

Laryngopharyngeal pH monitoring in patients with interstitial lung diseases

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Abstract

Background Patients with interstitial lung diseases (ILDs) often have irritating persistent dry cough. Possible correlations between dry cough and laryngopharyngeal reflux (LPR) remain unclear. **Methods** 44 patients with ILDs and 30 healthy individuals underwent 24-hour laryngopharyngeal pH monitoring. Ryan index score was calculated. Patients' demographic and clinical data were collected. **Results** 44 patients (23 cases of IPF and 21 cases of CTD-ILD) and 30 healthy individuals were included. The proportions of men and smokers were significantly higher in IPF group than in CTD-ILD group and control group (All $P < 0.01$). Other demographic and clinical data were similar in IPF and CTD-ILD group. According to the percentage duration of $pH < 6.5$, $pH 6.5-7.5$, and $pH > 7.5$ in the overall measure duration, the patients were classified into three pH groups. In entire pH monitoring duration, the proportion of $pH > 7.5$ group in ILD patients was higher than control group; at upright position, the proportion of $pH > 7.5$ group in ILD patients was higher than control group; at supine position, the proportion of $pH < 6.5$ group in ILD patients was higher than control group (All $P < 0.01$). Seven patients had Ryan index score > 9.41 at upright position. All patients had Ryan index score < 6.79 at supine position. Four patients showed significantly higher and one patient had significantly lower average pH at coughing than the overall average pH (All $P < 0.05$). **Conclusions** Patients with ILDs may have LPR. Basic and acidic LPR may likely occur at upright and supine position, respectively. Ryan index may not accurately reflect LPR in patients with ILDs.

Introduction

Interstitial lung diseases (ILDs) refer to a group of lung diseases characterized in alveolar inflammation and interstitial fibrotic lesions [1]. The etiology of ILDs is complex and diverse. Idiopathic pulmonary fibrosis (IPF) and connective tissue disease-related interstitial lung disease (CTD-ILD) are the most common types of ILD [2]. The main respiratory symptoms of ILDs include irritating cough and breathing difficulty.

Gastroesophageal reflux disease (GERD) is caused by the reflux of gastric acid and other stomach contents into the esophagus, and one of its typical clinical symptoms is cough [3-5]. GERD has been recognized as a common cause for chronic cough [5]. International diagnosis and treatment guidelines for IPF suggest an association between GERD and IPF onset and thus recommend anti-acid treatments for patients with IPF [6-9]. However, a previous report has shown that anti-acid treatments do not reduce the all-cause mortality and the rate of hospitalization of patients with IPF [10]. Moreover, Raghu and colleagues have found that approximately half of patients with IPF did not present gastroesophageal reflux (GER) symptoms, such as heartburn and sour regurgitation [6]. Extraesophageal reflux (EER) or laryngopharyngeal reflux (LPR) is the reflux of stomach contents into the throat and larynx, and patients with LPR usually do not present the classic symptoms of GERD [4]. An accurate diagnosis of LPR remains challenging in clinical practice.

LPR is the reflux of stomach contents into the area above the upper esophageal sphincter, such as the nasal cavity, mouth, throat, trachea, and lung [11]. Patients with LPR disease (LPRD) often presents

cough, laryngopharyngeal discomfort, and breathing difficulty [3, 11, 12]. Similar to GERD, LPRD can also cause chronic cough. Gaseous refluxate in the airway reduces the pH of the upper airway to < 6.5 , which activates the pepsin that is from the refluxate and deposited on the airway mucosal epithelial cells and consequently induces nonspecific inflammation in the airway mucosa [3, 11]. Previous studies have demonstrated that 32%-84% of patients with bronchial asthma had GERD and 50% of the patients with GERD did not present any obvious reflux symptoms such as heartburn and sour regurgitation [13, 14]. GERD can exacerbate asthma. Antacids and gastric pro-motility drugs can alleviate asthma symptoms in patients with GERD [15-17]. The association between LPR and ILDs remains unclear, and monitoring upper airway pH in patients with ILDs is essential to understand such association and may shed light on therapeutic strategies for LPR in patients with ILDs.

Materials And Methods

Study design

This single-center prospective study was conducted in Shanghai Pulmonary Hospital of Tongji University in Shanghai China. A total of 44 patients with ILDs treated in Shanghai Pulmonary Hospital from November 2016 to September 2017 were included in this study. The study protocol has been approved by the Ethics Committee of Shanghai Pulmonary Hospital (Approval No.: K16-296). The study was registered on the Chinese Clinical Trial Registry (<http://www.chictr.org.cn/abouten.aspx>, ChiCTR-ODC-16009478). Written informed consent was obtained from all the study participants prior to inclusion in the study.

Study participants

Patients with a confirmed diagnosis of IPF or CTD-ILD were enrolled. Patients with the following clinical characteristics were excluded: 1) had a malignancy or a history of malignancy; 2) were using glucocorticoid and/or immunosuppressants (including azathioprine, cyclophosphamide, mycophenolate mofetil, and cyclosporin A); 3) had serious systemic diseases and organ dysfunction; 4) refuse to do laryngophary reflux 24h monitor; 5) had incomplete clinical data. A total of 30 age-matched healthy individuals, who had routine physical examination in Shanghai Pulmonary Hospital, were included as controls.

Disease diagnostic criteria

IPF was diagnosed according to the 2013 American Thoracic Society/European Respiratory Society statement [1]. The diagnostic criteria for CTD followed the recommendations by the American Rheumatism Association and American College of Rheumatology, and patients with ILD who were also diagnosed with one type of CTD by rheumatologists were considered as CTD-ILD [2, 18-20].

Twenty four-hour laryngopharyngeal pH monitoring

The Restech® pH sensor (Respiratory Technology Corp., San Diego, CA) was first calibrated using two standard buffer solutions at pH 7 and pH 4, respectively. The nasal passage was topically anesthetized using Q-tips soaked with 2% lidocaine. The sensor was inserted into the nasal cavity and moved toward the throat until the flashing LED of the sensor was visible in the back of the throat, and then the sensor was positioned so that the flashing light was 5-10 mm below the uvula. The 5 mm-long LED light serves as a guide for the placement of the pH sensor. The catheter was first secured as close to the nares as possible on the face using a Tegaderm™ and then passed over the ear and secured on the neck using another Tegaderm™. The transmitter at the end of the catheter was either taped to the skin or attached to the study participant's clothing using a clip-on case. The data recorder was attached to the study participant's belt. The study participants were prohibited from taking a shower or bath during the recording period and were required to keep a diary to record meal periods and the time staying at supine and upright positions. The meal periods were excluded from data analyses. The data collected by the Restech® recorder and the information from the diary were analyzed [12, 21].

Ryan index calculation

Based on the data collected from the Dx-pH 24-hour laryngopharyngeal pH monitoring, a LPR episode was defined as a pharyngeal pH < 5.5 at upright position and/or < 5.0 at supine position. The number of LPR episodes, the longest duration of a LPR episode, and the proportion of total duration of LPR episodes in the total recording duration (episodes % time) were calculated, and the differences in these parameters between study participants and healthy population were determined according to a previous description [3]. The data analysis software of the Restech® recorder calculates patients' Ryan index based on the number of LPR episodes, duration of the longest LPR episode, and LPR episodes % time [3].

Blood tests and arterial blood gas test

Blood tests were performed to evaluate liver and kidney function, C-reactive protein (CRP) levels, and erythrocyte sedimentation rate (ESR). Partial pressure of oxygen (PaO₂), partial pressure of carbon dioxide (PaCO₂), and oxygen saturation (SaO₂) were also measured.

Chest high-resolution computed tomography (HRCT) score

The scoring criteria for chest HRCT followed a previous description and are described in Table 1 [18]. One radiologist and two pulmonologists scored chest HRCT results separately, and the average score was used for data analyses.

Pulmonary function test

Force vital capacity (FVC), FVC expressed as a percentage of predicted (FVC % pred), and carbon monoxide diffusing capacity of the lung expressed as a percentage of predicted (D_LCO % pred) were determined to assess study participants' pulmonary function.

Cough symptom score

Cough symptom score (CSS) was determined according to a previous description and the criteria are displayed in Table 2 [22]. Two pulmonologists independently evaluated daytime CSS, nighttime CSS, and total CSS. The average scores from the two pulmonologists were used for data analysis.

Statistical analysis

The statistical analysis software SPSS 16.0 was used. Measurement variables are presented as mean \pm standard deviation (SD). Inter-group comparison was examined by independent t-test. One sample t-test was used to compare the average pH at coughing versus the overall average pH. $P < 0.05$ was considered statistically significant. The constituent ratios of different pH range (pH < 6.5 , pH 6.5-7.5, and pH > 7.5) were analysed by chi-square test.

Results

General clinical data

The patient flowchart is displayed in Figure 1. A total of 44 patients with ILDs were included in the study. Of the 44 patients, 23 had IPF and 21 were diagnosed with CTD-ILD. The control group included 30 age-matched healthy individuals. The IPF group had significantly higher proportions of men (91.3% vs. 33.3% vs. 46.7%) and smokers (73.9% vs. 14.3% vs. 16.7%) than the CTD-ILD group and control group (All $P < 0.01$, Table 3). The average age was similar in the three groups (IPF group: 62 ± 8 years, CTD-ILD group: 60 ± 11 years, Control group: 61 ± 9 years), so were the other clinical data (Table 3). These results indicate that IPF and CTD-ILD group may have similar general physical condition, pulmonary function, and cough severity.

Twenty-four-hour laryngopharyngeal pH monitoring results of the three groups

The average laryngopharyngeal pH value for 24 hours was similar in the IPF (7.04 ± 0.11) and CTD-ILD (7.19 ± 0.12) group and control group (7.09 ± 0.06) (Figure 2). The typical results of 24-hour laryngopharyngeal pH monitoring of one patient with IPF are presented in Figure 3. We calculated the percentage duration of pH < 6.5 , pH 6.5-7.5, and pH > 7.5 in the overall measurement time of every patient and allocated the 44 ILD patients and 30 healthy individuals into pH < 6.5 , pH 6.5-7.5, and pH > 7.5

groups according to the highest percentage duration. When the entire pH measurement duration was used as the denominator to calculate the percentage duration, 11.4%, 61.3%, and 27.3% of the 44 ILD patients were in pH < 6.5, pH 6.5-7.5, and pH > 7.5 group, respectively. 3.3%, 93.4%, and 3.3% of the 30 healthy individuals were in each respective group. The proportion of pH>7.5 group in ILD patients was higher than control group ($P<0.01$); when the duration of upright position was used for the calculation, 6.8%, 63.6%, and 29.6% of the 44 ILD patients were in each respective group. 3.3%, 93.4%, and 3.3% of the 30 healthy individuals were in each respective group. The proportion of pH>7.5 group in ILD patients was higher than control group ($P<0.01$); when the duration of supine position was used, the proportions of 44 ILD patients in pH < 6.5, pH 6.5-7.5, and pH > 7.5 group were 27.3%, 54.5%, and 18.2%. The proportions of 30 healthy individuals in each respective group were 3.3%, 90.0%, and 6.7%. The proportion of pH<6.5 group in ILD patients was higher than control group (Table 4). Overall, 7 patients showed abnormal Ryan index score at upright position (Ryan index score > 9.41), including 5 cases of IPF and 2 cases of CTD-ILD. None of the 44 patients showed abnormal Ryan index score at supine position (Table 5). Abnormal Ryan index score was defined as > 6.79.

Correlation between pH value and cough

No heart burn event occurred in the 44 ILD patients and 30 healthy individuals during the 24-hour laryngopharyngeal pH monitoring. Comparison of the average pH value during coughing versus the overall average pH value showed that 4 ILD patients had significantly higher average pH at coughing than the overall average pH and one patient had significantly lower average pH at coughing (All $P < 0.05$, Table 6).

Discussion

IPF is a progressive lung disease with an unknown etiology. The pathology of IPF is characterized by slowly progressive diffuse alveolar inflammation and/or alveolar structural disorders, which eventually damage alveolar structure and result in pulmonary fibrosis and honeycomb lung. IPF has a poor prognosis and the survival time of patients with IPF is approximately 3-5 years [23]. CTDs are a group of heterogeneous, inflammatory, and immune-mediated diseases affecting multiple organs. Pulmonary interstitium and pleural are composed by rich connective tissues and thus become an important target for CTDs. ILDs that involve connective tissues are named as CTD-ILDs [24]. ILDs ultimately lead to scars in lung tissues although the clinical presentations of ILDs are highly heterogeneous.

Previous studies have suggested that IPF may be highly associated with GERD [6, 8]. Chronic inhalation of gaseous refluxate is a risk factor for airway and pulmonary inflammation and could induce or exacerbate IPF. Antacids, such as proton pump inhibitors and histamine H₂-receptor antagonists, have been found to reduce the risk of GER-associated pulmonary damages [8, 9]. Clinicians have routinely prescribed anti-acid drugs for patients with IPF [6, 7]. GER is caused by abnormal lower esophageal sphincter relaxation, which allows stomach contents to flow back to the esophagus. The majority of the

stomach contents in GER are liquid and stay inside the esophagus. Patients with GER and LPR may experience gaseous reflux into the upper airway. LPR is caused by abnormal upper esophageal sphincter relaxation and is mainly gaseous reflux into the throat, nose, and ear. The gaseous refluxate can then enter the lower airway and alveoli during breathing. Thus, compared with GER, LPR appears more likely to adversely affect the lower airway and lung parenchyma and exacerbate ILDs.

The etiology of GERD is associated with the dysfunction of gastric cardia and lower part of the esophagus. The clinical presentations of GERD are mainly digestive tract symptoms and occasional airway symptoms. The pathophysiology of GERD is characterized by acidic or basic gastric liquid and gaseous reflux into the esophagus and into the airway in severe cases. The etiology of LPR is associated with gastric empty dysfunction. LPR causes pathological changes in the airway. The clinical presentations of LPR are mainly airway symptoms but not digestive tract symptoms. The pathophysiology of LPR is characterized by acidic or basic gaseous reflux into the airway. Only 20% of patients with LPRD and GERD show low esophageal pH (the duration of $\text{pH} < 4.0$ is more than 4% of the total measurement time). Therefore, only monitoring esophageal pH could miss the diagnosis of LPRD in 80% of patients with LPRD [25, 26]. The 24-hour laryngopharyngeal pH monitoring (DX-pH) has been used to diagnose LPRD [21, 27, 28]. The diagnostic criteria for LPR based on DX-pH are the Ryan index at upright position > 9.41 and/or at supine position > 6.79 .

In the current study, we monitored the laryngopharyngeal pH of 44 patients with ILDs and 30 healthy individuals for 24 hours and explored the association between ILDs and LPR. The analysis of the overall 24-hour laryngopharyngeal pH showed that 61.3%, 27.3%, and 11.4% of the 44 ILD patients had neutral, basic, and acidic laryngopharyngeal pH, respectively. 93.4%, 3.3%, and 3.3% of the 30 healthy individuals had neutral, basic, and acidic laryngopharyngeal pH. The proportion of $\text{pH} > 7.5$ group in ILD patients was higher than control group. The normal pH in the lower airway is 7.0 to 7.5. Thus, both basic reflux ($\text{pH} > 7.5$) and acidic reflux ($\text{pH} < 6.5$) appear to occur in patients with ILDs. According to the diagnostic criteria for LPR (Ryan index at upright position > 9.41), only 7 patients including 5 cases of IPF and 2 cases of CTD-ILD met the criteria.

The normal pH in the lung is 7.0 - 7.5. $\text{pH} > 7.5$ may reduce enzyme activity in the lung tissues or even denature enzymes. Thus, basic reflux could affect lung function adversely, particularly for patients with ILDs, who often have poor pulmonary elasticity because of lung fibrosis. Patients with ILDs may have to inhale deeply to expand the alveoli because of the poor pulmonary elasticity. The deep inhalation may cause excessive negative pressure in the chest, which in turn may cause the basic contents including bile and pancreatic juice flow from the duodenal to the throat. The speed of this basic reflux may be too fast to allow the basic contents to be neutralized by gastric acid and to be cleared from the throat. The contents of basic refluxate and the adverse effects of basic refluxate on the laryngopharyngeal mucosa, the lower airway, and the lung need to be further investigated. Acidic reflux could activate the pepsin that has been deposited on the lower airway mucosa and alveoli and consequently result in nonspecific inflammation and trigger ILDs.

The analysis of the pH at supine position showed that 54.5%, 27.3%, and 18.2% of the 44 ILD patients had neutral, acidic, and basic laryngopharyngeal pH, respectively. 90.0%, 6.7%, and 3.3% of the 30 healthy individuals had neutral, acidic, and basic laryngopharyngeal pH. The proportion of pH<6.5 group in ILD patients was higher than control group. The supine position may actually facilitate gastric acid reflux into the throat. We found that using Ryan index only diagnosed 7 cases of LPR. For the entire pH monitoring duration and the duration at upright position, about 30% of the patients showed basic laryngopharyngeal pH, whereas for the duration at supine position, approximately 30% of the patients had acidic laryngopharyngeal pH. These findings indicate that the cutoff value of Ryan index for positive LPR (pH < 5.5 at upright position and/or pH < 5.0 at supine position) may not reflect LPR effectively in patients with ILDs. In addition, we found that only 5 of the 44 patients showed significant difference between the average pH at coughing and the overall average pH. This suggests that cough appears more likely to be associated with ILDs but not with LPR in patients with ILDs. Although the interpretation of the data is limited by small number of study participants, the current study was first to explore the possible association between LPR and ILDs. In addition, we will investigate the composition of gaseous refluxate and study possible mechanism underlying the adverse effects of LPR on ILD initiation and development in our future study.

Conclusion

We found that 50-60% of the patients had neutral laryngopharyngeal pH and did not need anti-acid treatments. Basic LPR may likely occur at upright position, whereas acidic LPR may probably occur at supine position. Patients with acidic LPR may use antacids [29-31] and gastric pro-motility drugs [32]. Patients with basic LPR may only need gastric pro-motility drugs. Ryan index score calculated based on acidic LPR may not reflect LPR accurately in patients with ILDs.

Declaration

List of Abbreviations

ILD: interstitial lung diseases

LPR: laryngopharyngeal reflux

IPF: idiopathic pulmonary fibrosis

CTD-ILD: connective tissue disease-related interstitial lung disease

GERD: gastroesophageal reflux disease

EER: extraesophageal reflux

ESR: erythrocyte sedimentation rate

CRP: c-reactive protein

PaO₂: partial pressure of oxygen

PaCO₂: partial pressure of carbon dioxide

SaO₂: oxygen saturation

CSS: cough symptom score

FVC: force vital capacity

FVC % pred: force vital capacity expressed as a percentage of predicted

D_LCO % pred: carbon monoxide diffusing capacity of the lung expressed as a percentage of predicted

Ethics approval and consent to participate

The study protocol has been approved by the Ethics Committee of Shanghai Pulmonary Hospital (Approval No.: K16-296). All the participating patients signed the informed consent.

Consent for publication

We have obtained consent to publish from all the participants.

Availability of data and material

Authors wish to share their data. The data used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

Author Contributions

HP Li, YL Su, L Shen, and F Zhang participated in the conception, hypothesis and design of the study. YL Su, L Shen, F Zhang, X Jiang and XF Jin performed the experiments. Y Zhang, Y Hu, Y Zhou and QH Li carried out the statistical analyses. All authors contributed to interpretation of the data. YL Su, L Shen, F Zhang and HP Li wrote the manuscript and all authors made critical revisions. All authors read and approved the final manuscript.

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Figures

Figure 1 Patient flow chart

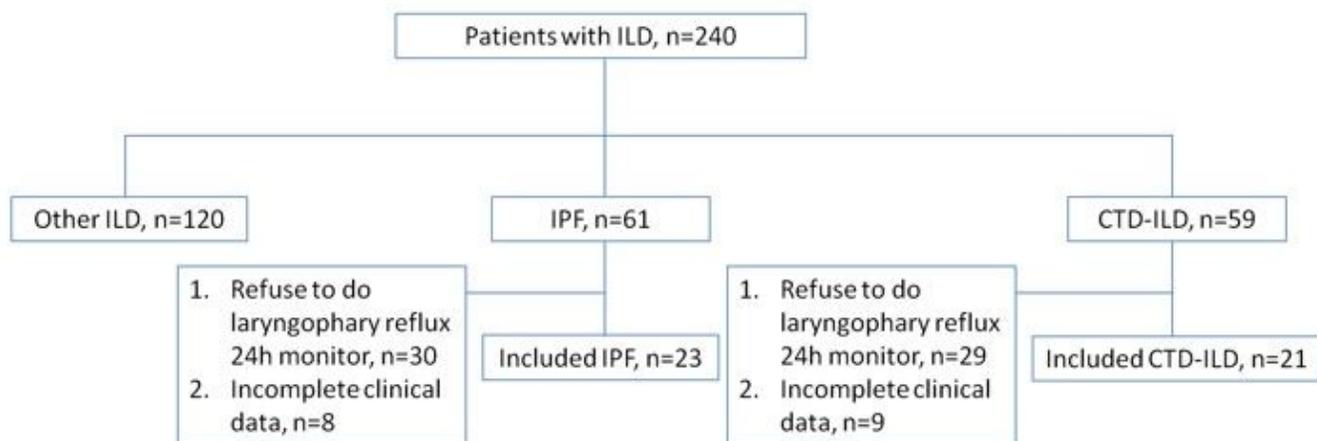


Figure 1

IPF = idiopathic pulmonary fibrosis, CTD-ILD = connective tissue disease-related interstitial lung disease, ILD = interstitial lung diseases A total of 240 patients were diagnosed with ILDs in our hospital between November 2016 and September 2017, including 61 cases of IPF, 59 cases of CTD-ILD, and 120 cases of other types of ILDs. Of the 61 cases of IPF, 30 rejected 24-hour laryngopharyngeal pH monitoring because of severe IPF; 8 did not have sufficient clinical data; 23 underwent 24-hour laryngopharyngeal pH monitoring. Of the 59 cases of CTD-ILD, 29 rejected 24-hour laryngopharyngeal pH monitoring; 9 did not have sufficient clinical data; 21 underwent 24-hour laryngopharyngeal pH monitoring.

Figure 2 Overall mean laryngopharyngeal pH values of IPF and CTD-ILD and control groups

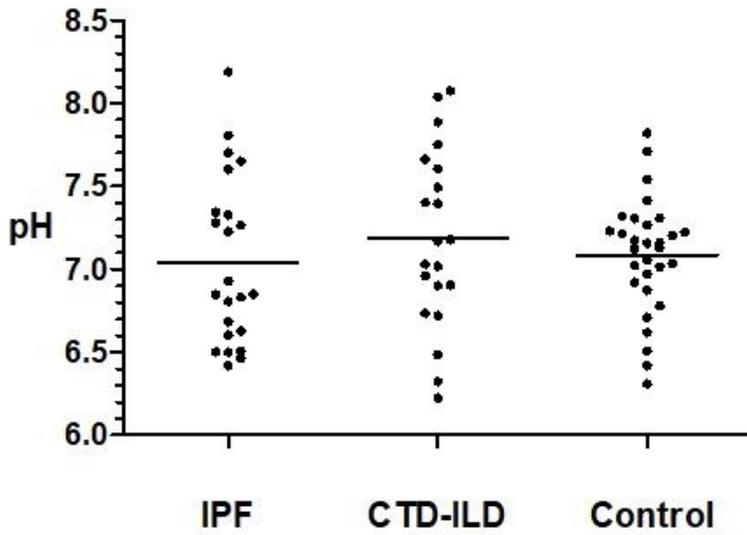


Figure 2

Control: healthy individuals. IPF = idiopathic pulmonary fibrosis, CTD-ILD = connective tissue disease-related interstitial lung disease. The overall average laryngopharyngeal pH of three groups were similar (IPF: 7.04 vs. CTD-ILD: 7.19 vs. Control 7.09, $P > 0.05$, Kruskal-Wallis test).

Figure 3 Results of 24-h pharyngeal pH monitoring of a patient with IPF

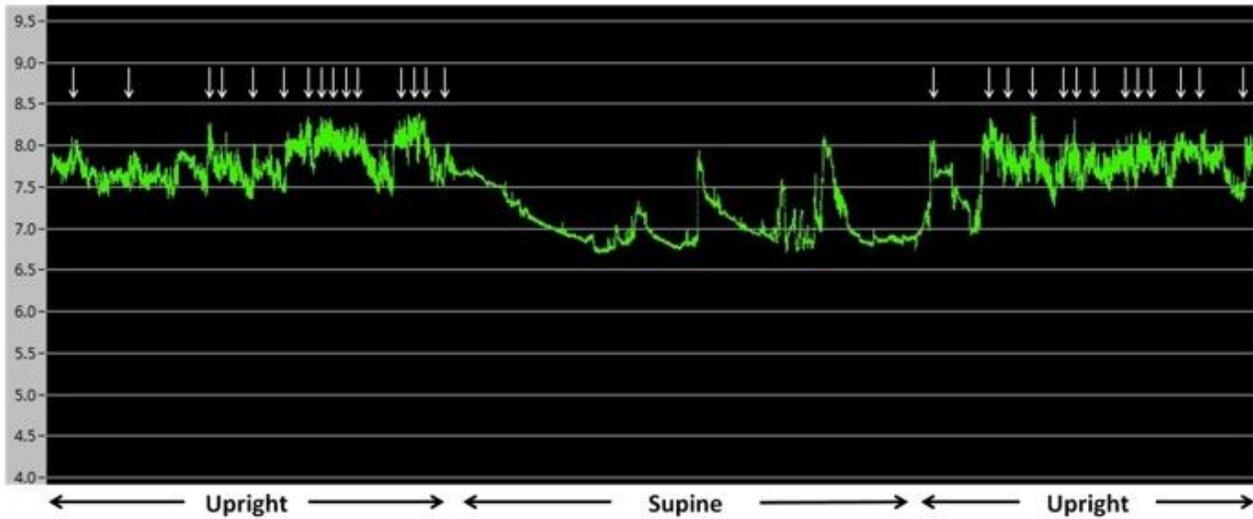


Figure 3

The upright and supine periods can be identified easily by the pattern of the pH recording. pH was more than 7.5 for the majority of the monitoring time. ↓ represent cough events. Cough occurred when pH was > 7.5.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Tables.docx](#)