

## Beta adrenergic influence on oesophageal peristalsis in man

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**SUMMARY** The effects of the beta-1 adrenergic agonist prenalterol and the beta-2 adrenergic agonist terbutaline on oesophageal peristalsis were studied in nine healthy volunteers with pressures recorded in the proximal, middle, and distal oesophagus. Two doses of the agonists were given after pretreatment with placebo, propranolol, or metoprolol in a double blind randomised fashion. Terbutaline  $0.25 \pm 0.25$  mg iv decreased peristaltic pressure in middle oesophagus from  $8.1 \pm 1.1$  to  $5.1 \pm 0.8$  kPa ( $p < 0.01$ ) and in the distal oesophagus from  $9.5 \pm 1.0$  to  $4.7 \pm 0.6$  kPa ( $p < 0.001$ ). Peristaltic velocity was decreased in the distal oesophagus after terbutaline from  $3.3 \pm 0.2$  cm/sec to  $2.9 \pm 0.2$  cm/sec ( $p < 0.05$ ). Prenalterol 1 mg iv was followed by a decrease of peristaltic pressure in the middle oesophagus from  $10.2 \pm 1.3$  to  $7.7 \pm 1.1$  kPa ( $p < 0.01$ ) and a decrease of peristaltic velocity in upper oesophagus from  $3.6 \pm 0.2$  to  $3.3 \pm 0.1$  cm/sec ( $p < 0.05$ ) while no significant changes were seen in the distal oesophagus. Pretreatment with the beta-1 blocker metoprolol 15 mg iv blocked the effects of prenalterol 1 mg iv but not the effects of terbutaline. Propranolol 10 mg iv blocked the effects of terbutaline on peristaltic pressure. After metoprolol infusion mean distal peristaltic amplitude was  $11.9 \pm 0.8$  kPa compared with  $8.5 \pm 1.2$  kPa after placebo ( $p < 0.01$ ). It is concluded that both beta-1 and beta-2 adrenoceptor stimulation significantly decrease oesophageal peristaltic pressure in man. The body of the oesophagus seems to be under beta adrenergic inhibitory influence under physiological conditions.

Adrenergic influence on gastrointestinal smooth muscle has been described in both animals and in man. Alpha adrenergic agonists have been shown to contract smooth muscles of the oesophageal body and the lower oesophageal sphincter.<sup>1-3</sup> Beta adrenergic substances have also been shown to influence oesophageal smooth muscle. The non-selective beta adrenoceptor antagonist alprenolol increased the amplitude of the peristaltic contraction in the distal oesophagus and increased lower oesophageal sphincter pressure in man.<sup>4</sup> The non-selective beta agonist isoproterenol reduces the force velocity characteristics of opossum oesophageal smooth muscle *in vitro*.<sup>5</sup> DiMarino and Cohen have recently shown an inhibitory effect on lower oesophageal sphincter pressure in man after administration of the beta-2 adrenergic agonist carbuterol.<sup>6</sup>

Studies of beta adrenergic influence on oeso-

phageal smooth muscle have mainly concerned with the lower oesophageal sphincter pressure but little is known of the corresponding influence on peristalsis of the oesophageal body in man. The clearing capacity of the oesophagus seems to be related to the peristaltic amplitude and pharmacologic inhibition of peristaltic pressure impairs oesophageal clearing.<sup>7</sup> Beta adrenergic agonists and antagonists are widely used in treatment of various clinical disorders. Some of these conditions - for example, bronchial asthma and angina of the heart may have a close association to oesophageal dysfunction.<sup>8,9</sup> Thus, from both a physiological and a clinical point of view it is of interest to study the role of beta adrenoceptors in oesophageal function.

The purpose of this study was to describe the effects of beta adrenergic agonists on oesophageal peristalsis in man. To elucidate the selectivity of these effects and the importance of adrenergic beta-1 and beta-2 receptors we also studied the influence of beta adrenergic blockade on the oesophageal response to the beta agonists.

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## Methods

### SUBJECTS

Nine healthy volunteers (eight men, one woman; aged 23–49 years) were studied. None of the subjects had a history of gastrointestinal disease. Each subject gave informed consent and the study was approved by the Ethical Committee of the University of Göteborg.

### DRUGS

The drugs used in the study were prenalterol (Hyprenan, AB Hässle) as beta-1 agonist,<sup>10</sup> terbutaline (Bricanyl, AB DRACO) as beta-2 agonist,<sup>11</sup> metoprolol (Seloken, AB Hässle) as beta-1 antagonist, and propranolol (Inderal, ICI) as non-selective beta antagonist.

### EXPERIMENTAL DESIGN

Manometric studies were done with a probe of three electronic semiconductor pressure catheters (Gaeltec, 16 CT/Sil) with the pressure sensitive tips 8 cm apart. The catheters were connected to a Grass RPS 7 C polygraph recorder. Before each recording session the catheters were calibrated with a liquid column at 37°C. After an overnight fast each subject was examined in a standardised sitting position with the manometric probe inserted through the nasal route. The probe was inserted so that the distal catheter passed the lower oesophageal sphincter and then withdrawn and fixed so that the distal recording point was 2 cm proximal to the lower oesophageal sphincter. Thus, pressures were recorded 18 cm proximal to the lower oesophageal sphincter (proximal oesophagus), 10 cm proximal to the lower oesophageal sphincter (middle oesophagus) and 2 cm proximal to the lower oesophageal sphincter (distal oesophagus). The study was randomised and double blind.

Each subject was investigated on five different days with at least five days between each registration

to avoid any possible influence of an earlier drug infusion. Oesophageal peristalsis was examined for three consecutive periods of 30 minutes (Table 1). The first period was preceded by infusion of either placebo (saline), metoprolol 15 mg, or propranolol 10 mg intravenously. The two following periods were each preceded by an infusion of terbutaline 0.25 mg iv to a total amount of 0.50 mg on one day, or prenalterol 1.0 and 4.0 mg iv on one day according to the randomised schedule. All doses of the drugs were given as infusion 1 ml/min for five minutes. With intervals of 10 minutes five wet swallows (water bolus of 5 ml, room temperature) were carried out with 30 seconds between each bolus.

### PERISTALTIC PARAMETERS MEASURED

Amplitude of the peristaltic contraction was measured as the change in pressure from the baseline resting oesophageal pressure to the peak of the contraction wave and expressed as kPa (1 kPa=7.5 mm Hg). The distances between the upper and the middle and the distal catheter tip were used for calculation of peristaltic velocity in the upper and lower oesophagus, respectively. The onset of the peristaltic wave was used for this calculation. The duration of the peristaltic pressure wave was measured from the onset of the major upstroke to the end of the peristaltic wave and expressed in seconds. The duration of the pressure waves was measured from the registrations of the middle catheter – that is, 10 cm proximal to the lower oesophageal sphincter.

The individual mean values of peristaltic parameters were calculated for the five swallows at each 10 minute interval. The swallows 28–30 minutes after the start of each drug infusion – that is, during the elimination phase of the drug, were used for statistical comparison of drug effects. The Student's *t* test for paired measurements was used to compare differences between periods of beta adrenergic stimulation and the preceding control period (placebo or beta blockade).

Table 1 Drug sequences and time for drug infusions and recording of swallows during the five different examinations. Each drug infusion given during five minutes

Time (min)	0	10	20	30	40	50	60	70	80	90
Drug infusion	×			×			×			
Swallows			×	×	×	×	×	×	×	×
Drug sequences	1 Placebo			Prenalterol 1.0 mg			Prenalterol 4.0 mg			
	2 Placebo			Terbutaline 0.25 mg			Terbutaline 0.25 mg			
	3 Metoprolol 15 mg			Prenalterol 1.0 mg			Prenalterol 4.0 mg			
	4 Metoprolol 15 mg			Terbutaline 0.25 mg			Terbutaline 0.25 mg			
	5 Propanolol 10 mg			Terbutaline 0.25 mg			Terbutaline 0.25 mg			

## Results

### AMPLITUDE OF PERISTALTIC PRESSURE

The time course of the effects of agonists on peristaltic pressure in the distal half of the oesophagus is illustrated in Figure 1. After a placebo control period infusion of the drugs was followed by a decrease in pressure amplitude. The maximum effect tended to appear earlier after terbutaline than after prenalterol.

Comparison of peristaltic amplitudes at the end of each test period showed that after terbutaline 0.25 mg pressure decreased in middle oesophagus from  $8.1 \pm 1.1$  to  $6.6 \pm 1.1$  kPa ( $p < 0.05$ ) compared with the placebo period (Fig. 2). After a total dose of 0.50 mg the amplitude decreased to  $5.1 \pm 0.8$  kPa ( $p < 0.01$ ). In the distal oesophagus terbutaline infusion was followed by a decrease from  $9.5 \pm 1.0$  kPa after placebo infusion to  $6.8 \pm 0.7$  kPa ( $p < 0.001$ ) after 0.25 mg and to  $4.7 \pm 0.6$  kPa ( $p < 0.001$ ) after 0.50 mg. After pretreatment with metoprolol 15 mg iv the decrease after terbutaline 0.25 mg was less marked but significant in both middle and distal oesophagus. After pretreatment with propranolol 10 mg iv terbutaline had no effect on peristaltic pressure.

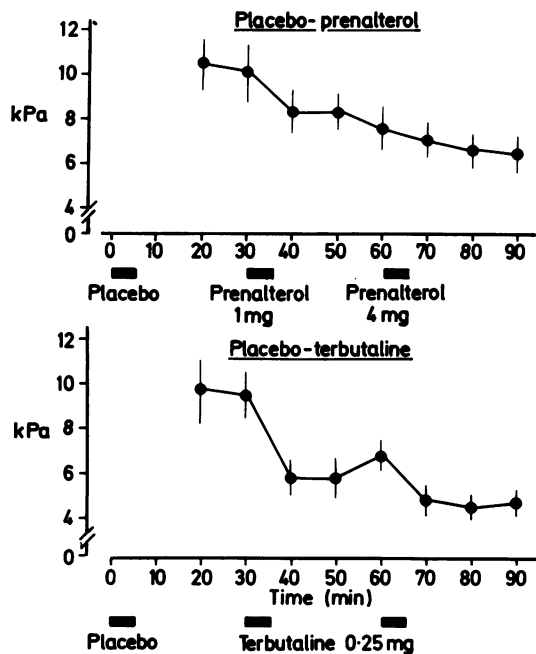


Fig. 1 Time course of the effects of prenalterol and terbutaline infusions on oesophageal peristaltic pressure after pretreatment with placebo.

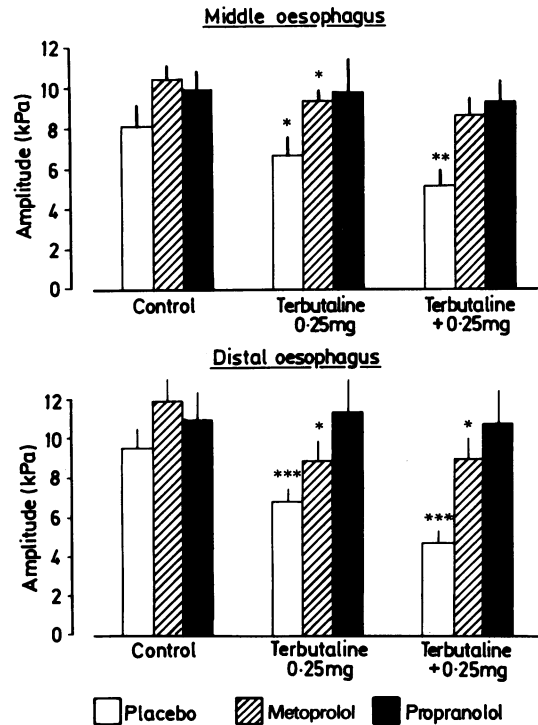


Fig. 2 Effects of terbutaline on peristaltic pressure in middle and distal oesophagus. Two doses of terbutaline 0.25 mg infused after pretreatment (control period) with placebo, metoprolol 15 mg or propranolol 10 mg iv. Asterisks indicate statistical differences compared with the preceding control period: \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ . 1 kPa = 7.5 mm Hg.

After prenalterol 1 mg (Fig. 3) peristaltic amplitude decreased in middle oesophagus from  $10.2 \pm 1.3$  to  $7.7 \pm 1.1$  kPa ( $p < 0.01$ ) and to  $6.6 \pm 0.9$  kPa after a total dose of 5 mg ( $p < 0.01$ ). In distal oesophagus peristaltic amplitude decreased significantly only after the highest dose of prenalterol. After pretreatment with metoprolol 15 mg iv pressure amplitudes did not change significantly after prenalterol 1 mg but decreased significantly in both locations after prenalterol 5 mg.

For each subject mean values were calculated for the swallows at the end of the two placebo periods and the two metoprolol periods (Fig. 4). After metoprolol 15 mg mean pressure amplitude in distal oesophagus was  $11.7 \pm 1.1$  kPa compared with  $9.3 \pm 1.3$  kPa after placebo infusion ( $p < 0.01$ ). After propranolol 10 mg the increase of peristaltic pressure did not reach significant level.

Registrations from the proximal catheter located

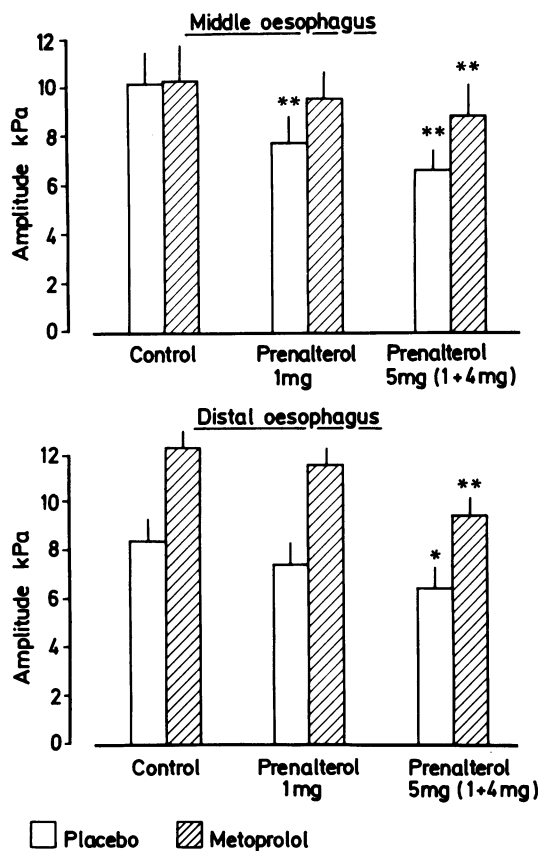


Fig. 3 Effects of prenalterol 1 mg and 4 mg iv on oesophageal peristaltic pressure compared with a preceding control period (placebo or metoprolol 15 g iv).

18 cm proximal to the lower oesophageal sphincter did not show any changes in peristaltic pressure after beta adrenergic agonist or antagonist infusion. After prenalterol 5 mg iv the mean amplitude was  $8.1 \pm 0.7$  kPa compared with  $7.9 \pm 0.5$  kPa after the preceding placebo infusion. After terbutaline  $0.25 \text{ mg} + 0.25 \text{ mg}$  the pressure was  $8.1 \pm 0.6$  kPa compared with  $8.3 \pm 0.9$  kPa after placebo.

#### PERISTALTIC VELOCITY

Table 2 shows the peristaltic velocity in the upper and lower oesophagus for the swallows done at the end of each test period. After infusions of prenalterol the velocity in upper oesophagus decreased significantly in a dose dependent way while no significant velocity changes were observed in the distal part. After pretreatment with metoprolol a decrease was seen only in the distal part after the highest dose of prenalterol.

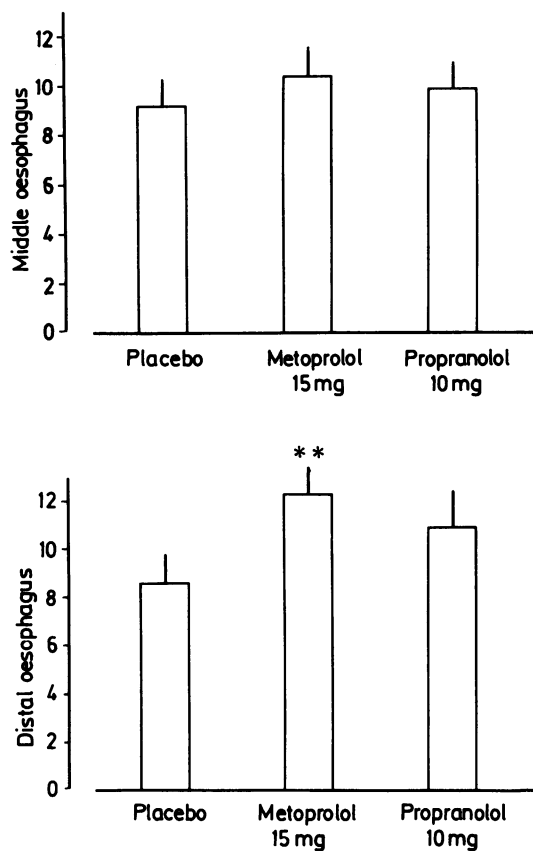


Fig. 4 Mean amplitude of oesophageal peristalsis after infusion of placebo, metoprolol 15 mg iv and propranolol 10 mg iv.

Infusion of terbutaline did not change peristaltic velocity in upper oesophagus compared with the preceding placebo period. In the distal oesophagus significant decrease in velocity was noted after terbutaline  $0.25 + 0.25 \text{ mg}$ . After pretreatment with metoprolol the decrease in velocity in the distal part did not reach significant level. After pretreatment with propranolol no significant effects of terbutaline on peristaltic velocity were observed.

#### DURATION OF THE PERISTALTIC PRESSURE WAVE

Peristaltic wave duration was estimated from the recording catheter 10 cm proximal to the lower oesophageal sphincter. After infusion of the beta agonists there was a tendency of shorter waves after the higher doses. After prenalterol 1+4 mg mean wave duration decreased from  $4.6 \pm 0.4$  to  $3.8 \pm 0.2$  sec ( $p < 0.01$ ). Also when pretreated with metoprolol, prenalterol 1+4 mg gave a significant decrease

Table 2 Peristaltic velocity after infusion of prenalterol and terbutaline. Asterisks indicate differences compared with the preceding control period (placebo, metoprolol, or propranolol)

Prenalterol experiments									
	Placebo	Prenalterol		Metoprolol 15 mg	Prenalterol				
		1 mg	+4 mg		1 mg	+4 mg			
Upper oesophagus	3.6±0.2	3.3±0.1*	3.0±0.1**	3.4±0.1	3.3±0.2	3.1±0.2			
Lower oesophagus	2.7±0.2	2.8±0.2	2.7±0.3	3.5±0.3	3.4±0.3	3.1±0.2*			
Terbutaline experiments									
	Placebo	Terbutaline		Metoprolol 15 mg	Terbutaline		Propranolol 10 mg	Terbutaline	
		0.25 mg	+0.25 mg		0.25 mg	+0.25 mg		0.25 mg	+0.25 mg
Upper oesophagus	3.5±0.3	3.5±0.2	3.7±0.3	3.4±0.2	3.5±0.2	3.4±0.2	3.9±0.5	3.6±0.5	3.7±0.4
Lower oesophagus	3.3±0.2	3.3±0.2	2.9±0.2*	3.3±0.4	3.0±0.2	3.1±0.3	3.7±0.4	3.5±0.4	3.4±0.4

from 4.3±0.3 to 3.9±0.2 sec ( $p<0.01$ ). After terbutaline 0.25+0.25 mg duration of the wave decreased in six of the nine subjects but the difference did not reach significant level for the whole group. After propranolol pretreatment there was no change of wave duration after terbutaline.

## Discussion

The present study was mainly aimed to evaluate the effects of beta adrenergic stimulation on oesophageal peristalsis. The results show that beta adrenergic stimulation influences oesophageal peristalsis, not only in the lower oesophageal sphincter region as earlier reported,<sup>4-6</sup> but throughout the whole smooth muscle part of the body of the oesophagus in man. The amplitude of the peristaltic pressure in the proximal, striated muscle part of the oesophagus seems not to be influenced by beta adrenergic stimulation.

There is clear evidence that beta-2 stimulation inhibits peristaltic pressure in the whole smooth muscle part. Thus, the beta-2 agonist terbutaline caused a dose dependent reduction of pressure. After pretreatment with the beta-1 adrenoceptor blocker metoprolol, terbutaline still depressed the peristaltic amplitude. Furthermore, the non-selective beta blocker propranolol completely blocked the effects of terbutaline. Thus beta-2 stimulation seems to depress not only the basal tone of the lower oesophageal sphincter<sup>6</sup> but also the oesophageal transport mechanism.

There is also strong evidence that stimulation of adrenergic beta-1 receptors affect oesophageal peristaltic pressure. In our study prenalterol caused a dose dependent reduction which was most prominent in the middle part of the oesophagus. Prenalterol is a partial agonist<sup>12</sup> and may, like other beta-1 agonists available have some affinity also to beta-2

receptors.<sup>13</sup> The effects of the lowest dose of prenalterol in our study was, however, selectively blocked by the beta-1 blocker metoprolol 15 mg iv, a dose which did not block the effects of the beta-2 agonist terbutaline. After prenalterol in a total dose of 5 mg significant inhibition of peristaltic pressure was seen also after pretreatment with metoprolol. This may be explained by an insufficient beta-1 blockade after this dose of metoprolol as has been discussed in studies of cardiovascular effects after similar doses of prenalterol and metoprolol.<sup>14</sup> Another possibility may be that the inhibition of peristaltic pressure observed after the highest dose of prenalterol was partly because of beta-2 stimulation.

The present results together with earlier reports on beta adrenergic blockade indicate that the oesophageal peristaltic contraction is under beta adrenergic inhibitory influence under physiological conditions. Non-selective beta blockade increases peristaltic pressure at the level of the lower oesophageal sphincter.<sup>4</sup> Our findings that peristaltic pressure is increased after metoprolol compared with placebo treatment indicate that beta-1 receptors are involved. At present it is not known how selective beta-2 blockade would affect oesophageal peristalsis. In our study the increase in peristaltic pressure after propranolol was not significant compared with placebo. This could, however, partly be because of the fact that fewer observations were made with propranolol than with metoprolol according to the design of the study. Thus, mean values for the propranolol period was more influenced by day to day variations in peristaltic pressure than was the mean value for metoprolol.

Peristaltic velocity decreased significantly in upper oesophagus after beta-1 stimulation by prenalterol. In contrast, beta-2 stimulation had no inhibitory effect on velocity in this part of the

oesophagus but decreased velocity in lower oesophagus. The inhibitory effect of beta-1 stimulation on peristaltic velocity in the transitional zone between oesophageal striated and smooth muscles is similar to that of atropine.<sup>15</sup> This effect of prenalterol and atropine seems not to be a direct consequence of the decreased force of oesophageal contraction as beta-2 stimulation influenced peristaltic pressure but not velocity at this level.

The site of action of beta adrenergic agents – that is, the location of beta adrenoceptors in the GI-tract is subject to some controversy. Sympathetic nerve fibres branch with synaptic contacts around the cell bodies of the myenteric plexus.<sup>16 17</sup> Direct contact with the intestinal smooth muscle cell has been shown as well.<sup>18</sup> It has been suggested that the inhibition of intramural cholinergic neurones is mediated through alpha receptors while the inhibitory effect on smooth muscle cells is achieved through beta receptors.<sup>19–21</sup> Further evidence for a location of the beta receptor on the smooth muscle cell was brought forward by Christensen,<sup>22</sup> and Goyal and Ratten.<sup>23</sup> Recent experiments, however, suggest that the beta-2 adrenoceptors are located postjunctionally on the smooth muscle cell while the beta-1 adrenoceptors may be prejunctionally located in the myenteric plexus.<sup>24 25</sup>

The significance of this proposed separation of receptor location in the effects of beta adrenergic agents is at the moment uncertain. In our study the effects of beta-1 and beta-2 stimulation on peristaltic velocity in the upper oesophagus suggest different locations of the two subgroups of receptors. The precise receptor location in the human oesophagus, however, remains to be shown.

The effects of beta adrenergic agonists and antagonists described here may have several clinical implications. We have earlier shown<sup>26</sup> that after infusion of terbutaline in the doses used here, plasma concentrations of the drug are at the level seen in patients treated for pulmonary disease.<sup>27</sup> It is noteworthy that oesophageal peristalsis may be considerably affected under these circumstances as oesophageal dysfunction with gastro-oesophageal reflux can be of pathophysiological importance for bronchial asthma and related disorders. In this group of patients it may be of relevance not to administer drugs which impair oesophageal clearing capacity.

Non-selective and beta-1 selective beta blockers are used for treatment of coronary artery disease and it is interesting to note that these drugs also increase oesophageal peristaltic pressure. It is not known whether this effect on the oesophagus is of clinical relevance. It remains to be studied if the effects of beta blockers on chest pain supposed to

emanate from the heart may instead be due to effects on a misinterpreted gastro oesophageal-disease. Although much is still unknown about beta adrenergic regulation of oesophageal function it seems reasonable to assume that increased knowledge in this field may have important clinical implications.

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