Viscerosensory-cardiovascular reflexes: altered baroreflex sensitivity in irritable bowel syndrome

Patrick P. J. van der Veek, Cees A. Swenne, Hedde van de Vooren, Annelies L. Schoneveld, Roberto Maestri, and Ad A. M. Masclee

Viscerosensory-cardiovascular reflexes: altered baroreflex sensitivity in irritable bowel syndrome. Am J Physiol Integr Comp Physiol 289: R970–R976, 2005. First published May 26, 2005; doi:10.1152/ajpregu.00607.2004.—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. Systolic 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. 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 intense stimulation. BRS was significantly higher in patients compared with 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. 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 tractus solitarii.

autonomic nervous system; colonic diseases; functional; blood pressure; heart rate; baroreflex

IRRITABLE BOWEL SYNDROME (IBS) is a frequently occurring functional disorder with a prevalence ranging from ~6 to 22% (7, 22). 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 (52).

Address for reprint requests and other correspondence: Cees A. Swenne, PhD, Dept. of Cardiology, Leiden Univ. Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands (e-mail: c.a.swenne@lumc.nl)

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
ulates sympathetic and parasympathetic autonomic outflow, but also affects cortical arousal (36, 44) and somatic (13, 36) and visceral (46) pain perception.

Thus far, no human studies have addressed BRS involvement in IBS. As, in general, BRS is reduced in disease (26, 50, 53), we expected that baseline BRS is depressed in IBS patients. Furthermore, we anticipated an exaggerated BRS reduction during gastrointestinal stress in IBS patients compared with healthy controls (45). Both assumptions would explain at least part of the previously observed abnormal activity of the autonomic nervous system (i.e., increased sympathetic predominance) and the increased visceral pain perception in IBS patients. The following study was done to corroborate this hypothesis.

METHODS

The ethics committee of the Leiden University Medical Center 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 (P. van der Wee). 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 cardiovascular or antihypertensive drugs were excluded. Other medications such as antispasmodics, laxatives, bulking agents, and occasional use of analgesics were permitted. All included patients met the Rome II criteria for IBS (52). 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, that is, 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 1,000 ml) tied to the end of a multilumen tube (19-fr) by injecting air when the bag is 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 Fig. 1. Each BRS measurement sequence consisted of a 5- to 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 (16, 19). Subjects were asked not to speak during metronome respiration, but to report any discomfort. Freely 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 anchored “none” to “unbearable” that was administered at every even pressure value (6, 8, 10,..., 30 mmHg). Pain perception scores >1 cm were considered significant. Perception measurements during the BRS measurement 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, nonpainful stimulus) and 35 mmHg (intense, mostly painful stimulus) (10). Each distension lasted 6 min and was preceded by a 4-min period at 5 mmHg. Metronome respiration commenced 1 min 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 Instrumentation

The finger cuff of a noninvasive blood pressure measurement device (Finapres, TNO, Amsterdam, The Netherlands) was attached to the middle finger of the subject’s right hand to continuously record arterial blood pressure and heart rate (HR). 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, Datascop, Montvale, NJ) was attached to the subject’s left upper arm. A surface ECG was obtained with a Marquette Case-12 electrocardiograph (Marquette Electronics, Milwaukee, WI). Thoracic impedance was measured by two electrodes attached to the lateral sides of the lower part of the thorax to monitor the subject’s compliance with 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).

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 mmHg. 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
Table 1. Baseline characteristics of IBS patients and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>IBS (n = 87)</th>
<th>Controls (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>40.0±13</td>
<td>39.5±15</td>
</tr>
<tr>
<td>Females</td>
<td>60 (69)</td>
<td>21 (58)</td>
</tr>
<tr>
<td>Bowel habit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31 (36)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>27 (31)</td>
<td>0</td>
</tr>
<tr>
<td>Alternating</td>
<td>22 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Currently unknown</td>
<td>7 (8)</td>
<td>–</td>
</tr>
<tr>
<td>Normal</td>
<td>–</td>
<td>36 (100)</td>
</tr>
</tbody>
</table>

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

BRS value. Then, BRS was computed in the selected episode using the POLYAN software (31). 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 s. 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 SBP in the 3 min before the BRS measurement procedure and the Finapres SBP during the subsequent BRS measurement procedure. This difference was added to the Accutorr SBP measured before 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). 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, and pain perception scores were analyzed as separate contributors. Subjects with missing data 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 with controls (7.9 ± 5.4 vs. 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.

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 vs. 9.2 ± 6.4 ms/mmHg, respectively, P = 0.68) and 35-mmHg distensions (7.3 ± 4.3 vs. 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)
Table 2. Mean systolic blood pressure at baseline and during mild and intense rectal stimulation in IBS patients and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>15 mmHg</th>
<th>P Value*</th>
<th>35 mmHg</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS patients (n = 87)</td>
<td>120.7±14.8</td>
<td>122.5±17.7</td>
<td>0.08</td>
<td>130.6±13.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Controls (n = 36)</td>
<td>116.4±12.7</td>
<td>121.6±12.8</td>
<td>0.002</td>
<td>129.5±14.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P value‡</td>
<td>0.23</td>
<td>0.91</td>
<td></td>
<td>0.90</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>15 mmHg</th>
<th>P Value*</th>
<th>35 mmHg</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS patients (n = 87)</td>
<td>67.1±10.1</td>
<td>64.0±9.6</td>
<td>&lt;0.001</td>
<td>72.0±14.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Controls (n = 36)</td>
<td>64.2±9.3</td>
<td>61.4±8.9</td>
<td>0.003</td>
<td>66.5±12.0</td>
<td>0.05</td>
</tr>
<tr>
<td>P value‡</td>
<td>0.14</td>
<td>0.33</td>
<td></td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

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

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 distension was similar in patients and control subjects. In contrast, the 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 with 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).

**DISCUSSION**

Our study demonstrates that stimulation of visceral afferents by a standardized stimulus, that is, 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 with 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 (46). Azpiroz and Malagelada (4) 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). Cardiovascular responses to colorectal distension were measured in rats (38) and in humans (39). In awake rats, blood pressure and heart rate increased during colorectal distension in a dose-dependent manner (38). In healthy volunteers, a similar graded response was observed in blood pressure (heart rate was not reported) (39). 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 that we applied is sympathetic activation. This hypothesis is supported by the consistent blood pressure increases as demonstrated in this study and by others (38, 39). The hypertension-associated baroreceptor loading reflexively 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, 49). To our knowledge, we are the first to demonstrate this phenomenon during visceral sensory 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 (14). 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, syncpe was recorded during colonic air insufflation in a patient with recurrent defecation syncpe that was not specifically associated with straining. A cardiac pacemaker resolved these symptoms completely (40). Hence, it is 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 with 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 be lower under stress. This expectation was based on a study in rats, showing that sympathetic output increased and baroreflex sensitivity decreased after stimulation of general gastric afferents (46). Several incompatibilities may account for this difference. First, anesthetized rats were used (46), while our study subjects were not sedated. Thus cortical perception (stimulus awareness) may have played a role in the BRS increase that we observed. In addition, it has been shown that the anesthetic agents used in the rat study considerably depress the arterial baroreflex (54). Second, the insertion of catheters into the femoral artery and vein may additionally have influenced the autonomic conditions (9) 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 surmised. 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 (32, 41). Substance P production at the level of the NTS has been demonstrated for somatosensory afferents (44), while a high density of substance P-containing fibers originating from the gastrointestinal tract have also been found in the pigeon NTS (6). Alternatively, enhanced parasympathetic tone as a reflex response to rectal stimulation may have enhanced BRS by facilitating deeper modulation of the parasympathetic outflow, that is, 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 nonsignificant trend \((P = 0.14)\) to higher supine baseline HR values in IBS patients that we observed was also reported by several other groups \((1, 17, 18, 24, 28, 43)\). 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. (28) found that baseline systolic blood pressure was significantly higher in patients.

The most striking difference between IBS patients and healthy control subjects was the 39% elevated BRS-value in patients \((7.9 \pm 5.4 \text{ vs. } 5.7 \pm 3.7 \text{ ms/mmHg}, P = 0.03)\). 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 \((20, 21, 41)\). 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 (19). Differences in HRV and HRV-derived assessments of the sympathovagal balance \((8, 15)\), as reported by several research groups \((20, 21, 41)\), might therefore, at least partly, be explained by differences in baroreflex function.

Our study does not provide information on the basis for 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 \((6, 32, 42, 44)\). 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 vagovagal reflex from/to the gastrointestinal tract (GI-GI reflex pathway) has been demonstrated involving the NTS, as well as the NA \((29)\). In analogy, spinospinal 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 \((36, 45)\) and visceral pain perception \((46)\) 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), because 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 with controls. Furthermore, the lack of baseline values in the patient group before 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 \((23)\).

In summary, our study provides evidence for the existence of 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 in-
crease heart rate and blood pressure, while baroreflex sensitivity seems to be impaired compared with mild stimulation. This reflex, which was evident in controls, as well as in IBS patients, might well be involved in defecation syncope.

Our study also provides evidence for baroreflex involvement in IBS, 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 baroreflex 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. Although 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 (30). The latter hypothesis requires further corroboration.

ACKNOWLEDGMENTS

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.

GRANTS

This study was supported by a grant from the Dutch Digestive Diseases Foundation (Maag Lever Darm Stichting). The Dutch Digestive Diseases Foundation was not involved in the development of the study design; the collection, analysis or interpretation of data; writing the report; or the decision to submit the paper for publication in any way. All investigators are independent from the Dutch Digestive Diseases Foundation.

REFERENCES


by 10.220.32.247 on July 5, 2017 http://ajpregu.physiology.org/ Downloaded from


