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# Bronchoalveolar pH and inflammatory biomarkers in newly diagnosed IPF and GERD patients: A case-control study

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**Background:** Several studies have suggested that idiopathic pulmonary fibrosis (IPF) may be related to repeated aspiration of gastric contents over long periods of time. We aimed to investigate differences between pH measured directly in the lung, and biomarkers of acute inflammation in patients with newly diagnosed IPF and in patients with newly diagnosed GERD.

**Material/Methods:** All subjects (N=61) underwent collection of medical history, physical examination, pulmonary function testing, bronchoscopy, endoscopy, arterial blood gas analyses, and biochemical testing.

**Results:** Previously diagnosed GERD was found in 56.7%, typical symptoms of reflux in 80%, and *Helicobacter pylori* in gastric biopsy specimens in 76.6% of the cases. pH in peripheral branches of bronchi in the cases was 5.32±0.44 and was 6.27±0.31 ($p<0.001$) in the control group. The average values of LDH, ALP, and CRP in bronchoalveolar aspirate and in serum, as well as TNF-α in bronchoalveolar aspirate, were significantly higher in IPF patients.

**Conclusions:** The more acidic environment in the bronchoalveolar aspirate of the IPF subjects could contribute to the development or progression of IPF, possibly via changes in local metabolism or by damaging local cells and tissue. However, further studies with larger numbers of patients are required to clarify the role of gastric fluid aspiration in IPF pathogenesis. Our preliminary work has identified inflammatory biomarkers LDH, ALP, and TNF-α as potentially important in the pathologic processes in IPF. Further research is needed to determine their importance in clinical intervention and patient care.

**MeSH Keywords:** **Bronchoscopy • Endoscopy • Idiopathic Pulmonary Fibrosis • Inflammatory Markers • Gastroesophageal Reflux**

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## Background

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease (ILD) characterized by formation of the scar tissue within the lung in absence of any known provocation [1]. Despite intensive research efforts, the cause of IPF is still unknown. It was hypothesized that a variety of causes, such as drug toxicities, environmental exposure, and connective tissue diseases, may be responsible for or contribute to IPF development [2]. IPF affects men more than women. The incidence of IPF increases with age, with the majority of the cases older than 60 years [3]. IPF does not have distinct geographic distribution and does not distinguish between particular races or ethnic groups [2]. Most of the patients present with dyspnea of insidious onset. Disease is characterized by chronic progression and death from respiratory failure [4]. Current therapies are not effective treating this progressive and fatal disease, which has a median survival of 2.8–4.2 years [5–7]. The findings of several studies indicate that IPF may be related to repeated aspiration of gastric contents over a long period of time. The role of gastroesophageal reflux (GER) in IPF has usually been studied using esophageal pH monitoring, and the results have shown a high prevalence of GER compared to the general population and patients with other interstitial lung diseases [7–10]. Research has suggested 2 potential mechanisms by which GER affects lung function. Acid fluid aspiration into the airways causes chronic inflammation, which may progress to pulmonary fibrosis [11]. On the other hand, a vaguely mediated reflex triggered by acid within the esophagus may lead to bronchial or laryngeal constriction and hyperresponsiveness [12]. Many animal studies have confirmed that continuous aspiration of acid fluid into the lung causes pulmonary inflammation and chronic pulmonary disease with or without pulmonary fibrosis [9,13–16]. Therefore, in the present study we aimed to evaluate the difference in the bronchoalveolar pH and inflammatory biomarkers in patients with newly diagnosed IPF and patients with newly diagnosed gastroesophageal reflux disease (GERD).

## Matherial and Methods

A total of 61 subjects were included in the current study: 30 newly diagnosed IPF patients (cases) and 31 newly diagnosed GERD patients (control group). This study was conducted from February 2006 to October 2010 at Split University Hospital.

Newly diagnosed IPF patients were enrolled based on the international consensus statement definition [3,17]. All subjects with other known causes of ILD (environmental/occupational exposure, collagen vascular disease, hypersensitivity pneumonitis, etc.) or presence of infection in bronchoalveolar aspirate were excluded. GERD patients were not treated with H2 blockers or proton pump inhibitors.

All subjects underwent collection of detailed medical history, physical examination, pulmonary function testing, endoscope procedures, arterial blood gas analyses, and biochemical testing.

Pulmonary function testing was performed using body plethysmograph (Jaeger Masterlab, Wurzburg, Germany). This included measurements of forced vital capacity (FVC), forced expiratory volume in the first second ($FEV_1$)/FVC, single-breath diffusing capacity of the lung for carbon monoxide ($DL_{co}$), and transfer coefficient of the lung (KCO). $DL_{co}$ was measured using a rapid carbon monoxide and methane analyzer, which was calibrated before each measurement.

Arterial blood gases were analyzed using a blood gas electrolyte analyzer (GEM Premier, 300, model 5700, Instrumentation Laboratory Lexington, MA).

Video-bronchoscopy (BSC) was performed under local anesthesia obtained with 2% lidocaine, using a video-bronchoscope (Olympus BF type 1T160, Tokyo, Japan). Lung specimens were sampled by transbronchial lung biopsy or open lung biopsy, performed by video-assisted thoracoscopy.

Biochemical testing and measuring pH in the lung were described in our previous study [18]. Briefly, acidity in peripheral branches was measured semi-quantitatively by means of test strips (Multistix 10 SG, Bayer AG, Leverkusen, Germany), which are otherwise used to determinate acidity in other fluids (urine, cerebrospinal liquid, and pleural effusions) within the range of 4.5–8.0. During BSC, a small piece of test strip was placed in biopsy forceps, which were then wedged into one of the peripheral branches of the right lower lobe, most frequently DB9 or DB10, for 15–20 s. The forceps were then pulled out, and pH was read immediately. Aspirate from peripheral branches of DB9 or DB10 was obtained with deep catheter aspiration using an 18 cm long and 2 mm wide catheter, which is otherwise used at BSC and is provided with a videobronchoscope. When the lumen of the catheter was completely filled with aspirate, the catheter was rinsed with 1.5 mL of distilled water [18].

The value of lactate dehydrogenase (LDH), C-reactive protein (CRP), and alkaline phosphatase (ALP) were measured by the Architect C-8000 device (Clinical Chemistry, Abbott Park, IL) within 1 h, in the laboratory located near the endoscopic cabinet. LDH, CRP, and ALP were also measured in the serum of the participants. Tumor necrosis factor alpha (TNF-α) was measured only in bronchial aspirate using the Elisys Uno Human device (Bender MedSystem, Vienna, Austria). We excluded the participants with evidence of infection or whose aspirate was bloody, or tinged with blood or pus, in order to avoid the influence of those contents on the value of pH and levels of biomarkers.





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**Table 1.** Subject characteristics. Data are presented as mean ±SD. For spirometry, $DL_{co}$ and KCO percentage predicted values individually achieved, were calculated according to expected for age, sex, weight, height and ethnicity.

| | Cases[a] (N=30) | Control group[b] (N=31) | P value[c] |
|---|---|---|---|
| Age (years) | 63.33±6.86 | 60.94±5.09 | 0.13 |
| Gender (male), N (%) | 17 (56.67) | 17 (54.84) | |
| Gastroesophageal reflux, N (%) | 24 (80.00) | 31 (100.00) | |
| Hiatus hernia, N (%) | 18 (60.00) | 11 (35.48) | |
| Gastritis, N (%) | 22 (73.33) | 24 (77.41) | |
| Gastric scars, N (%) | 4 (13.33) | 7 (22.58) | |
| FVC[d] (%) | 66.91±8.98 | 102.45±8.84 | <0.001 |
| $FEV_1$/FVC[e] (%) | 71.63±10.36 | 105.5±9.11 | <0.001 |
| DLCO[f] (%) | 52.71±9.80 | 101.36±9.92 | <0.001 |
| KCO[g] (%) | 53.32±11.15 | 88.55±9.98 | <0.001 |
| $pO_2$[h] (kPa) | 8.25±0.76 | 12.12±0.5 | <0.001 |
| $pCO_2$[i] (kPa) | 4.69±0.47 | 4.98±0.3 | 0.005 |

[a] Subjects with newly diagnosed idiopathic pulmonary fibrosis; [b] subjects with newly diagnosed gastroesophageal reflux disease; [c] Student's t-test; [d] forced vital capacity; [e] forced expiratory volume in 1 second/forced vital capacity; [f] diffusing capacity of the lung for carbon monoxide; [g] transfer coefficient of the lung; [h] partial pressure of $O_2$ in the arterial blood; [i] partial pressure of $CO_2$ in the arterial blood.

After diagnosis of IPF was made, esophagogastroscopy (EGS) was performed using a flexible video gastroscope (Olympus-Evis extra II GIF Type H-80, Tokyo, Japan) before medication treatment. The esophagogastroscopy was performed within 1 week after IPF was diagnosed. *Helicobacter pylori* was identified by rapid urease test from gastric biopsy specimens. The control group was age- and gender-selected, formed of newly diagnosed GERD patients, free of any pulmonary diseases. The diagnoses of GERD was made on the basis of symptoms such as heartburn or acid and food regurgitation and upon esophagogastroscopic findings based on work by Savary-Miller [19]. We excluded participants with fourth and fifth grade GERD. Video-bronchoscopy (BSC) was performed after esophagogastroduodenoscopy.

All patients who met inclusion criteria chose to participate in this study, and provided written informed consent. This study was approved by Ethics Committee of Split University Hospital.

The differences between groups were compared by Student's t-test. P value less than 0.05 was accepted as indicative of statistical significance. Statistical analyses were performed using Statistica 8 software.

## Results

Anthropometric data, esophagogastroscopic findings, pulmonary function testing, and arterial blood gas data are presented in Table 1. While the control group had results of the FVC, $FEV_1$/FVC, $DL_{co}$, KCO, $pO_2$, and $pCO_2$ in the normal range, all the measured parameters of the respiratory function in IPF patients were statistically significantly decreased.

All cases had at least 1 macroscopic pathological finding in the gastroesophageal system. Previously diagnosed GERD was found in the medical history of 17 (56.7%) IPF patients. *Helicobacter pylori* was found in gastric biopsy specimens in 23 (76.6%) of the cases, and in 11 (35.48%) of the controls. Since detection of *H. pylori* in lung biopsy specimens was negative in the first 8 participants with positive results from gastric biopsy specimens, no further detection from the lung biopsy specimens was done.

The average value of pH in peripheral branches of bronchi in the cases was 5.32±0.44, while in the control group it was 6.27±0.31 (mean ±SD). The difference in pH between these 2 groups was statistically significant (p<0.001). Biomarkers of acute inflammation LDH, CRP, and ALP in the bronchoalveolar aspirate and serum were significantly higher in the IPF patients (Table 2). Another biomarker of acute inflammation, TNF-α, measured only in the bronchoalveolar aspirate, was also statistically significant higher in IPF patients.

The average values of LDH, ALP, and CRP in bronchoalveolar aspirate and serum compared in cases and control group were all significantly different (Tables 3 and 4).





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**Table 2.** Levels of different parameters of cell and tissue injury in serum and brochioalveolar aspirate in cases[a] and control group[b].

| | Cases (N=30) | Control group (N=31) | P value[c] |
|---|---|---|---|
| pH | 5.32±0.44 | 6.27±0.31 | <0.001 |
| LDH[d] in bronchioalveolar aspirate (U/L) | 679.98±175.38 | 122.32±49.47 | <0.001 |
| LDH in serum (U/L) | 239.6±67.15 | 194.74±66.72 | 0.01 |
| CRP[e] in bronchioalveolar aspirate (mg/l) | 0.18±0.32 | 0.02±0.04 | 0.007 |
| CRP in serum (mg/l) | 16.53±10.51 | 5.03±3.35 | <0.001 |
| ALP[f] in bronchioalveolar aspirate (U/L) | 70.03±36.19 | 39.42±22.35 | <0.001 |
| ALP in serum (U/L) | 91.93±15.32 | 84.48±11.27 | 0.034 |
| TNF-α[g] in bronchioalveolar aspirate (pg/ml) | 21.99±7.09 | 5.36±3.23 | <0.001 |

[a] Subjects with newly diagnosed idiopathic pulmonary fibrosis; [b] subjects with newly diagnosed gastroesophageal reflux disesase; [c] Student's t-test; [d] lactate dehydrogenase; [e] C-reactive protein; [f] alkaline phosphatase; [g] tumor necrosis factor alpha.

**Table 4.** Levels of different parameters of cell and tissue injury in serum and brochioalveolar aspirate in control group (N=31).

| | Bronchiolaveolar aspirate level (mean ±SD) | Serum level (mean ±SD) | P value[a] |
|---|---|---|---|
| LDH[b] (U/L) | 122.32±49.47 | 194.74±66.72 | <0.001 |
| ALP[c] (U/L) | 39.42±22.35 | 84.48±11.27 | <0.001 |
| CRP[d] (mg/l) | 0.02±0.04 | 5.03±3.35 | <0.001 |

[a] Student's t-test; [b] lactate dehydrogenase; [c] alkaline phosphatase; [d] C-reactive protein.

**Table 3.** Levels of different parameters of cell and tissue injury in serum and brochioalveolar aspirate in cases (N=30).

| Parameter | Bronchiolaveolar aspirate level (mean ±SD) | Serum level (mean± SD) | P value[a] |
|---|---|---|---|
| LDH[b] (U/L) | 679.98±175.38 | 239.6±67.15 | <0.001 |
| ALP[c] (U/L) | 70.03±36.19 | 91.93±15.32 | 0.003 |
| CRP[d] (mg/l) | 0.18±0.32 | 16.53±10.51 | <0.001 |

[a] Student's t-test; [b] lactate dehydrogenase; [c] alkaline phosphatase; [d] C-reactive protein.

We also compared pH in peripheral branches of bronchi of IPF patients with actual GER symptoms and IPF patients without actual GER symptoms, and no statistical difference was found (Table 5). Comparison between inflammatory biomarkers from bronchoalveolar aspirate as well as from serum, in these groups, revealed no statistical difference (Table 5).

## Discussion

The most important finding from the current study is the more acid environment found in the peripheral branches of bronchi in newly diagnosed IPF patients compared to newly diagnosed GERD patients. Allaix et al. recently showed that aspiration of the gastric fluid into the airways and lung parenchyma in IPF patients is more common compared to GERD patients, due to more common proximal esophageal reflux, and the reflux coupled with a slower acid clearance in the supine position in IPF patients [20]. However, when IPF patients with actual GER symptoms are compared with IPF patients without actual GER symptoms, no difference between acidity in the peripheral branches of bronchi was observed (Table 5). A possible explanation is that chronic inflammation in the lungs of IPF patients, per se, results in a local acid environment with cell





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**Table 5.** Levels of different parameters of cell and tissue injury in serum and brochioalveolar aspirate in IPF patients with GER[a] *vs.* IPF patients without GER[b].

| | IPF/GER (N=18) | IPF/noGER (N=12) | P value[c] |
|---|---|---|---|
| Age (years) | 64.06±6.67 | 62.25±7.29 | 0.49 |
| pH | 5.36±0.41 | 5.25±0.5 | 0.51 |
| LDH[d] in bronchioalveolar aspirate (U/L) | 667.64±199.04 | 698.48±138.7 | 0.65 |
| LDH in serum (U/L) | 248±84.32 | 227±24.74 | 0.41 |
| CRP[e] in bronchioalveolar aspirate (mg/l) | 0.17±0.31 | 0.2±0.35 | 0.79 |
| CRP in serum (mg/l) | 18.29±11.52 | 13.89±8.56 | 0.27 |
| ALP[f] in bronchioalveolar aspirate (U/L) | 64.11±19.91 | 78.92±51.93 | 0.28 |
| ALP in serum (U/L) | 90.44±14.97 | 94.17±12.83 | 0.52 |
| TNF-α[g] in bronchioalveolar aspirate (pg/ml) | 21.72±7.19 | 22.37±7.22 | 0.81 |

[a] Patients with newly diagnosed idiopathic pulmonary fibrosis with GER; [b] patients with newly diagnosed idiopathic pulmonary fibrosis without GER; [c] Student's t-test; [d] lactate dehydrogenase; [e] C-reactive protein; [f] alkaline phosphatase; [g] tumor necrosis factor alpha.

injury, apoptosis, and necrosis; all known to elevate $H^+$ ions and lactic acid. Low pH at the alveolar-capillary membrane causes damage and loss of surfactant, with the resultant collapse of alveoli and development of microatelectasis, thus contributing to development and/or progression of IPF [21].

Previously was shown that pH mostly ranged between 6 and 8 in healthy subjects, measured in the exhaled breath condensate [22–25]. Until now, all studies that compared IPF and GERD patients were based on the 24-hour intraesophageal pH monitoring, with the observed pH mainly under 4 [9,25]. Tobin et al. suggested that IPF patients are at increased risk for gastroesophageal reflux due to increased pressure gradients across the diaphragm and changes in pulmonary mechanics [9]. Most of our newly diagnosed IPF patients had clear GER symptoms at the time of diagnosis or had previously diagnosed GERD before IPF was diagnosed, similar to findings recently reported [26,27]. A high percentage of hiatus hernia (60%) was found in our IPF patients, in contrast to findings in the general population (~20%) [28] and our control group (35.48%). The current study was not designed to investigate causal association between aspiration of the gastric acid fluid and IPF. However, animal studies lead to the conclusion that gastric acid contents in the lung may contribute to the inflammation and development of chronic pulmonary disease [13–16]. On the other hand, very few GERD patients develop IPF, considering that the prevalence of GERD in the general population is much higher [29,30] than the prevalence of IPF [31,32]. Other risk factors such as smoking, grain dust, medications, and radiation, as well as genetic susceptibility, may be involved in the development of IPF. To date, there is no effective management for the treatment of IPF. It is not clear if anti-reflux therapy has an influence on pulmonary function or respiratory symptoms in IPF [7], although Raghu et al. showed stabilization and improvement of the lung function, measured by FVC and/or DLco, after proton-pump inhibitor therapy [4].

A particularly intriguing finding in this study is that 76.6% of newly diagnosed IPF patients were *H. pylori* positive, in comparison to 35.48% newly diagnosed GERD patients. It was recently reported that *H. pylori*, not only GERD *per se*, may be related to IPF development [33].

The level of LDH, an indicator of cell injury and necrosis, was 2.84 times higher in bronchoalveolar aspirate than in serum of the IPF patients. The bronchoalveolar level of LDH was 5.56 times higher in IPF compared to GERD patients. Higher LDH found in the bronchoalveolar aspirate in cases compared to controls suggests local inflammation, cell injury, necrosis, and disease activity. Moreover, we have found higher levels of inflammatory biomarker TNF-α in bronchoalveolar aspirate in cases compared to controls. TNF-α stimulates fibroblasts and promote collagen production and was proposed by Coker et al. as one of the cytokines implicated in pathogenesis of lung fibrosis [34]. ALP, a biomarker of tissue damage and type II cell proliferation, was also more increased in the bronchoalveolar aspirate of IPF patients. Based on the results of this study, we do not suggest measuring CRP in bronchoalveolar aspirate, since their levels were low or even hardly detectable. The serum levels of inflammatory biomarkers LDH, ALP, and CRP were significantly higher in cases compared to controls, suggesting systemic inflammation.

In general, the role of inflammation in IPF is still controversial. Some of the prevailing hypotheses, which assumed that either an inflammatory process or an independent epithelial/





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fibroblastic disorder may propagate the disease process, need to be explained better in further studies [34–38].

In our study, several factors could have influenced the results. Our study was performed on a small number of subjects and the results therefore have to be viewed with caution. Further studies with larger numbers of patients are required to clarify the role of gastric fluid aspiration in IPF pathogenesis. We tried to avoid selection bias by offering enrollment in the study to all consecutive patients presenting with IPF and GERD to our hospital. Thus, patients were not selected because of presence or absence of GER symptoms.

We did not measure bronchoalveolar aspirate cell count. However, it is known that an early aspect of the disease is highly cellular with alveolar inflammation infiltrating. We were focused on the less-known measurement of pH and the levels of LDH, ALP, CRP, and TNF-α in the bronchoalveolar aspirate.

## Conclusions

To our knowledge, this is the first time that pH, LDH, ALP, and CRP were measured in the bronchoalveolar aspirate of IPF patients. Our study revealed a more acid environment in the peripheral branches of bronchi in newly diagnosed IPF patients compared to newly diagnosed GERD patients. When comparing IPF patients with actual GER symptoms and IPF patients without actual GER symptoms, no difference between acidity in the peripheral branches of bronchi was observed. This suggests that low pH in the peripheral branches of bronchi could be related to the underlying IPF itself, and not to gastric fluid aspiration. However, this study confirms, as has been reported many times by others, that IPF patients are more susceptible to gastroesophageal reflux, GERD, hiatal hernia, and gastritis compared to the general population. Further investigations of the role of gastric fluid aspiration in IPF pathogenesis is mandatory, as well as to clarify the association between GER and other interstitial lung diseases. All measured inflammatory biomarkers were higher in bronchoalveolar aspirate, as well as in the serum in IPF patients, compared to GERD patients.

Our preliminary work has identified inflammatory biomarkers LDH, ALP, and TNF-α as potentially important in the pathologic processes in IPF. Further research is needed to determine their importance in clinical intervention and patient care.

**Declaration of personal interests**

None.

**Declaration of funding interests**

None.

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