A Mathematical Modelling Study of the Effects of Air Expansion Inside the Brain on the Intracranial Pressure

Viruj Bala Soupramanien (27273652)
School of Engineering, Monash University Malaysia

Supervisor
Dr Ooi Ean Hin
School of Engineering, Monash University Malaysia

Summary

Following severe injury to the head, some patients may require surgery to relieve or prevent elevated intracranial pressure (ICP[1]). In some cases, medical air evacuation is required to reach the nearest neurosurgical operation centre. For patients that have previously had brain surgery, there is a chance of pneumocephalus, a collection of intracranial air, being present. However, the effects of pneumocephalus on ICP during air travel are poorly understood. This arises from the lack of clinical research and contradictions in literature. It is known that trapped air will follow the Boyle-Mariotte's law for ideal gases, causing changes in volumes and pressures of intracranial compartments. Cases of intracranial air resulting in elevated ICP have also been previously reported. The influence of temperature on pneumocephalus and ICP during air travel has not been investigated either. The purpose of this study is to investigate the effects of these parameters on ICP and provide an accurate mathematical model for this intracranial system. This paper reports the progress of the findings of this study during MEC4401.

[1] A list of abbreviations is provided in **Appendix A**.

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1.0 Introduction

Intracranial pressure (ICP) is the pressure within the cranial cavity relative to the ambient atmospheric pressure. It is the pressure exerted by the cerebrospinal fluid (CSF), blood and brain parenchyma inside the cranium. The contents of the skull, according to the Monro-Kellie doctrine, is assumed to be relatively constant and consists of the CSF (~10%), cerebral blood (~10%), and brain parenchyma (~ 80%). When there is a change in volume in one of the cranial contents, the volumes of the other contents will change accordingly to maintain a relatively constant cerebral volume. Compensatory mechanisms are used to maintain a suitable and stable blood flow during changes in ICP, this is known as cerebral autoregulation (Oswal & Toma, 2017; Oddo & Le Roux, 2010; "Intracranial Pressure (ICP) - Causes, Concerns and Management", 2016). The compensatory mechanisms involve shifting of the CSF into the spinal compartment, increased absorption rate of CSF and displacement of cerebral blood into the venous sinuses (Savoy, 1984).

If the cerebral autoregulation is impaired, i.e. when the compensatory reserves have been exhausted, a small change in intracranial volume will result in a steep increase in ICP. The volume-pressure relationship in the skull is non-linear which is quantified through the cerebral compliance. Altering intracranial compliance is the final mechanism for regulating ICP (Savoy, 1984). Compliance is a physical property of tissue that describes the ability of a chamber to accommodate a change in its volume or pressure ("CV Physiology | Compliance", 2015). Compliance is considered to be a crucial characteristic of the cerebral hemodynamic. Different methods have been developed to determine cerebral compliance. The Pressure Volume Index (PVI) proposed by Marmarou (Marmarou, 1973; Marmarou et al., 1987; Herman, 1993) and the Volume Pressure Response (VPR) of Miller (Miller & Garibi, 1972; Maset et al., 1987) are the most used techniques. PVI is the volume of CSF needed to raise the ICP ten-fold. VPR is defined as the change in ICP per unit volume of CSF infused.

There are numerous factors influencing increased ICP (Biersteker et al., 2012; Ugras & Yuksel, 2014). ICP may rise due to various stimuli in response to diseases, environmental conditions and normal bodily functions. Increased ICP can be caused by intracranial or extracranial changes. Blood pressure, heart function, intra-abdominal/intrathoracic infections, temperature and pain are some of the dominant factors that contribute to elevated ICP. These stimuli may cause a rapid or slow increase in ICP and these factors can be either non-pathological or pathological in

nature. Non-pathological causes involve coughing, sneezing, stress, blood pressure changes, emotional responses and changing body positions. Traumatic brain injury (TBI), e.g. concussions, contusions, and space occupying lesions are the main pathological conditions for elevated ICP. Space occupying lesions include hematomas, haemorrhages, hydrocephalus, tumours, oedema, abscess/infections and pneumocephalus ("Intracranial Pressure (ICP) - Causes, Concerns and Management", 2016).

TBI is a sudden damage to the brain caused by a blow or jolt to the head. A primary injury is present at the moment of impact. The injury may involve a specific lobe of the brain or the entire brain and may cause bruising, tearing of nerve fibres, bleeding and sometimes a fractured skull. The body has an inflammatory response to the primary injury resulting in a secondary brain injury. Fluid and nutrient accumulation is the bodies attempt at naturally healing the primary injury. However, owing to the rigidity of the skull, increased fluid accumulation can be dangerous and if cerebral autoregulation is faulty, ICP can rise to alarming levels. TBI is classified as mild, moderate or severe, in relation to the severity and mechanism of the injury. While mild TBI may be treated with rest and medication, severe TBI will require more intensive care and surgery (Mayfield Clinic - Brain & Spine, 2018). In some cases, an air ambulance is needed to transport the patient to the nearest operating centre, and this may entail more complications.

Craniotomy is a critical and complicated process that involves operating on the cranium. It is essential to repair fractures, ruptured vessels or remove large blood clots. During this procedure a hole is cut in the skull and a bone flap is removed to grant access to the brain. Once the neurosurgeon has repaired the damage, the bone flap is secured back in its initial position on the skull with plates and screws (Mayfield Clinic - Brain & Spine, 2018). This operation, however meticulously performed, often leaves trace amounts of air inside the cranial cavity. This minute volume of air is usually harmless and is spontaneously absorbed (Sharma et al., 1989). This phenomenon of intracranial gas collection is known as pneumocephalus and was first interpreted by Wolff in 1914. Of interest in this study is the effect of post-craniotomy pneumocephalus on ICP with varying atmospheric pressure.

Pneumocephalus is normally caused by trauma. Nonetheless, nontraumatic spontaneous pneumocephalus, from barotrauma, extracranial infections or by performing the Valsalva

manoeuvres, is not uncommon (Pribshin et al., 2015). Spontaneous pneumocephalus is rare and accounts for only 0.6% of all pneumocephalus cases (Mirone et al., 2009). Shelesko et al. (2017) reported only 8 clinical cases of spontaneous pneumocephalus from 1996 to 2016, portraying the rarity of this pathogen. The term "spontaneous pneumocephalus is used to describe intracranial air accumulation regardless of the cause. Since the etiological factors associated with pneumocephalus involve head injuries, surgical interventions and infections, and although being very rare, a defect in the cranial cavity will allow the development of spontaneous pneumocephalus (Shelesko et al., 2017). Pneumocephalus is a benign complication that can produce a mass effect on the brain should the rate of intracranial air accumulation continuously increase. This mass effect is known as tension pneumocephalus (TP) and may need operation to relieve ICP (Lindvall & Bergenheim, 2011). Air travel post-craniotomy increases the risk of TP. As a result, post-surgery patients are advised to avoid air travel for a certain period. Yet, these timescales provided, vary with each neurosurgeon. Literature on the topic provide controversial findings for the absorption of intracranial air. Goldmann in 1986 stated absorption occurs within a week but Reasoner et al. (1994) found that pneumocephalus may be present up to 3 weeks post operation. The timescales advised were found to range from less than 2 weeks to more than 8 weeks in the UK (Amato-Watkins et al., 2012).

The mass effect of pneumocephalus is caused by the expansion of the intracranial air following a decrease in ambient atmospheric pressure during ascension during air travel. Gas trapped in body cavities will expand when ambient pressure drops (Macmillan, 2000). Owing to the rigidity of the skull, intracranial air cannot expand readily. This limitation in air expansion will result in the compression of one or more of the intracranial components, increasing ICP. Several models for the hydrodynamic relationships of the intracranial system have been investigated and proposed (Marmarou et al., 1978; Eklund et al., 2007; Lakin et al., 2003). However, the validity of some of these models are still questioned and modified in various aspects. Anderson et al. (2003) developed a computer model to investigate the change in ICP during air travel with intracranial air. There are limited studies investigating the relationship between ICP and pneumocephalus during air travel. There is also a lack of literature exploring the effects of temperature on pneumocephalus and ICP. The aim of the present study is to mathematically model the effects of air expansion on ICP based on a modified model of Anderson et al. (2003). This will hopefully give a better

understanding of pneumocephalus and its effects on ICP during air travel. The modified model will also incorporate the effects of temperature on the system.

2.0 Literature Review

Following TBI, especially moderate and severe cases, there are moments when surgical interventions are required. Loss of consciousness between 20 minutes and 6 hours and limited response to stimuli are characteristics of moderate TBI. Patients having severe TBI may be unconscious for more than 6 hours and are unresponsive to stimulation. During a head impact, the brain is jerked in the cerebral cavity from the sudden motion. The soft brain tissue crashes against the walls of the skull causing bruising, bleeding and rupturing nerve fibres. After the initial impact, some of the symptoms are memory loss, confusion, disorientation or loss of consciousness or no symptoms may be seen but the person's condition soon rapidly declines. This period after the initial impact is known as the delayed trauma. The brain swells and pushes against the skull restricting the flow of oxygen-rich blood. This is called the secondary injury which is usually more dangerous than the primary injury (Mayfield Clinic - Brain & Spine, 2018). The causes and/or consequences of the primary and secondary injuries may cause ICP to rise to dangerous levels and thus, require operation to relieve pressure.

The procedure of the operation to the cranium is called craniotomy. This process involves the surgical removal of a section of the skull to access the intracranial compartments. According to the preoperative diagnostic imaging exam (from magnetic resonance imaging [MRI] or computerized tomography [CT]), the surgeon will use a special saw, called a craniotome, to remove a bone flap (the section of the skull removed to access the brain). Removing the bone flap exposes the dura, a protective membrane around the brain. To not cause any more unnecessary movement to the brain, neurosurgeons use very small instruments such as long handle scissors, dissectors and drills, lasers and ultrasonic aspirators (this uses fine jets of water to break up tumour and suck up the pieces), to work deep inside the brain. After completing the surgery, the dura is sewed closed and the bone flap is fixed back in place on the skull with plates and screws. During this procedure, surgeons take extra care to prevent closing the skull with trapped air. Although, no matter how careful, this process often leaves traces of air trapped in the cranium. ("Craniotomy", 2018; "Craniotomy Procedures | Goodman Campbell Brain and Spine", n.d.; "Craniotomy", n.d.)

Clinical studies have confirmed the presence of intracranial air post-operation. There have also been several reported cases of the complication arising from intracranial air following air travel in even pilots and soldiers who are used to flying (Canavan & Osborn, 1991; Chan, 2000; Jensen & Adams, 2004; Mirone et al., 2009; Javan et al., 2011; Huh, 2013). The advised rest time before air travel varies depending on the surgeon. Experimental and theoretical studies have also provided different timescales for the lifespan of intracranial air (Brändström et al., 2017; Seth et al., 2009; Ihab, 2012). Rest periods have been found to range from less than 2 weeks to more than 8 weeks (Amato-Watkins et al., 2012). Studies have shown that the size and incidence of intracranial air diminishes over time, but the time taken be completely absorbed has shown to vary. It was found in a study by Goodman (1986) that intracranial air will only stay for up to one week. Reasoner et al. (1994) estimated 25% of patients to still have trapped air in the skull, 11.8% of them having dangerous amounts of trapped air, up to 3 weeks post-operation.

Pneumocephalus, which is a collection of intracranial gas (Wolff, 1914), and its effects on the intracranial system are poorly understood. There is a lack of research and evidence in this field, especially following air travel. This information is useful to neurosurgeons and responders to medical air evacuation. Below pressures of 1500 mmHg (200 kPa), air can be treated as an ideal gas. As there is a rise in altitude, ambient atmospheric pressure will decrease and as a result the intracranial air pressure will reduce to maintain equilibrium. Following the Boyle-Mariotte's law for ideal gases, the trapped air is expected to expand to increase its volume and compensate for the fall in pressure (Zemansky & Dittman, 1987). However, due to the skull rigidity, the trapped air cannot readily expand and thus, compresses the brain. The cerebral autoregulation helps in the absorption of pneumocephalus but has a limit to the rate of absorption. As such, the compliance is the final compensatory mechanism. The Monro-Kellie hypothesis states that the intracranial volume is fixed, this includes the volume of any mass lesions occupying intracranial space like pneumocephalus.

Many studies conducted have considered the Monro-Kellie hypothesis (Anderson et al., 2003; Marmarou et al., 1978; Eklund et al., 2007). However, they assumed only one of the CSF to dictate the change in intracranial volume. During air travel when the atmospheric pressure drops, intracranial air volume will increase and following the Monro-Kellie doctrine, the volumes of one or more of the other intracranial compartments will reduce to maintain normal ICP ("trauma.org:

Neurotrauma: Intracranial Pressure", n.d.). In the study conducted by Anderson et al. (2003) and Eklund et al. (2007), the intracranial volume only represented the CSF volume and the intracranial air was assumed to behave independently of the other intracranial compartments. From Anderson's paper, the intracranial air pressure was said to vary with atmospheric pressure and ICP, however they neglected the effects of ICP since it is much lower than atmospheric pressure and thus derived the following expression using the hydrostatic equation for the standard atmosphere described by Lejenas (1989):

$$P_{IA}(t) = P_{atm} + P_{IC} \approx P_{atm}(t) \ = P_{atm_0}(1 - \alpha \frac{dH}{dt} t)^{\beta} \tag{1}$$

where P_{atm_0} is the atmospheric pressure at sea level, $\alpha = 2257 \times 10^{-8}$ and $\beta = 5.264$ are numerical constants and dH/dt is the constant rate of ascension. Combining equation (2) and the Boyle-Mariotte law gives the following expression for the intracranial air volume:

$$V_{IA} = \frac{V_{IA_0} P_{IA_0}}{P_{IA}(t)} \approx V_{IA_0}(1 - \alpha \frac{dH}{dt} t)^{-\beta} \tag{2}$$

where V_{IA_0} is the initial intracranial air volume present and P_{IA_0} is approximated by P_{atm_0}.

Due to limited knowledge on the effects of intracranial air, standard air ambulance procedures state that cabin pressure be maintained at sea level pressure (760 mm Hg). In order to achieve this, the operational ceiling of the aircraft must be reduced to lower altitudes where turbulent and air resistant effects are more prominent. Resorting to such precautions gives the pilot less control over the aircraft, causes more discomfort to the patient, increases fuel consumption and the risk of an accident. This is nonetheless, an expensive and technically demanding procedure (Seth et al., 2009). The standard procedures have been modified and updated over time, following published medical literature. Along with Amato-Watkins et al. (2012) and other authors, Seth et al. (2009) have pointed out the paucity in many research papers. There has also been much controversy from the multiple published studies in the field. In a simulated study by Peterson et al. (1944) it was found that altitude alone had little effect on ICP which contradicts findings of other authors (Kimoto et al., 2011; Herbrowski, 2016). In a study by Donovan et al. (2008), pneumocephalus was not found to cause any contraindication to air travel, contrary to the findings of Reasoner et al. (1994) and Anderson et al. (2003).

From the lack of evidence and contradiction from multiple studies, there is much controversy on the effects of pneumocephalus or intracranial air on ICP. It also known that temperature changes with altitude and volume, pressure and temperature are inter-dependent. To the extent of the author's knowledge, no research has investigated temperature effects on pneumocephalus and ICP. The proposed model will be designed to help shed some light on the contradictions and fill the porosity in the literature.

3.0 Work Completed for MEC4401

3.1 Methodology

The present study will aim to develop a mathematical model to simulate the effects of air expansion and change in temperature on ICP. This model will be adapted from that based on the proposed model by Anderson et al. in 2003. Like the Anderson model and other proposed models (Marmarou et al., 1978; Eklund et al., 2007; Lakin et al., 2003), the suggested model in this study will use an analogous electrical system to represent the intracranial system. The electrical analogy is used as a conceptual aid to approximate the hydrodynamics of the cerebral system. The model was modified to study essentially the behaviour of intracranial air and its influence on the intracranial system. The Anderson model, which is an extension of that proposed by Marmarou et al. (1978), incorporated intracranial air in the intracranial system. This model aimed to predict the influence of expanding intracranial air on the CSF. In this paper, the authors claimed the ICP to be a measure of the CSF pressure exerted on the brain tissue (Anderson et al., 2003).

The theoretical model was identified and evaluated analytically and described by a set of mathematical expressions. This was accomplished using MATLAB 2018b to mould these expressions into mathematical models to simulate the desired results. In the first part of this study, the results from Anderson et al. (2003) were reproduced. This was represented by **Model 1**. The parameters governing this model are given in *Table B1* in **Appendix B**. These parameters are the same as those described by Anderson et al. (2003) in *Table II* of their paper. In the Anderson model, the effects of ICP on intracranial air pressure (P_{IA}) was neglected and only atmospheric pressure was thought to influence the change in P_{IA}. In the next part of the study, **Model 2** was developed to include the effects of ICP on P_{IA}. The value of ICP in this model was the same as that proposed by Anderson et al. (2003). This model was further modified to incorporate ICP as a function of

time, instead of an absolute value. This was **Model 3**. The ICP function used was also proposed by Anderson and other authors have also derived or used this function in their models (Marmarou et al., 1978; Eklund et al., 2007). The system used for these models is illustrated in *Figure 1. It* was the same as used by Anderson.

Model 1:
$$P_{IA} = P_{atm} = P_{atm_0}(1 - \alpha \frac{dH}{dt} t)^{\beta} \quad (3)$$

Model 2:
$$P_{IA} = P_{atm} + P_{IC} = P_{atm_0}(1 - \alpha \frac{dH}{dt} t)^{\beta} + P_{IC_{absolute}} \quad (4)$$

Model 3:
$$P_{IA} = P_{atm} + P_{IC} = P_{atm_0}(1 - \alpha \frac{dH}{dt} t)^{\beta} + P_{IC}(t) \quad (5)$$

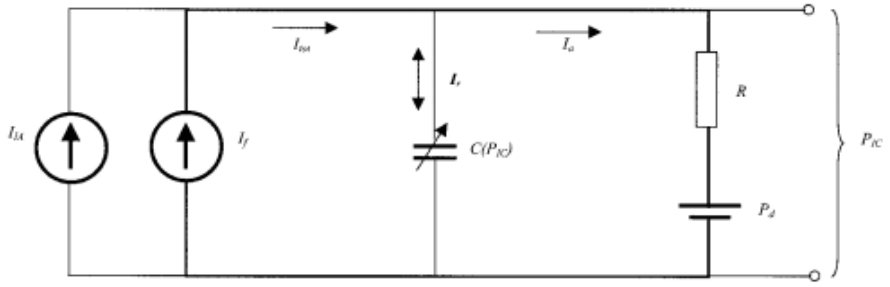

Fig. 1. Model describing the hydrodynamic system, incorporating intracranial pressure (P_{IC}), CSF production (I_f), expansion of intracranial air (I_{IA}), compliance (C), outflow resistance (R) and dural sinus pressure (P_d). I_{tot} is the total flow through the system, I_a is the part absorbed to venous blood, and I_r is that which remains.

Figure 1: The analogous electrical system proposed by Anderson et al. (2003) which was an extension of that by Marmarou et al. (1978)

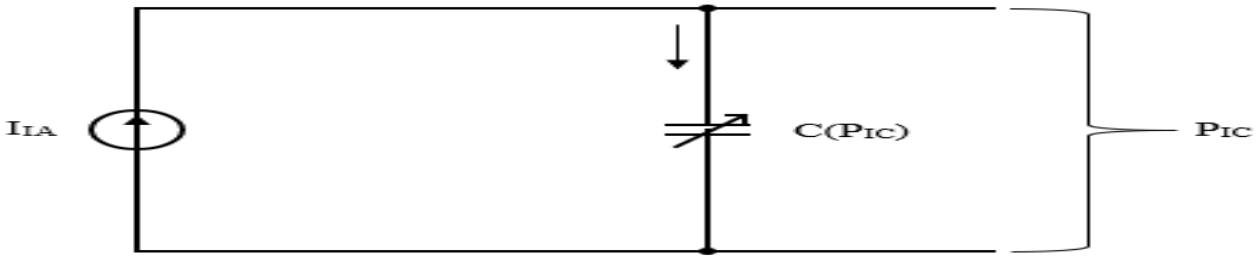

Figure 2: Proposed system depicted by an equivalent electrical circuit. P_{IC} is the intracranial pressure, I_{IA} represents the expansion of intracranial air and the compliance C shown as a variable capacitor as it is dependent on P_{IC}

The system being considered will comprise of the blood volume, brain tissue and the intracranial air. A schematic of the proposed analogous system is shown in *Figure 2*. Since this study desires to investigate the effects of the changes to intracranial air on the ICP, the proposed system neglected the rate of CSF production as well as the rate of fluid absorption into the venous blood. The other assumptions made follows those made by Anderson et al. (2003). The pressure

and flow are assumed to always be in a state of hydrodynamic equilibrium. In this system, I_{IA} is the total inflow/expansion of the intracranial fluid in the system as compared to the Anderson model, which took $I_{tot} = I_{IA} + I_f$ (where I_f is the CSF production rate) as the total inflow. Like the Anderson model, the air reabsorption rate and rate of fluid accumulation due to tissue swelling of this system were also considered to be negligible.

Anderson's proposed system considered the continuous fluid absorption into the venous blood, I_a and the part I_r that remains. The sum of these two components is equivalent to the total fluid flow in the system. In *Figure 1*, R represents the outflow resistance to the venous blood and P_d the dural sinus pressure. It is assumed that the absorption rate is linearly dependent on the difference in P_{IC} and P_d.

$$I_{tot} = I_{IA} + I_f = I_a + I_r \tag{6}$$

$$I_a = \frac{P_{IC} - P_d}{R} \tag{7}$$

P_{IC} is the ICP of the system. It governs the variation in the compliance C which will alter the brain blood volume and brain tissue compression. Compliance, as defined by Marmarou et al. (1978), is given by the ratio of change in volume to change in pressure and can also be determined from the volume-pressure curve of the system being studied. Cerebral compliance is thought to be an indication of the volume buffering capability of the brain (Portella et al., 2005).

$$C = \frac{dV_{IC}}{dP_{IC}} \tag{8}$$

The Pressure Volume Index (PVI) of Marmarou can also be used to determine the mathematical expression for cerebral compliance. PVI is clinically defined as the volume of fluid (in millimetres) needed to raise the ICP ten-fold (Robertson et al. 1993). Anderson's research assumed that PVI was a constant when assessed against a single individual.

$$PVI = \frac{P_{IC}}{0.4343} C \tag{9}$$

Marmarou found that due to the exponential nature of the volume-pressure relationship, the compliance will decrease as ICP increases and can thus be expressed by the following function:

$$C = \frac{1}{KP_{IC}} \tag{10}$$

where K is a mathematical constant given by $K = 1/(0.4343PVI)$. Combining equations (8) and (10) will yield an expression for the time rate of pressure change in the system.

$$\frac{dP_{IC}}{dt} = \frac{dP_{IC}}{dV_{IC}}\frac{dV_{IC}}{dt} = KP_{IC}\frac{dV_{IC}}{dt} \tag{11}$$

Since Anderson's model considered the volume variation to occur only in the CSF, i.e., blood volume remains constant, then dV_{IC}/t is represented by I_r. With this assumption and equations (6) and (11), the time rate of pressure change can be rewritten as:

$$\frac{dP_{IC}}{dt} = KP_{IC}I_r = KP_{IC}(I_{tot} - I_a) \tag{12}$$

When the rates of formation and absorption of fluid are in equilibrium, the system is in a steady state condition. The pressure difference is dependent on I_f and R. P_d is thus, thought to regulate the steady state ICP which is the resting ICP, P_{IC_r}, on the ground at equilibrium ($P_{IC_r} = P_d + I_f R$). Gjerris & Borgesen (1992) deduced that I_f, R, and P_d can be assumed to be independent of ICP within the interesting pressure range and so were approximated as constants in the model. From this relationship and equation (7), equation (12) can be rearranged to set up the following differential equation:

$$\begin{aligned}\frac{dP_{IC}}{dt} + \frac{KP_{IC}^2}{R} - \frac{KP_{IC}}{R}\left(RI_{IA} + P_{IC_r}\right) \\ = \frac{dP_{IC}}{dt} + \frac{KP_{IC}^2}{R} - \frac{KP_{IC}}{R}\left(R\frac{dV_{IA}}{dt} + P_{IC_r}\right) = 0\end{aligned} \tag{13}$$

Using the integrating factor method and substituting $x = 1/P_{IC}$ (Marmarou et al., 1978), the general, dynamic solutions to the differential equation (13) is given by:

$$P_{IC}(t) = \frac{e^{K(V_{IA}(t) + \frac{P_{IC_r}}{R}t - V_{IA_0})}}{\frac{K}{R}\int_0^t e^{K(V_{IA}(\tau) + \frac{P_{IC_r}}{R}\tau - V_{IA_0})}d\tau + \frac{1}{P_{IC_r}}} \tag{14}$$

The detailed derivation of equation (14) is provided in APPENDIX B of Anderson et al. (2003). From equations (2) and (14), an expression for ICP in terms of ascension rate and time can be found.

3.2 Results

3.2.1 Model 1

Model 1 was developed to replicate the results of the Anderson model. From their study, Anderson et al. (2003) deduced that the change in ICP had a strong dependence on the rate of change of cabin altitude. *Figures C1* and *C2* in **Appendix C** show the change in air volume (V_{IA}) and the rate of change of air volume ($dV_{IA}/dt = I_{IA}$) with altitude. Following the Boyle-Mariotte Law and the hydrostatic equation (P_{atm} equation), I_{IA} varied with altitude as expected and was larger with increasing V_{IA_0}. The simulations for I_{IA} ranged from 4.3 to 12.9 µl/s (4 to 13 µl/s in Anderson et al. (2003)). Ekstedt found in 1978 that the mean CSF production rate was 6.67±1.39 µl/s. Therefore, the rate of air expansion was of the same order as the CSF production rate. If all intracranial air is assumed to be absorbed, i.e., $I_{tot} = I_{IA} + I_f = I_a$, equation 7 would represent a system with no compliance as seen by the dotted line in *Figures C3* and *C4*. It was deduced from these figures that for small pressure changes, compliance is more dominant while the outflow resistance takes over at higher altitudes. The regular increments of ICP occurs from the continuously increasing I_{IA}. If I_{IA} was constant, ICP would tend to a state of equilibrium. Another of Anderson's major findings, was that intracranial air expanded by roughly 30% in volume from sea level to an altitude of 8000 ft, shown in *Figure C1*.

3.2.2 Model 2

Anderson et al. (2003) assumed that ICP was negligible compared to atmospheric pressure ($P_{IC} \approx$ *1-3 kPa* $<<$ $P_{atm} \approx$ *75-101 kPa*) and so was not thought to influence P_{IA}. However, it was not clear whether this value of ICP was gauge or absolute pressure. It was pointed out by Herbowski in 2016, that several papers had negligently taken gauge pressure as absolute ICP (Ragauskas et al. 2005; Nusbaum 2011; Siaudvytyte et al. 2015). As a result, **Model 2** assumed the range of ICP given by Anderson was gauge pressure and its influence on P_{IA} was taken into consideration. This gave rise to the following equation:

$$\begin{aligned} P_{IA} &= P_{atm} + P_{IC_{absolute}} \\ &= P_{atm_0}(1 - \alpha \frac{dH}{dt} t)^{\beta} + (P_{atm_0} + P_{IC_{gauge}}) \end{aligned} \tag{15}$$

where $P_{IC_{gauge}}$ ranged from 1-3 kPa (≈7.5-22.5 mm Hg) and P_{atm_0} was atmospheric pressure at sea level, taken to be 101 kPa (760 mm Hg). From the results in **Appendix C**, **Model 2** showed

little variation in intracranial air volume and pressure and their effects of ICP. In Herbowski's research on the influence of the atmosphere on ICP, the mean gauge ICP was found to be -1.0 mm Hg. This was an observational study on patients with suspected symptomatic normal pressure hydrocephalus however, and so may not apply to patients with pneumocephalus. It was also pointed out that in a study for the modelling and clinical evaluation of postural effects on ICP by Qvarlander et al. in 2013, the mean gauge ICP was found to be -2.2 mm Hg. Although **Model 2** had an identical volume-pressure curve to **Models 1** & **3**, and from the findings of Qvarlander et al. (2013) and Herbowski (2016), from the intracranial air volume-pressure graphs in **Appendix B, Model 2** simulated $P_{IA_0} \approx 1500\ mm\ Hg$ (well above P_{atm_0}). **Model 2** was thus, disregared.

3.2.3 Model 3

Model 3 was a further modification of **Model 2**. From the dynamic solutions given in equation (14), it is evident that ICP is a temporal function and not constant as was assumed in **Model 2**. From this the following equation was formed:

$$\begin{aligned} P_{IA} &= P_{atm} + P_{IC}(t) \\ &= P_{atm_0}(1 - \alpha \frac{dH}{dt} t)^{\beta} \\ &+ \frac{e^{K(V_{IA}(t) + \frac{P_{IC_r}}{R} t - V_{IA_0})}}{\frac{K}{R} \int_0^t e^{K(V_{IA}(\tau) + \frac{P_{IC_r}}{R} \tau - V_{IA_0})} d\tau + \frac{1}{P_{IC_r}}} \end{aligned} \tag{16}$$

Model 3 yielded similar results to **Model 1**. Intracranial air volume expanded by 1.7-4.5% less than **Model 1**. Increase in ICP was also less in **Model 3** by 0.48-6.89%. With higher P_{IC_r}, $V_{IA_0}$and dH/dt, the percentage difference in V_{IA} and ICP increased which is expected with normal cerebral autoregulation. **Model 3** provided a more accurate representation of the intracranial system. The percentage differences for each configuration, between **Models 1** & **3** are tabulated in *Tables B2 & B3 i*n **Appendix B**. The results are graphically represented in **Appendix C**.

3.3 Validity of Models

Initially, the goal set for MEC4401 in this study was to develop a model to accurately simulate, primarily the effects of air expansion on ICP using the system proposed in *Figure 2*. After analysing the assumptions made by Anderson et al. (2003) and a review of literature (Qvarlander et al., 2013; Herbowski, 2016; Portella; 2005), the objective of the study changed to evaluate and

improve the Anderson model (**Model 1**). Thus, **Model 3** was designed. It was thought that the assumptions and simplifications made by Anderson et al., were the reason that allowed for the steady increase in intracranial air volume and ICP. The models proposed are mathematically accurate; however, they allow for a continuous air expansion with decreasing ambient pressure, as the rigidity of the skull was not accounted for.

Hence, the influence of different parameter values, PVI and *R* (*Table* B4), based on values obtained from reviewing literature (Robertson et al., 1993; Shulman & Veredier, 1967), was studied to determine the predominant factor affecting ICP. *Figures C5-C12* show a comparison of the different parameters. It was found that *R* had little influence on ICP with changing intracranial volume, which was more visible at lower PVI. PVI had a greater impact on ICP. *Tables B5 & B6* in **Appendix B** represent the final simulated ICPs of **Models 1** & **3** respectively, for all initial conditions. The parameters used to simulate the results of *Tables B5* & *B6*, were the same as those used by Anderson et al. (2003).

Combining equations (8) and (10) will set up the following differential equation:

$$\frac{dV_{IC}}{dP_{IC}} = \frac{1}{KP_{IC}} \tag{17}$$

and when solved will give an expression for the change in CSF volume in terms of ICP. Normal adult CSF volume lies between 125-150 ml (Chazen et al., 2017). Using the definition of PVI and solving equation (17), the CSF volume needed for an increase in ICP ten-fold was found (*Figures C13-C16)* by extrapolating the volume-pressure curves. It was noticed from these figures that the simulated results gave a higher PVI than that used in the simulations, further questioning the validity of these models and the assumptions made for these models. When a PVI of 12.6 ml was used to simulate the results, the 3 models estimated a range of PVI from 32-61 ml which was roughly doubled when a PVI of 26 ml was used, as seen in *Figures C13-C16*. These results show that PVI should rather follow the expression provided by Marmarou (Marmarou et al., 1975; Chopp et al., 1983), than a constant value.

4.0 Work Planned for MEC4402

Anderson et al. (2003) proposed a model that would simulate the effects of air expansion on ICP with rising altitudes. Their research involved investigating the change in ICP with different

rates of ascension. Yet, they only studied the effects of different constant rates of ascension (250, 500 & 1000 ft/min). It was planned for MEC4401 to simulate the model using varying rates of ascension, i.e., the effect of accelerating or decelerating rates of ascension on ICP. However, after noticing ICP was not stated to be absolute or gauge pressure and from the research conducted by Portella et al. (2005), **Models 2** and **3** were proposed. **Model 2** will be disregarded, and **Model 3** will be investigated further. The aforementioned ascension rates will thus, be evaluated and their influence on ICP analysed in MEC4402. It has been established that the change in intracranial air volume depends less on the altitude than it does on the rate of ascension (Anderson et al., 2003). It was found that higher ascension rates had a greater impact on ICP, as seen from the volume-pressure curves in *Figures C17-C19*. Following these results, the effects of varying ascension rates on ICP were desired for analysis.

As mentioned in the literature review, volume and pressure are known to vary with temperature. Since no literature investigating temperature variations on pneumocephalus and ICP. The hydrostatic equation used by Anderson et al. (2003) to describe the change in atmospheric pressure, assumed temperature to remain constant. However, it is well known that with increasing altitude, temperature will fall. A fall in temperature is also known to cause a shrinkage in volume. In the case of pneumocephalus, a decrease in intracranial air volume is expected to result in intracranial pockets of vacuum giving rise to a negative pressure (Filippidis et al., 2011). These pockets of vacuum will offer no resistance and thus fluid will fill up the cerebral cavity. This is expected to cause an increase in ICP from the increased accumulation of fluid (McCullough & Fox, 1974). **Model 3** will be modified to incorporate the effects of temperature also.

4.1 Proposed Methodology

The temperature variation can be found by making use of the hydrostatic equation:

$$\partial P = -\rho g \partial H \tag{18}$$

and the ideal gas law:

$$\frac{P}{\rho} = R^* T \tag{19}$$

Combining equations (18) & (19) to eliminate ρ (the density of air) will yield:

$$\frac{\partial P}{\partial H} = -\frac{Pg}{R^*T} \tag{20}$$

where $\partial P/\partial H$ is the change in atmospheric pressure with altitude, g is the acceleration due to gravity, R^* is the universal gas constant and T is the ambient temperature (Lynch, 2004; Hall, 2006). Integrating equation (20) will lead to:

$$\frac{P}{P_0} = e^{-\frac{g}{R^*T}(H-H_0)} \tag{21}$$

for constant T, where P_0 is the atmospheric pressure at the reference height H_0 which would be at sea level for this study. For varying temperature, the temperature distribution can be obtained from standard atmosphere model provided in *Figure 3* or from the following equation (Hall, 2006):

$$T = T_0 + a(H - H_0) \tag{22}$$

where T_0 is the ambient temperature at the reference height H_0 and a is the lapse rate ("International Standard Atmosphere", n.d.). The rate of change of an atmospheric variable with altitude is known as the lapse rate ("Lapse rate", 2012). It can be obtained from the slope of the temperature distribution of the standard atmosphere (*Figure 3*). Atmospheric pressure is thus, related to the ambient temperature through:

$$\frac{P}{P_0} = \frac{T}{T_0} e^{-\frac{g}{R^*}(H-H_0)} \tag{23}$$

The standard atmosphere is a model used to describe the hypothetical distribution of atmospheric temperature, pressure and density. This representation of the atmosphere and its dependents is vital for pressure altimeter calibrations, aircraft performance calculations, aircraft and missile design, ballistic tables, etc. ("Standard Atmosphere", 2012).

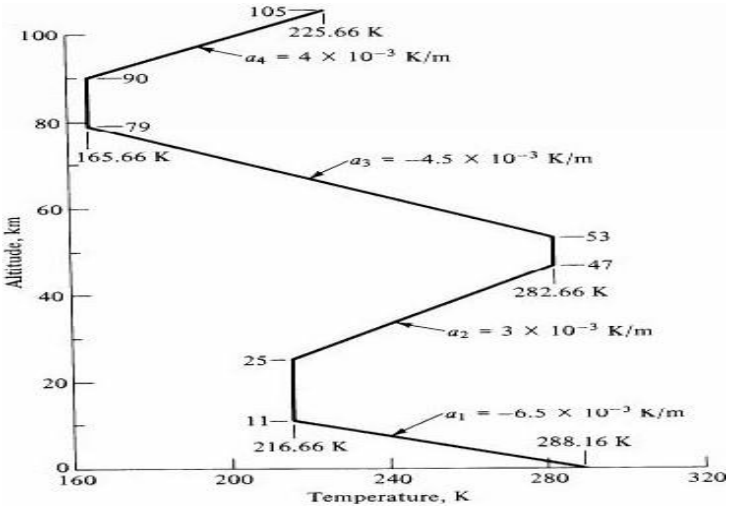

Figure 3: Temperature distribution in the standard atmosphere

5.0 Appendix

5.1 Appendix A

Abbreviations	
a	lapse rate (K/m)
α	numerical constant [2257E-8]
β	numerical constant [5.264]
C	compliance (m^3/Pa)
CSF	cerebrospinal fluid
g	acceleration due to gravity [9.8 m/s]
H	altitude [1 ft = 0.3048 m] (ft)
H_0	reference altitude [sea level] (ft)
I_a	absorption rate of CSF into venous blood (m^3/s)
I_f	production rate of CSF (m^3/s)
I_{IA}	expansion rate of intracranial air (m^3/s)
I_{tot}	total fluid flow rate in system (m^3/s)
K	mathematical constant [1/(0.4343PVI)] (m^{-3})
P, P_{atm}	atmospheric pressure [1 mm Hg = 133.322 Pa] (mm Hg)
P_0, P_{atm0}	atmospheric pressure at H_0 (mm Hg)
P_d	dural sinus pressure (mm Hg)
P_{IA}	intracranial air pressure (mm Hg)
P_{IA0}	initial intracranial air pressure at H_0 (mm Hg)
P_{IC}, ICP	intracranial pressure (mm Hg)
P_{ICr}	intracranial resting pressure (mm Hg)
PVI	pressure-volume index [1 ml = 1E-6 m^3] (ml)
R	outflow resistance of the system (mm Hg/[ml.min])
R*	universal gas constant [8.314 J/(mol.K)]
T	ambient temperature [1 °C = 273.15 K] (°C)
T_0	ambient temperature at H_0 (°C)
TBI	traumatic brain injury
TP	tension pneumocephalus
V_{IA}	intracranial air volume (ml)
V_{IA0}	initial intracranial air volume at H_0 (ml)
V_{IC}	intracranial volume (ml)
VPR	volume-pressure response

5.2 Appendix B

Table B1: Parameter values for CSF model and air ambulance

Parameter	Value
P_{ICr}	10 and 20 mm Hg
PVI	12.6 ml
R	16.1 mm Hg/(ml.min)
V_{IA0}	10, 20 and 30 ml
dH/dt	250, 500 and 1000 ft/min
H_{max}	8000 ft

*Table B2: Comparison between **Models 1** & **3** for 10 mm Hg resting pressure*

V_{IA0} (ml)	dH/dt (ft/min)	ΔV_{IA} (%)	ΔP_{IC} (%)
10	250	1.6981	0.4757
	500	1.7933	0.8214
	1000	1.8833	1.2101
20	250	1.8858	1.1411
	500	2.0889	2.1534
	1000	2.2959	3.4503
30	250	2.0740	1.9465
	500	2.3911	3.8502
	1000	2.7301	6.4674

*Table B3: Comparison between **Models 1** & **3** for 20 mm Hg resting pressure*

V_{IA0} (ml)	dH/dt (ft/min)	ΔV_{IA} (%)	ΔP_{IC} (%)
10	250	3.1820	0.4849
	500	3.3237	0.9147
	1000	3.4947	1.5599
20	250	3.3807	1.0710
	500	3.6617	2.1599
	1000	4.0092	3.9680
30	250	3.5757	1.7376
	500	3.9909	3.6309
	1000	4.5086	6.8933

Table B4: Parameter values found from literature

Authors	PVI [ml]	R [mm Hg/(ml.min)]	R [Pa/(m^3.s)]
Anderson et al. (2003)	12.6	16.1	1.29E+11
Robertson et al. (1993)	13-26	-	-
Shulman & Veredier (1967)	-	16.37-31.36	2.51E+11

*Table B5: Simulated results of **Model 1** using the Anderson parameters from Table B3*

V_{IA0} (ml)	dH/dt (ft/min)	ICP^2 (mm Hg)	ICP^3 (mm Hg)
10	250	11.8956	21.9899
	500	13.3047	23.7913
	1000	14.9662	26.6094
20	250	13.8486	23.9944
	500	16.9797	27.6972
	1000	21.2656	33.9594
30	250	15.8383	26.0102
	500	20.9013	31.6766
	1000	28.6926	41.8026

*Table B6: Simulated results of **Model 3** using the Anderson parameters from Table B3*

V_{IA0} (ml)	dH/dt (ft/min)	ICP^2 (mm Hg)	ICP^3 (mm Hg)
10	250	11.8132	21.8422
	500	13.1218	23.4745
	1000	14.6130	25.9172
20	250	13.6403	23.6621
	500	16.4205	26.9079
	1000	19.9070	31.9051
30	250	15.4638	25.4580
	500	19.7732	30.2739
	1000	25.4926	37.7573

[2] Final ICP at 8000 ft for a patient with 10 mm Hg resting pressure
[3] Final ICP at 8000 ft for a patient with 20 mm Hg resting pressure

5.3 Appendix C

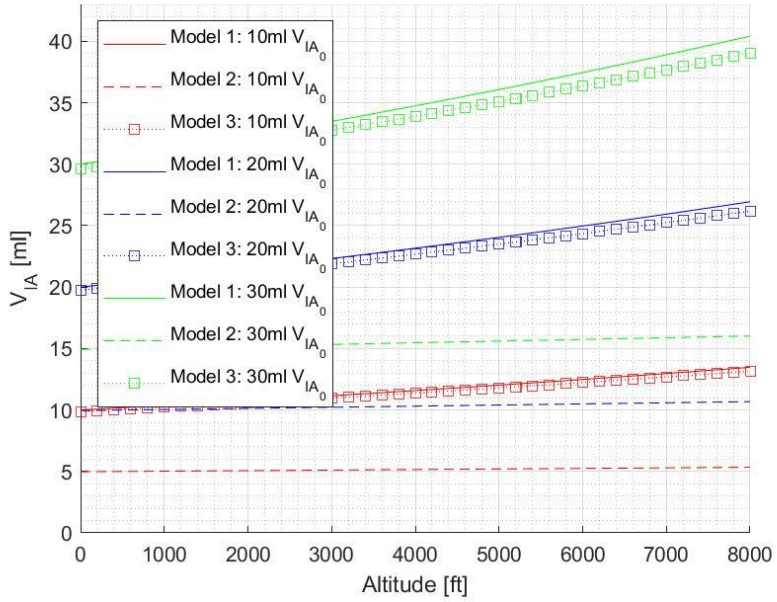

Figure C1: Simulated results of all 3 models for the change in intracranial air volume during ascent at a rate of 500 ft/min for 3 different initial volumes and normal resting ICP of 10 mm Hg.

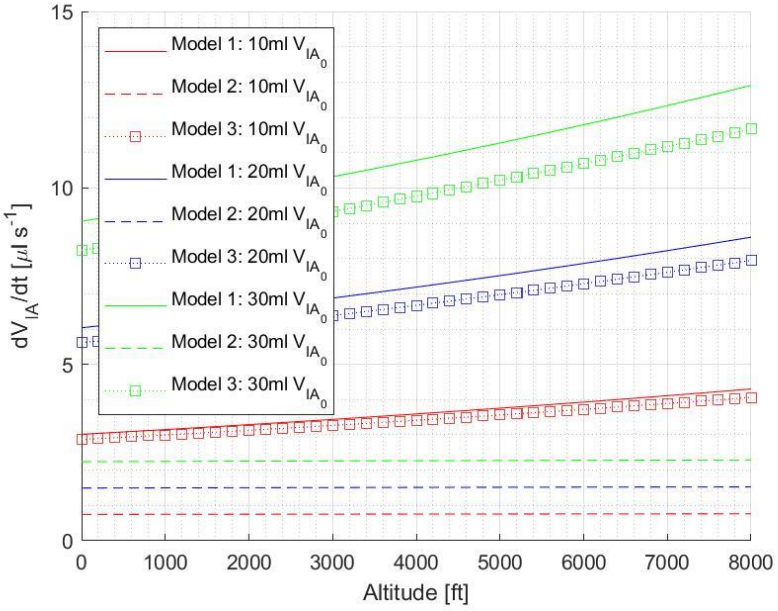

Figure C2: Simulated results of all 3 models for the rate of expansion of intracranial air volume during ascent at a rate of 500 ft/min for 3 different initial volumes and normal resting ICP of 10 mm Hg.

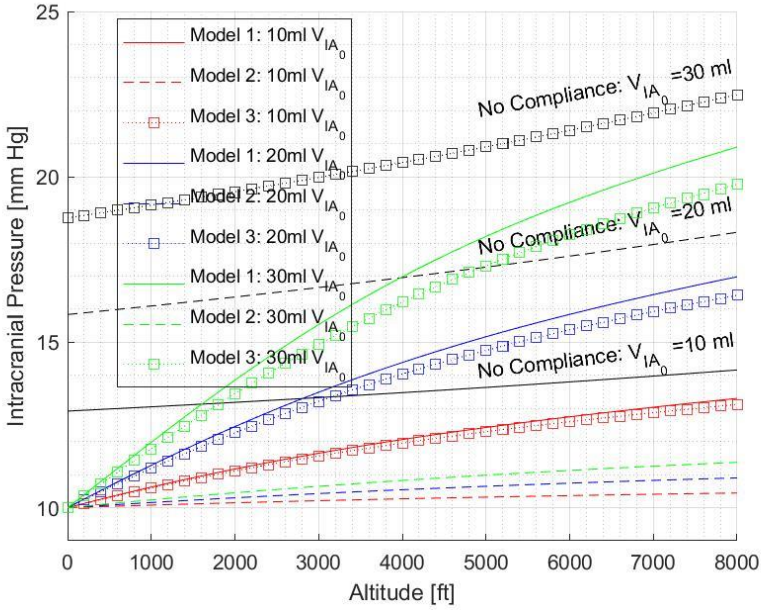

Figure C3: Simulated results for all 3 models for the change in ICP during ascent at a rate of 500 ft/min for 3 different initial volumes and normal resting ICP of 10 mm Hg. The black coloured line represents simulated ICP with no compliance for the 3 initial intracranial air volumes.

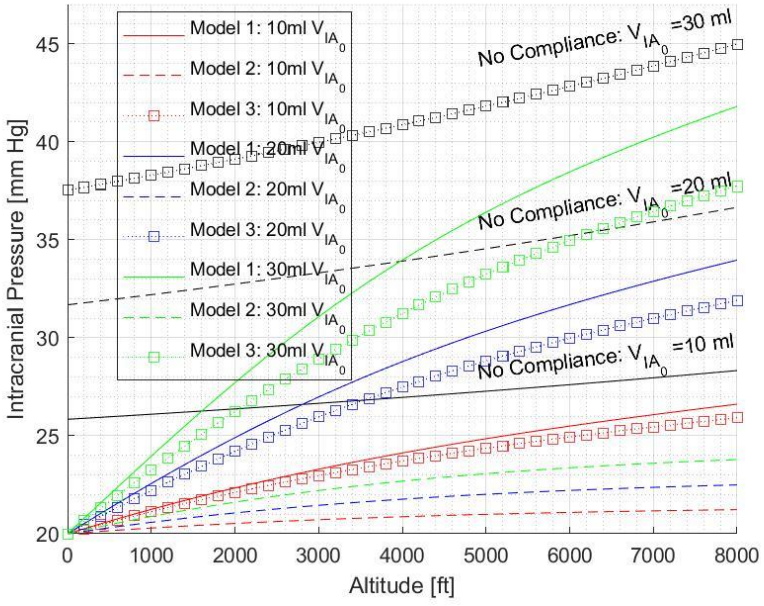

Figure C4: Simulated results for all 3 models for the change in ICP during ascent at a rate of 500 ft/min for 3 different initial volumes and normal resting ICP of 20 mm Hg. The black coloured line represents simulated ICP with no compliance for the 3 initial intracranial air volumes.

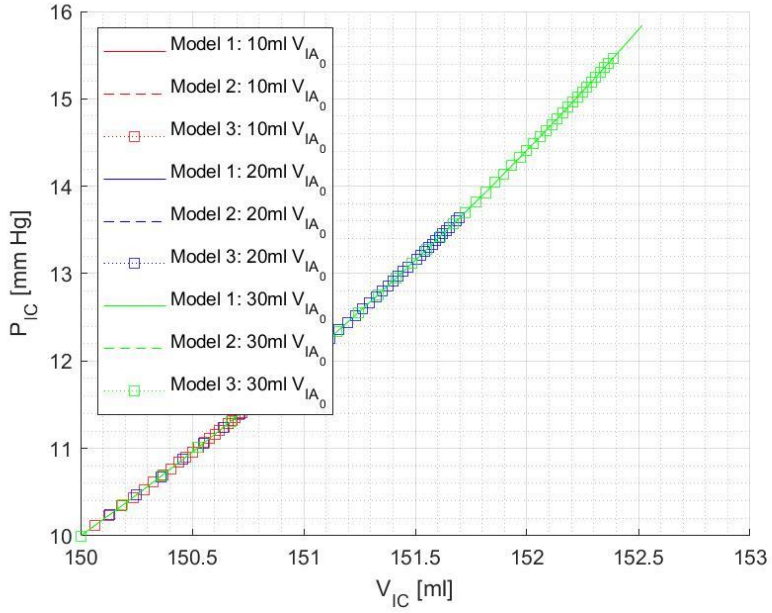

Figure C5: Intracranial volume-pressure relationship during ascent of 250 ft/min, PVI = 12.6 ml, R = 16.1 mm Hg/(ml.min) and a resting pressure of 10 mm Hg.

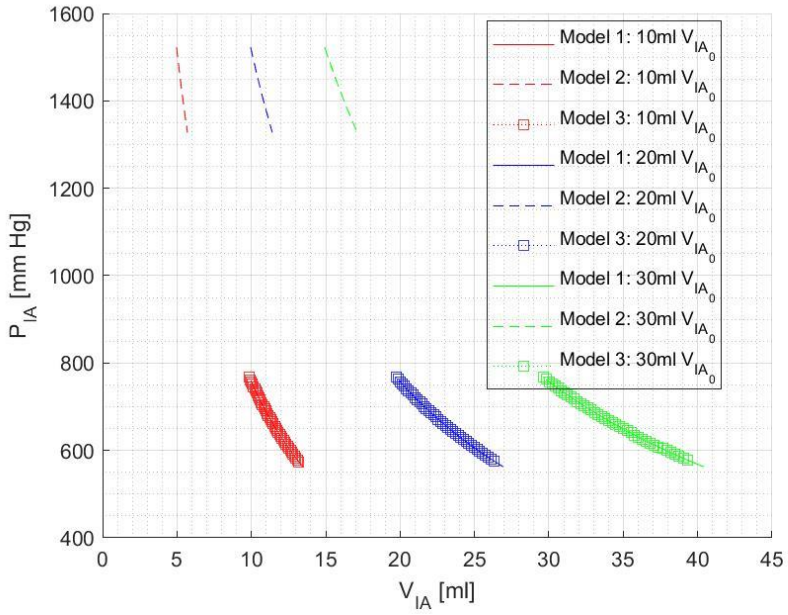

Figure C6: Intracranial air volume-pressure relationship during ascent of 250 ft/min, PVI = 12.6 ml, R = 16.1 mm Hg/(ml.min) and a resting pressure of 10 mm Hg.

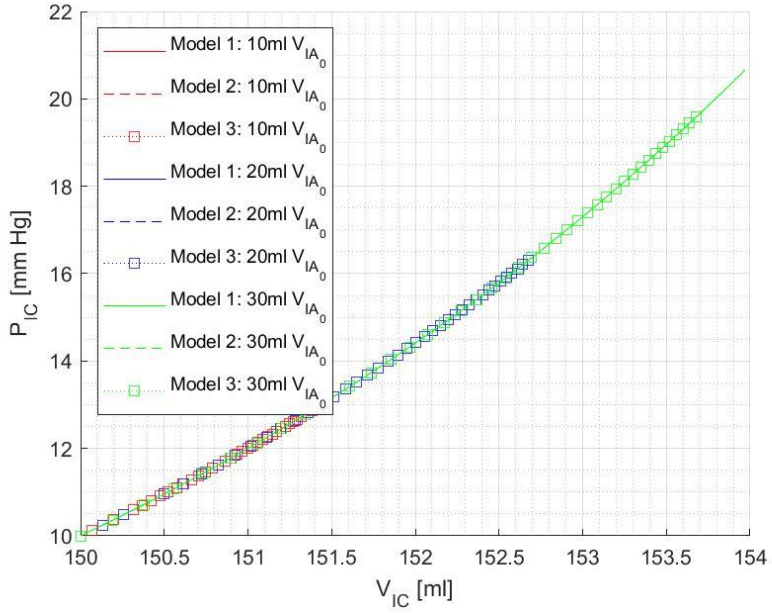

Figure C7: Intracranial volume-pressure relationship during ascent of 250 ft/min, PVI = 12.6 ml, R = 31.36 mm Hg/(ml.min) and a resting pressure of 10 mm Hg.

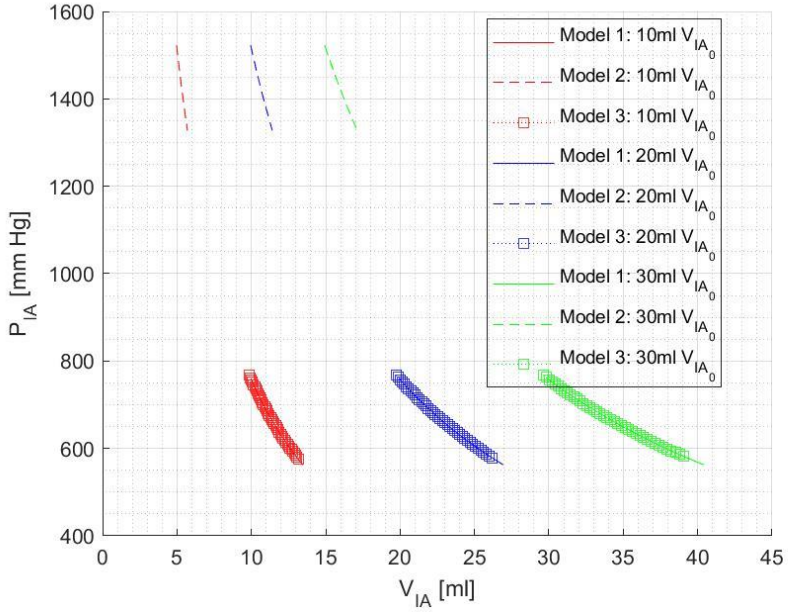

Figure C8: Intracranial air volume-pressure relationship during ascent of 250 ft/min, PVI = 12.6 ml, R = 31.36 mm Hg/(ml.min) and a resting pressure of 10 mm Hg.

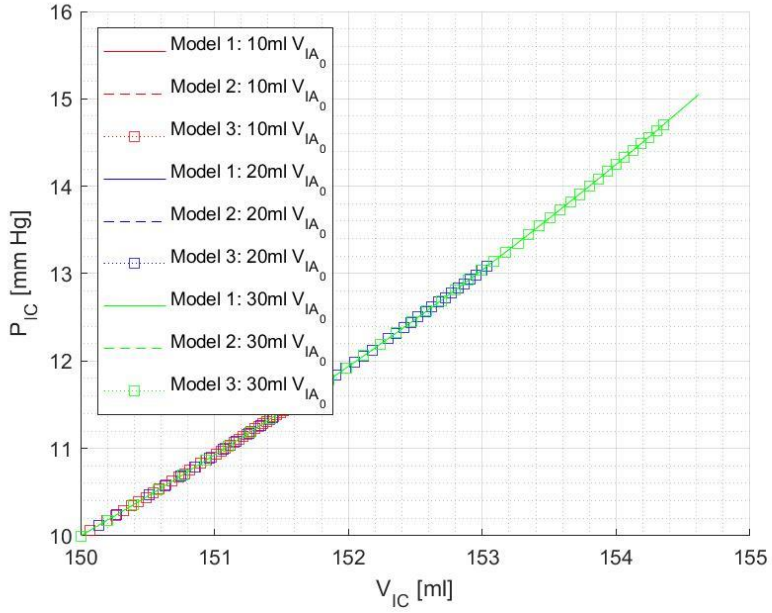

Figure C9: Intracranial volume-pressure relationship during ascent of 250 ft/min, PVI = 26 ml, R = 16.1 mm Hg/(ml.min) and a resting pressure of 10 mm Hg.

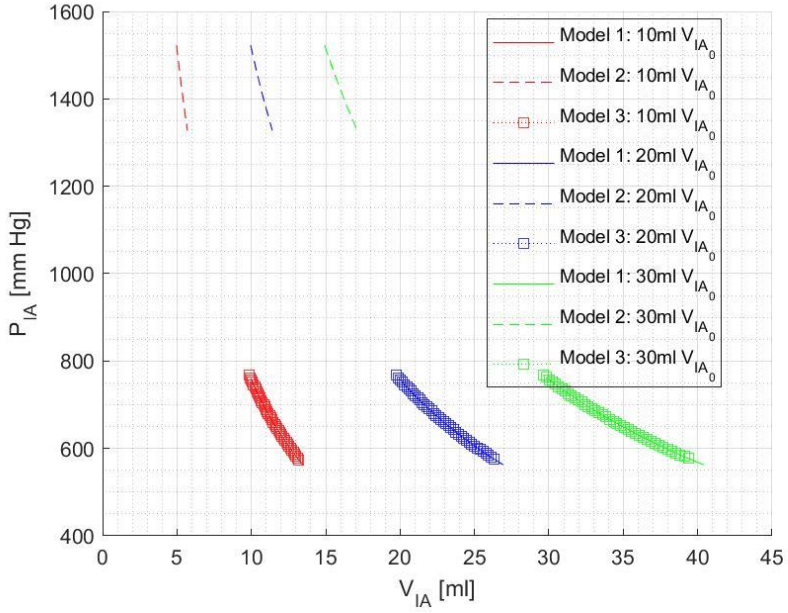

Figure C10: Intracranial air volume-pressure relationship during ascent of 250 ft/min, PVI = 26 ml, R = 16.1 mm Hg/(ml.min) and a resting pressure of 10 mm Hg.

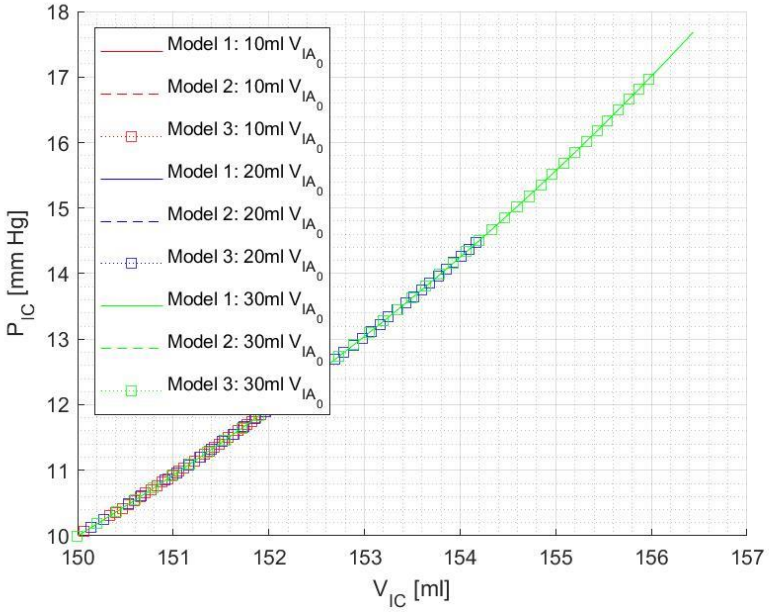

Figure C11: Intracranial volume-pressure relationship during ascent of 250 ft/min, PVI = 26 ml, R = 31.36 mm Hg/(ml.min) and a resting pressure of 10 mm Hg.

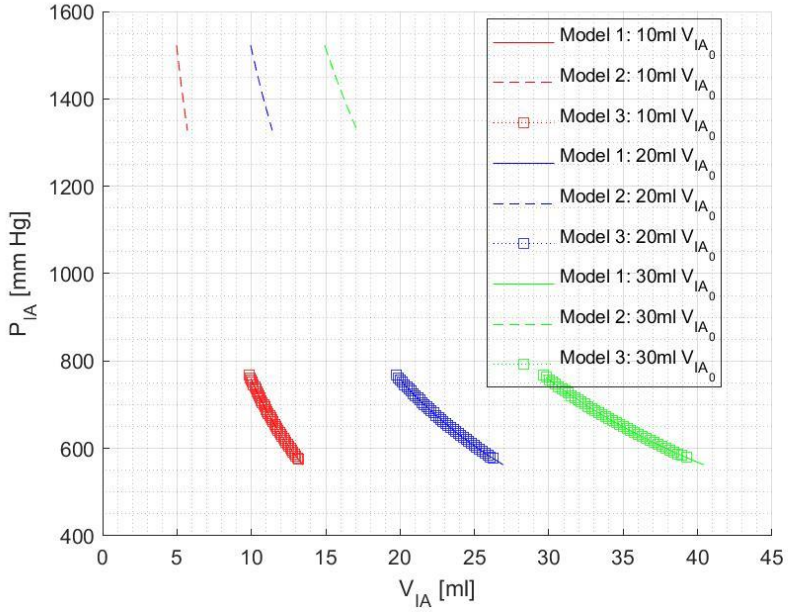

Figure C12: Intracranial air volume-pressure relationship during ascent of 250 ft/min, PVI = 26 ml, R = 31.36 mm Hg/(ml.min) and a resting pressure of 10 mm Hg.

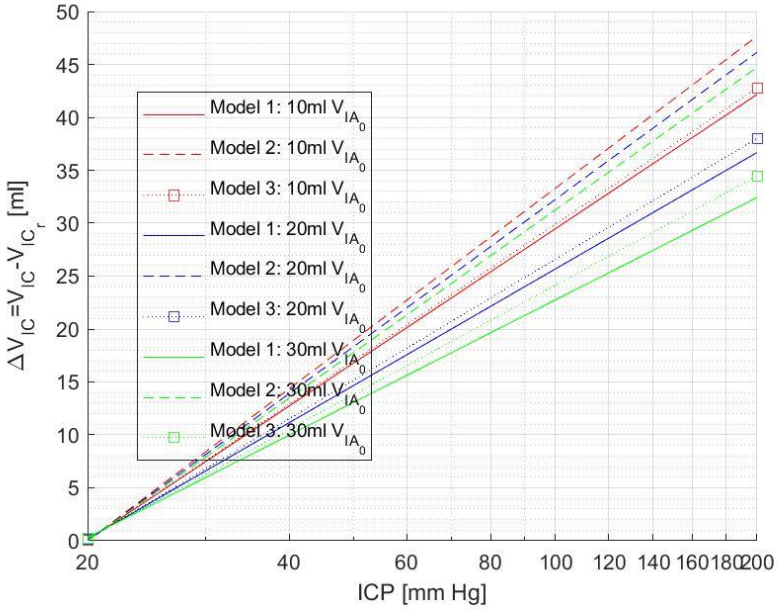

Figure C13: Change in intracranial volume with rise in ICP during ascent of 1000 ft/min with PVI of 12.6 ml, R = 16.1 mm Hg/(ml.min), resting pressure of 20 mm Hg and initial CSF volume of 120 ml.

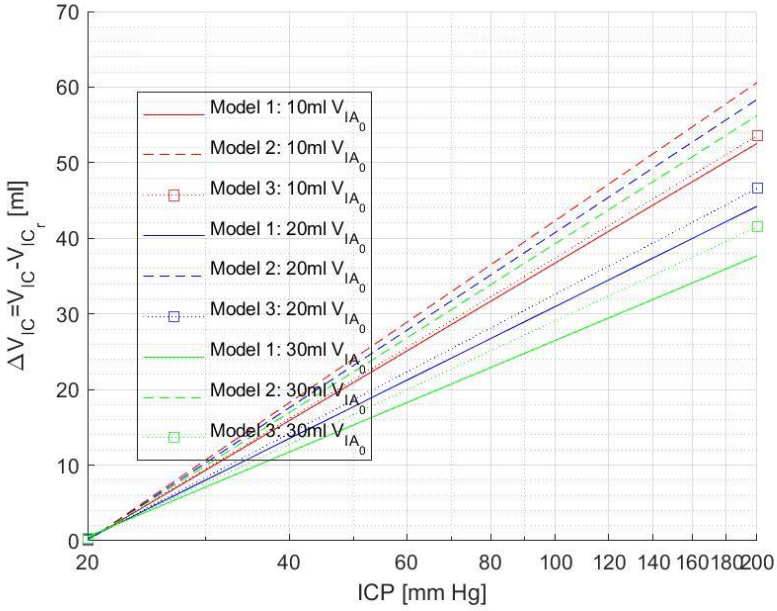

Figure C14: Change in intracranial volume with rise in ICP during ascent of 1000 ft/min with PVI of 12.6 ml, R = 31.36 mm Hg/(ml.min), resting pressure of 20 mm Hg and initial CSF volume of 120 ml.

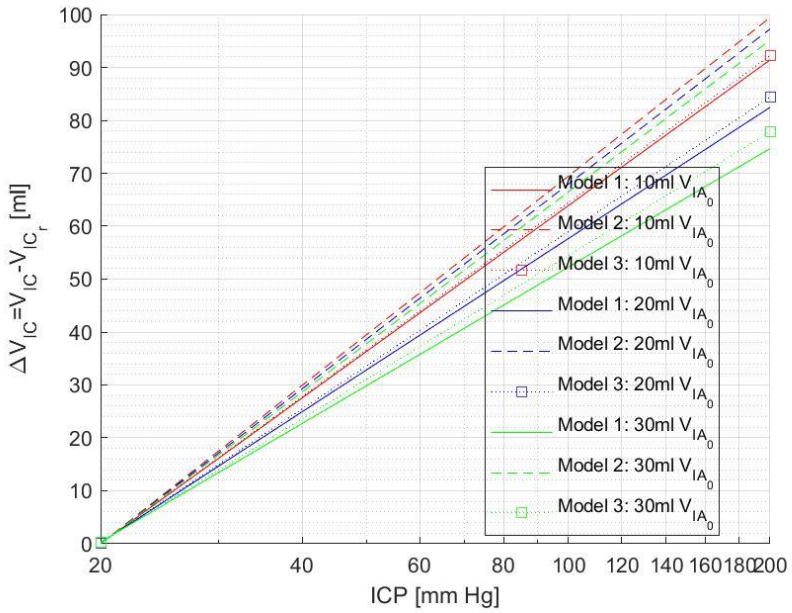

Figure C15: Change in intracranial volume with rise in ICP during ascent of 1000 ft/min with PVI of 26 ml, R = 16.1 mm Hg/(ml.min), resting pressure of 20 mm Hg and initial CSF volume of 120 ml.

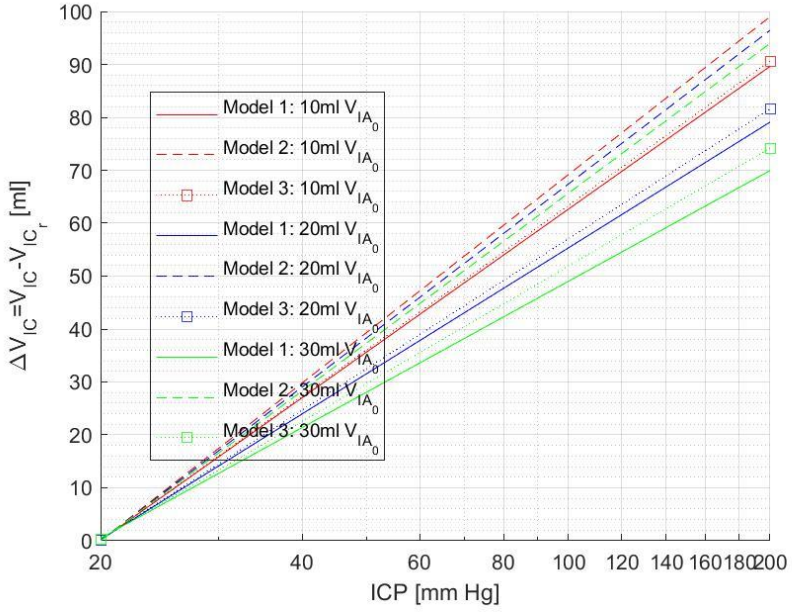

Figure C16: Change in intracranial volume with rise in ICP during ascent of 1000 ft/min with PVI of 26 ml, R = 31.36 mm Hg/(ml.min), resting pressure of 20 mm Hg and initial CSF volume of 120 ml.

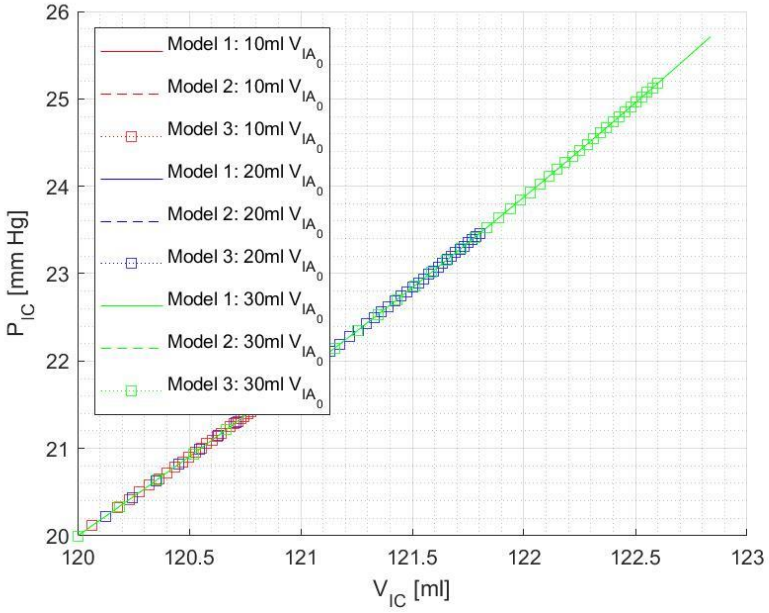

Figure C17: Intracranial volume-pressure curve during ascent of 250 ft/min for a patient with a resting pressure of 20 mm Hg, PVI of 26 ml and R = 31.36 mm Hg/(ml.min)

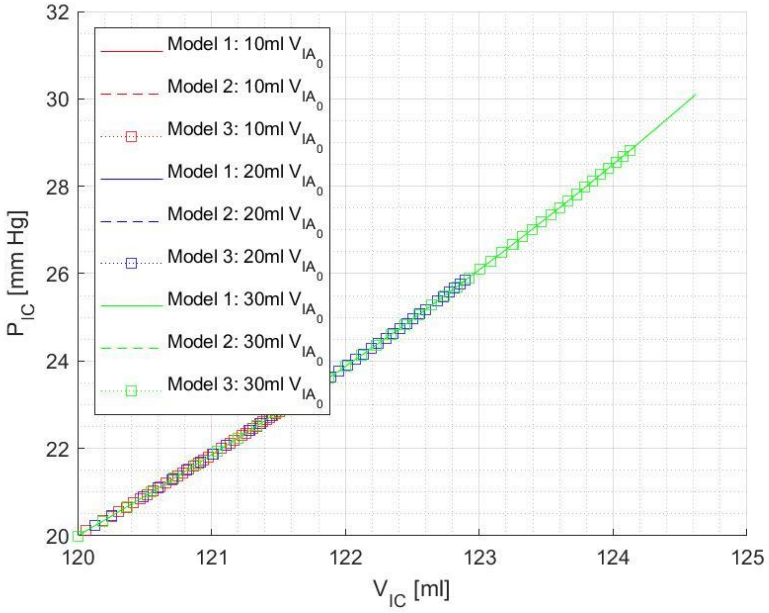

Figure C18: Intracranial volume-pressure curve during ascent of 500 ft/min for a patient with a resting pressure of 20 mm Hg, PVI of 26 ml and R = 31.36 mm Hg/(ml.min)

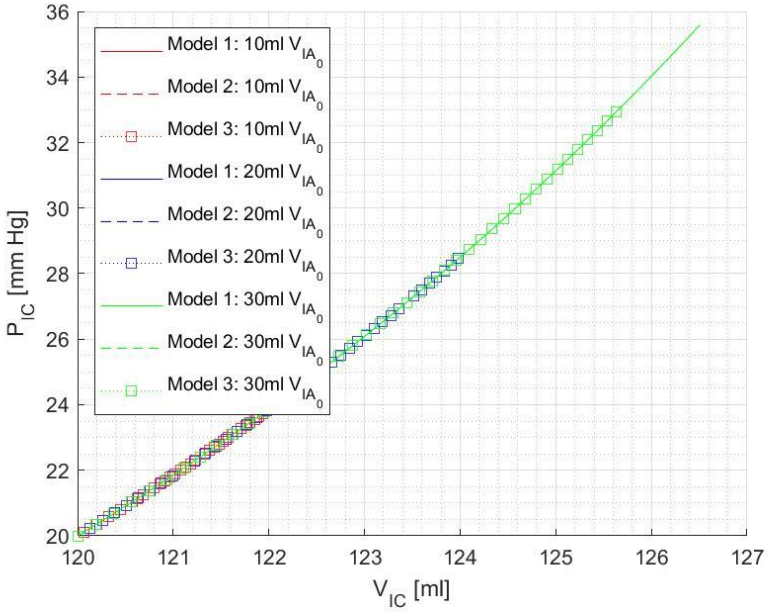

Figure C19: Intracranial volume-pressure curve during ascent of 1000 ft/min for a patient with a resting pressure of 20 mm Hg, PVI of 26 ml and R = 31.36 mm Hg/(ml.min)

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