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REVIEW

Brain ultrasonography: methodology, basic and advanced principles and clinical applications. A narrative review

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Abstract

Brain ultrasonography can be used to evaluate cerebral anatomy and pathology, as well as cerebral circulation through analysis of blood flow velocities. Transcranial colour-coded duplex sonography is a generally safe, repeatable, non-invasive, bedside technique that has a strong potential in neurocritical care patients in many clinical scenarios, including traumatic brain injury, aneurysmal subarachnoid haemorrhage, hydrocephalus, and the diagnosis of cerebral circulatory arrest. Furthermore, the clinical applications of this technique may extend to different settings, including the general intensive care unit and the emergency department. Its increasing use reflects a growing interest in non-invasive cerebral and systemic assessment. The aim of this manuscript is to provide an overview of the basic and advanced principles underlying brain ultrasonography, and to review the different techniques and different clinical applications of this approach in the monitoring and treatment of critically ill patients.

Keywords: Brain ultrasonography, Transcranial Doppler, Optic nerve sheath diameter, Neurosonology

Introduction

The use of ultrasound imaging in intensive care and perioperative medicine has increased enormously over the past decades. Brain ultrasonography, used to assess brain parenchyma and cerebral blood flow (CBF), is a generally safe, non-invasive and relatively low-cost neuromonitoring method that is easily applicable at the bedside. Potentially, it could provide crucially important information in the early detection and monitoring of neurological diseases, and to allow bedside assessment of cerebral haemodynamics in critically ill patients.

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It can be applied in a range of settings, including neurointensive and general intensive care units, the operating room and the emergency department. At present, however, brain ultrasonography is not routinely performed in critical care settings. The aim of this review is to provide a brief overview of the physical and anatomical principles underlying brain ultrasonography, and of its potential clinical applications.

The techniques

Basically, two brain ultrasound techniques are currently available: B-mode transcranial colour-coded duplex (TCCD) and transcranial Doppler (TCD) sonography. TCD, introduced in clinical practice approximately 40 years ago [1], identifies the cerebral arteries "blindly", on the basis of the spectral display and standard criteria (including arterial depth, arterial blood flow direction and waveform analysis). It allows assessment and continuous monitoring of CBF velocity, and is thus an excellent technique for use in multimodal brain monitoring and evaluation of basic and advanced parameters. Advanced parameters such as cerebral autoregulation, critical

closing pressure and cerebral compliance can be assessed with TCD, and it can also be used to perform functional tests for evaluating cerebrovascular reactivity [2].

TCCD, which combines colour-coded Doppler vessel representation with bi-dimensional pulsed-wave Doppler ultrasound imaging, has further improved the above technique, allowing direct visualisation and better identification of the cerebral arteries. TCCD is therefore a newer, more technically advanced tool, and it is useful for high-precision freehand real-time scanning and haemodynamic assessment of the brain. While it permits direct visualisation of the brain parenchyma and vessels, it does not allow prolonged continuous monitoring of CBF.

TCCD is usually performed using a 2–2.5-MHz probe that allows visualisation of the main cerebral structures and vessels. On duplex imaging, the midbrain can be identified through the transtemporal window (Fig. 1), and individual arteries of the circle of Willis can be then visualised. Each artery is identified by its depth and blood flow direction in relation to the probe and other visualised arteries. TCCD can provide basic information regarding blood flow velocity (systolic, diastolic and mean values) in an insonated artery, as well as the pulsatility index (PI).

This review focuses mainly on the expanding clinical applications of TCCD. The basic conditions allowing a complete TCCD-based brain examination (including normal anatomy and insonation windows, and normal blood flow velocity patterns of the cerebral arteries), as well as acquisition techniques and interpretation of images, are described in Figs. 1 and 2 and electronic supplementalmaterial (ESM1a–e). Basic and advanced TCD-derived parameters are described in detail in ESM2.

Clinical applications

Table 1 summarises all the clinical applications of brain ultrasonography. Below, we analyse the most common ones in the neurocritical care, general intensivecare unit (ICU), emergency department and prehospital medicine settings.

Brain ultrasonography in neurocritical care

Brain ultrasonography can be used in a wide range of clinical applications in neurocritical care, and the main ones are listed below. In general, although we recommend implementation of this technique in clinical practice, we also suggest that it should not replace invasive neuromonitoring techniques [such as invasive intracranial pressure (ICP) monitoring] or substitute diagnostic tools such as computed tomography (CT) or magnetic resonance imaging (MRI).

Take-home message

Brain ultrasonography enables assessment of the main structures of the brain, including the parenchyma and major cerebral vessels.

Brain ultrasonography can be performed using commonly used ultrasound systems, through four main acoustic windows (transtemporal, occipital, submandibular and transorbital).

Brain ultrasonography can be used for rapid bedside assessment of pathological changes in neurocritically ill patients, allowing, for example, evaluation of intracerebral haematomas, estimation of raised intracranial pressure, and detection of midline shift and intracranial masses.

Brain ultrasonography is not used exclusively in neurocritical care; clinical applications have been described in different settings, including general intensive care and the emergency department.

Intracranial haematomas

TCCD can identify and differentiate between intracranial haematomas and ischaemic strokes, with haematomas being hyperechogenic and ischaemic lesions hypoechogenic [1, 2]. In a cohort of 151 patients hospitalised with acute neurological deficits, TCCD, in comparison with CT, proved able to correctly detect the presence of intracranial haemorrhage or ischaemic stroke (Fig. 3) [3]. A poor acoustic window was present in 12% of the patients ($n=18$). In 126 of the remaining 133 patients, brain ultrasonography was concordant with CT findings (haemorrhagic stroke, ischaemic stroke or neither), demonstrating a sensitivity of 94% and a specificity of 95%. TCCD has also been shown to reliably estimate haematoma volume and expansion in patients with hyperacute intracranial haemorrhage (i.e., TCCD performed within 3 h of onset of symptoms). In a cohort of 52 patients eligible for TCCD assessment, 6 had a poor transtemporal acoustic window, and in 8, TCCD was not able to detect the intracranial haemorrhage (due to its small size as measured on CT or its brainstem/cerebellar location). In the 34 patients who underwent TCCD both within 3 h of onset and at 6 h post-admission, the technique showed good correlation with CT for haematoma volume quantification ($r=0.85$; $p=0.022$) and for detection of early haematoma expansion ($r=0.78$; $p=0.03$) [4]. We suggest performing daily measurement of the volume of cerebral haematomas for early detection of intracranial haemorrhage expansion.

Hydrocephalus

Cerebrospinal fluid (CSF) is anechoic, whereas the ependymal cells lining the cerebral ventricles are hyperechogenic. The third and lateral ventricles appear as double hyperechogenic lines containing the anechoic CSF. An excellent correlation has been observed between TCCD and CT measurements of the width of the third ventricle ($r=0.83$–0.95), right ($r=0.86$) and left ($r=0.92$) frontal

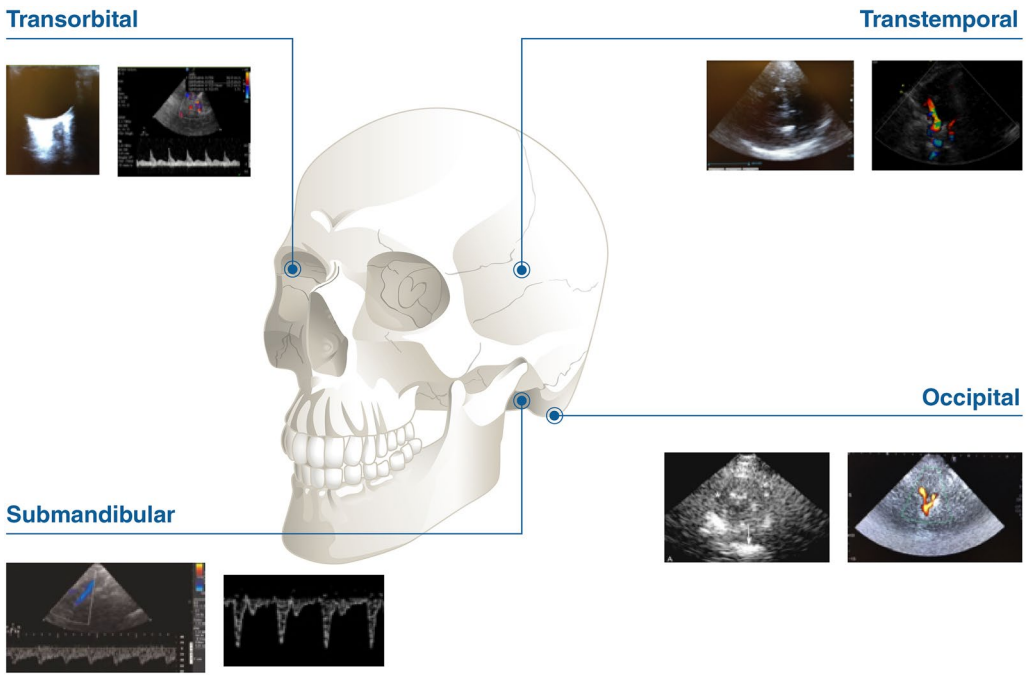

Fig. 1 Acoustic windows for brain insonation. The temporal window extends from the cephalad to the zygomatic arch between the tragus and lateral wall of the orbit. This area at the "temple" can be palpated as a 3–4-cm diameter depressed area in the skull. A phased-array transducer placed in this area allows insonation of basal structures at the base of the brain and the cerebral arteries at the level of the circle of Willis, as shown in the figure. By convention, the index marker points anteriorly towards the eyes. In the suboccipital window, the transducer is placed between the posterior margin of the foramen magnum and the spinous process of the first cervical vertebra, at the midline (or in proximity to it), with the ultrasound beam directed towards the bridge of the nose. The index marker points at the 3 o'clock position. This approach allows visualisation of the foramen magnum and the distal segment of the vertebral arteries (proximal insonation field) and of the basilar artery (distal insonation field). Insonation through the closed eyelid allows visualisation of the ophthalmic artery and the carotid siphon, as well as of the optic nerve sheath. Finally, a submandibular approach can be used to insonate the extra-cranial portion of the internal carotid artery (ICA) to calculate the mean flow velocity ratio between middle cerebral artery and the ICA (Lindegaard index)

horns, and middle part ($r = 0.73$) of the lateral ventricles [5, 6]. In patients with post-haemorrhagic hydrocephalus undergoing an external ventricular drain clamping trial, changes greater than 5.5 mm in the size of the lateral ventricles as assessed by TCCD were correlated with the need to reopen the drain (sensitivity 100%, specificity 83%) [7]. Therefore, ventricular width monitoring with TCCD may, in selected patients and in the hands of experienced operators, represent a valid alternative to CT scans. Finally, TCCD can also visualise the position of the external ventricular drain tip, especially in patients who have been submitted to decompressive craniectomy [8]. TCCD can be useful to assess bedside the diameter of the third ventricle and the position of the external ventricular drain, and to detect early the development of hydrocephalus and ventricular drain displacement.

Brain midline shift

Brain midline shift (MLS) is a life-threatening condition that requires urgent diagnosis and treatment. In 1996, Seidel et al. [9] in ischaemic stroke patients, described a simple sonographic method for determining the presence of MLS: it involved measuring, bilaterally, the distance between the skull and the third ventricle. MLS can be calculated as the difference between the two sides divided by two (Fig. 3, ESM3). Ultrasound MLS correlates well with findings on CT, and it is an early outcome predictor in acute stroke patients [10, 11]. Good agreement between CT and sonography for MLS assessment was recently confirmed in neurocritical care patients (Pearson's correlation coefficient 0.65; $p < 0.001$) [12]. Most study of ultrasound assessment of MLS has been conducted in malignant stroke and supratentorial intracerebral haemorrhage [13]. In a mixed population with a majority of traumatic brain injury (TBI) patients, a good correlation was found between ultrasound-measured MLS and CT scan measurement at the level of the third ventricle [area under the receiver operating curve (AUC) for 0.5-cm CT shift: 0.85, 95% confidence interval (CI): 0.73–0.94%] and at the level of the septum pellucidum (AUC for 0.5-cm CT shift: 0.86, 95% CI: 0.74–0.94%) [12]. Bedside assessment of MLS can be useful to detect early cerebral

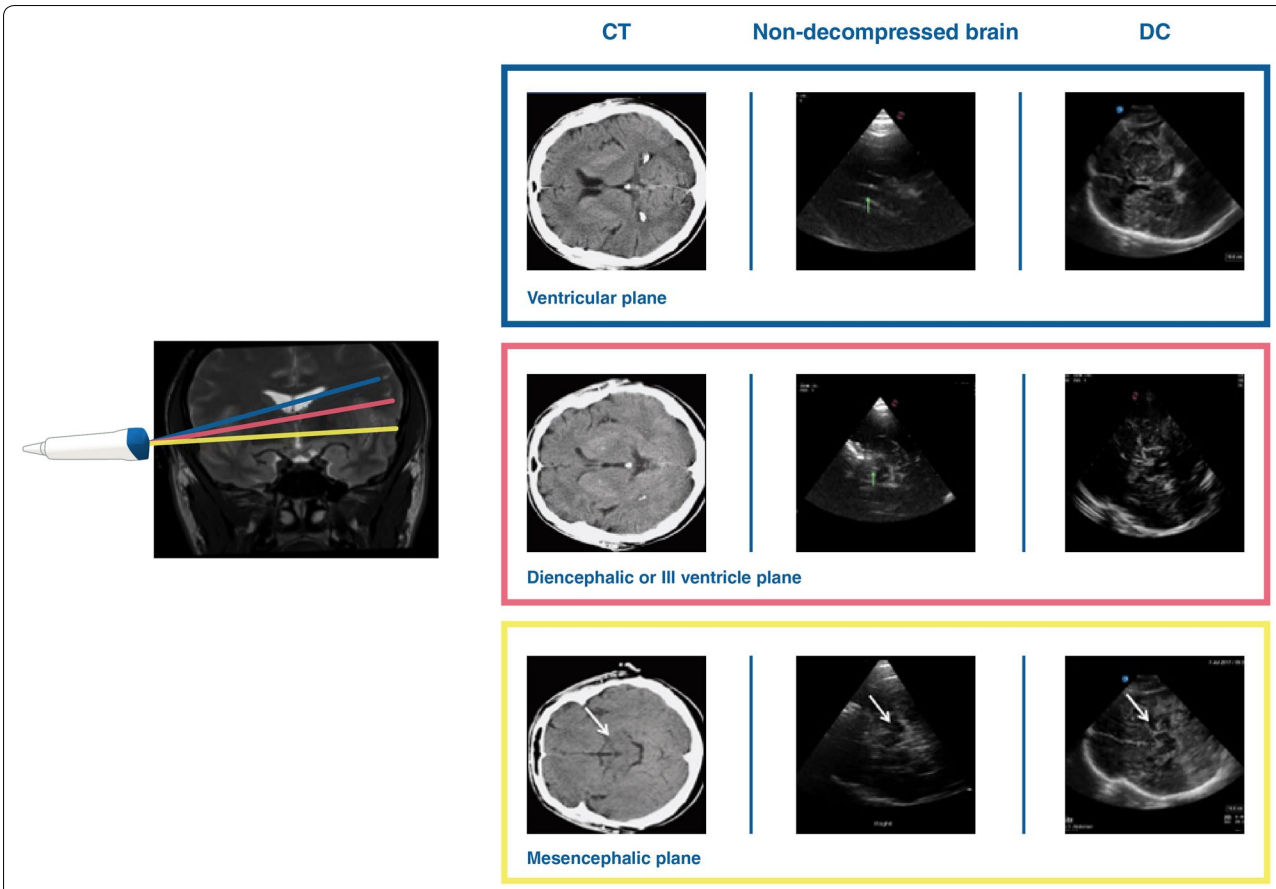

Fig. 2 Transtemporal axial insonation planes: brain ultrasonography images at three different insonation planes (mesencephalic, diencephalic, ventricular) in patients without and with decompressive craniectomy (DC). The mesencephalic plane is the most basal plane; the identification of the contralateral skull (usually at 12–15 cm) confirms the presence of an adequate insonation window; the midbrain is usually easily identified at the midline, and it resembles a butterfly with the wings directed anteriorly. Diencephalic plane—from the mesencephalic plane, an approximate 10° cranial tilting of ultrasound beam allows identification of the third ventricle, seen as two pulsating parallel lines (usually less than 10 mm apart) positioned slightly more cranial and anterior to the midbrain. Ventricular plane—further cranial tilting of the ultrasound beam allows visualisation of the thalami and frontal horns of the lateral ventricles

complications and the need for further imaging or neurosurgical intervention. However, these results suggest that MLS assessed using ultrasound should not be considered as an "absolute" number, but more as a trend.

Optic nerve sheath diameter

CSF circulates in the optic nerve sheath space, from the posterior to the anterior part. Due its particular trabecular architecture, the anterior (or retrobulbar) part of the optic nerve sheath is more distensible than the posterior part. Providing there is no CSF flow obstruction, a rise in CSF pressure is transmitted along the optic nerve sheath. Due to this "cul-de-sac" anatomy of the optic nerve sheath, in the event of an increase in ICP, CSF will accumulate in its retrobulbar part (Fig. 4, ESM5). This close relationship between ICP and dilation of the orbital perineural subarachnoid space has been confirmed by several studies using ultrasound [14, 15]. ICP changes, as detected by intraparenchymal probes, are followed very rapidly (within seconds) by changes in optic nerve sheath diameter (ONSD) [10, 12]. According to a recent systematic review and meta-analysis of seven studies (320 patients), performed to evaluate the diagnostic accuracy of sonographic ONSD measurements in adults [16], thresholds in the range of 4.80–6.30 mm were found to demonstrate robust prediction ability (AUC of 0.94) for the assessment of intracranial hypertension (applying a threshold of > 20 mmHg or > 25 cmH_20). The pooled diagnostic odds ratio, and positive and negative likelihood ratios were 67.5 (95% CI: 29–135), 5.35 (95% CI: 3.76–7.53) and 0.088 (95% CI: 0.046–0.152), respectively.

Table 1 Clinical applications of brain ultrasonography (morphological findings and basic/advanced TCCD-/TCD-derived parameters)

		Role of brain ultrasonography	Clinical conditions	Diagnostic performance	Limitations
Neurocritical care and emergency room	Ultrasound-derived parameters	Non-invasive ICP and CPP estimation	Any condition in which high ICP is suspected (e.g., TBI, hydrocephalus, SAH)	Non-invasive Good temporal resolution for detection of relative changes in ICP ONSD measurement allows identification of raised ICP with good accuracy.	Accuracy of TCD-derived ICP estimation is suboptimal (ICP overestimation ~ 10 mmHg) ONSD not suitable for continuous ICP monitoring ONSD measurements may be affected by optic nerve anatomical variations/diseases
		Cerebral autoregulation assessment	TBI, SAH	TCD with high temporal resolution of flow velocities allows continuous assessment of cerebral autoregulation distinguishing it from spontaneous changes in CBF	Measurements of FV are usually only performed from the MCA, and thus posterior circulation autoregulation changes may not be detected. TCD-based autoregulation assessment uses FV as a surrogate measure of CBF. However, FV proportionality to CBF is only maintained when the vessel crosssectional area remains constant.
		CrCP estimation	TBI, SAH, preterm neonates	Monitoring of CrCP makes it possible to assess the arterial blood pressure threshold below which the blood pressure in the brain microvasculature is inadequate to prevent the collapse of the vessels and cessation of blood flow	Some models of CrCP are limited by the possibility of obtaining negative values which cannot be clinically and physiologically explained
		Assessment of compliance and cerebrovascular dynamics	TBI	Monitoring of C_a and C_i makes it possible to evaluate the physiological interactions of the intracranial compartments undergoing volumetric changes during the cardiac cycle.	Only relative changes in C_a and C_i can be observed. The unknown cross sectional area of arterial vessels precludes the calibration of C_a and C_i
		Identification of vasospasm	TBI, SAH	High sensitivity and specificity for identification of MCA and BA vasospasm	Evidence for prognostic value in vasospasm is limited. Poor sensitivity for ACA and PCA vessels. Lack of clear correlation between TCD-measured vasospasm and delayed cerebral ischaemia
		Ancillary testing in the determination of brain death	Cerebral circulatory arrest	This assessment, easily and rapidly performed at the bedside, is aimed at demonstrating intracranial flow patterns compatible with a diagnosis of DNC.	Cerebral circulatory arrest findings cannot be taken to reflect brainstem function assessment. Lack of acoustic window in a non-negligible group of patients
	Imaging of intracranial anatomy	Identification of pathological findings	Intracranial haematoma	Good reproducibility in evaluating the volume of haematoma in the acute phase in comparison with CT scan	Volume of ischaemic brain is not accurately measured
			Hydrocephalus	Good reproducibility in evaluating the size of the third ventricle and portions of the lateral ventricles in comparison with CT scan.	Evaluation of the size of lateral ventricles may not be accurate due to the large inclination of insonation probe necessary in order to visualise this structure.
			Brain MLS	Good reproducibility in evaluating MLS in comparison with CT scan.	In conditions of disrupted intracranial dynamics following decompressive craniectomies, intracranial haematomas, skull fractures, cranial asymmetries, the measurement of MLS is inaccurate
			Prediction of neurological deterioration in mild to moderate TBI	TCD assessment on admission, complementing brain CT scanning, allows accurate screening of patients at risk of neurological deterioration.	Potential confounding factors (e.g., changes in $PaCO_2$, hematocrit) need to be taken into consideration to correctly interpret TCD measurements and determine their role as marker of neurological deterioration
General Critical Care		Non-invasive estimation of ICP and CPP	Liver failure and hepatic encephalopathy, postcardiac arrest syndrome, intraoperative assessment, sepsis	TCD monitoring of changes in ICP and CPP with reasonable temporal resolution. Enlarged ONSD allows the identification of potential high ICP episodes.	Most TCD-based models and ONSD thresholds are based on TBI populations, limiting the knowledge about the accuracy of such methods in different clinical conditions.
		Diagnosis and treatment of acute ischaemic and haemorrhagic events as complications in general ICU patients	Stroke, sickle cell disease	TCD monitoring in patients with ICA stenosis allows identification of stroke risk and of the need for carotid endoarterectomy. In malignant MCA stroke, it can be useful to predict the need for surgical decompression. TCD monitoring allows reliable prognosis in MCA occlusive stroke. TCD monitoring of children with sickle cell disease performed every 6-12 months allows the identification of those at risk of ischaemic stroke and guides transfusion therapy.	TCD monitoring thresholds of adult patients with sickle cell disease remain inconclusive because FV_m is lower than in children, but higher than in the normal population.
		Evaluation of paradoxical embolism	High-intensity transient signals in cryptogenic stroke and during ECMO	Good reproducibility to evaluate right-to-left shunts in comparison with invasive transoesophageal sonography.	TCD examination of the MCA does not provide additional information on patient's cardiac pathology.
		Assessment of cerebral autoregulation and perfusion changes	Sepsis, liver failure and hepatic encephalopathy post-cardiac arrest syndrome, pre-eclampsia, intraoperative assessment	Identification of significant alterations of cerebral haemodynamics.	Poor predictor of neurological prognosis; unclear role in clinical management.

BA basilar artery, C_a compliance of the cerebral arterial bed, *CBF* cerebral blood flow, C_i compliance of the intracranial space, *CPP* cerebral perfusion pressure, *CrCP* critical closing pressure, *CT* computed tomography, *DNC* death by neurological criteria, *ECMO* extracorporeal membrane oxygenation, *ER* emergency room, *FV* cerebral blood flow velocity ($_m$ mean, $_d$ diastolic, $_s$ systolic), *ICA* internal carotid artery, *ICP* intracranial pressure, *MCA* middle cerebral artery, *MLS* midline shift, *ONSD* optic nerve sheath diameter, $PaCO_2$ partial pressure of carbon dioxide, *PCA* posterior cerebral artery, *PI* pulsatility index, *SAH* subarachnoid haemorrhage, *Tau* cerebrovascular time constant, *TBI* traumatic brain injury, *TCD* transcranial Doppler ultrasonography

Nevertheless, the possible ONSD cut-off value for the detection of intracranial hypertension is still under debate, with most studies reporting an optimal cut-off in the 5.0–6.0-mm range [17].

Moreover, it has been demonstrated that combining ONSD measurement with other ultrasound modalities, such as venous transcranial Doppler assessment of the straight sinus, may provide better prognostic accuracy for the detection of intracranial hypertension than ONSD measurement alone. In a study by Robba et al. [18], the combination of ONSD and straight sinus systolic flow velocity showed a statistically significant improvement of

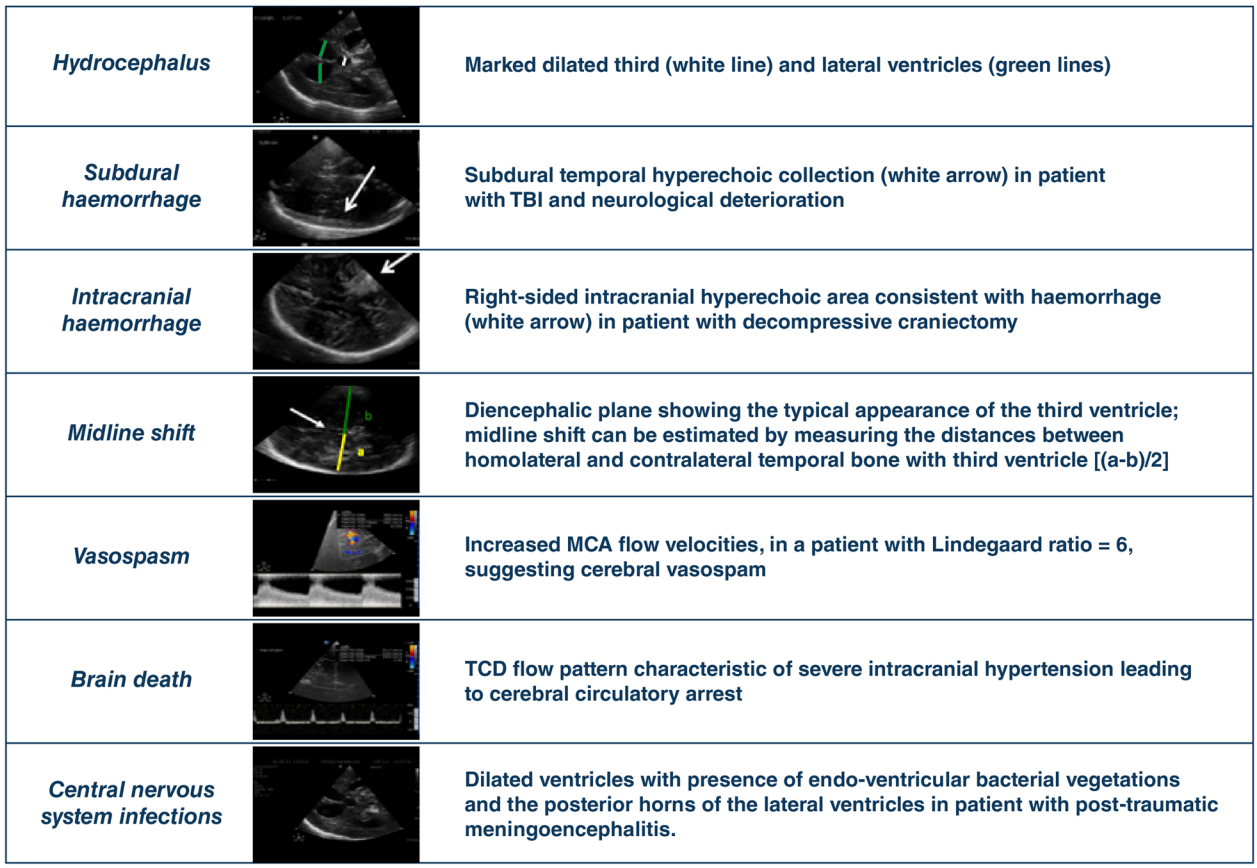

Fig. 3 Clinical applications of brain ultrasonography in neurocritical care

AUC values compared with the use of ONSD alone (0.93 and 0.91, respectively, $p = 0.01$).

Although ultrasound-based methods have several limitations (ESM16) and should not substitute invasive methods, they may help physicians to estimate high ICP, monitor treatment response, and manage ICP after TBI [through assessment of fluid loading effect, carbon dioxide optimisation by assessing cerebral resistance and TCCD waveform, vasopressor dose adjustment to obtain an appropriate cerebral perfusion pressure (CPP) etc.].

TCCD- and TCD-based methods for non-invasive intracranial pressure assessment

Intracranial pressure (ICP) evaluation and management is crucial in many neurological diseases. The currently available ICP monitoring methods require invasive procedures, and carry inherent risks such as haemorrhage, haematoma and infection [19].

CBF velocity waveform analysis is a widely explored non-invasive ICP (nICP) estimation technique. TCCD-/TCD-derived nICP estimation methods are based on the relationship between ICP and CBF velocity-derived indices. Because of the physiological relationship between blood flow velocity and pressure in cerebral vessels with compliant walls, increased ICP will affect CBF velocity measured by TCD, producing changes in the flow velocity waveform, such as low diastolic flow velocity, peaked waveform and a higher pulsatility index (PI) [20]. These "markers" of disturbed CBF have been applied in a variety of methods for describing cerebral haemodynamics, as well as in nICP monitoring [21]. nICP estimation methods can be divided into three categories (see ESM4 for more details):

I. Methods based on the TCCD-/TCD-derived PI, defined as the difference between maximum and minimum blood flow velocity normalised to the average velocity. The usefulness of this index for predicting ICP is controversial, as changes in PI are not dependent solely on changes in ICP, but also on cerebral perfusion pressure (CPP), arterial blood pressure and its pulsatility, and variations in partial pressure of CO_2;

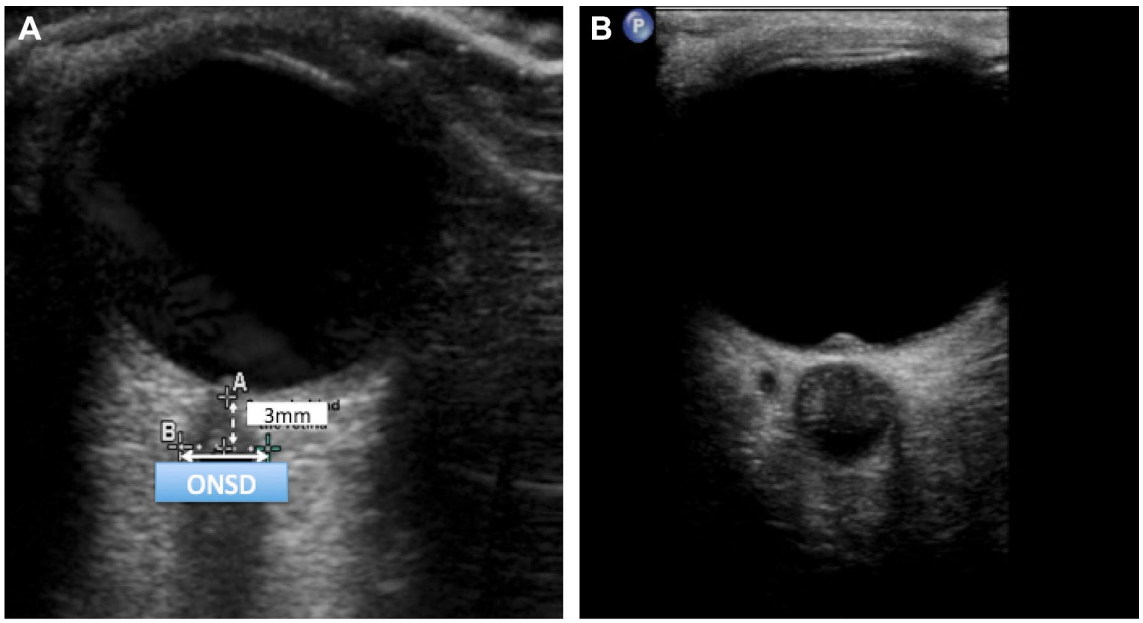

Fig. 4 Optic nerve sheath diameter (ONSD). **a** Axial image of the optic nerve sheath in a patient without increased ICP. The ONSD is measured perpendicularly to an electronic caliper positioned 3 mm behind the retina. **b** Axial image of the optic nerve sheath in a patient with increased ICP, demonstrating both bulging of the optic nerve disc in the vitreal space, consistent with papilloedema and widening of the ONSD

II. Methods based on non-invasive estimation of CPP (nCPP) and subsequent calculation of ICP, using the formula ICP = MAP − nCPP;
III. Methods based on mathematical models associating CBF velocity and arterial blood pressure (only for TCD, see ESM2, 4).

Schmidt et al. [22], using the formula $\mathrm{nCPP} = \mathrm{MAP} * \frac{\mathrm{FVd}}{\mathrm{FVm}} + 14$ mmHg, demonstrated a good correlation between nCPP estimation and invasive CPP measurement ($R = 0.61$; $p = 0.003$), with a 95% confidence limit range no greater than ± 12 mmHg, and with CPP ranging from 70 to 95 mmHg.

Non-invasive methods should not replace the use of invasive tools for invasive ICP estimation. However, when invasive ICP monitoring is not available or contraindicated (in patients with severe coagulopathy, such as hepatic encephalopathy), a reliable alternative nICP estimation method may be helpful for the screening of patients and for assessing their evolution and response to treatment interventions.

Vasospasm

Although vasospasm (VSP) and delayed cerebral ischaemia should not be considered synonymous [23], TCD-/TCCD-based methods can provide an indication of vessel narrowing (i.e., VSP) on the basis of elevated blood flow velocity, as first described by Aaslid, Huber and Nornes in the anterior circulation, and can also be used to assess cerebral autoregulation and its role as a predictor of the development of VSP and delayed cerebral ischaemia [24, 25]. Indeed, a clear correlation has been found between increased CBF velocity and reduced artery diameter on angiography [26–28]. TCCD can help to guide imaging decisions, and when tested directly against TCD, the sensitivity of TCCD CBF velocity measurement for detecting VSP was found to be higher [29]. There are four reasons why TCCD may be more sensitive to VSP detection than TCD. First, colour-coded Doppler sonography allows the vessel of interest to be visualised, which can allow the sonographer to select the site of highest velocity acceleration rather than discover it by trial and error as with "blind" TCD. Second, misinterpretation of the vessel source of the Doppler signal is a common error in conventional "blind" TCD [30]. Third, the guidance for imaging decisions provided by TCCD enables a higher rate of complete exams [bilateral middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery] [31]. Fourth, CBF velocity measurement is dependent upon the angle between the ultrasound beam and the direction of blood flow (Fig. 3, ESM6). The performance of TCD/TCCD has been tested against angiographic detection of VSP (generally defined as a > 25% narrowing of the artery) [32]. In an updated meta-analysis of high-quality TCD/TCCD studies ($n = 18$) [33], pooled sensitivities for the MCA (66.7%, 55.9–75.9)

and the basilar arteries (62.1%, 33.3–84.3) were higher than for the ACA (32.7%, 10.9–65.7). The pooled specificities were very similar for these three arteries: MCA 89.5% (80.3–94.7), basilar 84.5% (71.1–92.3), ACA 89.6% (48.2–98.7). For each artery there was great heterogeneity across the studies, with wide CIs. TCCD studies showed less heterogeneity than TCD ones for the MCA, and resulted in a better pooled estimate [sensitivity 81.5% (67.5–90.3); specificity 96.6% (93.2–98.3)], but this result was not statistically significant. Notably, only three studies using TCCD were included, and these did not include any head-to-head comparison [33]. TCD/TCCD is more specific than sensitive for detecting VSP. There are many possible reasons for the wide range of sensitivity, both sonographer-related (wrong vessel, missing peak velocity, inter-operator variability) and/or technology-related (inability to visualise peak velocity, inability to correct for angle of insonation). In patients at risk for VSP, we suggest performing daily TCD/TCCD for the early and bedside detection of patients at risk for neurological complications and requiring further imaging/treatment.

Brain death

Clinical examination of the patient is the mainstay for determining death by neurological criteria (DNC). However, clinical examination can be confounded by several factors, including metabolic disturbances, ocular injuries or pupillary paralysis, heavy sedation, and trauma to the middle or inner ears [34]. In this context, ancillary imaging techniques capable of demonstrating the absence of CBF have been proposed in order to complement the clinical assessment [35]. Robust techniques like angiography and radionuclear studies are currently the standard options for diagnosing cerebral circulatory arrest and the state of brain death. Nevertheless, such techniques might not be the most practical options in unstable patients who cannot easily be moved outside the ICU. By contrast, compared with these techniques, brain ultrasonography using TCD/TCCD may constitute a simpler, faster and more effective technique for demonstrating intracranial flow patterns compatible with DNC [36, 37].

Devastating brain injuries cause a significant increase in ICP and subsequent decrease in CPP; these intracranial haemodynamic changes are associated with characteristic, progressive changes in the cerebral vessel waveform spectrum [38] (Fig. 3, ESM7a, b). A recent meta-analysis exploring the accuracy of TCD for diagnosing DNC found pooled sensitivity and specificity estimates of 0.90 (95% CI, 0.87–0.92) and 0.98 (95% CI, 0.96–0.99), respectively [37]. These results suggest that TCD is a highly accurate ancillary test in the context of suspected DNC, allowing evaluation of cerebral circulatory arrest patterns.

Stroke

The use of brain ultrasonography for the diagnosis of arterial stenosis is being more frequently applied during the very early phase following stroke symptom onset.

In patients with acute stroke, TCCD is used mainly for diagnostic purposes, along with classical imaging techniques such as CT and MRI (see ESM8), and specifically for:

- Monitoring arterial recanalization and complications (mainly haemorrhagic) after thrombolytic therapy. During this acute phase, ultrasound imaging would be helpful for defining successful recanalization and for evaluating complications as haemorrhagic conversion of an ischemic lesion.
- Evaluating the evolution of brain shift in malignant MCA infarction. Brain ultrasonography can help verify the efficacy of blood pressure augmentation of CBF through the assessment of adequate cerebral perfusion. Cerebrovascular autoregulation is frequently compromised in the early phase of acute stroke [39], and this has led to the current treatment guidelines of permissive hypertension in the hyperacute phase [40]. However, stroke patients with compromised cerebrovascular autoregulation are more prone in developing either hypoperfusion or hyperperfusion, both of which can lead to brain oedema and increased ICP. Furthermore, cerebral infarcts may also be complicated to haemorrhagic infarction of the ischemic area. This later may also lead to intracranial hypertension [41–43].
- Diagnosing large vessel occlusion or stenosis and evaluating collateral circulation.

TCCD is complementary to CT angiography and angio-MRI and it is an exam that can be repeated at the bedside.

Other applications

Use of TCD/TCCD has been described in other conditions managed in the neurointensive care unit, such as central nervous system infections [8] and cerebral sinus thrombosis [44].

Brain ultrasonography in the general ICU

Although most of the applications of brain ultrasonography in critically ill patients are derived from "traditional" neurocritically ill patients, other potential uses of TCCD have been described in medical ICU patients at high risk

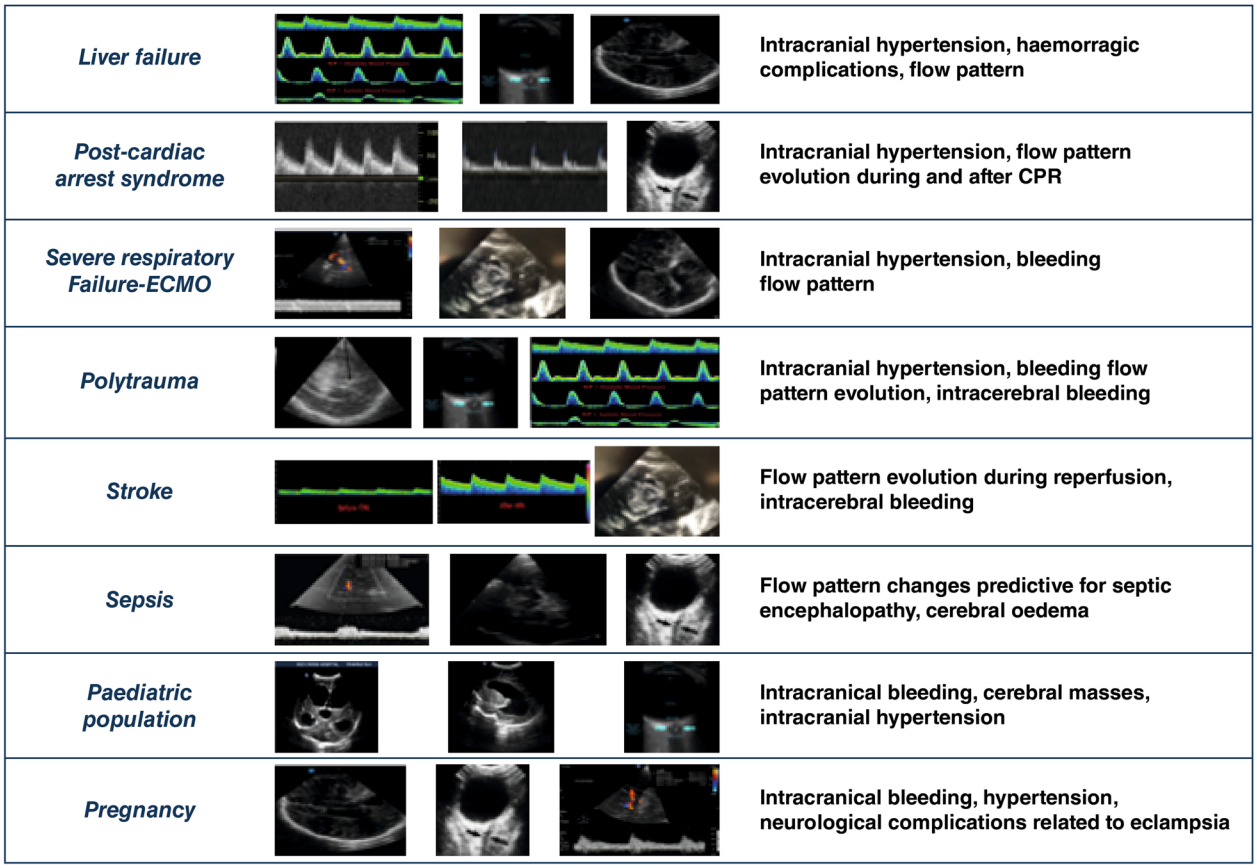

Fig. 5 Clinical applications of brain ultrasonography in the general ICU and in the emergency room

of developing brain injury (e.g., those with severe respiratory failure) or with secondary brain injury related to the primary insult (e.g., in patients presenting acute liver failure or post-cardiac arrest syndrome). Literature on these applications is still limited, and the studies described in this section should be seen more as hypothesis-generating literature rather than standard-of-care recommendations (Fig. 5).

Acute liver failure

Acute liver failure (ALF), a life-threatening multisystem critical illness caused by severe acute liver injury, is associated with encephalopathy and coagulopathy [45]. Despite significant improvements in incidence rates and outcome, intracranial hypertension is still detected in approximately 50% of comatose ALF patients [2, 46, 47] and it accounts for 20–25% of deaths in this population [48]. Due to the significant risks associated with invasive ICP monitoring in the context of ALF-associated coagulopathy [47], non-invasive techniques, including brain ultrasonography for monitoring CBF and ICP, may constitute a useful option. In ALF, both cerebral haemodynamic (hyperaemia and impaired cerebral autoregulation) and metabolic changes contribute to the development of encephalopathy, oedema and raised ICP. Hyperaemia is found in 80% of patients with ALF, and it seems to precede and contribute to the rise in ICP. Loss of cerebral autoregulation is also well-known in ALF patients. Interestingly, it can be promptly restored after improvement of hepatic function, whether spontaneous or post-liver transplant [49, 50]. It has also been shown that moderate hyperventilation may restore cerebral autoregulation in most patients with ALF, although concerns have been raised over the risk of hypoperfusion of certain areas, especially in patients with associated intracranial hypertension and when hyperventilation is performed in the absence of adequate monitoring of cerebral metabolism [51]. The use of nICP estimation in ALF is challenging due to the role simultaneously played in ICP by many physiological factors of sometimes unknown magnitude [e.g., mean arterial pressure (MAP), CO_2, vessel elasticity and volume, intracranial volume and temperature]. For example, the PI [20] reflects distal vascular resistance and vessel wall

elasticity and size, and it is influenced by heart rate, systolic blood pressure, and PaO_2 and $PaCO_2$ levels [52–54]. This could explain why, in a retrospective cohort study of patients with ALF undergoing invasive ICP monitoring, PI did not adequately discriminate ICP > 20 mmHg (AUC 0.55; 95% CI 0.34–0.75; $p = 0.70$) [46]. Conversely, in the same study, another commonly used TCD-derived parameter, CPPe/ICPtcd [i.e., ICP calculated from TCD flow velocities using the estimated cerebral perfusion pressure (CPPe) technique] [55], demonstrated a good intraclass correlation coefficient for IICP and ICPtcd (0.66; 95%CI: 0.31–0.85) and good discrimination for detection of concurrent IICP > 20 mmHg (AUC 0.90; 95% CI 0.72–0.98; $p < 0.00001$). Importantly, the TCD CPPe method was excellent in excluding elevated ICP (negative predictive value 100% for invasive ICP > 20 mmHg when ICPtcd ≤ 18.55 mmHg), and its use as a screening tool may be considered. Similarly, an increased ONSD in liver failure patients may be associated with high mortality (8/10; 80%) [56]. However, the largest published ($n = 23$) study correlating invasive ICP monitoring with ONSD measurements in ALF patients did not find the technique to adequately discriminate ICP > 20 mmHg (AUC 0.59; 95% CI: 0.37–0.79; $p = 0.54$). Altogether, TCCD and ONSD can be useful tools to monitor non-invasively ICP in this cohort of patients where the risk for intracranial hypertension is high and invasive methods are not indicated.

Post-cardiac arrest syndrome

Global cerebral ischaemia–reperfusion injury caused by cardiac arrest has a complex and still only partially understood pathophysiology [57, 58]. Prognostication after cardiac arrest can be challenging, and no single test has been shown to have a 0% false positive rate [59]. The role of TCCD as part of a whole-body ultrasound approach in cardiac arrest and post-resuscitation syndrome is described in detail in ESM9–10.

Four studies (185 patients) have investigated the relationship between ONSD measured on ultrasound after cardiac arrest and outcome (survival or neurological outcome) [60–63] (ESM11.Table 2a), and they all demonstrated a significantly larger ONSD in poor-outcome/non-surviving patients compared with good-outcome/surviving patients. However, optimal cut-offs spanned a wide range (5.11 to 6.7 mm), and prognostic performances were only moderate and therefore insufficient to warrant use of this parameter as an accurate prognostic tool.

More recently, Cardim et al. [64] measured ICP, both invasively and non-invasively, using both ONSD and a TCD-based method in a population of patients with hypoxic ischaemic brain injury after cardiac arrest. The study showed a linear relationship between ICP and nICP both when using ONSD ($r = 0.53$, $p < 0.0001$) and when using TCD ($r = 0.30$, $p < 0.01$). The ability of both ONSD and TCD to predict intracranial hypertension (ICP ≥ 20 mm Hg) in this population was strong [AUC = 0.96 (95% CI: 0.90–1.00) and AUC = 0.91 (95% CI: 0.83–1.00), respectively].

TCCD is an option in patients following cardiac arrest since, by allowing bedside monitoring of cerebral haemodynamic status, it may be used both for early identification of patients at higher risk of cerebral oedema and for haemodynamic/metabolic optimisation purposes.

TCCD during cardiac arrest has been shown to be feasible, especially insonation of the ICA through the transorbital window [65]. However, due to challenges in image acquisition, it cannot easily be implemented during cardiac arrest scenarios, except in situations (e.g., cardiac and aortic procedures) in which there is thought to be a high risk of cerebral hypoperfusion [66, 67], and should not be routinely used in this phase.

TCCD after cardiac arrest has been used in several studies (ESM11.Table 2b) [68–77], which have confirmed the presence of significant alterations of cerebral haemodynamics after cardiac arrest. Although TCCD does not seem to be a tool allowing accurate neuroprognostication, it may still have a role in haemodynamic and ventilatory optimisation, i.e., ensuring adequate cerebral perfusion and blood flow [71, 78]. TCD parameters may also be used to assess the safety of rewarming after targeted temperature management by measuring ICP and CBF [69, 75, 79]. Finally, diffuse, severe TCCD signs of hypoperfusion (e.g., reversal of diastolic flow or undetectable flow patterns) seem to be highly specific for bad neurological outcome [69], whereas regional asymmetries may predict the occurrence of stroke after cardiac arrest [80].

Severe respiratory failure

Severe respiratory failure is not uncommon in patients with acute brain injury [81, 82], and cognitive impairment is frequent in acute respiratory distress syndrome survivors, being present in 70–100% of patients at hospital discharge and in 20% at 5 years [83]. Commonly used ventilatory (e.g., high positive end-expiratory pressure, recruitment manoeuvres, lung-protective ventilation with permissive hypercapnia) and non-ventilatory strategies (e.g., prone positioning, extracorporeal membrane oxygenation) may affect cerebral perfusion and cerebral oxygen delivery [84–86]. Therefore, the use of ultrasound techniques aimed at monitoring CBF at the bedside, and the response to therapeutic interventions in patients with severe respiratory failure, is appealing. A lung- and

neuroprotective ventilatory strategy may be considered not only in patients with acute brain injury, but also in those without evidence of primary brain insult. However, evidence is still lacking in this context and further research is warranted to test our hypothesis.

Sepsis

Neurological dysfunction is a frequent complication during sepsis; 70% of patients with bacteraemia manifest symptoms of septic encephalopathy [87]. Its pathophysiology is poorly understood, with cytokine-induced damage of the blood–brain barrier, microvascular damage and impairment of cerebral autoregulation being some of the most commonly described contributory factors [88].

Brain ultrasonography might be helpful to optimise the haemodynamic management of these patients, by allowing the identification of MAP values associated with best cerebral autoregulation, and non-invasively providing information about cerebral perfusion and cerebrovascular resistance. Cerebral autoregulation is often impaired in patients with septic shock, and low CPP significantly correlates with elevated levels of protein S-100β, a biomarker of brain injury [89]. Furthermore, abnormal PI values and the presence of cerebral oedema are associated with severity of clinical symptoms and might show a correlation with the development of delirium. TCCD can be used as part of multimodal neuromonitoring to assess cerebrovascular resistance, as well as the optimal CPP to apply to this group of patients.

Brain ultrasonography in the emergency department and prehospital medicine

The bedside availability and dynamic nature of ultrasound techniques are two features that make them appealing in the emergency department and/or in prehospital scenarios as potential sources of real-time information on cerebral physiology.

Brain ultrasonography within the whole-body ultrasound approach in multiple trauma

Ever since the introduction, in the prehospital setting and emergency room, of the focused assessment with sonography for trauma (FAST) protocol [90] and the further development of its paradigm into a multi-organ approach [91, 92], point-of-care ultrasound (PoCUS) has become a widely used and extensively taught approach for the rapid evaluation of acute trauma patients. PoCUS involves multi-site investigation, and includes cardio-thoracic, abdominal, vascular and skeletal scans (Fig. 6), and it aims to detect life-threatening lesions and provide immediate assessment of the pathophysiology of the haemodynamic impairment [91]. Due to obvious technical limitations, both the prehospital scenario and the emergency department share a lack of information on ICP. TCCD screening for signs of intracranial hypertension could potentially fill this gap.

In a prospective multicentre study, TCD upon emergency department admission was able to predict neurological worsening after mild to moderate TBI with good sensitivity and specificity [92]. Although evidence on the prehospital feasibility and benefits of brain ultrasonography is still lacking, its role within the multi-organ PoCUS approach to trauma, namely to determine the need for neurosurgical care and allow the early implementation of neuroprotective strategies, is noteworthy. Preliminary data suggest that high-quality measurements of ONSD in the ambulance or helicopter, conducted to estimate the risk of raised ICP in TBI, are feasible [93]. In TBI patients, TCCD-estimated MLS demonstrated a mean difference of 0.12 ± 1.08 mm (95% CI, 0.15–0.41 mm, $p = 0.36$), a linear correlation of 0.88 ($p < 0.0001$), no significant bias and limits of agreement of +2.33 to −2.07 mm when compared with CT scan images [94]. TCD may also allow early detection of low CBF by detecting low MCA diastolic flow velocities and high PI values. In a pilot feasibility study, Tazarourte et al. [95] performed prehospital MCA TCD in severe TBI patients with the aim of improving cerebral perfusion by using an early goal-directed approach (norepinephrine infusion if PI was > 1.4 and MAP was < 80 mmHg; mannitol administration if PI was > 1.4 and MAP was > 80 mmHg). Although no statistically significant conclusions can be drawn from this small prospective study (nine patients with PI > 1.4), normalisation of TCD flows was obtained in the majority of the treated patients. Finally, a recently published multicentre prospective pilot study conducted in 38 ICU patients suggested that TCD could be used as an early tool to rule out raised ICP in severe TBI. In this study, Rasulo et al. [96], by comparing TCD-estimated ICP with invasive ICP monitoring, showed that TCD can detect ICP > 20 mmHg with high sensitivity. According to these results, TCCD can be useful not to assess ICP as a number, but to safely exclude patients with intracranial hypertension.

In all the above-mentioned settings, standardisation of clinical practice of brain ultrasonography and research is warranted. Data on clinical studies regarding the ultrasound-based management of patients are lacking, as is a standardised training and certification process. A panel of neurointensive care experts is currently finalising a consensus aimed at providing recommendations that will pave the way for standardisation of minimal requirements for brain ultrasonography and of the different levels of skills required. Also, several teaching programmes and courses are now being developed.

Other specific considerations, including application in the paediatric setting and in pregnancy, are described in

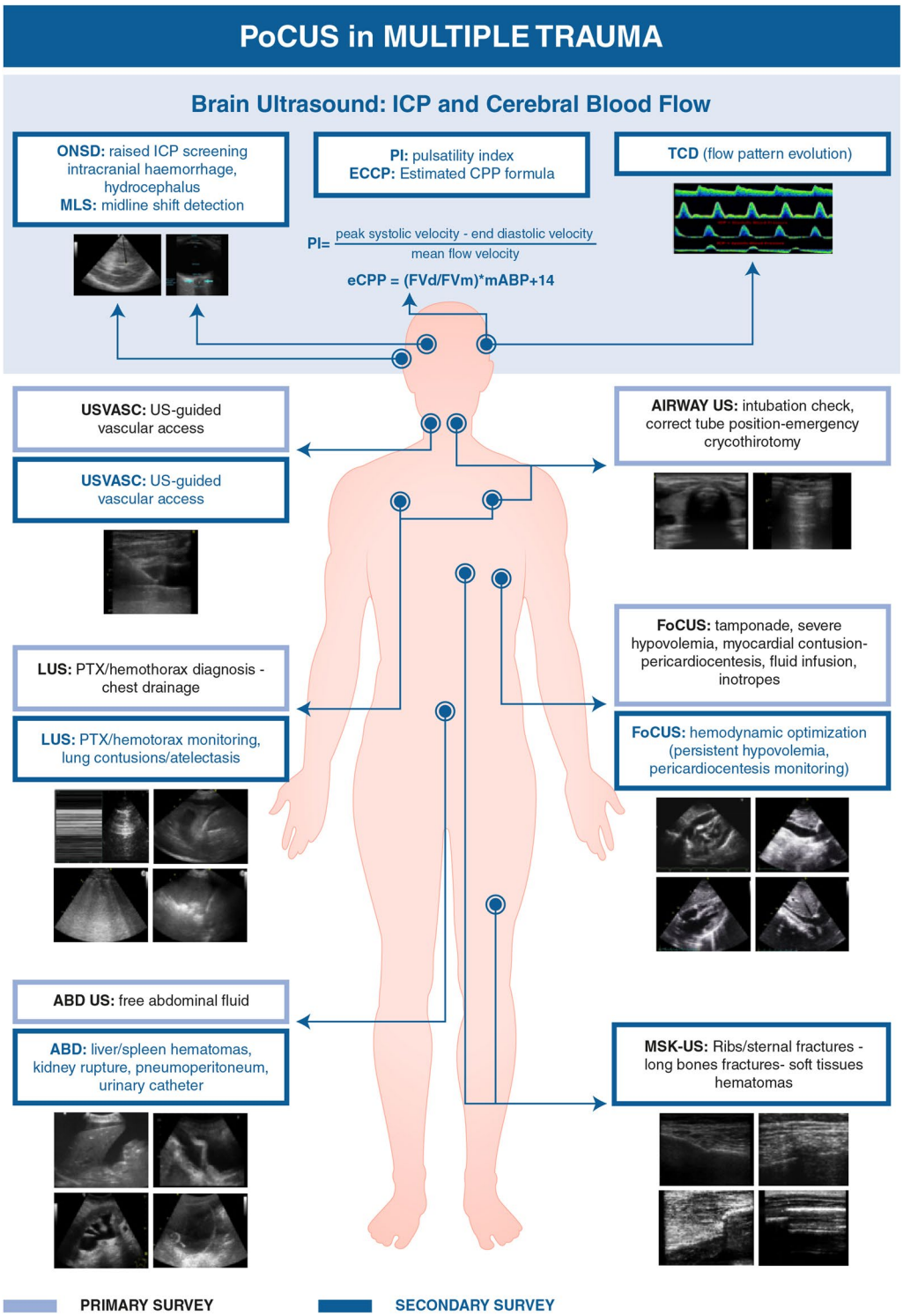

Fig. 6 Brain ultrasonography for the assessment of multi-system trauma. Implementation of brain ultrasonography in the context of extended focused assessment with sonography in trauma (E-FAST) in the emergency room for multi-system trauma patients, as part of both the primary and the secondary survey. Brain ultrasonography (using optic nerve sheath diameter measurement and either TCD or TCCD) can be applied for the non-invasive assessment of ICP and cerebral perfusion pressure, and for the assessment of flow patterns suggesting increased ICP, as well as for the assessment of brain anatomy, including the identification of midline shift and intracranial haemorrhage

ESM12–15. Possible pitfalls and artefacts of brain ultrasonography, as well as its safety limitations, are described in ESM16.

Conclusions

Brain ultrasonography is a non-invasive, low-cost, generally safe and readily available technique, which can potentially be used at the bedside for both diagnosis and monitoring of patients with brain insults. Assessment of brain anatomy and TCCD-derived indices may provide important bedside information regarding the onset and evolution of several cerebrovascular conditions and facilitate their clinical management. Brain ultrasonography is an evolving field; although there is a need for further clinical development, and research and training and teaching programmes are still lacking, efforts are now being made to address these gaps.

Despite presenting several limitations, brain ultrasonography has a strong potential for the assessment of cerebral haemodynamics in critically ill patients in many clinical settings.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05610-4) contains supplementary material, which is available to authorized users.

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