The pressure difference between eye and brain changes with posture

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Running title: Difference between IOP and ICP change with posture

Abstract

Objective: The discovery of a posture-dependent effect on the difference between intraocular pressure (IOP) and intracranial pressure (ICP) at the level of lamina cribrosa could have important implications for understanding glaucoma and idiopathic intracranial hypertension and could help explain visual impairments in astronauts exposed to microgravity. The aim of this study was to determine the postural influence on the difference between simultaneously measured ICP and IOP.

Methods: Eleven healthy adult volunteers (age 46±10 years) were investigated with simultaneous ICP, assessed through lumbar puncture, and IOP measurements when supine, sitting, and in 9° head down tilt (HDT). The trans-lamina cribrosa pressure difference (TLCPD) was calculated as the difference between the IOP and ICP. To estimate the pressures at the lamina cribrosa, geometrical distances were estimated from MRI and were used to adjust for hydrostatic effects.

Results: The TLCPD (mm Hg) between IOP and ICP was 12.3±2.2 for supine, 19.8±4.6 for sitting and 6.6±2.5 for HDT. The expected 24-hour average TLCPD on earth—assuming 8 h supine and 16 h upright—was estimated to be 17.3 mm Hg. By removing the hydrostatic effects on pressure, a corresponding 24 h-average TLCPD in microgravity environment was simulated to be 6.7 mmHg.

Interpretation: We provide a possible physiological explanation for how microgravity can cause symptoms similar to those seen in patients with elevated ICP. The observed posture dependency of TLCPD also implies that assessment of the difference between IOP and ICP in upright may offer new understanding of the pathophysiology of idiopathic intracranial hypertension and glaucoma.

Key words: Glaucoma, idiopathic intracranial hypertension, intracranial pressure, intraocular pressure, visual impairment, posture

Introduction

In recent years, there has been an increased interest in the balance between intracranial pressure (ICP) and intraocular pressure (IOP).[1] The subarachnoid space surrounding the optic nerve communicates with the rest of the cerebrospinal fluid (CSF) system, and thus allows transfer of the ICP to the posterior part of the lamina cribrosa (LC).[2,3] The anterior side of the LC membrane is in contact with the intraocular compartment, where the pressure is the IOP. Thus, the trans-lamina cribrosa pressure difference (TLCPD=IOP-ICP) will generate a mechanical force on the axons passing through the LC [4,5]. This may be important in diseases of the optic disc, e.g., in papilledema or optic atrophy[1]. Accordingly, TLCPD has been suggested to be a pathophysiological component in glaucoma[6] and idiopathic intracranial hypertension (IIH)[7].

We have identified a key property that has not been accounted for in the exploration of TLCPD, i.e, how it varies with posture. We identified this gap when studying visual impairment/intracranial pressure (VIIP)[8], which is a syndrome that affects astronauts in microgravity. Elevated ICP due to the absence of gravity has been suggested to be a potential cause[9] because the VIIP symptoms have many similarities to symptoms in IIH[10,11]. In microgravity, any posture-dependent effects that originate from hydrostatics will disappear, and the lack of hydrostatic forces could thus lead to a disturbance in the pressure balance between brain and eye and thus cause VIIP. The clinical symptoms in space indicate that, on earth, gravity assists in maintaining a healthy balance between ICP and IOP. This physiological function is critical in upright posture when there are hydrostatic columns in the body.

If microgravity can cause symptoms in space, potentially by generating a disturbed TLCPD, then it is an intriguing question how TLCPD balance is maintained on earth. Is it possible that a dysfunction in the hydrostatic regulatory system for ICP or IOP can cause an abnormal TLCPD and lead to diseases like papilledema or glaucoma? On earth, both IOP and ICP vary with posture[12-15]. In clinical practice however, ICP is exclusively investigated in the supine or recumbent position, while IOP is primarily investigated in the sitting position. Thus, retrospective data is not useful in answering questions about abnormal TLCPD.

In a recent study, we investigated posture-related changes in ICP and presented a model for how ICP is controlled by intracranial venous pressure[13]. We found a distinct reduction in ICP when moving from the supine to sitting position, and the results emphasized the importance of the hydrostatic pressure gradients and collapsible jugular neck veins for control of ICP.[13] Regarding IOP, we expect the posture-related change[15,16] to be smaller than that of ICP. This suggests a posture-dependent change in TLCPD. However, simultaneous assessment of the IOP and ICP is sparse[17-20]. Changes in TLCPD as a function of posture has not yet been studied.

Thus, there is a gap in knowledge regarding the within-subject variation in TLCPD with respect to body posture. The aim of this study was to perform simultaneous measurements of ICP and IOP to determine the TLCPD while supine and sitting and ultimately simulate TLCPD in microgravity.

Materials and method

Healthy subjects

The study included eleven healthy volunteers age 46 ± 10 years (eight women, mean±SD). The subjects were recruited through an advertisement in the local newspaper. The inclusion criteria included no past or present neurological or ophthalmologic diseases and age between 30 and 60 years. The Regional Ethical Review Board approved the study, and all participants signed an informed consent form.

Subjects were investigated with brain MRI to assess anatomical distances between the references points of the pressures and the LC. This was followed by simultaneous ICP, assessed through lumbar puncture, and IOP measurements. Pressure measurements were performed in the supine, sitting and 9° head down tilt (HDT) postures. The HDT position is a frequently used ground-based analogue for simulating microgravity.[21]

Investigational protocol

The ICP and IOP assessments were performed in supine, sitting and HDT postures (Fig. 1). The body positions were controlled using a tilt-function of the investigation bed. The protocol started with the patient in the supine posture for 15 minutes (= first-supine). It then proceeded with a 25-minute tilt protocol that included 5 tilt levels to slowly bring the subject from supine to sitting. The subject was then tilted to sitting position (= sitting). This was followed by a second recording while supine (= second-supine) and a final recording at 9º head down tilt (= HDT). In each position, the ICP was allowed to stabilize

for at least three minutes, and the ICP estimate for that level was calculated as the time averaged mean over the next two minutes, making the ICP results independent of waveform attenuation in the spinal canal; the IOP measurement procedure was repeated after each completed ICP recording (Fig. 1).

Intracranial pressure was measured with a CELDA lumbar pressure measurement apparatus (Likvor AB, Umeå, Sweden). We measured the lumbar CSF pressure, which was shown to agree with the ICP[22]. Through a hole in the back of the bed a ∅1.2 mm (18G) needle was placed in the spinal canal in contact with the CSF; care was taken to insert the needle with minimal CSF leakage. The lumbar puncture was performed by an experienced neurologist. CELDA Tools with standard tubing and pressure transducer were connected to the needle. The ICP contact was confirmed through detection of ICP pressure pulsations in the recording unit. In the supine position, the zero-pressure reference level of the pressure transducer was placed at the center of the auditory meatus using the built-in horizontal laser line. We further adjusted the pressure such that the auditory meatus was always the reference point independent of posture; this was accomplished by assessing the vertical distance between the auditory meatus and the sensor using a movable horizontal laser on a vertical rod mounted on the CELDA. Thus, we could assess the mean ICP at all postures.

An experienced ophthalmologist performed the IOP measurements. IOP was measured with the Applanation resonance tonometer (ART) (BioResonator Good Eye AB, Umeå, Sweden). By construction[23], this is independent of gravity and could be used in all body

postures. The ART used in this study was handheld with a supporting arm that is placed on the forehead of the measurement subject to enable a stable measurement. The ART technique has been described in detail elsewhere[24]. Prior to the IOP measurement at each position, a drop of lidocaine hydrochloride 4% and fluorescein sodium 0.25% (Chauvin Pharmaceuticals Ltd, Kingston-Upon-Thames, UK) was instilled in each eye. The IOP was measured at the first supine position, at the sitting position, and again at the second supine position and at HDT (Fig. 1). The IOP at each body position was calculated as the mean of six repeated measurements, three from the left eye and three from the right eye. Measurements at the second supine position was included as repeated IOP applanation measurements, without rest in-between, is known to potentially reduce IOP[25], and thus we wanted an additional supine baseline IOP estimate before the HDT measurement.

IOP was successfully assessed for all eleven subjects at first-supine, sitting, second-supine and at HDT. ICP was successfully assessed for all eleven subjects at first-supine and sitting. Suspicion of unreliable ICP estimation due to reduced CSF contact (as indicated by very low ICP pulsations) was noted in three subjects at second-supine. These measurements were therefore excluded, as was the corresponding HDT measurements. For another subject, the same problem was noted only in HDT. This resulted in n=8 ICP measurements for the second-supine and n=7 for HDT.

To calculate pressures at the LC, the geometrical distances corresponding to the hydrostatic columns affecting the two pressures were assessed using sagittal MRI T2-weighted images acquired with a 3T scanner (GE Discovery MR750; General Electric

Healthcare, Waukesha, WI). The images were analyzed to determine the (total) distance from the auditory meatus (reference point for the ICP) to the LC as well as the distance between the cornea and LC. The resulting vertical distances in the supine, sitting and HDT positions were then calculated for each subject (Fig. 2).

Analysis

ICP was estimated from the measured CSF pressure with the auditory meatus as the reference point. Using the distance from the auditory meatus to the LC as estimated by the MRI distance and tilt angle, the CSF pressure at the level of the posterior side of the LC (ICP_{LC}) was estimated for supine, sitting and HDT postures (Fig. 2). Similarly, the measured IOP was adjusted based on the bulb length and tilt angle to estimate the pressure at the anterior side of the LC (IOP_{LC}; Fig. 2). The trans-lamina cribrosa pressure difference was defined and calculated as $TLCPD = IOP_{LC} - ICP_{LC}$.

Based on the assessed IOP_{LC} and ICP_{LC}, we also estimated the expected daily 24-hour average TLCPD by assuming 16 hours of upright posture and 8 hours of supine. We further estimated the expected daily 24-hour average TLCPD in microgravity by assuming that without gravity, the subject would in a sense be put in a constant supine position without any gravitational (i.e. hydrostatic) effects on the pressures.

Statistics

Differences in pressure between postures were assessed with paired t-tests. All values are presented as a mean ± standard deviation; $P<0.05$ was set as a threshold for statistical significance.

Results

Both ICP and IOP changed with body posture. The ICP was higher in supine compared to sitting: 10.5 mm Hg versus -0.8 mm Hg ($p<0.001$, $n=11$) (Table 1). The IOP was also higher in the supine compared to sitting positions, but the difference was not as pronounced as with ICP: 17.2 versus 14.5 mm Hg ($p<0.001$, $n=11$). To investigate the effect of HDT, we compared it to the second-supine baseline. HDT caused an increase in both IOP (1.5 mm Hg, $p=0.003$, $n=11$) and ICP (4.3 mm Hg, $p>0.001$, $n=7$) (Table 1).

The measured IOP and ICP were translated to pressures at the lamina cribrosa and resulted in a TLCPD that displayed a strong posture dependence (Table 2). The TLCPD for the sitting position was 19.8 ± 4.6 mm Hg ($n=11$). For supine it was 12.3 ± 2.2 mm Hg ($p<0.001$, $n=11$), and for HDT 6.6 ± 2.5 ($p=0.002$, $n=7$, compared to second-supine) (Table 2).

With the assumed 16 hours of upright posture and 8 hours of supine posture we estimated the expected daily 24-hour average TLCPD to be 17.3 mm Hg (Table 2). In space, we would expect the TLCPD to always be approximately the difference in measured unadjusted supine IOP (17.2 mm Hg) and ICP (10.5 mm Hg) because there should be no hydrostatic effects at all. Accordingly, we estimated the simulated TLCPD in space to be about 6.7 mm Hg (Table 2).

We confirmed the expected reduction in IOP between the first- and second-supine measurements (-1.3 mm Hg, $p=0.03$, $n=11$). There was no significant difference in ICP between the first- and second-supine measurements ($p=0.19$, $n=8$).

Discussion

In this study, we show that the pressure difference over lamina cribrosa (TLCPD) depends on the hydrostatic effects related to changes in body posture. This is the first study to measure ICP and IOP simultaneously in subjects during standardized variations in body posture. Our findings support the hypothesis that the 24-hour average TLCPD in microgravity should be smaller than on earth. The distinct increases in TLCPD while upright suggests that diseases like Glaucoma and IIH—where TLCPD abnormality is suspected—should be investigated not only in the supine position, but also with the patient sitting or standing.

A review of previous studies (Table 3) clearly shows that the critical missing metric is a comparison of IOP and ICP at both postures. Most critically, ICP while upright is missing. This work adds critical information to the understanding of the mechanical stress applied to the axons in the LC. The relationship between IOP and ICP has been investigated before, but not with both variables assessed in the horizontal and upright posture or even in the same posture (Table 3). Studies investigating TLCPD have measured ICP while supine or recumbent as well as IOP while sitting. The exception is Morgan et al[20] who assessed ICP and IOP in nine sitting neurosurgical patients to investigate the timing of retinal venous pulsation in relation to the intraocular and intracranial pressure pulses.

Abnormal TLCPD values have been implicated in glaucoma. Specifically, for normal tension glaucoma, patients have a slightly reduced ICP[6] as measured with the patient in

horizontal position. TLCPD in a 24-hour perspective is primarily influenced by the ICP in the upright because people are upright approximately 16 hours per day. This posture had the largest TLCPD. We furthermore observed that the ICP variation in supine was small compared to the variation found in sitting (see Table 1) indicating inter-individual variation in the control system for upright ICP. Together, these findings strongly suggest that the continued work in addressing glaucoma pathophysiology based on a hypothesis of imbalance between IOP and ICP should include assessment and analysis of ICP in the upright posture.

In contrast to glaucoma, IIH can be expected to have a reduced or reversed TLCPD. Neurologists and neurosurgeons have traditionally attributed the bilateral papilledema in IIH to increased ICP[26]. In addition to the degree of ICP elevation, this study indicates that the counter pressure of the eye is important, and the pressure imbalance between ICP and IOP could be a key physiological cause of papilledema in IIH. This motivates posture studies in this patient group. ICP while upright should already be added to the protocol for IIH to fully understand the ICP stress on the back of the eye.

VIIP has been found in the majority of astronauts returning from the international space station[10], and VIIP is identified by NASA as one of the top risks to human space exploration[27]. The syndrome is suggested to originate from elevated ICP in microgravity. We give a potential explanation for the origin of a reduced TLCPD in space by revealing that ICP is much more posture dependent and thus more dependent on gravity than IOP. Gravity leads to a reduced ICP while upright. Thus, the absence of gravity increases ICP on a 24-hour basis, which is not balanced by the corresponding IOP

increase. Thus, the effective 24-hour average of TLCPD should be reduced (Table 2). A reduced TLCPD also agrees with what can be expected in IIH. Our results provide a possible physiological explanation for how microgravity can cause VIIP symptoms that are similar to the symptoms seen when elevated ICP causes IIH. Note also that the reduction in 24-hour average TLCPD in microgravity would persist even if the actual ICP compared to supine on earth is not elevated. On the topic of space medicine, it was interesting that the estimated TLCPD in microgravity corresponds to the TLCPD that we found in HDT posture. This supports a 9° supine head down tilt as a suitable microgravity analogue for simulating TLCPD on earth.

The intracranial and intraocular systems have analogue descriptions of what regulates the mean pressure in the respective system. This regulation is modeled with the formation of fluid (CSF or aqueous humor) and absorption of the fluid to venous blood over a resistive barrier[28,29]. According to these models, the change in IOP and ICP with respect to change in body posture should directly follow from the posture-induced change in venous pressure in the episcleral veins and dural sinuses, respectively. We found a marked ICP reduction in sitting, which agreed with previous findings[13,14]. This was explained by the hydrostatic reduction in venous pressure along with the effect of collapsible jugular veins[13]. In that study we investigated different models for ICP regulation with respect to posture changes and concluded that the model with a CSF indifference point according to Magnaes[12] does not describe measured ICP changes during head up tilt in a sufficient way, while a model that includes Davson equation and a venous indifference point together with a collapsible jugular system in upright did

predict ICP. It is based on these findings we emphasize the importance of the venous system in controlling ICP. However, as expected[15], the IOP was only slightly reduced in sitting indicating that there are additional control functions for the intraocular system; this is also supported by constant venous pressure in the episcleral veins while upright[30,31]. To further understand the postural effect on IOP and ICP, the hydrostatic regulating functions of their venous systems while upright should be studied. A dysfunction in these systems can be important in IIH and glaucoma.

In HDT, we noted a rise in ICP that corresponded to the expected venous hydrostatic column, suggesting that hydrostatic changes in the venous pressure induce a corresponding change in ICP. For the intraocular compartment, we again observed that the regulation of IOP during the hydrostatic load was more advanced and the increase was lower than the corresponding venous hydrostatic column. The 1.5 mm Hg increase in IOP at HDT agreed with recent findings in a long duration HDT bed rest study[32].

The choice of assessing ICP through the lumbar route and compensating for hydrostatic effects based on vertical distances assumes that CSF communication was maintained at all postures. In these healthy individuals MRI revealed a communicating CSF system between spinal and intracranial compartments. High correlation ($R>0.99$) in simultaneous measurements of mean ICP and mean lumbar CSF pressure has been shown in supine position[22] using a set-up similar to the one used in this study, and Eide et al[33] has shown a correlation of $R=0.91$ in lateral horizontal position. Furthermore, two recent studies with invasive ICP sensors found a pressure reduction (11.5-14 mm Hg) when going from supine to sitting posture[14,34] that corresponded well with the reduction

in this study (11.3 mm Hg), supporting the validity of assessing mean ICP with a lumbar CSF pressure measurement adjusted for the hydrostatic column.

The hydrostatic continuity between the subarachnoid space around the optic nerve and the rest of the CSF system (i.e. with the ICP) has been demonstrated[3]. However, animal studies[35,36] have indicated that at negative ICP values the CSF pathway around the optic nerve is occluded, suggesting that the CSF pressure at the LC (IOP_{LC}) should not drop below zero[35]. While sitting, ICP was negative for all but one of our subjects. If this occlusion of the CSF space holds true for humans as well, then our value for TLCPD while sitting would be reduced from 19.8 to 15 mm Hg, and the 24-hour average TLCPD would be reduced from 17.3 to 14 mm Hg. Thus, the main observation of a gravitational effect on TLCPD is still valid. If the occlusion of the optic nerve sheet while upright is a normal physiological property, then a non-occluding stiff nerve sheet could be a pathology that leads to elevated TLCPD while upright. In a paper by Morgan et al[37] they further suggest a four compartment model where in addition to the intracranial space, the orbital space and the optic nerve subarachnoid space, a retrolaminar tissue compartment is formed by the pia mater around the optic nerve, adding a compliance that further limits the minimum retrolaminar pressure in dog model to about 2.5 mm Hg. Again, if there is a similar effect in humans this would translate to a TLCPD in sitting of 12.5 mmHg, which is close the value we found in supine posture (Table 1). Although the corresponding 24-hour average TLCPD of approximately 12.5 mm Hg is still higher than the expected TLCPD in microgravity, this effect would describe the physiological mechanism needed to keep a posture independent TLCPD on earth. Together with the posture dependent difference between ICP and IOP this would indicate that a

suboptimal hydrostatic function in the pia mater compliance or an optic nerve sheet that does not occlude around the optic nerve at negative ICP, would not functionally counteract the large pressure difference between the brain and the eye, and could thus directly result in abnormal TLCPD in upright. Furthermore, it should be noted that Killer et al have demonstrated that the CSF turnover in the optic nerve subarachnoid space is reduced in papilledema[38] and in normal tension glaucoma[39], which could indicate a hampered fluid continuity and all this should be taken in consideration in future work on TLCPD in IIH and glaucoma.

Conclusions

Simultaneous measurements of ICP and IOP in supine and sitting positions revealed that the pressure difference between the eye and brain was posture-dependent. This study presents a possible physiological explanation for how the lack of hydrostatic forces in microgravity could lead to disturbances in the daily average pressure difference between the eye and brain. Accounting for the effect of postural dependency can provide new insights in research investigating the importance of TLCPD in glaucoma and IIH.

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Author Contributions

AE, JM and LOK contributed with conception and design of the study; AE, JM, GJ, SQ and LOK contributed with drafting a significant portion of the manuscript or figures. AE, GJ, EJ, PH, SQ, KA, AW, LOK and JM contributed with acquisition and analysis of data and contributed by critically revising the manuscript.

Conflicts of Interest

JM and AE holds patents assigned to Likvor AB, Umeå, Sweden related to the CELDA® device and has received royalties from Likvor AB. AE has a patent for ART IOP tonometry device assigned to BioResonator GoodEye AB, Umeå Sweden. GJ, EJ, PH, SQ, KA, AW and LOK have nothing to report.

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Figure legends

Figure 1 Investigational protocol. First, 15 minutes were spent supine followed by 25 minutes going in steps from supine to sitting without measurements followed by 7 minutes in sitting, 7 minutes in a second supine position and finally ending with 7 minutes in the HDT position. Black solid lines refer to periods of stabilization; grey lines refer to ICP measurements and black dotted lines to the period when the IOP measurements were performed.

Figure 2 Description of the vertical distances that were used to translate the ICP from the auditory meatus to the level of the posterior side of the LC (a). The IOP from the level of the cornea to the anterior side of the LC (b). Estimations were performed for supine (upper), sitting (lower) and head down tilt posture.

Tables

Posture	ICP (mm Hg)		IOP (mm Hg)	
	Mean±*SD*	n	*Mean*± *SD*	n
First-supine	10.5±1.5	11	17.2±1.8	11
Sitting	-0.8±3.8	11	14.5±2.3	11
Second-supine	11.5±0.8	8	16.0±1.9	11
Head down tilt	15.8±1.3	7	17.5±2.0	11

Table 1. ICP and IOP at different postures.
ICP: Intracranial pressure, IOP: Intraocular pressure, SD: Standard deviation.

Posture	Lamina cribrosa pressures (mm Hg)			Microgravity (simulated) (mm Hg)		
	ICP_{LC}	IOP_{LC}	*TLCPD*	ICP_{LC}	IOP_{LC}	*TLCPD*
Supine	6.6	18.9	**12.3**	10.5	17.2	**6.7**
Sitting	-4.7	15.1	**19.8**	10.5	17.2	**6.7**
Estimated 24-hour average	-0.9	16.3	**17.3**	10.5	17.2	**6.7**
Head down tilt	12.4	19.1	**6.6**	10.5	17.2	**6.7**

Table 2. Trans-lamina cribrosa pressure differences.
ICP_{LC} and IOP_{LC} are the measured ICP and IOP adjusted hydrostatically to the level of lamina cribrosa (n=11). The 24-hour daily average was calculated with an estimated 16 hours of upright posture and 8 hours in supine. Expected pressures in microgravity are the measured ICP and IOP in supine for all postures because there are no hydrostatic effects in microgravity.

Studies	Medical condition	Subjects; mean age	ICP (mmHg, mean±SD)		IOP (mmHg, mean±SD)		IOP-ICP (mmHg)		
			Supine*	Sitting	Supine	Sitting	Supine	Sitting	Sup/Sit
Berdahl[40]	Neurological	n=39; 55	11.5±3.3	✖	✖	16.1±2.2	✖	✖	4.6
Berdahl[40]	Neurological	n=66; 69	12.7±3.9	✖	✖	14.8±3.2	✖	✖	2.1
Berdahl[41]	Neurological	n=49; 69	13.0±4.2	✖	✖	14.9±3.0	✖	✖	1.9
Ren[6]	Neurological	n=71; 46	12.9±1.9	✖	✖	14.3±2.6	✖	✖	1.4
Morgan[20]	Neurosurgical	n=9; 39	✖	4.4±7.1	✖	15.1±8.9	✖	**10.7**	✖
Kirk[42]	Neurological	n=45, x	18.2±8	✖	✖	13.2±3.3	✖	✖	-5.0
Sajjadi[18]	Neurological	n=50; 34	19.0±1.4	✖	20.4±1.1	✖	**1.4**	✖	✖
Han[43]	Neurological	n=55; 38	20.1±7.5	✖	✖	14.4±2.7	✖	✖	-5.7
Current study	Healthy	n=11; 46	10.5±1.5	-0.8±3.8	17.2±1.8	14.5±2.3	**6.7**	**15.3**	4.0

Table 3. Literature review on ICP and IOP in humans with respect to postures. The review includes studies in which ICP and IOP were measured and reported in mean values. Note that ICP and IOP are the measured pressures according to their reference levels and not at the level of LC. ✖ denotes not measured. *Supine or recumbent. The Berdahl et al. and Ren et al. studies also presented data on glaucoma patients. The current study appended at the end is the only one that includes healthy and IOP and ICP in both postures. The Supine/Sitting column is greyed because it is not physiological.

Figure 1.

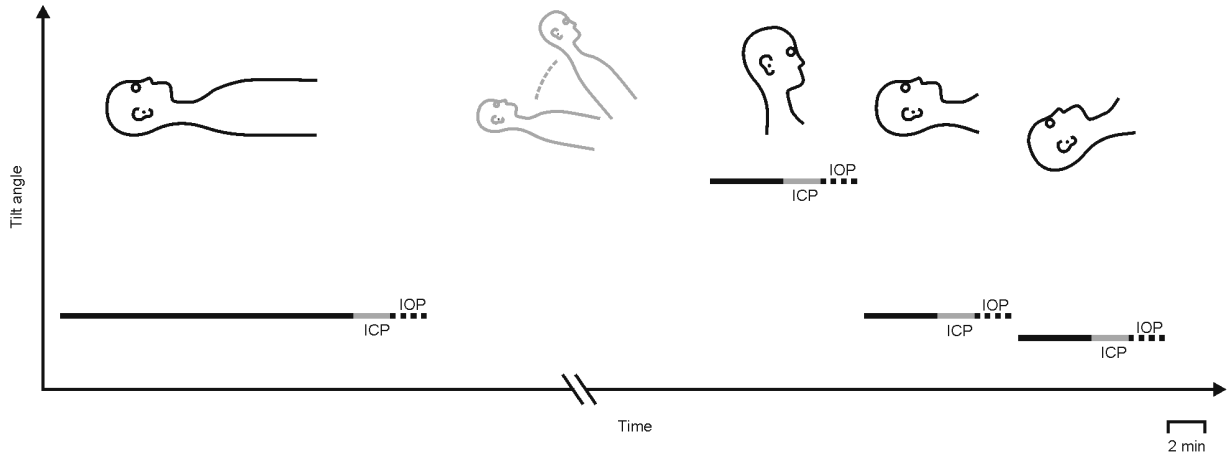

Figure 2