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Review Article

Transcranial Doppler Sonography for Detecting Stenosis or Occlusion of Intracranial Arteries in People with Acute Ischemic Stroke in Neurocritical Care Unit

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Abstract:

Introduction: A Transcranial Doppler (TCD) is an inexpensive noninvasive ultrasonography technique that helps provide a rapid real time measure of blood flow from the basal intracerebral vessels, which may be used for the diagnosis and follow-up of cerebrovascular disease. By placing the ultrasound probe on the scalp; it utilizes low frequency soundwaves to record cerebral blood flow velocity, and its change in multiple conditions. Technology offers several diagnostic tests available in the evaluation and treatment of cerebrovascular diseases (CVD). Transcranial ultrasonography may represent a valuable tool for patients with CVD in neurocritical care unit. However due to geographic, financial or patient tolerance of procedures, physicians may be limited to the tools they can utilize.

Method: Diagnostic accuracy of transcranial ultrasonography in acute stroke was subjected to systematic review. This study will set to demonstrate that the Transcranial Doppler (TCD) ultrasound is a viable piece of technology, which overcomes barriers mentioned in both the diagnosis and treatment of CVD. Cerebral flow peak systolic velocity (CBFVs), mean flow velocity (CBFVm), and the end diastolic velocity CBFVd) values are three components, which characterize the spectral waveform derived from TCD. These flow velocities provide valuable physiologic perspectives in various intracranial pathologies. We have demonstrated TCD to be highly predictive of evidence of vasospasm in patients with an aneurysmal subarachnoid hemorrhage with a 95% confidence interval. In patients with traumatic brain injury, TCD has been shown to be effective with a 95% confidence interval in the assessment of intracranial pressure and cerebral flow velocity. For strokes, TCD was shown to be effective with an overall sensitivity of 83% for the diagnosis, prognosis and treatment of ischemic strokes.

Results: Due to its portability, affordability, and noninvasive application along with the high confidence intervals seen in our study, our data suggests the successful application of TCD in various pathologies in both diagnosis and monitoring of patients with various CVD.

Key words: Neurocritical care unit, brain stem death, acute stroke, mean cerebral brain flow, paradoxical embolism, subarachnoid hemorrhage, transcranial doppler ultrasonography, traumatic brain injury, vasospasm, Neuroimaging.

Introduction

Common neurologic symptoms observed inacute cerebral ischemia usually manifests in the form of weakness affecting one side of the body, speech impairment, visual disturbances, unconsciousness and coordination problems. The majority of patients with a history of anacute ischemic stroke, hadan arterial thrombi that occlude extra- or intracranial vessels. Intravenously administered issue plasminogen activator (TPA) induces thrombolysis and remains the only the rapyand drug administration for ischemic strokes within a window of three hours from the onset of symptoms. Dramatic clinical recoveries can be seen after rapid dissolution of the thrombi. Several diagnostic tests are available in aiding the physicians in the evaluation of an

ischemic stroke. A non-contrast CT of the brain is currently the standard imaging test used in an acute stroke to differentiate ahemorrhagic stroke from that of an ischemic events. Patients with neurological deficits may have TPA administered if a CT scan reveals no intracerebral hemorrhage. A non-contrast CT scan of the brain, can also provide information regarding the extent and severity of ischemic injury, by visualization of early ischemic changes that can be present soon after the onset of symptoms. A CT scan may also show a "hyper-dense" artery, a sign that provides insight as to the location of an occlusion and its clot burden. An intravenous injection of a contrast bolus can then be administered to obtain a CTangiography (CTA) of extra- and intracranial vessels. This test can be performed rapidly and yields accuracy similar to that of invasive digital subtraction angiography. A Transcranial Doppler (TCD) ultrasound offers the most convenient way to assess vasculature at bedside and to monitorrecanalization in real time. After an occlusion is documented with a CTA, an ultrasound can be utilized to monitor recanalization during thrombolytic therapy and to assist select patients for further interventions. An ultrasound may also be used without aCTA as a screening tool for the rapid identification of anocclusion. This information is also useful indetermining the stroke pathogenic mechanism and in selecting the most appropriate subsequent measures in patient management. In an acute ischemic stroke, an ultrasound can be used as an adjunctive therapy for clot dissolution. Introduced inclinical practice in in 1982, Transcranial Doppler (TCD) ultrasonography is anoninvasive ultrasound, which has since been extensively applied in both outpatient and inpatient settings (White &Venkatesh, 2006). TCD ultrasonography involves the use of a low frequency (≤2 MHz) transducer which is placed on the scalp, to insonate thebasal cerebral arteries through relatively thin bone windows to measure the cerebral blood flow velocity (CBFV) and its alteration in different cerebrovascular diseases(CVDs) and traumatic brain injuries. Beingin expensive, repeatable, and portable allows for continuous use in bedside monitoring of CBFV, which is particularly useful in the intensive care setting.TCD utilization have gained an important role in the very early phase of critical cerebral pathologies, in addition to followup visits of patients with chronic CVDs. It is also useful amongst both adults and children in diagnosing and monitoring vasospasmaftershock after a subarachnoid hemorrhage of different etiologies (aneury smrupture and traumatic brain injury), and cerebralhemodynamic changes after a stroke including a cryptogenicstroke.

Significance

A Transcranial Doppler is a noninvasive ultrasound tool tha tinvolves the use of a low-frequency transducer probe to insonate the basal cerebral arteries through relatively thin bone windows. It allows dynamic monitoring of cerebral blood flow velocity with exceptional temporal and spatial resolution. It is relatively inexpensive, rapid, and repeatable. Given its small footprint and low weight, allows this portable technology to be utilized continuously in the bedside monitoring of cerebrovascular dynamics, which isparticularly useful in the neurointensive care setting.

Table1. Summary of Basic and Advanced Signals Derived fromTranscranial Doppler

Basic methods	Pulsatily Index, Flow Velocities
Advanced methods	Autoregulation Critical Closing Pressure (CrCp) Wall Tension (WT) Compliance (Ca, Ci) Cerebrovascular time constant (Tau) Non invasive cerebral perfusion pressure (nCPP) Non invasive intracranial pressure (nICP) Cerebrovascular reactivity

Basic Methods

TCD is called as the doctor's stethoscope of the brain. Introduced by Rune Aaslid in 1982 for detecting blood flow in the basal intracerebral arteries. Mark Moehring in 2002 invented the transcranial power-motion mode Doppler (PMD). Initially introduced for detecting the vasospasm following subarachnoid hemorrhage.

Flow velocities

Transcranial Doppler (TCD) is a noninvasive ultrasound it involves use of low frequency (≤2 MHz) US waves to insonate the basal cerebral arteries through relatively thin bone windows. The spectral waveform derived from TCD is characterized by three components: cerebral flow peak systolic velocity (CBFVs), mean flow velocity (CBFVm), and end diastolic velocity CBFVd) values (Figure 2; measured in cm/sec). Rather than depicting cerebral hemodynamics, FV systolic is predominantly dependent on the cardiac output (i.e., systemic haemodynamics). Utilizing diastolic flow velocity as a relevant parameter is currently thriving in clinical practice, especially in the intensive care. Authors have reported a reduction of CPP by rising ICP or decreasing systemic blood pressure in TBI (Trabold, Meyer, Blanot, Carli, & Orliaguet, 2004; Bouzat et al., 2016; O'Brien, Maa, & Reuter-Rice, 2015; Ziegler, Cravens, Poche, Gandhi, & Tellez, 2016). TCD cerebral blood FVs are commonly measured values in clinical practice and experimental models. Simultaneous monitoring of these variables along with intracranial pressure (ICP) and arterial blood pressure (ABP) can provide valuable physiologic perspectives in various intracranial pathologies. By analyzing TCD waveform, many researchers have attempted to investigate the correlation between cerebral blood flow (CBF) and cerebrospinal fluid (CSF) dynamics.

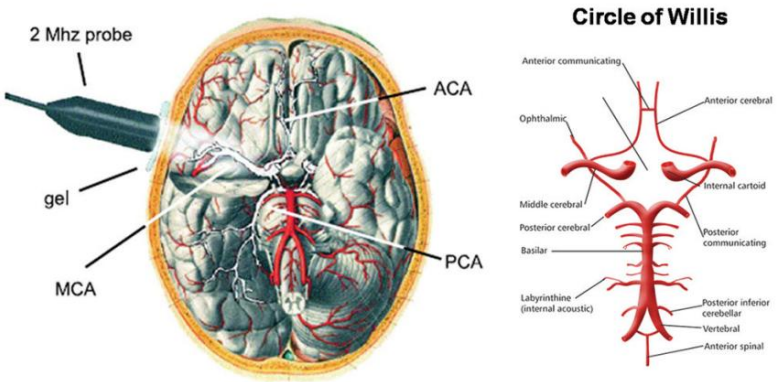

Figure 1: Left panel: Transmission of ultrasound beam through skull using Pulsed Doppler sectorial probe with a 2.0–3.5 MHz emission frequency. Probe is positioned on temporal window. Right panel = Circle of Willis

Pulsatility index

The pulsatility index (PI), measured by (TCD) ultrasonography, can reflect vascular resistance induced by cerebral small-vessel disease (SVD). We evaluated the value of TCD-derived PI for diagnosing SVD as compared with magnetic resonance imaging (MRI). PI is calculated from the relationship between systolic and diastolic flow velocities divided by the mean flow velocity (Naqvi, Yap, Ahmad, & Ghosh, 2013; Tegeler et al., 2013). Mathematically, PI is inversely proportional to the mean CPP and directly proportional to the pulse amplitude of the arterial blood pressure. Additionally, it is nonlinearly proportional to the compliance of the arterial bed (Ca), heart rate (HR), and peripheral cerebrovascular resistance (PCVR) (De Riva et al., 2012). The pulsatility index has been used in the assessment of distal PCVR (Giller, Hodges, & Batjer, 1990). Many experimental and clinical studies have supported the concept that PI is a reflection of the distal PCVR, attributing greater PI to higher PCVR (Bouma, Muizelaar, Bandoh, & Marmarou, 1992). However, research indicates that hypercapnia can cause a decrease in both PCVR and PI, while a reduction in CPP with intact autoregulation induces a decrease in PCVR, but an increasein PI. (Czosnyka, Richards, Whitehouse, & Pickard, 1996).

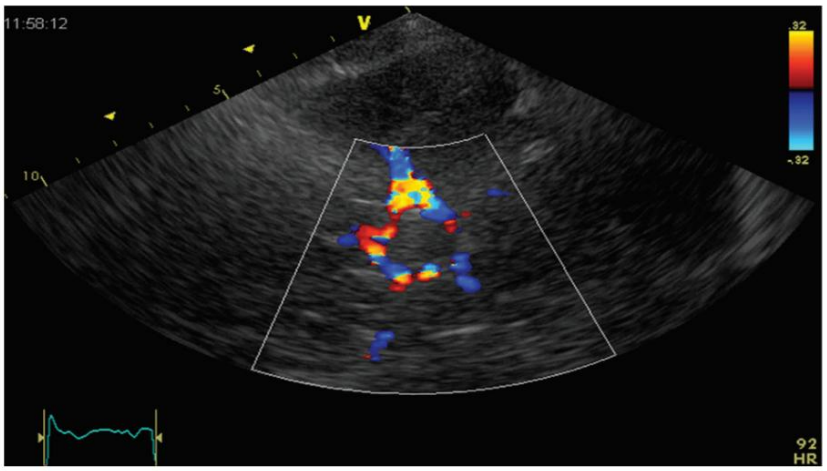

Figure 2: Mesencephalic view.
It is clearly distinguishable the middle cerebral artery

Advanced Methods

Advanced applications of transcranial Doppler (TCD) are possible due to its ability of continuous monitoring of blood flow in an intracranial artery over extended periods. Thus, the dynamic changes in cerebral hemodynamics as a result of the natural history of an intracranial disease and complications of a disease or secondary to an external provocative stimulus can be observed in real time and aid in the diagnostic, therapeutic as well as prognostic processes.(Nichol) Nichol, Girling, Jerrard, Claxton, & Burton, 1951). The vasomotor tone, which WT represents is the determinant of the critical closing pressure. Clinically, CrCP represents a lower threshold. By comparing the pulsatile waveforms of blood flow velocity and ABP, CrCP can be assessed non invasively through TCD. Given the association with the vasomotor tone of small blood vessels (wall tension), CrCP can provide important physiologic detail regarding cerebral haemodynamics and changes in cerebral perfusion pressure in several neurological conditions (Michel, Hillebrand, vonTwickel, Zernikow, & Jorch, 1997; Varsos et al., 2013a). The estimation of CrCP through TCD has been applied to estimate changes in ICP and cerebrovascular tone to direct therapies in patients at risk of developing vasospasms after a subarachnoidal hemorrhage (Panerai, 2003). Various methods for calculating CrCP have been proposed based on the assumption of a linear relationship between cerebral blood FV and ABP, and that PCVR is independent of the frequency of the cardiac cycle. Among these, the Michel's method (Michel & Zernikow, 1998), based on the fundamental harmonics of the pulse waveforms of ABP and FV is well studied. Nonetheless, a limitation of all methods for CrCP estimation consists in the possibility to obtain negative values of CrCP, which cannot be clinically and physiologically explained (Puppo et al., 2012; Soehle, Czosnyka, Pickard, & Kirkpatrick, 2004). A flow-limiting stenosis in a cervical or intracranial artery can produce cerebral ischemia by regional hypoperfusion, artery-to-artery embolization, or a combination of both. Extended monitoring of an intracranial artery distal to the steno-occlusive site can detect spontaneous embolic signals [microembolic signals (MES)] and quantify the embologenic potential of the atherosclerotic plaque. (Michel & Zernikow, 1998), The best method for monitoring of MES is to use a TCD probe fixation headframe that enables continuous recording of spectral flow from the desired intracranial artery.Detection of even a single MES during 40 min of monitoring is considered as clinically significant. According to this method, capacitance and resistance are in parallel such that the impedance to flow is considered a function of heart rate. This models advantage is that it does not take into account the negative values that can be seen in Michael's model which are not physiologically interpretable. Varsos et al. (2013b).

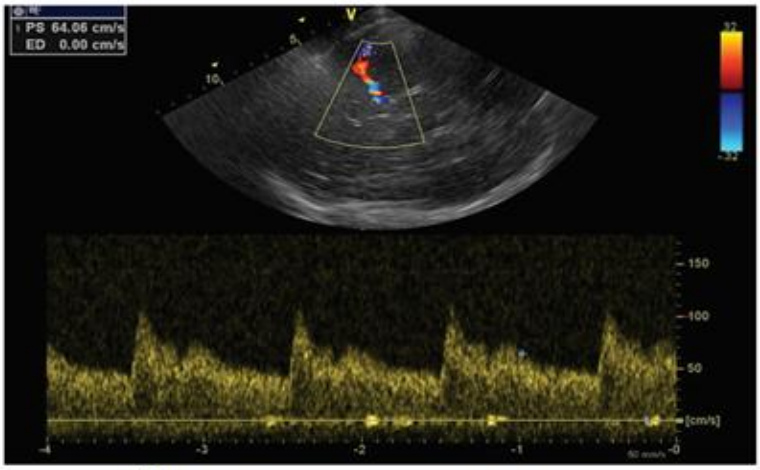

Figure 3: Transcranial Doppler spectral Doppler study of intracranial middle cerebral artery.0
MCA = Middle cerebral artery

Intracranial Pressure

ICP is essential to guide management of patients suffering from acute brain diseases, this signal is often neglected outside the neurocritical care environment. This is mainly attributed to the intrinsic risks of the available invasive techniques, which have prevented ICP monitoring in many conditions affecting the intracranial homeostasis, from mild traumatic brain injury to liver encephalopathy. In such scenario, methods for non-invasive monitoring of ICP (nICP) could improve clinical management of these conditions. (Bratton et al., 2007; Holloway et al., 1996). Hence, TCD waveform analysis has been widely investigated as a technique for noninvasive ICP estimation (nICP). Increased ICP may affect the blood flow velocity in major cerebral vessels and produce deviations in cerebral blood flow velocity such as decreased diastolic flow velocity and increased PI (Czosnyka et al., 1996; De Riva et al., 2012). PI and ICP correlation has been extensively studied (Bellner et al., 2004; Zweifel et al., 2012). Bellner et al., in a cohort of eighty-one patients with intracranial disorders, found a significant correlation (R 5 .94, p < .0001) between invasively measured ICP and PI and between ICP and PI in the ICP interval between 5 to 40 mmHg (Bellner et al., 2004). Zweifel et al., in a cohort of 290 patients, found a weak correlation between PI and ICP (.31; p < .001), with a 95% prediction interval of ICP values wider than 15 mmHg (Zweifel et al., 2012). Finally, Cardim et al. (Cardim et al., 2016a) demonstrated a nonsignificant correlation between nICP and_PI with a measured ICP of .15 (p > .05) and a predictive ability (AUC) for detecting mean values of ICP of 17 mmHg.

Mathematical Models

Models that stimulate CVD cerebrovascular dynamics using simultaneous FV and ABP have been proposed by numerous authors (Kashif, Verghese, Novak, Czosnyka, & Heldt, 2012). In a Black-Box model for estimation of ICP (nICP_BB), with ICP being a system response (output signal ICP) to the incoming signal ABP (input signal), noninvasive ICP estimation can be performed using signals obtained from ABP and cerebral blood FVs. In a cohort of 40 TBI patients, Cardim et al. (2016a) evaluated the black-box method and demonstrated a correlation with measured ICP of .39 (p < .05). The bias and 95% CI for the prediction of ICP were 2.50 6 5.07 and 9.94 mmHg, respectively. The predictive ability for detecting mean values of ICP 17 mmHg was .66 (AUC), which was measured through a receive operating characteristic (ROC) curve analysis. Aaslid et al. (1986) presented a mathematical model for the noninvasive estimation of CPP based on transcranial Doppler waveform analysis, the spectral pulsatility index (SPI), and the first harmonic component of the arterial blood pressure (A1). Czosnyka et al. (1998) proposed a similar, modified formula based on the waveform analysis of FV, which uses

the FVd for the estimation of nCPP. In 96 TBI patients, the correlation between nCPP and measured CPP was R 5 .73; p < 1026. In 71% of the examinations, the estimation error was found to be less than 10 mmHg, and in 84% of the examinations, the error was less than 15 mmHg. The method had a high positive predictive power (94%) for detecting low CPP (< 60 mmHg). The same method was applied in clinical and experimental studies (Robba et al., 2015; Cardim et al., 2016b; Rasulo et al., 2017) with promising results. Varsos et al. (2013b) used a method based on CrCP to provide information regarding the state of cerebral haemodynamics and reflection of changes in CPP (Czosnyka, Richards, Pickard, Harris, & Iyer, 1994; Michel et al., 1997; Nichol et al., 1951; Puppo et al., 2012). According to this method, nCPP seems to be correlated with measured CPP (R 5 .85, p < .001), with a mean SD difference of 4.02, 6.01 mmHg and 83.3% of the cases with an estimation error below 10 mmHg (Varsos et al., 2015). Cardim et al. (2016b) revealed that nICP measured by CrCP method, presented a correlation with measured ICP of .354Avoiding the complications of invasive monitoring, TCD can noninvasively estimate ICP and CCP.

The various formulas proposed for this purpose have demonstrated a wide confidence intervals which remains to be fully validated. Consequently, none of these methods appear to be accurate enough to be used as a replacement for invasive ICP measurements. At present, TCD is reserved for assessing changes of nICP, rather than absolute nICP. Although intracranial pressure (ICP) is essential to guide management of patients suffering from acute brain diseases, this signal is often neglected outside the neurocritical care environment. TCD waveform analysis has been widely investigated as a technique for non invasive ICP estimation (nICP). Increased ICP could affect the blood flow velocity in major cerebral vessels and produce changes in cerebral blood flow velocity such as decreased diastolic flow velocity and increased PI (Czosnyka et al., 1996; De Riva et al., 2012). The correlation between PI and ICP has been extensively studied (Bellner et al., 2004; Zweifel et al., 2012). Bellner et al., in a cohort of eighty-one patients with intracranial disorders, found a significant correlation (R = .94, p < .0001) between invasively measured ICP and PI and between ICP and PI in the ICP interval between 5 to 40 mmHg (Bellner et al., 2004); Zweifel et al., in a cohort of 290 patients, found a weak correlation between PI and ICP (.31; p < .001), with a 95% prediction interval of ICP values wider than ± 15 mmHg (Zweifel et al., 2012). Finally, Cardim et al. (Cardim et al., 2016a) demonstrated a non-significant correlation between *nICP_PI* with measured ICP of .15 (p > .05) and a predictive ability (AUC) for detecting mean values of ICP ≥ 17 mmHg of. Many authors have proposed mathematical models that simulate the cerebrovascular dynamics using simultaneous FV and ABP (Kashif, Verghese, Novak, Czosnyka, & Heldt, 2012). In a Black-Box model for estimation of ICP (*nICP_BB*), with ICP being a system response (output signal ICP) to the incoming signal ABP (input signal), noninvasive ICP estimation can be performed using signals obtained from ABP and cerebral blood FVs. Cardim et al. (2016a) evaluated the black-box method in a cohort of 40 TBI patients and demonstrated a correlation with measured ICP of .39 (p < .05). The bias and 95% CI for prediction of ICP were −.50 ± 5.07 and 9.94 mmHg, respectively. The predictive ability for detecting mean values of ICP ≥ 17 mmHg was .66 (AUC), measured through a receive operating characteristic (ROC) curve analysis.

Cerebrovascular Time Constant (CTAU)

The CTAU is a noninvasive TCD-based index, that theoretically indicates, the time required to establish a change in cerebral blood volume after a sudden change in arterial blood pressure during one cardiac cycle (Czosnyka et al., 2012). This analog to time constant is calculated as a product of brain arterial compliance (Ca) and resistance (PCVR), expressed in time units (seconds). Both Ca and PCVR are calculated from the relationship between pulsatile ABP and transcranial Doppler cerebral blood FVs. CTAU dependence on hemodynamic and cerebrovascular parameters was studied on 46 New Zealand

rabbits undergoing hemodynamic manipulation. An inverse correlation of CTAU was found with the changes in ABP (during arterial hypo- and hypertension) and CPP (during intracranial hypertension). In particular, during a decrease in CPP, Ca increased while PCVR decreased., the decrease in PCVR was more pronounced than the increase in Ca during hypercapnia, resulting in a total decrease in CTAU (Czosnyka et al., 2012). The assumption that CTAU is independent of the cross-sectional area of the insonated vessel allows the application of CTAU for quantitative hemodynamic study in different cerebrovascular diseases. In 50 patients with symptoms of normal pressure hydrocephalus undergoing infusion tests (Capel et al., 2014), the cerebral arterial time constant was directly linked to the dynamics of CSF circulation and pressure-volume compensation, however a significant correlation with changes in CPP was observed (R5 .33; p 5 .017). CTAU was also studied in healthy volunteers and in patients with severe stenosis of the internal carotid artery (ICA). CTAU was found to be significantly shorter in severe internal carotid artery stenosis (Kasprowicz et al., 2012a) than in controls, and that which correlated with the degree of stenosis (R 5 2.62, p 5 .001). Moreover, CTAU decreased significantly during vasospasm in patients SAH (Kasprowicz et al., 2012). In particular it was found to be shortened on the side of the aneurysmal SAH before the vasospasm was identified by clinical or conventional TCD signs of vasospasm. In another study, (Trofimov, Kalentiev, Gribkov, Voennov, & Grigoryeva, 2016) the cerebrovascular time constant was assessed in patients of TBI, with and without intracranial hematomas (epidural, subdural, and multiple hematomas). This study revealed that CTAU was shorter (p5 .05) in both groups in comparison with normal data, but in patients with intracranial hematomas, the time constant was found to be even shorter.

Compartmental Compliance

Compliance of arterial and CSF compartment Cerebral compliance (C) is the ability of the brain to adapt to changes in volume (dV) inside the cranium in response to a change in pressure (dP) in order to avoid intracranial hypertension. In particular, two main types of compliance are described: the cerebrovascular arterial compliance (Ca), which describes the change of arterial blood volume in response to change in arterial pressure and the compliance of the cerebrospinal space (Ci), which refers to changes of volume of the intracranial space in regards to changes in ICP. Ci represents the combined compliances of the venous bed and the CSF space, where Cv is generally considered as part of Ci (Czosnyka et al., 1999). The intracranial system consists of three different compartments: parenchymal, vascular, and CSF. Assuming that the parenchymal compartment is nearly incompressible, the changes of volume of the intracranial space through the foramen magnum strictly relate to the volume changes of the vasculature (venous pool) plus displacement of CSF down to the CSF spinal space. TCD noninvasively allows a calculation of cerebral arterial blood volume (CaBV); (Avezaat & Eijndhoven, 1984) and, based on the relationship between pulsatile changes in ABP, ICP, as well as CaBV, enables the assessment of the relative changes in the cerebrovascular arterial compliance. The model described is based on the mechanism of brain pulsatility that describes the physiological interactions of the intracranial compartments, that undergo volumetric changes during the cardiac cycle. This method was widely described in patients with TBI during “plateau waves” of ICP (Czosnyka et al., 1999), which were monitored using TCD. The origin of plateau waves includes intrinsic cerebral vasodilatation, with a rise in cerebral blood volume and ICP. Therefore, according to the vasodilatory cascade hypothesis, these changes are associated with a rapid increase in Ca caused by vasodilatation of cerebral resistive vessels during a wave and a reduction of Ci because of the decrease in cerebrospinal compensatory reserve that consequently leads to an increase in cerebral blood volume (Oktar et al., 2006; Rosner & Becker, 1984; Figure 4). The pulsatile component of ICP and clinical management guided by AMPICP has been shown to be a predictor of outcome in patients with SAH. Plateau waves affect the

balance between vascular and CSF compartments, which is reflected by the inverse change of compliance of the cerebral arterial bed and global compliance of the CSF space. (Eide et al., 2012)

Autoregulation of Cerebral Blood Flow

Impairment of CBF autoregulation may have serious implications for patients with cirrhosis if arterial hypotension occurs during coma, anesthesia, bleeding, or sepsis. Cerebral blood flow autoregulation refers to the intrinsic ability of the brain to maintain a stable cerebral blood flow (CBF) despite fluctuations in cerebral perfusion pressure between 50 to 150 mmHg in normotensive patients (Czosnyka, Smielewski, Piechnik, & Pickard, 2002). An abnormal balance between cerebral blood flow, blood volume, and of the metabolic requirement of the cerebral tissues, may result from disturbed autoregulation. In many neurological diseases, including TBI and stroke, an impairment of this autoregulatory response has been demonstrated (Bouma, Muizelaar, Bandoh, & Marmarou, 1992; Zweifel et al., 2008). It appears that the degree of impairment is related to a poor outcome. Evaluations of cerebral autoregulation tradaditionly have been performed under steady-state conditions at a constant baseline ABP and constant CBF. Numerous authors adopted TCD as a static model to autoregulatory testing in patients using the static autoregulatory index (sARI) or static rate of regulation (sROR), which is defined as the percentage change in PCVR% change in CPP (Panerai, 2009; Tiecks, Lam, Aaslid, & Newell, 1995). Although this classic static approach has been widely applied in clinical practice for decades, it does not take into account different factors including the different upper and lower limits of autoregulation or different slopes of the 'autoregulatory zone' among different individuals (Donnelly, Aries, & Czosnyka, 2015). Furthermore, static methods do not take in account the dynamic changes of autoregulation. They further require pharmacologic or mechanical manipulations of CPP, which may be inappropriate and unsafe in clinical practice and can fail in capturing the changes and latency of the autoregulatory response (Aries, Elting, De Keyser, Kremer, & Vroomen, 2010). Therefore, the investigation of dynamic cerebral autoregulation using TCD is an area of significant research, given that the high temporal resolution which allows measuring the timing and the magnitude of the changes of CBF to the CPP/(ABP) a challenge. This "dynamic" approach uses the induced or spontaneous rapid changes in ABP as an autoregulatory stimulus and compares ABP and CBF velocity during the entire autoregulatory process (dynamic pressure autoregulation); (Zhang, Zuckerman, Giller, & Levine, 1998). In neuromonitoring, TCD can be useful to calculate an index of autoregulation called the mean flow index (Mx), which is the correlation coefficient indices between FVm and CPP (Czosnyka, Smielewski, Kirkpatrick, Menon, & Pickard, 1996). To reduce the influence of cardiac pulse and respiration, ABP and CBF are time-averaged (usually > 10 seconds), and 30 such samples are usually used for the estimation of the correlation between the two parameters. Baseline CBF was measured using single-photon emission computed tomography (SPECT) with concomitant measurements of cerebral arteriovenous oxygen content differences ($AVDO_2$). CBF autoregulation was evaluated using the $AVDO_2$ method and changes in mean flow velocity in the middle cerebral artery (V_{mean}) as determined by transcranial Doppler (TCD). Mean arterial pressure (MAP) was increased by 30 mm Hg by intravenous norepinephrine, and subsequently decreased by a combination of lower body negative pressure and ganglion blockade, whereas $AVDO_2$ and V_{mean} were measured at each 5 mm Hg change in MAP. (Czosnyka, Smielewski, et al., 1996). Additionally there is a significant association with the outcome for both parameters. Despite the wide and generally accepted value of TCD in the assessment of cerebral autoregulation, this technique has some limitations. Measurements of FV are frequently taken only from the MCA, thus auto-regulatory changes in posterior circulation may not be detected (Aries et al., 2010). Moreover, TCD-based studies use CBF-V as a surrogate measure of CBF, however, CBF-V is only proportional to CBF

when vessel cross-sectional area remains constant. The assessment of cerebrovascular reactivity remains a fundamental diagnostic method for testing the cerebral hemodynamic reserve. There are several modalities available to assess cerebrovascular reactivity in clinical practice using different stimuli, such as carbon dioxide, breath-holding index, and acetazolamide injection (Smielewski, Czosnyka, Pickard, & Kirkpatrick, 1997; Mancini, De Chiara, Postiglione, & Ferrara, 1993). This parameter can be assessed using different tools, including near infrared spectroscopy (Smielewski et al., 1997) and positron emission tomography (PET) scanning (Herold et al., 1988). Yet still, the most commonly used is the assessment of changes in cerebral blood flow velocity through TCD (Markus & Cullinane, 2001). The hemodynamic reserve can be estimated by measuring cerebrovascular reactivity, induced by breathing CO2 and pressure-autoregulation by analyzing spontaneous slow fluctuations in the flow velocity measured through TCD and arterial pressure (Markus & Cullinane, 2001). In this, TCD has been widely used to assess CO2 reactivity in patients with carotid artery stenotic disease. FVs are measured during normo and hypercapnia, with the carbon dioxide used as a vasodilatory stimulus (Markus & Cullinane, 2001).

Clinical Applications

Traumatic Brain Injury

TBI is an important cause of morbidity and mortality. Several important disturbances of cerebral hemodynamics occur after TBI, including hyperemia, cerebral ischemia, and vasospasm. Monitoring and targeted management of ICP and CPP are necessary in patients with severe TBI. Intracranial hypertension and low CPP are associated with a poor outcome. Furthermore, the literature is solid to point out the importance of strict neuromonitoring in an effort to prevent secondary brain insult (Lane, Skoretz, Doig, & Girotti, 2000). In both human and animal studies, TCD has been widely applied in TBI patients, in particular for the assessment of ICP and CPP (Cardim et al., 2016a). Moreover, authors have shown that impaired autoregulation, determined by TCD methods (Mx or Sx index), is strongly associated with a poor outcome at 6 months (Czosnyka, Smielewski, et al., 1996; Budohoski, Reinhard, et al., 2012). TCD can also be useful in TBI patients to assess the cerebral dynamics and the entity of cerebral swelling through the calculation of cerebral compliance. Hyperemia may result a few hours after TBI, for a duration of two to four days, followed by Doppler patterns suggestive of high vascular resistance, which is consistent with elevated ICP (Muttaqin et al., 1993). TCD may also be used for diagnosis and monitoring of posttraumatic vasospasm and in the monitoring of treatment (Trabold et al., 2004) of ICP.

TCD Monitoring of Vasospasm in Subarachnoid Hemorrhage

TCD is the surveillance tool of choice in patients with aSAH for diagnosis vasospasm during the symptomatic phase as well as in the phase when there is no clinical suspicion (pre-symptomatic) or when the clinical suspicion is unreliable as in patients with poor neurological status. (Rincon, Rossenwasser, & Dumont, 2013), with a six-month mortality rate ranging from 32 to 67%, with 30% of survivors harboring permanent neurological impairment (Hop, Rinkel, Algra, & van Gijn, 1997). A vasospasm usually occurs 3 to 14 days following an aneurysmal subarachnoid hemorrhage (aSAH). It is known to be one of the causes leading to delayed cerebral ischemia (DCI) and poor outcomes (Diringer et al., 2011). Angiography is considered the gold standard for the detection of vasospasm; however, TCD has long been used for monitoring patients with SAH for vasospasm detection (Kumar, Shahripour, & Harrigan, 2015). TCD can detect vasospasms as the constriction of the cerebral vessels leads to an increase of cerebral blood flow velocities (Kumar et al., 2015). During the previous decade, numerous authors suggested various TCD criteria for the evaluation of vasospasm (Mascia et al., 2003; Toi et al.,2013). According to a recent meta-analysis, of 2870 patients, TCD was found to be highly predictive of evidence of vasospasm in patients with aSAH with a sensitivity 90%

(95% confidence interval [CI] 77%-96%), specificity 71% (95% CI 51%-84%), positive predictive value 57% (95% CI 38%-71%), and negative predictive value 92% (95% CI 83%-96%). Vora et al. (1999), in a retrospective study of 101 patients, found that mean flow velocity (FVM) > 120 cm/s on the MCA had a specificity of 72% and sensitivity of 88% for 33% angiographic vasospasm with a negative predictive value (NPV) of 94% for FVM < 120 cm/s. Moreover, FVM > 200 cm/s was 98% specific and 27% sensitive with a positive predictive value (PPV) of 87% for angiographic vasospasm of 33%. To differentiate an increase of the FV related to systemic hyperdynamic flow and vasospasm, the Lindegaard ratio ((LR); Linde Lindegaard, Nornes, Bakke, Sorteberg, & Nakstad, 1988) is typically used. LR is defined as FVm on the MCA divided for the extracranial ICA FVm. According to this assessment, LR indicates hyperdynamic flow and vasospasm. While TCD can also cerebral autoregulation after aSAH, TCD has also been extensively used for the detection of cerebral vasospasm showing good sensitivity and specificity. An Early detection of Impaired cerebral autoregulation in these patients (Budohoski et al., 2013) is associated with increased risk to develop delayed cerebral ischemia independently to the incidence of a vasospasm (Budohoski, Czosnyka, et al., 2012), and later shown to be associated with a poor outcome. (Budohoski et al., 2014).

Stroke

A distinct advantage of TCD is the ability to monitor blood flow in a blood vessel over prolonged periods of time, which has shown microembolic signals in acute ischemic stroke, carotid artery disease, atrial fibrillation and during angiography. In patients affected by ICA stenosis, impaired autoregulation assessed by significant increases in Mx and decreases in dARI are observed (Reinhard et al., 2003). TCD is a rapidly reproducible test which has been used for the diagnosis, prognosis and the treatment of ischemic strokes (Topcuoglu, 2012). In a cohort of 48 patients with angiographic occlusion, TCD showed an overall sensitivity of 83% and specificity of 94%, especially in anterior circulation (Demchuk et al., 2000). TCD can also be a reliable prognostic indicator in MCA occlusive stroke (Alexandrov, Burgin, Demchuk, El-Mitwalli, & Grotta, 2001). Its' role in the assessment of cerebral autoregulation after a stroke has been extensively studied.

Depending to the location and severity of the occlusion; TCD may also have a role in the prediction of outcome in stroke patients. In a study of 335 acute stroke patients who received thrombolytic treatment, distal MCA occlusions assessed through TCD were associated with the greatest probability of early re-canalization (44%), compared with 30% in the proximal MCA, 30% in the BA, and < 10% in the terminal ICA (Moppett & Mahajan, 2004). Regardless, TCD can play an important role in patients with ischemic stroke, CTA and MRA.

Another clinical application of TCD is seen in patients with a stroke, in the detection of paradoxical embolism through right to left cardiopulmonary shunts, such as in patent foramen ovale (Cabanes et al., 1993). A peripheral injection of agitated saline is typically administered. The patient is asked to perform a Valsalva maneuver. Thereafter the number of microembolic signals observed after the end of the injection are detected and counted through TCD and are correlated with the grade of shunting. TCD provides important information and serves as a rapid and reliable screening tool for the detection of an arterial occlusion, for monitoring of arterial patency during thrombolysis, as well as for the assessment of cerebral hemodynamic alterations in patients with acute ischemic stroke (Sarkar, Ghosh, Ghosh, & Collier, 2007).

Clinical Applications

A Doppler ultrasound may help in the diagnose many conditions, including: Blood clots. Poorly functioning valves in your leg veins, which can cause blood or other fluids to pool in your legs (venous insufficiency) Heart valve defects and congenital heart disease. TCD presents a wide range of clinical application in areas such as anesthesiology, neurology,

neurosurgery and in a neurointensive care settings. Aside from the previously described applications in neurointensive care settings, (TBI, SAH, Stroke) it has also been successful applied in the diagnosis of brainstem necrosis (Ducrocq et al., 1998) as seen in cerebral nervous system infections and in many ischemic cerebrovascular disease (sickle cell disease, right to left cardiac shunt, venous thrombosis) in both the adult and pediatric populations. TCD is also gaining particular traction in the intraoperative settings. It has been successfully applied in order to asses nCPP and nICP in surgical procedures with risk of increasing intracranial hypertension (Robba et al., 2016). These include procedures such as laparoscopic procedures with pneumoperitoneum and also when patients may require to be positioned in the Trendelenburg position (Robba et al., 2016). It has further been successfully used for neuromonitoring during carotid endarterectomy and cardiopulmonary bypass (Joshi et al., 2012). Recently, TCD has been applied in septic patients to assess nCPP and PI. Some authors have found higher values of PI and cerebral vascular constriction in septic patients, compared to that of the control group, suggesting a possible use of TCD in the assessment of the mechanisms underlying the pathogenesis of sepsis related encephalopathy. Transcranial Doppler (TCD) ultrasound provides rapid, noninvasive, real-time measures of cerebrovascular function.

TCD can be used to measure flow velocity in the basal arteries of the brain to assess relative changes in flow, diagnose focal vascular stenosis, or to detect embolic signals within these arteries. (Pierrakos et al., 2013).

Conclusion

Advances in technology have stimulated a renewed interest in the use of non-invasive, portable and easy to use tools for the monitoring of cerebral haemodynamics in a variety of disorders. Three-dimensional power Doppler ultrasonography imaging provides rapid, noninvasive visualization of ruptured intracranial aneurysms, including their relationship to other vascular structures. The noninvasive nature, repeatability, portability, and high temporal resolution of TCD have encouraged the use of this technique, especially in bedside monitoring of CBF in the neurocritical care settings. Invasive techniques still appear to remain the gold standard across the majority of clinical applications. Furthermore, operator dependency and the need for an appropriate temporal window are a significant limitation to its clinical utility. However, despite some limitations including operator dependency; 10–20% of patients have inadequate transtemporal acoustic windows. Yet, TCD still remains an important tool for the assessment of cerebral hemodynamics in critically ill patients and its wide utility as a diagnostic tool makes it a useful “stethoscope for the brain.” The future of TCD in intensive care Whilst class I data exist for the role of TCD in the management of patients with sickle cell disease, robust evidence for its usefulness in the critically ill is lacking. Although evidence of its diagnostic capabilities in a variety of conditions is emerging, its current application in intensive care is confined largely to the management of patients with aSAH, assessment of brain death and monitoring of cerebral haemodynamics in neurotrauma

Table2. Clinical Applications of Transcranial Doppler in NeurocriticalCare

CLINICALAPPLICATION	Role of TCD
TBI	Non invasive ICP and CPP estimation Autoregulation and cerebrovascular reactivity Compliance and cerebrovascular dynamics Detection of posttraumatic vasospasm Evaluation of effect of endovascular treatment of vasospasm with balloon angioplasty or injection of vasodilators
SAH (Aneurysms and AVM)	Vasospasm Autoregulation and cerebrovascular reactivity Non-invasive ICP evaluation

	Evaluation of effect of endovascular treatment of vasospasm with balloon angioplasty or injection of vasodilators
STROKE	Diagnosis and treatment of ischemicstroke Emboli monitoring especially after cardioembolic stroke,and in patients with fat embolism syndrome
HYDROKEPHALUS	Infusion study and cerebral reserve andcompliance Cerebral autoregulation and cerebrovascular reactivity
BRAIN TUMORS	Detection of vasospasm Non invasive intracranial pressure
BRAIN DEATH	Diagnosis of brain death
SICKLE CELL DISEASE	Screening and follow up of children
Right to Left CARDIAC SHUNT	Evaluation of paradoxical embolism through right left cardiopulmonary shunts to (e.g., patent foramen ovale)
CAROTID SURGERY	Postoperative evaluation of patients after Carotid endoarterectomyor carotidstenting (risk of brain hyperperfusionor emboli)
CEREBRAL NERVOUSSYSTEM INFECTION	Non invasive ICP and cerebrovascular dynamic
PERI-PROCEDURAL/ OPERATIVE	Autoregulation Non invasive ICP and CPP
LIVER FAILURE	Non invasive ICP estimation and prognosis for acute liver failure
PREECLAMPSIA	Assessment of autoregulation and FV as prognostic for preeclampsia
SEPSIS	Assessing cerebral perfusion changes in Septic patients as risk of sepsisassociated encephalopathy

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