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Review Article

REVIEW ARTICLE

Definition, evaluation, and management of brain relaxation during craniotomy

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Abstract

The term 'brain relaxation' is routinely used to describe the size and firmness of the brain tissue during craniotomy. The status of brain relaxation is an important aspect of neuroanaesthesia practice and is relevant to the operating conditions, retraction injury, and likely patient outcomes. Brain relaxation is determined by the relationship between the volume of the intracranial contents and the capacity of the intracranial space (i.e. a content–space relationship). It is a concept related to, but distinct from, intracranial pressure. The evaluation of brain relaxation should be standardized to facilitate clinical communication and research collaboration. Both advantageous and disadvantageous effects of the various interventions for brain relaxation should be taken into account in patient care. The outcomes that matter the most to patients should be emphasized in defining, evaluating, and managing brain relaxation. To date, brain relaxation has not been reviewed specifically, and the aim of this manuscript is to discuss the current approaches to the definition, evaluation, and management of brain relaxation, knowledge gaps, and targets for future research.

Key words: brain relaxation; definition; evaluation; intracranial pressure; management

Brain relaxation is an important aspect of anaesthetic care during intracranial surgery. Optimal brain relaxation improves the surgeon's operating conditions and is likely to minimizes the severity of retraction injury,[1–4] with the potential for providing the patient with a better outcome. Despite the practical and outcome relevance, the definition, evaluation, and management of brain relaxation have not been reviewed specifically. Our aim is to review the concept of brain relaxation, discuss the current approaches to management, and identify the knowledge gaps and targets for future research.

Definition of brain relaxation

The concept of 'brain relaxation' is routinely integrated into the perioperative communication between an experienced neurological anaesthetist and surgeon. After opening of the cranium and dura, the surgeon often makes note of how tight or relaxed the brain is. If a brain is perceived to be tight or swollen, various manoeuvres are instituted to soften the brain in order to improve the operating conditions and to protect the brain from retraction injury and ischaemia from compression. Brain relaxation is a term that is specifically used to describe the brain during craniotomy although the concept of brain relaxation has evolved over time to encompass many different terms.

In 1962, Hayes and Slocum[5] specifically discussed the problem of a swollen or tight brain and, for the first time, used the term 'brain relaxation' in the title of their paper. Other relevant terms that have been used include cerebral relaxation,[6 7] cerebral swelling,[8] brain swelling,[9] and brain herniation.[10] However, a consensus on the terminology is needed in order to facilitate

communication in clinical care and to provide consistent outcome measures for research purposes. We propose that brain relaxation should be used to describe a clinical entity that has anaesthetic, surgical, physiological, and outcome implications.

Brain relaxation describes the relationship between the volume of the intracranial contents and the capacity of the intracranial space when the cranium and dura are opened by the neurosurgeon. Therefore, it is a concept that should be applied specifically during an intracranial procedure when the content–space relationship can be assessed directly. Brain relaxation is adequate if the volume of intracranial contents is equal to or less than the capacity of the intracranial space. On the contrary, the brain relaxation is inadequate if the volume of intracranial contents surpasses the capacity of the intracranial space. This definition is lacking, however, as it omits the clinical outcome in assessing the adequacy of relaxation. The modern concept of brain relaxation should be defined as an ideal volume of the intracranial contents in relationship to the capacity of the intracranial space that provides optimal operating conditions during open intracranial surgery and a beneficial patient outcome afterwards.

We propose an analogy to illustrate the concept of brain relaxation by considering a spring (equivalent of intracranial contents) sitting in a rigid box (equivalent of intracranial space) with the top open. The spring is relaxed (potential energy=0) if the natural length of the spring matches (or is less than) the height of the box (Fig. 1A). On the contrary, the spring is compressed and tense (potential energy >0) if something extra is added between the spring and the bottom of the box, resulting in the protrusion of the spring outside of the open box (Fig. 1B).

There is another possibility to consider. When the spring is compressed it is also tense (potential energy >0) and able to stretch when the external compression is relieved (Fig. 1C). This may be of clinical relevance because an over-shrunken brain occurs when the surface of the brain is relatively lower than the cranial bone, with some distance between. This situation is frequently observed in the middle of an intracranial procedure even though the surface of the brain may be higher than cranial bone at the beginning of surgery. This dynamic change is attributable to several factors; the interventions for brain relaxation, the loss of cerebrospinal fluid (CSF); and debulking of the brain lesion. An over-shrunken brain because of parenchymal dehydration and cellular shrinkage, however, may still not be relaxed. This situation occurs because the brain tissue, like other tissue beds, resists sustained volumetric reduction and reacts to parenchymal shrinkage by cellular/tissue expansion.[11–13] At the moment when the shrinking force recedes, e.g. the mannitol effect wears off, the rebound process starts and typically takes place in minutes and is mediated by the re-uptake of free water and various electrolytes.[11] Although this situation is not optimal, an over-shrunken brain may be perceived as satisfactorily relaxed merely based on the intracranial content–space relationship. This dilemma can and should be resolved by correlation with the patient's outcome; an over-shrunken brain may be warranted if it is associated with beneficial patient outcomes, or vice versa pending on future research.

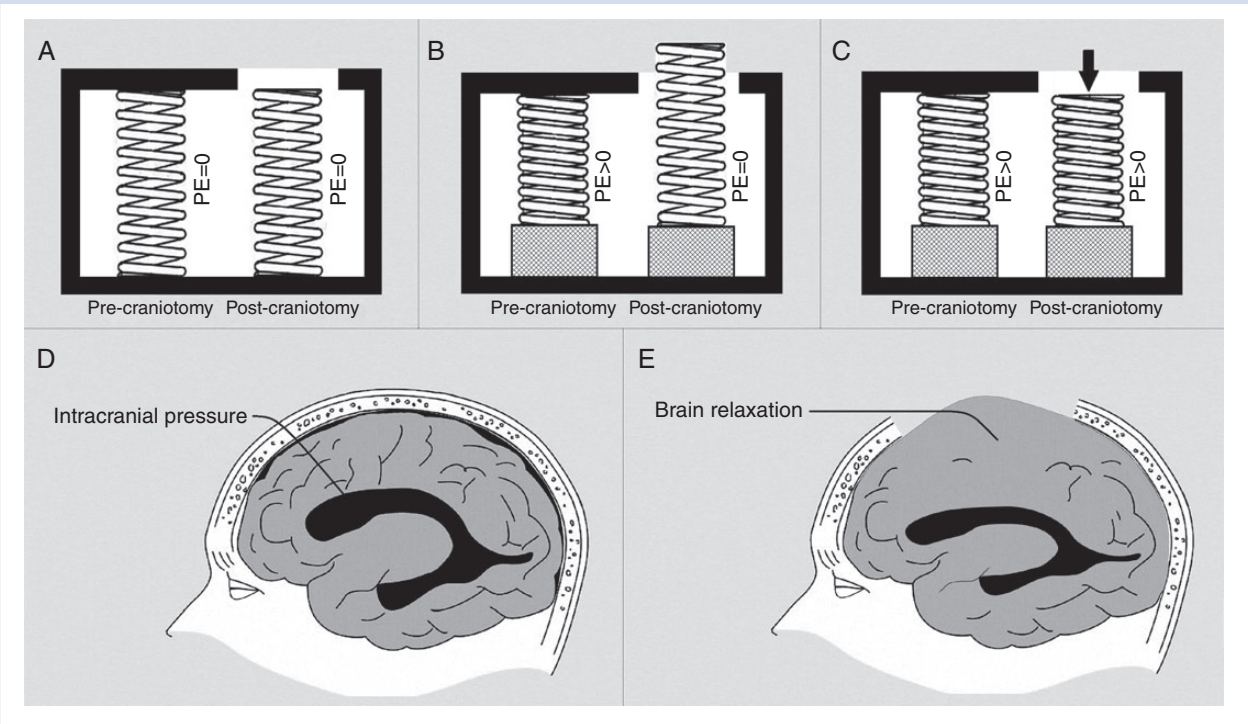

Fig 1 Diagram of intracranial content–space relationship. (A) If the intracranial contents and the intracranial space match, the potential energy (PE) of the intracranial contents represented by the spring is zero, and the spring does not protrude extracranially during craniotomy. (B) In contrast, the addition of extra intracranial content (represented by the cross-hatched block) renders the volume of all of the intracranial contents excessive to the capacity of the intracranial space, and the PE of the spring is greater than zero. As a result, the spring protrudes extracranially during craniotomy until its PE equals zero. (C) However, the spring may not protrude extracranially if it is pressed downward (represented by the black arrow). This is analogous to an over-shrunken brain as a result of hyperosmolar therapy-induced free water reduction and cellular shrinkage. In this situation, the brain tissue is prepared to expand (the PE of the spring is greater than zero) and will expand when the osmolality is restored. (D) The intracranial pressure is typically measured when the cranium and dura are closed (i.e. before craniotomy. (E) In contrast, brain relaxation is assessed when the cranium and dura are opened (i.e. after craniotomy).

In summary, the modern definition of brain relaxation should emphasize the outcome that is essential to patients, which is an improved definition that is above and beyond the traditional description of merely provision of ideal operating conditions to the surgeon. This is a rational proposal given both advantages and disadvantages related to each brain relaxation intervention and calls for outcome-oriented evidence to guide clinical management.

Comparison between brain relaxation and intracranial pressure

It is important to differentiate the concept of brain relaxation from the practice of measuring intracranial pressure (ICP). Intracranial pressure is the pressure in a closed cranium, i.e. it is an objective measure made with a transducer (Fig. 1D). Brain relaxation, in contrast, is a more subjective assessment by the surgeon primarily based on the intracranial content–space relationship when the cranium and dura are opened (Fig. 1E). Intracranial pressure decreases to the atmospheric level (referred to as zero) when both the cranium and dura are opened, yet the degree of brain relaxation may not change or may worsen if the brain tissue suddenly expands. However, these two entities are also intrinsically related. Physically, ICP results from the force exerted by the intracranial contents against the wall of the cranium. Intuitively, the greater the volume of the intracranial contents in relationship to the capacity of the intracranial space, the higher the ICP will be and *vice versa*. This relationship is corroborated by studies demonstrating that an elevated ICP correlates with a higher incidence of clinical brain swelling after dural opening.[14–16] A more detailed comparison between brain relaxation and ICP is provided (Table 1).

Diagrams frequently show the volume–pressure relationship (i.e. the relationship of the intracranial contents to ICP) as a relatively stable ICP in the face of an increase in intracranial contents as long as it is lower than the threshold volume.[19] The ICP increases quickly and substantially even with minimal incremental changes in the intracranial contents when it surpasses a critical volume threshold. The insignificant change in ICP before the threshold is attributed to compensatory mechanisms, such as the translocation of the CSF from the intracranial space to the extracranial intrathecal space or extrusion of some intracranial blood to an extracranial location (Fig. 2).[20] In order for the compensatory mechanism to occur, ICP must increase transiently in order to effect the volume reduction in CSF, cerebral blood volume (CBV), or both. This mechanism is in accordance with the Monro–Kellie doctrine.[20–22] The threshold is the turning point when the functional compensatory mechanism becomes exhausted.

However, the common rendition of the volume–pressure relationship is conceptually misleading.[19] The labelling of the abscissa of the volume–pressure curve needs to be defined carefully because the volume of the intracranial contents is the sum of all intracranial components, which is different from the volume of one specific intracranial component. When using the previously reported intracranial volume–pressure plot (Fig. 3A), the abscissa should be clearly labelled as the volume of the expanding intracranial component (Fig. 3B) in order to differentiate it from the volume of all of the components. The volumetric sum of all intracranial components does not change until the compensatory mechanism, whereby the increment of one component is counteracted by the decrement of other reducible components, is exhausted. If the abscissa represents the volume of all of the intracranial components, the volume–pressure plot should be revised by removing the threshold inflection point in order to fit the concept that a volumetric increase in the sum of all intracranial components, when compensation is exhausted, leads to an increase in ICP (Fig. 3C). Based on the available evidence,[14 15] we speculate that the volume–brain relaxation plot (Fig. 3D) is similar to the volume–pressure plot (Fig. 3C). The similarity implies that the concepts of ICP and brain relaxation are closely related.

In summary, brain relaxation and ICP are distinct concepts and are applied in different clinical scenarios. However, they overlap in some aspects of aetiology and management related to poor brain relaxation and intracranial hypertension.

Incidence of inadequate brain relaxation

The incidence of poor intraoperative brain relaxation, as manifested by brain swelling through the craniotomy site, is variably reported, depending on the definition used and population studied. A review of a spectrum of elective neurosurgical patients found an incidence of 0.7% of severe cerebral swelling.[23] Although all of these patients experienced profound swelling and herniation through the craniotomy site, interestingly, none of these patients experienced poor outcomes related to their intraoperative brain swelling. Other studies have reported an incidence from 5.0 to 6.1% for severe or pronounced swelling.[14 24] Mild or moderate brain swelling is relatively common, as Rasmussen and colleagues[14] reported an incidence of nearly 30% in a large series of patients undergoing resection of supratentorial brain tumours.

Aetiology of unsatisfactory brain relaxation

Unsatisfactory brain relaxation during craniotomy is caused by a mismatch between the intracranial contents and space. The primary cause of a tight brain is an excessive volume of intracranial contents. Various brain lesions, such as tumours, cysts, haematomas, and traumatic injury, together with the resultant cerebral oedema, enlarge the volume of intracranial contents without changing the capacity of the intracranial space, thus leading to content–space mismatch. Other factors that contribute to a tight brain include excessive CSF (e.g. hydrocephalus) and excessive CBV. Increases in CBV can result from increased cerebral blood flow [e.g. hypercapnia, high minimal alveolar concentration (MAC) of volatile anaesthetic agents] or reduced cerebral venous drainage (e.g. head-down tilt, extreme head/neck rotation, neck compression). Conversely, the reduction in capacity of the intracranial space such as that caused by a depressed cranial fracture can also lead to content–space mismatch and a poor brain relaxation. A pragmatic checklist is proposed to facilitate the differential diagnosis of unsatisfactory brain relaxation (Table 2).

Evaluation of brain relaxation

Prediction based on preoperative intracranial hypertension

The status of brain relaxation during craniotomy can be predicted by the severity of intracranial hypertension before craniotomy. A diagnosis of intracranial hypertension is a critical predictor and can be made based on history, symptoms and signs, imaging studies, and ICP measurement. Headache, nausea, and vomiting are common symptoms, while change in mental status, papilloedema, pupillary dilatation, decerebrate posturing, and bulging fontanel or scalp flap are common signs of intracranial

Table 1 Comparison between brain relaxation and intracranial pressure. CBF, cerebral blood flow; EVD, external ventricular drain; ICH, intracranial hypertension

Category	Brain relaxation	Intracranial pressure
Definition and clinical relevance		
Definition	Content–space relationship between the volume of the intracranial contents and the capacity of the intracranial space	Pressure as a result of the force exerted by the intracranial contents against the wall of cranium
Cranium and dura	Opened	Closed
Clinical relevance	Operating conditions, retraction injury, focal cerebral ischaemia, transdural brain herniation, patient's outcome	Cerebral perfusion pressure, global cerebral ischaemia, intracranial brain herniation, neurological well-being, patient's outcome
Aetiology		
Tumour, trauma, haemorrhage, abscess	Applicable	Applicable
Cerebral oedema	Applicable	Applicable
Excessive cerebrospinal fluid	Applicable	Applicable
Hypoventilation	Contributes to a tight brain	Rarely as the only cause of ICH
Head down	Contributes to a tight brain	Rarely as the only cause of ICH
Evaluation		
Symptoms and signs	Patients normally anaesthetized	Nausea, vomiting, headache, mental status change
Subjective assessment	Direct inspection and palpation during surgery (e.g. four-point scale)	Not applicable
Objective assessment	Subdural pressure before dural opening	Multiple options, invasive or non-invasive methods (e.g. EVD)
Imaging study	Valuable in predicting the degree of relaxation	Cerebral oedema, midline shift, mass lesion, reduced CBF
Management		
Goal	Relax or shrink the brain by the reduction of intracranial contents to improve operating conditions, reduce retraction injury, and improve patient's outcome	Decrease intracranial pressure to increase cerebral perfusion pressure, optimize CBF, prevent secondary injury, and improve patient's outcome
Hyperosmolar therapy	Applicable	Applicable
Hyperventilation	Applicable	Applicable
Head-up tilt	Applicable	Applicable
Cerebrospinal fluid drain	Applicable	Applicable
Anaesthesia	I.V. agents being preferred by some authors[17]	I.V. agents being preferred by some authors
Craniectomy	Not applicable	Applicable
Hypothermia	No evidence of being effective	May consider[18]

hypertension.[25] Measurement of ICP has been previously reviewed[26–29] and will not be discussed again. The findings on computed tomography (CT) scan, such as oedema, shallow sulcus, midline shift, and compressed basal cisterns, offer clues to the presence of intracranial hypertension.[30 31] Evidence shows that the oedema surrounding tumours based on CT scan predicts the severity of intracranial hypertension.[32] Likewise, a large study involving 692 patients undergoing supratentorial procedures found four significant predictors of poor intraoperative brain relaxation: diagnosis of glioblastoma multiforme, diagnosis of metastasis, midline shift on preoperative imaging, and elevated subdural pressure (a surrogate marker of ICP).[14] Interestingly, in this series the tumour size and location were not predictive of poor brain relaxation.

Subjective assessment

Once the bone and dura are opened, the status of brain relaxation can be evaluated by direct inspection and palpation. Different grading methods were used in previous studies. Bristow and colleagues[6] used a five-point scale assessing brain relaxation from excellent to poor, including ideal, less ideal, tense, bulging, and the worst conditions for surgery. Some studies simply categorized brain relaxation as satisfactory or not.[16 33] Other studies classified the brain as tight, adequate, or soft.[34 35] More recently, a four-point scale, grading the brain as completely relaxed, satisfactorily relaxed, firm, and bulging, has been used.[7 14 17 24 36–40] In general, it is best to avoid scales that have an easily defined midpoint (e.g. a three-point scale), as there is a tendency to select the midpoint level. However, direct visual and tactile assessment by the surgeon and the anaesthetist is subjective, which may be influenced by factors such as the firmness of the tumour and the size of the surgical opening. A previous study demonstrated that the neurosurgeon's tactile estimation of dural tension in posterior fossa surgery was poorly predictive of subsequent brain swelling or herniation.[9] Nevertheless, subjective assessment remains the most convenient and accessible method of grading brain relaxation during craniotomy and informs the surgeon in their discussion with the anaesthetist about additional treatments.

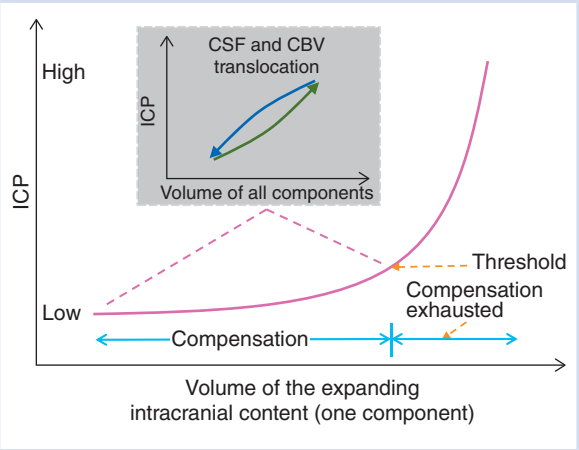

Fig 2 Relationship between intracranial pressure (ICP) and volume of the expanding intracranial content (one component). The ICP remains relatively stable when the increase in the volume of the expanding intracranial content (e.g. tumour) is compensated by the decrease in the volume of cerebrospinal fluid (CSF) and cerebral blood volume (CBV); i.e. translocation of CSF and CBV from the intracranial space to the extracranial space. The volume of all of the intracranial contents, including the expanding intracranial component (e.g. tumour), cerebral parenchyma, CSF, and CBV, remains relatively stable. However, the compensation is a process that is likely to take place over minutes. Mechanistically (the light grey inset), we speculate that there is a transient increase of both the volume of all of the intracranial contents and the ICP (indicated by the upward green arrow) when the volume of the expanding intracranial component (e.g. tumour) is increasing. The transiently increased ICP drives the translocation of CSF and CBV, which then restores both the volume of all of the intracranial contents and the ICP (indicated by the downward blue arrow).

Objective measurement

The subdural pressure measured when the cranium is opened while the dura is closed has been used as an objective indicator of brain relaxation. This method is relatively easy, reliable, and minimally invasive, as long as the dura is not torn during the craniotomy.[9 10 15] In patients with supratentorial tumours, Cold and colleagues[10] showed that the subdural pressure is correlated with the tactile estimation of dural tension and the risk of brain herniation. These authors found that brain herniation occurs rarely when the subdural pressure is <6 mm Hg, whereas pronounced brain herniation is much more likely at a subdural pressure that is ≥11 mm Hg.[10] Another study conducted during posterior fossa surgery showed that brain swelling/herniation occurs rarely if the subdural pressure <10 mm Hg, and some degree of brain swelling/herniation is always present if subdural pressure is ≥10 mm Hg.[9] A similar study conducted in patients undergoing infratentorial surgery showed that all patients with a subdural pressure >13 mm Hg had some degree of brain swelling.[15] When correlating with the subjective four-point scale used for estimating brain relaxation, it was shown that the subdural pressure in grade 1 and 2 patients is significantly different from that in grade 3 and 4 patients.[38] These studies suggest that the subdural pressure is an objective and valuable supplement to the surgeon's subjective estimation of brain relaxation.[14 38]

In summary, the surgeon's visual and tactile assessment remains the foundation of evaluation of brain relaxation during intracranial surgery, while the subdural pressure measurement provides objective and valuable information that supplements the subjective estimation and should be considered in high-risk patients. The existence and severity of intracranial hypertension before craniotomy has predictive value. Nonetheless, efforts should be made to standardize the method for evaluating brain relaxation in order to facilitate clinical communication and research collaboration, especially considering that the subjective assessment by the surgeon can be confounded by the surgeon's personal factors, such as experience and even mood. It needs to be emphasized that the ultimate goal of the evaluation of brain relaxation is not only to optimize operating conditions and minimize retraction injury but ideally also to improve the clinical outcomes. The method of evaluation of brain relaxation should be congruent with this goal.

Management of brain relaxation

A fundamental principle in medical management is that diagnosis precedes treatment. This applies equally well to the intraoperative management of the tight brain; therefore, the potential aetiologies (Table 2) must be considered before intervention. The management of brain relaxation is better guided by the differential diagnosis even though it revolves around the reduction of the intracranial contents in principle. Different interventions have different targets, mechanisms, rapidity, advantages, and disadvantages (Table 3). Most of the options overlap with those for treatment of intracranial hypertension. The advantages and disadvantages of the commonly applied approaches during intracranial surgery deserve a discussion.

Hyperosmolar therapy

Hyperosmotic agents, such as mannitol and hypertonic saline, are commonly used to improve brain relaxation. The mechanism relies on the extraction of the free water from the brain tissue to the intravascular space via the osmotic gradient across the blood–brain barrier that has low permeability to mannitol and sodium. Additionally, the translocation of free water from the extravascular space to the intravascular space decreases blood viscosity and may increase cerebral blood flow,[54 55] which leads to a reduction in CBV in an autoregulating brain as a result of vasoconstriction.[54 56] Therefore, the way in which hyperosmolar therapy effects brain shrinkage is likely to be multifactorial.

The efficacy of hyperosmolar therapy depends on the disease process. In the setting of acute ischaemic stroke or intracerebral haemorrhage, previous studies have found neither beneficial nor harmful effects on the outcome (fatality and dependency) associated with mannitol administration.[57] In a recent study conducted in patients with intracranial haemorrhage, hyperosmolar therapy was found to be associated with worse 3 month outcomes.[58] Although this is different from brain relaxation, it suggests that mannitol may not be as effective in treating a tight brain during craniotomy for acute stroke as for elective intracranial surgery. Additionally, there is concern that these therapies mostly shrink the normal brain, which could worsen midline shift and herniation in a patient with a grave neurological condition. Understanding this potential harm is important in the care of patients presenting to the operating room for decompressive craniectomy.

It is also important to recognize the potential risks associated with different hyperosmolar therapies. Mannitol can cause excessive urine output,[36] renal dysfunction,[18] electrolyte abnormalities,[24] and significant but short-duration alterations in preload, afterload, and cardiac output;[59] however, patients with normal cardiac and renal function can rapidly self-correct

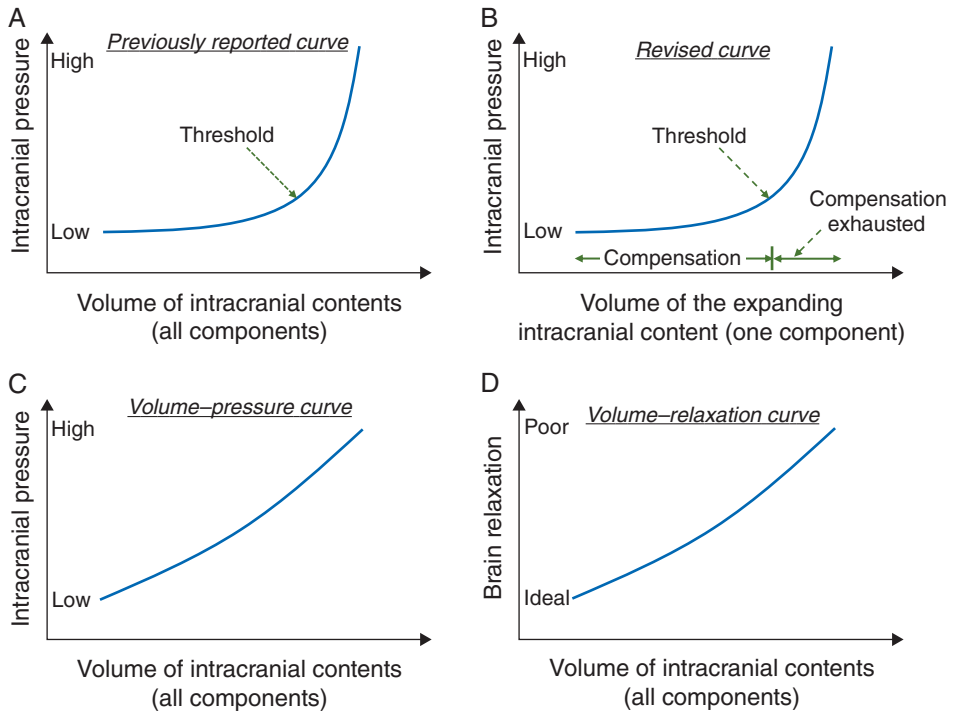

Fig 3 Intracranial volume–pressure and volume–brain relaxation curves. (A) The abscissa of the intracranial volume–pressure curve is commonly labelled as intracranial volume, implying that it is the volume of all of the intracranial contents combined.[19] However, as long as the compensatory mechanisms are still functional, even though the volume of one specific intracranial component increases, the volume of all of the intracranial contents (sum of all components) remains relatively constant. (B) Therefore, it is advisable to name the abscissa as the volume of the expanding intracranial content (one component) instead of the volume of all intracranial contents for the purpose of clarity. (C) The volume–pressure curve should be drawn in a different way if the abscissa represents all intracranial components, when there is an almost linear relationship between the intracranial pressure and the volume of all intracranial components. (D) It is speculated that the volume–brain relaxation curve is similar to the volume–pressure curve (C) if the abscissa also represents all intracranial components.

Table 2 A pragmatic checklist for determining the cause of unsatisfactory brain relaxation. CBF, cerebral blood flow; CBV, cerebral blood volume; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CT, computed tomography; $EtCO_2$, end-tidal carbon dioxide; EVD, external ventricular drain; MAC, minimal alveolar concentration; MRI, magnetic resonance imaging; Pa_{CO_2}, partial pressure of carbon dioxide in arterial blood

Parameters to check	Reasons
Oxygenation (oximetry or arterial blood gas)	Hypoxia results in an increase in CBF and CBV.
Carbon dioxide ($EtCO_2$ or Pa_{CO_2})	Increase in Pa_{CO_2} increases CBF and CBV. $EtCO_2$ may not accurately reflect Pa_{CO_2}.
Haemoglobin	Low arterial blood oxygen content results in an increase in CBF and CBV.
Blood pressure	In an autoregulating brain, hypotension results in cerebral vasodilatation to maintain CBF and a consequential increase in CBV. In a non-autoregulating brain, hypertension increases CBF and CBV.
Body position	Head-down position increases CPP and impedes cerebral venous drainage, with resultant increase of CBV. Head-down position also impedes the translocation of CSF from intracranial space to extracranial intrathecal location.
Neck position	Lateral flexion or torsion may obstruct venous drainage, with resultant increase of CBV.
Imaging study	CT and MRI studies offer clues of poor brain relaxation.
Masses	Could there be additional masses (e.g. contralateral subdural haematoma; enlarging pneumocephalus)?
Mannitol	Has mannitol, another hyperosmolar therapy, or both been given? Hyperosmolar therapy reduces cerebral parenchymal free water.
CSF drain	Is the CSF drainage functional? Check EVD or lumbar drain.
Volatile anaesthetics	Are volatile anaesthetics being used at >0.5 MAC? High-MAC volatile anaesthetics cause cerebral vasodilatation, with resultant increase in CBF and CBV.
Vasodilators	Are (cerebral) vasodilators being used (e.g. nitroglycerin and calcium channel blockers)?

Table 3 Interventions for improving brain relaxation. *Please go through the checklist provided in Table 2 first. †Based on personal experience if not referenced. Pa_{CO_2}, arterial blood partial pressure of carbon dioxide

Treatment*	Method	Advantages	Disadvantages	Speed of onset†
Hyperventilation	Increase minute ventilation but keep Pa_{CO_2}>3.33 kPa[18]	Effective	Cerebral blood flow reduction[41 42]	~5 min[43]
Mannitol	0.25–1 g kg^{-1} i.v.; redose if necessary	Effective	Diuresis, hypovolaemia, renal dysfunction[18]	~10 min[44]
Hypertonic saline	3–7.2% hypertonic saline,[24 35 36] 30–150 ml h^{-1}	Effective	Hypernatraemia,[24] hypokalaemia,[24] myelinolysis[18]	~10 min[44]
Head-up tilt	Reverse Trendelenburg position or head of table elevated position	Effective	Hypotension, venous air embolism,[45] pneumocephalus[46]	<5 min[43]
I.V. anaesthesia	Propofol instead of volatile agents[18]	Cerebral vasoconstriction,[47] less emergence agitation,[48] less nausea and vomiting[49]	Higher cost[34]	~10–20 min
Cerebrospinal fluid drainage	Lumber or ventricular drain	Reliable, intracranial pressure monitoring available	Invasive, infection, neurological injury, brain herniation	<5 min
Furosemide	10–20 mg i.v., redose if necessary	May potentiate cerebral dehydration effect of mannitol[50]	Hypovolaemia, hypokalaemia	~30 min
Steroids	Dexamethasone 4–10 mg, redose if necessary[51]	Reduce peri-tumour oedema[18]	Slow onset, not applicable in traumatic brain injury[18]	Hours[52 53]

mannitol-induced electrolyte abnormalities.[60] Mannitol can also paradoxically exacerbate cerebral oedema when used in patients with a disrupted blood–brain barrier.[61] In contrast, hypertonic saline does not cause diuresis and hypovolaemia,[36] although it carries potential risks of hypernatraemia,[24] hypokalaemia,[24] myelinolysis,[62] and pulmonary oedema.[63] Nonetheless, as most medical interventions are characterized by risk–benefit dilemmas, whether these potential adverse effects are outweighed by the intended therapeutic effect (i.e. a smaller brain) deserves more future outcome-oriented studies.

Previous studies have shown that hypertonic saline is at least as effective as, if not better than, mannitol in patients with intracranial hypertension.[64 65] Another study found that hypertonic saline is effective in treating mannitol-resistant refractory intracranial hypertension secondary to traumatic brain injury in paediatric patients.[66] Overall, the current evidence does not support choosing one agent over the other, especially given the lack of long-term outcome data.[67]

Furosemide is another agent that is often used alone or in combination with a hyperosmolar agent to treat a tight brain. Although earlier animal data suggested that furosemide acts synergistically with mannitol to reduce brain water content,[50] more recent studies demonstrated that furosemide does not reduce the brain water content even in combination with mannitol,[68] and its addition to hypertonic saline does not significantly augment the cerebral dehydration effect in comparison with that using hypertonic saline alone.[69]

Hyperventilation

Hyperventilation has been used for intraoperative brain relaxation for more than 50 yrs.[5 70] The mechanism of brain relaxation secondary to hyperventilation is attributed to the hypocapnia-induced cerebral vasoconstriction and the subsequent reduction of CBV and intracranial volume. The CBV reduction is accompanied by the reduction in cerebral blood flow that could render the brain at ischaemic risk, assuming that the cerebral metabolic activity remains the same before and after hyperventilation.[41 42 71–73] It is important to differentiate cerebral blood flow, a dynamic circulation concept, from CBV that is a static volume concept. Prophylactic prolonged hyperventilation correlates with poorer 3 and 6 months outcomes in head-injured patients and should be avoided.[74] A retrospective study conducted in patients undergoing endovascular thrombectomy for acute ischaemic stroke showed that the patients who had a favourable 90 day outcome had significantly higher 60 and 90 min end-tidal carbon dioxide during the procedure compared with those who had unfavourable outcomes.[75] The current consensus is to maintain normocapnia during intracranial surgery and to reserve hyperventilation as a temporary measure for brain relaxation when the tight brain is resistant to other means of treatment.[76] Nevertheless, hyperventilation is a valuable tool and one of the few interventions that has been documented to improve the brain relaxation score in intracranial surgery.[38] A practical approach is to consider hypocapnia in the same way one considers drugs; there must be an indication, the beneficial effect should be monitored, ideally adverse effects should also be monitored, and when there is no longer an indication, it should be stopped.

Cerebrospinal fluid drainage

Cerebrospinal fluid drainage is an effective means of improving brain relaxation via the reduction of intracranial CSF, a component of the intracranial contents. Drainage of CSF is invasive, however, and requires the insertion of drains, with the inherent associated risks of neural injury, haematoma, and infection. Cerebral herniation is also a potential risk of CSF drainage, especially if lumbar drainage is used.[77] In the setting of abnormally increased volume in the posterior fossa, upward cerebellar herniation is a potential risk with supratentorial external ventricular drains. In paediatric patients with traumatic brain injury, the biomarkers of injury and repair in CSF are two-fold greater with

intermittent CSF drainage compared with continuous CSF drainage, suggesting that the method of CSF drainage may impact outcomes, although long-term outcome data are lacking.[78]

Head-up tilt

Head-up tilt is easy to perform and can facilitate the reduction of intracranial contents via the relocation of CSF from the intracranial space to the extracranial intrathecal space, the reduction of CBV via the gravitational facilitation of cerebral venous blood drainage, and possibly, the gravitational traction on the brain. The concerns related to elevation of the head include an increased risk of cerebral hypoperfusion, venous air embolism, and pneumocephalus.[45 46] In head-injured patients, head elevation to 30 degrees significantly decreases ICP without affecting the cerebral perfusion pressure and blood flow.[79] In prone-positioned neurosurgical patients, 10 degrees of reverse Trendelenburg position significantly decreases ICP while the cerebral perfusion pressure remains unchanged.[80] Therefore, these studies suggest that a mild to moderate head-up tilt reduces ICP and is likely to improve brain relaxation, with minimal effect on cerebral perfusion. Overall, however, the effect of head-up tilt on long-term outcome remains unknown.

I.V. *vs* inhalation anaesthesia

Volatile and i.v. anaesthetic agents have distinctive effects on cerebral vasomotor tone and blood flow.[47 81–84] I.V. anaesthesia, represented by propofol, reduces cerebral blood flow and CBV, probably by its suppressive effect on cerebral metabolic activity (flow–metabolism coupling), whereas high-MAC inhalation anaesthesia increases cerebral blood flow and CBV by its intrinsic cerebral vasodilatory effect even though it also suppresses cerebral metabolic activity.[81–84] This distinction grants i.v. anaesthesia a unique position in neurosurgical anaesthesia for reasons including the belief that it promotes brain relaxation.[1 17 18] Several studies have demonstrated small reductions in intracranial pressure with i.v. anaesthesia, compared with volatile anaesthesia;[17 85 86] however, no difference in brain relaxation scores among different anaesthetic techniques has been demonstrated in several clinical trials.[34 38 39 49] To date, there are insufficient data to advocate one anaesthetic technique over another, or i.v. *vs* inhalation anaesthesia, especially given the lack of crucial outcome data related to neurological morbidity and mortality.[49] An important methodological consideration is the dose of volatile agent used. The commonly used volatile agents do not significantly increase ICP and brain bulk if <0.5 MAC is used.[38]

Steroids

Currently, glucocorticoids are not recommended in the care of patients with traumatic brain injury and might even worsen outcome.[18] Moreover, glucocorticoids have not been shown to reduce oedema (both vasogenic and cytotoxic) effectively in the setting of intracerebral haemorrhage or ischaemic stroke.[87] However, in patients undergoing brain tumour surgery, glucocorticoids such as dexamethasone are often administered in the perioperative period to reduce vasogenic tumour-associated oedema, although the precise mechanisms behind these effects are not clear.[52 88] Glucocorticoids have long been established as effective agents to reduce brain oedema, although the effect is delayed and may peak at 24–48 h after starting treatment.[52 53] Despite routine use, ongoing glucocorticoids are also associated with serious side-effects, including immunological suppression that may adversely affect the oncological outcome.[52 89]

Summary

Brain relaxation describes the intracranial content–space relationship when the cranium and dura are opened during craniotomy. Although brain relaxation is correlated with intracranial pressure, it remains a distinctive concept. The outcomes that matter the most to patients should be emphasized in defining, evaluating, and managing brain relaxation. A standardized approach to evaluate brain relaxation is warranted. Interventions for improving brain relaxation have both advantages and disadvantages that should be taken into consideration in patient care. The patient-centred outcome related to different interventions for a tight brain in different patient populations is an important gap in our knowledge and should be a target for future research.

Authors' contributions

Conceived this review article and revised every draft of this manuscript: L.M.
Literature search and prepararation of the first draft of this manuscript: J.L.
Substantial editing of every draft of this manuscript and contributed to the finalization of the idea: A.M.F., A.W.G., F.J.

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