Morphological analysis of cardiac-related waveforms of signals carrying information about cerebral dynamics

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Summary

Introduction

Cerebral homeostasis is dependent, among other factors, on the efficiency of the brain processes responsible for regulating intracranial pressure, cerebral blood flow and cerebrospinal fluid flow. Arterial blood supplies oxygen and nutrients to nerve cells, while cerebrospinal fluid supplies nutrients, drains metabolic products, and protects the brain from mechanical damage by cushioning vibrations and reducing overloads affecting the skull. High intracranial pressure can lead to reduced cerebral blood flow, which in turn can result in hypoxia of brain cells. The cerebral autoregulation mechanism prevents this by maintaining a constant cerebral blood flow through the constriction and dilation of cerebral blood vessels within the limited range of cerebral perfusion pressure (the difference between mean arterial blood pressure and intracranial pressure). In clinical practice, intracranial pressure and cerebral blood flow are commonly monitored, and clinical decisions are made based on the interpretation of the mean values of these signals. However, the mean value does not contain information about the dynamics of cerebral processes. Therefore, in order to improve the personalisation of patient therapy in medical intensive care units, multi-parameter monitoring of physiological signals with high sampling frequency is recommended. This allows for the analysis of the entire spectrum of fluctuations contained in the recorded signals. The fluctuations in brain signals can be divided into three categories: those related to respiration, vasomotor waves (which are associated with the active dilation and contraction of cerebral blood vessels, also known as cerebral autoregulation), and waves related to cardiac work. Recent studies have indicated that the signal fluctuations can provide additional information about the patient's state and the dynamics of cerebral processes. Currently, vasomotor fluctuations are most often analyzed in clinical practice. However, with the development of medical signal recording and processing technology, there is growing interest in the morphological analysis of cardiac-related waveforms of signals, such as: intracranial pressure and cerebral blood flow.

Cardiac-related waveforms are systematic oscillations of signals that are associated with cyclic heart rate. Cardiac-related waveforms of cerebral blood flow and intracranial pressure are linked. With each cardiac cycle, arterial blood flows into the closed intracranial space, which is bounded by the bones of the skull, and venous blood flows out, where the outflow of blood is characterized by smaller oscillations than its inflow. The inflowing blood exerts pressure on the walls of cerebral blood vessels, causing fluctuations in the diameter of these vessels, and consequently fluctuations of the volume of cerebral blood. These changes affect brain tissues and cerebrospinal fluid by modulating the cardiac-related waveform of intracranial pressure. The shape of the cardiac-realated waveform of intracranial pressure is also influenced by the mechanoelastic properties of the craniospinal space and cerebrospinal compliance, which describes the system's ability to buffer volume changes. Under conditions of high cerebrospinal compliance, an increase in intracranial volume results in a slight increase in the mean value of intracranial pressure. In contrast, when the compliance is low, the same increase in intracranial volume causes a significant increase in the value of mean intracranial pressure. This relationship is described by the pressure-volume curve.

Cardiac-related waveforms are also affected by pathologies, such as normal pressure hydrocephalus or traumatic brain injury, as well as by hemodynamic alterations, such as intracranial pressure plateau waves (a notable increase in intracranial pressure resulting from cerebral blood vessel dilatation in response to a decrease in arterial blood pressure) and hypocapnia (a reduction in intracranial pressure resulting from cerebral blood vessel constriction due to decrease in $PaCO_2$). The following issues were addressed in this thesis: 1) how hemodynamic changes affect the times of occurrence of characteristic local extremes of cardiac-related intracranial pressure and cerebral blood flow velocity waveforms, 2) whether an estimation of cerebral compliance is possible by concurrent analysis of cardiac-related intracranial pressure and cerebral blood flow velocity waveforms, 3) whether analysis the cardiac-related waveforms of the cerebral blood flow velocity signal may be useful in the diagnosis of normal pressure hydrocephalus, 4) whether changes in cerebral blood volume have a dominant effect on the shape of the cardiac-related intracranial pressure waveform during intracranial pressure plateau waves.

Results

In this study the morphologic features of the cardiac-related waveforms of intracranial pressure and cerebral blood flow velocity were analyzed in the context of the times of occurrence of the three characteristic local extremes of these waveforms. The intracranial pressure and cerebral blood flow velocity signals were recorded in patients with traumatic brain injury who were hospitalized at Addenbrooke's Hospital in Cambridge, UK. The recordings were analyzed during the occurrence of hemodynamic changes and at the steady baseline prior to the change (without sudden changes in the average values of the signals). The hemodynamic changes were related to the spontaneous changes linked with dilatation of cerebral blood vessels, which resulted in a significant increase in intracranial pressure in response to a sudden drop in arterial blood pressure (intracranial pressure plateau waves) and to controlled changes associated with the vasoconstriction, which resulted in a decrease of intracranial pressure in response to an increased minute tidal volume (hypocapnia). A number of significant changes were observed in the appearance times of the local extremes of cardiac-related intracranial pressure and cerebral blood flow velocity waveforms. Of these, the most noteworthy observation was an increase in the appearance time of all three local extremes of the non-invasively measured cerebral blood flow velocity during the increases in mean intracranial pressure. These results confirmed the first hypothesis of this thesis: **Hemodynamic changes influence the appearance times of local extremes of cardiac-realted cerebral blood flow velocity and intrecranial pressure waveforms in patients with traumatic brain injury.** The results were published in (Ziółkowski et al., 2023b). The apperance times of local extremes of cardiac-related waveforms of cerebral blood flow velocity has not previously been analysed in the context of changes in intracranial pressure. Consequently, the present study contributes to the development of knowledge regarding the morphology of these waveforms. Furthermore, the results suggest that the analysis of the times of appearance of local extremes of the cardiac-related cerebral blood flow velocity waveform may be useful for non-invasive detection of increases in intracranial pressure.

Subsequently, a simultaneous analysis of changes in the shape of cardiac-related intracranial pressure and cerebral blood flow velocity waveforms was conducted in patients suspected with normal pressure hydrocephalus, who were hospitalized at Addenbrooke's Hospital in Cambridge, UK. A novel parameter, RPS (ratio of pulse slopes), was developed, representing the ratio of the slopes of the ascending part of cardiac-related waveforms of intracranial pressure and cerebral blood flow velocity. This parameter can be automatically calculated during a measurement and its interpretation is intuitive and unambiguous. RPS takes values in the range of 0 to 1. A value close to 1 indicates high compliance, while values below 1 indicate reduced compliance. It was demonstrated that changes in RPS values reflect the state of cerebrospinal compensatory reserves even before the infusion test is performed. This implies that no additional volume manipulation is required to determine the cerebrospinal compliance. Furthermore, a decrease in the value of the RPS was observed during injection of an additional volume of saline solution into the craniospinal space. This suggests that the parameter is a useful tool for continuous monitoring of changes in the compliance, as it reflects the state of compensatory mechanisms. The second hypothesis of the present study was thus confirmed: **The analysis of the interrelationship between the cardiac-related waveforms of cerebral blood flow velocity and intracranial pressure allows for the assessment of cerebrospinal compliance without the need for an additional invasive procedure involving manipulation of craniospinal volume.** Furthermore, RPS was compared with other parameters known from the literature to be related to cerebrospinal compliance. It was observed that RPS exhibited the highest correlation (of all parameters analyzed) with elasticity (inverse of the compliance) calculated from the results of infusion tests. These results was published in (Ziółkowski et al., 2021) and presented at the international scientific conference Hydrocephalus2021, The 13th Annual 2021 Meeting of the Hydrocephalus Society.

The results of existing studies indicate that patients with normal pressure hydrocephalus often exhibit impaired cerebral blood flow. In light of these observations, the dissertation included an analysis of the waveform of cerebral arterial blood volume, estimated using a mathematical model of cerebral blood circulation and a noninvasively measured cerebral blood flow velocity signal. The study utilized two databases of signals: one recorded in patients with suspected normal pressure hydrocephalus who were hospitalized at Addenbrooke's Hospital in Cambridge and another recorded in healthy volunteers as part of projects conducted at the Wrocław University of Technology in the Neuroengineering Laboratory of the Department of Biomedical Engineering. The groups were age-matched. A novel method was proposed to quantitatively describe the waveform of cerebral arterial blood volume as a similarity to a triangle constructed by three points: 1) the beginning of the waveform, 2) the maximum of the waveform, and 3) the end of the waveform. A total of 27 parameters were defined and their values were calculated for patients with hydrocephalus symptoms and healthy volunteers. Significant differences were observed between groups for 18 parameters. A decision tree classifier was used to identify the parameter that most effectively distinguished patients suspected with hydrocephalus from healthy subjects. This parameter is the mean distance between the ascending slope of the waveform and the left arm of the triangle. This distance was smaller for subjects with hydrocephalus symptoms, manifesting as a "flattening"of the rising slope of the cerebral arterial blood volume waveform (the slope resembles the segment – arm of the triangle). This confirmed the third hypothesis of this thesis: **The morphology of cardiac-related changes in cerebral arterial blood volume, estimated from the cerebral blood circulation model using transcranial Doppler ultrasonography, differs between healthy volunteers and patients with normal pressure hydrocephalus.** The results was published in (Ziółkowski et al., 2023a) and presented at the international scientific conference Hydrocephalus2023, the 15th Meeting of the Hydrocephalus Society, Hamburg, Germany.

The objective of the last analysis was to determine whether alterations in cerebral blood volume influence the morphology of the cardiac-related intracranial pressure waveform. For the purpose of this study, intracranial pressure and cerebral blood flow velocity signals were analyzed during the plateau waves in patients with traumatic brain injury who were hospitalized at Addenbrooke's Hospital in Cambridge. The widely accepted mechanism for the increase in intracranial pressure during plateau waves is the dilatation of cerebral blood vessels in response to a vasodilatory stimulus (e.g., a sudden drop in arterial blood pressure) to maintain a constant flow of cerebral blood. Furthermore, during a plateau wave, there is an increase in the compliance of cerebral arterial bed, a decrease in cerebrospinal compliance, and a deformation of the cardiac-related intracranial pressure waveform. During the plateau wave, cerebral blood vessels effectively dilatate and contract in response to changes in cerebral blood volume. This results in alterations to the total craniospinal volume, which in turn influences the intracranial pressure waveform. Cardiac-related cerebral arterial blood volume waveforms were estimated, as in previous studies, using a mathematical model of cerebral blood circulation and cerebral blood flow velocity signal. A difference index betwen the waveforms of the pressure and the volume was proposed as the sum of the absolute differences between consecutive samples of synchronized waveforms. The results of the perfomed analyses indicates that the waveform of intracranial pressure becomes similar to the waveform of cerebral arterial blood volume during episodes of plateau waves. This result does confirm the fourth hypothesis of this thesis: **Changes in cerebral arterial blood volume have a dominant effect on the cardiac-related intracranial pressure waveform during intracranial pressure plateau wave in patients with traumatic brain injury.** These results was described in (Ziółkowski et al., 2024) and presented at the international scientific conference ICP2022, 18th International Symposium on Intracranial Pressure and Brain Monitoring, Cape Town, South Africa.

Conclusion

In the present study, the methods and research tools were developed for morphological analysis of cardiac-related waveform of signals that carry information about cerebral processes, such as intracranial pressure and cerebral blood flow velocity. The study analyzed the temporal changes in the appearance of local extremes characteristic of these waves during hemodynamic alterations associated with changes in intracranial pressure. The morphological relationships between intracranial pressure waves and cerebral blood flow velocity were also analyzed, which led to the development of a new index of cerebrospinal compliance (RPS). The primary advantage of this parameter is that compliance can be monitored without inducing volumetric changes. Furthermore, RPS is calculated in the time domain, which, in contrast to spectral parameters, makes this parameter resistant to errors resulting from variations in heart rate, the presence of respiratory and slow waves in physiological signals, and other hemodynamic changes that affect the mean value and variance of the signals. Furthermore, a novel approach for the analysis of non-invasively estimated cerebral arterial blood volume waveforms is proposed and demonstrated to may have a clinical applications in the diagnosis of normal pressure hydrocephalus. It was demonstrated that alterations in cerebral arterial blood volume have a dominant influence on the shape of the cardiac-related intracranial pressure waveform during plateau waves. This observation may be utilized in clinical practice for the non-invasive identification of intracranial pressure alterations. However, the results presented in this paper are from analyses performed on small study groups, and thus further studies are needed to verify the presented results and validate the proposed methods on other diseases.

The author of this thesis hopes that the results of the study will contribute to the state of knowledge about the morphology of cardiac-related waveforms of signals carrying information about cerebral processes and the proposed methods and research tools will be useful in the diagnosis and treatment of patients with disorders of cerebral fluid circulation, as well as in supporting physicians in making therapeutic decisions.

Bibliography

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