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MAGNETIC RESONANCE

Fetal dynamic phase-contrast MR angiography using ultrasound gating and comparison with Doppler ultrasound measurements

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Abstract

Objectives To investigate the feasibility of fetal phase-contrast (PC)-MR angiography of the descending aorta (AoD) using an MR-compatible Doppler ultrasound sensor (DUS) for fetal cardiac gating and to compare velocimetry with Doppler ultrasound measurements.

Methods In this prospective study, 2D PC-MR angiography was performed in 12 human fetuses (mean gestational age 32.8 weeks) using an MR-compatible DUS for gating of the fetal heart at 1.5 T. Peak flow velocities in the fetal AoD were compared with Doppler ultrasound measurements performed on the same day. Reproducibility of PC-MR measurements was tested by repeated PC-MR in five fetuses.

Results Dynamic PC-MR angiography in the AoD was successfully performed in all fetuses using the DUS, with an average fetal heart rate of 140 bpm (range 129–163). Time-velocity curves revealed typical arterial blood flow patterns. PC-MR mean flow velocity and mean flux were 21.2 cm/s (range 8.6–36.8) and 8.4 ml/s (range 3.2–14.6), respectively. A positive association between PC-MR mean flux and stroke volume with gestational age was obtained ($r = 0.66$, $p = 0.02$ and $r = 0.63$, $p = 0.03$). PC-MR and Doppler ultrasound peak velocities revealed a highly significant correlation ($r = 0.8$, $p < 0.002$). Peak velocities were lower for PC-MR with 69.1 cm/s (range 39–125) compared with 96.7 cm/s (range 60–142) for Doppler ultrasound ($p < 0.001$). Reproducibility of PC-MR was high ($p > 0.05$).

Conclusion The MR-compatible DUS for fetal cardiac gating allows for PC-MR angiography in the fetal AoD. Comparison with Doppler ultrasound revealed a highly significant correlation of peak velocities with underestimation of PC-MR velocities. This new technique for direct fetal cardiac gating indicates the potential of PC-MR angiography for assessing fetal hemodynamics.

Key Points

- *The developed MR-compatible Doppler ultrasound sensor allows direct fetal cardiac gating and can be used for prenatal dynamic cardiovascular MRI.*
- *The MR-compatible Doppler ultrasound sensor was successfully applied to perform intrauterine phase-contrast MR angiography of the fetal aorta, which revealed a highly significant correlation with Doppler ultrasound measurements.*
- *As fetal flow hemodynamics is an important parameter in the diagnosis and management of fetal pathologies, fetal phase-contrast MR angiography may offer an alternative imaging method in addition to Doppler ultrasound and develop as a second line tool in the evaluation of fetal flow hemodynamics.*

Keywords Fetal research · Magnetic resonance angiography · Ultrasonography, Doppler · Blood flow velocity

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Abbreviations

AoD Descending aorta
DUS Doppler ultrasound sensor

Introduction

Fetal Doppler ultrasound is an essential diagnostic tool in the evaluation of fetal blood flow. Assessment of fetal flow hemodynamics is, e.g., established in the diagnosis of intrauterine growth restriction (IUGR), where alterations of blood flow are also crucial for the timing of delivery and prediction of fetal outcome [1]. However, Doppler ultrasound flow measurements may be limited by technical difficulties in late gestation, e.g., fetal position or maternal obesity [2]. Also, methodological issues such as the correct angle of insonation and the assumption of uniform flow velocity across the vessel lumen may cause inaccuracy of measurements [3, 4]. Therefore, an alternative imaging modality would be desirable to further improve prenatal evaluation of fetal hemodynamics in cases where fetal ultrasound is of limited value.

Phase-contrast MR (PC-MR) angiography is the diagnostic reference standard for assessment of hemodynamics and blood flow quantification. PC-MR has been established as an accurate and reliable tool in children and adults with congenital heart disease (CHD) [5–7]. Although MRI is a standard approach in the prenatal evaluation of the fetal central nervous system and thoracic or abdominal pathologies [8–10], a comprehensive assessment of the fetal cardiovascular system lags behind due to technical limitations. In contrast to other organs, assessment of the fetal cardiovascular system requires dynamic imaging to resolve cardiac motion and blood flow. However, the intrauterine position of the fetus does not allow application of conventional surface electrodes for electrocardiogram gating. Therefore, the lack of a fetal cardiac gating signal prevented routine application of cardiovascular MRI during the fetal period.

The recent development of an MR-compatible Doppler ultrasound sensor (DUS) for tracking the fetal heartbeat revealed promising results to realize direct cardiac gating and dynamic imaging of the fetal heart [11]. However, this new technique has not been evaluated in the assessment of fetal hemodynamics using blood flow velocimetry measurements.

The aim of this study was to investigate the feasibility of dynamic fetal PC-MR angiography using the DUS for gating of the fetal heart and to compare blood flow measurements with standard fetal Doppler ultrasound velocimetry.

Materials and methods

Study population

Between October 2017 and September 2018, 12 pregnant women were included in this prospective study to undergo fetal echocardiography and fetal MRI in consecutive order. One woman had the history of neuroblastoma 20 years ago. Fetal Doppler ultrasound examinations and DUS-gated PC-MR angiography were assessed on the same day in varying order. Fetal MRI was performed for further evaluation of the central nervous system in five cases. Four pregnant women were referred for further evaluation of CHD. MRI was performed due to a fetal neck tumor in one case and in healthy pregnant volunteers in two cases, respectively. Mean gestational age was 32.8 weeks (range 28.7–36.7) and maternal age was 29.9 years (range 19.6–36.8). All participants gave their written informed consent. The local ethical committee approved the study.

Fetal PC-MR angiography

Two-dimensional (2D) PC-MR angiography of the fetal descending aorta was performed with a 1.5-T scanner (Achieva, Philips GmbH) using an eight-channel phased array cardiac coil, which was placed on the lower maternal abdomen. The pregnant women were positioned in the left decubital or supine position depending on individual preference of comfort.

A T2 turbo spin echo (TSE) sequence was performed for acquisition of transversal, coronal, and sagittal images of the fetal thorax (TE 90 ms, TR 1600 ms, FoV 430 × 360 mm, FA 90°, slice thickness 5 mm, matrix size 256 × 147, scan duration 32 s, sense factor 2). Following these images, a 2D phase-contrast angiography sequence was applied with the following parameters: TE 3 ms, TR 4.9 ms, FoV 250 mm, FA 15°, slice thickness 5 mm, acquisition matrix size 124 × 115 (reconstructed matrix size 192 × 192), slice thickness 5 mm, cardiac phases 10, velocity encoding factor 150 cm/s, NSA 2. Dependent on fetal heart rates, temporal resolution was 36–46 ms and scan duration was 12 s. All sequences were performed under maternal breath-hold or shallow free breathing to minimize motion artifacts. Measurements were performed in the fetal descending aorta (AoD) between the confluens of the arterious duct with the aorta and the diaphragmatic entering of the aorta. The respective slice was planned perpendicular to the direction of aortic blood flow, referring to sagittal and coronal T2-weighted images.

Gating of the PC-MR angiography sequence was realized using a recently developed MR-compatible DUS (sMaRT-sync, northh medical GmbH) that proved successful gating of the fetal heart recently [11]. After placing the pregnant women on the MR examination table, the DUS was placed

on the lower maternal abdomen at the position where a constant fetal cardiac signal was detected. The transducer was held in position by fitting an elastic belt around the maternal abdomen. The recorded DUS signals of the fetal heart beat were then transferred to the physiologic unit of the MR scanner and used as a cardiac gating signal.

Fetal Doppler ultrasound

Color and pulse-wave Doppler ultrasound of the descending aorta was performed using a convex curved array transducer with a frequency range of 2.0–6.0 MHz (Voluson E10, GE Healthcare). All measurements were performed by an experienced obstetric sonographer (MTS) and according to current guidelines [12]. The sample volume was set to cover the whole diameter of the fetal descending aorta. For accurate Doppler measurements, the angle of insonation was chosen as low as possible (< 30°).

Image analysis

PC-MR included assessment of peak flow velocity, mean flow velocity, mean flux, stroke volume, and regurgitation volume. Quantitative assessment of PC-MR measurements was focused on peak flow velocities in the fetal AoD and compared with standard Doppler ultrasound measurements. Flow-velocity curves in the fetal AoD were assessed from all 12 fetuses to calculate mean flow-velocity curves. In five fetuses, PC-MR angiography was performed twice to evaluate the reproducibility of flow measurements.

Segmentation of the aortic lumen was defined by manual delineation of a region of interest (ROI) encompassing the cross-sectional vessel area on a single frame of magnitude images. The vessel contours for the remaining phases were propagated and ROIs were superimposed to phase images by the software (IntelliSpace Portal, V. 9.0, Philips Medical Systems). All set ROIs in the AoD over the whole cardiac cycle were verified by visual inspection and manually corrected when necessary.

For fetal Doppler ultrasound measurements, peak systolic flow velocities were determined by definition of systolic peaks. The operators of PC-MR and Doppler ultrasound measurements were blinded for the other method, respectively.

Statistical analyses

Numbers are given as means and range (min–max). Students' *t* test was used to calculate differences between groups and quantitative measurements, with significant differences defined by $p < 0.05$. A Spearman rank analysis was performed to compare PC-MR and Doppler ultrasound peak velocities and for correlation of PC-MR velocities and volumes with gestational age. A paired Wilcoxon test was applied to calculate reproducibility.

Results

The MR-compatible DUS allowed successful fetal cardiac gating in all fetuses. In three fetuses, the DUS had to be repositioned during MR examination due to fetal movement and intermittent loss of fetal cardiac gating signal. The average fetal heart rate during MR examination was 140 bpm (range 129–163). No image distortions or artifacts related to the DUS were seen.

Fetal PC-MR angiography

In DUS-gated PC-MR cine images of the fetal AoD, the cross-sectional aortic lumen could be identified in all cases and ROIs in the vessel lumen could be reliably defined (Fig. 1). No phase aliasing was present with the selected velocity encoding factor of 150 cm/s. Mean vessel diameter of the AoD was 6.3 mm (range 5.2–6.8).

The assessed time-velocity curves revealed characteristic biphasic arterial flow waveform patterns with a high early systolic peak and continuously positive low diastolic blood flow (Fig. 2).

Peak velocity was 69.1 cm/s (range 39–125), mean flow velocity was 21.2 cm/s (range 8.6–36.8), and mean flux was 8.4 cm/s (range 3.2–14.6). Mean stroke volumes were 3.6 ml (range 1.5–5.7). There was no regurgitation volume in either of the fetuses, i.e., no pathological waveforms were observed. A summary of fetal characteristics and all assessed hemodynamic parameters is provided in Table 1.

Reproducibility of PC-MR was tested in five fetuses with two independent measurements each. No significant differences between the two settings were found for the peak velocity, mean flux, mean velocity, or stroke volume (SV) ($p = 0.12$–0.6).

A positive association with gestational age was assessed for PC-MR mean flux ($r = 0.66$, $p = 0.02$, 95%CI [0.13–0.9]) and stroke volume ($r = 0.63$, $p = 0.03$, 95%CI [0.07–0.89]), but not for mean flow velocity ($r = 0.5$, $p = 0.1$, 95%CI [− 0.12–0.84]).

Fetal Doppler ultrasound

Doppler ultrasound measurements in the fetal AoD were successfully performed in all 12 fetuses revealing typical biphasic arterial blood flow waveforms. In agreement to PC-MR measurements, no abnormal blood flow patterns were observed. The peak flow velocity assessed by Doppler ultrasound was 96.7 cm/s (range 60–142).

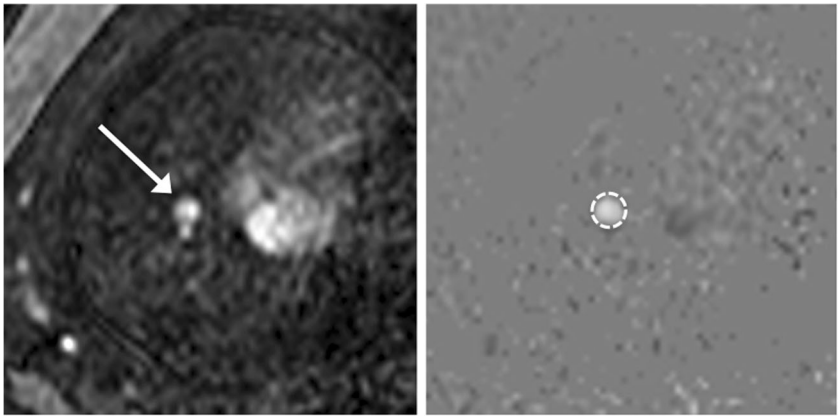

Fig. 1 PC-MR angiography images of a fetus (gestational age 34 + 3 weeks) illustrate a transversal slice of the fetal descending aorta (arrow in magnitude image, left) and placement of the region of interest (white dashed circle in phase image, right) for calculation of blood flow measurements

Comparison of PC-MR with Doppler ultrasound

A highly significant correlation of Doppler ultrasound with PC-MR peak flow velocities was assessed ($r = 0.8$, $p < 0.002$, 95%CI [0.41–0.95]) (Fig. 3). PC-MR-derived average peak flow velocities were generally lower than peak flows assessed by Doppler ultrasound in each fetus (69.1 cm/s vs. 96.7 cm/s; $p < 0.001$) (Fig. 4).

Discussion

This study demonstrates successful application of fetal PC-MR angiography for prenatal assessment of blood flow hemodynamics using a recently developed MR-compatible DUS for fetal cardiac gating. Comparison with Doppler ultrasound measurements revealed high correlation of peak flow velocities in the fetal AoD, with generally lower blood flow velocities for PC-MR measurements. The technical development of direct and non-invasive fetal cardiac gating allowed dynamic functional imaging of the fetal aorta and may offer a new possibility to assess the vascular system and blood flow measurements in the prenatal period.

PC-MR angiography is an accurate and reliable method for non-invasive blood flow quantification and established in the evaluation of hemodynamics in children and adults with CHD [7, 13]. PC-MR also allows estimation of pressure gradients associated with vascular stenosis, not being dependent on the acoustic window using Doppler ultrasound [5]. Clinical applications of PC-MR in the postnatal period or childhood include hemodynamic evaluation of aortic isthmic stenosis, congenital shunts, tetralogy of Fallot, or valve disease [5, 14, 15]. However, this method necessitates a cardiac gating signal to guarantee adequate spatial and temporal resolution. Due to the intrauterine fetal position, the inability of direct cardiac gating prevented the application of dynamic cardiovascular imaging in the prenatal period so far.

In recent studies, different strategies were introduced to overcome this technical challenge. The metric optimized gating (MOG) technique is an indirect gating technique that uses

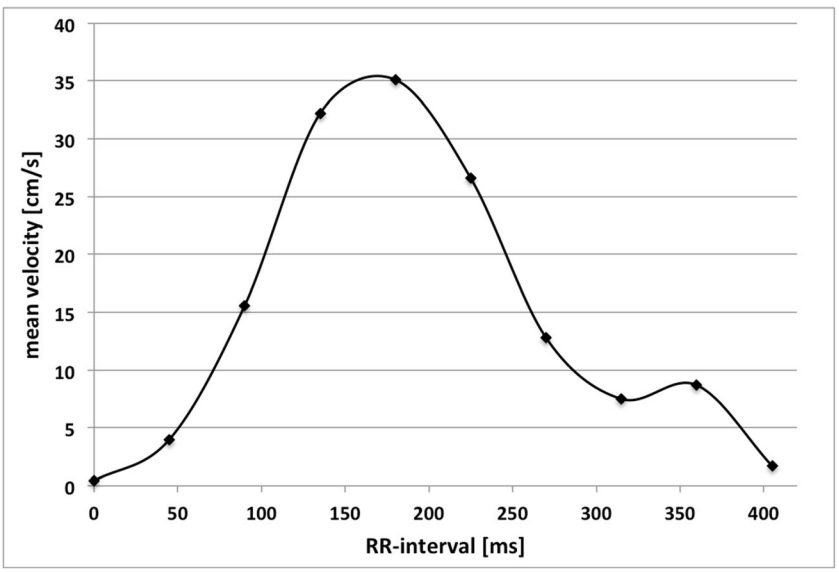

Fig. 2 DUS-gated PC-MR angiography-derived flow waveform (mean velocity) with typical strong early systolic peak and continuous positive diastolic flow of a fetus (gestational age 32 + 6 weeks)

Table 1 Summary of DUS-gated PC-MR angiography and Doppler ultrasound measurements

	GA (weeks)	HR (bpm)	aortic diameter (mm)	US peak velocity (cm/s)	MR peak velocity (cm/s)	MR mean velocity (cm/s)	MR mean flux (ml/s)	MR stroke volume (ml)	Diagnosis
Fetus 1	28 + 5	134	6.7	65	46	11.6	5.5	2.5	VMG
Fetus 2	28 + 5	131	5.6	60	53	9.8	3.3	1.5	IUD twin
Fetus 3	32 + 6	134	6.8	101	66	14.5	7.4	3.3	CoA
Fetus 4	33 + 2	147	6.7	80	39	20.9	7.1	2.9	IUD twin
Fetus 5	31 + 2	139	6.2	142	125	25.4	11.2	4.8	CoA
Fetus 6	35 + 4	163	6.5	105	73	16.9	14.6	5.4	RDA
Fetus 7	32 + 0	140	5.6	93	79	20.6	4.3	1.8	IUD twin
Fetus 8	33 + 2	155	5.2	64	39	18.5	6.1	2.4	Neck tumor
Fetus 9	34 + 3	134	6.5	105	83	23.2	8.5	3.8	PS
Fetus 10	33 + 6	136	6.2	130	78	19.7	9.9	4.4	Normal
Fetus 11	36 + 5	129	6.7	95	68	25.9	12.3	5.7	Normal
Fetus 12	33 + 0	138	6.7	120	80	31.2	10.7	4.7	ACC

GA gestational age (weeks + days), *HR* heart rate, *US* ultrasound, *VMG* ventriculomegaly, *IUD* intrauterine demise, *CoA* coarctation aorta, *RDA* right descending aorta, *PS* pulmonary stenosis, *ACC* agenesis of the corpus callosum

iterative reconstruction [16] to calculate a gating signal retrospectively [17]. PC-MR measurements using MOG were successfully performed in human fetuses demonstrating fetal blood flow distribution [18], assessing reference ranges in the major fetal vessels [19] and comparing PC-MR measurements at different field strengths [20]. However, this technique is limited by the inability to adjust for heart rate variations, which may influence precise measurements considering the physiologically strong variations of fetal heart frequencies between 138 and 175 bpm during MRI [16]. In addition, the need for a specialized software and prolonged post-processing with reported reconstruction times of up to 2 h complicates clinical application of MOG. A different method to synchronize the fetal heartbeat with image acquisition is the self-gating technique. This method recognizes periodic changes of the cardiac cycle to calculate a gating signal from acquired k-space data [21, 22]. Dynamic imaging of the fetal heart using the self-gating technique was reported recently [23, 24]. However, until now, there are no studies available performing self-gated PC-MR in human fetuses.

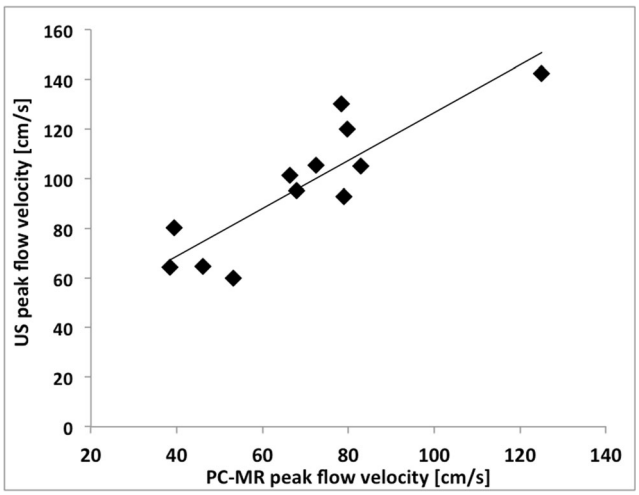

Fig. 3 Correlation of peak flow velocities assessed by DUS-gated PC-MR angiography and Doppler ultrasound (US)

The observed underestimation for PC-MR peak velocities in comparison to fetal Doppler ultrasound is a well-known phenomenon in adults [25–27] that may be enhanced by the choice of sequence parameters [28]. In agreement with our results, underestimation of aortic peak velocities by PC-MR of up to 30% though strong linear correlation with Doppler ultrasound was reported in adult patients [29, 30].

The flow profiles that were assessed by PC-MR in this study revealed characteristic waveforms of the fetal aorta with a steep systolic rise, a post-systolic notch, and a low end-diastolic forward flow [31]. The mean flow volume of 8.4 ml/s in this trial is lower than 13.2, 12.8, and 12.6 ml/s using MOG-gated PC-MR, which can be explained by a lower gestational age (33 weeks) of our fetuses compared to the other studies (36, 37, and 37 weeks) [18–20]. Flow volumes are known to describe a significant increase in late gestation [32], thus corresponding to the observed positive association of flow volumes and gestational age in this study. AoD flow volumes in this study were very similar to those assessed by Doppler ultrasound in term neonates with 8 ml/s [33] and in agreement with volumes adjusted for weight (3.8–4.2 ml/s per kilogram) and age (31–34 weeks of gestation) [34, 35].

PC-MR flow velocities in the fetal AoD (8.6–36.8 cm/s) were comparable to those assessed by Doppler ultrasound in term newborns (12.7–24.4 cm/s) [33] and late gestational fetuses 17–47 cm/s (27–40 weeks) [34, 36]. In contrast to flow volumes, the velocities in the AoD seem to be stable during late gestation [34].

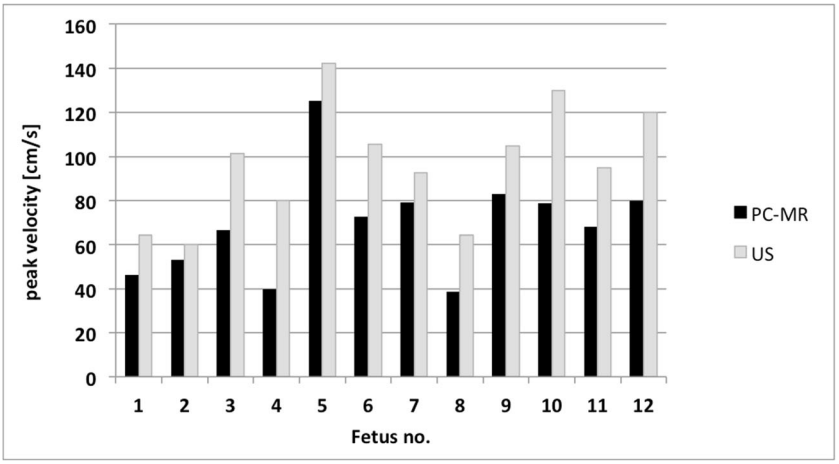

Fig. 4 Comparison of peak flow velocities in the fetal descending aorta as assessed by DUS-gated PC-MR angiography (PC-MR) and Doppler ultrasound (US)

Average peak velocities of 69 cm/s (PC-MR) and 97 cm/s (Doppler ultrasound) in our fetuses were comparable to reported velocities assessed by Doppler ultrasound in term neonates (55–117 cm/s) [33] and late-term fetuses (69–129 cm/s) [34, 36].

Measurement of flow hemodynamics and distribution in the fetus are commonly assessed by Doppler ultrasound to guide management in cases of fetal distress, intrauterine growth restriction (IUGR), and fetal cardiac disease [37–39]. In IUGR, assessment of fetal flow patterns is crucial for diagnosis and planning of delivery and further allows estimation of postnatal outcome [1]. In cases of suspected CHD, prenatal diagnosis is important for perinatal management including parental counseling and planning of delivery or surgical intervention. The presented new technique for direct fetal cardiac gating indicates the potential of PC-MR as an alternative diagnostic tool in the evaluation of fetal flow properties. This may be of importance in cases where cardiac or vascular anatomy is difficult to visualize, e.g., during later pregnancy where echocardiography is complicated by an inadequate acoustic window, ossification of the fetal skeleton or decreasing amniotic fluid. Also in the evaluation of aortic isthmus stenosis, the most commonly missed diagnosis in neonatal screening, estimation of aortic arch flow characteristics by PC-MR may help to increase diagnostic accuracy [40]. In other words, fetal PC-MR angiography may potentially offer a new diagnostic approach in the evaluation of fetal hemodynamics in addition or as an alternative to Doppler ultrasound. This may be of special interest for certain pathologies as IUGR, CHD, and aortic isthmus stenosis when Doppler ultrasound is inconclusive or technically challenging. However, the diagnostic performance of this technique is still unknown and requires validation in fetuses with the abovementioned abnormalities.

MRI is one of the most powerful diagnostic tools, and focused MRI examinations, e.g., of the breast or liver, have high and sometimes unique clinical impact [41]. On the other hand, MRI is an expensive diagnostic tool and is thus contributing to the increasing and unsustainable healthcare costs. To be of potential "value," this certain approach of fetal PC-MR angiography would therefore require clinical benefit over costs. Although adequate metrics assessing radiology's contribution to costs or outcomes are lacking or hard to define [41, 42], establishing fetal PC-MR into clinical routine would necessitate the proof of altering therapeutic decision-making and, in its best scenario, improving fetal outcome. In summary, although this is a promising technique to enhance the diagnostic yield of fetal MRI, further studies are needed to investigate the clinical impact and to avoid overestimation of this technique.

A limitation of our study is that the patient group is too small to claim overall consistency. In addition, fetal PC-MR was focused on the fetal AoD but not on other major fetal vessels.

In conclusion, this study demonstrated successful application of PC-MR using a MR-compatible DUS for fetal cardiac gating. Comparison of DUS-gated PC-MR with Doppler ultrasound measurements revealed a highly significant correlation, indicating the diagnostic potential of fetal DUS-gated PC-MR angiography. We believe that this novel technique of direct fetal cardiac gating is a promising approach in the prenatal evaluation of fetal hemodynamics, especially in cases where Doppler ultrasound is limited or inconsistent.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Prof. Dr. Gerhard Adam.

Conflict of interest The authors of this manuscript declare relationships with the following companies: The authors BS, JY, FK, KF, CR, and MTS are co-founders and stakeholders of northh medical GmbH, the developing company of the Doppler ultrasound gating device.

Statistics and biometry Dr. Roland Fischer, who is a co-author of this manuscript, kindly provided statistical advice for this manuscript.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Singular subjects of this study have been part of a previous publication performing fetal cardiac MRI, therefore investigating a different issue of fetal MR imaging than PC-MR angiography.

Methodology
- prospective
- experimental
- performed at one institution

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