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# Autonomic dysfunction and gastroparesis in Gulf War veterans

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## ABSTRACT

Over 25% of veterans with Gulf War illness developed chronic gastrointestinal (GI) symptoms of unknown etiology after they returned from deployment to the Persian Gulf. To determine the prevalence of delayed gastric emptying and its association with autonomic dysfunction in returning Gulf War (GW) veterans with chronic GI symptoms, we prospectively studied 35 veterans who were deployed to the Persian Gulf and developed chronic nausea, vomiting, postprandial abdominal pain, and bloating during their tour of duty and 15 asymptomatic controls. All veterans underwent 5 standardized cardiovascular tests to assess autonomic function. Each test was scored from 0 (normal) to 5 (severe disease) and the mean was calculated. A composite score >1.5 was considered abnormal, with 5 representing severe autonomic dysfunction. A standardized gastric emptying test with a solid phase was performed in each veteran. A gastric retention of >50% at 100 minutes was considered abnormal. The composite autonomic score was 3.7 in veterans with GI symptoms (vs 1.3 in controls) ( $p<0.01$ ). The mean solid phase retention at 100 minutes was 72.6% in the symptomatic veterans versus 24.6% in controls ( $p<0.001$ ). Our results suggest that autonomic dysfunction and delayed gastric emptying are common in returning GW veterans with GI symptoms. Autonomic dysfunction was positively correlated with the severity of delayed gastric emptying and may account for the GI symptoms of nausea, vomiting, postprandial abdominal pain, and bloating. These new findings are important for an increasing number of veterans who are serving in the Persian Gulf and are at a high risk of developing GI disorders while deployed.

## INTRODUCTION

Since 2001, more than 2.2 million US veterans have served in Operation Enduring Freedom in Afghanistan and Operation Iraqi Freedom in Iraq. The Persian Gulf Registry has identified a large number of Gulf War (GW) veterans with chronic illness complaints of undetermined etiology.<sup>1–3</sup> Approximately 25% of veterans have persistent gastrointestinal (GI) symptoms after returning home from deployment to the Persian Gulf.<sup>4–8</sup> The workup, treatment, and indirect costs such as lost work have cost

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Over 25% of Gulf War (GW) veterans returning home from deployment have persistent gastrointestinal (GI) symptoms of undetermined etiology.

## WHAT THIS STUDY ADDS

⇒ Autonomic dysfunction and gastroparesis are common in GW veterans and may account for the chronic GI symptoms such as nausea, vomiting, postprandial abdominal pain, and bloating.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Awareness for GI motility disorders and autonomic dysfunction is important for veterans who are serving in the Persian Gulf and are thus at a high risk of developing chronic GI disorders while deployed.  
⇒ These findings may lead to novel diagnostic and treatment paradigms for returning GW veterans who suffer from chronic GI disorders.

the military >\$900 million according to the Veterans Affairs (VA) Environmental Epidemiology Service. Many veterans are still serving in the Middle East and are at increased risk for developing chronic GI disorders, which will continue to be a large economic strain on the VA Health Care System.

Chronic fatigue, persistent headaches, frequent muscle and joint pain, and GI symptoms are common among veterans with Gulf War illness (GWI).<sup>1–3</sup> Nausea, vomiting, postprandial abdominal pain, and bloating are some of the most common GI symptoms that are experienced by these veterans. In many cases, there is no apparent etiology for their GI symptoms. GI symptoms such as nausea, vomiting, postprandial abdominal pain, and bloating have been described in GWI, and may be suggestive of an underlying motility disorder or altered GI transit time.<sup>6,7</sup> Another potential cause for these GI symptoms is autonomic dysfunction which has been previously reported to be a potential contributing factor in GWI.<sup>9–11</sup> Autonomic and peripheral neuropathies that have



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been described in diabetes are also seen in veterans with GWI.

In the current study, we investigated veterans who were deployed to the Persian Gulf who had GWI and developed persistent GI symptoms including nausea, vomiting, bloating, and postprandial abdominal pain during their tour of duty. The specific goals of the study were: (1) to determine the prevalence of gastroparesis in GW veterans with nausea, vomiting, postprandial abdominal pain, and bloating; (2) to quantify autonomic dysfunction in GW veterans with chronic GI symptoms versus asymptomatic GW veterans; and (3) to determine the relationship between gastroparesis and autonomic dysfunction in GW veterans who developed chronic GI symptoms during their tour of duty. These findings will be of concern to an increasing number of veterans currently serving in the Persian Gulf and who are therefore at high risk of developing chronic GI symptoms during and/or after deployment.

## MATERIALS AND METHODS

### GW veterans

Thirty-five consecutive GW veterans who were previously deployed to the Persian Gulf, and who were seen in the VA outpatient clinics, were screened. Included in the study were GW veterans who developed 3 out of the 4 chronic GI symptoms (postprandial abdominal pain, nausea, vomiting, bloating) during their tour and still had persistent symptoms. A total of 15 asymptomatic GW veterans who did not develop GI symptoms were included as controls. A complete history was taken from each veteran regarding dates and regions of deployment to the Persian Gulf. The questionnaire examined GI symptoms before, during, and after deployment to the Middle East. The presenting complaint to the clinic was persistent GI symptoms. All GW veterans had previously had upper endoscopy with biopsies that were normal; hydrogen breath test (to exclude bacterial overgrowth); a negative serum tissue transglutaminase; negative stool, hematologic, and biochemical studies.<sup>6</sup> Veterans with major medical illnesses such as acute infection, pancreatitis, inflammatory bowel and liver disease, or who were taking a medicine that affected bowel symptoms and function were excluded from the analysis.<sup>12 13</sup>

### Cardiovascular autonomic function tests

A total of 5 standardized cardiovascular tests were performed with each veteran to assess autonomic function.<sup>14</sup> These included the following: (1) Heart rate changes in the upright position: quantified as the longest R-R interval ratio at the 30th beat to the shortest R-R interval following the 15th beat on assuming the upright position.<sup>15</sup> (2) Deep breathing changes in heart rate response: this was determined as the minimum and maximum heart rates over each breathing cycle. The maximum-minimum heart rate was determined as the mean differences during 3 successive breathing cycles. (3) Blood pressure response to standing up: the difference between upright and supine systolic blood pressure was used to calculate postural blood pressure change. (4) Sustained hand grip changes in blood pressure: exertion of a hand grip at approximately 30% (on a visual analog scale) of maximal effort for 5 minutes was used to measure blood pressure changes to sustained

hand grip. Diastolic blood pressure just before starting and immediately before release was used as the measure of response. (5) Valsalva maneuver: a mouthpiece was used and each veteran was asked to blow at a pressure of 40 mm Hg for 15 seconds. The ratio between the longest R-R interval after the maneuver compared with the shortest R-R interval during the maneuver was used as the Valsalva ratio. The mean ratio from 3 repeated trials in each veteran was recorded.

Measured values for each test were used to calculate a standardized score in order to categorize autonomic damage severity.<sup>14 15</sup> Test results were documented from 0 (normal) to 5 (severe disease). The results were then placed into a specific category. These included: (a) normal—only 1 was borderline or all were normal; (b) early involvement—2 were borderline or 1 of the 3 heart rate tests was abnormal; (c) definite involvement—a total of 2 or more of the heart rate tests were abnormal; (d) severe involvement—1 or both blood pressure tests were abnormal or both were borderline plus 2 or more heart rate tests were abnormal. The mean of the 5 scores was used to calculate a final score of 0–5 for each veteran. A composite score >1.5 was considered abnormal with 5 representing severe autonomic involvement.<sup>14 15</sup> Controls had a mean composite score of <1.5.

### Measurement of gastric retention at 100 minutes

Following an 8-hour fast, each veteran underwent a solid phase gastric emptying study. A total of 0.5 mCi of Tc-99 in half-cup water was mixed with scrambled eggs and 1 pat margarine that was then consumed by each veteran. A gamma camera with a low energy high-resolution collimator was used to measure gastric emptying. Anterior and posterior images were obtained while the veteran was in the supine position after ingestion and then every 10 minutes for a total of 100 minutes. The study was then processed to evaluate % retention at 100 minutes. Gastric retention of >50% at 100 minutes was considered abnormal.

### Statistical analysis

Dependent variables (autonomic function scores and % retention) were evaluated with separate analysis of variance (ANOVA). Diagnosis was the independent variable in each of the ANOVAs. Post hoc Tukey tests were used to determine which groups differed following significant omnibus F-tests. A hierarchical regression was conducted with autonomic scores as the first block, and diagnosis (control vs control) as the second block to determine the effect of autonomic scores on gastric retention

## RESULTS

A total of 35 consecutive GW veterans (28 males, mean age 47.1±2.8 and 7 females, mean age 45.2±3.4) (table 1) were recruited and included in the study. All had been deployed to the Persian Gulf for 5–24 months (mean: 16.1 months). All 35 had documented chronic GI symptoms that consisted of postprandial abdominal pain, nausea, vomiting, and bloating that they developed during their deployment and continued on their return home from the GW. None of the participants had abnormal laboratory studies, abnormal stool studies, or abnormal endoscopic findings. Before deployment to the Persian Gulf, none of the veterans had

**Table 1** Demographics of GW veterans with GI symptoms

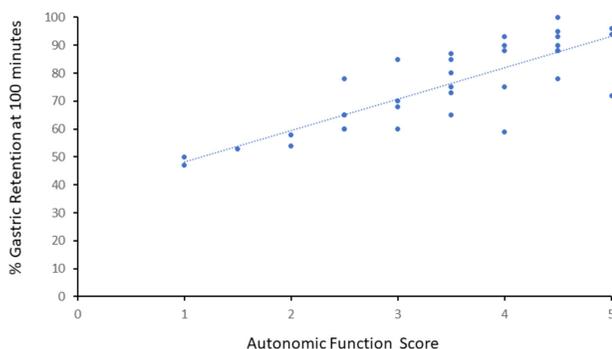
	Male	Female
Age (y)	47.1±2.8	45.2±3.4
Sex, n (%)	28 (80)	7 (20)
Ethnic group, n (%)		
White	18 (64)	4 (75)
Black	8 (29)	3 (25)
Hispanic	2 (7)	0
Asian	0	0
Other	0	0

Plus-minus values are means±SD.  
GI, gastrointestinal; GW, Gulf War.

any history of GI symptoms, functional bowel disorders, inflammatory bowel disease, celiac disease, or bacterial overgrowth. A total of 15 previously deployed GW veterans who did not develop any GI symptoms during their tour were included as controls (10 males, mean age 41.1±1.3 and 5 females, mean age 44.2±1.7). There were no significant differences in age or sex between the symptomatic GW veterans and the matched controls.

The mean per cent gastric retention at 100 minutes was 75.3±15.1 in the GW veterans with GI symptoms versus 26.1±8.2 ( $p<0.001$ ) in the control group. A total of 33/35 (94.2%) of veterans with GI symptoms had evidence of delayed gastric emptying with a gastric retention percentage of >50% at 100 minutes. A total of 33/35 (94.2%) of veterans with GI symptoms had evidence of abnormal autonomic composite scores of >1.5%. Interestingly, the 2 veterans with a normal autonomic score of 1 had borderline normal gastric retention of 47% and 50%, respectively. The composite autonomic score for GW veterans with GI symptoms was 3.4±1.1 vs 1.2±0.4 ( $p<0.001$ ) in the controls. Regression analysis revealed that neither age nor sex accounted for the variance in gastric emptying.

Correlation analysis revealed a positive correlation between the autonomic function score and the per cent gastric retention at 100 minutes ( $r=0.83$ , with 95% CIs) (figure 1). Thus, the higher autonomic scores were associated with longer mean gastric retention scores. This suggested that the more severe autonomic dysfunction led to greater gastric retention rates at 100 minutes. There was no specific autonomic test that correlated more tightly with

**Figure 1** Correlation between % gastric retention at 100 min and autonomic score.

gastric retention than the overall composite autonomic score.

## DISCUSSION

In our current study, we investigated GW veterans who had been deployed to the Persian Gulf and then had returned from active duty with persistent GI symptoms consisting of nausea, vomiting, postprandial abdominal pain, and bloating. We also investigated the prevalence of autonomic dysfunction and delayed gastric emptying in these GW veterans. Our current study showed several unique findings: (1) it identified the high prevalence of delayed gastric emptying in returning GW veterans that was not previously reported; (2) demonstrated the presence of autonomic dysfunction in GW veterans with GI symptoms; (3) suggested a positive correlation between gastroparesis and the severity of autonomic dysfunction. Thus, the development of nausea, vomiting, postprandial abdominal pain, and bloating is common among deployed GW veterans, and these symptoms usually persisted after the veteran returned from deployment. The etiology of these symptoms may be linked to several underlying factors including prolonged gastric retention and autonomic dysfunction.

The pathophysiological mechanisms of GI symptoms are not well understood, but these mechanisms cause significant morbidity in GW veterans. One of the earliest studies evaluated 57 deployed and 44 non-deployed members of a National Guard unit to better define the etiology and prevalence of chronic GI symptoms in Persian Gulf veterans.<sup>8</sup> After deployment to the Persian Gulf region, up to 80% reported chronic GI pain that persisted after their tour of duty. The abrupt onset of GI pain was coincidental with deployment to a stressful wartime environment. Veterans deployed to the Persian Gulf are exposed to a highly stressful environment that may make them more susceptible to chronic GI disorders. Some reports suggest that >50% of veterans deployed to the GW developed acute gastroenteritis that may be one of the underlying factors leading to chronic GI motility disorders and persistent GI symptoms.<sup>6,7</sup>

These abnormalities in motility are manifested as abdominal pain, delayed gastric emptying, altered small bowel and colonic transit, and bloating. The etiology of the GI motility disturbances is unknown, but clinical studies and experimental data suggest that gastric inflammation, possibly after gastroenteritis, can lead to persistent changes in GI smooth muscle function and in the myenteric plexus resulting in dysmotility and gastroparesis. Similarly, postinfectious dyspepsia has been reported after a *Salmonella* gastroenteritis outbreak.<sup>16</sup> It has been hypothesized that stress plays a role in the prolonged response to enteric infection and, in so doing, induces chronic functional GI disorders.<sup>17</sup> GI inflammation may sensitize receptors in the gut such that previously silent nociceptors trigger at a lower pain threshold.<sup>18–20</sup> Transient small bowel and colonic inflammation due to enteric infections acquired by deployed veterans may cause sensitization of the gut and enteric neurons to nociceptive stimuli, which can persist long after resolution of the inflammation, similar

to changes observed in animal models of functional GI disorders.<sup>21 22</sup>

GW shares symptoms with autonomic dysfunction, and autonomic dysfunction has been previously suggested as a potential contributing factor in GWI.<sup>9–11</sup> Given the nature of the vague symptoms in GW veterans, there is often a long delay in diagnosing autonomic disorders. The report of unexplained neurological symptoms suggests a high index of suspicion and requires availability of autonomic testing. Other unexplained GI disorders such as irritable bowel syndrome have been shown to have autonomic dysfunction.<sup>23 24</sup> Autonomic neuropathy has also been described in GI motility disturbances in patients with cirrhosis.<sup>25</sup> The presence of autonomic dysfunction in previously deployed GW veterans may be an important predictive factor to indicate which GW veterans are likely to develop chronic GI symptoms as a result of altered GI motility. Thus, using objective standards on autonomic function testing may be helpful in guiding more targeted therapy in GW veterans with multisymptom illnesses.

## SUMMARY

Our current study investigated GW veterans deployed to the Persian Gulf who returned from active duty with persistent GI symptoms including nausea, vomiting, post-prandial abdominal pain, and bloating. To the best of our knowledge, our study is the first to show a high prevalence of delayed gastric emptying in returning GW veterans that positively correlates with the severity of autonomic dysfunction. Thus, the presence of autonomic dysfunction was positively correlated with prolonged gastric retention at 100 minutes on a standard solid phase gastric emptying study. Some caution interpreting our results is needed as our present findings do not establish autonomic dysfunction as a cause of delayed gastric emptying in these GW veterans. Additional studies are needed with larger numbers of GW veterans to determine more details regarding the extent and causation of autonomic dysfunction in relation to gastroparesis. The conclusions of this study are important as they may lead to novel diagnostic testing of autonomic and gastric motility testing for returning GW veterans who suffer from chronic GI disorders.

**Contributors** ZTV conducted the experiments, and collected and analyzed the data. JZF edited the manuscript. BBZ conducted the data analysis. QZ designed the experiments and provided funding. QZ is responsible for the overall content as guarantor.

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**Competing interests** None declared.

**Patient consent for publication** Obtained.

**Ethics approval** This study involves human participants and was approved by the Veterans Affairs Medical Center Institutional Review Board; VA SCI (438190). Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available upon reasonable request.

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