Ischemic Hypersensitivity in Irritable Bowel Syndrome Patients

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Abstract

Objective. Mixed evidence exists regarding whether irritable bowel syndrome (IBS) patients show increased somatic pain perception compared with controls. The current study used a deep, tonic somatic pain stimulus (ischemic pain) to evaluate somatic hypersensitivity in IBS patients.

Methods. A total of 27 diarrhea-predominant and 15 constipation-predominant IBS patients, and 29 controls participated in the study. The modified sub-maximal effort tourniquet procedure was performed to induce ischemic arm pain, and the time required to reach pain threshold and pain tolerance were recorded in seconds. All subjects completed the Functional Bowel Disease Severity Index (FBDSI) scale as well as several psychosocial instruments. Group differences for threshold and tolerance were determined using a series of one-way ANOVA tests followed by Tukey comparisons.

Results. IBS patients had a shorter time to ischemic threshold ($F = 34.606, P < 0.001$) and tolerance ($F = 38.656, P < 0.001$) compared with controls; however, the groups did not differ on ratings of pain at the time of tolerance. IBS patients had a higher rating on the FBDSI scale compared with controls ($P < 0.001$), and ischemic pain threshold was negatively correlated with the FBDSI score.

Conclusions. The results of this study suggest that a widespread alteration in central pain processing in IBS patients may be present as they display hypersensitivity to ischemic arm pain, and ischemic pain threshold was associated with clinical symptoms. These findings could reflect a dysfunction in inhibitory pain systems in IBS patients, as ischemic (deep) pain may be under tonic inhibitory control.

Key Words. Irritable Bowel Syndrome (IBS); Ischemic Pain; Somatic Pain; Visceral Hypersensitivity; Somatic Hypersensitivity; Thermal Hypersensitivity

Introduction

Irritable bowel syndrome (IBS) represents one of the most common functional gastrointestinal (GI) disorders, with prevalence estimates indicating that approximately 10–20% of the general population is affected [1,2]. Despite the fact that only a minority of sufferers seeks treatment, IBS represents the most frequent complaint among patients visiting a gastroenterologist and is among the most common conditions seen in the primary care setting [3]. The primary symptom of IBS is recurrent abdominal pain associated with altered bowel habits, including changes in stool frequency and form as well as abdominal bloating [4]. While the pathophysiology of IBS is unclear, some IBS patients exhibit increased sensitivity to visceral stimuli, such as rectal distention [5–7]. This visceral hypersensitivity may help explain the clinical symptoms of IBS, such as abdominal pain, urgency, and bloating.

IBS is also frequently associated with extra-intestinal symptoms, including headache and musculoskeletal pain, fatigue, urinary symptoms, and dizziness [2,8]. Moreover, somatic conditions, such as fibromyalgia (FM), temporo-mandibular disorder, migraine headache, and chronic fatigue syndrome show high rates of comorbidity with IBS [2,8]. These clinical findings are consistent with the hypothesis that a subset of IBS patients may have heightened somatic pain sensitivity. However, there is contradictory evidence regarding somatic hypersensitivity in this population. For example, two groups of investigators reported reduced sensitivity to painful electrocutaneous stimuli among IBS patients compared with healthy controls [9,10]. Several studies have examined responses to cold pain, with some finding similar cold-pain tolerance in IBS patients vs controls [11,12], while others have reported lower cold-pain thresholds and tolerance in IBS patients [13,14]. Moreover, our recent studies using hot-water immersion of the foot have shown somatic hypersensitivity associated with IBS [7,15,16], and we recently...
demonstrated lower pain thresholds and tolerances for contact heat applied to the extremities among IBS patients vs healthy controls [17]. These inconsistent results regarding somatic sensitivity in IBS may derive from the varying modalities of painful stimuli employed. One criticism of these previous stimulation procedures is that they evoke pain primarily by activating cutaneous nociceptors [17,18], and such superficial stimuli may be less relevant to a painful condition such as IBS, which is characterized by deep, visceral pain.

In order to address this concern, we undertook a study to examine somatic pain sensitivity among patients with IBS using the submaximal effort tourniquet procedure, a stimulus that evokes deep, tonic, ischemic muscle pain [19–21]. In addition to its ability to produce deep pain, this procedure may be particularly appropriate for investigating somatic hypersensitivity in IBS for several reasons. First, increased ischemic pain sensitivity has been reported among patients with temporomandibular disorders (TMD) [22,23], FM [24], and interstitial cystitis [25], three pain conditions that show high rates of comorbidity with IBS. Second, it has been previously related to clinical pain severity in patients with TMD, in contrast to cutaneous thermal pain, which was not associated with clinical symptoms [21]. Finally, ischemic pain responses are more sensitive to modulation by endogenous opioids [26–28] and therefore may more readily reveal somatic hypersensitivity that results from deficiencies in endogenous pain inhibition, as have been suggested in IBS patients [29].

To evaluate sensitivity to a deep somatic pain stimulus in individuals with IBS, we compared ischemic pain responses in persons meeting criteria for IBS with those of healthy subjects. Moreover, previous case-control studies have compared primarily patient populations recruited from clinical settings to control subjects obtained via community-based recruitment methods. In order to avoid this potential sampling bias, we recruited both IBS and control participants from the community using posted advertisements. The aims of this study were 1) to determine whether individuals with IBS show increased sensitivity to experimental ischemic pain stimuli relative to controls; 2) to determine whether ischemic pain responses are associated with clinical symptoms among participants with IBS; and 3) to determine whether psychological factors account for any differences in ischemic pain responses between individuals with IBS and healthy controls.

Methods

Samples

The 71 subjects in this study were (52 female and 19 male participants) recruited from the community, and descriptive information is provided in Table 1. There was no difference in age, sex, or race/ethnicity between the groups (controls, diarrhea-predominant IBS [D-IBS], constipation-predominant IBS [C-IBS]). None of the control subjects had any evidence of acute or chronic somatic/abdominal pain or IBS based on a questionnaire and complete physical exam by an experienced gastroenterologist. Also, controls were free of any systemic medical disease or psychological conditions that could affect sensory responses. All IBS subjects had symptoms for at least 5 years but had never been given a diagnosis of chronic functional abdominal pain. The diagnosis of IBS was made by the same gastroenterologist who examined patients based on the ROME III criteria and exclusion of organic disease. All of the IBS patients had normal blood work, stool studies, and colonic biopsies. Patients with evidence of colonic inflammation and/or organic GI diseases were excluded from the study, including those patients with lactose intolerance or food allergies [30]. All subjects with IBS were examined for FM using the 1990 American College of Rheumatology criteria for FM [31]. None of the patients was diagnosed as having FM.

Table 1  Demographic variables for IBS patients and controls

<table>
<thead>
<tr>
<th></th>
<th>D-IBS (n = 27)</th>
<th>C-IBS (n = 15)</th>
<th>Controls (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>29.1 (6.5)</td>
<td>30.9 (7.3)</td>
<td>29.3 (10.0)</td>
</tr>
<tr>
<td>Sex (female, N [%])</td>
<td>21 (66%)</td>
<td>12 (80%)</td>
<td>19 (66%)</td>
</tr>
<tr>
<td>FBDSI</td>
<td>73.3 (22.5)†</td>
<td>51.8 (22.5)‡</td>
<td>1.1 (3.4)‡</td>
</tr>
<tr>
<td>Self-reported race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>16 (59%)</td>
<td>9 (60%)</td>
<td>24 (82%)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (15%)</td>
<td>5 (33%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (11%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (11%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>1 (4%)</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

† Scores on the FBDSI were different at P < 0.01 across the three groups. The groups were not different on age, sex, or race/ethnicity.

FBDSI = Functional Bowel Disorder Survey Index; D-IBS = diarrhea-predominant irritable bowel syndrome; C-IBS = constipation-predominant irritable bowel syndrome.

Columns may not sum to 100% because values were rounded to the nearest 1%.
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None of the IBS or control subjects were on pain medications (opioids), serotonin uptake inhibitors, serotonin antagonists, or tricyclic antidepressants for a period of at least 3 weeks prior to the study. In addition, none of the IBS patients or controls were taking calcium and/or sodium channel blockers or had received any nerve blocks for chronic pain. This study was approved by the University and Veterans Administration Institutional Review Boards. All subjects gave their informed consent once the procedures of the study had been thoroughly explained.

All subjects underwent the experimental psychophysical testing during a single session between 9 AM and 6 PM. Subjects were instructed to refrain from use of caffeine for 4 hours before their sessions. Prior to each session, participants received a reminder concerning the restrictions on analgesic medication and caffeine use before each session.

Female subjects participated during the follicular phase of their cycles (i.e., 4–9 days post onset of menses). This cycle phase was chosen because it is generally characterized by the least sensitivity to pain and by minimal menstrual cycle-related symptoms [32]. The menstrual cycle has been reported to alter pain perception in females, and IBS symptoms have also been reported to fluctuate across the menstrual cycle [33]. In addition, the follicular phase was chosen because some female subjects were using oral contraceptives (OC), and the follicular phase is the cycle phase during which women using OC and normally cycling women are the most similar in their responses to experimental pain [34].

Psychological Measures

Multiple psychological factors have been related to pain responses in a number of studies, and these factors may partially mediate group differences in pain sensitivity. Therefore, all participants completed psychological questionnaires assessing coping style, anxiety, depression, and hypervigilance prior to the experimental session. In addition, a measure of current affective state was administered prior to each experimental session. These measures were used as control variables to determine whether group differences in pain sensitivity remain significant after controlling for the influence of psychological variables.

The Coping Strategies Questionnaire (CSQ) consists of 44 items relating to how individuals cope with pain [35]. It yields seven subscales based on the pain coping strategies that individuals report using diverting attention, catastrophizing, praying and hoping, ignoring pain sensations, reinterpreting pain sensations, increasing behavioral activity, and coping self-statements. The CSQ also provides measures of subjects’ perceived ability to control and decrease pain. It has been widely used with various pain populations and has been modified for use with healthy pain-free subjects by having individuals respond to the instrument based on how they typically cope with day-to-day aches and pains [36]. Responses on the CSQ have previously been related to experimental pain responses [37] as well as clinical pain, including IBS [38–40]. We have used this scale in previous psychophysical and clinical research [22,41,42].

The Kohn Reactivity Scale consists of 24 items that assess an individual’s level of reactivity or central nervous system arousability. It has been used recently as a measure of the construct of hypervigilance [43]. This measure has been shown to correlate negatively with pain tolerance [43,44] and has been reported to have adequate internal consistency, ranging from alpha of 0.73 to 0.83 [16].

The State-Trait Anger Expression Inventory (STAXI) is a well-validated measure of the experience of anger for adults [45].

The Beck Depression Inventory (BDI) is a widely used, 21-item, self-report measure assessing common cognitive, affective, and vegetative symptoms of depression. Research evaluating the psychometric properties of the BDI suggests that it shows excellent reliability and validity as an index of depression [46]. Because chronic pain patients often endorse somatic symptoms assessed by the BDI, which may artificially inflate their scores [47], the BDI will be separated into its 13-item cognitive affective subscale and its 8-item somatic-performance subscale [48].

The Profile of Mood States-Bi-Polar (POMS-BI) consists of 72 mood-related items, and subjects are to indicate the extent to which each item describes their current mood [49]. This questionnaire assesses both positive and negative affective dimensions. The POMS-BI has been well validated with other mood measures and is sensitive to subtle differences in affective state. We have used this measure in previous psychophysical studies [41]. This mood measure was administered to determine current affective state at the beginning of each sensory testing session, and total positive and negative affect scores were computed.

The Functional Bowel Disorder Severity Index (FBDSI) comprises three variables: current pain (by visual analog scale [VAS]), diagnosis of chronic abdominal pain, and number of physician visits in the past 6 months [50]. The FBDSI is sensitive enough to distinguish among the different groups from healthy controls through IBS nonpatients (i.e., individuals meeting IBS diagnostic criteria but who have not sought treatment), to patients with IBS only, and, finally, IBS patients with concomitant FM. Severity is rated as none (0 points—controls), mild (1–36 points—IBS non-patients), moderate (37–110 points—IBS patients), and severe (>110 points—IBS and FM). All participants in the study were characterized with this index.

Psychophysical Measures

Ischemic pain was induced using a modified submaximal effort tourniquet procedure [20,21]. The right arm was exsanguinated by elevating it above the heart level for 60
seconds. The right arm was then occluded using a 10-cm wide straight segmental blood pressure cuff (model SC-10) inflated to 240 mm Hg using a Hokanson cuff inflator and air source (Hokanson, Bellevue, WA). Subjects were then instructed to perform 20 handgrip exercises of 2 seconds duration at 4-second intervals at 50% of their maximum grip strength. Subjects were instructed to say “pain” when they first felt pain and to continue until the pain became intolerable. Subjects continued until the perceived pain was intolerable or for 15 minutes, whichever came first. The time required to reach pain threshold and pain tolerance were recorded in seconds. All subjects were also asked to rate both the sensory (pain intensity) and affective (pain unpleasantness) dimensions of pain on a 0–100-point rating scale at the time of ischemic pain tolerance.

**Statistical Analysis**

Descriptive statistics were calculated for each of the IBS diagnostic groups and the asymptomatic control subjects. Group differences on demographic characteristics were tested with ANOVA or chi-square as appropriate. To test for differences in somatic pain sensitivity, a series of one-way ANOVAs was used with group as a between-subjects factor and VAS for Pain intensity, VAS for Pain unpleasantness, Ischemic pain threshold (ISTh) and Ischemic pain tolerance (ISTol) as the dependent variables. Group differences on the FBDSI and psychological inventories were also tested. To test whether somatic pain sensitivity gradients were associated with the FBDSI or psychological factors within persons with IBS, Pearson product moment correlation coefficients were calculated.

**Results**

**Differences in Ischemic Pain Sensitivity Between Controls and IBS patients**

Significant group differences emerged for ISTh ($F = 34.606, P < 0.001$) and ISTol ($F = 38.656, P < 0.001$) (Figure 1). The results of Bartlett’s test [51] for both ISTh and ISTol indicated that the null hypothesis of equality of group variances was rejected; consequently, the Dunnett T3 correction was used to adjust for multiple tests [52]. Post hoc tests revealed differences on the ISTh between the D-IBS and C-IBS groups compared with control subjects, both at $P < 0.001$. Differences between the D-IBS and the C-IBS groups failed to reach significance ($P = 0.053$). For ISTol, post hoc tests revealed differences between the D-IBS and C-IBS groups compared with control subjects, both at $P < 0.001$. There were no differences between the D-IBS and the C-IBS groups. No group differences were found for ratings of pain intensity or pain unpleasantness (Figure 2), indicating that both groups achieved pain tolerance at similar perceptual end points. As one would expect, the D-IBS and C-IBS groups reported greater symptoms on the FBDSI than control subjects, both at $P < 0.001$ (see Figure 2). In addition, the D-IBS group scored higher on the FBDSI than the C-IBS group ($P = 0.027$). The FBDSI total score was not associated with scores form the psychosocial measures among the persons with IBS ($n = 44$). There were no group differences on the Kohn, BDI, STAXI, CSQ, or Profile of Mood States (POMS). Overall means (SD) are presented in Table 2.

**Associations Between Pain, IBS Symptoms, and Psychological Variables**

Among persons meeting IBS diagnostic criteria, we also found interesting patterns between ischemic pain sensitivity measures and the IBS symptom scale and psychological measures. Because of the number of correlations tested, a critical value of $P = 0.010$ was used. Lower scores on the Copins Strategies Questionnaire (CSQ)
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Figure 2 VAS ratings and FBDSI by group. Data shown include the VAS ratings for the intensity and unpleasantness of ischemic pain at the time of tolerance and the FBDSI scores for controls, C-IBS, and D-IBS patients. C-IBS = constipation-predominant irritable bowel syndrome; D-IBS = diarrhea-predominant irritable bowel syndrome; FBDSI = Functional Bowel Disease Severity Index; VAS = visual analog scale.

Table 2 Mean and SD for psychosocial measures by group

<table>
<thead>
<tr>
<th>Instrument-subscale</th>
<th>D-IBS Mean (SD)</th>
<th>C-IBS Mean (SD)</th>
<th>Controls Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>4.0 (4.4)</td>
<td>5.1 (3.2)</td>
<td>3.5 (4.2)</td>
</tr>
<tr>
<td>STAXI</td>
<td>27.3 (4.3)</td>
<td>30.3 (4.7)</td>
<td>28.2 (4.4)</td>
</tr>
<tr>
<td>CSQ-catastrophizing</td>
<td>5.9 (6.0)</td>
<td>5.8 (7.1)</td>
<td>5.7 (5.5)</td>
</tr>
<tr>
<td>CSQ-diverting attention</td>
<td>9.0 (5.8)</td>
<td>11.6 (7.1)</td>
<td>8.8 (5.8)</td>
</tr>
<tr>
<td>CSQ-reinterpreting pain sensations</td>
<td>4.7 (5.5)</td>
<td>3.9 (5.6)</td>
<td>4.0 (4.6)</td>
</tr>
<tr>
<td>CSQ-praying or hoping</td>
<td>13.6 (4.5)</td>
<td>11.2 (5.7)</td>
<td>13.6 (4.8)</td>
</tr>
<tr>
<td>CSQ-ignoring pain sensations</td>
<td>10.4 (6.0)</td>
<td>11.9 (6.2)</td>
<td>10.9 (5.8)</td>
</tr>
<tr>
<td>CSQ-praying or hoping</td>
<td>4.0 (4.5)</td>
<td>4.3 (4.3)</td>
<td>4.6 (4.5)</td>
</tr>
<tr>
<td>POMS-positive</td>
<td>55.9 (16.3)</td>
<td>55.9 (16.3)</td>
<td>53.9 (15.9)</td>
</tr>
<tr>
<td>POMS-negative</td>
<td>28.3 (15.6)</td>
<td>29.3 (13.0)</td>
<td>30.3 (15.8)</td>
</tr>
<tr>
<td>Kohn</td>
<td>69.6 (9.3)</td>
<td>75.7 (9.0)</td>
<td>68.6 (8.6)</td>
</tr>
</tbody>
</table>

D-IBS = diarrhea-predominant irritable bowel syndrome; C-IBS = constipation-predominant irritable bowel syndrome; BDI = Beck Depression Inventory; STAXI = State-Trait Anger Expression Inventory; CSQ = Coping Strategies Questionnaire; POMS = Profile of Mood States.
Overall, our findings indicate the presence of ischemic hypersensitivity for both C-IBS and D-IBS patients relative to controls, with IBS patients reporting significantly lower pain threshold and pain tolerance times. These findings using an experimental ischemic pain stimulus have not been previously reported in IBS patients providing further support that a subset of IBS patients exhibits somatic hyperalgesia. Another unique finding of our study is that the shorter ischemic threshold times in IBS patients were related to greater IBS symptoms as measured by the FBDSI score, suggesting that sensitivity to ischemic pain may have clinical relevance in this population. In addition, while IBS patients and controls did not differ on POMS subscales, negative mood assessed by the POMS was associated with lower ischemic thresholds in IBS patients but not controls.

Consistent with the findings from the present study, other investigators have reported somatic hypersensitivity in IBS patients using cold pain [13,14], and we have shown similar results with hot-water immersion [7,15]. In contrast, several previous studies have reported no somatic hypersensitivity among IBS patients relative to controls based on cold-pain stimuli [11,12], and others actually showed higher electrocutaneous [9,10] and mechanical [53] pain thresholds among IBS patients relative to controls. Because we did not test other pain modalities, we cannot determine whether ischemic pain is more sensitive to group differences in somatic hypersensitivity than these other pain stimuli. However, the ischemic pain test produces a tonic, diffuse, deep pain that is associated with the activation of a large number of C fibers in the muscle, which is in contrast to other modalities, which include primarily cutaneous stimuli of shorter duration and activate a greater proportion of a-delta fibers which may also invoke endogenous pain modulatory pathways. The intense and tonic C-fiber activation induced by the ischemic test is more likely to uncover hypersensitivity than more brief, less intense stimuli that activate less C-fibers. While ischemic pain sensitivity has not been previously examined in IBS, others have reported hypersensitivity to this pain stimulus in TMD [22,23], FM [24], and interstitial cystitis [25], each of which is commonly comorbid with IBS. One potential explanation for heightened sensitivity to this type of pain across multiple idiopathic pain conditions is that it reflects diminished endogenous pain inhibitory function, given that ischemic pain has been shown to be influenced by endogenous opioids [26–28].

Another important aspect of our methodology is the nature of our IBS sample. In contrast to most prior investigations that recruited IBS patients from clinical settings [9–12], our IBS sample was recruited from the community using print and posted advertisements. Previous findings have demonstrated that for both IBS [54] and FM [55], treatment-seeking patients show greater psychological distress compared with individuals who meet diagnostic criteria for the condition but are not seeking treatment. Thus, our community-based recruitment approach may explain the absence of differences on psychological measures between our IBS sample and healthy controls. Importantly, given the absence of differences between our IBS and control groups, psychological factors cannot mediate the group differences in pain sensitivity that we observed in this study. Moreover, by using community-based recruitment for both cases and controls, we avoided one potential source of sampling bias that can emerge when clinic-based recruitment strategies are utilized for cases but not controls.

A few investigators have examined associations between visceral hypersensitivity and clinical symptoms in IBS, with inconsistent results [56–60], and several recent studies have shown that somatic measures of pain sensitivity and endogenous pain inhibition predict acute clinical pain [61]. However, little evidence exists regarding the association of somatic pain sensitivity and clinical symptoms in IBS. In the present study, the association of lower ischemic pain thresholds with greater IBS symptoms suggests that ischemic pain may have clinical relevance. These results are similar to our recent findings from a separate sample of IBS patients, in which heat pain threshold and tolerance were negatively correlated with FBDSI scores [17]. The current and previous findings suggest that somatic
hypersensitivity may be of clinical predictive value, in at least some patients with IBS, raising the possibility that the factors contributing to altered somatic pain sensitivity are also associated with clinical symptoms. The association of somatic pain responses with clinical symptoms in IBS has potentially important treatment implications. That is, in patients exhibiting generalized somatic hypersensitivity, centrally acting pharmacological and/or psychological treatments may prove more effective than those directed at peripheral targets.

Some limitations of this study deserve mention. First, somatic pain testing was limited to ischemic pain threshold and tolerance of the arm and did not include other stimulus modalities or body sites. Second, we did not assess sensitivity to visceral stimuli, and it would be interesting to know whether ischemic pain sensitivity is associated with visceral sensitivity. Finally, based on the current design, we are unable to identify the mechanisms underlying ischemic hyperalgesia and its association with clinical symptoms or whether expectancy and/or hypervigilance lead to differences in time to thresholds. Despite these limitations, the relatively large and well-characterized community-based sample, the use of ischemic pain measures, and the strong association between ischemic pain sensitivity and IBS symptom severity represent unique findings of our current study.

Conclusions

Our study indicates hypersensitivity to ischemic pain for both groups of IBS patients relative to controls, with IBS patients reporting significantly lower ischemic pain thresholds and tolerances. Moreover, ischemic pain threshold was associated with IBS symptoms. Further studies are warranted to evaluate somatic hypersensitivity as a predictor of clinical symptoms in IBS.

Acknowledgments

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References


