Transcranial Doppler Based Cerebrovascular Reactivity Indices in Adult Traumatic Brain Injury: A Scoping Review of Associations With Patient Oriented Outcomes

Alwyn Gomez1,2*, Logan Froese3, Amanjyot Singh Sainbhi3, Carleen Batson2 and Frederick A. Zeiler1,2,3,4,5

1Section of Neurosurgery, Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, 2Department of Human Anatomy and Cell Science, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, 3Biomedical Engineering, Faculty of Engineering, University of Manitoba, Winnipeg, MB, Canada, 4Centre on Aging, University of Manitoba, Winnipeg, MB, Canada, 5Division of Anaesthesia, Department of Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, United Kingdom

Background: Disruption in cerebrovascular reactivity following traumatic brain injury (TBI) is a known phenomenon that may hold prognostic value and clinical relevance. Ultimately, improved knowledge of this process and more robust means of continuous assessment may lead to advances in precision medicine following TBI. One such method is transcranial Doppler (TCD), which has been employed to evaluate cerebrovascular reactivity following injury utilizing a continuous time-series approach.

Objective: The present study undertakes a scoping review of the literature on the association of continuous time-domain TCD based indices of cerebrovascular reactivity, with global functional outcomes, cerebral physiologic correlates, and imaging evidence of lesion change.

Design: Multiple databases were searched from inception to November 2020 for articles relevant to the association of continuous time-domain TCD based indices of cerebrovascular reactivity, with global functional outcomes, cerebral physiologic correlates, and imaging evidence of lesion change.

Results: Thirty-six relevant articles were identified. There was significant evidence supporting an association with continuous time-domain TCD based indices and functional outcomes following TBI. Indices based on mean flow velocity, as measured by TCD, were most numerous while more recent studies point to systolic flow velocity-based indices encoding more prognostic utility. Physiologic parameters such as intracranial pressure, cerebral perfusion pressure, Carbon Dioxide (CO2) reactivity as well as more established indices of cerebrovascular reactivity have all been associated with these TCD based indices. The literature has been concentrated in a few centres and is further limited by the lack of multivariate analysis.
Conclusions: This systematic scoping review of the literature identifies that there is a substantial body of evidence that cerebrovascular reactivity as measured by time-domain TCD based indices have prognostic utility following TBI. Indices based on mean flow velocities have the largest body of literature for their support. However, recent studies indicate that indices based on systolic flow velocities may contain the most prognostic utility and more closely follow more established measures of cerebrovascular reactivity. To a lesser extent, the literature supports some associations between these indices and cerebral physiologic parameters. These indices provide a more complete picture of the patient’s physiome following TBI and may ultimately lead to personalized and precise clinical care. Further validation in multi-institution studies is required before these indices can be widely adopted clinically.

Keywords: cerebral autoregulation, cerebrovascular reactivity, scoping review, traumatic brain injury, transcranial Doppler, precision medicine

INTRODUCTION

The disruption of cerebral autoregulation (CA) following traumatic brain injury (TBI) has been known since the 1970s (Overgaard and Tweed, 1974; Cold and Jensen, 1978). At that time, evaluation of CA was cumbersome and involved perturbation of the patient’s blood pressure while low frequency measurement of cerebral blood flow (CBF) were obtained. This meant that assessment of dynamic changes in CA was limited and thus its utility in precision medicine limited.

Aaslid and colleagues first described transcranial doppler ultrasound (TCD) in 1982 as a non-invasive means of evaluating CBF through insonation of flow velocities (FV) in the basal arteries of the brain (Aaslid et al., 1982). Since then, the role of TCD in the management of TBI patients has grown substantially with widespread adoption in the neurocritical care setting. It has become one of the most commonly utilized methods for intracranial monitoring in the critically ill TBI patient, outside of ICP monitoring, and the most popular non-invasive cerebral monitoring modality for this population. While direct TCD measures, such as FV, have been measured for their association with secondary neurologic decline and global outcomes, derived TCD metrics have been developed to non-invasively estimate intracranial pressure (ICP), carbon dioxide (CO₂) reactivity and even CA (Gomez et al., 2021). Unfortunately, early methods of evaluating CA using TCD, such as the Thigh Cuff Deflation Technique (TCDT) and Orthostatic Hypotension Test (OHT), were intermittent in nature since they still depended on induced changes in arterial blood pressure (ABP) (Aaslid, 1986; Aaslid et al., 1989; Steinmeier et al., 2002).

TCD was first described as a tool to continuously evaluate CA following TBI by Czosnyka and colleagues in 1996 (Czosnyka et al., 1996). In this study, they described a time-domain based mean flow index (Mx), a continuously updating Pearson correlation coefficient between the natural fluctuations in cerebral perfusion pressure (CPP), equal to the difference between ABP and ICP, and mean FV through the middle cerebral artery (MCA) as measured by TCD. This method used mean FV as a surrogate measure for CBF with CPP used as the driving force in order to continuously interrogate cerebrovascular reactivity. It should be noted that cerebrovascular reactivity and CA are not synonymous as vascular reactivity can occur outside the limits of autoregulation (Varsos et al., 2014). Being a correlation coefficient, Mx ranged from +1 to −1 with a more negative correlation being associated with intact cerebrovascular reactivity and a more positive coefficient being associated with disrupted reactivity. In their study of 82 moderate and severe TBI patients, they found a correlation between the state of cerebrovascular reactivity, as measured by Mx, and 6-month outcomes (Czosnyka et al., 1996). Of note, for metrics to be designated as a CA measure, it must have some pre-clinical validation it its ability to measure aspects of the Lassen autoregulatory curve. To date, TCD-based metrics have not received such validation. As such, such measures are referred to as cerebrovascular reactivity metrics, as opposed to CA measures, as the provide surrogate assessments of cerebral vessel vasomotion, but have yet to be validated as CA measures. Subsequently, through the remainder of this article, such TCD-based measures will be referred to as cerebrovascular reactivity metrics.

Since then, a significant amount of research has been undertaken to examine the association between continuous TCD based indices of cerebrovascular reactivity and outcomes following TBI (It should be noted that cerebrovascular reactivity and CA are not entirely interchangeable as cerebrovascular reactivity can occur outside the limits of autoregulation. Cerebrovascular reactivity is the broader term that describes the physiologic process that is measured by these indices). Slightly modified indices that used the diastolic and systolic FV were examined (Dx and Sx, respectively) along with indices that utilized ABP, as opposed to CPP, as the driving force (Mx_a, Dx_a, and Sx_a). Table 1 summarizes these indices and their derivation. Notably, those that utilize ABP instead of CPP open the door to the entirely non-invasive measurement of cerebrovascular reactivity (Zeiler et al., 2018b; Zeiler et al.,2019b; Zeiler and Smielewski, 2018; Gomez et al., 2020). This has the potential to expand their application to the neurocritical care of patient populations that do not typically have ICP monitoring as well as to the outpatient setting. While not yet adopted widely in clinical
practice, these indices have an ever-growing body of evidence supporting their association with outcomes following TBI. The development of these indices has renewed the interest in leveraging measures of cerebrovascular reactivity in the development of personalized treatments following TBI. Further to this, adoption of this continuous non-invasive cerebrovascular reactivity assessment has expanded outside of TBI, including recent work in subarachnoid haemorrhage and general operative populations (Budohoski et al., 2012b; Klein et al., 2019). Thus, to aid with the development of further prospective studies in both TBI and non-TBI cohorts, a comprehensive understanding of the association between TCD based continuous time-domain cerebrovascular reactivity indices with patient-oriented outcomes is warranted. Given that the majority of the literature to date is focused in the TBI populations, the natural first step is to provide a comprehensive scoping overview of the association between TCD based cerebrovascular reactivity indices with: A. global patient outcomes, B. other cerebral physiologic correlates, and C. lesion change/progression on serial imaging. Thus, the aim of this study was to perform a systematically conducted review of the literature to evaluate the association between these continuous time-domain TCD based indices of cerebrovascular reactivity and the above outcomes, in adult moderate/severe TBI. In doing so, a better understanding of the role these indices play in describing the post-TBI physiome may be developed.

**METHODS**

A systematically conducted scoping review of the available literature was conducted based on the methodological framework described by Arksey and O’Malley (2005). The data was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR; Tricco et al., 2018). The search strategy and methodology used here is similar to other systematically conducted scoping reviews published by our group (Froese et al., 2020a, Froese et al., 2020b, Froese et al., 2020c; Hasen et al., 2020).

The review questions and search strategy were decided upon by the senior author (FAZ) and primary author (AG).

**Search Questions, Populations, and Inclusion/Exclusion Criteria**

The question of this systematically conducted scoping review was: What is the association of continuous time-domain TCD based indices of cerebrovascular reactivity, with: A. global functional outcomes, B. cerebral physiologic correlates, and C. imaging evidence of lesion change following moderate-to-severe TBI?

All English language studies, either prospective or retrospective, with 20 or more adult (age 18 years or older) moderate and severe TBI patients, were included. Moderate TBI is defined as an admission Glasgow coma scale (GCS) of 9–12 while a GCS of 3–8 defines severe TBI.

Only continuous time-domain TCD based cerebrovascular reactivity metrics were of interest, excluding both intermittent techniques (Zeiler et al., 2017a) and those based in frequency-domain (i.e., transfer-function techniques; Czosnyka et al., 2008). The eligible time-domain TCD based cerebrovascular reactivity indices of interest were Mx, Sx, Dx, Mx_a, Sx_a, and Dx_a. Table 1 outlines the components of these indices and their derivation.

The primary outcome of interest was the statistically significant association between these indices and morbidity/mortality following TBI. Secondary outcomes included statistically significant associations with severity of injury and age. Additionally, associations with various cerebral physiologic parameters such as ICP, CPP, brain tissue oxygenation (PbtO2), and CO2 reactivity were also examined. Give that the pressure reactivity index (PRx) has become a widely accepted continuous measures of cerebrovascular reactivity (Czosnyka et al., 1997; Zeiler et al., 2018d), its associations with TCD based indices were also collected. Associations between TCD based indices and more novel ICP based indices of cerebrovascular reactivity, such as PAx and RAC, were excluded as these indices are not as well established despite their evidence of their prognostic utility in TBI (Zeiler et al., 2017b). Table 2 outlines the cerebral physiologic parameters that were examined for their association with TCD based indices. All parameters selected as secondary outcomes are known to be associated with global outcomes and/or are physiologic targets in guideline based management following moderate to severe TBI (Carney et al., 2017; Zeiler et al., 2018d; Hawryluk et al., 2019).

Studies relating to TCD time-domain based cerebrovascular reactivity measures and imaging changes were searched for. Specifically, studies examining the association of these indices with changes in CT score (Marshall, Rotterdam, Helsinki, or Stockholm), midline shift, and hematoma volume as well as the development on new lesions were all considered relevant.

Exclusion criteria for studies were the following: non-English, non-human, non-TBI, mild TBI, paediatric cohorts, non-time-

| Index | Surrogate for cerebral blood flow | Surrogate for driving force | Signal averaging (s) | Calculation windows (s) | Update frequency (min) |
|-------|----------------------------------|----------------------------|----------------------|-------------------------|------------------------|
| Mx    | Mean CBFV                        | CPP                        | 10                   | 300                     | 1                      |
| Sx    | Systolic CBFV                     | CPP                        | 10                   | 300                     | 1                      |
| Dx    | Diastolic CBFV                    | CPP                        | 10                   | 300                     | 1                      |
| Mx_a  | Mean CBFV                         | ABP                        | 10                   | 300                     | 1                      |
| Sx_a  | Systolic CBFV                     | ABP                        | 10                   | 300                     | 1                      |
| Dx_a  | Diastolic CBFV                    | ABP                        | 10                   | 300                     | 1                      |

ABP, Arterial blood pressure; CBFV, Cerebral blood flow velocity (measured by transcranial Doppler); CPP, Cerebral perfusion pressure.
TABLE 2 | Outline of Cerebral Physiologic Parameters of Interest

| Cerebral Physiologic Parameter | Description | Clinical relevance |
|-------------------------------|-------------|--------------------|
| Intracranial pressure (ICP)   | An invasively measured physiologic parameter obtained through either the placement of an intraparenchymal probe or placement of an intraventricular catheter. It represents the pressure experienced by the brain | Following TBI values greater than 20–22 mmHg are associated with worse outcomes. Current guideline-based management recommends maintain ICP less than 22 mmHg post injury (Carney et al., 2017) |
| Cerebral perfusion pressure (CPP) | This is a derived physiologic parameter equal to the difference between ABP and ICP, it represents the net pressure gradient that drives oxygen delivery to the brain | Following TBI values greater than 70 mmHg and less than 60 mmHg are associated with worse outcomes. Current guideline-based management recommends maintain CPP between 60 and 70 mmHg post injury (Carney et al., 2017) |
| Brain tissue oxygenation (PbtO2) | An invasively measured physiologic parameter obtained through the placement of an intraparenchymal Clark electrode. It measures extracellular oxygen content and is thought to reflect cerebral oxygenation. | Following TBI values less than 20 mmHg are associated with worse outcomes. Current guideline-based management recommends maintain a PbtO2 greater than 20 mmHg (Hawryluk et al., 2019) |
| CO2 reactivity | This is the propensity of the brains vasculature to dilate in the setting of elevated PaCO2 and constrict in the setting of a reduced PaCO2. It can be measured in numerous methods, including TCD, and can be leveraged in the acute management of TBI | Following TBI, if CO2 reactivity is intact, elevated ICP can be treated transiently with hyperventilation to reduce PaCO2 which reduces CBV and results in a decrease in ICP (Carney et al., 2017) |
| Pressure reactivity index (PRx) | This derived invasive index is a moving Pearson correlation coefficient between ICP and ABP. It ranges in value from −1.0 to +1.0 and is thought to represent cerebrovascular reactivity with higher correlation (and therefore higher values) being associated with disrupted cerebrovascular reactivity | Recently it has been found that following moderate-to-severe TBI PRx values of +0.35 are associated with increased morbidity and mortality (Zeiler et al., 2018d) |

ABP, arterial blood pressure; CBV, cerebral blood volume; CO2, carbon dioxide; CPP, cerebral perfusion pressure; ICP, intracranial pressure; mmHg, millimetres of mercury; PaCO2, partial pressure of carbon dioxide; PbtO2, brain tissue oxygenation; PRx, pressure reactivity index; TBI, traumatic brain injury; TCD, transcranial doppler.

domain TCD based indices, non-continuous TCD metrics, cohort < 20 TBI patients, or no relevant outcome (functional or physiologic) association. Review studies and meta-analysis were also excluded from consideration.

**Search Strategy**

BIOSIS, Cochrane Library, EMBASE, MEDLINE, and SCOPUS were searched from inception to November 2020 using individualized search strategies for each database. The search strategy for SCOPUS can be seen in Supplementary Appendix A with similar strategies used for each of the other databases. Finally, the reference lists of each article were reviewed to ensure no studies were missed. Search results were then combined, and deduplication was performed.

**Study Selections**

Using two reviewers (AG and LF) a two-step review of all articles returned by our search strategies was performed. In the first filter phase, each reviewer independently screened all studies identified using the above-described search strategy and determined if they met the inclusion criteria based on their title and abstract. The resulting list of studies was then passed through the second filter phase where once again each reviewer independently determined if the studies met the inclusion criteria, but this time based on the full text. Any discrepancies between the two reviewers were resolved by a third party (FAZ).

**Data Collection**

Data was extracted from the selected articles and compiled into various data fields. These fields included the following: number of patients, study design, institution, mean age, mean GCS on presentation, number of male patients, additional patient characteristics, goals of the study, indices examined, duration of insonation, outcomes evaluated, key results, and conclusions.

**Bias Assessment**

Given the goal of this review was to provide a comprehensive scoping overview of the available literature, a formal bias assessment was not conducted.

**Statistical Analysis**

Due to the heterogeneity of the results/study design no meta-analysis was performed.

**RESULTS**

**Search Results and Study Characteristics**

The results of the search and filtration strategy can be seen in Figure 1. Overall, the search strategy identified 617 articles with 296 remaining following deduplication. Following the first filtration stage, based on article title and abstract, 187 articles were removed for not fitting into the inclusion/exclusion criteria. Full text documents were reviewed on the remaining 109 articles in the second filtration phase with 73 articles being found to not meet the inclusion/exclusion criteria for this study. This left 36 articles to be included in this scoping review. Figure 1 provides the PRISMA flow-diagram.

Table 3 summarizes general characteristics of each study while Table 4 outlines the key results, conclusions, and limitations of each study. Mx was the most common time-domain TCD index that was studied, with all but one study reporting on it (Czosnyka...
et al., 2005). It was also the only index with evidence showing that it worsened with injury severity (Czosnyka et al., 1996; Czosnyka et al., 1999; Czosnyka et al., 2000) and with advanced age (Czosnyka et al., 2005; Czosnyka et al., 2008). The next most common index was Mx_a with it being measure in nine studies (Lang et al., 2003a; Lang et al., 2003b; Lewis et al., 2007; Sorrentino et al., 2011; Budohoski et al., 2012c; Liu et al., 2015; Zeiler et al., 2017b; Zeiler et al., 2018a; Zeiler et al., 2018c). Notably, Mx, and Mx_a have been found to be strongly associated with one another (Schmidt et al., 2003a; Lewis et al., 2007; Sorrentino et al., 2011). The remainder of time-domain TCD based indices were examined only in a minority of studies. The number of patients with TCD recordings included in each study varied from as few as 20 TBI patients to as many as 347 (Schmidt et al., 2016b; Zeiler et al., 2018a). The evidence for the association between other TCD based indices and mortality is not as clear with a 2018 study by Zeiler and colleagues having most comprehensively examined this relationship in a cohort of 281 TBI patients (Zeiler et al., 2018a). Sx and Sx_a were found to have the strongest associations with mortality for indices with CPP and ABP as inputs, respectively, while Mx and Mx_a were also found to have some association. Neither Dx nor Dx_a were found to have any correlation with mortality.

**Mortality**

There is strong evidence of an association between dysfunctional cerebrovascular reactivity, as measured by continuous time-domain TCD based indices, and mortality following TBI, with numerous studies finding a higher Mx correlating with mortality (Czosnyka et al., 2002; Schmidt et al., 2003b; Schmidt et al., 2016a; Budohoski et al., 2012a; Budohoski et al., 2012c). A notable exceptions to this was a 2016 study by Schmidt and colleagues which contained a mixed cohort of 20 TBI patients and 21 non-TBI patients (Schmidt et al., 2016b).

The evidence for the association between other TCD based indices and mortality is not as clear with a 2018 study by Zeiler and colleagues having most comprehensively examined this relationship in a cohort of 281 TBI patients (Zeiler et al., 2018a). Sx and Sx_a were found to have the strongest associations with mortality for indices with CPP and ABP as inputs, respectively, while Mx and Mx_a were also found to have some association. Neither Dx nor Dx_a were found to have any correlation with mortality.

![PRISMA flow-diagram](image-url)
### TABLE 3 | Study Characteristics of Included Studies.

| Reference | Number of Patients | Institution | Study design | Mean age (Range) | Mean admission GCS (Range) | Number of male Patients | Additional patient characteristics | Duration of insonation | Relevant indices evaluated |
|-----------|--------------------|-------------|--------------|------------------|---------------------------|-------------------------|-------------------------------|--------------------------|--------------------------|
| Budohoski et al. (2012a) | 201 | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 23 (11–78) | 6 | 157 | None reported | Not reported | Mx/PRx |
| Budohoski et al. (2012c) | 300 | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 29 (6–14) | 6 | 226 | None reported | Not reported | Mx/Sx/Dx/ Mx_a/ Sx_a/ Dx_a |
| Czosnyka et al. (1996) | 82 | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 36 (7–75) | 6 (3–13) | 55 | No patients with craniectomy | Daily for 20 min -2 h | Mx/Sx |
| Czosnyka et al. (1997) | 82 | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 37 (6–75) | 7 (3–13) | 55 | No patients with craniectomy | Not reported | Mx/PRx |
| Czosnyka et al. (1998) | 82 | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 36 (7–75) | 6 (3–13) | 55 | None reported | Daily for 20 min-2 h | Mx/PRx |
| Czosnyka et al. (1999) | 98 | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 38 (14–76) | < 8 (3–13) | 68 | None reported | Daily for 20 min–4 h | Mx |
| Czosnyka et al. (2000) | 166 | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | None reported | None reported | Not reported | None reported | Daily 30 min–2 h | Mx |
| Czosnyka et al. (2001) | 187 | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 36 (8–75) | 6 (3–13) | 143 | 31% SDH 28% ICH 10% EDH 11% DAI 57% Brain Swelling 38% MLS 25% tSAH | Daily for 20 min–2 h | Mx |
| Czosnyka et al. (2002) | 188 | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | None reported | None reported | Not reported | None reported | Daily for 30 min–2 h | Mx/PRx |
| Czosnyka et al. (2005) | 358 | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | None reported | None reported | Not reported | 237 patients with TCD data | Daily for 20 min–2 h | Sx/PRx |
| Czosnyka et al. (2008) | 50 | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 31 (17–75) | 6 (3–13) | 34 | 15% SDH 20% ICH 10% EDH 10% DAI 50% Brian Swelling 22% MLS 25% tSAH | Daily for 20 min–2 h | Mx |
| Lang et al. (2003a) | 37 | Christian-Albrechts-Universität, Ger. and University of Sydney, Aus. | Retrospective analysis of prospectively collected data | 41 | 8.4 | 30 | 6 EDH 23 SDH 19 Contusion 2 DAI | Not reported | Mx/Mx_a |
| Lang et al. (2003b) | 25 | Christian-Albrechts-Universität, Ger. and University of Sydney, Aus. | Retrospective analysis of prospectively collected data | 38 (16–58) | 7.1 | 18 | None reported. | 18 min | Mx_a |
| Lewis et al. (2007) | 151 | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 36 (16–75) | 6 (3–13) | 121 | 30% SDH 25% ICH 13% DAI 59% Brain Swelling | Daily for 20 min–2 h | Mx/Mx_a |

(Continued on following page)
TABLE 3 | (Continued) Study Characteristics of Included Studies.

| Reference          | Number of Patients | Institution                          | Study design                                      | Mean age (Range) | Mean admission GCS (Range) | Number of male Patients | Additional patient characteristics | Duration of insonation | Relevant indices evaluated |
|--------------------|--------------------|--------------------------------------|--------------------------------------------------|------------------|----------------------------|------------------------|-----------------------------------|--------------------------|------------------------|
| Lewis et al. (2012) | 187                | Addenbrookes Hospital, United Kingdom | Retrospective analysis of prospectively collected data | None reported   | None reported              | Not reported           | 32% MLS 23% tSAH                  | Not reported             | Mx                     |
| Liu et al. (2015)  | 288                | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 33               | 6                          | Not reported           | None reported                    | Daily for 20 min–1 h     | Mx/Mx_a                |
| Radolovich et al. (2011) | 293              | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 37 (13–78)      | 6                          | Not reported           | None reported                    | Daily for 10 min–3 h (mean 32 min) | Mx                     |
| Schmidt et al. (2016a) | 30                | Chemnitz Medical Centre, Ger.       | Retrospective analysis of prospectively collected data | 51.4             | None reported              | Not reported           | 23 patients with TBI 7 patients with other cerebral disease | Not reported             | Mx/PRx                 |
| Schmidt et al. (2016b) | 41               | Chemnitz Medical Centre, Ger.       | Retrospective analysis of prospectively collected data | 52 (18–77)      | None reported              | 28                     | 20 TBI patients 21 patients with other cerebral disease | Not reported             | Mx/PRx                 |
| Sorrentino et al. (2011) | 248              | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 28 (3–78)       | 6 (3–15)                   | 195                    | None reported                    | Daily for 20 min–2 h      | Mx/Mx_a                |
| Zeiler et al. (2017b) | 37                | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 33 (18–76)      | 8 (3–14)                   | Not reported           | None reported                    | Two separate recordings of 60 min | Mx/Sx/Dx/ Mx_a/ Sx_a/ Dx_a/PRx |
| Zeiler et al. (2018a) | 281              | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | 33.5             | 6                          | 231                    | None reported                    | 30 min or greater        | Mx/Sx/Dx/ Mx_a/ Sx_a/ Dx_a/PRx |
| Cerebral physiologic correlates | | | | | | | | | |
| Czosnyka et al. (2003) | 345 (243 TBI)      | Addenbrooke’s Hospital, United Kingdom | Retrospective analysis of prospectively collected data | None reported   | None reported              | Not reported           | The cohort included: 14 Healthy Volunteers 243 TBI Patients 15 aSAH Patients 15 tSAH Patients 38 Patients with Carotid Stenosis 35 Patients with Hydrocephalus | Daily for 20 min–2 h | Mx                     |
| Haubrich et al. (2011) | 30                | Addenbrooke’s Hospital, United Kingdom | Prospective Observational                        | 39               | None reported              | Not reported           | 20 min at normocapnia 30 min at hypocapnia 20 min at normocapnia 30 min at hypocapnia | Not reported             | Mx                     |
| Haubrich et al. (2012) | 29                | Addenbrooke’s Hospital, United Kingdom | Prospective Observational                        | 39               | None reported              | Not reported           | None reported                    | Not reported             | Mx                     |
| Lang (2003)         | 40                | Christian-Albrechts-Universität, Ger. and University of Sydney, Aus. | Retrospective analysis of prospectively collected data | 40 (16–78)      | 8 (3–15)                   | 32                     | 6 EDH 23 SDH 21 contusion 4 DAI 2 MH | Not reported             | Mx                     |

(Continued on following page)
| Reference                  | Number of Patients | Institution                                      | Study design                                      | Outcome Metric Evaluated | GCS Admission (Range) | Number of Male Patients | Duration of Insonation | Mean Admission GCS (Range) | Number of Patients | Outcome Metric Used | Relevant Indices Evaluated |
|---------------------------|--------------------|--------------------------------------------------|--------------------------------------------------|--------------------------|-----------------------|------------------------|------------------------|--------------------------|------------------------|----------------------|------------------------|
| Lewis et al. (2014)       | 21                 | Addenbrooke’s Hospital, United Kingdom           | Retrospective analysis of prospectively collected data | Mx                       | 24 (17-71)            | 17                     | Not reported           | 4 (3-11)                  | 10 Focal Haemorrhage   |                      | Mx                    |
| Liu et al. (2016)         | 24                 | Addenbrooke’s Hospital, UK                       | Retrospective analysis of prospectively collected data | Mx /Mx_a                 | None reported         | None reported          | Not reported           | None reported            | 135 TBI patients      | 10 haemorrhagic stroke patients |
| Schmidt et al. (2003a)    | 145                | Addenbrooke’s Hospital, United Kingdom; Munich-Bogenhauses Medical Centre, Ger.; Munich-Schwabing Medical Centre, Ger.; Chemnitz Medical Centre, Ger.; and Frankfurt Medical Centre, Ger. | Retrospective analysis of prospectively collected data | Mx/Mx_a                  | 35 (3-76)            | 111                    | Not reported           | None reported            | The cohort included 135 TBI patients (39 SDH, 35 ICH, 68 Brain Oedema) and 10 haemorrhagic stroke patients |
| Schmidt et al. (2003b)    | 96                 | Addenbrooke’s Hospital, United Kingdom           | Retrospective analysis of prospectively collected data | Mx                       | 31 (16-76)           | 84                     | Daily for 20 min-2 h    | 6 (3-14)                  | 27 patients with MLS   |                      | Mx                    |
| Schmidt et al. (2009)     | 53                 | Addenbrooke’s Hospital and Chemnitz Medical Centre, Ger. | Retrospective analysis of prospectively collected data | Mx/Mx_a                  | None reported         | None reported          | None reported           | None reported            | 135 TBI patients      |                      | Mx/Mx_a               |
| Schmidt et al. (2012)     | 62                 | Addenbrooke’s Hospital and Chemnitz Medical Centre, Ger. | Retrospective analysis of prospectively collected data | Mx                        | None reported         | None reported          | None reported           | None reported            | 135 TBI patients      |                      | Mx                    |
| Zeiler et al. (2018c)     | 40                 | Addenbrooke’s Hospital, United Kingdom           | Retrospective analysis of prospectively collected data | Mx/Sx/Sx_a/Dx_a/Sx_a/PRx  | 31.1                 | 5                      | None reported           | 30 min to 1 h            |                      | Mx/Sx/Sx_a/Dx_a/Sx_a/PRx | Mx/Sx/Sx_a/Dx_a/Sx_a/PRx |
| Zeiler et al. (2018e)     | 347                | Addenbrooke’s Hospital, United Kingdom           | Retrospective analysis of prospectively collected data | Mx                        | 33.7                 | 250                    | None reported.          | 30 min-3.26 h           |                      | Mx                    |
| Zhang et al. (2016)       | 31                 | Addenbrooke’s Hospital, United Kingdom           | Retrospective analysis of prospectively collected data | Mx                        | None reported         | None reported          | 17 Craniectomy            | 33 (16-79)                | 17 Craniectomy         |                      | Mx                    |
| Zweifel et al. (2006)     | 398                | Addenbrooke’s Hospital, United Kingdom           | Retrospective analysis of prospectively collected data | Mx                        | None reported         | None reported          | None reported           | 314                      | Not reported           |                      | Mx                    |

**Global Functional Outcomes**

Most studies chose to use Glasgow Outcome Scale (GOS) as their outcome metric of choice, while opting to dichotomize outcome into favourable/unfavourable or good/poor (with favourable typically denoted as GOS of 5 or above and unfavourable as GOS 4 or less). Follow up was usually collected at 6 months post-injury. Once again, Mx seems to have the strongest body of evidence supporting its association with outcomes with studies consistently finding that a higher Mx was associated with poor or unfavourable outcome at follow up (Czosnyka et al., 1996; Czosnyka et al., 1997; Czosnyka et al., 1999; Czosnyka et al., 2000; Czosnyka et al., 2001; Czosnyka et al., 2002; Czosnyka et al., 2008; Lang et al., 2003a; Lewis et al., 2007; Lewis et al., 2012; Radolovich et al., 2011; Sorrentino et al., 2011; Budohoski et al., 2012a; Budohoski et al., 2012c; Liu et al., 2015; Schmidt et al., 2016a). When Mx was found to not be associated with outcomes, it was often attributed to small sample sizes (Schmidt et al., 2016b; Zeiler et al., 2017b).
### TABLE 4 | Study goals, findings and limitations of included studies.

| Reference | Relevant Goals of the Study | Key Relevant Results | Conclusion | Study Limitation |
|-----------|-----------------------------|---------------------|-------------|------------------|
| Budhoski et al. (2012a) | Primary: To assess the association of Mx with functional outcomes. Secondary: To assess the association of Mx with PRx. | Mx was significantly different between those that had unfavourable outcomes and those that had favourable outcomes (0.09 ± 0.26 vs. -0.03 ± 0.25, p = 0.002). Mx was significantly different in those that died and those that survived (0.12 ± 0.29 vs. 0.01 ± 0.25, p = 0.018). Mx and PRx correlated well (r = 0.58, p = 0.01). | Mx was significantly lower in those with good functional outcomes and those that survived. Mx and PRx covary with one another. | ABP, ICP and GCS were all significantly different between those that survived and those that died, and GCS and ABP were significantly different between those with favourable and unfavourable functional outcomes, but this was not controlled for when assessing the association with outcomes and Mx. |
| Budhoski et al. (2012c) | Primary: To assess the prognostic utility of Mx, Sx, Dx, Mx_a, Sx_a, and Dx_a. Secondary: To assess the association of Mx/Sx with severity of injury, age, CPP and ICP. | Mx (F = 16.86, p = 0.0003), Sx (F = 20.11, p = 0.0002), Dx (F = 7.07, p = 0.008), Mx_a (F = 8.88, p = 0.003), and Sx_a (F = 12.49, p = 0.0005) were all able to discriminate between patients with favourable and unfavourable functional outcomes at follow up. Mx (F = 6.93, p = 0.009), Sx (F = 13.10, p = 0.0003) and Sx_a (F = 5.32, p = 0.02) were all able to discriminate between those that survived and those that did not at follow up. Mx was significantly different between patients with favourable and unfavourable functional outcomes with Mx positively correlated with PRx (r = 0.41, p < 0.0002) and Sx (r = 0.48, p < 0.00004) correlated with 6-month GOS. Mx (r = 0.34, p = 0.0025) and Sx (r = 0.38, p = 0.0008) correlated with admission GCS. | Mx and Sx correlate with both injury severity and functional outcome. There is good correlation between Mx and PRx in non-craniectomy patients. | No multivariate analysis performed. |
| Czosnyka et al. (1996) | Primary: To assess the association of Mx with global outcomes. Secondary: To assess the association of Mx/Sx with severity of injury, age, CPP and ICP. | Mx (r = 0.41, p < 0.0002) and Sx (r = 0.48, p < 0.00004) correlated with 6-month GOS. | There is good correlation between Mx and PRx in non-craniectomy patients. | No multivariate analysis performed. |
| Czosnyka et al. (1997) | Primary: To assess the prognostic ability of PRx. Secondary: To assess the covariance of PRx and Mx. | Mx positively correlated with PRx (r = 0.63, p < 0.00001). Mx (r = 0.41, p < 0.0002) correlated with 6-month GOS. Median Mx significantly different in those with a favourable vs. unfavourable outcome (−0.26 vs. 0.03, p < 0.00006). | Mx and Sx correlate with both injury severity and functional outcome. There is good correlation between Mx and PRx in non-craniectomy patients. | No multivariate analysis performed. |
| Czosnyka et al. (1998) | Primary: To assess the prognostic ability of PRx. Secondary: To assess the correlation of Mx and PRx. | Mx (r = 0.41, p < 0.0002) correlated with 6-month GOS. Mx positively correlated with PRx (r = 0.63, p < 0.00001). Mx correlated with 6-month GOS (r = 0.39, p = 0.05). Mx correlated with admission GCS (r = −0.28, p = 0.05). | There is good correlation between Mx and PRx in non-craniectomy patients. | No multivariate analysis performed. |
| Czosnyka et al. (1999) | Primary: To assess the correlation of Mx with functional outcomes. Secondary: To assess the association of Mx with admission GCS, CPP and ICP. | Mx correlated with admission GCS (r = −0.39, p = 0.05) and ICP and CPP (r = −0.45 and r = −0.34, p = 0.05). | Mx was associated with functional outcomes at 6 months and injury severity. Mx was associated with both ICP and CPP. | No multivariate analysis performed. |
| Czosnyka et al. (2000) | Primary: To assess the association of Mx with global functional outcomes. Secondary: To assess the association of Mx with CPP. | Mx was significantly greater in those with an unfavourable outcome (p < 0.001). Mx correlated with 6-month GCS and admission GCS (ANOVA, F value 17 and 15, p < 0.05) and Mx dependent on CPP (ANOVA, p < 0.0001) and became positive at CPP < 60 mm Hg. | Mx was associated with functional outcomes at 6 months and injury severity. Mx was associated with CPP with a lower threshold of CPP at 60 mm Hg. | No multivariate analysis performed. |
| Czosnyka et al. (2001) | Primary: To assess the association of Mx with ICP and CPP. Secondary: To assess the association of Mx with 6-month outcomes. | The relationship between Mx and CPP is characterized by a U-shaped curve. Mx worsened with increasing ICP with the steepest rise between 20 and 30 mm Hg. Those with a favourable outcome at 6 months had a lower mean Mx (−0.08 ± 0.26 vs. 0.15 ± 0.31, p < 0.00002), lower mean ICP (17.0 ± 8.9 vs. 23.0 ± 13, p < 0.0003), higher GCS on admission (6 vs. 4, p < 0.0018) and younger age (27 vs. 32, p < 0.015). | Mx has a U-shaped relationship with CPP and worsens with increasing ICP. A favourable outcome was associated with lower Mx, lower ICP, Higher admission GCS, and younger age. | No multivariate analysis performed. |
| Czosnyka et al. (2002) | Primary: To assess the association of Mx and PRx with outcomes. Secondary: To identify a threshold value for Mx. | Those with a favourable outcome had a lower mean Mx (−0.06 ± 0.26 vs. 0.15 ± 0.31, p < 0.00002), lower mean ICP (17.0 ± 8.9 vs. 23.0 ± 13, p < 0.0003), higher GCS on admission (6 vs. 4, p < 0.0018) Mx (r = −0.2562, p < 0.0001), PRx (r = 0.278, p < 0.0001), ICP (r = −0.195, p < 0.01) and GCS (r = −0.18, p < 0.014) were all correlated with 6-month GOS. Thresholds of Mx (0.23) and PRx (0.31) were found by identifying where there was associated with 6-month outcomes with an increased mortality at Mx > 0.23. | Mx is associated with 6-month outcomes with an increased mortality at Mx > 0.23. | No multivariate analysis performed. |

(Continued on following page)
**TABLE 4** (Continued) Study goals, findings and limitations of included studies.

| Reference                  | Relevant Goals of the Study                                                                 | Key Relevant Results                                                                                                                                                                                                 | Conclusion                                                                 | Study Limitation                                                                 |
|----------------------------|--------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Czosnyka et al. (2005)     | Primary: To assess the association of Mx with functional outcomes                             | Sx not associated with 6-month GOS in multiple regression models                                                                                                                                                    | Sx was not found to be associated with outcome through multiple regression but cerebrovascular reactivity did worsen with age | Single institution dataset                                                        |
|                            | Secondary: To assess the association of Mx with age                                          | Sx was significantly worse with age (\( \tau = 0.26, p = 0.002 \))                                                                                                                                                |                                                                          |                                                                                  |
|                            | Primary: To assess the association of Mx with functional outcomes                             | Those with a favourable outcome had a lower Mx than those with an unfavourable outcome (\( -0.12 \pm 0.28 \) vs. \( 0.21 \pm 0.35, p = 0.0062 \)) independent of age  |                                                                           |                                                                                  |
|                            | Secondary: To assess the association of Mx with age, ICP, CPP and admission GCS              | Mx was worse with age (\( \rho = 0.30, p = 0.034 \)) Mx correlated positively with mean ICP (\( \tau = 0.31, p = 0.028 \)) and negatively with CPP (\( \tau = -0.33, p = 0.016 \)) |                                                                           |                                                                                  |
|                            |                                                                                             | There was no association with Mx and GCS on admission                                                                                                                                                    |                                                                          |                                                                                  |
| Lang et al. (2003a)        | Primary: To assess the association of Mx and Mx_a with functional outcomes at discharge       | Mx_a was associated with outcome (\( \tau = -0.42, p < 0.05 \)) Mx was associated with outcome (\( \tau = -0.56, p < 0.01 \))                                                                                       | Mx and Mx_a are associated with functional outcomes at discharge          | No long-term follow-up                                                          |
|                            | Secondary: To assess the covariance of Mx and Mx_a                                          | Mx and Mx_a did not correlate with ABP, CPP, ICP and CBFV                                                                                                                                                |                                                                          | No indication of duration of insonation                                           |
|                            |                                                                                             | Hemispheric asymmetry in cerebrovascular reactivity is relatively common following TBI but its impact on outcomes is unclear                                                                               |                                                                          |                                                                                  |
| Lang et al. (2003b)        | Primary: The incidence of hemispheric asymmetry (a difference of Mx_a > 0.2) and its association with outcome | 12 of the 25 patients had a hemispheric asymmetry in Mx_a                                                                                                                                                    |                                                                          |                                                                                  |
|                            | Hemispheric asymmetry had no impact on outcomes at discharge                                  |                                                                                                                                                    |                                                                          |                                                                                  |
| Lewis et al. (2007)        | Primary: To assess the association of Mx and Mx_a with functional outcomes                   | There was no statistical association between outcome and Mx_a                                                                                                                                                    | While Mx was associated with functional outcomes Mx was not Mx and Mx_a were found to be associated with one another | No multivariate analysis performed so unclear if association of Mx with outcomes is mediated through ICP, CPP, admission GCS, age etc. |
|                            | Secondary: To assess the covariance of Mx and Mx_a                                          | Mx was significantly different in those with a favourable vs. unfavourable outcome (\( -0.072 \pm 0.21 \) vs. \( 0.12 \pm 0.24, p = 0.007 \)) Mx and Mx_a were associated with each other (\( \tau = 0.71, p < 0.05 \)) |                                                                          | Single institution dataset                                                      |
| Lewis et al. (2012)        | Primary: To assess the association of Mx with functional outcome                              | Mx was statistically different across GOS at 6 months (\( \tau = 0.39, p = 0.0013 \))                                                                                                                                | Mx is associated with functional outcomes There is a U-shaped relationship between Mx and CPP indicating the possibility to identify a CPP > opt | No multivariate analysis performed so unclear if association of Mx with outcomes is mediated through ICP, CPP, admission GCS, age etc. |
|                            | Secondary: To assess the relationship between Mx and CPP                                      | Mx was able to discriminate between those with a favourable and unfavourable functional outcome (\( \tau = 1.42, p = 0.0002 \)) Plotting Mx vs. CPP shows a U-shaped curve indicating a CPP at which Mx is at a minimum |                                                                          | No reporting on the relationship between CPP and Mx in individual patients      |
| Liu et al. (2015)          | Primary: To assess the association of Mx, Mx_a with functional outcomes                      | Mx was significantly different in those with favourable vs. unfavourable outcomes (\( -0.04 \pm 0.29 \) vs. \( 0.03 \pm 0.28 \), respectively, \( p < 0.0001 \), \( \text{F value} = 53.38, \text{AUC} = 0.647 \) ) Mx_a was significantly different in those with favourable vs. unfavourable outcomes (\( 0.18 \pm 0.24 \) vs. \( 0.26 \pm 0.21 \), respectively, \( p = 0.002, \text{F value} = 10.08, \text{AUC} = 0.627 \) ) | Mx_a and Mx were both able to discriminate favourable vs. unfavourable functional outcomes but Mx had the stronger association with outcomes than Mx_a | No multivariate analysis performed so unclear if association of Mx/Mx_a with outcomes is mediated through ICP, CPP, admission GCS, age etc. |
|                            |                                                                                             | Mx_a and 3-month GOS (\( \tau = -0.54, p = 0.005 \)) Mx was higher in the non-survivor group compared to the survivor group (\( 0.28 \pm 0.4 \) vs. \( 0.03 \pm 0.21, p = 0.04 \) ) |                                                                           | No multivariate analysis performed so unclear if association of Mx with outcomes is mediated through ICP, CPP, admission GCS, age etc. |
| Radulovich et al. (2011)   | Primary: To assess the prognostic ability of Mx                                              | Mx was strongly predictive of poor functional outcome (\( \text{AUC} = 0.69, p < 0.001 \) )                                                                                                                      | Mx was predictive of poor functional outcome                               | No multivariate analysis performed so unclear if association of Mx with outcomes is mediated through ICP, CPP, admission GCS, age etc. |
|                            |                                                                                             |                                                                                                                                                    |                                                                          |                                                                                  |
| Schmidt et al. (2016a)     | Primary: To assess the association of Mx with functional outcomes following TBI              | Mx correlated with 3-month GOS (\( \tau = -0.54, p = 0.005 \))                                                                                                                                             | Mx was associated with functional outcome and survival following TBI     | Single institution dataset                                                      |
|                            | Secondary: To assess the correlation of Mx with PRx                                          | Mx was higher in the non-survivor group compared to the survivor group (\( 0.28 \pm 0.4 \) vs. \( 0.03 \pm 0.21, p = 0.04 \) )                                                                                                   | Mx and PRx correlate positively with one another                         | No indication of duration of insonation                                           |
|                            |                                                                                             | PRx and Mx correlated (\( \tau = -0.56, p < 0.001 \) )                                                                                                                                                    |                                                                          |                                                                                  |
| Schmidt et al. (2016b)     | Primary: Examine the association of Mx and PRx with mortality and functional outcomes       | Mx was not significantly different between those that died in hospital and those that survived Mx and not PRx was significantly different                                                                       | Mx was not able to predict mortality and but was significantly different in those with good functional outcomes compared with those with poor functional outcomes | Heterogenous patient population                                                  |
|                            |                                                                                             |                                                                                                                                                    |                                                                          | Single institution dataset                                                      |

(Continued on following page)
(Continued) Study goals, findings and limitations of included studies.

| Reference | Relevant Goals of the Study | Key Relevant Results | Conclusion | Study Limitation |
|-----------|-----------------------------|----------------------|------------|-----------------|
| Sorrentino et al. (2011) | Secondary: To identify a critical threshold for Mx and Mx_a where survival and functional outcomes worsen | The threshold (by 2x2 chi square analysis) was 0.3 for survival and good functional outcome | Mx has a threshold for worsening survival at 0.3 while outcomes worsen above 0.05 | No multivariate analysis performed |
| Zeiler et al. (2017b) | Primary: To assess the covariance of various indices of cerebrovascular reactivity | Mx correlated well with Dx (r = -0.991, p < 0.0001) and Sx (r = -0.726, p < 0.0001) | CPP based TCD indices correlated well with one another | No multivariate analysis performed |
| Zeiler et al. (2018a) | Primary: To confirm the covariance of TCD and ICP derived indices such as PRx | Sx and Sx_a displays the strongest correlation with ICP based indices compared to other TCD based indices | Sx and Sx_a seem to be the most strongly associated with ICP indices of all TCD based indices | No multivariate analysis performed |
| | Secondary: To identify thresholds for Sx, Sx_a, Dx, and Dx_a associated with functional outcomes | Principle Component Analysis also found Sx and Sx_a to be most associated with ICP based indices | Sx and Sx_a are discriminating between alive/dead and favourable/unfavourable outcomes | Single institution dataset |
| | | Sx and Sx_a also co-clustered with ICP based indices by Agglomerative Hierarchal Clustering and K-Means Cluster Analysis | Sx was superior to Sx_a when predicting functional outcome | Small patient population with limited recording time |
| | | Sx was able to discriminate between alive/dead (AUC = 0.930, p = 0.005) and favourable/unfavourable (AUC = 0.946, p = 0.001) by univariate logistic regression and performed better than Dx and Mx | Sx was only found to be able to discriminate between favourable and unfavourable outcomes with a threshold of -0.10 | |
| | | Mx was found to have a critical threshold of -0.15 for unfavourable outcome (p = 0.001) and -0.20 for mortality (p < 0.0001) by sequential chi-square thresholding | Dx failed to display any prognostic value | |
| | | Sx_a was able to discriminate between alive/dead (AUC = 0.582, p = 0.006) and favourable/unfavourable (AUC = 0.652, p = 0.001) by univariate logistic regression and performed better than Dx_a and Mx | No multivariate analysis performed |
| | | Sx_a was found to have a critical threshold of -0.10 for unfavourable outcome (p = 0.0001) and -0.05 for mortality (p = 0.019) by sequential chi-square thresholding | Single institution dataset |
| | | Chi-square values of Sx were higher than for Sx_a in thresholding analysis indicating a stronger relationship between thresholds and outcomes for Sx than Sx_a | |
| | | Dx was able to discriminate between favourable/unfavourable outcomes (AUC = 0.592, p = 0.012) but failed to reach significance when predicting mortality by univariate logistic regression | |
| | | Dx was found to have a threshold of -0.10 (p = 0.005) for unfavourable outcomes | |
| | | Sx_a failed to reach significance for 6-month outcomes and mortality | |

Cerebral physiologic correlates

(Continued on following page)
TABLE 4 | (Continued) Study goals, findings and limitations of included studies.

| Reference | Relevant Goals of the Study | Key Relevant Results | Conclusion | Study Limitation |
|-----------|-----------------------------|----------------------|------------|------------------|
| Haubrich et al. (2012) | Primary: To assess if CPPopt, as determined by Mx, was altered by hypocapnia | Hypocapnia improved cerebrovascular reactivity in those where it was impaired (Mx > 0.25) | In those with impaired cerebrovascular reactivity, hypocapnia improves Mx and may aid its detection | Single institution dataset Short recording period especially for determine a CPPopt |
| Haubrich et al. (2011) | Primary: To assess if CPPopt, as determined by Mx, was altered by hypocapnia | Hypocapnia improved cerebrovascular reactivity in those where it was impaired (Mx > 0.25) | In those with impaired cerebrovascular reactivity, hypocapnia improves Mx and may aid its detection | Single institution dataset Short recording period |
| Haubrich et al. (2012) | Secondary: To assess if hypocapnia alters the ability to detect CPPopt with Mx | Hypocapnia did not change cerebrovascular reactivity in those where it was intact (Mx < 0.25) | | |
| Lang (2003) | Primary: To assess the association of Mx with PRx. | There was a significant overall correlation between PRx and Mx (Pearson correlation: r = 0.42, p < 0.007, Spearman correlation: r = 0.49, p < 0.009) | Mx and PRx correlate with one another. | Single institution dataset No indication of duration of isononation |
| Lewis et al. (2014) | Primary: To evaluate the behavior of Mx during plateau waves of ICP | Mx during plateau wave was significantly more positive when compared to pre-plateau and post-plateau recordings (0.91 vs. 0.27 and 0.29, p = 0.001) | Cerebrovascular reactivity, as measured by Mx, is significantly disrupted during plateau waves of ICP. | Small number of events observed. |
| Liu et al. (2016) | Primary: To evaluate the behavior of Mx and Mx_a during plateau waves of ICP | Mx increased from 0.12 to 0.47 at baseline to 0.47 ± 0.47 at plateau, p = 0.004 | The deterioration of cerebrovascular reactivity during plateau waves of ICP was detected by Mx but not Mx_a | Small number of events observed |
| Schmidt et al. (2003a) | Primary: To assess the association of Mx with Mx_a | Mx and Mx_a correlated well with one another (r = 0.86, p < 0.001) | Mx and Mx_a correlate with one another | No indication of duration of isononation |
| Schmidt et al. (2003b) | Primary: To assess the prognostic value of hemispheric asymmetry in Mx | Asymmetry was higher in those that died than survived (0.14 ± 0.18 vs. 0.08 ± 0.1, p = 0.04) | Hemispheric asymmetry in Mx was independently associated with outcome following TBI | Single institution dataset |
| Schmidt et al. (2009) | Primary: The assess if Mx/Mx_a were different during increases of CPP than during decreases of CPP | Mx was significantly different during increases of CPP than during decreases of CPP (0.05 ± 0.49 vs. 0.14 ± 0.54, p < 0.005) | Cerebrovascular reactivity, as measured by Mx, appears to be stronger during increases in CPP than during decreases in CPP | During analysis, a large proportion of data was discarded with data from 53 out of 210 patients used in the study |
| Schmidt et al. (2012) | Primary: To evaluate if cerebrovascular reactivity differs during increases in CPP as compared to decreases in CPP | Cerebrovascular reactivity appears to be stronger during increases of CPP than during decreases of CPP | | Data used in study represented only a small amount of original dataset due to limited availability of TCD recordings |

(Continued on following page)
Once again, the evidence supporting other TCD based indices is not as prevalent. Mx_a was found to be associated with global functional outcomes in four different articles with higher values being associated with worse outcomes (Lang et al., 2003a; Sorrentino et al., 2011; Liu et al., 2015; Zeiler et al., 2018a). Dx and Dx_a have been more recently examined with Dx having a weak association with functional outcomes and Dx_a failing to demonstrate any predictive value. In the original 1996 study by Czosnyka and colleagues Sx was correlated with 6-month GOS (Czosnyka et al., 1996). More recently, Sx and Sx_a showed a stronger association with ICP based indices than other TCD based indices (Zeiler et al., 2018b). Of note, a 2005 study by Czosnyka and colleagues noted in their 2003 study that Mx was worse on the side of contusion or expansion if the patient had midline shift. They also noted that a hemispheric asymmetry was significantly more common in patients that died than those that survived (Czosnyka et al., 2003). In a follow up study Schmidt and colleagues found that the magnitude of hemispheric asymmetry, as determined by Mx, was higher in patients that died compared to those that survived and that hemispheric asymmetry was independently associated with functional outcome by multiple regression analysis (Schmidt et al., 2003b). Interestingly, hemispheric asymmetry, as determined by Mx_a was not found to be associated with outcomes by Lang and colleagues in their 2003 study (Lang et al., 2003b).

### Thresholds

Thresholds values of indices, where outcomes or mortality significantly increases, was the focus of 4 articles. In a 2002 study by Czosnyka and colleagues they found a threshold for Mx of 0.23, above which mortality went from 11 to 47% (Czosnyka et al., 2002). A similar threshold for mortality, Mx = 0.3, was found in a follow up study by Sorrentino and colleagues in 2011. In that same study, a threshold of 0.05 for Mx was found to be where functional outcomes most drastically worsened while Schmidt and colleagues found a threshold for unfavourable outcomes closer to that of the mortality threshold at Mx = 0.2 (Sorrentino et al., 2011; Schmidt et al., 2016b).

In the 2011 study by Sorrentino and colleagues, Mx_a was found to have a threshold at 0.3 where both mortality and functional outcome both worsened in their cohort (Sorrentino et al., 2011). Zeiler and colleagues found in 2018 that in their cohort of 281 TBI patients, Sx had thresholds of −0.15 and −0.20 while Sx_a had thresholds of −0.10 and 0.05 for functional outcome and mortality, respectively. They also identified a threshold of −0.10 for Dx where outcomes worsened (Zeiler et al., 2018a).

### Hemispheric Asymmetry

TCD can be utilized to insonate the left and right MCA of the patient without any increased risk to the patient and so a number of studies examined the effect of hemispheric asymmetry of TCD based indices of cerebrovascular reactivity. Czosnyka and colleagues noted in their 2003 study that Mx was worse on the side of contusion or expansion if the patient had midline shift. They also noted that a hemispheric asymmetry was significantly more common in patients that died than those that survived (Czosnyka et al., 2003). In a follow up study Schmidt and colleagues found that the magnitude of hemispheric asymmetry, as determined by Mx, was higher in patients that died compared to those that survived and that hemispheric asymmetry was independently associated with functional outcome by multiple regression analysis (Schmidt et al., 2003b). Interestingly, hemispheric asymmetry, as determined by Mx_a was not found to be associated with outcomes by Lang and colleagues in their 2003 study (Lang et al., 2003b).

### Established Measure of Cerebrovascular Reactivity

Cerebrovascular reactivity is often measured by the fluctuation of ICP in response to changes in ABP in a more established index known as the pressure reactivity index (PRx). There has been a building body of evidence supporting cerebrovascular reactivity, in the form of PRx, being an important physiologic measure in TBI and so several studies have assessed the covariance of PRx and TCD based indices (Czosnyka et al., 1997; Czosnyka et al., 2002; Lang, 2003; Zweifel et al., 2008; Budohoski et al., 2012a; Schmidt et al., 2016a; Zeiler et al., 2017b; Zeiler et al., 2018a; Zeiler et al., 2018c).

Once again, Mx has been the most well examined TCD based index

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**TABLE 4 | (Continued) Study goals, findings and limitations of included studies.**

| Reference                     | Relevant Goals of the Study                                                                 | Key Relevant Results                                                                 | Conclusion                                                                                           | Study Limitation                        |
|-------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------|
| Zeiler et al. (2018d)         | Primary: To evaluate the association of various TCD based indices with ICP based indices, such as PRx | Mx and PRx were correlated (r = 0.346, p = 0.006)                                      | PRx and Mx are correlated with one another                                                             | Single institution dataset              |
|                               |                                                                                             | Sx and Sx_a were moderately correlated with ICP based indices such as PRx               |                                                                                                       | Short recording period                  |
|                               |                                                                                             | ICP based indices, such as PRx, were found to be most associated with Sx and Sx_a       |                                                                                                       |                                         |
|                               |                                                                                             | by Principal Component Analysis and by Agglomerative Hierarchical Clustering             |                                                                                                       |                                         |
| Zeiler et al. (2018e)         | Primary: To determine if PRx can be estimated by Mx_a and Sx_a                               | The model of PRx using Sx_a correlated well with PRx (r = 0.794, 95% CI 0.788–0.799, p < 0.0001) | PRx can be estimated using ABP and TCD bases indices Mx_a and Sx_a                                     | Model development cohort was the same as the validation cohort |
|                               |                                                                                             | The model of PRx using Sx_a and Mx_a correlated well with PRx (r = 0.809, 95% CI 0.809–0.819, p < 0.0001) |                                                                                                       | Single institution dataset              |
| Zhang et al. (2016)           | Primary: To assess the association of Mx with CO2 reactivity                                | CO2 reactivity was correlated with Mx (r = −0.37, p = 0.04)                            | Cerebrovascular reactivity, as measured by Mx, is associated with CO2 reactivity                       | Small sample size with limited recording time |
|                               | Secondary: To assess the impact of Hyperventilation of Mx                                  | Mx did not significantly change with hyperventilation                                    | Cerebrovascular reactivity, as measured by Mx                                                        |                                         |
| Zweifel et al. (2008)         | Primary: To assess the correlation between Mx and PRx                                       | There was good correlation between Mx and PRx (r = 0.36, p < 0.001)                    | Both measures of cerebrovascular reactivity, Mx and PRx, correlated with one another                    | No indication of duration of insonation |
|                               |                                                                                             |                                                                                        |                                                                                                       | TCD was not available for each patient   |
|                               |                                                                                             |                                                                                        |                                                                                                       | Single institution dataset              |

ABP, arterial blood pressure; CBFV, cerebral blood flow velocity; CPP, cerebral perfusion pressure; CPPopt, optimal CPP, Dx, diastolic flow index with ccpp, Dx_a, diastolic flow index with ABP; GCS, glasgow coma scale; GOS, glasgow outcome scale; ICP, intracranial pressure; Mx, mean flow index with ccpp; MLS, midline shift; Mx_a, mean flow index with ABP, PRx, pressure reactivity index; Sx, systolic flow index with ccpp; Sx_a, systolic flow index with ABP
with eight studies demonstrating some degree of correlation between Mx and PRx (Czosnyka et al., 1997; Czosnyka et al., 2002; Lang, 2003; Zweifel et al., 2008; Budohoski et al., 2012a; Schmidt et al., 2016a; Zeiler et al., 2017b; Zeiler et al., 2018c). Despite this, recent work comparing various TCD based indices found that Sx had the strongest correlation with PRx (Zeiler et al., 2017b; Zeiler et al., 2018a; Zeiler et al., 2018c), and both Sx and Sx_a appear to closely approximate PRx through advanced time-series modeling (Zeiler et al., 2018c). Finally, utilizing complex time-series analysis, PRx has been found to be estimated well with Mx_a and Sx_a based models (Zeiler et al., 2018c).

Cerebral Perfusion Pressure and Intracranial Pressure

The relationship between TCD based indices and ICP seems to be somewhat independent with Mx being found to be positively correlated with ICP in early studies and a notable increased in Mx with ICPrs above 20 mm Hg (Czosnyka et al., 1999; Czosnyka et al., 2001; Czosnyka et al., 2003; Czosnyka et al., 2008). Notably, during measurements of plateau waves of ICP, Mx was greater than the threshold of 0.2 and significantly more positive than pre-plateau and post-plateau periods (Czosnyka et al., 2003; Lewis et al., 2014). This difference during plateau waves was not found in Mx_a (Liu et al., 2016). The association between TCD indices and CPP is slightly more complex. While early studies showed a negative correlation between Mx and CPP (Czosnyka et al., 1999; Czosnyka et al., 2000) subsequent studies have found that when plotting Mx vs. CPP a U-shaped distribution is observed (Czosnyka et al., 2001; Czosnyka et al., 2003; Lewis et al., 2012). This may indicate that an optimal CPP (CPPopt) may exist where Mx is at a minimum, and therefore cerebrovascular reactivity may be best preserved, for individual patients. Cerebrovascular reactivity may then be disrupted both when CPP is inadequate or insufficient and this has been postulated as a means of identifying individual CPP targets based on a CPPopt derived from Mx. Interestingly, some studies have also found that Mx was significantly lower when CPP was increasing compared to when it was decreasing and that the correlation between Mx and CPP is stronger during increases in CPP than decreases in CPP (Schmidt et al., 2009; Schmidt et al., 2012). This may indicate that current management generally places patients at a CPP less than their CPPopt.

CO₂ Reactivity

A number of smaller studies have explored the relationship between TCD based indices and hypocapnia as well as CO₂ reactivity (Haubrich et al., 2011; Haubrich et al., 2012; Zhang et al., 2016). In general, those with disrupted cerebrovascular reactivity (Mx ≥ 0.25), moderate hypocapnia seemed to significantly decreased Mx while those with intact reactivity (Mx ≤ 0.25) saw no significant change with hypocapnia (Haubrich et al., 2011, Haubrich et al., 2012). Of note, while less than half of the patients examined had an identifiable CPPopt at normocapnia, nearly all of them had one with hypocapnia (Haubrich et al., 2011). In a similar study, Zhang and colleagues found that CO₂ reactivity was correlated with Mx but did not find any significant changes in Mx with hyperventilation (Zhang et al., 2016).

Radiographic Evolution of Injury

No study was identified that examined the association between time-domain TCD based indices of cerebrovascular reactivity and the evolution of imaging findings following TBI.

DISCUSSION

A strong relationship between time-domain TCD based indices of cerebrovascular reactivity and mortality/functional outcome following TBI has been demonstrated through this scoping review of the literature (Czosnyka et al., 1996; Czosnyka et al., 1997; Czosnyka et al., 1999; Czosnyka et al., 2000; Czosnyka et al., 2001; Czosnyka et al., 2002; Lang et al., 2003a; Schmidt et al., 2003b; Lewis et al., 2007; Radolovich et al., 2011; Sorrentino et al., 2011; Budohoski et al., 2012a; Budohoski et al., 2012c; Lewis et al., 2012; Schmidt et al., 2016a). The prognostic utility of TCD based indices has been emphasized with the identification of thresholds for most indices at which outcomes worsen and mortality increases (Czosnyka et al., 2002; Sorrentino et al., 2011; Schmidt et al., 2016b; Zeiler et al., 2018a). Hemispheric asymmetry of cerebrovascular reactivity, as measured by TCD based indices, also seems to pertain a poor prognosis following TBI (Czosnyka et al., 2003; Lang et al., 2003b; Schmidt et al., 2003b). There also seems to be a reasonable degree of covariance between TCD based indices of cerebrovascular reactivity and more established measures, such as PRx (Czosnyka et al., 1997; Czosnyka et al., 2002; Lang, 2003; Zweifel et al., 2008; Budohoski et al., 2012a; Schmidt et al., 2016a; Zeiler et al., 2017b, Zeiler et al., 2018c). Elevations in ICP seem to be associated with the disruption of cerebrovascular reactivity (Czosnyka et al., 1999; Czosnyka et al., 2001; Czosnyka et al., 2003; Czosnyka et al., 2008) while a U-shape relationship exist between CPP and Mx indicating the possibility of a CPPopt where cerebrovascular reactivity is the least disrupted (Czosnyka et al., 2001; Czosnyka et al., 2003; Lewis et al., 2012). Finally, hyperventilation seems to improve cerebrovascular reactivity when it is already disrupted but does not significantly change it when already intact (Haubrich et al., 2011; Haubrich et al., 2012; Zhang et al., 2016). These findings highlight the utility of these indices in not only providing a greater understanding of the post-TBI physiome but also indicate a role for these measure of cerebrovascular reactivity in precision medicine by aiding in developing personalized targets for physiologic parameters following injury.

This review has also identified some major limitations to this body of literature. Perhaps, most obvious, is that the predominance of data supporting these findings comes from a single institution. This limits the confidence in the generalizability of these findings. A more subtle corollary of this is that there is significant overlap in cohorts used over various articles and so while there may be numerous publications finding prognostic utility in these indices, the strength of these finding may be somewhat overstated as the data is not wholly unique between them.

There are also limitations to the assessment of global outcomes measured at follow up. None of the studies identified in this
scoping review utilized pathology specific, detailed quality of life measures such as the Quality of Life after Brain Injury (QOLIBRI) instrument. Assessments such as these would have provided a more comprehensive understanding of a patient’s health-related quality of life following their injury (von Steinbüchel et al., 2020). Additionally, trends in functional outcome, identified through serial measurements collected over multiple timepoints, were not investigated by any of the studies. As a result, no comments can be made about the utility of TCD based indices of cerebrovascular reactivity to stratify various trajectories of functional recovery.

Another weakness is in the analysis performed in these studies. We have seen that these indices are related to age, severity of injury and ICP (Czosnyka et al., 2006; Czosnyka et al., 2003; Czosnyka et al., 2005), however, what is unclear is if these indices provide prognostic utility independent of these associated variables as no multivariate analysis was performed. Without multivariate analysis, the role of TCD based indices as an independent prognostic tool remains unclear. Further to this, the studies identified reduced measures of TCD indices to grand averages over the recording period or over the length of stay with no study performing time-series analytics to evaluate causal relationships. While this simplifies analysis, it is at the cost information encoded in the fluctuations of these indices over a recording period or over the entire length of stay.

The literature also seems to mainly focus on Mx as the TCD based index most studied. This is likely due to it being the first TCD based index described (Czosnyka et al., 1996). While this means there is a large volume of evidence supporting its use, studies exploring other indices are limited. Of note, systolic TCD based indices (Sx and Sx_a) were only examined in seven studies (Czosnyka et al., 1996; Czosnyka et al., 2005; Budohoski et al., 2012c; Zeiler et al., 2017b; Zeiler et al., 2018a; Zeiler et al., 2018c; Zeiler et al., 2018e). This is especially unfortunate given recent studies finding systolic based indices to closest association with more established ICP based indices of cerebrovascular reactivity and provide better prognostic utility than mean flow (Mx and Mx_a) and diastolic (Dx and Dx_a) TCD based indices(Zeiler et al., 2018a). Diastolic TCD based indices (Dx and Dx_a) were only examined in four studies and were found to have the weakest outcome associations of all modalities (Budohoski et al., 2012c; Zeiler et al., 2017b; Zeiler et al., 2018a; Zeiler et al., 2018c). However, generalization of the findings of diastolic (Dx and Dx_a) and systolic (Sx and Sx_a) modalities are limited not only by the small number of studies but also due to the fact that all of the identified studies evaluating them draw from a single institution’s database (Addenbrooke’s Hospital, United Kingdom).

There are also some limitations inherent to TCD that become apparent when reviewing the literature. Due to the difficulty in obtaining prolonged recordings of TCD data, most studies report only data collection during a small proportion of time spent in ICU with some studies reporting as little as 10 min of insonation a day (Radolovich et al., 2011) and no study reporting more than 4 h per day. Given the dynamic nature of cerebrovascular reactivity, as demonstrated by the PRx literature (Adams et al., 2017), it is hard to believe that prognostic utility would not benefit from longer periods of insonation. In addition to the variable duration of insonation, there is also inconsistent timing and rate of measurements with some studies performing serial daily measurements (Czosnyka et al., 1996; Czosnyka et al., 1998; Czosnyka et al., 1999; Czosnyka et al., 2000; Czosnyka et al., 2001; Czosnyka et al., 2002; Czosnyka et al., 2003; Schmidt et al., 2003b; Czosnyka et al., 2005; Lewis et al., 2007; Czosnyka et al., 2008; Radolovich et al., 2011; Sorrentino et al., 2011; Schmidt et al., 2012; Liu et al., 2015) while others reported only performing one recording session over the course of admission (Lang et al., 2003b; Zeiler et al., 2018a; Zeiler et al., 2018c; Zeiler et al., 2018e). A number of studies also failed to report any details around duration and frequency of insonation as well as timing of measurement following injury(Czosnyka et al., 1997; Lang et al., 2003a; Lang, 2003; Schmidt et al., 2003a; Zweifel et al., 2008; Schmidt et al., 2009; Budohoski et al., 2012a; Budohoski et al., 2012c; Lewis et al., 2012; Lewis et al., 2014; Schmidt et al., 2016a; Schmidt et al., 2016b; Liu et al., 2016; Zhang et al., 2016). In those studies, in which serial assessments were performed, no comment was made on the progression of cerebrovascular reactivity over time.

Finally, there seems to be an absence of any literature evaluating the link between cerebrovascular reactivity, as measured by time-domain TCD based indices, and the evolution or progression of imaging findings in the setting of TBI. Similar reports have been published with regards to PRx and have found a link between cerebrovascular reactivity and lesion progression following TBI (Mathieu et al., 2020a; Mathieu et al., 2020b; Zeiler et al., 2020). A link between similar TCD based indices may provide a less invasive means of predicting radiographic progression and should be explored further.

**Limitations**

This scoping review does, in and of itself, have some limitations. Articles included in this study were limited to those that contained cohorts of greater than 20 TBI patients. This was done in order to limit the prevalence of small case series and case reports, however, this may have limited the diversity of institutions included in this review. Additionally, this review was limited to continuous time-domain TCD based indices at the exclusion of frequency domain based TCD indices. While this was done to avoid excessive heterogeneity in indices examined, there is evidence that these indices do associate with outcomes following TBI, but to a lesser degree (Liu et al., 2015). Additionally, the inclusion articles in journal supplements resulted in some very similar reports being included in this review (Haubrich et al., 2011; Haubrich et al., 2012). Finally, given that TBI has a global burden of disease, the exclusion of non-English language articles may have further narrowed the institutional diversity as well as likely skewed the ethnocultural diversity of the patient cohorts included in this review.

**Future Directions**

This review highlights some key areas for further development. First, before TCD based indices are adopted clinically, validation of these findings will need to occur on more diverse datasets. Large multi-institutional/multi-national collaborative networks such as the ones found in the CENTER-TBI study and CANadian High-
Resolution TBI (CAHR-TBI) Research Collaborative are ideal for such validation studies (Bernard et al., 2020). In order to identify the true prognostic utility of TCD based indices, these studies should ideally examine the unique contributions of these indices in and above ICP, age and injury severity through multivariant analysis.

The clinically applicability of these indices may also be expanded past prognostication. Further exploration of utilizing TCD based indices to identify personalized CPP targets in critically ill patients following TBI must be undertaken. Precision medicine with personalized targets derived from these indices may provide the means to significantly alter outcomes following TBI and is already being explored utilizing more established measure of cerebrovascular reactivity, such as PRx (Zeiler et al., 2019a).

Further investigation of TCD based indices, aside from Mx, should also be done given the evidence of the strength of correlation with outcome Sx has demonstrated. Additionally, ABP based indices are of particular interest given the recent description of entirely non-invasive methods of collecting the requisite physiologic data (Zeiler et al., 2018b; Zeiler et al., 2019b; Zeiler and Smielewski, 2018; Gomez et al., 2020).

Finally, advances in TCD technology, such as robotic TCD has allowed for prolonged recording in and above 4 h due to the continuous robotic optimization of probe position. This has already been described as a means of assessing cerebrovascular reactivity for extended periods of time and may extend the percentage of time monitored while in ICU (Zeiler et al., 2018b; Zeiler and Smielewski, 2018). This may prove to further improve the association of these indices with outcomes following TBI while providing a more complete picture of the post-TBI physiome.

**CONCLUSION**

This systematic scoping review of the literature identifies that there is a substantial body of evidence that cerebrovascular reactivity as measured by time-domain TCD based indices have prognostic utility following TBI. To a lesser extent, the literature has also explored some associations between these indices and cerebral physiologic parameters in this patient population. Notably, there is lack of evidence evaluating the correlation between these indices and radiographic progression following injury. Further research needs to be done to expand the generalizability of these results and identify optimal inputs and collection methods for these indices before they can be widely clinically adopted. However, their role in precision medicine following traumatic brain injury is promising.

**AUTHOR CONTRIBUTIONS**

AG: Designed the search strategy and search terms, collected articles for review, undertook review and screening of the literature, and prepared the manuscript. LF: Undertook review and screening of the literature as well as aided in preparing the manuscript. AS: Aided in preparation of the manuscript. CB: Aided in preparation of the manuscript. FZ: Responsible for conceptual development of this article, development of search strategy, undertook screening of the literature, and aided in preparation of the manuscript.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.690921/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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