Three-Dimensional Volumetric Spatially Angle-Corrected Pixelwise Fetal Flow Volume Measurement

Dreidimensionale, raumwinkelkorrigierte, fetale Volumenflussmessungen mit der PixelFlux-Methode

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Zusammenfassung

Ziel: Frühere Versuche, mithilfe von zweidimensionalen Sonogrammen die fetale Gesamtperfusion zu berechnen, scheiterten an methodischen Grenzen. Daher wird zur fetalen Beurteilung noch heute die Bestimmung des Resistance-Indexes der Nabelarterie benutzt, wenngleich dessen methodische Basis unzureichend ist. Wir entwickelten daher ein neuartiges Verfahren der Flussvolumenkalkulation aus dreidimensionalen Farbdoppler-Bildern der Nabelschnur, welches hier vorgestellt wird.

Material und Methoden: Aus 281 dreidimensionalen Farbdoppler-Bildern der Nabelschnur von 124 Einlingen in der 23. – 41. Schwangerschaftswoche wurden mit der PixelFlux-Software der Raumwinkel der Nabelvene und deren horizontale Querschnittsfläche pixelweise bestimmt. Daraus wurde der Volumenfluss errechnet. Zur Evaluierung der PixelFlux-Methode wurden Phantomflussmessungen vorgenommen.

Ergebnisse: Die Phantomflussmessungen erbrachten eine hochsignifikante Korrelation der tatsächlichen und der mit der PixelFlux-Methode ermittelten Flussvolumina ($p < 0{,}001$; rPearson $= 0{,}987 - 0{,}991$) bei einer exzellenten Interobserver-Korrelation ($p < 0{,}001$; rPearson $= 0{,}997$). Wir konnten einen signifikanten Zusammenhang der raumwinkelkorrigierten fetalen Globalperfusion mit dem Fetalgewicht ($r = 0{,}529$ bei Raumwinkeln kleiner 30° bis zu $r = 0{,}724$ bei Raumwinkeln kleiner 5°) und der Schwangerschaftsdauer nachweisen, einen signifikanten Einfluss des Raumwinkels auf diesen Zusammenhang ($p = 0{,}003$; $r = -0{,}865$) sowie den Effekt der maximal darstellbaren Flussgeschwindigkeit auf die Messungen beschreiben.

Schlussfolgerung: Die neuartige Methode der raumwinkelkorrigierten fetalen globalen Perfusionsmessung überwindet methodische Schwächen herkömmlicher Verfahren der fetalen Perfusionsbeurteilung, ist schnell und einfach

Abstract

Purpose: Early attempts to calculate fetal global perfusion used 2 D images. The results were not sufficiently reliable. That's why RI measurements are still in use despite the fact that they do not reflect the amount of blood passing through the fetus. We present a novel three-dimensional approach to overcome these limitations.

Materials and Methods: In 124 singleton pregnancies between the 23rd and 4st gestational week, a three-dimensional color Doppler sonographic record of the umbilical cord was made, resulting in 281 volume data sets. With dedicated software (PixelFlux) the spatial angle of the umbilical vein was calculated and the true global fetal perfusion was calculated from its horizontal transection as the product of the area of all pixels and the spatial angle-corrected velocity. To validate the PixelFlux technique, phantom flow measurements were carried out.

Results: Phantom flow measurements revealed a highly significant correlation of actual flow volumes and those measured by the PixelFlux technique ($p < 0.001$; rPearson $= 0.987 - 0.991$) with an even higher interobserver correlation ($p < 0.001$; rPearson $= 0.997$). We found a significant correlation of fetal volume flow to gestational age and weight ($r = 0.529$ at spatial angles below 30° to $r = 0.724$ at spatial angles below 5°) and a significant influence of the spatial angle on this correlation ($p = 0.003$; $r = -0.865$).

Conclusion: Spatial angle-corrected global fetal perfusion measurement improves existing approaches to fetal perfusion evaluation, and is feasible, simple and fast. Thus, it can be recommended to explore the relationship of fetal perfusion and disturbances of fetal development.

durchführbar. Sie kann für weitergehende Untersuchungen von Feten, deren Entwicklung und Erkrankungen empfohlen werden.

Introduction

Detailed knowledge of the perfusion of various fetal organs is of fundamental interest for confirming a normal supply of blood to the fetus as well as for evaluating deviations which might cause or reflect diseases of the fetus or the mother. Today, the evaluation of the perfusion of various fetal organs and the fetus as a whole is evaluated by measurements of two flow velocities, peak systolic and end-diastolic flow velocity to calculate the resistance index in a variety of fetal vessels [1] or in a similar way to calculate the pulsatility index (PI) [2]. The main focus is on the umbilical artery [3]. A rising RI is a crucial sign of deteriorating fetal perfusion [4]. Despite its broad use in obstetrics, there are basic objections to the RI [5], since it cannot describe the volume of blood flow [6] through a fetus and thus cannot deliver important information about the supply with oxygen and nutrients. Therefore, attempts to overcome this limitation date back to the 1980 s. First attempts were made at that time to calculate the volume flow inside the umbilical vein as the product of the mean flow velocity and the transsectional area of the vein [7 – 9]. Technical limitations caused substantial uncertainties which resulted in a discontinuation of this method [10].

We present a completely new approach to the volumetric global fetal perfusion measurement. Spatial angle correction and horizontally cut vessel transsections from three-dimensional data as well as the pixelwise evaluation of all moving red blood cells [11 – 13] are the cornerstones of this PixelFlux technique [14].

Aim

Our aim was to investigate whether volume flow measurements using the PixelFlux method could yield a correlation to fetal age and estimated fetal weight in normal pregnancies. We first investigated the optimal technical and imaging conditions for such PixelFlux measurements and performed a phantom flow measurement to validate the PixelFlux technique.

Patients

In 124 singleton pregnancies between 23 and 41 gestational weeks (minimum 161 /mean 237 /maximum 285 days), a three-dimensional record of the umbilical cord was carried out under strictly standardized conditions. During 172 examinations, 281 volume data sets were recorded at various times of pregnancy. The estimated fetal weights were below the 3rd percentile in 19 cases and above the 97th percentile for gestational age in 7 cases. 213 datasets were recorded with a maximum of the color scale of 31 cm/sec and 68 with 23 cm/sec. 245 data sets from 107 women were sufficient for flow calculations, 183 (86 %) with a maximum flow of 31 cm/sec and 62 (91 %) with 23 cm/sec.

Methods

Phantom flow measurements

To measure the volume flow under externally controlled conditions, a phantom was constructed. A Teflon tube with an internal diameter of 2.0 mm was placed in a water basin and fixed so that the tube was running straight at a steep angle towards the ultrasound transducer. The transducer was held by a clamp fixed to a tripod. The tube was perfused with a 4 % rice starch solution in water. This solution was homogeneous and yielded a good color Doppler signal when pumped by a precision laboratory pump through the tube. Color Doppler videos were recorded under standardized imaging conditions (ultrasound device: S2000, Siemens, Germany, linear transducer, color Doppler frequency 4 MHz, the angle of the tube towards the ultrasound propagation line was 36°). The pump rate was changed and repeated color Doppler recordings were made.

To calculate the tube's perfusion, the diameter of 2 mm was sliced into 5 regions of interest of equal size which symmetrically encompassed the entire lumen of the tube. The central ROI was used to calculate the area of a central cylinder, while the neighboring pairs of ROIs parallel to the central ROI were used to calculate the areas of rings surrounding the central ROI in 2 concentric rings. The flow velocity of these ROIs was measured with the PixelFlux software. The flow velocities of two symmetric ROIs were averaged to calculate the mean flow velocities of the ring surrounding the central cylinder or the velocity of more peripheral rings. The transsectional area of these rings and of the central cylinder was calculated and separately multiplied by the respective flow velocity. In this way three distinct flow volumes were calculated using the PixelFlux technique corresponding to the flow volume of the central cylinder and the two surrounding hollow cylinders, which emanate from the four ROIs parallel to the central ROI. The flow volume of the tube was then calculated as the sum of these three separate flow volumes. The flow volumes at different pump rates measured by the PixelFlux method were correlated to the actual flow volumes as pumped by the precision pump. Two separate investigators independently performed these PixelFlux measurements from 87 datasets (mean values based on 191 recordings) at 22 different pump rates.

To evaluate the effect of different measurement depths in a watery fluid, we compared PixelFlux measurements at various measurement sites inside the Teflon tube. A 16-mm section of the tube lying in water at an angle of 36° towards the ultrasound propagation line was equally divided into 10 ROIs one lying upon the other. The rectangular distance of the topmost ROI from the transducer was 15 mm and that of the lowermost was 29 mm. A single focus was placed at a depth of 25 mm corresponding to the fourth lowest ROI. 18 phantom flow measurements were made (180 equal ROIs at 10 different depths).

3 D color Doppler sonography of the umbilical cord

All 3 D sonographic examinations were done with a Voluson 730 Expert ultrasound system (GE Medical Systems, Zipf, Austria) and a 4 – 8 MHz transabdominal transducer. All imaging features were fixed. At the beginning of the study optimum imaging conditions were sought and defined as a preset which was stored on the machine. This preset was always used and not changed. The fixed parameters included among others gain, color Doppler frequency and transducer type. Only the pulse repetition frequency was changed to record videos with a color scale with maximum flow velocities of 23 or 31 cm/sec. Volume data files were recorded and sent to a personal computer which was equipped with the 4 D View software 5.0 (Kretz, Austria).

Transformation of the volume data files

1. The volume data files were opened with the 4 D View software.
2. The frontal and sagittal imaging planes were shifted in parallel shifts to locate a suitable segment of the umbilical vein (UV) which is defined as follows:
   a) The UV should run as steep as possible towards the horizontal plane to reduce measurement errors as a consequence of the dependence of measured flow velocities by the cosine of the angle between the ultrasound propagation line (perpendicular to the transducer surface) and the UV
   b) The resulting horizontal plane should show a well defined section of the UV with clear borders and an area as small as possible.
   c) The scale of the images was maximized by the respective software tool to reduce measurement errors of distances and areas.
3. After completing this, a bitmap file (*.bmp) of the horizontal section of the UV was stored for further use in the PixelFlux software (▶ **Fig. 1**).

These preparatory steps aimed at the selection of a transsection of the umbilical vein at a point where the sagittal and frontal angles of this vessel were as small as possible while the vein itself was clearly discernible from the arteries and the amniotic fluid. This is to provide a template for the essential pixelwise measurement of velocities and area inside the vein. The following steps such as spatial angle calculation, velocity measurements from each pixel's color hue, the angle correction of this measurement and the measurement of the vessel's transsectional area were then performed by the PixelFlux software.

Spatial PixelFlux measurements of the umbilical vein volume flow

The bitmap file produced with the 4 D View software was loaded by the PixelFlux software [14]. To calculate areas, a distance calibration of the image is necessary. The distances of the image and the color scale were calibrated by the investigator by clicking on a one centimeter distance at the distance scale displayed on the lateral border of the image. To calculate the flow velocity of each pixel it was necessary to calibrate the color hues according to the color bar which was provided by the ultrasound machine. This color bar indicated at the top the maximum velocity which was encoded in color in the respective image. The PixelFlux software read out the color bar with all its hues and the maximum velocity. Then the software assigns individual flow velocities to each color hue. These velocity values, which were translated from the color hues, were the basis for the calculation of flow velocities by the software.

The next step was the calculation of the spatial angle of the umbilical vein. For this the angles of the UV in the frontal (the image in the upper left quadrant of the three-dimensional image-set delivered by the ultrasound machine) and the sagittal plane (in the right upper quadrant) towards the horizontal plane were measured by clicking on the center of the vessel (which is marked by a red dot by the 4 D View software) and by then clicking on the axis of the vessel. Both clicks define the angel of the vessel in the respective planes from which the spatial angle is then calculated by the software. After this, the transverse section of the UV in the horizontal plane (left lower quadrant of the image) was encircled. Each color pixel inside the lumen of the UV was assigned its spatially angle-corrected velocity value by the software and the mean flow velocity of all color pixels inside the UV was calculated. The area of all UV pixels was calculated and multiplied with the mean spatially angle-corrected flow velocity of all UV pixels by the software. The result was the true flow volume per time running through the UV.

It took about 30 sec to 1 min with the 4 D View software to find the appropriate measurement plane in the 3 D dataset by performing parallel shifting of the three major planes (frontal and sagittal planes and consequently the horizontal plane) and about 10 sec to do the perfusion measurement with the PixelFlux software.

Statistics

Statistical calculations were done with the PASW 18.0.0 software (IBM Corp. Somers, NY, USA). Correlations were calculated according to Pearson, groups were compared with the Mann-Whitney-U-test. P-values less than 0.05 were regarded as statistically significant.

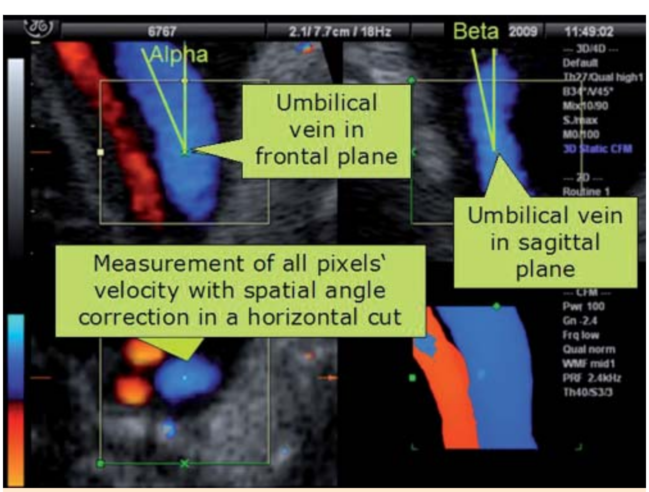

Fig. 1 3 D image of the umbilical vein after selection of a suitable segment. The angles of the UV in the frontal as well as in the sagittal planes are indicated.

Abb. 1 3-D-Abbildung der Nabelvene nach Auswahl eines geeigneten Segments. Die Winkel der Vene mit der Ultraschallausbreitungslinie in der Frontal- und der Sagittalebene ist angegeben.

Results

Phantom flow measurements with the PixelFlux software showed an excellent correlation to pump rates (▶ **Table 1**, ▶ **Fig. 2**). The Pearson correlation coefficient of the pump rate and the PixelFlux measurements of investigator 1 was 0.987 and for investigator 2 it was 0.991. The measurements of both investigators correlated with 0.997. The measurement results in stacked ROIs in different depths varied significantly. The ROIs around the focus zone showed nearly no significant differences but ROIs more proximal to the transducer had significantly higher flow measurements. There was no clear linear relation between the depth of the ROI and the measurement results. The position of the focus was more relevant than the depth (▶ **Fig. 3**).

UV volume flow data correlated significantly with the gestational ages of the fetuses and the estimated fetal weights (▶ **Table 2**). The weakest correlation was achieved if mixed recordings with 23 as well as 31 cm/sec were evaluated together (▶ **Table 3**). The correlation was better in ultrasound recordings with the maxi-

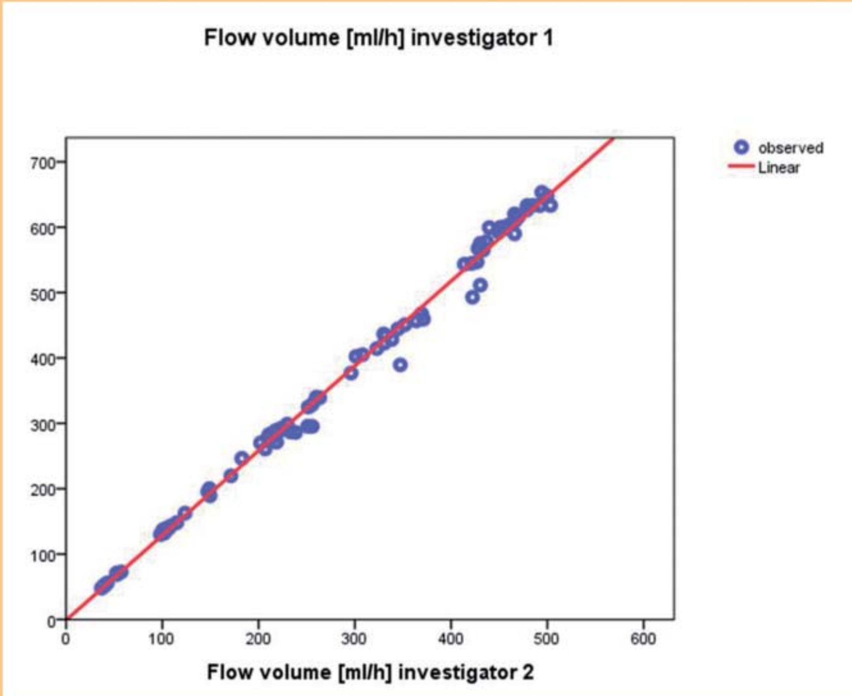

Fig. 2 Correlation of PixelFlux-perfusion measurements in a Teflon-tube-phantom made by two investigators.

Abb. 2 Korrelation der PixelFlux-Perfusionsmessungen zweier Untersucher in einem Teflonschlauchphantom.

Table 1 Correlation of PixelFlux volume flow measurements by two investigators with pumped volumes per time in a Teflon-tube-phantom.

		flow volume (ml/h) investigator 1	flow volume (ml/h) investigator 2
pump flow (ml/h)	correlation (Pearson)	0.987	0.991
	significance (2-sided)	< 0.001	< 0.001
	n	87	87
flow volume (ml/h) investigator 1	correlation (Pearson)		0.997
	significance (2-sided)		< 0.001
	n		87

Table 2 Correlation of volume flow measurements with fetal weight and fetal age.

		volume flow (ml/sec)
estimated fetal weight (g)	Pearson correlation	0.227
	sig. (2-tailed)	0.000
	n	245
gestational age (d)	Pearson correlation	0.187
	sig. (2-tailed)	0.003
	n	245

Table 3 Correlation of volume flow measurements with fetal weight and fetal age depending on the maximum flow velocity applied.

maximum flow velocity	correlation of flow volume to gestational age		correlation of flow volume to estimated fetal weight	
	r	p	r	p
23 cm/sec n = 62	0.287	0.024	0.323	0.010
31 cm/sec n = 183	0.190	0.010	0.245	0.001

mum flow velocity of 23 cm/sec compared to those with 31 cm/sec (▶ **Table 3**).

The correlation coefficients were significantly better with smaller angles of the UV vein with respect to the ultrasound propagation line (▶ **Fig. 4**). A remarkable and significant increase in correlation was achieved by decreasing the UV angle to less than 40° (▶ **Fig. 5**; $r = -0.856$; $p = 0.003$).

Discussion

The evaluation of fetal blood supply is of great interest for perinatologists for the purpose of evaluating the status of the fetus and making sound decisions concerning the initiation of labor or measures to prolong pregnancy. Color Doppler ultrasound has a pivotal role in such evaluations. Today fetal perfusion is mainly evaluated by resistance index (RI) measurements. This does not allow volumetric measurements.

The PixelFlux technique offers the opportunity to measure the area of the umbilical vein regardless of its shape from three-dimensional data. In the horizontal transsection each pixel of the vein is measured and the total area is summed up from all colored pixels. This can reduce the error resulting from the assumption of a circular vessel. In the past the area was calculated under this assumption by measuring of the vessel's diameter.

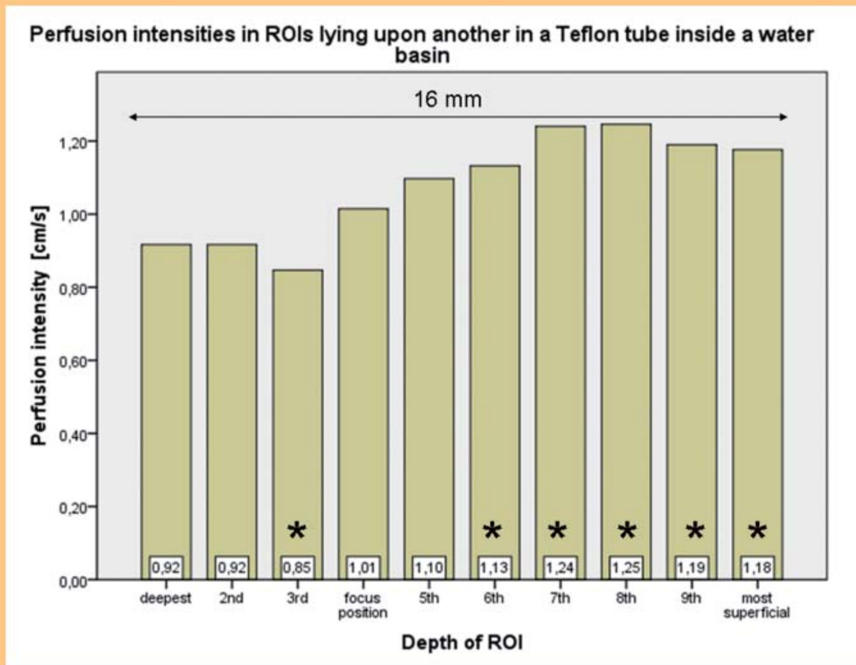

Fig. 3 Comparison of PixelFlux-perfusion measurements in a Teflon-tube-phantom with 10 equal ROIs lying one upon another in different depths. The focus was within ROI 4. Significant differences compared to ROI 4 are highlighted by asterisks.

Abb. 3 Vergleich der PixelFlux-Perfusionsmessungen in verschiedenen Tiefen des Wasserbads in 10 identischen übereinanderliegenden ROIs in einem Teflonschlauchphantom. Der Fokus war auf ROI 4 eingestellt. Signifikante Unterschiede zu den Messungen in ROI 4 sind durch Sterne gekennzeichnet.

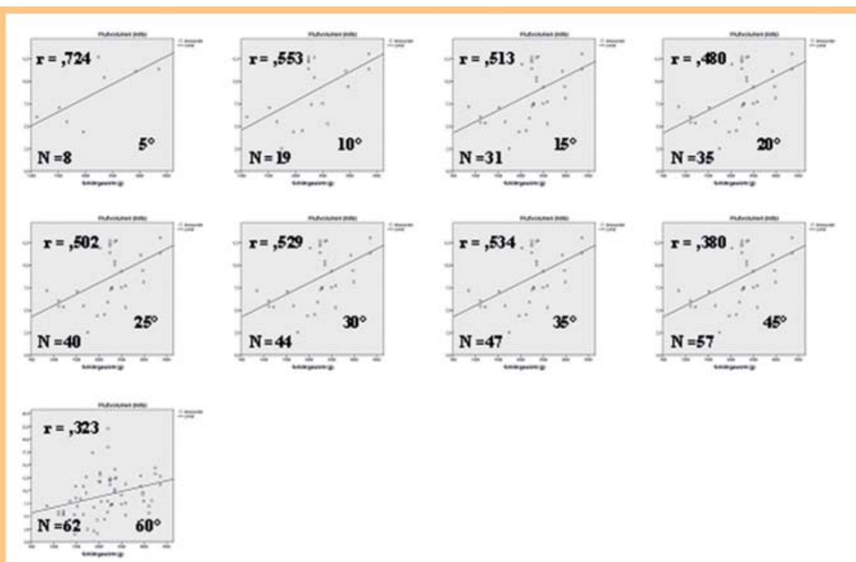

Fig. 4 Correlation of volume flow measurements compared to fetal weight with continually increasing spatial angles of the UV towards the ultrasound propagation line demonstrating a decrease of correlation with an increase of spatial angle.

Abb. 4 Korrelation der Flussvolumenmessungen zum Fetalgewicht bei kontinuierlich ansteigenden Raumwinkeln.

Spatial angle calculation is another important feature of the PixelFlux technique. The spatial angle of the umbilical vein at its crossing point with the horizontal plane is calculated from the angles in the frontal and sagittal plane. The true flow velocity of each pixel is then calculated by dividing the velocity value of each color pixel by the cosine of this spatial angle. Both innovations, pixelwise vessel area measurement and spatial angle correction of flow velocities, should help to improve the evaluation of fetal perfusion.

To prove this assumption we performed phantom flow measurements with a Teflon tube in a water basin perfused by rice starch solution. Here we could demonstrate a highly significant correlation of PixelFlux volume flow measurements with the actual pumped volumes per time. This underscores the reliability of the PixelFlux method per se. The interobserver correlation of such flow volume measurements was excellent, stressing the feasibility of the measurement procedure.

With the novel spatially angle-corrected PixelFlux measurements in horizontal transsections of the umbilical vein, we performed a pilot study to investigate the feasibility of fetal volume perfusion measurements. Here we could demonstrate a significant correlation of fetal volume perfusion and the estimated fetal weight. This result, which is in accordance with findings of other techniques [15], allows the assumption that spatial PixelFlux measurements can describe the relationship between fetal weight and fetal blood flow volume. It makes sense that blood supply to the fetus is a predictor of fetal weight gain, which in turn, can be understood as the accumulation of substances delivered by the bloodstream. This is further supported by our observation that the correlation of perfusion is less but likewise significant to fetal age. Fetal growth differs among individual fetuses. The weaker

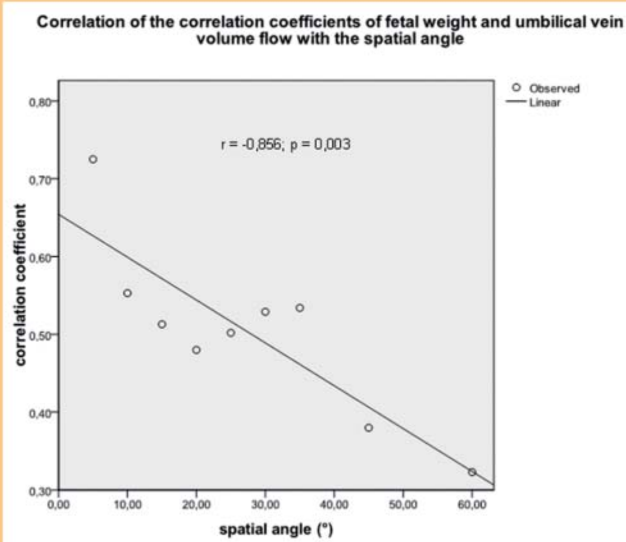

Fig. 5 A significant inverse correlation of spatial angle of the UV and the degree of correlation between flow volume calculations and fetal weight exists.

Abb. 5 Nachweis der signifikant abnehmenden Korrelation von Flussvolumenmessungen und Fetalgewicht bei zunehmenden Raumwinkeln.

correlation of blood flow volumes to fetal age than to fetal weight might mirror this fact.

The degree of correlation to fetal weight lies in the range of other methods and investigators published so far [16, 17]. A volume flow measurement could be seen as the evaluation of the momentary metabolic demand of the fetus.

PixelFlux measurements depend on the imaging conditions since they quantify what is displayed on the screen. It is therefore important to define an optimum preset of all parameters, which could influence the image. Such a preset must be defined in advance and must not be changed. Crucial parameters to be kept constant (gain, color Doppler frequency, transducer type, type of the ultrasound machine, wall filters, type of color bar, spatial and time resolution, persistence and smoothing of the coloration).

The pulse repetition frequency (PRF) which influences the maximum value of the velocities encoded in color which are displayed without aliasing can be changed. The PixelFlux software recognizes this and uses the maximum value as shown at the top of the color bar to calculate the actual velocity of each pixel.

Different stages of fetal development require different blood volumes to be delivered via the umbilical vessels. It is a common observation that umbilical venous blood flow velocity changes during pregnancy. To avoid color dropouts in fetuses with low flow velocities it may be necessary to adapt the actual PRF. We tested different PRFs which resulted in detectable maximum flow velocities of 23 and 31 cm/sec. The correlation of perfusion and fetal weight and age in our population was better in ultrasound recordings with 23 cm/sec compared to those with 31 cm/sec. This might reflect the influence of the wall filter which cuts out low flow signals regarded as wall vibrations. The higher the maximum flow velocity, the higher the respective wall filter. This creates a loss of low flow signals. In the umbilical vein relatively low flow velocities are found. Thus, a higher wall filter might cause a relevant loss of flow data in a setting with 31 cm/sec compared to 23 cm/sec. We therefore recommend using 23 cm/sec recordings in the fetal age group from 23 to 41 gestational weeks.

The depth of the measurement zone may also have an influence on the PixelFlux measurements. The umbilical vein is embedded in amniotic fluid. To evaluate the effect of different depths in a fluid, we compared measurement positions at different depths along the Teflon tube flow phantom (**Fig. 3**). The results show that it is important to place the focus in the region of the PixelFlux measurement. Measurements around the focus were comparable.

Several drawbacks and theoretical flaws of the traditional techniques can be overcome with the PixelFlux techniques.

The traditional RI (resistance index) consists of the values of maximum systolic (v_{sys}) and end-diastolic flow velocities (v_{dia}) as follows: $RI = (v_{sys} - v_{dia})/v_{sys}$. The transsectional area of the vessel is not regarded, thus no evaluation of perfusion volume is possible with RI. Not surprisingly, the value of umbilical artery RI calculation to predict IUGR is low [18] and its correlation to umbilical volume flow is also weak [17].

Until today, angle corrections are made in the frontal imaging plane only. Only the angle inside the imaging plane can be calculated and corrected [16]. This is too simplistic. A vessel might apparently run straight toward the transducer from the perspective of the frontal plane but may for example actually have an inclination of 45° from the perspective of the sagittal plane. The traditional assumption would be to calculate with a cosine of 0° = 1, resulting in an exact match of apparent vector and effective vector. The true spatial angle instead is 45° in our example resulting in a cosine 45° = 0.71. The difference of flow volume calculation, which is a product of velocity and perfused area, will be 29 %. Even more deleterious than the fact that the difference is remarkable is the fact that the true difference is unknown and indeterminable if the measurements are made from a two-dimensional perspective. This problem is compounded by the fact that the shape of the vein is often quite different from round. The two-dimensional perspective might display parallel vessel borders which have so far been accepted as the projection of a round-shaped tube. Many other shapes (e. g., bean shape) might mimic a round vessel in a 2 D projection thus causing relevant errors.

Pixelwise flow measurements (PixelFlux method) rule out that solely the central flow inside a vessel is regarded (such as in conventional PW Doppler measurements) and PixelFlux respects non-circular distribution of flow velocities inside the vessel which are missed in a 2 D technique.

It is evident from these considerations that substantial and unpredictable errors can result in erratic measurements in a 2 D model which in turn must result in a rejection of the method. Some tried to overcome this limitation by combining several parameters [19 – 22].

We present a new approach with a sound theoretical basis. Nevertheless technical restrictions from the imaging procedure and signal processing inside the ultrasound device need to be observed. Our results demonstrate that spatially angle-corrected pixelwise volume flow measurements from three-dimensional datasets might offer an attractive alternative to traditional techniques. Further studies are necessary to describe the prospects and limitations of the technique in clinical settings.

References

1 *Hoskins PR, Haddad NG, Johnstone FD et al.* The choice of index for umbilical artery Doppler waveforms. Ultrasound Med Biol 1989; 15: 107 – 111
2 *van Huisseling H, Hasaart TH, Muijsers GJ et al.* Umbilical artery pulsatility index and placental vascular resistance during acute hypoxemia in fetal lambs. Gynecol Obstet Invest 1991; 31: 61 – 66
3 *Al-Gazali W, Chapman MG, Chita SK et al.* Doppler assessment of umbilical artery blood flow for the prediction of outcome in fetal cardiac abnormality. Br J Obstet Gynaecol 1987; 94: 742 – 745
4 *Woo JS, Liang ST, Lo RL.* Significance of an absent or reversed end diastolic flow in Doppler umbilical artery waveforms. J Ultrasound Med 1987; 6: 291 – 297
5 *Scholbach T, Girelli E, Scholbach J.* Tissue pulsatility index: a new parameter to evaluate renal transplant perfusion. Transplantation 2006; 81: 751 – 755
6 *Scholbach TM.* Changes of renal flow volume in the hemolytic-uremic syndrome–color Doppler sonographic investigations. Pediatr Nephrol 2001; 16: 644 – 647
7 *Gill RW, Trudinger BJ, Garrett WJ et al.* Fetal umbilical venous flow measured in utero by pulsed Doppler and B-mode ultrasound. I. Normal pregnancies.. Am J Obstet Gynecol 1981; 139: 720 – 725
8 *Eik-Nes SH, Marsal K, Brubakk AO et al.* Ultrasonic measurement of human fetal blood flow. J Biomed Eng 1982; 4: 28 – 36
9 *Sauders JB, Wright N, Lewis KO.* Measurement of human fetal blood flow. Br Med J 1980; 280: 283 – 284
10 *Erskine RL, Ritchie JW.* Quantitative measurement of fetal blood flow using Doppler ultrasound. Br J Obstet Gynaecol 1985; 92: 600 – 604
11 *Scholbach T, Dimos I, Scholbach J.* A new method of color Doppler perfusion measurement via dynamic sonographic signal quantification in renal parenchyma. Nephron Physiol 2004; 96: 99 – 104
12 *Scholbach T, Herrero I, Scholbach J.* Dynamic color Doppler sonography of intestinal wall in patients with Crohn disease compared with healthy subjects. J Pediatr Gastroenterol Nutr 2004; 39: 524 – 528
13 *Scholbach T, Hormann J, Scholbach J.* Dynamic tissue perfusion measurement of the intestinal wall – correlation to histology in ulcerative colitis. Journal of Medical Ultrasound 2010; 18: 62 – 70
14 Chameleon-Software. PixelFlux 2009, www.chameleon-software.de
15 *Link G, Clark KE, Lang U.* Umbilical blood flow during pregnancy: evidence for decreasing placental perfusion. Am J Obstet Gynecol 2007; 196: e489 – e487
16 *Rizzo G, Capponi A, Pietrolucci ME et al.* Umbilical vein blood flow at 11 + 0 to 13 + 6 weeks of gestation. J Matern Fetal Neonatal Med 2010; 23: 315 – 319
17 *Sutton MS, Theard MA, Bhatia SJ et al.* Changes in placental blood flow in the normal human fetus with gestational age. Pediatr Res 1990; 28: 383 – 387
18 *Favre R, Ditesheim PJ.* Value of Doppler velocimetry of the umbilical artery, aorta, cerebral artery, and uterine artery in pathological pregnancies. J Gynecol Obstet Biol Reprod 1991; 20: 253 – 259
19 *Gasser B, Ditesheim PJ, Willemetz JC.* Measuring fetal ischemia using multichannel pulsed Doppler sonography of the aorta and umbilical vein. Preliminary results in normal pregnancy. Gynakol Rundsch 1989; 29: 22 – 31
20 *Tchirikov M, Rybakowski C, Huneke B et al.* Umbilical vein blood volume flow rate and umbilical artery pulsatility as "venous-arterial index" in the prediction of neonatal compromise. Ultrasound Obstet Gynecol 2002; 20: 580 – 585
21 *Chen HY, Chang FM, Huang HC et al.* Antenatal fetal blood flow in the descending aorta and in the umbilical vein and their ratio in normal pregnancy. Ultrasound Med Biol 1988; 14: 263 – 268
22 *Tchirikov M, Strohner M, Forster D et al.* A combination of umbilical artery PI and normalized blood flow volume in the umbilical vein: venous-arterial index for the prediction of fetal outcome. Eur J Obstet Gynecol Reprod Biol 2009; 142: 129 – 133