

The Effect of Life Stress on Symptoms of Heartburn

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Objective: Psychosocial stressors have been associated with exacerbations of symptoms in functional and inflammatory disorders of the gastrointestinal tract. The present longitudinal study tests the general hypothesis that life stressors can exacerbate symptoms in patients with chronic heartburn. **Methods:** Sixty subjects with current heartburn symptoms were recruited by community advertisement and assessed for presence of stressful life events retrospectively over the preceding 6 months and prospectively for 4 months. Symptom severity by daily diary, quality of life, and psychological symptoms of anxiety, depression, and vital exhaustion were also measured. **Results:** The presence of a severe, sustained life stress during the previous 6 months significantly predicted increased heartburn symptoms during the following 4 months. In addition, symptoms showed a strong, independent correlation with vital exhaustion. Affective and subjective stress ratings were not strongly related to heartburn severity; however, anxiety showed the strongest relationship to impaired quality of life and depression to heartburn medication use. **Conclusions:** As with other chronic conditions such as irritable bowel syndrome (IBS), heartburn severity appears to be most responsive to major life events and not an accumulation of more minor stressors or fluctuations in mood. In addition, vital exhaustion, which may in part result from sustained stress, may represent the psychophysiological symptom complex most closely associated with heartburn exacerbation. Potential mechanisms for these results include increased level and frequency of esophageal acid exposure, inhibition of gastric emptying of acid, or stress-induced hypersensitivity. **Key words:** vital exhaustion, visceral sensitivity, gastroesophageal reflux disease.

ANOVA = analysis of variance; **BDI** = Beck Depression Inventory; **BAI** = Beck Anxiety Inventory; **EPI-N** = Eysenck Personality Inventory Neuroticism Scale; **GERD** = gastroesophageal reflux disease; **GI** = gastrointestinal; **HIS** = high-impact stressors; **IBS** = irritable bowel syndrome; **LEDS** = Life Events and Difficulties Schedule; **LSI** = UCLA Life Stress Interview; **MQ** = Maastricht Questionnaire; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **NUD** = non-ulcer dyspepsia; **SRLE** = Survey of Recent Life Experience.

INTRODUCTION

Psychosocial stressors have been associated with exacerbation of symptoms in several functional disorders of the gastrointestinal (GI) tract (1–5) (and reviewed in Mayer et al. (6)). Stress may also play a significant role in heartburn; a majority of patients surveyed with symptoms of heartburn reported an increase in symptoms related to stressful life events (7). Although acute heartburn symptoms have been shown to respond to both laboratory psychological stress (8) and muscle relaxation (9), no previous studies have directly examined the relationship between heartburn symptoms, mood, and naturalistic stressors.

Heartburn symptoms are very common, with reports of 20% to 30% of the population in Western countries having some heartburn symptoms and 20% reporting heartburn at least once per month (10,11). Although a significant number

of upper gastric symptoms, including heartburn, are associated with acid reflux, nonacid-related (or functional) heartburn has often been associated with anxiety and emotional lability (12). Perception of acid events is also greater in subjects with greater anxiety, even though acid levels are within the normal range. In a recent study, Fass et al., using a dichotomous listening task, demonstrated that acute laboratory stress increased sensitivity to esophageal acid exposure in patients with both gastroesophageal reflux (GERD) and nonerosive reflux disease (8). Relaxation training, in contrast, has been shown to decrease both heartburn symptoms and acid sensitivity in GERD patients (13). These data are consistent with patient surveys and clinical experience that suggest that life stress may be a significant contributor to heartburn symptoms in patients with both GERD and functional heartburn. Substantial decrements in well-being or quality of life are common consequences of chronic heartburn, and are more frequently being used as measures of illness impact and treatment outcome and may also be related to life stress (14).

Several different methods have now been validated to study life stress in relation to medical and/or psychiatric symptoms. These include retrospective and diary self-reports of the frequency and severity of stressful life events as well as patient reports of mood or their own stress response. Two newer measures may be especially relevant for assessment of the impact of stress on heartburn. The first is the assessment of vital exhaustion. Although cumulative stress often has an impact on general mood including anxiety and depression, a more direct manifestation of the physiological consequences of chronic stress or allostatic load (15) is the syndrome of vital exhaustion. This includes a cardinal symptom of fatigue coupled with irritability and demoralization (16). Although not previously studied in functional GI disorders, vital exhaustion has been shown to have a significant association with heart disease even after controlling for other psychological symptoms such as depression and anxiety (17). A second innovation in stress measurement is assessments designed to separate out presence of stressful life events from the subjective re-

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sponse to such events. In order to gain a more objective measure of the amount of life stress a person has experienced, Brown and Harris (18) developed the Life Events and Difficulties Schedule (LEDS). This is a structured interview approach that defines the severity of a life event based on the context in which the event happens but independent of the subject's reaction. Recent studies using this approach have shown clear associations between presence of major life events and exacerbations of symptoms in psychiatric disorders (19) as well as functional GI disorders such as irritable bowel syndrome (IBS) (1) and nonulcer dyspepsia (NUD) (20). The present study is aimed to test the general hypothesis that life stressors can enhance symptoms in patients with chronic heartburn. We therefore examined the relationship between several measures of life stress and symptom severity in patients with frequent heartburn. Based on the small literature linking stress with symptom exacerbation in other functional GI disorders, we hypothesized that severe, sustained life stressors, vital exhaustion, and psychological symptoms would be predictive of heartburn symptom severity and health-related quality of life over a 4-month follow-up period.

METHODS

Subjects

Sixty-three subjects with current heartburn symptoms were recruited by community advertisement. Mean age of the subjects was 48 years ($SD = 13.9$, range = 25–74 years). Forty-three percent of the sample were men. All subjects had at least a 3-month history of heartburn symptoms during 2 or more days or nights per week. Subjects were evaluated by physical examination, and a medical history was obtained by a gastroenterologist or a nurse practitioner to rule out previous diagnoses or symptoms suggestive of GERD complications, gastric disorders, or prior surgery in the upper gut. Other exclusionary criteria included history of alcoholism or drug abuse in the past 12 months; use of any drug that might significantly alter gastric motility or gastric acid secretion (except for antacids and H₂ blockers) in the month before the start of the study; and regular use of nonsteroidal antiinflammatory drugs (NSAIDs), or any psychiatric medications. Occasional use of NSAIDs was permitted (<10 days per month).

Procedure

After screening, subjects were evaluated at study entry and at 2- and 4-month follow-ups. No specific interventions were given or recommended by the study staff. Subjects were told that the purpose of the study was to examine how heartburn symptoms varied over time.

Measures

Symptoms

Symptoms and symptom impact were recorded daily on diary cards. Patients were instructed to complete the diary every day before bedtime for 2 weeks at study entry and for 2 weeks before each follow-up assessment. The diary card for each day included 11-point severity ratings (nothing to unbearable) of overall heartburn severity, other bodily pain, and stressfulness of the day as well as overall symptom impact (none to most). Also recorded were frequency of daytime and nighttime heartburn episodes, frequency of regurgitation, frequency of medication use, and total hours of symptoms.

Life Stress

UCLA Life Stress Interview (LSI): The LSI is a validated system similar to the LEDS for objective assessment of stressful life events (chronic strain and episodic life events) based on detailed structured interviews (21).

Chronic Strain

The interviewer, using established criteria, rated the degree of chronic strain during the past 6 months in 6 areas: intimate relationships, family, friends, work, finances, and health. Stressors directly related to heartburn or GERD were categorized separately and not included in the analysis. The overall ongoing stress (chronic strain) in each area was rated on a 5-point scale by the interviewer with specific criteria set for each content area. To check for interrater reliability in application of the criteria, 2 trained interviewers independently rated the interviews of 34 subjects. Reliability coefficients for the 6 areas ranged from 0.81 to 0.99, indicating excellent agreement on the amount of stress for all categories. In the present study, the chronic strain ratings for the 6 categories were averaged to give a general measure of chronic life stress.

Episodic Stressors

Subjects were also queried regarding episodic life events. Based on the method of Brown and colleagues (18), the interviewer elicited not only the occurrence of stressors, but also the surrounding circumstances in which they occur and that may modify the understanding of their impact. The severity and independence (how much the subject had some influence on the event) of each episodic event was rated by a consensus panel of 3 trained raters who had not interacted with the subject directly, and do not know the subject's actual reaction to the stress. Thus, objective ratings of the event were based on knowledge of the event in its context and a judgment of how much impact the event would have on a typical person under identical circumstances. Severity ratings were made on a 5-point scale based on the information supplied by the interviewer and established criteria for each type of event (1 = no impact, not considered an event; 2 = mild impact; 3 = significant impact, important, but limited consequences; 4 = marked impact, very stressful, many consequences; 5 = severe). The subject also made a rating of each event on a similar scale. Consistent with previous studies (1), we initially examined both the number of episodic events (all events rated 2 or more) and the presence of high-impact stressors (HIS; those events rated 4 or 5). The total number of events was not related to any of the dependent variables, and total events are also captured in the Survey of Recent Life Experience (SRLE) scale described below. Therefore, the present analysis focused on the presence of HIS. HIS were found in 24% of the subjects by team rating, while 66% of the subjects self-rated at least 1 stressor as having high impact. Examples of team-rated HIS were death or serious illness of a spouse, primary fault in a serious motor vehicle accident, miscarriage, and divorce. Chronic strain and episodic events were assessed at intake.

Daily Stress

A measure of average daily stress was computed from the daily diary card question: "How stressful was your day?" rated on an 11-point scale.

Survey of Recent Life Experience

The SRLE (22) is a well-validated self-report measure of daily stressors (hassles). It contains 51 items describing typical daily stressful events, each rated on a 4-point scale (1 = not at all part of my life, 4 = very much part of my life). Alpha reliability of the total score = 0.91 (22). It differs from the original Hassles scale (23) in that SRLE was designed to lessen influence of subjective mood or stress responses on ratings of the presence of typical daily stressors. The mean stressor frequency was used as total score.

Affective Symptoms

Beck Depression and Anxiety Inventories

Both the Beck Depression (BDI) and the Anxiety Inventories (BAI) are reliable and validated inventories for assessment of symptoms of depression and anxiety, respectively (24,25). Total scores were used for both scales. Scale scores of 11 or greater are indicators of possible psychiatric diagnosis.

Maastricht Questionnaire

The Maastricht Questionnaire (MQ) is a 21-point scale that has been validated as a measure of vital exhaustion and shows good discriminant validity from

traditional measures of depression (17) and predictive validity for increased risk of myocardial infarction and coronary artery disease (26–28).

Eysenck Personality Inventory Neuroticism Scale

The Eysenck Personality Inventory Neuroticism Scale (EPI-N) is a well-validated measure of stress vulnerability and has been linked to development of functional GI disorders (29).

Quality of Life

The GERD-specific Quality of Life scale is a 37-item inventory composed of 6 scales reflecting the impact of GERD on daily life, relationships, quality of life, worries and concerns, sleep, and eating (30,31). For the purposes of this study, the individual scales were averaged to yield a global score for quality of life.

Statistical Analysis

Descriptive data on symptoms for the sample were tabulated. Intercorrelations among the diary measures (at intake) were then examined to determine whether a single measure of symptom severity could be found for use in the prediction models. Bivariate correlations were performed to examine the relationships between GERD symptoms and measures of stress and psychological status. Multiple linear regression analyses were used to test the interdependent relationships among the predictor variables (stress and psychological status) at intake and the dependent variables of symptom severity and quality of life. Finally, an analysis of longitudinal changes in symptoms was carried out to examine whether initial life stress would predict GERD symptoms over the 4-month follow-up period. This was done using a 2-group (presence or absence of HIS) \times 4 time period repeated measures analysis of variance (ANOVA).

RESULTS

Diary Variables

The initial diary ratings are shown in Table 1. There was a wide range of symptom frequency and severity within the

sample. Examination of the correlations among the various diary measures indicated that the general GERD severity rating was highly related to frequency of daytime symptoms ($r = 0.58, p < .001$), total hours of symptoms ($r = 0.81, p < .001$), regurgitation ($r = 0.52, p < .001$), and symptom impact ($r = 0.91, p < .001$). It was less related to nighttime symptoms ($r = 0.37, p < .01$) and medication use ($r = 0.32, p < .05$). On the basis of these high intercorrelations, the diary severity rating was used in subsequent analyses as a global measure of daytime symptom severity, whereas medication use is included as a separate variable.

Prediction of GERD Severity

Table 2 shows the individual correlations between GERD symptom severity and medication use, and the psychological and stress variables. Significant relationships were found for depression, anxiety, vital exhaustion, and presence of HIS. A somewhat different pattern of correlations was found for prediction of medication use. The affective variables and vital exhaustion showed strong correlations with medication use, but of the stress measures only the extent of daily hassles (from the SRLE) was significantly related.

Further exploration of these relationships was carried out using multiple linear regression. Table 3a shows the results for the regression for the diary GERD severity measure. Predictor variables include chronic strain (from the UCLA LSI), depression, anxiety, presence of a HIS by the team and the subject's rating, vital exhaustion, and stress vulnerability (EPI-N). The overall prediction equation was significant ($R^2 = 0.59, p <$

TABLE 1. Initial Daily Diary Ratings (Averaged During 2 Weeks)

	N	Mean	SD	Minimum	Maximum
Freq. of daytime symptoms	62	2.44	2.22	0.00	9.29
Freq. of PM symptoms	62	0.79	1.11	0.00	5.71
Freq. of regurgitation	62	1.79	1.86	0.00	10.00
Hours of GERD symptoms	62	2.78	2.41	0.21	10.00
Overall GERD severity (0–10)	62	2.93	1.85	0.29	9.86
Daily stress (0–10)	62	3.05	1.80	0.14	8.50
Impact on life today (0–10)	62	2.42	2.00	0.00	10.00
Number of GERD meds today	59	0.43	0.54	0.00	2.21

GERD = gastroesophageal reflux disease.

TABLE 2. Correlations of GERD Symptoms and Quality of Life With Psychological and Stress Measures

	GERD symptom severity	N	GERD medications	N	Impact on daily life	N	Overall quality of life	N
BDI	0.384**	62	0.472**	59	0.465**	62	0.529**	62
BAI	0.384**	61	0.505**	58	0.549**	62	0.495**	62
MQ	0.431**	61	0.295*	58	0.553**	62	0.614**	62
HIS-Team	0.451**	55	0.075	55	0.150	56	0.139	56
HIS-Self	0.286*	55	0.084	53	0.225	56	0.236	56
Hassles	0.184	61	0.343**	58	0.489**	62	0.486**	62
Chronic strain	0.069	62	0.183	59	0.040	63	0.231	63
EPI-N	0.123	60	0.173	57	0.347**	61	0.429**	61

* $p < .05$ (2-tailed). ** $p < .01$ (2-tailed).

BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; EPI-N = Eysenck Personality Inventory Neuroticism Scale; GERD = gastroesophageal reflux disease; HIS = high-impact stressors; MQ = Maastricht Questionnaire.

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TABLE 3a. Regression Predicting GERD Diary Severity

ANOVA						
Model		Sum of squares	df	Mean Square	F	Sig.
1	Regression	92.400	8	11.550	5.233	0.000
	Residual	90.502	41	2.207		
	Total	182.902	49			

Coefficients						
Model		Unstandardized coefficients		SE	Standardized coefficients	
		B	t		Beta	
1	(Constant)	2.991	1.674	1.786	0.052	0.252
	BDI	1.293E-02	0.051	0.047	0.025	0.130
	BAI	6.115E-03	0.037	0.677	0.473	3.100**
	MQ	0.114	0.612	0.543	-0.086	-0.894
	HIS-Team	2.015	3.354**	0.601	-0.150	-0.371
	HIS-Self	-0.333	-0.213	0.587	-0.044	-1.227
	Hassles	-0.613	-0.213	0.685	-0.213	
	Chronic	-0.217		0.587		
	Strain					
	EPI-N	-6.876E-02		0.056		

** $p < .01$ (2-tailed).

For abbreviations, see Table 2.

.001). The presence of a HIS during the past 6 months by team rating and vital exhaustion were the only significant independent predictors of GERD symptoms.

The pattern of GERD symptoms associated with a team-rated HIS is shown in Figure 1 and differences between subjects with and without a team-rated HIS were compared with t -tests. Subjects with presence of HIS had greater sever-

ity, mood disturbance, and impact of their GERD symptoms compared with those without HIS, but did not report greater frequency of heartburn episodes during the day or night, or increased medication use.

Because medication use did not cluster with the other diary variables of symptom severity, a similar regression analysis using the same predictor variables as described above was

TABLE 3b. Regression Predicting GERD Medication Use

ANOVA						
Model		Sum of squares	df	Mean square	F	Sig.
1	Regression	4.963	8	0.620	3.364	0.005
	Residual	7.192	39	0.184		
	Total	12.154	47			

Coefficients						
Model		Unstandardized coefficients		SE	Standardized coefficients	
		B	t		Beta	
1	(Constant)	0.381	0.716	0.533	0.769	3.263**
	BDI	4.950E-02	1.253	0.015	0.266	-1.393
	BAI	1.717E-02	-0.807	0.014	-0.337	0.017
	MQ	-1.502E-02	-0.537	0.011	0.003	-0.073
	HIS-Team	3.040E-03	-0.387	0.175	-0.124	-0.189E-02
	HIS-Self	-0.127	-0.537	0.158	-0.073	-7.763E-02
	Hassles	-7.763E-02	-0.387	0.201	-0.071	-9.189E-02
	Chronic	-9.189E-02	-0.537	0.171	-0.013	-1.156E-03
	Strain					
	EPI-N	-1.156E-03	-0.070	0.016		

** $p < .01$ (2-tailed).

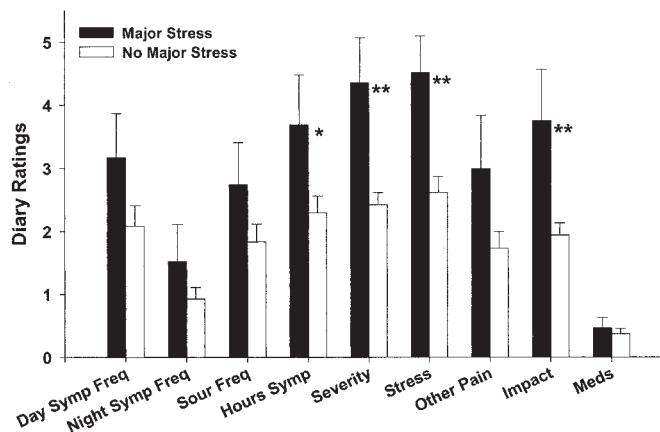


Figure 1. Impact of major life stress in previous 6 months on diary ratings. Subjects with presence of HIS during the past 6 months by team rating show increased heartburn symptom severity, impact, daily stress, and other pains on daily diary. Error bars represent SD. * $p < .05$ level (2-tailed). ** $p < .01$ level (2-tailed).

done to predict average number of GERD medications taken per day. The results are shown in Table 3b. Unlike global severity, medication use was significantly related independently to depression but not to presence of life stressors.

Quality of Life

The various life stress and psychological variables were also examined as predictors of GERD impact on quality of life. Table 2 shows the individual correlations, and the regression analysis is shown in Table 4. Although a variety of the psychological variables were related to quality of life and the overall prediction was significant ($R^2 = 0.50, p < .001$), only

anxiety was a significant independent predictor in the regression.

Longitudinal Changes in Symptoms

Forty-five of the initial subjects had complete follow-up data (75%). Overall, GERD symptoms were very stable over the course of the study. Symptom severity at entry was strongly related to symptom severity at 2-month ($r = 0.83, p < .001$) and 4-month ($r = 0.85, p < .001$) follow-up. Presence of at least 1 HIS during the 6 months preceding study entry was found in 29% of patients with follow-up data. A repeated measure ANOVA examining subjects with and without at least 1 HIS showed a significant main effect of Group, $F(1,38) = 8.31, p = .006$, but not a significant Time or Group \times Time interaction. As shown in Figure 2, post hoc tests indicated that subjects with at least 1 HIS continued to have significantly greater symptom severity at the follow-up evaluations (p values $< .01$). Similarly, vital exhaustion as measured at intake continued to be strongly related to GERD severity symptoms at 2-month ($r = 0.56, p < .001$) and 4-month ($r = 0.56, p < .001$) follow-up.

Attempts to model change in symptoms over time as a function of changes in psychological factors were not successful. Generally symptoms, stress, and psychological factors were highly consistent across time.

Sex-Related Effects

The regression analyses described above were repeated using a hierarchical design with sex entered as a predictor on the first step and the other psychological and stress variables entered on the second step. Sex was not significantly related to

TABLE 4. Regression Predicting GERD Quality of Life

ANOVA							
Model		Sum of squares	df	Mean square	F	Sig.	
1	Regression	14.463	8	1.808	5.340	0.000	
	Residual	14.220	42	0.339			
	Total	28.683	50				
Coefficients							
Model	Unstandardized coefficients			Standardized coefficients		<i>t</i>	
	B	SE	Beta				
1	(Constant)	1.725	0.685		2.516*		
	BDI	-5.753E-04	0.020	-0.006	-0.029		
	BAI	3.932E-02	0.018	0.413	2.136*		
	MQ	1.052E-02	0.014	0.162	0.731		
	HIS-Team	-3.070E-02	0.233	-0.019	-0.132		
	HIS-Self	0.167	0.212	0.109	0.786		
	Hassles	0.428	0.268	0.270	1.596		
	Chronic	-0.224	0.224	-0.119	-0.999		
	Strain						
	EPI-N	-8.791E-03	0.022	-0.070	-0.401		

* $p < .05$ (2-tailed).

For abbreviations, see Table 2.

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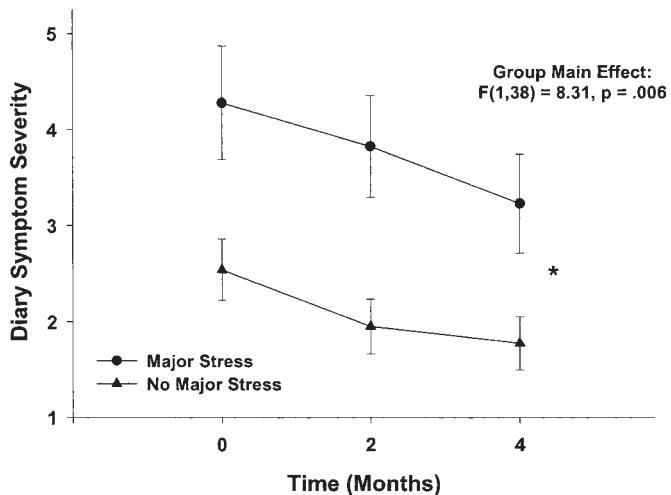


Figure 2. Symptom severity during 6 months for subjects with a major life stressor versus no major life stressor in past 6 months. Subjects with the presence of high-impact stressors by team rating show greater heartburn severity at 0, 2, and 4 months. Error bars represent SD. * $p < .05$ level (2-tailed).

severity of GERD symptoms and did not affect the prediction equation for the other variables. This indicates that there are similar overall relationships between psychological and stress variables and GERD severity in both men and women. In a similar regression prediction of quality of life, sex was related to quality of life ($r = 0.33$, $p < .02$), with men reporting significantly greater GERD impact on their quality of life ($p < .01$). However, sex did not significantly alter the prediction equation for the other variables.

DISCUSSION

The current study examines both cross-sectional and longitudinal relationships between life stress and heartburn symptoms. In patients with mild to moderate heartburn symptoms, significant cross-sectional relationships were found between certain measures of life stress and severity of heartburn: 1) Higher levels of heartburn symptoms were associated with the presence of a severe, sustained life stressor during the past 6 months. 2) Heartburn symptoms showed a strong, independent correlation with another measure of sustained stress, "vital exhaustion." This correlation persisted even after controlling for anxiety, depression, and life stress. 3) In contrast, other stress variables such as ratings of chronic strain, number of minor stressors, or even the subject's own assessment of presence of a major stressor were not related to heartburn symptoms. 4) Mood variables had their strongest relationship with disease outcomes other than heartburn severity. Anxiety was the only independent predictor of quality of life and depression the only independent predictor of medication use. 5) A longitudinal analysis of heartburn symptoms indicated that presence of a severe, HIS in the 6 months before study entry predicted continued increased symptoms during a 4-month follow-up period. In the following, we will discuss these findings in terms of possible underlying mechanisms

and in the context of related reports of chronic stress in the literature.

Impact of Acute Stress on Heartburn Symptoms

There are a variety of possible mechanisms that might account for the relationship between a life stressor and heartburn severity. Even though most of these mechanisms have been reported in the context of acute, experimental studies, they nevertheless provide plausible hypotheses to be tested in future studies on the impact of chronic stress on gut physiology. For example, experimental studies suggest that acute stress may increase the level and frequency of esophageal acid exposure by several mechanisms including increased gastric acid production (32), stress-induced inhibition of gastric emptying of acid (33), and impairment of the diaphragmatic component of the lower esophageal sphincter mechanism by stress-related breathing patterns (34). More recently, Fass et al. have demonstrated that the perceptual sensitivity to acid is increased under even mild acute laboratory stressors, such as dichotic listening (8). Dichotic listening has also been shown to enhance perception of colonic distension in healthy control subjects (35). Animal experimental evidence supports the concept of stress-induced visceral hyperalgesia, an increase in visceral pain perception during acute laboratory stress (36).

Relationship of Major Life Events With GI Symptom Severity

Although the physiological studies discussed above relate directly only to acute stressors, the current results are consistent with a growing literature linking chronic, high-impact stressors with symptom exacerbation in a variety of somatic conditions, including those involving the GI tract (37). In contrast, short-term stressors (those occurring over a few days to a week), or multiple less severe stressors may be less important. For example, Levenstein et al. (5) found a significant relationship between exacerbation of ulcerative colitis and long-term stress rated on the Perceived Stress Questionnaire (but not acute stress). A similar result was found in a 16-month prospective study of IBS in which symptom exacerbations were predicted by presence of a major threatening life stress but not daily stressors (1). Gwee et al. (4) also reported that the presence of a major life stress during the 12 months preceding hospitalization for gastroenteritis was significantly related to development of postinfectious IBS, and this relationship was independent of anxiety and neuroticism.

Although acute stressors are associated with transient autonomic, neuroendocrine, and pain modulatory responses of central stress circuits, severe, sustained stressors may produce persistent or even permanent alterations in stress responsiveness and therefore longer-lasting changes in symptom patterns. In addition to the mechanisms discussed above for acute stressors, mechanisms engaged by sustained stressors may include changes in central afferent processing, such as changes in attention or in affective responses (37). They may also include alteration in endogenous pain modulation systems, or the stress-induced generation of peripheral mediators,

such as proinflammatory cytokines (38,39). The fact that patients in this study with a history of major life events did not report a greater frequency of heartburn episodes, but only greater symptom severity, may suggest that stress has its most powerful impact on the perceptual processes that lead to the judgment of how "bad" the symptoms are, rather than modulation of mechanisms influencing acid reflux (which should be more closely associated with increased episodes of heartburn). Consistent with the requirement for sustained high-impact stress for symptom modulation is the current observation that the number of stressors was not a significant predictor. In addition, it was the team rating of stress impact and not the more subjective assessment of stress impact by the subject that predicted symptom severity. This supports the hypothesis that significant life stressors are important predictors of illness regardless of self-perceived impact. Subjective ratings of stressors may not capture the impact of life events due to reporting bias, influence of mood, and poor insight.

Vital Exhaustion and Cognitive Factors in GI Symptoms

The data from this study linking heartburn symptoms to vital exhaustion reinforce the supposition that heartburn symptoms are related to global stress responses, particularly those that are of significant magnitude and chronicity to result in symptoms of fatigue and "burnout." Although the neurobiological mechanisms underlying the construct of vital exhaustion (fatigue, irritability, demoralization) are incompletely understood, they may be attributable to alterations in central arousal systems (including ascending noradrenergic systems), hypothalamic–pituitary–adrenal axis dysregulation, and the generation of proinflammatory cytokines (40). Development of vital exhaustion has also been linked to the "type D" (distressed) personality, which is defined as negative affectivity and the tendency to inhibit the expression of this affect in social interaction (41). The finding that vital exhaustion and presence of a HIS were independent predictors of heartburn symptoms suggests multiple pathways for stress affecting heartburn severity. Vital exhaustion is closely associated with negative affect and has high correlations in this sample with neuroticism ($r = 0.71$), depression ($r = 0.78$), and anxiety ($r = 0.65$). Presence of a HIS, on the other hand, is associated with symptom severity but is not strongly related to vital exhaustion or negative affect. These data therefore suggest several mechanisms by which heartburn severity may be enhanced. One mechanism involves a cognitive or physiological change resulting from the occurrence of a HIS, but perhaps due to good support, coping, or predisposition does not lead to a generalized change in mood, quality of life, or need to increase medications (or even high ratings of subjective stress). A second pathway is marked by presence of vital exhaustion and is part of a more generalized decline, including alterations in mood, quality of life, and increased subjective stress. Further research is needed to both verify these independent pathways as well as examine whether the differential mechanisms are perceptual, physiological, or both.

Subjective ratings of stress and standard measures of mood were not the strongest predictors of symptoms in the current study. Measures of anxiety and depression have also not been shown to be as strong predictors of symptoms as life stress in several previous studies (1,4); however, other subjective ratings of stress do predict symptom changes. Dancey et al. (42) found that severity of daily hassles, recorded on a daily basis, predicted symptoms over the next 4 days, but that symptoms also predicted the stress ratings. Levenstein et al. (5) found that a self-report measure of perceived stress was a better predictor of symptoms in ulcerative colitis than either life events or mood. In the current study, vital exhaustion may represent a good measure of overall stress impact and was significantly associated with symptoms independent of the other mood variables. Further research is clearly needed to pinpoint the best technique for assessment of the impact of stress, especially in terms of the quality of stress response that is most directly tied to physiological changes for a particular disorder. It is noteworthy that illness-specific quality of life was strongly associated with the affective measures and that anxiety was the only independent predictor of this measure. Thus, general illness impact is more closely associated with affective measures than specific symptom severity.

Heartburn Medication Use and Chronic Stress

Medication use is commonly used as an outcome measure in clinical trials of acid peptic-related disorders of the esophagus and stomach. Surprisingly, reported medication use did not cluster with the other variables of heartburn symptom severity. Although multiple measures of negative affect including depression, anxiety, and vital exhaustion were related to medication use, depression was the only significant independent predictor in the regression analysis. Of the life stress measures, only daily hassles showed a relationship with medication use, but this was not independent of depression. These findings are consistent with the concept that medication use is a distinct outcome variable from symptom frequency and severity, and that patients with greater negative mood, especially depression, more frequently turn to medications for relief (43).

Strengths and Limitations

The major strength of this study is the fact that it represents the first longitudinal study evaluating the impact of stressful life events on symptoms of heartburn. Other strengths are the inclusion of a validated objective measure of episodic life stress and examination of vital exhaustion in addition to the standard mood measures of anxiety and depression. Several limitations of the current study should be mentioned. One involves the subject sample. Subjects were obtained via advertisement and therefore probably represent a population in between those recruited from GI clinics and those randomly selected from the general population in terms of severity and impact of symptoms on

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quality of life. A second limitation is the length of the follow-up period. Although this study examines heartburn symptoms during a 4-month period, it may be that the length of the study was not sufficient to test within subject stress-symptom relationships. The natural history of heartburn is not well characterized, but our results do indicate that 6 months or longer may be required to examine individual variation in symptom patterns. In addition, many of the associations are based on a cross-sectional analysis, and therefore direction of causation should be interpreted cautiously. A final limitation is the lack of physiological measures. Future studies that include potential mediator variables such as esophageal pH or neuroendocrine variables may help clarify the mechanisms behind the results reported here.

CONCLUSION

In summary, we found significant relationships between the presence of a severe, sustained life stress during the previous 6 months and increased severity of heartburn symptoms during the following 4 months. Affective and subjective stress ratings were not strongly related to heartburn; however, symptoms were highly correlated with a measure of sustained stress symptoms, "vital exhaustion."

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