MANAGEMENT OF INCREASED INTRACRANIAL PRESSURE

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OVERVIEW

Intracranial pressure (ICP) is the pressure within the dura. In health, homeostatic mechanisms maintain ICP in a range from 3 to 15 mm Hg (or 5 to 20 cm H$_2$O). Elevated ICP is rapidly detrimental to brain function and can cause secondary cerebral ischemia and herniation. Treatment to restore ICP to normal must be given expeditiously and constitutes a cornerstone of acute care neurology.

EPIDEMIOLOGY

Traumatic brain injury (TBI) is the most common cause of intracranial hypertension (1). TBI has an annual incidence of about 200 cases per 100,000 population (2). Injury severe enough to warrant ICP therapy, known as severe TBI, occurs in only 10% of cases.

PATHOPHYSIOLOGY

Any condition that adds volume to the intracranial vault may raise ICP (Table 1). For example, increased blood volume may occur in trauma or sinus thrombosis; increased cerebrospinal fluid (CSF) volume may occur in obstructive or non-obstructive hydrocephalus; and increased brain tissue volume may occur in tumor, trauma, or cerebral edema.

The acuity with which a mass lesion develops corresponds with the magnitude of any increase in ICP. In circumstances where a large mass lesion develops slowly over time, ICP may increase minimally or not at all. Examples are slow-growing tumors such as meningiomas, or chronic hydrocephalus. In these cases, the intracranial compartment is able to compensate for the increased volume, and ICP is preserved, although symptoms and signs chronically elevated ICP (i.e. headache and papilledema) may occur.

Monroe-Kellie Doctrine

The Monroe-Kellie doctrine dictates that the cranial vault is a fixed space containing three volumes; blood, CSF, and brain. As a space-occupying lesion or any of these volumes are increased beyond capacity, ICP will rise (3). In the average adult, the brain volume is 1400 ml, the blood volume is 150 ml, and the CSF volume is 150 ml. CSF is produced by the choroid plexus at a rate of approximately 20 ml/hr. The CSF drains into the venous system via the arachnoid villi and granulations. This outflow is normally of low-resistance; hence, central venous pressure is the chief determinant of ICP in healthy patients.
**Intracranial Compliance**

Intracranial compliance is defined as the change in volume over the change in pressure \((dV/dP)\). Compliance decreases as intracranial volume increases (Figure 1). In the initial phases of an ICP elevating process, as volume is added to the skull (Point A), CSF is displaced into the spinal thecal sac and blood is decompressed from the distensible cerebral veins. Once these compensatory redistribution mechanisms are exhausted, however, ICP can increase profoundly with small increments of additional volume (Point B). The amplitude of the ICP pulse wave may provide a clue that compliance is reduced; as compliance falls, the ICP pulse amplitude increases Point B, inset).

**Cerebral Perfusion Pressure**

The main untoward consequence of elevated ICP is lowering of cerebral blood flow (CBF) and secondary hypoxic-ischemic injury. Cerebral perfusion pressure (CPP) is calculated as mean arterial pressure (MAP) minus ICP. CPP in turn determines CBF; normally, autoregulation of the cerebral vasculature maintains CBF at a constant level between a CPP of 50 to 100 mm Hg. Brain injury can impair autoregulation and cause CBF to approximate a more straight-line relationship with CPP (4). Although the optimal CPP for a given patient may vary, as a rule of thumb, CPP should be maintained above 60 (to avert ischemia) and below 110 mm Hg (to avoid breakthrough hyperperfusion and cerebral edema) (5,6). To accurately measure CPP in the ICU, the pressure transducer used to measure mean arterial pressure must be set at head level.

**Pathological Pressure Waves**

In patients with raised ICP, pathologic ICP waveforms may occur (Figure 2). Lundberg A waves (or plateau waves) represent prolonged periods of profoundly high ICP (7). They are ominous, and abruptly occur when either CPP or intracranial compliance is low. Their duration is from minutes to hours, and levels as high as 50 to 100 mm Hg may be reached. Lundberg B waves are shorter duration, lower amplitude elevations that indicate that intracranial compliance reserves are compromised.

**CLINICAL FEATURES**

The clinical manifestations of increased ICP are varied and unreliable. If ICP is becomes acutely increased, depressed level of consciousness may occur. Other symptoms may include nausea and vomiting, headache, blurring of vision, and diplopia (from sixth nerve palsies). In some cases Cushing’s triad may be observed: increased arterial blood pressure associated with bradycardia and irregular respirations.

ICP elevation may become compartmentalized as a result of the rigid boundaries created by the falx and tentorium cerebelli. Compartmentalized mass effect and pressure differentials in turn can lead to herniation of brain tissue from the area of higher to lower pressure. Different herniation syndromes are each marked by characteristic signs (Table 2).
DIAGNOSIS

Indications for ICP Monitoring

The diagnosis of increased ICP should not be made on clinical grounds alone. In order diagnose increased ICP it must be directly measured. Because of the invasive nature of ICP monitoring, and the need for ICU management, patients should generally meet three criteria prior to placement of an ICP monitor: 1) brain imaging reveals a space-occupying lesion or cisternal effacement, suggesting that the patient is at risk for high ICP; 2) the patient is comatose (Glasgow Coma Scale score of \( \leq 8 \)); and 3) the prognosis is such that aggressive ICU treatment is indicated.

ICP Monitoring Devices

Several types of ICP monitors exist (Figure 3). The external ventricular drainage (EVD) catheter is the gold standard; it consists of a water-filled catheter which is placed through a burr hole into the ventricle and connected to a pressure transducer set at head level. It allows for both ICP monitoring and the ability to perform therapeutic CSF drainage. Its major drawback is the risk of infectious ventriculitis, which occurs in approximately 10-15% of patients and steadily increases until the 10\(^{th}\) day of use \((8,9)\). The best alternatives to EVD include fiberoptic transducers (Integra\(^{\circledR}\)) or pressure microsensors (Codman\(^{\circledR}\)) placed through a burr hole either into the parenchyma or ventricle. These devices carry a minimal risk of infection and are highly reliable.

TREATMENT

ICP Management Protocols

The clinician must implement an orderly and sequential approach when managing raised ICP. Considering the sizeable number of effective treatments available, use of these should occur in a logical step-wise fashion. There are two scenarios for ICP management. First is the hyperacute situation during which brain herniation is taking place.

Treatment is an all-out approach to immediately protect the brainstem pending definitive surgical intervention or placement of an ICP monitor (Table 3). The second scenario is for the monitored patient in the ICU setting (Table 4). This algorithm should be initiated any time ICP remains greater than 20 mm Hg for more than 10 minutes.
General Measures for ICP Control

These general measures apply to all patients at risk for elevated ICP.

Head Position

Elevation of the head to 30 degrees is advised in patients with raised ICP, with one study confirming that this degree of elevation produces consistent reduction in ICP (10). Although some investigators advocate a head flat position to preserve CPP, moderate elevation is safe as long as CPP is continuously maintained at greater than 60 mm Hg.

Body Temperature

Fever may potentiate ischemic brain injury and contribute to elevated ICP. It has been demonstrated that increases in brain temperature are correlated with ICP elevations, as CBF and cerebral blood volume (CBV) increase disproportionately in relation to the cerebral metabolic rate of oxygen consumption (CMRO₂) (11). Acetaminophen and cooling blankets are the first line of therapy and should be instituted when temperature is sustained over 101°F (38.3°C). Whether the prophylactic maintenance of mild hypothermia (34-35 °C) can reduce the number of ICP crises remains unknown. Early mild-to-moderate hypothermia (32-34 °C) within 8 hours of onset has not been found to be effective for improving outcome after severe TBI, even though a modest benefit on ICP was seen (12).

Seizures

Seizures cause an increase in CMRO₂ and hence CBV. These alterations tend to be abrupt and marked, and in patients with reduced cerebral compliance, can trigger plateau waves. Patients at risk for raised ICP it is reasonable to administer prophylaxis with an intravenous anticonvulsant. In TBI patients prophylaxis was shown to reduce the frequency of seizures during the first week from 14% to 4%. Fosphenytoin or phenytoin (15-20 mg/kg bolus followed by 300 mg daily) has traditionally been the agent of choice.

Fluid Management

Historically, raised ICP had been managed by fluid restriction. It was later found that this effort to dehydrate the brain actually worsened hypoxic-ischemic injury because the hypovolemia led to reduced CPP (15). Patients with high ICP states should be kept well-hydrated with isotonic saline.

Free water in any form (e.g. 0.45% saline, D₅W, or enteral water) must be avoided because it will accumulate through an osmotic gradient in regions of injured brain, and aggravate brain swelling.
Some centers use a continuous infusion 2% or 3% saline at 1 ml/kg as an alternative to normal saline for patients at risk for ICP, directed toward establishing and maintaining a hypernatremic (goal Na$^+$ $\sim$155 mEq/L) hyperosmolar (goal osmolality $\sim$320 mOsm/L) environment for the injured brain. Whether this strategy is effective for reducing ICP crises or improving outcome, however, is unknown.

**Corticosteroids**

Corticosteroids such as dexamethasone are not effective as a general measure to treat elevated ICP, and also carry risks: the most common are nosocomial infection, hyperglycemia, impaired wound healing, muscle catabolism, and psychosis. Steroids are effective only for reducing the volume of mass lesions related to abscess or neoplasm.

**Stepwise Treatment Protocol for ICP Control in a Monitored Patient**

1. **Cranial Decompression**

Whenever a sustained ICP elevation of 20 mmHg or more occurs, the clinician should consider (or reconsider) surgical cranial decompression. A CT scan should be considered, and if increased mass effect or CSF volume is detected, surgical intervention such as CSF drainage, mass evacuation, or hemicraniectomy should be considered. CSF drainage can be accomplished with a ventricular drain or by using a lumbar spinal drain, which is safe only if the basal cisterns are open.

By opening the cranial vault, hemicraniectomy can reverse brain tissue displacement and herniation, and definitively normalizes ICP. Hemicraniectomy is increasingly being used as a final salvage therapy for patients with malignant middle cerebral artery territory infarction and other space-occupying mass lesions. It is usually considered as a definitive therapeutic option as an alternative to instituting barbiturate therapy or mild-to-moderate hypothermia. Several studies have found that hemicraniectomy improves survival after MCA infarction (14). A meta-analysis of hemi-craniection for MCA infarction found that survival with a good functional outcome is most likely among younger patients (15).

2. **Sedation**

Agitation must be avoided, because it can aggravate ICP elevation through straining (increasing thoracic, jugular venous, and systemic blood pressure) and increased CMRO$_2$. During an ICP spike, sedation must be maximized, and may be all that is necessary to control the ICP. The patient should be made quiet and motionless.
The preferred regimen is the combination of a short-acting opioid such as fentanyl (1 to 3 µg/kg/hr) or remifentanil (0.03-0.25 µg/kg/min), to provide analgesia, and propofol (0.3 to 3 mg/kg/hr), because of its extremely short half-life, which makes it ideal for periodic interruption for neurological assessments. Bolus injections of opioids, however, should be used with caution in patients with elevated ICP because they can transiently lower MAP and increase ICP due to autoregulatory vasodilation of cerebral vessels (16). Compared to an opioid-based sedation regimen, in one trial propofol was been associated with lower ICP and fewer ICP interventions in patients with severe traumatic brain injury (17).

**3. CPP optimization**

After maximal sedation, if ICP remains elevated, attention should be directed to optimizing CPP. CPP low enough to induce ischemia can trigger reflex vasodilatation and aggravate ICP elevation (24). Conversely, a high CPP (greater than 110 mm Hg) can sometimes cause breakthrough cerebral edema and also potentially elevate ICP (24) (Figure 4). For these reasons, in most cases CPP should be maintained between 60 and 110 mm Hg. Appropriate vasopressors to raise blood pressure and CPP include phenylephrine (2 to 10 µg/kg/min), dopamine (5-30 µg/kg/min), or norepinephrine (.01 to .6 µg/kg/min). Useful agents to lower blood pressure and CPP include labetolol (5-150 mg/hr) and nicardipine (5-15 mg/hr); nitroprusside should be avoided because of its dilating effects on the cerebral vasculature.

Many studies have attempted to define optimal CPP management in acute traumatic brain injury, with differing conclusions. In recent years, two distinct approaches have developed with differing views on whether CPP should be maintained at a higher or lower level. The high CPP approach, popularized by Rosner, focuses on pharmacologic means to elevate mean arterial pressure (MAP) and CPP in order to maintain adequate CBF (18,19). Support for this method comes from case series demonstrating good clinical outcomes and higher brain tissue oxygen levels with this management approach, and clinical examples demonstrating that induced hypertension can lead to the termination of plateau waves, presumably by causing reflex vasoconstriction (20). The main argument against the high CPP approach comes from a randomized trial by Robertson et al. that found no clinical benefit with CPP targeted therapy (CPP >70 mmHg) compared with traditional ICP targeted therapy (CPP >50 mmHg)(21). In this study, the high CPP approach led to fewer jugular venous desaturations, but a five-fold increase in the risk of acute respiratory distress syndrome (ARDS).

The low CPP approach, popularized in Lund, Sweden, concentrates on ICP reduction by minimizing CPP and reducing CBV and intravascular hydrostatic pressure (22). The fundamental principles of the Lund approach include the maintenance of normal colloidal pressure to prevent extravascular fluid shifts, reduction of intra-capillary hydrostatic pressure through systemic blood pressure reduction, and minimization of CBV by suppressing CMRO$_2$ with thiopental and promoting pre-capillary vasoconstriction with dihydroergotamine.
Evidence in support of the Lund approach includes case series managed according this protocol with good outcomes (22), and cerebral microdialysis studies demonstrating that significant oxidative stress in the form of increased lactate/pyruvate ratios does not consistently occur until CPP falls below 50 mm Hg (23).

It seems most likely that both the high and low CPP strategies described above are valid, depending on the individual circumstances of the patient. In this view, no single approach should be generalized to all patients; instead, CPP should be optimized based on individualized physiological monitoring. Advanced multilodality monitoring techniques such as brain tissue oxygen monitoring, jugular bulb oximetry, signal-processed EEG and microdialysis may eventually allow clinicians to fine tune CPP based on the specific physiological circumstances in a particular patient at a any given point in time.

4. **Osmotherapy**

If CPP is optimized, the patient is sedated, and ICP remains elevated, osmotherapy should be initiated. Mannitol, given in a 20% solution at a dose of 0.25 to 1.5 g/kg, mediates an ICP lowering effect through two mechanisms. First, it is an osmotic diuretic that creates a concentration gradient across the blood-brain barrier, and pulls free water from the brain. This decreases brain volume and lowers ICP (20). Also, mannitol increases CPP through plasma expansion, and promotes vasoconstriction and CBV reduction by decreasing blood viscosity and improving CBF (24). Mannitol can lower ICP within minutes. It should be given in a single rapid bolus (.25 gm/kg to 1.5 gm/kg), and may be repeated as frequently as once an hour when ICP is elevated. Complications of mannitol therapy include dehydration and renal failure. A widened gap >10 mOsms between the measured and calculated osmolality may indicate incomplete mannitol clearance by the kidneys and an increased risk of renal tubular necrosis.

Hypertonic saline (2 to 5 ml/kg of 7.5% saline, or .5 to 2 ml/kg of 23.4% saline, over 30 minutes) is an alternative to mannitol for treating acutely elevated ICP. It has been shown to be at least as effective (25,26) for acutely lowering ICP, and has the advantage of boosting MAP, CPP and intravascular volume when patients are dehydrated. The main complication specific to hypertonic saline therapy is congestive heart failure due to fluid overload.

At this time there is insufficient data to suggest one concentration or method (continuous or bolus) over another. Hypertonic saline bolus therapy does appears to be as effective as mannitol in reducing refractory elevated ICP and improving CPP transiently. However, many issues remain to be clarified including the exact mechanism of action of hypertonic saline, the best mode of administration and concentration, and its risks and complications.

5. **Hyperventilation**

Hyperventilation has long played a role in ICP therapy. A decrease in pCO₂ causes vasoconstriction, which lowers cerebral blood volume (CBV) and thus ICP. The effect is immediate, but often shortlived, with a steady loss of within 1 to 24 hours.
In conditions characterized by excessive vasodilation and cerebral hyperemia, the effect of hyperventilation may be sustained for days. Intracranial pressure is directly related to CBV. Hyperventilation acts by directly reducing cerebral blood flow (CBF) through vasoconstriction. A reduction of CBF could potentially limit blood flow to ischemic areas of brain with only a modest reduction in ICP through its indirect effects on CBV.

Recent studies have demonstrated a risk of exacerbation of cerebral ischemia with ongoing hyperventilation. The routine application of extreme hyperventilation (<30 mm Hg) within the first few hours of TBI is generally considered harmful because of the risk of exacerbation of ischemia (27).

If necessary, jugular venous oxygen saturation or brain tissue oxygen monitoring can be used as a guide during hyperventilation to ensure adequate brain oxygen delivery (28,29).

6. Pentobarbital infusion

Failure of hyperventilation and mannitol to control ICP should prompt consideration of the initiation of pentobarbital infusion (30). Consideration of pentobarbital in this setting should also trigger reconsideration of performing hemicraniectomy or the application of hypothermia. The mechanism of action of pentobarbital is a profound reduction of cerebral metabolic rate. Pentobarbital can be given in repeated 5 mg/kg boluses every 15 to 30 minutes until ICP is controlled (usually 10 to 20 mg/kg is required), and then continuously infused at 1 to 4 mg/kg/hr. An electroencephalogram (EEG) should be continuously recorded, and the pentobarbital titrated to produce a burst-suppression pattern, with approximately 6 to 8 second interbursts, to avoid over-medication. The most common complication of pentobarbital therapy is hypotension, and vasopressors are usually needed for hemodynamic support. Ileus may occur as well, and feeding may have to be given parenterally during treatment.

7. Hypothermia

If pentobarbital fails to control ICP, induced hypothermia to 32-34 °C can effectively lower otherwise refractory ICP. Hypothermia reduces ICP by lowering CMRO$_2$ requirements and thus CBV. The recommended temperature goal is 32-34 °C, so-called mild-to-moderate hypothermia, because there are fewer complications than at lower temperatures. Hypothermia can be achieved using various surface and endovascular cooling methods coupled to a rectal, esophageal, pulmonary artery, or bladder thermometer. Rapid infusion of large volume cold fluids (30 ml/kg of 0.9% saline cooled to 5 °C) may be suitable for core cooling. Hypothermia has been demonstrated to control ICP in a small series of patients refractory to pentobarbital (31), but large controlled studies are lacking. Common complications of hypothermia include nosocomial infection, hypotension, cardiac arrhythmias, coagulopathy, shivering, hyperkalemia, hyperglycemia, and ileus. Particular caution should be exercised when rewarming patients, because rebound ICP readily occurs. Rewarming must be done slowly (0.10 to 0.33 °C per hour) and in a controlled fashion.
### TABLE 1: Conditions Associated with Increased ICP

<table>
<thead>
<tr>
<th>I. Intracranial mass lesions</th>
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<tr>
<td>Subdural hematoma</td>
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<td>Epidural hematoma</td>
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<td>Brain tumor</td>
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<td>Cerebral abscess</td>
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<td>Intracerebral hemorrhage</td>
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<th>II. Increased brain volume (cytotoxic edema)</th>
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<tr>
<td>Cerebral infarction</td>
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<tr>
<td>Global hypoxia-ischemia</td>
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<tr>
<td>Reye's syndrome</td>
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<td>Acute hyponatremia</td>
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<th>III. Increased brain and blood volume (vasogenic edema)</th>
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<tr>
<td>Hepatic encephalopathy</td>
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<td>Traumatic brain injury</td>
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<td>Meningitis</td>
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<td>Encephalitis</td>
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<tr>
<td>Hypertensive encephalopathy</td>
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<tr>
<td>Eclampsia</td>
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<tr>
<td>Subarachnoid hemorrhage</td>
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<td>Dural sinus thrombosis</td>
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<td>Eclampsia</td>
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<th>IV. Increased CSF volume</th>
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<tr>
<td>Communicating Hydrocephalus</td>
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<tr>
<td>Non-communicating Hydrocephalus</td>
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<tr>
<td>Choroid Plexus Papilloma</td>
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### TABLE 2: Herniation Syndromes

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<tr>
<th>TYPE</th>
<th>CLINICAL HALLMARK</th>
<th>CAUSES</th>
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| Uncal (lateral transtentorial) | • Ipsilateral CN 3 palsy  
• Contralateral or bilateral motor posturing | Temporal lobe mass lesion           |
| Central transtentorial      | • Progression from bilateral decorticate to decerebrate posturing  
• Rostral-caudal loss of brainstem reflexes | Diffuse cerebral edema, hydrocephalus |
| Subfalcine                  | • Asymmetric (contralateral > ipsilateral) motor posturing  
• Preserved oculocephalic reflex | Convexity (frontal or parietal) mass lesion |
| Cerebellar (upward or downward) | • Sudden progression to coma with bilateral motor posturing  
• Cerebellar signs | Cerebellar mass lesion              |

### TABLE 3: Emergency measures for ICP reduction in an unmonitored comatose patient with clinical signs of herniation

1. Elevate head of bed 30-45 degrees
2. Normal saline (0.9%) at 80-100 cc/hr (avoid hypotonic fluids)
3. Intubate and hyperventilate (target pCO2 = 28-32 mm Hg)
4. Mannitol 20% 1-1.5 g/kg via rapid IV infusion
5. Foley catheter
6. CT scan and immediate neurosurgical consultation
TABLE 4: Stepwise treatment protocol for elevated ICP (>20 mmHg for >10 minutes) in a monitored patient

1. Consider repeat CT scanning and surgical removal of an intracranial mass lesion, or ventricular drainage
2. Intravenous sedation with fentanyl and propofol to attain a motionless, quiet state
3. Reduction of blood pressure if CPP remains >110 mmHg, or pressor infusion if CPP <70 mmHg
4. Mannitol .25-1 g/kg IV (repeat every 1-6 hours as needed)
5. Hyperventilation to pCO2 levels of 28-32 mmHg
6. High dose pentobarbital therapy (load 5-20 mg/kg and infuse 1-4mg/kg/hr)
7. Hypothermia with external cooling to 32-34° C

Refer to text for details

FIGURES

Figure 1. Intracranial pressure-volume curve. At point A, on a flatter portion of the curve, the amplitude of the arterial reflection in the ICP waveform is small (inset), and the addition of the same amount of volume leads to a smaller increase in pressure (A'). At point B, on a steep portion of the curve, the intracranial compartment is relatively noncompliant, the amplitude of the arterial reflection in the ICP waveform is large (inset), and the addition of volume leads to a large increase in pressure.
Figure 2. Pathologic ICP waves. A, Lundberg A (plateau) wave. B, Lunberg B waves.

**Figure 4.** Cerebral autoregulation curve (black line) and relationship between CPP and ICP in states of abnormal intracranial compliance (grey line). Under normal circumstances CBF is held constant across a wide range of CPP (50-150 mmHg), and changes in vessel caliber have no effect on ICP. In disease states with reduced intracranial compliance, however, ICP can become elevated when CPP is low due to autoregulatory vasodilation and increased CBV (vasodilatory cascade physiology), or when CPP is too high due to passive increases in CBV due to increased hydrospatic pressure and hyperemia (autoregulation breakthrough physiology).

**REFERENCES**


