Altered gastroesophageal motility in patients with idiopathic orthostatic hypotension[1]

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Although a variety of neurologic and systemic disorders are associated with abnormal gastroesophageal motility, little is known of gut involvement in patients with idiopathic orthostatic hypotension. To assess upper gastrointestinal motility, five patients with idiopathic orthostatic hypotension underwent esophageal manometry and esophageal and gastric radionuclide transit studies. Three patients had abnormal esophageal manometric studies, and two had abnormal gastric transit. The esophageal emptying study was abnormal in one of two patients. These results and the diversity of findings suggest that the upper gastrointestinal tract is involved in idiopathic orthostatic hypotension, although further work is needed to delineate the extent and the site of the abnormality. Esophageal manometry and gastroesophageal transit studies provide a means of diagnosing patients with idiopathic orthostatic hypotension.

Index terms: Esophagus • Hypotension, orthostatic

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More than 50 years have elapsed since the first description in the American literature of primary idiopathic orthostatic hypotension (IOH) by Bradbury and Eggleston.[1] Since then, a variety of conditions mimicking the syndrome have been described.[2] In 1960, Shy and Drager[3] provided the first clinical-pathologic evaluation and description of nervous system involvement in the disorder. Idiopathic orthostatic hypotension together with somatic neurologic manifestations, such as Parkinsonism, is labelled as Shy-Drager syndrome.[4] Idiopathic orthostatic hypotension is a disease of middle to old age. The usual presenting com-

Table 1.   Characteristics and test results

Patient	Age/Sex	Diagnosis	GI Symptoms	Esophageal Manometry	Esophageal Emptying	Gastric Emptying	
						Liquid	Solid
1	51/M	Shy-Drager syndrome	none	DES, hypotensive UES	—	delayed	delayed
2	63/F	IOH	early satiety, nausea, fecal incontinence	normal	normal	normal	normal
3	52/F	Shy-Drager syndrome	none	hypotensive UES and LES, aperistalsis in proximal one-third	significant delay in distal one-third	normal	normal
4	81/M	IOH	none	normal	—	—	—
5	49/F	IOH	none	hyperdynamic esophagus	—	delayed	delayed

IOH = idiopathic orthostatic hypotension; *DES* = diffuse esophageal spasm; *UES* = upper esophageal sphincter; *LES* = lower esophageal sphincter.

plaint is weakness, and progressive orthostatism occurs along with a relatively fixed heart rate.[5] Some patients present with angina pectoris, Parkinsonism, postprandial fainting, or a variety of other complaints.[6] Many neurologic and systemic disorders are associated with altered gastroesophageal motility,[2,7] but little information is available about gastrointestinal involvement in IOH or Shy-Drager syndrome.[8,9]

We performed esophageal manometry and esophageal and gastric radionuclide transit studies in five patients with IOH and Shy-Drager syndrome. Only one patient had gastrointestinal complaints, including nausea, early satiety, diarrhea, and fecal incontinence. The results of this study form the basis of this report.

Materials and methods

Three patients with IOH and two with Shy-Drager syndrome agreed to participate in this study, which was approved by the Investigation Review Board of The Cleveland Clinic Foundation. All had been followed by the Research Division of the Cleveland Clinic and before our studies had undergone extensive studies to establish the diagnosis, including serum electrolytes, fasting glucose testing, syphilis serology, Westergren sedimentation rate, rectal biopsy, supine and upright plasma catecholamine and renin activity, and blood volume analysis. All had abnormal supine and upright arterial hemodynamic analysis results including tilt test, Valsalva maneuver, cold pressor testing, and/or baroreceptor testing.[5] With informed consent and after an overnight fast, esophageal manometry was performed followed by esophageal and gastric radionuclide analysis.

Esophageal manometry was performed with patients supine. A four-lumen catheter with openings 5 cm apart at 90° angles was passed nasally. Each lumen was perfused at a constant rate of 0.5 mL/min by a pneumohydraulic pump (Arndorfer Medical Specialties). Recorded pressures were transmitted to a Hewlett-Packard 775A recorder. The lower esophageal sphincter (LES) pressure was measured by standard station pull-through technique as previously described.[10] The LES pressure was measured in mmHg with intragastric pressure as zero reference. The tube was then positioned with its distal tip above the LES and ten wet swallows of 5 mL of water were given. The amplitude of the contractions was measured in mmHg with esophageal resting pressure as baseline. The upper esophageal sphincter (UES) pressure was measured anteroposteriorly and laterally. All tracings were reviewed by one of us (EA) who had no knowledge of the clinical history. Results were compared with previous age-matched normal subjects in our laboratory.

Esophageal transit studies were performed after manometry and in conjunction with the radionuclide gastric emptying procedure. Subjects were placed in the supine position. Two separate boluses of 100 mCi (3700 MBq) In-111-labelled DTPA (pentetic acid) in 15 mL tap water were swallowed by the patient and were recorded by the gamma camera and stored by a minicomputer at 0.5 seconds per frame for 50 seconds. Esophageal transit time was defined as the time from the entrance of radioactivity into the proximal esophagus until there was 90% clearance of the bolus from the distal esophagus, as previously reported.[11] Areas of interest for calculation of esophageal transit were defined manually with
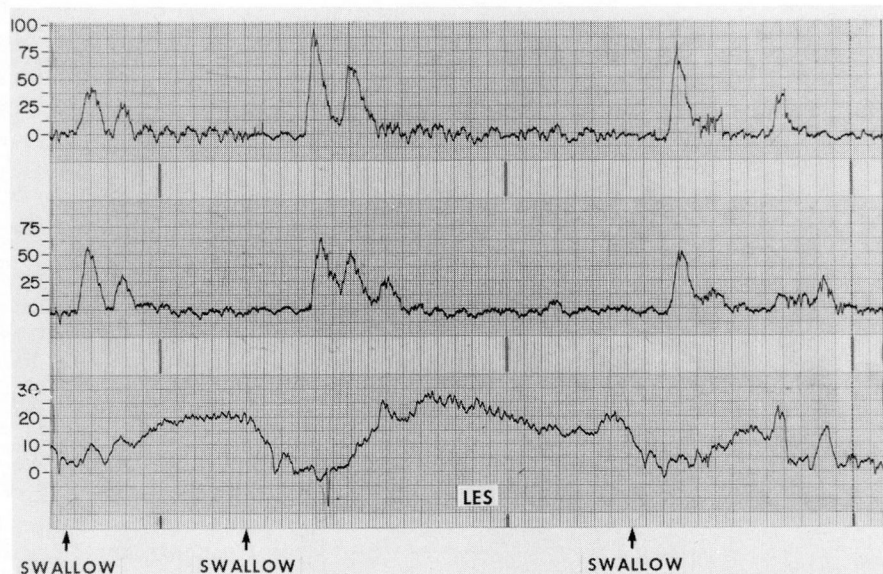
Fig. 1. Manometric tracing showing diffuse esophageal spasm. The two upper leads show simultaneous repetitive contractions. The lower lead shows normal lower esophageal sphincter relaxation.

the use of a cursor-type software program. The entire esophagus region encompassed the column of radioactivity from the cricoid cartilage to the gastroesophageal junction. This region was also divided into three equal regions for further quantification of proximal, mid, and distal esophageal transit.

Gastric emptying was evaluated by serial imaging of the abdomen for two hours at 15-minute intervals. A solid meal of cooked eggs labelled with Tc-99m-labelled sulfur colloid and the above-described liquid phase of In-111-labelled DTPA in water were employed using the technique of Malmud et al.[12] Regions of interest for gastric activity were drawn for both solid and liquid phases at each time frame. After appropriate correction for radioisotopic decay of Tc-99m and for crossover interference between the two isotopes, time-activity curves were generated, which represented the rate of gastric emptying. The derived quantitative percent gastric emptying values were then compared with established normal subjects[12,13] and with normal controls in our clinic. The results were expressed as percent of liquid emptied at one hour and two hours, and as percent of solid emptied at one hour and two hours.

Results

Five patients completed the study; three had IOH and two had Shy-Drager syndrome. There were two males and three females; ages ranged from 49–81 years. The results are summarized in *Table 1.*

Esophageal manometry

All five patients underwent esophageal manometry. The test was normal in two. One of them had a history of nausea, diarrhea, and fecal incontinence (patient 2). Three patients, free of gastrointestinal symptoms, had an abnormal esophageal motility tracing. One had diffuse esophageal spasm (DES), with a normal LES and a majority of repetitive simultaneous contractions (*Fig. 1*). This patient also had a hypotensive upper esophageal sphincter, with an average resting pressure in the lateral position of 12 mmHg (normal, 20–40 mmHg) and 51 mmHg in the anteroposterior position (normal, 60–110 mmHg). The second patient demonstrated high-amplitude peristaltic contractions consistent with the hyperdynamic "nutcracker" esophagus (*Fig. 2*). The mean contraction amplitude in the distal esophagus was 202 mmHg (normal mean ± S.D. 79.9 ± 41.05 mmHg). The third patient exhibited a nonspecific motor abnormality including a hypotensive LES (mean resting pressure, 7.5 mmHg; normal mean ± S.D. 16.6 ± 2.55 mmHg), low-amplitude nonperistaltic contractions of the striated part of the esophagus (mean pressure, 7.8 mmHg; normal mean ± S.D. 48.2 ± 21.2 mmHg), and a hypotensive upper esoph-
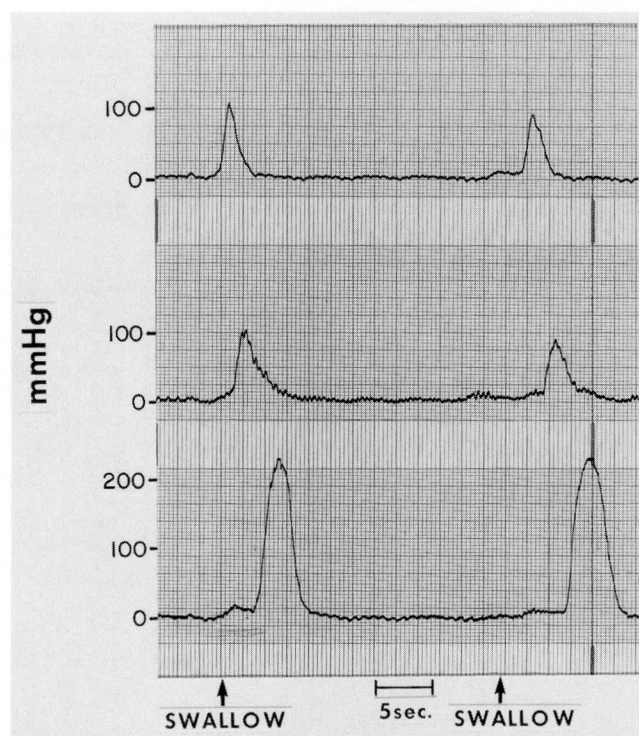
Fig. 2. Manometric tracing showing hyperdynamic esophagus with peristaltic high-amplitude contractions.

ageal sphincter with pressures in the lateral position of 10 mmHg and 12.5 mmHg in the anteroposterior position (*Fig. 3*).

Radionuclide transit studies

Radionuclide transit studies were completed in two patients. The test was normal in one patient and abnormal in another. The latter demonstrated a significant delay in emptying of the distal one-third of the esophagus when compared with controls (21 seconds vs. control <9 seconds).

Gastric emptying studies were performed in four patients. Two out of the four (patients 1 and 5) demonstrated delayed emptying of liquids at one hour and of solids at two hours after ingestion (*Table 2*).

Discussion

Idiopathic orthostatic hypotension is a rare disorder of the autonomic nervous system that tends to be progressive and disabling.[14] Most patients present with fainting spells, dizziness, or syncope. Other organ systems may be involved as well, as in two of our patients, resulting in impotence, anhidrosis, and bladder dysfunction.[5,9] The diagnosis of IOH can be made only after excluding a multitude of causes, including

pharmacologic agents, decreased circulating blood volume, adrenal insufficiency, diabetes mellitus, electrolyte abnormality, and amyloidosis.[2] Multiple system atrophy (Shy-Drager syndrome) is characterized by autonomic failure with associated somatic neurologic manifestations, such as Parkinsonism.[4]

Many disorders of the central and peripheral nervous system can influence gastroesophageal function, including diabetes mellitus, alcoholism, brain stem lesions, Parkinson's disease, amyotrophic lateral sclerosis, familial dysautonomia (Riley-Day syndrome), and congenital insensitivity to pain.[15-22] Little, however, is known regarding gastrointestinal involvement in patients with IOH or Shy-Drager syndrome. Clinical manifestations of the disorders include early satiety, nausea and vomiting, postprandial bloating, constipation, and fecal incontinence,[8,9] presumably related to the observed motility dysfunction. One of our patients with IOH had gastrointestinal symptoms, yet esophageal motility and gastric and esophageal emptying studies were normal. The exact site of the defect is unknown, but probably resides in the efferent adrenergic system with interruption of the baroreceptor reflex arc.[23] Ziegler et al[24] reported that those with central nervous system (CNS) involvement are unable to activate appropriately an otherwise normal sympathetic nervous system, whereas in those without CNS disease the deficit affects peripheral sympathetic nerves. Camilleri et al[8] noted that all four of their patients had evidence of involvement of the efferent sympathetic pathway, and Khurana et al[9] reported two patients with cholinergic and adrenergic dysfunction, and suggested that vagal denervation of the esophagus and stomach was a factor in causing symptoms.

There is currently no universally effective treatment for these disorders, and a better understanding of gastrointestinal involvement may provide a more rational approach to therapy. The pharmacologic agents currently being employed or investigated include 9-alpha fluorohydrocortisone,[5] midodrine,[25] indomethacin,[26] lisuride,[27] dihydroergotamine,[28] and lidamidine.[29] As gastrointestinal symptoms may be a cause of significant morbidity, therapeutic agents affecting gut motility such as peripheral dopamine antagonists (metoclopramide, domperidone), cholinergic agents (bethanechol), and sympathetic agonists (lidamidine, clonidine) may play a
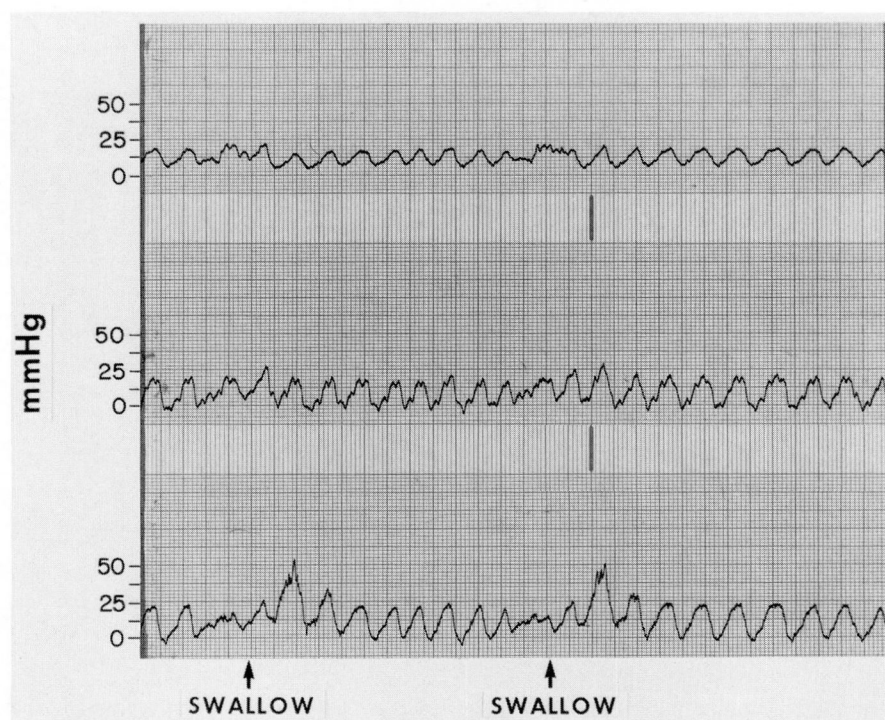
Fig. 3.   Manometric tracing showing weak, nonperistaltic esophageal contractions.

role in the treatment of these poorly understood disorders.

Camilleri et al[8] have suggested that gastric and small bowel motility studies may provide a means of documenting gut involvement in these disorders, although they are somewhat cumbersome and generally not available. Because esophageal manometry and gastroesophageal transit studies are readily available and easy to perform, they provide a means of evaluating the gastrointestinal tract in patients with this selective group of disorders.

Although esophageal transit studies were unavailable in three patients and gastric emptying studies in one, three had evidence of esophageal or gastric dysmotility. There was a spectrum of esophageal manometric disorders, including diffuse esophageal spasm, hyperdynamic esophagus,[30] and a nonspecific disorder characterized by low-amplitude contractions. We have no explanation for the diversity of findings, or why our symptomatic patient had no detectable abnormalities. Our results suggest that the upper gastrointestinal tract is involved in IOH and Shy-Drager syndrome, although further work is needed to find the extent and degree of involvement.

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Table 2.   Gastric emptying

	Percentage Emptied			
	Solid Phase		Liquid Phase	
Patient	1-hour	2-hour	1-hour	2-hour
1	21	48	22	60
2	55	96	76	99
3	45	73	80	87
4	—	—	—	—
5	16	43	46	75
Normal (mean ± 1 SD)	27 ± 10	63 ± 8	66 ± 7	87 ± 6

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