Terminal veins and neonatal intraventricular haemorrhage of prematurity: a sonographic approach

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Abstract

Purpose: To evaluate the sonographic appearance and velocities of terminal veins (TVs) in premature neonates without/with germinal matrix (GMH) or intraventricular haemorrhage (IVH), and to investigate for an early sonographic finding, helpful in the prognosis of IVH.

Material and Methods: Two groups of premature babies (24-36 gestational weeks) were prospectively studied. Group I included 60 neonates without haemorrhage and Group II 40 neonates with GMH/IVH. TVs were evaluated for their presence, type of flow, time-averaged maximum (Tmax) and time-averaged mean (Tmean) velocity by colour and pulsed Doppler.

Results: In Group I, 117 out of 120 TVs (97.5%) were visualised, with continuous, monophasic flow pattern. Statistical analysis of Tmax and Tmean velocities documented that both increased in a linear association with gestational weeks. Tmax velocities ranged from 2.04 cm/sec (24 gestational weeks) to 4.63 cm/sec (36 gestational weeks); Tmean velocities ranged from 1.16 cm/sec to 2.81 cm/sec, respectively. In Group II, 14 GMHs, 33 IVHs Grade II, 17 IVHs Grade III and 4 parenchymal haemorrhagic infarcts (PHIs) were demonstrated. One large GMH, two IVHs Grade II and one IVH Grade III with no flow in the ipsilateral TV progressed to PHI. In 4 more PHIs already
developed in the initial sonogram, no TV flow was demonstrated. 

**Conclusions:** TVs can be sonographically visualised in almost all prematures. When a GMH-IVH has occurred, TV demonstration represents a good prognostic sign for the haemorrhage evolution. In contrary, no TV flow seems to be a bad prognostic sign preceding the PHI appearance.

**1. Introduction**

Brain haemorrhagic disease in premature neonates presents as a continuum of germinal matrix haemorrhage (GMH), intraventricular haemorrhage (IVH) and periventricular parenchymal haemorrhagic infarct (PHI). It occurs in the first three days of life in 75% of cases [1, 2]. Epidemiologic studies have shown that the incidence of severe GMH-IVH has declined since the 1980s, but has remained substantially stable throughout the 2000s, in contrast with a significant decrease in mortality rates observed among extremely immature neonates due to the improved perinatal care [3-9]. Thus, brain haemorrhage continues to be a key abnormality of prematurity [10]. A large IVH and especially the presence of PHI is a main underlying cause of short-term mortality, whereas in the remaining cases it is often associated with an adverse neurologic outcome. Inevitably, the outmost clinical significance of PHI is obvious.

The physiopathogenic mechanisms that cause brain haemorrhagic disease are better known today than in the past, but yet not fully elucidated. Systemic haemodynamic instability and immature cerebral blood pressure autoregulation of prematurity are key factors predisposing to the development of haemorrhage at the germinal matrix area (GMH or IVH Grade I) [2, 11-18]. Blood may rupture through the ventricular wall and spread into the ventricular lumen, without or with dilatation of the lateral ventricle (IVH Grade II or III, respectively). Clot’s mass effect in the germinal matrix causes congestion, stasis and thrombosis of the ipsilateral terminal vein (TV), as it passes near the germinal matrix and it is compressed or even displaced. Subsequent compression of medullary veins and impaired venous return in the veins draining white matter results in the development of PHI [19-22].

The systematic use of gray-scale brain sonography with its well-known advantages has already offered a lot in early diagnosis and grading of IVH of prematurity, when haemorrhage has already developed [23-25]. However, it does not offer prognostic information about IVH progression, future neurologic sequelae and developmental outcome. In addition, cerebral venous vasculature, including TVs, is poorly described in the literature, especially in infants and few colour Doppler data exist [26-30]. However, it is assumed that TVs are directly implicated to the pathogenesis and evolution of GMH-IVH [19, 20]. Anatomically TVs are formed by the confluence of the anterior septal, thalamostriate, superior choroidal veins and several medullary veins. They course beneath the stria terminalis, posterior to the foramen of Monro, and continue as the internal cerebral veins.

Given the paucity of relative studies, we conducted this prospective study: a) to investigate if TVs can be sonographically visualised in premature neonates without/with GMH-IVH, which are their velocities and if their patency and velocities are affected by GMH-IVH and b) to answer our primary question, if there is an early sonographic finding, related to TV implication in IVH, which could be helpful in the prognosis of IVH evolution and should probably allow for clinical neonatology efforts to minimise subsequent sequelae.

**2. Material and Methods**

The study was approved from the local ethics com-
mittee and it was performed according to the ethical standards as described by the Declaration of Helsinki. Informed consent for participation in the study was obtained from all parents.

This prospective study enrolled two groups of premature neonates [gestational age (GA) 24-36 weeks (mean age 28.7 gestational weeks-GWs)] who were admitted in the Neonatal Intensive Care Unit of our hospital during a two-year period. Group I consisted of 60 premature neonates without GMH-IVH. Group II included 40 neonates with uni- or bilateral GMH-IVH.

Gray-scale sonographic examinations of the brain were performed via the anterior fontanelle. Accessory windows were complementarily used. All sonograms were performed with a GE Logic 5 ultrasound unit using a microconvex 5-8 MHz and a linear 10-12 MHz transducer. Colour and pulsed Doppler technique were applied to coronal sections of the brain for the TVs evaluation.

Each neonate was examined for the presence of GMH, IVH and PHI. Maximum transverse diameter was obtained for each GMH. Each normal positioned TV was illustrated with colour Doppler, laterally and inferiorly to the floor of each lateral ventricle near the germinal matrix, coursing inferiorly and centrally to merge to the ipsilateral internal cerebral vein. A displaced TV was shown either away from the lateral ventricle’s wall, due to an intervening GMH or with a more inferior and lateral course due to ventricular dilatation. Since TVs flow velocities were low, the wall filter was set at the lowest setting and the colour scale at the minimum setting (2 cm/sec). Colour gain was set individually to maximise vascular signal intensity and minimise tissue motion artefacts.

The type of flow was evaluated with the use of pulsed Doppler. Tmax (time-averaged maximum) and Tmean (time-averaged mean) velocities were automatically calculated on representative tracings of velocity.

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**Fig 1.** Normal TVs: a. Coronal colour Doppler sonographic image of the brain shows TVs at the floor of the lateral ventricles (arrows). b. Pulsed Doppler study of normal TVs with continuous flow pattern and Tmax/Tmean estimation. c. Coronal colour Doppler image of another neonate shows a displaced right TV (narrow arrow) due to a large right GMH (transverse diameter 8.2 mm-horizontal yellow line) and a normal positioned left TV (wide arrow).
waveforms lasting at least 3 seconds. Optimal technical conditions were required for reliable values of flow velocities. A correct beam axis and sample volume was placed and spectral analysis was obtained. The angle of insonation was held at ≤60°.

In group I, brain ultrasound examination was performed in the first week of life. The capability and incidence of left/right TV visualisation, their flow spectrum and velocities were recorded.

In group II, brain ultrasound was performed between day 1 and 3 of life and was repeated every 3 days for the 10 days after the initial diagnosis of haemorrhage. Two to four sonographic weekly re-examinations followed, depending on size and evolution of haemorrhage. The grade and size of the haemorrhage, the presence of flow in normal positioned or displaced TVs, their flow spectrum and velocities were evaluated. The course of every haemorrhage was followed, as well as the possible reappearance of the ipsilateral TV and its velocities. No flow in the TV was attributed to its thrombosis. The reliability and prognostic significance of this sonographic finding for the development of PHI was investigated.

**Statistical Analysis**

Continuous variables were summarised using mean (SD), while the categorical variables as count (percentages), separately for Group I and Group II neonates. In Group I neonates, a linear model was used for assessing the association of gender, age at the examination day and GWs to Tmax/Tmean velocity of right/left TV (Four models). The differentiation of Tmax/Tmean velocities between right/left TV was investigated, after adjusting for gender, age at the examination day and GWs. In Group II neonates, the relationship between Tmax/Tmean velocity, right/left TV with gender, age at the examination, GWs, initial grade of haemorrhage, evolution of haemorrhage and TV displacement was investigated with the use of a linear model (four models). The differentiation of Tmax/Tmean velocities between right/left TV was investigated, taking into consideration gender, age at the examination, GWs, initial and final grade of hemorrhage and TV displacement. In all analyses, statistically significant variables were selected with the use of backward stepwise procedure. Type I level of significance was set at 5% and the statistical package R was employed for all analyses.

**3. Results**

**Group I**

Group I consisted of 60 premature neonates of GA 24-36 weeks, (mean age 28.5 GWs), 37 males (61.7%) and 23 females (38.3%) without GMH-IVH: 117 out of 120 TVs were visualised with the colour Doppler technique (Fig. 1a). TVs of a 26-GW premature neonate could not be detected, as well as the right TV of a 28-GW neonate. TV flow pattern was continuous and monophasic. Tmax and Tmean velocities were estimated (Fig. 1b). Univariate analysis showed that the mean/median value and the variance of Tmax of right and left TVs had
no significant difference. Similar analysis showed that the mean/median value of Tmean for right and left TVs were significantly different (p=0.04 and p=0.05 respectively), but Tmean velocity variance was not significantly different (p=0.4) (Fig. 2).

The association of gender, age at examination day and GWs to Tmax and to Tmean of right and left TVs respectively was also investigated. The only variable that significantly correlated to Tmax, as well as Tmean was “GWs” (p<0.01), revealing a linear relationship, which was not statistically different for the two TVs (Tables 1, 2). Tmax velocities ranged from 2.04 cm/sec at 24 GW to 4.63 cm/sec at 36 GW and Tmean velocities from 1.16 cm/sec to 2.81 cm/sec, respectively.

**Group II**

Group II consisted of 40 preterm neonates, 24–36 GW (mean age 29 GW) (Table 3). There were 23 (57.5%) males and 17 (42.5%) females. The initial sonographic examination was performed during the first 3 days of life; 12 (30%) were examined at day 1 after birth, 9 (22.5%) at day 2 and the remaining 19 (47.5%) at day

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<th>Gestational weeks</th>
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<td>24</td>
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<tr>
<td>26</td>
<td>2.47</td>
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<td>36</td>
<td>4.63</td>
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<tr>
<th>Gestational weeks</th>
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<td>24</td>
<td>1.16</td>
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<td>36</td>
<td>2.81</td>
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3. The grade of intracranial haemorrhage was determined on the findings of the initial sonogram. Sonographic follow-up was determined for each neonate, according to the study protocol. Fourteen GMHs, 33 IVHs Grade II, 17 IVHs Grade III and 4 parenchymal haemorrhagic infarcts (PHIs) were demonstrated. No TV flow was demonstrated in the ipsilateral TV in all four cases of PHI. Moreover, in one case of large GMH, two IVHs Grade II and one IVH Grade III where no TV flow was detected, progression to PHI was shown. In all other cases TVs were patent, although inferiorly and laterally displaced in some cases. The evolution of brain haemorrhage during the sonographic follow-up is shown in detail in Tables 3 and 4. In addition, it was estimated that mean Tmax of right and left TV was 2.5 ± 1.4 cm/sec and 2.8 ± 1.1 cm/sec respectively, while mean Tmean of right and left were TV 1.4 ± 0.8 cm/sec and 1.5 ± 0.7 cm/sec, respectively. The mean/median Tmax and Tmax variance for the right and left TVs did not statistically differ. The same was noted for the

### Table 3. Group II (40 neonates, 24-36 GWs)

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<th>GMH (IVH Grade I)</th>
<th>TV</th>
<th>IVH Grade II</th>
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<th>PHI</th>
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<tr>
<td>8 neonates GMH</td>
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<td>(+): 4 (d): 6 (-): 1</td>
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<td>20 neonates IVH Gr II</td>
<td>2</td>
<td>(+): 1 (d): 1</td>
<td>32</td>
<td>(+): 8 (d): 22 (-): 2</td>
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<td>1</td>
<td>(d): 1</td>
<td>16</td>
<td>(d): 15 (-): 1</td>
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<tr>
<td>3 neonates PHI</td>
<td>1</td>
<td>(d): 1</td>
<td>4</td>
<td>(-): 4</td>
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* (+): TV patent in normal position, (d): TV patent but displaced, (-): no TV flow

**Fig 3.** Neonate 27 GWs with bilateral IVH Grade II: a. Colour Doppler image showing left TV (arrow). Right TV was not depicted. Thrombi within lateral and 3rd ventricles. b. Two days later. Right PHI has occurred and left IVH Gr II remains. Right TV was again not demonstrated with colour Doppler. The left IVH Grade II progressed later to Grade III with patent, though displaced left TV (not shown).
mean/median of Tmean and Tmean variance of the right and left TVs. In a univariate analysis, no significant difference was found between Tmax and Tmean of the right and left TVs. In a univariate analysis, no significant difference was found between Tmax and Tmean of the right/left TV and either IVH grade, IVH evolution or TV displacement. A linear model examining the relationship of gender, age at examination, GWs, initial IVH grade, IVH evolution, TV displacement on Tmax of the right and left TV respectively was considered. The same model was filtered for Tmean. Notably, TV Tmax and Tmean velocities were highest in neonates with IVH Grade II to III. A linear association between either Tmax or Tmean and GWs was shown, similar for right/left TV.

### 4. Discussion

Our study showed that TVs are depicted with the Doppler technique in the vast majority (97.5%) of premature neonates without brain haemorrhage. TV flow pattern is monophasic, continuous, and velocities are increasing in a linear association to GWs. In addition, in premature neonates with GMH-IVH, the detection of ipsilateral TV seems to represent a favourable prognostic sign, while the absence of TV flow is an accurate sonographic sign for the forthcoming development of PHI.

A review of the literature revealed only a few studies accessing cerebral venous vasculature in infants, including TVs. Taylor was the first who used colour Doppler technique to investigate cerebral veins in normal and abnormal neonates and reported TV velocities [21, 29]. He also observed a significant trend between GMH size and decreasing TV velocities and noted that there was no TV flow when a PHI had already developed. In 2004 Schneider studied the TVs of 86 premature (29-36 GWs) [31] and found that 94% of TVs were detected and a linear association of GA to max TVs velocity was demonstrated, without difference between right and left TV [31]. In 2006, Deeg and Lode analysed Doppler contribution to the study of intracranial veins of infants with various pathologies and described the alterations of TV flow during the evolution of an IVH Grade III to PHI [32]. They presented one case of a neonate with IVH Grade II (and patent TV) which progressed to IVH Grade III (with increased velocity of the ipsilateral TV) and sequentially to PHI a (with no TV flow).

Our measurements, regarding the 60 normal preterm neonates (24-36 GWs) (see Results), cannot be compared to those of Taylor (1992), because he studied full-term neonates and doesn’t refer to TVs [29]. Hypothetically however, given that in that study subependymal veins’ mean velocity was 3 cm/sec and internal cerebral veins’ 3.3 cm/sec, it should be ex-
Expected that TVs velocities range in between. Indeed, Tmean TV velocities were lower in our premature neonates. Only in 1995, when Taylor studied 24 abnormal preterm neonates, he reported that TVs of the normal cerebral hemisphere had time average velocities of 2.6 ± 3 cm/sec, with a comment that velocities of the abnormal hemisphere were lower [21]. It should be noted however, that our study includes more abnormal neonates (40 vs 24) of a wider spectrum of prematurity (24-36 vs 24-29 GWs) and more haemorrhages (68 vs 32).

In the current study, 97.5% of TVs of the normal premature neonates were detected with colour Doppler. This percentage is higher than that of Schneider. This could be attributed to the fact that our study is more recent, and brain sonograms were performed in a modern sonographic unit, with higher resolution transducers and more sensitive vascular flow analysis. The velocities

Fig 4. Neonate 29 GWs with bilateral IVH Grade III and haemorrhage in the 3rd ventricle: a. Colour Doppler image. Bilateral TVs are demonstrated, patent though displaced (arrows). b. Gray-scale coronal image of the same neonate six weeks later. The bilateral IVH has regressed.

Fig 5. Neonate 29 GWs with bilateral PHI: a. Colour Doppler image-coronal section. No TV flow is detected bilaterally, whereas internal cerebral veins are apparent (arrows). b. Ten days later. Hypoechoic thrombi remain within the dilated lateral ventricles and porencephalic cysts have already developed.
and the linear relationship between GA and TV max velocity that we noted are consistent with the findings of Schneider [31]. No statistically significant difference was noted between the right and left TV velocities. Moreover, the statistical analysis of simultaneous effect of gender, age at the examination day and GWs on Tmax or Tmean of right/left TV revealed that the only variant that relates significantly to the Tmax or Tmean is “GWs”.

In abnormal neonates, TVs were also detected in all cases, except in the cases of PHI in the initial sonogram and those who progressed to PHI. It should be then emphasised that the illustration of ipsilateral TV was in fact a good prognostic sign in premature neonates of our study. In contrast, no TV flow in a large GMH, 2 IVH Grade II and 1 IVH Grade III preceded the sonographic depiction of PHI. In our opinion, the above findings strongly indicate the TV implication in the pathogenesis of PHI.

5. Conclusions

TVs are depicted with the Doppler technique in the vast majority of normal premature neonates. TV velocities are increasing in a linear association to GWs. In premature neonates with GMH-IVH, the absence of TV flow is an accurate sonographic sign for the forthcoming development of PHI. Thus, in clinical practice, we recommend to look for TV flow when GMH-IVH is detected, in order to predict the pending PHI, with therapeutic and prognostic implications.

Conflict of interest

The authors declared no conflicts of interest.

References


31. Schneider A. [Normal values of blood flow velocity in the terminal vein of preterm infants] [Article in German]. Ultraschall in Med 2004; 25(2): 137-140.
