IMPACT OF ALTERED AIRWAY PRESSURE ON INTRACRANIAL PRESSURE, PERFUSION AND OXYGENATION - *A NARRATIVE REVIEW*

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Key Words: mechanical ventilation; positive pressure ventilation, negative pressure ventilation, Intracranial pressure, cerebral perfusion, cerebral oxygenation.

Conflict of Interest: BPK has a patent pending for a device for mechanical ventilation.

ABSTRACT

Objectives: A narrative review of the pathophysiology linking altered airway pressure and intracranial pressure (ICP) and cerebral oxygenation.

Data Sources: Online search of PubMed and manual review of articles (laboratory and patient studies) of the altered airway pressure on ICP, cerebral perfusion or cerebral oxygenation.

Study Selection: Randomized trials, observational and physiological studies.

Data Synthesis: In the normal brain, positive pressure ventilation (PPV) does not significantly alter ICP, cerebral oxygenation or perfusion. In injured brains, the impact of airway pressure on ICP is variable and determined by several factors; a cerebral venous Starling resistor explains much of the variability. Negative pressure ventilation can improve cerebral perfusion and oxygenation and reduce ICP in experimental models, but data are limited, and mechanisms and clinical benefit remain uncertain.

Conclusions: The effects of airway pressure and ventilation on cerebral perfusion and oxygenation are increasingly understood, especially in the setting of brain injury. In the face of competing mechanisms and priorities, multimodal monitoring and individualized titration will increasingly be required to optimize care.

INTRODUCTION - Mechanical ventilation is a core management of patients with acute intracranial hypertension; while the relationships among ventilation, $PaCO_2$ and intracranial pressure (ICP) are well understood, the impact of altering airway pressure (P_{aw}) is less well appreciated. It is often assumed that raising P_{aw} will invariably elevate ICP, but recent data indicate that this is not always the case. The effect of altering P_{aw} depends on several factors (*e.g. respiratory mechanics, lung recruitability, baseline ICP*), and the resulting ICP may be unchanged, increased or decreased. Furthermore, the impact on cerebral oxygenation is often unknown. This *Review* considers the pathophysiology linking altered P_{aw} and ICP, the impact of pleural and venous pressures, and the consequences for cerebral oxygenation. Data from patient (***Table 1***) and laboratory (***Table 2***) studies are synthesized, and the importance of titrating P_{aw} against individual responses considered.

PUBLICATION SEARCH STRATEGY - Words used were "airway pressure, positive pressure ventilation, negative pressure ventilation, mechanical ventilation, PEEP, ICP, cerebral perfusion pressure, cerebral oxygenation, brain tissue oxygenation, cerebral blood flow". References from articles were also searched to identify additional studies.

BASIC CONCEPTS - The Monroe-Kellie doctrine dictates that the contents of the cranium consist of the combined volume of the brain, the blood and the cerebrospinal fluid (CSF); and, because the skull is rigid (and its contents non-compressible), increases in the volume of the contents exponentially increases the ICP (***Figure 1***). Since the components are non-compressible and the overall volume cannot be increased, an increase in intracranial mass (edema, hydrocephalus, tumor, hematoma, etc.) results in displacement of the fluid components (*i.e.* blood and CSF) out of the cranium (1). Once the capacity to displace CSF and blood volume is exhausted, additional increases in any of the intracranial contents is associated with precipitous increases in ICP (1).

An increase in P_{aw} increases pleural pressure, which in turn elevates central (and jugular) venous pressure. Because increased jugular venous pressure impedes cerebral venous return, the cerebral blood volume (CBV) -and the ICP- increases (2). Raised ICP may occur because of greater intracranial

blood volume due to greater arterial inflow, or less venous outflow (3, 4).

The effectiveness of the transmission of P_{aw} to the pleural space and the intra-thoracic veins depends on the relative compliance of the lung and chest wall (5); transmission of pressure from the thoracic veins to the neck and cranial veins can be impeded by head position, or by the effect of a cranial 'Starling resistor' (6).

A Starling resistor is a collapsible tube on which the external pressure exceeds the outflow pressure (**Figure 2**), and depending on that pressure difference, provides a 'variable' resistor. The anatomic basis is the cranium (*i.e.* a sealed, rigid compartment that determines the external pressure), the non-collapsible cerebral artery (upstream), the non-collapsible superior sagittal sinus (downstream), and the intervening collapsible cerebral veins.

Evidence for this phenomenon comes from hemodynamic (6-8) and imaging (9) studies. In graded elevations in ICP, the P_{aw} was altered (6, 7) (**Figure 2**) and an abrupt drop in venous pressure (a 'resistor') demonstrated by passing a catheter from the cerebral vein into the sagittal sinus (6). Raised ICP compressed the cerebral veins and decreased downstream venous pressure; thus, the increased pressure gradient between the cerebral vein and the sagittal sinus constitutes a vascular 'waterfall' impeding the transmission of central venous pressure (CVP) into the cranium and regulating outflow. In this scenario, increases in P_{aw} will be incompletely transmitted and will not (or only marginally) further increase ICP (6, 7). However, if P_{aw} exceeds a threshold, the CVP (and downstream venous pressure) exceeds the ICP; this opens the resistor and establishes a direct (venous) connection between the thorax and the cranium: here, elevating P_{aw} raises ICP.

Finally, decreased venous return also lowers the cardiac output, which if it reduces systemic arterial pressure, will lower the cerebral perfusion pressure (CPP). If cerebral autoregulation is intact, CBF may be maintained despite a lower CPP, but if impaired, decreased CPP may lower cerebral blood flow (CBF) and CBV, and thereby decrease ICP. Brain injury raises the lower limit of CPP at which autoregulation is active (10-12), resulting in differential effects on ICP with reductions in CPP that depend on how much CPP has already been reduced. Above the (elevated) lower limit of autoregulation, reduced CPP will result in vasodilatation, which in a non-compliant intracranial cavity will increase ICP and further reduce

CPP (and potentially CBF). Reduced CPP below the lower limit of autoregulation will not trigger autoregulatory vasodilatation -and regardless of ICP- will nonetheless reduce CBF. CBF appears not to be closely related to cardiac output (13). A conceptual framework of the integrated regulation of brain perfusion suggests that CBF is regulated by multiple factors including sympathetic activity, renin–angiotensin action, cardiac output, blood pressure, metabolic products, nitric oxide etc. (14).

The concept of intracranial compliance is important. Impaired compliance is not synonymous with elevated ICP. Although comparable in shape, individual patient ventricular volume-pressure curves may demonstrate important differences. A similar level of ICP might occur in the face of a higher *vs*. a lower compensatory reserve. Measurement of intracranial compliance is performed (in experimental models) by injecting a known (small) amount of fluid into the CSF and noting the increment in ICP.

Thus the two key determinants of the impact of elevating PEEP are the intracranial compliance, and the 'net' change of CBV, which is determined by the relative inflow (regulated by preload, cerebral autoregulation, respiratory mechanics, CO_2, etc.) and outflow (regulated by CVP, Starling resistor, etc.; *Figure 1*).

POSITIVE PRESSURE VENTILATION - This can be divided into two components: static (*i.e*. PEEP or continuous positive airway pressure, CPAP), and dynamic (*i.e*. the changes with each tidal volume); an increase in either will increase mean P_{aw}, but can have different hemodynamic consequences (15). Increased 'static' pressure causes a proportionate decrease in cardiac output, whereas increased dynamic pressure has minimal impact on cardiac output until a threshold is reached. Elevated static pressure elevates systemic venous pressure whereas increased dynamic pressure can lower it (15). Nonetheless, most studies focus on the effects of static P_{aw} (usually PEEP) on ICP, cerebral perfusion and oxygenation. ICP elevation (variable, not sustained) may accompany elevation of peak P_{aw} (16).

Normal Brain: Few data exist describing the influence of P_{aw} on ICP in patients without intracranial pathology (unsurprising - ICP not ordinarily be monitored). Using non-invasive assessment of ICP (*e.g*. transcranial Doppler, optic nerve sheath diameter) in patients undergoing elective surgery, PEEP of 8 cmH_2O (P_{aw} increase ≈ 4 cmH_2O) has minimal impact on ICP (17, 18).

The impact P_{aw} on cerebral perfusion and oxygenation has been examined in patients without brain injury during elective surgery (17-23). The most common non-invasive assessment of cerebral perfusion is Transcranial Doppler (TCD) ultrasound (19, 24-26), while cerebral oxygenation is estimated using near-infrared spectroscopy (NIRS) (18, 20-23, 27). Increased P_{aw} can increase (28), decrease (29), or not alter (30) CBF velocity; however, even if velocity is altered, regional oxygenation is usually maintained (31).

To accurately measure CBF using TCD, the diameter of the imaged artery must be constant (32). In the setting of intact autoregulation (no brain injury), the cerebral artery may constrict (or dilate) to maintain constant CBF (33), because the cardiac output fluctuates with P_{aw}. However, while the middle cerebral artery diameter is sensitive to exercise (34), $PaCO_2$ (35, 36) and hypoxemia (37), it is unknown if it responds to altered P_{aw}.

Injured Brain – ICP: In patients with brain injury, ICP may be normal (or normalized by medical management), or elevated. The responses of ICP to increases in P_{aw} are not predictable based on its initial level (38, 39). Some studies report that increased PEEP may have no impact on ICP if not initially elevated, but may have impact if initially elevated (39). However, the opposite has also been reported: raised P_{aw} had no impact on already elevated ICP, but increased it if initially normal (38). Finally, increased P_{aw} may decrease ICP (40).

In attempting to reconcile these disparate reports, three issues are key. *First*, the ability to perform interventional testing in patients with intracranial hypertension is limited, as such patients are vulnerable. *Second*, assessment is confounded by analgesics, sedatives, anesthetics and anticonvulsants, as well as deliberate control of blood pressure, blood gases, acid-base status, plasma osmolality, glucose and temperature (41-44). *Third*, intracranial veins can behave as either veins in series without threshold flow characteristics (45), or as a 'Starling Resistor' (6, 7). If intrathoracic pressures are transmitted into the intracranial veins, this can increase the volume of intracranial blood (even if only slightly). If an incremental increase in the volume of the intracranial contents exceeds the 'compensatory reserve', ICP will rise precipitously (1). In summary, modest levels of positive P_{aw} can potentially increase ICP, but may conversely have no significant effects.

Injured Brain – Cerebral Perfusion and Oxygenation: There are few reports of the effects of altered P_{aw}

on cerebral perfusion or oxygenation, likely in part, because accurate non-invasive assessment is not generally available. The most widely used non-invasive assessment of CBF is TCD and, as with ICP, results are variable (46-48). Although widely used in non-brain injured patients, non-invasive assessment of cerebral oxygenation (*e.g.* NIRS) has not been well investigated.

Direct measurement of CBF using intracranial flow probes (49), radioactive microspheres (50, 51) or arterial flow probes (52), suggest decreased (52) or unchanged (49-51) ICP following increases in P_{aw}. However, in patients with subarachnoid hemorrhage, increases in PEEP (5-20 cmH$_2$O) that are sufficient to decrease mean arterial pressure (MAP), reduce regional CBF and brain tissue oxygenation (49). More recent multimodal monitoring that incorporates ICP, cerebral perfusion and cerebral oxygenation may provide better insight (53, 54). In summary, altered P_{aw} may change cerebral perfusion or oxygenation before any change in ICP can be observed; such effects have not been extensively investigated and, at the bedside, are likely under-recognized. Ultimately, the focus must be on identifying vulnerable regions and determining the impact on perfusion or oxygenation in these areas.

Compliance of the Lung and the Chest Wall: Understanding the relationships between respiratory mechanics and vascular physiology may help predict how changes in P_{aw} will influence ICP (48, 55, 56). Increases in P_{aw} are transmitted to the pleural space and raise the P_{pl}, which in turn raises the CVP. The elevation in CVP reflects a reduced venous return, and the lowered CO can initiate autoregulatory cerebral vasodilation and increase ICP. Elevated CVP can also directly increase ICP by decreasing jugular venous outflow; or, in the presence a Starling resistor, open the resistor, increase outflow and lower ICP (15, 57).

The first 'linkage' is the impact of P_{aw} on P_{pl}. The transmission of changes in P_{aw} to the pleural space depends on the relative compliance of the lung and the chest wall. If the lung compliance is high and the chest wall compliance is low, then the transmission is highly 'efficient' (5). This can be conceptualized as an elevation in P_{aw} maximally extending through the highly compliant lung to the pleural space, but because expansion of the pleural space is prevented by a non-compliant chest wall, the P_{pl} rises in close approximation to the P_{aw}. By contrast, if the lung is non-compliant, the transmission of a change in P_{aw} is poor; moreover, even if P_{aw} transmission is efficient, a highly compliant chest wall

can dissipate swings in P_{pl} (*Figure 3*).

The local static pressure in any part of the pleural space (P_{pl}) depends on the body position, the contents of the thorax and abdomen, and the distance between the dependent and nondependent thoracic margins (58). In normal lung a 'swing' in pleural pressure (*e.g.* inspiratory or expiratory effort) is transmitted -almost instantaneously- to all parts of the pleural space; this reflects normal or, 'fluid like' lung behavior (59). However, if injury or atelectasis is present, the transmission of swings in P_{pl} through abnormal areas may be impaired; this reflects 'solid like' lung behavior (60). Thus, with dependent atelectasis, a deflection in P_{pl} near the diaphragm caused by spontaneous inspiratory effort will be poorly transmitted to the rest of the pleural space (61). In contrast, with positive pressure ventilation and dependent atelectasis, dynamic changes in P_{aw} will be greatest in the pleura around ventilated regions; but will not be effectively dissipated and not impact on venous pressure as effectively as with normal lungs.

P_{pl} is contiguous with the pericardial space (62), thus an increase in P_{pl} increases CVP. Increased PEEP raises the mean systemic and the right atrial pressures to the same extent, thereby maintain an unchanged gradient for venous return (63). However, cyclic positive pressure reduces venous return, notwithstanding an unchanged mean P_{aw} (64).

The transmission of CVP to the internal jugular vein is direct (65), but the vein can collapse and regulate an abrupt decrease in downstream pressure (CVP) from an accompanying increase in the gradient between CVP and the pressure in the internal jugular vein (*e.g.* negative pressure ventilation, vigorous spontaneous breathing). By contrast, an increase in CVP can be transmitted to the internal jugular vein without being impeded by such an extracranial 'waterfall' (65), provided any intracranial resistor is overcome (6, 7).

Impact of Concomitant Medical Management: A stepwise approach to escalating treatment intensity has evolved (66, 67) and may impact the effects of mechanical ventilation. For example, sedation or barbiturate coma can induce a redistribution of intravascular volume and increase the risk of arterial hypotension due to vasodilatation. Hyperosmolar agents (*e.g.* mannitol) acutely increase intravascular

volume, but subsequent diuresis causes hypovolemia, which can amplify the depressant effects of positive-pressure ventilation on hemodynamics and cerebral perfusion (68).

Impact on Clinical Outcomes: Although associations between intermediate (patho)physiological endpoints (*e.g.* ICP, CBF, $P_{ti}O_2$) and clinical outcomes (*e.g.* mortality, disability) have been shown (44, 69), the impact of altered P_{aw} on clinical outcomes is rarely investigated, probably because mechanical ventilation is a 'support' rather than a therapy. In respiratory failure mechanical ventilation is more likely seen as a central modality, and studies in respiratory failure generally exclude patients with brain injury. However, a ventilation strategy that improves intermediate endpoints may facilitate optimal brain recovery and improve outcome.

Management of Concomitant ARDS and Intracranial Hypertension: Favorable effects of PEEP must be balanced with impact on hemodynamics and cerebral perfusion. The impact of PEEP on ICP are lessened if lung compliance is low (***Figure 3***). However, 'trade off' of lung protection (permitting some hypercapnia) and brain protection (avoiding abrupt hypercapnia, sometimes rapidly inducing hypocapnia) need to be considered (***Figure S1***, supplement). With elevated PEEP, individual titration may be essential.

Monitoring and Individualization: The effect of positive-pressure ventilation on ICP (and probably on cerebral perfusion and oxygenation) is determined by several factors including the nature of the lesion (*e.g.* traumatic brain injury, subarachnoid hemorrhage, thrombotic stroke), concomitant conditions (*e.g.* coexisting ARDS, septic shock), and adjunct therapies (***Figure S1***, supplement). Because of the 'interdependence' among these parameters, no single value can be considered in isolation, and the net impact may be difficult to predict. Thus, individualized monitoring and titration is key.

NEGATIVE PRESSURE VENTILATION - Negative intrathoracic pressure decreases the impedance to venous return which may in turn decrease ICP. The increased venous return may increase cardiac output and

potentially increase MAP, and the latter may increase cerebral perfusion (70-74).

Two types of negative thoracic pressure devices are described: the intrathoracic pressure regulator, and the inspiratory impedance threshold device. These can decrease ICP in brain injury following experimental cardiac arrest (70-72). The regulator decreases ICP in an experimental brain injury (73), and in patients (74). However, the effect of negative thoracic pressure on cerebral oxygenation is unknown (74). Continuous negative abdominal pressure (CNAP) has been reported as an adjunct to conventional ventilation for intra-abdominal hypertension (75-77). Subsequently, different forms of CNAP have been shown to selectively recruit basal atelectasis, increase end-expiratory lung volume and improve oxygenation (60, 78-80). Although CNAP can decrease intra-abdominal and intrathoracic pressure, the overall impact of CNAP on ICP, and cerebral perfusion or oxygenation is not well studied. In experimental intra-abdominal hypertension, CNAP reduced both intra-abdominal pressure and ICP (77). Negative pressure ventilation is not widely used and experience is limited.

IMPORTANT UNKNOWNS - Although the effect of positive P_{aw} on ICP has been widely studied, it is poorly understood, especially regarding regional cerebral oxygenation. Negative pressure ventilation may decrease ICP and possibly increase cerebral perfusion and oxygenation, but the impact -and determinants- need to be better understood. Finally, the effects of P_{aw} on the brain in patients with different mechanisms of (and therapies for) brain injury, need individual design and assessment of long-term impact.

CONCLUSIONS: The effect of P_{aw} on ICP is determined by several factors, and the net impact may be unpredictable. In the face of competing mechanisms and a spectrum of priorities, individualized titration is required to optimize care, especially in patients with severe respiratory failure (*e.g.* ARDS).

FIGURE LEGENDS

Figure 1 - Relationships among Changes in Airway Pressure and Intracranial Pressure: An increment of airway pressure, if transmitted to the pleural cavity, will increase pleural pressure. The transmission is determined by the mechanics of the lung and the chest wall. The increase in pleural pressure impedes venous return, which can reduce cardiac preload (and output), as well as cerebral venous outflow (and this may increase cerebral blood volume; CBV). Reduced cardiac output may reduce CBV due to decreased cerebral artery inflow, and this is regulated by sympathetic activity, renin–angiotensin action, blood pressure, metabolic products, nitric oxide etc. A conceptual framework of the integrated regulation of brain perfusion has been proposed (Meng L *et al*: Anesthesiology, 2015, 123:1198-1208). If increased airway pressure accompanies an increase in minute ventilation, hypocapnic alkalosis may in addition cause cerebral vasoconstriction. The net impact on ICP reflects the balance of changes in CBV caused by altered (venous) outflow and (arterial) inflow.

Figure 2 - Intracranial Starling Resistor: An intracranial Starling resistor consists of a 'rigid' cerebral artery, sagittal sinus and a compressible cerebral vein. In this system, a pressure gradient (caused by the higher CSF pressure external to the cerebral vein, arrow) regulates cerebral venous outflow. Elevated intracranial pressure (ICP) compresses the cerebral veins and increases upstream venous pressure (P_v) while the sagittal sinus pressure (P_{ss}) is not impacted by the raised ICP (the sinus wall is rigid). Thus, the increased pressure gradient between the cerebral vein and the sagittal sinus constitutes a vascular 'waterfall' (arrows in *Panel A*), and this external vascular compression impedes the transmission of central venous pressure (CVP) into the cranium. Under these circumstances, increased airway pressure (P_{aw}) will not be transmitted *via* increased CVP into the cranium and will not elevate ICP. Above a threshold level, the CVP exceed P_{ss} and thus P_v, and this will open the resistor and establish a direct (venous) connection between the thorax and the cranium. In this setting, increased P_{aw} elevates ICP (*Panel A*). The 'vascular waterfall' is seen on angiography as a decreased vein diameter (with increased velocity), and the smaller caliber vessel is termed the 'void sign' (arrows in *Panel B*). *Panel A* - Modified from Luce et al: J Appl Physiol Respir Environ Exerc Physiol, 1982, 53: 1496-1503. *Panel B* - Reproduced

from Simone et al: Panminerva Med, 2017, 59: 76-89. ***Abbreviations***: CVP central venous pressure, ICP intracranial pressure, MAP mean arterial pressure, P_{aw} airway pressure, P_{ss} sagittal sinus pressure, P_v (cerebral) venous pressure.

Figure 3 - Transmission of Deflections in Airway Pressure to the Pleural Space: The transmission of a positive deflection of P_{aw} to the pleural cavity is determined by both the compliance of the lung and the chest wall (***Panel A***). The transmission is more effective when the chest wall is stiff and/or the lung is compliant, resulting in a larger deflection or 'swing' in P_{pl} in response to a positive pressure inflation (***Panel B***). In the presence of injury or atelectasis, the transmission of 'swings' in P_{pl} through abnormal lung regions may be impaired (so called 'solid like' lung behavior). Therefore, during positive pressure ventilation, dynamic changes in P_{pl} are greater in the pleural space surrounding ventilated regions, than in the non-ventilated (*e.g.* dependent, atelectatic) regions (***Panel C***). ***Abbreviations***: P_{aw} airway pressure, P_{pl} pleural pressure.

On-Line Supplement

Figure S1 - Algorithm for Management of Mechanical Ventilation Strategy in Concomitant Brain Injury and ARDS *This threshold has not been validated. Because SaO_2 90% appears to be the threshold of hypoxic cerebral vasodilatation (Anesth Analg. 85:817-820, 1997) and there is significant heterogeneity in vascular responses in traumatic brain injury, it may be prudent to target SaO_2 95% in such patients. Further study is needed. ***Abbreviations***: ARDS Acute Respiratory Distress Syndrome, CBF Cerebral Blood Flow, CPP Cerebral Perfusion Pressure, $ECCO_2R$ Extracorporeal CO_2 Removal, ECMO Extracorporeal Membrane Oxygenation, ICP Intracranial Pressure, PBW Predicted Body Weight, PEEP Positive End-Expiratory Pressure, SaO_2 arterial oxygen saturation. Adapted from Oddo et al: Intensive Care Med, 2016; 42:790-793.

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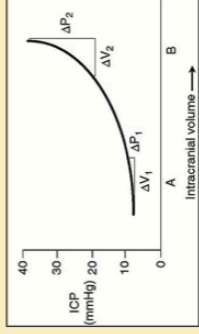
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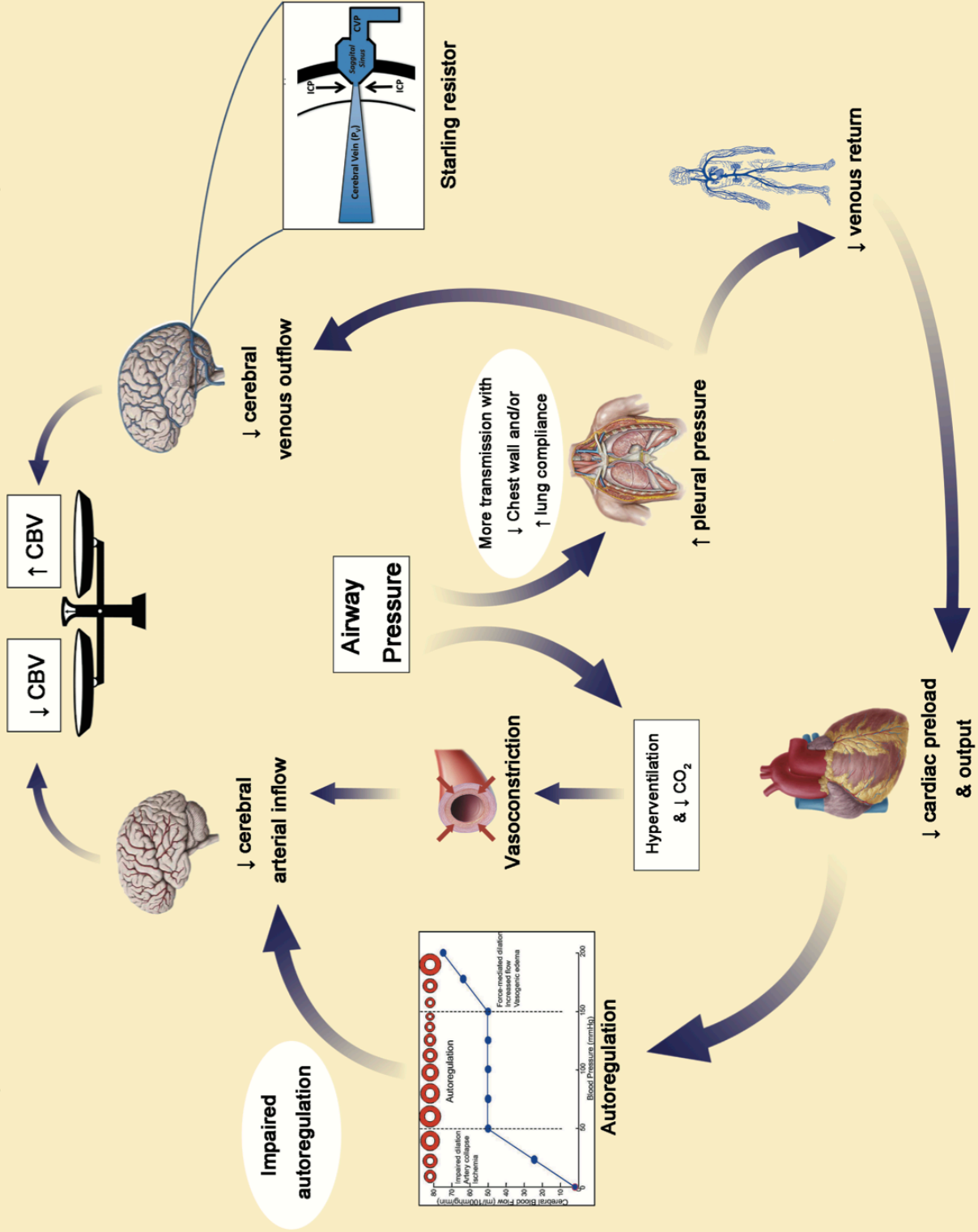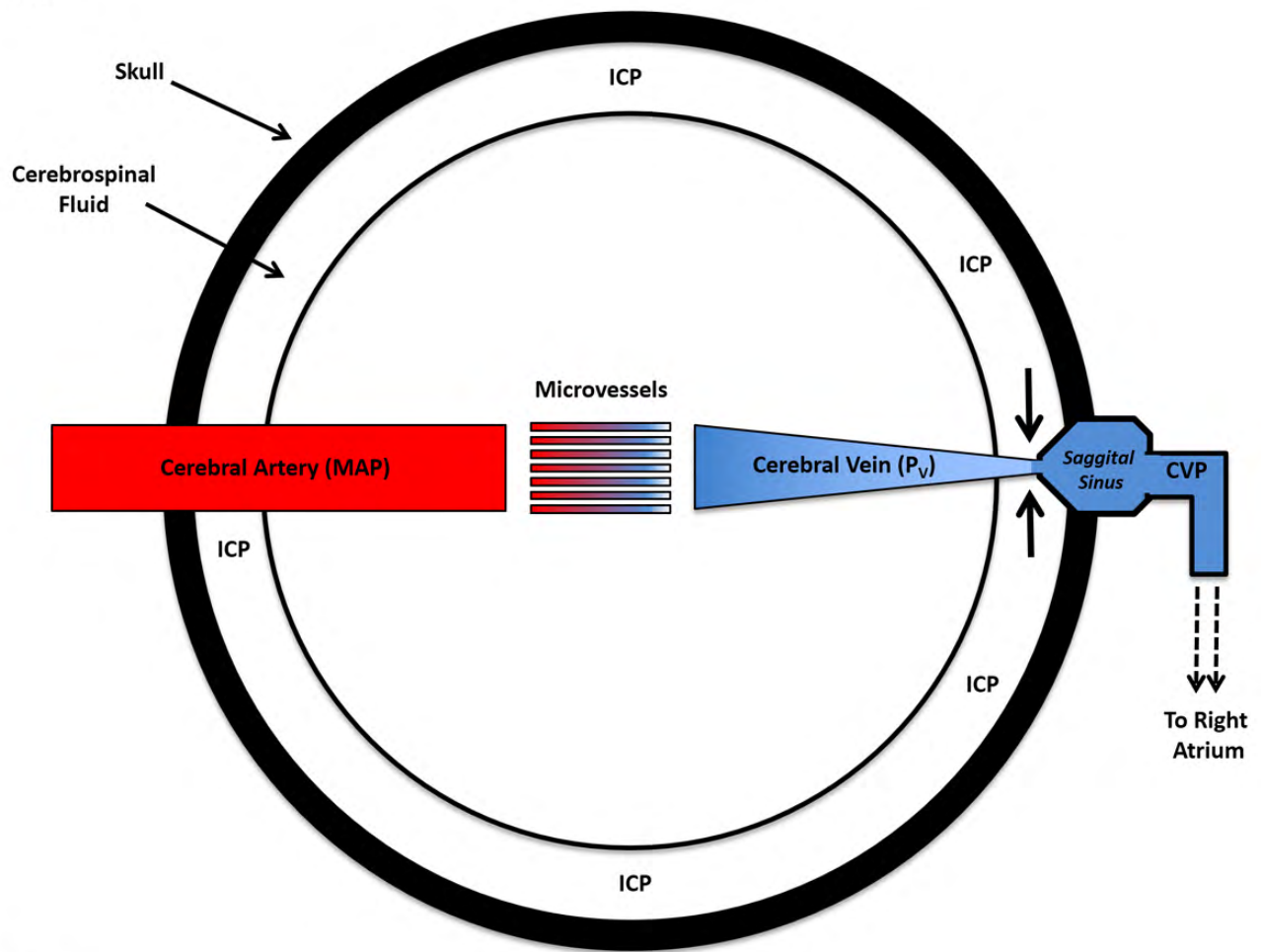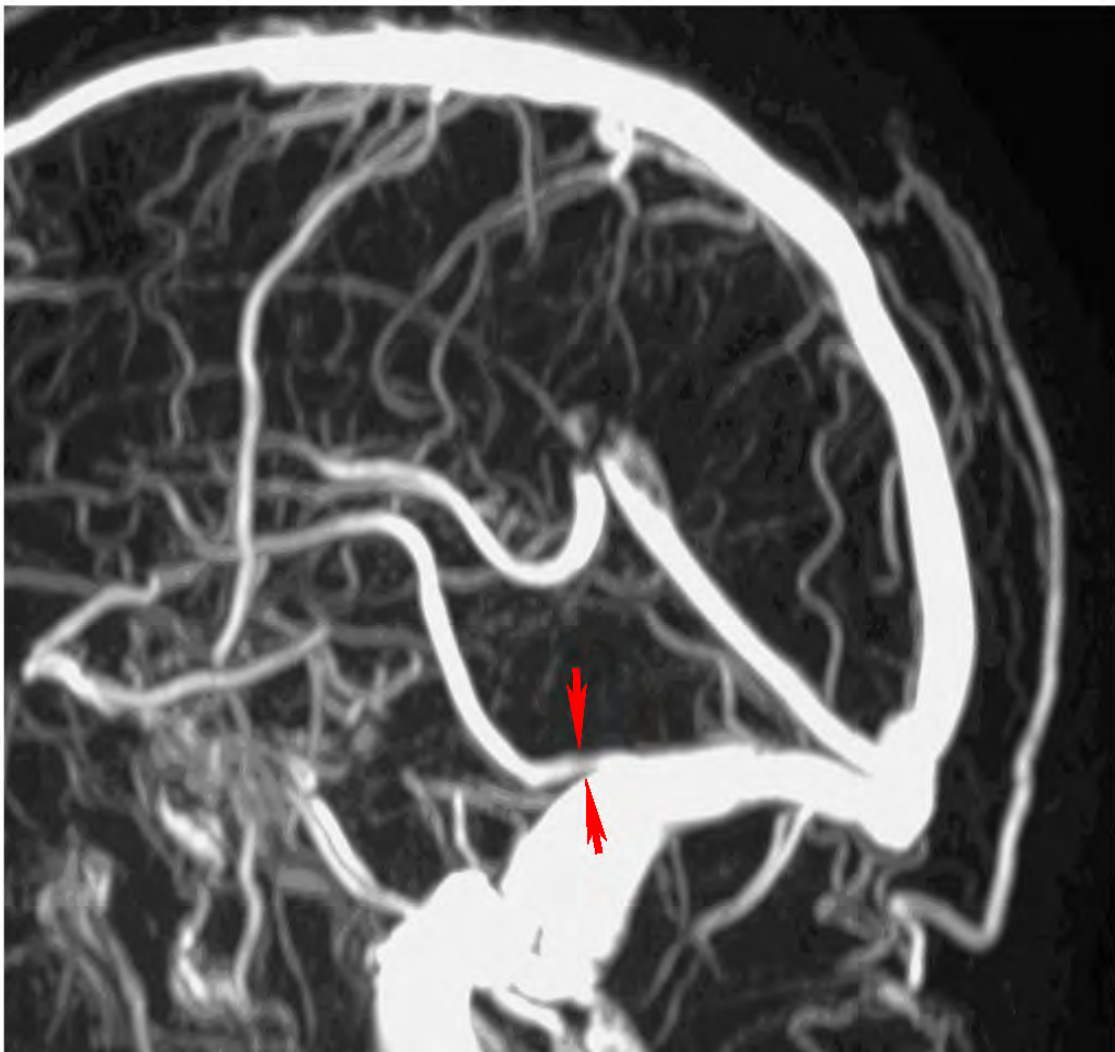
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Intracranial compliance

Starling resistor

↑ ICP

↓ ICP

↓ cerebral venous outflow

↑ CBV

↓ CBV

↓ cerebral arterial inflow

Vasoconstriction

Hyperventilation & ↓ CO_2

Airway Pressure

More transmission with ↓ Chest wall and/or ↑ lung compliance

↑ pleural pressure

↓ venous return

↓ cardiac preload & output

Impaired autoregulation

Autoregulation

A

Skull

Cerebrospinal Fluid

ICP

ICP

ICP

ICP

ICP

Microvessels

Cerebral Artery (MAP)

Cerebral Vein (P_V)

Saggital Sinus

CVP

To Right Atrium

B

A

P$_{aw}$

Normal

P$_{pl}$ swing

P$_{pl}$ P$_L$

B

P$_{aw}$

High Compliance

Low Compliance

P$_{pl}$ swing

P$_{pl}$ P$_L$

C

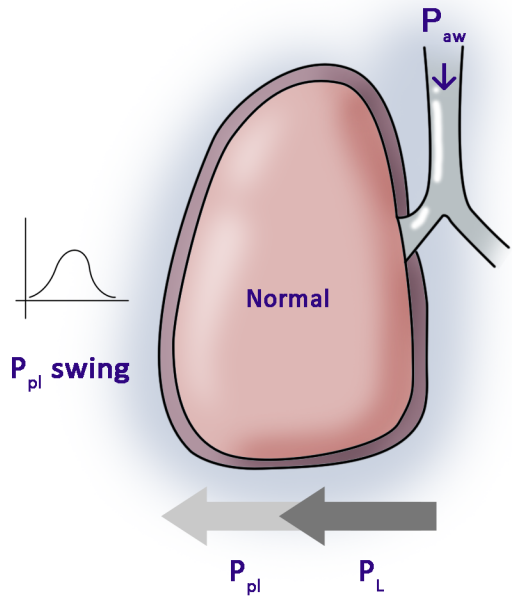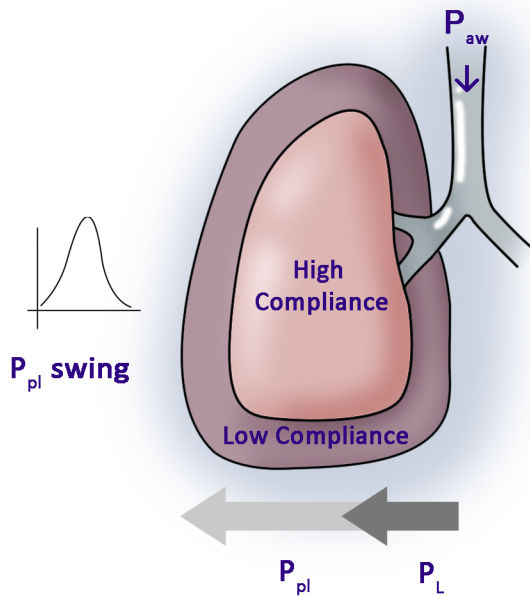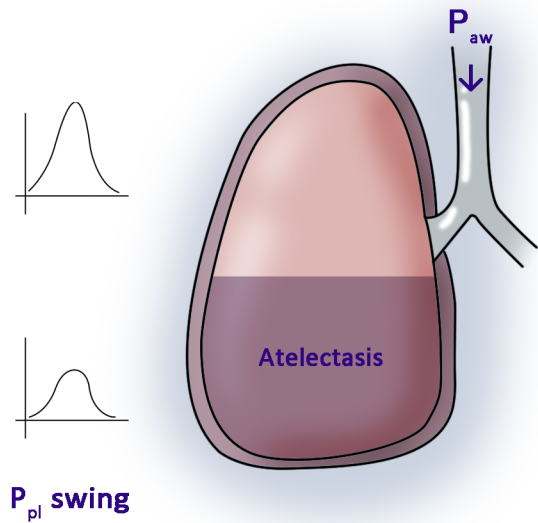P$_{aw}$

Atelectasis

P$_{pl}$ swing

Table 1 MAIN IMPACT OF INCREASING AIRWAY PRESSURE OR PEEP IN PATIENTS WITH BRAIN INJURY

AUTHOR (#)	YEAR	SUBJECTS	MAIN IMPACT OF INCREASING AIRWAY PRESSURE OR PEEP
ICP INCREASED			
Ludwig (16)	2000	TBI (n=10)	PEEP increases ICP; Increasing peak P_{aw} increases variability of ICP, CPP and V_mMCA
Burchiel (55)	1981	TBI (n=16), SAH (n=2)	PEEP increases ICP; decreases CPP if cerebral compliance low & lung compliance normal
Shapiro (81)	1978	TBI (n=12)	PEEP increases ICP in 50% of patients
Muench (82)	2005	SAH (n=10)	PEEP increases ICP; decreases rCBF and $P_{ti}O_2$.
Mascia (47)	2005	TBI & ARDS (n=10)	ICP, V_mMCA and S_jO_2 unchanged if lungs recruitable; deteriorate if lungs unrecruitable
Cooper (83)	1985	TBI (n=33)	PEEP increases ICP (not if baseline ICP elevated)
McGuire (38)	1997	N/Surg (n=18)	PEEP increases ICP (not if baseline ICP elevated)
Apuzzo (39)	1977	N/Surg (n=25)	PEEP increases ICP if cerebral elastance elevated
Cunitz (84)	1979	N/Surg (n=24)	PEEP increases ICP
Lima (85)	2011	ICH (n=25)	PEEP increases ICP (not CPP)
Videtta (86)	2002	N/Surg (n=20)	PEEP increases ICP (not CPP)
NO IMPACT ON ICP			
Solodov (87)	2016	ICH (n=39)	PEEP non-significant increase in ICP (no effect on CPP)
Zhang (88)	2011	TBI & ARDS (n=9)	No change in ICP or CPP
Martinez-Perez (89)	2004	TBI & ARDS (n=7)	No changes in hemodynamic or cerebral parameters
Caricato (48)	2005	TBI, SAH (n=21)	PEEP reduces CPP and V_mMCA if respiratory compliance normal; no impact on ICP or S_jO_2.
Frost (90)	1977	Coma (n=7)	No increase in ICP if normal/low intracranial compliance; no increase ICP in absence of pulmonary disease.
Nemer (91)	2015	TBI & ARDS (n=20)	PEEP increases $P_{ti}O_2$, no impact on ICP or CPP
Pulitano (46)	2013	Ped. Tumor (n=21)	No change in ICP, CPP or V_mMCA
OTHER EFFECTS			
Georgiadis (92)	2001	N/Surg (n=20)	Complex effects, 3 patterns observed

Abbreviations: ARDS (Acute Respiratory Distress Syndrome), CPP (Cerebral Perfusion Pressure), ICH (Intracranial Hemorrhage), ICP (Intracranial Pressure), N/Surg (Neurosurgery), P_{aw} (Airway Pressure), Ped. Tumor (pediatric brain tumor), PEEP (Positive End-Expiratory Pressure), $P_{ti}O_2$ (brain tissue oxygenation), rCBF (regional cerebral blood flow), SAH (Subarachnoid Hemorrhage), S_jO_2 (jugular saturation of oxygen), TBI (Traumatic Brain Injury), V_mMCA (mean blood flow velocity, middle cerebral artery).

Table 2 MAIN IMPACT OF INCREASING AIRWAY PRESSURE OR PEEP IN ANIMAL STUDIES

Author	Year	Subjects	Brain injury	MAIN IMPACT OF INCREASING AIRWAY PRESSURE OR PEEP
ICP INCREASED				
Sun (93)	2014	Dogs	N	PEEP increases ICP, Hyperbaric oxygen leads to a smaller ICP increase
Luce (6)	1982	Dogs	Y	PEEP increases ICP (less if baseline ICP elevated)
Huseby (7)	1981	Dogs	Y	PEEP increases ICP (less if baseline ICP elevated)
Doblar (52)	1981	Goats	N	PEEP increases ICP and decrease CBF, complex impact of mannitol
Cotev (94)	1981	Dogs	Y	PEEP increases ICP (more if baseline ICP elevated)
Huseby (95)	1978	Dogs	N	PEEP increases ICP, decrease CPP
Aidinis (96)	1976	Cats, ARDS	Y	PEEP increases ICP, less impact if lung injury present
O'Rourke (97)	2007	Sheeps	Y	P_{aw} increases ICP; mode of ventilation (conventional, HFOV) no impact on ICP, S_jO_2 or CBF
Walker (98)	1992	Lambs	N	P_{aw} increases ICP and decreases CPP, no impact of ventilation mode (conventional, HFOV)
NO IMPACT ON ICP				
Muench (49)	2005	Pigs	N	No impact on ICP, $P_{ti}O2$ or CBF
Toung (50)	1988	Dogs	N	ICP increased by Jugular compression (not by PEEP); No impact on CBF or $CMRO_2$
Heuer (99)	2012	Pigs	Y	$P_{ti}O_2$ decreased with increased P_{aw}; CPP, CBF increased with HFOV (ICP unchanged)
OTHER EFFECTS				
Feldman (100)	1997	Rabbits	Y	PEEP reduces Intracranial compliance
Walfisch (51)	1997	Dogs, ARDS	N	No impact on CBF

Abbreviations: ARDS (Acute Respiratory Distress Syndrome), $CMRO_2$ (Cerebral Metabolic Rate of Oxygen), CPP (Cerebral Perfusion Pressure), HOFV (High Frequency Oscillatory Ventilation), ICP (Intracranial Pressure), P_{aw} (Airway Pressure), PEEP (Positive End-Expiratory Pressure), $P_{ti}O_2$ (brain tissue oxygenation), CBF (Cerebral Blood Flow), S_jO_2 (jugular saturation of oxygen).

Brain Injury & ARDS

- V_T 6-8 mL•kg^{-1} — Monitor ICP, adjust RR to PaCO$_2$
- SaO$_2$ 88-92% — Monitor brain oxygen if SaO$_2$ low
- Titrate PEEP — Monitor MAP, SaO$_2$, ICP, CPP, CBF
- Recruit Lungs — Monitor MAP, SaO$_2$, ICP, CPP, CBF

Consider venous return & cardiac output; caution with high PEEP

- Rescue Therapy
  - Prone Position — Monitor ICP, CPP
  - ECCO$_2$R, ECMO — Caution: PaCO$_2$, coagulation