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DISSERTATION

Telemetrische Messung des intrakraniellen Drucks in der pädiatrischen Neurochirurgie

Telemetric intracranial pressure monitoring in Pediatric Neurosurgery

zur Erlangung des akademischen Grades
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Vorwort

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- ***Pennacchietti V, Schaumann A, Thomale U-W, Maneuver protocol for outpatient telemetric intracranial pressure monitoring in hydrocephalus patients, Child´s Nervous System,*** 2022 Sep 13. Doi: 10.1007/s00381-022-05659-5. Online ahead of print.

Ein Ethikvotum zur Durchführung der retrospektiven Ausarbeitung der Daten liegt vor (Antragsnummer EA2/132/17).

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Abbreviations

AMP – amplitude

BMI – body mass index

CSF – cerebrospinal fluid

ETV – endoscopic third-ventriculostomy

EVD – external ventricular drainage

ICP – intracranial pressure

IIH – idiopathic intracranial hypertension

MMC – myelomeningocele

ONSD – optic nerve sheath diameter

PHH – posthemorrhagic hydrocephalus

P-TEL – Neurovent-P-Tel

RAP – correlation coefficient (R) between amplitude and mean pressure

SR – sensor reservoir

tICPM – telemetric intracranial pressure measurement

VPS – ventriculo-peritoneal shunt

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Abstract (English)

Introduction: Telemetric intracranial pressure measurement (tICPM) enables the measurement of intracranial pressure (ICP) in different conditions, such as body posture and activity. Neurovent-P-Tel (P-Tel, Raumedic, Helmbrechts, Germany) and sensor reservoir (SR, Miethke, Potsdam, Germany) are among the most used systems, and their employment influences the management of patients with cerebrospinal fluid (CSF) circulation disturbances. The SR has added several advantages in the follow-up of patients. The aim of this work is to assess the *in vitro* and *in vivo* performance of tICPM devices and to describe new achievements in maneuver measurements in pediatric neurosurgery.

Materials and methods: Six SRs were tested and compared to standard invasive ICP measurement methods in an experimental setting. *In vivo* data from 21 patients in a mixed P-Tel and SR population (8 with a P-Tel and 13 with an SR) was retrospectively evaluated. Additionally, a specific measurement protocol, combining different body positions, ventilation patterns and jugular compression, was developed and applied in 17 SR-implanted patients.

Results: *In vitro* testing showed a significant similarity between SRs and invasive pressure measuring systems. The *in vivo* dataset contained measurements from a total of 21 patients (median age 16.5 years, range 10–39.5 years). A maneuver protocol was applied in one population with a ventriculoperitoneal shunt system, and in another with a stand-alone SR for diagnostic purposes only. There were 13 shunted patients (median age 15.8 years, range 4.0–35.2 years), and 6 were non-shunted (median age 11.9 years, range 3.6–17.7 years). A total of 480 measurements were performed. tICPM-guided shunt adjustments led to clinical improvements in 7 P-Tel (75%) and 6 SR (76.9%) patients, with shunt survival rates of 44.4% at 77.9 months and 83.3% at 42 months, respectively. Three secondary shunt implantations were indicated in the stand-alone population. Comparative analysis in intracranial pressure and amplitude among stand-alone and shunted SR patients showed differences in the changes of these two parameters: in the shunted group, intracranial pressure showed more significant variations, while the non-shunted population showed a more drastic change in amplitude.

Conclusions: SRs were confirmed to have a good reliability *in vitro*. tICPM is well-established and helpful in clinical practice – especially in complex shunt-dependent patients with chronic symptomatology. The introduction of an analysis tool improved the throughput of the data analysis, but data processing remains cumbersome. Future improvements will focus on the

elaboration of relevant parameters and performing tests.

Abstrakt (Deutsch)

Fragestellung: Die telemetrische intrakranielle Druckmessung (tICPM) ermöglicht die Messung des intrakraniellen Drucks (ICP) unter verschiedenen Bedingungen (Körperhaltung, Aktivität). Neurovent-P-Tel (P-Tel, Raumedic, Helmbrechts, Deutschland) und Sensor-Reservoir (SR, Miethke, Potsdam, Deutschland) gehören zu den am häufigsten verwendeten Systemen, und ihr Einsatz hat Einfluss auf das Management von Patienten mit Liquorzirkulationsstörungen. Das SR hat mehrere Vorteile in der Patientenbehandlung gebracht. Ziel dieser Arbeit ist es, die *In-vitro-* und *In-vivo*-Leistung von tICPM-Geräten zu bewerten und neue Perspektiven bei Manövermessungen in der pädiatrischen Neurochirurgie zu beschreiben.

Materialien und Methoden: Sechs SR wurden experimentell getestet und mit invasiven Standardmethoden zur ICP-Messung verglichen. In-vivo-Daten von 21 Patienten aus einer gemischten P-Tel- und SR-Population (8 P-Tel und 13 SR) wurden retrospektiv ausgewertet. Darüber hinaus wurde ein spezifisches Messprotokoll entwickelt, das verschiedene Körperpositionen, Beatmungsmuster und Jugularkompression kombiniert und bei 17 SR-implantierten Patienten angewendet wurde.

Ergebnisse: *In-vitro*-Tests zeigten eine signifikante Ähnlichkeit zwischen SRs und invasiven Druckmesssystemen. Der *In-vivo*-Datensatz enthielt Messungen von 21 Patienten (mittleres Alter 16.5 Jahre, Range 10-39.5 Jahre). Ein Manöverprotokoll wurde bei einer Population mit einem Shuntsystem und bei einer mit „stand-alone“ SR zu rein diagnostischen Zwecken angewendet. An 13 Shunt-Patienten (medianes Alter 15.8 Jahre, Range 4.0-35.2 Jahre) und 6 Nicht-Shunt-Patienten (medianes Alter 11.9 Jahre, Range 3.6-17.7 Jahre) wurden 480 Messungen durchgeführt. Die tICPM-gesteuerten Shuntanpassungen führten bei 7 P-Tel- (75 %) und 6 SR-Patienten (76.9 %) zu klinischen Verbesserungen, mit Shunt-Überlebensraten von 44.4 % nach 77.9 Monaten bzw. 83.3 % nach 42 Monaten. Drei sekundäre Shunt-Implantationen waren in der Stand-alone-Population indiziert. Eine Vergleichsanalyse des intrakraniellen Drucks und der Amplitude zwischen „stand-alone“- und Shunt-SR-Patienten zeigte Unterschiede in den Veränderungen dieser beiden Parameter: In der Shunt-Gruppe wies der intrakranielle Druck deutlichere Veränderungen auf, während die nicht geshuntete Population eine drastischere Veränderung der Amplitude zeigte.

Schlussfolgerungen: Es wurde bestätigt, dass die SRs in vitro eine gute Zuverlässigkeit aufweisen. tICPM ist in der klinischen Praxis gut etabliert und hilfreich - insbesondere bei komplexen

shuntabhängigen Patienten mit chronischer Symptomatik. Die Einführung eines Analysetools verbesserte den Durchsatz der Datenanalyse, aber die Datenverarbeitung ist umständlich. Künftige Verbesserungen werden sich auf die Ausarbeitung der relevanten Parameter und die Durchführung von Tests konzentrieren.

1 Introduction

Intracranial pressure (ICP) is the result of the volumetric balance between the three components of the intracranial space (Monro-Kellie doctrine): blood (about 15%), cerebrospinal fluid (CSF, <5%) and parenchymal compartments (about 80%). It is strictly regulated by compensatory mechanisms, which, for example, rely on the caliber regulation of the cerebral vascular system, the venous outflow, and CSF resorption (1). Those fast and continuous reactions mirror the compensatory capacities of the brain, which depend on the arterial, venous and liquoral districts. A decompensation of this volumetric equilibrium results in intracranial hypertension, whose causes are variable and often intertwined. In order to manage and treat CSF, blood, or parenchymal pathologies in clinical practice, ICP measurements play a pivotal role.

The first notions of increased ICP caused by brain edema were developed in ancient Egypt, and were later expanded by Hippocrates and Galen, who were the first to introduce an initial notion of CSF. Starting from the sixteenth century, other anatomists developed the concept of CSF production and circulation (Massa in 1538, Cotugno in 1764, Magendie in 1842, Retzius and Key in 1875, Cushing in 1926). In the eighteenth century, Monro and Kellie further elaborated this concept (2). It was only in the nineteenth century that the first data on liquoral pressure interpreted as an expression of intracranial pressure and measured via lumbar puncture were published by Quincke (1891). This practice was, however, lethal in most of the investigated subjects because of intracranial masses, which resulted in brain-herniation events after CSF subtraction. In 1951, Guillaume and Janny described an invasive measurement of the ICP by means of an electromagnetic transducer, while the first ICP curve analysis was carried out by Lundberg in 1960 for patients with intracranial masses and in 1965 for individuals with head traumas (3). The measurements were performed through a transducer integrated in an external ventricular drainage. Lundberg named the three waves which characterize the ICP curve “P1”, “P2” and “P3” (4). After these acquisitions, the practice of ICP monitoring increased and developed quickly (5), (6), (7), but the knowledge of the potential damage created by increased ICP became more obvious from the studies of Miller (8). The first applications of ICP monitoring were mostly in acute situations, such as severe traumatic brain injuries. In those cases, the ICP is the most important parameter to rule out the necessity of conservative or invasive therapies to reduce secondary damage intracranial hypertension. It has been demonstrated that not only the absolute ICP value, but also the cumulative duration of ICP peaks play a role in determining the outcome of the patient and, therefore, the prognosis in response to an increased ICP. Children appear to be particularly sensitive to an increased ICP: ICPs over 20 mmHg are tolerated for a maximum of 7 minutes, versus 37 minutes in the adult population (9). The normal range in adults is 7–15 mmHg (9.5–20.4

cmH_2O). Normal ICP values in children are described to be under 10 mmHg (13.6 cmH_2O) (10). Those normal values are the results of studies in comatose patients in a lying and static position, and therefore do not represent the dynamic and physiologic variations which characterize the ICP. The large variety of pathologies in which the knowledge of the ICP is fundamental have extended the field of research to ICP measurement methods which could also be applied in active subjects and in different body postures. The definition of normal values in children and in dynamic conditions is today still a challenge because of the lack of literature on pediatric head traumas or on pathological situations, such as hydrocephalus or craniosynostosis.

CSF circulation disturbances, in particular, include a very large spectrum of pathologies involving the liquoral component, which appear to be particularly complex in the pediatric age. The challenge lies principally in the fact that the brain grows relatively fast and the bony skull is still elastic. Thus, the intracranial volume is variable, making the Monro-Kellie doctrine relative. Another difference in comparison to adults is the fact that a venous blockage would lead to an increased cranial circumference and to an enlargement of the subarachnoid and/or ventricular spaces, and not to an IIH with normal ventricular width as would happen in an adult population (11).

Moreover, in patients treated with a shunt system, the diagnosis of shunt dysfunction might be particularly challenging. In selected cases, the lack of consistent symptomatology and the difficulty in interpreting neurological disturbances makes the necessity of measuring the ICP pivotal to further proceed with the diagnostic and therapeutic iter.

1.1 Indications for ICP measurement

ICP monitoring methods are helpful and needed nowadays for several reasons in neurosurgery. In general, the need for monitoring ICP is to control patients in a comatose state, caused by different conditions involving brain edema and/or expansive masses.

The classical use has been extensively described in the literature, especially in adult populations, and concerns *severe TBI*. The extreme inhomogeneity of pediatric patients and the current lack of consistency in the literature on the subject is mainly due to the limited knowledge on normal ICP ranges in childhood (10). ICP monitoring is a fundamental tool for the management and therapy of increased ICP in this particular application, starting from the very first moments after diagnosis. Radiological signs of increased ICP might also be an acute indication to proceed with an invasive ICP measurement and monitoring device placement. The use of ICP monitoring devices has been thoroughly analyzed and discussed in the past few years and has led to different guidelines, which unanimously propose pathological imaging findings, and/or a severe injury, and/or a severely impaired neurological status as criteria (2), (12).

ICP monitoring also has an application in patients with *intracranial hemorrhage* such as subarachnoid hemorrhages or intraparenchymal hematomas, if the clinical condition of the patient makes a neurological evaluation unfeasible and/or the hemorrhage is particularly large.

In severe *infections* of the central nervous system, an ICP monitoring may also be applied. This is true mainly in situations in which the patient is comatose, and in particular in cases of cerebral edema induced by venous drainage impairment, or in cases of brain compression due to purulent collections.

Patients with *hydrocephalus* carrying a shunt in a comatose state require ICP monitoring in order to proceed to further treatment.

Other cases of particular pediatric neurosurgical interest comprise clinical *unclear situations*, where the typical stigmata of increased ICP have no classical clinical or radiological expression:

- In patients *without a shunt system*. For instance, an ICP measurement may help in the further management of a diagnosed *chronical ventricular enlargement*, by means of transfontanellar ultrasound or through a cranial MRI (or, more rarely, CT scan), where high ICP is not necessarily present. This may happen, for instance, in the case of a pressure-compensated hydrocephalus. This has to be differentiated from a condition known as brain atrophy, in which ventricular enlargement is secondary to “loss of substance” (hydrocephalus ex vacuo). Another valuable application would be in the diagnosis and characterization of an *IIH*, where some of the classical signs and symptoms may be lacking. Furthermore, measuring the ICP may also help defining unclear *indications* to implant a ventriculoperitoneal shunt.
- In patients *with a shunt system*. An ICP measurement can be determinant in some cases of suspected *shunt dysfunction*, which usually might be handled through a shunt tapping and measurement of the column of water. In more acute settings, e.g., in patients with sudden clinical signs such as consciousness impairment, a shunt externalization to measure the ICP is indispensable for further management. Knowing the ICP might improve the *shunt adjustment* in outpatient clinical practice as well. Furthermore, ICP might be a fundamental parameter to handle *differential diagnosis* between shunt-related symptoms and other causes of headache or unspecific clinical signs.

The development of ICP monitoring methods also makes it possible to expand on research on pathophysiological aspects which are still only partially known, i.e., the ICP behavior in dynamic conditions (walking, standing for a long time).

1.2 ICP measurement methods

Several methods have been developed over time to measure ICP and they may be direct as well as indirect, both detecting values either as single or continuous data points.

To the *indirect* and non-invasive single method tools giving morphological information belong, for example, brain imaging (ultrasound, MRI or CT are currently the most used in neurosurgery), optic nerve sheath diameter (ONSD, estimated sonographically) and fundoscopy (13). It has to be specified, though, that imaging does not give a direct measurement of the ICP. Other non-invasive tools offer physiological information and include ophthalmic and transcranial Doppler (TCD)(14), tympanometry (Doppler-based impedance), near-infrared spectroscopy, otoacoustic emissions and electroencephalography (13). Furthermore, automated pupillometry has gradually increased in use in the ICU practice in some centers (15). In the case of tympanometry, continuous data points may alternatively be collected. Introduced in the 1990s, ONSD appears to be a valuable indirect method since it offers a measurement of the subarachnoid space around the optic nerve, although with some exceptions, e.g., patients younger than 1 year or with an open fontanelle. A linear individual correlation as well as the fact that ONSD is not sensitive to treatment in patients with IIH are also to be taken into account while using this technique (16), (17), (18).

Direct methods are invasive because they rely on direct contact to the intrathecal or intracranial compartment. Therefore, an indication for placement should be established, balancing the risks and benefits of the procedure. Overall, the methods should be feasible, precise, safe, and cost-effective. The gold standard to measure the ICP is achieved by placing an intraventricular catheter, which may sometimes be challenging because of narrow ventricles, can be subjected to misplacements and measurement inaccuracy, and can cause secondary infections (19). Intraparenchymal probes present less risks but do not offer the possibility to drain CSF for diagnostic or therapeutic purposes. Subdural and epidural transducers do not present the same reliability as the previously mentioned methods (2).

Among the direct methods there are shunt tapping in shunt/reservoir-bearing patients (puncture of the reservoir gives a measurement of the ICP at a particular moment), lumbar puncture (in those two modalities a hypercapnia following sedation may increase the ICP, thus resulting in false values), lumbar drainage (enabling a more continuous measurement, but may not be reliable in case of non-communicating CSF compartments or bear complications in case of intracranial masses), and telemetric methods. If the measurement is done through a lumbar puncture, an intracranial mass or a tonsillar herniation have to be ruled out.

Continuous direct ICP measurements are obtained through intraparenchymal ICP probes, shunt infusion tests and telemetric methods. Using those methods, it is possible to perform overnight monitoring of the ICP, e.g., in the case of a difficult diagnosis (asymptomatic enlarged ventricles and macrocephaly, to differentiate compensated hydrocephalus and brain atrophy) (20). This offers the possibility to get measurements without artifacts in awake patients. It also enables the calculation of different parameters, such as the RAP (pressure-amplitude coefficient), AMP, and slow waves. Moreover, an infusion test gives unique information about the functioning of a shunt (21).

1.3 Telemetric measurement of the ICP

A non-invasive repeated and continuous measurement of the ICP can be performed through a ventricular or intraparenchymal probe connected to a sensor or transducer. Telemetry refers to the collection of data from a source and their transfer to receiving tools in order to manage them. Because of the possibility of being performed in an outpatient regimen, it is particularly suited to chronic or subacute clinical contexts, e.g., some forms of hydrocephalus. It is a direct ICP measurement method and has been extensively used over the last two decades (22). Multiple devices have been introduced on the market, offering the chance to collect intracranial pressure data at different frequencies and modalities: Osaka Telesensor (Nagano Keiki Seisakusho Co. Ltd., Tokyo, Japan), P-tel sensor (Raumedic, Helmbrechts, Germany), and the SR (Miethke, Potsdam, Germany) (23), (24), (25), of which currently the most used telemetric systems are the P-tel sensor and the SR (*Figure 1*). These telemetric systems are able to work in different ways: the SR detects the ICP through a sensor directly connected to the CSF system, while in the P-tel sensor a microballoon at the extremity transmits ICP fluctuations (3).

1.4 The impact of posture on the ICP

A huge advantage, common to all telemetric methods, is the possibility to also perform measurements in different so-called physiological and paraphysiological conditions, thus contributing to deepen the knowledge on posture- or maneuver-induced changes to ICP. Studies about normal values of ICP focus on the crucial role of the venous system in different body postures (20), (26), (27), (28), (29), (30), (31), (32). It has largely been demonstrated that negative ICPs are physiological in the upright position, due mainly to the venous outflow, which is then reduced because of internal jugular veins collapse (33). The first study to document and describe ICP in different body postures and, in particular, negative values in the upright position was conducted by Juhler et al. (34); a study which also further investigated the phenomenon of venous collapse in order to avoid too extremely negative ICPs (29). Studies on astronauts investigated the risks of prolonged high ICP, focusing on the application of negative body pressure in order to reduce ICP, thus maintaining a normal cerebral perfusion pressure (35), (36). Other studies also describe ICP-lowering measures in order to avoid cerebral damage in intensive care unit settings (37). In shunted patients, the impact of posture also has an influence on the valve function: the hydrostatic pressure increases in the vertical position, thus letting the resistance of the valve automatically rise in systems hosting a differential pressure and a gravitational unit, which are routinely used in our center.

1.5 Intracranial compliance and other ICP-related parameters

To date, an important issue has also been the analysis process of the ICP data; the development of a reading and analysis software has been a necessity in order to improve the interpretation of the ICP data.

ICP might be characterized better and in more detail in combination with other related parameters. As stated by the Monro-Kellie doctrine, the intracranial compartment has a compensation capacity towards an increase in volume in order to keep ICP constant. This is called *intracranial compliance*. The most direct parameter associated to it may be the pulse amplitude (AMP) - the difference between diastolic and systolic ICP. Brain compliance behavior has been long debated, but recent studies have confirmed that it is increased in the vertical position in comparison to the horizontal, i.e., the ICP is lower in the former and higher in the latter state (38). This behavior of the cerebral compliance has also been demonstrated in patients bearing a CSF shunting system (38).

Other parameters may also indirectly characterize the ICP, but they are not easily detectable and interpretable in everyday clinical practice. Using spectral analysis of ICP, Lundberg proposed the already mentioned *ICP waveform peaks* (*P1*, *P2*, *P3*, in *Figure 1*), which are the result of CSF circulation and intracranial blood flow. The three peaks represent accurate parameters to support the clinical management of increased ICP: P1 is determined by the cardiac cycle and therefore related to the arterial pressure (percussion wave); P2 has a correlation to the brain compliance by being the combination between blood pulsation in the intracranial vessels and brain resistance (tidal wave); and P3 is a lower amplitude wave determined by the closure of the aortic valve (dicrotic wave) (39). In particular, the dicrotic waves represent the equivalent amplitude of the slow waves (association to blood flow velocity, arterial blood pressure, and brain oxygenation) (40). A physiological configuration implies that P1 is higher than P2 and P2 higher than P3.

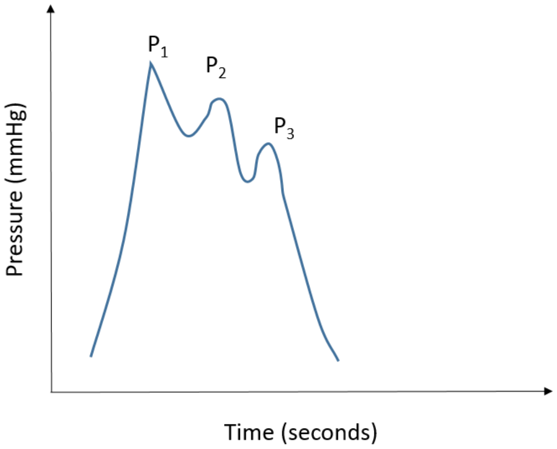


Figure 1: ICP waveforms.

ICP waveforms with waveform peaks P1, P2, and P3.

An increase in the ICP has a direct impact on the shape of the waves, as depicted in *Figure 2*. P2 becomes the higher peak, meaning an impairment of cerebral compliance. The additional presence of vasogenic A and B waves in the mean ICP may also help in detecting an altered status of the intracranial compensation.

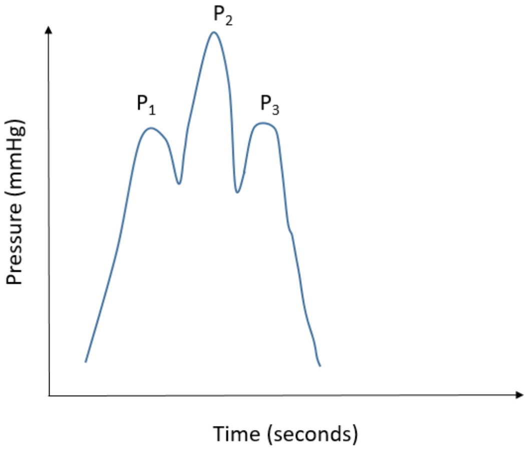


Figure 2: Pathological ICP waveforms.

Schematic representation of ICP waveforms in the case of increased ICP.

The *RAP index* (RAP), depicted in *Figure 3*, represents the correlation coefficient between mean ICP and ICP mean pulse amplitude (AMP) (41), and is an index of compensatory reserve capacity in clinical practice (42). The RAP takes a value between +1 and -1. If the RAP index exceeds 0.6, the compensatory reserve appears to be low, thus indicating a low compliance (43).

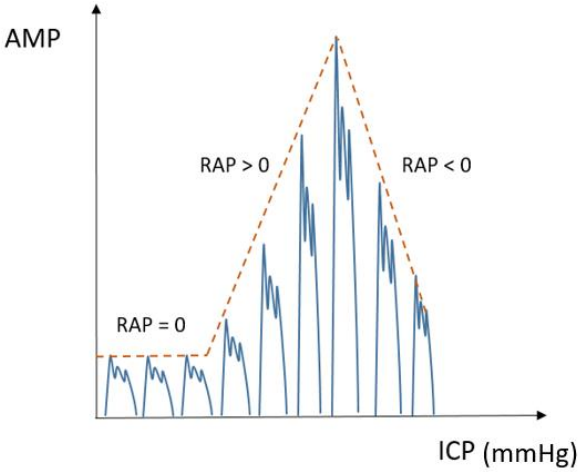


Figure 3: RAP index representation.

RAP index, the ratio between ICP mean pulse amplitude (AMP) and ICP.

The *ICP mean pulse amplitude* (AMP) depicts the difference in the ICP values between the highest and lowest pressure value during one cardiac cycle. It has been reported that AMP may, in some cases, offer a better understanding of patients with raised ICP, especially in chronic situations where venous and/or CSF outflow are more important than acute compensatory reserve. Increased ICP is reflected in raised AMP until the critical ICP is reached, resulting then in decreased AMP (44), (42). It is challenging to interpret the compliance alone with singular AMP values without knowing if it is detected in the range of increase or decrease together with elevated ICP measures. The *intracranial elastance coefficient* (E) is one of the most significant parameters, since it indicates the pressure change per unit of volume removed from or gained by the system. This represents the ability of the CSF compartment to store an extra volume amount (“buffering capability”) (45), (46), (47). There is no direct correlation between E and RAP, and no correlation at all with AMP.

The *pressure reactivity index* (PRX) is the correlation coefficient between ICP and mean arterial blood pressure, representing cerebral autoregulation. It varies with the concurrent cerebral perfusion pressure in a U-shaped way (48), (49), as depicted in *Figure 4*.

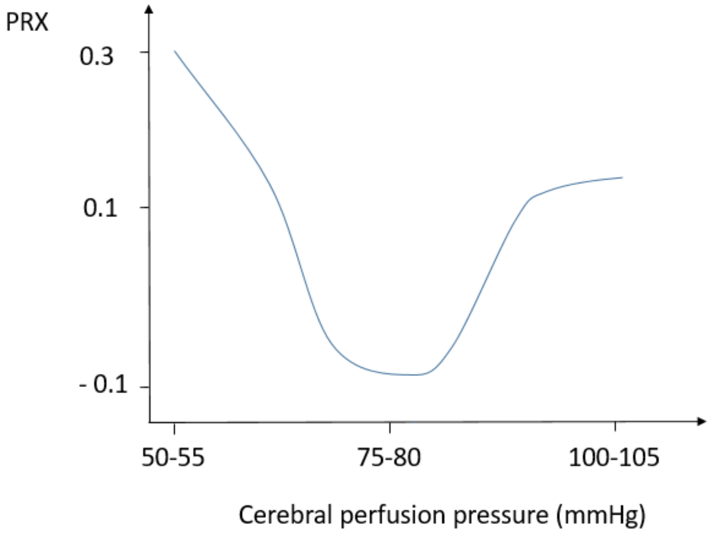


Figure 4: Pressure reactivity index (PRX) and cerebral perfusion pressure correlation.

1.6 Study purpose

The aim of this study is to analyze the use of telemetric intracranial pressure measurements (tICPM) in the clinical practice of hydrocephalus treatment. Firstly, *in vitro* characteristics of the telemetric device and, secondly, *in vivo* maneuver measurements in patients were investigated.

tICPM techniques are still not used on a broad scale for clinical neurosurgical investigations because of their limited applicability in the everyday routine and because of the cost and time effort to follow-up the implanted patient population. The main purpose of the presented work is to investigate if tICPM may support the treatment of patients with hydrocephalus or intracranial hypertension.

At this point, an *in vitro* set-up is (why present, "is", not "was" in this para up to "reported"?) used in order to compare an established ICP measurement with a tICPM method, specifically the sensor reservoir (SR). The aim of the laboratory testing of SR is to evaluate the accuracy of ICP measurements in the telemetric pressure measurement method. Furthermore, a retrospective sample of shunted and non-shunted patients and their clinical management during follow-up and therapeutic or conservative decision making is reported. Additionally, the study focused on the potential of tICPM to extrapolate ICP together with AMP and its relevance for cerebral compliance evaluation. Lastly, ICP and amplitude response to physiological and paraphysiological maneuvers in shunted and non-shunted patients were characterized. Thereby, postural, ventilation, and venous congestion maneuvers are evaluated in measuring protocols and integrated in the routine patient follow-up.

2 Materials and methods

For this retrospective study, intracranial pressure data from registrations in different settings, *in vitro* as well as *in vivo* were collected and evaluated. The tICPMs were performed using two telemetric systems, the P-Tel and the SR.

2.1 Neurovent-P-Tel

The P-tel consists of a 25 mm catheter hosting silicone and a piezoelectric pressure-detecting sensor on its proximal end. On the distal end, a flat round structure allows transduction of measuring data through a portable system collecting radiofrequency signals.

The catheter has to be placed intraparenchymally, usually at the level of the precoronal Kocher´s point. In shunted patients, the location of choice is opposite to the ventricular catheter.

As recommended by the producers, the device is CE certified and has to be explanted until 90 days after implantation surgery. The measurement frequency rate is 1–5 Hz.

Although the device has a low sampling rate, the possibility to further analyze the data through the ICM+ software (ICM+ software, Cambridge, UK) enables the investigator to extrapolate additional information, such as ICP-related parameters, which are mentioned further in the text (50).

2.2 Sensor Reservoir

The SR consists of a detecting unit protected by a titanium shield, encased in a circular polymeric structure and with a silicone dome on top, which offers the possibility to inject fluids or extract CSF. The sensor detects intracranial pressure having a direct contact with CSF through a proximal intraventricular catheter, which lies ipsilateral on one of the frontal horns of the lateral ventricles. The reservoir also hosts a distal connector, which can be connected to a CSF shunting system (51). An alternative off-label use of the SR is to obliterate the distal connector to a blind end, thus allowing tICPM and reservoir tapping at a pure diagnostic level.

The requisite for optimal function and measurement collection is a correct position of the proximal end of the ventricular catheter in the ventricle: several guiding methods have been described, e.g., the use of a guide using imaging and anatomical landmarks of the patient (52).

A portable device allows direct measurement from the sensor, showing parameters such as ICP, amplitude, temperature of the system, and time.

The measurement modalities are single, high (fast) and low (continuous) frequency detection. The single type of measurement offers one value collected at the exact time of the detection. The frequency rate reaches 44 Hz. The screen of the measuring device shows an ICP wave if a continuous or a fast measurement is performed.

The manufacturer provides an SD card uniquely paired to each SR. If used, the card is able to save the measurement data anonymously, and they can be exported to a computer in order to perform further analysis.

The analysis software (ICPicture, Miethke, Potsdam, Germany) was recently introduced (2020) by the company: the data, saved as CSV files, can be renamed and managed through the program, which permits the visualization of an ICP curve, in which an AMP analysis can be performed. The additional extrapolated data was further exported as Excel for further analysis.

The device is CE certified and no explantation surgery of the reservoir is indicated, since the drift 4 years after implantation is under 2 mmHg (53), (54), (55).

Potential use, feasibility and reliability have been partially analyzed by the existing literature, reporting mainly experiences with shunted patients (53), (54), but only a few concern laboratory experimental settings and there is little data about the real long-term performance and reliability of the obtained values.

2.3 Experimental measurements

In a laboratory setting, SR models were tested in different conditions. A simplified simulation of a ventricular system was reconstructed in laboratory, consisting of a pressure chamber (a column of water acting on the sensor, simulating the ventricular system) and communicating through a catheter with the proximal connector of the SR (*Figure 5*).

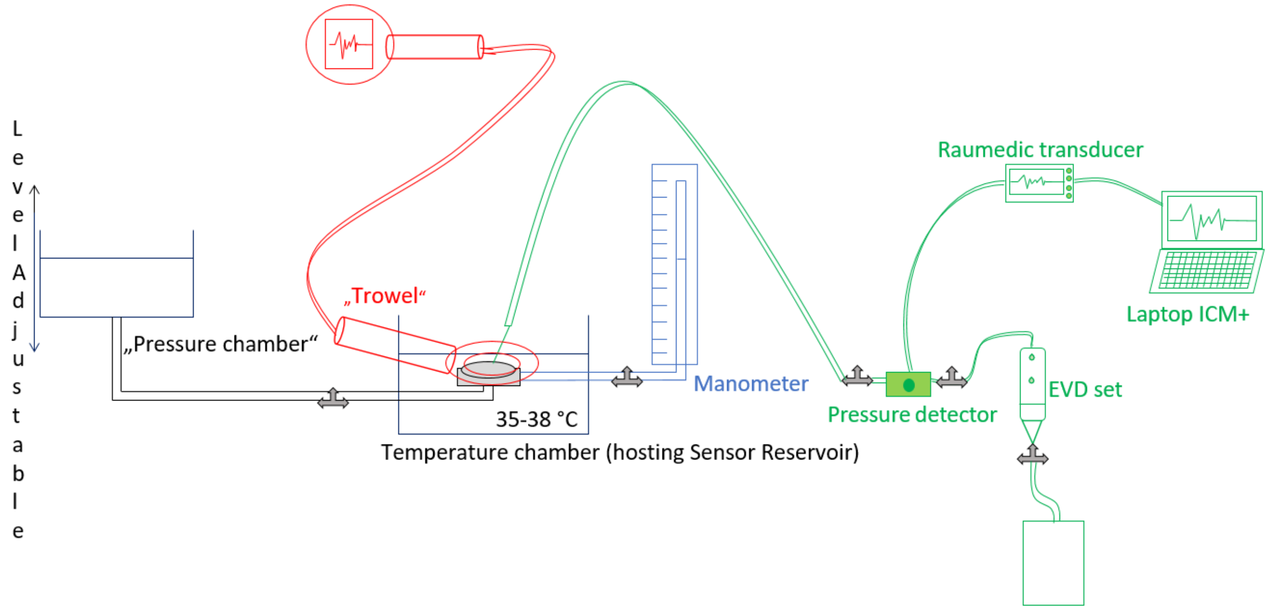


Figure 5: Schema of the in vitro SR testing.

Schema of the laboratory setting for the *in vitro* testing of SR samples. In black, communicating vessels simulating the ventricular system with the SR (on the left, the “ventricle” connected to a chamber to maintain the SR temperature constant, on the right). In red, the SR measuring system. In blue, a manometer to check the pressure in the system. In green, the invasive puncture of the SR to cross-check the measured pressure, through a Raumedic transductor, connected to the ICM+ software.

As depicted in the scheme, the “pressure” and “temperature” chambers were containers with physiological saline (0.90% sodium chloride) solution, in order to perform a pressure on the SR and maintain the temperature in a physiological range, respectively. Specifically, the temperature in the system was maintained between 35°C and 38°C. This was achieved by placing a stove under the container hosting the SR and periodically checking the water temperature with a thermometer. In this setting, the SR was put in the “temperature chamber”, with the proximal connector connected to the “pressure chamber” and the distal connector to a manometer, in order to cross-check the pressure of the column of water. The “pressure chamber” established the pressure, which had to be cross-checked by the measuring systems. This was recreated using a centimeter column and a laser system to control the “zero” level and estimate the measured pressure levels with precision.

A total of 6 SRs were tested through this laboratory model. Three of them were inline reservoirs, and the other three were burr-hole reservoirs. During the measurements on each sensor, an additional puncture of the reservoir was conducted and the needle was connected to an external ventricular drainage (EVD) set with a sensor for the intracranial pressure monitoring (Raumedic AG, Helmbrechts, Germany). Using the Raumedic transducer, a visualization with the ICM+

computer program was also performed (ICM+ software, Cambridge, UK), in order to compare the pressures detected by the three different tools. The measurements were performed at different pressures/levels of the column of water in the "pressure chamber": -20, -10, 0, 10 and 20 cmH$_2$0 (-14.71; -7.36; 0; 7.36; 14.71 mmHg). The tICPM from the SR was conducted through a single measurement modality, because no pulsation could be recreated to simulate a physiological system.

In *Figure 6*, photographic details of the laboratory setting are presented. The telemetric measurement with the trowel was performed in parallel through a continuous measurement mode and registered through the SD card connected to each of the 6 SRs.

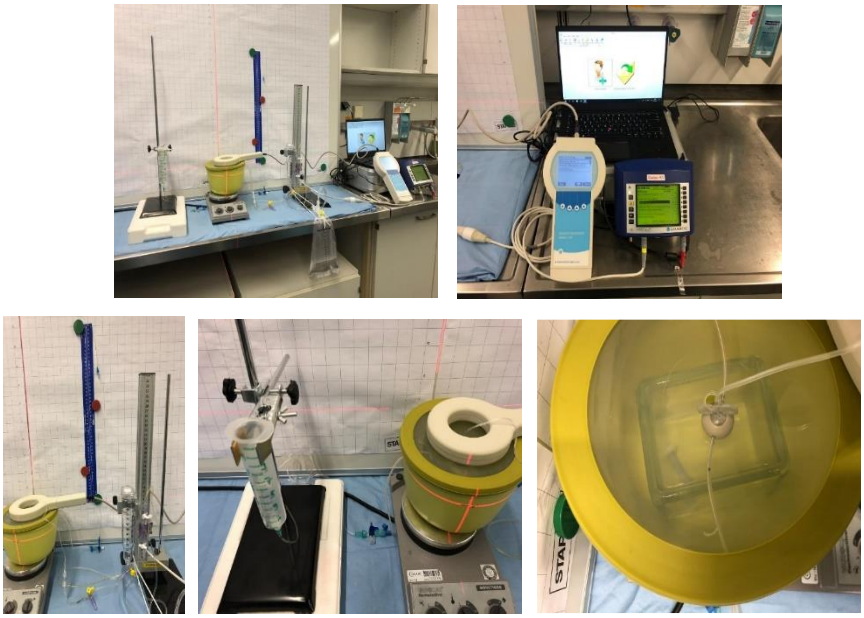


Figure 6: Picture of the in vitro SR testing.

Laboratory setting for the *in vivo* measurements. General setting of the different compartments (left above); tICPM methods (right above) manometer and EVD set system to cross-check the pressure detections (left below); pressure and temperature chamber (middle below) in which the SR is positioned (right below).

2.4 ICP measurements in patients

A measurement session was performed in patients already bearing a shunting system with challenging clinical pictures of hydrocephalus and with difficulty in managing the shunt with a regular valve adjustment protocol. The cases were selected when symptoms and imaging were not matching and in case of failure of shunt adjustment to reduce the clinical disturbances. In this session, a first sample of eight shunted patients implanted with a P-tel device (*Figure 7a*) and a second sample of seven shunted patients carrying a SR (*Figure 7b*) were retrospectively analyzed and the consequent valve adjustments and clinical outcomes were extrapolated and reported. Even though the 90-day explantation period of the P-tel was part of the informed consent, patients and families decided whether or not to undergo further surgery.

In an additional cohort of six patients carrying a stand-alone SR (*Figure 7c*), indication for device implantation was of diagnostic nature. Patient selection was addressed to ambiguous clinical signs, hinting at an intracranial hypertension. As already described, the distal extremity of the sensor was closed in this case, while the proximal was normally introduced in one of the frontal horns with the help of a guiding system. Measurement sessions were in this case also performed after puncture of the reservoir, in order to rule out the need for a shunt through pre- and post-puncture clinical and ICP measurements. Precise indication parameters for a shunt implantation were: ICP > 20 cmH_2O in the supine position, and/or > 0 cmH_2O in the upright position and/or clinical improvement after reservoir tapping test, performed at least 3 times. The tICPM protocol sessions were carried out before and 10–15 minutes after reservoir tapping: 10–20 ml were extracted (conditioned by patient weight, age and clinical condition). A measurement session had a duration of 30–60 seconds for each analyzed posture.

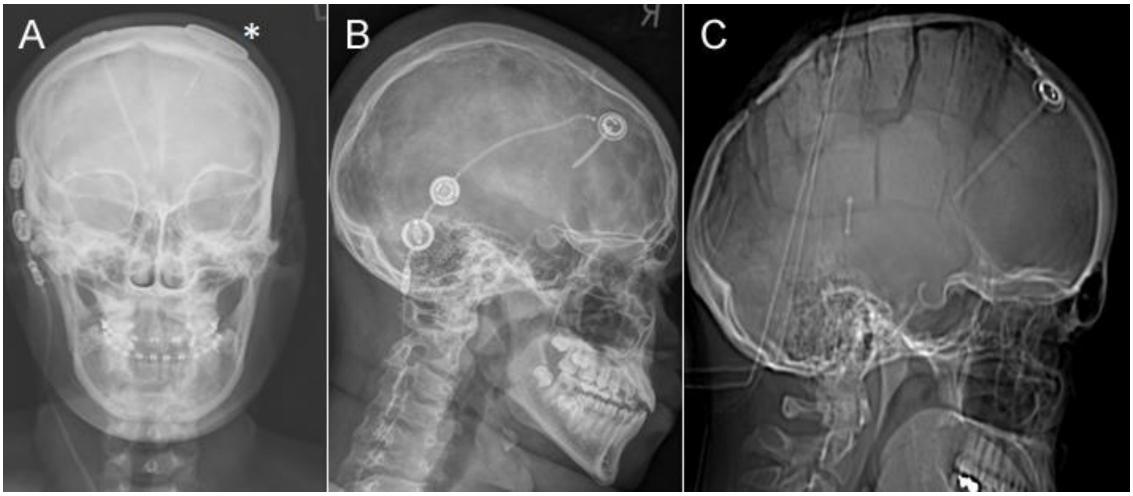


Figure 7: X-ray representation of tICPM devices.

Radiological depiction of (a) P-tel (Raumedic, Helmbrechts, Germany) and of SR (Miethke, Potsdam, Germany), integrated to a shunt system (b) and stand-alone (c).

TICPMs were conducted in the outpatient clinic, performing postural changes in the following order: standing, sitting, and lying, during which the head was kept slightly elevated with the use of a pillow. The single measurement modality was conducted. Four to six single measurement series were done and the mean resulting ICP was reported. An intracranial pressure of -10 up to 0 cmH_2O was considered the optimal range in the upright postures, while an optimum of 5–15 cmH_2O was set as the target in the supine position. All the patients filled out a daily report with headache scale evaluations (interval: 0, no headache, to 10, maximal intensity headache). In the shunted populations, shunt adjustments were towards higher resistances in the differential pressure unit (usually two cmH_2O on the valve scale) in case of low values in the lying posture and in the gravitational unit (four cmH_2O) in case of low values in the elevated positions (both hyperdrainage conditions). In underdrainage situations, the differential pressure unit was adjusted towards lower values in case of increased ICP in horizontal postures, while the gravitational unit was set lower in case of high ICP in the vertical positions.

An informed consent signed by the patients, parents or caregivers was obtained before every invasive procedure described, including reservoir punctures.

Perioperative complications, clinical follow-up and subsequent surgeries were registered and reported.

2.5 Telemetric intracranial pressure measurements

The maneuver measuring protocol was composed of 12 different maneuvers. These were performed in a purely SR-carrying patient group of 17 individuals (13 shunted and 6 non-shunted), in order to observe significant physiological, paraphysiological and interpersonal variations in the intracranial pressure values. Four non-shunted patients were later implanted with a ventriculo-peritoneal shunt and two of them were also subjected to maneuver measurements after that, and therefore included in the shunted group.

The patients investigation took place in an outpatient basis.

Among the patients hosting a ventriculoperitoneal shunt system, four were diagnosed with an IIH, three with myelomeningocele and Chiari malformation type 2, two with a PHH in combination with prematurity, one with an aqueductal stenosis, and one patient with craniopharyngioma. Median age was 15.8 years (range 4.1–35.2 years),

In the non-shunted subgroup, the indication to implant a SR was set in order to objectify an IIH in a patient previously operated for a craniosynostosis and in a patient with macrocrania and MCM-syndrome (megalencephaly-capillary malformation syndrome). Among the non-shunted patients, two were later implanted with a ventriculoperitoneal shunt. The mean age n the non-shunted group was 11.9 years (range 3.6–17.7 years) (for details about the population characteristics, see *Table 2*, in the Results chapter).

The positional maneuvers were: standing, lying supine in a +10° (anti-Trendelenburg) position, lying supine in a 0° position, and lying supine in a -10° (Trendelenburg) position. Breathing maneuvers were partially combined with the positional ones, in particular with the +10° lying and the 0° lying and were: fast breathing in and out (hyperventilation), breath keeping (hypoventilation), Valsalva maneuver, and slight jugular veins pressure exerted at the neck (compatible with the cooperation of the investigated subject) (*Figure 8*).

Every single measurement had a duration of 30–60 s. The interval time between the measurements was 1 min. All the investigations were conducted by the same physician and in an ambulatory setting as well as using the fast measurement modality. The frequency of the measurements was principally based on the clinical status of the individual patient. In particular, in the non-shunted population, the measurement interval was always no longer than 4 weeks, while in the shunted group it varied from 2 weeks to 3 months, according to the necessity to adjust the shunt or not.

The measurement data were collected by the SR reader unit, composed of a trowel, which was positioned 2–3 cm above the skin on the SR implantation site of the patient. The samples were saved on a SD card, which permitted moving the files in an anonymized way to a laptop in the CSV format. The further elaboration of the collected data in tables or in diagrams was possible through a Beta ICP-Viewer software related to the SR and developed by the company (ICPicture, Miethke, Potsdam, Germany). Through the program, the additional information about AMP was extracted from the ICP curves with a 44 Hz frequency. The ICP and AMP data were finally exported as excel files and further analyzed for the purposes of this work.

As with the previous series of patients (*in vivo* measurements), a CSF puncture was also performed in the non-shunted individuals if the measured ICP exceeded 15 cmH_2O in the lying 0° position and 0 cmH_2O in the standing one. A maximum of 15 ml were subtracted from the SR by means of a sterile procedure. If the post-puncture status included a clinical improvement and lower ICP values, and if it was observed after a minimum of 3 reservoir tappings, the surgical indication for shunt placement was set.

The measurements were performed between May 2020 and February 2022, and all the subjects in this study were admitted and discharged in an outpatient regimen. In the invasive maneuvers (reservoir tapping), an informed consent from the caregivers/parents/patients was collected before the procedure. A total of 480 measurements and corresponding evaluations were conducted.

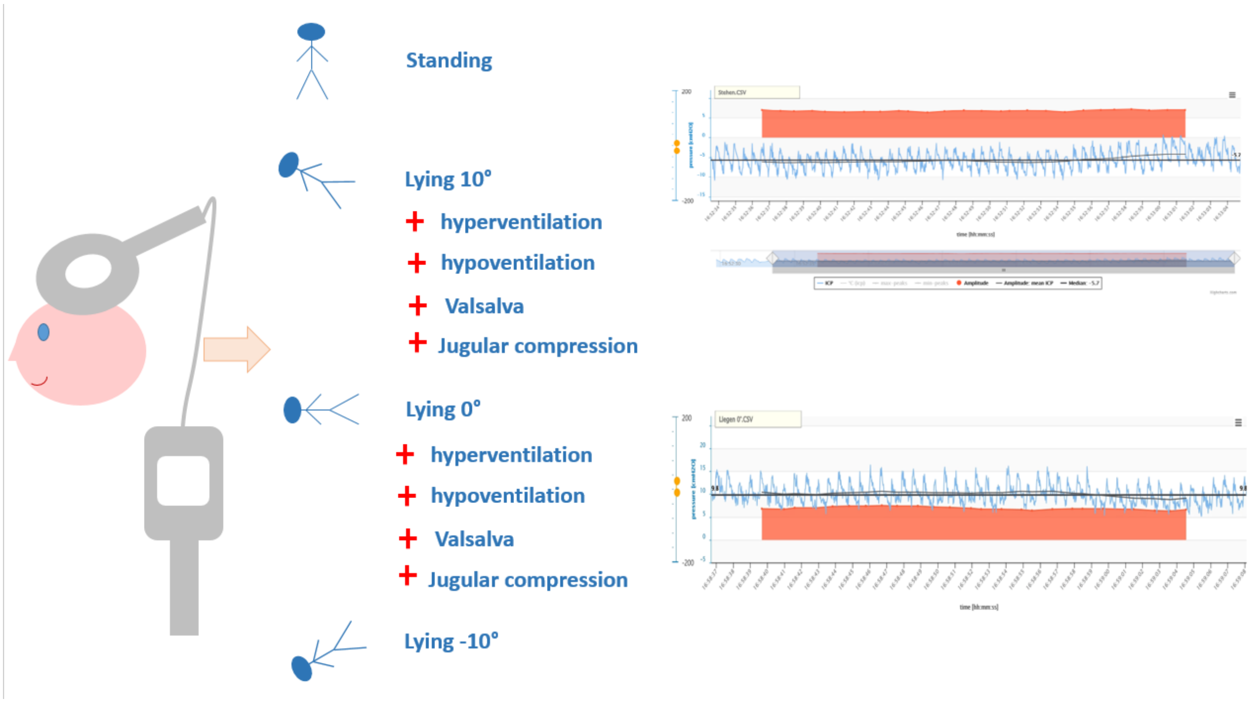


Figure 8: tICPM protocol.

Schematic view of the tICPM protocol, from the measurement to the translation of the data in the software. In the middle column are the different positional, ventilation and compression maneuvers.

2.6 Statistics

Values are given as median with range or mean and standard deviation. For comparison of multiple measurements *in vitro* and *in vivo*, such as the comparison among the experimental SRs and the maneuver measurements a paired t-test was used. Values < 0.05 were considered statistically significant. To evaluate the survival rate of P-Tel and SR and the shunt survival after their implantation a survival curve comparison was performed. The shunt setting adjustment of the gravitational and differential pressure unit after ICP measurement was examined by means of a Wilcoxon test. Statistical analysis was performed using Excel and Prism 9 software (Graphpad, San Diego, CA, USA).

3 Results

3.1 Experimental measurements

In an experimental setting, a communicating vessels system was reconstructed simulating a ventricular system and six SRs (three of them burr hole reservoir models, three inline reservoirs models) were positioned in it and tested. A baseline "zero" registration of values from each sensor was also carried out, outside and in water, showing a drift range of -0.22–2.40 mmHg (-0.3–3.3 cmH_2O). A total of 30 measurements and their relative analysis was performed. The results from the experimental data depicted a difference in the two measurement systems varying from a minimum of 0.3 cmH_2O (0.2 mmHg) to a maximum of 6.8 cmH_2O (5.0 mmHg). In particular, in four out of six samples, the values fluctuate from 0.3–1.9 cmH_2O (0.2–1.4 mmHg), a range considered normal. In two devices, the delta values were 0.7–6.8 cmH_2O (0.5–5.0 mmHg) and 2.6–4.5 cmH_2O (1.9–3.3 mmHg), respectively (*Figure 9*). In general, the values obtained with the two pressure detection systems were comparable, thus showing a good reliability in the laboratory setting of the SR ($p < 0.0001$).

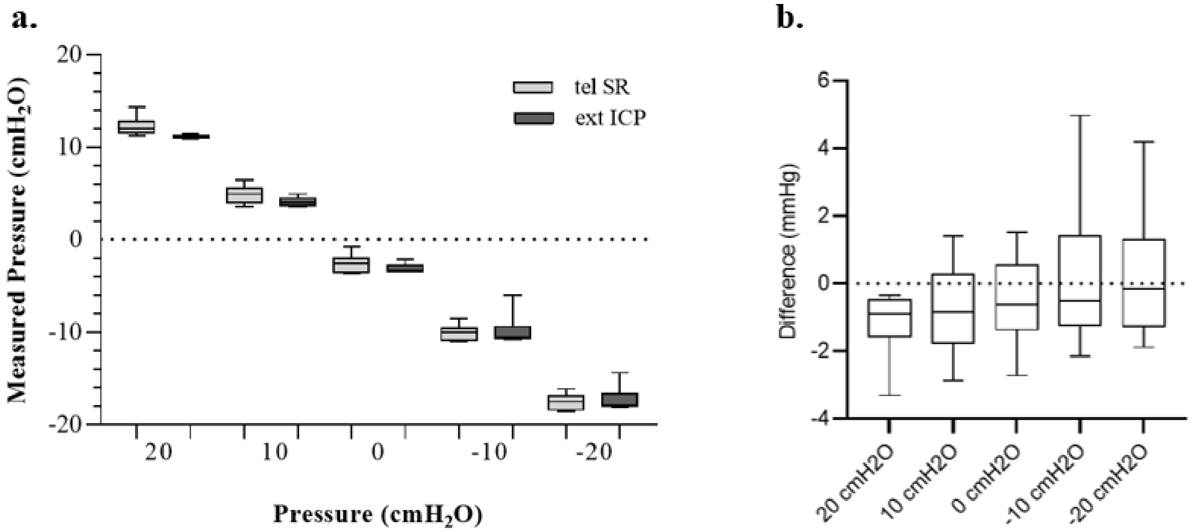


Figure 9: Comparison of the in vitro SR measurements.

a. comparison of *in vitro* measurement of the 6 SR samples in different pressure systems with telemetric detection of pressure (tel SR, light gray), and by means of invasive puncture of the reservoir and transduction through a Raumedic device (ext ICP, dark gray). *b.* differences among the SR and "invasive measurement": at around 20 cmH_2O the difference among the two systems appears to be more enhanced.

3.2 ICP measurements in patients

The data were collected in an 80-month period (December 2010–July 2018) in our center on 21 patients, 15 females and 6 males, with median age 16.5 years (age range 10–39.5 years).

A P-tel was implanted in eight cases, with a median age of 16.3 years (age range 10–21.6 years) between December 2010 and March 2015. The original diagnoses were as follows: 2 craniopharyngiomas, 2 Crouzon syndromes, one glioma and one myelomeningocele.

In 13 subjects, ten females and three males, with a median age of 16.4 years (age range 13.1–39.5 years), an SR was used, between December 2015 and July 2018. Primary diagnosis in this population was myelomeningocele in four cases, three posthemorrhagic hydrocephalus, one craniopharyngioma, one scaphocephaly, one traumatic brain injury, one suprasellar arachnoid cyst, one idiopathic intracranial hypertension, and one aqueductal stenosis following ETV (*Table 1*).

Population		**N.**	**Median Age (years)**	**Diagnosis**	**Outcome**	
P-Tel		8	16.3	3 Gliomas 2 Craniopharyngiomas 2 Crouzon Syndromes 1 Spina Bifida	Shunt Weaning 1	
					Shunt Adjustments 7	
SR	**Non-Shunted**	6	16.0	2 Spina Bifida 1 Craniosynostosis 1 Arachnoid Cyst 1 IIH 1 PHH	Secondary Shunt 4	
	Shunted	7	16.7	2 Spina Bifida 2 PHH 1 Craniopharyngioma 1 TBI 1 Aqueductal Stenosis	Shunt Adjustments 7	Symptoms Resolution 1
						Improvement 5
						Stability 1

Table 1: Population characteristics from in vivo analysis.

General characteristics of the mixed population P-Tel and SR in the *in vivo* analysis.

Concerning the follow-up data after the P-tel or SR implantation, further surgical indications to solve shunt issues were necessary in six patients belonging to the P-tel group and in two in the SR group. Different combinations of differential pressure and gravitational units were in use in our cohort, thus reflecting a high heterogeneity of the population.

Two post-implantation complications were identified in the P-tel group (one case of infection and one case of symptomatic, confined intracerebral bleeding), both requiring explantation of the devices. Among the SR patients, one case of infection occurred which also imposed explantation surgery. Mean implant survival time was 4.2 months (range 4–13 months) for P-tel and 35.5

months for the SR (*Figure 10c*).

In both shunted cohorts, the overall shunt survival rate was 68.3% in 77.9 months (*Figure 10b*). A clinical improvement after serial tICPM-targeted shunt adjustments was registered in nine cases, and a disappearance of the cephalalgic symptomatology in three. In the non-shunted population, which was later treated with a VPS (4 out of 6 patients), a clinical improvement was always assessed, with two cases being symptom-free at follow-up. The two remaining patients did not show any response to CSF puncture in terms of symptoms and intracranial pressure change.

From the tICPM, according to the already described protocol, a significant difference was found between the sitting and standing values of ICP and the lying ones ($p < 0.0001$). Statistical significance was also found in ICP measurements in standing and sitting among shunted and non-shunted subjects ($p < 0.0001$ and $p < 0.001$, respectively). After shunting, stand-alone patients showed statistically significant differences in the lying position ($p < 0.05$) (*Figure 10a*).

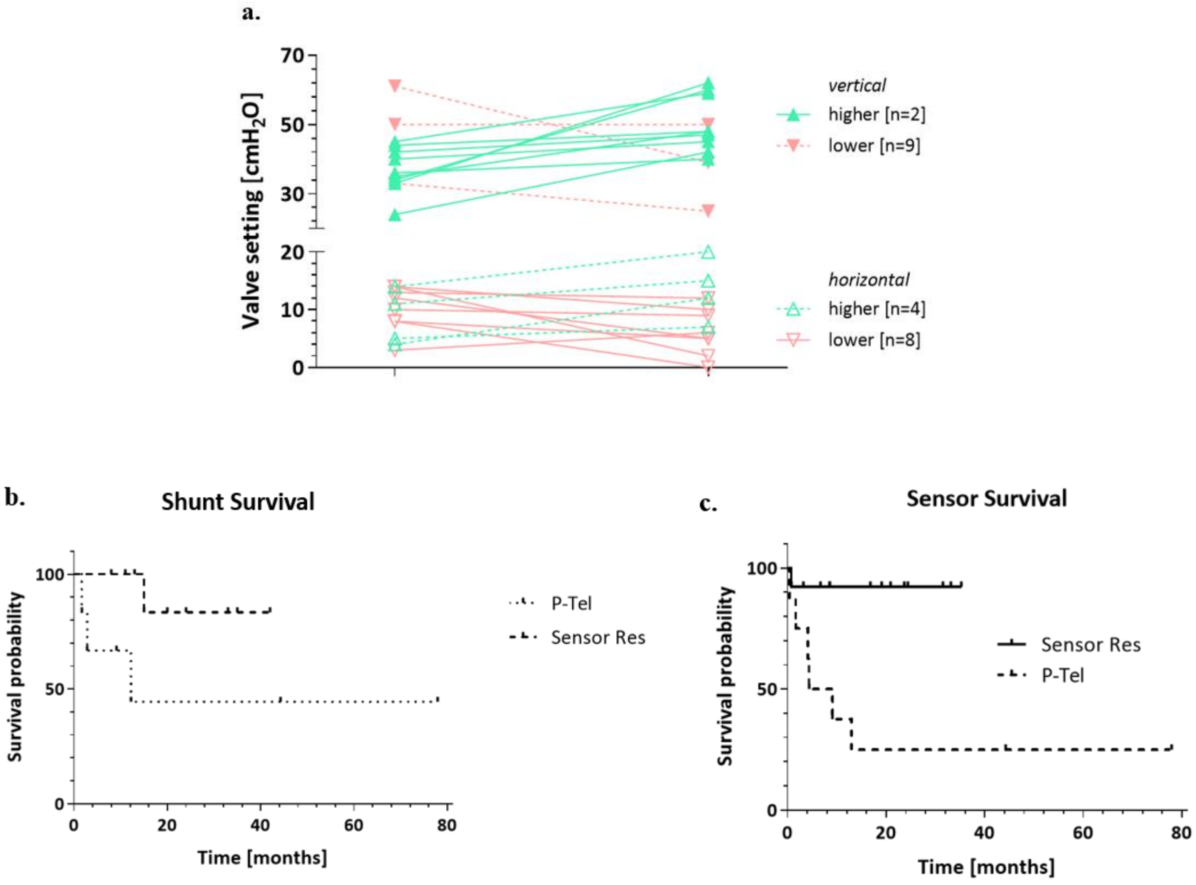


Figure 10: a. tICPM-induced shunt adjustments; b. shunt survival after tICPM; c. sensor survival after tICPM.

Valve adjustments after tICPMs in most of the cases brought a change in the differential pressure units (DP) towards lower values and of the gravitational unit (GA) towards higher pressures (a.). In b., survival curve showing the revision surgery survival of a shunt after implantation of a tICPM system. In c., survival curve of the two tICPM systems analyzed in the series.

3.3 Telemetric intracranial pressure measurements

In 17 patients, 6 non-shunted, two of which were then added to 11 shunted, measurements in different positions (standing, lying 10°, lying 0° and lying -10°) and breathing pattern protocols were performed. As already stated, all the patients were investigated on an outpatient regimen. Among the shunted patients, four suffered from an idiopathic intracranial hypertension, three were followed for a myelomeningocele and Chiari malformation type 2, two for a posthemorrhagic hydrocephalus due to prematurity, one for an aqueductal stenosis, and one patient had a craniopharyngioma. Among the non-shunted population, the SR was implanted to rule out an intracranial hypertension mostly to diagnose an IIH in a patient operated for craniosynostosis and in a patient with macrocrania affected by MCM-syndrome (megalencephaly-capillary malformation syndrome). The two non-shunted patients which were later treated with a shunt were affected by an IIH and a macrocrania in the context of an MCM-syndrome. Median age in the shunted group was 15.8 years (range 4.1–35.2 years), and in the non-shunted group 11.9 years (range 3.6–17.7 years) (*Table 2*).

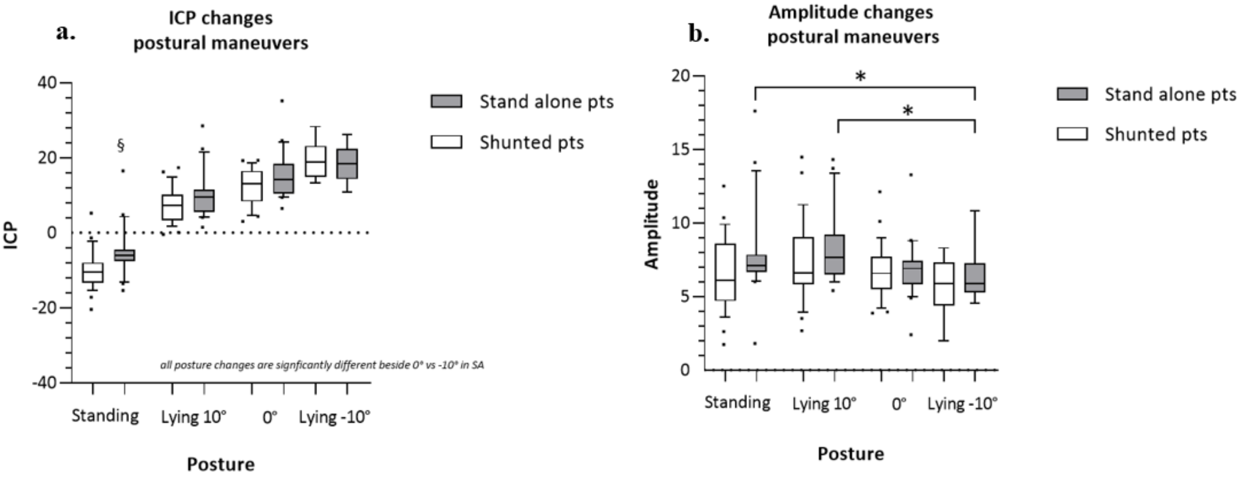
	N.	**Age (years)**	**Sex**	**Diagnosis**	**Shunt Duration (months)**	**BMI**	**Punctures (n)**
Shunted	1	35.2	F	IIH	35	22.9	-
	2	13.4	F	PHH	144	25.9	-
	3	21.9	F	IIH	47	43.2	-
	4	16.5	F	MMC	55	31.8	-
	5	13.1	F	IIH/PHH	16	27.9	-
	6	24.5	F	MMC	294	20.6	-
	7	15.6	M	IIH	34	21.5	-
	8	15.8	F	Tumor	46	33.7	-
	9	21.0	F	Aqueductal stenosis	50	19.4	-
	10	5.9	F	PHH	5	12.4	-
	11	4.0	F	IIH	9	16.3	-
	12	7.1	M	MCM	6	16.2	-
	13	18.2	F	MMC	66	26.5	-
Median (range)		15.8 (4.0–35.2)			80.1 (16–294)	24.5 (12.4–43.2)	-
					Secondary Shunt implantation (months)		
Non-Shunted	14	17.7	F	Craniosynostosis	-	29.7	3
	15	6.9	M	MCM	3	16.2	4
	16	4.2	F	IIH	24	14	4
	17	3.6	M	IIH	5	16.3	3
	18	17.0	F	IIH	-	24.3	4

	19	17.2	F	IIH	3	20.3	3
Median (range)		11.9 (3.6–17.2)			10.7 (3–24)	20.1 (14–29.7)	3 (3–4)

Table 2: Maneuver protocol tICPM population characteristics.

Characteristics of the population subjected to the maneuver measurements (IIH: idiopathic intracranial hypertension, PHH: posthemorrhagic hydrocephalus, MMC: myelomeningocele).

From the maneuver sessions, we compared the shunted with the non-shunted group. First of all, we observed the differences and similarities in the postural maneuvers: standing, lying 10°, lying 0° and lying -10°. A statistically significant difference was noticed among the shunted and the non-shunted groups in both amplitude and ICP in the standing position and in the ICP in the lying 0° position (*Figure 11a* and *b*). A significant change in the ICP was also registered for the relative values in the lying -10° position (*Figure 11b*). Ventilation maneuvers applied to postural variations (hyperventilation and hypoventilation in lying 10° and lying 0°) showed a significant change in both ICP and amplitude in the lying 10° hyperventilating maneuver (*Figure 11e* and *f*). Significant changes in ICP among the two groups were also detected in the lying 0° hyperventilating activity. An analysis of the compression maneuvers (Valsalva and jugular compression, in both lying 10° and lying 0°) did not reveal any significant variation among patients with or without a shunting system (*Figure 11c* and *d)*.



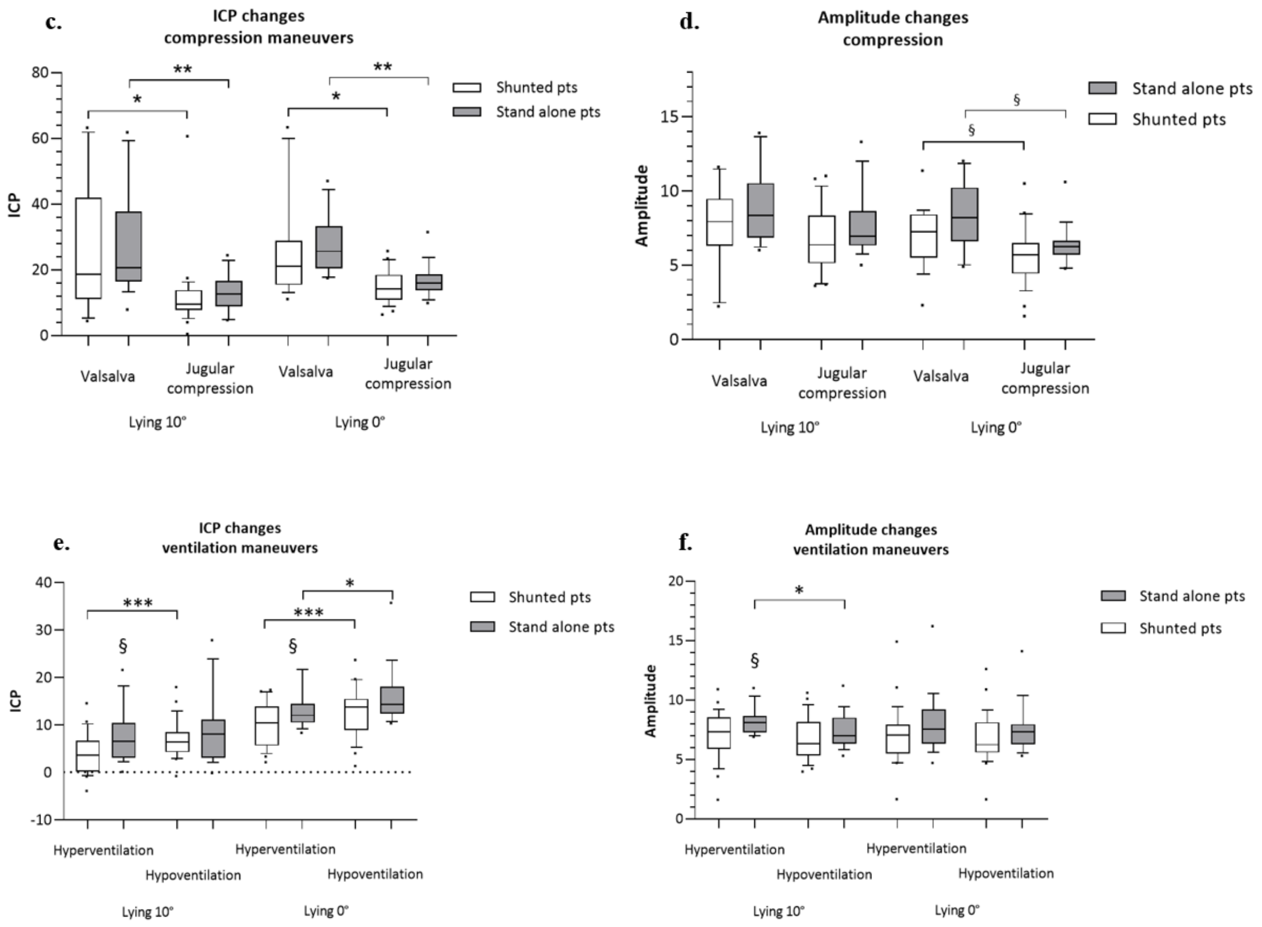


Figure 11: ICP and AMP comparison between shunted and non-shunted patients in postural, compression and ventilation maneuvers.

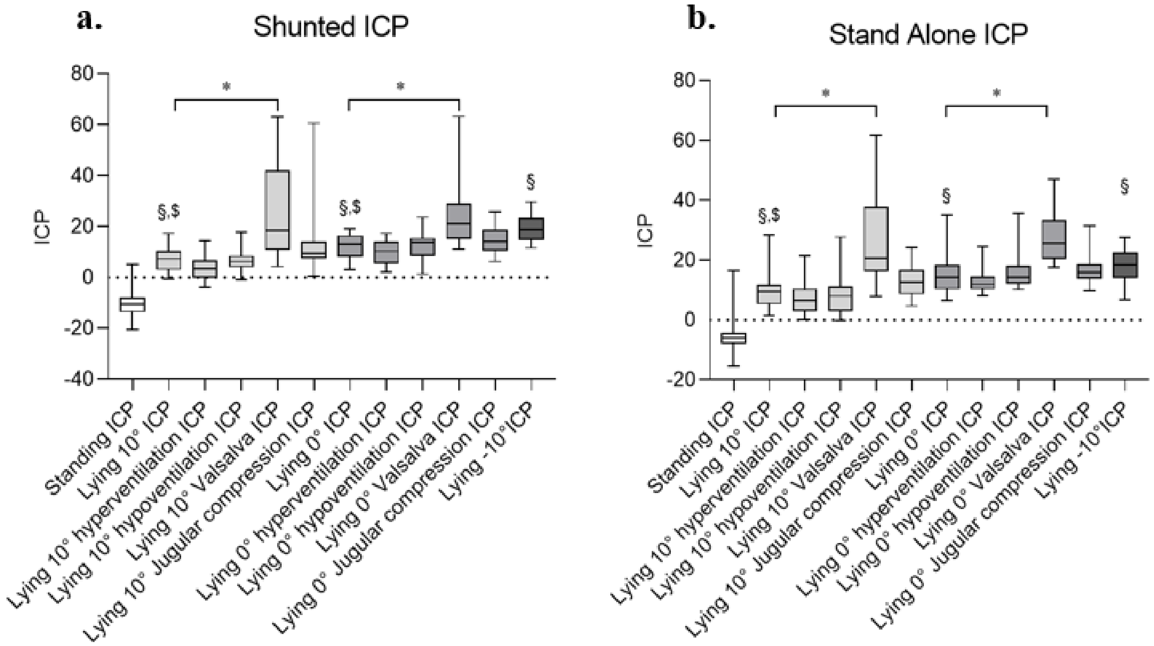
Boxplots on maneuver differences in ICP and amplitude in shunted and non-shunted patients: postural maneuvers (a. ICP and b. amplitude), compression maneuvers (c. ICP and d. amplitude), and ventilation maneuvers (e. ICP and f. amplitude).

In standing and lying 0° positions, but also - even though not significantly in our data - lying 10° and -10° positions, the patients with a shunt presented more negative values of ICP, while the amplitude ranges appear to be bigger in the stand-alone population. While a change in ICP is observed in both groups, though with differences, the amplitude appears to be more constant in the two investigated populations.

Under ventilation maneuvers, implemented to the positional changes, we observed that hyperventilation also makes the amplitude change (significantly only in lying 10°) and that this is more enhanced in the non-shunted population. ICP also differs, but only in hyperventilation is this change significant. Although not significantly, similar changes are also observed in hypoventilation.

Jugular compression and Valsalva maneuvers may evoke increases in amplitude in stand-alone patients and in ICP in the shunted patients, although no evidence of a statistical significance in those variations was noticeable in our populations.

In general, it was observed that ICP values showed more variations among the shunted group of patients (*Figure 12a* and *b*), while amplitude changes were particularly enhanced in the non-shunted cohort (*Figure 12c* and *d*).



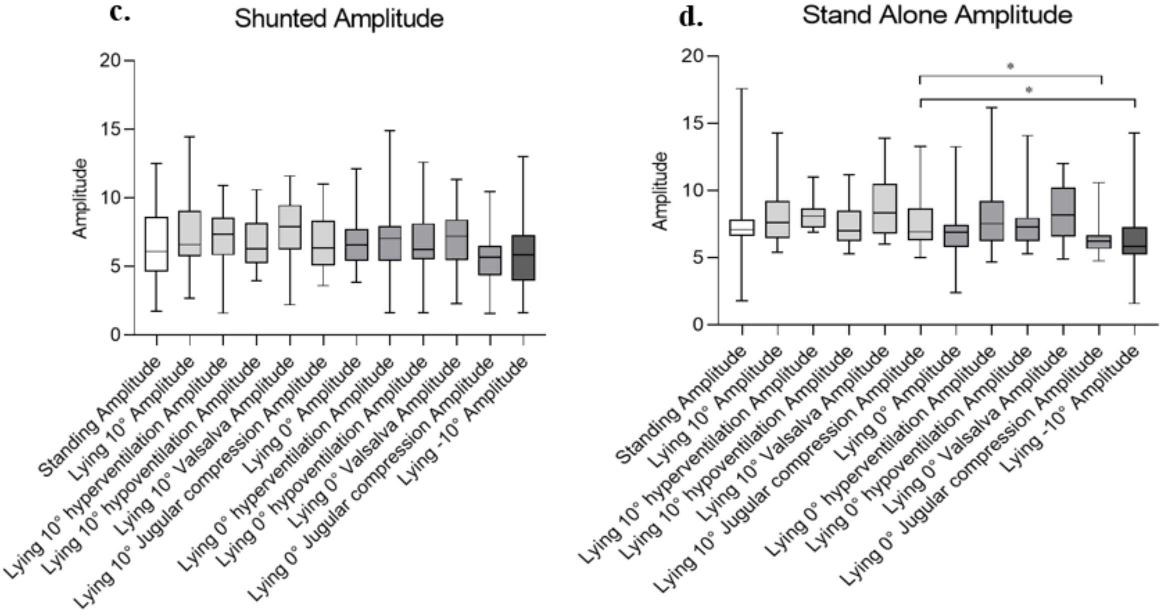


Figure 12: ICP and amplitude changes in shunted and non-shunted patients.

Box-plot tables on maneuvers: ICP in shunted (a.) and non-shunted patients (b.), and amplitude in shunted (c.) and non-shunted (d.), respectively.

The correlation analysis between ICP and AMP showed a significant relation in almost all body positions and maneuvers investigated in the stand-alone population, with the exception of the lying 0° position and in the same position during hyperventilation. In the shunted group, the relation was not so strong, but < 0.05 in the standing, lying 0° and 10° positions as well as in the hyperventilation maneuvers (*Table 3*).

Stand-Alone	**Patients (n)**	**Maneuvers (n)**	**R^2**	**P**	**Slope (95% CI)**
Standing	6	20	0.5	**0.0009**	1.4 (0.7–2.2)
Lying 10°	6	20	0.4	**0.002**	1.7 (0.7–2.7)
Hyperventilation 10°	6	18	0.51	**0.001**	3.5 (1.7–5.3)
Hypoventilation 10°	6	19	0.4	**0.005**	3.1 (1.1–5.1)
Valsalva 10°	6	16	0.8	**<0.001**	5.7 (3.9–7.5)
Jugular compression 10°	6	18	0.6	**<0.001**	2.0 (1.1–2.9)
Lying 0°	6	20	0.06	0.3	0.7 (-0.8–2.2)
Hyperventilation 0°	6	18	0.02	0.54	0.6 (-0.6–1.1)

Hypoventilation 0°	6	17	0.6	**0.0003**	2.2 (1.2–3.3)
Valsalva 0°	6	15	0.7	**<0.001**	3.2 (1.9–4.6)
Jugular compression 0°	6	18	0.5	**0.002**	2.7 (1.1–4.2)
Lying -10°	6	20	0.2	**0.03**	-1.0(-1.9–0.08)
Shunted			**R^2**	**P**	**Slope (95% CI)**
Standing	13	29	0.2	**0.02**	0.9 (0.2–1.7)
Lying 10°	13	28	0.2	**0.009**	0.8 (0.2–1.4)
Hyperventilation 10°	13	26	0.2	**0.04**	0.8 (0.04–1.6)
Hypoventilation 10°	13	26	0.1	0.09	0.7 (-0.1–1.6)
Valsalva 10°	13	18	0.0003	0.9	0.1 (-3.8–4.1)
Jugular compression 10°	13	26	0.08	0.2	1.5 (-0.6–3.6)
Lying 0°	13	29	0.2	**0.01**	1.1 (0.2–2.0)
Hyperventilation 0°	13	26	0.1	**0.04**	0.8 (0.02–1.5)
Hypoventilation 0°	13	27	0.02	0.5	0.06 (-0.1–0.2)
Valsalva 0°	13	19	0.04	0.4	1.5 (-2.1–5.2)
Jugular compression 0°	13	27	0.04	0.3	0.5 (-0.5–1.5)
Lying -10°	13	27	0.004	0.7	0.1 (-0.7–1.0)

Table 3: Correlation between ICP and AMP in the maneuver protocol in shunted and non-shunted patients.

Correlation between ICP and AMP in the different maneuvers in the stand-alone and in the shunted groups.

An association between age and amplitude and ICP values in both investigated groups was done in order to detect a linear regression. In the lying 10° position, the ICP is increasing with age among shunted patients, while it is decreasing among non-shunted, as well as in lying 10° and 0° hyper- and hypoventilating maneuvers. In the lying 10° jugular compression maneuver, ICP also shows a tendency to increase with age in the shunted population, while there is a stable tendency in the non-shunted population. In the lying 0° position, the amplitude decreases with age in the shunted group, while it increases in non-shunted group. All the changes do not show any statistical significance, however.

Additionally, a correlation between BMI and ICP was analyzed in the population, not showing statistical significance, but the higher the BMI value, the lower was the ICP in the standing and lying 10° positions, in particular in shunted patients. A comparison between BMI and difference in ICP among standing-lying 0° positions and lying 10°-lying 0° positions revealed a statistically significant difference in the shunted population at the lying -10° position. Nevertheless, the lying position 10° also showed an important correlation between BMI and ICP variations (*Figure 13a and b*).

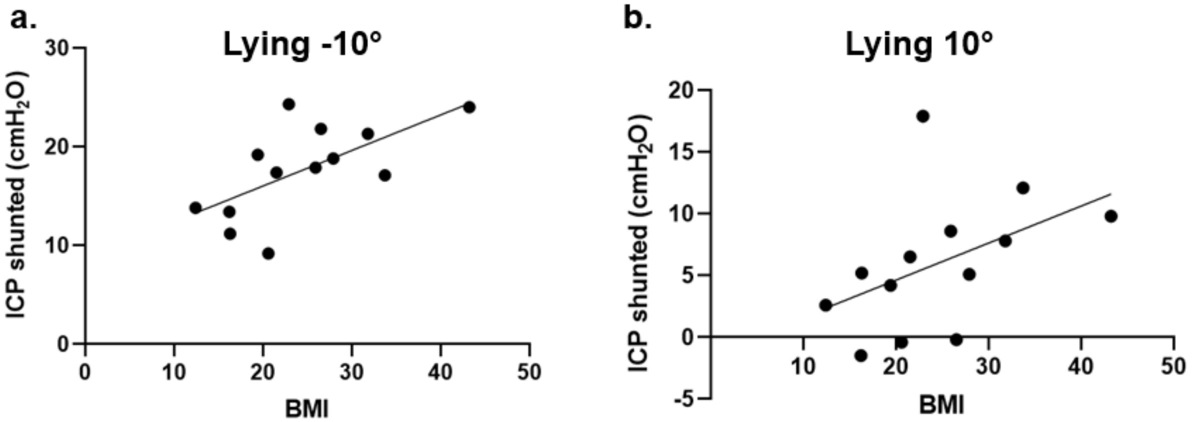
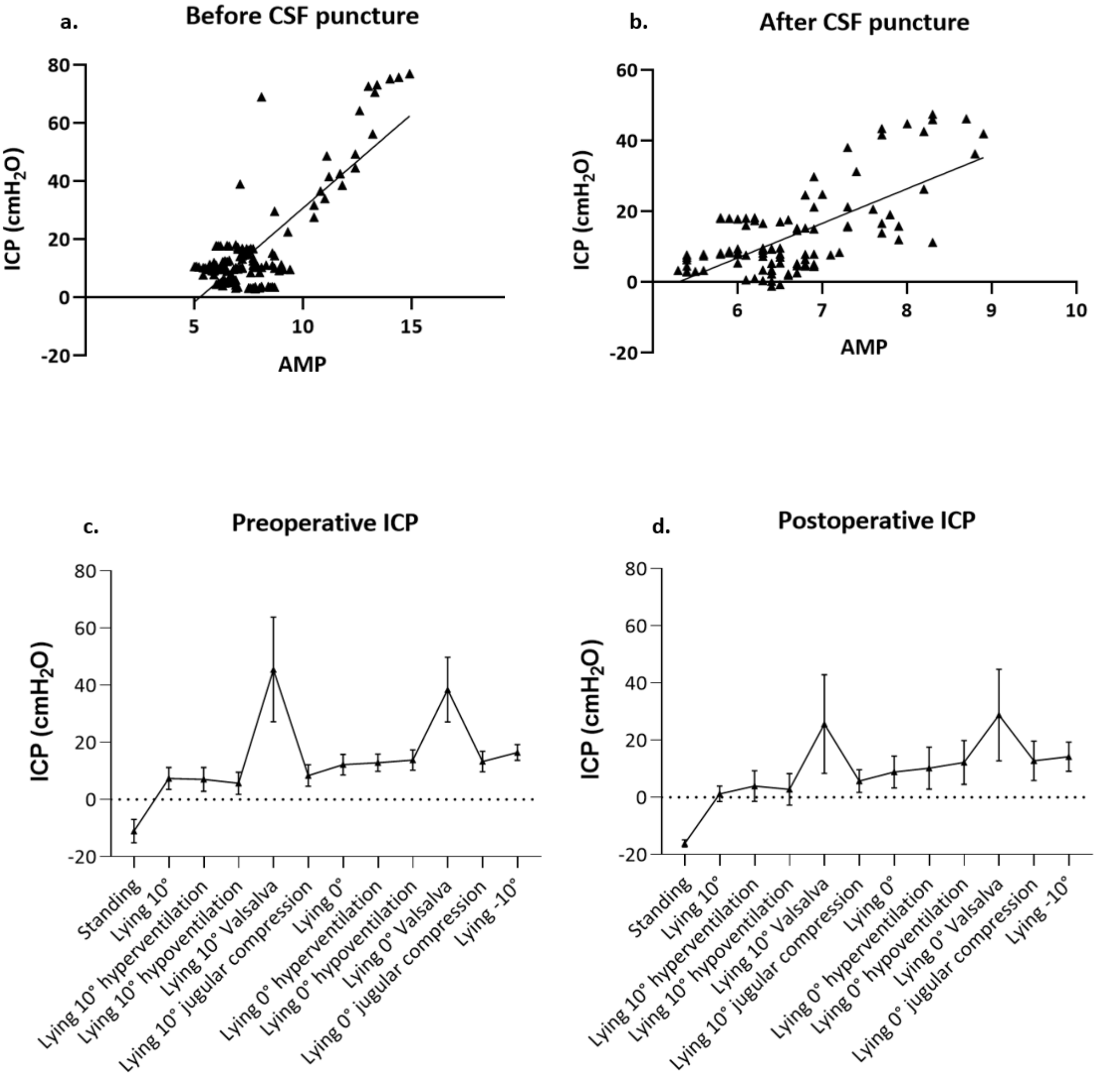


Figure 13: BMI and ICP correlation in shunted patients.

BMI and ICP variations in lying -10° (a.) was revealed to be statistically significant in shunted patients and showed a good correlation in the shunted population also in the lying 10° position (b.).

3.3.1 Case example

After lumbar punctures with an ICP over 30 cmH_2O accompanied by headaches and visual field disturbances, a 17-year-old female patient was admitted into our outpatient clinic with suspected IIH, though lacking papilledema and MRI signs of increased ICP. Because of the side effects of the high doses of acetazolamide (1.5 g/d), a shunting necessity had to be ruled out. An attention deficit hyperactivity disorder partially complicated the definitive diagnosis, and we indicated the implantation of a stand-alone SR in order to proceed with ICP measurements with our maneuver protocol. The ventricular catheter placement was performed through a guide in the right frontal horn and was anchored to the skull at the burr hole through the SR, which was closed with a blind connector at the other extremity. The follow-up was then carried on for three months, and the tICPMs confirmed the clinical suspect of IIH, with high ICP and AMP values in the maneuvers and positions. SR tapping tests were also performed three times, with extraction of ~10ml CSF, and the patient also described a regression of the headaches and of the visual issues. TICPM revealed a reduction of both ICP and AMP (*Figure 14a and b*). With those observations we suggested the implantation of a ventriculo-peritoneal shunt: a M.blue valve with 15/+30cmH2O opening pressures was used, and it was connected with the distal end of the SR. Acetazolamide therapy was decreased and then interrupted. The patient is still on a 6-months follow-up, presenting an amelioration of the preoperative clinical disturbances. Values measured before and after the shunt show both in the ICP values (*Figure 14c and d*) as well as in the AMP values (*Figure 14e and f*) a significant reduction. The correlation between ICP and AMP was also found to be reduced after shunt implantation in a significant way.



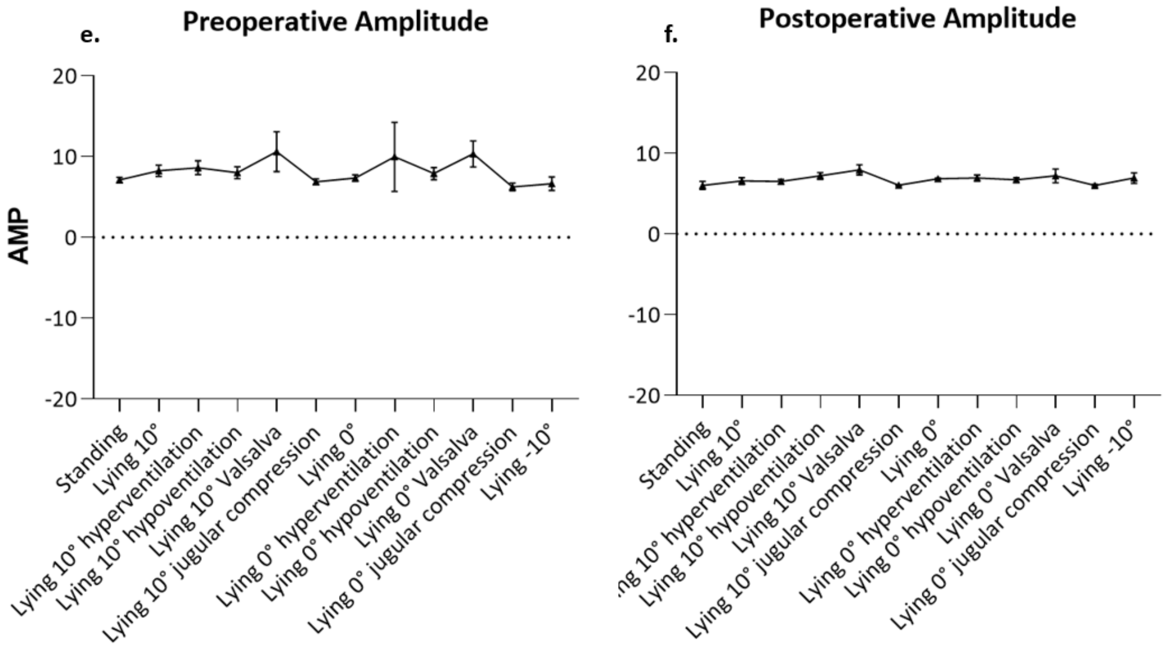


Figure 14: Clinical case.

Clinical example illustrating the case of a 17-year-old female patient diagnosed with IIH, but presenting with untypical signs of increased ICP. After implanting a stand-alone SR, a significant reduction in the ICP and AMP values was observed after SR puncture (a, b), together with a subjective clinical improvement. Those observations led to the implantation of a ventriculoperitoneal shunt, after which tICPMs were further investigated, revealing a significant response of ICP (c, d) and AMP (e, f).

4 Discussion

4.1 Reproducibility and limitations of telemetric devices

Laboratory measurements in the reconstructed system, simulating a water column at variable heights enabled us to establish the differences between the SR, a manometer, and the Raumedic system, which was also connected to the ICM+ software. As already stated, the difference in the two measurement systems was found to range from a minimum of 0.3 cmH_2O (0.2 mmHg) to a maximum of 6.8 cmH_2O (5.0 mmHg). This huge difference may be due to temperature oscillations during measurements. In two out of six devices, the difference was statistically significant. In general, the values obtained with the two pressure detection systems were comparable, thus showing a good reliability of the SR in a laboratory setting. Keeping the temperature constant in the system appears to be a critical point of concern, in order to avoid measurement errors and unreliability in an experimental setting (56). This issue is of lesser importance *in vivo*, but should not be underestimated in, for example, patients with temperature dysregulations.

In the same way, it was also possible to apply the double measurement in a small subgroup of patients that hosted an SR for more than one year. This allowed assessment of the ***long-term reliability*** of the values measured from the SR. A good agreement was found between the long-implanted sensors with the standard method. The setting of the "zero" was important for these measurements: in fact, the zero on the EVD has to be placed at the level of the sensor and not, as usually done with patients with an EVD, at the external auditory meatus. This is because the detection has to be performed considering that the column of water does not burden the sensor and, in order to obtain comparable results, it has to be applied and considered also for the EVD measurement. The big difference of standing in comparison to the other body positions may be due to this discrepancy, which has been an underestimated and barely mentioned parameter in the literature until now (56).

4.2 State-of-the-art tICPM methods

Already apparent from the published data, but also from the further analysis of them described here, it appears mandatory to distinguish shunted patients from non-shunted patients; not only due to the obvious pathophysiological differences, but also because of the behavior of ICP and ICP-related parameters. To date, there has been no literature describing a "stand-alone" population, while studies have been done about shunted patients hosting SRs and/or P-tel devices. A schematic view on the state-of-the-art in the literature is described in *Table 4*.

Study	Number of patients	Mean age / age range (years)	tICPM device	Results
Rot et al. (2020)	17	57 / 26–80	SR/P-tel	Comparison of the measured values through the two systems in shunted patients and analysis of the ICP-changes related to the body position
Antes et al. (2018)	25	53.6 ± 20.7	SR/P-tel	70% improvement after tICPM-tailored shunt adjustment – clear difference among upright and lying postures
Norager et al. (2018)	119	30 / 2–80	P-tel	Clinical and technical aspects
Pedersen et al. (2018)	21 adults (>18 years); 14 children	Adults: 18–85 Children: 4–17	P-tel	Age-related ICP decrease in a linear fashion
Barber et al. (2017)	4	4–16	P-tel	Clinical and economic implications, purely pediatric cohort
Erlt et al. (2017)	2	72 / 66–78	SR	Feasibility analysis in shunted patients
Antes et al. (2016)	247	59.3 ± 20.7 / 4–91	P-tel	Technical, clinical, and handling aspects, data analysis
Lilja et al. (2014)	21	28 / 2–83	P-tel	Challenging shunt patients; 1/3 tICPMs indicated surgical shunt revision

Table 4: Literature on tICPM.

Schema of the review of the current literature on tICPM methods in shunted patients.

The SR presents the possibility of being connected to a shunting system as a clear advantage over a P-Tel. On the other hand, P-tel has the advantage to collect long-term and dynamic measurements. At present, the SR offers the opportunity to perform tICPMs in different positions and maneuvers, as described, while P-Tel can also perform longer measurement sessions during movements, such as walking. Measurement frequency is higher for the SR (40 Hz versus 5 Hz), and the implantation time is also longer (3 years versus 3 months). Both systems are accompanied with data analysis software, which, in the case of the P-tel, appears to be more developed in terms of further parameters, such as RAP, AMP or slow waves. From an economic point of view, the SR comes with slightly lower costs in comparison to the P-tel (55), (56), (57), (58). In fact, Norager et al. described costs around €17,380 for the P-Tel versus €15,790 for the SR, including implantation, explantation, and reimplantation surgeries (56).

4.3 Feasibility of tICPM implantation surgery

Our experimental exemplification and the investigated series of patients were numerically limited, and it is therefore difficult to reach a final and definite statement. Nevertheless, it is a starting point for the development of a structured tICPM protocol and collects a number of patients hosting a stand-alone construct. Since following shunted and non-shunted patients with an SR and analyzing their ICP values and other parameters is quite challenging, and the modalities are evolving, the indication for device implantation is reserved to difficult and selected cases. In fact, over the last 10 years among all shunt operations performed in our center, 2.3% involved the use of a tICPM device.

The small number of these procedures and their management may be the cause of the relatively high complication rate observed in our cohort (14.3%). Reservoir and shunt placements are, in general, routine procedures in our institution and, after including SR and P-Tel implantations to the regularly performed procedures, the general complication rate is reduced. Moreover, if complications, such as shunt dysfunctions, are included, the implantation of a tICPM device increases the probability of shunt revision. This is explainable through the low threshold in detecting a shunt dysfunction if ICP is measured and considered as a clinical parameter.

tICPM-tailored shunt adjustments brought a surgical revision of the shunt in 20% of the patients, in accordance to current literature data (59), (60).

The already analyzed pros and cons of the SR over the P-tel have considered structural, technical, and also economic factors (56). Particular consideration must be given to the fact that the pressure is measured at the tip of the intraparenchymal catheter in the case of the Raumedic device, while the SR is located extracranially. This may mean that pressure values might be lower when an SR is used and that pressure variations might be detected in the vertical position. Contralateral implantation side, limited certification time, lower registration frequency, and the impossibility to perform a CSF sample collection have been issues described in the literature concerning the P-tel device (61), (62), (63), (64). However, capable and reliable analysis software favor it, even though a more advanced analysis tool is still actively being developed for the SR, as attested by our initial experience.

4.4 tICPM-tailored shunt adjustments

Among the shunted groups in both of our series, SR-implantation surgery was indicated to better manage the shunting system function. In our center, the use of valve systems with a differential and gravitational pressure unit are routinely employed (Miethke, Potsdam, Germany) (59) as the pediatric population is particularly prone to develop overdrainage, due to the hydrostatic forces in the vertical position adding to the draining force of the shunting system. With the additional work of a gravitational unit, this mechanism is prevented and avoided, and the function of a valve presents no difference in regard to the activity and/or position of a patient and, of course, to their age. In fact, since different age groups have different body pressures as well as positional and activity habits, an adjustment protocol for the valve system is recommended. The adjustments for differential pressure units are around 10 cmH_2O for children under 1 year of age and gradually higher for older patients, and for gravitational units, 25 cmH_2O for children under 2 years of age and 30 cmH_2O for older subjects (65), (66) (*Table 5*).

Age group (years)		**Differential pressure unit**	**Gravitational unit**
Infants	<1	5–10 cmH_2O	25/30 cmH_2O
Younger children	1–2	8–12 cmH_2O	25/30 cmH_2O
Children	3–12	12–16 cmH_2O	25/30 cmH_2O
Adolescents	13–18	12–16 cmH_2O	25/30 cmH_2O

Table 5: Age-oriented shunt adjustment protocol.

Age-oriented shunt adjustment protocol: body activity and eventual limitations of the motility also have to be considered when implanting and/or adjusting a valve.

As described in the results, tICPM in shunted patients brought, in most cases, the decision for an adjustment of the valve of the gravitational unit towards higher pressures and of the differential pressure unit towards lower pressures. This indicates that the measurements detected an overdrainage with low ICP in the vertical positions and an underdrainage with high ICP in the horizontal positions more frequently.

4.5 Maneuver analysis and parameters evaluation

A standardized measurement and tICPM-analysis procedure has not yet been developed. The present study enabled the systematic acquisition of both ICP and AMP, whose variations were induced in different postural and physiological conditions. The maneuver protocol was developed in order to better investigate possible variations of ICP and AMP among the two groups, and was usable for almost all of our examined populations. The exceptions were small children under 6 years of age, who were not always able to cooperate with ventilation and compression maneuvers. Moderate venous obstruction was reproduced by Valsalva and jugular veins compression at the base of the neck, while intracranial blood volume was influenced by hyper- and hypoventilation maneuvers.

In summary, in standing, lying 10°, and lying 0° positions, the patients with a shunt presented lower values of ICP, while the amplitude ranges appeared to be bigger in the stand-alone population. While a significant change in ICP is observed in both groups, though with differences, the amplitude appears to be constant in the two investigated populations. This is in accordance with the literature, even though there is no study directly comparing the two categories of patients to date (28), (27).

The most relevant changes in ICP were noticed in positional maneuvers, affecting both the shunted and the non-shunted groups, as confirmed in previous studies (31), (29). In general, similarly to previous literature, it is possible to observe the most significant ICP changes between horizontal and vertical postures at a 20° angulation. It is well known and demonstrated by several studies that ICP values in healthy individuals are negative in the upright position (51), (29), (67), (34). In our series, it was possible to observe the same tendency in both the shunted and non-shunted population. The mechanism causing this involves an enhanced hematic outflow from the intracranial compartment to the heart in the orthostatic position, resulting in jugular vein collapse. Shunted patients were observed to have a lower ICP than non-shunted ones. Compression maneuvers, particularly Valsalva, evoked the highest ICP. Additionally, hypoventilation was more effective in increasing the ICP than hyperventilation.

The most significant variations between the shunted and stand-alone groups were seen in a combination of lying 10° position and ventilation maneuvers.

AMP appeared to be more effectively influenced in non-shunted patients applying postural maneuvers and in shunted patients combining postural and venous compression maneuvers. Ventilation maneuvers in lying 10° positions in the stand-alone group and hyperventilation comparing the two groups in examination were particularly effective.

These observations in combination with literature data contribute to define normal ICP in the standing posture as negative (27), (38), with lower values in shunted individuals (53), (25). The ICP is affected by shunt valve adjustments (53, 55, 66), but the clinical implications on the patient may be variable. For this reason, it might be useful to also consider the AMP as an indicator of cerebral compliance (28), (38), (25). On the one hand, tICPM is demonstrated to be an aid in complicated cases (55); on the other hand, it still represents a challenging method concerning data analysis.

ICP values are largely variable, and their fluctuations are only partially correlated with AMP variations. This concept is in accordance with the literature (27), (28). Until now, no published study has described a comparison among a pediatric cohort of shunted and non-shunted patients.

As already stated, AMP changes showed far less variability than ICP. Other authors have described the correlation between these two parameters, more specifically the RAP index, as an indicator of cerebral compliance (21), (68). However, it is still difficult to gain a valuable indication of cerebral compliance: when the ICP rises, the AMP may also show an increase. In having the limitation of short measuring time with tICPM, the advantage of introducing a maneuver protocol in order to detect a change in the ICP/AMP relation may become evident. It also would make it possible to avoid hospital admission and more cumbersome overnight or infusion tests. Nevertheless, it has to be considered that AMP is not only influenced by posture, but also by the cardiac volume and the cerebrovascular resistance (29), (28), (30).

This study depicts for the first time ICP changes in children with and without a shunt system, implementing a venous compression maneuver to postural tests. By performing a Valsalva or a moderate neck compression, it was possible to evoke ICP and AMP variations and put them in correlation to figure out implications on the cerebral compliance. Non-shunted subjects of our study are demonstrated to have more enhanced ICP, statistically significant AMP variations, as well as a correlation between ICP and AMP, when compared to the shunted (*Table 7*).

A similar comparison study in an adult population showed a relevant correlation between ICP and AMP in postural maneuvers and at different times of the day (38). Other authors demonstrated the "normalization" of ICP and AMP after shunting (25), and the effect of shunt adjustments on those parameters in ambulation (30).

In general, we can state that in the stand-alone population, maneuver-related changes are more sensitive to both ICP and AMP changes. This may be explained by those subjects having no system regulating, eventually increased ICP, although the examined population is limited in terms of number, age and pathology.

This work may offer a standardized protocol which may lead the surgeon to diagnose unclear pathological conditions affecting the CSF system after implanting an SR. As an additional diagnostic item, the tapping of the SR and the possibility to compare measurements before and after puncture maneuvers might also support the indication for shunt surgery.

In a presented clinical case, a patient with IIH and no papilledema, though high ICP after lumbar puncture, was implanted with a stand-alone SR and then consecutively measured following our maneuver protocol. Increased levels of ICP and AMP were detected, with a good response after SR puncture. The shunting procedure resulted in a permanent decrease of ICP and AMP. This reduction in both parameters agrees well with an improvement in cerebral compliance, which is ameliorated after shunt placement in comparison to the stand-alone population.

4.6 ICP correlation to age and BMI

In our population no particular correlation was noticed between the age of the patient and the ICP. Additionally, BMI and ICP were not statistically significantly correlated, with the exception of the lying -10° position in the shunted population. This is partially explainable by the larger number of patients in the shunted group, which also hosted a wider spectrum of this biological parameter. Moreover, although the most frequent diagnosis among non-shunted patients was IIH, their median age was lower in comparison to the shunted patients. In the shunted group, the patients diagnosed with IIH typically had a high BMI and an older age, thus matching better with the association of increased ICP and high BMI.

4.7 Conclusion

In conclusion, the SR represents a feasible instrument to measure ICP in an outpatient regimen in challenging hydrocephalus cases and its reliability has been proven to last over time. The implementation of the data analysis software provides the opportunity to compare parameters in different conditions. However, the impossibility until now to perform long-term measurements, as in some animal samples (69), still limits the potential use of the tool, e.g., for overnight studies, infusion tests, or for prolonged tailored measuring sessions. The relationships between raised ICP and AMP variations might reveal a disturbance of the cerebral compliance. Postural maneuvers in combination with compression maneuvers, such as mild jugular vein obstruction, may be used instead of a more invasive and expensive infusion test on outpatient regimens. The same applies for reservoir tapping.

Further investigations need to focus and elaborate on the feasibility of those tests and maneuvers in a more extensive and heterogeneous way, in order to be able to propose them as a valuable alternative to classic long-term ICP studies, such as overnight and infusion tests.

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6 Eidesstattliche Versicherung

„Ich, Valentina Pennacchietti, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Telemetrische Messung des intrakraniellen Drucks in der pädiatrischen Neurochirurgie“ – „Telemetric intracranial pressure monitoring in pediatric neurosurgery“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum 13.02.2023 Unterschrift

7 Anteilserklärung an erfolgten Publikationen

Valentina Pennacchietti hatte folgenden Anteil an den folgenden Publikationen:

1) ***Pennacchietti V, Prinz V, Schaumann A, Finger T, Schulz M, Thomale U-W, Single center experiences with telemetric intracranial pressure measurements in patients with CSF circulation disturbances, Acta Neurochirurgica, (Wien). 2020 Oct;162(10):2487-2497***. Doi: 10.1007/s00701-020-04421-7. Epub 2020 Jun 3. PMID: 32495080.

   Beitrag im Einzelnen:

   - Konzeption, Gestaltung und Studienplanung (Kooperation mit Prof. U.-W. Thomale);
   - Durchführung der Datenerhebung, insbesondere retrospektive Erhebung von den Daten bezüglich der zwei examinierten Patientengruppen (Neurovent- P-Tel-implantierten und der SR-implantierten Patienten); (Kooperation mit Dr. med. A. Schaumann);
   - Statistische Auswertung der Daten und der Ergebnisse, insbesondere Vergleich von den obengenannten 2 Populationen und der Untergruppe der „stand-alone“ Patienten, Evaluation der „survival“ Kurven bezüglich der tICPM Geräte und der Shuntsysteme in den untersuchten Gruppen mithilfe der Programme Excel und Graph Pad Prism (inklusiv Entwicklung von Graphen); (Kooperation mit Prof. U.-W. Thomale);
   - Selbstständige Erstellung aller Anteile des Manuskriptes und Literaturrecherche (Korrektur durch Prof. U.-W. Thomale);
   - Korrekturen im Review – Verfahren (Federführung des Reviewverfahrens durch Prof. U.-W. Thomale);

     - Verantwortung für folgende Anteile des Papers: Einführung, Materialien und Methoden, statistische Auswertung, Ergebnisse, Diskussion und Literatur.

Pennacchietti V, Schaumann A, Thomale U-W, Maneuver protocol for outpatient telemetric intracranial pressure monitoring in hydrocephalus patients, Chid´s Nervous System. 2022 Sep 13. Doi: 10.1007/s00381-022-05659-5. Online ahead of print.

Beitrag im Einzelnen:

- Konzeption, Gestaltung und Studienplanung (Kooperation mit Prof. U.-W. Thomale);
- Selbstständige Durchführung der Datenerhebung und Bearbeitung, insbesondere selbständige Durchführung der protokollgemäßen tICPMs in den Patientengruppen und

weitere Bearbeitung der relativen Dateien (Export der Dateien durch das Programm ICPicture);

- Statistische Analysen, insbesondere Vergleich der Amplituden- und ICP-Dateien unter den Patientengruppen mit dem Programm Excel und Graph Pad Prism und Entwicklung von dazugehörigen Graphen (Überprüfung durch Prof. U.-W. Thomale);
- Selbstständige Erstellung aller Anteilen des Manuskriptes und Literaturrecherche (Korrektur durch Prof. U.-W. Thomale);
- Einreichen des Papers und Korrekturen im Review – Verfahren (Federführung des Reviewverfahrens durch Prof. U.-W. Thomale);
- Verantwortung für folgende Anteile des Papers: Einführung, Materialien und Methoden, statistische Auswertung, Ergebnisse, Diskussion und Literatur.

13.02.2023

Unterschrift, Datum und Stempel des erstbetreuenden Hochschullehrers

Unterschrift der Doktorandin

8 Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht

9 List of publications

- F. Zenga, G. Pecorari, I. Baudracco, **V. Pennacchietti**, A. Berton, A. Ducati: Adenomi ipofisari PRL-secernenti: quale spazio per la chirurgia? L'Endocrinologo. 2013, dicembre, vol. 14, n.6.
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- ***Pennacchietti V,*** Schaumann A, Thomale U-W, Maneuver protocol for outpatient telemetric intracranial pressure monitoring in hydrocephalus patients, Child´s Nervous System. 2022 Sep 13. Doi: 10.1007/s00381-022-05659-5. Online ahead of print.

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11 Statistical certification

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Bescheinigung

Hiermit bescheinige ich, dass Frau Valentina Pennacchietti innerhalb der Service Unit Biometrie des Instituts für Biometrie und Klinische Epidemiologie (iBikE) bei mir eine statistische Beratung zu einem Promotionsvorhaben wahrgenommen hat. Folgende Beratungstermine wurden wahrgenommen:

- Termin 1: 18.03.2021
- Termin 2: 29.03.2021
- Termin 3: 12.04.2021

Folgende wesentliche Ratschläge hinsichtlich einer sinnvollen Auswertung und Interpretation der Daten wurden während der Beratung erteilt:

- Anwendung verbundener und unverbundener t-Tests, nötige Anordnung der Daten in GraphPadPrism
- Korrelation, Regression, graphische Darstellung von Zusammenhängen metrischer Variablen; overlap-Grafiken mit zwei Gruppen zum Erkennen von unterschiedlichen Korrelationsmustern, Interpretationder Grafiken
- Behandlung von Mehrfachmessungen durch Gewichtung
- Vergleichsmöglichkeiten für verbundene Daten

Diese Bescheinigung garantiert nicht die richtige Umsetzung der in der Beratung gemachten Vorschläge, die korrekte Durchführung der empfohlenen statistischen Verfahren und die richtige Darstellung und Interpretation der Ergebnisse. Die Verantwortung hierfür obliegt allein der Promovierenden. Das Institut für Biometrie und klinische Epidemiologie übernimmt hierfür keine Haftung.

Datum: 07.12.2021

Name des Beraters/ der Beraterin: Dr. Dörte Huscher

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