Summary of doctoral dissertation
Assessment of cerebral compliance based on analysis of the shape of intracranial pressure pulse waveform

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Patient management in modern neurocritical care units relies heavily on brain multimodal monitoring, including secondary indices describing the homeostasis of the nervous and circulatory systems. Interdisciplinary approaches combining the field of medicine with technological advances play a crucial role in improving patient care through development of novel diagnostic tools, predictive models, and therapeutic strategies. Still, despite decades of study, our understanding of the pressure–volume relationships in the intracranial space, and consequently, available management approaches for treatment of intracranial pathologies, remain incomplete. Since Lundberg's seminal 1965 paper on continuous intracranial pressure (ICP) monitoring, various attempts have been made to precisely characterise traumatic brain injury (TBI) patients and predict impending deterioration of their condition. Cerebrospinal compliance, defined as the ratio of change in volume to change in pressure and describing the cerebrospinal system's ability to buffer changes in volume without potentially threatening increases in pressure, is often considered as a promising tool to improve patient care. Diminished compliance indicates that even a relatively small volume increment may produce disproportionately large increase in ICP. In turn, ICP elevation is a hazardous condition as it may lead to restricted cerebral blood flow or mechanical damage to the brain. Therefore, identification of TBI patients at risk of increases in ICP before a hypertension episode occurs could allow for early therapeutic intervention and help prevent the adverse effects from taking place, in contrast to currently employed protocols where ICP elevation is managed rather than averted. Compliance could also complement the current methods of assessing cerebrospinal fluid dynamics in hydrocephalus, as in this group evaluation of the patient's volume–pressure compensation is included in the decision process for shunt implantation.

However, none of the methods of compliance estimation suggested to date have been successfully incorporated into routine clinical practice. The earliest proposed approaches, dating back to the 1970s, are based on manipulation of intracranial volume through either bolus injection or constant rate infusion of fluid. Although these techniques remain the primary method of direct compliance assessment, their clinical applicability is limited due to the fact that they are additionally invasive, can only be performed intermittently, and may be too dangerous in patients already at risk of uncontrolled ICP elevation. Imaging techniques such as magnetic resonance imaging can be used to measure changes in intracranial volume without external manipulation, but they cannot be employed in continuous monitoring, and the measurements are still relatively expensive. On the other hand, it has been shown in the 1980s that information on cerebrospinal compliance may be derived indirectly through analysis of the ICP pulse waveform, i.e. the shape of the signal over a single cardiac cycle. In normal conditions, the waveform contains three characteristic local maxima, called peaks P1, P2, and P3. As compliance decreases and ICP increases, the height of the second peak increases to a greater extent than the other two. Therefore, it has been suggested that the height ratio of the first two peaks may be used to estimate compliance. However, the ICP pulse waveform presents a large variety of complex shapes, changing both over time and between subjects, which makes peak detection a highly challenging task. The solutions proposed so far have not gained widespread acceptance or been introduced to clinical practice, and the validity of the peak ratio as a measure of compliance has never been conclusively proven. Moreover, it has been shown that at very high ICP the pulse waveform becomes rounded and the peaks are no longer distinguishable, which causes peak detection to fail. More recently, a different approach was proposed. In this technique, four characteristic shapes of the ICP pulse waveform, roughly reflecting the changing configuration of peaks associated with changes in compliance, were described using radial basis function approximation and classified using an artificial neural network. A study in hydrocephalus patients showed that automatic morphological classification is a promising new tool for indirect compliance estimation, although further results using this method have not been published.

Building upon the groundwork laid down in previous studies, this dissertation addresses the problem of compliance estimation through analysis of the shape of ICP pulse waveform. Firstly, the peak ratio approach is compared with other known methods of compliance estimation during controlled changes in mean ICP in order to confirm the validity of using ICP pulse morphology as an indirect measure of cerebrospinal compliance. Secondly, the existing body of knowledge on compliance-related changes in ICP pulse waveform morphology is integrated with new developments in the field of machine learning in order to propose a novel solution for continuous monitoring of compliance. As ICP measurement in TBI patients is usually performed over several days, producing recordings that contain hundreds of thousands of individual pulses, assessment of ICP pulse morphology is already a challenging task due to the sheer volume of generated data. Taking that difficulty into account, the abovementioned pulse shape classification approach is combined for the first time with deep learning algorithms that rose to prominence in recent years as a tool for big data analysis. A deep neural network model, capable of classifying characteristic shapes of the ICP pulses and simultaneously detecting artefactual waveforms is developed, and a new index describing the ICP pulse morphology, termed pulse shape index (PSI), is introduced. It is demonstrated through a series of studies in patients with intracranial pathologies that features of the ICP pulse waveform can be used to monitor cerebrospinal volume compensation continuously and that assessment of the shape of the ICP pulse waveform using deep learning has the potential to improve neurocritical care management of TBI patients.

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- **Kazimierska, A.**, Kasprowicz, M., Czosnyka, M., Placek, M. M., Baledent, O., Smielewski, P., and Czosnyka, Z. (2021). Compliance of the cerebrospinal space: comparison of three methods. *Acta Neurochirurgica*, 163(7):1979–1989.
- Mataczyński, C.*, **Kazimierska, A.***, Uryga, A., Burzyńska, M., Rusiecki, A., and Kasprowicz, M. (2022). End-to-end automatic morphological classification of intracranial pressure pulse waveforms using deep learning. *IEEE Journal of Biomedical and Health Informatics*, 26(2):494–504. *joint first authorship
- **Kazimierska, A.**, Uryga, A., Mataczyński, C., Burzyńska, M., Ziółkowski, A., Rusiecki, A., and Kasprowicz, M. (2021). Analysis of the shape of intracranial pressure pulse waveform in traumatic brain injury patients. In *43rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC 2021)*, pages 546–549, Mexico. IEEE.

and are part of unpublished works:

- **Kazimierska, A.**, Uryga, A., Mataczyński, C., Pelah, A., Czosnyka, M., Kasprowicz, M., and the CENTER-TBI high resolution sub-study participants and investigators. The shape of intracranial pressure pulse waveform in traumatic brain injury: a CENTER-TBI study. Submitted to *Scientific Reports* journal in March 2022.
- Mataczyński, C., **Kazimierska, A.**, Uryga, A., Kasprowicz, M., and the CENTER-TBI high resolution sub-study participants and investigators. Intracranial pressure pulse morphology-based definition of life-threatening intracranial hypertension episodes. Accepted for publication at the *44th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC 2022)* (planned date: 11–15 July 2022; Glasgow, UK).

This dissertation includes six chapters.

Chapter 1 presents a review of ICP monitoring and the pressure–volume relationships in the cerebrospinal space, including the relevant physiology and clinical significance of compliance assessment, as well as an overview of the estimation methods proposed so far with emphasis on analysis of the ICP pulse waveform.

In Chapter 2, the aims of this thesis and the research hypotheses are outlined.

Chapter 3 discusses a comparison study in hydrocephalus patients between the 'gold standard' method of compliance estimation based on external manipulation of the intracranial volume and two indirect methods: an approach based on analysis of characteristic features of the ICP pulse waveform and another based on evaluation of changes in ICP pulse pressure in relation to changes in cerebral blood volume. The results of this study confirm the validity of using the P1/P2 ratio of the ICP pulse waveform as a measure of relative changes in compliance.

In Chapter 4, the feasibility of using deep learning to automatically classify characteristic shapes of the ICP pulse waveform, and therefore overcome the need for precise peak identification, is discussed. A residual neural network is proposed as a tool for morphological classification of individual ICP pulses and used to assess the potential clinical usefulness of this approach in long-term recordings obtained from TBI patients. The results show that it is possible to classify the ICP pulse waveform using deep neural networks with high accuracy and good generalisation.

Chapter 5 continues the investigation into ICP pulse waveform classification as a potential tool for continuous monitoring of the cerebrospinal volume compensation. A new index describing the ICP pulse waveform, PSI, is introduced and investigated in a large, multi-centre cohort of TBI patients. The relationship between PSI and other ICP-derived metrics is discussed in relation to the pressure–volume relationships in the cerebrospinal space. The results also show the link between the shape of ICP pulse waveform and outcome after TBI as well as the presence of mass lesions in the brain.

Conclusions of this dissertation along with suggestions for further investigations are presented in Chapter 6.