Injury, Int. J. Care Injured 40 (2009) 33–39

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Associations between intracranial pressure, intraocular pressure and mean arterial pressure in patients with traumatic and non-traumatic brain injuries☆

Tomasz Czarnik[a,*], Ryszard Gawda[a], Waldemar Kolodziej[b], Dariusz Latka[b], Katarzyna Sznajd-Weron[c], Rafal Weron[d]

[a] Department of Anaesthesia and Critical Care, Regional Medical Centre, Aleja Witosa 26, 45-418 Opole, Poland
[b] Department of Neurosurgery, Regional Medical Centre, Aleja Witosa 26, 45-418 Opole, Poland
[c] Complex Systems and Nonlinear Dynamics Division, Institute of Theoretical Physics, University of Wroclaw, Pl. M. Borna 9, 50-204 Wroclaw, Poland
[d] Hugo Steinhaus Center for Stochastic Methods, Institute of Mathematics and Computer Science, Wroclaw University of Technology, ul. Janiszewskiego 14a, 50-372 Wroclaw, Poland

ARTICLE INFO

Article history:
Accepted 8 October 2008

Keywords:
Intracranial pressure
Intraocular pressure
Mean arterial pressure
Ocular tonometry
Correlation
Brain injury

ABSTRACT

Introduction: Anatomical proximity of the eye and the intracranial space is a fact but the existence of physiological and pathophysiological relationships between them is elusive. The objective of this study was to explore anatomical and pathophysiological interactions between the eye and the intracranial space and to assess clinical utility of intraocular pressure measurement in estimation of intracranial pressure in patients with brain injuries and to discover how haemodynamic instability could influence these interactions. Controversy surrounds the recent literature concerning this problem and the consensus has not been achieved.

Materials and methods: We evaluated the correlation between intracranial pressure and intraocular pressure, intracranial pressure and mean arterial pressure, intraocular pressure and mean arterial pressure in 40 patients with brain injuries initially comatose, admitted to our hospital. All patients required the intracranial pressure monitoring on clinical grounds. Simultaneous recordings of intracranial pressure, intraocular pressure and mean arterial pressure were performed.

Results: We calculated both the linear correlation coefficient and the Spearman rank-order correlation coefficient for all three relations. We found significant correlation between intraocular pressure and mean arterial pressure in 63% of the tested population. When the power of the test was increased, by considering only patients with 11 or more observations, this ratio increased to 76%. However, the correlation between intraocular pressure and intracranial pressure, as well as, between intracranial pressure and mean arterial pressure was not significant.

Conclusions: There is no anatomical and pathophysiological basis for the statement that intraocular pressure can be used as an indirect estimator of intracranial pressure.

Introduction

Intracranial hypertension is one of the most important therapeutical problems in the neurocritical care. The pathophysiology, monitoring and treatment of intracranial pressure (ICP) are relatively well known problems.[7,30,34] Measurement of ICP is the gold standard in neurocritical care worldwide despite the fact that close relation between invasive ICP monitoring and better outcome is observed but still not well documented.[5,17] Estimation of cerebral perfusion pressure (CPP) is the mainstay of ICP/CPP directed therapy of intracranial hypertension especially in severe traumatic brain injury (severe TBI).[10,13,23,33,39] Calculation of CPP is performed by intraventricular or intraparenchymal ICP measurement and invasive mean arterial pressure (MAP) monitoring according to the equation CPP = MAP-ICP. ICP sensor is usually implanted in the neurocritical care unit, the emergency department or operating room at the day of admission after initial diagnostic procedure (computed tomography, CT, magnetic resonance imaging, MRI).

Anatomical proximity of the eye and the intracranial space is a fact, but the existence of physiological and pathophysiological

☆ Work should be attributed to the Department of Anaesthesia and Critical Care, Regional Medical Centre, Aleja Witosa 26, 45-418 Opole, Poland.

* Corresponding author at: Department of Anaesthesia and Critical Care, Regional Medical Centre, Aleja Witosa 26, 45-418 Opole, Poland. Tel.: +48 669906333.
E-mail addresses: antocz@mp.pl, tczarnik@mac.com (T. Czarnik).

0020–1383/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.injury.2008.10.010

relationships between them is elusive. Some authors claim that it is possible to estimate ICP in an alternative way using intraocular pressure (IOP) as an indirect surrogate for ICP. Potential clinical utility concerns prehospital and initial hospital period of brain injury when the invasive ICP measurement procedure has not been yet established and the indirect estimation of ICP can lead to significant clinical conclusions, modification of the therapeutic protocol and elimination of the potential risk of secondary insults to the brain which are the most important problems the physician has to face during the management process of brain injury. Other ways of indirect assessment of ICP much as pulsatility index calculated from transcranial Doppler measurement, evoked potentials, impedance audiometry, ophthalmodynamometry and scalp blood flow are not widely used in clinical practice.[1,20,26,37]

The objective of this study was to explore anatomical and pathophysiological interactions between the eye and the intracranial space and to assess clinical utility of IOP measurement as an indirect estimation of ICP in patients with brain injuries. Our aim was also to discover how haemodynamic instability (fluctuations of MAP), which is a relatively often observed phenomenon in this group of intracranial pathologies, could modify these interactions and influence the absolute values of IOP and ICP. Controversy surrounds the recent literature concerning this problem and the consensus has not been achieved. We would like to contribute our view to this clinical dilemma. We present the final data of clinical series. A preliminary report of this study was published earlier.[6]

Patients and methods

The methodology of this prospective cohort study included invasive, continuous monitoring of ICP and MAP. Periodical IOP measurements were performed using contact Schioetz Eye Tonometer. Invasive, continuous ICP measurements were instituted on clinical grounds in every patient according to the Brain Trauma Foundation existing guidelines.[10] The study was approved by the local ethics committee in Opole (decision number 96/2003). Informed consent was obtained from the patient's closest relative. We explored the correlation between IOP and ICP, IOP and MAP, ICP and MAP.

The study was performed in the Department of Neurosurgery, Regional Medical Centre, Opole, Poland between December 2003 and September 2006. The Regional Medical Centre in Opole is the main trauma centre in Opole Region and serves a population of 1 million people.

Comatose patients with traumatic and non-traumatic brain injuries caused by brain trauma, subarachnoid haemorrhage (SAH) and spontaneous intracerebral haemorrhage (ICH) who were admitted to the emergency department were enrolled. All patients were in coma at the time of admission with a Glasgow Coma Scale score (GCS) between 3 and 8. After initial resuscitation, physical examination and diagnostics including CT, patients were transferred to the operating room or neurosurgery unit. Investigators were called by treating neurosurgeon and a final inclusion decision was made. Final inclusion criteria were: isolated TBI, SAH, ICH, coma (GCS score 3–8), clinical indications for ICP monitoring according to Brain Trauma Foundation guidelines, time less than 6 h from impact, age above 14 years. Exclusion criteria were: multiply injured patients, spinal cord injury, high-dose steroid therapy, significant facial and ocular trauma, a history of glaucoma, corneal disease and age of 14 years or less.

Invasive ICP measurement included intraparenchymal placement of the Microchip microtransducer (Codman MicroSensor Basic Kit, Johnson & Johnson, Berkshire, UK) in the operating room on the day of admission. The tip of the microtransducer was positioned 3–4 cm within the brain parenchyma via a frontal burr hole after calibration. ICP Express Monitor interface (Codman & Shurtleff Inc., Raynham, MA, USA) and Spacelabs Medical monitor type PC Scout (Spacelabs Medical, Issaquah, WA, USA) were used for measurement. A value of 20 mmHg was regarded as the cut-off for normal ICP. After 5–7 days of measurement the ICP microtransducer was removed.[15,38] Continuous invasive MAP measurement was performed using bedside transducers (Gabarith, Becton Dickinson Medical, Sandy, Utah, USA) zeroed to the heart and intraarterial cannula 20G Venflon Pro (Becton Dickinson Infusion Therapy, Helsingborg, Sweden) for radial artery cannulation and single lumen catheter 16G type CV-04306 (Arrow International Inc., Reading, PA, USA) for femoral artery cannulation.[2]

Additional bedside monitoring procedures fulfilled the criteria of critical care monitoring and included electrocardiography (ECG), arterial saturation (SpO_2), central venous pressure (CVP), respiratory rate (RR). Analogue signals from bedside monitors were transformed to digital signals by the card number BNC-2110 (National Instruments Corporation, Austin, TX, USA) and stored on the hard disc of a personal computer using LabVIEW 7.0 (National Instruments Corporation, Austin, TX, USA).

The IOP was measured by using the Schioetz Eye Tonometer (Rudolf Riester GmbH & Co, Jungingen, Germany) in both eyes and mean IOP was calculated. Immediately before the IOP measurement was taken the tonometer was cleaned and then placed on the test block (testing procedure). If the pointer had been set to zero, the start of measurement was possible. The patient was in a recumbent position. The patient was sedated if necessary for proper measurement and patient safety (to stop intracranial and haemodynamic response). Midazolam was used for sedation (Midanium, Polfa Warsaw, Warsaw, Poland) in a dose of 2–5 mg (0.05 mg kg^{-1}) intravenously. After anaesthetising the cornea with the proxymetacaine (Alcaine-Proxymetacaini hydrochloridum, Alcon-Couvreur S.A/N.V., Puurs, Belgium), the tonometer was placed in a vertical position at the centre of the cornea. Reliable pressure values were recorded when the pointer had shown a pulse. According to the manufacturer, the pressure of a healthy eye was approximately 16 mmHg (average value). The cut-off point for normal IOP was defined as 21 mmHg.

Simultaneous measurement values of MAP, ICP and IOP were recorded in the measurement protocol. IOP calculation was performed at 8-h intervals and (depending on availability of the investigator) if ICP value had changed by 5 mmHg or more. All IOP measurement procedures were performed by the same person (Tomasz Czarnik) with the same equipment. The study protocol was initiated within 24 h after brain injury in every patient and terminated after 1–8 days (mean measurement period, 4.5 days; S.D., 1.7) (Table 1). The approach to the therapy of patients followed general critical care principles and was ICP/CPP-directed. All patients were initially mechanically normoventilated without positive end-expiratory pressure (PEEP) institution. The management of elevated ICP included 15–30° head-up position, sedation, osmotherapy, avoidance of jugular venous obstruction, normovolaemia, prevention of hyperthermia, moderate cooling, surgical intervention and barbiturate coma as the last resort. The treatment for ICP was initiated at an upper threshold of 20 mmHg. The aim of the therapeutic protocol was to maintain CPP above 60 mmHg (above lower limit of cerebral autoregulation) with norepinephrine or dopamine intravenous infusion if necessary.

To determine correlations between IOP, ICP and MAP we calculated the linear correlation coefficient and the Spearman rank-order correlation coefficient.[24] The dependence was treated as significant if the p-value <0.05 for both methods simultaneously (in a two-sided test with the null hypothesis of no correlation). The

Table 1
Demographic data of the study group. No.: patient number, GCS: Glasgow Coma Scale score estimated on admission, *M*: monitoring period in days, *N*: number of simultaneous measurements of IOP, ICP, MAP in the sample, TBI: traumatic brain injury, SAH: subarachnoid haemorrhage, ICH: spontaneous intracranial haemorrhage.

No.	Age	Sex	Diagnosis	GCS	*M*	*N*
1	34	M	TBI	4	5	11
2	74	M	ICH	7	6	18
3	64	M	SAH	4	6	17
4	53	M	TBI	4	7	19
5	69	M	ICH	5	2	6
6	65	M	TBI	4	4	9
7	46	F	ICH	5	6	19
8	56	M	TBI	4	5	15
9	57	M	SAH	4	4	11
10	74	M	ICH	7	6	13
11	42	M	TBI	4	5	12
12	36	M	TBI	8	6	12
13	55	M	TBI	4	5	15
14	59	M	ICH	4	8	18
15	70	M	SAH	4	3	10
16	26	M	TBI	6	3	6
17	36	M	SAH	5	5	14
18	67	M	TBI	6	5	14
19	64	F	TBI	3	6	14
20	74	M	TBI	4	4	8
21	43	F	SAH	4	3	10
22	68	F	TBI	3	7	16
23	70	M	TBI	7	7	13
24	62	M	TBI	4	2	5
25	51	F	SAH	5	4	10
26	62	F	ICH	6	3	9
27	51	M	TBI	5	4	12
28	50	M	TBI	5	1	5
29	58	M	TBI	6	7	16
30	22	M	TBI	4	4	9
31	42	M	TBI	4	6	16
32	15	F	TBI	4	3	10
33	53	M	ICH	4	2	10
34	48	F	ICH	4	5	12
35	70	M	ICH	7	3	7
36	53	M	ICH	4	3	9
37	63	M	TBI	6	4	13
38	25	M	TBI	5	6	13
39	69	M	TBI	5	3	11
40	61	M	TBI	4	4	11

idea of using two statistical methods in this study was to augment the reliability of results. All statistical analyses were performed using Matlab 7.2 (The Math Works Inc., Natick, MA, USA). The power analysis was independently confirmed with PASS 2008 (NCSS, Kaysville, Utah, USA).

Results

Forty patients, 8 females and 32 males were enrolled in the trial. Their ages ranged from 15 to 74 years (mean value, 53.9; S.D., 15.3). Patients sustained such intracranial pathologies as severe TBI (24 patients) with intracranial contusions, haematomas and diffuse axonal injury (DAI), subarachnoid haemorrhage (6 patients) and spontaneous intracerebral haemorrhage (10 patients). Demographic data of the study group are presented in Table 1. In all, 478 simultaneous recordings of IOP, ICP, MAP were performed (5–19 per patient; mean, 12; S.D., 3.75). The lowest IOP value recorded was 4.2 mmHg and the highest, 46.9 mmHg (mean value, 14.2 mmHg; S.D., 6.6), for ICP and MAP, respectively: lowest, 0 mmHg; highest, 150 mmHg (mean value, 29.3 mmHg; S.D., 23.0), and lowest, 47 mmHg; highest, 170 mmHg (mean value, 97.8 mmHg; S.D., 21.6).

All calculated linear correlation coefficients and Spearman rank-order correlation coefficients are presented in Tables 2 and 3. Out of the 40 patients, 6 patients had a significant (and positive) correlation of MAP to ICP. In the whole group of 40 patients both positive and negative linear correlation coefficients were estimated (mean value, 0.1992; S.D., 0.4367). This, together with the fact that similar results were obtained for the Spearman rank-order correlation coefficient, indicates that the MAP-ICP dependence is no more than very weakly positive.

Statistically significant correlation of ICP to IOP appeared in eight patients (20% of the tested population). In seven patients of this group the correlation was positive, but in patient number 5 the correlation was negative. As in the analysis of MAP-ICP dependence, in the whole group of 40 patients both positive and negative linear correlation coefficients were estimated (mean value, 0.2273; S.D., 0.4488). Together with the fact that similar results were obtained for the Spearman rank-order correlation coefficient, this indicates that the ICP-IOP dependence is no more than very weakly positive.

Significant (and positive) correlation of MAP to IOP was found in 25 patients. The range for the value of the linear correlation coefficient was 0.5890–0.9812 (mean value, 0.8466; S.D., 0.1044), whereas for the Spearman rank-order correlation coefficient 0.6436–1 (mean value, 0.8402; S.D., 0.1099). Unlike in the case of previous two correlation studies, in the whole group of 40 patients only positive linear correlation coefficients between MAP and IOP were estimated (mean value, 0.7337; S.D., 0.2323). Also the Spearman rank-order correlation coefficients were positive (except for one patient, no. 15).

Power analysis reveals the fact that a sample size of 11 observations achieves 73%, 82% and 90% power to detect a difference between the null hypothesis of no linear correlation and the alternative hypothesis correlation of 0.7, 0.75 and 0.8, respectively, using a two-sided hypothesis test with a significance level of 0.05. In our previous study[6] the median value (the median is more robust to outliers, hence it is used here instead of the mean) of the linear correlation between MAP and IOP was found to be ca. 0.75. Taking this value as a benchmark and considering only patients with at least 11 observations allows us to say that the power (the probability of rejecting a false null hypothesis) of the test for linear correlation is 'on average' above 80%, which is a commonly acceptable value. Consequently, we repeated the MAP-IOP correlation study selecting only patients who had at least 11 measurements (there are 25 such patients in the whole study group). Significant (and positive) correlation of MAP to IOP was found in 19 patients. The range for the value of the linear correlation coefficient was 0.5890–0.9711 (mean value, 0.8205; S.D., 0.1053), whereas for the Spearman rank-order correlation coefficient 0.6436–0.9908 (mean value, 0.8121; S.D., 0.1094).

Globally, only the correlation between MAP and IOP was significant, but neither ICP and IOP nor MAP and ICP could be considered as correlated. Linear dependence was observed only between MAP and IOP (see Fig. 1).

Discussion

We hypothesised that there were two possible ways of interaction between the eye and the intracranial space which could be the source of relationships between ICP and IOP. First, there was the anatomical proximity of the eye and the intracranial space and probable mechanism of direct pressure transmission through the cerebrospinal fluid surrounding the optic nerve sheath exactly at the point where the optic nerve enters the orbit. The second mechanism (treated by us as more probable) was pressure transmission through the venous and/or arterial system of the brain and the ocular bulb to the intraocular fluid.

Table 2
Calculated linear correlation coefficients; bold numbers represent significance at the usual 5% level. No.: patient number, *N*: number of simultaneous measurements of IOP, ICP, MAP in the sample.

No.	*N*	Linear correlation coefficient			*p*-Value		
		MAP ↔ ICP	MAP ↔ IOP	ICP ↔ IOP	MAP ↔ ICP	MAP ↔ IOP	ICP ↔ IOP
1	11	−0.0480	0.5878	0.4916	0.8886	0.0572	0.1246
2	18	−0.1813	0.8526	−0.0783	0.4716	<**0.0001**	0.7575
3	17	0.5250	0.8013	0.6142	**0.0305**	**0.0001**	**0.0087**
4	19	0.3137	0.7164	0.0765	0.1909	**0.0006**	0.7555
5	6	−0.6748	0.9160	−0.8252	0.1414	**0.0103**	**0.0432**
6	9	−0.0397	0.9233	0.0946	0.9193	**0.0004**	0.8087
7	19	−0.0068	0.8744	0.2765	0.9779	<**0.0001**	0.2518
8	15	0.6523	0.1301	0.0394	**0.0084**	0.6439	0.8891
9	11	0.7993	0.9711	0.8762	**0.0032**	<**0.0001**	**0.0004**
10	13	0.7326	0.4899	0.0397	**0.0044**	0.0893	0.8976
11	12	−0.1911	0.4519	0.4971	0.5519	0.1403	0.1001
12	12	−0.2981	0.8026	0.0940	0.3466	**0.0017**	0.7713
13	15	0.1439	0.9650	0.1642	0.6090	<**0.0001**	0.5588
14	18	0.0743	0.2305	0.5838	0.7696	0.3575	**0.0110**
15	10	−0.4196	0.8726	−0.6566	0.2274	**0.0010**	**0.0392**
16	6	0.4645	0.0056	−0.4869	0.3534	0.9916	0.3274
17	14	0.2953	0.7863	0.6709	0.3053	**0.0009**	**0.0086**
18	14	−0.0270	0.6518	0.4731	0.9269	**0.0115**	0.0875
19	14	−0.3976	0.8560	−0.4056	0.1592	**0.0001**	0.1502
20	8	0.1757	0.6620	0.2310	0.6773	0.0737	0.5820
21	10	−0.6114	0.5815	−0.4150	0.0604	0.0779	0.2330
22	16	0.3288	0.5202	0.5457	0.2137	**0.0389**	**0.0288**
23	13	0.3230	0.7877	0.0801	0.2818	**0.0014**	0.7948
24	5	0.5406	0.8288	0.7632	0.3469	0.0828	0.1333
25	10	0.5227	0.4588	−0.0383	0.1211	0.1822	0.9163
26	9	0.5097	0.9273	0.6951	0.1610	**0.0003**	**0.0376**
27	12	0.2372	0.9095	0.2584	0.4578	<**0.0001**	0.4174
28	5	0.8606	0.9675	0.7831	0.0612	**0.0070**	0.1172
29	16	0.6383	0.5890	0.2320	**0.0078**	**0.0164**	0.3873
30	9	−0.5111	0.6873	−0.3664	0.1597	**0.0408**	0.3321
31	16	0.4928	0.8340	0.4136	0.0525	**0.0001**	0.1112
32	10	0.3529	0.7479	0.0722	0.3172	**0.0129**	0.8428
33	10	0.9026	0.9038	0.8725	**0.0004**	**0.0003**	**0.0010**
34	12	0.0269	0.6801	0.3795	0.9339	**0.0150**	0.2237
35	7	−0.4109	0.9812	−0.3912	0.3598	**0.0001**	0.3855
36	9	0.2754	0.8860	0.2403	0.4732	**0.0015**	0.5335
37	13	0.6174	0.8908	0.7267	**0.0246**	<**0.0001**	**0.0049**
38	13	0.4056	0.7772	0.7066	0.1692	**0.0018**	**0.0069**
39	11	0.8883	0.9270	0.9040	**0.0003**	<**0.0001**	**0.0001**
40	11	−0.3123	0.9159	−0.1411	0.3498	**0.0001**	0.6789

The results of our study reveal that in general the correlation between ICP and IOP does not exist. Eight patients with a positive correlation of ICP to IOP can be treated as a minority. There were no special features which could lead to any conclusion and point at the probable reason for the appearance of the positive correlation of ICP to IOP in such a small group of patients. Aetiologically, it was a heterogenic group. The correlation between MAP and ICP revealed in six patients of the tested population is globally insignificant too. In fact, lack of correlation between MAP and ICP should be treated with caution. Relationships between MAP and ICP are used for the assessment of cerebral autoregulation. The negative correlation of MAP to ICP is observed when the mechanism of cerebral autoregulation is preserved whereas the positive correlation exists when this mechanism is impaired. These relations are described by the pressure–reactivity index (PRx) which reflects changes of ICP as a consequence of spontaneous MAP fluctuations.[8,18] We used single measurements of MAP and ICP for estimating the correlation between these variables but it seems that long term continuous recordings should be used for such estimations, especially in conditions of haemodynamic instability. Statistically significant correlation between MAP and IOP was observed in 63% of the tested population. Moreover, when the power of the test was increased, by considering only patients with at least 11 observations, this ratio increased to 76%. Our results contribute to the controversy that surrounds the recent literature exploring the problem of relation between the eye and intracranial space in patients with intracranial pathologies.

Salman claims that tonometric measurement of IOP is a good estimator of ICP value.[35] He concludes that the cerebrospinal fluid surrounds the optic nerve sheath to the point where the optic nerve enters the orbit so elevations of ICP could be directly transmitted to the eyeball. A second potential mechanism according to Salman is the rise of the ophthalmic venous pressure as a direct consequence of the ICP increase. He cites Lehman et al.'s study on Rhesus monkeys.[21] Lehman et al. used an intracranial balloon to raise the ICP and then measured the IOP. The increase of IOP was not rapid and started when the ICP value reached 46.8 mmHg (mean value). The IOP rise curve reached a plateau at ICP values about 74 mmHg and the mean IOP increase was only 6.4 mmHg. We think that Lehman et al.'s study is not a proof of the utility of IOP in the indirect estimation of ICP. The IOP rise was not high and started when the ICP reached very high values. Such ICP values are relatively rare phenomena in the initial phase of brain injury and the therapy for intracranial hypertension starts usually at the ICP threshold of 20 mmHg.

Hayreh was raising ICP to 50 mmHg in 27 Rhesus monkeys and did not observe increases in IOP.[11] He claims that there is no anatomical and pathophysiological basis to explain relationships

Table 3
Calculated Spearman rank-order correlation coefficients; bold numbers represent significance at the usual 5% level. No.: patient number, *N*: number of simultaneous measurements of IOP, ICP, MAP in the sample.

No.	*N*	Spearman rank-order correlation coefficient			*p*-Value		
		MAP ↔ ICP	MAP ↔ IOP	ICP ↔ IOP	MAP ↔ ICP	MAP ↔ IOP	ICP ↔ IOP
1	11	−0.2965	0.0151	0.4567	0.3759	0.9648	0.1579
2	18	−0.1172	0.8272	0.0927	0.6432	<**0.0001**	0.7146
3	17	0.4760	0.8323	0.6551	0.0535	<**0.0001**	**0.0043**
4	19	0.3033	0.7174	−0.0825	0.2069	**0.0005**	0.7372
5	6	−0.4638	0.7143	−0.8117	0.3542	0.1108	**0.0499**
6	9	−0.0681	0.9132	0.0934	0.8618	**0.0006**	0.8111
7	19	0.0704	0.8745	0.3499	0.7747	<**0.0001**	0.1419
8	15	0.7242	0.0437	0.3636	**0.0023**	0.8772	0.1827
9	11	0.7969	0.9908	0.7972	**0.0033**	<**0.0001**	**0.0033**
10	13	0.6792	0.7052	0.2401	**0.0107**	**0.0071**	0.4294
11	12	−0.2228	0.3926	0.4809	0.4863	0.2069	0.1135
12	12	−0.2340	0.8182	−0.0186	0.4642	**0.0011**	0.9543
13	15	0.0497	0.9409	0.1895	0.8603	<**0.0001**	0.4987
14	18	0.0281	0.3432	0.5267	0.9120	0.1632	**0.0247**
15	10	−0.3884	0.9077	−0.5276	0.2674	**0.0003**	0.1170
16	6	0.2273	−0.0455	−0.3636	0.6650	0.9319	0.4786
17	14	0.1536	0.9014	0.4602	0.6001	<**0.0001**	0.0978
18	14	0.0058	0.6520	0.4465	0.9843	**0.0115**	0.1095
19	14	−0.5056	0.9110	−0.3369	0.0651	<**0.0001**	0.2388
20	8	0.1520	0.6121	0.0132	0.7193	0.1068	0.9752
21	10	−0.4692	0.2006	−0.1354	0.1713	0.5784	0.7092
22	16	0.2230	0.4608	0.5949	0.4065	0.0724	**0.0151**
23	13	0.3833	0.7418	0.1294	0.1960	**0.0037**	0.6735
24	5	0.3947	0.2895	0.7895	0.5108	0.6366	0.1122
25	10	0.5836	0.4360	0.2530	0.0765	0.2078	0.4806
26	9	0.3629	0.9061	0.4292	0.3371	**0.0008**	0.2490
27	12	−0.0319	0.9056	0.0565	0.9216	**0.0001**	0.8614
28	5	0.6000	0.9747	0.6669	0.2848	**0.0048**	0.2189
29	16	0.7384	0.6457	0.3326	**0.0011**	**0.0069**	0.2082
30	9	−0.5788	0.4702	−0.2684	0.1025	0.2016	0.4850
31	16	0.4048	0.6436	0.5329	0.1199	**0.0071**	**0.0335**
32	10	0.4195	0.5858	0.1305	0.2276	0.0752	0.7194
33	10	0.7744	0.8750	0.6962	**0.0085**	**0.0009**	**0.0253**
34	12	0.0248	0.7018	0.3762	0.9390	**0.0110**	0.2281
35	7	−0.3670	1.0000	−0.3670	0.4181	<**0.0001**	0.4181
36	9	0.3361	0.6629	0.5224	0.3765	0.0516	0.1490
37	13	0.5155	0.8705	0.7047	0.0714	**0.0001**	**0.0072**
38	13	0.0347	0.7030	0.4092	0.9105	**0.0074**	0.1650
39	11	0.8545	0.9245	0.8925	**0.0008**	<**0.0001**	**0.0002**
40	11	0.0484	0.8268	−0.0399	0.8877	**0.0017**	0.9073

between IOP and ICP. The cerebrospinal fluid is separated from the eyeball and the optic nerve by fibrous tissue which limits pressure transmission. The hypothesis that elevation of ICP could be transmitted via the cavernous sinus to the superior ophthalmic vein was clinically verified by Lirng et al.[22] He observed a widening of the superior ophthalmic vein in intracranial hypertension on MRI, but high pressure in the superior ophthalmic vein was not transmitted to IOP. We think that it could be explained by the fact that the superior ophthalmic vein is connected not only with the cavernous sinus but also with the facial vein (via the angular vein). Pressure elevation in the cavernous sinus theoretically might divert blood flow toward the facial vein via the superior ophthalmic vein, preventing IOP rise (there are no valves in the superior ophthalmic vein). This could explain the lack of correlation between ICP and IOP in our study.

Firsching et al. and Motschmann et al. confirmed the lack of correlation between IOP and ICP but observed strict relations between IOP and venous outflow pressure (VOP) from the central retinal vein in 31 patients with intracranial hypertension.[9,26] They used venous ophthalmodynamometry to estimate VOP. Querfurth et al. used venous ophthalmodynamometry to estimate VOP and transcranial Doppler to measure blood flow velocity in the central retinal artery and ophthalmic artery.[29] He assessed the Gosling pulsatility index (PI) for these arteries which is used for a non invasive estimation of ICP. He proposed a new index of VOP/PI as a better predictor of ICP rises. We think that these observations could also be anatomically explained. The central retinal vein directly enters the cavernous sinus and does not have a major alternative anastomosis. That is why the VOP elevation reflects intracranial hypertension, while it has no influence on IOP.

Sheeran et al. observed considerable correlation between IOP and ICP in 31 patients with various intracranial pathologies (77% of the tested population).[36] The mean increase in ICP per 1 mmHg rise in IOP was 11 mmHg but a significant diversity was observed in the tested group. Sheeran et al. claimed that the variability in the value of the relation of IOP to ICP with this method of indirect estimation of ICP is not useful in clinical practice. Our study uses a slightly different approach, which might be the cause of the lack of correlation of IOP to ICP. Each patient was observed for a longer period of time. The minimum number of measurements per day was 3. Haemodynamic instability was not the cause of exclusion and this instability seemed very interesting to us. Frequent changes in MAP, which is a relatively often observed phenomenon in patients with brain injuries, were associated with significant IOP value changes in most patients (positive correlation) without marked changes in ICP. It could suggest that MAP-related regulation of IOP is present in patients with intracranial pathology. We think that the rise of MAP could be directly transmitted to the arteries of the eyeball and then to the ocular fluid arising the IOP. The eyeball is supplied with arterial blood by the ophthalmic

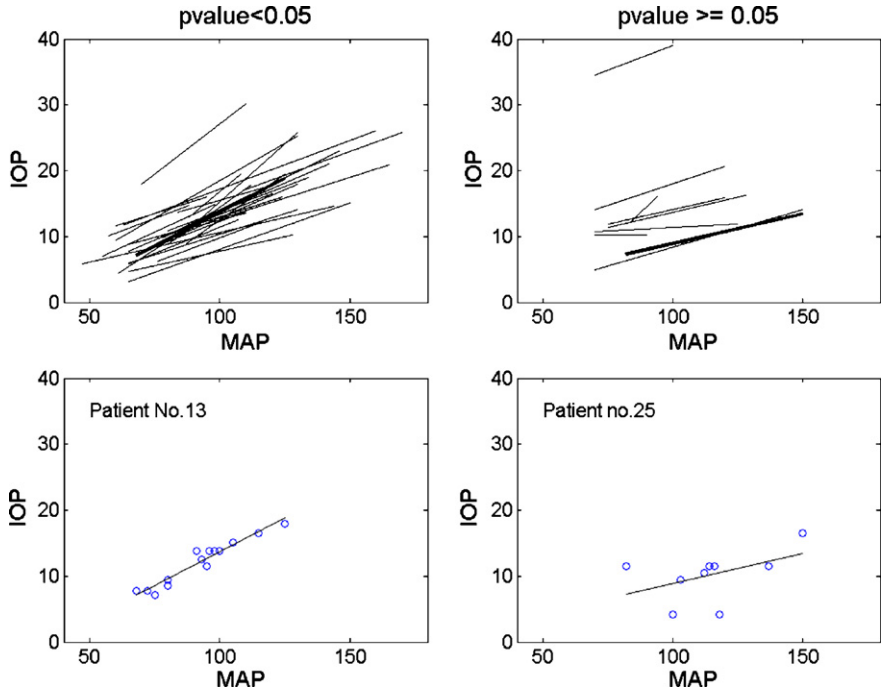

Fig. 1. (Top left) Linear regression lines, corresponding to linear correlation between IOP and MAP, for 30 patients with significant (at the 5% level) linear correlation. Globally, significant linear correlation can be observed for these data. The regression line emphasised in bold corresponds to patient no. 13. (Top right) Linear regression lines for the remaining 10 patients. The regression line emphasised in bold corresponds to patient no. 25. (Bottom right) Correlation plot for a sample patient (no. 13) with significant linear correlation. (Bottom right) Correlation plot for a sample patient (no. 25) with insignificant linear correlation.

artery, which is the intracranial branch of the internal carotid artery. The ophthalmic artery enters the eyeball with the optic nerve through the optic canal.

Raitsamer et al. studied the relation between ocular haemodynamics and IOP in rabbits.[31,32] According to him IOP is dependent on ocular perfusion pressure (OPP), which can be defined according to the equation OPP = MAP-IOP. There is a direct link between production of ocular fluid, the value of IOP and the blood flow through the ciliary body of the eye. The rise of MAP can directly stimulate the IOP increase. Nagdeve et al. studied the IOP rise after ketamine administration in children.[27] Ketamine stimulates ciliary blood flow and as a consequence indirectly elevates the IOP. We think that the close relation of MAP to IOP observed in our study can be explained in the same way. Because of the nonexistence of the mechanism of autoregulation in the ciliary body we can make the assumption that there is probably a linear relation of IOP to ciliary blood flow and, as a consequence, to MAP. The absence of such correlations in 40% of the tested population could be caused by considerable influences of other mechanisms of IOP regulation (extraocular muscles contraction or central regulation). Close relation between MAP and IOP is observed in anaesthetic practice. The IOP rises after anaesthesia induction and endotracheal intubation can be caused by inadequate analgesia, stress reaction, catecholamine stimulation, increase of ciliary blood flow and, finally, high values of MAP.[14,16,25,28]

Laschutka et al. claim that high tonometric values of IOP are good predictors of intracranial hypertension but the strict calculation of ICP from IOP is not possible.[19] We think that an absolute high value of IOP is not a good predictor of intracranial hypertension. In a small group of humans after the age of 40 years, IOP values higher than 20 mmHg are observed and this is not treated as pathology, if only IOP measurement trends are analysed. Laschutka et al. performed 3 simultaneous measurements of IOP in each patient (mean value) which is a relatively small number. They did not analyse correlations of IOP to ICP in every patient but rather summarised the results for all 76 simultaneous measurements. If such a methodology was applied to our dataset (with the outlier–patient 14–excluded) we would find significant correlations for all three pairs: MAP-ICP, MAP-IOP and ICP-IOP. But this information is meaningless as population-wide values do not necessarily translate into values for individual patients, and it is the latter that we are truly interested in. Moreover, in the scatter plot of ICP versus IOP presented by Laschutka et al. a significant dispersion appears in the range of high values of IOP and ICP, which is rather a proof of poor agreement between these two measurements.

Limitations

The significant limitation of our study was the availability of the person performing IOP measurement (Tomasz Czarnik). We assumed that measuring IOP by one person only eliminates the bias related to different techniques of measurement. But as a consequence it was not possible to react to every change of ICP value of 5 mmHg and more. The measurement regime of 8-hour intervals was preserved.

The second limitation was the influence of drugs on IOP. The IOP value can be modified by mannitol, carbonic anhydrase inhibitors, beta-adrenergic receptor antagonists and midazolam. Carbonic anhydrase inhibitors and beta-adrenergic receptor antagonists were not administered in the study group but almost every patient received mannitol (osmotherapy) and midazolam (sedation). Mannitol is administered intravenously before ocular surgical procedures in a dose of 1.5–2 g kg^{-1} to lower IOP. Patients of the study group were receiving mannitol in a doses of 0.5–0.8 g kg^{-1} every 4–6 h. Mean sedative intravenous doses of midazolam in the study group were 0.1–0.2 mg kg^{-1} per hour and additional doses administered before the measurement procedure were 0.5 mg kg^{-1}. Carter et al. claim that intravenous administration of midazolam in a dose of 1 mg does not lower IOP,[3] whereas Hirlinger et al. observed a reduction in intraocular pressure after

administration of midazolam at a much higher dose of 0.15 mg kg^{-1} intravenously with other anaesthetic drugs after induction of anaesthesia.[12] Cesati et al. measured IOP after intravenous midazolam premedication (0.05 mg kg^{-1}) and anaesthesia induction.[4] No reduction in IOP was observed. We assumed that mannitol and midazolam doses administered in the study group had limited influence on IOP.

We wondered whether mechanical ventilation could have modified the results. We did not observe peak inspiratory pressures above 30 cmH_2O, PEEP was not used. However, Theba et al. claims that long lasting mechanical ventilation with PEEP of 15 cmH_2O can elevate IOP.[40] The clinical necessity of the PEEP institution did not appear in the study group.

Conclusions

There is no anatomical and pathophysiological basis for the statement that IOP can be used as an indirect estimator of ICP. Ocular tonometry is not a useful method for the assessment of ICP in prehospital and initial hospital period in patients suffering from brain injuries. The lack of correlation between MAP and ICP, which appeared in our study, should be treated with caution. It seems that that long term continuous recordings should be rather used for such estimations, especially in conditions of haemodynamic instability. Considerable correlation of MAP to IOP in 63% of patients of the study group (when the power of the test was increased, by considering only patients with 11 or more observations, this ratio increased to 76%) appeared probably because there is a direct link between production of ocular fluid, the value of IOP and the blood flow through the ciliary body of the eye. The absence of such correlations in 40% of the tested population could have been caused by considerable influences of other mechanisms of IOP regulation, like extraocular muscles contraction or central regulation. On the other hand, the moderately large values of the correlation coefficient suggest that with much larger samples, almost all subjects would be shown to have a significant positive association.

Conflict of interest

The authors disclose any financial and personal relationships with other people, or organizations, that could inappropriately influence (bias) their work, all within 3 years of the beginning the work submitted.

Acknowledgments

Authors would like to thank Professor Wojciech Gaszynski MD for his advice in designing this study and scientific support.

References

1. Bellner J, Romner B, Reinstrup P, et al. Transcranial Doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP). Surg Neurol 2004;62:45–51.
2. Bessman ES. Invasive monitoring, pacing techniques and automated and implantable defibrillators. In: Tintinalli JE, Kelen GD, Stapczynski JS, editors. Emergency medicine. A comprehensive study guide. 6th ed., McGraw-Hill; 2004. p. 132–8.
3. Carter K, Faberowski LK, Sherwood MB, Berman LS, McGorray S. A randomized trial of the effect of midazolam on intraocular pressure. J Glaucoma 1999;8:204–7.
4. Cesati A, Aldegheri G, Fanelli G, et al. Lightwand intubation does not reduce the increase in intraocular pressure associated with tracheal intubation. J Clin Anesth 1999;11(3):216–9.
5. Cremer OL, Dijk van GW, Wensen van E, et al. Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. Crit Care Med 2005;33(10):2207–13.
6. Czarnik T, Gawda R, Latka D, et al. Non-invasive measurement of intracranial pressure—is it possible? J Trauma 2007;62(1):207–11.
7. Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. J Neurol Neurosurg Psychiatry 2004;75:813–21.
8. Czosnyka M, Smielewski P, Kirkpatrick P, et al. Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 1997;41:11–9.
9. Firsching R, Schutze M, Motschmann M, et al. Non-invasive measurement of intracranial pressure (letter). The Lancet 1998;351:523–4.
10. Guidelines for the management of severe traumatic brain injury, 3rd ed. A joint venture of the Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, AANS/SCN Joint Section on Neurotrauma and Critical Care. Brain Trauma Foundation; 2007 (www.braintrauma.org).
11. Hayreh SS. Non-invasive measurement of intracranial pressure (letter). The Lancet 1998;351:524–5.
12. Hirlinger WK, Wick C, Stodtmeister R. Comparative study of the behavior of intraocular pressure in anesthesia induction by diazepam and midazolam. Anasth Intensivther Notfallmed 1986;21(6):324–6.
13. Johnston AJ, Steiner LA, Coles JP, et al. Effect of cerebral perfusion pressure augmentation on regional oxygenation and metabolism after head injury. Crit Care Med 2005;33:189–95.
14. Kelly RE, Dinner M, Turner LS, et al. Succinylcholine increases intraocular pressure in the human eye with the extraocular muscles detached. Anesthesiology 1993;79(5):948–52.
15. Koskinen LOD, Olivecrona M. Clinical experience with the intraparenchymal intracranial pressure monitoring Codman MicroSensor system. Neurosurgery 2005;56:693–8.
16. Lamb K, James MFM, Janicki PK. The laryngeal mask airway for intraocular surgery: effects on intraocular pressure and stress responses. Br J Anaesth 1992;69(2):143–7.
17. Lane PL, Skoretz TG, Doig G, Girotti MJ. Intracranial pressure monitoring and outcomes after traumatic brain injury. CJS 2000;43(6):442–8.
18. Lang EW, Lagopoulos J, Griffith J, et al. Cerebral vasomotor reactivity testing in head injury: the link between pressure and flow. J Neurol Neurosurg Psychiatry 2003;74:1053–9.
19. Lashutka MK, Chandra A, Murray HN, et al. The relationship of intraocular pressure to intracranial pressure. Ann Emerg Med 2004;43(5):585–91.
20. Layon AJ, Gabrielli A. Elevated intracranial pressure. In: Layon AJ, Gabrielli A, Friedmann WA, editors. Textbook of neurointensive care. Philadelphia: Saunders; 2004. p. 709–32.
21. Lehman RAW, Krupin T, Podos SM. Experimental effect of intracranial hypertension upon intraocular pressure. J Neurosurg 1972;36:60–6.
22. Lirng JF, Fuh JL, Wu ZA, et al. Diameter of the superior ophthalmic vein in relation to intracranial pressure. Am J Neuroradiol 2003;24:700–3.
23. Marin-Caballos AJ, Murillo-Cabezas F, Cayuela-Dominguez A, et al. Cerebral perfusion pressure and risk of brain hypoxia in severe head injury: a prospective observational study. Crit Care 2005;9(6):670–6.
24. Mickey RM, Dunn OJ, Clark VA. Applied statistics: analysis of variance and regression. Hoboken, NJ: Wiley; 2004.
25. Moeini HA, Soltani HA, Gholami AR, Masoudpour H. The effect of lidocaine and sufentanil in preventing intraocular pressure increase due to succinylcholine and endotracheal intubation. Eur J Anesthesiol 2006;23:739–42.
26. Motschmann M, Muller C, Kuchenbecker J, et al. Ophthalmodynamometry: a reliable method for measuring intracranial pressure. Strabismus 2001;9(1):13–6.
27. Nagdeve NG, Yaddanapudi S, Pandav SS. The effect of different doses of ketamine on intraocular pressure in anesthetized children. J Pediatr Ophthalmol Strabismus 2006;43:219–23.
28. Ng HP, Chen FG, Yeong SM, et al. Effect of remifentanil compared with fentanyl on intraocular pressure after succinylcholine and tracheal intubation. Br J Anaesth 2000;85(5):785–7.
29. Querfurth HW, Arms SW, Lichy CM, et al. Prediction of intracranial pressure from noninvasive transocular venous and arterial hemodynamic measurements: a pilot study. Neurocrit Care 2004;1(2):183–94.
30. Ravi R, Morgan RJ. Intracranial pressure monitoring. Curr Anaesth Crit Care 2003;14:229–35.
31. Reitsamer HA, Kiel JW. Relationship between ciliary blood flow and aqueous production in rabbits. Invest Ophthalmol Vis Sci 2003;44:3967–71.
32. Reitsamer HA, Kiel JW. A rabbit model to study orbital venous pressure, intraocular pressure and ocular hemodynamics simultaneously. Invest Ophthalmol Vis Sci 2002;43:3728–34.
33. Robertson CS. Management of cerebral perfusion pressure after traumatic brain injury. Anesthesiology 2001;95:1513–7.
34. Ross N, Eynon CA. Intracranial pressure monitoring. Curr Anaesth Crit Care 2005;16:255–61.
35. Salman MS. Can intracranial pressure be measured non-invasively? The Lancet 1997;350:1367.
36. Sheeran P, Bland JM, Hall GM. Intraocular pressure changes and alterations in intracranial pressure (letter). The Lancet 2000;355:899.
37. Shimbles S, Dodd C, Banister K, et al. Clinical comparison of tympanic membrane displacement with invasive ICP measurements. Acta Neurochir Suppl 2005;95:197–9.
38. Signorini DF, Shad A, Piper IR, Statham PFX. A clinical evaluation of the Codman MicroSensor for intracranial pressure monitoring. Br J Neurosurg 1998;12(3):223–7.
39. Stover JF, Steiger P, Stocker R. Treating intracranial hypertension in patients with traumatic brain injury during neurointensive care. Eur J Trauma 2005;31:308–30.
40. Teba L, Viti A, Banks DE, et al. Intraocular pressure during mechanical ventilation with different levels of positive end-expiratory pressure. Crit Care Med 1993;21(6):867–70.