

## Feasibility of Ultrafast Doppler technique for cranial ultrasound in neonates

Hyun Gi Kim<sup>1,2</sup>, Jang Hoon Lee<sup>3</sup>

<sup>1</sup>Department of Radiology, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, <sup>2</sup>Department of Radiology, Ajou University School of Medicine, Ajou University Medical Center, Suwon, <sup>3</sup>Department of Pediatrics, Ajou University School of Medicine, Ajou University Medical Center, Suwon, Korea

### Abstract

**Aims:** The aim of this study was to compare the performances of Ultrafast Doppler ultrasound (US) with classic Doppler US, for cranial ultrasound in neonates. **Materials and methods:** We measured the peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistive index (RI) of the anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) in neonates using both conventional and Ultrafast Doppler US and acquisition times were compared. Distal ACA branches were assessed with Ultrafast Doppler US. **Results:** A total of 138 neonates were included. The PSV and EDV of the cranial arteries were comparable between the two Doppler methods (PSV, 64.6-85.5 cm/s vs. 63.4-84.1 cm/s,  $p=0.100-0.510$ ; EDV, 19.1-26.5 cm/s vs. 17.8-24.2 cm/s,  $p=0.100-0.981$ ). The RIs of the ACA and PCA were not significantly different (0.69-0.73 vs 0.68-0.74,  $p=0.174-0.810$ ). Ultrafast Doppler US required shorter acquisition times than conventional Doppler US (6.7 s vs. 11.0 s,  $p=0.003$ ). The PSV and EDV of the distal ACA were higher than the proximal ACA (20.1-63.3 cm/s vs. 9.4-36.7,  $p<0.001$ ) although the RI was similar (0.69 vs. 0.68,  $p=0.251$ ). **Conclusions:** Ultrafast Doppler US provides comparable values to conventional Doppler US with shorter acquisition times. This novel imaging technique provides quantitative information and is suitable for distal cranial artery evaluation.

**Keywords:** infant; brain; cerebral hemodynamics; ultrasonography; fast Doppler

### Introduction

Cranial ultrasound (US) is one of the most powerful tools for neonatal brain imaging [1] because of its lower expense and higher portability in addition to its avail-

ability without sedation or radiation. Addition of Doppler images to B-mode brain US images is a widely used protocol. With color and spectral Doppler US, systolic and diastolic velocities can be obtained. As a result, the resistive index (RI) can be calculated and pathological situations such as increased cranial pressure or hypoxia can be evaluated [2,3].

Although some studies have stratified the significance of term-equivalent MRI in neonates [4,5], cranial US with advanced techniques has shown comparable diagnostic accuracy to MRI [6,7]. To develop cranial US as a more potent tool, we need to determine how it reflects the hemodynamic features of the brain. Doppler studies add value to conventional cranial imaging, as they show quantified information of brain hemodynamics [8,9]. Yet, evidence is still not robust enough to allow longitudinal

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Corresponding author: Hyun Gi Kim, MD, PhD

Department of Radiology, Eunpyeong  
St. Mary's Hospital, College of Medicine,  
The Catholic University of Korea,  
1021 Tongil-ro, Eunpyeong-gu,  
Seoul, Korea, 03312

E-mail: catharina@catholic.ac.kr

Phone: 82-2-2030-2970

Fax: 82-2-2030-2965

studies with Doppler US alone, since Doppler findings are sensitive to various factors such as angle or location [10].

A new Doppler technique called Ultrafast Doppler, which can overcome these limitations, has been developed. This technique makes it possible to obtain several images 1,000 frames per second, which is about 100 times faster than conventional techniques [11]. With this method, color and spectral Doppler US are merged into one feature and after acquiring 2 to 4 seconds of Ultrafast Doppler data, it is possible to retrospectively review the images, select the best frame for flow and make a spectral analysis. This has potential for future studies because less acquisition time is required [12,13] and quantified information can be obtained [14]. In addition, Ultrafast Doppler US can store data and display spectral waves of multiple locations with a single acquisition and allow deep tissue penetration with high spatial resolution [8].

To the best of our knowledge, *in vivo* studies of this new technique have been done with only a limited number of neonates or nonhuman primate models with dedicated software to evaluate cranial flow [8,9,11]. Before it can be clinically applied within commercialized US settings, it is important to compare the performances of Ultrafast Doppler US with conventional color Doppler US. Therefore, the objective of this study was to compare the velocities, RI values and acquisition times of Ultrafast and color Doppler US. In addition, we assessed the cerebral blood flow of distal cranial arteries.

## Materials and methods

### *Study subjects and study phases*

This study was approved by our hospital's institutional review board and informed consent was waived. The subjects were neonates who underwent screening cranial US from December 2016 to August 2018. Both preterm and full-term neonates were included. We excluded US studies of neonates who showed intracranial abnormalities, such as intracranial hemorrhage, hydrocephalus, or encephalomalacia. The neonates did not undergo further imaging studies or follow-up with neurodevelopmental assessments.

The study was divided into three phases. In the first phase, neonates who underwent cranial US with Aixplorer (Supersonic Imagine, Aix-en-Provence, France) were assessed using both conventional and Ultrafast Doppler US. At least two among three major cranial arteries (anterior cranial artery [ACA], middle cranial artery [MCA], and posterior cranial artery [PCA]) were assessed.

In the second phase, either conventional or Ultrafast Doppler imaging was used for cranial US with Aixplorer.

The difficulty level of the scan, depending on neonates' cooperation, was assessed after US: Grade 1, easy and Grade 2, difficult.

In the third phase, both the proximal ACA (vertical segment of the ACA, from anterior communicating artery to the origin of the callosomarginal artery) and distal ACA (distal to the origin of the callosomarginal artery, including the pericallosal artery, callosomarginal artery, or medial frontal branches of callosomarginal artery) were assessed using Ultrafast Doppler US.

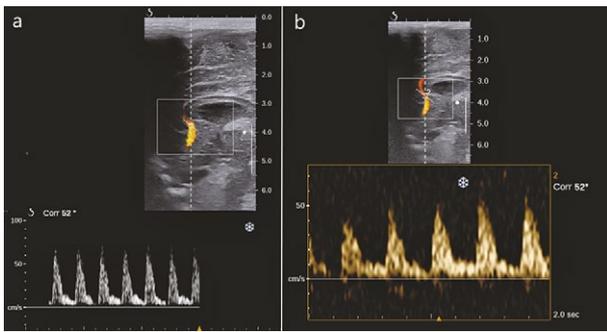
### *Ultrasound*

Cranial US was performed with both a convex probe (SMC12-3; Supersonic Imagine) and linear array probe (SL10-2; Supersonic Imagine). For conventional and Ultrafast Doppler US, we used the linear array probe. For conventional Doppler US, the frame rate was 16 Hz. For Ultrafast Doppler US, the compounded frame rate was 45-56 Hz. For ACA evaluation, we used the sagittal view through the anterior fontanel. For MCA and PCA evaluation, the temporal view through the mastoid fontanel was used.

For arterial waveform acquisition using conventional Doppler US, the following steps were performed: 1) the color Doppler box was displayed on the US machine monitor; 2) the selected cranial artery was positioned in the Doppler box by adjusting the location and size of the box; 3) after displaying the selected vessel, the probe was immobilized at the site; 4) the Doppler mode was switched to the spectral Doppler mode; 5) the sampling cursor of the spectral acquisition line was placed at the vessel; 6) the acquisition angle was adjusted according to the direction of the vessel between 30 to 60 degrees; 7) the US performer pressed the 'update' button for spectral wave acquisition. When at least three constant and even spectral wave forms were displayed, the spectral wave was considered adequate for measuring flow velocity.

For arterial waveform acquisition using Ultrafast Doppler US, the following steps were performed: 1) the color Doppler box was displayed; 2) the proper cranial artery was positioned in the Doppler box by adjusting the location and size of the box; 3) the 'Ultrafast Doppler acquisition button' was pressed; 4) both color and spectral information was acquired for 2 seconds and stored in the US machine; 5) positioning and angle adjustment were made right after the stored color Doppler movie was automatically displayed on the US monitor. Figure 1 shows the acquired spectral waves of a subject.

Spectral waveforms were used to measure the peak systolic velocity (PSV) and end-diastolic velocity (EDV). The RI value was defined as the difference between the PSV and EDV divided by the PSV.



**Fig 1.** Doppler US of a neonate's brain. Sagittal images of the brain with the anterior cerebral artery are shown. The spectral waves were obtained with conventional (a) and Ultrafast (b) Doppler US.

### Acquisition time

Acquisition times were measured for both techniques. The acquisition time was the total time that the US probe needed to be placed on a neonate's head. For the conventional method, the starting time point was step 1 (Doppler box display) and the end time point was step 7 (spectral wave acquisition). For the Ultrafast method, the starting time point was step 1 (Doppler box display) and the end time point was step 4 (information acquisition and storage).

### Statistical analysis

For each parameter, the normality of data was assessed with the Kolmogorov-Smirnov test. To compare the velocities and RI values obtained with conventional and Ultrafast Doppler US, the paired t-test was used. To determine the correlation between the two Doppler US studies for values with statistical differences on the paired t-test, Pearson's correlation analysis was used. For non-normality data such as the EDV values in the distal and proximal ACA vessels, the Wilcoxon signed-rank test was used. To compare acquisition times, the independent t-test was used. A p value less than 0.05 was considered statistically significant. SPSS v.25.0 (SPSS, Chicago, IL) was used for analysis.

## Results

### Patients

Demographic characteristics of the subjects are summarized in Table I. In the first phase, a total of 30 neonates underwent both conventional and Ultrafast Doppler US. Among the 30 neonates, 2 did not have PCA velocity measurements. In the second phase, 23 neonates underwent conventional Doppler US and 22 underwent Ultrafast Doppler US. There were no differences in corrected gestational age, chronological age and gender between the conventional and Ultrafast Doppler US groups. In the third phase, both the proximal and distal ACA of 63 neonates were assessed.

### Flow velocity and RI values

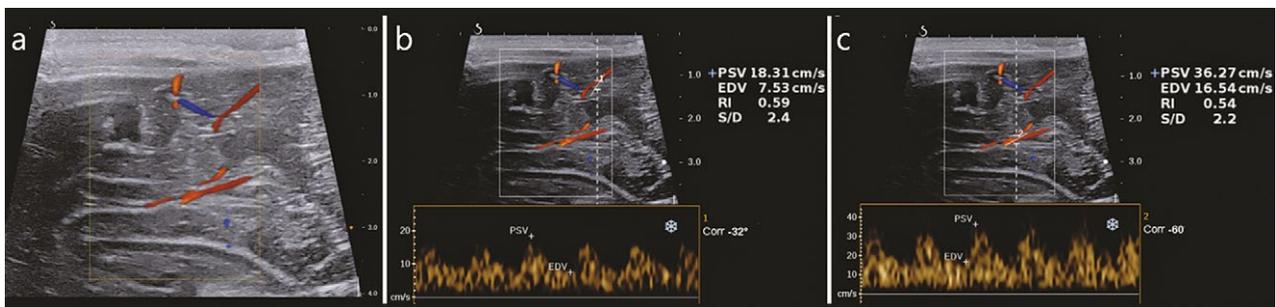
The flow velocity and RI values of the 30 neonates who underwent both conventional and Ultrafast Doppler US are summarized in Table II. There were no statistical differences in the PSV and EDV of the ACA, MCA and PCA between conventional and Ultrafast Doppler US. The RI values of the ACA and PCA were not different. The RI value of the MCA was higher with Ultrafast Doppler US compared to conventional Doppler US (0.71 vs. 0.69,  $p=0.011$ ). When the correlation analysis was performed, there was significant positive correlation between RI values of MCA with conventional and Ultrafast Doppler US ( $R=0.852$ ,  $p<0.001$ ).

### Acquisition time

Ultrafast Doppler US showed shorter acquisition time compared to conventional Doppler US (6.7 seconds vs. 11.0 seconds,  $p=0.003$ ). When the difficulty level was assessed in 45 neonates, 38 were assessed as grade 1 and 7 as grade 2. Among the 7 neonates assessed as grade 2, 4 underwent Ultrafast Doppler US (acquisition time range 6-7 seconds) and 3 underwent conventional Doppler US (acquisition time range 15-28 seconds).

### Distal vessel evaluation

When the distal ACA vessels were evaluated (fig 2), the mean (standard deviation) PSV value of the proximal



**Fig 2.** Ultrafast Doppler US at the distal anterior cerebral arteries. After a single acquisition of Ultrafast Doppler US (a), spectral waves at different locations of the distal anterior cerebral arteries could be evaluated (b and c).

Table I. Demographic characteristics of the subjects

Study phase	First	Second	Third		
Doppler method	Conventional & Ultrafast	Conventional	Ultrafast	p value	Ultrafast
Number of subjects	30	23	22		63
Mean corrected GA (weeks)	38.0 (2.2)	39.7 (4.2)	38.6 (6.5)	0.502	39.6 (4.5)
Age (days)	15 (10)	30 (22.3)	28.5 (39.4)	0.875	30.3 (17.8)
Male/Female	18/12	16/7	12/10	0.465	29/34

Data are means (standard deviations); GA, gestational age

Table II. Velocity and resistive index value comparison between conventional and Ultrafast Doppler ultrasonography

Cranial artery		Conventional		Ultrafast		p value
ACA (n = 30)	PSV (cm/s)	70.9	(23.0)	66.5	(22.2)	0.100
	EDV (cm/s)	19.1	(9.6)	17.8	(9.3)	0.274
	RI	0.73	(0.08)	0.74	(0.09)	0.810
MCA (n = 30)	PSV (cm/s)	85.5	(25.3)	84.1	(24.8)	0.510
	EDV (cm/s)	26.5	(10.6)	24.2	(10.8)	0.100
	RI	0.69	(0.09)	0.71	(0.10)	0.011
PCA (n = 28)	PSV (cm/s)	64.6	(21.3)	63.4	(20.1)	0.484
	EDV (cm/s)	20.4	(10.4)	20.4	(8.2)	0.981
	RI	0.69	(0.09)	0.68	(0.08)	0.174

Data are means (standard deviations). ACA, anterior cranial artery; MCA, middle cranial artery; PCA, posterior cranial artery; n, number of subjects

ACA was higher than the distal ACA (63.3 [16.3] cm/s vs. 36.7 [14.5] cm/s,  $p < 0.001$ ). The median (interquartile range) EDV value of the proximal ACA was higher than the distal ACA (20.1 [12.5] cm/s vs. 9.4 [7.7] cm/s,  $p < 0.001$ ). There was no significant difference for the mean (standard deviation) RI value between the proximal ACA and distal ACA (0.69 [0.09] vs. 0.68 [0.09],  $p = 0.251$ ).

## Discussions

Cranial Doppler US plays an important role in the diagnosis and management of brain damage in neonates [8,9,15]. We showed that the vascular velocity values obtained using the new Doppler technique, Ultrafast Doppler US, are comparable with those obtained using conventional Doppler US. Acquisition times were shorter with Ultrafast Doppler US and the flow dynamics of the distal ACA could be evaluated. When compared with the proximal ACA, the distal ACA had lower PSV and EDV values. However, the RI values did not significantly differ between the proximal and distal ACA.

The absolute values of PSV and EDV are useful as they quantitatively reflect the cranial hemodynamics of neonates. However, values acquired with Doppler US are affected by various factors. These factors include the baseline, pulse repetition frequency/wall filter, angle cor-

rection, sample volume gate length, packet size and the position of the sample volume. Although the RI value is less sensitive to the above factors [16] and has high interobserver reliability [17], its application is limited because it is related to the caliber of the insonated artery and cannot reflect changes due to similar PSV and EDV alterations [18]. As these factors can be adjusted retrospectively after Ultrafast Doppler images are acquired, Ultrafast Doppler US might be suitable for longitudinal comparison studies.

The comparable velocity and RI values obtained in our study using the two US techniques are consistent with a previous study that applied Ultrafast Doppler US to liver imaging [13]. A strong positive correlation between the flow velocities of conventional and Ultrafast Doppler US was found ( $R = 0.806$ ) [13]. The study also demonstrated no differences between techniques concerning clinical decisions.

We showed that the acquisition time of Ultrafast Doppler US was shorter than conventional Doppler US, similar with Bercoff et al [12]. With conventional Doppler US, there is compromise between spatial and temporal resolution, but with Ultrafast Doppler US, it is possible to simultaneously acquire full quantitative Doppler information without limited sample volume (i.e., with a large region of interest) [12]. The reduced acquisition time seen in our study reflects the technical improvement of

the Doppler US method. Another reason for the reduced acquisition time could be the lower number of manual steps required for the procedure. With conventional Doppler US, the color flow and power wave Doppler cannot be displayed and controlled at the same time. In addition, to acquire adequate PSV and EDV values in conventional Doppler US, the power Doppler angle has to be placed and adjusted before spectral wave acquisition. In comparison, angle adjustments can be done after images are acquired with Ultrafast Doppler US.

The acquisition time with Ultrafast Doppler US was shorter than that with conventional Doppler US in poorly cooperating neonates. This result is consistent with the previous study on liver imaging [13] in which the poor breath-holders showed significantly shorter acquisition times with Ultrafast Doppler US than with conventional Doppler US [13]. Since we had a small number of patients with grade 2 level of difficulty, it was hard for us to statistically evaluate the role of Ultrafast Doppler US on poorly cooperating neonates. We postulate that Ultrafast Doppler US will reduce the time and effort needed to examine moving neonates, but this needs to be validated with a larger number of subjects.

We evaluated the distal arteries of the ACA and showed that Ultrafast Doppler US can be used to obtain the spectral waves of small arteries. This is related to the fact that Ultrafast Doppler US allows deep tissue penetration with high spatial resolution [9,11,19]. In fact, during one acquisition of Ultrafast Doppler US in 14 neonates a quantitative mapping of deep brain vascular dynamics was realized [11]. The authors determined specific RI values in 6 arteries and artery segments. We obtained lower RI values of the ACA branches probably related to the higher age of included neonates in our study. A decrease in RI values according to higher age was already reported [20,21]. In addition, Montaldo et al [19] used a dedicated Ultrafast Doppler sequence relying on Compound Plane-Wave and we used a commercialized version that was setup on the US machine itself.

There are some limitations in our study. First, the US was performed by one pediatric radiologist and the intra- and interobserver agreement were not evaluated. In a previous study, the reproducibility of measuring the RI values of the ACA was fair to good (intraclass correlation coefficient, 0.73) [8]. Secondly, we did not measure velocities or RI values in the thalamus, as our study was focused on the feasibility of using Ultrafast Doppler US in clinical setting. A previous study that used a hypoxic ischemic model revealed that thalamic RI, not ACA RI, was highly associated with disease severity and reflected the treatment response of hypothermia [8]. Third, there was a limited number of subjects who underwent both

Doppler US methods. The higher RI value of the MCA with Ultrafast Doppler US compared to conventional Doppler US could be related to the limited number of subjects.

### Conclusion

Our study showed that Ultrafast Doppler US can be used to retrospectively analyse the acquired vascular waveforms and that the acquired vascular velocity values are comparable to those acquired with conventional Doppler US. Also, this new technique allows the evaluation of multiple branches with a single acquisition and in shorter time. Therefore, Ultrafast Doppler US is thought to be a feasible and safe method for cranial US in neonates at risk for altered hemodynamic conditions of the brain. Future validation of intra- and interobserver variability may further contribute to supporting the reproducibility of this method.

**Conflict of interest:** none

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