Transcranial Doppler to Predict Neurologic Outcome after Mild to Moderate Traumatic Brain Injury

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ABSTRACT

Background: To assess the performance of transcranial Doppler (TCD) in predicting neurologic worsening after mild to moderate traumatic brain injury.

Methods: The authors conducted a prospective observational study across 17 sites. TCD was performed upon admission in 356 patients (Glasgow Coma Score [GCS], 9 to 15) with mild lesions on cerebral computed tomography scan. Normal TCD was defined as a pulsatility index of less than 1.25 and diastolic blood flow velocity higher than 25 cm/s in the two middle cerebral arteries. The primary endpoint was secondary neurologic deterioration on day 7.

Results: Twenty patients (6%) developed secondary neurologic deterioration within the first posttraumatic week. TCD thresholds had 80% sensitivity (95% CI, 56 to 94%) and 79% specificity (95% CI, 74 to 83%) to predict neurologic worsening. The negative predictive values and positive predictive values of TCD were 98% (95% CI, 96 to 100%) and 18% (95% CI, 11to 28%), respectively. In patients with minor traumatic brain injury (GCS, 14 to 15), the sensitivity and specificity of TCD were 91% (95% CI, 59 to 100%) and 80% (95% CI, 75 to 85%), respectively. The area under the receiver operating characteristic curve of a multivariate predictive model including age and GCS was significantly improved with the adjunction of TCD. Patients with abnormal TCD on admission (n = 86 patients) showed a more altered score for the disability rating scale on day 28 compared to those with normal TCD (n = 257 patients).

Conclusions: TCD measurements upon admission may provide additional information about neurologic outcome after mild to moderate traumatic brain injury. This technique could be useful for in-hospital triage in this context.
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PATIENTS with mild to moderate traumatic brain injury (TBI) constitute the majority of the patients admitted to the emergency room (ER).[1] Despite their reassuring presentation, 5 to 20% of these patients will develop secondary neurologic deterioration (SND) within the first post-traumatic week.[2,3] Neurologic worsening adds to the burden of initial lesions and influences neurologic outcome.[4] Clinical examination including the Glasgow coma score (GCS) and pupil size measurements is not accurate enough to detect these high-risk patients. While cerebral computed tomography (CT) scan has an excellent negative predictive value (NPV),[5] mild to moderate brain lesions on CT weakly correlate with SND.[6] Therefore, triage of patients with minor to moderate TBI and minor lesions on CT scan is challenging in the emergency department (ED) and requires additional tool to screen this population.

Transcranial Doppler (TCD) is a technique that explores cerebral blood flow velocities.[7] In patients with TBI, this technique can reveal low diastolic blood flow velocity (FVd) and high pulsatility index (PI) values induced by

What We Already Know about This Topic

- A substantial proportion of patients with mild to moderate traumatic brain injury, and who have minor lesions on an initial computed tomography scan, undergo secondary neurologic deterioration within the first week
- Transcranial Doppler thresholds for flow velocity and pulsatility index might allow for the differentiation of those patients who undergo secondary neurologic deterioration from those who do not
- In a multicenter study, the transcranial Doppler thresholds for pulsatility index and flow velocity were validated for outcome prediction in mild to moderate traumatic brain injury

What This Article Tells Us That Is New

- Transcranial Doppler parameters had excellent negative predictive value in that patients who did not undergo secondary neurologic deterioration were readily identifiable
- Patients with abnormal transcranial Doppler patterns had greater disability 4 weeks after injury
- In combination with clinical examination and computed tomography scan, transcranial Doppler monitoring can inform clinicians about neurologic outcome in patients with mild to moderate traumatic brain injury

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high vascular bed resistance. TCD has been used on admission to improve cerebral hemodynamics in patients with severe TBI.[8,9] In a previous study including patients with normal or mild brain lesions on initial CT scan, we found a correlation between TCD measurements on admission and early neurologic status.[10] The thresholds of 1.25 and 25 cm/s for PI and FVd accurately predicted neurologic worsening with 90% sensitivity and 91% specificity. However, these cut-offs were proposed from one single-center study and an external validation of TCD from multiple sites is required to promote the use of TCD in the ED. The aim of the current study was to validate these TCD thresholds for outcome prediction in a large multicenter cohort study population after mild to moderate TBI and minor lesions on initial CT scan.

Patients and Methods

We conducted an observational prospective multicenter study in 17 French EDs, including 7 university and 10 general hospitals (see appendix) between February 2011 and January 2013. The Regional Institutional Ethics Committee approved the study design (*Comité d'Ethique des Centres d'Investigation Clinique de l'inter-région Rhône-Alpes-Auvergne*, institutional review board number 2007–24, Clermont-Ferrand, France). This study is registered with ClinicalTrials.gov No. NCT01291706 (Principal Investigator: J.-F.P., registered on February 7, 2011). Patients were individually informed, but no written informed consent was required. Patients had the opportunity to decline their participation in the study.

Patients aged more than 15 yr admitted to the ED after mild to moderate TBI (GCS, 9 to 15) were included in the study if they underwent TCD within 8 h post injury and their initial CT scan satisfied the Traumatic Coma Data Bank (TCDB) II classification: diffuse injury with cisterns present, a midline shift between 0 and 5 mm, and/or no high- or mixed-density lesions of at least 25 ml. CT scans were all classified by a senior radiologist from each center. Initially, patients more than 18 yr were planned to be included. Due to a lower rate of recruitment, we extended the inclusion criterion to 15-yr-old patients because their TCD velocities were not different from those of adult patients. Patients were excluded if they met one of the following criteria: previous treatment with anticoagulant or antiplatelet drugs except aspirin, mechanical ventilation with sedation on admission, systolic arterial blood pressure less than 90 mmHg, arterial pulse oximetry less than 92%, no CT scan on admission, evidence of moderate or severe brain lesions on initial CT scan (*i.e.,* TCDB classification III-VI), any craniotemporal lesion impeding satisfactory TCD examination, more than 8-h delay between initial injury and TCD measurements, or a history of intracranial procedures. Data collected on admission were age, mechanism of injury, time from trauma to initial CT scan, time from trauma to TCD, heart rate, arterial blood pressure, respiratory rate, and score for the visual analog pain scale. Biologic data consisted of serum sodium concentration, serum glucose concentration, hemoglobin concentration, platelet count, coagulation parameters, and arterial blood gases if available. An injury severity score (ISS) was also measured upon admission.

Transcranial Doppler

Centers were visited by P.B. before their participation in the study. The reliability of TCD recordings was checked. Physicians with an adequate background in transcranial ultrasonography were allowed to include patients in each center. TCD measurements were performed in the ED within the first 8 h post-TBI using a Doppler instrument operating at 2 MHz or an echo-Doppler device with a 1- to 5-MHz transducer. In all patients, both middle cerebral arteries were insonated through the transtemporal window at a depth of 50 to 60 mm, and tracings were recorded for at least 10 cardiac cycles in patients showing stable conditions, *i.e.*, no agitation or pain, no cardiorespiratory distress. For echo-Doppler measurements, the clinoid process of the sphenoid bone and the brain stem were initially identified. Color-coded sonography enabled identification of the circle of Willis. The M1 segment of the middle cerebral artery (MCA) was identified and manual angle correction then applied to measure blood flow velocity in each MCA (in centimeter per second) by the inbuilt software. Tracings had to be stable over a 30-s recording period. Time-averaged mean blood flow velocity (FVm), systolic blood flow velocity (FVs), and FVd (in centimeter per second) and the PI [(FVs – FVd)/FVm] were then calculated. The higher PI and the lower flow velocity between the right and left MCAs were considered for statistical analysis. According to our previous study,[10] normal TCD pattern was defined as the combination of FVd greater than 25 cm/s and PI less than 1.25. An abnormal TCD pattern was one in which FVd less than or equal to 25 cm/s or PI greater than or equal to 1.25.

Study Endpoints

The primary endpoint of this study was early neurologic worsening. Clinical observation lasted 7 days, after which

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neurologic outcome was determined either by physical examination or by telephone interview if the patient had already been discharged from the hospital. Neurologic worsening was defined as one of the two following objective criteria[11]: (1) a decrease in GCS of greater than 2 points from the initial GCS in the absence of pharmacologic sedation and (2) a deterioration in neurologic status sufficient to warrant intervention, *i.e.*, mechanical ventilation, sedation, osmotherapy, transfer to the intensive care unit (ICU), or neurosurgic intervention. All cases with SND were reviewed at the end of the study by a panel of experts blinded to the TCD findings.

Secondary outcomes were: (1) variables independently associated with the development of early SND and their potential value to predict neurologic outcome; (2) the influence of TCD pattern: ICU admission (yes/no), length of stay in the ICU (number of days), intracranial pressure (ICP) monitoring (yes/no), and number of repeat CT scans after trauma; and (3) neurologic outcome assessed on day 28 using the disability rating scale (DRS). A score for the DRS was given as a result of a centralized telephone interview, and all scores were reviewed by a neurorehabilitation specialist blinded to the TCD findings. DRS scores were divided into four categories[12]: no/mild disability for scores 0 and 1, moderate disability for scores between 2 and 6, severe disability for scores between 7 and 21, vegetative/dead for scores between 22 and 30.

Data Collection and Quality Control

Inclusions were prospectively recorded in an electronic data capture form. Any inconsistency in the TCD values led to manual queries: contradictions between velocity measurements and PI, outliers in any TCD value, and strong asymmetry between values of the right and the left hemisphere. For every query, investigators had to check for TCD values. In centers with multiple discrepancies or for patients with ongoing discrepancies, initial TCD images were monitored. In addition to TCD values, data quality check was performed before statistical analysis on every abnormal values: vital signs, inclusion criteria, CT descriptors, SND description, and 1-month follow-up. ISSs were all derived from CT description present in the electronic data capture form by a single assessor. A 7-day follow-up was performed by each site investigator with the help of a centralized clinical research associate for patients difficult to contact. A 28-day follow-up was performed by a centralized clinical research associate. Because endpoint collectors were not blinded to TCD values, all cases of SND were reviewed by a blinded panel of experts and all DRS scores were reviewed by a blinded neurorehabilitation specialist (cf. endpoints section).

Study Size

The diagnostic performance of a test is assessed by its sensitivity and specificity. Sensitivity is the ability to detect a disease in patients in whom the disease is truly present (*i.e.*, a true positive), and specificity is the ability to rule out the disease in patients in whom the disease is truly absent (*i.e.*, a true negative). Although sensitivity and specificity are the most commonly provided variables in diagnostic studies, they do not directly apply to clinical situations because the physician wants to know the probability that the disease is truly present or absent if the diagnostic test is positive or negative rather than probability of a positive test given the presence of the disease (sensitivity). These more clinically interesting probabilities are provided by the positive predictive value (PPV) and NPV. Although sensitivity and specificity are not influenced by the prevalence of the disease, NPV and PPV are affected by prevalence.[13] Because true prevalence of SND in this specific multicenter population was unknown, we pragmatically used the observed rate in an interim analysis to reevaluate the sample size in this multisite application.

To estimate the sample size of the study and to validate TCD as a routine exam for clinical practice, we used the 95% CI lower limit of the NPV. We proposed that the lower NPV limit should not be less than 95% to be clinically relevant. Based on previous monocentric study, we hypothesized that 600 patients out of 1,000 would have normal TCD values upon admission. Among them 3% would suffer neurologic worsening (95% CI, 1.7 to 4.7%) giving a NPV of 97% (95% CI, 95 to 98%). Sample size was reevaluated after the first 228 included patients according to observed prevalence and negative test findings. It appeared that (1) patients with normal TCD values were more frequent than expected (73 *vs.* 60%) and (2) the incidence of neurologic worsening was lower than expected (1.2 *vs.* 3%). Therefore, the steering committee reevaluated the sample size at 360 patients. With 73% patients with normal TCD values and 2% with neurologic worsening, this sample size should allow the determination of a lower NPV limit not less than 95%.

Statistical Analysis

Descriptive statistics included frequencies and percentages for categorical variables, and the median and interquartile range (25th to 75th percentile) for continuous variables. The performance of the TCD was evaluated based on measurements of cut-off sensitivity, specificity, PPV, NPV, and positive (LR+) and negative (LR–) likelihood ratios. To describe spectrum effect in our cohort, we also evaluated diagnostic performance of TCD in two subpopulations: minor TBI (GCS, 14 to 15) and moderate TBI (GCS, 9 to 13). The spectrum effect is a sampling bias that refers to subgroup variation in diagnostic test evaluation. To evaluate the additional value of TCD on neurologic prognostication, we built a multivariate predictive model using classic parameters for neurologic outcome prediction, *i.e.*, age and GCS. The diagnostic performance of this model was then compared with another predictive model including age, GCS, and TCD using the determination of the area under the receiver operating characteristic (AUC–ROC) curves. The AUC–ROC curves were compared using a test for dependent ROC curves

(same sample). For each variable, 95% confidence intervals of estimates were provided (Stata 13.0; Stata Corp, USA).

Results

A total of 369 patients were consecutively included over the 2-yr period. Twelve of these patients were then excluded due to the use of mechanical ventilation during TCD (n = 1), a CT scan not corresponding to the TCDB II definition according to the expert's reviewing (n = 2), a nontraumatic lesion on CT scan (n = 1), no acoustic window (n = 4), missing TCD values (n = 1), an inability to consent due to legal protection (n = 2), and a withdrawal of consent (n = 1). For one patient who had two distinct episodes of moderate TBI during the study period, the first event was considered for the analysis. A total of 356 patients were thus analyzed. TCD was performed with an echo-Doppler in 283 (80%) patients and with a Doppler device in 73 (20%) patients. Across the different centers, 107 physicians performed TCD recordings. Characteristics of the studied population are summarized in table 1. The majority of the patients were male, and 63% of the patients had been managed by prehospital emergency medical services. Injury severity was moderate with a median ISS of 16. One hundred eighty-two patients (51%) were discharged from hospital on day 7. A second cerebral CT scan to monitor initial lesions was performed in 279 patients (78%). Of the 194 patients (55%) admitted to the ICU, 24 (13%) stayed in the ICU for longer than 7 days. Six patients (1.7%) died, 4 due to SND within the first week after trauma and 2 due to complications unrelated to the initial TBI (severe respiratory complications in one and a second TBI after day 7 in the other).

Table 1. Demographic Data Collected on Admission of the Study Population (n = 356 Patients)

Variable	Value
Age (yr)	42 (29–61)
Male/female, n	277/79
ISS	16 (14–22)
Circumstances, n (%)	
Road traffic accident	139 (39)
Falls	59 (17)
Sport	76 (21)
Admission, n (%)	
Emergency room	173 (49)
Emergency service	151 (42)
ICU	32 (9)
Pre–hospital medical care, n (%)	225 (63)
GCS on admission	14 (14–15)
Alcohol intoxication, n (%)	61 (17)
Aspirin, n (%)	22 (6)
Mean arterial pressure (mmHg)	93 (84–105)
Heart rate (beats/min)	80 (70–90)
Respiratory rate (breaths/min)	16 (15–20)
Arterial oxygen saturation (%)	98 (97–100)
Temperature (°C)	36.9 (36.4–37)
VAS (n)	2 (1–4)

Continuous values are medians (25th to 75th interquartiles).

GCS = Glasgow coma scale; ICU = intensive care unit; ISS = injury severity score; VAS = visual analog pain scale.

Primary Endpoint

Twenty patients (6%) developed SND within the first week after trauma. All patients received therapeutic interventions: 14 patients for a decrease in GCS score and 6 patients for neurologic worsening without GCS decrease (agitation, focal deficit, seizure). The median GCS at the time of SND was 9 (7 to 12). Neurologic worsening occurred within the first 48 h after trauma in 16 patients. Therapeutic interventions included mechanical ventilation (n = 11), osmotherapy (n = 2), antiepileptic drugs (n = 4), decompressive craniectomy (n = 1), evacuation of intracranial hematomas (n = 4), and external ventricular drainage (n = 2). Nine patients had ICP monitoring for neurologic worsening. In addition to the four patients who died from early SND, nine had severe disability on day 28 according to the DRS (DRS = 11 [8 to 20]), three had moderate disability (DRS = 4, 5, and 6), and four had minor or no disability (DRS = 30 for each).

Of the 20 patients who suffered SND, 16 showed an abnormal TCD pattern on admission (individual data for IP and FVd in figure 1). Among the patients who did not suffer any SND (n = 336 patients), 265 (79%) showed normal TCD values and only 71 (21%) an abnormal TCD pattern (fig. 1). Therefore, TCD thresholds (PI greater than or equal to 1.25 and FVd less than or equal to 25 cm/s) had 80% sensitivity (95% CI, 56 to 94%) and 79% specificity (95% CI, 74 to 83%) to predict early neurologic worsening. This resulted in a NPV of 98% with a 95% CI of 96 to 100% and PPV of 18% (95% CI, 11 to 28%). In this population, LR+ and LR– of TCD were 3.8 and 0.2, respectively.

Subgroup variation in the TCD diagnostic performance was analyzed to assess spectrum effect in this cohort. In the subgroup of minor TBI patients (GCS, 14 to 15; n = 281 patients), 11 patients had a neurologic deterioration within the first week after trauma. Only one patient (1 of 11) had normal TCD pattern on admission. Sensitivity of TCD thresholds was 91% (95% CI, 59 to 100%) and specificity was 80% (95% CI, 75 to 85%) in this subgroup. NPV reached 100% (95% CI, 97 to 100%), whereas PPV was 15.6% (95% CI, 8 to 30%). LR+ was 4.5 and LR– was 0.1 for these patients. In the subgroup of moderate TBI patients (GCS, 9 to 13; n = 75 patients), TCD thresholds had lower diagnostic performance: 67% (95% CI, 30 to 93%) sensitivity, 74% (95% CI, 62 to 84%) specificity, 94% (95% CI, 84 to 99%) NPV, and 26% (95% CI, 10 to 48%) PPV. LR+ was 2.6 and LR– was 0.4 for these patients.

Secondary Endpoints

Patients who suffered SND and those who did not suffer SND showed significant differences with regard to initial GCS, FVm, FVd, and PI (table 2). The AUC–ROC curve of the predictive model including age, GCS, and TCD

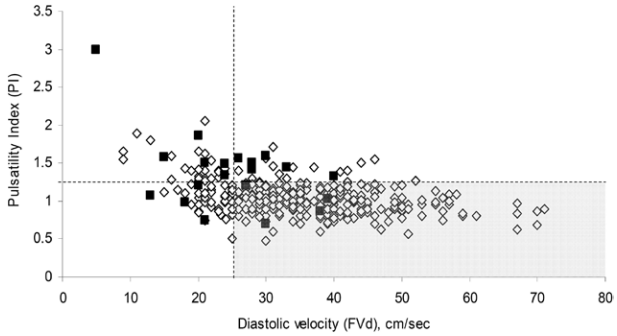

Fig. 1. Individual data for pulsatility index (PI) and diastolic blood flow velocities (FVd). Patients with neurologic aggravation (N = 20 patients) are represented by *black squares,* and patients without neurologic aggravation (N = 336 patients) are represented by *white diamonds*. The *gray zone* indicates the normal transcranial Doppler pattern (PI less than 1.25 and FVd greater than 25 cm/s).

measurements was significantly higher than the AUC–ROC curve of the model including age and GCS: 0.86 (95% CI, 0.82 to 0.89) *versus* 0.68 (95% CI, 0.63 to 0.73), respectively (fig. 2).

Eighty-seven patients displayed an abnormal TCD pattern (abnormal TCD group) *versus* 269 patients for whom it was normal (normal TCD group). Patients in the abnormal TCD group were generally older and had more comorbidities compared to those in the normal TCD group (table 3). The two groups showed no differences with regard to the number of ICU admissions or the length of stay in the ICU. More patients with abnormal TCD pattern required monitoring of ICP with probes (9 *vs.* 0) and their initial brain lesions *via* repeat CT scans.

Of the 356 patients studied, 343 were followed-up on day 28 after trauma. At this time, 167 (77%) of the 218 patients in professional employment before TBI had returned to work. According to the DRS performed during this follow-up, 207 patients had none/mild disability (DRS, 0 to 1), 101 had partial/moderate disability (DRS, 2 to 6), 29 had severe disability (DRS, 7 to 21), and 6 were in a vegetative state or had died (DRS, 22 to 30). Of note was the association between DRS and TCD pattern: patients with abnormal TCD on admission (n = 86 patients) had a significantly more severe DRS on day 28 compared to those with normal TCD (n = 257 patients; table 4).

Discussion

In this large multicenter cohort study, we showed that TCD was feasible in various EDs upon admission after mild to moderate TBI. Sensitivity and specificity of TCD thresholds (PI greater than or equal to 1.25 and FVd less than or equal to 25 cm/s) to detect early neurologic worsening were acceptable in this context. While NPV was high, PPV was poor, meaning that normal TCD pattern was more indicative of predicting outcome than abnormal pattern. In addition, TCD measurements on admission were associated with the neurologic outcome on day 28. These findings provide an external validation of our previous studies in patients with mild to moderate TBI,[10,14] and may highlight the potential use of TCD in the ED for in-hospital triage of such patients.

Initially used to diagnose cerebral vasospasm after subarachnoid hemorrhage,[15] TCD is now used to monitor various brain injuries such as stroke and TBI (see review[7,16,17]). As TCD provides a noninvasive assessment of cerebral blood flow, this monitoring approach has been extensively studied in patients with severe TBI to detect episodes of low brain perfusion after trauma, to assess cerebral autoregulation and vasoreactivity, and to estimate ICP and cerebral

Table 2. Univariate Analysis of Data Collected on Admission in 359 Patients with Mild to Moderate Traumatic Brain Injury According to Their Neurologic Status on Posttrauma Day 7: Patients with and without Secondary Neurologic Deterioration

	No SND (N = 336 Patients)	SND (N = 20 Patients)	Missing Value
Age (yr)	42 (28–61)	58 (38–67)	0
	42.6–46.7	43.8–64.1	
Initial GCS			
9–13	66 (20%)	9 (45%)	0
	15.5–24.3	23.1–68.5	
14–15	270 (80%)	11 (55%)	
	75.7–84.3	31.5–76.9	
Mean blood pressure (mmHg)	93 (84–104)	102 (91.5–110)	0
	91.2–98.0	91.4–108.9	
Heart rate (beats/min)	80 (70–90)	85 (66–95)	0
	80.0–83.3	72.2–90.1	
Respiratory rate (breaths/min)	16 (15–19)	17 (14–20)	0
	16.7–17.6	16.3–20.2	
Arterial oxygen saturation (%)	98 (97–100)	98 (96–100)	0
	97.7–98.1	96.7–98.6	
Temperature (°C)	36.9 (36.4–37)	37 (36.3–37)	0
	36.6–36.8	36.5–37.1	
Pain VAS (n)	2 (1–4)	2 (0–3)	39
Injury to TCD time (h)	4.5 (2.8–6.2)	4.1 (2.8–5.2)	27
	4.3–4.7	3.3–5.4	
Injury-to-CT scan time (h)	2.5 (1.7–3.5)	2.2 (1.4–3.2)	28
	2.5–2.9	1.8–3.2	
ISS	16 (14–22)	17 (16–22)	0
	17.7–19.3	15.6–20.6	
FVs (cm/s)	82 (69–100)	83 (51–99)	8
	83.0–88.2	64.9–93.1	
FVm (cm/s)	51 (41–62)	45 (25–52)	50
	50.7–54.1	34.6–49.8	
FVd (cm/s)	34 (27–42)	25 (20–31.5)	2
	33.8–36.2	34.6–49.8	
PI	0.9 (0.8–1.1)	1.2 (1.0–1.3)	0
	0.9–0.9	1.0–1.4	
Patients with aspirin, n (%)	19 (6)	3 (15)	0
	3.4–8.7	1.0–1.4	

Continuous values are medians (25th to 75th interquartiles) and 95% CI.

CT = computed tomography; FVd, FVm, and FVs = time-averaged diastolic, mean, and systolic values of blood flow velocities, respectively; GCS = Glasgow coma scale; ISS = injury severity score; PI = pulsatility index; SND = secondary neurologic deterioration; TCD = transcranial Doppler; VAS = visual analog scale.

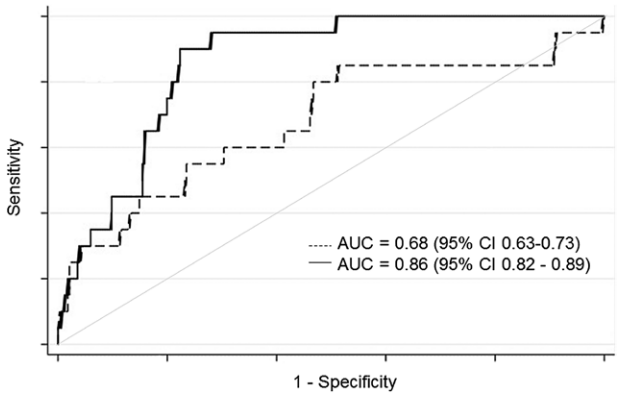

Fig. 2. Receiver operating characteristic (ROC) curves of predictive models for neurologic worsening after mild to moderate traumatic brain injury in our cohort (n = 356 patients). The *black line* represents the ROC curve of the multivariate model using age, Glasgow coma score, and transcranial Doppler (TCD) as predictors of secondary neurologic deterioration. The *dashed line* represents the ROC curve of the multivariate predictive model with age and Glasgow coma score. Area under the curve (AUC) was higher adding TCD in the predictive model (0.86 [95% CI, 0.82 to 0.89] *vs.* 0.68 [95% CI, 0.63 to 0.73]).

perfusion pressure.[18] However, the use of TCD after mild to moderate TBI has received little attention. Common barriers against the extensive use of TCD in the ER have included its restricted use by well-trained physicians aimed at limiting TCD operator dependency and the absence of data from multicenter studies with several operators. Here our findings support and extend those from our previous small single-center cohort[10] and show that TCD measurements are feasible in various ED settings including general hospitals. Any physician with sufficient relevant training in charge of patients with TBI can obtain reliable TCD tracings at the ER provided that they avoid confounding factors such as pain, agitation, and cardiorespiratory distress, and that they ensure all criteria required for high-quality TCD tracings have been fulfilled. The prominent use of echo-Doppler in our study population might have ensured an optimum TCD signal from the middle cerebral arteries. Indeed only six patients (1.6%) were excluded from analysis due to technical TCD problems.

We confirmed that PI and FVd were associated with early neurologic worsening. FVd reflects the degree of downstream vascular resistance, whereas FVs depends on upstream determinants such as cardiac output, arterial blood pressure, and carotid blood flow. The flow velocity waveform is determined by the arterial blood pressure waveform, the viscoelastic properties of the vascular bed, and blood rheology. Therefore, in the absence of vessel stenosis, vasospasm, arterial hypotension, or profound anemia, PI reflects the distal cerebrovascular resistance. In patients with severe TBI, a low FVd, a peaked waveform, and high PI values can be observed during high vascular bed resistance induced by increased ICP or hypocapnia.[19,20] Our findings indicate that small changes in PI and FVd reflect an alteration in downstream vascular resistance even after mild to moderate TBI, and expose the patient to a higher risk of SND. Not surprisingly, the PI and FVd threshold values to detect unfavorable outcome in severe TBI patients under mechanical ventilation were found to be different from those defined in spontaneously breathing patients with a lower severity of TBI.[8–10] We applied PI and FVd thresholds from our previous cohort and found relatively low sensitivity and specificity. Interestingly, these values improved when considering the subgroup of patients with

Table 3. Univariate Analysis of Data Collected on Admission in 356 Patients According to Their TCD Pattern on Admission

	Normal TCD (N = 269 patients)	Abnormal TCD (N = 87 patients)
Age (yr)	39 (27–54)	62 (34–73)
	39.7–43.9	50.8–60.2
Male, n (%)	207 (76.9%)	70 (80.5%)
	71.4–81.8	70.6–88.2
Comorbidities		
High blood pressure, n (%)	29 (10.7%)	27 (31.0%)
	7.3–15.1	21.5–41.8
Thromboembolic event, n (%)	0	3 (3.5%)
	0–0.1*	0.7–0.1
Coronary artery disease, n (%)	5 (1.8%)	4 (4.6%)
	0.6–4.3	1.3–11.3
Atrial fibrillation, n (%)	1 (0.4%)	2 (2.3%)
	0.0001–0.2	0.03–0.08
Stroke, n (%)	20 (0.4%)	16 (2.3%)
	0.5–0.11	0.11–0.28
Mean blood pressure, mmHg	90 (83–103)	98 (91–105)
	90.6–97.2	93.7–105.2
Heart rate, beats/min	80 (70–90)	78 (70–90)
	80.3–84.2	76.5–82.6
Respiratory rate, breaths/min	16 (15–19)	17 (15–20)
	16.5–17.5	16.9–18.7
Arterial oxygen saturation, %	98 (97–100)	97 (96–99)
	97.9–98.3	96.7–97.6
Temperature, °C	36.9 (36.4–37.0)	36.9 (36.4–37.0)
	36.6–36.8	36.6–36.8
Number of repeat CT scan		
0	63 (23.4%)	14 (16.1%)
	18.4–28.9	9.1–25.5
1	158 (58.7%)	48 (55.2%)
	52.6–64.7	44.1–65.8
≥2	48 (18%)	25 (29%)
	13.4–22.9	19.5–39.4
ICU stay		
Number of patients	148 (55%)	46 (53%)
	48.9–61.2	41.8–63.7
Length of stay in ICU (d)	1 (0–4)	1 (0–5)
	1.7–2.2	1.6–2.7

The normal transcranial Doppler (TCD) group had a combination of diastolic blood flow velocity (FVd) greater than 25 cm/s and pulsatility index (PI) less than 1.25. The abnormal TCD group had FVd less than or equal to 25 cm/s and/or PI greater than or equal to 1.25. Continuous values are medians (25th to 75th interquartiles) and 95% CI.

*One-sided, 97.5% CI.

CT = computed tomography; ICU = intensive care unit.

Table 4. Univariate Analysis of DRS Collected at Day 28 in 343 Patients According to Their TCD Pattern on Admission

DRS Categories of Disability	Normal TCD (N = 257 Patients)	Abnormal TCD (N = 86 Patients)
0–1 (none/mild)	156 (60.7%) (54.4–66.7)	51 (59.3%) (48.2–69.8)
2–6 (partial/moderate)	83 (32.3%) (26.7–38.4)	18 (20.9%) (12.9–31.0)
7–21 (severe)	17 (6.6%) (3.9–10.4)	12 (13.9%) (7.4–23.1)
22–30 (vegetative/dead)	1 (0.4%) (0.0001–2.1)	5 (5.8%) (1.9–13.0)

The normal transcranial Doppler (TCD) group had a combination of diastolic blood flow velocity (FVd) greater than 25 cm/s and pulsatility index (PI) less than 1.25. The abnormal TCD group had FVd less than or equal to 25 cm/s and/or PI greater than or equal to 1.25. 95% CI is given for each variable in brackets.

DRS = disability rating scale.

GCS 14 to 15. We also found a NPV as high as 98% (96 to 100%). At its lowest limit, NPV compared favorably with the value obtained for troponin I to exclude acute myocardial infarction[21] and with d-dimer to exclude venous thromboembolism.[22] Four of our patients had false-negative results, *i.e.*, a normal TCD at presentation but developed SND. One patient (age, 74 yr; GCS, 11) had brain lesions located in the cerebral posterior fossa, which exerted a compression on the brainstem with no impact on supratentorial circulation. While the GSC score did worsen as early as day 1 in 2 patients (age, 41 yr and 62 yr, both GCS, 9), both spontaneously recovered with no or minor disability on day 28. Finally, one patient (age, 52 yr, GCS, 14) had borderline TCD measurements: FVd = 27 cm/s and PI = 1.20. These situations underscored the limits of TCD for detecting neurologic worsening. For instance, infratentorial trauma lesions cannot be associated with changes in TCD measurements from MCA. A low PPV also indicated poor diagnostic properties of abnormal TCD pattern. While PI reflects both extrinsic resistance (such as during increased ICP) and intrinsic resistance (such as during hyperventilation or administration of barbiturates/propofol), the inherent change in vascular tone with age or diabetes may also influence PI value.[23] Another confounding factor might be the systemic pulse pressure amplitude. Indeed, the cerebral flow velocity is a dynamic measurement reflecting the instantaneous driving pressure, *i.e.*, systolic and diastolic blood pressure. A low diastolic blood pressure should inevitably result in a high PI value. For instance, a patient with significant aortic insufficiency will have a high PI value, irrespective of ICP measurements. Large pulse pressure amplitude is not uncommon in older patients, as their blood vessels become stiff and lose their compliance. Taken together, these factors should explain why the PPV of TCD could be low, particularly in elderly patients.

Patients with abnormal TCD pattern had poorer DRS score on day 28 compared to those with normal TCD. This result further confirmed the relationship between early TCD measurements and delayed neurologic outcome in our cohort. However, differences between the abnormal and normal TCD groups of patients in terms of age and comorbidities might also be misleading. These differences might be misleading and might explain the observed differences in DRS. Although beyond the scope of this study, the use of advanced magnetic resonance imaging methods such as susceptibility-weighted imaging and diffusion tensor imaging on day 28 would have been of interest to investigate potential lesions of the white matter in patients with initial abnormal TCD.[24]

From these results, clinical perspectives of TCD in mild to moderate TBI patients may include an impact on monitoring level, in-hospital triage, and hospital discharge. Indeed, patients with a normal TCD pattern might not even need a control CT scan and might have a reduced stay in the hospital. Conversely, abnormal TCD pattern might lead to unnecessary high-level monitoring with repeated CT scans or abusive stay in ICU. Whether TCD-guided management would benefit all patients with mild to moderate TBI remains to be further evaluated and potential beneficial effect of TCD-based management for some patients should be balanced by possible overuse of high-level monitoring for others.

This study has several limitations. First, the PPV of TCD to predict SND was low. Indeed, the proportion of patients with SND was lower than expected and accounted for only 6% of our study population, much lower than the 20% reported in our previous studies.[10,14] It should be noted that, in the current study, each operator was not blinded for TCD results. This information might have had an impact on the patient care, as was perhaps reflected by the greater requirement for ICP measurements and repeat CT scans in the group of patients with abnormal TCD patterns. An uncontrolled, preventive management against subsequent neurologic deterioration might also have occurred in these patients. Second, an abnormal TCD pattern was not predictive of a patient developing early SND although it was found associated with altered DRS score on day 28. Using strict thresholds for PI and FVd, we deliberately chose a restrictive approach to rule out the risk of SND: measurements of the two middle cerebral arteries to consider the most pejorative TCD, and a combination of both FVd and PI normal values to define a normal TCD pattern. Clearly such an approach was at the expense of poor accuracy to predict the occurrence of SND. Third, we only investigated the yield of TCD in highly selected patients in the ED. We cannot generalize our findings to all patients presenting with mild to moderate TBI. General management of these patients with TCD will require a randomized controlled trial to further assess the beneficial effect of TCD after TBI. Finally, the low incidence of neurologic worsening in our cohort affected the NPV and artificially improved its value. However, 95% CI was narrowed with a lower limit above 95%, which indicated high NPV of TCD despite low incidence.

In conclusion, TCD measurements upon admission to the ED may provide additional information regarding neurologic outcome in patients with mild to moderate TBI and mild lesions on brain CT scan. Our findings suggest the use of TCD in complement to the clinical examination and initial CT scan. Whether a medical strategy including TCD measurements may improve the management of these patients warrants further investigation.

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Competing Interests

The authors declare no competing interests.

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Appendix: Traumatic Brain Injury—Transcranial Doppler (TBI-TCD) Investigators

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Great-grandson Restout's 1771 Painting, Exhibited as *Morpheus* in 1783

Highly popular in 18th-century France, the *Metamorphoses* written by Ovid of Rome characterized Morpheus as a cave-bound, winged god of dreams who was surrounded by opium poppies. Ovid's vivid description likely influenced the 1771 painting (*above), Morpheus,* by Jean-Bernard Restout (1732 to 1797). As the youngster of the celebrated Restout Dynasty of French painters, Jean-Bernard flourished in the artistic tradition of his great-grandfather Marc-Antoine, grandfather Jean the Elder (1666 to 1702), and father Jean the Younger. In fact, just two years before painting *Morpheus*, Jean-Bernard Restout had been inducted into France's Royal Academy of Painting and Sculpture. During the French Revolution, Restout led the Commune des Arts in suppressing the Academy, the very society most responsible for cultivating Restout's clinical attention to anatomic detail. Missing from Restout's rendering of his god of dreams is Ovid's description of how the shape-shifting "Morpheus … express'd the shape of man, and imitated best…. but all his action is confined, extending not beyond our humankind." (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology)

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