Open access • Journal Article • DOI:10.1088/1361-6579/ABB145

RAQ: a novel surrogate for the craniospinal pressure-volume relationship.

Andreas Spiegelberg, Matthias Krause, Juergen Meixensberger, Vartan Kurtcuoglu

Institutions: University of Zurich

Published on: 05 Oct 2020 - Physiological Measurement (IOP Publishing)

RAQ: a novel surrogate for the craniospinal pressure-volume relationship

Spiegelberg, Andreas ; Krause, Matthias ; Meixensberger, Juergen ; Kurtcuoglu, Vartan

Abstract: OBJECTIVE The intracranial pressure-volume relation contains information relevant for diagnostics of hydrocephalus and other space-occupying pathologies. We aimed to design a noise-resilient surrogate for this relationship that can be calculated from intracranial pressure (ICP) signals. APPROACH The new surrogate, termed respiratory amplitude quotient (RAQ), characterizes the modulation of the cardiac pulse wave amplitude by the respiratory wave in the ICP time course. RAQ is defined as the ratio of the amplitude of the respiratory wave in the ICP signal to the amplitude of the respiration-induced variation in the course of the cardiac pulse wave amplitude. We validated the calculation of RAQ on synthetically generated ICP waveforms. We further extracted RAQ retrospectively from overnight ICP recordings in a cohort of hydrocephalus patients with aqueductal stenosis, age 55.8 ± 18.0 years, and a comparison group with hydrocephalus diagnosed by morphology in MRI, but not responsive to either external lumbar drainage or ventriculo-peritoneal shunting, age 72.5 ± 6.1 years. RAQ was determined for the full recordings, and separately for periods containing B-waves. MAIN RESULTS We found a mean difference of less than 2% between the calculated values of RAQ and the theoretically determined equivalent descriptors of the synthetic ICP waveforms. In the overnight recordings, we found significantly different RAQ values during B-waves in the aqueductal stenosis (0.86 ± 0.11) and non-responsive hydrocephalus patient groups (1.07 ± 0.20), $p = 0.027$. In contrast, there was no significant difference in other tested parameters, namely pressure-volume index, elastance coefficient, and resistance to outflow. Neither did we find significant difference when considering RAQ over the full recordings. SIGNIFICANCE Our results indicate that RAQ may function as a potential surrogate for the intracranial pressure-volume relation.

DOI: https://doi.org/10.1088/1361-6579/abb145

RAQ – A novel surrogate for the craniospinal pressure-volume relationship

Andreas Spiegelberg[1,*], Matthias Krause[2], Juergen Meixensberger[2], Vartan Kurtcuoglu[1,3,*]

[1] University of Zurich, The Interface Group, Institute of Physiology, Switzerland
[2] Universitaetsklinikum Leipzig AoeR, Klinik und Poliklinik für Neurochirurgie, Germany
[3] University of Zurich, Zurich Center for Integrative Human Physiology and Neuroscience Center Zurich, Switzerland

* Corresponding authors: University of Zurich, Institute of Physiology, Winterthurerstrasse 190, 8057 Zurich, Switzerland, andreas.spiegelberg@uzh.ch, vartan.kurtcuoglu@uzh.ch

Abstract

Objective: The intracranial pressure-volume relation contains information relevant for diagnostics of hydrocephalus and other space occupying pathologies. We aimed to design a noise-resilient surrogate for this relationship that can be calculated from intracranial pressure (ICP) signals.

Approach: The new surrogate, termed respiratory amplitude quotient (RAQ), characterizes the modulation of the cardiac pulse wave amplitude by the respiratory wave in the ICP time course. RAQ is defined as the ratio of the amplitude of the respiratory wave in the ICP signal to the amplitude of the respiration-induced variation in the course of the cardiac pulse wave amplitude. We validated the calculation of RAQ on synthetically generated ICP waveforms. We further extracted RAQ retrospectively from overnight ICP recordings in a cohort of hydrocephalus patients with aqueductal stenosis, age 55.8 ± 18.0 years, and a comparison group with hydrocephalus diagnosed by morphology in MRI, but not responsive to either external lumbar drainage or ventriculo-peritoneal shunting, age 72.5 ± 6.1 years. RAQ was determined for the full recordings, and separately for periods containing B-waves.

Main results: We found a mean difference of less than 2 % between the calculated values of RAQ and the theoretically determined equivalent descriptors of the synthetic ICP waveforms. In the overnight recordings, we found significantly different RAQ values during B-waves in the aqueductal stenosis (0.86 ± 0.11) and non-responsive hydrocephalus patient groups (1.07 ± 0.20), p=0.027. In contrast, there was no significant difference in other tested parameters, namely pressure volume index, elastance coefficient, and resistance to outflow. Neither did we find significant difference when considering RAQ over the full recordings.

Significance: Our results indicate that RAQ may function as a potential surrogate for the intracranial pressure-volume relation.

Keywords: Intracranial pressure, Waveform analysis, Respiratory Amplitude Quotient, Pressure-volume relationship

1. Introduction

Proper function of the central nervous system (CNS) is dependent on pressure homeostasis within the cranial and spinal compartments. Due to limited available space, intracranial pressure (ICP) is tightly coupled to changes in the volumes of cerebrospinal fluid (CSF), blood and interstitial fluid (ISF). This pressure-volume relationship is influenced by various factors, including space-occupying pathologies such as hydrocephalus. Consequently, the ICP signal contains information on the biomechanical state of the CNS.

The pressure-volume relationship can be derived with methods that rely on volume loading, as well as using approaches based on the analysis of temporal variations of ICP. Whereas the former are more invasive and carry a higher risk of infection, the latter are influenced by modulations of ICP that do not reflect changes in the pressure-volume relationship. Herein, we present a surrogate that does not rely on volume loading and that is influenced to a considerably smaller degree by ICP changes not originating in the pressure-volume relationship.

Since the first ICP monitoring in 1959 by Lundberg [1], a number of metrics linking biomechanical changes reflective of craniospinal pathophysiology to the ICP signal have been developed. Marmarou defined the pressure volume index (PVI) as the increase in craniospinal volume needed to elevate ICP to ten times the baseline level [2], [3]. Provided that the pressure-volume curve has the expected exponential form, PVI is constant and fully describes the curve in conjunction with an anchor point, e.g., with volume change defined as zero at baseline ICP.

Avezaat and Eijndhoven [4] showed that PVI can also be determined by a constant infusion volume loading technique. Furthermore, they extended the original exponential pressure-volume relation with a constant term:

$$ICP = ICP_0 + ICP_1 \cdot e^{k \cdot \Delta V} \quad (1)$$

Here, ICP_0 and ICP_1 are constant pressure terms, k is the elastance coefficient, and ΔV is the change in craniospinal volume with respect to equilibrium.

Next to PVI, volume loading gives access to further metrics that describe the pressure-volume relation. Maramarou et al. defined the resistance to outflow (R_O) as the resistance needed to maintain a certain pressure plateau above the resting ICP [3]. While R_O can be calculated from a single bolus injection or from constant volume infusions, differences in the values obtained with these methods have been observed. These may be attributed, in part, to viscoelastic properties of the CNS and its surroundings [5].

Procedures based on volume loading are time consuming and carry the risk of infection. These disadvantages have to be weighed against a possible diagnostic value. For idiopathic normal pressure hydrocephalus, evaluation of the response to lumbar drainage is a guideline recommendation in [6], whereas the assessment of R_O is described as optional and no further methods requiring volume loading are advocated. For severe traumatic brain injury, even with concomitant increase in ICP and danger of cerebral herniation, diagnostics based on volume loading are not even mentioned in the current guidelines [7].

While volume loading provides well-interpretable quantitative data on the craniospinal pressure-volume relation, the ICP signal in itself also carries substantial information. Lundberg referred to waveforms in the ICP time course as cardiac pulse waves (origin in

cardiovascular action), respiratory waves (induced by effects of respiration), and A-, B- and C-waves. The frequency, duration, and magnitude of B-waves have been considered for use in hydrocephalus diagnostics [8], but are currently not part of any standardized diagnostic regime.

Hu et al. described an algorithm for extracting the amplitudes and positions of sub-components of the cardiac pulse waveform [9]. Phenomenologically, these sub-components are indicative of the pressure-volume relationship and/or the compliance as also described by Kiefer et al. [10]. Associations with other parameters and diagnoses were described as well [11], [12]. The method was also used to characterise cerebral vascular changes during acute ICP drop in SAH [13], [14]. However, it has not found widespread entry into clinical routine so far. Price et al. first described the metric RAP, regression coefficient of the amplitude/pressure characteristic [15], which Czosnyka et al. later redefined as follows: “The rate of increasing amplitude per rise in ICP is called AMP/P slope, where P represents pressure“ [16]. Lenfeldt et al. introduced the parameter RPPC as the slope (k) of the linear regression equation $\Delta p = k \cdot p_{mean} + m$, where Δp is the amplitude of each individual cardiac pulse wave, p_{mean} the mean ICP during that cardiac pulse wave, and m the y-intercept of the linear regression curve [17]. Furthermore, a parameter also called RAP was described as "the moving correlation coefficient between mean ICP and associated changes in pulse amplitude" [18].

All current parameters derived from the ICP signal have one thing in common: They are influenced by changes in ICP not caused by changes in the pressure-volume relationship. For instance, a patient’s transient shift in body position may change ICP in a fashion similar to the occurrence of a B-wave. Consequently, both will influence pressure-volume parameters derived from ICP similarly, even though the former does not reflect a pathologic change whereas the latter might. This explains, at least in part, why current methods that rely solely on pressure recordings and that do not require volume loading have not had a substantial clinical impact.

As a step towards improving this situation, we describe herein a new surrogate termed respiratory amplitude quotient (RAQ) that does not rely on volume loading and that is affected to a lesser degree by changes in ICP that are not reflective of an altered pressure-volume relation. Therefore, RAQ can be derived from ICP signals with only partial calibration. We further present an algorithm for computing RAQ and its application for possible discrimination of two patient groups with different types of hydrocephalus.

2. Methods

2.1 Calculation of RAQ

We take advantage of the fact that in the ICP signal, the amplitude of the cardiac pulse wave varies periodically with the respiratory wave. When ICP rises in the expiratory phase of spontaneous respiration, the cardiac pulse wave amplitude increases. Conversely, it decreases with falling ICP in the inspiratory phase. For the definition of RAQ, we assume that respiration-induced changes in ICP follow the pressure-volume curve, and that the shape of the curve stays constant during respiratory and cardiac cycles.

RAQ quantifies the change in the amplitude of the cardiac pulse component with the time course of the respiratory component in the ICP signal. We define RAQ as the ratio of the

amplitude of the respiratory wave to the amplitude of the respiration-induced variation in the course of the cardiac pulse wave amplitude,

$$RAQ = \frac{A_{rp}}{AA_{vp}} \quad (2)$$

The individual parts of Equation 3 are illustrated in Figs. 1 - 4 using a synthetic ICP time course consisting of two sinusoidal components, one representing the cardiac pulse wave and the other the respiratory wave: ICP (black line) is drawn over ten cardiac cycles. The mean ICP calculated over each cardiac half-period (MICP, blue line) as well as the peak-to-valley and valley-to-peak cardiac pulse wave amplitude for each half period (A_{vp}, orange line) are also shown. The peak-to-valley amplitude of the respiratory wave in the MICP curve (A_{rp}) reflects the level of mean ICP change with respiration, while the peak-to-valley amplitude of the respiratory wave of the A_{vp} curve (AA_{vp}) reflects the level of cardiac pulse wave amplitude modulation by respiration.

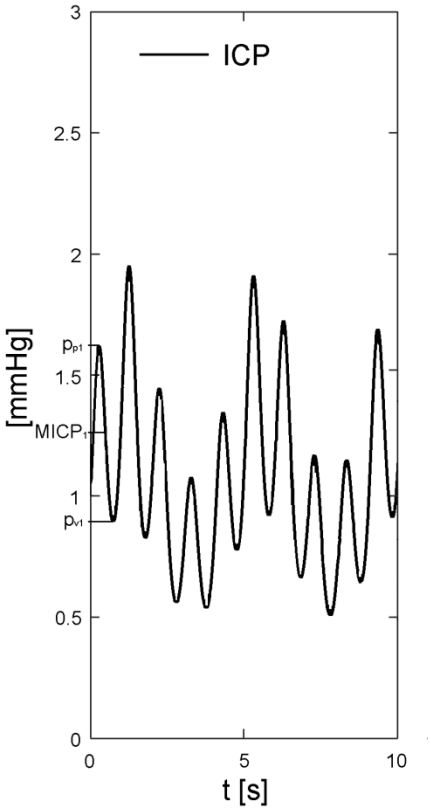

Fig. 1a. Illustration of the calculation of MICP, the mean ICP determined over each cardiac half-period. A synthetic ICP time course (black line) consisting of two sinusoidal components representing cardiac pulse and respiratory waves, respectively, is shown. The first MICP value, $MICP_1$, is determined from the first peak of the ICP (p_{p1}) to its first valley (p_{v1}).

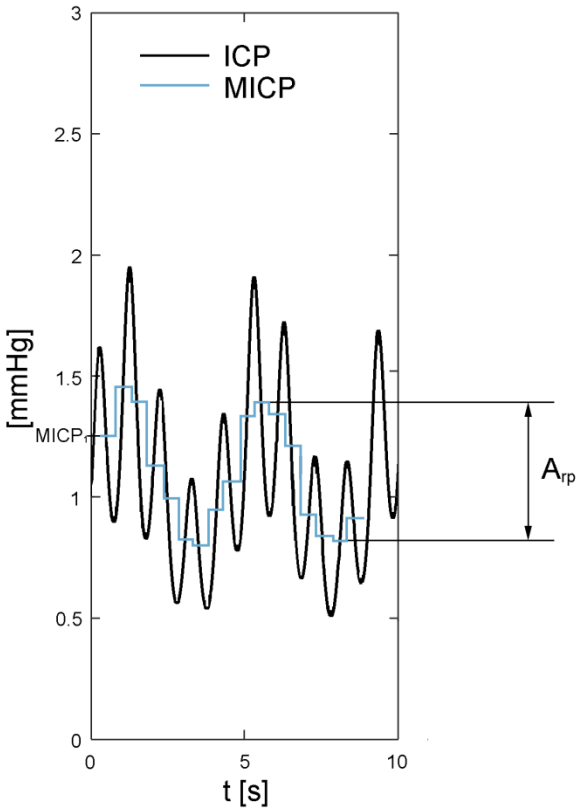

Fig. 1b. Calculation of A_{rp}, the amplitude of the respiratory wave in the MICP curve (blue line). To establish MICP, $MICP_1$ is plotted for the duration of the first cardiac half-period. Then, the mean pressures are continuously determined for each half-period from peak-to-valley and valley-to-peak, respectively, yielding the respective new value of MICP. The respiratory amplitude A_{rp} is subsequently determined from the MICP curve as the highest amplitude in the respiratory frequency range (see Fig. 3).

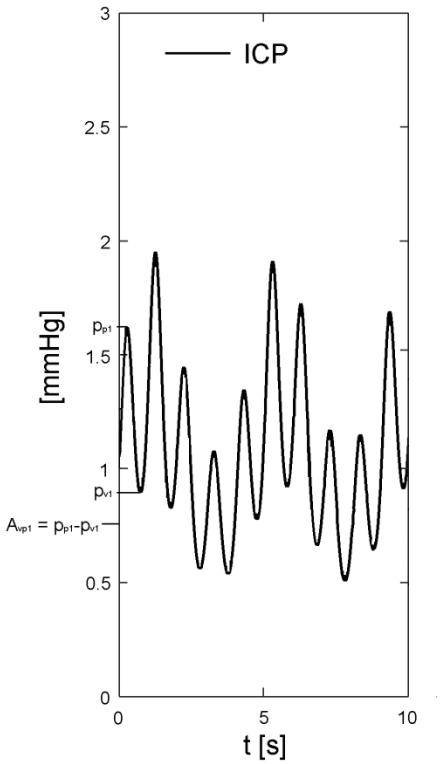

Fig. 2a. Illustration of the calculation of A_{vp}, the cardiac pulse wave amplitude for each half-period of the ICP time course (black line). The cardiac pulse wave amplitude of the first half period is determined from the first peak (p_{p1}) to the first valley (p_{v1}) as $A_{vp1} = p_{p1} - p_{v1}$.

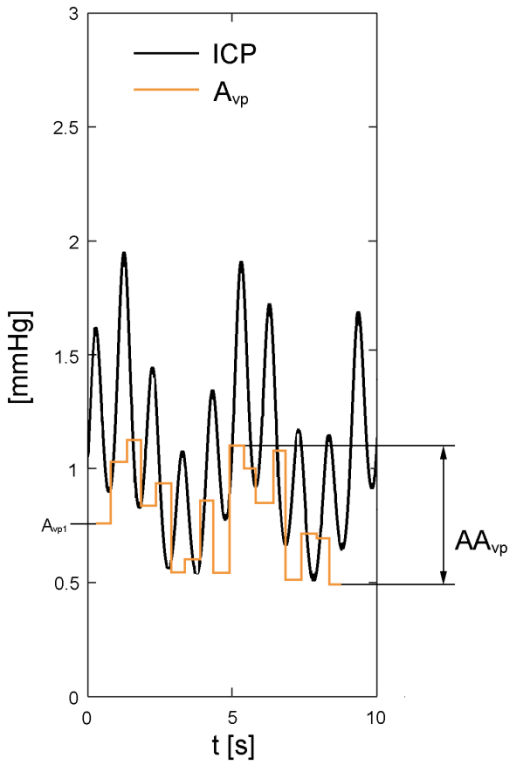

Fig. 2b. Calculation of AA_{vp}, the amplitude of the respiratory wave of the A_{vp} curve (orange line). To establish AA_{vp}, A_{vp1} is plotted for the duration of the first cardiac half-period. Then the cardiac pulse wave amplitudes are continuously determined for each half-period from peak-to-valley and valley-to-peak, respectively. The respiratory amplitude AA_{vp} is subsequently determined from the A_{vp} time course as the highest amplitude in the respiratory frequency range (see Fig. 4).

For the calculation of RAQ, pulse amplitudes have to be determined. We use the automatic multiscale-based peak detection algorithm (AMPD) for this purpose [19]. AMPD finds the systolic and diastolic points of the ICP signal in the time domain. We then calculate the peak-to-valley and valley-to-peak cardiac pulse wave amplitudes for each half-period and form a time series consisting of those. We further calculate for each half-period the mean ICP and again form a time series. To determine the respiratory amplitudes of mean ICP and cardiac pulse amplitude courses, we apply fast Fourier transform (FFT) [20] on both time series, calculate the amplitude spectra, and then select the highest amplitude within the respiratory frequency range as shown in Figs. 3 and 4. We found that determining the amplitudes of the respiratory waves in the course of mean ICP and cardiac pulse amplitude was more reliably done in the frequency domain than in the time domain. A pseudocode describing a reference approach for calculating RAQ is shown in List 1 in Appendix I. The code is derived from a Matlab (The MathWorks, Inc., Natick, MA, USA) implementation that we used for the calculation of the RAQ values presented herein.

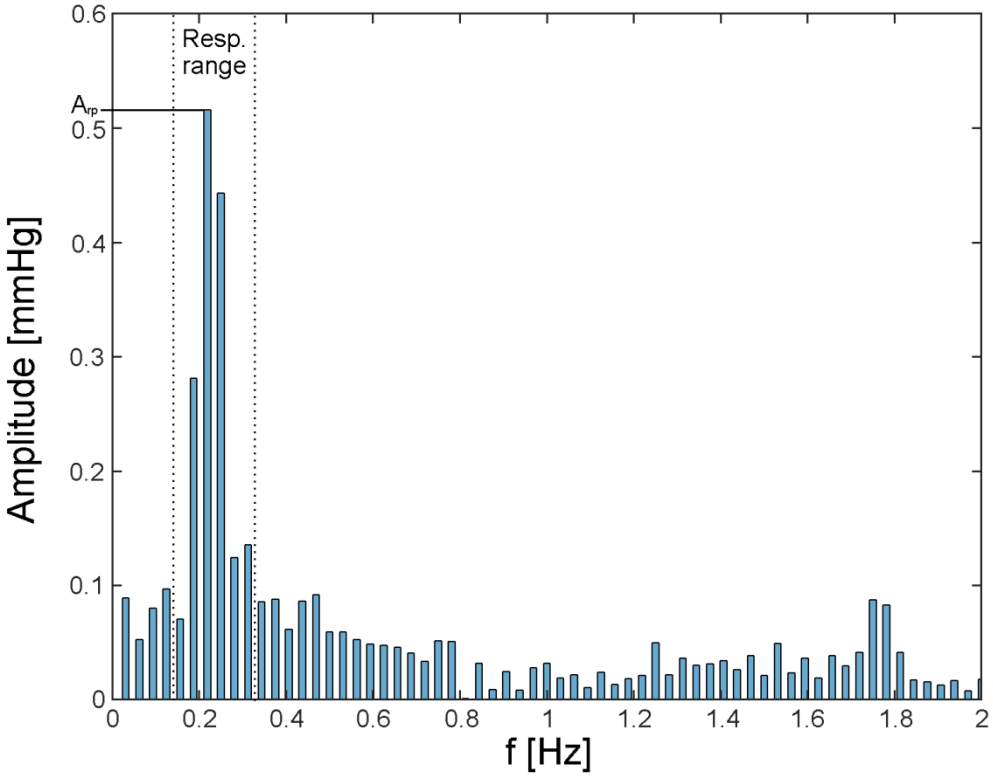

Fig. 3. Amplitude spectrum of the MICP signal shown in Figure 1b. A_{rp} is determined as the highest peak in the respiratory frequency range (0.166 to 0.33 Hz).

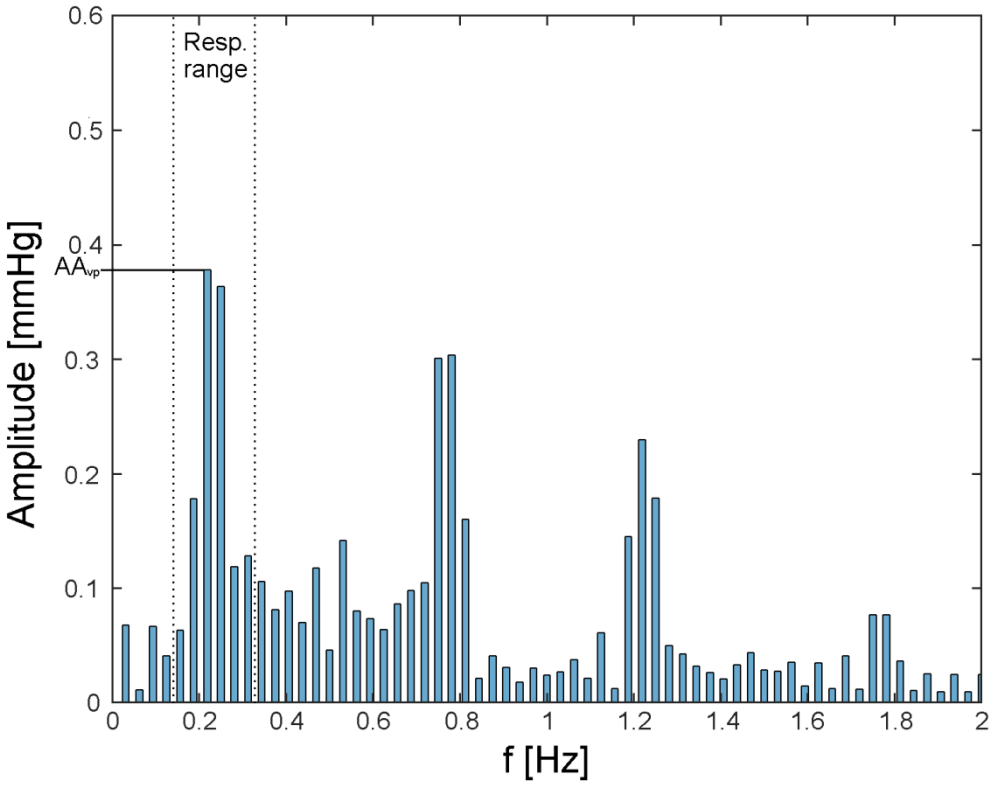

Fig. 4. Amplitude spectrum of the A_{vp} signal shown in Figure 2b. AA_{vp} is determined as the highest peak in the respiratory frequency range (0.166 to 0.33 Hz).

2.2 Numerical simulations

To characterize RAQ under idealized conditions and to validate our Matlab program used to calculate RAQ in ICP recordings, we produced synthetic ICP time series by employing Eq. (1) and prescribing sinusoidal volume changes, V_p, in the cardiac pulse frequency range, f_p, and sinusoidal volume changes, V_r, in the respiratory frequency range, f_r:

$$ICP = ICP_0 + ICP_1 \cdot e^{k \cdot (V_p + V_r)}, \quad (3)$$

where

$$V_p = \frac{\Delta V_p}{2} \cdot \sin(t \cdot f_p \cdot 2 \cdot \pi) \quad (4)$$

and

$$V_r = \frac{\Delta V_r}{2} \cdot \sin(t \cdot f_r \cdot 2 \cdot \pi) \quad (5)$$

Here, ΔV_p is the craniospinal volume change induced by cardiovascular action during each cardiac cycle, and ΔV_r is the craniospinal volume change due to respiration during each respiratory cycle. The courses of two exemplary synthetic ICP curves over 30 seconds are shown in Fig. 5. The black curve in Fig. 5 reflects the output of a system described by Eq. 3 with k=0.1/ml, which is indicative of a normal pressure-volume relationship. The orange curve with k=0.15/ml reflects a system with reduced overall compliance. Both the cardiac pulse wave amplitude and the respiratory amplitude of ICP are higher with k=0.15/ml. The modulation of the cardiac pulse wave amplitude by respiration is clearly visible. Whether or not the modulation of the cardiac pulse wave amplitude is "stronger" with k=0.15/ml cannot be determined visually, but - as we will show - can be quantified with RAQ. We calculated RAQ numerically using a time window of 6000 seconds and compared the values obtained to those representative of the system used to generate the ICP curves in the first place.

To test whether the algorithm is resilient to a very common type of disturbance that does not have an influence on compliance, we furthermore produced synthetic ICP time series, again 6000 seconds long, that feature pressure steps of 1, 2, and 3 mmHg at the 3000 second mark (see Fig. 6). Typically, such pressure steps occur when the head elevation is changed during ICP recording. A 1 mmHg increase in ICP corresponds to a decrease in head elevation with respect to heart level by about 1.4 cm (not accounting for potential concomitant changes in central venous pressure and collapse of jugular veins).

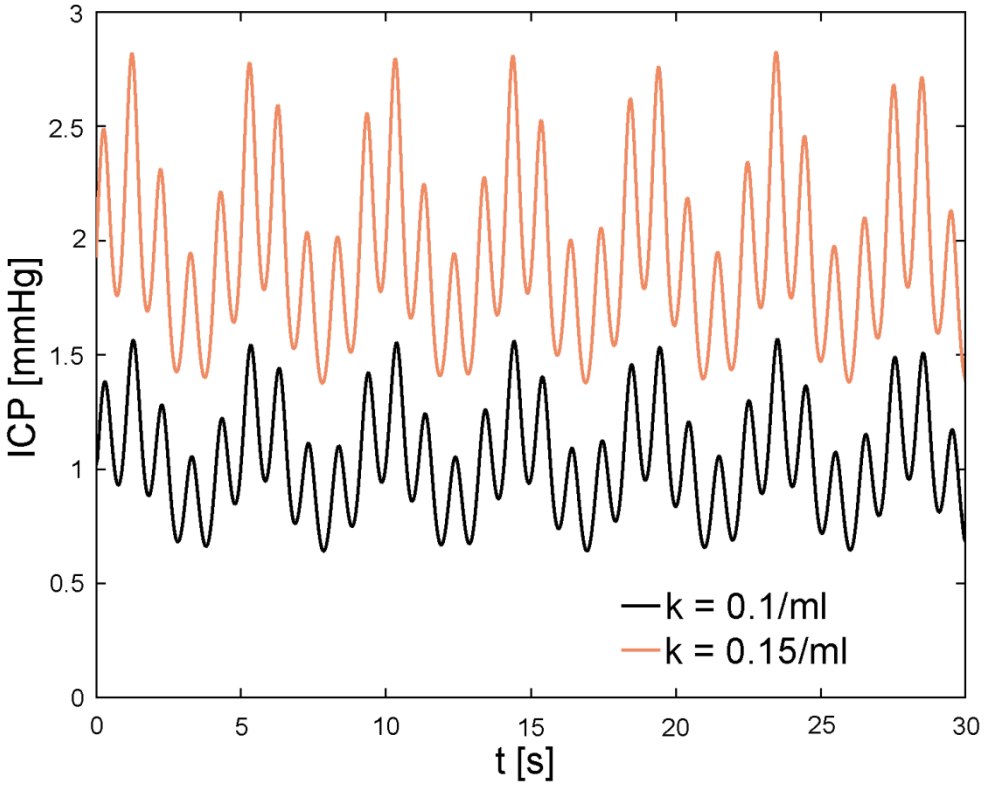

Fig. 5. Synthetic ICP signals consisting of cardiac pulse waves and respiration-induced waves that are idealized as sine-shaped. Black line: k = 0.1/ml, orange line: k = 0.15/ml (for better discernibility drawn with an offset of ICP_0 = 1 mmHg). The cardiac pulse waves (produced by cardiovascular action) and the respiration-induced waves are clearly discernible. The cardiac pulse wave amplitude is visibly larger at the peak of the respiration-induced wave. Both cardiac pulse wave amplitudes and respiration-induced wave amplitudes are higher for k=0.15.

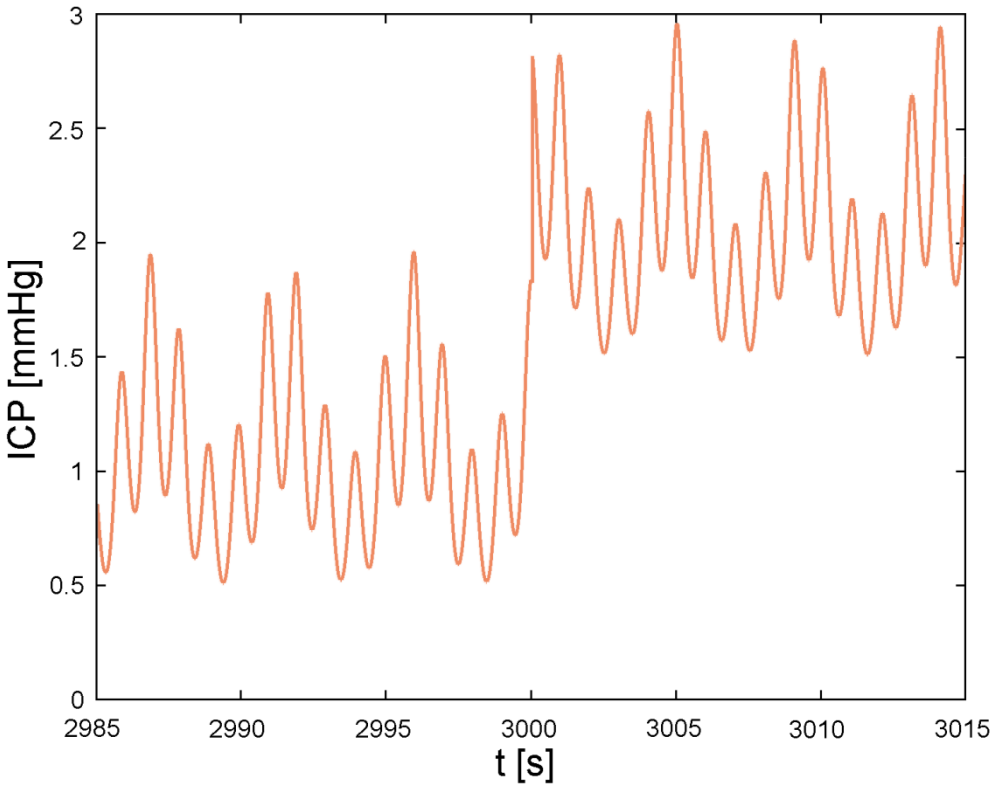

Fig. 6. Synthetic ICP signal with pressure step of 1 mmHg at 3000 s.

2.3 Patient selection

To assess a possible clinical application, we evaluated RAQ retrospectively in intraparenchymal ICP signals recorded with a sampling rate of 50 Hz overnight in two groups of patients with different aetiology of hydrocephalus. The study was approved by the local ethics committee (Ethikkommission Universität Leipzig, Az 014-13-28012013), and written informed consent was obtained from the patients.

The first group, hereinafter referred to as AQS, consisted of 6 hydrocephalus patients with aqueductal stenosis diagnosed by magnetic resonance imaging (MRI), 55.8 ± 18.0 years of age (mean and standard deviation), 4 males, 2 females. The second group consisted of 17 hydrocephalus patients diagnosed by morphology with MRI who were non-responsive to external lumbar drainage or ventriculo-peritoneal shunting (non-normal pressure hydrocephalus, NNPH), age 72.5 ± 6.1 years, 8 males, 9 females. In the AQS group, concurrent neurological and metabolic diseases were ruled out; the aqueductal stenosis was the only evident cause of hydrocephalus. These patients responded to CSF diversion surgery. The two groups were chosen to represent both cases with (AQS) and without (NNPH) obvious impairment of CSF circulation.

2.4 Data analysis

We determined RAQ after upsampling the ICP time series to 100 Hz. First, we calculated RAQ over the full recording period (RAQ_C). Because the pressure-volume characteristic is influenced by the occurrence of slow vasogenic waves (B-waves), we further calculated RAQ for periods containing such waves.

To identify B-wave containing periods, we applied the method described in [21]. Briefly, the ICP signal is compared to a set of B-wave templates and, using the cross-correlation function, the similarity of the ICP signal to the templates is quantified. For each recording, we calculated the following parameters that describe the power and occurrence of B-waves as described in [21]: ICP_S, the root mean square amplitude of the B-waves, averaged over the B-wave containing time; TF_S, the time fraction of the total recording containing B-waves; and $ICP_{Smean} = ICP_S \cdot TF_S$. After computing the RAQs of all B-wave containing periods, we calculated their mean value, RAQ_B.

2.5 Statistical Analysis

Anderson-Darling tests indicated that some parameters were not normally distributed. Therefore, we used two-sided Mann-Whitney U tests to identify statistical differences between the two patient groups (AQS and NNPH) for each parameter. The significance level was set at $\alpha=0.05$ for all statistical tests.

3. Results

3.1 Influence of k, ΔV_p, ΔV_r , depth of respiration and zero point and span errors on RAQ

To characterize RAQ under changing physiological conditions, we varied the coefficient k in the exponent of the pressure-volume relation, the craniospinal volume change induced by cardiovascular action during each cardiac cycle, ΔV_p, as well as the craniospinal volume change during each respiratory cycle due to respiration, ΔV_r. Figure 7 shows RAQ as a function of k and, additionally, as a function of PVI, since the latter is more commonly used in the clinical setting. It is evident that RAQ is linearly dependent on PVI. Furthermore, ΔV_p strongly influences RAQ, as is clearly visible in Fig. 8. Finally, Figure 9 shows that RAQ does not depend on ΔV_r.

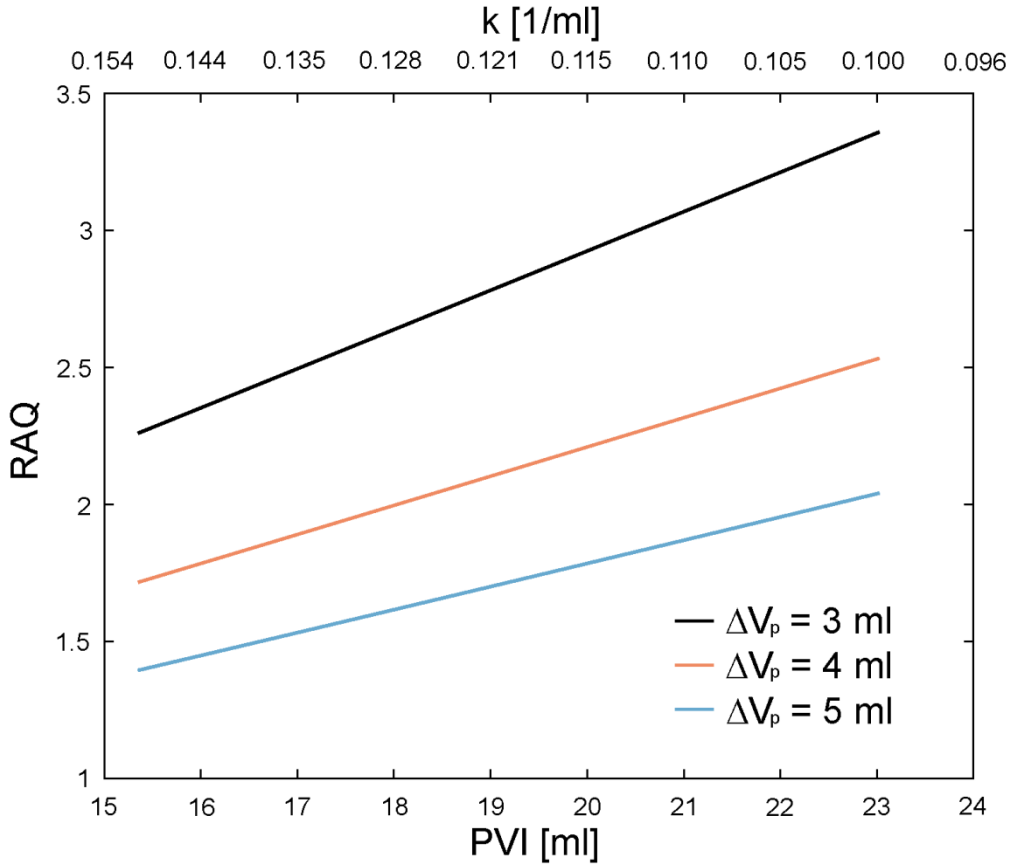

Fig. 7. RAQ as a function of k, PVI and ΔV_p, the craniospinal volume change due to cardiac action within each cardiac cycle.

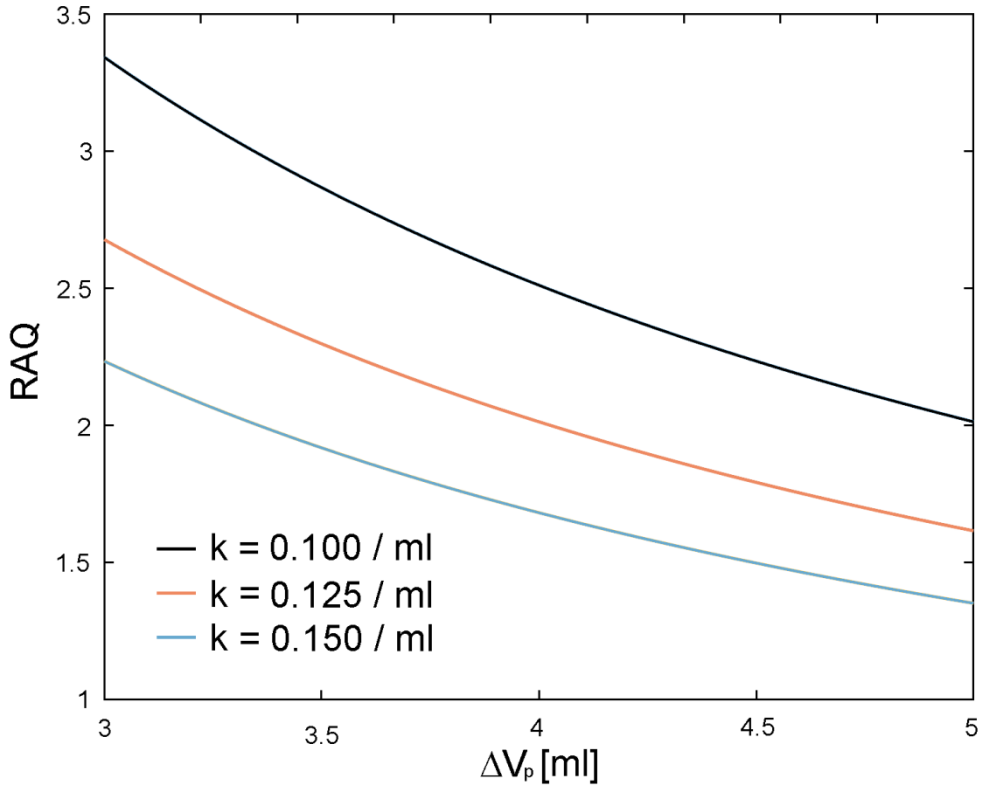

Fig. 8. RAQ as a function of ΔV_p, the craniospinal volume change due to cardiac action within each cardiac cycle, and k.

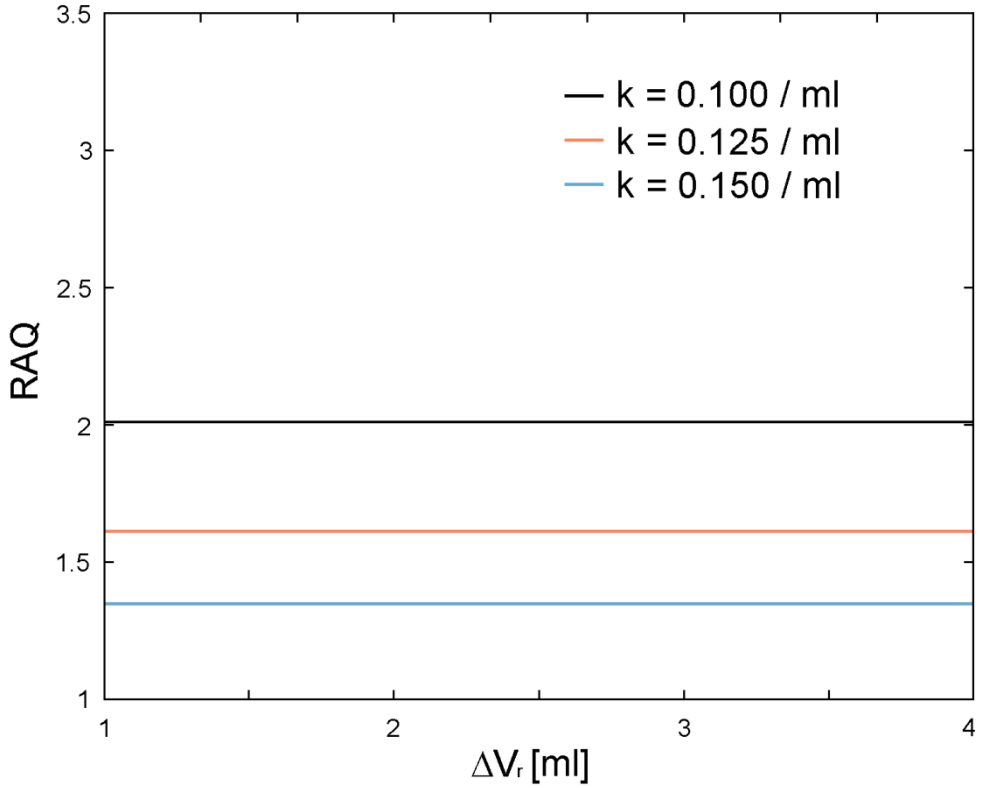

Fig. 9. RAQ as a function of ΔV_r, the craniospinal volume change due to respiration within each respiratory cycle, and k. ΔV_p = 5 ml.

To determine possible influences of zero-point and span errors in the ICP signal, we introduced such errors analytically in Equation 2, the definition of RAQ. The effect of a zero-point calibration error, e_z, is shown in Equation 6: With p_1 the inspiratory minimum ICP and p_2 the expiratory maximum, Δp_1 the amplitude of the cardiac pulse wave in inspiration and Δp_2 the amplitude of the cardiac pulse wave in expiration, we obtain

$$RAQ = \frac{p_2 + e_z - p_1 - e_z}{\Delta p_2 + e_z - \Delta p_1 - e_z} = \frac{p_2 - p_1}{\Delta p_2 - \Delta p_1} . \quad (6)$$

It is evident that the zero-point error does not affect RAQ, since the error terms in both the numerator and denominator add up to zero. Similarly, RAQ is not influenced by a span calibration error, e_s, as shown in Equation 7. This is because e_s scales numerator and denominator equally:

$$RAQ = \frac{e_s \cdot p_2 - e_s \cdot p_1}{e_s \cdot \Delta p_2 - e_s \cdot \Delta p_1} = \frac{p_2 - p_1}{\Delta p_2 - \Delta p_1} \quad (7)$$

3.2 Analysis of synthetic ICP signals

For the synthetic ICP time course shown as orange line in Fig. 5 (k=0.15), an RAQ value of 1.349 was expected, while numerically we obtained 1.327 (Table 1). Similar results were seen for k=0.1 and k=0.125, as well as for the ICP signal with a step increase in mean value shown in Fig. 6. Taken together, these results indicate that our algorithm and its implementation are sound, and that RAQ is insensitive to step changes in ICP caused by exogenous factors.

k [1/ml]	Step [mmHg]	RAQ_e	RAQ_{calc}	RAQ_e - RAQ_{calc}	Relative Error [%]
0.100	0	2.011	1.971	0.040	1.99
0.100	1	2.011	1.971	0.040	1.98
0.100	2	2.011	1.971	0.040	1.99
0.100	3	2.011	1.971	0.040	1.99
0.125	0	1.613	1.585	0.028	1.75
0.125	1	1.613	1.585	0.028	1.73
0.125	2	1.613	1.586	0.028	1.72
0.125	3	1.613	1.586	0.028	1.72
0.150	0	1.349	1.327	0.023	1.67
0.150	1	1.349	1.327	0.022	1.62
0.150	2	1.349	1.328	0.021	1.59
0.150	3	1.349	1.328	0.021	1.59
				Mean	1.78

Table 1. Comparison of expected (RAQ_e) and calculated (RAQ_{calc}) values for three systems described by Eq. 3 with k of 0.1, 0.125 and 0.15 ml^{-1} and steps of 1, 2, and 3 mmHg. RAQ_{calc} values were determined numerically with a Matlab implementation of the pseudocode shown in List 1 in Appendix I.

3.3 Analysis of ICP measured in patients

We found significantly different RAQ_B values in the two patient groups, namely 0.857 in AQS compared to 1.065 in NNPH, p = 0.027. In contrast, there was no significant difference between the respective RAQ_C values. For cases where lumbar infusion testing had been performed, we also calculated k, R_O, and PVI, finding no significant difference between the two patient groups. Table 2 and Fig. 10 summarize these findings. Table 2 also contains the values ICP_S, ICP_{Smean}, and TF_S, which quantify the B-waves and their occurrence, as well as heart rate (HR) and respiratory rate (RR). Tables 3 and 4 in Appendix II show the individual values for each patient.

Group	Parameter												
	ICP [mmHg]	RAQ_B [-]	PVI [ml]	R_O [mmHg / (ml / min)]	k [1 / ml]	Age [years]	RR [1 / min]	HR [1 / min]	RAQ_C [-]	ICP_{Smean} [mmHg]	TF_S [-]	ICP_S [mmHg]	n [-]
NNPH	5.76 ± 4.94	1.065 ± 0.195	16.08 ± 11.53	12.14 ± 6.39	0.206 ± 0.127	72.5 ± 6.1	15.1±0.7	65.6±15.6	1.38 ± 0.32	0.367±0.135	0.377±0.11	0.987±0.264	17
AQS	8.96 ± 4.49	0.857 ± 0.109	18.26 ± 9.84	11.63 ± 5.38	0.232 ± 0.159	55.8 ± 18.0	15.0±0.6	60.9±14.1	1.20±0.21	0.785±0.290	0.572±0.12	1.337±0.240	6
p-value	0.31	**0.027**	0.621	0.823	0.983	**0.015**	0.860	0.462	0.220	**0.001**	**0.013**	**0.025**	
Female	6.43 ± 4.52	1.001 ± 0.119	14.23 ± 4.69	10.51 ± 4.26	0.216 ± 0.118	69.2 ± 6.8	15.3 ± 0.8	63.3 ± 11.7	1.34 ± 0.18	0.426 ± 0.151	0.409 ± 0.112	1.028 ± 0.193	11
Male	6.75 ± 5.45	1.020 ± 0.251	18.84 ± 14.36	13.35 ± 7.19	0.211 ± 0.151	67.2 ± 16.5	14.9 ± 0.5	65.3 ± 18.0	1.33 ± 0.39	0.521 ± 0.327	0.444 ± 0.166	1.124 ± 0.366	12
p-value	0.926	0.735	0.842	0.278	0.589	0.440	0.339	0.781	0.442	0.976	0.902	0.580	

Table 2. Differences in age, craniospinal pressure-volume parameter values, and B-wave parameters between the NNPH and AQS patient groups, as well as between female and male patients. P-values indicating a statistically significant difference are shown in bold numbers. With the exception of the sample size n and p-values, numbers indicate mean ± standard deviation. The significance level was set at α=0.05.
ICP: intracranial pressure; RAQ_B: mean RAQ during B-waves; PVI: pressure volume index; R_O: outflow resistance; k: elastance coefficient; RR: respiratory rate; HR: heart rate; RAQ_C: mean RAQ during the recording; TF_S: time fraction of recording containing B-waves; ICP_S: root mean square amplitude of the B-waves, averaged over the B-wave containing time; ICP_{Smean}: product of ICP_S and TF_S.

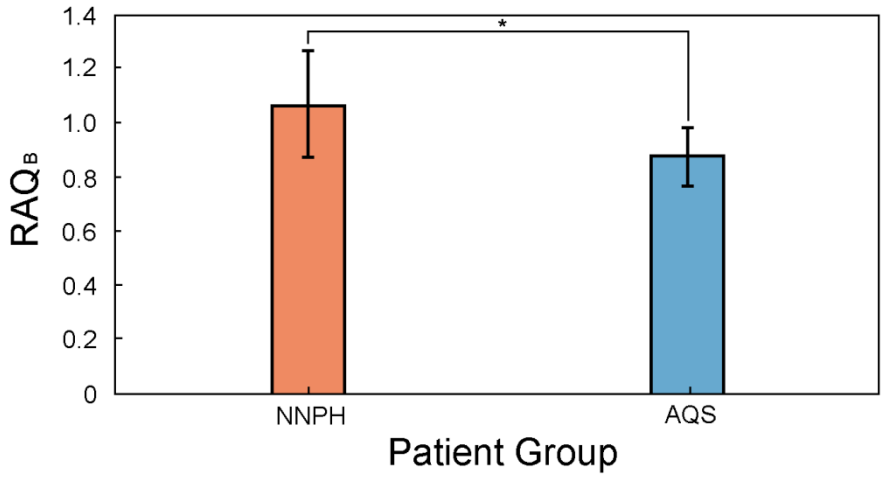

Fig. 10. Mean RAQ_B and standard deviation for the NNPH and AQS patient groups. RAQ_B differs significantly between the two groups (p-value 0.027).

4. Discussion

We defined the new surrogate RAQ, respiratory amplitude quotient, as the ratio of the amplitude of the respiratory wave in the ICP signal to the amplitude of the respiration-induced wave in the course of the ICP cardiac pulse wave amplitude. We determined RAQ retrospectively in the ICP recordings of two groups of patients with different types of hydrocephalus. Comparing, between these two groups, the respiratory amplitude quotient averaged over the full recording time, RAQ_C, and over the B-wave containing periods, RAQ_B, as well as pressure volume index, resistance to outflow and elastance coefficient, we found

that only RAQ_B differed significantly ($p = 0.027$). Since RAQ may provide information for the discrimination of the two groups included in this study, its potential as a tool for stratification of patients with suspected space occupying pathologies should be further investigated.

4.1 Resilience to errors and changes in ICP not caused by altered pressure-volume relationship

Our results demonstrate that RAQ is resilient to certain types of errors in the assessed signal. As a quotient of amplitudes, RAQ is not affected by zero-point calibration errors of the ICP signal. It is also not influenced by span calibration errors, as these scale numerator and denominator of Equation (2) equally. Consequently, RAQ is also not affected by zero-point drifts as encountered in epidural pressure monitoring [22] and long-term telemetric monitoring [23]. However, linearity calibration errors are not inherently compensated and must still be considered. Also, we did not investigate the effect of other sources of disturbance and noise, such as line frequency noise, electromagnetic disturbances and vibrations. Future studies are needed to assess those.

Next to errors in the ICP signal, another potential source of disturbance is the numerical implementation of RAQ. We found good agreement of RAQ values determined with the Matlab implementation compared to the theoretically expected values when analysing synthetically produced waveforms. The deviation was below 2% for all assessed cases, which is well acceptable for potential clinical applications.

RAQ shows a level of resilience to changes in ICP that are not caused by an altered pressure-volume relationship. A typical example of such ICP changes encountered in clinical practice are pressure steps or drops when the position of the patient is changed. Algorithms based on mean ICP and amplitude, such as the RAP described by Price et al. [15], are not resilient to positional changes in ICP.

Taken together, RAQ shows promise as a potentially resilient surrogate for the pressure-volume relationship that can be calculated from signals with span and/or zero-point calibration errors, including non-invasively obtained ICP time courses with unknown calibration constants.

4.2 Underlying physiological assumptions

We defined RAQ based on the assumption that during normal tidal respiration, ICP moves along the pressure-volume curve. In other words, the shape of the pressure-volume curve is presumed to be unaltered by the respiratory changes of ICP, and that, therefore, RAQ does not change during the respiratory cycle. Since this assumption is very difficult to verify, it constitutes currently one of the limitations of the new surrogate.

Our results show that ΔV_p, the transient craniospinal volume change during a cardiac cycle, has a strong influence on RAQ. Cerebral perfusion is relatively constant at 45 – 55 ml/100g/min [24] and is kept constant by cerebral autoregulation. Consequently, an increase in heart rate should result in a decrease in ΔV_p and vice versa. In our patient cohort, there was no significant difference in the mean heart rates between the two groups. For a given cerebral perfusion and heart rate, ΔV_p will depend on brain size. In this retrospective study, we did not

have information on patients' brain sizes or on other parameters based on which we could have estimated them.

4.3 Interpretation and potential applications of RAQ

RAQ reflects the exponential character of the pressure-volume relationship in regions I (high compliance, low ICP, high RAQ) and II (decreased compliance, increased ICP, lower RAQ) as shown in Fig. 11. In region III, where the cerebral compensatory reserve is impaired, the pressure-volume curve is characterized by a decreasing slope [18]. At the transition to this region, where $V = V_{krit}$ and $p = p_{krit}$ (limit of impaired cerebral compensatory reserve), the curvature changes from convex to concave. RAQ tends to infinity as this point is approached. $\Delta V/\Delta p$ increases with increasing V in region III, and RAQ is negative. This is evident in Equation 8, where p_1 is the inspiratory minimum ICP and p_2 the expiratory maximum, Δp_1 the amplitude of the cardiac pulse wave in inspiration and Δp_2 the amplitude of the cardiac pulse wave in expiration:

$$RAQ = \frac{p_2 - p_1}{\Delta p_2 - \Delta p_1} \tag{8}$$

In region III, Δp_2 is smaller than Δp_1. The denominator of the equation is thus negative, while the numerator is positive and, therefore, RAQ is negative. Δp_2 is equal to Δp_1 at the transition between regions II and III. As the denominator tends to zero, the quotient tends to infinity.

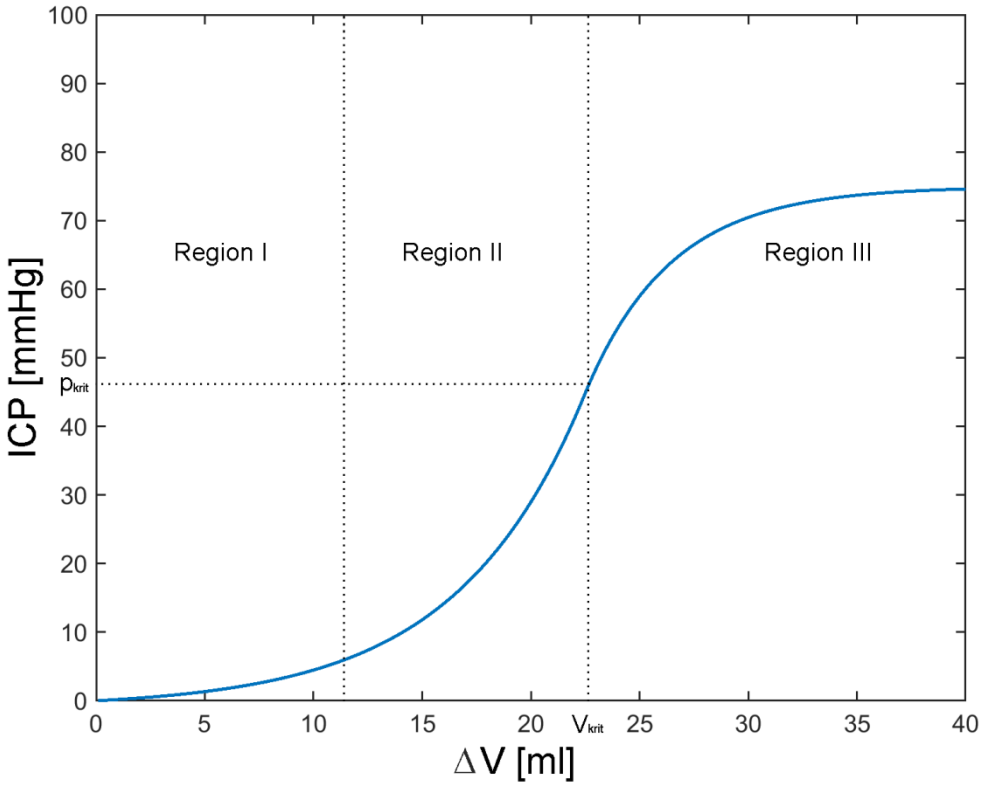

Fig. 11. Generic representation of three characteristic regions of the craniospinal pressure-volume curve. Region I: Characterized by comparably small cardiac pulse wave amplitudes. Region II: Exponential relationship as in the first region, but characterized by fast increase in cardiac pulse wave amplitudes with increasing craniospinal volume. Region III: Diminishing cardiac pulse wave amplitudes. For lack of an established quantitative description in humans, a logarithmic relationship is used here for illustrative purposes.

Before a potential clinical use as a surrogate for the pressure-volume relationship can be targeted, RAQ may be of value for pathophysiological investigations. For instance, B-waves are a sign of reduced craniospinal compliance in hydrocephalus patients. The fact that our AQS-patients had increased B-waves (as quantified by ICP_S) and, at the same time, reduced RAQ during B-waves (as quantified by RAQ_B), could indicate that not only compliance is reduced during periods of B-waves, but also that the pressure-volume relationship is altered. Furthermore, the shift from positive values of RAQ to negative ones in the transition between regions II and III could serve as an indicator for impaired cerebral compensatory reserve.

4.4 Limitations

The main limitations of the methodology for calculating RAQ are the assumptions that ΔV_p is constant, and that RAQ does not change during each cardiac cycle, respiratory cycle and over the observation period. While we have shown that RAQ possesses a level of resilience to some measurement errors and to changes in ICP that are not caused by an altered pressure-volume relationship, we did not perform an exhaustive investigation of the effects of other disturbances and noise. Care must be taken when using RAQ in the transition to impaired cerebral compensatory reserve, where the slope of the pressure-volume curve shifts from positive to negative, and RAQ tends to infinity.

The clinical arm of our study is limited by the fact that no invasive ICP data could be obtained from healthy subjects serving as a control group. Therefore, we did not compare impaired to normal CSF circulation cases, but impaired (AQS) to possibly not impaired ones (NNPH). The former group included a relatively low number of patients, and the two groups were not age and sex matched. The study's primary technical shortcoming is the low ICP sampling rate of 50 Hz. The sampling rate needs to be sufficiently high to capture high frequency components that may contribute to signal peaks used in the derivation of RAQ. Currently, we do not have data to assess the influence of the sampling rate on the calculation of RAQ in ICP recordings of patients.

5. Conclusion

RAQ is a new surrogate for the craniospinal pressure-volume relationship. Since it can be calculated directly from ICP signals, it does not require volume loading and, therefore, has a lower degree of invasiveness and carries a lower risk of infections. Furthermore, alterations of ICP introduced by changes in body position that do not affect the pressure-volume relationship, as well as span and zero-point calibration errors are not reflected in RAQ.

Once RAQ is better understood, it might prove useful for the characterization of space occupying pathologies such as traumatic brain injury, tumors, postoperative swelling and hydrocephalus. Until then, observations made in the current investigation need to be confirmed in prospective studies. Further research is required to characterize both physiological and exogenous factors that may affect RAQ without influencing the pressure-volume relationship. These include the inter- and intra-patient variability of the craniospinal volume change due to cardiac action within each cardiac cycle, possible change of the pressure-volume curve with respiration, as well as line frequency and other noise.

6. Acknowledgments

This study was financed in part by the Swiss National Science Foundation through grant 182683 and through NCCR Kidney.CH.

Vartan Kurtcuoglu and Andreas Spiegelberg are inventors, Andreas Spiegelberg and the University of Zurich are applicants of patent applications DE102018100697A1 and WO2018206799A1. Andreas Spiegelberg is the owner of Cephalotec, a manufacturer of devices that use RAQ. Matthias Krause and Juergen Meixensberger declare that they have no conflict of interest.

Bibliography

[1] N. Lundberg, "Continuous recording and control of ventricular fluid pressure in neurosurgical practice.," *Acta Psychiatr. Scand. Suppl.*, vol. 36, no. 149, pp. 1–193, 1959.

[2] A. Marmarou, "A theoretical and experimental evaluation of the cerebrospinal fluid system. Drexel University." PhD thesis, 1973.

[3] A. Marmarou, K. Shulman, and J. Lamorgese, "Compartmental analysis of compliance and outflow resistance of the cerebrospinal fluid system," *J. Neurosurg.*, vol. 43, no. 5, pp. 523–534, 1975.

[4] C. Avezaat and J. H. M. van Eijndhoven, *Cerebrospinal fluid pulse pressure and craniospinal dynamics: a theoretical, clinical and experimental study*. 1984.

[5] S. Bottan, M. S. Daners, D. de Zelicourt, N. Fellner, D. Poulikakos, and V. Kurtcuoglu, "Assessment of intracranial dynamics in hydrocephalus: effects of viscoelasticity on the outcome of infusion tests," *J. Neurosurg.*, vol. 119, no. 6, pp. 1511–1519, 2013.

[6] A. Marmarou, M. Bergsneider, P. Klinge, N. Relkin, and P. M. Black, "The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus," *Neurosurgery*, vol. 57, no. 3, pp. S2-17, 2005.

[7] N. Carney *et al.*, "Guidelines for the management of severe traumatic brain injury," *Neurosurgery*, vol. 80, no. 1, pp. 6–15, 2017.

[8] A. Spiegelberg, M. Preuß, and V. Kurtcuoglu, "B-waves revisited," *Interdiscip. Neurosurg. Adv. Tech. Case Manag.*, vol. 6, pp. 13–17, May 2016.

[9] X. Hu and M. Bergsneider, "Morphological clustering and analysis of intracranial pressure pulses (mocaip)." Google Patents, 18-Aug-2011.

[10] M. Kiefer and W.-I. Steudel, "Moderne Hirndruckmessung Grundlagen und Praxis," *Unfallchirurg*, vol. 105, no. 7, pp. 578–586, 2002.

[11] R. Hamilton, J. Fuller, K. Baldwin, P. Vespa, X. Hu, and M. Bergsneider, "Relative position of the third characteristic peak of the intracranial pressure pulse waveform morphology differentiates normal-pressure hydrocephalus shunt responders and nonresponders," in *Intracranial Pressure and Brain Monitoring XV*, Springer, 2016, pp. 339–345.

[12] M. Kasprowicz, M. Bergsneider, M. Czosnyka, and X. Hu, *Association Between ICP Pulse Waveform Morphology and ICP B Waves*. Springer, 2012.

[13] X. Liu, L. L. Zimmermann, N. Ho, P. Vespa, X. Liao, and X. Hu, "Cerebral vascular changes during acute intracranial pressure drop," *Neurocrit. Care*, vol. 30, no. 3, pp. 635–644, 2019.

[14] X. Liu *et al.*, "Morphological changes of intracranial pressure quantifies vasodilatory effect of verapamil to treat cerebral vasospasm," *J. Neurointerv. Surg.*, 2020.

[15] D. J. Price, M. Czosnyka, and M. Williamson, "Attempts to continuously monitor autoregulation and compensatory reserve in severe head injuries," in *Intracranial*

Pressure VIII, Springer, 1993, pp. 61–66.
[16] M. Czosnyka *et al.*, "Pulse pressure waveform in hydrocephalus: what it is and what it isn't," *Neurosurg. Focus*, vol. 22, no. 4, pp. 1–7, 2007.
[17] N. Lenfeldt *et al.*, "Cerebrospinal fluid pulse pressure method: a possible substitute for the examination of B waves," *J. Neurosurg.*, vol. 101, no. 6, pp. 944–950, 2004.
[18] D.-J. Kim *et al.*, "Index of cerebrospinal compensatory reserve in hydrocephalus," *Neurosurgery*, vol. 64, no. 3, pp. 494–502, 2009.
[19] F. Scholkmann, J. Boss, and M. Wolf, "An efficient algorithm for automatic peak detection in noisy periodic and quasi-periodic signals," *Algorithms*, vol. 5, no. 4, pp. 588–603, 2012.
[20] J. W. Cooley and J. W. Tukey, "An algorithm for the machine calculation of complex Fourier series," *Math. Comput.*, vol. 19, no. 90, pp. 297–301, 1965.
[21] A. Spiegelberg, M. Krause, J. Meixensberger, B. Seifert, and V. Kurtcuoglu, "Significant Association of Slow Vasogenic ICP Waves with Normal Pressure Hydrocephalus Diagnosis," in *Intracranial Pressure & Neuromonitoring XVI*, Springer, 2018, pp. 243–246.
[22] M. A. Poca, J. Sahuquillo, T. Topczewski, M. J. Peñarrubia, and A. Muns, "Is intracranial pressure monitoring in the epidural space reliable? Fact and fiction," *J. Neurosurg.*, vol. 106, no. 4, pp. 548–556, 2007.
[23] M. Kiefer *et al.*, "Telemetric ICP measurement with the first CE-approved device: data from animal experiments and initial clinical experiences," in *Intracranial Pressure and Brain Monitoring XIV*, Springer, 2012, pp. 111–116.
[24] H. C. Hemmings and T. D. Egan, *Pharmacology and Physiology for Anesthesia E-Book: Foundations and Clinical Application*. Elsevier Health Sciences, 2012.

Appendix I

List 1

```
program determineRAQ

// functions minimax(ICP[],i) and maximin(ICP[],i) return "true" if ICP[i] are recognized as minimum or maximum, respectively
// minimax and maximin can make use of the AMPD algorithm or a zero crossing technique

// function target[1:n]= transfer(source[],pointer,n) transfers n samples from the ring-memory source[] into target[1:n]
// pointer points to the oldest sample

// initialize variables

fsample=100                                          // sample rate for ICP
fsampleampmean=4                                     // sample rate for the ICPamps and ICPmeans time series

i25=0                                                // counts to 25 to determine 250 ms intervals for the ICPamps and ICPmeans
time series
pointer=1                                            // pointer into ICPmeans[] and ICPamps[]
pointercounter                                       // counts 4 entries into the means and amps time series
sumRAQ=0                                             // cumulated RAQ values
countRAQ=0                                           // counter for cumulated RAQ values
fl=10/60                                             // 0.1666 Hz, 10 per minute, lower limit for respiration frequency
fu=20/60                                             // 0.3333 Hz, 20 per minute, upper limit for respiration frequency

// the following limit indices might have to be adjusted to the respective FFT function
// depending on how the FFT function arranges the resulting complex numbers
// also the calculation of magnitudes might have to be adjusted

l=7                                                  // index for 0.1875 Hz line in the amplitude spectrum to approximate fl
u=11                                                 // index for 0.3125 Hz line in the amplitude spectrum to approximate fu

ii=0                                                 // the running index into ICP[]

imin=0                                               // point to local maximum and minimum
imax=0



mmin=false                                           // marker minimum found
```

```
// find the first diastolic minimum

repeat
    ii++

    if minimax(ICP[],ii)                          // diastolic minimum identified?

        ICPmin=ICP[ii]
        imin=ii
        mmin=true

until (mmin)

// the main loop

for ii=iibegin to iend                            // go through the time series sampled at 100 Hz

    if (mmin)                                     // search for maximum
        if maximin(ICP[],ii)                      // systolic maximum identified?
            ICPmax=ICP[ii]
            imax=ii
            ICPamp=ICPmax-ICPmin
            ICPmean=mean(ICP[imin:imax])
            mmin=false


    if (min==false)
        if minimax(ICP[],ii)                      // diastolic minimum identified?
            ICPmin=ICP[ii]
            imin=ii
            ICPamp=ICPmax-ICPmin
            ICPmean=mean(ICP[imax:imin])
            mmin=true

    i25++                                         // 250 ms ?

    if (i25==26)                                  // yes
        i25=1
        ICPmeans[pointer]=ICPmean                 // enter mean and amp into the respective time series
        ICPamps[pointer]=ICPamp
        pointer++

        if pointer>64
            pointer=1

        pointercounter++
        if (pointercounter==5) // 1 second?
            pointercounter=1

// calculate RAQ

            fftinput[1:64]=transfer (ICPmeans[],pointer,64)          // transfer the time series in ICPmeans to fftinput[]
            fftinput[1:64]=fftinput[1:64]-mean(fftinput[1:64])       // remove offset
            fftinput[65:128]=0 // pad with zeroes
            fftoutput[] = fft(fftinput[],128)                        // 128 point fft returns complex spectral lines
            magnitudes[l:u]=abs(fftoutput[l:u])                      // the magnitudes calculated from the complex spectral
                                                                     // lines in the respiratory frequency range
            Arp=mean(magnitudes[l:u])                                // highest spectral line in the respiratory frequency
                                                                     // range

            fftinput[1:64]=transfer (ICPamps[],pointer,64)           // transfer the time series in ICPamps to fftinput[]
            fftinput[1:64]=fftinput[1:64]-mean(fftinput[1:64])       // remove offset
            fftinput[65:128]=0                                       // pad with zeroes
            fftoutput[]=fft(fftinput[],128)                          // 128 point fft returns complex spectral lines
            magnitudes[l:u]=abs(fftoutput[l:u])                      // the magnitudes calculated from the complex spectral
                                                                     // lines in the respiratory frequency range
            AAvp=mean(magnitudes[l:u])                               // highest spectral line in the respiratory
                                                                     // frequency range

            RAQ=Arp/AAvp

            sumRAQ=sumRAQ+RAQ
            countRAQ++
next ii

RAQresult=sumRAQ/countRAQ                         // the final value for RAQ

end determineRAQ
```

List 1. Pseudocode for calculating RAQ within a given time window

Appendix II

NNPH													
Pat. Nr.	**Age** [years]	**sex**	**ICP** [mmHg]	**RR** [1/min]	**HR** [1/min]	**RAQ_R**	**RAQ_C**	**ICP_{Smean}** [mmHg]	**TF_S**	**ICP_S** [mmHg]	**PVI** [ml]	**R_O** [mmHg/(ml/min)]	**k** [1/ml]
75	68	f	9.11	16.6	70.8	1.075	1.479	0.488	0.394	1.240	11.66	12.40	0.20
114	77	m	5.35	14.5	98.4	0.957	0.873	0.265	0.533	0.498	19.63	32.96	0.10
51	77	m	6.91	15.3	65.7	1.472	1.943	0.462	0.296	1.564			
81	73	f	3.03	14.6	69.0	0.845	1.173	0.441	0.510	0.864	14.32	7.76	0.16
63	72	f	8.94	15.8	58.4	1.138	1.210	0.132	0.139	0.952	20.75	14.53	0.11
125	83	m	9.68	15.3	70.0	0.975	2.002	0.416	0.310	1.344	5.59	14.17	0.41
49	72	f	8.57	15.2	76.5	0.886	1.518	0.457	0.488	0.937	19.48	7.33	0.12
32	76	m	12.59	14.4	83.0	0.885	1.176	0.389	0.510	0.763	16.40	10.76	0.14
55	83	f	2.55	16.7	71.5	1.212	1.643	0.217	0.345	0.629			
87	58	f	-3.41	14.9	34.9	1.075	1.349	0.452	0.457	0.990			
94	69	m	8.29	14.7	60.6	1.239	1.635	0.155	0.224	0.693	52.90	15.78	0.04
37	72	m	6.34	15.0	69.7	1.502	1.711	0.298	0.314	0.950	9.62	10.80	0.24
110	73	m	-6.78	15.4	28.9	1.088	1.052	0.418	0.356	1.176	6.84	10.85	0.34
10	70	f	10.77	15.1	63.9	0.827	1.171	0.693	0.564	1.229	20.16	7.13	0.11
61	70	m	3.90	14.7	71.1	0.866	0.911	0.248	0.278	0.892	4.54	7.17	0.51
99	76	f	2.28	15.0	68.3	1.067	1.356	0.380	0.331	1.148	13.71	9.55	0.17
100	63	f	9.78	14.1	54.0	0.998	1.213	0.322	0.355	0.905	9.52	8.78	0.24

Table 3. Values of craniospinal pressure-volume parameters and age for individual patients in the NNPH group

AQ													
Pat. Nr.	**Age** [years]	**sex**	**ICP** [mmHg]	**RR** [1/min]	**HR** [1/min]	**RAQ_R**	**RAQ_C**	**ICP_{Smean}** [mmHg]	**TF_S**	**ICP_S** [mmHg]	**PVI** [ml]	**R_O** [mmHg/(ml/min)]	**k** [1/ml]
105	63	f	12.41	14.7	53.5	0.911	1.093	0.546	0.502	1.088	6.55	6.79	0.35
54	53	m	14.31	15.3	55.0	0.804	1.070	1.041	0.715	1.455	33.83	7.49	0.07
47	64	m	1.51	14.3	41.7	0.650	1.073	1.297	0.720	1.800	25.05	8.01	0.09
43	63	f	6.66	15.5	75.0	0.980	1.556	0.558	0.419	1.331	11.93	20.35	0.48
60	74	m	6.33	15.8	83.5	0.947	1.432	0.530	0.461	1.148	13.95	15.51	0.17
57	18	m	12.55	14.4	56.4	0.851	1.021	0.737	0.614	1.200			

Table 4. Values of craniospinal pressure-volume parameters and age for individual patients in the AQS group