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Magnetic Resonance Imaging Relaxation Time Measurements of the Placenta at 1.5 T

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Abstract

Placental insufficiency is a major cause of fetal growth restriction (FGR) and accumulating evidence indicates several aspects of placental morphology are altered in this condition. MRI provides quantitative indices that may be used in non-invasive assessment of the human placenta, such as relaxation time measurements, T1 and T2. We hypothesised that placental relaxation times relate to alterations in placental tissue morphology and hence may be useful in identifying the changes associated with FGR. We report on the first phase of testing this hypothesis, in a study of women in normal pregnancy.

Aims—To assess relaxation time measurements in the placenta in normal pregnancy and correlate these with gestational age and stereological analyses of placental morphology following delivery.

Methods—30 women underwent MRI examination (1.5 T) between 20 and 41 weeks gestation. Placental T1 and T2 measurements were acquired from a mid-depth placental region, co-localised to a structural scan. Fixed, wax-embedded sections of these placentas collected at delivery were stained with hematoxylin/ eosin and subjected to stereological analysis.

Results—Placental T1 and T2 show a significant negative correlation with gestation, (Pearson correlation $p=0.01$, 0.03 respectively). 17 placentas were analysed stereologically. In the group as a whole there was no significant correlation between T1 and T2 and morphological features. However, in a subset of 7 pregnancies scanned within a week of delivery, a significant positive correlation was observed between the fibrin volume density and the ratio of fibrin: villous volume densities and T2 (Spearman correlation $p=0.02$, 0.03 respectively).

Discussion—The correlations between placental T1 and T2 and gestation show that these variables are clearly influenced by changes in placental structure. Fibrin might be a key component but further work is needed to fully elucidate the major structural influences on placental T1 and T2.

Keywords

Fetus; Placenta; MRI; Relaxation Times; IUGR (FGR); Stereology

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Introduction

Fetal growth restriction (FGR) is a serious complication of pregnancy in which the fetus fails to reach its own genetically determined growth potential. It is common, affecting 3-10% of all first time births[1] and is linked to a third of all antepartum deaths[2]. Placental insufficiency is a major cause of FGR and accumulating evidence indicates that several aspects of placental structure and function are specifically altered in this condition, including gross morphology[3], tissue morphology at a microscopic level[4], blood flow in the uteroplacental circulations and placental transport mechanisms for nutrients and ions[5].

In clinical obstetrics, ultrasound biometry and Doppler ultrasound of the uterine and umbilical vessels are the main investigations available to diagnose and predict FGR. However, it may not always be possible to differentiate the small but healthy fetus from one affected by FGR. These difficulties particularly affect the large heterogeneous groups of women with suspected FGR (on the basis of biometric measurements, reduced amniotic fluid volumes, abnormal uterine artery Dopplers or risk factors for FGR), all undergoing intensive fetal surveillance or facing unnecessary intervention, as prognosis for the fetus is difficult to predict and a deterioration may only occur late in disease, if at all.

Doppler ultrasound of umbilical blood flow is an assessment of only one aspect of placental function (and does not directly measure blood flow in the placental microcirculations, the site of increased resistance), whilst several other aspects of placental structure and function are altered in FGR[5]. Various morphological changes occur in placental tissue in association with FGR. Gross placental lesions are detected occasionally and are associated with poorer fetal outcomes and abnormal Doppler waveforms[6, 7]. However, there are often more subtle alterations, such as impoverished development of the villi[4] and changes in placental exchange barrier surface area and thickness[4, 8-10]. Such subtle changes are not directly detectable using routine ultrasound, although altered vessel morphometry may in turn influence umbilical Doppler waveforms[11]. The constellation of specific morphological and physiological abnormalities in the placenta has been proposed to represent a placental phenotype(s) of FGR[5]. The development of tools to identify a placental FGR phenotype *in utero*, may allow more rigorous definitions of the condition, improve our ability to stratify disease and potentially provide specific predictive tests.

Magnetic Resonance Imaging (MRI) provides a range of quantitative indices that may be used in non-invasive assessment of the human placenta. At the gross morphology level, MRI has been shown to detect changes in placental thickness and volume in FGR as compared to normal pregnancy[12]. However, other MRI markers may relate to fine tissue structure and function and therefore be good candidates for more detailed *in utero* placental assessment, with greater discrimination between placental phenotypes. The major source of image contrast in MRI comes from the variation in relaxation times between tissues. Relaxation times are MRI measurements that reflect the rate of hydrogen nucleus recovery following perturbation using a radiofrequency pulse in the scanner. The relaxation times are determined by the molecular environment of the hydrogen atoms within the tissue, these atoms being mostly associated with tissue water and fat content *in vivo*. Relaxation occurs by two independent processes, referred to as longitudinal (T_1) and transverse (T_2) relaxation. The relaxation times T_1 and T_2 characterise these processes and may be measured non-invasively *in vivo*. These parameters have been studied in many clinical disorders but, although generalisations can be made regarding their histopathological correlates, it is not known specifically what changes in the placenta influence relaxation: previous studies have not reported on the relationship between placental relaxation times and histologically identified features. In studies examining other tissue types, water content (related to vascular

and intervillous volumes in the placenta) and membrane surface areas were found to be important influences on relaxation times[13].

In this study we have examined relaxation time measurements in the placenta in normal pregnancy and evaluated evidence for correlations between these measurements and postnatal histology of the placenta using stereological techniques. Based on the work described above in other tissues, indices relating to blood and non-blood volumes of the placenta were examined as potential structural correlates, as well as consideration of villous and vascular surface areas. The fibrin content of the placenta was also assessed; this is an important general marker of tissue damage and repair, and thought to be related to relaxation time values in other disease processes such as atherosclerosis and liver cirrhosis [14, 15]. In previous MRI studies at lower field strengths (0.5 T), a trend for shorter relaxation time measurements, T_1 and T_2 , was observed in pregnancies complicated by pre-eclampsia and FGR [16]. We hypothesised that the differences observed at 0.5 T in FGR placentas were related to the altered placental morphology associated with this condition. To begin testing of this hypothesis, we investigated placental relaxation times in normal pregnancies at the increased field strength of 1.5 T, allowing improvements over the 0.5T measurements in signal-to-noise ratio and spatial resolution.

Methods

Subjects

Ethical approval was obtained from the local NHS Research Ethics Committee and all women gave written informed consent. Women with normal pregnancies between 20 and 42 weeks gestation were recruited. Participants included had apparently uncomplicated pregnancies and subsequently delivered normal infants at term without adverse outcomes. Exclusion criteria were co-existing maternal systemic disease such as diabetes, renal disease or microvascular disease, multiple pregnancies, fetal anomalies and antenatal complications including pre-eclampsia, fetal growth restriction and pre-term delivery. Neonates with an individualised birthweight ratio (IBR) less than the 5th centile, a surrogate for FGR[17], were excluded.

MRI

Women underwent a single MRI examination including acquisition protocols for placental structure and relaxation time measurements (T_1 and T_2). All scans were carried out on a 1.5 T Philips Achieva scanner using a 5 channel phased array cardiac coil positioned to optimise the signal from the placenta. The pregnant women were positioned supine, using a foam wedge to support a left-lateral tilt (preventing vena cava compression) and introduced feet first into the scanner, with their heads outside the bore to reduce potential for claustrophobia. Although no evidence has demonstrated any detrimental effects to the fetus as a result of MRI, in the interests of adopting a cautious approach, “SofTone” imaging magnetic field gradients were used, keeping gradient ramp speeds to below 50% of maximum to reduce noise exposure. Furthermore, the specific absorption rate (SAR) was restricted to 2 W/kg to minimise thermal effects. These restrictions represent hard limits on acquisition protocol optimisation, which aimed to achieve measurements within reasonable time limits, reducing issues of fetal motion and maximising patient comfort. All scanning sessions were limited to a maximum of 40 minutes, which was well tolerated by the women.

Women first underwent a series of 3 localising images, for orientation, followed by structural and relaxation time acquisitions, taking slices along the long axis of the placenta and through the shortest axis, giving disc shape placental images. This allowed whole placental coverage with the minimum number of slices. Structural scans were carried out

using an implementation of the single shot fast spin echo sequence used routinely in fetal scanning; with a field of view of $384 \times 384 \text{ cm}^2$, matrix size 128×128 , 30 slices (interleaved), resolution $3 \times 3 \times 3 \text{ mm}^3$ and half scan (55%) to obtain the image in a single acquisition lasting 36 seconds. T_1 and T_2 measurements were acquired with whole placental coverage, co-localised with the structural scans. T_1 measurements were achieved using a 3D multiple flip angle fast field echo (FFE; spoiled gradient echo) technique with angles 2, 10 & 20 degrees with an acquisition time of 10 seconds for each volume[18]. T_2 measurements, with the same geometry, were acquired with a double echo spin echo sequence using echo times of 6.3 ms and 200 ms on a slice by slice basis, repetition times 400ms each echo, taking 4 seconds per slice.

T_1 and T_2 values were calculated by fitting the relevant signal intensity relationships to the signal intensities recorded using the acquisitions outlined above using Matlab (The Mathworks). Relaxation times were recorded as median values from the distribution of fits obtained from each voxel across a selected region of interest (ROI).

The ROI was drawn as the largest placental region possible ensuring that the outer borders were not crossed and typically encompassed between 500 – 1500 voxels. The ROI was marked on a scan slice passing at a mid-depth through the placenta and was always first selected on the structural image, (where the placental outline and cord insertion are most clearly seen) and then checked against the co-localised relaxation time scans and repositioned if affected by obvious artefact or patient movement. Figure 1 shows a typical structural image through the placenta with the ROI selected.

Stereology

All stereological analyses were made in placentas collected from women undergoing MRI using methods adopted from those reported by Mayhew[9, 10]. Placental tissue samples were collected in 17 subjects delivered at term. Placentas were collected postnatally within 30 minutes of delivery time. A systematic random sampling method was devised that would later allow more in-depth analysis of placental heterogeneity. Taking the placental cord insertion as the central point, a circle was marked out on a transparent sampling grid with a diameter half that of the longest axis of the placenta. Within this circle was marked as 'central' and outside this circle was 'peripheral'. Full-depth columns of tissue were dissected by superimposing the transparent grid over the placenta, bearing a systematic array of sampling windows (4cm apart). Using a random computer-generated number sequence, 3 tissue samples were taken from windows overlying the central region and 5 from the peripheral region (This method was chosen so that central and peripheral regions were approximately equally represented; the central region being thicker and to also allow comparison of central and peripheral regions in subsequent analyses). The resulting full depth tissue samples were then dissected into a top (fetal facing), middle and bottom (maternal facing) placental section and fixed in 10% buffered formalin. Only middle sections are considered in this analysis, to correspond with the mid-depth level of the MRI scan plane. These samples were diced and embedded with random orientation in paraffin wax blocks and processed for histology.

Before imaging, cut sections (5 micrometres) were mounted on microscope slides, stained with hematoxylin and eosin (H&E), and observed under a Leitz (Dialux 22) microscope at a magnification of x250. 8 sections were investigated per placenta. For image analysis, a Q-Imaging (Fast 1394) digital camera acquired images from each sample. In total, 40 high-power fields of view were analysed per placenta.

Images were acquired using Image-Pro Plus software (Version 6.3). Test point counting was employed to obtain volume densities. Intersection counting using a superimposed grid lattice

was used to calculate surface area densities. Indices calculated included villous volume density, fetal capillary volume density, fibrin (intervillous fibrin deposition) volume density, villous surface area density, capillary surface area density. From this intervillous space (IVS) volume density (1 – villous volume density), total blood volume density (IVS + capillary volume density), ratio of fibrin: villous volume densities, ratio of capillary: villous volume densities and total surface area density (villous + capillary surface area densities) were calculated.

Statistics

The normality of the distribution of the median relaxation time and stereological values across the subject group was tested using D'Agostino and Pearson omnibus normality test: T_1 and T_2 results were normally distributed and therefore analyses of their relationships with gestation were performed using parametric tests. Not all stereological variables were normally distributed, therefore non-parametric tests were used for all analyses involving stereological variables. Test of correlations were consistently two-tailed. Linear regression analysis was performed to define linear trends in the data. Graphpad Prism (Version 4.01) was used for statistical analysis. No corrections were made for multiple statistical comparisons.

Results

Relationship between placental relaxation times and gestation

30 women underwent a single MRI examination at a range of gestations between 21.9 and 41.7 weeks (mean 32.9). Of the 30 women scanned, one scan was terminated before completing the entire T_1 sequence due to maternal claustrophobia, thus there were 29 remaining T_1 results.

Figure 2 shows the relationship between relaxation times and gestational age at the time of scan. A significant negative correlation was seen between both T_1 and gestational age (Pearson's $p = 0.01$) and T_2 and gestational age (Pearson's $p = 0.03$). When expressed as a linear regression, this showed a fall in T_1 across gestation of 20.2 ms/week (95% confidence interval -35.1 to -5.2 ms/week, intercept = 1684ms, $r^2 = 0.22$, $p = 0.01$) and in T_2 of 2.4 ms/week (95% confidence interval -5.6 to -0.3 ms/week, intercept = 280 ms, $r^2 = 0.16$, $p = 0.03$).

Correlations between placental stereological analyses and relaxation times

From the 29 patients who were scanned, 17 placentas were analysed stereologically following delivery. No significant correlations were observed between relaxation times measured at time of scan and placental stereological variables (Table 1).

As placentas were collected at term, often some time after the MRI scan, and bearing in mind the change in T_1 and T_2 over gestation, three further analyses were performed. In the first, a subgroup population who all had scans within a week of delivery were analysed. In this subgroup ($n = 7$), significant correlations were observed between T_2 relaxation time and the fibrin volume density and fibrin: villous densities ratio (Spearman's $p = 0.02$ and 0.03 respectively) (Table 1 and Figure 3). In the second analysis, a subgroup of women who were scanned within 2 weeks of delivery ($n = 10$), were analysed: no significant correlations between relaxation times and stereological variables were observed (Table 1).

In the third analysis, the linear regression model for the relationship between gestational age and relaxation times (Figure 2) was used to predict T_1 and T_2 values for each of the seventeen women (whose placentas had been analysed stereologically) for the exact day of

their delivery. Using this method no significant correlations were found between T_1 and T_2 values and placental stereological variables (Table 1).

Discussion

The most important finding in this study is a clear correlation and linear relationship between placental T_1 and T_2 measurements at 1.5T and gestational age. T_1 and T_2 relaxation times are shown to decrease by 20.2 ms and 2.4 ms per week of gestation respectively, giving a total fall of in T_1 of 400 ms and in T_2 of 50 ms between 20 and 40 weeks. The existence of this relationship supports the proposition that changes in placental tissue structure or composition that occur with advancing gestation significantly influence relaxation times.

Our observations on gestational changes in placental T_1 and T_2 are similar to those seen at 0.5 T [16]. However, our study at 1.5T shows a sharper decline in T_1 across gestation than was reported at 0.5 T. It is known that field strength strongly influences T_1 [19] and the trend for a steeper decline across gestation at 1.5 T than at 0.5 T (gradient 20.2 ms/week at 1.5 T and gradient 9.1 ms/week at 0.5 T) suggests an enhanced ability to differentiate placentas with longer or shorter relaxation times at the higher field strength. This additional differentiability may be important, as shorter relaxation times have previously been associated with complicated pregnancies [16].

The origin of the observed change in relaxation times with advancing gestational age remains a matter for conjecture. In this study, relaxation time values did not correlate with villous volume densities or total blood volume densities, indicating that other changes in morphology or function, rather than just increases in solid or blood volumes, lead to the fall in T_1 and T_2 towards term. The total volume of the maternal vascular bed increases with gestational age [20], but if this was the major influence on relaxation times then a rise rather than fall would be seen, as the T_1 and T_2 of oxygenated maternal blood *in vivo* is around the upper end of the placental values [21]. That other changes in placental morphology may influence relaxation times, rather than the balance of vascular and non-vascular volumes, is supported by studies looking at MRI magnetisation transfer (an *in-vivo* measure of bound protons to total protons) in the placenta which demonstrated no changes in these values or in non-vascular: total placental volume ratios assessed stereologically across gestation [22]. Other studies have also supported the view that the ratios of total volumes of blood and non-blood placental compartments remain fairly static across gestation [23] and if so, the fall in T_1 and T_2 observed across gestation must be due to other changes within placental tissue, rather than blood volume alone.

Our data show a correlation between T_2 and placental fibrin deposition, but only when scan and delivery were within one week of each other (Figure 3). These data suggest that fibrin content might be one of the contributors to the fall in T_2 over gestation. However, intuitively, a negative rather than positive correlation between fibrin and relaxation times would be expected as we might assume that the complex macromolecular structure of fibrin deposits would result in shorter relaxation times. Fibrin may, however, be a surrogate marker for a wider change in tissue quality that is influencing T_1 and T_2 . Villous surface area may be a factor influencing relaxation times, (surface area of the villi expands with advancing gestation [23-25]) but we did not find a significant correlation between these variables. Other potential factors not investigated here include reduced blood oxygenation (for example, deoxygenated blood generally has lower T_1 values [26] and changes in the tissue hydration fraction [13]).

In this study, women were scanned deliberately at a range of gestations in order to assess the effect of gestational age on relaxation times. This caused difficulties in the analysis when relating MRI findings to stereology, as the stereological variables were always measured at delivery. There was a correlation between T_2 and fibrin content when only those placentas delivered within one week of scan were considered, but not when all delivered within two weeks of scan were included, emphasising the importance of taking gestational changes into account. We attempted to do this by modelling the gestational changes in T_1 and T_2 and using the predicted values for day of delivery in correlations with stereological values. For several indices, a tighter relationship was seen using this approach but none reached significance at the 5% level. Although a significant linear relationship was observed between relaxation times and gestation, the broad confidence interval surrounding this slope may have hindered the linear regression model as an accurate predictor of T_1 and T_2 at delivery. In future studies we hope to scan more women closer to term in order to closely assess the links between MRI biomarkers and morphology, removing the influence of gestation. In practical terms this can be problematic, as delivery may be unpredictable, MR scanning may be prevented due to size of the gravid uterus or discomfort lying flat/still and women may also be less amenable to participation in research in the last few days before delivery.

Histological studies have demonstrated a range of differences in placentas from FGR pregnancies including evidence of tissue damage and repair, increased inter-villous fibrin deposition and reduced villous volume, surface area and capillary surface area[4, 8-10]. Previous studies at 0.5 T demonstrated that in pregnancies complicated by pre-eclampsia and FGR, relaxation times were generally lower and frequently below the 90% confidence interval for the healthy population. From the stereological data presented in this current study it is unclear which morphological variables, if any, directly influence placental relaxation times and therefore whether a difference in relaxation times in FGR could be expected. However, the clear correlation with both T_1 and T_2 and gestation at scan supports the view that relaxation times may be important biomarkers of placental tissue change and therefore may be useful in detecting pathological conditions such as FGR. Further work to test this hypothesis requires stereological measurements of the placenta together with measurement of relaxation times and other MRI variables closer to term. These structural measurements might also be combined with MRI assessment of placental blood flow such as those measured by Intra-Voxel Incoherent Motion and/or Arterial Spin Labelling.

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Figure 1. Structural scan through the placenta at 36 weeks showing placental ROI outline

Figure 2. Graph showing relaxation times plotted against gestational age at time of scan. The linear regression lines for T_1 and T_2 are also shown

Figure 3.

Graphs showing relationships between a) fibrin volume density and b) the fibrin: villous volume densities ratio and relaxation times in the subgroup population scanned within 1 week of delivery. Significant correlations were observed with T_2 (a) $p=0.02$ and b) $p=0.03$). Linear regression analysis demonstrated a linear trend (plotted line) between T_2 and fibrin volume density, $r^2=0.57$, $p=0.05$, and the ratio of fibrin: villous volume density, $r^2=0.59$, $p=0.04$.

Table 1

Table summarising Spearman's ρ values for correlations between measured stereological variables and relaxation times for a) all 17 participants in whom stereological analysis was performed, b) only the 7 participants that were scanned within a week of delivery c) only in the 10 participants scanned within 2 weeks of delivery and c) correlations based on a predicted T_1 and T_2 value, estimated for date of delivery.

Stereological Variable	A. Whole group, n=17		B. Subgroup scanned within a week of delivery, n=7		C. Subgroup scanned within 2 weeks of delivery, n=10		D. T_1 and T_2 value predicted for day of delivery, n=17	
	T_1	T_2	T_1	T_2	T_1	T_2	T_1	T_2
Villous volume density	P=0.93	P=0.43	P=0.71	P=0.35	P=0.95	P=0.80	P=0.72	P=0.35
Fibrin volume density	P=0.90	P=0.46	P=1.04	P=0.02*	P=0.81	P=0.48	P=0.70	P=0.35
Capillary volume density	P=0.59	P=0.65	P=0.35	P=0.40	P=0.63	P=0.29	P=0.74	P=0.51
Intervillous space volume density	P=0.93	P=0.43	P=0.71	P=0.35	P=0.95	P=0.80	P=0.72	P=0.35
Total blood volume density	P=0.83	P=0.42	P=0.24	P=0.44	P=0.92	P=0.96	P=0.93	P=0.37
Fibrin:Villous density ratio	P=0.99	P=0.41	P=0.84	P=0.03*	P=0.17	P=0.65	P=0.78	P=0.34
Capillary:Villous density ratio	P=0.99	P=0.93	P=0.50	P=0.50	P=0.81	P=0.56	P=0.85	P=0.90
Villous surface area density	P=0.84	P=0.26	P=0.91	P=0.91	P=0.66	P=0.35	P=0.43	P=0.15
Capillary surface area density	P=0.66	P=0.86	P=0.91	P=0.78	P=0.89	P=0.93	P=0.88	P=0.68
Total surface area density	P=0.80	P=0.28	P=0.96	P=0.71	P=0.84	P=0.35	P=0.73	P=0.20

* significant correlation taken as $p < 0.05$ in two-tailed Spearman's test.