Title

Uterine artery pulsatility and resistivity indices in pregnancy: comparison of MRI and Doppler US.

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Abstract

Objective

The aim of this work was to evaluate whether the uterine arteries (UtA) could be identified and their flow profiles measured during a fetal MRI examination. A comparison was performed against same day routine sonographic Doppler assessment.

Methods

35 normal, healthy, singleton pregnancies at 28-32 weeks gestation underwent routine Doppler examination, followed by MRI examination. The resistivity index (RI) and pulsatility index (PI) of the left and right UtA were measured using phase contrast MRI. Bland Altman statistics were used to compare MRI with the ultrasound results.

Results

Sixty-nine comparable vessels were analysed. Six vessels were excluded due to artefact or technical error. Bland-Altman analysis demonstrated the ultrasound indices were comparable, although systematically lower than the MRI indices; Right UtA RI bias -0.03 (95% limits of agreement -0.27 to +0.20), and left UtA RI bias -0.06 (95% limits of agreement -0.26 to +0.14); Right UtA PI bias -0.06 (95% limits of agreement -0.50 to +0.38), Left UtA PI bias -0.11 (95% limits of agreement -0.54 to +0.32). The inter-rater agreement for the MRI derived PI and RI analysis was good.

Conclusion

This study demonstrates that in the majority of early third trimester pregnancies, the uterine arteries can be identified, and their flow profiles measured using MRI, and that the derived PI and RI values are comparable with Doppler ultrasound values. MRI may prove a useful future technique to complement the use of ultrasound in the assessment of fetal well-being.

Introduction

Prior to pregnancy, the uterine circulation is high resistance. As the placenta develops in the first and second trimesters, extravillous trophoblast invades the walls of the resistance vessels in the myometrial layer of the uterus, and the vascular resistance of the uterine circulating declines[1]. This physiological process is mirrored by an increasingly low resistance pattern of flow in the uterine arteries[2]. Failure of trophoblast invasion of the uterine resistance vessels is implicated in a number of the major complications of pregnancy such as pre-eclampsia and fetal growth restriction[3]. Consistent with this, the presence of a high resistance pattern of UtA Doppler flow in mid-gestation is associated with an increased risk of these complications[4]. UtA Doppler flow velocimetry has been shown to provide useful prediction of the risk of pre-eclampsia and stillbirth[5]. However, its use is generally confined to women who are high risk. Currently, the primary method for assessing the vascular resistance of the uterine circulation is ultrasonic Doppler flow velocimetry of the uterine arteries[6]. Commonly measured indices include the pulsatility index (PI) and the resistivity index (RI)[7,8]. PI describes the variability of blood velocity across the cardiac cycle; peak systolic velocity (S), minus minimum diastolic velocity (D), divided by the time averaged mean (M) ((S-D)/M), while RI is calculated from (S-D)/S[9,10].

MRI (magnetic resonance imaging) is becoming more widely used in fetal imaging, and in placental studies[11,12]. It is particularly valuable when ultrasound is technically problematic due to maternal body habitus, fetal position or advanced gestational age[13,14,15]. Previous studies of placental MRI have reported a decrease in placental volume with an increase in UtA Doppler PI[16], however, there is little literature on whether PI and RI are reproducible using MRI, and whether MRI could provide more detailed information on placental function[17].

An initial small-scale study reported difficulty in UtA localisation, and MRI blood flow measurements were not successfully obtained.[18]. Phase-contrast methods have been developed for measuring arterial blood flow[19,20] and Issa et al. were the first to describe successful UtA blood flow measurements using phase-contrast MRI[21]. To our knowledge, there are no MRI studies estimating UtA PI and RI during pregnancy, however, studies in sheep have proved that phase-contrast methods demonstrate high inter-operator agreement and good reproducibility when calculating flow velocities and when compared with Doppler ultrasound[22]

The aim of this work is to establish if phase contrast MRI can identify the UtA, measure the PI and RI, and compare these with Doppler indices measured at same day ultrasound examination in the early third trimester.

Method

Ethical approval was obtained from the NRES Committee East of England-Cambridge Central, reference number 12/EE/0169. Participants provided written informed consent and between 1st May 2013 and 28th May 2014, 35 normal singleton pregnancies were recruited at routine 20-22 week ultrasound examination. Subjects with multiple pregnancies were excluded. All women then underwent routine fetal ultrasound examination between 28-32 weeks gestation followed by same-day MRI examination which was then analysed by two independent observers. This formed part of a larger study evaluating amniotic fluid measurements.

Ultrasound

Following routine biometry measurements, transabdominal colour Doppler US was used to identify each UtA. The in-room time was 20 minutes and the US examination was performed by a single investigator (RH) with 5 years obstetric

ultrasound experience as guidelines and recent research state Doppler ultrasound is reproducible[23,24]. All the examinations were performed using the same GE Voluson E8 (GEHC, Waukesha, WI, USA) ultrasound machine with a 2-5MHz multi-frequency curvilinear transducer adhering to the following standardised guidelines[24]. The Doppler measurement was taken 10mm anterior to the point at which the UtA crosses the external iliac artery, as it passes anteriorly in the uterine wall (Figure 1a)[24]. The sample gate was set at 3mm to include the whole vessel and an angle of insonation $<40^{o}$ was used. Pulse-wave Doppler US was used to obtain three separate UtA waveforms, and the inbuilt automatic waveform analysis calculated the mean UtA RI and PI[24,25,26,27]. The mean of three consecutive measurements was recorded (Figure 1b).

MRI

All MRI examinations were performed using an 8-channel cardiac array coil and the same 1.5T MRI system (MR450), GE Healthcare, Waukesha, WI, USA). Initial breath-hold sagittal and axial imaging through the uterus was obtained with a fast-imaging employing steady-state acquisition (FIESTA) pulse sequence. Following these, an oblique coronal image plane was positioned immediately superior to, and parallel with, the external iliac arteries. A cardiac-gated cine phase-contrast study was performed using this plane, with the following parameters: TR/TE 6.45/3.1msec, slice thickness 7mm, FOV 36cm, matrix 192x256, flip angle 30^{o}, retrospective gating with 60 cardiac phases, two views per segment, velocity encoding parameter (venc), 80-90cm/sec. The in-room total examination time ranged from 25-30 minutes.

Data analysis

A computer based imaging software ClearCanvas (ClearCanvas Inc, Toronto, ON) was used for vessel identification by co-locating the UtA between the phase-contrast image and reference images. Axial and sagittal FIESTA images and an oblique coronal phase-contrast image were used to identify each vessel (Figure 2). Correct identification was based on the following features: the presence of one or more vessels passing through the plane in the expected location, flow predominantly in an anterior direction, image correlation confirming that the vessel was positioned within the uterine wall rather than in adjacent structures such as fetal body parts, maternal bowel, or the umbilical artery. Vessels were excluded if they did not fulfil the criteria, or if the vessel could not be discretely identified owing to motion or blurring artefacts. If more than one artery was identified on each side of the uterus, both were evaluated, but the largest vessel was used for comparison with ultrasound as this was the criterion applied during routine US examinations.

An in-house flow analysis program was developed using Matlab (The Mathworks, Nattick, MA), was used to evaluate the phase-contrast images of the selected vessels. Two observer's independently traced manual regions of interest (ROI) around each identified UtA, and an adjacent artefact-free area of stationary tissue to provide background correction. Velocity aliasing was also corrected. A corresponding flow profile was generated, and from this a RI and PI value for each artery was calculated (Figure 3b).

Statistical analysis

Bland Altman comparison statistics were used to investigate the relationship between the PI and RI values from the reference Doppler ultrasound, and MRI examinations[28]. The standard deviation, bias, and 95% limits of agreement were

calculated[28]. Using reference standards, normal US PI and RI reference values at 30 weeks gestation were defined as a PI value of 0.35-1.21 and an RI of 0.27-0.54[25,26,27,29]. Inter-rater variability was calculated using the intra-class correlation (ICC) statistic to assess the study repeatability[28]. Two investigators independently analysed each UtA on the stored MR images. All statistical analysis was performed in R (version 3.1.1, The R Foundation for statistical Computing, Vienna, Austria).

Results

Data from 35 women examined at a mean gestational age of 30 weeks (range 28-32 weeks) were analysed. The MRI scan was well tolerated, with all participants completing the examination. A total of 76 UtA, including six duplicate arteries, were initially identified for analysis. At ultrasound, one artery could not be identified, leaving a total of 69 single arteries for comparison with MRI. At MRI, six UtA were excluded from this total, leaving 63 arteries in 34 patients for analysis. Three right, and three left UtA were excluded; two UtA were not identified due to motion artefact corrupting the PC acquisition, one was not identified due to an adjacent pulsatile vessel creating a ghosting artefact, and three were not identified due to technical error where the PC acquisition plane was incorrectly positioned. Only in one patient were both UtA excluded.

Of the remaining 34 participants, 30 were Caucasian, two were Oriental, and two were Asian with a mean maternal age of 32 years (range, 20-41 years). There were no adverse outcomes and all 34 women had normal live births. The mean birth weight was 3405g (range 2520g-4180g) and the mean gestation at delivery was 40 weeks (range, 37-42 weeks).

The level of agreement or bias between phase contrast MRI and ultrasound is shown in Table 1. This demonstrates a relatively small difference in values for the less well established PC method, with an overall relatively small bias which are illustrated graphically in figure 4. All the results from both US and MRI examinations were within normal ultrasound reference values (Table 2) with the MRI values being slightly higher than the ultrasound values. There was no relationship or trend between the differences in the MRI and ultrasound measurements and the magnitude of the measurements.

Intra-rater variability for the MRI measurements is reported in (Table 3) and demonstrates very good inter-rater agreement based on benchmarking set by Altman[28] with ICC values for the left UtA PI and RI (0.876 and 0.865) and good agreement for the right UtA PI and RI (0.704 and 0.746) when using the MR PC technique.

Discussion

To our knowledge, the use of MRI in the early third trimester of pregnancy for identifying the UtA and calculating a PI and RI has not been previously reported. Previous MRI studies have attempted to quantify blood flow in the UA[18,21]. Our results show that in the majority of cases it is possible to identify the UtA using phase-contrast MRI, obtain a PI and RI value similar to that of ultrasound, and record flow waveforms that are comparable to those acquired using Doppler ultrasound. Issa et al. used echo-planar imaging (EPI) to achieve the first report of reproducible and consistent UtA blood flow velocity and volumes recorded in 9 participants[21], however, RI and PI were not calculated. To our knowledge, the only other MRI study was conducted by Pates et al[18] who reported difficulties with UtA localisation which prevented accurate blood flow assessment in their 13 participants.

In this study, the MR indices obtained had good agreement with only small biases. Results were comparable with the ultrasound Doppler indices and within the normal reference range for 30 weeks gestation (Table 2). Although the MRI PI and RI values obtained were comparable with the ultrasound values, there was some irregularity in several of the MRI flow profiles. This finding could be attributed to several technical factors such as the small artery size, poor cardiac gating, vessel motion, fetal motion, background correction artefacts or very high velocity blood flow producing undetected aliasing during systole. Figure 5a illustrates a smooth flow profile with a single peak consistent with systole, replicating that of the Doppler ultrasound flow profile (figure 3a). An example of an irregular profile with a less well defined definite systolic peak is illustrated in figure 5b. The aliasing correction algorithm may also have contributed to the irregular profiles and influenced the results. Other factors affecting the profiles could be the small vessel cross-sectional area available for analysis, the non-zero background phase-shifts due to eddy currents (affecting the accuracy of the volumetric flow), acquiring data during breathing and time-averaging over a number of heartbeats.

Our study used a larger cohort of women compared with other studies, and the MRI in-room time of 25-30 minutes was better than previous studies that reported 40 minutes[14]. This did not include analysis time, therefore, the ultrasound examination time of 20 minutes including analysis and reporting was, as expected, more efficient. The MRI examination was well tolerated by the participants, although the extended scan time remains a disadvantage, with analysis currently being labour-intensive. Calculating the PI and RI using our software was quick, however, manually drawing a ROI around each artery to calculate the PI and RI, along with the initial UtA identification was relatively time consuming and not yet suitable for use in the clinical

setting. Although motion artefact is a common problem in MRI, owing to these longer acquisition times, this only resulted in one case being excluded from analysis. Continued advances in the optimisation of MRI will, over time, improve these limitations. An advantage of the MRI technique, if future studies prove that data is reliable, is that it allows retrospective analysis with no impact on the patient experience. Analysis time was not recorded in this study, however Issa et al[21] report the flow measurements on average took an additional 13 minutes to assess.

This data set was collected as part of an earlier AFI (amniotic fluid index) study; therefore, women were assessed at 30 weeks gestation, when in practice the UtA would routinely be evaluated at 20-24 weeks gestation. Many early first trimester and second trimester studies indicate that abnormal Doppler ultrasound RI and PI help predict conditions such as PE or IUGR, however, there are fewer third trimester studies reported to be of clinical value[25]. Future studies using second trimester participants would be more clinically relevant and may prove more challenging regarding MRI measurements.

This study has a number of limitations. First only a single investigator undertook the Doppler ultrasound. However, good reproducibility and reliability of the UtA Doppler using two sonographers, performing blinded measurements in the same woman, has been previously reported[23]. A further limitation of the present study is that the reproducibility of the MRI was not assessed, just the inter-rater agreement. Further studies should address the reproducibility and reliability of two separate and blinded MRI examinations on the same patient. This study assumes that ultrasound is the gold-standard. However, the reason why notable variation between the ultrasound and MRI exists as demonstrated by the range in the 95% LOA may be due to a lack of 'true' gold standard i.e. an invasive intra-arterial measurement. Further work could

compare MRI and ultrasound using either clinical outcome or histopathological assessment of the placental bed as the gold standard. There are several limitations associated with measuring flow using Doppler ultrasound. Even though the spatial resolution of ultrasound images may be superior to MRI in this application, we do not know the precise volume from which the Doppler signal is obtained. In MRI, the phase shift measurement is calculated for every pixel. The angle of insonation with Doppler ultrasound is operator dependant which will affect the measured velocities and flow, whereas MRI is relatively robust to errors in angulation, and may also be useful for assessing small vessel sizes[30].

Future work will also need to include studies using larger populations at differing gestational ages. The published studies to date have used normal sample populations. Studies examining high risk third trimester pregnancies are necessary to evaluate pregnancies with abnormal PI and RI values. Future studies will benefit from including a more diverse range of gestational ages from 20 - 40 weeks to correlate with the current Doppler ultrasound reference standards, and assessing participants with a high BMI as this is a growing population, and a cohort that is technically difficult to evaluate using ultrasound[31].

It can be argued that Doppler ultrasound PI and RI simply provide a ratio of measurements and do not truly reflect absolute flow quantification, and their limitations have been acknowledged[21,32]. MRI may prove an alternative, quantitative technique to complement the use of ultrasound and with further optimisation such as using 3 Tesla scanners with an improved signal-to-noise-ratio could potentially estimate absolute flow, which may provide a more accurate biomarker for predicting PE and IUGR thus leading to more in depth information on the placenta.

Conclusion

This early third trimester study, in normal singleton pregnancies, demonstrates that MRI can identify the majority of uterine arteries, and that derived PI and RI MRI values are comparable with Doppler ultrasound values. It shows that the analysis methods used in this study are reproducible, adding validity to the work. PE and IUGR continue to be major causes of third trimester morbidity and mortality, and remain difficult to predict. The known accuracy of MRI ensures the imaging plane is perfectly orthogonal to the vessel, where there is variability in ultrasound, and although further work is required to improve validation of the MRI technique at different gestational ages, and to evaluate its prognostic value in the management of adverse outcome pregnancies, it may provide a potential alternative technique.

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Tables

	n sample size	US Median, LQ, UQ	MRI Median, LQ, UQ	sd	Bias (average)	95% LOA (limits of agreement)
PI RIGHT	31	0.61 [0.53-0.68]	0.66 [0.57-0.82]	0.22	-0.06	-0.50 to +0.38
PI LEFT	32	0.60 [0.52-0.66]	0.74 [0.58-0.84]	0.22	-0.11	-0.54 to +0.32
RI RIGHT	31	0.43 [0.39-0.48]	0.47 [0.42-0.56]	0.12	-0.03	-0.27 to +0.20
RI LEFT	32	0.42 [0.39-0.46]	0.50 [0.43-0.56]	0.10	-0.06	-0.26 to +0.14

Table 1 Bland-Altman comparison statistics assessing the relationship between the ultrasound and MRI techniques in relation to both the PI and RI values

RI	reference	US right UtA	US left UtA	MRI right UtA	MRI left UtA
Median	0.40	0.43	0.42	0.47	0.50
3^{rd} - 97^{th} percentile	0.27 -0.54	0.39-0.48	0.39-0.48	0.42-0.56	0.43-0.56
PI					
Median	0.72	0.61	0.60	0.66	0.74
3^{rd} - 97^{th} percentile	0.35-1.21	0.53-0.68	0.52-0.66	0.57-0.82	0.58-0.84

Table 2 Normal reference ranges for PI and RI as set by Schaffer 1998 and Mertz 2005 at 30 weeks gestation compared with the results obtained in this study;

	MRI ICC	MRI 95% CI
RI – Left	0.865	0.735-0.935
RI – Right	0.746	0.535-0.87
PI – Left	0.876	0.752-0.94
PI – Right	0.704	0.469-0.847

Table 3 Illustrates the MRI ICC based on benchmarks set by Altman[35]. Results demonstrate "good" inter-rater agreement for the right UtA PI and RI and "very good" inter-rater agreement for the left PI and RI

Figures

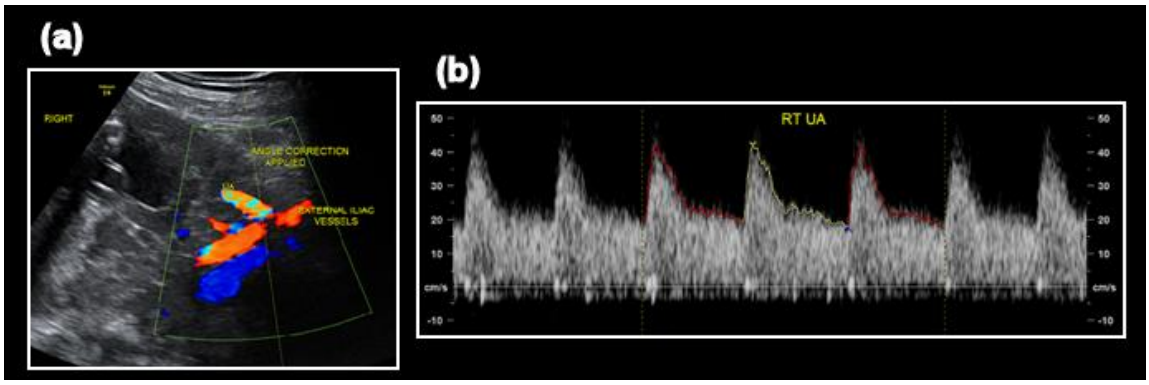

Figure 1

Illustrates the UtA location on ultrasound (a), and the resulting waveform (b) at 30 weeks gestation.

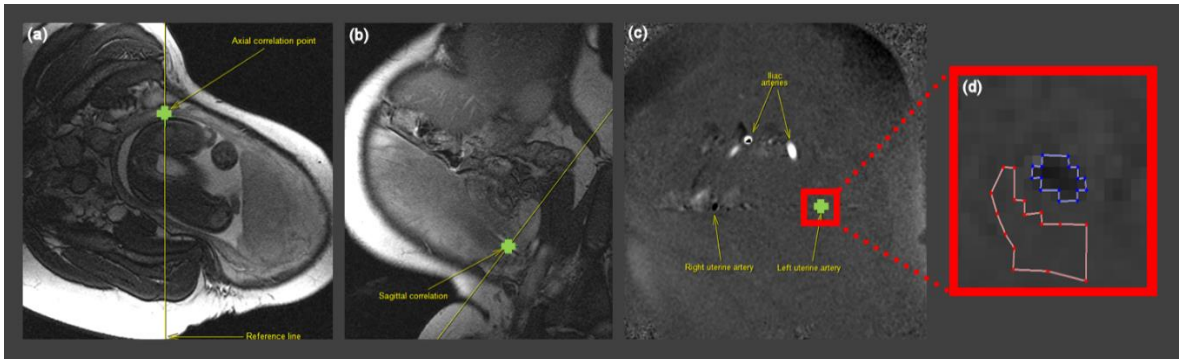

Figure 2

UtA identification (green x) with MRI. Correlation is demonstrated in three planes using ClearCanvas; axial FIESTA (a), sagittal FIESTA (b) and phase-contrast (c). A ROI was drawn around each UtA (blue) and an area of representative background tissue (red) using the in-house Matlab software (d).

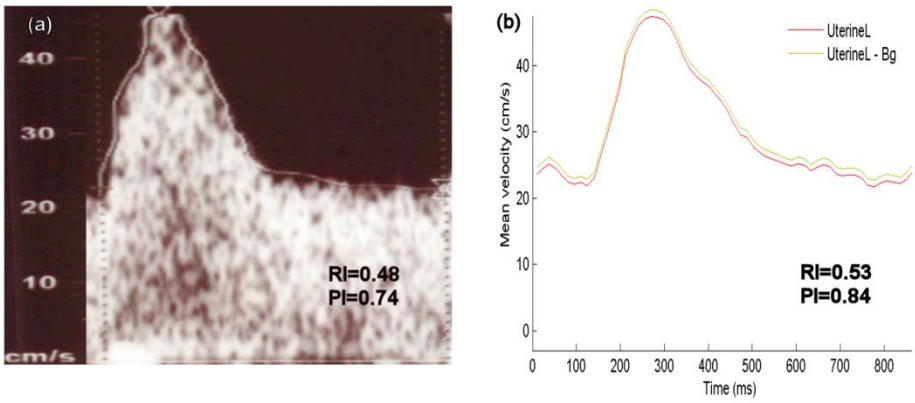

Figure 3

Correlation between Doppler ultrasound (a) and MRI flow profiles (b) with PI and RI values.

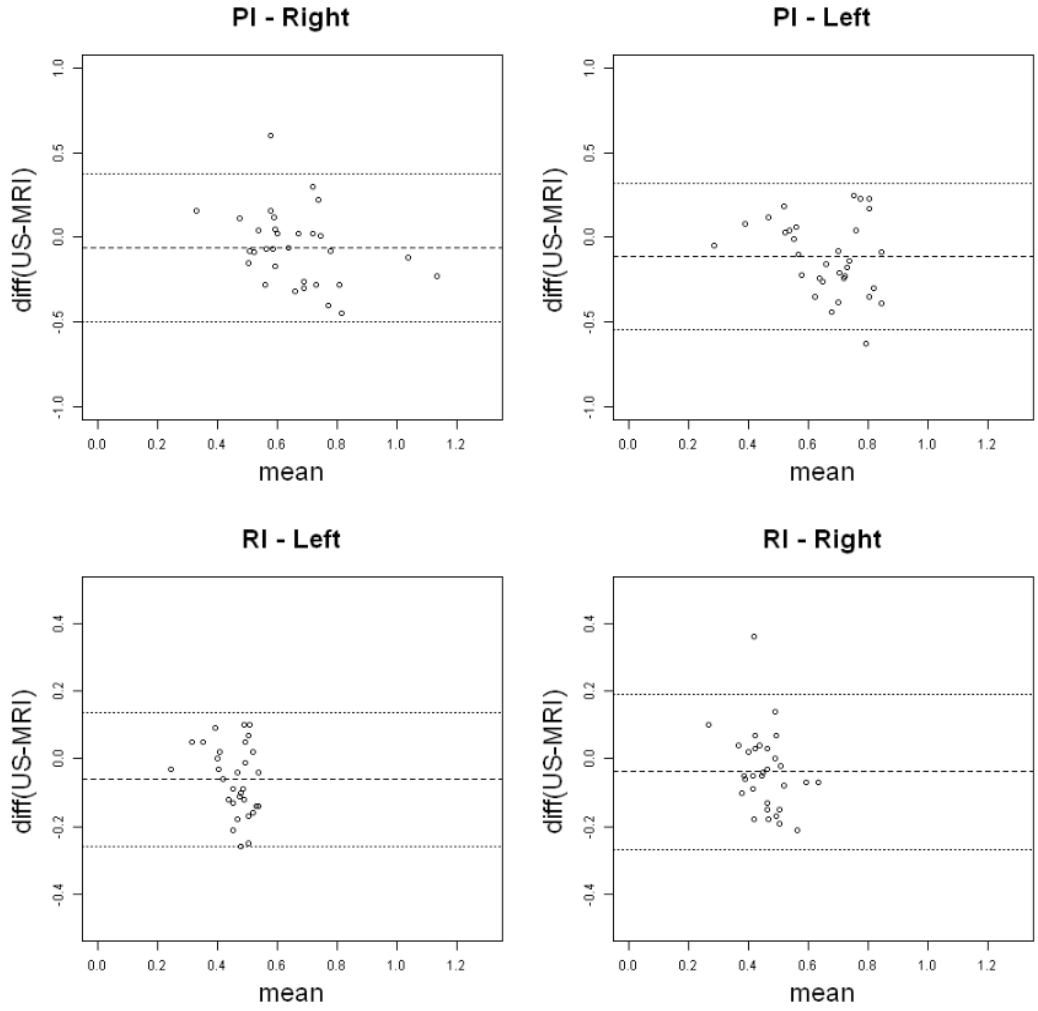

Figure 4.

Bland-Altman comparison plots comparing MRI PI and RI values with the reference standard ultrasound. The dashed line represents the bias and the dotted line represents the 95% limits of agreement. Points are clustered around the bias and there is no trend, suggesting MRI values are comparable with ultrasound.

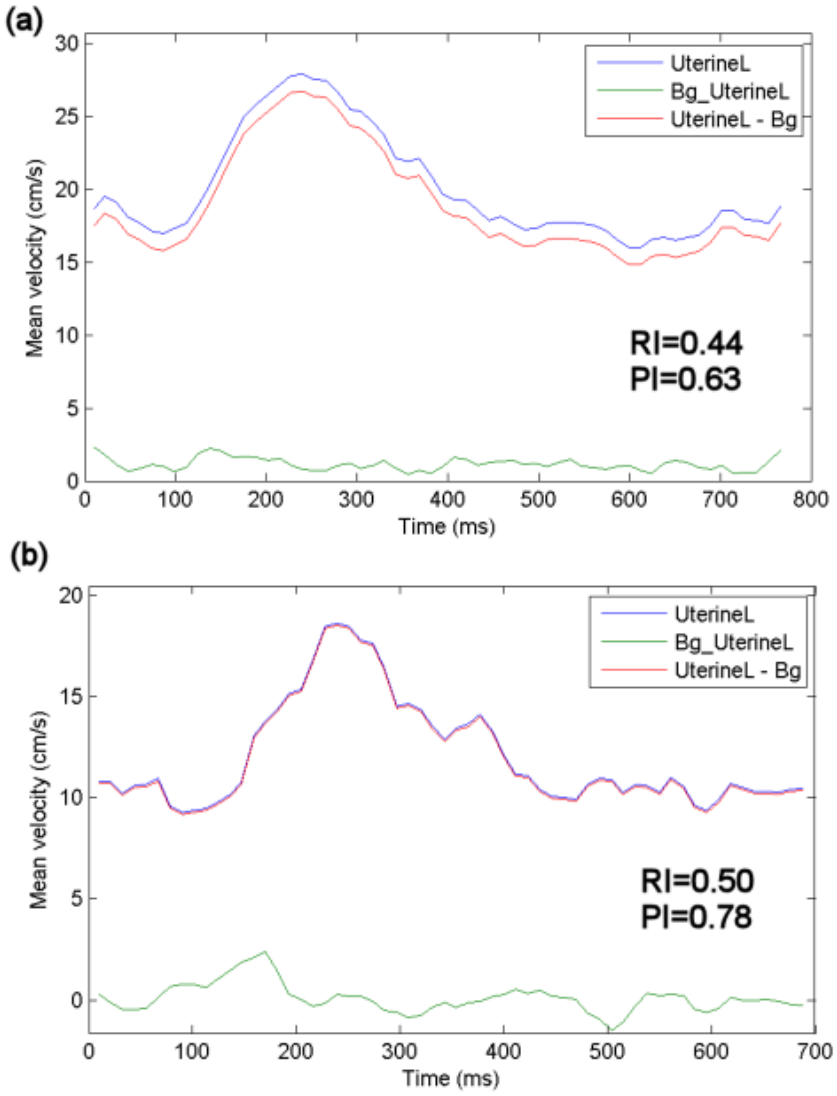

Figure 5

A smooth MRI profile (a) and an irregular MRI profile (b). Both produce values for RI and PI that are within the normal reference range. The irregular profile may be attributed to the small vessel cross-sectional area, the pulsatile nature of the arterial flow or aliasing.

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