Preterm neonatal lateral ventricle volume from three-dimensional ultrasound is not strongly correlated to two-dimensional ultrasound measurements

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Abstract. The aim of this study is to compare longitudinal two-dimensional (2-D) and three-dimensional (3-D) ultrasound (US) estimates of ventricle size in preterm neonates with posthemorrhagic ventricular dilatation (PHVD) using quantitative measurements of the lateral ventricles. Cranial 2-D US and 3-D US images were acquired from neonatal patients with diagnosed PHVD within 10 min of each other one to two times per week and analyzed offline. Ventricle index, anterior horn width, third ventricle width, and thalamo-occipital distance were measured on the 2-D images and ventricle volume (VV) was measured from 3-D US images. Changes in the measurements between successive image sets were also recorded. No strong correlations were found between VV and 2-D US measurements (R^2 between 0.69 and 0.36). Additionally, weak correlations were found between changes in 2-D US measurements and 3-D US VV (R^2 between 0.13 and 0.02). A trend was found between increasing 2-D US measurements and 3-D US-based VV, but this was not the case when comparing changes between 3-D US VV and 2-D US measurements. If 3-D US-based VV provides a more accurate estimate of ventricle size than 2-D US measurements, moderate–weak correlations with 3-D US suggest that monitoring preterm patients with PHVD using 2-D US measurements alone might not accurately represent whether the ventricles are progressively dilating. A volumetric measure (3-D US or MRI) could be used instead to more accurately represent changes.

Keywords: three-dimensional ultrasound; intraventricular hemorrhage; ventricle dilatation; hydrocephalus; preterm neonate.

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1 Introduction

Posthemorrhagic ventricle dilatation (PHVD) is characterized by an enlargement of the cerebral ventricles and commonly occurs in preterm neonates with moderate to severe intraventricular hemorrhages (IVHs), grades II–IV, as graded by the clinical standard system. 1 PHVD can lead to lifelong neurological complications such as cerebral palsy as well as visuospatial disorders and lower developmental quotient. 2,3 Transfontanel cranial ultrasound (US) is sensitive and specific for detection of PHVD and is used clinically to diagnose and monitor this condition. 4 However, 2-D images cannot provide accurate volume measurements, thus ventricle volume (VV) is often estimated and monitored qualitatively. To address this, several quantitative measurements [ventricle index (VI), anterior horn width (AHW), thalamo-occipital distance (TOD), third ventricle width (3rd)] have been derived for 2-D US images. 5 These measurements rely on the linear widths of ventricles to estimate the changes in VV as the disease progresses. Such measurements have not been standardized across neonatal intensive care units (NICUs), therefore, there is a wide variation in the interpretation of 2-D US-based measurements’ utility. This is further confounded by the user-dependent nature of 2-D US as the technician only records some image planes, furthermore, there has been no consensus on what should be measured by a radiologist to best illustrate VV. 6

The “gold standard” to quantify VV makes use of three-dimensional (3-D) MR images, but can only be acquired once the patient is stable enough to be transferred to the imaging suite—often weeks after initial diagnosis and intervention for PHVD. Indeed, only a few studies directly comparing 2-D US and MRI measurements of the ventricles have been done. 7,8 Specifically, Horsch et al. 7 found that the AHW was strongly correlated with MRI VV (R^2 = 0.88) when preterm born infants with varying ventricle sizes were imaged at term equivalent age.

In contrast to the “gold standard” MRI-based measurements, 3-D US images can be attained multiple times per week—early after birth—with limited adverse effects to the patient, as the imaging procedure is done within the incubator and takes only a few minutes to complete. 9 Additionally, serial 3-D US is far less expensive than longitudinal monitoring with MRI.

3-D US imaging studies have been able to attain VV measurements from preterm neonates with both normal ventricles...
2.2.2 Three-dimensional ultrasound images

3-D US images were acquired using a 3-D US motorized attachment developed in our laboratory, which housed the US transducer [Fig. 1(a)]. Technical details of the 3-D US system were previously described.\textsuperscript{16,18,19} The 3-D US images were acquired by locating the midline in the sagittal plane, then firmly holding the motor encasement to allow the device to mechanically tilt the transducer about the axis at the probe tip along parasagittal slices, while the technician’s hand remained as still as possible.

This image can be viewed through any reconstructed plane (i.e., sagittal, axial, coronal, or oblique) using a multiplanar reformatted 3-D visualizer [see Fig. 1(b)] at the bedside to determine that the full VV was acquired with limited motion from either the patient or the technician during the scan.\textsuperscript{20} An example of motion artifact that would require additional scans can be seen in Fig. 2(a), whereas Fig. 2(b) shows the same patient’s “acceptable” 3-D US image from the same scanning session. Imaging specifications are such that 2-D US images were acquired with an angular spacing of 0.3 deg at 25 frames/s over a scan angle of 60 deg to 72 deg, making total 3-D image acquisition between 8 and 9.6 s. 3-D US images ranged from 300 × 300 × 300 to 400 × 400 × 400 pixels with voxel sizes ranging from 0.2 × 0.2 × 0.2 mm\textsuperscript{3} for 7.1-cm depth to 0.24 × 0.24 × 0.24 mm\textsuperscript{3} for 9.9-cm depth. The same depth settings were used in 2-D and 3-D images on the same day for the same patient. Under ideal circumstances, a single sweep of the mechanical tilting device is able to capture the entire ventricular system in 3-D US. Generally, an acceptable image [Fig. 2(b)] was acquired in two to three sweeps of the device, taking between 2 and 10 min for the entire 3-D US examination. Some patients with extremely dilated ventricles required acquisition of two separate 3-D US images to capture the entire ventricular system, one of the right lateral ventricle and one of the left.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{(a) The mechanical “tilting” 3-D US transducer device being held in position next to a preterm-sized mannequin. This is approximately the position used for neonates scanned while intubated or while on continuous positive airway pressure during a 3-D US acquisition. (b) A representative “cube” view cut through three orthogonal planes of a 3-D US image of a patient with PHVD.}
\end{figure}
2.3 Image Analysis and Ventricle Segmentation

2.3.1 Two-dimensional ultrasound

Two observers (FS and WR) analyzed the 2-D US images and reported the VI and AHW for the left and right lateral ventricles as well as the third ventricle width (3rd) and the largest TOD. Reporting a single TOD was the standard at our institution and was used as there were often large differences between the left and right sides, with one much larger than the other. Therefore, to attain the best correlation possible, we used the largest TOD, as we believed this would be a better representative of both VV and change in the VV. Measurements are described in detail in Davies et al. and examples are shown in Fig. 3. The differences (Δ) obtained between consecutive time points (i.e., between scans 2 and 3 and scans 3 and 4, but not between 2 and 4) were calculated for all 2-D US-based measurements.

2.3.2 Three-dimensional ultrasound

VV was obtained by manually segmenting the ventricles from the 3-D US images by a single trained observer (JK) and verified by an experienced clinician (SdR). Due to the high volume of images to be segmented (N = 255), each image was only segmented once in order to mitigate user-fatigue, which can cause an increase in variance of segmentation. The segmentation was performed on parallel sagittal slices on the reconstructed 3-D image. The manually segmented boundaries included the intraventricular blood clot as well as the choroid plexus, but not porencephalic cysts if they were present. Slice spacing was set at 0.5 or 1 mm depending on the amount of ventricular dilatation. Patients with smaller ventricles (that could be captured in a single image) required smaller slice spacing (0.5 mm) due to the highly irregular shape, as well as the thinness of the anterior and temporal horns. Patients with severe PHVD who required two 3-D US images to fully capture the ventricles (one image for right and one for the left lateral ventricle) had slice spacing set at 1 mm as the ventricles were much less irregular in shape and the segmentation of these patients required the most time and most contours to segment for determination of VV. For these patients, each of the left and right lateral VVs were segmented from separate images and added together. Each image set required an average of 20 min to segment, with 30 to 70 contours segmented per 3-D US image set. Figure 4 shows the 3-D US segmented image and volume rendered ventricle surface for a patient with mild ventricle dilatation as well as a patient with PHVD. The difference in 3-D US VVs (ΔVV) between successive time points was calculated and recorded.

2.4 Observer Agreement in Reported Two-Dimensional Ultrasound Measurements

As there were two observers (FS and WR) for the 2-D US images, a small subset of the images was measured by both observers to determine measurement agreement. Seventeen
images were analyzed, and they were all from different neonates with varying severities of IVH and ventricle dilatation. VI and AHW for the left and right lateral ventricles as well as the 3rd and the largest TOD were reported by the two observers.

2.5 Two-Dimensional Ultrasound Measurements Made on Two-Dimensional Ultrasound Images

In order to further validate our 3-D US system, VI, AHW, and TOD were measured on approximately the same plane on the 3-D US images as would be used for 2-D US. A 3rd was excluded as images were taken too close to the midline to visualize this structure in most “acceptable” 3-D US images. A single observer (FS) performed measurements on both the 3-D US images and time-matched 2-D US images. Twenty-eight image sets from different neonates with varying severities of IVH and ventricle dilatation were analyzed for this study.

2.6 Statistical Analysis

Linear regression ($R^2$) was performed using GraphPad Prism 6 (GraphPad Software, San Diego, California). A regression of $R^2 > 0.7$ was considered strong, 0.7 to 0.5 moderate, and <0.5 weak. Observer agreement between the two observers on the same 2-D US images was performed through absolute agreement, two-way random ICC using SPSS v.20 (IBM Corp, Armonk, New York). Absolute agreement, two-way random ICC was additionally performed to determine agreement between 2-D US images made on both 2-D and 3-D US for the same observer.

3 Results

3.1 Patient Characteristics

Forty-two neonates were enrolled into the study following an initial diagnosis of IVH and subsequent ventricle dilatation between April 2012 and February 2015. The median age of enrollment was 9 days of life (range 4 to 30 days). Patient characteristics are summarized in Table 1. A total of 265 image sets (2-D and 3-D US images acquired on the same day) were collected for this study. Two hundred and fifty-five 2-D/3-D US exams provided all the required US measurements, with eight image sets missing a 3rd measurement and two missing TODs. Scans were performed between 25 and 42 2/7 weeks corrected gestational age (GA) with the median GA at imaging being 30 3/7 weeks (Fig. 5).

To compare changes between images, patients required at least two 3-D/2-D US image sets, and seven patients were discharged to a secondary care center or home after only a single imaging session leaving 35 to be used in the change study, with their 248 images for a total of 213 comparison points with a median of 6.5 days in between scans (range 3 to 46 days). These change scans were over the same GA range as the direct comparisons (25 to 42 2/7 weeks). Of the 35 patients who had >1 imaging session, the median number of images per patient was 7 (range 2 to 14).

<table>
<thead>
<tr>
<th>Clinical Characteristics of the Study Population. Interventions include ventricle taps, external ventricle drains, and VP shunts.</th>
<th>Direct comparisons (N = 42)</th>
<th>Changes (N = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks ± SD)</td>
<td>27.6 ± 3.0</td>
<td>27.3 ± 3.1</td>
</tr>
<tr>
<td>Birth weight (g ± SD)</td>
<td>1105 ± 450</td>
<td>1062 ± 480</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>30:12</td>
<td>25:9</td>
</tr>
<tr>
<td>Patent ductus arteriosus (%)</td>
<td>30 (66%)</td>
<td>24 (71%)</td>
</tr>
<tr>
<td>Antenatal steroids (%)</td>
<td>24 (37%)</td>
<td>20 (57%)</td>
</tr>
<tr>
<td>IVH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>7 (11%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Grade II</td>
<td>17 (58%)</td>
<td>16 (46%)</td>
</tr>
<tr>
<td>Grade III</td>
<td>10 (21%)</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>8 (11%)</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Required intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (16%)</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>No</td>
<td>32 (84%)</td>
<td>26 (74%)</td>
</tr>
</tbody>
</table>
VVs ranged from 2.7 cm³ (GA at scan 25 weeks) to 96.2 cm³ (GA at scan 26 5/7 weeks), where the overall median was 10.3 cm³ for patients ranging in GA from 25 to 42 2/7 weeks. In comparison, normal preterm neonates without IVH between 25 and 40 weeks GA would have VVs in the range of 0.4 to 2 cm³. 

### 3.2 Observer Agreement

There was a high ICC (>0.95) between the two observers for all 2-D US measurements, which can be seen in Table 2.

### 3.3 Two-Dimensional Ultrasound Measurements Made on Three-Dimensional Ultrasound Images

There was a high ICC (>0.70) between measurements made by a single observer on both 2-D and 3-D US images for VI, AHW, and TOD, which is presented in Table 3.

### 3.4 Ventricle Volumes Compared with Two-Dimensional Ultrasound Parameters

Linear regressions were performed between 3-D US VV and the corresponding 2-D US-based measurements recorded at the same time. Figure 6 shows the linear regressions (bold line) and 95% confidence intervals (CIs) (thin lines) of VV as measured using 3-D US images against the corresponding 2-D US-based measurements (VI, AHW, 3rd, and TOD). While there were trends toward increasing 2-D US measurements with increased VV, the Pearson correlation coefficients were between 0.69 and 0.36. For the left lateral ventricle measurements, there was a single patient (open circles) who tended to have high 2-D US measurements in the coronal plane (VI and AHW), but relatively low VV [Figs. 6(b) and 6(d)]. This appeared to be due to a very large porencephalic cyst on the left side that was communicating with the ventricular system and was erroneously included in the coronal measurements. This patient was removed from the analysis, the correlation for the left side VI and AHW became 0.65 and 0.69, respectively, and the linear regression line on Fig. 6 reflects this patient being removed from analysis.

### 3.5 Changes in Ventricle Volumes Compared with Changes in Two-Dimensional Ultrasound Parameters

We investigated the differences in 2-D and 3-D measurements between successive imaging sessions as an indication of how ventricular size changes post-IVH. Since there can be substantial differences in rates of change from one patient to the next, and due to the various numbers of imaging points per patient, linear regression between adjacent time points was used instead of multilevel modeling, or ANOVA. We believed that the linear regression on the difference of measurements at two time points would be fairly representative of what would happen on a day-to-day use of measurements when comparisons are made with the previous scans. Figure 7 shows the linear regressions (bold line) and 95% CIs (thin lines) of ΔVV as measured using 3-D US images against the corresponding change in 2-D US-based measurements. The Pearson correlation coefficients found between ΔVV estimated using 3-D US and the measured change in 2-D US parameters were between 0.13 and 0.02.

### 4 Discussion

As expected, there was a trend toward increasing 2-D US-based measurements with increased VV (Fig. 6), though there was no 2-D US measurement that “best” correlated with 3-D US VV. Additionally, due to the longitudinal nature of this study, we were able to show that changes in serial 2-D US measurements are weakly correlated to changes in VV and, indeed, there was

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**Table 2** Interobserver agreement through ICC of the VI and AHW for the left and right lateral ventricles as well as the 3rd and the largest TOD. 95% CI are within brackets.

<table>
<thead>
<tr>
<th></th>
<th>VIR</th>
<th>VIL</th>
<th>AHWL</th>
<th>AHWR</th>
<th>3rd</th>
<th>TOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICC</td>
<td>0.98</td>
<td>0.99</td>
<td>0.97</td>
<td>0.99</td>
<td>0.95</td>
<td>0.96</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[0.99 to 0.91]</td>
<td>[0.99 to 0.98]</td>
<td>[0.99 to 0.92]</td>
<td>[0.99 to 0.98]</td>
<td>[0.98 to 0.86]</td>
<td>[0.89 to 0.89]</td>
</tr>
</tbody>
</table>

**Table 3** Intraobserver agreement though ICC between 2-D and 3-D US measurements (ICC) of the VI and AHW for the left and right lateral ventricles as well as the 3rd and the largest TOD. 95% CI are within brackets.

<table>
<thead>
<tr>
<th></th>
<th>VIR</th>
<th>VIL</th>
<th>AHWR</th>
<th>AHWL</th>
<th>TOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICC</td>
<td>0.70</td>
<td>0.70</td>
<td>0.85</td>
<td>0.87</td>
<td>0.77</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[0.91 to 0.50]</td>
<td>[0.90 to 0.54]</td>
<td>[0.93 to 0.70]</td>
<td>[0.93 to 0.73]</td>
<td>[0.89 to 0.56]</td>
</tr>
</tbody>
</table>
not an obvious trend. This is possible due to the variability in 2-D US-based measurements. Previously reported standard deviations of measurements ranged from 2 mm for the AHW\(^9\) to 2.5 mm for the VI and 4 mm for the TOD,\(^8\) whereas the mean absolute change between imaging sessions was 1.4 mm for AHW, 1.2 mm for VI, and 2.7 mm for TOD—less than measurement variability. In comparison, we previously found variance (standard error of measure) to be 0.23 cm\(^3\) for intrauser and 0.24 cm\(^3\) for interuser through a study of 3-D US ventricle segmentation using three different observers.\(^6\) An additional study found variability in 3-D US as measured through standard deviation to be an average of 0.95 cm\(^3\) (range 0.31 to 2.03 cm\(^3\)) for preterm patients born less than 32 weeks GA with ventricles that ranged in size from 5 to 34 cm\(^3\).\(^2\) Given that a single observer, who was the one previously used in the prior published work,\(^6,23\) was used in the present study for 3-D US VV, the mean absolute change in VV of 4.1 cm\(^3\) was much higher than the intrauser variability reported in either previous study.

Attempting to estimate change in an irregular 3-D volume, such as the lateral ventricles, with a linear measurement obtained from 2-D US has obvious limitations other than high measurement error as well. This could explain why, to our knowledge, no previous papers have found strong correlations between VV and linear measurements. This could partially be due to a higher variance in volume measurement made on 3-D US in comparison with MR images as the boundaries are less clear in US images.\(^14\) In Horsch et al.’s MRI-based VV study, they were only able to make one comparison at a single time point per patient at term equivalent age, and only 4 of 28 patients analyzed had ventricle dilatation. As most of the patients in that study would have clustered near the lower “normal” end of VV, the four with ventricle dilatation would have driven the linear regression and strengthened the correlation in that study, especially with such a relatively low sample size. In comparison, in the present study, we had patients with ventricle sizes along the continuum of both normal (2.7 cm\(^3\)) to very large (96.2 cm\(^3\)) and included a total of 255 image sets from 42 patients.

An additional strength of the present study is that we were able to make 3-D US-based VV measurements prior to term equivalent age in every preterm neonate studied with varying severities of ventricle dilatation throughout the course of their stay in the NICU as opposed to only when stable enough to be transferred to an MRI suite. This is in keeping with when

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**Fig. 6** VI (a) right (R) and (b) left (L), AHW (c) right (R) and (d) left (L), (e) third ventricle width (3rd), and (f) TOD measurements against VV from 3-D US. Linear regression is indicated by the bold line along with 95% CI (thin lines). A single patient (open circles) was excluded from regression analysis for VIL and AHWL (b, d) as the measurements included a left side porencephalic cyst and are represented as the cluster of points well above the linear regression.
Recent studies\textsuperscript{6,24} have advised using the >97th percentile of 2-D US measurements as the “action line” for when interventional therapies should begin. While this may provide guidance as to when the first intervention should occur, often patients with severe PHVD will remain over the 97th percentile even after intervention. Thus, subsequent interventions can no longer be guided by 2-D US measurements. The change in 3-D US-based VV as opposed to 2-D US-based measurements might be a better indicator as to when subsequent interventions are required and would provide another metric to those already proposed. Although outside the scope of this study, a future study should be performed using 3-D US VV to determine thresholds for interventional therapy while the patient is in the NICU and during follow-up to determine whether or not a neonate requires shunting, or whether or not the shunt has failed, as there are also no consensus imaging guidelines for that intervention.

The main limitation in our study from a translational standpoint is that the methodology involves manual segmentation of the images offline and does not provide timely data for routine patient care. For 3-D US to become a viable method for determining the VV at the bedside, an automated or semiautomated approach must be developed. This was beyond the scope of this pilot study. Neonates with PHVD pose a particularly challenging segmentation problem as the ventricles change fairly significantly in shape as well as echogenicity over time. For example, the ventricles become rounder over time, and the bleed, initially hyperechoic, slowly breaks down over time and becomes indistinguishable from the hypoechoic cerebrospinal fluid (CSF) (Fig. 8). The change in echogenicity over time makes simple thresholding or local optimization-based methods like active contour or level set methods not useful for this application, while the dramatic change in shape makes atlas-based approaches challenging. Given the inherent variability and prohibitively long segmentation times in manual segmentation, our lab has developed a semiautomated approach based on convex optimization with some encouraging preliminary results\textsuperscript{25} and we have integrated this new software into our acquisition software and are currently piloting this new protocol in a small sample of patients. The semiautomated segmentation algorithm has been validated through a multiobserver study and compared with multiuser manual segmentation.\textsuperscript{26} The segmentation time was reduced to approximately 2 min in comparison to an average of 20 min for manual segmentation. In Chen et al.,\textsuperscript{26} a new framework for future validation of both manual and algorithm-based ventricle segmentation was presented and gave us knowledge on areas of local segmentation variability that were not easily seen using global metrics such as VV agreement, or dice coefficient. In particular, the temporal and posterior horns have the largest segmentation variability in both manual and
obtain the clinical standard set of measurements, while potentially enhancing the ability to determine whether or not a new clinical standard could be developed using 3-D US-based VV estimates. We have presented further evidence that 3-D cranial US has potential as valuable tool; however, a future study with a larger cohort would be necessary before guidelines for intervention could be suggested for the clinical management of PHVD.

Acknowledgments

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References

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