The use of transcranial Doppler pulsatility index to guide hyperosmolar therapy

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ABSTRACT

يعد علاج الضغط داخل القحف من أساسيات الرعاية الطبية العصبية الدقيقة، وبغض النظر عن الإصابات الرضحية للدماغ فإنه لا يوجد حتى الآن توجيهات واضحة حول مراقبة الضغط داخل القحف. كما ويعد إدخال أدوات مراقبة الضغط داخل القحف من الإجراءات المعقدة التي قد يترتب عليها العديد من المخاطر والتي من شأنها منع استعمال مثل هذه الأدوات في حالة حدوث الاعتلالات الخثرية. يعد مؤشر النبض باستخدام التصوير بأشعة دوبلر فوق السمعية عبر الدماغ من العلامات البديلة لحدوث الضغط داخل القحف. يناقش هذا المقال استخدام مؤشر النبض من أجل التحكم بالحالات الشديدة من ارتفاع الضغط داخل القحف وذلك من أجل التوجيه إلى تحديد الجرعات المثالية من عوامل فرط الأسمولية المستخدمة في مستشفانا. ويعد اللجوء إلى مؤشر النبض باستخدام التصوير بأشعة دوبلر فوق السمعية عبر الدماغ من الطرق المهمة أثناء العلاج بعوامل فرط الأسمولية وذلك في كثير من الحالات المصابة بالضغط داخل القحف. كما أننا سوف نناقش إمكانية الجمع بين استخدام مؤشر النبض والتقييم التشريحي للقطر العصبي العيني من أجل تقليل نسبة العوامل المربكة أثناء استخدام مؤشر النبض.

Management of intracranial hypertension is a major cornerstone of neurocritical care. Apart from traumatic brain injury, there are no clear guidelines for intracranial pressure (ICP) monitoring. The insertion of ICP monitors is an invasive procedure with inherent risks and could be contraindicated in case of severe coagulopathy. The transcranial Doppler (TCD) pulsatility index (PI) has emerged as a surrogate marker for ICP. This is a technical report with illustrative cases on the use of PI in the management of high ICP, as a guide for optimal dosing of hyperosmolar agents we use in our institution. The use of TCD PI is a useful adjunct to guide the use of hyperosmolar therapy in various conditions with raised intracranial hypertension. We will discuss the combination of the PI determination with an anatomical evaluation of the optic nerve diameter to eliminate confounding factors in PI determination.

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Intracranial hypertension is a major determinant of poor outcome in a variety of neurological and neurosurgical diseases. Determination and control of intracranial pressure (ICP) have long been of paramount importance to optimize cerebral perfusion pressure (CPP) and as a result cerebral homeostasis.[1] Apart from traumatic brain injury, there are no clear guidelines for ICP monitoring.[2] The insertion of ICP monitors, in the form of external ventricular drains or intraparenchymal pressure sensors, is an invasive procedure with inherent risks and could be contraindicated in case of severe coagulopathy. The transcranial Doppler (TCD) pulsatility index (PI) has emerged as a surrogate marker for ICP.[3] For the most part, it is currently used as a snap shot screening tool, mainly because it is cumbersome to utilize in a continuous monitoring fashion, and secondly because there is a lack of consensus as to the accuracy and applicability in therapeutic decision making.[4]

There are variable pharmacological and non-pharmacological approaches to the treatment of high ICP. One of the major components of the pharmacological options is the use of hyperosmolar

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therapy, namely, mannitol and hypertonic saline.[5] The use of hyperosmolar agents, the doses, and the protocols for their use all suffer from inter-institutional variability as well as inter-physician variability within the same institution. This is reflective of our incomplete understanding of the mechanism of action of these agents. In this article, we describe the novel use of the transcranial Doppler pulsatility index (PI) as a non-invasive tool to guide optimal dosing of hyperosmolar agents in our institution in order to control intracranial hypertension.

This is a technical report with illustrative cases on the use of PI in the management of high ICP. A transcranial Doppler ultrasonography (Zone.one, ZONARE Medical Systems, Inc., Mountain View, CA, USA) was used at the Montreal Neurological Institute/Hospital Neurocritical care unit to obtain the PI and predict the ICP. All TCD examinations were performed by a single operator, using a P4-1c Phased Array (ZONARE Medical Systems, Inc., Mountain View, CA, USA), operated at 2-3 mHz to insonate the temporal windows bilaterally. The target vessels were the middle cerebral artery (MCA) and the anterior cerebral artery (ACA). For each case the PI was obtained immediately before the hyperosmolar therapy in the form of Mannitol 20% (Hospira, Montreal, QC, Canada), or 3% hypertonic saline (Baxter, Corporation, Mississauga, ON, Canada) was initiated, and 15 minutes after the dose was completed. These exams were repeated twice daily, to determine the PI dynamics for each hyperosmolar agent. As an internal control, we used a previously described optic nerve ultrasonography as a reflection of the ICP to objectively corroborate the trend seen in the PI.[6,7]

Case Reports. *Patient 1.* A 78-year old right-handed male, longstanding smoker, with a history of atrial fibrillation, chronic obstructive pulmonary disease, and previously unrecognized rigidity later attributed to Parkinson's disease. He presented with a 2-day history of confusion and headaches for which he took 180 mg of aspirin (Bayer Inc., Toronto, Canada) the night prior to admission. On the morning of admission, he fell twice and was brought to hospital by the emergency medical services. Upon evaluation in the emergency room, he was found to have a decreased level of consciousness, with a Glasgow Coma Scale (GCS) of 12 out of 15 withdrawing weakly to pain in the extremities. The CT scan on admission showed a large left frontal intracerebral hematoma (ICH) with surrounding edema causing mass effect on the frontal horn of the lateral ventricle and a 7 mm midline shift to the right side associated with mild engagement of the uncus without definite herniation. Thereafter, he was admitted to the neurocritical care unit for observation. Surgical intervention including invasive ICP monitoring was deferred because he was cachectic and was not considered a candidate for surgical intervention.

A few hours into his admission, his neurological condition deteriorated further. He was not arousable to deep central or peripheral pain, except for a triple flexion response in the lower limbs. His deep tendon reflexes were diffusely brisk, yielding a GCS of 4 out 15. He was intubated and was treated with standard blood pressure control (target kept below 180/100 mm Hg) and received Dilantin (Phenytoin sodium, Mylan Laboratories, Morgantown, WV, USA) for seizure prophylaxis. More aggressive therapy was being considered and so the TCD was used to attempt to non-invasively assess the ICP. The first TCD assessment of the MCA on the left side showed a PI of 1.7 (normal value is 0.8±0.1).[8] This was judged to be indicative of a raised ICP, and hyperosmolar therapy was initiated. He was given 3% saline 150 ml over 15 minutes. The PI dropped to 1.3, 15 minutes after the hyperosmolar dose. He was put on a regimen of alternating 150 ml of 3% saline and 20% Mannitol alternating every 6 hours. His neurological exam improved significantly within 12 hours of therapy; he became alert, answering simple questions and obeying simple commands yielding a GCS of 14-15. No lateralizing findings were elicited, and hemodynamically he was always stable and able to protect his airway throughout his stay. The repeat PI in 24 hours showed a baseline PI of 1.3 that dropped to 1.1 after the morning dose of the hyperosmolar agent. He was weaned from the hyperosmolar therapy over 3 days and continued to do well. He was later discharged to a convalescent center prior to returning home.

Patient 2. A 61-year-old right-handed male with a complex medical history that included a remote metallic mitral valve replacement receiving anticoagulation therapy for 18 years, and being investigated for a possible mitral valve leak one week prior to this admission. He also suffered from a sick sinus syndrome and was status post pacemaker insertion. He presented to our hospital with a sudden left sided weakness, right gaze preference, and slight dysphasia detected when he woke up from sleep that morning. His CT scan on admission showed a large right frontal ICH with mass effect causing a slight midline shift of 3 mm towards the left. His therapeutic anticoagulation (International normalized ration [INR] 2.5) was reversed appropriately using prothrombin complex concentrate (Octaplex, Octapharm Canada, Scarborough, ON, Canada), vitamin K, and later fresh frozen plasma to achieve a

normal INR. During the observation period in the neurocritical care unit, he suffered from worsening headache, nausea, and vomiting. Repeat imaging at that time showed expansion of the ICH with an increase in the edema and worsening midline shift to 6 mm. The insertion of an ICP monitor was deemed too dangerous because of the location of the hematoma in the right frontal lobe, and the concern of promoting the midline shift with left sided intervention. The PI was carried out at that time and was determined to be 1.9 with an optic nerve diameter of 5.8 mm (upper limit is 3 mm). He received a dose of hyperosmolar therapy (mannitol alternating with 3% saline every 6 hours) of 150 mL and the repeat PI after the initial dose at 15 minutes and 30 minutes were 1.8 and 1.9 in the ACA and the MCA, denoting lack of effective response to the given dose. The subsequent doses were increased to 250 mL of both agents. The baseline PI was 1.8 and went down to 1.4 after the higher dose, corresponding to an optimal response. He was followed with twice daily TCD examinations and optic nerve ultrasonography, documenting an appropriate response to the given doses during the weaning of the hyperosmolar therapy, for example, on the second day of the treatment in the ICU, the PI was 1.4 and after the dose of Mannitol it came down to 1.14 denoting an appropriate response to the dose (**Figure 1**). The baseline PI at the completion of the weaning period was 0.8 and the optic nerve diameter was 3 mm. He was always hemodynamically stable in the neurocritical care unit and remained off anticoagulation for 11 days until his bleed was deemed stable. His neurological status improved, and he was discharged to a rehabilitation center for further physiotherapy.

Patient 3. A 27-year-old right-handed healthy male, presented to our hospital with a 2-week history of severe headaches, at its worst in the morning. For the 6 months prior to admission, he suffered from intermittent headaches as well as occasional sensory phenomena on the left side. On arrival to the emergency room, he had decreased sensation on the left side including the face, arm, and the leg. His neurological exam was also remarkable for a left sided pronator drift, difficulty standing without assistance, and trouble with gait. His medication history included only non-steroidal anti-inflammatory drugs (NSAID's) for his migraines. The CT and MRI carried out at our institution showed a right fronto-temporal-insular lesion surrounded by edema with significant mass effect leading to a 1.1 cm midline shift. There was evidence of compression of the cerebral peduncle on the right side. He was started on medical therapy including a steroid loading dose (dexamethasone 20 mg, followed by 4 mg every 6 hours) and was admitted to the neurocritical care unit for close monitoring. The insertion of an ICP monitor was deferred for fear of complications related to insertion of monitors into edematous brain, and the risk of further shift with contralateral device insertion. The initial PI was shown to be 1.9 with an optic nerve diameter of 6.7 mm. He received 150 mL of 3% hypertonic saline and the PI failed to correct after neither 15 minutes nor 30 minutes. The subsequent dose was increased to 250 mL. This elicited a clear response in the PI, from 1.68 to 1.2. On the fourth day of his hospitalization, he was already started on a weaning protocol of the hyperosmolar therapy, guided by a favorable trend of PI and optic nerve diameter. However, he started

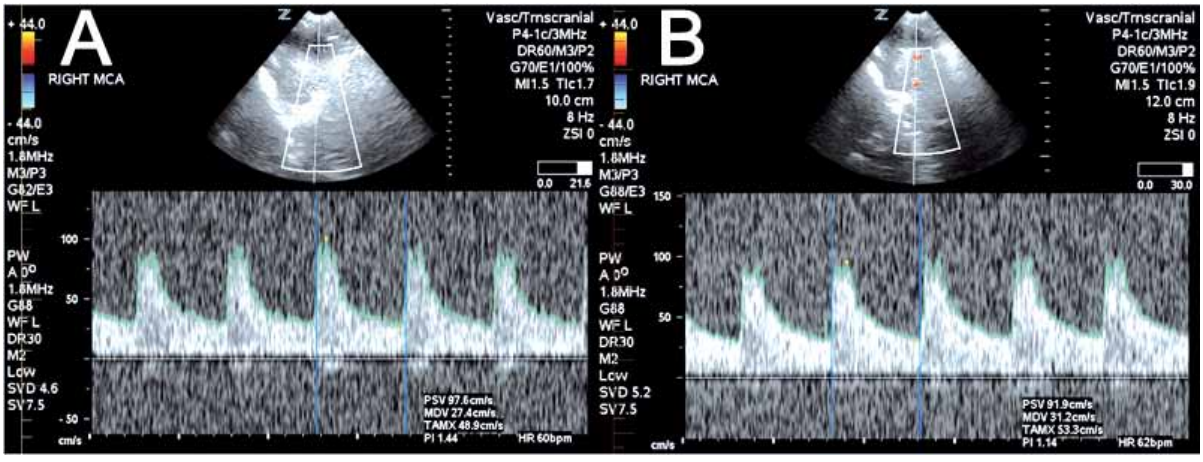

Figure 1 - The transcranial Doppler tracing is an example of the serial examinations carried out for patient 2. The insonation is carried out for the right middle cerebral artery in which **A)** was prior to the hyperosmolars dose showing a PI of 1.4, and **B)** is after the dose showing a PI of 1.1, denoting an appropriate response to the given dose. PI - pulsatility index

complaining of a severe headache upon rising from his sleep. The PI was repeated at that time and was found to be 0.6-0.8, and the optic nerve diameter was 2.2. Based on these findings, the hyperosmolar therapy was not adjusted. Instead, the pain medication regimen was adjusted to include narcotics, after which he responded well and underwent a frameless stereotactic biopsy. The pathology showed a high-grade glioma. On the first post-operative day, the PI was found to be 1.2 and the optic nerve diameter increased to 2.7. Both these findings led to an increase of the dexamethasone dose and prolongation of the hyperosmolar therapy for 48 hours prior to starting the weaning protocol. He continued to improve his motor function. He was able to walk unassisted, perform tandem gait, and his pronator drift completely resolved. Paresthesia of the face, hand, and leg on the left side continued, and he also suffered occasional blurring of vision. According to his wishes, he was later transferred to another hospital for scheduled radiotherapy, chemotherapy, and definitive surgery for his tumor.

Discussion. Transcranial Doppler was introduced in 1982 by Aaslid[9] as a tool to assess flow velocities in the basal vessels of the brain. The TCD gained popularity for its application in patients with subarachnoid hemorrhage and the diagnosis of vasospasm. This fell out of favor because of the lack of consistency of TCD findings and clinical outcome of subarachnoid patients, and the concern that flow velocity alone is not sufficient for prediction and proper guidance of therapy. The mobility of the TCD machines, the refinement of the ultrasound probes, and the development of reliable machines to calculate various indices, have led to a renewed interest in the application of TCD into the neurocritical care arena. The TCD-PI was described first by Gosling,[10] as the peak systolic velocity minus the end diastolic velocity divided by the mean flow velocity, irrespective of the angle of insonation. It is thought to reflect the impedance of the environment around intracerebral vessels during the cardiac cycle. This makes the PI an acceptable parameter to objectively estimate the ICP, and also to provide an estimation of the status of cerebral autoregulation.[11] With this case series, we present a novel use for the PI in neurocritical care units. In these patients, there was equipoise in terms of candidacy for invasive ICP monitoring options. The PI was instrumental in objectively guiding the therapy. The PI was used to guide the initiation (patients 1, and 2), weaning (patients 1, and 2) and adjustment (patients 2, and 3) of the hyperosmolar therapy protocol.

There are factors that can influence the PI determination. These include general hemodynamic and respiratory parameters, the extent of tissue compliance and the severity of any cerebrovascular disease that increases the rigidity of the vessels, thus seriously affecting the PI determination.[11] The presence of extensive microvascular disease, as in diabetics, could also potentially affect the PI determination.[12] As a consequence, there is a concern as to the reliability of the TCD-PI assessment as a surrogate marker of ICP, without a definitive ICP monitoring device. For these reasons, we used the optic nerve ultrasonography to objectively judge the pressure in the intracranial compartment. In our series there was significant correlation between the TCD-PI assessment and the optic nerve sonography measurements, making the PI result more robust and more reliable. Our case series is limited in number and is representative of patients with focal mass lesions. Future work is necessary to objectively assess the generalizability of this interesting technique. If results remain reliable, the PI could guide the use of osmolar agents and even determine the indication for invasive ICP monitoring devises in cases of clinical equipoise.

In conclusion, the use of TCD-PI is a useful adjunct to guide the use of hyperosmolar therapy in various conditions with raised intracranial hypertension. It is useful to combine the PI determination with an anatomical evaluation of the optic nerve diameter to eliminate confounding factors in PI determination.

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