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Echo-Planar Imaging Relaxometry to Measure the Viscosity of a Model Meal

L. Marciani,* P. Manoj,† B. P. Hills,† R. J. Moore,* P. Young,* A. Fillery-Travis,† R. C. Spiller,‡ and P. A. Gowland*,[1]

*Magnetic Resonance Centre, Department of Physics, University of Nottingham, Nottingham NG7 2RD, United Kingdom; †Institute of Food Research, Colney, Norwich NR4 7UA, United Kingdom; and ‡Gastroenterology, Queen's Medical Centre, University Hospital, Nottingham NG7 2UH, United Kingdom

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A method for measuring noninvasively the viscosity of a polysaccharide model meal using the known relationship between relaxation times and polysaccharide concentration in solution *in vitro* **is presented. The aim is to develop a method for monitoring digesta viscosity** *in vivo,* **using EPI to capture the motion of the gastrointestinal lumen. The transverse relaxation rate T_2^{-1} of locust bean gum solutions was calibrated against the zero-shear viscosity at 37°C. Differences in viscosity were distinguished significantly using T_2^{-1} measurements. T_2^{-1} and viscosity were insensitive to exposure to gastric juice and changes in pH, and the model meal was well received by volunteers and provided good contrast** *in vivo* **in EPI images. Therefore it would be possible to use this method to monitor the changes in meal viscosity within the gastric lumen** *in vivo.*

Key Words: **EPI; relaxation rate; viscosity; polysaccharide.**

INTRODUCTION

Increasing interest has been shown in imaging the gastrointestinal tract using MRI since the introduction of ultrafast sequences which can overcome abdominal motion artifacts (*1, 2*). Different aspects of gastric physiology such as the effect of meal viscosity on gastrointestinal motor function are so far poorly understood, and generally studied in invasive animal models (*3, 4*). It would be useful to be able to measure meal viscosity noninvasively within the human gastric lumen as knowledge of digesta viscosity, combined with gastric emptying and motility measurements (*4–9*), is essential to study the mechanics of food processing in the stomach, and it is also probably an important factor in determining the response of the stomach to different meals (*10*).

In recent years the field of NMR rheology has been subject to fast developments. It has been shown that it is possible to use MRI to measure velocity fields and pressure drop measurements in shear-thinning polysaccharide solutions and hence to calculate the shear viscosity (*11–15*). It has been known since the early days of NMR that the relaxation times of water–polysaccharide solutions are related to their viscosity (*16, 17*) and the possibility of using this relationship and MRI to measure viscosity has been reported (*18*).

This paper aims to investigate *in vitro* the possibility of using simple NMR relaxometry techniques to measure the viscosity of a polysaccharide model meal. Viscosity has been calibrated against the relaxation rates and apparent diffusion coefficient of a polysaccharide locust bean gum (LBG) nonnutrient model meal. It also addresses the question of whether it would be possible to use this technique *in vivo.* For this reason a whole-body scanner and a body coil were used to acquire images with a single-shot echo-planar imaging (EPI) (*19*) technique. EPI is particularly suitable for abdominal imaging as it is able to freeze motion artifacts arising from the gastrointestinal tract and respiration.

EXPERIMENTAL

Solutions were prepared by adding appropriate amounts of the LBG powder (food grade Lucas Meyer Colloids Ltd., Chester, UK) to water and blending them. Samples were prepared either at room temperature and left to rest for 1 h, meal (a), or using boiling water and keeping the solution at 90°C for 1 h and then allowing it to cool down slowly overnight, meal (b). Measurements were carried out on six different batches for each LBG concentration, eight in the range 0–3% (w/w) for meal (a) and nine in the range 0–2% (w/w) for meal (b). A little precipitation occurred in the low-concentration (<1%, w/w) meal (a), in which case only the supernatant fraction was used for measurements. To investigate the effect of pH on the NMR and viscosity parameters, six test samples were prepared over the pH range 1.9 to 6.5 by adding microquote aliquots of sodium hydroxide and hydrochloric acid from concentrated stock solutions as required. pH measurements were performed with a Corning 240 pH meter calibrated against Aldrich solutions at pH 4 and 7. The complete effect of gastric juice on NMR and viscosity parameters was investigated by adding either 15% (w/w) gastric juice (retrieved from a healthy volunteer via a nasogastric tube) or 15% (w/w) water (for a

[1] To whom correspondence should be addressed. Fax: +44 115 9515166. E-mail: Penny.Gowland@nottingham.ac.uk.

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control) and then keeping samples at 37°C for 40 min before measurements.

A double-vessel water jacket, connected via plastic pipes to a water bath in the magnet room, was used to keep samples at 37°C inside a whole-body 0.5-T purpose-built EPI scanner equipped with actively shielded gradient coils. A 50-cm-diameter bird-cage coil was used to acquire single-shot MBEST EPI (*20*) images in 130 ms, with a slice thickness of 1 cm and using a 128 × 128 matrix with 4.3 × 2.6-mm in-plane resolution. T_1 data were acquired using an inversion recovery EPI sequence at eight different inversion times varying from 0 to 1000 ms, repeated once, with a hyperbolic secant inversion pulse. A spin-echo EPI sequence was used to acquire data to measure T_2 at eight echo times varying from 60 to 960 ms, repeated once. A PGSE EPI sequence was used to acquire data to measure the apparent water diffusion coefficient, D, at eight diffusion encoding levels varying from $b = 0$ to 912 s/mm^2, repeated once. The total acquisition time for each data set was less than 3 min. Stress viscometry measurements were carried out using a CSR10 (Bohlin Instruments Ltd., Cirencester, UK) temperature-controlled rheometer. Thirty logarithmically spaced shear rates ranging from 10^{-1} to 10^3 s^{-1} were acquired at 37°C using double-gap and concentric cylinder geometries. The low-shear-rate viscosity plateau was used to determine the zero-shear viscosity η_0 values (*21, 22*). Data were analyzed using Student's t test and Pearson's correlation coefficient.

Two healthy volunteers ingested 500 ml of 3% (w/w) LBG meal (a) (4 Pas), and for each a transverse rapid multislice set of MBEST EPI images was acquired over the abdomen, to determine the acceptability of the meal to volunteers and the contrast available to delineate the stomach *in vivo.*

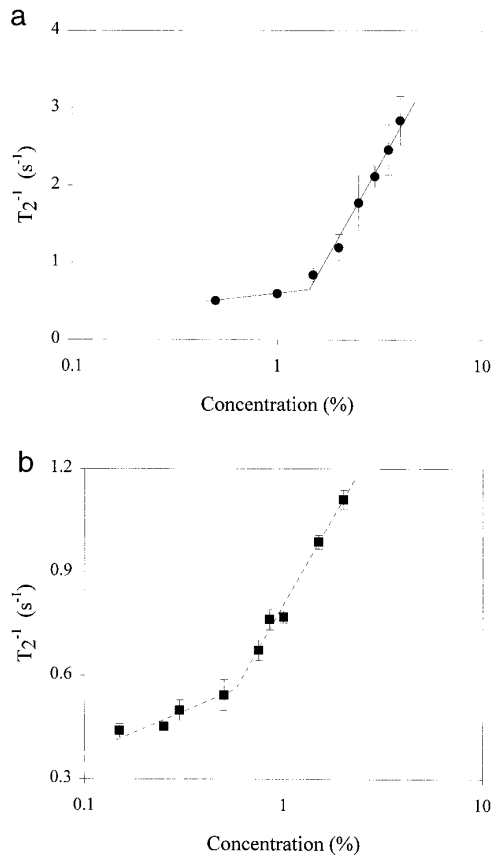

FIG. 1. Variation of the proton transverse relaxation rate T_2^{-1} on concentration at 37°C for nonheated locust bean gum meal (a) and heated meal (b). $n = 6$ for each data point.

RESULTS

The transverse relaxation rate T_2^{-1} data showed a two-phase linear dependence on the logarithm of LBG concentration for both meals (a) and (b), as shown in Fig. 1. The data were grouped into two phases by performing a separate linear regression on each phase and optimizing the total correlation coefficient R^2 as the points were moved between groups. Only a few data points were acquired in the low-concentration phase and the linear fit is therefore only approximate in that interval, whereas in the high-concentration phase the linear fit modeled the data well. The intersection of the lines of best fit yielded the critical LBG concentration c^* separating the two phases (*21*), 1.4% (w/w) for meal (a) and 0.6% (w/w) for meal (b). The T_2^{-1} values corresponding to c^* are 0.65 s^{-1} for meal (a) and 0.55 s^{-1} for meal (b). R^2 for the high-concentration phase was 0.98 for meal (a) and 0.99 for meal (b). Repeatability of EPI T_2 measurements was within 10% over the entire range of LBG concentrations. T_2 values were insensitive to *in vitro* exposure to gastric juice and changes in pH (Pearson's correlation coefficient $p < 0.4$).

The steady-shear viscosity η remained at a fixed, maximum value (η_0) at low shear rates and decreased at higher shear rates due to shear thinning. Repeatability of η_0 measurements for six different samples run at each concentration was within 34% for meal (a) and 13% for meal (b). A two-phase linear variation in zero-shear viscosity η_0 with LBG concentration was found for both meals (a) and (b), as shown in Fig. 2 ($R^2 = 0.99$ for the high-concentration phase in both cases). The values of the critical concentrations c^* separating the two phases were found to be 1.2% (w/w) ($\eta_0 = 0.1$ Pas) for meal (a) and 0.6% (w/w) ($\eta_0 = 0.25$ Pas) for meal (b). η_0 values were found to be independent of pH and of *in vitro* exposure to gastrointestinal juice.

The calibration curves of T_2^{-1} against η_0 for the two LBG solutions were obtained by direct comparison of the data at each LBG concentration and are shown in Fig. 3. T_2^{-1} values and η_0 values correlate with a two-phase linear relationship, the two phases being separated at the concentration c^* corresponding to $T_2^{-1} = 0.70$ s^{-1} ($\eta_0 = 0.3$ Pas) for meal (a) and $T_2^{-1} = 0.57$ s^{-1} ($\eta_0 = 0.24$ Pas) for meal (b) ($R^2 = 0.99$ for both meals in the higher LBG concentration phase). T_2^{-1} can be used to significantly distinguish differences in viscosity corresponding to 0.5% (w/w) changes in LBG concentration (Student's t test, $p < 0.01$ for LBG concentrations <3%, w/w,

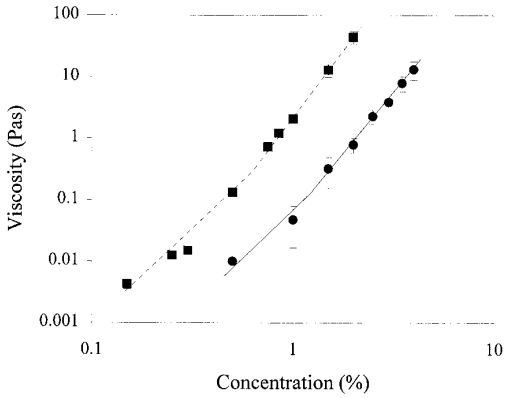

FIG. 2. Variation of the zero-shear viscosity η_0 on concentration at 37°C for nonheated locust bean gum meal (a) (●) and heated meal (b) (■). $n = 6$ for each data point.

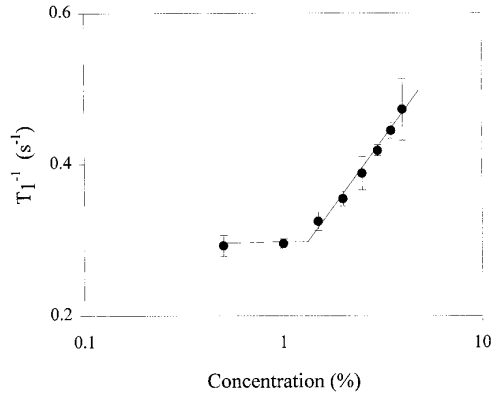

FIG. 4. Variation of the proton longitudinal relaxation rate T_1^{-1} on concentration at 37°C for nonheated locust bean gum meal (a). $n = 6$ for each data point.

and $p < 0.05$ for concentrations >3%, w/w) for meal (a) and to 0.3% (w/w) (Student's t test, $p < 0.05$) for meal (b).

The average apparent water diffusion coefficient D measured for meal (a) was $2.23 \pm 0.13 \times 10^{-9}$ m^2/s and did not show significant variation with LBG concentration over the range investigated. The dependence of the longitudinal relaxation rate T_1^{-1} on the logarithm of LBG concentration again showed (Fig. 4) a two-phase linear relationship ($c^* = 1.3\%$, w/w, T_1^{-1} at $c^* = 0.30$ s^{-1}, $R^2 = 0.99$ for the high-concentration phase) for meal (a) with a very low gradient for the low-concentration phase. Data repeatability was within 10%.

The viscous LBG model meal was well received by volunteers and provided good contrast between the stomach and the surrounding organs in EPI images (Fig. 5).

DISCUSSION

The relaxation process can be modeled by a two-pool exchange formalism (*23, 24*). According to this, the water proton relaxation is dominated by the fast exchange between water and hydroxyl protons on the LBG and the model proposed by Bloembergen *et al.* (*16, 17*) is not applicable. The observed relaxation is single exponential, so in the limit of long 90°–180° pulse spacings, the observed relaxation rate is generally given by the Swift–Connick expression:

$$T_2^{-1} = T_{2w}^{-1} + P_b k_b \left\{ \frac{(T_{2b}^{-1})^2 + T_{2b}^{-1} k_b + (\delta\omega)^2}{(T_{2b}^{-1} + k_b)^2 + (\delta\omega)^2} \right\}. \qquad [1]$$

Here we have assumed that the fraction of exchangeable LBG protons, P_b, is $\ll 1$. T_{2w}^{-1} is the intrinsic relaxation rate of the water protons, T_{2b}^{-1} is the intrinsic transverse relaxation rate of the exchangeable LBG protons, and k_b is the exchange rate, defined as the reciprocal lifetime of a proton on the LBG hydroxyl site. $\delta\omega$ is the difference in resonance frequencies between the water and exchangeable LBG protons. Previous work on polysaccharide systems suggests that k_b is of the order of 10^3 s^{-1} at neutral pH,

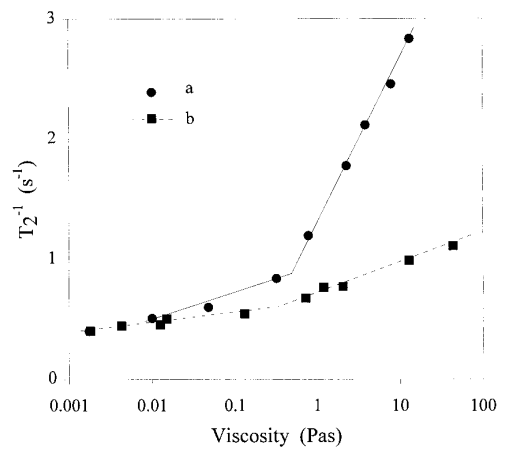

FIG. 3. The dependence of proton transverse relaxation rate T_2^{-1} on zero-shear viscosity η_0 at 37°C for nonheated locust bean gum meal (a) and heated meal (b). Each data point represents a direct comparison between viscometry and relaxation time measurement for six samples.

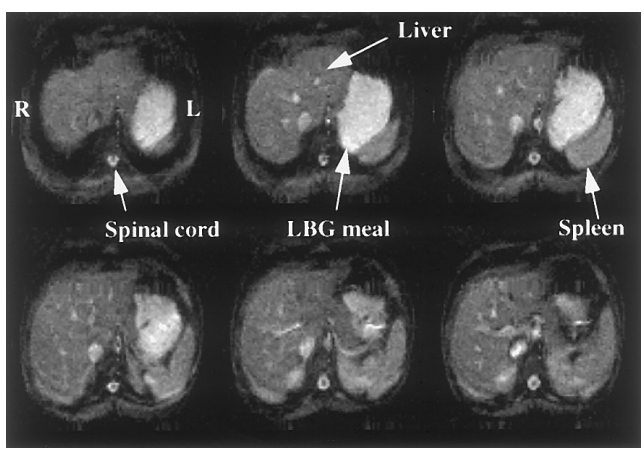

FIG. 5. Transverse multislice MBEST EPI set acquired over the abdomen of a normal volunteer after ingesting a 3% (w/w) nonheated locust bean gum meal (a).

and $\delta\omega$ is of the order of 1 ppm or 25 s^{-1} at the operational frequency of this scanner. Acid–base catalysis is expected to dramatically alter k_b; therefore the experimental observation that the relaxation rate is independent of pH strongly suggests that the relaxation is in the fast exchange limit (k_b and $T_{2b}^{-1} \gg \delta\omega$). In this limit, Eq. [1] reduces to

$$T_2^{-1} = T_{2w}^{-1} + \frac{P_b}{k_b^{-1} + T_{2b}}. \quad [2]$$

The fact that the relaxation is pH independent further suggests that $k_b \gg T_{2b}^{-1}$, which would be true if T_{2b}^{-1} is $>\approx 1$ ms, so that we finally arrive at the well-known two-site, fast exchange limiting expression,

$$T_2^{-1} = T_{2w}^{-1} + P_b T_{2b}^{-1}. \quad [3]$$

This predicts a linear dependence of T_2^{-1} on LBG concentration. In fact the T_2^{-1}/concentration and the viscosity/concentration curves show a dramatic change in gradient at the critical concentration c^*. In water solution the LBG polysaccharide coils entangle, leading to a rapid increase in viscosity with LBG concentration. The extent of the entanglement modifies the mobility and the conformation of the chains, affecting the values of T_{2b}^{-1} and hence the observed T_2 as well. Below c^* the polysaccharide coils are isolated and moving randomly, whereas above c^* the coils entangle and a long-range network is formed (*21*, *22*).

Heating increases the degree of entanglement and of hydration. Increased entanglement increases the viscosity and the increased hydration increases the LBG chain flexibility and hence reduces T_{2b}^{-1} as observed for meal (b). Therefore the solutions prepared in heated water, meal (b), had longer T_2 values and higher viscosities than those obtained for the same concentrations of LBG in cold water, meal (a). Overall this reduced the dynamic range in T_2^{-1} values available to predict viscosity (Fig. 3). This was partly counteracted by the fact that the heating preparation method (b) produced a more homogeneous meal, which was stable with respect to precipitation and yielded lower errors on viscosity measurements. Therefore with the heated solution (b) it was still possible to statistically distinguish different LBG concentrations from the T_2 data sets. Equation [3] is also expected to describe the longitudinal relaxation behavior if subscript 2 is replaced with subscript 1. However, the changes observed in T_1^{-1} with LBG concentration were less marked because this parameter is less sensitive to the low-frequency components of molecular motion and to chain entanglement and hydration (*25*). T_{1b}^{-1} is very long and in the low-concentration phase T_1 is insensitive to concentration. Therefore T_1 only varied over a limited range with changing LBG concentration and thus provided a less sensitive indicator of viscosity of the LBG solutions. For meal (a) it was found that the increase in viscosity did not affect the bulk water diffusion properties as the calculated apparent water diffusion coefficient D did not vary significantly over the investigated range of viscosity (*26*).

The EPI viscosity measurements possible with this model LBG meal, the acceptability of the meal to volunteers, and the inherent contrast between the organs surrounding the stomach and the meal indicate that this meal provides a suitable method for monitoring digesta viscosity *in vivo.*

CONCLUSIONS

This paper shows that it would be possible to carry out viscosity measurements *in vivo* within the gastric environment using EPI, by calibrating *in vitro* the transverse relaxation rate of a simple polysaccharide model meal against its viscosity. It would be therefore possible to extend MRI investigations of the gastrointestinal system to the study of the effects of meal viscosity on digestion.

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