Umbilical vein blood volume flow rate and umbilical artery pulsatility as ‘venous–arterial index’ in the prediction of neonatal compromise

M. TCHIRIKOV†, C. RYBAKOWSKI*, B. HÜNEKE*, V. SCHODER‡ and H. J. SCHRÖDER†

*Universitätsklinikum Hamburg-Eppendorf, Klinik für Frauenheilkunde und Geburtshilfe, †Abteilung für Experimentelle Gynäkologie, ‡Institut für Mathematik und Datenverarbeitung in der Medizin, Hamburg, Germany

KEYWORDS: Doppler sonography, Fetal compromise, Human fetus, Pulsatility index, Umbilical vein volume flow rate

ABSTRACT

Objective To assess the diagnostic power of the umbilical venous arterioarterial index (VAI) for the prediction of poor fetal outcome.

Subjects and methods This was a retrospective, cross-sectional clinical study in which normalized umbilical vein blood volume flow rate (nUV) (mL/min/kg estimated body weight), umbilical artery pulsatility index (UAPI), the newly developed VAI (nUV/UAPI), and the uterine artery resistance index (UTRI) were determined in 85 fetuses once (17–41 gestational weeks) during pregnancy using standard ultrasound Doppler equipment. A risk score based on umbilical blood pH, 1-min Apgar score, birth weight, duration of gestation, type of respiratory support, and referral to the pediatric department was constructed, and fetuses were assigned to a control or a pathological group accordingly. Logistic regression and analysis of fitted receiver–operating characteristics curves were performed to evaluate the diagnostic power of nUV, UAPI, UTRI, and VAI.

Results The incidence of compromised neonates was 17.6%. The area under the receiver–operating characteristics curve was larger for VAI than for UTRI or for UAPI (P < 0.002). At a cut-off value of 100 mL/min/kg, the sensitivity of VAI to predict poor neonatal outcome was 85% with a 15% false-positive rate.

Conclusion Determination of the VAI has a greater diagnostic power to predict poor fetal outcome than the pulsatility index in the umbilical artery or the resistance index in the uterine artery.

INTRODUCTION

For the fetus, placental blood volume flow rate is as important as cardiac output and lung perfusion in adults. Volume flow rate determinations based on the Doppler principle require the measurement of the angle of insonation and the vessel’s diameter as well as measurement of the intensity-weighted mean Doppler shift frequency which reflects the spatial mean blood flow velocity at any given moment. The accurate determination of blood volume flow rate is time consuming, and precise measurement of the vessel diameter is a major obstacle. Therefore, for assessment of the fetal state, the focus clearly is on the analysis of frequency or temporal velocity 'profiles'. They can be more easily determined than volume flow rates, and the profiles can be evaluated quantitatively as angle-independent Doppler indices, such as the S/D ratio, pulsatility index (PI), and resistance index (RI). Thus, nowadays, clinical assessment of the fetal condition in utero tends not to be based on flow rates but rather on Doppler indices, although, as indicators of vascular resistance, they reflect perfusion rates only indirectly.

Recently, attention has turned towards the fetal venous circulation. Our previous studies have shown that variations of mean volume flow rates in the ductus venosus and in the proximal umbilical vein are related to intrauterine growth restriction. In this study we set out to demonstrate that, in a standard clinical setting, the measurement of normalized placental blood volume flow rate, i.e. umbilical venous blood volume flow rate per kilogram estimated fetal body weight, in combination with the umbilical artery PI (UAPI) is a promising tool to identify a fetus that may be compromised during and after delivery.

MATERIALS AND METHODS

The protocol of this retrospective, cross-sectional clinical study followed the ethical guidelines of our institution. Originally, Doppler ultrasound investigation was carried out in 178 patients with singleton pregnancies and no signs of fetal malformation by B-mode ultrasound. Gestational age was...
determined based on the last menstrual period and on ultrasound examination in the first trimester. Fetal estimated weight was derived from measurements of the head and abdominal circumferences, and from femur length.

The patients who were finally included in the study (n = 83) were either attending our hospital for antenatal care and had no known pathologies (51% or 43 patients) or were referred for a variety of obstetric indications (n = 42). The most frequent indications besides small-for-gestational age (n = 19) were breech presentation (n = 5) and gestational diabetes without insulin treatment (n = 2), or patients with well-controlled (normoglycemia, normal HBA₁, normally sized fetus) type I diabetes (n = 6).

**Doppler ultrasound measurements**

Ultrasound measurements were performed with an Ultramark 9, an HDI ESP 3000 (both Advanced Technology Laboratories, Solingen, Germany) or a Kranzbühler GE LOGIQ 500 (Kranzbühler Medizinische Systeme, Solingen, Germany) system, all three Doppler ultrasound devices being equipped with 5–7-MHz convex transducers (acoustic output less than 100 mW/cm² spatial peak time average intensity). Doppler evaluations were carried out with the mother in the left lateral recumbent position and in the absence of fetal breathing and body movements. Recordings were made when at least three nearly identical consecutive waveforms, typical for the vessel under investigation, were visible on the screen.

The seven Doppler indices determined in each patient as part of our clinical routine included the PI in the umbilical artery (UAPI), in the aorta, in the middle cerebral artery, and in the ductus venosus, the RI in both uterine arteries, and the aortic mean velocity (time-averaged maximum velocity). The eighth variable, i.e. the cerebral–placental ratio (CPR), was calculated as CPR = cerebral artery PI/UAPI. Umbilical vein blood volume flow rate (UV) was measured as described below and normalized by the estimated fetal weight (nUV = UV/fetal weight in kg). The ratio of nUV/UAPI was calculated as the ‘venous–arterial index’ (VAI). A detailed description of the results is restricted to VAI, nUV, UAPI, and the RI of the uterine artery (UTRI) on the opposite side to the placenta (although if the side of the placenta could not be determined, the uterine artery with the higher RI was considered to be the non-placental-side uterine artery).

**Umbilical vein blood volume flow rate**

For umbilical vein blood volume flow measurement, a straight segment of the intra-abdominal part of the umbilical vein upstream of any hepatic branches was selected, and the Doppler gate was positioned to completely cover the vessel’s diameter. Both the intensity-weighted mean velocity (iVmean) and the vessel diameter were determined using a longitudinal section of the umbilical vein in real-time mode following the ‘maximum principle’. The goal was to acquire three maximum values. The lines representing the vessel walls on screen should appear as straight lines for as long as possible (maximum length). In this case, lateral tilting is minimal at a given angle of insonation.

![Figure 1 Schematic diagram illustrating the ‘maximum principle’. The paraboloid of revolution emerging from the cylinder (vessel) indicates the spatial distribution of blood flow velocities (streamlines). The vertical planes represent three possible ultrasound beams for imaging or Doppler measurements; the Doppler angle is zero. Determination of vessel diameter and mean velocity can only be correct if the plane of the ultrasound beam runs parallel to, and through, the vessel’s longitudinal axis. A tilted ultrasound plane will yield curved vessel walls instead of straight lines, and velocity calculation will be (slightly) erroneous because of the non-zero Doppler angle in the horizontal plane. Flow determinations will be correct if diameter and mean velocity as well as straightness and length of vessel walls on screen are maximal (maximum principle).](image)
biometry measurements. Most of the remaining ultrasound data were obtained by C.R. and B.H.

The results of volume flow rate measurements in the umbilical vein were unavailable to the obstetricians in charge of the patients and did not influence the management of care.

Outcome score
As shown in Table 1, basic score values of 0, 1, or 2 were assigned to each of six outcome variables (umbilical arterial blood pH, Apgar score after 1 minute, birth weight, duration of gestation, type of respiratory support, and admission to the pediatric department), and the basic score values were summed to obtain an ‘outcome score’. This outcome score was constructed for each newborn before further statistical evaluation but after data had been collected. As described below, neonates with outcome scores of 0, 1, or 2 were assigned to the control group, whereas those with scores of 3–12 made up the group of compromised neonates.

Statistics
The study aimed to compare established Doppler parameters and the new VAI as diagnostic tools for detection of fetuses at risk. Two statistical approaches to achieve this goal were used. In the logistic regression analysis, the dependence of outcome on the above variables and on time was explored, and the effect of various definitions of ‘fetal compromise’ on the results was also tested. We selected for analysis VAI, UAPI, and UTRI, because they demonstrated the smallest area under the ROC curve compared between the pathological and the control groups. Because sensitivity and specificity depend strongly on the respective cut-off values, receiver–operating characteristics (ROC) analysis was used to assess the diagnostic performance. ROC curves (sensitivity vs. 1 – specificity) were constructed by a fitting procedure based on the usual assumption of binormality (Figure 2). For each Doppler parameter, the area under the ROC curve was computed as a measure of diagnostic quality and pairwise comparisons of these areas were performed using the area test.

Average data are presented as mean and 95% confidence interval (CI), or median and range when appropriate. Relationship between variables was examined using regression analysis and by computing correlation coefficients (Pearson, Spearman). The significance of differences between means was established with Student’s unpaired t-test, whereas different proportions were verified with a χ² test. The level of significance was accepted at P < 0.05. The statistical software packages used were Statistica® (Statsoft, Tulsa, OK, USA), SPSS (SPSS, Chicago, IL, USA), and ROC-FIT (Department of Radiology, University of Chicago, IL, USA).

RESULTS
Patient recruitment
Table 2 summarizes the reduction of the study group from 178 to 85 patients. Most frequently (34.8%) patients were excluded because our criteria for good quality volume flow measurements were not met. The other cases were excluded because the patients developed complications during pregnancy, unrelated to placental blood volume flow. Gestational age at the time of measurement of the 85 patients ranged from 17 to 41 weeks.

Outcome data
Outcome data are shown in Tables 3 and 4. The incidence of fetal compromise (outcome score ≥ 2) was 17.6% (15 of 85). The proportion of non-spontaneous deliveries was significantly higher (P = 0.011) in the group of compromised fetuses, and birth weight and duration of pregnancy were less than in controls. The median outcome score was 0 (range 0–2) in controls and 5 (range 3–9) in the compromised group. Thirteen neonates in the control group (Table 4) presented with an admission status of NICU, neonatal intensive care unit.
an outcome score value of 2, which in three cases was based on one single scoring parameter (pH, 1-min Apgar, or birth weight percentile). Of the remaining ten neonates five acquired one scoring point because they were transferred to the pediatric department but respiratory support or intensive care was not necessary.

Doppler recordings

The angle of insonation was kept below 60° (median 26.5°, range 0–60°), with no significant differences between the two groups.

As illustrated in Figure 3, UV increased significantly (Figure 3, solid line; controls: $r = 0.87$, estimated slope 17 (CI, 15–19) mL/min/week) with gestational age in both groups. Vessel diameter as well as $\text{iVmean}$ increased significantly with gestational age in the control group ($r = 0.75$ and $r = 0.51$, respectively). Compromised fetuses (Figure 3, closed symbols) tended to have lower volume flow rates. If a curvilinear relationship is assumed, the estimated equation is $nUV = 0.06 \times (\text{gestational week})^{2.4}$ (Figure 3, dotted line). Four compromised fetuses with apparently normal volume flow rates (closed squares) had outcome score values of 3 each; they represent four of six cases with this score value in the compromised group. nUV significantly decreased with gestational age in controls ($r = -0.56$; estimated slope $-2.2$ (CI, 1.4 to $-3.0$) mL/min/kg/week) but did not change significantly in compromised fetuses. The differences for the mean values of VAI, UAPI, UTRI, and nUV between control and compromised fetuses were significant ($P < 0.005$). Figure 4 demonstrates that VAI decreased with the outcome score (Spearman rank order correlation coefficient $r = -0.48$). UAPI and nUV were significantly related to outcome score as well (not shown), but not UTRI. The VAI did not depend on the age of gestation ($r = 0.09$) as expected, because both the nUV and the UAPI decreased with gestational age.

As illustrated in Figure 2, the ROC curves for VAI, UAPI, and UTRI were different. The differences in area between VAI and UAPI or UTRI, respectively, were significant ($P < 0.002$).

The definition of ‘compromise’ will affect the results, and the effects of varying the cut-off value were explored. Univariate logistic regressions were calculated for VAI, nUV, UAPI, and UTRI at five different outcome score values which defined the threshold between normal and compromised fetuses.
neonates. Based on the respective regression coefficients, odds ratios and their CI (95%) were derived. The odds ratios reflect the change of risk to be included in the group of compromised fetsuses per unit increase (UAPI, UTRI, 0.1; VAI, nUV, 10 mL/min/kg). Figure 5 illustrates that both VAI and UAPI independently show odds ratios significantly different from 1 regardless of the cut-off value chosen for the outcome score. At a cut-off value of > 2 for neonatal compromise the odds ratio is distinctly separate from the line of unity. Figure 5 also indicates the prevalence of compromise, which is almost 40% or higher when the cut-off value is less than 2. We chose an outcome score of > 2 as the minimal value to define ‘compromise’.

In a second step a multiple logistic regression was performed to account for the correlation between variables. This led to VAI being the single predictor of poor fetal outcome (odds ratio per 10 mL/min/kg change, 0.43 (CI, 0.27–0.69)) which is not surprising because by definition VAI combines UAPI and nVU. The addition of UTRI to VAI did not improve the model or change the odds ratio significantly. Gestational age at the time of measurement also had no significant influence on the odds ratio for VAI. When the inclusion of time in the regression was repeated using absolute UV (Figure 3) instead of nUV or VAI, gestational age significantly influenced the model (results not shown). This is expected because compromised fetsuses were delivered earlier (Table 3) and nUV is distinctly lower at early gestational ages (Figure 3).

**DISCUSSION**

In this study, blood volume flow rate in the umbilical vein (Figure 3) was similar to that previously reported, and the volume flow values measured by us were comparable to those of others. For example, mean placental blood volume flow rate at week 38 was 320 mL/min (Figure 3) and others have reported this value to be 270 mL/min and 400 mL/min, respectively. The increase of UV with gestational age (Figure 3) is plausible and generally accepted. It has been suggested to fit placental volume flow rate to gestational age using a power function. The coefficient of determination of this function (r² = 0.76) within the given range of gestational weeks, however, is not different from that of a linear relation.

The decrease of normalized placental blood volume flow with gestational age has been observed in human fetuses even if only as a trend.

**Doppler results as indicators of the compromised neonate**

It is evident that setting outcome score value limits to define ‘compromise’ is arbitrary. The basis for our definition of ‘compromise’ is six factors that are in widespread clinical use, and the limits chosen for assignment of the basic score values are reasonable. The significance of each of the basic scores varies. For example, a basic score of 2 because a neonate had to be intubated for respiratory support is more indicative of distress than two scoring points which are the result of an abnormal Apgar score and cord blood pH value. Instead of
applying a weight function to each parameter, we decided to include in the control group neonates with summed score values up to 2. Clinical experience demonstrates that basic score values of 1 can readily be gained during routine medical care, and that several factors should accumulate to justify the diagnosis of ‘compromise’. Table 4 demonstrates that both groups overlap with respect to the outcome variables, but the significant difference in mode of delivery (Table 3) indicates, for example, that our definition (sum of basic scores > 2) of fetal ‘compromise’ is meaningful. Because we further consider the assumed prevalence of 40%–50% of ‘fetal compromise’ at lower outcome score limits (Figure 5) as unrealistic, we believe that our choice of an outcome score limit > 2 is justified. The increased distance of odds ratios from a value of 1 at this value (Figure 5) is additional support for this decision.

From Figure 5 it can be deduced that both the UAPI, and the VAI are related to outcome in comparable strength. Because the effort involved in determining UAPI is minimal, the benefits of measuring nUV or VAI appear to be dubious. However, the ROC curves in Figure 2 and the results of multiple logistic regression indicate that there is a significant gain in diagnostic power when VAI is used, and this benefit justifies, in our opinion, the extra effort.

The data show that determination of the nUV combined with UAPI once during gestation improves the chance of detecting a fetus which presents signs of compromise after delivery. The analysis of ROC curves in combination with logistic regression provides evidence that measuring the VAI is advantageous compared to the PI alone, or to the RI in one uterine artery. From the ROC curve in Figure 2 it can be seen that at a cut-off value of 90 mL/min/kg the sensitivity to predict a compromised neonate is 76% with a false-positive rate of 9%. The same sensitivity can be achieved for UAPI (by using a cut-off value of approximately 1.03), but this will result in a false-positive rate of 40%.

Figure 3 conveys the impression that measuring absolute UV (mL/min) would suffice to discriminate between healthy and compromised fetuses. Multiple logistic regression reveals that this is true, but at the same time gestational age influences the statistics. Normalizing UV by the estimated fetal weight effectively removes this dependence on gestational age.

We conclude that based on the ‘maximum principle’ nUV can be measured with sufficient accuracy in human fetuses. High quality ultrasound equipment is capable of obtaining adequate UV measurements. Combining nUV with the UAPI as the VAI yields a Doppler parameter which may prove useful in future studies to predict neonatal compromise. This is reasonable because VAI reflects and enhances changes of UAPI and/or nUV associated with fetal compromise. In the present data, at a cut-off value of about 100 mL/min/kg the proportions of true and false positives for neonatal compromise are close to 85% and 15%, respectively. As is typical for retrospective studies, it remains to be examined whether these results can be generalized. Prospective studies will have to be performed to ascertain whether the VAI contributes to the detection of the neonate and/or fetus at risk. It also needs to be established whether this knowledge should influence medical care management by, for example, a more frequent control of fetal intrauterine development.

ACKNOWLEDGMENTS

We are grateful to Dr E. Schairen, Department of Physiology, University of Hamburg, Germany, for construction of Figure 1.

REFERENCES

10 Kiserud T, Rasmussen S. How repeat measurements affect the mean diameter of the umbilical vein and the ductus venosus. Ultrasound Obstet Gynecol 1998; 11: 419–25