



Review

A Scoping Review of Cerebral Doppler Arterial Waveforms in Infants

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Cerebral Doppler ultrasound has been an important tool in pediatric diagnostics and prognostics for decades. Although the Doppler spectrum can provide detailed information on cerebral perfusion, the measured spectrum is often reduced to simple numerical parameters. To help pediatric clinicians recognize the visual characteristics of disease-associated Doppler spectra and identify possible areas for future research, a scoping review of primary studies on cerebral Doppler arterial waveforms in infants was performed. A systematic search in three online bibliographic databases yielded 4898 unique records. Among these, 179 studies included cerebral Doppler spectra for at least five infants below 1 y of age. The studies describe variations in the cerebral waveforms related to physiological changes (43%), pathology (62%) and medical interventions (40%). Characteristics were typically reported as resistance index (64%), peak systolic velocity (43%) or end-diastolic velocity (39%). Most studies focused on the anterior (59%) and middle (42%) cerebral arteries. Our review highlights the need for a more standardized terminology to describe cerebral velocity waveforms and for precise definitions of Doppler parameters. We provide a list of reporting variables that may facilitate unambiguous reports. Future studies may gain from combining multiple Doppler parameters to use more of the information encoded in the Doppler spectrum, investigating the full spectrum itself and using the possibilities for long-term monitoring with Doppler ultrasound.

Introduction

Doppler ultrasound represents an important bedside tool for assessing cerebrovascular status in infants; it has been an integral part of the care of sick infants for decades [1]. Infants, and especially preterm neonates, are particularly vulnerable to disturbed cerebral blood perfusion. Altered cerebral blood flow and fluctuations in systemic blood flow in combination with impaired cerebral autoregulation can cause permanent brain damage or, in the worst case, death. Thus, techniques for monitoring cerebral blood perfusion have an important clinical potential for diagnostics as well as for assessing vulnerability and risks, need for intervention and response to treatment.

Doppler ultrasound possesses a range of properties that make its application especially well-suited for infants. The open fontanelle of infants provides an acoustic window through which ultrasound waves can pass unhindered by the cranium, providing high signal quality. Because the instrument is portable, it can readily be used bedside without interfering with other monitoring systems or disturbing the access to continuous life-support systems. Doppler ultrasound is safe when the settings and exposure are within the recommended limits [2]. Because the technology provides a real-time overview of cerebral perfusion, its

potential clinical value is substantial: the need for intervention can be detected immediately, the effect of treatment can be assessed during the application and the response to interventions such as pressure provocation and tilt can be determined.

Despite the potential for longitudinal monitoring of blood flow, conventional bedside Doppler measurements offer only a “snapshot” status of the cerebral circulation, typically in the form of numerical parameters. Currently, there is a lack of evidence to support that the single measurement of Doppler parameters, such as pulsatility index (PI), in the cerebral arteries can predict well-being, brain injury and long-term neurodevelopmental outcome in infants and fetuses [3,4]. One reason for this lack of evidence could be that reducing the Doppler spectrum into single parameters removes significant information of clinical interest; when only parameters such as indices and velocities are studied, the complexity of the Doppler spectrum is lost. Studying the full Doppler spectrum may strengthen the clinical value of Doppler ultrasound in pediatric practice.

There is currently a lack of systematic characterization of what is known about cerebral velocity waveforms in infants. Waveforms from various conditions are displayed in several textbooks [5–7] and case studies, but these presentations are typically collected from the authors’

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clinical practice. A more systematic approach could support the clinical interpretation of bedside Doppler examination. To this end, a scoping review was conducted to summarize existing research on cerebral Doppler spectra and identify possible research gaps.

The main research question for this review was: “what information can cerebral Doppler velocity waveforms provide in healthy and sick infants below one year of age?” Specific sub-questions were formulated: (i) What conditions and states have been related to characteristic Doppler velocity waveforms in infants less than 1 y of age? (ii) What is reported in the literature regarding single Doppler measurements (“snapshots”) versus long-term monitoring using transcranial/transfontanellar Doppler in infants less than 1 y of age? (iii) What knowledge gaps provide objectives for possible future research? The review was confined to arterial waveforms as these are most common in clinical practice.

Methods

A protocol was drafted under guidance of the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist [8] and pre-registered with the Open Science Framework on March 30, 2021 (<https://osf.io/zk7r9>) before the search was conducted [9].

Literature search

A structured literature search was performed in the bibliographic databases MEDLINE, Embase and Web of Science Core Collection on April 6, 2021. The search strategy included three main concepts: “Doppler,” “cerebral” and “infant.” Alternative free text terms for the concepts were used consistently across the databases. Additionally, relevant thesaurus terms for each concept were also included for MEDLINE and Embase. Alternative thesaurus and free text terms for each concept were combined using the Boolean operator OR, before combining the concepts using the Boolean operator AND. The literature search was updated on April 7, 2022. All identified references were exported to the reference manager EndNote 20, where duplicates were removed before screening of titles and abstracts. Bibliographies of identified reviews were also hand searched to identify studies potentially overlooked by the structured literature search. See Appendix S1 (online only) for a detailed description of the specific search strategies used for the different databases.

Study selection

Articles that met the following criteria were included: (i) arterial Doppler velocity waveform(s) were reported in graphical form; (ii) the study population contained infants younger than 1 y of age; (iii) the methodology included transcranial or transfontanellar Doppler ultrasound; (iv) the article was published in a scientific journal; and (v) the article was written in English. Case studies, reviews and studies with fewer than five infants less than 1 y of age were excluded. The study selection was performed by A.H.J, and borderline cases were resolved by consensus with S.A.N.

Data charting

Information on all Doppler spectra and general data were extracted from the included studies. A large number of included studies made it necessary to extract fewer details than originally planned [9]. Data items are listed in Table S1 (online only). Tables with artificial spectra were made for a selection of pathological conditions and medical interventions as detailed below. The conditions and medical interventions were selected based on assumed clinical utility and/or the number of studies describing the condition/intervention.

Table 1

Quality scores were calculated from traceability and reporting of time and velocity scales

Score	Criterion
<i>Traceability</i>	
0	Only a sketch or trace is given, not the entire spectrum
1	The spectrum or parts of the spectrum are not traceable because of a weak signal, unsatisfactory gain or contrast, aliasing or other causes
2	The spectrum can be traced with high confidence
<i>Velocity scale</i>	
0	Scale not indicated
0.5	Scale indicated but not clearly marked with numerical values
1	Scale clearly marked
<i>Time scale</i>	
0	Scale not indicated
0.5	Scale indicated but not clearly marked with numerical values
1	Scale clearly marked

A custom quality score scale was designed to support the selection of relevant spectra for conditions for which several alternative spectra were available. A score (ranging from 0–4) was assigned to each spectrum based on the combination of traceability (sufficient gain and contrast) and reporting of velocity and time scales (see Table 1 for a more detailed description of the scale). The time design of the studies was classified along two dimensions: (i) single or repeated examinations and (ii) measurements or longitudinal monitoring (Table 2; Fig. S1, online only). These classification criteria were designed after the initial assessment of the included papers to distinguish methodological approaches to the Doppler spectrum as snapshot or time signal. Studies were classified as repeated if at least one part of the study comprised repeated examinations.

Adaption of Doppler spectra

To present the characteristic Doppler spectra in a comparable manner, and to avoid copyright issues, we traced original spectra and reproduced them by simulation with in-house software (Fig. 1). Original spectra were manually traced with the Engauge Digitizer tool [10] and post-processed in MATLAB [11] by interpolation and circular convolution. The latter allowed repeating the trace without gaps between repetitions. Final adopted spectra were generated by in-house software [12]. In-phase and quadrature (IQ) Doppler signal was obtained by a complex, Gaussian random number generator, lowpass filtered to give a stationary complex Gaussian process. The signal was then resampled with time

Table 2

Classification of time designs (Fig. S1)^a

<i>Single versus repeated examination</i>	
Single examination	Participants examined under only one experimental condition or on one occasion. One or more arteries may have been examined by one or more investigators, but the hemodynamic state of the infant is constant across examinations.
Repeated examinations	Participants examined under different experimental conditions or at distinct time points, such as at different stages of a procedure or disease or at increasing age
<i>Measurement versus longitudinal monitoring</i>	
Measurement	The Doppler recording is summarized as single Doppler parameters
Longitudinal monitoring	The Doppler recording is analyzed as a continuous time signal or Doppler parameters are calculated on a beat-for-beat basis

^a Studies were classified as either single or repeated examinations and as either measurement or longitudinal monitoring.

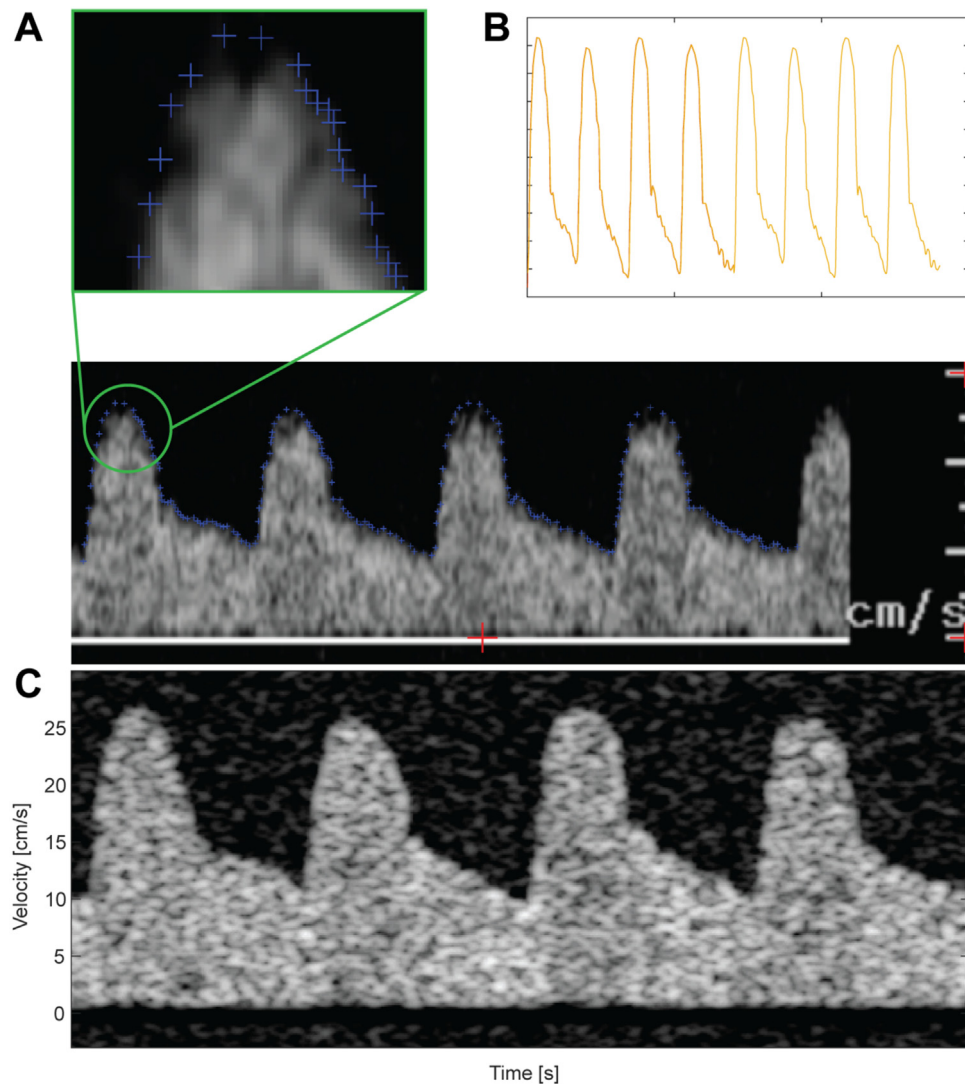


Figure 1. Depiction of how Doppler spectra were traced and regenerated. (A) The original Doppler spectrum was manually traced (blue crosses). The red crosses define the axes. (B) The trace was then post-processed by interpolation and modulo- n circular convolution. (C) New Doppler spectra were generated from the trace with in-house software. The time scale has been removed as it is missing in the original figure. Spectrum adapted from Camfferman et al. [3], licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

intervals proportional to the instantaneous velocity value from the traced velocity curve. Independent white noise was added to the signal to obtain the requested signal-to-noise ratio (SNR) of 15 dB. The resulting Doppler signal was processed and displayed by standard spectrogram methods, with a 35-dB dynamic range. When velocity or time scale was missing, approximate values were used during tracing and the corresponding scale was removed from the regenerated spectrum (Fig. 1). In this way, valuable previous research was used.

Statistical analysis

The average spectrum quality was calculated by study, and the correlation to publication year was assessed with Spearman's correlation coefficient. R software (Version 4.0.2) was used for statistics and statistical figures [13–17].

Results

Search summary and study characteristics

The literature search resulted in 8693 records, which were reduced to 296 after the removal of duplicates and screening of title and abstract

(Fig. 2 [18]). Of these, 117 were excluded because of lack of Doppler spectrum, unfit study population or being reviews. Another study, by Wang et al. [19], could not be obtained and was therefore also excluded. One article by our research group was manually added as it was published the day following the literature search update [20]. Thus, 179 studies were included in the final review (Table S2, online only).

The 179 studies contained 655 Doppler spectra in total. The median number of spectra per study was 2 (range: 1–31). Most studies were either published before 2000 (56%), or had fewer than 50 participants (65%, data missing for 3 studies) (Fig. 3). The median size of the study population was 32 (range: 5–18,194, data missing for three studies), and 150 studies (84%) had fewer than 100 participants. Most study populations were from developed countries (Fig. 3A, 3B; data missing for 3 studies), most frequently the United States ($n = 57$), Germany ($n = 16$), the United Kingdom ($n = 14$), Japan ($n = 10$) and The Netherlands ($n = 11$). However, Figure 3A illustrates worldwide use.

Spectrum quality and descriptive variables

Doppler spectrum quality was assessed with a custom scale (range: 0–4) based on traceability and on whether scales were properly reported (Fig. 3D). In total, 75 spectra from 21 different studies were rated as

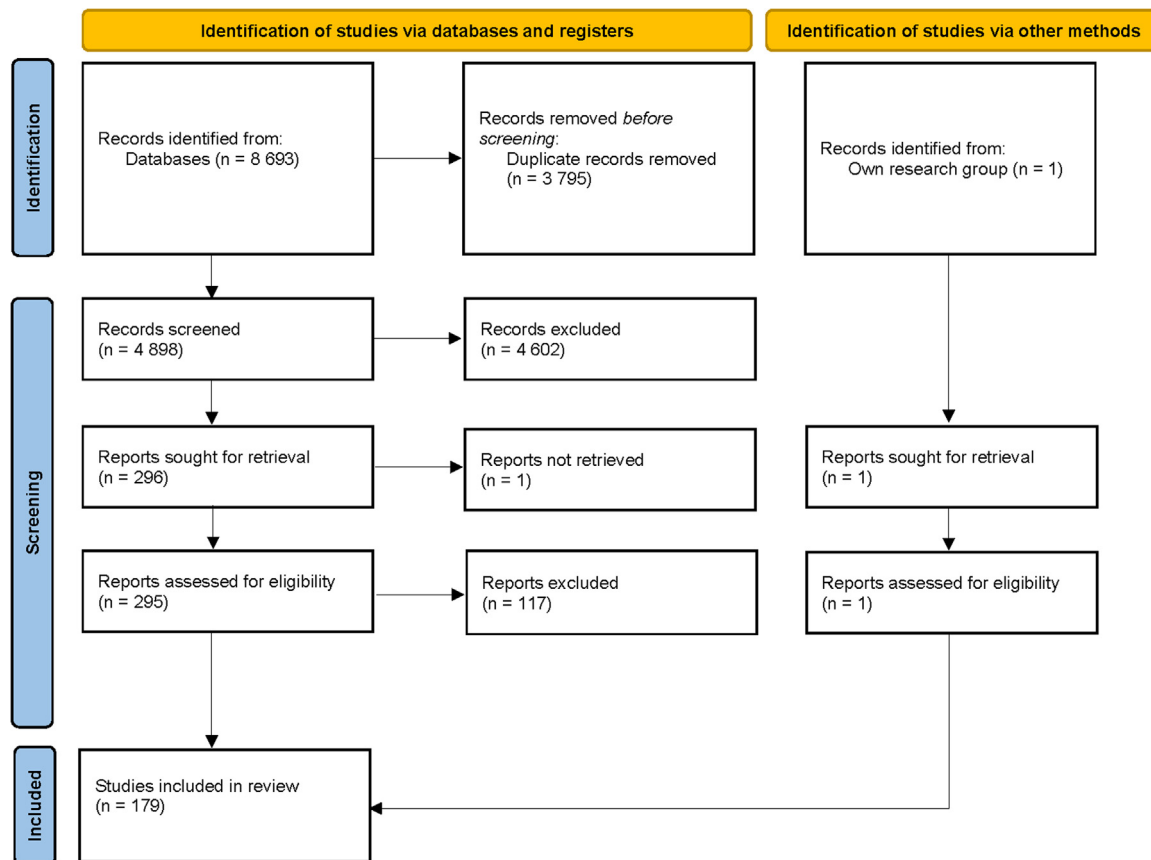


Figure 2. Flowchart of study inclusion. Adapted from Page et al. [18].

excellent (score 4), whereas 47 spectra from 18 studies were reported as a simple trace without time or velocity scales (score 0). The average spectrum quality by paper increased with the year of publication ($r = 0.40$, $p < 0.001$), but most of the increase in quality took place before 1995 (Fig. S2, online only).

The Doppler spectra were quantitatively described by a wide range of variables (Table 3, Fig. 4). The three most common variables were resistance index (RI, 64% of the studies), peak systolic velocity (PSV, 43% of the studies) and end-diastolic velocity (EDV, 39% of the studies) (Fig. 4). A large proportion of studies reported only RI (18%), whereas 10% also included PSV and EDV in addition to RI. Sixteen studies (9%) lacked a description of the spectra in terms of quantitative variables (Table S3, online only). The number of high-intensity transient signals (HITS) in the Doppler spectra represents a distinct kind of variable as it relates to the presence of characteristic high-intensity signals in the Doppler spectrum rather than the Doppler waveform itself [20].

Several uncommon variables, as well as variations of common variables, were identified (Tables 3 and S2). Prior to 1995, what we today know as RI and PI were commonly reported as “PI” (Fig. S3, online only), sometimes—but not always—specified by reference to either Gosling et al. [21] or Pourcelot [22].

Time design of the studies

Most studies employed a repeated-measures ($n = 100$, 56%) or single-measure ($n = 62$, 35%) design (Fig. S1). Only 17 studies (9%) used a longitudinal or heartbeat-for-heartbeat approach, 13 of them with repeated examinations. The classifications are listed in Table S2. The classification was, however, difficult in some cases as the design was either not properly described by the authors or not easily assessed by the classification criteria.

The Doppler spectrum in health and disease

Studies have examined the effects of a wide range of conditions on cerebral Doppler spectra in neonates and infants, including physiological variations ($n = 77$, Table S3), pathology-associated changes ($n = 111$; Table S4, online only) and the impact of medical interventions ($n = 71$; Table S5, online only). Typical spectra from selected, central conditions are provided in Tables 4–6. In terms of number of studies, the most frequently studied conditions were patent ductus arteriosus (PDA, $n = 22$), effect of postnatal age ($n = 17$), hydrocephalus ($n = 16$), asphyxia ($n = 16$), hypoxic–ischemic encephalopathy (HIE, $n = 16$), effect of gestational age ($n = 14$) and extracorporeal membrane oxygenation (ECMO, $n = 12$).

All major cerebral arteries were extensively examined (Table S2). The anterior cerebral artery ($n = 106$, including the pericallosal artery), middle cerebral artery ($n = 75$) and internal carotid artery ($n = 47$) were most frequent, followed by the basilar artery ($n = 21$), posterior cerebral artery ($n = 9$) and vertebral artery ($n = 4$). Three studies examined the lateral striate or lentostriate arteries, two studies the circle of Willis, one study the common carotid artery, one study the pial artery and one study the full brain; 10 studies did not specify artery [20,23–110].

Discussion

This scoping review identified 179 studies spanning four decades and populations from more than 30 countries describing how the Doppler spectrum is affected by a wide range of physiological factors, pathological conditions and medical interventions. Our study complements existing reference works in the field [5–7] by presenting an unbiased list of additional and alternative references. The thorough characterization of the literature offers a detailed overview for researchers and

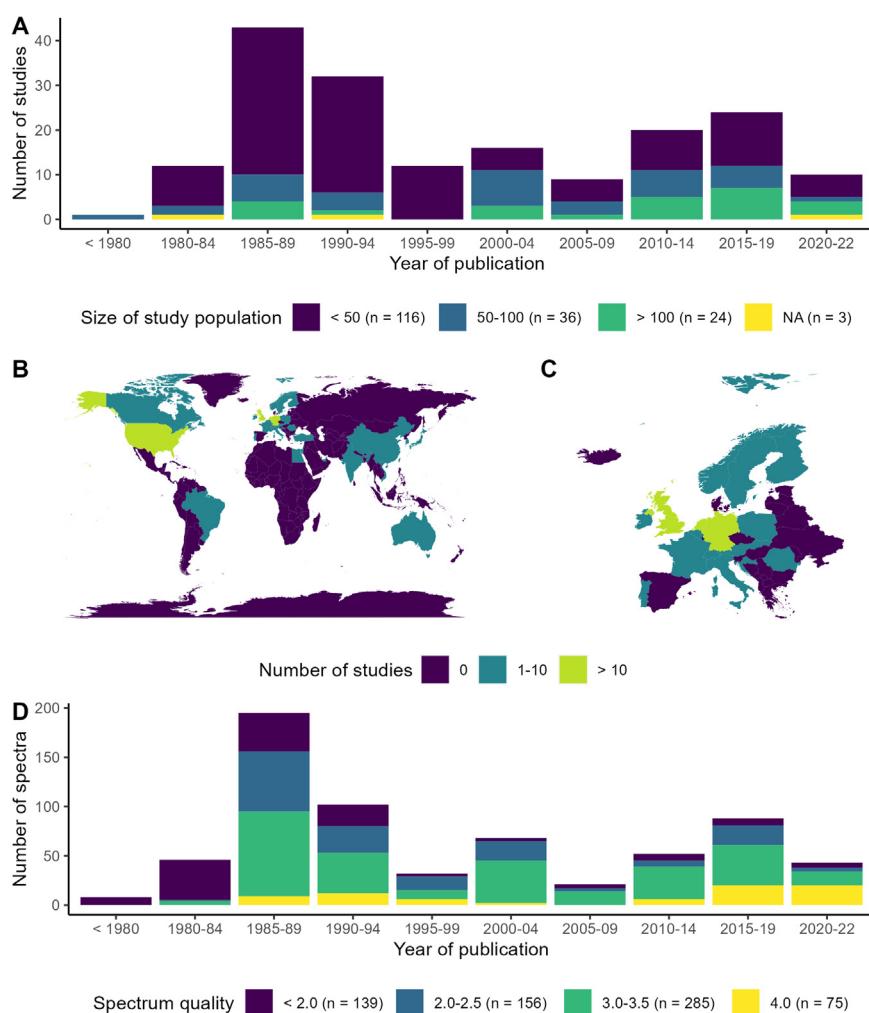


Figure 3. Characteristics of studies on cerebral Doppler waveforms in neonates. (A) Study size by year of publication. n = total number of publications in each group. Data were not available (NA) for three studies. (B) Number of studies conducted in various countries worldwide and in Europe (C), based on the location of the study population. Data are missing for three studies. (D) Spectrum quality by year of publication. The number of spectra reported by five-year span. n = total number of spectra in each group.

clinicians approaching the Doppler spectrum and identifies several areas where systematic reviews and meta-analyses would be useful.

Characteristic Doppler velocity waveforms in infants less than 1 y of age

This article provides the first scoping review of studies reporting Doppler velocity waveforms for infants less than 1 y of age. We have identified studies investigating a wide range of conditions in infants, but four main categories seem to stand out. First, many studies focused on normal physiological properties relating to the infant, such as birth weight, gestational age at birth and postnatal age. Others investigated factors related to the examination itself, such as artery, artery depth and infant head position or behavioral state. A third study category was Doppler spectra related to pathology and disease, both the progression of such conditions and whether Doppler ultrasound could assist the evaluation of diagnosis and prognosis. The fourth and final set of studies examined how medical interventions affect cerebral perfusion in infants, ranging from ECMO and cardiopulmonary bypass to more gentle treatments such as mydriatics and kangaroo mother care. The studies indicate that cerebral Doppler ultrasound can be employed in diverse settings, but interpretation is demanding because of inter-individual variation in the spectrum (Fig. 5).

Physiologic ductus arteriosus closure, or persistent patent ductus arteriosus (PDA), was most frequently studied. The clinical importance of PDA in premature infants is controversial, as induced closure or ligation has failed to improve adverse outcomes [117,118]. Most premature infants eventually experience spontaneous closure [119], and no international consensus has been reached regarding management. There is, however, increased mortality among infants with PDA [120,121], and

Doppler ultrasound reveals higher RI and lower mean velocity in the cerebral arteries of infants with hemodynamically significant PDA [3]. It is thus possible that some infants with PDA will gain from medical intervention and that Doppler ultrasound can assist in the identification of these infants. Currently, few studies have assessed whether longitudinal neurovascular monitoring can improve the care of PDA infants [122], and more studies using (semi-)continuous monitoring, including studies of veins, have been encouraged [3].

The current lack of standardized descriptions of the Doppler spectrum makes it challenging to compare studies precisely. However, standardized terminology for describing peripheral Doppler signals was recently proposed [123]. The Doppler parameters represent attempts to derive numerical characteristics of the curve, and the complexity of the Doppler spectrum has given birth to many such numerical characteristics. A different approach was taken by Evans et al. [30], who used principal component analysis to analyze the Doppler waveform, later combined with compensatory fuzzy neural networks to distinguish healthy from pathological signals [37,38]. Although other approaches have been tested on non-cerebral arteries [37] or were developed in later years [124–127], the research on automatic classification of cerebral ultrasound signals from infants is scarce.

The diastolic portion of the Doppler spectra is most sensitive to hemodynamic changes. Two classifications of cerebral Doppler arterial waveforms have been proposed by Deeg et al. [6, pp.136,209]. The first system reflects the sensitivity of the diastolic portion and divides the flow profiles into (i) normal flow, (ii) increased diastolic flow, (iii) decreased diastolic forward flow, (iv) missing diastolic flow and (v) negative/retrograde diastolic flow. Many conditions, such as asphyxia and PDA, can produce waveforms that fit this system (Table 5). For example,

Table 3
Common parameters used to describe the Doppler spectra

Symbol	Variable	Definition	Also known as
<i>Continuous variables</i>			
Velocities			
V_{\max}	Maximal velocity curve	Calculated from the maximal frequency shift in the Doppler spectrum	
V_{mean}	Mean velocity curve	Calculated from the intensity-weighted mean frequency shifts in the Doppler spectrum	
<i>Variables calculated per heartbeat</i>			
Velocities			
TAV_{\max}	Time-averaged maximum velocity (cm/s)	Average of V_{\max} over one heartbeat	TAV, TAM, TAMX, TMFV
TAV_{mean}	Time-averaged mean velocity (cm/s)	Average of V_{mean} over one heartbeat	TMVF, TAMn, V_m , V , average velocity (AV), mean flow velocity (MFV)
AUVC	Area under the velocity curve (cm)	Area under the curve V_{\max} or V_{mean}	AUC
EDV	End-diastolic velocity (cm/s)	Of V_{\max} curve	V_{eds} , end-diastolic flow velocity (EDFV)
PSV	Peak systolic velocity (cm/s)	Of V_{\max} curve	V_{ps} , peak systolic flow velocity (PSFV), maximal systolic velocity, systolic velocity
Indices			
RI	Resistance index	$(\text{PSV} - \text{EDV})/\text{PSV}$	Pourcelot's index, resistive index, resistivity index
PI	Pulsatility index	$(\text{PSV} - \text{EDV})/TAV$	Gosling's index, resistance index (RI)
<i>Less frequently used variables</i>			
t_a	Acceleration time	Time from onset of ejection to PSV	
ESV	End-systolic velocity		
FIP	Frequency index profile		
SIP	Specific index of pulsatility		
VAS	Velocity acceleration slope	$(\text{PSV} - \text{EDV}_{\text{previous heartbeat}})/t_a$	Rise slope
LSDS	Late systolic deceleration slope		Fall slope
APHT	Acceleration pressure half-time		
DPHT	Deceleration pressure half-time		
<i>Variables relating to speckle patterns</i>			
HITS	(Number of) high-intensity transient signals		Microembolic signals (MES)
EBR	Embolus-to-blood ratio		

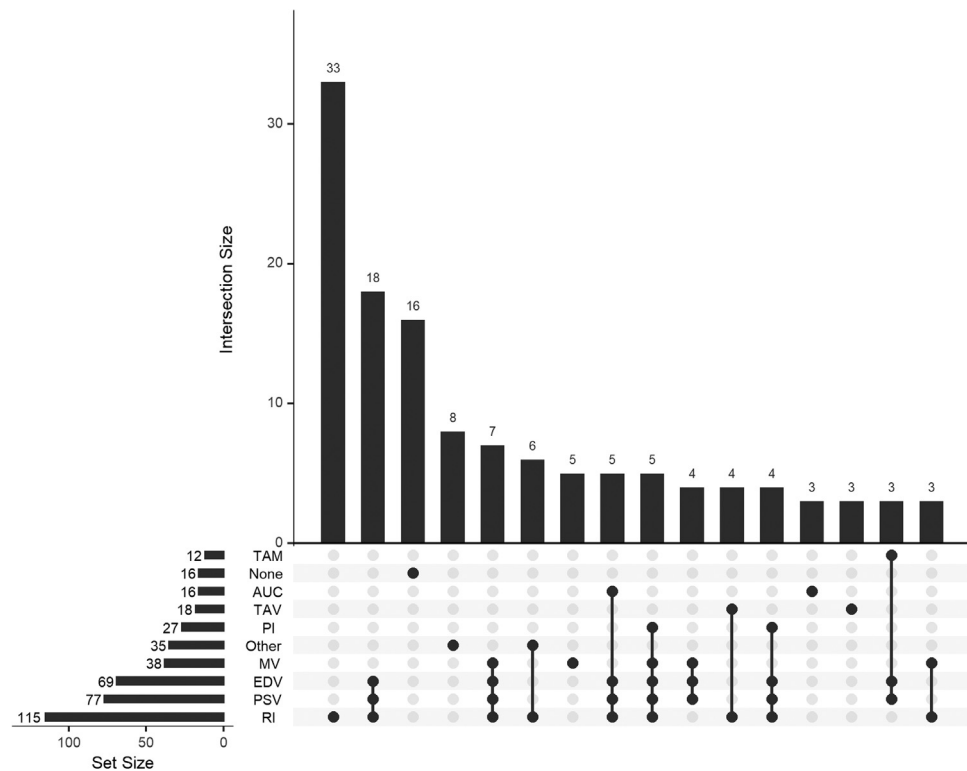
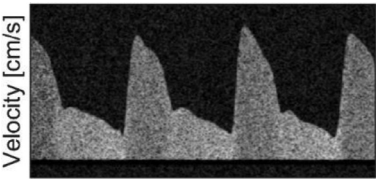
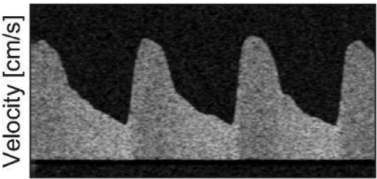
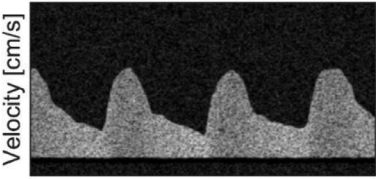
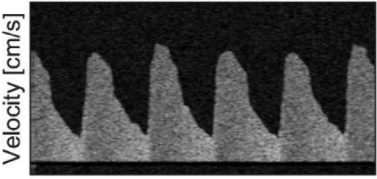
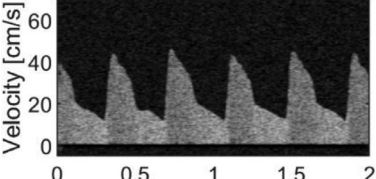
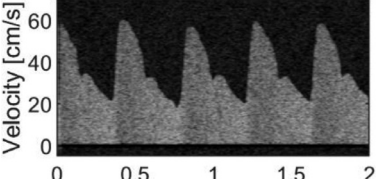


Figure 4. Most frequently reported variables describing the Doppler spectrum. Set size is the number of papers reporting the corresponding variable, whereas intersection size is the number of papers reporting various combinations of variables. Most frequent were papers reporting only resistance index (RI, $n = 33$), followed by the combination of peak systolic velocity (PSV), end-diastolic velocity (EDV) and RI ($n = 18$).

Table 4
Characteristic Doppler waveforms in healthy infants

Waveform		Reference ^a
 <p>Velocity [cm/s]</p> <p>Time [s]</p> <p>Proximal section of the anterior cerebral artery. Figure adopted from Archer et al. [23].</p>	 <p>Velocity [cm/s]</p> <p>Time [s]</p> <p>Distal section of the anterior cerebral artery. Figure adopted from Archer et al. [23].</p>	Archer et al. [23] Forster et al. [24] Fukuda et al. [25] Maesel et al. [26]
 <p>Velocity [cm/s]</p> <p>Time [s]</p> <p>Pericallosal artery (branching of the anterior cerebral artery). Figure adopted from Archer et al. [23].</p>	 <p>Velocity [cm/s]</p> <p>Time [s]</p> <p>Posterior cerebral artery. Figure adopted from Fukuda et al. [25]</p>	
 <p>Velocity [cm/s]</p> <p>Time [s]</p> <p>Middle cerebral artery, 20 min after birth. Figure adopted from Maesel et al. [26].</p>	 <p>Velocity [cm/s]</p> <p>Time [s]</p> <p>Middle cerebral artery, approximately 33 h after birth. Figure adopted from Forster et al. [24].</p>	

^a An overview of studies presenting data on the respective waveforms is provided in this column.

altered diastolic flow following asphyxia is related to vasoparalysis and loss of autoregulation, in addition to molecular stress responses and changes in metabolism, so that both increase (“luxury perfusion”) and decrease can be seen depending on the systemic blood pressure [128,129]. In contrast, PDA causes decreased diastolic flow by left-to-right shunting (“diastolic steal”) through an open ductus arteriosus [130]. A different diastolic phenomenon, reported by Rupprecht et al. [58], is increasing flow during diastole (“Inverted diastolic flow” in Table 5). This phenomenon is probably caused by increased venous pressure and is included in the second system proposed by Deeg et al. [6, p. 209]: (i) normal flow profile, (ii) inverted flow profile, (iii) systolic and diastolic increased flow profile and (iv) negative diastolic flow profile. In contrast to the diastolic portion of the Doppler signal, the systolic portion is less affected by intracranial factors but reflects systemic parameters such as cardiac performance, volume status and distribution and changes in larger arteries. The systolic portion of the waveform reveals variation in parameters such as peak velocity, deceleration and acceleration times, peak sharpness, catacrotic shoulder and dicrotic notch (Fig. 5).

Various conditions can produce similar changes in the spectrum, and a condition can typically cause various changes in the spectrum. An abnormal Doppler spectrum is, however, indicative of ongoing pathological processes regardless of etiology. Similarly, a specific condition can involve different etiologies, stages and pathological processes, which contribute to diversity in both hemodynamic disturbance and alteration of the Doppler spectra. This makes it difficult to use simple cutoff values of indices such as RI to guide clinical decisions [3]. Several studies described distinct disease stages or grades with characteristic Doppler spectra for each stage/grade [6,27,29,131]. These observations suggest that repeated Doppler examinations may be more useful than a single

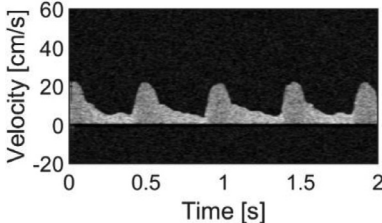
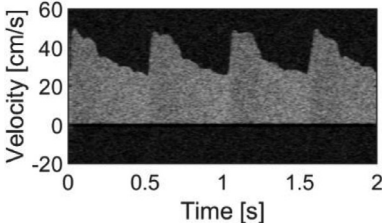
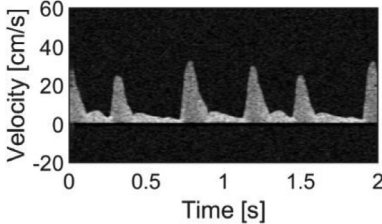
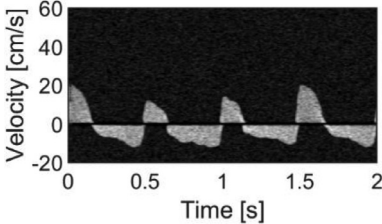
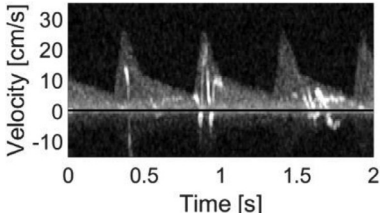
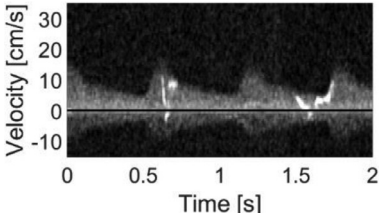
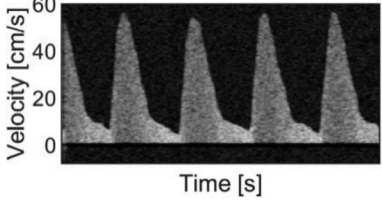
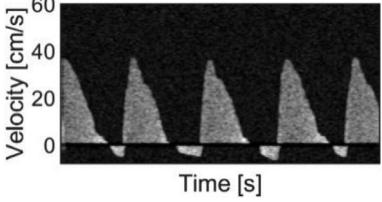
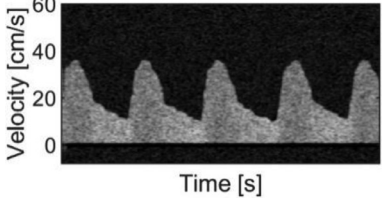
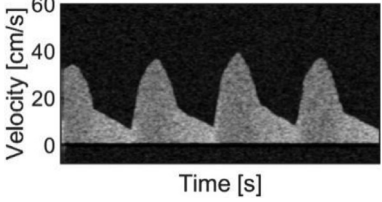
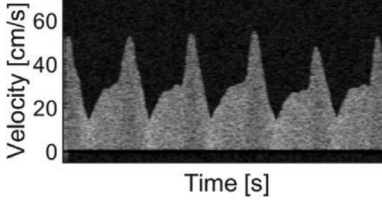
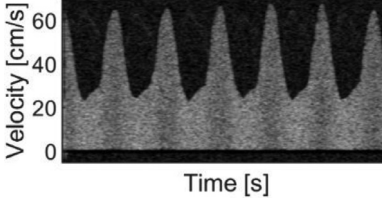
snapshot of the cerebral perfusion to assess the degree of distress as well as progression of disease.

Single Doppler measurements (“snapshots”) versus long-term monitoring using transcranial/transfontanellar Doppler

Ultrasound is unique among medical imaging modalities with respect to time resolution and monitoring capabilities, and many of the included studies used these properties by applying repeated or longitudinal study designs. Most studies focused on “snapshots” where Doppler parameters were averaged over the recording. This approach has multiple advantages: Doppler parameters are easily calculated, reported and communicated, and can be subjected to common statistical analyses. Moreover, repeated “snapshot” examinations can account for the significant inter-individual differences in blood flow, which otherwise make Doppler measurements difficult to interpret [3,4]. Mapping the intra-individual variability of the Doppler spectrum over time is important as some degree of flow fluctuation is normal in both term and preterm infants and may render “snapshots” unrepresentative [132,133].

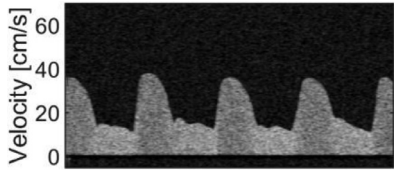
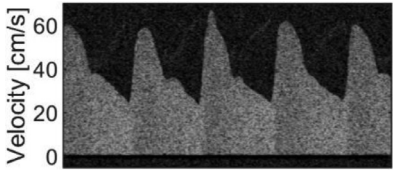
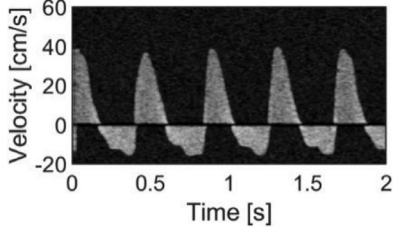
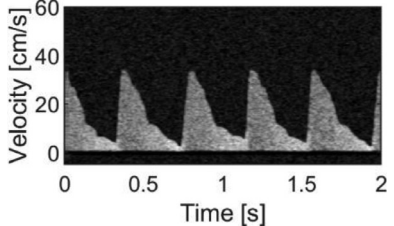
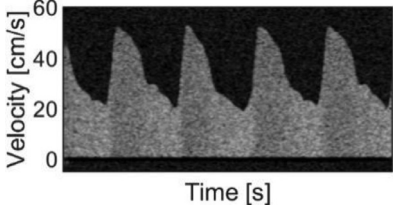
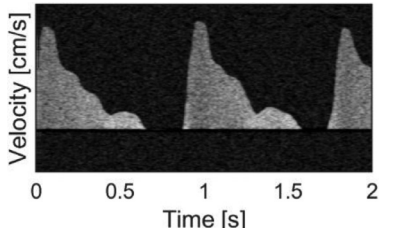
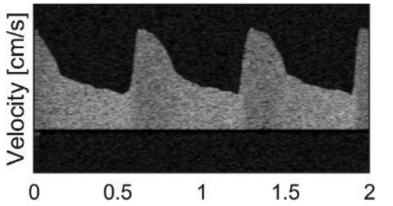
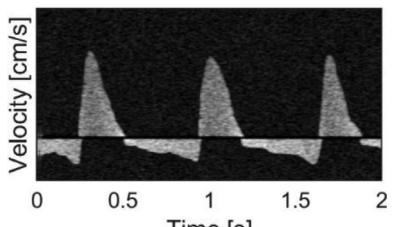
Longitudinal ultrasound monitoring has been sparsely used but can add valuable information and complement “snapshot” measurements. Our group and other research groups have found that combining longitudinal time series analysis with Doppler parameters averaged over given time intervals can be useful in analyzing responses and dynamic phenomena [134,135]. In addition, prolonged monitoring is required to detect low-frequency oscillations in blood flow that are otherwise invisible in short-term recordings [12]. Prolonged ultrasound exposure is safe within recommended limits [136,137] and longitudinal monitoring with Doppler ultrasound is achievable within these limits [12,20]. However, care must be taken when designing protocols to ensure safety for

Table 5
Characteristic Doppler waveforms for selected medical conditions

Waveform		Reference
<i>Asphyxia and hypoxic ischemic encephalopathy (HIE)</i>		
		Bada et al. [27] D'Orey et al. [28] Deeg et al. [29] Evans et al. [30] Julkunen et al. [31] Kirimli et al. [32] Lin et al. [33] Molicki et al. [34] Nishimaki et al. [35] Sato et al. [36] Seker et al. [37,38] Sevely et al. [39] Shen et al. [40] Stark et al. [41] Wazir et al. [42]
Stage I. Normal waveform.	Stage II. Increased flow.	
		
Stage IIIA. Decreased DF.	Stage IIIB. Bi-directional flow with retrograde DF.	
Figures adopted from Deeg et al. [29].		
<i>High-intensity transient signals (microembolic signals)</i>		
		Leth-Olsen et al. [20]
The figures depict high-intensity transient signals (HITS) during cardiac surgery. Examples kindly provided by Martin Leth-Olsen.		
<i>Hydrocephalus</i>		
		Ahmad et al. [43] Couture et al. [44] De Oliveira et al. [45,46] Dirrichs et al. [47] El-Shafei et al. [48] Fischer et al. [49] Goh et al. [50] Grant et al. [51] Kolarovszki et al. [52] Nishimaki et al. [53] Riggo et al. [54] Seibert et al. [55] Sevely et al. [39] Svrckova et al. [56] Westra et al. [57]
ACA of premature neonate with hydrocephalus. Decreased DF and increased pulsatility.	Positive pressure provocation test (RI > 0.90 or RI > 25% increased from baseline).	
		
After drainage.	After drainage, negative pressure provocation test	
Figures adapted from Kolarovszki et al. [52].		
<i>Inverted diastolic flow</i>		
		Rupprecht et al. [58]
Vertebral artery. Two-day-old with co-arcuation of the aorta and right aortic arch.	ACA. After the Senning procedure for D-transposition of the great arteries. One-year-old.	
Figures adapted from Rupprecht et al. [58].		

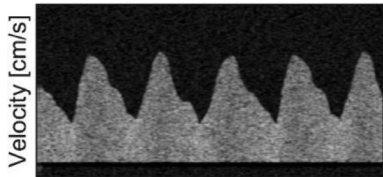
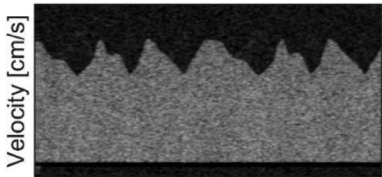
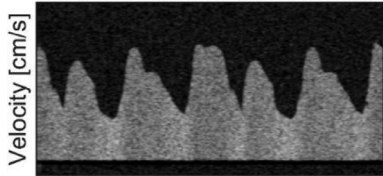
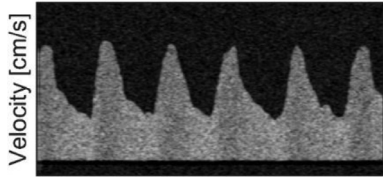
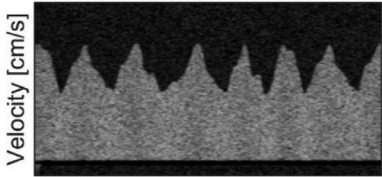
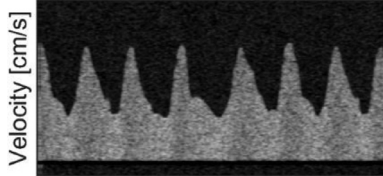
(continued)

Table 5 (Continued)

Waveform		Reference
<i>Neonatal sepsis: Early onset</i>		
		
MCA. Increased flow and decreased pulsatility.	ICA. Increased flow, especially in diastole, and decreased pulsatility.	
Figures adapted from Ratnaparkhi et al. [60].		
<i>Neonatal sepsis: Late onset</i>		
		Yengkhom et al. [61]
Retrograde DF. Figure adapted from Yengkhom et al. [61].		
<i>Patent ductus arteriosus (PDA)</i>		
		Benders et al. [62] D'Orey et al. [63] Ichihashi et al. [64] Keusters et al. [65] Lipman et al. [66] Lundell et al. [67,68] Martin et al. [69] Mellander et al. [70] Mullaart et al. [71] Perlman et al. [72] Rodriguez et al. [73] Saliba et al. [74] Seibert et al. [55] Sevely et al. [39] Snider [75] Sonesson et al. [76] Van Bel et al. [77–79] Wright et al. [80] Wu et al. [81]
Subclinical PDA in term neonate. Decreased flow, especially in diastole. Figure adapted from Wright et al. [80].	The infant to the left after closure. Normalized flow. Figure adapted from Wright et al. [80]	
		
Hemodynamically significant PDA in preterm. DF → zero. Figure adapted from Martin et al. [69]	The infant to the left after closure. Normalized flow. Figure adapted from Martin et al. [69]	
		
Hemodynamically significant PDA in preterm. Retrograde DF/ductal steal. Figure adapted from Martin et al. [69].		

(continued)

Table 5 (Continued)

Waveform		Reference
<i>Pneumothorax</i>		
		Hill et al. [82]
Time [s] Normal flow before pneumothorax.	Time [s] During pneumothorax. Increased flow, especially in diastole, and decreased pulsatility.	
		
Time [s] Normalisation of flow after the pneumothorax is resolved. Figures adapted from Hill et al. [82]		
<i>Seizure</i>		
		Perlman and Volpe [83]
Time [s] Before seizure, normal flow.	Time [s] During seizure. Increased DF and decreased pulsatility.	
		
Time [s] Five minutes after cessation of seizure. Figures adapted from Perlman and Volpe [83].		

ACA, anterior cerebral artery; DF, diastolic flow; MCA, middle cerebral artery; PDA, patent ductus arteriosus.

the patients, and the general recommendation is to keep exposure *as low as reasonably achievable* (ALARA principle).

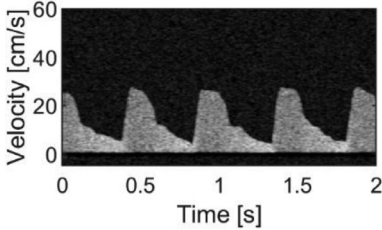
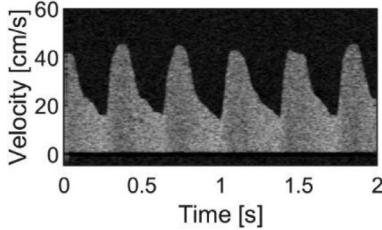
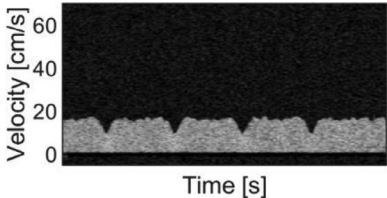
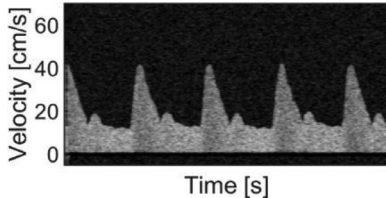
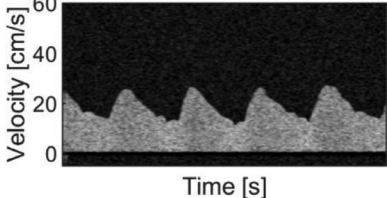
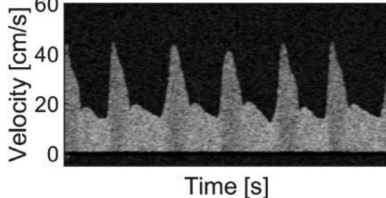
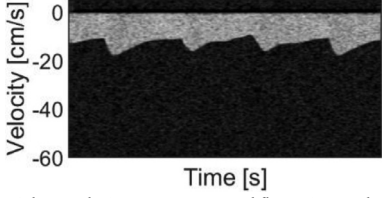
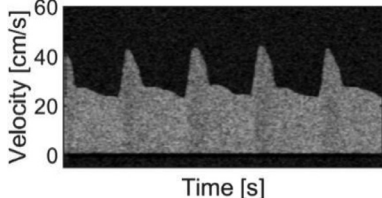
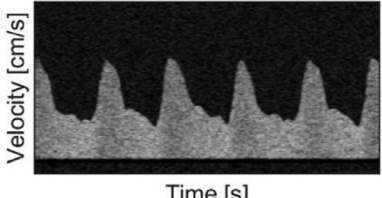
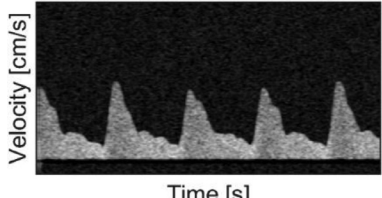
Future research

Technological innovations involving Doppler ultrasound continue to emerge, providing new avenues of research. Ultrafast Doppler ultrasound is a technique used to collect quantitative Doppler data from a large region of interest and create a 2-D map of the blood flow of the region. A Doppler spectrum can then be produced for each point on the map. The technique offers exciting possibilities for bedside visualization of blood flow velocities and resistance mapped over the whole brain with high resolution and in real time and has been used with success in neonates [106,138]. The high temporal and spatial resolution and the high sensitivity of ultrafast Doppler ultrasound have made it possible to assess global and local changes in perfusion in response to changes in cerebral activity. Demene et al. [139,140] reported that bedside functional ultrasound is feasible in human neonates, and Baranger et al. [141] used this technique to map deep brain connectivity at high spatio-temporal resolution (<250 μm, 1-s scale). The potential of functional

ultrasound monitoring as a bedside alternative to functional magnetic resonance imaging (fMRI) bears promise of exciting possibilities for both pediatricians and researchers. Another innovation is the NeoDoppler ultrasound system consisting of a coin-shaped probe, a scanner and software [12]. The probe can be fixed to the anterior fontanelle and used for longitudinal monitoring of cerebral blood flow. Although similar systems have previously been employed in research settings [134,142,143], the NeoDoppler system is also designed for use in the clinic. Combining longitudinal Doppler ultrasound with other modalities of neuromonitoring such as electroencephalography (EEG) and near-infrared spectroscopy (NIRS) may provide a way to gain a more complete understanding of the pathophysiology of neonatal brain injury.

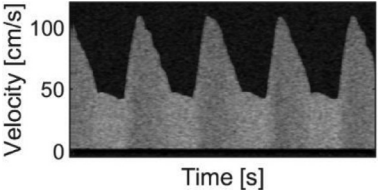
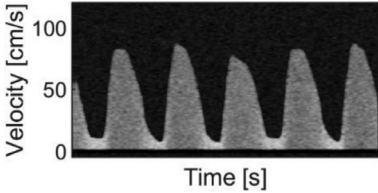
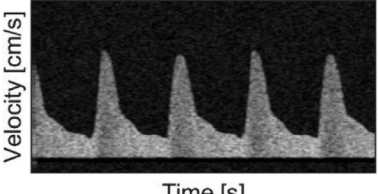
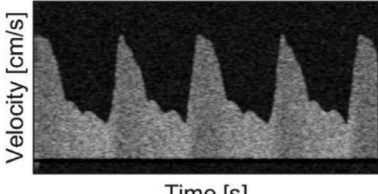
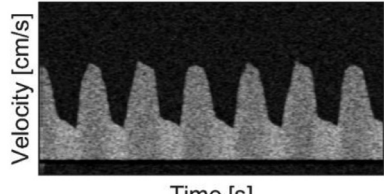
Future Doppler studies would benefit from a more standardized and precise terminology. A consensus statement has recently been made that includes recommendations for terms to describe peripheral Doppler spectra [123]. However, the recommended terms are broad and lack modifier terms for the diastolic alterations seen in the cerebral Doppler spectra of infants with various conditions. The problem of terminology also extends to quantitative descriptors of the Doppler spectrum. In Doppler ultrasonography, several variables, as listed in Table 3, can be

Table 6
Characteristic Doppler waveforms for selected medical interventions

Waveform	Reference
<p><i>Blood transfusion because of anemia</i></p> <div></div> <p>Before tranfusion, anemic preterm infant. Compensatory increased flow. Figures adapted from Ramaekers et al. [84].</p> <p>The same infant as to the left, 24 hours after infusion. Normalized flow.</p>	Ramaekers et al. [84]
<p><i>Cardiopulmonary bypass (CPB)</i></p> <div></div> <p>Before CPB but after induction of anesthesia, pericallosal artery. After CPB but before sternum closure, same infant and location. Figures adapted from Park et al. [88].</p> <p>During CPB, same infant and location.</p>	Abdul-Khaliq et al. [85] Astudillo et al. [86] Jonassen et al. [87] Park et al. [88] Su et al. [89]
<p><i>Extracorporeal membrane oxygenation (ECMO)</i></p> <div></div> <p>Before ECMO, pericallosal artery. Figure adapted from Taylor et al. [97]. ECMO for 48 hours, pericallosal artery. Reduced pulsatility. Figure adapted from Taylor et al. [97].</p> <div></div> <p>Left ICA during ECMO. Figure adapted from Lohrer et al. [93]. Right ICA during ECMO, reversed flow. Figure adapted from Lohrer et al. [93].</p>	Alexander et al. [90] De Mol et al. [91] DeAngelis et al. [92] Lohrer et al. [93] Matsumoto et al. [94] Mitchell et al. [95] Svrckova et al. [56] Taylor et al. [96–98] Weber et al. [99] Zamora et al. [100]
<p><i>Partial plasma exchange because of polycythemia</i></p> <div></div> <p>Before tranfusion, ACA. Decreased DF. Same infant, three hours after tranfusion, ACA. Normalized flow.</p>	Bada et al. [101] Maertzdorf et al. [102] Rosenkrantz et al. [103]

(continued)

Table 6 (Continued)

Waveform	Reference
Figures adapted by Maertzdorf et al. [102].	
<i>Sevoflurane</i>	
	
Awake, MCA. Admitted for elective abdominal or urological surgery.	After induction of anesthesia by inhalation of sevoflurane, steady-state. Decreased DF and increased pulsatility.
Figures adapted from Rhondali et al. [104].	
<i>Therapeutic hypothermia</i>	
	
Normothermia (36°C).	Moderate hypothermia (22°C–35°C). Decreased flow (velocity scale not reported).
	
Deep hypothermia (<18°C). Decreased flow, especially in diastole, and increased pulsatility.	
Figures adapted from Abdul-Khaliq et al. [85].	

ACA, anterior cerebral artery; CPB, cardio-pulmonary bypass; DF, diastolic flow; ECMO, extra-corporeal membrane oxygenation; ICA, internal carotid artery; MCA, middle cerebral artery; PDA, patent ductus arteriosus.

calculated per heartbeat, based on a continuous velocity curve, derived from the Doppler spectrum (spectrogram). The continuous velocity curve can be estimated in two different ways: either from the intensity-weighted mean frequency shifts in the Doppler spectrum (V_{mean} in Table 3) or from the maximum velocity (V_{max} in Table 3). The two methods yield similar estimates for the Doppler indices RI and PI, as well as acceleration time, under certain conditions but are not interchangeable [144–147]. V_{max} is most common in the clinic and has some advantages compared with V_{mean} : the envelope can be validated visually, and vessel curvature, clutter and insonation of neighboring vessels have less impact on the estimated velocity. However, the V_{max} envelope can be affected by instrument settings (compression, image scale, gain, filters) and spectral broadening. Spectral broadening comprises at least three components: (i) the velocity distribution of the blood cells in the insonated vessel [148], (ii) transit-time broadening and (iii) local geometrical broadening from the shape of the ultrasound beam [149]. As the velocity distribution in a vessel can be of clinical interest, attempts have been made to remove the two latter sources of spectral broadening [148,150,151]. Spectral broadening has, however, little impact on RI and PI as the broadening is proportional to velocity. Another approach to calculating mean velocity was reported by Vu et al. [152] who calculated mean velocity per heartbeat as $(\text{PSV} + \text{EDV})/4$. Variations also exist in the definition of RI. For example, some define $\text{RI} = 1.0$ when diastolic flow is retrograde so that $\text{RI} \leq 1.0$ by definition [69], whereas others have used *peak*-diastolic velocity instead of *end*-diastolic velocity for calculating RI [153]. In addition, the terms *pulsatility index* and *resistance index* were often interchanged before 1995 so that the reader must pay attention to which definition is used.

There is a need for improved methods to analyze Doppler recordings that conserve the complexity of the Doppler waveform, can use data from longitudinal monitoring and yet produce results that are reproducible, reliable, interpretable and easily communicated. One possible approach may be to combine different Doppler parameters, such as velocity indices and time measures, and use multivariate statistics to investigate the impact of various aspects of the Doppler waveform. Research on photoplethysmograms and pulse waves has generated several parameters with clinical correlates that may be translated to Doppler waveforms, including the interest in the derivatives of the waveform [154]. Pulse waves and Doppler waveforms share the challenge of diverse morphology and studies in adults have identified 128 interesting features (morphological clustering and analysis of intracranial pulse [MOCAIP] metrics) that include amplitudes, delays, slopes, curvatures and their ratios [155–157]. As some features may be unavailable because of disease or other factors, finding alternative methods for automatic classification of waveforms is an active field of research [e.g., 158–160]. Thus, the available technology is rapidly developing which enables exciting possibilities for further research. Dedication to open science with sharing of software and source code is, however, a prerequisite for broader use of these techniques.

More standardized terminology and research protocols for studies on cerebral Doppler ultrasound in infants are warranted. Study protocols should ideally contain precise instructions on where the Doppler signals should be recorded, how Doppler parameters are to be calculated and reported, including the number of cycles, and which parameters and statistics are to be reported. It is possible that the combined evaluation of multiple parameters would retain more of the information encoded in

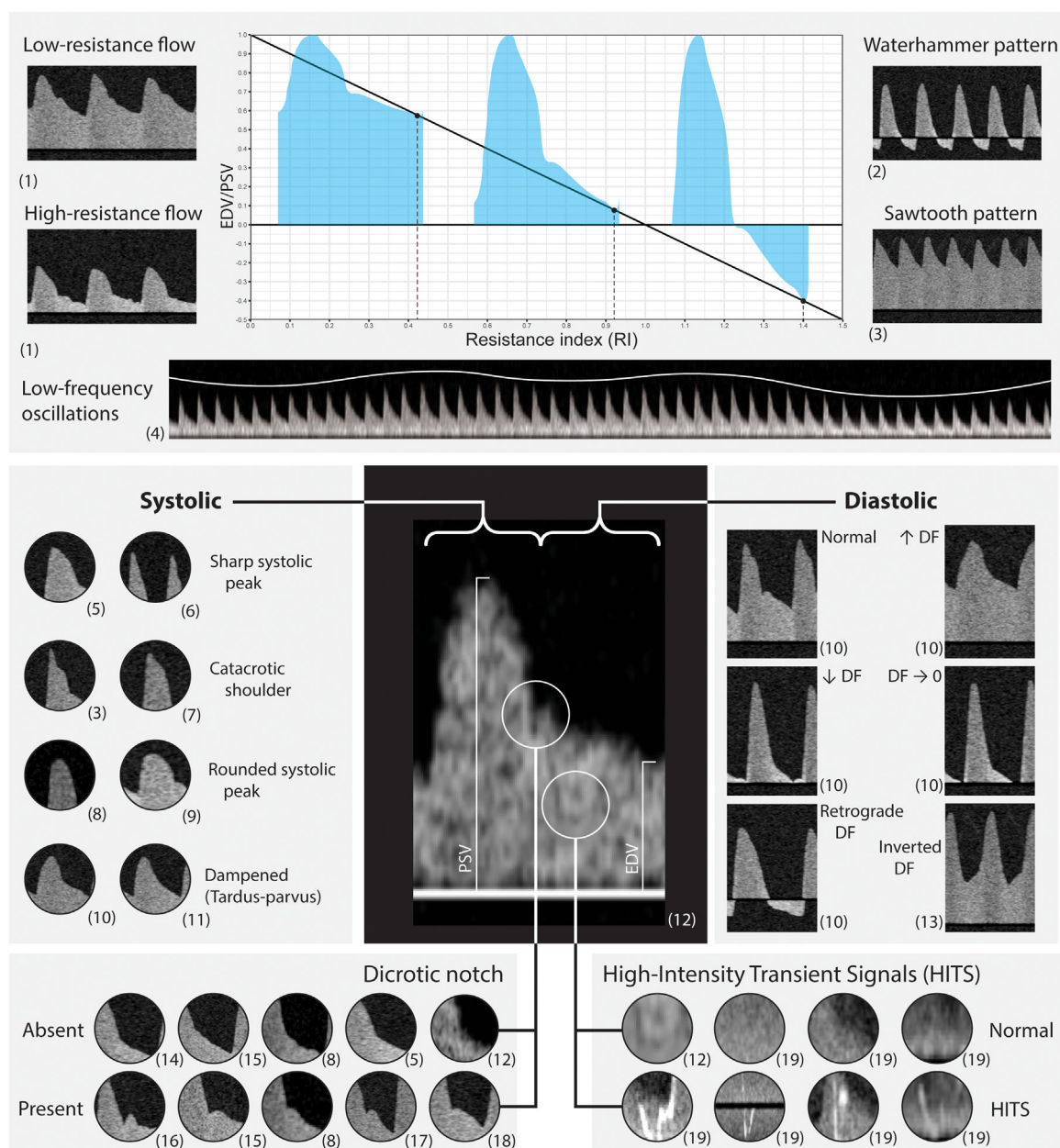


Figure 5. Characteristics of the cerebral Doppler spectrum. The cerebral arteries usually exhibit low resistance with relatively high diastolic flow (DF) velocity. By definition, there is a direct, inverse, linear relationship between the resistance index (RI) and the relative difference between peak systolic (PSV) and end-diastolic flow velocity (EDV). Of note, healthy neonates exhibit oscillating blood flow velocity in addition to the impact of activity and breathing. Other characteristic patterns exist as well, such as the waterhammer and sawtooth patterns. The systolic portion of the Doppler waveform is strongly affected by systemic factors such as cardiac parameters and the condition of larger arteries. In contrast, the diastolic portion of the Doppler waveform is sensitive to cerebral factors such as intracranial pressure and vasodilatation but is also influenced by systemic factors and diastolic steal. The dicotic notch is another feature of the Doppler waveform that may be present in some arteries. Finally, the Doppler spectrum contains information beyond the waveform itself and can display high-transient intensity signals (HITS) that correspond to gaseous or solid emboli in the bloodstream. (1) Adapted from Shen et al. [40]. (2) Adapted from Deeg et al. [29]. (3) Adapted from Liu et al. [111]. (4) Excerpt from Vik et al. [12] licensed under CC BY 4.0. (5) Adapted from Deeg and Rupprecht [112]. (6) Adapted from Huang et al. [113]. (7) Adapted from Venkatesh et al. [114]. (8) Adapted from Couture et al. [44]. (9) Adapted from Stritzke et al. [115]. (10) Adapted from the textbook by Deeg et al. [6]. (11) Adapted from Epelman et al. [116]. (12) Excerpt from Camfferman et al. [3], licensed under CC BY 4.0. (13) Adapted from Rupprecht et al. [58]. (14) Adapted from Kolarovszki et al. [52]. (15) Adapted from Archer et al. [23]. (16) Adapted from Park et al. [88]. (17) Adapted from Forster et al. [24]. (18) Adapted from Maertzdorf et al. [102]. (19) Excerpt from Leth-Olsen et al. [20], licensed under CC BY 4.0. License: <https://creativecommons.org/licenses/by/4.0/>.

the Doppler spectrum and thus provide a more sensitive overview of the infant's hemodynamic state. Standardized terminology and procedures for qualitative descriptions of the Doppler spectra [123] should be adapted to the specific features of the infant [6]. In addition, the impact of the instrument, technique and signal processing must be appreciated; Doppler ultrasound has a tendency to overestimate blood flow velocity, and occasional calibration may be beneficial

[161]. Separate protocols must be developed for studies employing longitudinal monitoring. Such experimental protocols will ensure high quality and low risk, and ease the comparison of studies in the future, as well as lower the barrier of initiating studies on Doppler ultrasound in infants. The latter may encourage more research into the possible clinical benefits of Doppler ultrasound in resource-limited settings [162,163].

Table 7

Suggested items for a transcranial/transfontanellar Doppler ultrasound on toddlers and infants (TC-DUTI) reporting checklist

	Reference
<i>Experimental design and statistics</i>	
<input type="checkbox"/> Number of times participants were examined	
<input type="checkbox"/> Explicit definitions of all reported Doppler indices and parameters	
<input type="checkbox"/> Method used for calculating mean velocity	
<input type="checkbox"/> Number of heartbeats used to calculate average velocities and indices	
<i>Equipment</i>	
<input type="checkbox"/> Brand and model of ultrasound device	[165,166]
<input type="checkbox"/> Whether ultrasound device (or software) was changed during the study	[165]
<input type="checkbox"/> Type and model of transducer	[165,166]
<input type="checkbox"/> Frequency of probe	
<i>Scanning/acquisition procedures</i>	
<input type="checkbox"/> Vessel(s)/vessel segment(s)/anatomical structure(s) studied	[165]
<input type="checkbox"/> How structures were identified (relation to landmarks or color mode image)	
<input type="checkbox"/> Acoustic window used	
<input type="checkbox"/> Approximate angle between vessel and probe direction	
<input type="radio"/> <i>Optional:</i> Depth of sampling volume	
<input type="checkbox"/> Whether probe moved during examination or not	
<input type="checkbox"/> On which side were structures studied? (left/right/both)	
<input type="checkbox"/> Rationale for choosing this/these vessel(s)	[165]
<input type="checkbox"/> Patient position (e.g., prone, supine)	[165,166]
<input type="checkbox"/> Head position (midline/tiled left/right, extended/flexed)	
<input type="checkbox"/> Head position relative to heart	
<input type="checkbox"/> Number of sonographers	[165]
<input type="checkbox"/> In longitudinal studies, whether the same sonographer scanned the same patient at each assessment	[165]
<input type="radio"/> <i>Optional:</i> Information on experience of the sonographer(s) and reader(s) (e.g., numbers of scans performed, certification, qualification)	
<input type="checkbox"/> Whether clinical information on the participant was available to sonographer before or during examination or not. Procedures for blinding of sonographers and participants	[165,166]
<input type="checkbox"/> Duration of ultrasound examination when relevant for the study question	[165]
<input type="radio"/> <i>Optional:</i> Whether ambient conditions (e.g., temperature, time of day) were kept stable during the study	[165]
<input type="radio"/> <i>Optional:</i> Potential confounding factors	[165]
<input type="checkbox"/> Maternal factors such as exercise, alcohol, caffeine, smoking	
<input type="checkbox"/> Factors relating to the infant such as medication (e.g., morphine, inotropics), respiratory support, PaCO ₂ , etc	
<i>Ultrasound settings</i>	
<input type="checkbox"/> Whether angle correction was applied or not	
<input type="radio"/> <i>Optional:</i> Envelope detection algorithm	
<i>Figures</i>	
<input type="checkbox"/> Information identifying patient is deleted	[165]
<input type="checkbox"/> Figures match the content of the manuscript	[165]
<input type="checkbox"/> Quality of the figures is adequate	[165]
→ If the figure contains a Doppler spectrum	
<input type="checkbox"/> The time scale is clearly visible.	
<input type="checkbox"/> The velocity scale is clearly visible.	
<input type="checkbox"/> The gain is adjusted so that the spectrum is easily traceable.	
<input type="checkbox"/> Low velocities are not removed by wall filtering.	
<input type="checkbox"/> Relevant clinical information is given about the examined subject (gestational/postnatal age, vessel, condition, etc.).	

Until consensus can be reached on terminology and research protocols, we recommend precise and comprehensive reporting of methodology and results. Our literature search did not contain any reporting checklist for transcranial/transfontanellar Doppler ultrasound studies of young children, and this scoping review has identified several elements that are important to ensure the clarity and unambiguity of study results. Further, for published Doppler spectra to be able to inform clinical practice, sufficient quality of the figures is necessary, as is information on the examined patients. The development of a reporting checklist is an international effort requiring a systematic approach [164]. Pending such an initiative, we have suggested variables for reporting in Table 7 that may assist researchers during writing to remember which details are useful for reproducibility and clinical utility [165,166].

Strengths and limitations

Strengths of this review include a pre-registered protocol, objective yet liberal inclusion criteria and no limitations on publication date. The

study was designed and performed by a cross-disciplinary team comprising clinicians, technologists and a senior research librarian. Some deviations from the pre-registered protocol [9] were necessary because of the large number of relevant studies identified by the systematic search. Venous waveforms were excluded in the current review as described in the pre-registered protocol and may be an interesting topic for a separate review. To help prioritize the identified spectra, we devised a custom quality scale. However, the search strategy and criteria for inclusion and exclusion were kept as originally planned to avoid bias in study selection. In contrast to systematic reviews and meta-analyses, scoping reviews do not aim to assess the quality of evidence or critically extract findings from them [8,167]. Thus, no critical appraisal was conducted. The exclusion of non-English papers may have led to the omission of relevant studies and may also have contributed to fewer studies from non-Western populations (Fig. S1). The age limitation was important to isolate findings that are characteristic of younger infants but also implied that several articles were excluded as they studied only older children. For example, hypercapnia is an important clinical condition and pCO₂ is

an important regulator of cerebral blood flow but spectra in patients with hypo- and hypercapnia were only found for older age groups [e.g., 168]. Some articles with longitudinal monitoring were excluded as the Doppler spectra were not interpretable [e.g., 132,133]. A single author assessed the studies, increasing the probability of bias and errors, whereas uncertain studies were discussed among authors. Another important limitation of the article is that selecting characteristic waveforms from various pathological conditions is challenging because of differences in how pathology presents and variations in the severity and comorbidity among the study populations. The extraction and regeneration of spectra aimed to compensate for differences in presentation but may also have contributed to loss of details. Most articles did not focus on the spectrum and merely provided them for illustration. Thus, the spectra in Table 5 are neither definitive nor exclusive for the given conditions.

Conclusions

The Doppler spectrum from cerebral arteries provides comprehensive and real-time information on the hemodynamic state, especially in infants with open fontanelles. Standardized terminology and systematic descriptions of the cerebral Doppler spectrum are still missing, despite four decades of research and widespread clinical use. Nevertheless, a rich literature exists on the cerebral Doppler spectrum in infants, reporting primarily Doppler indices and parameters, that warrants a systematic review of specific conditions to improve clinical utility. Few studies seem to have made use of the possibility of longitudinal monitoring with Doppler ultrasound. There is a need for more standardized terminology and protocols that include how Doppler parameters should be calculated and how Doppler spectra should be described. As a temporary measure, we suggest elements for a potential reporting checklist for transcranial/transfontanelar Doppler ultrasound in infants.

Conflict of interest

The Norwegian University of Science and Technology (NTNU)/St. Olav's Hospital and Trondheim University Hospital may benefit financially from a commercialization of the NeoDoppler used for cerebral Doppler monitoring in infants through future possible intellectual properties. H.T. and S.A.N. are co-inventors of NeoDoppler. S.A.N. is a board member of CIMON Medical. H.T. and S.A.N. have part-time positions and are among shareholders in CIMON Medical, the company responsible for commercialization of NeoDoppler. J.D., S.A.P. and A.H.J. declare no conflicts of interest.

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Data availability statement

A complete overview of the articles included in this study can be found in Table S2. Further inquiries can be directed to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ultrasmedbio.2022.12.007.

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