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Prognostic Value of Pulmonary Doppler to Predict Response to Tracheal Occlusion in Fetuses with Congenital Diaphragmatic Hernia

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Abstract
Pulmonary Doppler may play an important role in the prediction of survival and postnatal morbidity in fetuses with congenital diaphragmatic hernia treated with fetoscopic tracheal occlusion (FETO). Spectral Doppler indexes such as pulsatility index and peak early diastolic reversed flow could help to refine the selection of fetuses that might benefit from fetal therapy. When combined with lung-to-head ratio (LHR), these Doppler indices allow to discriminate cases with moderate-to-high survival rates from fetuses with extremely low chances to survive after FETO. In addition, they discriminate groups with a high or low risk of serious neonatal morbidity in surviving fetuses. After therapy, the combined evaluation of the relative increase of LHR with the increase in lung tissue perfusion by power Doppler seems to improve the prediction of fetal survival. In conclusion, while LHR remains the strongest predictive index, Doppler measurements allow to substantially improve the accuracy in the prediction of the chances of survival of fetuses with congenital diaphragmatic hernia treated with FETO.

Introduction

Congenital diaphragmatic hernia (CDH) is associated with a high mortality rate primarily due to lung hypoplasia and/or pulmonary hypertension [1]. In an attempt to improve survival, prenatal therapy with fetoscopic tracheal occlusion (FETO) is offered in cases with estimated chances of poor neonatal survival [2]. Clinical series have demonstrated relative increments in overall survival rates ranging from 24 to 49% in left-sided CDH, and from 0 to 35% in right-sided CDH [3]. In addition, preliminary evidence suggests that tracheal occlusion may improve the neonatal pulmonary function among survivors by increasing the alveolar-arterial oxygen difference and lung compliance [4].

Clinical evidence demonstrates that there is a wide individual variability in the response to FETO [3]. Refining

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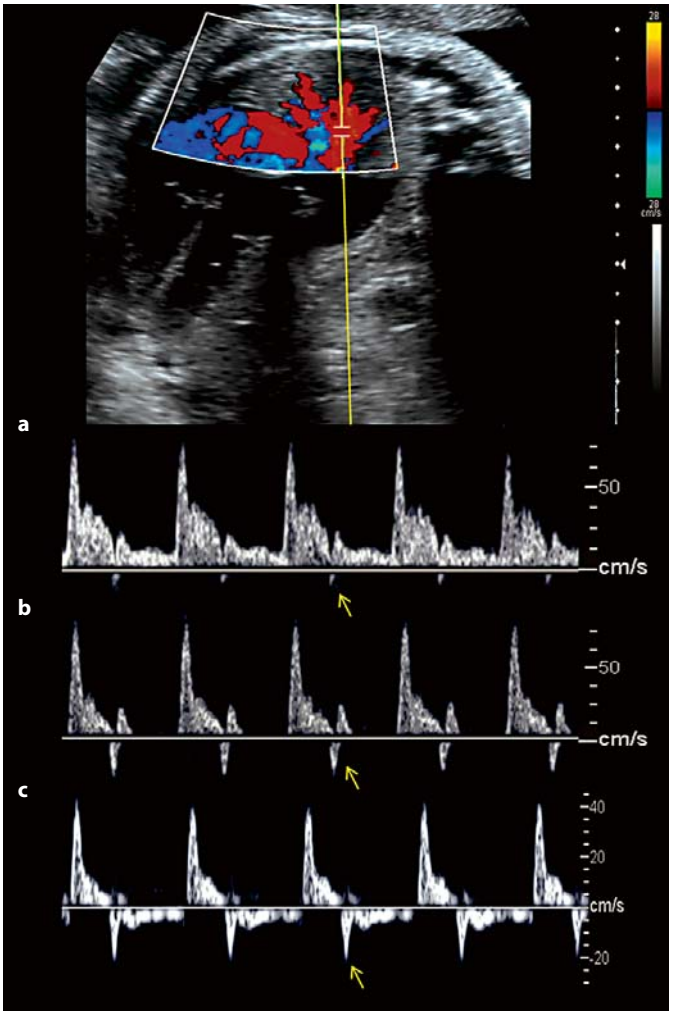

Fig. 1. Color Doppler evaluation of the proximal branch of the intrapulmonary artery in CDH, and progression of spectral Doppler patterns with the severity of lung hypoplasia. **a** Typical features of the Doppler waveform in normal lungs and mild CDH cases showing low velocities in the PEDRF (arrow) and positive diastolic flow. **b** Cases of severe CDH are normally associated with abnormal intrapulmonary impedance showing an increased PEDRF and absent diastolic flow. **c** Exceptionally, extremely severe cases may present holodiastolic reversed flow.

the identification of cases with high probability of responding to fetal therapy is of high relevance for parents' counseling and decisions. So far, the best parameter to establish the severity of CDH and predict the chances of survival after FETO is the observed to expected lung-to-head ratio (LHR) in combination with the presence or absence of intrathoracic liver herniation [5–8]. However, the survival rates after FETO in fetuses with intermediate LHR values range from 45 to 55%. These rates leave considerable uncertainty and may have a negative impact on parents' decisions. Recent evidence demonstrates that the predictive capacity of LHR can be notably improved if combined with the evaluation of the lung circulation by means of several Doppler methods [9–11]. In this concise review, we will summarize current evidence supporting the use of these techniques to improve individual prediction of the chances of survival of fetuses with CDH treated with FETO.

Intrapulmonary Spectral Doppler

Background

CDH is associated with profound changes in the pulmonary vasculature [12]. Histopathological studies have demonstrated that lungs of CDH fetuses have a decreased number of arterial branches and increased muscular thickness in the wall of the intrapulmonary vessels [13, 14]. Histological changes of CDH are reflected as increased impedance in the vascular blood flow of the intrapulmonary vessels estimated by spectral Doppler [15]. The association between abnormal Doppler waveforms and the risk of lung hypoplasia was first described by Laudy et al. [16]. The authors evaluated cases with CDH but also with oligohydramnios and premature rupture of membranes, and demonstrated a relation between poor survival rates and increased impedance values in the main branches of the intrapulmonary arteries. These findings were confirmed by other research groups and as a consequence, fetal lung evaluation was proposed as a potential prognostic parameter for lethal pulmonary hypoplasia [17, 18]. In studies focusing only on CDH-affected fetuses, intrapulmonary Doppler showed a progressive increase in the lung impedance (fig. 1) in relation to the severity of lung hypoplasia [unpubl. data], which had a negative correlation with the degree of lung growth and neonatal survival [19]. However, the good performance of LHR in the prediction of survival in CDH fetuses has gained wide acceptance [20–22] and the use of spectral Doppler for these purposes became almost abandoned.

The role of Doppler in CDH fetuses has been revived with its potential application to predict the chances of survival in cases treated with FETO. The rationale is as follows. While it is clear that in CDH the vascular tree suffers a disruption in normal development, this has traditionally been considered to be the consequence of the compressive mechanical effect of the herniated abdominal viscera. In line with this notion, experimental studies

with animal models had demonstrated that histological vascular changes were reversed after tracheal occlusion [23–25]. However, clinical experience has demonstrated that this was not always the case in human fetuses. Thus, a subset of fetuses treated with FETO still present severe forms and die as a consequence of pulmonary hypertension. This has led to the suggestion that certain forms of CDH are characterized by intrinsic changes in the pulmonary vascular tree [9] that might not be identifiable by LHR measurements.

Technical Aspects of Spectral Lung Doppler

Laudy et al. [26, 27] described the Doppler waveform in three different locations of the intrapulmonary circulation: proximal, medial and distal branches. The morphological characteristics are a rapid increment in the time-to-peak systolic velocity described as the 'needle-like' waveform, followed by an initially rapid but then more gradual velocity deceleration characterized by forward diastolic flow which is interrupted by a short reversed flow at the beginning of the diastolic phase named the peak early diastolic reverse flow (PEDRF). This pattern changes in relation to the location. Whereas in proximal branches there are always high peak systolic velocities (>50 cm/s), in the distal arterial branches peripheral resistance and peak systolic velocities decrease, with a reduction in both pulsatility index (PI) and PEDRF velocity. Nevertheless, all branches maintain the 'needle-like' time-to-peak systolic component. Normal reference ranges for the different components have already been published [19, 26] and showed an increment in the intrapulmonary impedance with advancing gestational age. The pulmonary veins [28] and the intrapulmonary venous circulation have also been studied [29]. The lung vein waveform shows a pulsatile pattern during systole and diastole in all branches. Location is generally easy as the vein runs together with the arteries and usually both components could be recorded in the same waveform [30]. The role of lung veins Doppler in CDH has not been investigated.

In normal fetuses the intrapulmonary circulation is evaluated in a cross-sectional view of the fetal thorax in a lateral projection, at the level of the four-chamber view of the heart. The visualization improves trough the intercostal space as the ribs make an acoustic shadow affecting the ultrasound (US) signals. The directional color Doppler box is placed in the lung closer to the US probe in order to identify the proximal intrapulmonary branch. Recordings in the middle and distal branches are more difficult and frequently the angle of insonation is not 0°, affecting the real estimation of velocities. In contrast, the proximal branch is clearly identified, and due to its position it assures an angle of isonation closer to 0°. The pulsed Doppler sample size is set to 2 mm and placed just after the proximal origin of vessel, before any bifurcation can be visualized, with an angle of insonation as close to 0 as possible and with a high-pass wall filter of 70 Hz. Evaluation of the proximal branch of the intrapulmonary artery had demonstrated an acceptable repeatability with an interobserver variability below 15% [31].

In fetuses with CDH, Doppler studies can be performed in both the ipsi- and contralateral lung to the side of the hernia, but the examination is much more demanding in the ipsilateral lung. In experienced hands, the contralateral lung could be satisfactorily examined with Doppler in all cases, while the ipsilateral lung could not be identified in 22% of the fetuses with left-sided CDH [19]. In CDH, the anatomical landmarks described above are displaced, but the best approach is also to start from a four-chamber view of the heart, with the contralateral lung closer to the anterior uterine wall. In this view, the proximal intrapulmonary branch runs slightly medial and posterior with respect to the left atrium (fig. 1). The branch can also be visualized by following the arterial vessel emerging from the bifurcation of the main pulmonary artery, by means of a slight cephalic movement, just below the plane of the three-vessel tracheal view [26, 27, 31, 32]. The waveform analysis includes the PI and the PEDRF velocity.

Lung Doppler evaluation in CDH requires a trained operator and very strict guidelines for acquisition and measurement to ensure reproducibility. In experienced hands, waveform analysis of the proximal intrapulmonary branch shows good reproducibility with intra- and interobserver intraclass correlation coefficients of 0.87 and 0.82, respectively [19].

Spectral Doppler before Therapy to Predict Survival in CDH Fetuses Treated with FETO

All studies have been performed in left-sided CDH. In a recent study on 41 severe cases (LHR <30% and liver herniation) treated with FETO, we demonstrated that increased values of PI and PEDRF between 24 and 28 weeks of gestation and before FETO were significantly and independently associated with postnatal survival [9]. More interestingly, the combination of both parameters with the LHR improved the accuracy in the prediction of survival. Thus, LHR was the best initial predictor of prognosis with a survival rate up to 90% for cases with LHR ≥26%. For cases with LHR <26%, intrapulmonary PI

and PEDRF allowed to discriminate a group with moderately good (66–71% survival) prognosis when both parameters were normal (PI <1.0 and PEDRF <3.5 z-scores), from another group with very poor (0% survival) prognosis when both parameters were abnormal. These findings remain to be confirmed by further studies, but they support the hypothesis that abnormal Doppler values might allow to identify fetuses with similar lung size but differences in the degree and/or type of vascular disruption. In addition to prediction of survival, preliminary evidence suggests that intrapulmonary Doppler may also play a role in the prediction of morbidity among survivors managed with FETO. In a recent study on 25 neonates with CDH who survived after FETO, patients with increased PI and PEDRF values during fetal life showed higher rates of neonatal morbidity, with average increases of 14 days in the duration of mechanical ventilation, 32 days of oxygen requirement, 12 days of parenteral feeding and 28 days of stay at the neonatal intensive care unit [11].

Hyperoxygenation Test for Pulmonary Vascular and Spectral Doppler Evaluation in CDH-Affected Fetuses Treated with FETO

In addition to spectral Doppler before therapy, hyperoxygenation tests based on Doppler evaluation may also improve prediction of postnatal evolution in cases treated with FETO. In the third trimester of pregnancy, fetal pulmonary arterial resistance can be lowered by maternal oxygen administration [33]. This phenomenon has been studied clinically in patients with pulmonary hypertension and in animal models [34, 35]. Changes in the vascular resistance can be measured by pulmonary Doppler studies using the hyperoxygenation test for pulmonary vascular reactivity (HPVR) [33–36]. Broth et al. [36] showed that HPVR is a reproducible test, highly predictive of lung function in the neonatal period. The proximal branch of the fetal pulmonary artery of the contralateral lung to the CDH is evaluated before and after maternal hyperoxygenation using a mask with oxygen at 60%, between 31 and 36 weeks of gestation [36]. A reduction of ≥20% of the pretest PI is considered as a reactive test. In a recent study, we applied HPVR to predict neonatal survival and the risk of pulmonary hypertension in a population of 38 fetuses with severe CDH treated with FETO [37] and demonstrated that fetuses that survived had a larger decrease of resistance after HPVR. Hemodynamic changes related to HPVR are still under research and merit further studies in expectantly managed cases.

Lung Tissue Perfusion by Power Doppler

Background

Estimation of tissue blood perfusion can provide additional information on the pulmonary hemodynamic processes in fetuses affected with CDH. Despite the fact that real perfusion values are obviously difficult to quantify, different estimation methods based on power Doppler ultrasound (PDU) have been proposed. PDU is a pulsed Doppler technique that displays the amplitude (power) component of the backscattered US signals, and therefore by means of mathematical methods it allows to infer the magnitude of perfusion in a given region of interest. PDU is very sensitive to slow movements, which renders it particularly suitable for evaluation of tissue blood perfusion [38].

Application in CDH Fetuses and Technical Aspects

Lung perfusion has been evaluated by two- and three-dimensional methods. Fortunato [39] was first to describe the use of qualitative PDU assessment for the visualization of the fetal lung vasculature. Dubiel et al. [40] evaluated PDU changes in the fetal lung after administration of steroids for lung maturation by the quantification of the pixel intensity of the backscattered PDU signals. Concerning the prediction of survival in CDH fetuses, Mahieu-Caputo et al. [41] qualitatively applied PDU for the identification of the pulmonary arterial vascular segments in a cohort of 42 (32 left and 10 right) CDH fetuses and reported that visualization of less than three segments of the pulmonary branches was associated with a higher neonatal mortality. All these studies applying PDU used qualitative or semiquantitative approaches to estimate the increment or reduction in blood movements.

Ruano et al. [42] applied three-dimensional PDU in the lung of 21 CDH fetuses and reported a decrease in the vascular flow and vascular/flow indices in cases showing pulmonary hypertension neonatally. However, currently available three-dimensional PDU methods represent estimations subjected to substantial bias due to a lack in correction for attenuation and depth, and the potential variation by the power Doppler settings [43, 44]. Therefore, although these studies support the concept that PDU may be useful to predict severity and postnatal evolution in CDH, they may be limited by a low reproducibility.

Recently, fractional moving blood volume (FMBV) has been applied to evaluate fetal blood perfusion. This technique is based on offline analysis of power Doppler recordings by means of algorithms that compensate for

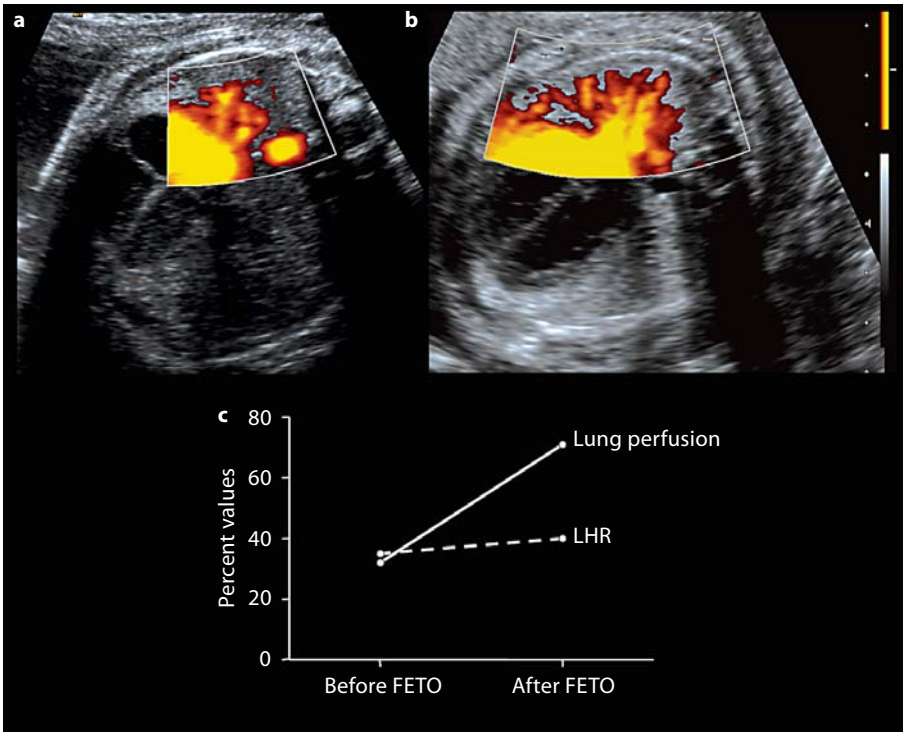

Fig. 2. Illustrative picture of a CDH fetus treated successfully with FETO. **a** Lung perfusion as measured with power Doppler before therapy. **b** One week after FETO a substantial increase is subjectively observed, with quantitative values similar to normal fetuses. **c** Relative postoperative increment of the LHR and lung perfusion recorded in this fetus. LHR increased very modestly after FETO. Prediction of survival on the sole basis of the relative increment in LHR values was 30%, but when both the increment in LHR and lung perfusion were combined, the predicted survival was 73%.

attenuation and depth. The technique has been validated against gold standards in the estimation of true tissue blood flow in animal experiments [45] and has shown a good reproducibility in the assessment of lung perfusion in human fetuses [46]. The methodological aspects for the quantification of lung FMBV have previously been described [47]. Briefly, in a cross-sectional view of the fetal thorax at the level of the four-chamber view of the heart, the power Doppler color box is placed including all the lung area, maintaining the color box as small as possible to include most of the lung and minimum of flash artifacts from the heart (fig. 2). Five consecutive high-quality images are recorded using fixed US settings. Images are examined offline and FMBV estimated within a specific region of interest using purpose-designed software. FMBV is expressed as the percentage of blood movements occupying the region of interest. This technique has been previously applied to evaluate the fetal lung in normally grown and growth-restricted fetuses showing a significant reduction in the lung of cases with intrauterine growth restriction [48].

Similarly, our group evaluated the lung tissue perfusion in 95 CDH human fetuses and 95 normal fetuses and demonstrated that lung FMBV is significantly reduced in CDH fetuses in comparison with controls (26.8 vs. 37.9%, $p < 0.001$) [49]. Thus, FMBV correlated positively with the degree of lung growth ($r = 0.37$, $p < 0.001$) and negatively with the intrapulmonary impedance as measured by spectral Doppler indices such as PI ($r = -0.31$, $p < 0.001$) and PEDRF ($r = -0.43$, $p < 0.001$) [49].

Use of Lung Perfusion to Predict Response to Therapy in CDH Fetuses Treated with FETO

In a rabbit model of CDH treated with FETO, lung FMBV values consistently showed a significant increment in lung perfusion closer to values observed in normal fetuses [50]. However, as discussed above, the vascular response in humans is more heterogeneous. In a recent study on human fetuses, we assessed the potential association between lung FMBV changes and the survival probability in a cohort of 62 left-sided CDH fetuses managed with FETO [10]. Lung tissue perfusion was evaluated 1 day before and 7–14 days after fetal intervention. While preoperative lung FMBV values were not associated with the likelihood of survival, the relative postoperative increment in FMBV with respect to preoperative values, in combination with the relative increase in LHR, significantly correlated with the probability of survival. Thus, a 100% survival rate was observed in cases with an increment in lung FMBV of ≥30% and LHR of ≥50%.

On the contrary, the subgroup with none or minor changes in both lung perfusion and size was associated with a very poor prognosis (10% survival). These findings suggest that lung perfusion could be used to evaluate the response to FETO, and thus improve the prediction of survival after fetal therapy. Nevertheless, clinical application of this technique is still limited since current US devices do not yet incorporate FMBV algorithms for automatic calculation of tissue perfusion.

Conclusions

The data provided by the studies summarized in this review suggest that fetuses with similar lung size as assessed by LHR may present substantial differences in spectral or power Doppler indices, and that these differences may help in the prediction of the response to FETO and consequently of the chances of survival. Although preoperative LHR remains the most powerful predictor of survival, incorporation of intrapulmonary Doppler evaluation may help to stratify the probability of survival in severe CDH, and particularly to identify a subgroup of fetuses with very low chances of survival after FETO treatment. Combination of LHR with Doppler information might thus facilitate comparison between clinical studies and influence parents' decisions by providing more accurate predictions of the individual prognosis at the time of considering FETO.

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