

Autonomic control of colonic tone and the cold pressor test

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Abstract

Background—Cardiovascular responses to cold stimulation are well characterised. It is unclear, however, whether cold pain stimulates responses in colonic tone in the transverse and sigmoid regions.

Aims—To assess the effects of cold stimulation on tone and motility in the transverse and sigmoid colon and on cardiovascular autonomic activity.

Methods—Phasic and tonic motility of the transverse and sigmoid colon, pulse rate, and beat to beat pulse variability (which are measures of centrally mediated changes in autonomic function) were measured before, during, and after a standard cold pressor test in 22 healthy volunteers.

Results—Cold pain induced a significant increase in colonic tone but not phasic contractility in the transverse and sigmoid regions. Simultaneously, cold pain increased pulse interval variability.

Conclusion—The findings are consistent with the hypotheses that cold pain produces coactivation of both the sympathetic and parasympathetic limbs of the autonomic nervous system and that cold induced changes in colonic tone are temporally associated with alterations in central autonomic nervous activity.

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Keywords: colonic motility, colonic tone, cold pressor, autonomic.

Physical, mental, and emotional stressors induce significant changes in oesophageal, gastric, small intestinal, and colonic motility in healthy subjects; furthermore, the effects of acute stress on the gut often differ from those induced by chronic stress.^{1,2} Though neural and humoral systems link the gastrointestinal tract to the central nervous system, the interplay between the two systems in mediating the effects of stress on the gut is complex and incompletely understood. Central command mechanisms evoked by changes in arousal states change craniospinal autonomic outflow and probably mediate some of the central effects of stress.³

The effects of the cold pressor test as a non-specific stimulant of central autonomic nervous system activity have been extensively studied.³⁻⁶ Gastrointestinal motility responses to the cold pressor test have previously shown significant changes in phasic contractility in the oesophagus,⁷⁻⁹ stomach,¹⁰⁻¹³ small intestine,¹⁴⁻¹⁶ and colon,¹⁷⁻¹⁹ although its effects on

colonic tone have not been reported. Cold pressor responses are dependent on pain perception, and responses are abolished by denervation of the limb or by hysterical conversion hemianaesthesia.⁴ As central processing of cold pain is essential for the pressor response to occur, the effect of the cold pressor test on colonic tone should relate to the severity of cold pain and produce coactivation of both the sympathetic and parasympathetic limbs of the autonomic nervous system.⁶

Cold induced pain is one of many acute stressors that increase autonomic neural activity. Different stimuli, however, induce different effects on gastrointestinal motility. For example, hand immersion in cold water delays small bowel transit without any change in heart rate, whereas dichotomous listening mental stress has no demonstrable effect on small bowel transit while inducing a sustained increase in heart rate.¹⁴ Furthermore, the same stimulus can have contrasting motility effects in different regions of the gut; for example, cold induced pain inhibits gastric antral motility yet increases colonic motility.^{1,2} Gastrointestinal motility responses to autonomic stimulation indicate both stimulus and site specificity. Given that enteric nerve and smooth muscle cell activity are influenced by α and β adrenergic innervation, and that the cold pressor test increases blood pressure and total vascular resistance due to α adrenergically mediated vasoconstriction,²⁰ we hypothesised that, like gastric wall tone and motility, colonic wall tone and motility should decrease if the colon is perturbed during activation of a centrally mediated 'sympathetic brake'.⁹ Our aim therefore was to evaluate proximal and distal colonic tone and phasic motility together with cold pain perception and autonomic cardiovascular responses to cold stimulation.

Methods

Healthy volunteers

Twenty two healthy volunteers, aged 19-62 years (mean (SEM)=31 (2.1); 12 M and 10F), were recruited by public advertisement. None had previous gastrointestinal surgery. Irritable bowel syndrome, anxiety, and depressive disorders were excluded using validated, screening questionnaires,^{21,22} a clinical interview, and physical examination. The studies were approved by Mayo Clinic's Institutional Review Board.

Colonic motor function

A multilumen, combined manometric and

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barostat assembly was placed in the prepared colon with the aid of colonoscopy and fluoroscopy.^{23 24} Tonic and phasic contractile activity of the colon were measured by barostat balloons and conventional manometry respectively. The combined assembly comprised six manometric ports, one 10 cm orad to a 10 cm polythene balloon positioned in the transverse colon, one 10 cm aborad to a similar balloon in the sigmoid colon, and four ports, 10 cm apart, between the two balloons, the latter being 50 cm apart. Each balloon was linked to a strain gauge and an electromechanical air injection device. The barostat balloons were inflated to a minimum distending pressure, defined as the pressure (and volume) at which respiratory excursions were regularly recorded as changes in the barostat volume. The operating pressure was set 2 mm Hg above the minimum distending pressure (median pressure 10 mm Hg, range 8–14 mm Hg). Intraballloon volumes and manometric pressure changes in response to contractile activity were monitored continuously throughout the study. The technique and its use in healthy and clinical states has previously been shown to be both safe and effective.^{23 24}

Cold pressor test and haemodynamic function

The cold pressor test was performed in a conventional manner as previously described in 22 subjects.^{5 11} Subjects were asked to immerse the non-dominant hand up to the wrist in ice cold water (0°C) for 60 seconds, withdraw the hand for 15 seconds, and then reimmerse the hand; the sequence of immersion and rewarming was continued to the point of maximum tolerance or for a maximum of five minutes. The potency of the stimulus could therefore be maintained throughout the procedure, and the tendency to pain adaptation minimised. Test responses were assessed using the maximum duration of pain tolerance in seconds and pain intensity scores using 100 mm visual analogue scales.

The arterial pulse rate was monitored continuously using conventional digital pulse plethysmography (CO₂SMO, Novamatrix Medical Systems, Wallingford, CT). The mean pulse rate and beat to beat pulse interval were calculated for each 60 second time frame, the second of these being achieved using a modification of the VAX LAB peak finding programme. To obtain a dynamic measure of cardiovascular autonomic activity, the coefficient of variation of the pulse interval per minute (standard deviation/mean pulse peak interval) was then calculated. Thus, an increase in the coefficient of variation in pulse interval implies increased parasympathetic activity or decreased sympathetic activity, or both.^{25 26}

Experimental design

All subjects were admitted to the General Clinical Research Center at St Marys Hospital for bowel preparation, comprising 1.5–2.0 l oral colonic lavage solution (polyethylene glycol and electrolyte solution) on the evening prior to the study. All signed informed consent and women

of childbearing potential had a negative plasma human chorionic gonadotrophin pregnancy test. After an overnight fast, colonoscopy was performed under conscious sedation with intravenous midazolam (0.07 mg/kg); sedation was reversed immediately after the procedure with intravenous flumazenil (0.2–0.5 mg) to ensure return to full consciousness. No endoscopic abnormalities were seen, and the combined manometry and barostat assembly was introduced into the colon over a guidewire and positioned under fluoroscopic control. After 60 minutes of equilibration, the experiment was started. Colonic tone and motility and digital pulse plethysmography were assessed continuously during five minute periods before, during, and after the cold pressor test.

Colonic motor parameters

Phasic manometric pressure activity and changes in both pressure and volume of the two barostat balloons were sampled as analogue signals at 8 Hz and converted to digital signals before entry into a computer. As in previous studies, movement and respiratory artefacts were filtered out using a modified VAXLAB filtering program (Digital Equipment Corporation, Boston, MA) to remove waveforms with a frequency of greater than 10 per minute, pressure changes of less than 10 mm Hg amplitude or less than four seconds duration.^{23 24} Phasic pressure activity measured manometrically was expressed as the activity index – that is, the area under the contraction curve for each 60 second period. The mean manometric phasic activity in the transverse and sigmoid colon was calculated from the mean values recorded from two sensors positioned proximal and distal to the barostat balloons. The barostat balloon volumes recorded in the transverse and sigmoid colon were similarly computer analysed to separate baseline balloon volume from phasic volume events (PVEs). PVEs were defined as changes in volume greater than 10% of baseline volume and occurring at a frequency of one to four per minute. Baseline volumes were calculated by computerised exclusion of the PVEs from the barostat recordings and averaged over 60 second time frames during each five minute period to represent colonic tone.

Statistical analysis

The five minute period before and consecutive one minute periods during the tests were compared using paired *t* tests for normally distributed data, non-parametric paired Wilcoxon rank sum tests, and Bonferroni's correction as appropriate for multiple pairwise comparisons.

Results

Cold pressor test, somatic pain tolerance, and pulse rate variability

The initial one minute period of cold pain was tolerated by all 22 healthy subjects; 19 completed two minutes of the cold pressor test,

12 lasted three minutes, eight subjects four minutes, and only five subjects were able to withstand five minutes or more of the cold pressor test (Table I). There was a highly significant inverse correlation between cold pain ratings, as measured by visual analogue scores (vas), both of cold pain at first onset (threshold score) and maximum tolerable cold pain and the duration of maximum tolerance of cold pain ($r=-0.67$, $p<0.001$ and $r=-0.42$, $p<0.05$ respectively). Although the cold pressor test did not induce any significant change in pulse rate, there was a significant change in the coefficient of variation of the pulse interval from baseline during the period from minute 2 to minute 5 after the onset of the cold pressor test

TABLE I Cold pressor test and pain perception (mean (SEM))

Time to onset of pain	48.4 (6.3) sec
Threshold pain rating (vas)	69.5 (3.3) mm
Time to maximum pain tolerance	169.9 (19.6) sec
Maximum pain rating (vas)	88.5 (1.4) mm

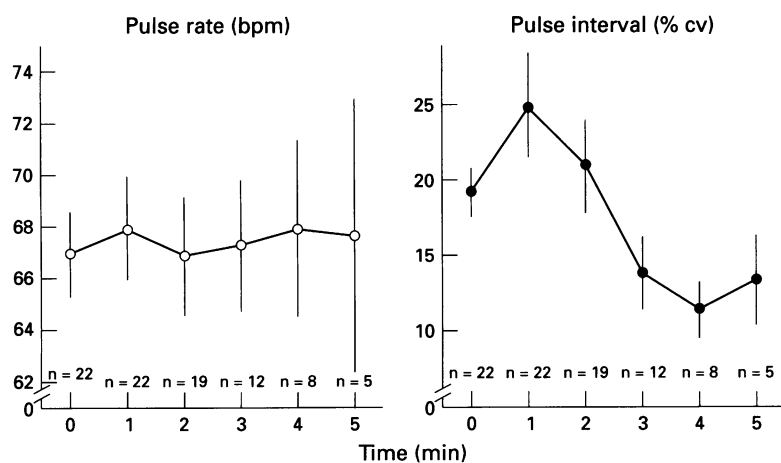


Figure 1: Pulse rate and variability (mean (SD)) during cold pressor test. Note the lack of any significant change in pulse rate, but a significant change in the coefficient of variation of the pulse interval from minute 2 to minute 5. n =number of subjects in whom observations were available during each minute of the cold pressor test.

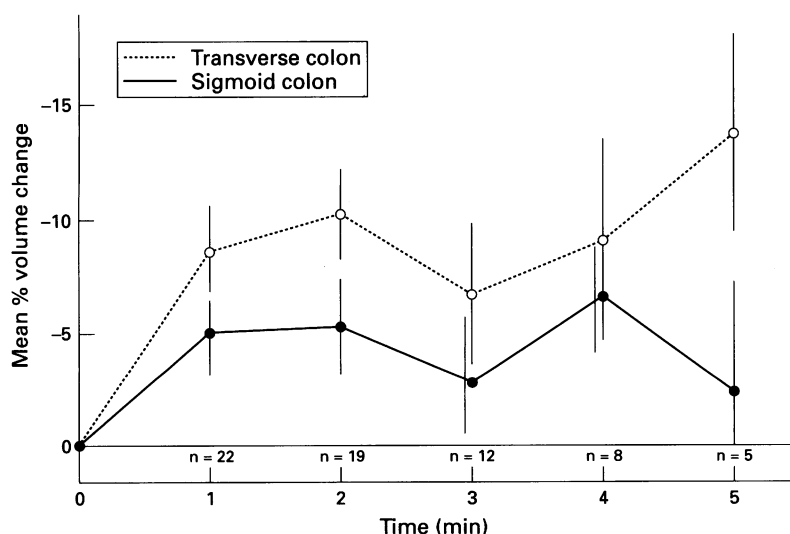


Figure 2: Percentage of change in colonic balloon volume (mean (SD)) in the transverse and sigmoid colon in response to the cold pressor test in healthy controls. Note the significant reduction in balloon volume, consistent with increases in colonic tone. n =number of subjects in whom observations were available during each minute of the cold pressor test.

(ANOVA, Duncan's test, $p<0.05$, Fig 1). Cold pain ratings did not correlate with pulse rate or pulse rate variability.

Cold pressor test and colonic tone and motility

Colonic tone (Fig 2), but not phasic motility (Fig 3), increased significantly during the cold pressor test in both the transverse and sigmoid colon. The mean (SD) barostat baseline volumes prior to the cold pressor test were 150.4 (9.5) ml in the transverse colon and 122.8 (9.6) ml in the sigmoid colon. During the initial one minute of the cold pressor test, mean barostat volumes fell significantly to 138.1 (9.5) ml and 115.1 (8.6) ml ($p=0.0013$ and $p=0.005$ respectively). After the initial one minute period (averaged for minute 2 to minute 5), the significant fall in mean barostat volumes was maintained at 140.2 (8.6) ml and 109.5 (8.9) ml ($p=0.0004$ and $p=0.0004$ respectively, Table II). There was no significant difference quantitatively or qualitatively between the initial and later responses of the transverse or sigmoid colon to the cold pressor test.

Cold pain, as reflected by the times to first onset of pain and to maximum tolerable pain, was inversely correlated with mean barostat volume reductions in both the transverse and sigmoid colon during the period from minute 2 to minute 5 after the onset of the cold pressor test ($r=-0.44$, $p<0.05$ and $r=-0.66$, $p<0.001$ respectively). In the sigmoid colon, the time to first onset of pain was also inversely correlated with the barostat volume reduction during the initial one minute of the cold pressor test ($r=-0.51$, $p<0.02$).

Discussion

The cold pressor test produces an increase in heart rate, total vascular resistance, arterial blood pressure, and cardiac output attributable to increased sympathetic vasomotor neuronal activity.^{3,6} The resulting cardiac autonomic response, however, is complex. In the first minute of the cold pressor test, the increase in heart rate seems to be a central command effect associated with the onset of cold pain and an increased state of arousal. The respiratory rate and tidal volume both increase in response to cold pain, an effect that increases both sympathetic and parasympathetic neural activity.^{3,6} As the initial increase in heart rate is attenuated by β adrenoreceptor blockade, sympathetic activation rather than parasympathetic inhibition seems to be the principal mediator of the initial chronotropic response to the test.^{3,5,6} The later pressor responses to the cold pressor test are associated with a pronounced increase in muscle rather than skin sympathetic neural activity, an effect that is not blocked by α or β adrenoreceptor blockade.²⁷⁻³⁰ In addition to the neural mediators of the cold pressor test, numerous humoral mechanisms are also at play, including the release of β endorphin, corticotrophin releasing hormone, and a variety of vasoactive catecholamines and neuropeptides.^{3,11,12,15,31-35}

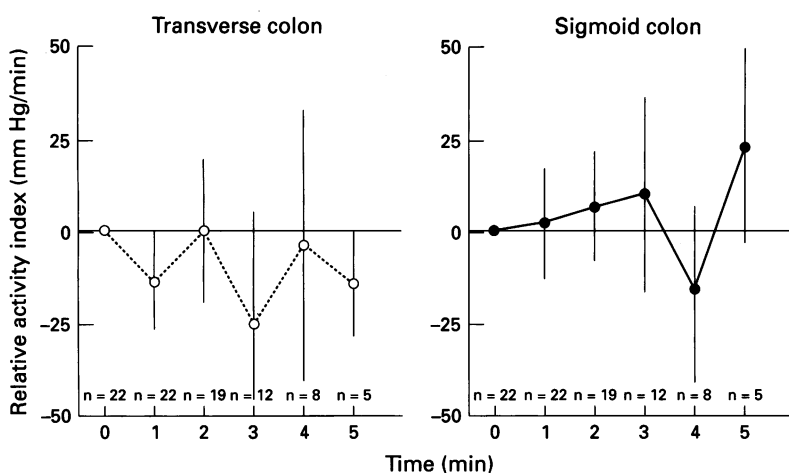


Figure 3: Phasic pressure activity (area under contraction curve) in the transverse and sigmoid colon of health controls during the cold pressor test. Data are expressed as the relative activity index, that is, the difference between phasic pressure activity for each one minute time frame during the cold pressor test minus the mean minute activity during the five minute epoch prior to the cold pressor test.

The initial increase in colonic tone during the first minute of the cold pressor test thus occurs during a period of central sympathetic stimulation. Our current studies do not permit an unequivocal understanding of the receptor subtypes involved.

Enteric smooth muscle cells have predominantly β adrenergic receptors, while enteric ganglia cells have predominantly α adrenergic receptors.^{36 37} This preferential localisation of α and β adrenergic receptors may help explain why colonic wall tone can be selectively increased without any demonstrable effect on colonic phasic motility. Enteric responses to the cold pressor test do not correlate closely with the cardiac autonomic responses to the cold pressor test nor do they correlate with the release into the circulation of catecholamines or β endorphin.^{11 14} Colonic wall tone and motility should decrease, like gastric wall tone and motility, if the cold pressor test is a predominantly sympathomimetic stimulus.^{6 9 37} Colonic phasic motility and myoelectric activity,^{18 19} and now colonic tone have, however, been shown to increase during the cold pressor test. It is likely, therefore, that additional factors are also involved. Power spectral analysis of the variability in pressor and heart rate responses after two minutes of the cold pressor test has shown that the increase in the low frequency component of systolic blood pressure fluctuations is consistent with coactivation of both sympathetic and parasympathetic cardiac neural activity.⁶ It has been suggested that, as the heart rate and blood

pressure effects are temporally dissociated, there may be differential sympathetic effects at play.³⁸ Given that the relative interplay between sympathetic and parasympathetic activity differs throughout the gut and that regions of the gut exhibit contrasting sensitivities to sympathetic and parasympathetic stimulation, it would be surprising if cold induced stress did not result in different effects in the various regions of the gut.³⁶⁻³⁸

How does stimulation of colonic tone during the cold pressor test compare with other effects of the test on gut function? The cold pressor test increases oesophageal contractility and decreases lower oesophageal sphincter and gastric tone.^{8 9 39} Inhibition of gastric antral motility and delayed gastric and oro-caecal transit induced by the cold pressor test is attenuated by combined α and β adrenoreceptor blockade or by the opioid receptor antagonist, naloxone, without inhibiting the increase in plasma norepinephrine or β endorphin. Such data strongly suggest that the motility changes induced during the cold pressor test are not directly humorally mediated.^{12 15 16} It has been shown that the cold pressor test exerts a biphasic effect on both gastric and pancreatic enzyme secretion, that is, an initial inhibition followed by stimulation of secretion during the post-stimulation period.¹⁰ This biphasic effect is consistent with coactivation of both the sympathetic and parasympathetic limbs of the autonomic nervous system, or initial activation of a non-adrenergic, non-cholinergic system. The finding that the cold pressor test also inhibits salt and water absorption from the human jejunum¹⁷ is consistent with such hypotheses. Increases in both systolic blood pressure and plasma epinephrine and norepinephrine concentrations in response to the cold pressor test are significantly enhanced by naloxone, indicating that μ -opioid receptor mechanisms may have important inhibitory effects on the stress responses.³⁶ The interplay between adrenergic and opioid control of colonic tone during the stress response requires further study.

Cold induced pain is a useful tool with which to explore the autonomic control of gut motility; however, its physiological effects may not parallel the complexity of motility changes evoked by the stresses of everyday life events and difficulties. For example, emotive interviews provoking anger induce colonic hypermotility; in marked contrast, those provoking sadness or despair induce colonic hypomotility.⁴⁰ Therefore, caution must be exercised before extrapolating the results of experimental studies in attempting to explain motility patterns that characterise dysautonomic states such as the irritable bowel syndrome and autonomic neuropathies.^{16 41} Our studies have shown that human colonic tone is increased during the cold pressor test. The data strongly suggest that both the sympathetic and parasympathetic limbs of the autonomic nervous system are involved in gut responses to cold induced pain and that the increase in parasympathetic activity is relatively greater than the increase in sympathetic activity, a

TABLE II Cold pressor test and barostat volumes (mean (SEM))

	Volume (ml)	Volume reduction (%) (increase in colonic tone)
<i>Transverse colon</i>		
Baseline volume	150.4 (9.5)	
Minute 1	138.1 (9.5)	8.5
Minutes 2-5	140.2 (8.6)	12.7
<i>Sigmoid colon</i>		
Baseline volume	122.7 (9.6)	
Minute 1	115.1 (8.6)	5.0
Minutes 2-5	109.5 (8.9)	7.8

finding consistent with the cardiovascular responses to the cold pressor test previously reported.⁶

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