

Latency Relationships Between Cerebral Blood Flow Velocity and Intracranial Pressure

Shadnaz Asgari, Paul M. Vespa, Marvin Bergsneider, and Xiao Hu

Abstract Pulsatile intracranial pressure (ICP) is a key to the understanding of several neurological disorders in which compliance is altered, e.g., hydrocephalus. A recently proposed model suggests that ICP pulse is a standing wave and not a transmitted wave. The present work, aimed at obtaining a better understanding of the pulsatility in the cranium, tries to test the following hypotheses: first, ICP pulse onset latency would be lower than that of cerebral blood flow velocity (CBFV) pulses measured at a distal vessel; second, CBFV pulse at different intracranial arteries will have different pulse onset latencies, and hence they are not generated as a standing wave. The dataset used in the present study consists of ICP and CBFV signals collected from 60 patients with different diagnoses. The results reveal that the ICP pulse leads CBFV for 90% of the patients regardless of the diagnosis and mean ICP value. In addition, we show that CBFV pulse onset latency is roughly determined by the distance of the measurement point to the heart. We conclude that the ICP signal is not generated as a standing wave and that ICP pulse onset may be related to the arteries proximal to the heart.

Keywords Intracranial pressure • Cerebral blood flow velocity • Pulse onset latency • Pulsatility

S. Asgari

Department of Neurosurgery, Neural Systems and Dynamics Laboratory, The David Geffen School of Medicine, University of California, Los Angeles, CA 90095, USA

P.M. Vespa

Neurocritical Care Program, Department of Neurosurgery, The David Geffen School of Medicine, University of California, Los Angeles, CA 90095, USA

M. Bergsneider and X. Hu (✉)

Department of Neurosurgery, Neural Systems and Dynamics Laboratory, The David Geffen School of Medicine, University of California, Los Angeles, CA 90095, USA

Biomedical Engineering Graduate Program, Henry Samueli School of Engineering and Applied Science, University of California, Los Angeles, CA 90095, USA
e-mail: xhu@mednet.ucla.edu

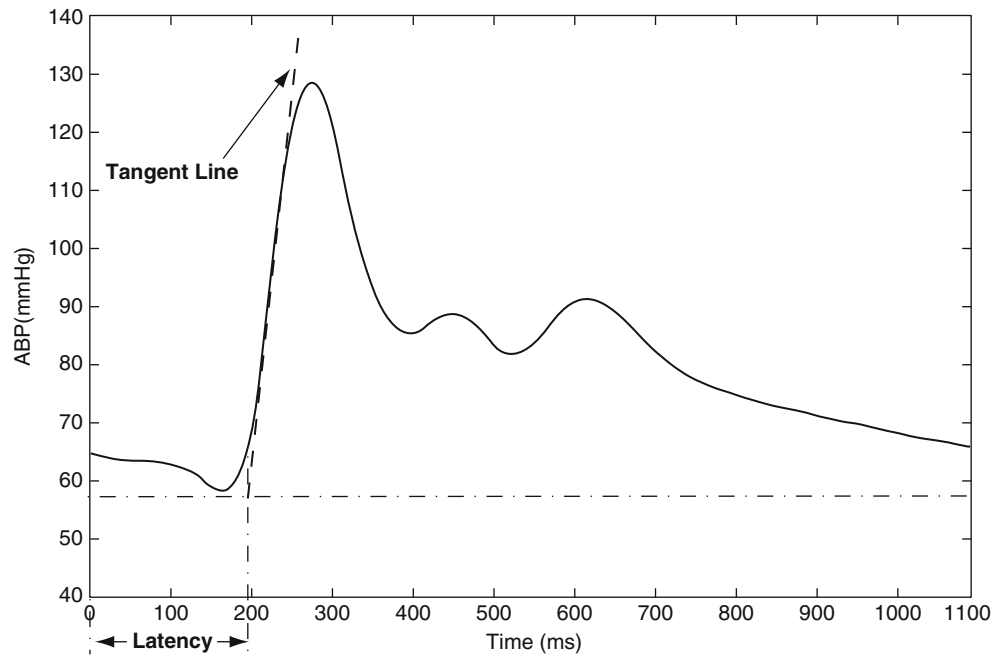
Introduction

For three decades, many clinical investigators have indicated that abnormalities of intracranial pulsations could play an important role in the pathophysiology of several neurological conditions (e.g., hydrocephalus) and have consequently employed the intracranial pressure (ICP) response to cardiac pulsations for characterization of compliance [5, 7, 10, 20]. In 1981, Foltz underlined the significance of intraventricular cerebral spinal fluid (CSF) pulsatility as the cause of hydrocephalus by showing that the power of intraventricular CSF pulsations is augmented by four times in chronic hydrocephalus [13, 14]. Since then, several interesting models of normal CSF pulsations have been proposed that relate CSF pulsatile flow to ICP, cerebral blood flow (CBF) or arterial blood pressure (ABP). While each model has its own specific set of assumptions, all of them suggest a major role of pulsatility in the cranium [4, 12, 14].

In 2000, Bateman reported decreased pulsatility at the cortical veins; measured for the first time in hydrocephalus patients, using magnetic resonance imaging (MRI) [3]. He suggested that reversible elevation in cortical vein pressure and reversal of the normal absorption pathway for CSF may be behind the pathophysiology of normal pressure hydrocephalus (NPH). Other studies have also employed the advanced magnetic resonance measurements of the transfer function between vascular pulsations and the pulsatile response of CSF to characterize intracranial mechanical factors [2, 8, 9, 18].

A recently proposed pulsatile CSF model postulates that the ICP pulse is a standing pulse and hence could even lead the carotid arterial pressure pulse if the mean ICP value is not high [11]. This theory has been shown to be valid to certain degree in animal data. To shed some light on the issue of timing of the ICP pulse, we test the following hypotheses in the present work, using a dataset of ICP and cerebral blood flow velocity (CBFV) signals collected from 60 patients with different neurological disorders: first, the ICP pulse onset latency would be lower than that of CBFV pulses measured at a distal vessel, regardless of mean ICP value; and second,

Fig. 1 Example of arterial blood pressure (ABP) pulse waveform recorded at the left radial artery and the estimated latency using an intersecting tangent line. $t=0$ corresponds to the onset of ventricular ejection (i.e., R-wave on the ECG)



the CBFV pulse at different intracranial arteries will have different pulse onset latencies (proportional to the distance of the measurement point to the heart). This study may help us to re-evaluate our current understanding of the way in which the ICP pulse is generated and processed. Consequently, it may affect the management of several neuropathological conditions not limited to hydrocephalus, e.g., traumatic brain injury (TBI) and arteriosclerosis.

Materials and Methods

Definition of Pulse Latency and Its Importance

To develop clinically viable tools that are capable of continuously assessing the cerebral vasculature, a focus of our laboratory has been to explore novel methods of extracting physiological information by analyzing continuously acquired signals of intracranial origin [16, 17]. Latency of the onset of a vascular pulse relative to an extracranial timing signal (i.e., time delay between the electrocardiogram (ECG) QRS peak and the initial inflection in the resulting blood pressure pulse) is one of the parameters that could be continuously extracted from an intracranial signal.

Moens–Korteweg equation (Pulse Wave Velocity = $PWV = \sqrt{\frac{Eh}{2\rho_b R}}$), establishes a deterministic relationship between

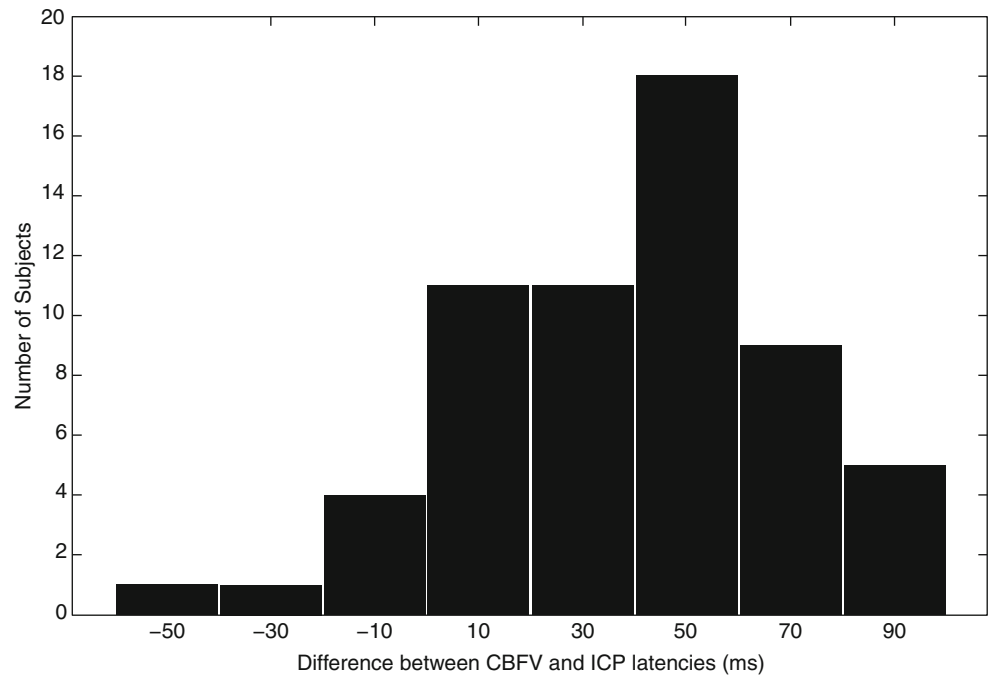
PWV (the velocity at which a blood pressure or a flow velocity pulse travels through the cerebral vasculature) and the basic properties of this vascular route, including Young's elastic modulus E , wall thickness h , internal radius R , and the

blood density ρ_b . As the changes in PWV would manifest with reciprocal changes in pulse waveform latency, the latency of a pulsatile intracranial signal could be considered to be a cerebrovascular index. Figure 1 shows an example of an ABP signal for one cardiac cycle and its extracted latency using the tangent intersect method [6].

Patient Data

The ECG, ICP, and CBFV data were collected from 60 inpatients including 20 female and 40 male, who were treated for various ICP-related conditions at UCLA Ronald Regan Medical Center; 21 cases of TBI, 21 cases of subarachnoid hemorrhage (SAH), 10 cases of hydrocephalus, 4 cases of intracerebral hemorrhage (ICH) and 4 cases of headaches. Patients' ages ranged from 18 to 89 years with the mean and standard deviation of 48 and 20 respectively. No explicit criteria were used to select the aforementioned patients other than the availability of ECG, ICP, and CBFV signals. ICP was monitored continuously using Codman intraparenchymal microensors (Codman and Schurtleff, Raynaud, MA, USA) placed in the right frontal lobe. Simultaneous cardiovascular monitoring was performed using the bedside GE monitors and CBFV was measured using transcranial Doppler (TCD) machines (Multi-Dop X, Compumedics DWL, Singen, Germany). ICP, CBFV, and lead II of the ECG signals were archived using either a mobile cart at the bedside that was equipped with the PowerLab SP-16 data acquisition system (ADInstruments, Colorado Springs, CO, USA) with sampling frequency of 400 Hz or the BedMaster system

Fig. 2 Histogram of the latency difference between cerebral blood flow velocity (CBFV) and intracranial pressure (ICP) signals over 60 patients



that collects data (sampling frequency of 240 Hz) from the GE Unity network to which the bedside monitors were connected. The use of these archived waveform data in an anonymous fashion has been granted a waiver of consent by the UCLA IRB.

To verify the hypothesis that CBFV pulse at different intracranial arteries will have different pulse onset latencies (and hence they are not generated as a standing wave), the CBFV signal was measured for two healthy subjects (subject 1: a 24-year-old woman and subject 2: a 29-year-old man), at the following vessels: intracarotid artery (ICA), vertebral (VERT), posterior cerebral artery (PCA), middle cerebral artery (MCA), anterior cerebral artery (ACA).

Data Analysis

All the signals were time synchronized and re-sampled at 400 Hz. ECG QRS detection was performed using a previously published algorithm [1] on lead II of the ECG. Then, an ECG-aided pulse detection algorithm [17] was used to delineate each pulse of ICP and CBFV. In addition, each detected ICP and CBFV pulse was saved and visualized using the custom software developed in-house to screen obvious noise or artifacts, so that only clean beats were further processed. Latencies were measured from the onset of each clean pulse relative to ECG QRS as described in the previous subsection. Then all extracted latencies were corrected based on the subjects' heart rate using Weissler's regression equation [15, 22, 23].

Table 1 The mean and standard deviation of the heart rate corrected CBFV pulse latencies (in ms) measured at different intracranial arteries for two healthy subjects

Measured artery	Subject 1 (a 24-year-old woman)	Subject 2 (a 29-year-old man)
ICA	Not measured	140.3 ± 4.4
VERT	155.7 ± 4.6	152.2 ± 4.1
PCA	172.8 ± 6.6	Not measured
MCA	175.9 ± 5.6	169.2 ± 8.3
ACA	194.7 ± 9.4	167.4 ± 8.5

Results

The mean and standard deviation of the corrected ICP and CBFV latencies over all 60 patients were $120.85 \pm 29.6(ms)$ and $160.1 \pm 30.93(ms)$ respectively.

Figure 2 demonstrates the histogram of the corrected latency difference between CBFV and ICP (corrected CBFV latency – corrected ICP latency) over all 60 patients. The mean and standard deviation of this latency difference is $40 \pm 30(ms)$. As the histogram shows, only 6 out of 60 subjects had a negative latency difference. These subjects had a different diagnosis: two cases of TBI, two cases of ICH, one case of NPH, and one case of SAH. As a result, ICP pulse leads CBFV pulse measured at MCA for 90% of the patients in this study. A simple correlation analysis reveals that the amount of leading does not seem to be related to the mean ICP value ($\rho = -0.16, p = 0.22$).

Table 1 summarizes the results of the corrected CBFV pulse latencies measured at different intracranial arteries for

the two healthy subjects. We observe that the latency results for each of the two subjects are consistent with the distances of the measurement points to the heart ($Latency_{ICA} \leq Latency_{VERT} \leq Latency_{PCA} \leq Latency_{MCA} \leq Latency_{ACA}$). In other words, as the measurement point of CBFV at the ICA is closer to the heart than that of VERT, one would expect to have a shorter CBFV latency measured at ICA than at VERT. We also observe that the corrected CBFV latency measured at MCA for the two normal subjects is at least 12 ms longer than those of the patients (average of 160 ms). This observation is consistent with the fact that patients may have stiffer vessels and consequently a higher pulse wave velocity, which itself results in a shorter pulse latency.

As the mean of the corrected ICP latency for the patients was 120 ms; considering the latency difference between healthy subjects and the patients, we can conclude that the latency of ICP is close to the latency of the CBFV measured at the ICA; a point relatively closer to the heart than the MCA.

Discussion

While several clinical investigations have focused on studying the intracranial pulsations in hydrocephalus and the effect on treatment, there have only been a few studies that explain the underlying physiological causes [21]. In a recent study, Egnor et al. proposed that the ICP pulse is a standing wave and hence could even lead the carotid arterial pulse [11]. In addition, a negative correlation between mean ICP and the latency difference between the ICP and the carotid arterial pulse has been found in dogs when the mean ICP is not high.

Our results show that the ICP pulse leads CBFV measured at the MCA for 90% of the patients in the study and there is no significant correlation between the amount of leading and the value of mean ICP. Also, the results of a multi-vessel TCD study on two normal subjects revealed that CBFV pulse at different intracranial arteries have different pulse onset latencies that are proportional to the distance of the measurement point to the heart; hence, these pulsatile signals cannot be generated as standing waves.

The observation that the ICP pulse precedes the CBFV is counterintuitive, because, first, the location of the ICP measurement is further away from heart than that of the CBFV; and second, a flow pulse usually leads the pressure pulse [19]. We propose that the following factors could contribute to the observed leading phase of the ICP versus CBFV:

1. As the ICP pulse is the summation of all cerebral blood volume and CSF pulsations in the cranium, ICP pulse onset may be related to the arteries proximal to the heart.
2. The current definition of the onset of a pulse is not compatible for different pulses and needs to be modified accordingly.
3. Different analog filter settings on the amplifier of ICP and CBFV recording systems can affect the estimated latency of the pulses.

Conclusion

The latency relationship between the ICP and CBFV signals was described in studies in 60 patients with different neurological disorders. It was found that ICP pulse leads CBFV, but no significant correlation between mean ICP and the latency difference was observed. The leading phase of the ICP relative to the CBFV measured at the MCA could be explained by the fact that the ICP pulse is the summation of all cerebral blood volume and CSF pulsations in the cranium. As a result, ICP pulse onset may be related to the arteries proximal to the base of the skull rather than the MCA. An additional intracranial multi-vessel study on two normal subjects confirmed that the CBFV latency is roughly determined by the distance of the corresponding measurement site to the heart and thus intracranial pulsatile signal cannot be generated as a standing wave. Gaining a deeper insight into the mechanisms underlying the link between pulsations and hydrocephalus and other pathophysiological conditions involving the cerebral blood flow could be helpful in the design of therapies based on the regulations of intracranial dynamics.

Conflict of interest statement We declare that we have no conflict of interest.

References

1. Afonso VX, Tompkins WJ, Nguyen TQ, Luo S (1999) ECG beat detection using filter banks. *IEEE Trans Biomed Eng* 46:192–202
2. Alperin N, Vikingstad EM, Gomez-Anson B, Levin DN (1996) Hemodynamically independent analysis of cerebrospinal fluid and brain motion observed with dynamic phase contrast MRI. *Magn Reson Med* 35:741–754
3. Bateman GA (2003) The reversibility of reduced cortical vein compliance in normal-pressure hydrocephalus following shunt insertion. *Neuroradiology* 45:65–70
4. Bergsneider M, Alwan AA, Falkson L, Rubinstein EH (1998) The relationship of pulsatile cerebrospinal fluid flow to cerebral blood flow and intracranial pressure: a new theoretical model. *Acta Neurochir Suppl* 71:266–268
5. Cardoso ER, Rowan JO, Galbraith S (1983) Analysis of the cerebrospinal-fluid pulse-wave in intracranial-pressure. *J Neurosurg* 59:817–821
6. Chiu YC, Arand PW, Shroff SG, Feldman T, Carroll JD (1991) Determination of pulse wave velocities with computerized algorithms. *Am Heart J* 121:1460–1470

7. Chopp M, Portnoy HD (1980) Systems-analysis of intra-cranial pressure – comparison with volume-pressure test and csf-pulse amplitude analysis. *J Neurosurg* 53:516–527
8. Chu D, Levin DN, Alperin N (1998) Assessment of the biomechanical state of intracranial tissues by dynamic MRI of cerebrospinal fluid pulsations: a phantom study. *Magn Reson Imaging* 16:1043–1048
9. de Marco G, Idy-Peretti I, Didon-Poncelet A, Baledent O, Onen F, Feugeas MC (2004) Intracranial fluid dynamics in normal and hydrocephalic states: systems analysis with phase-contrast magnetic resonance imaging. *J Comput Assist Tomogr* 28:247–254
10. Dubin MJ, Magram G, Prasad AK (1998) Intracranial pressure waveform analysis: computation of pressure transmission and waveform shape indicators. *Neurol Res* 20:533–541
11. Egnor M, Wagshul M, McCormack E, McAllister P, Madsen J, Zou R, Zhen L, Peng J (2006) Pressure phase relationships between carotid arterial pressure and intracranial pressure: the ‘violin’ analogy of intracranial pulsations. 50th annual meeting of the Society for Research into Hydrocephalus and Spina Bifida Cambridge, UK.
12. Egnor M, Zheng L, Rosiello A, Gutman F, Davis R (2002) A model of pulsations in communicating hydrocephalus. *Pediatr Neurosurg* 36:281–303
13. Foltz EL, Aine C (1981) Diagnosis of hydrocephalus by CSF pulse-wave analysis: a clinical study. *Surg Neurol* 15:283–293
14. Greitz D (2004) Radiological assessment of hydrocephalus: new theories and implications for therapy. *Neurosurg Rev* 27:145–165, discussion 166–147
15. Hassan S, Turner P (1983) Systolic time intervals: a review of the method in the non-invasive investigation of cardiac function in health, disease and clinical pharmacology. *Postgrad Med J* 59:423–434
16. Hu X, Subudhi AW, Xu P, Asgari S, Roach RC, Bergsneider M (2009) Inferring cerebrovascular changes from latencies of systemic and intracranial pulses: a model-based latency subtraction algorithm. *J Cereb Blood Flow Metab* 29:688–697
17. Hu X, Xu P, Lee DJ, Vespa P, Baldwin K, Bergsneider M (2008) An algorithm for extracting intracranial pressure latency relative to electrocardiogram R wave. *Physiol Meas* 29:459–471
18. Miyati T, Mase M, Banno T, Kasuga T, Yamada K, Fujita H, Koshida K, Sanada S, Onoguchi M (2003) Frequency analyses of CSF flow on cine MRI in normal pressure hydrocephalus. *Eur Radiol* 13:1019–1024
19. Nichols WW, O'Rourke MF (2005) McDonald's blood flow in arteries: theoretical, experimental and clinical principles. Hodder Arnold, London
20. Piper IR, Chan KH, Whittle IR, Miller JD (1993) An experimental study of cerebrovascular resistance, pressure transmission, and craniospinal compliance. *Neurosurgery* 32:805–815, discussion 815–806
21. Wagshul ME, Kelly EJ, Yu HJ, Garlick B, Zimmerman T, Egnor MR (2009) Resonant and notch behavior in intracranial pressure dynamics. *J Neurosurg Pediatr* 3:354–364
22. Weissler AM, Harris WS, Schoenfeld CD (1968) Systolic time intervals in heart failure in man. *Circulation* 37:149–159
23. Weissler AM, Kamen AR, Bornstein RS, Schoenfeld CD, Cohen S (1965) The effect of deslanoside on the duration of the phases of ventricular systole in man. *Am J Cardiol* 15:153–161

Intracranial Pressure and Brain Monitoring XIV

Schuhmann, M.; Czosnyka, M. (Eds.)

2012, XIV, 421 p., Hardcover

ISBN: 978-3-7091-0955-7