

# $\beta$ Adrenergic modulation of human upper intestinal propulsive forces

N K Ahluwalia, D G Thompson, J Barlow, L Heggie

## Abstract

$\beta$  Adrenoceptor blockade is known to accelerate transit through the small intestine without changing either the number or pattern of intestinal contractions. This study therefore tested the hypothesis that an increase in intraluminal aboral propulsive force may contribute to this transit acceleration. Twenty paired studies were performed, in 10 healthy volunteers, after oral administration of either 100 mg atenolol (a selective  $\beta_1$  antagonist) or matched dummy tablets according to a double blind, randomised protocol. The frequency of occurrence of, and the propulsive force exerted by, traction events related to intestinal contractions were measured, using a combined traction force detector and manometry assembly. After atenolol, a consistent increase in the force generated per traction event was noted, both for propagating contractions mean (SEM) (12.0 (1.8) g *v* control 5.9 (0.07) g;  $p < 0.05$ ) and for stationary (11.6 (1.4) g *v* control 7.0 (0.7) g;  $p < 0.05$ ). In contrast no change in the number of traction events was noted (control *v* atenolol = 1.6 (0.3) *v* 1.64 (0.4) per min for propagating and 0.7 (0.1) *v* 0.85 (0.16) per min for stationary contraction;  $p > 0.05$ ).  $\beta$  Adrenoceptor blockade thus increases the propulsive force generated by intestinal contractions, possibly by removing a sympathetic neural inhibition of intestinal tone.

(Gut 1994; 35: 1356-1359)

Experimental sympathetic stimulation has been shown to delay upper intestinal transit in humans,<sup>1</sup> an effect that is reversed by  $\beta$  adrenoceptor blockade<sup>2</sup> and seems to be mediated by  $\beta$  adrenoceptors located on intestinal smooth muscle.<sup>3</sup> It has also been shown that upper intestinal transit is modulated by a  $\beta$  adrenoceptor mediated pathway even under resting conditions,<sup>2</sup> as administration of atenolol (a selective  $\beta_1$  receptor antagonist) accelerates postprandial transit. The mechanism by which this transit acceleration occurs remains uncertain, however, because neither the amplitude or the frequency of small intestinal contractions seem to be changed by  $\beta$  blockade.<sup>1</sup> Other, hitherto unexplored factors that might explain this transit acceleration, include the length of propagation of a contraction along the small intestine and the propulsive force generated by it.

It has recently been shown that in humans<sup>4 5</sup> as in other species<sup>6 7</sup> two main types of small

intestinal contraction exist. One type (propagating contractions) travel over a distance of 2 cm or more and propel intraluminal contents aborally. The other type (stationary contractions) travel less than 2 cm and seem to serve a mixing rather than propulsive function.<sup>6-8</sup> We hypothesised that the transit accelerating effect of  $\beta$  blockers might be exerted either, by an increase in propulsive force exerted by contractions or, by a change in the proportion of propagating/stationary contractions. This study was designed to test this hypothesis by measuring the effect of  $\beta$  adrenoceptor blockade on both the contraction type and on the aboral forces generated in the small intestine after ingestion of a meal.

## Methods

### SUBJECTS

Ten healthy volunteers (six males, four females; mean age 28 years; range 21-39) without a past or current history of gastrointestinal disease, participated in the study after providing informed consent.

### THE TRACTION FORCE DETECTOR

This device, which has been previously described in detail in this journal,<sup>5 9</sup> consisted of a miniature electronic strain gauge force transducer (Gaeltec Ltd, Dunvegan, Isle of Skye, UK) mounted on a catheter to which a silicone extension was attached by Kevlar threads. The inelastic Kevlar threads ensured that aboral traction forces acting on the extension were transferred directly to the force transducer without damping.

The force transducer was calibrated before and after each study by suspending the catheter vertically and applying known weights to the extension piece. The voltage output from the transducer amplifier was recorded on a Polygraph (Grass Instruments Co, Quincy, MA, USA) calibrated so that a 10 mm pen deflection was equivalent to 10 g force.

A latex balloon 1.5 cm in length (HSC4 Precision Dippings Marketing, Stover Trading Estate, Yate, UK) was attached to the silicone extension 3 cm proximal to the end of the catheter. During each experiment the balloon was inflated with 1.5 ml air through a channel running through the catheter, this volume being chosen from the results of pilot studies because it permitted the detection of pressure changes and aboral forces generated by contractions without inducing any distension related contractile responses.

Department of  
Medicine, University  
of Manchester Medical  
School, Hope Hospital,  
Manchester  
N K Ahluwalia  
D G Thompson  
J Barlow  
L Heggie

Correspondence to:  
Dr D G Thompson,  
Department of Medicine,  
Hope Hospital, Eccles Old  
Road, Salford M6 8HD.

Accepted for publication  
9 February 1994

## INTRALUMINAL MANOMETRY

Intraluminal pressure activity was measured, both proximal and distal to the balloon, by attaching two polyvinyl chloride perfusion catheters (internal diameter 0.63 mm, Portex Ltd, Hythe, Kent, UK) to the traction catheter. The perfusion port of one catheter was sited 2 cm proximal, while the other was sited 2 cm distal, to the midpoint of the balloon. Two additional perfusion catheters with ports 7 and 17 cm proximal to the balloon were also attached to the catheter to aid the location of the device in the upper small intestine. All the perfusion catheters were bonded to the traction catheter using tetrahydrofuran. The external diameter of the entire catheter assembly was 4.5 mm.

Each of the four channels was perfused with degassed water at a rate of 0.5 ml/min using a low compliance pneumohydraulic perfusion system (Arndorfer Medical Specialties Inc, Greendale, WI, USA) run at a pressure of 15 pounds per square inch. A transducer (Statham P23-ID, Gould Inc, Oxnard, CA 93030, USA) was attached to the proximal end of each of the four perfused channels, the outputs of each transducer amplifier being recorded on the polygraph, run at a paper speed of 50 mm/min, and calibrated so that a pen deflection of 10 mm on the chart recorder corresponded with a pressure change of 10 mm Hg. Sudden complete occlusion of each channel gave a pressure rise of >400 mm Hg/s.

To provide a measure of contractile activity at the site of the balloon, the intraballoon pressure was also recorded continuously on the chart recorder using a similar Statham P23 transducer connected to the balloon inflation channel.

## TEST MEAL

A mixed nutrient test meal was used for all studies (H J Heinz and Co Ltd, Cream of Chicken Soup 360 ml; 425 g; 200 kcal; fat=11.5 g; protein=5.5 g). Before ingestion, the meal was warmed to a temperature of 37°C in a microwave oven.

## DRUGS

Atenolol (Tenormin 100 mg, Stuart Pharmaceuticals Ltd, UK) a predominantly  $\beta_1$  selective, peripherally acting,  $\beta$  adrenoceptor blocker was given orally 60 minutes before meal ingestion, a regimen that has previously been shown to achieve optimal  $\beta$  blockade.<sup>2</sup>

In the control experiments a matched dummy tablet (methyl-cellulose) was used.

## STUDY PROTOCOL

The study protocol was submitted to, and approved by, the Salford District ethics committee.

All studies were conducted in the morning after an overnight fast of at least 11 hours. The subjects reclined supine with their trunk at an angle of 30° to the horizontal throughout the study. The distal end of the catheter assembly

was first passed through the nose into the stomach and then through the pylorus and into the duodenum, its position being monitored by the pattern of the manometric events recorded from the perfusion channels. The identification of a typical duodenal manometric pattern from the three distal perfusion channels and an antral pattern from the most proximal port, was taken to indicate that the balloon was sited in the upper small intestine, 12–15 cm beyond the pylorus. After correct placement, the catheter was tethered to the cheek with adhesive tape to prevent further aboral movement, and the balloon was inflated.

The subject then ingested the test meal over a three to five minute period and after a further five minutes to permit a fed pattern to develop, a 30 minute recording of manometric and traction activity was made on the chart recorder.

To provide an index of the drug effect, the radial pulse rate and the brachial blood pressure were measured, both before and for 60 minutes after drug ingestion.

## DEFINITION OF TERMS

The nomenclature and criteria used for the classification of small intestinal contractions in this study are identical to those previously reported for humans, and are based on the assumption that the aboral propagation velocity of a contraction would be about 1 cm per second.<sup>4</sup>

*Contraction* – was defined as the occurrence of a manometric event at either a perfusion port or the balloon.

*Propagating contraction* – was defined as a contraction at the balloon that occurred between one to two seconds after a contraction in the proximal channel or between one to two seconds before a contraction in the distal channel, or both.

*Stationary contraction* – was defined as a contraction at the balloon that did not occur between one to two seconds after a proximal contraction or between one to two seconds before a distal contraction.

The simultaneous occurrence of pressure activity in all channels was considered to result from an extraintestinal artifact and was not included in data analysis.

*Traction events* – all events recorded by the traction force detector, other than those associated with artifacts as described above, were defined as traction events. These were subdivided as being either: (a) *related to propagating contractions*, those that occurred synchronously with a propagating contraction or, (b) *related to stationary contractions*, those that occurred synchronously with a stationary contraction.

*Traction force* – this was defined as the force in grams (g) exerted by a traction event, measured from the amplitude of the deflection on the chart recorder.

## DATA COLLECTION

*Contractions* – both the number and amplitude of contractions were counted at the

proximal and distal perfusion ports, and at the balloon.

**Traction events** – all traction events were noted and the force generated by each was measured. Each traction event was then classified as being related to either a propagating or a stationary contraction and the force associated with each event was measured.

**STATISTICAL METHODS**

The distribution of the data was first tested by applying the Shapiro-Wilk test<sup>10</sup> and because all data seemed to be normally distributed, the

results are expressed in the text as mean (SEM).

Student's paired *t* test<sup>11</sup> was used for comparison of paired data, a *p* value of less than 0.05 being taken to represent a biologically relevant difference.

The interindividual variability in the magnitude of change in force generated by contractions after  $\beta$  blockade was calculated by the method of Altman and Bland<sup>12</sup> and results expressed as median and interquartile range (IQR).

**Results**

**CARDIOVASCULAR DATA**

The pulse and blood pressure were unaffected by the dummy tablet. Atenolol, however, induced a consistent decrease in both pulse rate and arterial blood pressure (Fig 1).

**CONTRACTIONS**

After atenolol the number and the amplitude of both stationary and propagating contractions were similar to control values (Fig 2).

**TRACTION EVENTS**

After atenolol, both the number of traction events and the proportion related to propagating and stationary contractions was similar to the control study (Fig 2) indicating that traction event occurrence was not influenced by  $\beta$  blockade.

**TRACTION FORCE**

After atenolol, traction events generated greater force per minute than during the control study, and traction forces generated per event were also increased (Figs 3 and 4). The magnitude of the  $\beta$  blocker related increase in force generated varied widely between subjects both for traction events related to propagating contractions (median (IQR) 5.7 (3.0–12.0) g/min and 3.7 (0.1–11.6) g/event) as well as those related to stationary contractions (6.2 (2.3–3.9) g/min and 3.9 (3.1–7.0) g/event).

There was a poor correlation between the effect of atenolol on pulse rate and on the traction force ( $r^2=0.02$ ), suggesting that the intraindividual variation in the intestinal effects of  $\beta$  blockade was not related to the degree of cardiovascular blockade achieved.

**Discussion**

Our experiments have shown that  $\beta$  adrenoceptor inhibition by atenolol increases the aboral traction force associated with small intestinal contractions without changing either their type or number. As there is a direct relation between tone and force of contraction of an intestinal smooth muscle segment *in vitro*,<sup>13–15</sup> it seems probable that this increase in traction force is the result of the abolition of a  $\beta$  adrenergic mediated inhibitory influence

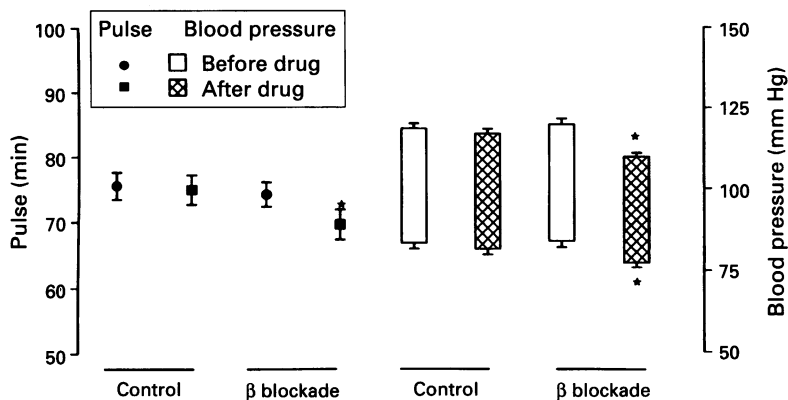


Figure 1: The pulse rate and blood pressure, before and 60 minutes after oral administration of placebo and atenolol. \*= $p < 0.01$ .

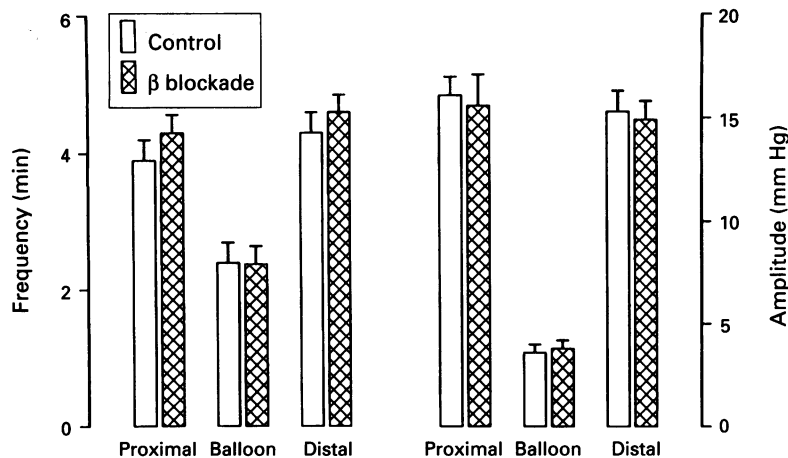


Figure 2: The frequency and amplitude of contractions (mean (SEM)) at the three recording sites.

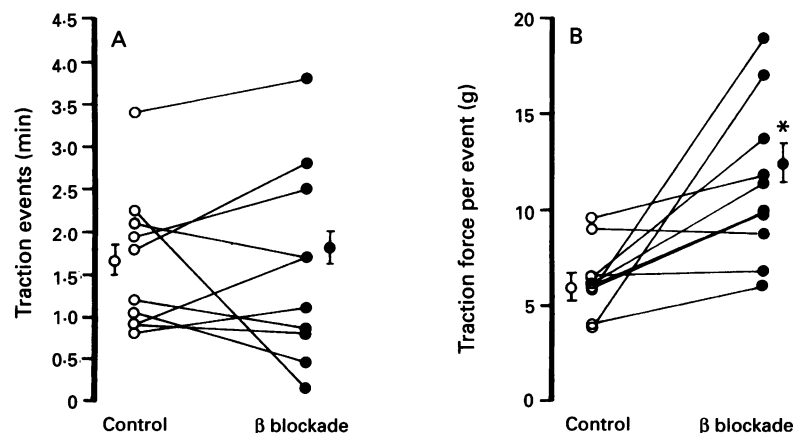


Figure 3: The numbers (A) and force (B) generated by traction events related to propagating contractions. The circle and vertical bars represent mean (SEM). \*= $p < 0.05$ .

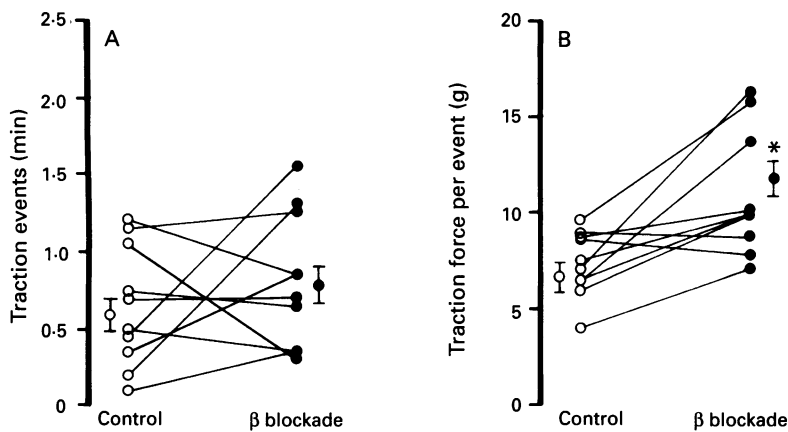


Figure 4: The numbers (A) and force (B) generated by traction events related to stationary contractions. The circle and vertical bars represent mean (SEM). \* =  $p < 0.05$ .

on small intestinal muscle tone, a conjecture consistent with the reported location of  $\beta$  receptors on gut smooth muscle rather than enteric nerves.

It is of interest to note that, despite an increase in propulsive force generated the amplitude of contractions was unchanged after  $\beta$  blockade. This suggests that the magnitude of the propulsive force associated with an intestinal contraction is not closely related to its amplitude, a finding similar to that reported in the gastric antrum.<sup>16</sup> A lack of relation between manometric amplitude and tone was also noted recently in a combined barostat and manometry study of the human small intestine.<sup>17</sup>

A wide interindividual variation in the degree of enhancement of contractile force after  $\beta$  blockade was found in our study independent of any effect on the cardiovascular system suggesting the existence of an equally large interindividual variation in the expression of sympathetic neural regulation of intestinal tone. These results are in keeping with earlier studies<sup>2</sup> that showed a similar range of transit acceleration in response to  $\beta$  blockade. Further studies are now required to determine the relation between the effects of  $\beta$  blockade on transit and on aboral traction forces.

The lack of a  $\beta$  blocker related effect on the type of contraction excludes the possibility that the  $\beta$  blocker related transit acceleration is exerted by a change in length of propagation.

In conclusion, our study has shown that  $\beta$  adrenoceptor blockade increases the propulsive force associated with small intestinal contractions without changing either their pattern or number. This finding supports the existence of a tonic inhibitory  $\beta$  adrenergic influence on the aboral movement of nutrients, which seems to vary in its degree of expression among normal subjects.

- O'Brien JD, Thompson DG, Day SJ, Burnham WR, Walker E. Perturbation of upper gastrointestinal transit and antroduodenal motility by experimentally applied stress: the role of beta-adrenoceptor mediated pathways. *Gut* 1989; 30: 1530-9.
- McIntyre AS, Thompson DG, Burnham WR, Walker E. Modulation of human upper intestinal nutrient transit by a beta-adrenoceptor mediated pathway. *Gut* 1992; 33: 1062-70.
- Hedges A, Turner P. Effect of five  $\beta$ -adrenoceptor antagonists on the effect of isoprenaline and acetylcholine on human isolated smooth muscle. *Br J Pharmacol* 1971; 41: 426-9.
- Sarna SK, Soergel KH, Harig JM, Loo FD, Wood CM, Donahue KM, et al. Spatial and temporal patterns of human jejunal contractions. *Am J Physiol* 1989; 257: G423-32.
- Ahluwalia NK, Thompson DG, Barlow J, Heggie L. Human small intestinal contractions and aboral traction forces during fasting and after feeding. *Gut* 1994; 35: 625-30.
- Schemann M, Ehrlein H-J. Postprandial patterns of canine jejunal motility and transit of luminal content. *Gastroenterology* 1986; 90: 991-1000.
- Siegle M-L, Ehrlein H-J. Digestive motor patterns and transit of luminal contents in canine ileum. *Am J Physiol* 1988; 254: G552-9.
- Ramorino MA, Colagrande C. Intestinal motility: preliminary studies with telemetry capsules and synchronized fluorocinematography. *Am J Dig Dis* 1964; 9: 64-71.
- Williams D, Thompson DG, Marples M, Heggie L, O'Hanrahan T, Mani V, et al. Identification of an abnormal esophageal clearance response to intraluminal distension in patients with esophagitis. *Gastroenterology* 1992; 103: 943-53.
- Minitab. *Minitab Statistical Software, DOS microcomputer version, release 7*. Minitab Inc, 3081 Enterprise Drive, State College PA 16801-2756, USA, 1989.
- Armitage P, Berry G. *Statistical methods in medical research*. Oxford: Blackwell Scientific, 1987: 141-59.
- Altman DG, Bland JM. Measurement in medicine: the analysis of method of comparison studies. *Statistician* 1983; 32: 307-17.
- Salimi M. Comparison of  $\beta$ -adrenoceptor blocking properties of Sotalol, Oxprenol, Propranolol and pindolol on rabbit intestinal smooth muscle. *Pharmacology* 1975; 13: 441-7.
- Arner A. Mechanical characteristics of chemically skinned guinea-pig taenia coli. *Pfluegers Arch* 1982; 395: 277-84.
- Gordon AR. Contraction of detergent treated smooth muscle. *Proc Natl Acad Sci USA* 1978; 75: 3527-30.
- Vassalo MJ, Camilleri M, Prather CM, Hanson RB, Thomforde GM. Measurement of axial forces during emptying from the human stomach. *Am J Physiol* 1992; 263: G230-9.
- Rouillon J-M, Azpiroz F, Malagelada J-M. Reflex changes in intestinal tone: relationship to perception. *Am J Physiol* 1991; 261: G280-6.