Future applications of advanced neonatal cerebral ultrasound

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Abstract

Ultrasound is a superb neonatal neuroimaging technique as it is non-invasive, easily accessible and safe. Ultrasound is still seen as complementary to other neonatal neuroimaging techniques (such as MRI) because it still lacks several important neuroimaging features such as quantitative tissue analysis. However, developments in ultrasound technology are predicted to follow each other in rapid succession and are expected to have a major impact on clinical neonatal cerebral ultrasound applications in the near future. Elastography, Ultrafast Doppler, Shear Wave imaging, Contrast Enhanced ultrasound and functional ultrasound are examples of techniques being discussed. The aim of this review is to provide a compact overview of current ultrasound developments which are likely to have an impact on neonatal cerebral ultrasound use.

Keywords brain; neuroimaging; preterm infant; technology; ultrasonography

Introduction

Critically ill newborns are at high risk for brain injury and subsequent abnormal neurodevelopment. Timely and accurate diagnosis of brain injury is important for treatment, prediction of outcome and guidance of long-term follow up. Cerebral ultrasound (CUS) is the most frequently use neuro-imaging modality in the neonatal intensive care unit (NICU).

Ultrasound (US) was first used on a large scale as medical imaging device in the 1960s. Reports on CUS go as far back as 1967, scanning in A-mode ("Amplitude modulation") and showing a correlation between US and pathology in postmortem neonatal brains. Since then, on average every decade has seen a major technological breakthrough allowing better visualization of brain structures and pathology. To date, CUS is the gold standard for bedside detection of common neonatal brain lesions (e.g. haemorrhages, venous infarctions, cystic white matter injury, hypoxic ischaemic injury) and is used complementary to magnetic resonance imaging (MRI). The advantage of CUS is that it allows serial real-time bedside imaging at low cost, without ionizing radiation exposure, and is nearly universally available in developed countries. The spectrum of brain injury that can be identified with CUS is constantly evolving due to the increased use of high resolution CUS, improved Doppler techniques and the use of alternative acoustic windows.

Unexpectedly, it is demands for enhanced computing power for leisure purposes which has driven advances in medical imaging. The current demands in computer processing and display performances needed for the gaming industry have reduced the costs and boosted the processing power available to assist with medical imaging technologies. Parallel processing by multicore central processing units (CPUs), together with advanced graphical processing units (GPUs), now allow extremely fast processing.

This technology has been implemented in the new US and changes the way US can be used to assess the neonatal brain. The aim of this review is to provide a compact overview of current US developments that are likely to have an impact on the application of CUS in neonates.

High frame rate, Ultrafast Doppler

B-mode imaging (Brightness mode or grayscale mode) is the most used technique in neonatal brain imaging (Figure 1). To create a B-mode image, conventional US devices send and receive sequential US beams: each beam allows the reconstruction of a single image line (one line is being processed at a time), giving a 2D view.

Conventional B-mode imaging provides only static information about anatomy and pathophysiology of the brain. Besides B-mode imaging, US has a unique feature: live visualization of arterial and venous flow with the use of Doppler. Making use of the Doppler-effect, US devices calculate the absolute blood flow velocity by measuring the frequency shift of the reflected US beam. It is one of the most useful applications US has to offer. In cardiology, US is by the far the most utilized imaging modality because of its flow visualization capabilities.

In neonates, maintenance of adequate blood flow and oxygenation is central to normal brain development and function. There is evidence that neonates are less able to regulate the cerebral blood flow (CBF) in response to perfusion pressure changes in comparison to adults, while sick infants cannot regulate this at all. It is a challenge to study neonatal brain perfusion systematically. Methods to approximate blood flow, like blood pressure, limb oxygen saturation, diuresis, and

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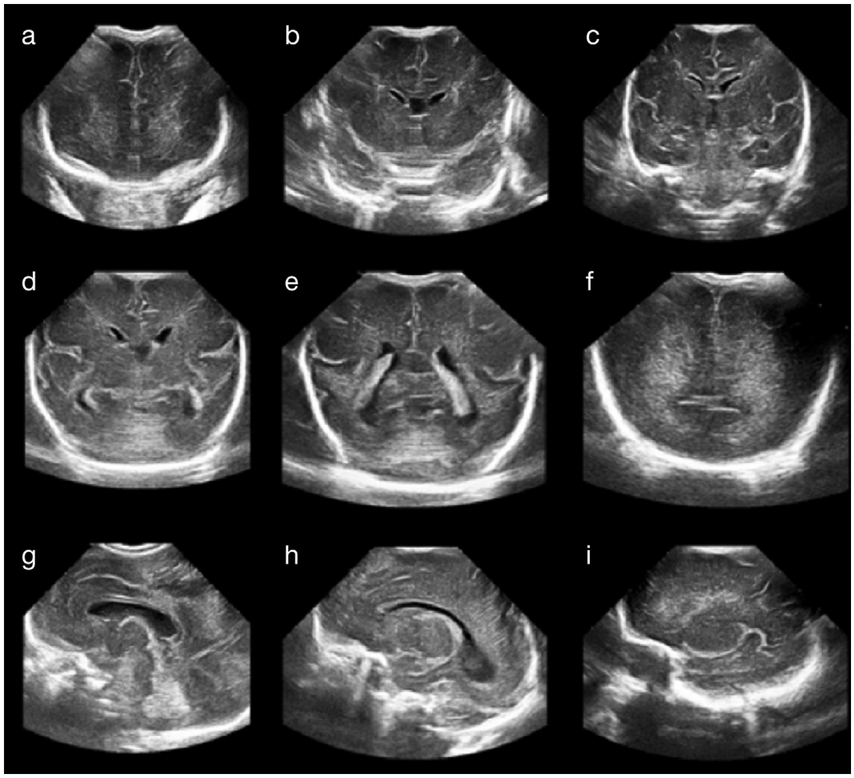

Figure 1 Conventional B-mode cerebral ultrasound images. (**a**)–(**f**): Standard coronal views. (**g**)–(**i**): Standard sagittal and parasagittal views.

heart rate are poor surrogates of actual neonatal brain perfusion. A reliable, objective, repeatable, safe, and bedside method to determine neonatal blood perfusion is therefore needed. Color Doppler (CD) has already found an application in the analysis of cerebral effects of patent ductus arteriosus and birth asphyxia. Indices like pulsatility index (PI) and resistance index (RI) have been developed from analysis of the spectral waveform, and these are used as proxies for vascular autoregulation and intracranial hypertension. A great limitation of flow visualization, however, is the low frame rate. Fortunately, most recent US devices can now scan several lines in parallel, called “multi line processing”. Several lines are computed for each transmit beam and frame rates of hundreds of frames per second can be recorded and processed. These recent advances in US technique have enabled visualization of small diameter vessels (microcirculation). Using high-frequency linear probes it is possible to visualize vessels with a diameter below 200 μm. Therefore, visualization of the brain microcirculation of the preterm infant is feasible, making this a potential tool for *in vivo*, safe, bedside, repeatable measurement of blood flow. In Figure 2, the effect of a germinal matrix haemorrhage on venous flow is shown.

Using plane waves and multi-core CPUs, “ultrafast ultrasound” devices can now even compute a full image from just one single US transmitter. Thousands of frames per second can be processed with this technique. These new ultrafast US imaging systems provide increased temporal resolution and sensitivity, allowing for high definition images of the neonatal brain. The high-resolution imaging enables very precise quantitative mapping of vascular dynamics and RI of the neonatal brain. In a recent (2014) study, Ultrafast Doppler was used to provide *in vivo* mapping of the full vasculature dynamics of the neonatal brain. Simultaneous estimations of full Doppler spectra in all pixels of wide field-of-view images within a single cardiac cycle were obtained with ultrafast frame rate (5000 Hz) imaging (Figure 3).

Ultrafast Doppler also allows US systems to merge two Doppler modes (Color Flow imaging and Pulsed wave Doppler) into a single acquisition. This way the examiner can record all data during one cardiac cycle, place a caliper afterwards in any place in the vessel and measure parameters such as flow velocity, pulsatility index and resistance index.

Functional ultrasound scanning (fUS)

Using high frame rate imaging “functional” US (fUS) was demonstrated in the rat brain in 2011. Based on the same basic principles as functional MRI, the investigators could quantify differences in blood perfusion of the brain due to vasodilatation in active parts of the brain by whisker stimulation. It was even possible to visualize ‘waves’ of epileptic activity ‘traveling’ through the brain. This technique has been successfully translated to humans, with fUS in human neonates being reported in 2017. It was achieved by mounting a lightweight US probe on their heads together with EEG electrodes. By evaluating cerebral perfusion, researchers were able to accurately distinguish quiet sleep from active sleep. In addition, they localized epileptic foci in neonates suffering from seizures. fUS and Ultrafast Doppler could provide more insight in the neonatal brain and may help to better understand human brain functionality.

One of the remaining challenges of US is that the vessel caliber cannot be accurately measured, so that flow cannot be

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