Transient intracranial pressure elevations are associated with sleep apnea

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Abstract

Background

Repetitive transient intracranial pressure waveform elevations up to 50 mmHg (ICP B-waves) are often used to define pathological conditions and determine intracranial pressure-reducing treatment indications. We recently showed that nocturnal transient ICP elevations are present in patients without structural brain lesions or hydrocephalus in whom they are associated with sleep apnea. However, whether this signifies a general association between intracranial pressure patterns and sleep apnea is still unknown.

Methods

We included 34 patients with hydrocephalus, or idiopathic intracranial hypertension (IIH), referred to the Neurosurgical Department, Copenhagen, Denmark, from 2017 to 2021. Every patient underwent a diagnostic overnight intracranial pressure monitoring on clinical indications with simultaneous polysomnography (PSG) sleep studies. All transient ICP elevations were objectively quantified for all patients. Three patients were monitored with continuous positive airway pressure (CPAP) treatment for an additional night.

Results

All patients had transient intracranial pressure elevations associated with sleep apnea. The mean temporal delay from sleep apnea to transient intracranial pressure elevations for all patients was 3.6 seconds (SEM 0.2 seconds). High amplitude ramp-type transient intracranial pressure elevations were associated with rapid eye movement (REM) sleep and sinusoidal-type elevations with non-REM (NREM) sleep. CPAP treatment reduced the number of transient intracranial pressure elevations in all three patients (mean 37%). CPAP treatment elevated the mean intracranial pressure during sleep in two patients by 1.2 and 5.6 mmHg, respectively, and reduced the mean intracranial pressure in one patient with a ventriculoperitoneal shunt by 1.0 mmHg.

Conclusion

The findings suggest that sleep apnea causes a significant proportion of transient intracranial pressure elevations, and sleep apnea should be considered in intracranial pressure evaluation. Continuous positive airway pressure (CPAP) treatment can reduce their occurrence. However, CPAP may concurrently elevate the mean intracranial pressure. More research is needed on the impact of slow oscillating mechanisms on transient intracranial pressure elevations during high intracranial pressure and REM sleep.

Background

Intracranial pressure (ICP) measurement is a cornerstone of diagnostics in neurology and neurosurgery. Lundberg initially described different macro-patterns of ICP and categorized them as A-, B-, and C-waves based on frequency, amplitude, and duration.[1] Lundberg B-waves (0.5 to 2 waves per minute and amplitude up to 50 mmHg), being the most common and generally seen as indicative of a pathological condition, are this paper's primary focus.

Historically, transient ICP elevations such as B-waves have been considered pathological when observed overnight. Despite their use in guiding decisions for invasive ICP management, the underlying physiology of these transient elevations remains elusive. Previous studies have reported their occurrence in healthy individuals,[2–4] and associated with sleep-disordered breathing, like sleep apnea.[1, 4–7] However, this has not attracted much attention, and transient ICP elevations are generally considered a result of altered cerebral blood flow (CBF) due to changes in blood gasses, especially CO_2. We recently showed that transient ICP elevations are highly associated with sleep apnea, with high-amplitude ramp-like transient ICP elevations accompanying rapid eye movement (REM) sleep. In contrast, more minor sinusoidal waves primarily occurred with non-REM (NREM) sleep stages.[4] Additionally, we suggested that pressure changes in the thoracic cavity caused by respiratory movement and sleep apnea could contribute to a significant proportion of transient ICP elevations.

Several underlying physiological mechanisms probably cause transient ICP elevations, depending on ICP level and clinical conditions. We propose that there is a strong connection between transient ICP elevations and sleep-disordered breathing, like sleep apnea, in patients with idiopathic normal pressure hydrocephalus (iNPH). Since both transient ICP elevations (B-waves)[8–10] and sleep apnea[11–13] are highly prevalent in these patients. We also propose similar patterns in patients with other neurosurgical conditions.

By exploring the connection between transient ICP elevations, sleep stages, and sleep apnea, this study aims to provide valuable insights into a better understanding of the underlying mechanisms of transient ICP elevations. This was done by recording ICP signals and conducting simultaneous polysomnography sleep studies in 34 patients with different types of hydrocephalus and idiopathic intracranial hypertension (IIH). The study also examined the effects of continuous positive airway pressure (CPAP) treatment on the number of sleep apnea-associated transient ICP elevations by monitoring three patients for an additional night when treated with CPAP.

Methods

This prospective observational study was conducted and reported according to the STROBE guidelines for cohort studies. It focuses mainly on the nocturnal occurrence of transient ICP elevations in neurosurgical patients and is part of a more extensive research program investigating sleep and the glymphatic system in humans.

Study Population

The cohort included 34 patients with hydrocephalus or IIH referred to the Neurosurgical Department, Copenhagen, Denmark, from 2017 to 2021. To confirm the diagnosis, every patient underwent a physical, neurological, and radiological evaluation. ICP monitoring was performed for diagnostic purposes. The patients were asked to participate in an additional voluntary sleep evaluation study performed together with ICP monitoring. Upon enrollment, a hydrocephalus expert classified the patients with the following diagnoses: iNPH, adult-onset obstructive hydrocephalus, pediatric-onset hydrocephalus, following the ASPECT Hydrocephalus System for evaluation of hydrocephalus patients[14] or IIH (Table 1).

Table 1
Demographic and clinical data.

	Type of patient				
	iNPH (n = 5)	Adult-onset (n = 4)	Pediatric-onset (n = 13)	IIH (n = 12)	P value
Men/Women	4 (20%) / 1 (20%)	1 (25%) / 3 (75%)	5 (45%) / 6 (55%)	1 (8%) / 11 (92%)	
Age, years	67.4 (6.6)	60.0 (7.2)	42.9 (20.5)	33.0 (8.0)	**< 0.001**
BMI	25.4 (3.4)	26.1 (3.0)	26.5 (6.4)	36.5 (9.6)	**0.005**
ESS	4.8 (3.1)	7.8 (5.3)	10.5 (6.1)	9.1 (4.3)	0.23
	General disease and risk factors				
Hypertension	4 (80%)	1 (25%)	1 (8%)	3 (25%)	
Heart disease	3 (60%)	0	0	1 (10%)	
	CNS				
Dementia	4 (80%)	0	3 (23%)	0	
Psychiatric	0	0	0	2 (17%)	
Epilepsy	2 (40%)	1 (25%)	3 (23%)	0	
Evans ratio	0.44 (0.05)	0.33 (0.08)	0.34 (0.07)	0.26 (0.04)	**< 0.001**
DESH	3 (60%)	0	1 (8%)	0	
Obstruction	0	4 (100%)	9 (69%)	0	
	Treatment				
Shunt	0	4 (100%)	2 (15%)	4 (33%)	
ETV	1 (20%)	1 (25%)	7 (54%)	0	

Summary statistics include the mean and the standard deviation (SD) to summarize continuous variables and numbers and (percentages) to summarize categorical variables. BMI = Body mass index (kg/m^2); DESH = Disproportionately enlarged subarachnoid space hydrocephalus; Epworth sleepiness scale (ESS, normal < 10)); ETV = Endoscopic third ventriculostomy; Evans ratio = ventricular size ratio (normal ≤ 0.30); Standard deviation (SD). P value of one-way analysis of variance (ANOVA).

The iNPH diagnosis was based on the iNPH symptom triad and imaging. None of the iNPH patients had a previous history of tumors, subarachnoid hemorrhage, head injury, or meningitis and had no visible obstruction of CSF flow on imaging. All adult-onset hydrocephalus patients showed signs of CSF flow obstruction on imaging. The pediatric-onset patients had a documented pediatric-onset or a clinical

presentation compatible with pediatric-onset, e.g., congenital malformations and a large head circumference. The patients with IIH were diagnosed based on the Friedman criteria with normal brain parenchyma without hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement or venous sinus thrombosis.[15] Three patients with IIH were included upon an acute diagnosis with papilledema. The demographic and clinical data of the patient groups are summarized in Table 1. Except for one patient with pediatric-onset hydrocephalus, the prevalence of sleep apnea has been reported previously for all the patients with hydrocephalus.[11]

Surgery and ICP catheter

All patients underwent surgery by inserting a commercially available ICP catheter (RAUMEDIC AG, Helmbrechts, Germany). Fourteen patients were measured with Neurovent-P catheter and seven with Neurovent-P-tel catheter (telemetric catheter), both inserted 2 cm into the brain parenchyma in the right frontal region (Kocher's point) and measuring the ICP in the parenchyma. The remaining nine patients were measured with a Neurovent catheter, measuring ICP in the lateral ventricle (Supplementary Table 1). All operations were completed without complications, and all patients were discharged after their diagnostic ICP measurement or the next day for patients with Neurovent-P-tel. Calibration is not necessary before insertion, as these systems auto-calibrate against atmospheric pressure.

Polysomnography

As previously described, the sleep evaluation was performed during in-hospital diagnostics with ICP measurements.[4] Polysomnography (PSG) is a standard criterion method and was performed according to the American Academy of Sleep Medicine (AASM) standards (electroencephalogram (EEG), electrooculography (EOG), submental- and anterior tibialis electromyography (EMG), electrocardiography (ECG), airflow, respiratory inductance plethysmography (RIP), snoring, and oxyhemoglobin saturation (SaO_2)), and was recorded with Domino™ software (SOMNOmedics GmbH, Germany). Recordings were scored manually according to the AASM by an independent trained professional supervised by an experienced expert in neurophysiology, both blinded to the diagnosis of the patients. Sleep-Disordered Breathing is reported as Apnea-Hypopnea Index (AHI) following the AASM 2012 standard. In addition, two patients with IIH and two with pediatric-onset were monitored with end-tidal CO_2 (LoFlo, Respironics, Inc), performed according to the manufacturer's protocol.

Continuous positive airway pressure

Three patients with sleep apnea were monitored for two days with ICP and PSG. Continuous positive airway pressure (CPAP) treatment was added for the second night of monitoring. None of the three patients were known to have sleep apnea prior to our investigation and had not tried CPAP treatment before.

Intracranial pressure and polysomnography recordings

As previously described,[4] simultaneous recording of PSG (SOMNOscreen™ plus, Somnomedics) and ICP (RAUMEDIC AG) was performed. Briefly, during PSG recording, the ICP signal was transferred from the Datalogger (MPR1, RAUMEDIC AG) to the SOMNOscreener by an analog cable to ensure the correct and fully synchronized time incorporation of the ICP signal into the PSG data. After manually scoring the PSG, all data were transferred to Matlab 2020b (MathWorks®). Two sensors recorded the signals: the Datalogger MPR1 and the PSG. The data were collected asynchronously by these two sensors, so time alignment was necessary to remove the delay between them. As a result, the signal recorded by the Datalogger MPR1 was integrated into the PSG signal. Only the synchronized Datalogger MPR1 ICP signal was analyzed further. Before conducting the ICP analysis, artifacts were identified and removed from the Datalogger MPR1 ICP signal.

Transient intracranial pressure elevations

All transient ICP elevations were identified by the recently described method for automatic macro-pattern identification in the ICP signal[16] and subdivided into occurring during REM sleep vs. NREM sleep and into occurring with or without apnea or hypopnea. Briefly, artifacts were removed with an Empirical Decomposition (EMD) based method. Afterward, the ICP signal was smoothed via a linear phase FIR lowpass filter, with a cut-off frequency (Fpass) set to 0.05–0.1 Hz. Then ICP signal was segmented into subsequences of duration varying from seconds to minutes by finding the local maxima and minima in the smoothed ICP signal. The derived subsequences were Z-normalized to ensure that the subsequences were linearly transformed to have zero mean and standard deviation close to one. In the end, five representative k-Shape clusters were identified and used to quantify transient ICP elevations. The amplitude was calculated as the difference between the lowest and highest ICP value during a transient ICP elevation. The mean ICP value during sleep for each patient was calculated from the sleep onset to sleep offset in the hypnogram (including positional change, apneas, and short awake periods).

The causal relationship between transient intracranial pressure elevations and sleep-disordered breathing

To determine the relationship between sleep apnea and transient ICP elevations, we measured the time difference between the onset of all apneas and the local minima (lowest value) of a transient ICP elevation detected by the automatic macro-pattern identification method.

Statistical analysis

Descriptive statistics were obtained for each variable. Summary statistics included the continuous variables' mean, median, range, standard deviation (SD), and standard error of the mean (SEM). Percentages and sample sizes were used to summarize categorical variables. One-way analysis of variance (ANOVA) was used to compare the groups' mean for continuous variables. Linear regression was applied to test for the association of two independent variables. Values of $P < 0.05$ were considered statistically significant.

Data availability statement

Anonymized data are available upon reasonable request from the corresponding author and after clearance by the competent ethics committee.

Results

Transient ICP elevations

All patients had transient ICP elevations associated with sleep apnea (Table 2 & Figs. 1, 2 & 3). The mean temporal delay between sleep apnea and transient ICP elevations for all patients was 3.6 seconds (SEM 0.2 seconds) in 3273 apneas, without differences between the groups ($P = 0.59$). Thus, on average, the apnea started 3.6 seconds before the transient ICP elevation, proceeded through most of the upslope of the ICP elevation, and terminated just before the peak of the ICP elevation. Transient ICP elevations of higher amplitude were associated with increased activity in the abdominal respiratory belt and low activity in the thoracic respiratory belt and vice versa for low amplitude transient ICP elevations. Sleep apnea during REM sleep was associated with transient ICP elevation with higher amplitude and ramp-type morphology (Figs. 1 & 2), and sinusoidal-type elevations occurred with NREM sleep.

Table 2
Quantification of transient ICP elevations.

	Transient ICP-elevations			**Sleep apnea**
	Total	Apnea	without apnea	AHI
iNPH (*n* = 5)	361 (148)	125 (67)	236 (118)	34.9 (6.4)
Pediatric (*n* = 13)	398 (175)	47 (52)	351 (199)	13.8 (16.8)
IIH (*n* = 12)	451 (171)	57 (70)	394 (151)	9.9 (8.9)
Adult (*n* = 4)	180 (90)	16 (8)	165 (97)	5.7 (4.3)

Transient ICP elevation values are mean and standard deviation (SD). Adult = adult-onset obstructive hydrocephalus; AHI = apnea-hypopnea index; IIH = idiopathic intracranial hypertension; iNPH = Idiopathic normal pressure hydrocephalus; Pediatric = pediatric-onset hydrocephalus; Ratio = the ratio between transient ICP elevation with apnea and without apnea.

All patients had transient ICP elevations not associated with sleep apnea. However, most of these transient ICP elevations had changes in the respiratory signals not meeting the criteria for apneas or hypopneas; thus, in all patients, transient ICP elevation was seen without apneas, most often caused by irregular breathing with altered thoracic and abdominal movement (Supplementary Fig. 1).

The number of ICP elevations associated with sleep apnea out of the total number of transient ICP elevations varied between the patient groups. The percentage reflects the mean AHI found in each patient group (Table 2).

REM sleep ICP elevations

In one patient with iNPH, one with pediatric-onset, and one with adult-onset hydrocephalus, plateau ICP wave morphology was observed with a prolonged desaturation at the onset of REM sleep periods (Fig. 1).

In eight out of 12 patients with IIH and eight out of 13 patients with pediatric-onset hydrocephalus, REM sleep onset was associated with marked ICP elevations, standing out from the ICP measurement. REM sleep ICP elevations followed the same pattern in all these patients, with the highest ICP values at REM sleep onset followed by a declining trend and ending with a decrease when the REM sleep ended (Supplementary Fig. 3). This pattern was not observed in patients with iNPH or adult-onset obstructive hydrocephalus.

One patient with IIH and four out of 13 patients with pediatric-onset hydrocephalus had transient ICP elevations not associated with apneas or irregular breathing with altered thoracic and abdominal movement, predominantly during REM sleep and without any change in O_2 saturation, which was constant at 98–99% (Fig. 4).

CO_2

Two patients with IIH and two with pediatric-onset hydrocephalus measured with end-tidal CO_2 had non-oscillating CO_2 levels within normal limits (35–45 mmHg) during their transient ICP elevations (Supplementary Fig. 4).

ICP

The mean ICP was highest in the patients with IIH (15.1 (6.6)), with only one patient with a mean ICP below 10 mmHg (7.3 mmHg). The mean ICP was 10.4 (6.7) for the pediatric-onset, 7.2 (2.3) for the adult-onset, and 6.7 (1.9) for the patients with iNPH (ANOVA, $P = 0.036$). Posthoc confirmatory t-test showed the only significant difference between patients with iNPH and IIH ($P = 0.0014$) and adult-onset and IIH ($P = 0.0035$). Linear regression showed no association between the total number of ICP elevations and the mean ICP for any patient groups (Supplementary Fig. 4, $R^2 = -0.019$, $P = 0.54$). However, as expected, there was a significant association between the mean amplitude of the transient ICP elevations and the mean ICP (Supplementary Fig. 5, $R^2 = 0.32$, $P = 0.00031$ and Supplementary Table 1).

Continuous positive airway pressure

Three patients were monitored during an additional night with CPAP treatment (two patients with iNPH, one with pediatric-onset hydrocephalus, and a ventriculoperitoneal (VP)-shunt). All three patients used the CPAP treatment most of the night, and all were above the compliance threshold of > 4 hours per night. Furthermore, they all had a low level of leakage, indicating a good mask fit, and the mean pressure applied by the CPAP was within normal limits (Supplementary Table 2).

The mean reduction in all three patients of transient ICP elevations with CPAP treatment was 37% (Table 3). There was an apparent reduction in transient ICP elevations with and without apneas for one of the patients with iNPH and the pediatric-onset patient. However, the second patient with iNPH had

predominantly central apneas unaffected by CPAP. Accordingly, there was no reduction in transient ICP elevations associated with apneas but only in transient ICP elevations without apneas. CPAP treatment elevated the mean ICP during sleep in the two patients with iNPH and reduced the mean ICP in the patient with pediatric-onset hydrocephalus and a VP-shunt (Supplementary Table 2).

Table 3
Quantification of transient ICP elevations in three patients measured with and without continuous positive airway pressure (CPAP).

	First night			Second night with CPAP			
	Total	Apnea	without apnea	Total	Apnea	without apnea	Change
iNPH 1	439	193	246	210	38	172	-52.2%
iNPH 2	379	96	283	223	105	118	-41.2%
Pediatric	241	106	135	200	1	199	-17.0%
Mean	353	132	221	211	48	163	-37.0%

The change indicates the reduction in the total number of transients ICP elevation with CPAP treatment. iNPH = Idiopathic normal pressure hydrocephalus; Pediatric = pediatric-onset hydrocephalus.

Discussion

Our main finding is that transient ICP elevations are highly associated with sleep apnea in all patients. High amplitude ramp-type transient ICP elevations were related to sleep apnea during REM sleep and sinusoidal-type with NREM sleep. All patients have transient ICP elevations without sleep apnea, especially those with IIH and pediatric-onset hydrocephalus, with similar ICP changes during REM sleep periods. Furthermore, CPAP treatment reduced the number of transient ICP elevations and changed the mean ICP during sleep.

Transient ICP elevations and sleep apnea

Intracranial pressure is influenced by various factors, including the volume of intracranial components (e.g., brain tissue, blood, CSF), the compliance of the intracranial cavity, and the resistance to cerebrospinal fluid outflow. Sleep apnea has been linked to various physiological changes affecting ICP, including heart rate, blood pressure, and respiratory function. Here we found that sleep apnea induced transient ICP elevations in all patients, like in patients without intracranial pressure disturbances[4], suggesting this is a general physiological consequence of sleep apnea. The relationship between sleep apnea and patients with ICP changes has been known for many years.[1, 5–7] Patients with iNPH frequently have severe sleep apnea.[11–13] Accordingly, the patients with iNPH have the highest number of sleep apnea-associated transient ICP elevations of the four groups of patients (Table 1).

CO_2 and transient ICP elevations

Traditionally, CO_2 has been considered essential in generating transient ICP elevations, but several studies have shown mixed results.[1,4,17–19] Recently, we have shown that transient ICP elevations (B-waves) can be generated by sleep apnea and abnormal respiratory movements in the chest and not by elevated levels of $PaCO_2$ when ICP is below 20 mmHg.[4] Cerebral blood flow (CBF) regulation, through vasodilation or constriction of the cerebral blood vessels, is critical for the cerebrovasculature to respond to changes in O_2 and CO_2, resulting in changes in cerebral blood volume (CBV) and ICP.[20–22]

Furthermore, ventilation and $PaCO_2$ are closely linked. Thus, CO_2 is critical for CBF regulation and stable breathing, and compromised regulation of CBF can lead to irregular breathing. Accordingly, CO_2 is most likely a modulator of transient ICP elevations when ICP is within normal levels and may primarily affect transient ICP elevations by influencing the rhythm of breathing and secondary in changing the arterial CBV. Accordingly, our results show sleep apnea-associated transient ICP elevations without changes in CO_2 or O_2 (Fig. 3 & Supplementary Fig. 4). However, increased CO_2 is probably an important factor in the transient ICP elevations with plateau morphology seen in the three patients with REM sleep prolonged desaturation.

Physiology transient ICP elevations

The total CBV consists of 70% capillary and venous blood and only 30% arterial blood,[23] and changes in CBV during hypercapnia and hypocapnia only causes changes in arterial blood volume without changes in venous and capillary blood volume.[24] Thus, rapid changes in the outflow of venous blood, not affected by CO_2, have significant potential to alter ICP.

Respiratory inhalation drives deoxygenated venous blood outflow from the brain and induces a counterbalancing of CSF inflow, following the Monro–Kellie doctrine of relative compartment changes.[25,26] A temporary cessation of breathing, as during an apnea, will generate negative intrathoracic pleural pressure increasing venous return and initially decreasing ICP. However, as the apnea precedes, an excessively venous return to the heart will raise the central venous pressure (CVP)[5] and ultimately decrease cerebral venous blood's outflow, increasing CVP and ICP. When the apnea stops and breathing is restored, the intrapleural pressure will change to positive instantly, thus further increasing CVP and ICP. Our results are consistent with this physiological association between sleep apnea and transient ICP elevations, as there is a close temporal delay between the onset of the apnea and the subsequent increase in ICP. On average, in a total apnea count of 3270 in all patients, the apnea starts 3.6 seconds before the lowest ICP level and proceeds throughout the ICP elevation ending close to the peak of the ICP increase. The ICP peak coincides with a ventilatory overshoot when respiration resumes. This is supported by a highly significant phase correlation of transient ICP elevations with the peak of respiratory movements, CVP, and arterial blood pressure, with or without changes in CO_2.[5,19,27]

The magnitude of ICP and the manifestation of transient ICP elevations might concurrently reflect the level of compliance of the intracranial cavity. In situations where the ICP is elevated or the CSF compartment is less able to compensate for acute changes, e.g., changes in blood flow or irregular breathing (especially during REM sleep or sleep apnea), the transfer of these changes to the intracranial compartment as transient ICP elevations may be accentuated. Thus, resulting in increased and more pronounced transient ICP elevations. Furthermore, the timing of the apnea in the respiratory cycle, the level of negative intrathoracic pleural pressure, or the apnea duration could explain the heterogeneity in the amplitude of sleep apnea generated transient ICP elevations we observed since short apneas and irregular breathing only caused transient ICP elevation with small amplitudes.

Transient ICP elevations without sleep-disordered breathing

ICP elevations in patients with IIH and pediatric-onset hydrocephalus during the REM sleep phase were also observed without changes in respiration (Fig. 4) and oxygen saturation or CO_2 (Supplementary Fig. 4). This suggests that other mechanisms generate transient ICP elevations and that the mechanism may differ depending on the underlying clinical condition. Especially patients with IIH and pediatric-onset hydrocephalus display similar ICP morphology compared to patients with iNPH and adult-onset hydrocephalus.

Surges in cardiac sympathetic and parasympathetic activity are an essential REM sleep feature, increasing cardiovascular variability. In REM sleep, a rapid and rhythmic increase in CBF occurs,[28–30] and there is a causal influence of slow waves in CBF velocity on slow waves in ICP with a frequency between 0.095 and 0.155 Hz magnified by increasing ICP.[31] Increased CBV is the critical factor in increasing ICP, whether due to decreased venous outflow, increased arterial inflow, or a combination of the two. CSF only has limited buffering capacity for acute and sudden changes in ICP. Thus changes in CSF volume are less likely to be involved in the sudden ICP increase we observed with REM onset due to the speed of changes, at least in patients with normal CSF circulation. However, the slowly declining ICP level through the REM sleep phase could be caused by a slowly adapting CSF circulation, where CSF is removed from the ventricles into the spinal canal. Accordingly, in patients with pediatric-onset hydrocephalus and IIH, the rapid increase in the ICP during the REM phase of sleep suggests that changes in CBF and CBV mainly cause the changes in ICP. We speculate if different underlying mechanisms cause transient ICP elevations during REM sleep, but most often is caused by sleep apnea or changes in respiration. However, in some patients, especially during high ICP or reduced venous buffer capacity due to venous hypertension, transient ICP elevations may be generated by oscillating changes in the cardiovascular system dictated by the autonomic nervous system (Fig. 5). Future studies should try to pinpoint the mechanism generating these slow oscillations.

Clinical implications

Idiopathic normal pressure hydrocephalus and sleep apnea

Patients with iNPH often suffer from severe sleep apnea,[11–13] which is also linked to cerebral microbleeds and brain ischemias.[35,36] It is possible that the transient increases in intracranial pressure caused by sleep apnea, as shown here and previously,[4,5,32] could damage the brain's periventricular tissue and capillaries, leading to decreased compliance and the progression of chronic hydrocephalus, particularly in patients with iNPH. Furthermore, pressure peaks resulting from sleep apnea and the retrograde flow of venous blood through incompetent jugular valves [33,34] may enlarge the ventricles through transient venous hypertension hindering CSF absorption, particularly in the presence of brain atrophy. These factors may play a role in the pathogenesis of iNPH and warrant further investigation.

Idiopathic intracranial hypertension and pediatric-onset hydrocephalus

The exact pathophysiology of IIH is still unclear. However, several studies have shown that patients with IIH often have increased venous pressure, intracranial or systemic, and compromised venous outflow.[37–39] Some have suggested that elevated intracranial venous pressure may be a universal mechanism in patients of various etiologies.[37] This study does not address the metabolic and hormonal factors involved in the pathophysiology of IIH, which could also alter central venous pressure.

However, of particular interest is the relationship between increased intraabdominal pressure associated with central obesity and IIH. We note that gastric bypass is reported to achieve a much higher success in relieving symptoms than CSF VP-shunting.[39] Furthermore, increased intrathoracic pressure results in increased ICP in animal models,[40,41] in severely obese patients with IIH,[38] and head trauma patients.[42] Increased intrathoracic or abdominal pressure possibly increases superior vena cava pressure and secondarily cerebral venous pressure resulting in the decreased cerebral venous outflow.[41] Interestingly, one of the patients with pediatric-onset hydrocephalus had similar REM sleep-associated high amplitude transient ICP elevations without sleep apnea, and a subsequent invasive venous pressure measurement revealed a moderately elevated superior sagittal venous pressure (12 mmHg). Furthermore, high-grade venous stenoses and cerebral hyperemia are common in childhood hydrocephalus.[43] Thus, we speculate if cardiovascular changes and increased CBF during REM sleep are causing high amplitude ramp-type transient ICP elevations in patients with elevated venous pressure (and thereby lower compensatory reserve).

Venous system and intracranial pressure disturbances

The jugular veins are open when lying down, connecting the central venous system directly to the brain. Thus allowing changes affecting the CVP, e.g., during apnea or increased abdominal pressure, to be transmitted to the brain and affect ICP. The brain is protected during a seated or standing position by collapsing jugular veins, uncoupling the brain from the central venous system. Could abnormal positional changes in ICP or high ICP during REM sleep be diagnostic markers for increased CVP in patients with IIH? The role of the venous system in patients with ICP disturbances could be underestimated, and studies of the venous system a highly needed in future studies of these patients.

Continuous positive airway pressure

Continuous positive airway pressure reduced the number of transient ICP elevations with waveform abnormalities in all three patients. The increase in mean ICP in the two patients with iNPH could result from increased resistance to venous return caused by CPAP but could also be a general consequence of CPAP treatment. A case report has described a patient with iNPH who experienced worsening symptoms after starting CPAP treatment but saw improvement after a VP-shunt was inserted. Patients with iNPH have a higher frequency of retrograde jugular venous flow, possibly because of incompetent jugular valves, which may also contribute to the observed increase in ICP during CPAP treatment.[33] To fully understand the impact of CPAP on ICP and venous pressure in patients, future studies should measure ICP and pressure in the venous system during CPAP treatment. Interestingly CPAP treatment in the patient with pediatric-onset hydrocephalus and a VP-shunt reduced the mean ICP (Supplementary Table 2), but the generalizability of this finding to other types of hydrocephalus and iNPH requires further study. If CPAP treatment increases ICP in patients with iNPH, it could potentially be harmful, making it essential to understand the effects of CPAP on ICP in this patient population. This study showed an increase in mean ICP in two patients with iNPH after CPAP treatment, raising concerns about the treatment's safety.

Transient ICP elevations

Transient ICP increases do not occur with regular intervals or duration. They have very different appearances and durations between patients and within patients, which speaks against a universal underlying and generating mechanism. This favors a role for sleep apnea in generating transient ICP elevations in a significant proportion of the observed ICP elevations, as apneas and hypopneas vary in duration, degree, and timing. However, several mechanisms are probably responsible for generating transient ICP elevations. When ICP is pathologically raised, physiological changes during REM sleep can play an essential role in generating transient ICP elevations (Fig. 5).

Furthermore, changes in the venous system, whether intermittent or chronic, could have a previously underestimated role in patients with ICP disturbances, which should be investigated to clarify the role of possibly elevated venous pressure in different clinical conditions. It could also be relevant to question whether transient ICP elevations generated by sleep apnea could be involved in the well-known association of sleep apnea with stroke and cardiovascular disease.[44] Additionally, it will be helpful to establish an animal model of sleep apnea with simultaneous ICP measurement to elucidate the mechanism of sleep apnea in generating transient ICP elevations.

Limitations

The primary limitation of this study is the relatively small sample size (n = 34). However, even though the sample size was small, the results are consistent within each patient group regarding the association of sleep apnea with transient ICP elevations. Although this study has a relatively small sample size, it is the most extensive ever conducted.

We used an objective method to detect the number of transient ICP elevations. Thus, we most likely overestimated the number of transient ICP elevations in some patients since regular small movements and positional changes are reflected in the ICP signal and count as a transient ICP elevation. However, the objective method used in this study reduces bias and makes the data more reproducible. Others have used objective methods to calculate transient ICP elevations and found an association between transient ICP elevations and the mean ICP.[10] In contrast, we found no association between transient ICP elevations and the mean ICP but only, as expected, an association between the mean amplitude of the transient ICP elevations and the mean ICP. The algorithm and the threshold used could explain differences since they used a 0.5 to 5.0 mmHg threshold. This highlights the importance of selecting a proper threshold for detecting clinically relevant transient ICP elevations, which probably should be > 5.0 mmHg.

A telemetric ICP probe was used in one patient with pediatric-onset hydrocephalus and six with IIH (Supplementary Table 1). Zero-offset drift is a potential source of error in the telemetric probe, but this becomes relevant only after very long-term implantation, well beyond the three-month utility period set by the manufacturer.[45] Recognizable morphological changes are still detectable in the signal, like transient ICP elevations.[4] There were no technical differences in the ICP signal in patients with telemetric probes compared to the remaining patients. Fourteen patients were measured with a parenchymal ICP probe, with the same high sampling rate and no zero-offset drift as the golden standard ventricular probe used in the remaining patients (Supplementary Table 1). Thus, minor deviations in absolute ICP may occur depending on the pressure gauge's tip location.

Some patients were treated with a VP-shunt or an ETV, possibly affecting the measured mean ICP (Supplementary Table 1). However, we and others have previously shown that VP-shunt treatment does not change the prevalence of sleep apnea in patients with iNPH,[11–13] suggesting treatment changes the absolute ICP level without affecting sleep apnea and transient ICP elevations. However, we can not exclude that treatment with a VP-shunt or an ETV can affect the macro ICP pattern seen, e.g., during REM sleep.

Conclusion

The findings suggest that sleep apnea causes a significant proportion of transient intracranial pressure elevations, and sleep apnea should be considered in intracranial pressure evaluation. Continuous positive airway pressure (CPAP) treatment can reduce their occurrence. However, CPAP may concurrently elevate the mean intracranial pressure. More research is needed on the impact of slow oscillating mechanisms on transient intracranial pressure elevations during high intracranial pressure and REM sleep.

Abbreviations

Cerebral blood flow (CBF); Cerebral blood volume (CBV); continuous positive airway pressure (CPAP); Endoscopic third ventriculostomy (ETV); idiopathic normal pressure hydrocephalus (iNPH); intracranial

hypertension (IIH); Intracranial pressure (ICP); polysomnography (PSG); Ventriculoperitoneal shunt (VP-shunt)

Declarations

Ethics

The study protocol was approved by the Committee on Health Research Ethics for the Capital Region of Denmark (H-1-2014-123) and was performed according to the Helsinki declaration standards. All patients gave their written informed consent.

Availability of data and materials

Anonymized data are available upon reasonable request from the corresponding author and after clearance by the competent ethics committee.

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Competing Interests

The authors report no competing interests

Authors' contributions

C.S.R., P.J., and M.J. formulated and planned the study. I.M., M.A., J.E.W. developed the algorithm for automatic macro-pattern identification in the ICP signal. C.S.R. collected, analyzed, and interpreted the patient data. C.S.R. and I.M. prepared the figures. C.S.R. wrote the main manuscript. All authors read and approved the final manuscript.

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References

1. Lundberg, N. Continuous recording and control of ventricular fluid pressure in neurosurgical practice. *Acta Psychiatr Scand Suppl* **36**, 1–193 (1960).

2. Mautner-Huppert, D. *et al.* B-waves in healthy persons. *Neurol. Res.* **11**, 194–196 (1989).
3. Droste, D. W. & Krauss, J. K. Oscillations of cerebrospinal fluid pressure in nonhydrocephalic persons. *Neurol. Res.* **19**, 135–8 (1997).
4. Riedel, C. S. *et al.* B-waves are present in patients without intracranial pressure disturbances. *J. Sleep Res.* **30**, e13214 (2021).
5. Jennum, P. & Børgesen, S. E. Intracranial pressure and obstructive sleep apnea. *Chest* **95**, 279–283 (1989).
6. Yokota, A., Matsuoka, S., Ishikawa, T., Kohshi, K. & Kajiwara, H. Overnight recordings of intracranial pressure and electroencephalography in neurosurgical patients. Part II: Changes in intracranial pressure during sleep. *J. UOEH* **11**, 383–91 (1989).
7. Cooper, R. & Hulme, A. Intracranial pressure and related phenomena during sleep. *J. Neurol. Neurosurg. Psychiatry* **29**, 564–570 (1966).
8. Symon, L., Dorsch, N. W. & Stephens, R. J. Pressure waves in so-called low-pressure hydrocephalus. *Lancet (London, England)* **2**, 1291–2 (1972).
9. Krauss, J. K. *et al.* The relation of intracranial pressure B-waves to different sleep stages in patients with suspected normal pressure hydrocephalus. *Acta Neurochir. (Wien).* **136**, 195–203 (1995).
10. Stephensen, H. *et al.* Objective B wave analysis in 55 patients with non-communicating and communicating hydrocephalus. *J. Neurol. Neurosurg. Psychiatry* **76**, 965–970 (2005).
11. Riedel, C. S., Milan, J. B., Juhler, M. & Jennum, P. Sleep-disordered breathing is frequently associated with idiopathic normal pressure hydrocephalus but not other types of hydrocephalus. *Sleep* **45**, 1–8 (2022).
12. Kristensen, B., Malm, J. & Rabben, T. Effects of transient and persistent cerebrospinal fluid drainage on sleep disordered breathing in patients with idiopathic adult hydrocephalus syndrome. *J. Neurol. Neurosurg. Psychiatry* **65**, 497–501 (1998).
13. Román, G. C., Verma, A. K., Zhang, Y. J. & Fung, S. H. Idiopathic normal-pressure hydrocephalus and obstructive sleep apnea are frequently associated: A prospective cohort study. *J. Neurol. Sci.* **395**, 164–168 (2018).
14. Milan, J. B. *et al.* The ASPECT Hydrocephalus System: a non-hierarchical descriptive system for clinical use. *Acta Neurochir. (Wien).* (2022) doi:10.1007/s00701-022-05412-6.
15. Friedman, D. I. & Jacobson, D. M. Diagnostic criteria for idiopathic intracranial hypertension. *Neurology* **59**, 1492–1495 (2002).
16. Martinez-Tejada, I., Riedel, C. S., Juhler, M., Andresen, M. & Wilhjelm, J. E. k-Shape clustering for extracting macro-patterns in intracranial pressure signals. *Fluids Barriers CNS* **19**, 12 (2022).
17. Børgesen, S. E. & Espersen, J. . The correlation between A- and B-waves and arterial CO2 tension. *Intracranial Press. VI* 298–304 (1986) doi:10.1007/978-3-642-70971-5_56.
18. Venes, J. L. B waves. A reflection of cardiorespiratory or cerebral nervous systems rhythm? *Childs. Brain* **5**, 352–360 (1979).

19. Tindall, G. T., McGraw, C. P., Vanderveer, R. W. & Iwata, K. Cardiorespiratory Changes Associated with Plateau Waves in Patients with Head Injury. in *Intracranial Pressure* 227–231 (Springer Berlin Heidelberg, 1972). doi:10.1007/978-3-642-65486-2_39.
20. Ainslie, P. N. & Duffin, J. Integration of cerebrovascular CO2 reactivity and chemoreflex control of breathing: Mechanisms of regulation, measurement, and interpretation. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.* **296**, (2009).
21. Brian, J. E. Carbon Dioxide and the Cerebral Circulation. *Anesthesiology* **88**, 1365–1386 (1998).
22. Wilson, M. H. Monro-Kellie 2.0: The dynamic vascular and venous pathophysiological components of intracranial pressure. *J. Cereb. Blood Flow Metab.* **36**, 1338–1350 (2016).
23. Ito, H. *et al.* Arterial fraction of cerebral blood volume in humans measured by positron emission tomography. *Ann. Nucl. Med.* **15**, 111–6 (2001).
24. Ito, H., Ibaraki, M., Kanno, I., Fukuda, H. & Miura, S. Changes in the arterial fraction of human cerebral blood volume during hypercapnia and hypocapnia measured by positron emission tomography. *J. Cereb. Blood Flow Metab.* **25**, 852–7 (2005).
25. Dreha-Kulaczewski, S. *et al.* Identification of the Upward Movement of Human CSF In Vivo and its Relation to the Brain Venous System. *J. Neurosci.* **37**, 2395–2402 (2017).
26. Vinje, V. *et al.* Respiratory influence on cerebrospinal fluid flow – a computational study based on long-term intracranial pressure measurements. *Sci. Rep.* **9**, 1–13 (2019).
27. Einhäupl, K. M. *et al.* Oscillations of ICP related to cardiovascular parameters. in *Intracranial Pressure VI* 290–297 (Springer Berlin Heidelberg, 1986). doi:10.1007/978-3-642-70971-5_55.
28. Ingvar, D. H. Cerebral blood flow and metabolism related to EEG and cerebral functions. *Acta Anaesthesiol. Scand. Suppl.* **45**, 110–4 (1971).
29. Reivich, M., Isaacs, G., Evarts, E. & Kety, S. Regional cerebral blood flow during REM and slow wave sleep. *Trans. Am. Neurol. Assoc.* **92**, 70–4 (1967).
30. Reivich, M., Isaacs, G., Evarts, E. & Kety, S. The effect of slow wave sleep and REM sleep on regional cerebral blood flow in cats. *J. Neurochem.* **15**, 301–6 (1968).
31. Martinez-Tejada, I., Czosnyka, M., Czosnyka, Z., Juhler, M. & Smielewski, P. Causal relationship between slow waves of arterial, intracranial pressures and blood velocity in brain. *Comput. Biol. Med.* **139**, 104970 (2021).
32. Kuchiwaki, H. *et al.* Pressure wave with apnoea evaluated by sleep level in patient with ventricular dilation. *Neurol. Res.* **10**, (1988).
33. Kuriyama, N. *et al.* Retrograde jugular flow associated with idiopathic normal pressure hydrocephalus. *Ann. Neurol.* **64**, 217–221 (2008).
34. Williams, H. The venous hypothesis of hydrocephalus. *Med. Hypotheses* **70**, 743–747 (2008).
35. Johansson, E. *et al.* Cerebral microbleeds in idiopathic normal pressure hydrocephalus. *Fluids Barriers CNS* **13**, 1–4 (2016).

36. Fisher, M., French, S., Ji, P. & Kim, R. C. Cerebral microbleeds in the elderly: A pathological analysis. *Stroke* **41**, 2782–2785 (2010).
37. Karahalios, D. G., Rekate, H. L., Khayata, M. H. & Apostolides, P. J. Elevated intracranial venous pressure as a universal mechanism in pseudotumor cerebri of varying etiologies. *Neurology* **46**, 198–202 (1996).
38. Sugerman, H. J., DeMaria, E. J., Felton, W. L., Nakatsuka, M. & Sismanis, A. Increased intra-abdominal pressure and cardiac filling pressures in obesity-associated pseudotumor cerebri. *Neurology* **49**, 507–11 (1997).
39. Sugerman, H. J. *et al.* Gastric surgery for pseudotumor cerebri associated with severe obesity. *Ann. Surg.* **229**, 634–40; discussion 640-2 (1999).
40. Bloomfield, G. L., Ridings, P. C., Blocher, C. R., Marmarou, A. & Sugerman, H. J. Effects of increased intra-abdominal pressure upon intracranial and cerebral perfusion pressure before and after volume expansion. *J. Trauma* **40**, 936–41; discussion 941-3 (1996).
41. Luce, J. M., Huseby, J. S., Kirk, W. & Butler, J. Mechanism by which positive end-expiratory pressure increases cerebrospinal fluid pressure in dogs. *J. Appl. Physiol. Respir. Environ. Exerc. Physiol.* **52**, 231–235 (1982).
42. Citerio, G., Vascotto, E., Villa, F., Celotti, S. & Pesenti, A. Induced abdominal compartment syndrome increases intracranial pressure in neurotrauma patients: a prospective study. *Crit. Care Med.* **29**, 1466–71 (2001).
43. Bateman, G. A., Yap, S. L., Subramanian, G. M. & Bateman, A. R. The incidence of significant venous sinus stenosis and cerebral hyperemia in childhood hydrocephalus: Prognostic value with regards to differentiating active from compensated disease. *Fluids Barriers CNS* **17**, 1–12 (2020).
44. Sánchez-de-la-Torre, M., Campos-Rodriguez, F. & Barbé, F. Obstructive sleep apnoea and cardiovascular disease. *Lancet. Respir. Med.* **1**, 61–72 (2013).
45. Norager, N. H., Lilja-Cyron, A., Bjarkam, C. R., Duus, S. & Juhler, M. Telemetry in intracranial pressure monitoring: sensor survival and drift. *Acta Neurochir. (Wien).* **160**, 1–8 (2018).

Figures

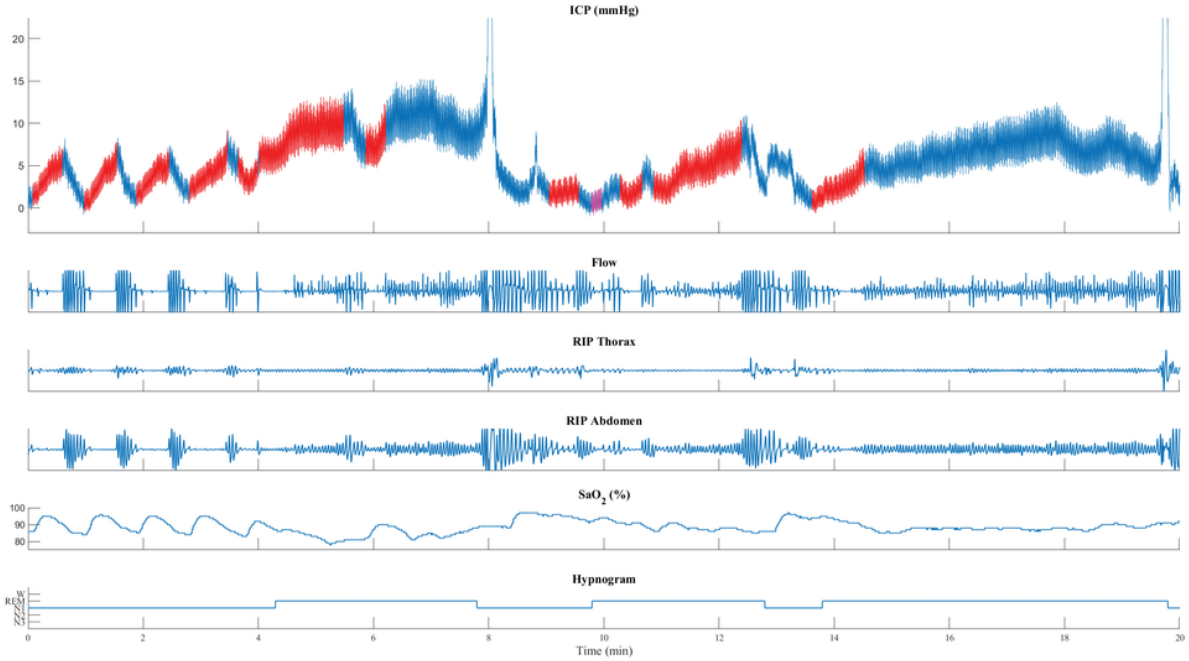

Figure 1

Patient with iNPH with the transition from NREM to REM sleep. The peak in the transient ICP elevations is when respiration resumes, after an apnea, with a ventilatory overshoot marked by increased flow and respiratory movements in the thorax and abdominal RIP. In NREM, in the beginning, repeated transient ICP elevations with low amplitude are seen together with desaturations. During the transition to REM sleep, the transient ICP elevation amplitude increases with more significant desaturations and more prolonged apneas. ICP is shown in blue, with red and purple indicating the duration of apneas and respiratory disturbances. Flow: nasal cannula registering flow changes (arbitrary units). RIP, respiratory inductance plethysmography; thorax and abdomen movements (arbitrary units). SaO_2 (%), oxyhemoglobin saturation measured on the finger. Heart rate, beats/min. Hypnogram with awake and sleep stages.

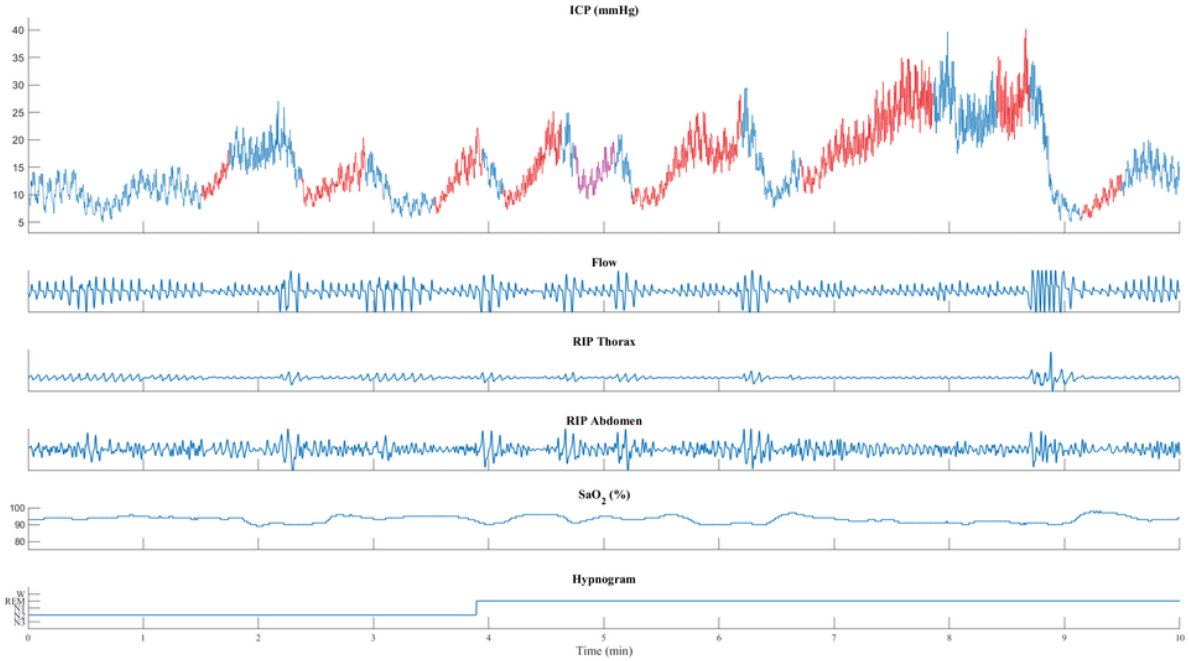

Figure 2

Patient with IIH transitioning from NREM to REM sleep. ICP elevations with sleep apnea start when transitioning from NREM to REM. More activity in the abdominal RIP than in the thoracic RIP. ICP is shown in blue, with red and purple indicating the duration of apneas and respiratory disturbances. Flow: nasal cannula registering flow changes (arbitrary units). RIP, respiratory inductance plethysmography; thorax and abdomen movements (arbitrary units). SaO_2 (%), oxyhemoglobin saturation measured on the finger. Heart rate, beats/min. Hypnogram with awake and sleep stages.

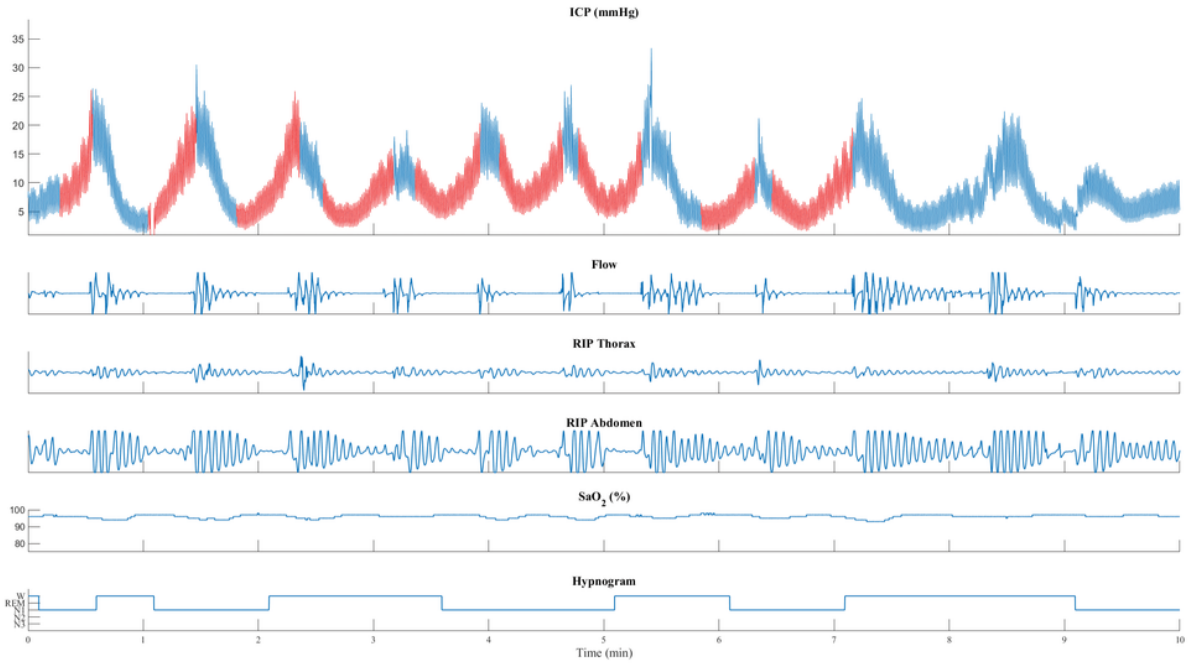

Figure 3

Patient with iNPH and SLEEP APNEA during NREM with frequent arousals and awakenings. The peak of the transient ICP elevation is seen when respiration resumes with a ventilatory overshoot, marked by increased flow and respiratory movements in the thorax and abdominal RIP. All transient ICP elevations in this example are seen with stable oxygen saturation. ICP is shown in blue, with red and purple indicating the duration of apneas and respiratory disturbances. Flow: nasal cannula registering flow changes (arbitrary units). RIP, respiratory inductance plethysmography; thorax and abdomen movements (arbitrary units). SaO_2 (%), oxyhemoglobin saturation measured on the finger. Heart rate, beats/min. Hypnogram with awake and sleep stages.

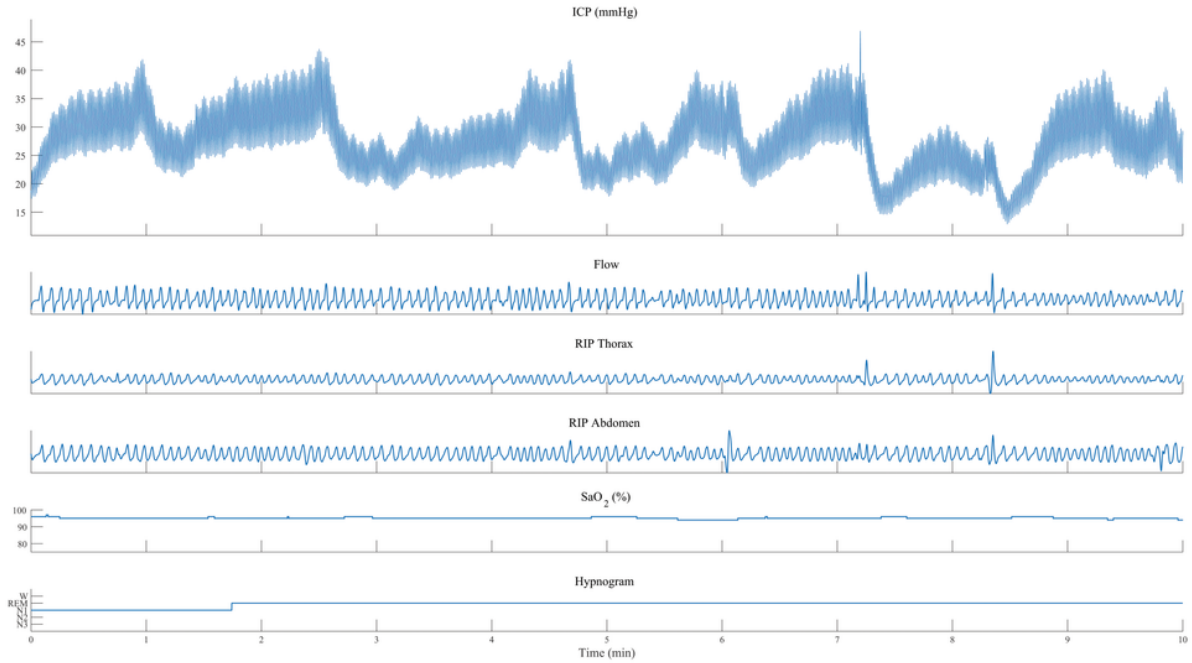

Figure 4

Patient with IIH and repeating ramp-type transient ICP elevations with the onset of REM without apneas, respiratory disturbances, or desaturation. ICP is shown in blue, with red and purple indicating the duration of apneas and respiratory disturbances. Flow, nasal cannula registering flow changes (arbitrary units). RIP, respiratory inductance plethysmography; thorax and abdomen movements (arbitrary units). SaO_2 (%), oxyhemoglobin saturation measured on the finger. Heart rate, beats/min. Hypnogram with awake and sleep stages.

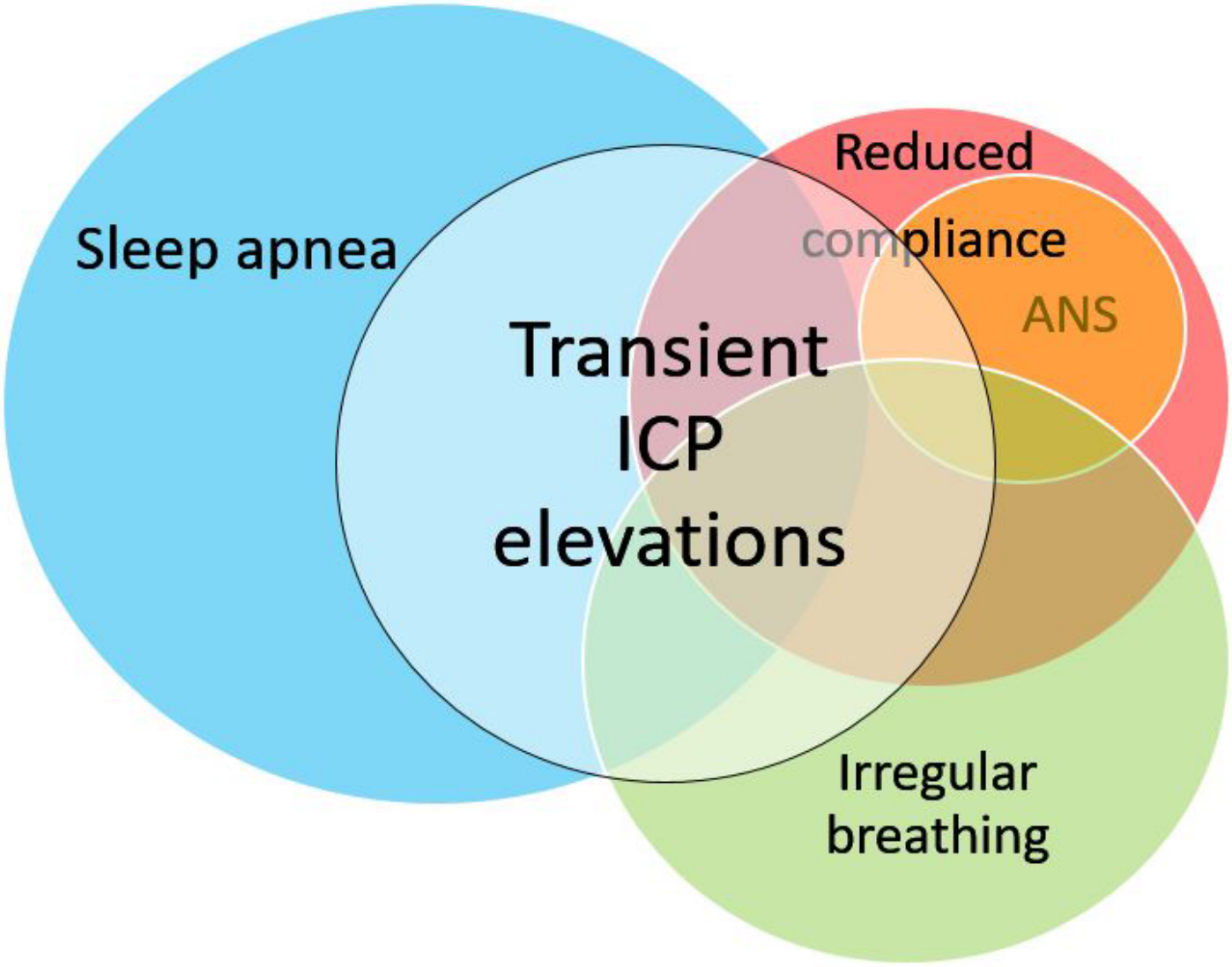

Figure 5

Different mechanisms are generating transient ICP elevations. Sleep apnea generates a significant proportion of transient ICP elevations, followed by irregular breathing with altered thoracic and abdominal movement. However, during reduced compliance, often seen by pathologically high ICP >20 mmHg, transient ICP elevations are generated by slow oscillating changes in the autonomic system (ANS) reflected in the cardiovascular system.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementarymaterialSleepapneaICP.pdf