Gastroparesis After Lung Transplantation*
Potential Role in Postoperative Respiratory Complications

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Background: We observed an unexpectedly high incidence of postoperative gastroparesis among lung and heart-lung transplant recipients.

Purpose: To identify the incidence of GI complications and to describe the clinical profiles of patients who developed symptomatic gastroparesis after lung transplantation.

Patients and methods: Retrospective study of GI symptoms and complications identified during 3 years of follow-up of 38 adult lung and heart-lung transplant recipients.

Results: Sixteen of 38 patients (42%) reported one or more GI complaint and received a specific GI diagnosis. Nine of 38 patients (24%) complained of early satiety, epigastric fullness, anorexia, nausea, or vomiting. Gastroparesis was suspected when endoscopic evaluation revealed undigested food in the stomach after overnight fast and symptoms could not be attributed to peptic disease or cytomegalovirus gastritis. Delayed gastric emptying was confirmed by gastric scintigraphy. Mean gastric emptying (t½) was 263±115 min (normal <95 min). Gastroparesis occurred in 4 of 13 right lung, 2 of 12 left lung, 1 of 9 bilateral single lung, and 2 of 4 heart-lung recipients (p=NS). Patients responded partially to metoclopramide or cisapride, with the exception of two patients who required placement of jejunal feeding tubes secondary to severe symptoms. In long-term follow-up, symptoms resolved in all patients and treatment with medications or mechanical intervention was successfully discontinued.

Four of nine patients (44%) suffering from gastroparesis developed obliterative bronchiolitis (OB). Food particles were discovered in the BAL fluid of two such symptomatic patients. In contrast, only 6 of 29 (21%) nonsymptomatic patients developed OB (p=0.16).

Conclusion: Symptomatic gastroparesis is a frequent complication of lung or heart-lung transplantation that may promote microaspiration into the lung allograft.

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CMV=cytomegalovirus; OB=obliterative bronchiolitis; t½=mean gastric emptying

Key words: bronchiolitis obliterans; gastric stasis; immunosuppression

Recipients of solid organ transplants often complain of diverse abdominal symptoms that may develop from stress, intercurrent infections, or medications. The frequency of GI complaints after transplantation is variable, but may approach 35% in heart-lung transplant recipients.1 Most GI symptoms are associated with peptic ulcer disease, cytomegalovirus (CMV) gastritis, and pancreatitis, but rarer symptoms and underlying causes have been reported. One condition, gastroparesis, presents with nonspecific complaints of dyspepsia, early satiety, epigastric fullness, and occasionally nausea and vomiting.2 This condition can be easily overlooked in immunosuppressed patients treated with numerous medications. Thorough GI evaluation of symptomatic patients who had received lung or heart-lung transplants at our institution revealed an unusually high incidence of this postoperative complication.

In the present report, we review the clinical features of nine patients diagnosed as having gastroparesis following lung transplantation. Specifically, endoscopic and radioscintigraphic findings consistent with gastric stasis in the absence of current gastritis, peptic ulcer disease, or CMV infection are identified among patients complaining of nausea, vomiting, dyspepsia, and early satiety. In addition, we report an expected incidence of GI complaints and complications following lung transplantation at our institution. While gastric stasis has been reported among heart and heart-lung transplant patients,1,2 to our knowledge, this is the first description of this syndrome among lung transplant recipients.

METHODS

The study population consisted of 38 consecutive adult patients who survived lung or heart-lung transplantation at the Presbyterian
Hepatitis in New York City between 1989 and 1992. Of these 38 patients, 25 received single lung transplants (13 right lung, 12 left lung) for emphysema (n=18), pulmonary fibrosis (n=4), or pulmonary hypertension (n=3). Nine patients received bilateral single lung transplants for cystic fibrosis (n=7) or bronchiectasis (n=2). Four patients received combined heart-lung transplants for pulmonary hypertension. Eighteen (47%) patients were men and 20 (53%) were women. Mean age at the time of surgery was 42±13 years (range, 21 to 64 years). Omentectomy was not used during lung transplant surgery.

After surgery, patients underwent intensive postoperative surveillance in the hospital, followed by regular, frequent visits in the outpatient department. Complete physical examination and laboratory tests were performed weekly for the first 2 months, biweekly for the next 2 months, then at monthly intervals indefinitely. The mean follow-up time for all the patients was 19±12 months (range, 6 to 71 months) and no patients were unavailable for follow-up. Seven (18%) of the 38 patients died during the study period.

Standard immune suppression consisted of cyclosporine, azathioprine, and prednisone. Cyclosporine dosage was adjusted to maintain serum cyclosporine levels near 200 ng/mL (by fluorescent polarization immunoassay) and to maintain a serum creatinine level of 175 µmol/L or less. After the first 6 postoperative months, cyclosporine levels were maintained near 150 ng/mL. After 1 year of surgery, maintenance levels were near 100 ng/mL. Treatment with prednisone, 1 mg/kg/d, was begun immediately postoperatively and tapered to 0.1 to 0.15 mg/kg/d by 3 months after surgery. Treatment with azathioprine, 2 mg/kg/d, was adjusted to maintain the WBC count above 4,000/µm³ and platelet count above 100,000/µm³. Episodes of rejection were treated with daily infusion of methylprednisolone, 1 g IV for 3 days.

In the absence of symptoms, surveillance fiberoptic bronchoscopy with transbronchial biopsies were performed routinely at 1 month postoperatively and then every 3 months for the first postoperative year. Alternatively, bronchoscopy and biopsies were performed for clinical indications (suspicion of infection or rejection). During the second postoperative year, surveillance biopsies were performed every 4 months, and thereafter, biopsy specimens were obtained every 6 months.

Patients complaining of persistent and severe GI symptoms, not occasional discomfort, were referred for further evaluation. Those describing abdominal symptoms suggestive of delayed gastric emptying (n=9; 24%), such as nausea, vomiting, early satiety, or epigastric fullness, underwent upper endoscopy (n=8) and/or radioscintigraphy (n=7).

Upper GI endoscopy was performed after overnight fast to examine the esophagus, stomach, and duodenum. After visual inspection, gastric biopsy specimens were taken from areas of inflammation or randomly if the mucosa appeared normal. Biopsy specimens were sent for pathology and CMV cultures. Patients demonstrating CMV gastritis on gastric biopsy specimen (n=2) were treated with ganciclovir for 14 days and then underwent another endoscopic examination before undergoing radioscintigraphic tests for delayed gastric emptying.

The kinetics of gastric emptying were evaluated scintigraphically according to standard protocol.3 Oral administration of a bread and egg meal containing 0.5 mCi of technetium 99m-labeled sulfur colloid was followed by serial scintiphotos of the stomach obtained at 1-min intervals for 60 min. If gastric emptying was delayed, serial scanning was continued for a maximum of 360 min. The mean gastric emptying (t½) was extrapolated and compared with controls. The upper limit of normal for gastric emptying t½ at this institution is 35 min.

Comparison of observed proportions was performed by χ² test, or by two-tailed Fisher’s Exact Test when the numbers were small. A p value of less than 0.05 was considered significant.

### RESULTS
Persistent GI symptoms were described on follow-up clinic visits for 16 of 38 (42%) patients (Table 1). Specific symptoms were abdominal pain (n=10), dyspepsia (n=8), nausea and vomiting (n=7), early satiety (n=6), and severe diarrhea (n=1). There were 29 specific GI diagnoses in 16 (42%) of 38 patients (Table 1). The most common diagnoses were gastritis (n=9) and gastroparesis (n=9). Three patients had symptomatic cholelithiasis and required cholecystectomy. Rarer complications included duodenal ulcer (n=2) and one case each of intussusception, ileal ulcer, upper GI bleeding, small bowel obstruction, pancreatitis, and rectal polyps. The endoscopic biopsy specimens of two patients with gastritis were diagnostic for CMV disease. Following pharmacotherapy, subsequent endoscopic biopsy specimens did not indicate CMV disease.

Nine patients with persistent symptoms of nausea, vomiting, dyspepsia, or early satiety were evaluated with endoscopy (n=8) and gastric scintigraphy (n=7). Clinical features of these nine patients are listed in Table 2. The average age of affected patients was 39±2 years, and similar to the age of unaffected patients (41±3 years; p=NS). Six of nine patients described nausea and vomiting, six reported early satiety, and four complained of dyspepsia. The mean onset of symptoms was 3.4±2.4 months (median, 3.0 months; range, 1 to 8 months) after surgery. Evidence of delayed gastric emptying (retained food on endoscopy or gastric emptying t½>95 min) was demonstrated in all patients. The average t½ gastric emptying of the seven patients in whom it was measured was 263±115

| Table 1—GI Symptoms and Diagnoses Among Lung and Heart-Lung Transplant Recipients |
|-----------------------------------|-------------------|
| GI symptoms                        | No. of Patients   |
| Abdominal pain                     | 10                |
| Dyspepsia                          | 8                 |
| Nausea and vomiting                | 7                 |
| Early satiety                      | 6                 |
| Severe diarrhea                    | 1                 |
| No. of patients with one or more GI symptoms | 16 (42%) |

<table>
<thead>
<tr>
<th>GI diagnosis</th>
<th>No. of Patients</th>
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<tbody>
<tr>
<td>Gastroparesis</td>
<td>9</td>
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<tr>
<td>Gastritis</td>
<td>9</td>
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<td>GI ulcer</td>
<td>3</td>
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<td>Cholelithiasis/cholecystitis</td>
<td>3</td>
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<tr>
<td>Pancreatitis</td>
<td>1</td>
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<td>Upper GI bleed</td>
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<td>Small bowel obstruction</td>
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<td>Intussusception</td>
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<td>Rectal polyps</td>
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<td>No. of patients with one or more GI diagnoses</td>
<td>16 (42%)</td>
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min (range, 105 to 360 min). Two of these patients had essentially no gastric emptying after 360 min. In these two instances, the used for calculations was 360 min with the understanding that this represented a minimum estimation based on the limits of the test performed.

Gastroparesis occurred in 4 of 13 right lung, 2 of 12 left lung, 1 of 9 bilateral single lung, and 2 of 4 heart-lung recipients (p=NS). Patients were treated initially with metoclopramide. Five patients who failed to respond to metoclopramide were given cisapride. Two patients who were unable to maintain adequate caloric intake required jejunal feeding tubes. Ultimately, symptoms gradually abated over 3 to 6 months in surviving patients and treatment with medications or mechanical intervention was successfully discontinued.

Lung biopsy specimens were reviewed for correlation with symptomatic gastroparesis. Acute inflammation and or acute pneumonia was noted in the biopsy specimens of 4 of 9 patients (44%) with gastroparesis and 5 of 29 (19%) without gastroparesis. Obliterative bronchiolitis (OB) was diagnosed in biopsy specimens of 10 of 38 (26%) patients. These specimens were obtained at autopsy (n=4), transbronchial biopsy (n=3), or open lung biopsy (n=3). Four of the 9 (44%) patients with documented gastric stasis developed OB, whereas only 6 of the remaining 29 (21%) patients developed OB (p=0.16). Food particles were observed in the BAL fluid of two patients with OB and symptomatic gastroparesis.

**Case Reports**

A 23-year-old-woman with idiopathic pulmonary hypertension underwent right lung transplant. The early postoperative course was complicated by severe ischemia-reperfusion injury, respiratory insufficiency, and bilateral pneumonitis. She recovered sufficiently to leave the hospital 2 months after transplant. One month later, she developed upper abdominal pain, nausea, and vomiting. Upper endoscopy revealed retained food particles, but no ulcers or CMV gastritis. Gastric scintigraphy showed markedly prolonged gastric emptying (t½=337 min; normal <95 min). There was little response to metoclopramide and cisapride therapy. The patient failed to maintain an adequate caloric intake and received a gastrostomy with jejunal feeding tube for nutrition. As her pulmonary function declined, a transbronchial biopsy specimens revealed bronchiolitis obliterans. In addition, food particles were observed in the BAL fluid and lung parenchyma.

A 62-year-old-man with emphysema underwent right lung transplant. The early postoperative course was complicated by Pseudomonas pneumonia. Two months after surgery, the patient complained of nausea and abdominal fullness. Endoscopy revealed gastritis and biopsy specimens were positive for CMV. Repeat endoscopy after a 2-week course of ganciclovir showed massive retention of food particles. Biopsy specimens were negative for CMV. Scintigraphy revealed essentially no gastric emptying after 360 min. The patient suffered repeated respiratory infections. BAL demonstrated numerous food particles. The patient died of Pseudomonas sepsis. Postmortem examination revealed OB in the transplanted lung.

A 51-year-old-man with emphysema underwent left lung transplant. He had a history of peptic disease and selective vagotomy and pyloroplasty 15 years earlier. Two months after surgery, he complained of early satiety and abdominal pain. Upper endoscopy revealed a patent pyloroplasty and mild gastric erythema, with biopsy specimens that did not show CMV. By scintig-
raphy, he had essentially no gastric emptying after 6 h. After only minimal improvement with metoclopramide therapy, he was treated with cisapride. The patient’s condition failed to improve; he had persistent intermittent nausea but no weight loss. His respiratory function deteriorated and he died of OB and respiratory insufficiency. Evidence for aspiration of gastric contents was not documented.

A 45-year-old-man with emphysema experienced peptic ulcer disease 25 years earlier, but was without abdominal pain for at least 10 years prior to left lung transplant. His postoperative course was complicated by recurrent bacterial pneumonia and acute rejection. Four weeks after transplant, he developed nausea and vomiting with postprandial abdominal distress. Endoscopy was significant only for prepyloric erythema. Gastric emptying was prolonged (t½ emptying=162 min). A trial of metoclopramide therapy resulted in some improvement, although symptoms waxed and waned over the next 6 months until they finally resolved completely.

A 22-year-old-woman with congenital heart disease and resultant Eisenmenger’s syndrome underwent combined heart and lung transplant. The posttransplant course was complicated by early lung rejection and an episode of CMV pneumonitis. Four months after surgery, she complained of progressive abdominal pain, vomiting, and inability to tolerate oral feedings. Endoscopy showed a large amount of retained food, a patent pylorus, and gastric erythema. Biopsy specimens did not show CMV, and no ulcers were noted. The patient experienced a dystonic reaction to metoclopramide and was started on a regimen of cisapride. Symptoms were refractory to high doses of cisapride, and she required percutaneous gastrostomy and a jejunal feeding tube. Over the next 6 months, symptoms abated and the patient no longer required jejunal feeding.

A 30-year-old-woman with cystic fibrosis underwent bilateral single lung transplant. Two months after transplant, she complained of epigastric pain and vomiting. Upper endoscopy revealed a pyloric channel ulcer and small erosions. Gastric biopsy specimens showed the presence of CMV inclusion cells. She was treated with ranitidine and ganciclovir. After brief improvement, her symptoms recurred. Repeated endoscopy 1 month later revealed large amounts of retained food, without ulcerations, erosions, or erythema. Biopsy specimens did not show CMV. The patient was treated with metoclopramide and her symptoms improved but never resolved completely.

**DISCUSSION**

Lung and heart-lung transplantation have become accepted treatment modalities for end-stage pulmonary disease at many institutions worldwide. In recent years, operative mortality has declined and 1- and 3-year survival rates have improved. Respiratory infection and chronic allograft rejection, however, remain important causes of postoperative mortality. One study of heart-lung transplant recipients identified GI complications as a potential precipitant of respiratory infection and as a factor in up to 35% of cases of perioperative mortality. The present report describes GI symptoms and complications exhibited by a population of lung transplant recipients. Nearly half of all patients experienced at least one GI complication after lung transplantation. This incidence of GI symptoms and complications is similar to that observed among heart and heart-lung transplant recipients.

In this study population, we noted an unusually high incidence of symptomatic gastroparesis (9/38, 24%). The diagnosis of gastroparesis was established by direct endoscopic demonstration of retained food after overnight fast in patients who commonly complained of nausea, vomiting, and abdominal pain within 3 to 6 months of surgery. The diagnosis was further confirmed by markedly prolonged gastric emptying during scintigraphic studies. Patients frequently required cholinergic stimulants or dopamine antagonism for symptomatic relief; two required jejunal feeding tubes. All surviving patients eventually had improved conditions without additional surgical intervention.

The differential diagnosis of gastroparesis can be subdivided into several categories that include inflammatory disease, infectious disease, mechanical obstruction, drug toxicity, and metabolic disease, neuropathic or idiopathic. Lung transplant recipients, by virtue of their immunosuppression and previous surgery, may be predisposed to many of these inciting factors. The delayed onset, waxing, and waning course is most suggestive of a neuropathic or idiopathic cause of gastroparesis. Patients variably reported symptoms within several weeks to months after surgery (mean, 3.4±2.4 months) without a distinct precipitating event. No patient described symptoms immediately after surgery or within several days of an acute infectious or inflammatory disease. Symptoms were especially pronounced after meals and the vomitus tended to be characterized by partially digested food. Symptoms exhibited a waxing and waning pattern that ultimately led to partial or complete remission. This clinical presentation does not support the chronic, progressive pattern of obstructive gastric dysmotility or the acute presentation of postinfectious gastroparesis. Rather, the late onset, chronically waxing and waning course would be expected from idiopathic or neuropathic gastroparesis. We suspect that some of the delay in the patient’s reporting of gastroparesis symptoms relates to postoperative respiratory difficulties, poor oral intake, and general lack of appetite. Furthermore, other postoperative medical conditions (such as pain, pleural effusions,
chest tubes, narcotics, high-dose corticosteroids, etc) disrupt the normal homeostatic humoral regulation of gastric emptying (gastrin, secretin, motilin, cholecystokinin, etc). All of these difficulties generally resolve by 1 month after surgery, when patients begin to feel well, go home, and eat well (in part due to appetite stimulation of corticosteroids and in part due to general well-being).

It has long been known that truncal vagotomy decreases antral motility and slows gastric emptying of solid foods by interfering with receptive relaxation of the proximal stomach in response to distention of the throat or esophagus.\(^5\,^9\) Even after vagotomy, patients experience the sensation of gastric distention, as the distal stomach is still innervated by splanchnic nerves that contain an afferent pathway that may transmit the sensation of visceral stretch receptor stimulation. Gastroparesis has been reported, albeit infrequently, among heart-lung transplant recipients,\(^1,\,^2,\,^10\) and it has been postulated in such cases that inadvertent vagotomy or vagal injury (thermal, ischemic) during dissection of the posterior mediastinum may cause this postoperative complication. It remains unclear, however, if inadvertent vagal injury is the cause of gastroparesis in single lung transplant recipients. The vagus nerve bundles are well guarded and generally unexposed during the operation, and the affected population included patients who had received either right lung, left lung, or combined heart-lung transplants. The former two procedures can at best be expected to lead to unilateral vagotomy, while only bilateral vagal injury is thought to cause gastric dysmotility.

An alternative cause of gastric stasis in these patients could be a direct toxic effect of the immunosuppressive medications—cyclosporine, azathioprine, and prednisone. The absence of gastroparesis among liver and kidney transplant recipients and the paucity of reporting among heart transplant recipients,\(^1,\,^2,\,^10\) mitigates against the suggestion that immunosuppressive medications are the causative agents. However, the use of higher-maintenance doses of cyclosporine to control smoldering airway rejection in the transplanted lung complicates any such comparison. Additionally, as cyclosporine becomes increasingly implicated in the derangement of cardiovascular tone and the development of peripheral neuropathy, its contribution to the development of gastroparesis becomes more tenable.

Gastroparesis could be a sequel of GI infection in the immunosuppressed host. Viral illness has been reported to precede the appearance of gastric stasis\(^11\) and immunosuppression could increase the likelihood of such a temporal association. In two of our patients, CMV gastritis preceded the onset of abdominal bloating. Nevertheless, symptoms of gastroparesis persisted even after resolution of CMV gastritis. In the remain-}

ing patients of the study, biopsy specimens did not show viral and bacterial pathogens. Because this syndrome is rare in other solid organ recipients, it does not appear to be simply an effect of immunosuppression and secondary infection.

The two major respiratory complications of lung transplantation are pulmonary infection and rejection. The high incidence of respiratory infection after lung transplantation may be a consequence of immunosuppression and the sequelae of surgery that include tissue ischemia, denervation, interruption of lymphatic drainage, and altered mucus transport.\(^12,\,^13\) OB is an inflammatory process affecting small airways that probably represents chronic rejection. Tissue biopsy specimens reveal a cellular infiltrate of lymphocytes, plasma cells, histiocytes, and some neutrophils but, in later stages, fibrosis is the major pathologic finding.\(^14\)

In light of these findings, gastroparesis is of special relevance to the lung transplant recipient because by promoting bacterial overgrowth and enabling gastro-esophageal reflux, it may predispose to microaspiration\(^9\) and lead to respiratory infection and rejection. The inflammatory response induced by microaspiration may augment transplant rejection by facilitating the encounter of alloreactive lymphocytes with foreign tissue and antigens. Although we noted a trend toward a relation between gastroparesis and OB, it did not achieve statistical significance. Other risk factors for OB, including CMV infection and repeated episodes of acute rejection, may obscure the contribution of microaspiration to OB. Nevertheless, improved recognition and early treatment of gastroparesis may reduce or limit the progression of OB in lung transplant recipients.

In summary, GI symptoms are a common postoperative complication of lung and heart-lung transplantation. This report describes an association between lung transplantation and symptomatic gastroparesis that has strong clinical implications regarding maintenance of GI and lung function after transplantation.

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