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REGULAR ARTICLE

Ultrasound lineal measurements predict ventricular volume in posthaemorrhagic ventricular dilatation in preterm infants

Isabel Benavente-Fernandez (isabenavente@gmail.com)[1,2], Manuel Lubián-Gutierrez[3], Gema Jimenez-Gomez[4], Alfonso M. Lechuga-Sancho[4], Simon P. Lubián-López[1,2], on behalf of Neonatal Neurology Foundation (Fundación Nene)

1.Neonatology Department, "Puerta del Mar" University Hospital, Cadiz, Spain
2.Fundación Nene (Neonatal Neurology Research Group), Madrid, Spain
3.Faculty of Medicine, University of Cádiz, Cádiz, Spain
4.Research Unit, "Puerta del Mar" University Hospital, Cadiz, Spain

Keywords
Cranial ultrasound, Posthaemorrhagic ventricular dilatation, Preterm infant, Three-dimensional ultrasound, Ventricular volume

Correspondence
Isabel Benavente-Fernandez, Neonatology Department, "Puerta del Mar" University Hospital, 3ª Planta, Avenida Ana de Viya 21, 11009 Cadiz, Spain.
Tel: +34 956002314 |
Fax: +34 956002347 |
Email: isabenavente@gmail.com

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ABSTRACT

Aim: Posthaemorrhagic ventricular dilatation (PHVD) is monitored by conventional two-dimensional ultrasound (2DUS). The aims of this study were to determine the volume of the lateral ventricles using three-dimensional ultrasound (3DUS) in preterm infants with PHVD and to evaluate the relationship between volume and linear measurements.

Methods: Serial 2DUSs and 3DUSs were performed on preterm infants with PHVD admitted to the neonatal intensive care unit at Puerta del Mar Hospital, Cádiz, Spain, from January 2013 to December 2014. The ventricular index, anterior horn width and thalamo-occipital distance were used as ventricular lineal measurements. Ventricular volume was calculated offline.

Results: Serial ultrasounds from seven preterm infants were measured. Each linear measurement was significantly associated with volume, and an equation was obtained through a significant multilevel mixed-effects lineal regression model: ventricular volume (cm^3) = −11.02 + 0.668*VI + 0.817*AHW + 0.256*TOD. Intra-observer and interobserver agreement was excellent with an intraclass correlation coefficient of 0.99.

Conclusion: Lateral ventricular volumes of preterm infants with PHVD could be reliably determined using 3DUS. Ventricular volume could be accurately estimated using three lineal measurements. More studies are needed to address the importance of volume determination in PHVD.

INTRODUCTION

Despite advances in neonatal care, germinal matrix intraventricular haemorrhage (GM-IVH) is a complication that occurs frequently in preterm neonates (1). The incidence of this entity ranges from 18% to 38% and is inversely related to gestational age (2). Posthaemorrhagic ventricular dilatation (PHVD) occurs in approximately one-third of preterm neonates with severe GM-IVH (1). It is most commonly defined as a ventricular enlargement, with a ventricular index (VI) according to Levene, that exceeds the 97th percentile for gestational age (3,4). PHVD secondary to GM-IVH that requires at shunt has shown to be a marker of poor neurodevelopmental outcome (3). Serial two-dimensional ultrasound (2DUS) measurements allow the diagnosis and follow-up of PHVD. Several lineal measurements have been described by different research groups (4–7), but the ones that are most widely used in routine practice are VI, anterior horn width (AHW) and thalamo-occipital distance (TOD).

Ventricular volume through three-dimensional ultrasound (3DUS) appears to be an accurate technique that

Abbreviations
2DUS, Two-dimensional ultrasound; 3DUS, Three-dimensional ultrasound; AHW, Anterior horn width; GM-IVH, Germinal matrix intraventricular haemorrhage; ICC, Intraclass correlation coefficient; NICU, Neonatal intensive care unit; PHVD, Posthaemorrhagic ventricular dilatation; r, Pearson's correlation coefficient; TOD, Thalamo-occipital distance; VI, Ventricular index; VOCAL, Virtual organ computer-aided analysis.

Key notes
- Posthaemorrhagic ventricular dilatation (PHVD) in preterm infants is usually monitored by two-dimensional ultrasound using lineal measurements, but little is known about how they reflect ventricular volume.
- This study showed how three-dimensional ultrasound (3DUS) produce highly accurate serial volume measurements of lateral ventricles and how lineal measurements were related to volume.
- Further research is needed to address the role of 3DUS in PHVD in preterm infants.

enables volume calculation without prolonging a routine cranial sonographic examination of infants (8). 3DUS ventricular volume calculation has also been shown to have good correlation to ventricular volume through magnetic resonance imaging (9,10). Ventricular size has been related to structural brain damage and neurodevelopment (11–15).

The aims of this study were to determine the volume of the lateral ventricles using 3DUS in preterm infants with PHVD and to evaluate the relationship between volume and ventricular linear measurements.

PATIENTS AND METHODS

Very low birthweight preterm infants admitted to the neonatal intensive care unit in Puerta del Mar hospital who developed PHVD were prospectively included in this study. The study period was from January 2013 to December 2014.

Informed consent was obtained from all parents of infants included in the study.

Perinatal data and clinical courses were prospectively collected. Exclusion criteria included chromosomal disorders, congenital abnormalities, congenital infections and proven metabolic or malignant disorders.

Two-dimensional ultrasound and 3DUS were both carried out in the same ultrasonography study with the infant lying supine with his or her head turned to the right.

Two-dimensional ultrasound

Study patients underwent cranial 2DUS ultrasound every day to monitor ventricular size and determine their treatment based on linear measurements.

A coronal view, with the plane of the scan at the level of the interventricular foramina of Monro, was obtained to evaluate the VI according to Levene, known as the distance between the falx and the lateral wall of the anterior horn in a horizontal direction (4) and the AHW according to Davies, described as the distance between the medial wall and floor of the lateral ventricle at the widest point (7). The last lineal measurement was taken in an oblique parasagittal view, which demonstrated the entire lateral ventricle. The TOD was then measured from the outermost point of the thalamus at its junction with the choroid plexus to the outermost part of the occipital horn posteriorly (5,7).

Three-dimensional ultrasound

Volume acquisition was carried out through the 4D option in the 3D/4D Voluson i portable ultrasound system (GE Healthcare, Milwaukee, WI, USA). First, the transducer (S-VNA5-8B, 5–8 MHz), using a centre frequency of 6.5 MHz, was situated in the third coronal plane, and the scan angle was settled to 90°. With the transducer fixed in that position, the beam would move from anterior to posterior planes and from side to side through lateral planes. Volumes were saved, and analysis was performed offline with 4D-view version 10.0 software (GE Healthcare).

Volume measurements were then obtained by the Virtual Organ Computer-Aided Analysis (VOCAL) method (General Electric Medical Systems, Kretztechnik, Zipf, Austria), which has been evaluated both *in vitro* (16) and *in vivo* (17–19), with high reliability, validity (16) and good intra-observer and interobserver agreement (10,16,17,20–22). In fact, the VOCAL method is considered the gold standard 3DUS method for performing volumetric measurements (22).

This software tool allows the performance of volume measurements, by rotating the organ or structure of interest around a fixed axis, while 2DUS contours are manually or automatically delineated on each plane. Different rotation angles (6°, 9°, 15° and 30°) for each contour plane can be selected, which are related to the number of rotation steps necessary to perform the measurements. For this study, we used a rotation angle of 15°, because it allows accurate measurements with high accuracy (22).

The starting plane was the view of the three horns of the lateral ventricle (23), obtained once orthogonal planes were optimised and rotated to a position where the anteroposterior ventricular axis was perpendicular to the vertical rotation axis (Fig. 1). Measurements were carried out through manual delimitation of the lateral ventricle contour in the 12 given planes (Fig. 2).

Once accomplished, the software presented the twelve planes of measurement for eventual contour corrections, automatically calculated the final volume and rendered the respective ventricular surface (Fig. 3).

One observer (IBF) was responsible for the lineal measurements. No intra-observer or interobserver variability of the linear measurements (VI, AHW, TOD) was assessed, as they have been studied and reported elsewhere and this study was not intended for that purpose.

Two observers (IBF and MLG) carried out volume measurements on stored images. Intra-observer variability was evaluated by calculating the intraclass correlation coefficient (ICC) of the three volume measurements that each observer obtained in 30 ventricles. They were blinded to previous measurements. We determined the interobserver reliability by calculating the ICC for the first of the three measurements of each observer. Both observers were blinded to the other's data.

Statistical analysis

Data are first presented in a descriptive manner using the average standard deviation (±) or the median (minimum–maximum) according to the variable's distribution. Simple correlations – namely Pearson's correlation coefficient – and linear regressions were calculated for lineal measurements and volumes. The aim of this study was to create a predictive model of volume calculation through lineal measurements (VI, AHW, TOD). We used multilevel linear mixed-effects models to adjust for correlation as we made repeated observations for the same subject.

To assess interobserver and intra-observer variability, the ICC was calculated as mentioned before. The strength of agreement scale of Fleiss (24) was used for interpretation.

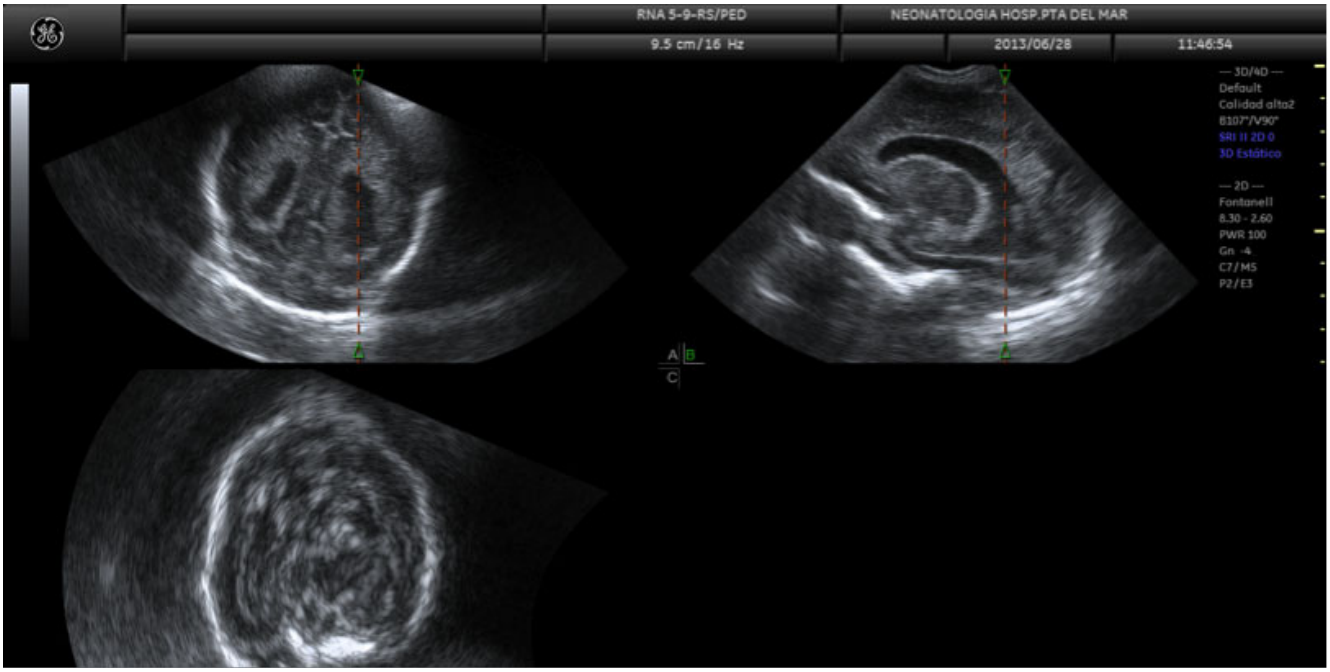

Figure 1 Three orthogonal planes view. On plan B, we obtained three horn views of the lateral ventricle.

The strength of agreement or reliability was considered poor if the ICC was <0.4, low to good from 0.4 to 0.75 and excellent if higher than 0.75.

Statistical analysis was conducted using Stata 13.0 (StataCorp. 2013. *Stata Statistical Software: Release 13*; StataCorp LP, College Station, TX, USA). A result was considered statistically significant at $p < 0.05$.

The study was approved by the Ethical Committee of Hospital Puerta del Mar following the Declaration of Helsinki recommendations and based on the Oviedo Apostille Convention, which accounts for current Spanish legislation. Written informed parental consent was obtained in each case.

RESULTS

Of all the patients with a birthweight of <1500 g born during the study period, 14 developed PHVD. Of those, seven met inclusion criteria (Fig. 4). Serial 2DUS and 3DUS were performed to monitor evolution and indicate neurosurgical treatment if necessary. A total of 130 ventricles with PHVD were measured with determination of linear measurements in 2DUS and 3DUS ventricular volume.

The mean VI was 12.9 mm (±1.7), the median AHW was 7.8 (3.6–16.68 mm) and the median TOD was 26.1 (14.15–37.97).

Each predictor variable, namely linear measurements, was significantly correlated using Pearson's correlation coefficient, with each other predictor variable and with volume as shown in Table 1. VI and AHW accounted for the most elevated correlation (84%), while both frontal horn measures had poor correlation with TOD (28% VI-TOD and 38% AHW-TOD). VI was found to explain 39.4% of the volume variability as shown by adjusted R-squared (R^2_{adj}) in the simple lineal regression analysis ($p < 0.0001$) with the equation: volume = $-12.26 + 1.81 \times$ VI. AHW was found to explain 49.8% of volume variability with the equation: volume = $-0.41 + 1.43 \times$ AHW ($p < 0.0001$). TOD was found to explain 51.9% of volume variability with the equation: volume = $-7.99 + 0.75 \times$ TOD ($p < 0.0001$) (Fig. 5). Head circumference showed no significant correlation with VI, AHW or volume. The major correlation coefficient was found to be related to TOD ($r = 0.29$; $p = 0.007$) with a $R^2_{adj} = 0.0747$, which means that this association was of no clinical relevance.

Linear mixed-effects model

As the measurements were only carried on a few patients, we used multilevel mixed-effects linear regression to statistically correct for repeated measurements, with maximum likelihood as estimation method. The main objective was to develop a predictive model of ventricular volume through linear measurements: VI, AHW and TOD. Regression coefficients and a summary of statistics determining independent variable contributions to regression effects are shown in Table 2.

Each of the predictor variables had a significant effect in the full model ($p = 0.001$ for VI and $p < 0.0001$ for AHW and TOD). The three-predictor model was able to account for 0.75% of the variance in ventricular volume: $F_{3,126} = 128.92$, $p < 0.0001$, $R^2_{adj} = 0.75$.

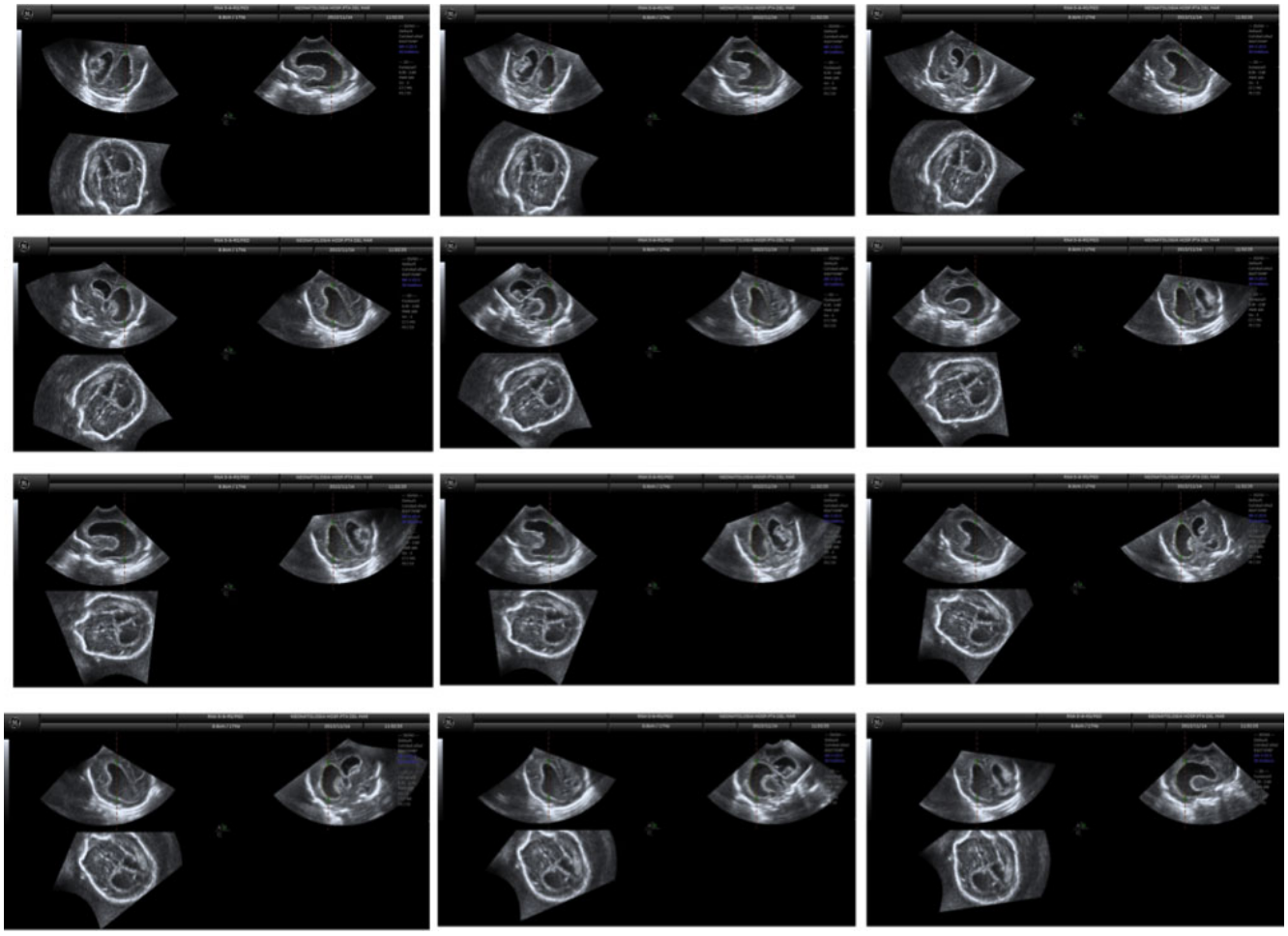

Figure 2 Illustration of the 12 planes obtained to measure volume by virtual organ computer-aided analysis (VOCAL) method.

The intra-observer and interobserver reproducibility for the various ventricular volume measurements was excellent. The resulting ICC obtained to estimate intra-observer and interobserver reliability is shown in Table 3. We found a high degree of agreement with minimal amounts of measurement error introduced by the independent observers. As the 30 ultrasounds selected for intra-observer and interobserver variability belonged to four patients, we measured ICC again, only considering measurements in different subjects – therefore not repeated measurements – with no substantial changes (ICC: 0.999; 95% confidence interval 0.984–0.9999).

DISCUSSION

We analysed 130, 2DUS and 3DUS cranial ultrasounds of seven very low birthweight preterm infants with PHVD and found a strong correlation between lineal measurements and ventricular volume. This correlation was an important finding and, in addition, our study was the first to report a predictive model of ventricular volume in PHVD in preterm infants using the given equation.

Lineal measurement of the lateral ventricles using 2DUS is the gold standard to monitor ventricular size and assess the need for neurosurgical intervention (7,25). However, there is significant heterogeneity in the diagnostic and therapeutic approach of PHVD among different neonatal units (26). VI, AHW and TOD are most frequently used to monitor ventricular dilatation through 2DUS and many studies have demonstrated high intra-observer and interobserver reliability in these measurements. Given the complex morphology and disposition of the lateral ventricles, in an oblique plane with respect to the sagittal axis, the study aimed to determine how well one, two or three of these measurements would reflect the dynamic and progressive change in volume in PHVD. To our knowledge, there have been no studies that have related linear measurements to ventricular volume through serial ultrasounds in preterm infants with PHVD.

To answer the above, this study demonstrated that calculation of ventricular volume through VOCAL is a reproducible, easy and reliable technique, with a very high intra-observer and interobserver reliability in PHVD. The procedure has been described before in foetal brains

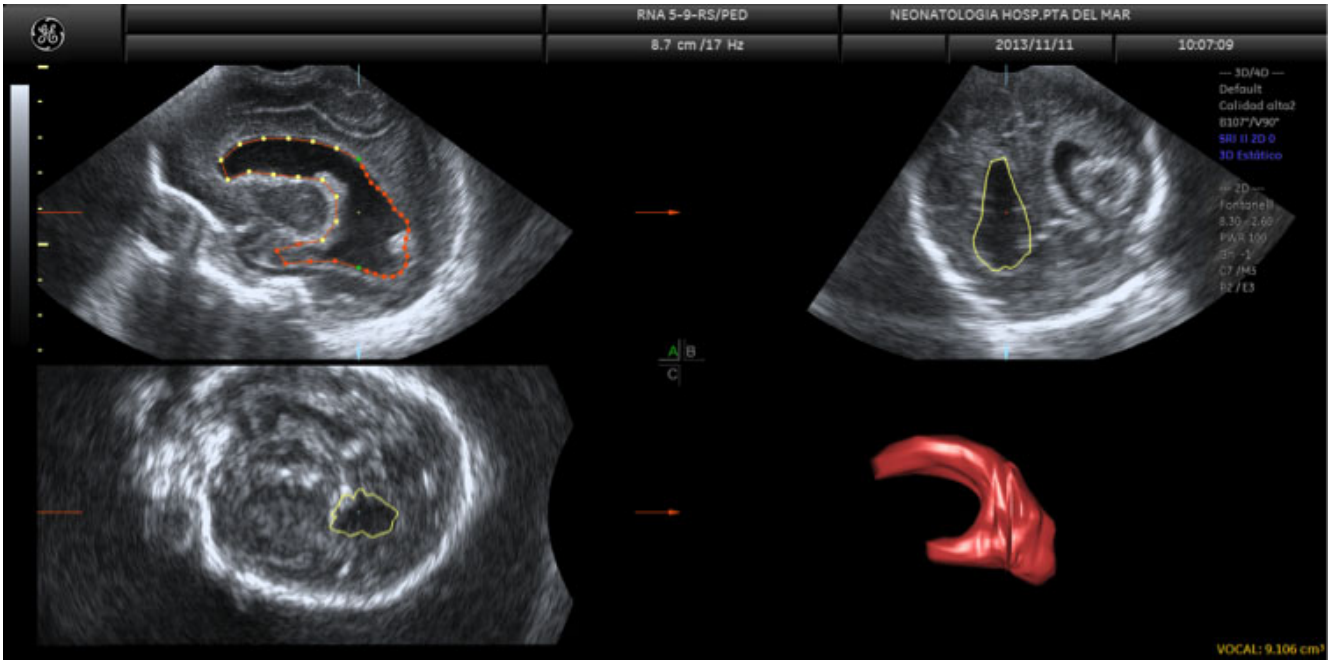

Figure 3 Final ventricular rendering.

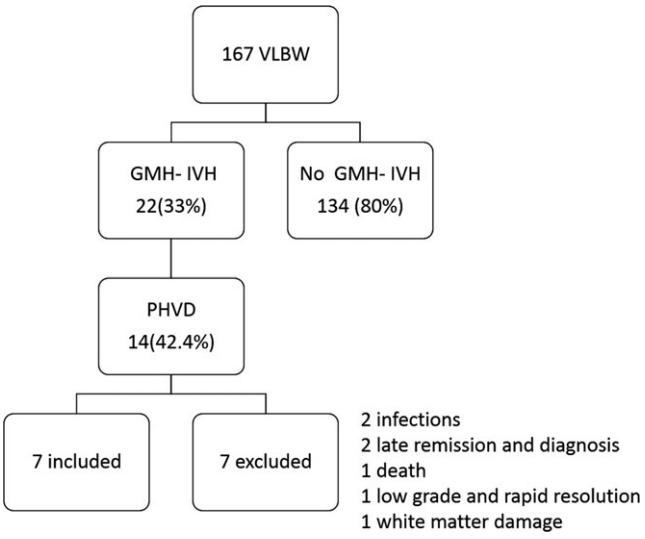

Figure 4 Flow diagram.

Table 1 Correlation coefficients

	Volume	VI	AHW
VI	0.6317		
AHW	0.7084	0.8359	
TOD	0.7233	0.2780	0.3821

VI = Ventricular index; AHW = Anterior horn width; TOD = Thalamo-occipital distance.

(10,20,27), in normal preterm infants at different gestational ages (28) and at term-equivalent age to study correlation with magnetic resonance imaging scans (9). However, a common limitation of these studies is that they failed to give volume an important role in monitoring ventricular size. Our study was the first to prospectively carry out these measurements in serial 3DUS ultrasound in preterm infants with PHVD.

All three lineal measurements were studied in terms of their independent correlation with ventricular volume and, to our knowledge, this has not previously been explored. Findings showed that either VI, AHW or TOD taken singularly, or in pairs, would better describe ventricular volume than all three measurements together. The three measurements explained 75% of the volume variation. Given the heterogeneity in the diagnostic and therapeutic approaches among European neonatal units reported by Brouwer et al. (25), the equation obtained could suggest that the three lineal measurements should be the standard approach to PHVD. This model could also be used as a predictive model and guide future studies that relate to ventricular volume, the neurosurgical approach and patient prognosis as it can be used in units that work with 2DUS.

It is necessary to highlight the absence of any association between head circumference, ventricular volume, VI and AHW. This finding supports previous studies that demonstrated how ultrasound measurements were superior to clinical findings that suggested elevated intracranial pressure, such as a tense fontanelle, sunset phenomena of the eyes or measurements of the head circumference (25,29). This enhances the need for serial cranial ultrasounds in the neonatal intensive care unit to assure an adequate diagnosis

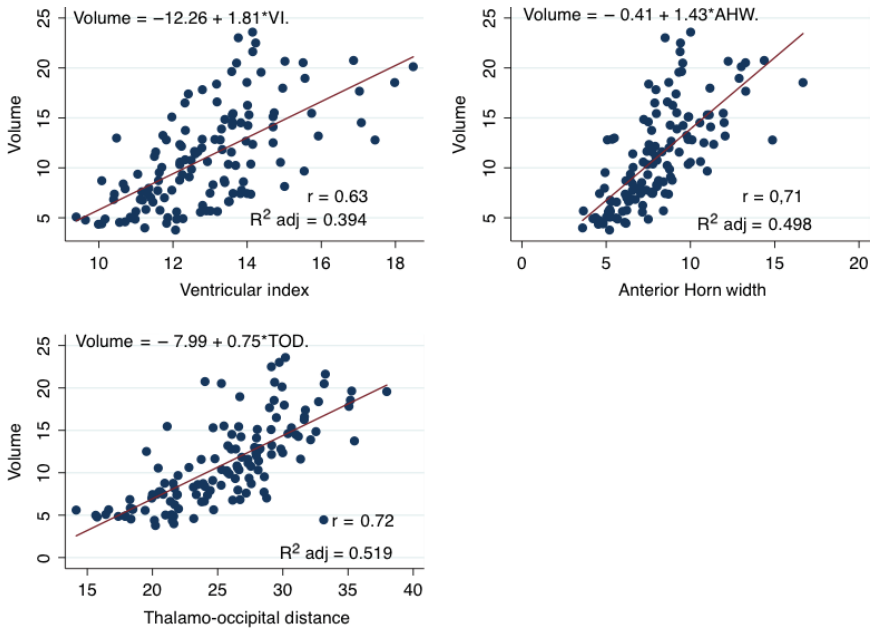

Figure 5 Bivariate analysis. Correlation and simple lineal regression.

Table 2 Mixed-model effect parameters and equation of predictive ventricular volume

	Coefficients	Standard error	p
VI	0.668	0.195	0.001
AHW	0.817	0.134	0.0001
TOD	0.256	0.055	0.0001
Constant	−11.025	2.176	0.0001

Number of observations = 130; Number of groups = 7
Observations per group: minimum = 4; average = 18.6; maximum = 45
Log likelihood = −281.205; p = 0.0000; R^2_{adj} = 0.75
Random-effects covariance = 4.980; Std err = 2.949
Equation ventricular volume (cm^3)
= −11.025 + 0.668×VI + 0.817×AHW + 0.256×TOD

VI = Ventricular index; AHW = Anterior horn width; TOD = Thalamo-occipital distance; Std err = Standard error.

Table 3 Interobserver variability and intra-observer reproducibility of ventricular volume measurements

	ICC	CI 95%	p
Interobserver (IBF-MLG)	0.999	0.998–0.999	0.0001
Intra-observer 1 (IBF)	0.993	0.986–0.996	0.0001
Intra-observer 2 (MLG)	0.997	0.994–0.999	0.0001

ICC = Intraclass correlation coefficient; CI = Confidence interval.

and follow-up of GM-IVH and its complications for an early therapeutic approach to PHVD.

A limitation of our study was the small sample size, as only seven patients were included in the study. Nevertheless, an advantage of the statistical approach we carried out, through mixed-effects models, is that they do not require a minimum sample size for a particular group (30). Given the significant results obtained through this model, we think it can be generalised, while new studies with bigger sample size are recommended.

CONCLUSION

VI, AHW and TOD were related to, and represented, dynamic and progressive change in the ventricular system volumes of preterm infants with PHVD. This study suggests an optimal approach to ventricular volume estimation in patients with PHVD that uses all three measurements rather than one or two measurements. Estimating ventricular volume using 2DUS measures can lead to greater knowledge of the course of PHVD. Future studies can help to determine the role of ventricular volume as a predictive marker of neurological outcome in preterm infants with PHVD.

FUNDING

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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