Sole Treatment of Acid Gastroesophageal Reflux in Idiopathic Pulmonary Fibrosis*

A Case Series

Ganesh Raghu, MD, FCCP; Steve T.-Y. Yang, MBBS; Carolyn Spada, RN; Jennifer Hayes, RN; and Carlos A. Pellegrini, MD

Rationale: Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal disease despite the available treatment regimes. Increased acid gastroesophageal reflux (GER) occurs in IPF patients.

Objectives: To follow the course of IPF in patients while being treated for acid GER alone.

Methods: A retrospective review of the clinical outcomes of four patients with newly diagnosed IPF and increased acid GER who chose to be treated solely with anti-acid GER therapy were followed up regularly with pulmonary function tests (PFTs) [measuring FVC and the diffusing capacity of the lung for carbon monoxide] over a period of 2 to 6 years. Anti-acid GER therapy was administered using proton-pump inhibitors and fundoplication, if needed. Adequate suppression of acid GER was ascertained by 24-h esophageal pH monitoring.

Main results: PFT results in all four patients stabilized or improved while their conditions were maintained with adequate treatment for acid GER. All patients were alive at the last follow-up, and none manifested an acute exacerbation of IPF or needed treatment for respiratory problems during this period. After maintaining 4 years of improved status (based on PFT and exercise testing findings) while adhering to treatment for acid GER, one patient’s deterioration correlated with poor compliance to daily treatment during the fifth year, although the PFT results at the sixth year showed stabilization compared to baseline values. The condition of another patient was stabilized by adhering to anti-acid GER treatment after an initial period of deterioration that was associated with nonadherence.

Conclusions: Future clinical studies are indicated to clarify the role of acid GER in IPF and to determine whether adequate treatment for increased acid GER in part improves the outcome of patients with IPF.

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Key words: acid gastroesophageal reflux; fundoplication; idiopathic pulmonary fibrosis; proton pump inhibitor

Abbreviations: ATS = American Thoracic Society; DLco = diffusing capacity of the lung for carbon monoxide; GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease; HRCT = high-resolution CT; IPF = idiopathic pulmonary fibrosis; PFT = pulmonary function test; PPI = proton pump inhibitor; 6MWT = 6-min walk test; SLB = surgical lung biopsy; SpO2 = pulse oximetric saturation; UIP = usual interstitial pneumonitis; UWMC = University of Washington Medical Center

Idiopathic pulmonary fibrosis (IPF) is a relentless, progressive disease that usually leads to death within 5 years of diagnosis.1–5 Usual interstitial pneumonitis (UIP) is the underlying lesion in IPF, which is the most common subset of the idiopathic interstitial pneumonias. In most patients, the disease occurs in adults >50 years of age, who present with dyspnea of insidious onset that is characterized by chronic progression, failure to respond to corticosteroid and immunosuppressive therapy, and death from respiratory failure unless the patient undergoes lung transplantation. In the appropriate clinical setting, the definitive diagnosis of IPF relies on the histologic appearance of UIP on surgical lung biopsy (SLB) specimens.6 In the absence of a SLB specimen, the likelihood of a correct diagnosis of IPF is increased by using major and minor clinical criteria, as outlined in the American Thoracic Society (ATS)/European Respiratory Society consensus statement.7–9

Optimal therapy for IPF is problematic.10 To date, treatment strategies have been based on eliminating or suppressing inflammation and/or fibroproliferation. However, such therapeutic interventions have been ineffective.

Current concepts about the pathogenesis of IPF speculate that recurrent insults to the lung epithelium play a key role.11 Different strategies have not addressed possible etiologic and risk factors associated with IPF. Since >90% of patients with IPF have increased acid gastroesophageal reflux (GER),12 we hypothesize that increased acid GER is an important risk factor for IPF development and/or progression. We describe the cases of four selected patients with IPF whose pulmonary function either stabilized or improved with adequate treatment for increased

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acid GER alone. Their course of IPF was influenced by their compliance with adequate treatment for increased acid GER alone.

**Materials and Methods**

A retrospective review of patients who met all of the following inclusion and exclusion criteria and had been managed for IPF at the University of Washington Medical Center (UWMC), Seattle, WA, were selected in this case series. The IPF patient database that is maintained in the Interstitial Lung Disease Clinic at the UWMC was reviewed for potential subject inclusion in this study. The clinical data were gathered in a retrospective manner and with the approval of the University of Washington Human Subjects Review Committee.

**Inclusion Criteria**

1. New-onset IPF (ie, gradual progression of exertional dyspnea during the 24 months preceding the confirmation of diagnosis)
2. Meeting the criteria for IPF, which were in accordance with the ATS/European Respiratory Society consensus statement on IPF (sensitivity, 69%; specificity, 95%)7,8:
   - The presence of symptoms and/or documented GER disease (GERD) or increased acid GER as determined by 24-h esophageal pH probe testing
   - Refusal to receive conventional therapy for IPF (ie, low-dose prednisone and azathioprine or cyclophosphamide); and
   - Refusal to participate in available clinical trials and/or to receive any other medical treatment (including over-the-counter N-acetyl-cysteine) or agents that could potentially target cytokine mediators and their effects, which are implicated in the pathogenesis of inflammation and fibrosis, and/or drugs that are considered experimental or off-label for the treatment for IPF (see “Exclusion Criteria” subsection).

**Exclusion Criteria**

1. Advanced IPF (ie, diffusing capacity of the lung for carbon monoxide [DLCO], <30% predicted; FVC, <30% predicted; and unable to perform adequate pulmonary function tests [PFTs] because of extreme shortness of breath or intractable cough) at baseline
2. Received conventional medical treatment for IPF (ie, prednisone, azathioprine, cyclophosphamide, immunosuppressive agents, and colchicine) prior to initiating treatment for GER (see below), and any other concurrent medication implicated for treatment of IPF, including N-acetyl-cysteine or any concurrent new/experimental drugs implicated for the treatment of IPF (eg, agents known to modulate the effects of specific cytokines implicated in the pathogenesis of IPF, such as γ-interferon, etanercept, mycophenolate, imatinib, pirfenidone, pentoxifylline, infiximab, leflunomide, bosentan, and sildenafil);
3. Evidence of air-trapping and/or bronchodilator response on baseline PFT (FEV1/FVC ratio, < 0.7; residual volume by body plethysmography, > 120% predicted; and 10% improvement in FVC after treatment with inhaled bronchodilators or 15% improvement in FEV1 after treatment with inhaled bronchodilators9); and
4. Any comorbid conditions affecting the overall outcome and clinical course of IPF (eg, neoplasms, severe hepatic, renal, and cardiac disease, uncontrolled diabetes mellitus, angina, deep venous thrombosis, pulmonary embolism, and collagen vascular disease).

**Documentation of Acid GER and Treatment for Acid GER**

The presence of increased acid GER was confirmed by ambulatory 24-h esophageal pH probe monitoring. A DeMeester score of > 14.72 was considered to be positive for increased acid GER (sensitivity, 96%; specificity, 96%).14 All patients were prescribed daily proton pump inhibitor (PPI) therapy (initial dose, 40 mg of omeprazole or its substitute 30 min before dinner) and were advised to follow conservative measures to decrease GER (ie, elevation of the head of the bed by placing 8-inch blocks on the floor, minimizing foods and beverages known to provoke acid GER, avoiding bedtime snacks, and lying supine for 3 to 4 h after a meal).

**Follow-up**

All patients were seen at baseline and during regular follow-up appointments at the UWMC, and all interim clinical events, if any, were reviewed with the patient and noted in clinic records. All PFTs and 24-h esophageal pH monitoring tests were performed at the UWMC.

Patients were followed up at regular intervals (ie, every 3 to 6 months during the first year, and, if stable, every 4 to 6 months during the second year, and every 6 to 12 months during the subsequent years). Spirometry and DLCO measurements (corrected for hemoglobin level) were routinely performed in accordance with ATS recommendations at intervals of 6 months.15,16 Exercise testing was performed in accordance with the protocol followed at our center for similar patients. This included performing a 6-min walk test (6MWT) while breathing room air on a premeasured, designated, flat surface and continued exertion in patients demonstrating pulse oximetric saturation (SPO2) of >80% during the 6MWT by stair climbing (climbing consecutive steps as a continuum of the 6MWT) escorted by a designated respiratory therapist with continuous pulse oximetry monitoring. For patients demonstrating a resting SPO2 of < 85%, the 6MWT is performed using supplemental oxygen that was titrated to keep the SPO2 at > 80% during the 6MWT. For all patients with an SPO2 of > 85% while breathing air at rest, the 6MWT and exercise test is performed while breathing room air first and then with supplemental oxygen in patients demonstrating an SPO2 of ≥ 88% during the 6MWT.17 While the exercise test was performed during follow-up at variable intervals for all patients, only one patient had baseline exercise test data available to compare with the results of subsequent exercise tests during follow-up.

None of the patients underwent pulmonary rehabilitation during this period. Patients were considered to be stable, improved, or deteriorated based on the ATS international consensus statement on IPF.7

**Case 1**

IPF was diagnosed in a 68-year-old woman based on typical clinical features, nondiagnostic bronchoscopy findings (ie, using BAL and transbronchial lung biopsy), and high-resolution CT (HRCT) scan of the chest findings consistent with a UIP pattern.4,7 Baseline patient demographics and PFT results are summarized in Table 1. The results of the patient’s 6MWT and exercise test results at baseline and during follow-up are shown in Table 2. An esophagogastrarduodenoscopy performed for longstanding symptoms of GERD revealed a hiatal hernia and grade 4 esophagitis with linear erosions and ulceration. She was started on home oxygen therapy for the noted hypoxemia and on daily PPI therapy (omeprazole, 40 mg) for GERD. Because of persistent symptoms of GERD, PPI therapy was maximized (omeprazole, 40 mg bid 30 min before meals). A 24-h esophageal pH probe study that was performed 6 weeks later revealed persis-
tently increased acid GER despite receiving the maximum omeprazole dosage during the 24-h pH probe test (DeMeester score, 76.5; normal score, 14.72).14

The patient underwent laparoscopic repair of the hiatal hernia with Nissen fundoplication. Six months after undergoing fundoplication, a significant decrease in acid GER was documented by a 24-h pH probe test (DeMeester score, 25.9). She became asymptomatic, and objective measurements of PFT results, 6MWT distance, and exercise test results showed an improvement during follow-up (Table 2). The patient did not feel the need to take PPIs on a daily basis. Six months later, she began to experience exertional dyspnea again. Her PFT results and 6MWT distance demonstrated a downward trend (Table 2). A repeat 24-h esophageal pH probe study showed a recurrence in increased acid GER with a DeMeester score of 57.0 (12 months after fundoplication). Treatment with twice daily PPIs and

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>68</td>
<td>65</td>
<td>57</td>
</tr>
<tr>
<td>Gender†</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>IPF diagnosis</td>
<td>All major and minor criteria</td>
<td>All major and minor criteria</td>
<td>UIP on SLB, all major and minor criteria</td>
</tr>
<tr>
<td>Duration of symptoms prior to diagnosis of IPF, mo</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Ex-smoker</td>
<td>Ex-smoker</td>
<td>Nonsmoker</td>
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<tr>
<td>Baseline PFT results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC, L (% predicted)</td>
<td>2.18 (74)</td>
<td>3.29 (97)</td>
<td>2.56 (67)</td>
</tr>
<tr>
<td>DLco, mL/min/mm Hg (% predicted)</td>
<td>10.7 (45)</td>
<td>14.4 (67)</td>
<td>15.0 (60)</td>
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</tbody>
</table>

Reflex assessment for acid GER

Baseline positive EGD* and 24-h pH probe results;
Positive 24-h pH probe results despite maximal PPI dose (40 mg of omeprazole bid);
Negative 24-h pH probe results after fundoplication;
Positive 24-h pH probe results 1 yr postfundoplication;
Subsequent negative 24-h pH probe results while receiving PPIs and H2- antagonists

Baseline positive 24-h pH probe result;
Negative 24-h pH probe results while receiving PPIs (40 mg of omeprazole qd);
Baseline positive 24-h pH probe result;
Baseline positive 24-h pH probe result;
Baseline positive 24-h pH probe results;
Negative 24-h pH probe results while receiving PPIs (40 mg of omeprazole qd)

Treatment for acid GER

PPIs, fundoplication, and conservative measures
PPIs and conservative measures
PPIs and conservative measures
PPIs and conservative measures

*EGD = esophago-gastro-deodenoscopy.
†Acknowledging that IPF is more prevalent in men, the fact of female gender in all of these four patients is coincidental.

The patient underwent laparoscopic repair of the hiatal hernia with Nissen fundoplication. Six months after undergoing fundoplication, a significant decrease in acid GER was documented by a 24-h pH probe test (DeMeester score, 25.9). She became asymptomatic, and objective measurements of PFT results, 6MWT distance, and exercise test results showed an improvement during follow-up (Table 2). The patient did not feel the need to take PPIs on a daily basis. Six months later, she began to experience exertional dyspnea again. Her PFT results and 6MWT distance demonstrated a downward trend (Table 2). A repeat 24-h esophageal pH probe study showed a recurrence in increased acid GER with a DeMeester score of 57.0 (12 months after fundoplication). Treatment with twice daily PPIs and

Table 2—Sequential PFTs, 6MWTs, and Exercise Tests in Case 1 and Association With Acid GER

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>6 mo</th>
<th>12 mo</th>
<th>24 mo</th>
<th>36 mo</th>
<th>48 mo</th>
<th>60 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L (% predicted)</td>
<td>2.18 (74)</td>
<td>2.47 (84)</td>
<td>2.44 (85)</td>
<td>2.91 (101)</td>
<td>2.61 (93)</td>
<td>2.46 (86)</td>
<td>2.11 (73)</td>
</tr>
<tr>
<td>DLco, mL/min/mm Hg (% predicted)</td>
<td>10.7 (45)</td>
<td>14.5 (62)</td>
<td>11.6 (50)</td>
<td>13.6 (59)</td>
<td>13.4 (58)</td>
<td>13.2 (58)</td>
<td>11.2 (50)</td>
</tr>
<tr>
<td>Acid GER determined by 24-h esophageal pH probe</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise test on room air</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO2 at rest, %</td>
<td>95</td>
<td>97</td>
<td>98</td>
<td>97</td>
<td>98</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Lowest SpO2 during 6MWT, %</td>
<td>93</td>
<td>96</td>
<td>92</td>
<td>93</td>
<td>93</td>
<td>95</td>
<td>94</td>
</tr>
<tr>
<td>6MWT, feet</td>
<td>700</td>
<td>800</td>
<td>1000</td>
<td>1400</td>
<td>1500</td>
<td>1220</td>
<td></td>
</tr>
<tr>
<td>Lowest SpO2 during climbing stairs,* %</td>
<td>85</td>
<td>93</td>
<td>93</td>
<td>93</td>
<td>96</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Dyspnea grade (Borg scale) at end of exercise</td>
<td>7</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

*Stairs were 60 consecutive steps (each step was 6.5-in high) as a continuum of 6MWT (three floors or 32.5 feet in vertical height).
H₂-receptor antagonists was reinitiated. The results of another 24-h esophageal pH probe study performed 6 weeks later was normal (DeMeester score, 8.3). PFTs and the 6MWTs performed 1 year after the reinitiation of PPI and H₂-receptor antagonist therapy (2 years after fundoplication) showed stability (Table 2). The patient felt well and became asymptomatic. Based on the subjective and objective perceptions of stability, she discontinued receiving anti-reflux medication. During the subsequent follow-up, the FVC demonstrated a downward trend (Fig 1, top, a); she was advised to resume treatment for increased acid GER. At the last follow-up (6 years after presentation), the patient was alive and asymptomatic. However, the FVC deteriorated compared to the improved status noted at 2 years of follow-up (Fig 1, top, a), but, compared to her condition at baseline, her condition remains stable.

**Case 2**

A 65-year-old woman with clinical features of IPF including chest HRCT scan findings that were consistent with a UIP pattern had a strong family history of definite IPF affecting the patient’s mother and a maternal aunt (UIP confirmed by autopsy). The baseline patient demographics and initial PFT results are summarized in Table 1. The patient had symptomatic heartburn that was worse when in the supine position. She was treated with daily PPI therapy (omeprazole, 40 mg), and her GER symptoms subsided. Six weeks later, the patient underwent 24-h esophageal pH probe testing while receiving PPIs to ascertain whether the acid GER was adequately suppressed. This testing confirmed no increased acid exposure (DeMeester score, 5.7).

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**Figure 1.** Change in predicted FVC and DLCO over time.
She was followed regularly over the next 5.5 years while still receiving daily PPI therapy alone, and her PFT results remained unchanged from baseline. A repeat chest HRCT scan revealed no progression when compared to the baseline chest HRCT scan findings. However, she complained of an increase in cough. In view of the downward trend in DLco at 5.5 years (Fig 1, top middle, b) as well as symptoms of cough despite daily PPI therapy, she was prescribed twice-daily therapy with PPIs. Her cough subsided, and 1 year later (6.5 years after presentation) she remained stable (Fig 1, top middle, b).

Case 3

The patient was a 69-year-old woman in whom definite IPF with exertional dyspnea was diagnosed, with chest HRCT scan findings consistent with the UIP pattern as well as SLB findings with lung histology revealing UIP. Baseline patient demographics and initial PFT results are summarized in Table 1. A 24-h esophageal pH probe test revealed increased acid GER (DeMeester score, 32.7) despite the patient being asymptomatic for GER. She elected to undergo sole therapy for acid GER. A repeat 24-h esophageal pH probe test performed 6 weeks later while receiving PPI was negative (DeMeester score, 5.4). At the 2-year follow-up, the patient felt stable subjectively with PFT results showing stability (Fig 1, bottom, d).

Case 4

The patient was a 57-year-old woman in whom definite IPF was diagnosed based on a chest HRCT scan and an SLB showing the UIP pattern. Baseline patient demographics and initial PFT results are summarized in Table 1. Six months after diagnosis, she was noted to have had deteriorating PFT results (FVC, 2.27 L [63% predicted]; DLco, 15.0 mL/min/mm Hg [60% predicted]). She had symptomatic acid GER, and a 24-h esophageal pH probe test was positive (DeMeester score, 40.2; normal score, <14.72). The patient began receiving daily PPI therapy (omeprazole, 40 mg). One year later, she had worsening exertional dyspnea and persistent symptoms of GER; her PFT results showed a decline (Fig 1, bottom, d). When questioned about compliance with treatment for acid GER with PPIs, the patient admitted not being compliant with anti-acid GER therapy despite increased symptoms and objective deterioration. She refused to receive conventional treatment with combined prednisone and azathioprine as well as other treatment options including participating in clinical trials. Since her decline in PFTs coincided with her stopping the treatment for acid GER, she opted to resume and adhere to treatment for acid GER. During subsequent follow-ups, she became asymptomatic for GER and felt subjectively stable; PFT results showed stability. A repeat 24-h esophageal pH probe test while receiving PPI therapy was negative (DeMeester score, 9.1). At the last follow-up (2 years after presentation), she remained subjectively and objectively stable (Fig 1, bottom, d).

**DISCUSSION**

The direct relationship between lung injury induced by acid and pulmonary fibrosis has been demonstrated in animals. We have demonstrated an increased acid GER in 87 to 91% of patients with IPF in two prospective studies. In these studies, 25 to 47% of patients with IPF exhibited classic symptoms of GER such as heartburn or regurgitation despite having objective evidence of abnormal acid GER. Furthermore, treatment with standard doses of PPIs suppressed acid GER in only 37% of patients with IPF.

With increasing awareness of IPF as a predominantly fibrotic disease, treatment strategies have been based on eliminating or suppressing the inflammatory component and/or aborting the fibrotic component in the fibrotic lung. However, an effective treatment regime has yet to be determined. Acknowledging that the cause of IPF is yet to be identified and the nature of the apparent recurrent injury to the lung is unknown, treatment strategies have been unable to address the effect of decreasing or avoiding possible etiologic factors/risk factors that are associated with IPF. The international consensus statement on IPF lists GER as one of the five risk factors for IPF. In this regard, no study has been undertaken to explore the possibility of the treatment of IPF with the suppression of acid GER. Our case series of four patients is the first to document that the treatment of increased acid GER in IPF results in the stabilization or improvement of lung function (as measured by FVC and/or DLco). We hypothesize that acid GER is an important factor for the development and/or progression of IPF. With the suppression of acid GER in these patients, we speculate that the lungs are given an opportunity to recover rather than progressing to fibrosis that is perpetuated by recurrent injury by acid by preventing recurrent and chronic microaspiration of acid droplets and by the consequent inflammation. The patients in cases 1 and 4 demonstrated an association between a trend toward deterioration and poor adherence to anti-acid GER treatment, stabilization on reinitiating treatment for acid GER, and the demonstration of the adequate suppression of acid GER by 24-h pH monitoring. The correlations of physiologic abnormality with acid GER were striking in case 1 as this patient required maximal medical and surgical treatment interventions that were guided by repeated 24-h pH monitoring testing for acid GER. It is also of interest that none of the patients manifested an acute exacerbation of IPF, needed hospitalization for respiratory problems, or received antibiotics during the follow-up period while receiving maintenance therapy with PPIs.

The long-term stabilization in both FVC and DLco in these patients with new-onset IPF who received no other treatment other than that for increased acid GER is encouraging. In this regard, changes in the FVC and DLco at 6 to 12 months after diagnosis has been associated with survival in patients with IPF. In addition, there was an improvement in oxygen saturation during the 6MWT and exercise test in case 1. The other three patients also demonstrated stability in oxygen saturation and walk distances during follow-up 6MWTs and exercise tests (data not shown as results from baseline walk tests within 2 to 3 months of the initiation of anti-acid GER therapy was not available in those patients). Since oxygen saturation during the 6MWT has been correlated with survival and the deterioration of the patient’s condition during the first 2 to 3 years following the diagnosis of IPF is common, the response of these patients to the suppression of acid GER raises interesting questions about the pathogenesis and management of IPF.

The prevalence rates of IPF have been estimated to be 20.2 and 13.2 per 100,000, respectively, in men and women, whereas the rates of acid GER vary from 9 to 20.
42% in the general population. Clearly, not all patients with increased acid GER develop lung fibrosis. We hypothesize that pulmonary fibrosis occurs only in individuals who are genetically susceptible to developing fibrosis from recurrent insults such as chronic acid GER and/or other unknown intrinsic or extrinsic factors. It is hoped that ongoing molecular genetic studies in patients with IPF and familial IPF will yield the needed insight into the genetic basis for the development of IPF and that this hypothesis can be tested in appropriate patient populations in the future.

Several questions about the relationship between IPF and acid GER and GERD need to be answered in future studies. Among them are the following: (1) the cause-effect relationship of the anatomical extent of acid GER and IPF needs to be clarified; (2) the efficacy of adequate treatment for acid GER in IPF patients; and (3) the role of overall gastric reflux (ie, acid, alkali, and gastric contents) in the context of the cause of IPF and acute exacerbations of IPF needs to be explored. Since the 24-h esophageal pH probe testing is the most sensitive in diagnosing acid GER and the vast majority of patients with IPF have no symptoms of acid GER, we routinely discuss the role of formal 24-h esophageal pH monitoring with our IPF patients; the intensity, severity, and anatomical extent of increased acid GER detected by the 24-h pH probe testing will guide the optimal treatment for acid GER and may prevent other comorbid problems associated with acid GER, independent of IPF. The limitations in the retrospective observations made in case reports/series are inevitable. Such case reports do not have control patients, and thus treatment recommendations and conclusions cannot be drawn from this report. Only a proper randomized controlled trial will ascertain the efficacy of the aggressive suppression of acid GER in IPF patients. The causality or pathophysiologic mechanisms of acid GER in IPF patients was not determined in this case series. Acknowledging these limitations, the results in these patients whose conditions may have otherwise deteriorated during the follow-up period of 2 to 6 years are informative and provocative. Given the lack of an effective treatment for IPF despite new interventions with antifibrotic agents having been tried, we think that the design of future clinical trials in IPF patients should consider a treatment strategy using PPIs in prospective protocols.

REFERENCES
Glucose-Insulin and Potassium Infusions in Septic Shock*

Shahir S. Hamdulay, BSc, MRCP; Ali Al-Khafaji, MD, MPH, FCPP; and Hugh Montgomery, MD, MRCP

Glucose-insulin and potassium (GIK) infusions are beneficial in treating ischemic myocardial depression. Myocardial depression is also an important feature in septic shock. We describe two cases of pressor-resistant hypodynamic septic shock that responded to high-dose GIK infusions. In each case, hemodynamic profiles improved sufficiently to allow withdrawal of vasopressor agents. Further assessment of GIK in patients with hypodynamic septic shock is necessary to confirm efficacy and prognostic significance. (CHEST 2006; 129:800–804)

Key words: antiinflammatory; glucose-insulin and potassium; insulin; myocardium; sepsis; shock

Abbreviations: APTT = activated thromboplastin time; CVP = central venous pressure; FFA = free fatty acid; GIK = glucose-insulin and potassium; IL = interleukin; MAP = mean arterial pressure; PT = prothrombin time; SV = stroke volume; TNF = tumor necrosis factor; TT = thrombin time

S eptic shock carries a high attendant risk of death to which impaired myocardial contractility may contribute. Recent interest in the use of glucose-insulin and potassium (GIK) infusions as therapy in ischemic myocardial depression has extended to septic myocardial depression. Few studies have demonstrated an improvement in the hemodynamics of hypodynamic septic shock on commencing GIK infusions. We describe two cases of hypodynamic septic shock in which such intervention was associated with an improvement in hemodynamic profile.

**CASE 1**

A 51-year-old woman with high-grade B-cell lymphoma (stage IIIb) had dyspnea 2 days following a second course of chemotherapy with cyclophosphamide, Adriamycin, vincristine, and prednisolone. She was jaundiced, febrile (39°C), tachycardic (120 beats/min), and hypotensive (90/60 mm Hg) with evidence of right middle lobe consolidation. Investigations revealed low arterial oxygen saturation (88% on room air); pancytopenia (hemoglobin, 7 g/dL; WBC, 1.6 × 10^9/L; neutrophils, 0.8 × 10^9/L); platelets, 18 × 10^9/L; coagulopathy (prothrombin time [PT], 18 s; activated thromboplastin time [APTT], 38 s; thrombin time [TT], 12 s); deranged liver function test results (bilirubin, 266 μmol/L; alanine aminotransferase, 542 IU/L; alkaline phosphatase, 90 IU/L; albumin, 17 g/dL); and abnormal biochemistry results (urea, 12.2 mmol/L; creatinine, 112 mmol/L; sodium, 140 mmol/L; potassium, 5.1 mmol/L; C-reactive protein, 280 mg/L). Neutropenic septic shock with right middle lobe pneumonia was diagnosed. Therapy was commenced with fluid resuscitation, antibiotics (piperacillin/tazobactam, gentamicin, fluconazole, cotrimoxazole), and bone marrow stimulation (filgrastim). Spiral CT of the chest excluded pulmonary embolus. Echocardiography showed a dilated left ventricle with trivial mitral regurgitation and ejection fraction of 70%. Progressive hypoxemia (pH 7.37; PaO₂, 56 mm Hg; PaCO₂, 47 mm Hg; base excess, −4; bicarbonate, 20 mmol/L) despite noninvasive ventilatory support required endotracheal intubation and mechanical ventilation. Transesophageal Doppler analysis revealed a baseline cardiac output of 4.5 L/min (cardiac index, 2.8 L/min/m²) with stroke volume (SV) of 40 mL. Within 1 h of admission to the ICU, atrial fibrillation developed with a ventricular rate of 150 beats/min. Chemical (IV magnesium sulfate and amiodarone) and electrical cardioversion failed to re-establish sinus rhythm, although rate declined to 105 beats/min. Over the following 4 h, cardiac output declined (to 2.8 L/min; cardiac index, 1.6 L/min/m²; SV, 26 mL) despite a central venous pressure (CVP) of 15 mm Hg. Oliguria and acidemia ensued (pH 7.25; PaCO₂, 56 mm Hg; PaO₂, 47 mm Hg; base excess, −4; bicarbonate, 20 mmol/L) necessitating continuous venovenous hemofiltration. Over the following 8 h, increasing infusions of epinephrine (rising to a maximum of 56 μg/min) and colloid challenges (totaling 4 L) failed to significantly improve mean arterial pressure (MAP) [55 mm Hg] or cardiac output (3.1 L/min; cardiac index, 1.9 L/min/m²; SV, 26 mL; CVP, 26 mm Hg). A repeat echocardiogram showed poor left ventricular contractility with biventricular dilatation and poor ejection fraction (40%). An infusion of GIK (30% glucose with 50 units of actrapid insulin and 80 mmol/L potassium at 1.5 mL/kg/h) was associated with a dramatic increase in cardiac output (Fig 1; Table 1). Within 4 h of commencing GIK, it was possible to start weaning the epinephrine infusion; the greatest reduction occurred in the first 14 h (from 56 to 16 μg/min), with an infusion rate of just 6 μg/min at 72 h, when GIK was ceased, and cessation of epinephrine at 130 h (MAP, 72 mm Hg; cardiac output, 5.5 L/min; SV, 44 mL). The patient required no further pressor support for the next 4 days. Glucose concentrations throughout the ICU stay ranged from 5 to 8 mmol/L. Ten days after hospital admission, systemic Staphylococcal infection and candidiasis developed, resulting in death.

**CASE 2**

A 23-year-old man with a history of paroxysmal nocturnal hemoglobinuria was admitted to the ICU with neutropenic septic shock. He had received cyclosporine, mycophenolate mofetil,