Colonic response to an experimental model of human diarrhoeal disease

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Introduction We have been developing MRI techniques that allow us to monitor colonic function, without invasive bowel preparations, which are often used to improve anatomical detail in clinical MRI of the colon, but which disturb colonic function. Our ultimate aim is to study the perturbation of normal physiological function in diseases such as diarrhoea predominant Irritable Bowel Syndrome. This work uses MRI to study the colonic response to two contrasting test meals: a readily absorbable glucose drink and a non absorbable mannitol drink. The mannitol provides a model of acute diarrhoeal disease while the glucose acts a well absorbed control meal.

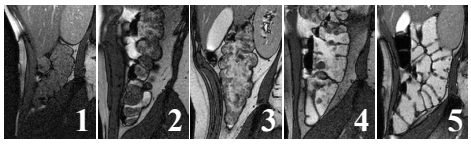

Figure 1 bTFE scans for the subjective heterogeneity measures of the AC: 1 (all dark) to 5 (all bright).

Methods 8 healthy volunteers were imaged on two different occasions, using a 1.5 T Philips Achieva scanner with a SENSE 4-element abdominal body coil. The volunteers were fasted overnight and then after a baseline scan, they were given a drink containing either 5% mannitol or 5% glucose powder in 350 ml of water (conditions randomized). Mannitol is a common laxative known to stimulate small intestinal secretion and can be used as a model for a range of diarrhoeal diseases, while glucose is known to be rapidly absorbed. Volunteers were scanned at 30 minutes intervals for three hours after the drink, when they were fed a large 1000 kcal test meal (400 g macaroni cheese, 100 g cheese cake and 250 ml still water) to elicit the colonic response to feeding. They were then scanned again every 30 minutes for 5 hours after the drink (8 hours for 2 additional pilot subjects). A range of MRI sequences were used to image the ascending colon (AC): high resolution bTFE (TE=1.7 ms, rec. res = 0.86 mm x 0.86 mm, 8 slices of 5 mm thickness, 1 mm gap) to image colonic contents; dual echo FFE (TE_1= 2.3 ms, TE_2=4.6 ms, rec. res. = 1.76 mm x 1.76 mm, 24 slices of 7 mm thickness) to estimate colonic volumes; MRCP (TE=320 ms, rec. res = 0.78 mm x 0.78 mm, 24 slices of 7 mm thickness) used to measure free water content using a previously described analysis method[1]. The AC contents showed varying signal characteristics and since there is little independent information about the nature of the contents of the AC, at this stage subjective assessment was used to grade the AC contents: 2 observers (E.P. and C.L.H.) independently graded the high resolution bTFE images (single score per time point covering all 8 slices), between 1 (all dark) and 5 (all bright) with 3 having a mixture of dark and bright patches (Fig. 1). The inter-observer and intra-observer variability for the subjective measurements were assessed by calculating the weighted kappa from the subjective data[2].

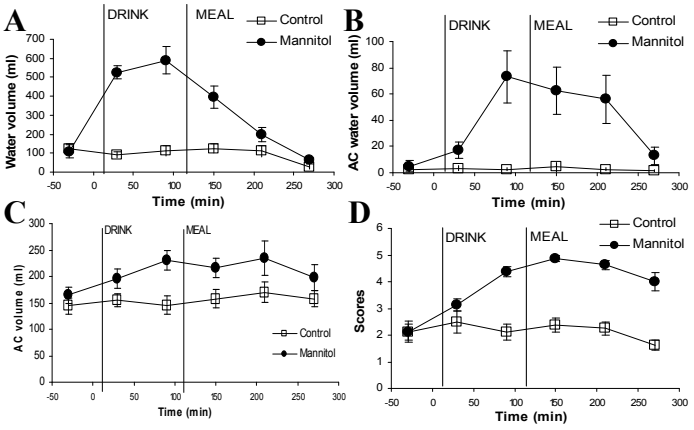

Figure 2 Total water content of the whole bowel (A) and AC only (B) measured using a MRCP sequence showing a larger quantity of fluid after the mannitol drink compared to after the control drink. C shows the AC volumes calculated from the dual echo FFE sequences. D shows the average scores versus time for the 8 volunteers scored by E.P. All graphs show (mean ± standard error averaged over all subjects).

Results Figure 2A and B show the variation in water content for the whole bowel and the AC averaged over the 8 volunteers, quantified from the MRCP sequence: very little free water was seen in the small bowel and in the AC after the control drink, while a large amount of free water was visible in both regions after the mannitol drink. This was also reflected in the total volume of the AC (Fig. 2C*)*. The high resolution bTFE images clearly showed the colonic response to feeding over time for both conditions (Fig. 3). After the mannitol drink the arrival of water in the AC was observed at 90 minutes, which readily mixed with the colonic contents and caused distension of the colon. At 150 minutes it was possible to observe a bright, homogeneous signal in the AC. The following scans showed that as the water signal was declining darker material appeared particularly around the folds. After the control drink the scans showed at all times a very heterogeneous, low signal in the colon. Figure 2D shows the average subjective scores of the heterogeneity of the high resolution images for the two meals. The weighted kappa for the inter-observer agreement was 0.83 and for the intra-observer was 0.84, which indicates very good agreement in both cases, and the trend is similar to that for the AC water contents and volumes (Fig. 2B-C), showing that the scoring system is robust.

Discussion These images clearly show that the unabsorbable osmotically active mannitol solution causes secretion in the small bowel whose volume starts to fall within two hours and when the secretions arrive in the colon they distribute heterogeneously. Figure 2B and C show that the water carried into the colon by the mannitol was a small fraction of the total colonic contents which was otherwise dominated by solid material and gas. The change in total AC volume with mannitol can largely be explained by the increase in free water content, although this was not true at the last time point, possibly due to the increase in the mass of the bacterial biofilm, where intracellular water will give reduced signal compared to free water in the colon. In the colon mannitol is rapidly fermented to short chain fatty acids which are known to be co-transported with sodium causing associated water absorption. The mannitol metabolism will also increase bacterial mass which will incorporate water intracellularly where it would appear to give a low signal. These methods will be useful in future studies to evaluate mechanisms of diarrhoea and drug intervention and in clinical studies of diarrhoeal disease.

References [1] Hoad et al Phys. Med. Biol. **52** (2007) p.6909–6922 [2] Altman DG. Practical statistics for medical research. London: Chapman & Hall; 1991. p. 403-9.

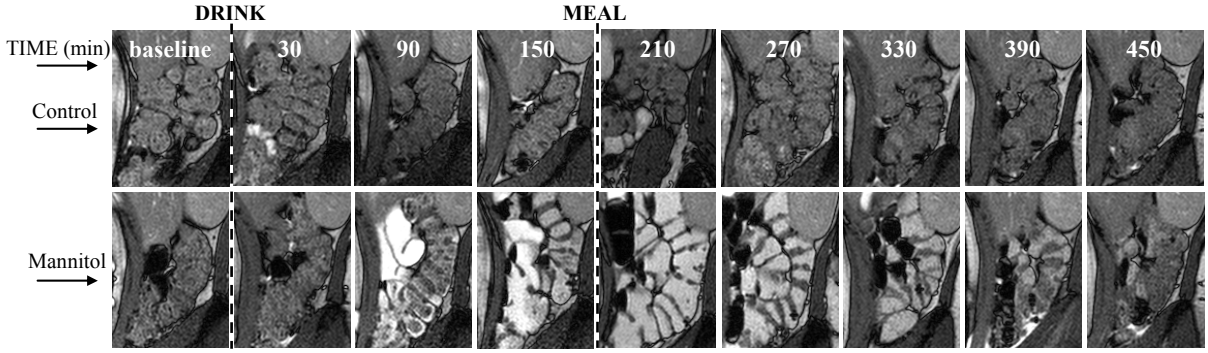

Figure 3 High resolution bTFE sagittal images of the AC after the glucose and the mannitol drink for the same volunteer.