxygen saturation 67% to 90% on FiO₂ 1.0. With potential risk of additional end-organ compromise from high-dose therapy with 2 vasopressors, a low-flow state from generalized vasoconstriction and potential for refractory cardiovascular instability, consideration was given to treatment of additional causes of hypotension. To that end, location of M.H. within the continuum following massive TBI was determined. Currently, he was approximately 9 to 10 hours following injury, which placed him within the interval of decreased thyroid hormone bioavailability and significant inflammatory state from mobilization of cytokines/inflammatory mediators from damaged/necrotic brain tissue. The pronounced inflammatory state was one probable mechanism of hypoxemia refractory to high FiO₂. Appropriate mechanism-based therapeutics for these causes of hypotension/hypoxemia even before formal brain death declaration included high-dose steroids, insulin, thyroid hormone replacement, and vasopressin.

Vasopressin (0.04 U per minute) was already being administered. At 9:00 AM, an L-thyroxine (T-4) 20-mcg bolus was administered and followed by infusion dosing at 20 mcg per hour in addition to methylprednisolone 2-g IV bolus and IV insulin. Within 1 hour following these interventions, dramatic improvement in BP/cardiovascular stability was evident, enabling downward titration of norepinephrine, which was titrated to off by 11:00 AM. Gas exchange improved markedly as evidenced by improved oxygen saturation from 67% to 100% over 1 hour following methylprednisolone administration. M.H. was stabilized to the point where the second of 2 formal brain death examinations was possible, as was safe transport for a radionuclide flow study. The second brain death examination, apnea testing, and radionuclide flow study were consistent with brain death. He was pronounced dead by neurological criteria at 1:05 PM on ICU day 2. His family consented to organ donation and his organs were recovered for transplant. Figure 4 illustrates the timeline and trajectory of care and timing of metabolic/cellular-level resuscitation.

Discussion
Patients who experience catastrophic TBI progressing to terminal brain stem herniation despite aggressive, mechanism-based care for primary and secondary brain injury can be extraordinarily challenging in critical care practice, which is true through the entire trajectory of care from initial resuscitation and managing intracranial dynamics through identification and management of global consequences of final brain stem herniation. The focus of care at the outset is control of devastating ICP elevations and modulating effects of secondary brain injury. In the event that injury progression or ICP elevations or both are not halted, pressure builds inexorably to the terminal event of brain stem herniation. Once this event occurs, characteristic physiological events follow. These events include phase 1 through phase 2 cardiovascular instability as well as endocrine dysfunction. Endocrine dysfunction may be manifested as refractory hypotension from decreased thyroid hormone bioavailability and marked elevation of urine output from ADH depletion. The pronounced inflammatory state consequent to catastrophic TBI can contribute to hypotension as well as impaired gas exchange. These events can and do contribute to tremendous cardiopulmonary instability and may begin before initiating or completing brain death protocols and formal declaration of death by neurological criteria. Customarily, metabolic/cellular-level resuscitation with HRT is typically initiated following declaration of death by neurological criteria as well as following consent for organ donation. The initiation of metabolic/cellular resuscitation and HRT prior to formal declaration of brain death or initiating formal brain death protocol can be considered once certain conditions are met, including (1) severe brain injury with loss of consciousness; loss of brain stem reflexes; fixed, dilated, and midpoint pupils; (2) hypotension and hypoxemia refractory to aggressive cardiopulmonary support; (3) determination of a temporal relationship between TBI and onset/progression of cardiopulmonary instability; and (4) the absence of a “do not
Figure 4: Timeline and trajectory of care from emergency (ED) admission through operating room (OR) holding area and surgical intensive care unit management with completion of brain death protocol including timing of metabolic/cellular-level resuscitation. Significant improvement in cardiovascular stability is evident consequent to mechanism-based interventions (hormonal replacement therapy protocol) for causes of hypotension. Abbreviations: BD, brain death; HRT, hormonal replacement therapy; IV, intravenous; MAP, mean arterial pressure.

resuscitate” status with aggressive physiological support remaining the goal of care. In these circumstances, aggressive management of cardiopulmonary instability with mechanism-based therapeutics as outlined can be clinically appropriate ICU care in addition to vasoactive and inotropic agents, volume resuscitation, and controlled ventilation.

Future Directions
The clinical management of the patients in these case examples encompassed aggressive ICU care and more timely initiation of mechanism-specific care for cardiopulmonary and neurohormonal instability following terminal brain stem herniation. The hormonal resuscitation protocol used in these cases is generally consistent with HRT recommended by the United Network for Organ Sharing. Future directions for research might include additional study evaluating effectiveness of individual components and organ-specific outcomes, such as cardiac function and/or oxygenation. One placebo-controlled study found that hormonal resuscitation therapy alone had no significant effect on cardiac output and/or heart recovery for transplant as compared with aggressive organ-specific management. In addition, on systematic review, routine use of hormonal replacement therapies is noted as effective in retrospective review and in case series; however, randomized controlled trials do not show significant benefit. As such, future directions for well-constructed research can explore additional evidence related to this practice.

Summary and Practice Implications
Clinical management of patients following catastrophic TBI and consequent terminal brain stem herniation can appropriately include metabolic/cellular-level resuscitation including HRT. The focus on prompt attention to mechanism-specific therapeutics for hypoxemia and cardiovascular instability with the intent to stabilize BP, minimize vasopressor dosing, and improve oxygenation is appropriate. Establishing a timeline between cardiopulmonary instability and onset of catastrophic TBI with neurological assessment findings can establish a presumptive diagnosis of terminal brain stem injury. Within this context, multidisciplinary collaboration in evaluating differential causes of cardiopulmonary instability can provide
clinical justification for appropriate and earlier, mechanism-based interventions and improved physiological stability at the tissue and cellular levels.

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