INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and disability around the world and presents a major worldwide social, economic, and health problem.[1] It is the number one cause of coma and is the leading cause of brain damage in children and young adults.[2] In Europe it is responsible for more years of disability than any other cause.[3]

Epidemiology of head injury

The number of patients with TBI presenting to the hospital vary widely in accordance with hospitals admission policies and capabilities. Typical figure of all-case head injury admission in developed countries range from 200 to 300 per 100 000 patients per year.[4] Causes include road traffic accidents (RTA), falling from height, sport injuries, and assault.[5]

TBI accounts for approximately 40% of all deaths from acute injuries in the United States. Annually, 200,000 victims of TBI need hospitalization, and 1.74 million persons sustain mild TBI requiring an office visit or temporary disability for at least 1 day. The financial cost is estimated at approximately $4 billion per year.[6]

In Egypt, RTA is the leading cause of TBI, 70% of accidents are due to ignorance and carelessness, and 30% are the result of mechanical problems and poor road conditions. These include insufficient pedestrian crossing facilities and deficient traffic signs at intersections.[7]

The situation in Egypt is serious and getting worse year by year, especially exacerbated by the progressing density of traffic, with an annual increase of 80,000 vehicles.[7]

The risk of experiencing TBI is not equally divided among all age groups. Adolescents, young adults and persons older than 70 years have the highest risk of TBI. Because TBI is more common in young people, its costs to society are high due to the loss of productive years to death and disability.[8]

Regardless of age, TBI rates are higher in males. Men suffer twice as many TBIs as women do and have a fourfold risk of fatal head injury.[9] Socioeconomic status also appears to affect TBI rates; people with lower levels of education and employment and lower socioeconomic status are at greater risk.[10]

Classification of TBI:

Head injuries most often have been classified according to:

(1) Severity.
(2) Mechanism.
(3) Pathology.
(4) Pattern of injury.
(5) CT findings.

1- Classification by injury severity:

Severity of head injuries can be classified into mild, moderate and severe categories according to Glasgow Coma Score (GCS).[11]

Traumatic brain injury represents a range of injury from mild head injury (GCS 13 to 15) that may be fully recovered to moderate head injury (GCS 9 to 12) and severe injury (GCS 8 or less) associated with high mortality or high rate of disability.[12] Although the majority of head injury (70-80%) is minor, a significant proportion of these patients may have poor functional outcomes duo to secondary insults, missed injuries and co-morbidities. Of the 20-30% who constitute moderate and sever head injury, approximately 10% of these are dead on admission, while the remainders will usually require admission to the intensive care unit (ICU) for management in the first 7-10 days.[11]

Table (1): Glasgow Coma Scale[11]:

Glasgow Coma Scale		**Score**
Eye opening	spontaneously	4
	To speech	3
	To pain	2
	None	1
Verbal response	Oriented	5
	Confused	4
	Inappropriate wards	3
	Incomprehensible sounds	2
	None	1
Motor response	Obeys commands	6
	Localizes to pain	5
	Withdraws from pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1
Maximum score		15

2- Mechanism related classification:

Head injuries can be classified according to whether the head is struck or strikes an object (contact or impact loading) and/or the brain moves within the skull (noncontact or inertial loading). The magnitude and direction of each type or combination of loading forces may predict type and severity of injury. There is considerable but not perfect correlation between physical mechanism of injury and the resulting pathological

features.[13] For instance, most focal injuries, such as skull fracture, brain contusion, and epidural hematoma, result from impact loading, whereas inertial loading generally causes more diffuse injuries such as concussion and diffuse axonal injury (DAI).[13] Also TBI is divided into closed and penetrating head injury.[3] A closed injury occurs when the brain is not exposed. While penetrating head injury occurs when an object pierces the skull and breaches the dura mater.[14]

3- Pathological classification:

TBI can be classified according to its pathological features. Lesions can be extra-axial, (occurring within the skull but outside of the brain) such as subdural, extradural, subarachnoid, and intraventricular hemorrhage, or intra-axial (occurring within the brain tissue) such as brain contusions, lacerations, and hematomas.[15,16] Damage from TBI can be focal or diffuse, confined to specific areas or distributed in a more general manner, respectively. However, it is common for both types of injury to exist in a given case.[17]

4- Classification by pattern of injury:

It divides TBI into primary and secondary brain injuries.

Primary brain injury:

It is the damage that occurs at the moment of trauma when tissues and blood vessels are stretched, compressed and torn.[17]

Primary brain injury is the result of acceleration-deceleration forces that result from the impact during falls and motor vehicle accidents. The resulting tissue deformation may cause axonal dysfunction and injury, brain contusions, epidural, subdural, subarachnoid or parenchymatous hemorrhages.[17]

This macroscopic injury is associated with microscopic changes and metabolic derangements including ischemic cytotoxic edema, astrocyte swelling with microvascular occlusion or dysfunction, and blood brain barrier disruption.Theses initial injury processes are closely linked with early gene activation which results in subsequent recruitment of inflammatory cells and repair mechanisms.[18]

Secondary brain injury:

It is a complex set of cellular processes and biochemical cascades that occur in minutes to days following the trauma.[18] These secondary processes can dramatically worsen the damage caused by the primary injury [19] and accounts for the greatest number of TBI deaths occurring in hospitals.[20]

Ischemia has been implicated as a major cause of secondary brain injury and death following TBI.[21] Inadequate oxygen supply to the traumatized brain results in the conversion of aerobic metabolism to anaerobic metabolism. Anaerobic metabolism results in acidosis and depletion of cellular energy.[22] As the demands for energy production are no longer met, the brain cells lose their ability to maintain ionic homeostasis.[22] Abnormally high intracellular concentrations of calcium result. A combination of cellular acidosis and excessive concentrations of calcium activate various important intracellular proteins. This abnormal cellular environment results in the release of excitatory amino

acids and in the formation of highly reactive free radicals that are extremely damaging to cell membranes.[23] The high levels of calcium also have been shown to lead to excessive calcium being absorbed on neuronal mitochondria membranes leading to the impairment of mitochondrial respiratory chain-linked oxidative phosphorylation leading to further functional failure of aerobic metabolism. Mitochondrial dysfunction can persist for days following the initial insult.[24]

Paradoxically, during this early phase of injury, metabolic needs of the injured brain tissue are increased and cerebral blood flow and oxygen delivery are decreased. This results in what is called a "flow/metabolism mismatch". Oxygen delivery to the brain tissue is impaired not only by decreased cerebral blood flow but also by reduced oxygen diffusion into cells caused by vasogenic and cytotoxic edema.[24]

Ischemia leads to anaerobic metabolism with increased lactate production and cellular acidosis. Many studies indicate that increased cerebrospinal fluid (CSF) lactate product is a marker for this anaerobic metabolism status caused either by a lack of oxygen and/or damage to the mitochondria. A continued high level of lactate in the brain has been shown to be a poor prognostic indicator after brain injury.[25]

The time from the primary brain injury to the occurrence of irreversible cell damage resulting from ischemia and hypoxia varies considerably, depending upon the severity of the injury and the degree of hypoxia.[26]

Predisposing factors of secondary brain injury:

I-Hypotension:

Systemic hypotension is a major contributor to secondary brain injury and is found in at least one third of patients who presents with severe TBI.[27]

During the first 24 hours after severe head injury, cerebral blood flow (CBF) is less than half of that of normal individuals and may approach to ischemic threshold. The reduction in CBF following trauma together with the vulnerability of the traumatized brain to ischemia makes hypotension a potentially lethal complication.[28]

It has been proven that hypotension is associated with great increase in morbidity and doubling the mortality in severe TBI.[27] Studies have proposed that one attack of hypotension was among the most powerful predictors of poor outcome.[29]

The normal amount of cerebral blood flow (CBF) equals to 750 ml/min this is 50-54 ml blood/100 gm of brain tissue per minute.[30] Critical levels of hypotension were identified as 20 ml/100 gm of brain tissue/min with failure of electrical activity occurring at 15-20 ml/100 gm/min, and failure of energy metabolism at 10 ml/100gm/min.[31]

II-Hypoxia and anemia:

Traumatic brain injury is characterized by imbalance between cerebral oxygen delivery and cerebral oxygen consumption that leads to brain tissue hypoxia.[21] Measurements of brain tissue oxygen tension ($PtiO_2$) has identified the critical threshold for $PtiO_2$ as 10-15 mmHg, below which infarction of neuronal tissue occur.[32] Normally the brain compensates for hypoxia by cerebral vasodilatation on the account of increasing

cerebral blood volume (CBV) and intracranial pressure (ICP) and when the compensatory mechanisms are fully mobilized; further decrease in oxygen supply will result in hypoxia of the brain tissue.[31]

Hypoxia may occur as a result of obstructed airway duo to hypotonia or a foreign body, central depression of respiration secondary to loss of consciousness, chest injury, aspiration of gastric contents, neurogenic pulmonary edema or any combination of the above.[28]

Hypoxia is among the powerful predictors of poor outcome, that should be corrected as soon as possible with establishing clear airways and ensuring adequate breathing.[29]

III- Hypocapnia and hypercapnia:

Hypercapnia has long been known to increase CBV and CBF, which may lead to increased ICP due to reduced intracranial compliance, while hypocapnia may reduce CBF and CBV, worsening the ischemic damage and shifting O_2 dissociation curve to the left making O_2 release to the tissues more difficult.[33]

IV- Hyperthermia and hypothermia:

After TBI, fever frequently develops secondary to infection, thrombophlebitis, drug reaction or defect in central thermoregulatory system. Moreover, some studies found that brain temperature exceeds systemic temperature in head injured patients.[34] Severe hypothermia < 32 C should be avoided in patients with TBI as it may be associated with ventricular fibrillation (VF), cardiac asystole, respiratory failure , coagulopathy and ileus.[35]

V- Hyperglycemia and hypoglycemia:

Hyperglycemia has been associated with exacerbation of brain damage with both head trauma and ischemia. In patients with TBI, approximately 50% of patients present with blood glucose > 200 mg/dl. Peak levels greater than that are associated with significantly worse outcome up to 1 year post-injury.[36] Hypoglycemia should be carefully watched in TBI patients as it was found to decrease seizure threshold and worsen neurological damage.[37]

VI-Acid base and electrolyte disturbances:

Acidosis may increase CBF and ICP while alkalosis may decrease CBF and worsen the ischemic damage.[38] Patients should be kept with normal PH unless hyperventilation is to be done for refractory increased ICP.[33]

Hyponatremia after TBI (due to cerebral salt wasting (CSW), syndrome of inappropriate anti-diuretic hormone secretion (SIADH), or hypopituitarism or hypovolemia) may decrease seizure threshold and exacerbate brain edema.[39]

Patients with severe TBI have a higher risk of developing hypernatremia over the course of their ICU stay, due to the coexistence of predisposing conditions such as impaired sensorium, altered thirst, central diabetes insipidus (CDI) with polyuria and increase insensible losses. Unless properly corrected it may worsen the outcome as it was shown that people with TBI that developed hypernatremia have a higher mortality than those who did not.[40]

5- CT based classification:

Marshall and colleagues devised a CT-based classification scheme that proved prognostically useful.[41]

Table (2): Marshall's classification of CT brain findings in head trauma.

Category	Definition
• Diffuse injury I	No visible intracranial pathology
• Diffuse injury II	Cistern present, with midline shift 0 to 5 mm; no high density lesion > 25 ml
• Diffuse injury III (swelling)	Cisterns compressed or abscent, with midline shift 0 to 5 mm; no high density lesion > 25 ml
• Diffuse injury IV (shift)	Midline shift> 5mm; no high density lesion > 25ml
• Evacuated mass lesion	Any lesion surgically evacuated
• Non-evacuated mass lesion	High density lesion > 25 ml ; not surgically evacuated

Signs and symptoms of TBI:

Symptoms are dependent on the type of TBI (diffuse or focal) and the part of the brain that is affected.[42] Unconsciousness tends to last longer for people with injuries on the left side of the brain than for those with injuries on the right.[15] Symptoms are also dependent on the injury's severity. With mild TBI, the patient may remain conscious or may lose consciousness for a few seconds or minutes. Other symptoms of mild TBI include headache, vomiting, nausea, lack of motor coordination, dizziness, difficulty balancing, lightheadedness, blurred vision or tired eyes, ringing in the ears, bad taste in the mouth, fatigue or lethargy, and changes in sleep patterns. Cognitive and emotional symptoms include behavioral or mood changes, confusion, and trouble with memory, concentration, attention, or thinking.[43]

A person with a moderate or severe TBI may have a headache that does not go away, repeated vomiting or nausea, convulsions, an inability to awaken, dilation of one or both pupils, slurred speech, aphasia , dysarthria, weakness or numbness in the limbs, loss of coordination, confusion, restlessness, or agitation. Common long-term symptoms of moderate to severe TBI are changes in appropriate social behavior, deficits in social judgment, and cognitive changes, especially problems with sustained attention, processing speed, and executive functioning.[43]

When the pressure within the skull (intracranial pressure) rises too high, it can be deadly. Signs of increased ICP include decreasing level of consciousness, paralysis or weakness on one side of the body, and a blown pupil, one that fails to constrict in response to light or is slow to do so. Cushing's triad, a slow heart rate with high blood pressure and respiratory depression is a classic manifestation of significantly raised ICP. Anisocoria, unequal pupil size, is another sign of serious TBI.[44]

Abnormal posturing, a characteristic positioning of the limbs caused by severe diffuse injury or high ICP, is an ominous sign.[44]

Assessment of head injured patient:

1- Primary trauma survey:

The widespread knowledge of the American College of Surgeons Advanced Trauma Life Support (ATLS) courses improved the initial management of trauma victims. This approach is based on the identification of the sequential variables that could cause the victim's death. It includes[45]:

A: airway with cervical spine conrol.
B: breathing (ensure adequate breathing)
C: circulation (maintenance of blood pressure, control of hemorrhage)
D: disability (assessment of the level of consciousness)
E: examination from head to toe

2- Secondary trauma survey[45]:

After stabilization of the patient, a secondary survey of the patient includes:

- Obtaining history including time and mechanism of injury and the presence of any past medical disease.
- Conducting "head to toe" examination with systemic approach in order not to miss any associated injuries.
- Neurological assessment and estimation of the level of consciousness with GCS (table 1) as the most widely used method, pupils size and reactivity as well as ocular movements which provide important information about the brain and brain stem functions.

Radiological studies:

1- Plain skull radiography:

The role of skull X-ray in head injury has assumed progressively less importance with the wide spread availability of computerized tomography (CT) scanning. The value of plain skull films is in the diagnosis of skull fractures and occasionally to help localize intracranial foreign bodies as missile fragments.[46]

2- Computed tomography (CT scan):

CT scan without contrast enhancement that extends from the skull base to the vertex defines intracranial lesions and determines whether urgent neurosurgical intervention is required. Obtaining both brain and bone windows helps in determination of the etiology and significance of focal neurological findings and whether a skull fracture is present.[41]

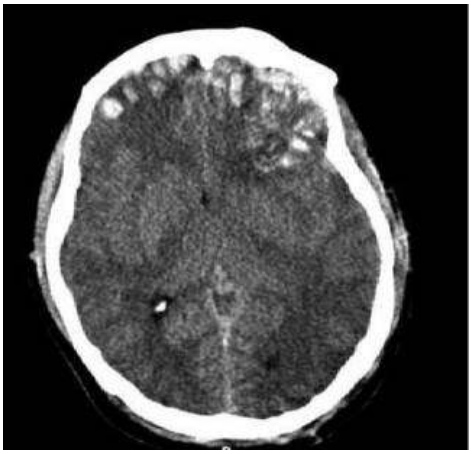

Figure (1): CT scan showing cerebral contusions, hemorrhage within the hemispheres, and subdural hematoma.

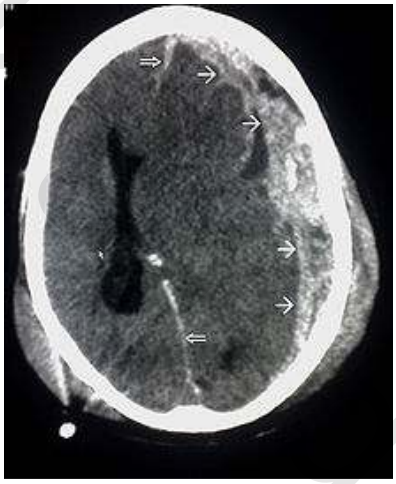

Figure (2): CT scan Spread of the subdural hematoma and midline shift.

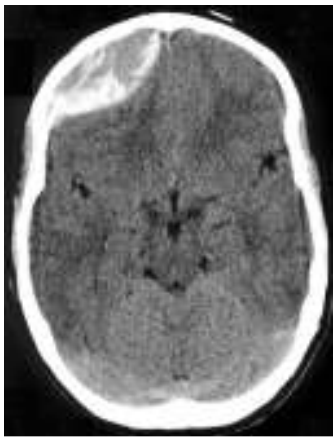

Figure (3): CT brain showing sizable extradural hematoma.

3- Magnetic resonance imaging (MRI)

MRI has been used on limited basis with head injured patients. MRI is better than CT scan in detecting some types of small extra-axial fluid collection and parenchymal injuries. However, it offers no advantage in detecting hematomas requiring surgical intervention. A potential application is to inprove identification of parenchymal changes following mild and moderate head injury that have been shown to correlate with neuropsychological sequel of head injury.(47)

4- Other studies include:

a- Transcranial Doppler ultrasonography:

Transcranial Doppler provides a great potential in cerebrovascular investigations for assessment of cerebrovascular autoregulatory reserve, reactivity,cerebral perfusion pressure, cerebral hyperemia, post-traumatic spasm and in estimation of cerebral tamponade.(48)

b- Laser Doppler flowmetry:

It provides real time measure of relative changes in capillary perfusion, which is suitable for assessing the microcirculatory response to therapeutic challenge.(49)

c- Transcranial near-infrared spectroscopy:

It is used to detect accurately the presence of an acute intracranial hematoma in head injured patients. So this procedure may have its greatest use in the hemodynamically unstable patients.(50)

d- **Positron Emission Tomography (PET scan):**

Many of the research work in brain metabolism has involved the use of PET tracers such as short lived tracers labeled with carbon-11 or flow studies using oxygen-15 labeled water as a marker.(50)

e- **Electroencephalography (EEG), Evoked potentials** (visual, auditory, somatosensory) could also be used as adjunctive measures.(51)

f- Cerebral microdialysis

The technique of microdialysis enables sampling and collecting of small-molecular-weight substances from the interstitial space. Cerebral microdialysis (MD) has been used to monitor patients with TBI for over a decade, but the methodology has not yet found a clear place in the intensive care unit.(52) The commonly monitored parameters that are advocated to follow dynamic metabolic changes in viable but vulnerable tissue (and their current predominant interpretations) are lactate, pyruvate, glucose, glutamate (excitotoxic marker) and glycerol (phospholipid degradation as a marker of cell breakdown and death).(52)

g- Lactate oxygen index (LOI):

Lactate oxygen index is the ratio between jugular-arterial lactate difference and arterio-jugular oxygen content difference.[53]

Levels of jugular venous bulb oxygen saturation ($SjvO_2$) and lactate have been proposed as indicators of cerebral ischemia and prognosis.[54] Lactate-oxygen index uses both parameters for better assessment of changes in brain metabolism.[53] It is measured by the following calculation:

$$\frac{(\text{Lactate})\text{jv} - (\text{lactate})\text{art}}{(\text{Hbx1.34xSaO2})(0.003\text{xPaO2}) - (\text{Hbx1.34xSvO2})(0.003\text{xPvO2})}$$

Where: Hb: hemoglobin, (lactate)jv: lactate concentration in the juglar venous bulb, (lactate)art: lactate concentration in the arterial blood, $SaO_{2:}$ arterial oxygen saturation, $SvO_{2:}$ jugular bulb venous oxygen saturation, $PaO_{2:}$ arterial oxygen tension, $PvO_{2:}$ jugular bulb oxygen tension

Treatment of TBI

It is important to begin emergency treatment within the so-called "golden hours" following the injury. The management of the primary insult comprises providing the injured brain the best possible physiological milieu that allows the recovery of the sublethally injured neurons.(55)

Whilst the management of the acutely head injured patient depends primarily on the prevention of secondary insults and if these eventually happen, timely diagnosis and management of these secondary insults. Surgically correctable intracranial lesions should be recognized early and treated accordingly. On the other hand, concomitant injuries should be recognized and stabilized.(55)

I. Prehospital Care:

The pre-hospital phase is an important interval in determining the ultimate outcome after TBI. The initial goals are to maintain a patent airway, begin fluid resuscitation and proper immobilization technique at the accident site and during patient transport.(56) All patients with a suspected spinal cord injury are immobilized in a rigid cervical collar and placed on a spine board for transport.(57)

II. In hospital management:

1- Airway and breathing:

Early endotracheal intubation should be performed for patients with a GCS of 8 or less, or are unable to protect their airways. Extreme caution must be exercised when intubating head injured patients as evidence suggests that the prevalence of cervical spine injury is fourfold to eightfold higher in patients with concomitant head injuries . Orotracheal intubation allows for airway protection in patients who are severly obtuned and allows for better control of oxygenation and ventilation.(58)

Rapid sequence intubation should be performed to all head injured agitated or combative patients. If possible, a brief neurologic examination should be performed before the patient is given any sedative or neuromuscular blocking agents. Nasotracheal intubation should be avoided because of the risk of direct intracranial injury, especially in patients with basilar skull fractures.(59)

2- **Oxygenation** should be monitored and hypoxia (PaO_2<60 mm Hg or saturation <90) should be avoided.(59)

3- **Blood pressure** should be monitored and hypotension should be avoided.(60)

Aggressive fluid resuscitation with isotonic fluids until euvolemia is achieved. Isolated TBI rarely leads to severe hypotension. Other possible injuries (e.g. spinal cord trauma), ongoing occult blood loss, and reasons for cardiac tamponade, including hemothorax or pneumothorax, should be identified and quickly treated.(60)

4- **Hypercarbia and hypoxia** must be avoided. In the initial resuscitation period, efforts should be made to maintain eucapnia at the low end of the reference range ($PaCO_2$ of 35-40 mmHg) and prevent hypoxia to prevent or to limit secondary brain injury.(61)

5- **Fever (**temperature >38 C) is not uncommon following TBI. Temperature control through the treatment of fever can aid in decreasing systemic and cerebral metabolic requirements. Fever also decreases the seizure threshold. Efforts should be made to avoid hyperthermia using medications and cooling devices.(61)

6- **Sedation and analgesia** are also important adjuncts to minimize the increase in ICP. However, sedatives and analgesics must be judiciously chosen to prevent unwanted side effects (e.g. hypotension). Short acting and reversible medications, such as fentanyl, are commonly used. Short acting benzodiazepins, such as midazolam, are also commonly used and have the added benefit of increasing the seizure threshold.(62)

7- Measures to decrease the intracranial pressure (ICP):

As the cranial vault is essentially a closed, fixed, bony box, its volume is constant. This volume was described by Monro-Kellie in the early part of the 19th century (63):

Intracranial volume (constant) = volume of brain + volume of CSF + volume of blood + volume of blood vessels.

As all theses components are fluids, and non-compressible, once the cranial vault is filled (as in intracranial hemorrhage or brain edema), its pressure rises dramatically.(63) This intracranial pressure rise can lead to interruption of cerebral blood flow by reducing cerebral perfusion pressure which depends on both intracranial pressure and mean arterial blood pressure.(64)

Cerebral perfusion pressure = mean arterial blood pressure – intracranial pressure.

As an intracranial mass lesion or edematous brain expands, some compensation is possible as Cerebrospinal fluid (CSF) and blood move into the spinal canal and extra cranial vasculature respectively. Beyond this point, further compensation is impossible and ICP rises dramatically.(64)

The normal ICP is 5-10 mmHg. Intracranial hypertension is defined as sustained ICP greater than 20 mmHg. Several clinical studies have found that mortality and morbidity increase significantly when the ICP persistently remains above this threshold.(65)

Indications of intracranial pressure monitoring (66):

1- Comatose head injury patients (GCS 3-8) with abnormal CT scan.
2- Comatose patients with normal CT scan if they have two or more of the following features on admission:

   a- Age over 40.
   b- Unilateral or bilateral motor posturing.
   c- A systolic blood pressure of less than 90 mmHg.

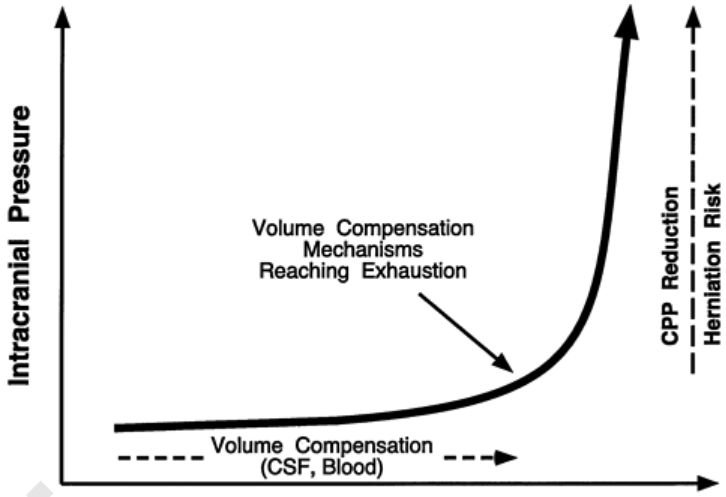

Figure (4): Pressure volume curve.

The spaces most frequently monitored are [66]:

1- Intraventricular spaces.
2- Subarachnoid spaces.
3- Subdural space.
4- Epidural space.
5- Intraparenchymal space.

Recommendations for intracranial pressure monitoring technology:

In patients who require ICP monitoring, a ventricular catheter connected to an external strain gauge transducer or catheter tip pressure transducer device is the most accurate reliable method of monitoring ICP and enables therapeutic CSF drainage.[67] Clinically significant infections or hemorrhage associated with ICP devices are rare and should not deter the decision to monitor ICP.[68] Parenchymal catheter tip pressure transducer devices measure ICP similar to ventricular ICP devices but have the potential for significant measurement differences and drift due to the inability to recalibrate.[68] These devices are advantageous when ventricular ICP is not obtained or if there is obstruction in the fluid couple. Subarachnoid or subdural coupled devices and epidural ICP devices are currently less accurate.[67]

Treatment of intracranial hypertension:

Treatment of patients with intracranial hypertension should proceed in a stepwise manner and measures be instituted immediately.

Basic measures of increased ICP control are [61]:

a. Keeping the head elevated at 45 degrees and in neutral position.
b. Adequate analgesia and sedation.
c. Good control of fever.
d. Effective seizure management.

If these are not adequate, further management includes:

A- Osmotherapy

Hemodynamic and osmotic effects of osmotic agents induce ICP reduction and CBF increase (in areas of preserved autoregulation). Ideally, an osmotic agent should reduce ICP while preserving or improving cerebral perfusion pressure (CPP).

Mannitol is widely used in the control of raised ICP following TBI. It may act by immediate plasma expansion, which reduces the haematocrit, increases the deformability of red blood cells and thereby reducing blood viscosity, increases CBF and increases cerebral oxygen delivery. Another action of mannitol is its osmotic effect that creates a fluid gradient out of cells, with consequent dieresis. This osmotic effect initially decreases intracellular edema, thus decreasing ICP.[69,70]

Over time, mannitol may accumulate in the brain and result in reverse osmotic shift potentially increasing ICP (rebound brain edema).

Mannitol is given as an intravenous rapid infusion of 0.25 to 1 gm per kg per dose and will maximally reduce the ICP within 10 minutes of administration. The reduction in ICP usually persists for 3 to 4 hours. However the main concern of mannitol is lowering blood pressure and consequently CPP through its diuretic effect.[71]

Hypertonic saline typically 3% saline can be used for lowering ICP. The principle effect is through osmotic mobilization of water across the intact blood brain barrier (BBB) which reduces cerebral water content.[72,73] Moreover, effects on the microcirculation by dehydrating endothelial cells and erythrocytes which increases the diameter of the vessels and deformability of erythrocytes and leads to plasma volume expansion with improved blood flow.[74]

Risks of hypertonic saline administration include rebound intracranial hypertension after withdrawal of therapy and central pontine mylinolysis.[73]

Furosemide is used in the management of increased ICP. As a loop diuretic, it decreases CSF production and increases serum osmolarity by increasing the free-water clearance by the kidneys. Given along with mannitol, furosemide results in a greater (62% vs. 57%) and more sustained (5 hours vs. 2 hours) decrease in ICP than mannitol alone.[75]

B- Hyperventilation:

In cases of refractory intracranial hypertension, mild hyperventilation ($PaCO_2$ <30 mmHg) may be necessary in emergency situations such as impending herniation, it is not commonly used as a prolonged therapy for the reduction of ICP due to its association with decreased cerebral blood flow as it causes cerebral vasoconstriction and consequently augmenting brain ischemia.[76]

C- Barbiturates:

Barbiturate coma which decreases the basal metabolic rate of the brain is another treatment modality that has been used to lower ICP in TBI patients. This class of medications suppresses cerebral metabolism, thus decreasing oxygen demand. Barbiturates

also have the added benefit of neuroprotection through mechanisms such as inhibition of free radical lipid peroxidation and neuronal membrane disruption.(77)

Treatment with barbiturates is indicated in non responders who are patients with a positive gain in ICP/CPP without a decrease in arterial pressure.(77)

Mechanical ventilation (MV) and electroencephalogram (EEG) monitoring are recommended during that. Complications occurring during treatment with barbiturate coma have been reported to include hepatic dysfunction in 87%, hypokalemia in 82%, respiratory complications in 76%, hypotension in 58%, infections in 55% and renal dysfunction in 47% of the patients. Also the ability to perform neurological examination is lost during barbiturate coma.(78)

D- Therapeutic hypothermia:

First reported as a treatment for brain injury in the 1950s, induced or therapeutic hypothermia has remained a controversial issue in the debate concerning the management of elevated ICP.(79)

Hypothermia decreases cerebral metabolism and may reduce CBF and ICP. Initial studies were limited by systemic side effects, including cardiac arrhythmias and severe coagulopathy. However, later work has demonstrated that hypothermia can lower ICP and improve patient outcomes up to six months after injury.(80)

Hypothermia may also be effective in lowering ICP after other therapies have failed. The body temperature is lowered to 32 to 33 C as soon as possible and kept at that temperature for 24 to 48 hours using surface cooling techniques.(80)

E- Drainage of cerebrospinal fluid (CSF):

Ventriculostomy catheter as a gold standard for monitoring of ICP allows evacuation of CSF for treatment of intracranial hypertension. Potential complications include trapping a ventricle, infection or hemorrhage.(81)

F- Decompressive craniotomy:

Prompt evacuation of surgical mass lesion is clearly beneficial for treatment of intracranial hypertension and clinical outcome. But the role of decompressive surgical procedure as a specific treatment modality for intracranial hypertension remains controversial. No clearly defined indications are presently available.(81)

Neurosrgical consultation:

Once the patient's condition is stabilized, early neurosurgical consultation is required. The critical factors in deciding whether to proceed directly with surgical evacuation of an intracranial hematoma are the patient's neurological status and CT scan findings.

In general, any acute traumatic extra-axial hematoma more than or equal 1 cm in thickness warrants evacuation. A subdural or epidural hematoma more than 5 cm in thickness with an equivalent midline shift in a comatose patient should be evacuated urgently. Surgical repair is also required in patients with depressed, open and compound skull fractures.(81)

Adjunctive therapy:

a- Nutrition:

Early enteral nutrition is a priority. Parentral nutrition should be used only if an absolute contraindication of enteral route exists. Head-injured patients have caloric requirements that approach the requirements of patients with significant burns.[82]

b- Ulcer prophylaxis:

Stress gastritis following head injury is common. Hypersecretion of acid and splanchnic ischemia play a role in stress gastritis.[82] Gastric feeding in adequate volume is often sufficient propylaxis. However, stress ulcer prophylaxis using medications as H_2 blockade or sucralfate is also indicated.[83]

c- Deep venous thrombosis prophylaxis:

Deep vein thrombosis (DVT) and pulmonary embolism are frequent complications in head injured patients. The incidence of DVT in patients with major head injuries who are not receiving thrombo-prophylaxis is reported to be as high as 54%.[84] Low dose heparin and low molecular weight heparin are contraindicated in patients with head injuries. So sequential compression devices should be used (if possible) in all patients with TBI.[85]

d- Infection:

It has been debatable whether or not to use antibiotics in the prophylaxis of infection in patients with an open head injury, particularly duo to fracture at the base of the skull resulting in CSF rhinorrhea or otorrhea, or intracranial air.

Systemic sepsis is frequently associated with pulmonary sepsis that may take place few days in comatose patients duo to aspiration pneumonia. This can be minimized by early intubation, frequent gentle sterile suction, positional change and chest physiotherapy. So the use of antibiotics should be reserved for those with established infection documented by radiological evidence, fever and leucocytosis. Also urinary bladder catheter may be another source of sepsis in TBI patients.[86]

e- Antiseizure prophylaxis:

Anticonvulsants (especially epanutin) are indicated to decrease the incidence of early post-traumatic seizures (within 7 days of injury). Prophylactic use of phenytoin or valproate is not recommended for preventing late post-traumatic seizures.[87,88]

Outcome and prognosis of TBI

Several clinical and radiologic criteria have been used to predict outcome in order to help in guiding acute and chronic care for the typical recovery process.

Among predictors of outcome which proved to be powerful are age, initial GCS, pupil's size and reaction to light, ICP, the nature and extent of intracranial injury and the presence of associated systemic injuries. However, these factors proved to be more reliable in predicting death rather than predicting normal function or mild dysfunction.[89]

In most published data, mortality from severe TBI varies from 30% to just above 50%. In 30 to 60%, there is a good outcome or moderate disability.[23] In addition to those patients who die, small numbers will be left in a persistent vegetative state or alert but totally dependent. The numbers of such patients have not increased in those series of patients in which mortality was reduced by early aggressive management of head injury. Recovery may continue for up to 18 to 24 months after head injury, although the most significant gains are made during the first 6 months.[89,90)]

Many outcome measuring scales have been used in the literature to assess outcome from head trauma and to assess degree of disability. Popularly used are Glasgow outcome scale (GOS), extended Glasgow outcome scale (EGOS), disability rating score (DRS), Apathy evaluation score (AES) and many more. The most commonly used is GOS as shown in table 3.[91]

Table (3): Glasgow outcome scale (GOS): [91]

1	**Dead**
2	**Vegetative state**
3	**Severe disability** Able to follow commands/ unable to live independently
4	**Moderate disability** Able to live independently but unable to return to work or school
5	**Good recovery** Able to return to work or school

.

Apathy evaluation scale (AES): [93]

Apathy is defined as indifference, or a reduced emotional, cognitive, and behavioral state. It is common after TBI and is related to frontal lobe and limbic system damage, both of which are common areas of injury.[93]

Apathy evaluation scale has been used to assess apathy following TBI. It contains 18 statements that require an answer on a 4-point scale. Examples of statements on the Apathy Evaluation Scale are “Getting together with friends is important to them” and “When something good happens, she/he gets excited”.[93]

Disability Rating Scale (DRS): [94]

Table (4): Disability rating scale:

Category	Item	Instructions	Score
Arousability, Awareness and Responsivity	Eye Opening	0 = spontaneous 1 = to speech 2 = to pain 3 = none	3
	Communication Ability	0 = oriented 1 = confused 2 = inappropriate 3 = incomprehensible 4 = none	4
	Motor Response	0 = obeying 1= localizing 2= withdrawing 3=flexing 4 = extending 5 = none	5
Cognitive Ability for Self Care Activities	Feeding	0 = complete 1 = partial 2 = minimal 3 = none	3
	Toileting	0 = complete 1 = partial 2 = minimal 3 = none	3
	Grooming	0 = complete 1 = partial 2 = minimal 3 = none	3
Dependence on Others	Level of Functioning	0=completely independent 1= independent in special environment 2 = mildly dependent 3 = moderately dependent 4 = markedly dependent 5 = totally dependent	5
Psychosocial Adaptability	Employability	0 = not restricted 1= selected jobs 2 = sheltered workshop (non-competitive) 3 = not employable	3
Total score			29

Table (5): Disability Categories: [94]

Total DR Score	Level of Disability
0	None
1	Mild
2-3	Partial
4-6	Moderate
7-11	Moderately Severe
12-16	Severe
17-21	Extremely Severe
22-24	Vegetative State
25-29	Extreme Vegetative State

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is defined as breathing 100% oxygen while under increased atmospheric pressure.[95]

All the previously methods for treatment of TBI have failed to show improvement in the functional outcome and mortality rates in patients suffering from TBI. In recent years, however, there has been promising animal and clinical research in the area of oxygen therapy, especially hyperbaric oxygen (HBO) therapy and normobaric hyperoxia (NBH) , for the treatment of TBI.[95]

Historical Review

Hyperbaric oxygen therapy (HBOT) is a treatment that can be traced back to the 1600s. The first well-known chamber was built and run by a British clergyman named Henshaw. He built a structure called the "domicilium" that was used to treat a multitude of diseases. The chamber was pressurized with air or unpressurized using bellows. The idea of treating patients under increased pressure was continued by the French surgeon Fontaine, who built a pressurized, mobile operating room in 1879.[96]

Dr. Orville Cunningham, a professor of anesthesia, ran what was known as the "Steel Ball Hospital." The structure, erected in 1928, was 6 stories high and 64 feet in diameter. The hospital could reach 3 atmospheres of pressure. The hospital was closed in 1930 because of the lack of scientific evidence indicating that such treatment alleviated disease . It was deconstructed during World War II for scrap.[96]

HBO was tested and developed by the U.S. Military after World War I. It has been used safely since the 1930's to help treat deep sea divers with decompression sickness. Clinical trials in the 1950's uncovered a number of beneficial mechanisms from exposure to hyperbaric oxygen chambers. These experiments were the forerunners of contemporary applications of HBO in the clinical setting.[96]

Physiology of Oxygen Transport

The transport of oxygen from the ambient air to the mitochondria (sites of oxygen utilization) of tissue cells occurs by diffusion down a stepwise decrease in the driving oxygen pressure gradient. This gradual decline is termed the "oxygen cascade" [97]. The oxygen is transported in the blood from the lung alveoli to the tissues through two forms; either bound to hemoglobin or dissolved in the plasma.[98] The arterial oxygen content (CaO_2) is the summation of both forms which is calculated as follows: [99]

Blood oxygen content $= (SO_2 \text{ X Hb X } 1.39) + (0.003 \text{ X } PaO_2)$

Under normal conditions, when one is breathing room air (20.9% oxygen at 1 ATA), 97% of oxygen is transported bound to hemoglobin and only about 3% is dissolved.[98] Normally an individual's blood contain about 15 grams of hemoglobin for every 100 milliliters of blood. Each gram of hemoglobin can bind to 1.34 milliliters of oxygen, so when hemoglobin is 100% saturated, 20 milliliters of oxygen can be transported for every 100 milliliters of blood.[98,99] Under normal physiological conditions, arterial blood is only 97% saturated, so 19.4 milliliters of oxygen is transported bound to hemoglobin for every

100 milliliters of blood. As blood flows from the arterial side to the venous side of the circulatory system, the O_2 carried on hemoglobin drops from 19.4 to 14.4.[97] At normal arterial PO_2 levels , 0.29 milliliters of oxygen is physically dissolved in 100 milliliters of blood which brings the total amount found in 100 milliliters of blood (bound+dissolved) to 19.7 millilters of oxygen. Hence, the oxygen carrying capacity of the blood is largely equivalent to the concentration of hemoglobin while the dissolved oxygen is largely negligible.[100]

Physics of hyperbaric oxygen:

The physics behind HBOT lies within the ideal gas laws.

- The application of Boyle's law ($p_1\ v_1 = p_2\ v_2$) [where: p= pressure; v = volume]. This can be useful with embolic phenomena such as decompression sickness (DCS) or arterial gas emboli (AGE). As the pressure is increased, the volume of the concerning bubble decreases. This also becomes important with chamber decompression; if a patient holds her breath, the volume of the gas trapped in the lungs over expands and causes a pneumothorax.
- Charles' law ($[p_1\ v_1]/T_1 = [p_2\ v_2]/T_2$) [where: T = temperature] explains the temperature increase when the vessel is pressurized and the decrease in temperature with depressurization. This is important to remember when treating children or patients who are very sick or are intubated.
- Henry's law states that the amount of gas dissolved in a liquid is equal to the partial pressure of the gas exerted on the surface of the liquid. By increasing the atmospheric pressure in the chamber, more oxygen can be dissolved into the plasma than would be seen at surface pressure.

The clinician must be able to calculate how much oxygen a patient is receiving. In order to standardize this amount, atmospheres absolute (ATA) are used. This can be calculated from the percentage of oxygen in the gas mixture (usually 100% in HBOT; 21% if using air) and multiplied by the pressure. The pressure is expressed in feet of seawater (fsw), which is the pressure experienced if one were descending to that depth while in seawater. Depth and pressure can be measured in many ways; some common conversions are 1 atmosphere (atm) = 33 feet of seawater (fsw) = 10 meters of sea water (msw) = 14.7 pounds per square inch (psi) = 1.01 bar = 760 mmHg.

Oxygen delivery by HBO

Most oxygen carried in the blood is bound to hemoglobin, which is 97% saturated at standard pressure. Some oxygen, however, is carried in solution, and this portion is increased under hyperbaric conditions due to Henry's law.[95] Tissues at rest extract 5-6 mL of oxygen per deciliter of blood, assuming normal perfusion.[97] Administering 100% oxygen at normobaric pressure increases the amount of oxygen dissolved in the blood to 1.5 mL/dL; at 3 atmospheres, the dissolved-oxygen content is approximately 6 mL/dL, which is more than enough to meet resting cellular requirements without any contribution from hemoglobin. Because the oxygen is in solution, it can reach areas where red blood cells may not be able to pass and can also provide tissue oxygenation in the setting of impaired hemoglobin concentration or function.[101]

Table (6): Oxygen carrying capacity in arterial blood with increasing oxygenation at one, two and three atmospheres absolute (ATA)

Variable	AT 1 ATA		At 2 ATA	At 3 ATA
Inspired gas	Air	Oxygen	Oxygen	Oxygen
Inspired gas PO_2 (mm Hg)	150	713	1426	2139
PaO_2 (mm Hg)	100	600	1313	2026
CaO_2 (ml / 100 ml)	19.3	21.3	23.4	25.5
A-V O_2 (ml / 100 ml)	5	5	5	5
VO_2 (ml / 100 ml)	14.3	16.3	18.4	20.5

Cerebral response to hyperoxia:

The cerebrovascular response to hyperoxia has been investigated in physiologic and pathologic conditions, and it has been shown that there is a cerebral blood flow (CBF) reduction in response to hyperoxia ranging from 9% to 27%.[102] Menzel *et al.* studied the cerebral oxygen vasoreactivity after TBI using stable xenon CT.[103] In regions of interest corresponding with normal-appearing tissue, they observed a mean CBF reduction of 19%. The degree of this response was proportional to the level of the regional baseline CBF.[103]

Hyperoxia is followed by an increase in brain tissue oxygen tension, increase in blood oxygen saturation measured in the jugular bulb and by a decrease in arteriovenous oxygen difference (AVDO2), suggesting that the ratio between oxygen demand and supply is shifted either to a lower cerebral metabolic rate of oxygen consumption or to a better oxygen delivery.[104]

However, in a swine model of progressive global brain ischemia, it has been shown that when CBF is reduced to 30%, AVDO2 is not changed by hyperoxia, suggesting that increasing PaO2 does not always influence brain oxygen delivery.[105]

Mechanism of action of HBO in TBI:

Hyperoxia caused by HBO leads to vasoconstriction of the cerebral blood vessels which leads to decreased brain edema and ICP.[102] The vasoconstriction was not found to be deleterious because O_2 availability to the injured cells was greatly increased. Experimental research showed that HBO decreases cerebral edema and stabilized blood brain barrier as well leading to decrease of ICP. [106]

Following TBI, there is a relative energy crisis with depression of cerebral mitochondrial function. Impaired mitochondrial respiration results in a shift from aerobic to anaerobic metabolism with resultant increased lactate and reduced ATP production.[24] HBO appears to improve aerobic metabolism in brain injured patients.[104]

In TBI, delivery of O_2 to brain tissue is reduced by both decreased local CBF as well as diminished O_2 diffusion secondary to cerebral edema. [22] HBO allows the delivery of supra normal amounts of O_2 to the injured brain cells through increased dissolved oxygen in the blood and decreasing cerebral edema.[106]

HBO allows the injured brain to utilize oxygen more efficiently and has a persistent effect on the injured brain tissue. There is a growing evidence that this change occurs at the mitochondrial level. The exact mechanism by which HBO may enhance mitochondrial recovery is unknown. [106]

Other actions of HBO

HBO increases generation of oxygen free radicals, which oxidize proteins and membrane lipids, damage DNA and inhibit bacterial metabolic functions. HBO is particularly effective against anaerobes, and facilitates the oxygen-dependent peroxidase system by which leukocytes kill bacteria. [107] HBO also improves the oxygen-dependent transport of certain antibiotics across bacterial cell walls.[108]

HBO improves wound healing by amplifying oxygen gradients along the periphery of ischaemic wounds, and promoting oxygen-dependent collagen matrix formation needed for angiogenesis.[109]

During reperfusion, leukocytes adhere to ischaemic tissues, releasing proteases and free radicals, which leads to pathological vasoconstriction and tissue destruction.[110] This worsens crush injuries and compartment syndromes, and causes failure of skin flaps, grafts and reattachment procedures. [111] This free radical damage has been implicated in neuronal injury following ischemia and exposure to drugs and poisons. Zamboni[112] demonstrated reduced leukocyte adherence and post-ischaemic vasoconstriction with HBO in ischaemic rat tissue, and more recently Thom [113] demonstrated reduced lipid peroxidation with HBO in rats with carbon monoxide poisoning.

Hyperoxia in normal tissues due to HBO causes rapid and significant vasoconstriction,[114] but this is compensated for by increased plasma oxygen carriage, and microvascular blood flow in ischaemic tissue is actually improved with HBO.[112] Such vasoconstriction does however reduce post-traumatic tissue oedema, which contributes to the treatment of crush injuries, compartment syndromes and burns.[115]

Approved indications for HBO by the Undersea and Hyperbaric Medical Society: [116]

- Air or gas embolism.
- Carbon monoxide poisoning; cyanide poisoning; smoke inhalation.
- Clostridial myostitis and myonecrosis (gas gangrene).
- Decompression sickness.
- Crush injuries, compartment syndrome, and other acute traumatic ischemias.
- Enhancement of healing in selected problem wounds.
- Exceptional blood loss anaemia.
- Intracranial abscess.
- Necrotizing soft tissue infections.
- Refractory osteomyelitis.
- Skin flaps and grafts (compromised).
- Delayed radiation injury (soft tissue and bony necrosis).
- Thermal burns.
- Idiopathic Sudden Sensorineural Hearing Loss.

Complications:

HBO is a relatively safe treatment, but does carry some risks, due to the increased pressure and hyperoxia. The commonest effect of oxygen toxicity is a progressive, reversible myopia, thought to be due to physical lens deformation. [117] There is no evidence for other optical side-effects such as cataracts.[117]

CNS toxicity may occur, and has been known since Paul Bert documented the seizure-potentiating effect of HBO in 1878.[118] Interestingly, a 2003 paper reported an apparent increase in oxygen-induced convulsions over recent years, though the reasons for this were unknown.[119]

Middle ear and sinus barotraumas are preventable by equalization techniques or tympanostomy tubes, and otitis media can be prevented with pseudoephidrine.[120] Inner ear barotrauma is extremely rare, but tympanic rupture can result in permanent hearing loss, tinnitus and vertigo. Pulmonary barotrauma and pneumothorax are extremely rare, particularly without pre-existing lung disease. Dental barotrauma may rarely cause pain under a dental filling.

Accidents are a risk due to the enriched oxygen and inaccessibility, with over 50 reported deaths due to fire in the last 20 years.[121]

Contraindications:

Table (7): Absolute Contraindications to Hyperbaric Oxygen Therapy: [122]

Absolute Contraindications	Reason Contraindicated	Necessary Conditions Prior to HBOT
Untreated pneumothorax	Gas emboli Tension pneumothorax Pneumomediastinum	Thoracostomy
Bleomycin	Interstitial pneumonitis	No treatment for extended time from use of medication
Cisplatin	Impaired wound healing	No treatment for extended time from use of medication
Disulfiram	Blocks superoxide dismutase, which is protective against oxygen toxicity	Discontinue medication
Doxorubicin	Cardiotoxicicity	Discontinue medication

Table (8): Relative Contraindications to Hyperbaric Oxygen Therapy: [122]

Relative contraindication	Reason contraindicated	Necessary Conditions Prior to HBOT
Claustrophobia	Anexiety	Treatment with benzodiazepines
Congenital spherocytosis	Severe hemolysis	None; HBOT for emergencies only
COPD	Loss of hypoxic drive to breathe	Observation in chamber
Eustachian tube dysfunction	Barotrauma to tympanic membrane	Training, PE tubes
High fever	High risk of seizures	Provide antipyretic
Pace-makers or epidural pain pump	Malfunction or deformation of device under pressure	Ensure company has pressure-tested device and learn to what depth
Asthma	Air trapping upon ascent leading to pneumothorax	Must be well controlled with medications
Pregnancy	Unknown effect on fetus (Previous studies from Russia suggest HBOT is safe.)	None, but HBOT may be used in emergencies
Seizures	May have lower seizure threshold	Should be stable on medications; may be treated with benzodiazepines
Upper respiratory infection	Barotrauma	Resolution of symptoms or decongestants

Chambers of HBOT [123]

The patient can be administered systemic oxygen via 2 basic chambers: Type A, multiplace; and Type B, monoplace. Both types can be used for routine wound care, treatment of most dive injuries, and treatment of patients who are ventilated or in critical care.

Multiplace chamber

Multiplace chambers treat multiple patients at the same time, generally with a nurse or another inside observer who monitors the patients and assists with equipment manipulation or emergencies. Patients in a multiplace chamber breathe 100% oxygen via a mask or close-fitting plastic hood. Multiplace chambers can usually be pressurized to the equivalent of about 6 atmospheres of pressure.

All equipment used with patients, such as ventilators and intravenous lines, is put into the chamber with the patient. Since the employee is breathing air during the treatment (not using a mask), his or her nitrogen intake must be monitored, as this presents a risk for problems similar to those sometimes developed by scuba divers (eg, decompression sickness [DCS]).

Monoplace chamber

A monoplace chamber compresses one person at a time, usually in a reclining position (see image below). The gas used to pressurize the vessel is usually 100% oxygen. Some chambers have masks available to provide an alternate breathing gas (such as air). Employees tend to the patient from outside of the chamber and equipment remains outside the chamber; only certain intravenous lines and ventilation ducts penetrate through the hull. Newer Duoplace chambers can hold 2 people; their operation is similar to that of a monoplace chamber.

Other chambers

Two other types of chambers are worth mentioning, although they are not considered HBOT.

Topical oxygen, or Topox, is administered through a small chamber that is placed over an extremity and pressurized with oxygen. The patient does not breathe the oxygen, nor is the remainder of the body pressurized. Therefore, the patient cannot benefit from most of the positive effects of HBOT, which are systemic or occur at a level deeper than topical oxygen can penetrate. Topox is based on the concept that oxygen diffuses through tissue at a depth of 30-50 microns. [124]This method does not treat DCS, arterial gas emboli (AGE), or carbon monoxide (CO) poisoning.[124]

The other type of chamber is the portable "mild" hyperbaric chamber. These soft vessels can be pressurized to 1.5-1.7 atmospheres absolute (ATA). They are only approved by the FDA for the treatment of altitude illness. The number of these chambers has increased, as they are being used more commonly in off-label indications.

Figure (5): Multiplace chamber

Figure (6): Multiplace chamber

Figure (7): Monoplace chamber.

Oxygen toxicity

The lung is the organ most commonly damaged by hyperoxia since the oxygen tension in the lungs is substantially higher than in other tissues.[125] The mechanism by which pulmonary injury occurs has been termed oxidative stress.[126] Central to this process is the release of proinflammatory cytokines by alveolar macrophages, specifically IL-8 and IL-6, and the subsequent influx of activated cells into the alveolar air space.[127] Measurements of these proinflammatory cytokines in bronchial alveolar lavage has been shown to be predictive of acute lung injury and pulmonary infection in exposure to super physiological concentrations of inspired oxygen.[128]

The concept of a "unit pulmonary toxic dose" (UPTD) has been developed and allows comparison of the pulmonary effects of various treatment schedules of hyperoxia.[129] One UPTD is equal to one minute of 100% O_2 at 1 ATA. Appropriate conversion factors (kp), that is, multipliers of one minute of 100% O_2 at 1 ATA, allow one to quantitate the pressure (ATA) of oxygen exposure.

In general, it is recommended that total oxygen exposure in a single treatment be limited to a UPTD of 615 or less. The extreme limit of a single O_2 exposure is 1425 UPTD. This dose will produce a predicted 10% decrease in vital capacity in a normal individual. A one-hour HBO treatment at 1.5 ATA is equal to 106.8 UPTD which is considered a low dose of O_2. While 3 hours of 100% oxygen at 1 ATA is equal to 180 UPTD which is also considered a low dose of O_2.

Oxygen, especially under increase pressure, also may cause potential cerebral toxicity.[119] Brain tissue is especially vulnerable to lipid peroxidation because of its high rate of oxygen consumption and high content of phospholipids. Additionally the brain has

limited natural protection against free radicals; it has limited scavenging ability, poor catalase activity, and is rich in iron, which is an initiator of radical generation in brain injury.[130] However, there is no clinical evidence for cerebral toxicity using an HBO treatment paradigm of 1.5 ATA for 60 minutes.[130]

In conclusion, HBO treatments at depth of 1.5 ATA can be delivered to TBI patients with or without multiple injuries in either a monoplace or multiplace chamber with relatively safety and low risk of O_2 toxicity.

Practical Aspects of Hyperbaric Therapy

Patient Monitoring

Important parameters to monitor include the conscious state, presence of cyanosis, chest movement and pulse rate. Inside the chamber, there is a built-in multi-parameter physiological monitoring system for the monitoring of vital signs including ECG, heart rate, SpO2, plethysmography, respiratory rate, capnography and blood pressure. For invasive arterial pressure monitoring (continuous), the pressure bag volume and pressure should be monitored during descent and ascent. No bubble is allowed within any tubings.[131] For non-invasive blood pressure (intermittent), it is made preferably by the automatic oscillometric method; mercury sphygmomanometer should not be used to avoid the risk of spillage of mercury and the resulting contamination. While the monitoring module is placed inside chamber, the monitor screen should be placed outside chamber. No monitor with hot-wire stylus and no battery-run monitor should be allowed inside the pressure chamber because of fire risk. For pulmonary artery catheter (Swan Ganz catheter), the balloon port should be left open if not measuring wedge pressure. Measuring wedge pressure during descent/ascent is not advisable.[132]

Defibrillation could generate a fire if there is sparking and combustible materials in the vicinity of the paddles. Sparking and heat generation can be minimized by using a low resistivity conductive gel between the electrodes and the skin or pre-applied conductive disposable pads. To avoid pressure-related malfunction of the device, the defibrillator can remain outside the chamber and connection to the patient via through-hull high voltage wiring. Despite the fear of causing fire, defibrillation has been carried out in multiplace chambers numerous times without arcing, fire, or explosion.[133] Defibrillation cannot be safely performed inside a monoplace chamber compressed with O_2.[133]

Intravenous Fluid Administration

In multiplace chambers the air volume within the drip chamber will shrink during the compression phase of the HBO treatment and expand during decompression (which could force air into the intravenous line).Trapped air inside bottle during ascent may cause an increased rate of infusion and also increase the risk of air embolism. Collapsible bag is preferable, but make sure there is no bubble in the tubing. Safeguard against disconnection. Intravenous infusion pump or syringe pump with battery should not be used unless it is purged continuously with nitrogen because of fire risk.[134]

Administration of fluids to patients inside a pressurized monoplace chamber requires an infusion pump capable of handling the pressure differential (up to 3 ATA or 1500 mm Hg pressure gradient across the chamber wall). Check valves can prevent unintended

backflow of blood from the patient in the event of disconnection of the pump. Rigid arterial-pressure transducer tubing will help to prevent kinking while the patient is inside the chamber.[135]

Avoid the intramuscular or subcutaneous routes because hyperbaric therapy-induced vasoconstriction could cause delayed or erratic absorption.[134,135]

Blood Gas Assessment and Ventilator Management

For arterial blood gases analysis, when a specimen taken inside the chamber and analyzed at surface, the PH and PCO2 are reasonably accurate, but PO2 must be analysed with a specially adjusted equipment within the chamber, or otherwise expect a spurious result due to the "off-gassing" effect. The effect is due to the fact that O2 gradient between blood and bubble is higher at 1 ATA than 3 ATA, therefore, O2 would tend to escape from blood to bubble faster at 1 ATA than at 3 ATA, hence a spuriously low PaO2 at 1 ATA if at which it is measured outside the chamber.[136]

Normal values for pH and $PaCo_2$ under resting clinical hyperbaric conditions are the same as they are at 1 ATA. $PaCo_2$ (and hence pH) do not change significantly in blood samples that are decompressed.[136]

Several types of ventilators have been used and tested in hyperbaric chambers. Pressure-cycled devices have been used with some success, because their compactness fulfills the requirement for small size. [137]

As ambient pressure increases, gas density is proportionately raised, whereas there is relatively little change in gas viscosity.[138] Therefore, in regions of turbulent flow (i.e., in the large airways) airway resistance increases. The higher gas density results in a less efficient distribution of ventilation, manifested by an increase in physiologic dead space. If ventilator settings are not adjusted to compensate for the higher dead space, a rise in $PaCO_2$ will occur.[137]

Figure (8): Mechanical ventilation inside a hyperbaric chamber.

When the chamber pressure is increased, the tidal volume delivered to the patient will diminish accordingly and the scale on the ventilator no longer reflects the actual volume. To solve this issue, one may refer to the calibration table provided by the chamber, or one may use a Wright's spirometer, with prior calibration to make sure that it is accurate, which can be connected to the ventilator circuit for tidal volume monitoring.(139)

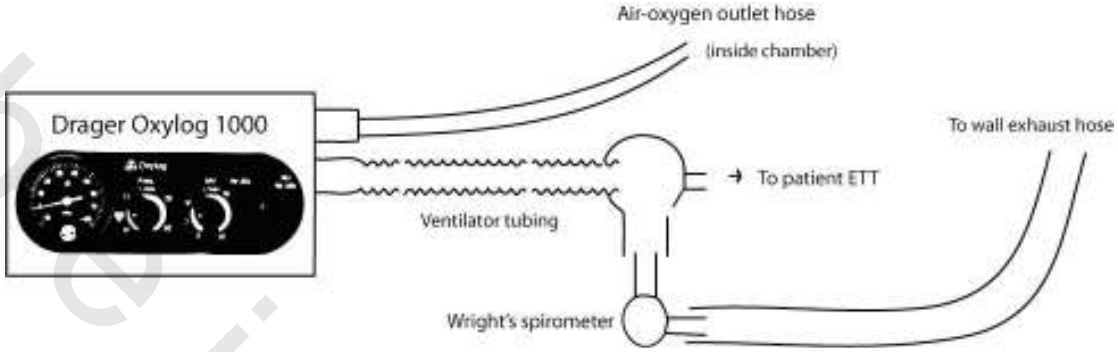

Figure (9): Ventilator circuit.

Air-filled endotracheal tube cuffs will tend to lose volume during compression and reexpand during compression. Appropriate cuff inflation volume can be maintained either by manual adjustment of the air pressure within the cuff during compression and decompression or filling the cuff with saline.(140)

For suction, a hand-held aspirator with in-line trap and vacuum regulator can be used. Prepare a chest tube drainage system ready within vicinity of chamber for emergency chest drain insertion for pneumothorax. Monitor chest drain box air-fluid level during descent and ascent.(141)

Atmosphere Control

Chamber atmosphere safety includes management of levels of O_2, CO_2, and trace gases. In a multiplace chamber it is essential that the patient breathe as high a concentration of O_2 as possible (usually 98% or greater) while maintaining the chamber O_2 concentration close to 21% to minimize fire hazard. In some hyperbaric units, head-tent O_2 concentration is routinely monitored. In others, the concentration is assumed to be high because of a high rate of O_2 flow through the head tent. Leakage of O_2 from head tents, masks, and ventilators will tend to raise the chamber O_2 concentration. Typically, an upper limit of around 23% is used as a criterion for ventilating the chamber with air or small volumes of 100% nitrogen until the O_2 concentration decreases.(142)

Fire Hazards

Although fires in hyperbaric chambers are rare, they are usually lethal. The effects of fire at elevated ambient pressure are so devastating and so fast that fire extinguisher systems may not be effective. Minimization of this risk involves the following:(143)

- Control of chamber O_2 concentrations (irrelevant in a monoplace chamber)
- Minimizing the use of combustible materials within the chamber
- Controlling sources of heat and spark
- Chamber fire extinguisher system

The increase in burning rate with increases in O_2 concentrations mandates careful monitoring of chamber O_2, as already noted. At increased ambient pressure, burning occurs more rapidly, even when O_2 concentration is 21%. Cotton garments are recommended because of their reduced risk of static electricity.[143]

The following items should be strictly prohibited inside chamber because they are potentially inflammable and/or may lead to explosion from air pressure changes: cigarette, match or lighter, oil-based cosmetic, face cream, body oil, hair spray, nail polish, nylon clothing, ink-filled pen, electronic instrument, mobile phone, and watch (except the type for designed for diving which contains no battery).

Evaluation of a Patient for Safety of HBO Treatment

In addition to ensuring that HBO is indicated for the disease process in question, it is important to assess the patient in terms of general effectiveness and safety of HBO. The following issues are pertinent: [144]

- Whether a sufficient elevation in PaO_2 can be obtained.
- Whether the patient can equilibrate middle ear pressure.
- Optimization of reversible obstructive lung disease and the presence of pulmonary bullae or blebs.
- Whether the patient is susceptible to claustrophobia.

The ability to vent the middle ears may be assessed before treatment by observing directly the tympanic membrane with an otoscope while the patient holds his or her nose or performs a Valsalva maneuver. Movement of the eardrums indicates a patent eustachian tube and the ability to equilibrate middle ear pressure. If otic barotrauma is unlikely to be avoided (e.g., with mental obtundation or the presence of an endotracheal tube) or because of a condition that may render the patient susceptible to inner ear injury, myringotomy or tube placement can be performed before HBO treatment.[144] The presence of pulmonary bullae or blebs represents a relative contraindication to HBO because of the possibility of barotrauma, although a large clinical experience suggests that the risk is extremely low.[144]

For patients requiring more than 20 to 30 HBO treatments, periodic checks of visual acuity may be useful to assess hyperbaric myopia.[117]

Because most hyperbaric chamber systems are small and cramped, patients who cannot tolerate enclosed spaces may require anxiolytic therapy to facilitate toleration of the HBO therapy.

Normobaric hyperoxia (NBO)

Hyperoxia has been investigated as a potential treatment strategy for increasing aerobic metabolism after TBI and hyperbaric hyperoxia (HBH) in particular has shown beneficial effects in both animals and humans. However chambers capable of delivering HBH to critically ill patients are expensive and availability is severely limited. Interest has therefore grown in the use of normobaric hyperoxia (NBH) which is cheap and simple to administer.[95]

Normobaric hyperoxia means inhalation of a high oxygen fraction up to 100% while under normal atmospheric pressure (1 ATA).

The poor clinical outcomes of earlier HBOT studies combined with the relative success of normobaric oxygen therapy (NBOT) in TBI have lead some to propose that normobaric oxygen therapy should be used preferentially in brain-injured patients. There are numerous studies that demonstrate an enhanced clinical outcomes by treatment with normobaric oxygen .[145] Much of the enthusiasm for use of NBOT is based on a prospective study of severe TBI patients.[146] Narotam and colleagues[147] evaluated brain tissue oxygen concentrations in patients with severe TBI. Using Licox oxygen probes, 139 patients were studied using a pO_2 protocol that maintained brain oxygen levels to > 20 mm Hg. They elegantly demonstrated that normobaric oxygen therapy significantly reduced mortality, but moreover, they showed improved clinical outcomes at 6 months post-severe TBI. A similar study found that hyperoxia improved the cerebral metabolic rate of oxygen in severe TBI patients using O15-postiron emission tomography, but they did not compare to HBOT treated patients.[148] Thus, at a minimum, NBOT could be beneficial for TBI patients.

Studies investigating the use of NBH in adults after TBI have consistently shown increases in brain oxygen tension and reductions in microdialysis measured brain tissue lactate concentration. [147] But interpretation of these findings is controversial. Some investigators conclude that they support a beneficial role for NBH while others suggest that NBH may be detrimental.

Normobaric hyperoxia (NBO) has been shown to effectively reduce tissue infarction and protect the blood brain barrier (BBB) in animal ischemic stroke models.[148] These neuro- and vaso-protective effects make NBO a promising approach to expand the narrow time window of the reperfusion therapies for ischemic stroke. Indeed, recent studies showed that NBO treatment during cerebral ischemia significantly reduced the neurovascular complications in delayed tPA treatment in a rat model of ischemic stroke.[149] In human studies, NBO treatment was associated with improvements in clinical deficit and survival in selected stroke patients. Increasing oxygen level, particularly over-oxygenation, with oxygen therapy may result in oxidative stress and free radical damage. Interestingly, NBO treatment for ischemic stroke does not increase oxidative stress[150], instead, it may decrease reactive oxygen species (ROS) production. However, it remains to be elucidated how NBO affects ROS production in the ischemic brain.[149]