Towards an integrated psychoneurophysiological approach of irritable bowel syndrome

Veek, P.P.J. van der

2

VISCEROSENSORY-CARDIOVASCULAR REFLEXES: ALTERED BAROREFLEX SENSITIVITY IN IRRITABLE BOWEL SYNDROME

Patrick P.J. van der Veek[1], Cees A. Swenne[2], Hedde van de Vooren[2], Annelies L. Schoneveld[3], Roberto Maestri[4], and Ad A. M. Masclee[1]

Departments of [1]Gastroenterology and Hepatology and [2]Cardiology, Leiden University Medical Center, Leiden, The Netherlands, [3]Leiden Foundation for ECG Analysis (SEAL), Leiden, The Netherlands, and [4]Department of Biomedical Engineering, S. Maugeri Foundation - IRCCS, Scientific Institute of Montescano, Montescano, Italy

Am J Physiol Regul Integr Comp Physiol 2005;289:R970-6

ABSTRACT

Background: Animal studies have demonstrated that visceral afferent stimulation alters autonomic cardiovascular reflexes. This mechanism might play an important role in the pathophysiology of conditions associated with visceral hypersensitivity, such as irritable bowel syndrome (IBS). As such studies in humans are lacking, we measured viscerosensory-cardiovascular reflex interactions in IBS patients and healthy controls.

Methods: Blood pressure (SBP), heart rate (HR) and arterial baroreflex sensitivity (BRS) were studied in 87 IBS patients and 36 healthy controls under baseline conditions and during mild (15 mmHg) and intense (35 mmHg) visceral stimulation by rectal balloon distension. BRS was computed from continuous ECG and arterial blood pressure signals (Finapres-method) during 5 min periods of 15/min metronome respiration.

Results: Baseline SBP and HR were not different between patients and controls. In both groups, SBP increased similarly during rectal stimulation, whereas HR decreased during mild and increased during intense stimulation. BRS was significantly higher in patients compared to controls at baseline (7.9±5.4 *vs.* 5.7±3.7 ms/mmHg, P=0.03) and increased significantly in both groups during mild stimulation. This increase persisted in controls during intense stimulation, but BRS returned to baseline in patients. BRS was not significantly different between groups during rectal distension.

Conclusion: This study demonstrates the presence of a viscerosensory-cardiovascular reflex in healthy individuals and in IBS patients. The increased BRS in IBS patients at baseline may either be a training-effect (frequent challenging of the reflex) or reflects altered viscerosensory processing at the nucleus tracti solitarii.

INTRODUCTION

Irritable bowel syndrome (IBS) is a frequently occurring functional disorder with a prevalence ranging from approximately 6 to 22%[1,2]. It is characterized by recurrent abdominal pain and disturbed bowel habits. In the absence of an established biological substrate, the diagnosis is symptom-based and made according to the Rome II criteria[3].

IBS is a multifactorial condition in which disturbances in the brain-gut axis have been identified. In particular, visceral hypersensitivity, which may be induced by a number of factors such as post-inflammatory tissue injury[4] or persistent mucosal immune activation[5,6], is thought to play a central role in the pathophysiology[7,8]. In addition, abnormal activity of the autonomic nervous system, reflected in the cardiovascular system by altered heart rate variability (HRV)[9,10] and in the gastrointestinal tract by disturbed motility[11,12], has been reported. These observations suggest disturbed viscerosensory-autonomic reflexes in IBS.

Gastrointestinal functioning is controlled by the dorsal vagal complex (DVC)[13]. This is an integrated structure comprising the motor nucleus of the vagus (DMV) from which autonomic outflow to the colon arises; the nucleus ambiguus (NA), where parasympathetic outflow to the cardiovascular system is generated; and the nucleus tracti solitarii (NTS), which integrates viscerosensory input from the gut, cardiovascular system (e.g. carotid and aortic baroreceptors) and other organs[14,15]. Interneurons from the NTS also reach the NA.

Noxious viscerosensory information from the gut down to the splenic flexure is transmitted by sympathetic spinal fibers, while physiological information is carried by cranial nerve afferents that terminate in the NTS. From here, interneurons project to the ventrolateral medulla (VLM), which governs sympathetic outflow, and to higher centers. Sensory information from the descending colon and rectum is exclusively conveyed by spinal afferent fibers that terminate in the thalamus, but collaterals also reach the NTS and VLM[16,17]. The key role of the NTS suggests that the altered autonomic outflow observed in IBS may result from an abnormal reflex response to disturbed afferent viscerosensory information from the gut.

Results of a study by Saleh et al. point to the possible involvement of the arterial baroreflex in IBS. They demonstrated that, in rats, electrical stimulation of abdominal vagal afferents increased sympathetic outflow and also decreased baroreflex sensitivity (BRS)[18]. Altered baroreflex functioning during gastrointestinal stress may constitute a pathophysiological key in IBS, as the arterial baroreflex not only modulates sympathetic and parasympathetic autonomic outflow, but also affects cortical arousal[19,20] and somatic[19,21] and visceral[18] pain perception.

Thus far, no human studies have addressed BRS involvement in IBS. As, in general, BRS is reduced in disease[22-24], we expected that baseline BRS is depressed in IBS patients. Furthermore, we anticipated an exaggerated BRS reduction during gastrointestinal stress in IBS patients compared to healthy controls[25]. Both assumptions would explain at least part of the previously observed abnormal activity of the autonomic nervous system (*i.e.*, increased sympethetic predominance) and the increased visceral pain perception in IBS patients. The following study was done to corroborate this hypothesis.

METHODS

The local ethics committee approved the study protocol.

Participants

Between March 2001 and July 2002, IBS patients were recruited through the outpatient department of Gastroenterology and Hepatology of the Leiden University Medical Center and through local advertisement. Eligible patients were seen by one of the investigators (PvdV). Exclusion criteria were the presence of organic disease, previous major abdominal surgery apart from cholecystectomy and appendectomy, dependence on analgesics and pregnancy. Patients who were taking cardio-active or antihypertensive drugs were excluded. Other medication such as antispasmodics, laxatives, bulking agents and occasional use of analgesics was permitted. All included patients met the Rome II criteria for IBS[3]. Age and sex matched healthy volunteers were recruited by advertisement. Each participant provided informed consent before entering the study.

Visceral stimulator

An electronic visceral stimulator, *i.e.* barostat (Synectics Visceral Stimulator, Synectics Medical, Stockholm, Sweden), was used to study the effect of a visceral stressor on blood pressure, heart rate and BRS. Using electronic feedback regulation, this device is able to apply isobaric distensions. Constant pressure is maintained within a highly compliant, polyethylene bag (maximum capacity 1000 mL) tied to the end of a multilumen tube (19 Fr) by injecting air when the rectal wall relaxes and aspirating air during rectal contraction[26]. Intrabag pressure is directly measured via a separate lumen.

BRS instrumentation

The finger cuff of a noninvasive blood pressure measurement device (Finapres, TNO, Amsterdam, NL) was attached to the middle finger of the subjects' right hand to continuously record arterial blood pressure and heart rate. When this did not yield a good signal, the cuff was attached to another finger on the same hand. The cuff of an automatic sphygmomanometer (Accutorr, Datascope Corp, Montvale, NJ, USA) was attached to the subject's left upper arm. A surface ECG was obtained with a Marquette Case-12 electrocardiograph (Marquette Electronics Inc., Milwaukee, USA). Thoracic impedance was measured by two electrodes attached to the lateral sides of the lower part of the thorax to monitor subject's compliance with the metronome respiration protocol described below. An indicator for metronome respiration was visualized on a computer screen. The ECG, finger blood pressure and thoracic impedance signals were digitally stored (sampling rate 500 Hz, sample size 16 bits).

Study design

Recordings were performed in a quiet, air-conditioned room with a constant temperature of 20 °C. No individuals except the investigator were allowed to enter the room during measurements. Subjects were allowed a standardized small, fat-free breakfast at 8:00 am. Upon arrival at our department at 11:00 am, a tap water enema was given to empty the rectosigmoid area. Next, subjects were placed in a bed, which was in a 6° head-down position to abolish gravitational effects of the abdominal contents on the rectal balloon. The bag was inserted into the rectum and the catheter was connected to the barostat. Subsequently, ECG, Finapres and Accutorr devices were connected during a 30 min adaptation period. In this period, aortic and carotid baroreceptors could adjust to the supine blood pressure that was maintained throughout the entire recording period.

The experimental procedure is outlined in Figure 1. Each BRS measurement sequence consisted of a 5-min 15/min metronome respiration episode, preceded by three Accutorr blood pressure measurements to determine systolic blood pressure (SBP). Metronome respiration at 0.25 Hz prevents the direct mechanical component of respiration and the respiratory gating effect to enter the low-frequency band (0.04-0.15 Hz) in which we compute baroreflex sensitivity[27,28]. Subjects were asked not to speak during metronome respiration, but to report any discomfort. Free chosen tidal volume was permitted to assure comfortable breathing.

After a baseline BRS measurement procedure at 0 mmHg rectal pressure, a slow ramp distension (5-30 mmHg, 1 mmHg/min) was performed to measure rectal pain perception. This was done using a 10 cm Visual Analog Scale (VAS) anchored 'none' to 'unbearable' that was administered at every even pressure. Pain perception scores > 1 cm were considered significant. Perception measurements during the BRS mea-

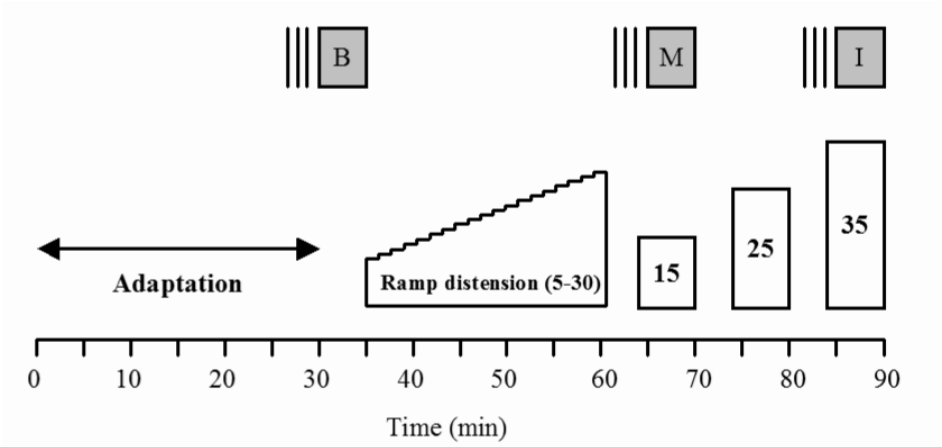

Figure 1. Study design. The three vertical lines next to shaded boxes denote the Accutorr systolic blood pressure measurements. Shaded boxes denote metronome respiration period for baroreflex sensitivity (BRS) assessment. B, baseline, M, mild rectal stimulation, I, intense rectal stimulation. Open boxes denote ramp distension (5-30 mmHg) or phasic rectal distensions of 15, 25 and 35 mmHg.

surement sequence were not feasible because of interference with metronome respiration. After balloon deflation, BRS measurement sequences were carried out during isobaric phasic distensions of 15 mmHg (mild, non-painful stimulus) and 35 mmHg (intense, mostly painful stimulus)[29]. Each distension lasted 6 min and was preceded by a 4-min period at 5 mmHg. Metronome respiration commenced one minute after each rectal distension onset. A 25 mmHg isobaric distension was performed in between the mild and strong stimuli to provide a gradual transition.

BRS signal analysis

To characterize arterial baroreflex function we computed baroreflex sensitivity (BRS), the reflex-induced increase/decrease of the interval between heart beats in milliseconds when arterial blood pressure rises/falls by 1 mm Hg. First, the longest arrhythmia free and stationary period in each metronome respiration episode was selected (sinus rhythm and a stationary signal are prerequisites for a reliable BRS value). Then, BRS was computed in the selected episode using the POLYAN software[30]. This algorithm calculates the transfer function between the systolic blood pressure variability (baroreflex input) and the interbeat interval variability (output), averaged over the 0.04-0.15 Hz band. BRS assessment was deemed impossible if this period was less than 90 seconds. Data selection and BRS computations were performed by two independent analysts.

The Accutorr arm cuff was not inflated during the BRS measurement procedures to avoid any possible interaction with the rectal distension stimulus. Instead, we calculated blood pressure during this period by computing the difference between the Finapres BP in the 3 min prior to the BRS measurement procedure and the Finapres

BP during the subsequent BRS measurement procedure. This difference was added to the Accutorr BP measured prior to the BRS assessment.

Statistical analysis

Linear mixed model analysis was used to detect overall differences in BRS, SBP and HR between IBS patients and controls (SPSS for Windows 11.0, Chicago IL, USA). Condition (baseline or rectal distension), group (IBS patients or controls), and condition by group interaction were analyzed as separate contributors. Subjects with missing data were not excluded from the analysis. Within-group changes from baseline in BRS, SBP, HR, and pain perception scores were analyzed using t statistics or Wilcoxon Signed Ranks Tests, and between-group differences were compared by t statistics or Mann-Whitney tests where appropriate. Data are expressed as mean ± SD in text and tables and, for clarity purposes, as mean ± SE in figures. The level of significance was set at $P \leq 0.05$.

RESULTS

Subject characteristics

We screened 130 patients, 26 of whom did not meet Rome II criteria, and 40 healthy volunteers. All 40 volunteers and 104 patients provided informed consent. From these, 17 patients and 4 control subjects were excluded from the analysis: 10 patients and 1 control subject used cardio-active or antihypertensive medication, 4 patients and 3 controls had cardiac arrhythmias and 1 patient had a pacemaker. Two more patients were excluded due to technical difficulties during the BRS measurements. Thus, 87 patients and 36 controls were included in the final analysis. Mean age and gender distribution were comparable in patients and controls (Table 1). Pain perception was significantly increased in patients from 8 mmHg onward, but in controls from 22 mmHg onward, indicating hypersensitivity to balloon distension in patients (Fig 2).

Baseline assessment

Opposite to what we expected, baseline BRS was higher in IBS patients compared to controls (7.9 ± 5.4 versus 5.7 ± 3.7 ms/mmHg, $P=0.03$) (Fig 3). Baseline SBP (Table 2) and HR (Table 3) were not significantly different between patients and controls.

Table 1. Baseline characteristics of IBS patients and healthy controls

	IBS (n=87)	Controls (n=36)
Age (yr)	40.0 ± 13	39.5 ± 15
Females	60 (69)	21 (58)
Bowel habit		
diarrhea	31 (36)	0
constipation	27 (31)	0
alternating	22 (25)	0
currently unknown	7 (8)	-
normal	-	36 (100)

Numbers within parentheses show percentages. IBS, irritable bowel syndrome; n, number of patients or controls.

BRS, blood pressure and heart rate during phasic rectal distension

BRS

Figure 3 shows mean BRS in patients and controls during baseline and 15 and 35 mmHg rectal distensions. The condition by group interaction was significant (P=0.01). BRS was not different between patients and controls during 15 mmHg (9.0 ± 5.7 versus 9.2 ± 6.4 ms/mmHg, respectively, P=0.68) and 35 mmHg distensions (7.3 ± 4.3 versus 7.9 ± 4.3 ms/mmHg, respectively, P=0.40). BRS was significantly increased in controls (P<0.0001) and in patients (P<0.05) during 15 mmHg, but only in controls (P=0.002) and not in patients (P=0.25) during 35 mmHg distensions.

Systolic blood pressure

Mixed model analysis showed that neither condition by group interaction nor the group factor was significant for systolic blood pressure (P=0.37 and P=0.41, respectively), indicating that the SBP response to rectal distensions was similar in patients and control subjects. In contrast, condition was significant (P<0.0001), indicating that blood pressure changed similarly in both groups. SBP was significantly increased in controls (P=0.002) with a similar trend in patients (P=0.08) during 15 mmHg distension, and in both groups during 35 mmHg distension (P<0.001) (Table 2).

Heart rate

HR condition by group interaction was not statistically significant (P=0.13), nor was group (P=0.07), but condition was significant (P<0.0001). Compared to baseline, HR decreased significantly in patients (P<0.0001) and controls (P=0.003) during 15 mmHg and increased significantly in patients (P<0.0001) and controls (P=0.05) during 35 mmHg distension (Table 3).

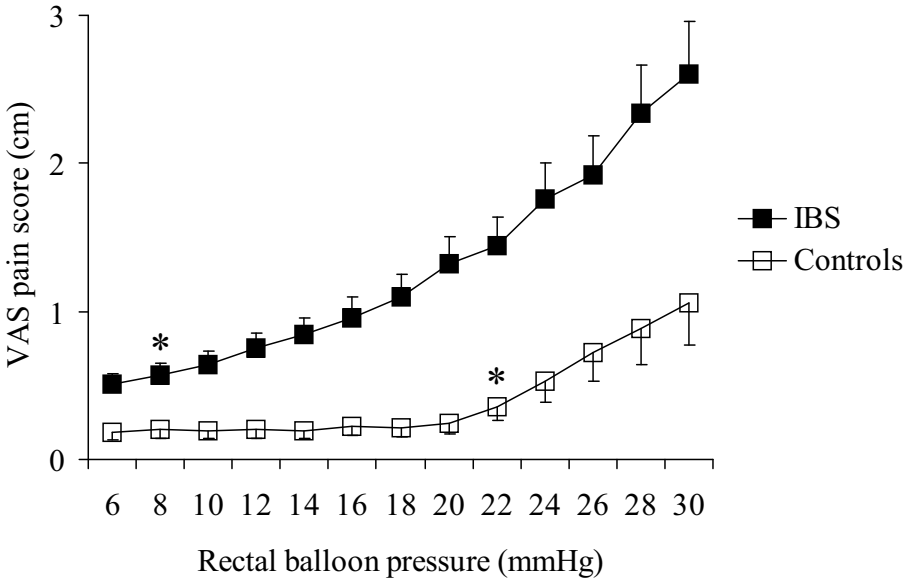

Figure 2. Pain perception during ramp distension. Visual Analog Scale (VAS, range 0-10) scores for rectal pain perception (mean ± SE) during the ramp distension procedure in IBS patients (closed squares) and healthy controls (open squares). Asterisks denote the first pressure at which the perception score was significantly increased compared to 6 mmHg ($P<0.05$), which was at 8 mmHg for IBS patients and at 22 mmHg for controls.

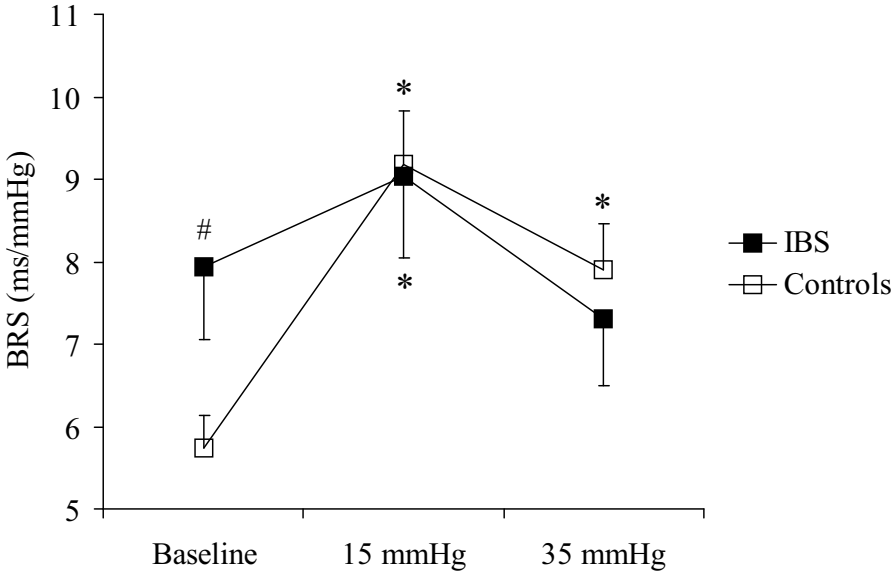

Figure 3. BRS (mean ± SE) at baseline and during mild (15 mmHg) and intense (35 mmHg) rectal stimulation in IBS patients (closed squares) and healthy controls (open squares). Baseline BRS was significantly larger in patients compared to controls (#, $P=0.025$). * significant increase from baseline ($P<0.05$).

Table 2. Mean systolic blood pressure at baseline and during mild and intense rectal stimulation in IBS patients and healthy controls

	baseline	15 mmHg	P-value*	35 mmHg	P-value†
IBS (n=87)	120.7± 14.8	122.5 ± 17.7	0.08	130.6 ± 13.6	<0.001
Controls (n=36)	116.4 ± 12.7	121.6 ± 12.8	0.002	129.5 ± 14.5	<0.001
P-value‡	0.23	0.91		0.90	

Data are expressed as mean ± SD. * 15 mmHg versus baseline; † 35 mmHg versus baseline; ‡ IBS patients versus control subjects.

DISCUSSION

Our study demonstrates that stimulation of visceral afferents by a standardized stimulus, *i.e.,* pressure-driven rectal balloon distension, produces significant changes in systolic blood pressure and heart rate in healthy subjects and in patients with IBS. Moreover, this stimulus increases baroreflex sensitivity in healthy individuals and in IBS patients. In addition, resting BRS is significantly larger in IBS patients compared to healthy subjects.

Physiologic mechanisms underlying the cardiovascular response to rectal distension

Heart rate and blood pressure

Several studies have reported that stimulation of visceral afferents produces cardiovascular responses, notably in blood pressure and heart rate. Yet, the results are contradictory, which may be caused by widely varying experimental designs. For instance, abdominal vagal nerve stimulation in anesthetized rats did not alter blood pressure and heart rate[18]. Azpiroz and colleagues reported that neither jejunal balloon distension below the perception threshold, nor distension at the discomfort threshold or above affected heart rate in healthy volunteers (blood pressure data were not reported)[31]. Cardiovascular responses to colorectal distension were measured in rats[32] and in humans[33]. In awake rats, blood pressure and heart rate increased during colorectal distension in a dose-dependent manner[32]. In healthy volunteers, a similar graded response was observed in blood pressure (heart rate was not reported)[33].

Table 3. Mean heart rate at baseline and during mild and intense rectal stimulation in IBS patients and healthy controls

	baseline	15 mmHg	P-value*	35 mmHg	P-value†
IBS (n=87)	67.1 ± 10.1	64.0 ± 9.6	<0.001	72.0 ± 14.7	<0.001
Controls (n=36)	64.2 ± 9.3	61.4 ± 8.9	0.003	66.5 ± 12.0	0.05
P-value‡	0.14	0.33		0.07	

Data are expressed as mean ± SD. * 15 mmHg versus baseline; † 35 mmHg versus baseline; ‡ IBS patients versus control subjects.

Our findings are consistent with a graded hypertensive response in healthy individuals and in IBS patients. The response in heart rate was, however, biphasic in both groups: heart rate decreased during mild rectal distension (15 mmHg) but increased during more intense stimulation (35 mmHg).

Most likely, the primary autonomic response to the stimulus we applied is sympathetic activation. This hypothesis is supported by the consistent blood pressure increases as demonstrated in this study and by others[32,33]. The hypertension-associated baroreceptor loading reflexly reduces the increase in sympathetic outflow (thereby reducing the original blood pressure rise and tachycardic response) while enhancing vagal outflow (which lowers heart rate, but not peripheral vascular resistance and thereby blood pressure). Thus, a mild hypertensive stressor may leave heart rate unaffected or even cause a slight decrease. Thus far, heart rate decreases have been reported during mental stress[34,35]. To our knowledge, we are the first to demonstrate this phenomenon during viscerosensory stimulation.

In contrast, a high blood pressure increase (e.g. during 35 mmHg distension) will be counteracted by the baroreflex to a lesser degree as the baroreceptor firing characteristic is S-shaped[36]. Consequently, the significant baroreceptor loading during high pressure rectal distension will lead to less reduction of the increase in sympathetic tone and less stimulation of parasympathetic outflow. This may explain our finding that during high rectal distension pressure, not only blood pressure but also heart rate increased.

Individual heart rate responses differed in sign and magnitude. Approximately 80% of our study population (IBS patients plus control group) exhibited a heart rate decrease during mild stimulation. Six percent (5/87 patients and 2/36 controls) had a heart rate decrease of more than 10 bpm and in one subject in the IBS group, heart rate lowered by 12 bpm from 62 to 50 bpm. On intake, this patient had reported defecation syncope on several occasions. It has been long hypothesized that straining during defecation (Valsalva maneuver) plays a dominant role in this form of fainting. However, recently, syncope was recorded during colonic air insufflation in a patient with recurrent defecation syncope that was not specifically associated with straining. A cardiac pacemaker resolved these symptoms completely[37]. It is hence conceivable that the colorectal-cardiovascular reflex response to mild distension as measured in our study provides an alternative clue to the mechanism that underlies this form of syncope.

Baroreflex sensitivity

We measured an increase in baroreflex sensitivity under mild rectal distension in healthy subjects and in IBS patients. During intense stimulation, the BRS increase compared to baseline persisted in healthy controls, albeit to a lesser extent, whereas

BRS returned to baseline in patients. These findings are opposed to our original hypothesis that BRS would lower under stress. This expectation was based on a study in rats, showing that sympathetic output increased and baroreflex sensitivity decreased following stimulation of general gastric afferents[18]. Several incompatibilities may account for this difference. First, anesthetized rats were used[18], while our study subjects were not sedated. Thus, cortical perception (stimulus awareness) may have played a role in the BRS increase we observed. In addition, it has been shown that anesthetic agents as used in the rat study considerably depress the arterial baroreflex[38]. Second, the insertion of catheters into the femoral artery and vein may additionally have influenced the autonomic conditions[39] in the rat experiment. Third, it cannot be ruled out that the spinal afferent viscerosensory input caused by the rectal distensions in our study is processed differently at the level of the brainstem from the cranial nerve (vagal) afferent input in the rat study.

The mechanism responsible for the BRS increase can only be speculated upon. Possibly, projections of the viscerosensory afferents ending at the NTS produce a neurotransmitter that directly enhances the baroreflex gain. Substance P, which is known to enhance the baroreflex by modulating the transmission from the baroreceptive afferents to the NTS neurons, would be a candidate neurotransmitter to achieve this effect[10,40]. Substance P production at the level of the NTS has been demonstrated for somatosensory afferents[20], while a high density of substance-P-containing fibers originating from the gastrointestinal tract have also been found in the pigeon NTS[41]. Alternatively, enhanced parasympathetic tone as a reflex response to rectal stimulation may have enhanced BRS by facilitating deeper modulation of the parasympathetic outflow, *i.e.* allowing increased heart rate fluctuation, rather than by increasing baroreflex gain.

Differences between IBS patients and healthy control subjects

Baseline supine heart rate and blood pressure were not significantly different between IBS patients and controls, although patients tended to have slightly higher values (Tables 2 and 3). The non-significant trend (P=0.14) to higher supine baseline HR values in IBS patients we observed was also reported by several other groups[9,42-46]. HR was similar during mild distension in patients and controls (P=0.33), but again tended to be higher in IBS patients during intense rectal distension (P=0.07). Few published numerical data are available regarding baseline blood pressure differences between IBS patients and healthy controls. Levine et al. found that baseline systolic blood pressure was significantly higher in patients[45].

The most striking difference between IBS patients and healthy control subjects was the 39% elevated BRS-value in patients (7.9 ± 5.4 versus 5.7 ± 3.7 ms/mmHg, P=0.03). This difference no longer existed during mild and intense rectal distension.

The marked elevated baseline BRS in IBS patients may provide an explanation for autonomic alterations reported in patients[10,47,48]. The baroreflex plays a key role in the generation of heart rate variability as it transfers respiration induced blood pressure variability into fluctuations in sympathetic and parasympathetic outflow, eventually leading to modulation of the discharge rate of the cardiac pacemaker[28]. Differences in heart rate variability (HRV) and HRV-derived assessments of the sympathovagal balance[49,50] as reported by several research groups[10,47,48] might therefore at least partly be explained by differences in baroreflex function.

Our study does not provide information on the basis of which the elevated baseline BRS value in IBS patients and its functional role in IBS can be explained. We speculate that the frequently experienced viscerosensory stimuli, *e.g.*, abdominal pain, entail a training-effect, possibly materialized in chronic elevated substance P concentrations at the NTS level[20,40,41,51]. Such a training-mechanism can only be further investigated in animal models of visceral afferent stimulation. Alternatively, the elevated baseline BRS value may reflect an intrinsic autonomic characteristic in which IBS patients differ from healthy individuals. Altered baroreflex function could witness altered information processing at the NTS level. For the esophagus, a vago-vagal reflex from/to the gastrointestinal tract (GI-GI reflex pathway) has been demonstrated involving the NTS as well as the NA[52]. In analogy, spino-spinal GI-GI sensorimotor reflex pathways, although not identified yet, may be involved in reflexes regarding the distal gut.

It is tempting to interpret the enhanced baseline baroreflex vigor as an anticipatory phenomenon and to expect benefits from that anticipation in the form of inhibition of cortical arousal[19,25] and visceral pain perception[18] during irritating stimuli such as abdominal pain. However, our finding that no differences in BRS values exist between IBS patients and control subjects during rectal distension renders such a hypothesis unlikely.

A limitation of our study was that we did not measure rectal perception during the applied rectal stimuli (phasic distensions), as this was not feasible due to the imposed metronome respiration. It may, however, be inferred from the pain scores during ramp distension (Fig 2) that pain perception was increased in IBS patients compared to controls. Furthermore, the lack of baseline values in the patient group prior to disease onset should be appreciated when interpreting our results. Finally, although we controlled for age and gender in this study, which have been shown to be strong determinants of spontaneous baroreflex sensitivity, there are other variables that may also affect baseline BRS[53].

Conclusions

In summary, our study provides evidence for the existence for a colorectal-cardiovascular reflex, characterized by a blood pressure increase, slight heart rate decrease, and an increase of baroreflex sensitivity during mild stimuli. Intense stimuli increase heart rate and blood pressure, while baroreflex sensitivity seems to be impaired compared to mild stimulation. This reflex, that was evident in normals as well as in IBS patients, might well be involved in defecation syncope.

Our study also provides evidence for baroreflex involvement in irritable bowel syndrome, as IBS patients have a higher baseline BRS-value than healthy controls. This finding renders the hypothesis unlikely that IBS patients are hypersensitive due to diminished baroflex function. We provide two possible explanations for the higher baseline BRS in IBS: 1) a "training-effect" (frequent challenging of the reflex by IBS-associated abdominal discomfort); 2) altered information processing at the NTS that causes BRS increases and, in parallel, abnormal GI-GI sensorimotor reflexes. While the first explanation considers the autonomic changes as a consequence of IBS, the second one recognizes a role for the autonomic nervous system in the pathophysiology of IBS and explains both altered HRV and changes in gastrointestinal motility as observed in this condition[54]. The latter hypothesis requires further corroboration.

ACKNOWLEDGEMENTS

We thank our colleagues at the research unit of the Department of Gastroenterology and Hepatology of the Leiden University Medical Center for their assistance in performing the measurements.

REFERENCES

1. Boekema PJ, van Dam van Isselt EF, Bots ML, Smout AJ. Functional bowel symptoms in a general Dutch population and associations with common stimulants. Neth J Med 2001;59:23-30.
2. Jones R, Lydeard S. Irritable bowel syndrome in the general population. BMJ 1992;304:87-90.
3. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. Gut 1999;45(2):II43-7.
4. Mayer EA, Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. Gastroenterology 1994;107:271-93.
5. Chadwick VS, Chen W, Shu D, Paulus B, Bethwaite P, Tie A, Wilson I. Activation of the mucosal immune system in irritable bowel syndrome. Gastroenterology 2002;122:1778-83.
6. Spiller RC, Jenkins D, Thornley JP, Hebden JM, Wright T, Skinner M, Neal KR. Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute campylobacter enteritis and in post-dysenteric irritable bowel syndrome. Gut 2000;47:804-11.
7. Lembo T, Munakata J, Mertz H, Niazi N, Kodner A, Nikas V, Mayer EA. Evidence for the hypersensitivity of lumbar splanchnic afferents in irritable bowel syndrome. Gastroenterology 1994;107:1686-96.
8. Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology 1995;109:40-52.
9. Karling P, Nyhlin H, Wiklund U, Sjoberg M, Olofsson BO, Bjerie P. Spectral analysis of heart rate variability in patients with irritable bowel syndrome. Scand J Gastroenterol 1998;33:572-6.
10. Orr WC, Elsenbruch S, Harnish MJ. Autonomic regulation of cardiac function during sleep in patients with irritable bowel syndrome. Am J Gastroenterol 2000;95:2865-71.
11. Bassotti G, Sietchiping-Nzepa F, De Roberto G, Chistolini F, Morelli A. Colonic regular contractile frequency patterns in irritable bowel syndrome: the 'spastic colon' revisited. Eur J Gastroenterol Hepatol 2004:16:613-7.
12. Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. Gastroenterology 1987;92:1885-93.
13. Tache Y, Stephens RL Jr, Ishikawa T. Central nervous system action of TRH to influence gastrointestinal function and ulceration. Ann N Y Acad Sci 1989;553:269-85.
14. Altschuler SM, Bao XM, Bieger D, Hopkins DA, Miselis RR. Viscerotopic representation of the upper alimentary tract in the rat: sensory ganglia and nuclei of the solitary and spinal trigeminal tracts. J Comp Neurol 1989;283:248-68.
15. Ciriello J. Brainstem projections of aortic baroreceptor afferent fibers in the rat. Neursci Lett 1983;36:37-42.
16. Monnikes H, Ruter J, Konig M, Grote C, Kobelt P, Klapp BF, Arnold R, Wiedenmann B, Tebbe JJ. Differential induction of c-fos expression in brain nuclei by noxious and non-noxious colonic distension: role of afferent C-fibers and 5-HT3 receptors. Brain Res 2003;966:253-64.
17. Saper CB. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. Annu Rev Neurosci 2002;25:433-69.
18. Saleh TM, Connell BJ, Allen GV. Visceral afferent activation-induced changes in sympathetic nerve activity and baroreflex sensitivity. Am J Physiol 1999;276:R1780-91.
19. Mini A, Rau H, Montoya P, Palomba D, Birbaumer N. Baroreceptor cortical effects, emotions and pain. Int J Psychophysiol 1995;19:67-77.
20. Potts JT. Neural circuits controlling cardiorespiratory responses: baroreceptor and somatic afferents in the nucleus tractus solitaries. Clin Exp Pharmacol Physiol 2002;29:103-11.
21. Dworkin BR, Elbert T, Rau H, Birbaumer N, Pauli P, Droste C, Brunia CH. Central effects of baroreceptor activation in humans: attenuation of skeletal reflexes and pain perception. Proc Natl Acad Sci USA 1994;91:6329-33.

22. Lefrandt JD, Hoogenberg K, van Roon AM, Dullaart RP, Gans RO, Smit AJ. Baroreflex sensitivity is depressed in microalbuminuric Type I diabetic patients at rest and during sympathetic manoeuvres. Diabetologia 1999;42:1345-49.
23. Szili-Torok T, Kalman J, Paprika D, Dibo G, Rozsa Z, Rudas L. Depressed baroreflex sensitivity in patients with Alzheimer's and Parkinson's disease. Neurobiol Aging 2001;22:435-38.
24. Toniyama O, Shiigai T, Ideura T, Tomita K, Mito Y, Shinohara S, Takeuchi J. Baroreflex sensitivity in renal failure. Clin Sci (Lond) 1980;58:21-7.
25. Rau H, Pauli P, Brody S, Elbert T, Birbaumer N. Baroreceptor stimulation alters cortical activity. Psychophsyiology 1993;30:322-5.
26. Azpiroz F, Malagelada JR. Gastric tone measured by an electronic barostat in health and postsurgical gastroparesis. Gastroenterology 1987;92:934-43.
27. Eckberg DL. The human respiratory gate. J Physiol 2003;548:339-52.
28. Frederiks J, Swenne CA, TenVoorde BJ, Honzikova N, Levert JV, Maan AC, Schalij MJ, Bruschke AV. The importance of high-frequency paced breathing in spectral baroreflex sensitivity assessment. J Hypertens 2000;18:1635-44.
29. Bouin M, Plourde V, Boivin M, Riberdy M, Lupien F, Laganiere M, Verrier P, Poitras P. Rectal distention testing in patients with irritable bowel syndrome: Sensitivity, specificity, and predictive values of pain sensory thresholds. Gastroenterology 2002;122:1771-7.
30. Maestri R, Pinna GD. POLYAN: a computer program for polyparametric analysis of cardiorespiratory variability signals. Comput Methods Programs Biomed 1998;56:37-48.
31. Azpiroz F, Malagelada JR. Isobaric intestinal distension in humans: sensorial relay and reflex gastric relaxation. Am J Physiol 1990;258:G202-7.
32. Ness TJ, Gebhart GF. Colorectal distension as a noxious visceral stimulus: physiologic and pharmacologic characterization of pseudoaffective reflexes in the rat. Brain Res 1988;450:153-69.
33. Ness TJ, Metcalf AM, Gebhart GF. A psychophysiological study in humans using phasic colonic distension as a noxious visceral stimulus. Pain 1990;43:377-86.
34. McCanne TR, Lyons GM. Decelerative changes in heart rate are associated with performance on tasks that assess intelligence. Int J Psychophysiol 1990;8:235-48.
35. Swenne CA, Bootsma M, Van Bolhuis HH. Different autonomic responses to orthostatic and to mental stress in young normals. Homeostasis 1995;36:287-92.
36. Eckberg DL. Nonlinearities of the human carotid baroreceptor-cardiac reflex. Circ Res 1980;47:208-16.
37. Newton JL, Allan L, Baptist M, Kenny R. Defecation syncope associated with splanchnic sympathetic dysfunction and cured by permanent pacemaker insertion. Am J Gastroenterol 2001;96:2276-8.
38. Zatman ML, Thornhill GV .Effects of anesthetics on cardiovascular responses of the marmot Marmota flaviventris. Cryobiology 1988;25:212-26.
39. Bootsma M, Swenne CA, Lenders JW, Jacobs MC, Bruschke AV. Intravenous instrumentation alters the autonomic state in humans. Eur J Appl Physiol Occup Physiol 1996;73:113-6.
40. Martini F, Reynaud JC, Puizillout JJ. Effects of substance P on cardiovascular regulation in the rabbit. J Auton Nerv Syst 1995;51:143-52.
41. Berk ML, Smith SE, Karten HJ. Nucleus of the solitary tract and dorsal motor nucleus of the vagus nerve of the pigeon: localization of peptide and 5-hydroxytryptamine immunoreactive fibers. J Comp Neurol 1993;338:521-48.
42. Adeyemi EO, Desal KD, Towsey M, Ghista D. Characterization of autonomic dysfunction in patients with irritable bowel syndrome by means of heart rate variability studies. Am J Gastroenterol 1999;94:816-23.
43. Elsenbruch S, Lovallo WR, Orr WC. Psychological and physiological responses to postprandial mental stress in women with the irritable bowel syndrome. Psychosom Med 2001;63:805-13.

44. Elsenbruch S, Orr WC. Diarrhea- and constipation predominant IBS patients differ in postprandial autonomic and cortisol responses. Am J Gastroenterol 2001;96:460-6.
45. Levine BS, Jarrett M, Cain KC, Heitkemper MM. Psychophysiological response to a laboratory challenge in women with and without diagnosed irritable bowel syndrome. Res Nurs Health 1997;20:431-41.
46. Posserud I, Agerforz P, Ekman R, Bjornsson ES, Abrahamsson H, Simren M. Altered visceral perceptual and neuroendocrine response in patients with irritable bowel syndrome during mental stress. Gut 2004;53:1102-8.
47. Heitkemper MM, Burr RL, Jarrett M, Hertig V, Lustyk MK, Bond EF. Evidence for autonomic nervous system imbalance in women with irritable bowel syndrome. Dig Dis Sci 1998;43:2093-8.
48. Heitkemper MM, Jarrett M, Cain KC, Burr RL, Levy RL, Feld A, Hertig V. Autonomic nervous system function in women with irritable bowel syndrome. Dig Dis Sci 2001;46:1276-84.
49. Bootsma M, Swenne CA, Janssen MJ, Manger Cats V, Schalij MJ. Heart rate variability and sympathovagal balance: pharmacological validation. Neth Heart J 2003:250-9.
50. Eckberg DL. Sympathovagal balance: a critical appraisal. Circulation 1997;96:3224-32.
51. Petty MA, Reid JL. Opiate analogs, substance P, and baroreceptor reflexes in the rabbit. Hypertension 1981;3:I142-7.
52. Lu WY, Bieger D. Vagovagal reflex motility patterns of the rat esophagus. Am J Physiol 1998;274:R1425-35.
53. Kardos A, Watterich G, de Menezes R, Csanady M, Casadei B, Rudas L. Determinants of spontaneous baroreflex sensitivity in a healthy working population. Hypertension 2001;37:911-6.
54. Mach T. The brain-gut axis in irritable bowel syndrome-clinical aspects. Med Sci Monit 2004;10:RA125-31.