Exhaled nitric oxide measurements in patients with acute-onset interstitial lung disease

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Abstract

It is important to identify the underlying cause of acute-onset interstitial lung disease (ILD). This study aims to assess whether there are differences in the exhaled nitric oxide (eNO) level between different subtypes of acute-onset ILD. Forty patients with a combination of illness ≤4 weeks in duration and diffuse radiographic infiltrates were classified into groups based on the etiology. The eNO at a flow rate of 50 ml s⁻¹ (FeNO), the alveolar nitric oxide concentration (Calv), and the systemic inflammatory markers of the groups were compared. The median FeNO value of patients with acute eosinophilic pneumonia (AEP) (48.1 ppb) was significantly higher than that of the other groups (17.4 ppb in cryptogenic organizing pneumonia, 20.5 ppb in hypersensitivity pneumonia, and 12.0 ppb for sarcoidosis) (p < 0.0005) as well as blood eosinophils (p < 0.005) and Calv levels (p < 0.005). The area under the receiver’s operating characteristic curve (AUC) for FeNO to identify AEP was 0.90 with a cut-off of 23.4 ppb. The AUC for Calv and blood eosinophils was 0.85 and 0.82, respectively. Even in patients with blood eosinophil numbers <5 × 10⁶ cells µl⁻¹, FeNO maintained a good diagnostic value for AEP (AUC = 0.85). eNO can be useful for differentiating AEP from other types of acute-onset ILD, regardless of the blood eosinophil levels.

Introduction

Acute-onset interstitial lung diseases (ILD) comprise a group of heterogeneous disorders of the lung. Diagnostic considerations in acute-onset ILD include infection and noninfectious ILD, acute interstitial pneumonia (AIP), acute eosinophilic pneumonia (EP), diffuse alveolar haemorrhage (DAH), acute hypersensitivity pneumonitis (HP), acute cryptogenic organizing pneumonia (COP) and drug toxicity or acute exacerbation of previously undiagnosed idiopathic pulmonary fibrosis (IPF) [1]. It is important to identify the underlying lung disease, as it may influence the clinical outcome or appropriate choice of treatment. A chest computed tomography (CT) scan may help to differentiate the cause of ILD. However, CT scans are not specific and a surgical lung biopsy is sometimes required to confirm the diagnosis. Establishing a non-invasive diagnostic tool would be useful for the management of ILD.

Exhaled nitric oxide (eNO), which is a gaseous molecule generated by NO synthase (NOS), is enhanced by inflammatory stimuli [2]. The exhaled nitric oxide fraction (FeNO) has been proposed as a marker of airway inflammation and a guide for anti-inflammatory therapy in asthma [2–4]. Recently, it was made possible to measure local NO production by partitioning eNO into an alveolar NO concentration (Calv) and a conducting airway wall flux of NO (JawNO), with the Calv levels found to reflect NO production at the lung parenchyma [5]. We considered the possibility that NOS up-regulation would be quite different in the lung parenchyma than in the airway. If the eNO levels are elevated in some subtypes of acute-onset ILD, eNO measurements might be a useful approach for identifying the underlying lung disease.

This study aims to assess whether there are differences in the exhaled nitric oxide (eNO) level between different subtypes of acute-onset ILD. We consecutively recruited patients whose symptoms were consistent with the definition of acute-onset ILD. The patients were divided into four groups based on the ILD etiology: acute EP, acute COP, sarcoidosis and
HP. Lung function, FeNO, Calv, inflammatory markers in the blood and cellular patterns in the bronchoalveolar lavage fluid (BALF) of each group were compared.

Methods

Study patients
According to the current guidelines, acute-onset ILD was defined as a combination of illnesses ≤ 4 weeks in duration, shortness of breath, hypoxemia and diffuse radiographic infiltrates in a patient with no history of lung disease and no risk factors for acute respiratory distress syndrome such as infection or trauma [6]. We consecutively recruited patients whose symptoms were consistent with the definition of acute-onset ILD from the Wakayama Medical University Hospital. Current smokers were not included in this study since they can demonstrate chronically reduced levels of FeNO [7–12]. A few patients were excluded because of clinical severity and/or because of inadequate cooperation in performing technically acceptable and repeatable FeNO measurements as well as spirometry. Patients were also excluded if they had no clear etiology of acute-onset ILD and if a lung tissue biopsy was not available. Causes of acute-onset ILD were divided into four groups: acute EP, acute COP, sarcoidosis and HP. The diagnosis of EP was based on the modified Philit criteria [13] (BALF showing >25% eosinophils or eosinophilic pneumonia on the lung biopsy specimen and the absence of known causes of lung eosinophilia). Acute COP is defined histopathologically by intra-alveolar buds of granulation tissue, consisting of intermixed myofibroblasts and connective tissue, together with the exclusion of any possible cause of organizing pneumonia [14]. The diagnosis of sarcoidosis was confirmed by histological evidence of noncaseating epithelioid cell granuloma in one or more tissues with typical clinical features [15]. The diagnosis of HP was based on the criteria reported by Lacasse et al [16] BALF lymphocytosis (≥30%) [17] and bilateral ground-glass or poorly defined centrilobular nodular opacities on chest CT [18], and serum precipitating antibodies against potential antigens were required for a diagnosis of HP [16]. Diagnosis of the ILD etiology was made by two lung specialists who were blinded to the eNO values. The study was approved by the ethics committee of Wakayama Medical University (IRB #526) and all patients gave informed consent.

Study assessments
The level of eNO was measured in accordance with the current guidelines [2]. We measured eNO in triplicate prior to conducting spirometry at four separate, constant expiratory flow rates (50, 100, 175 and 370 ml s⁻¹) by using a chemiluminescence-based exhaled NO analyzer (NA-623 N, Chest Co. and Kimoto Electric Co., Tokyo, Japan), and the mean of three values is reported. The eNO at a flow rate of 50 ml s⁻¹ is represented as FeNO levels [2]. The technique of Tsoukias and George was used to calculate the peripheral airway/alveolar NO concentration (Calv, ppb) by using a linear regression line for each subject with a minimum of three expiratory flow rate data points [5]. To adjust for possible spurious overestimation of the values for Calv NO, the initial, uncorrected large airway NO flux (ml s⁻¹) was divided by a correction factor and subtracted from the initial uncorrected small airway/alveolar Calv NO [19]. Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and the diffusion lung carbon monoxide (DLCO) were measured using a dry-rolling seal spirometer (CHESTAC-8800; Chest Co., Tokyo, Japan). The predictive values were estimated by the prediction formula of the Japanese Respiratory Society. Complete blood cell count, the differential count of leukocytes, sialylated carbohydrate antigen KL-6 (KL-6), c-reactive protein (CRP), pulmonary surfactant protein A and D (SP-A and SP-D), total serum immunoglobulin E (IgE) levels, and specific IgE for common inhaled allergens including Dermatophagoides pteronyssinus (DP), Dermatophagoides farina (DF) and the house dust mite (HD) were also examined. A specific IgE positive for at least one allergen was assumed to confirm the presence of atopy. All asthmatic patients had a history of episodic dyspnea, wheezing and documented significant airway reversibility.

Statistical analysis
All data was expressed as median and interquartile ranges (IQR) for continuous variables. The numbers of observations and percentages are given for each category of data. The clinical and demographic characteristics of each acute-onset ILD group were compared using the Kruskall–Wallis test or Fisher exact test as appropriate. The Mann–Whitney test was used to compare eNO values with the blood eosinophil status. A p-value of <0.05 was considered statistically significant. Receiver operating characteristic (ROC) analysis was used to assess FeNO, Calv and blood eosinophils as a potential marker of acute EP. The sensitivity and specificity of these parameters for acute EP diagnosis were also determined.

Results
A total of 50 patients were recruited for the study, and 40 patients were enrolled and analyzed. A lung tissue biopsy was not available in three patients and seven patients had no clear etiology of acute-onset ILD. The causes of acute-onset ILD were divided into four groups. Eighteen patients (45%) had acute EP, sixteen had eosinophilic pneumonia on their lung biopsy specimens and eight had >25% eosinophils in BALF. Fourteen patients...
(35%) had acute COP, based on their histological and clinical features; sarcoidosis and HP were identified in five and three patients, respectively.

The clinical and biological characteristics for each cause of acute-onset ILD are shown in Table 1. The age, gender, BMI, smoking history and presence of atopy were no different between the groups, although the acute EP group had a higher proportion of patients with asthma history (p < 0.05) and higher levels of blood eosinophils (p < 0.005) (figure 1). None of the other systemic inflammatory markers showed a significant difference. As shown in Table 2, there was no significant difference for VC, FVC, FEV1 or DLCO, but the median FeNO value of patients with EP (48.1 ppb) was significantly higher than that of the other groups (17.4 ppb in COP, 20.5 ppb in HP and 12.0 ppb for sarcoidosis) (p < 0.0005) as well as Calv levels (p < 0.005) (figure 1). As shown in Figure 2, the area under the ROC curve (AUC) for FeNO to identify an acute EP was 0.90 with a cut-off of 23.4 ppb and a sensitivity and specificity of 94% and 73%. The AUC for Calv and blood eosinophils to identify an acute EP was 0.85 and 0.82; a Calv cut-off of 10.2 ppb had a sensitivity and specificity of 71% and 96%, and a blood eosinophils cut-off of 692 cells μl⁻¹ had a sensitivity and specificity of 53% and 100%.

Next, we dichotomized the patients with acute EP into two groups based on the blood eosinophil levels. We labeled those whose levels were less than the 50th percentile as non-high blood eosinophils (<5 × 10⁵ cells μl⁻¹), and those whose levels were greater than the 50th percentile as high blood eosinophils. As shown in Figure 3, both patients with non-high and high blood eosinophils had higher levels of FeNO compared to the patients with other etiologies of ILD (p < 0.005 and p < 0.0001, respectively). In the patients with non-high blood eosinophils, the AUC for FeNO to identify an acute EP was 0.85 with a cut-off of 23.2 ppb having a sensitivity and specificity of 88% and 73%. In patients with high blood eosinophils, the AUC was 0.96 with a cut-off of 24.2 ppb having a sensitivity and specificity of 100% and 77% (figure 4).

**Discussion**

Our study revealed two important clinical issues. FeNO was a value for differentiating EP from other types of acute-onset ILD regardless of the blood eosinophil levels. The Calv levels in the patients with EP were significantly higher than in those with other types of acute-onset ILD.

First, FeNO was a value for differentiating EP from other types of acute-onset ILD, regardless of the blood eosinophil levels. BALF or lung biopsy is necessary to confirm the diagnosis of EP and these procedures are occasionally difficult to perform on patients with hypoxemia [13]. FeNO does not substitute these procedures for definitive diagnosis of EP; however, it can contribute to the possibility of EP. Although CT findings are useful for differentiating the causes of ILD, EP and COP share many features in CT findings, and some authors have concluded that CT cannot differentiate them [20]. A FeNO level > 23.4 ppb yielded 94% sensitivity and 73% specificity for differentiating patients with EP from other types of acute-onset ILD. To our knowledge, there is only one study that analyzed the FeNO levels in patients with acute EP [21]. Lee et al reported that the FeNO levels were significantly higher in 31 patients with acute EP than in 29 patients without it. However, the study population only included young males, and the patients without acute EP had community-acquired pneumonia in all cases. Therefore, it was questionable whether FeNO measurements should be used as a diagnostic tool for differentiating patients with acute EP from those without it. Our study population consisted of middle-aged and aged patients and the causes of acute-onset ILD were various. Regardless of the blood eosinophil levels, FeNO maintained a good diagnostic value for acute EP. Peripheral
blood eosinophilia is not usually observed in the initial stage of EP [22], and thus our results may be helpful for the early diagnosis of EP in the clinical setting. For these reasons, our results demonstrated that FeNO levels.

Table 2. The lung function and airway inflammatory parameters for etiologies of acute-onset interstitial lung disease.

|                | EP               | COP              | Sarcoidosis      | HP               | p value |
|----------------|------------------|------------------|------------------|------------------|---------|
| VC, L          | 2.57 (2.13–3.34) | 2.40 (1.71–3.48) | 3.26 (3.07–3.53) | 3.31 (2.71–3.34) | 0.24    |
| VC % of predicted, % | 80.5 (70.4–93.4) | 82.3 (77.3–103.1) | 113.9 (107.1–113.3) | 96.3 (80.5–100.6) | 0.10    |
| FVC, L         | 2.61 (2.16–3.34) | 2.40 (1.82–3.42) | 3.34 (3.11–3.62) | 3.24 (2.68–3.30) | 0.17    |
| FEV1 / FVC ratio, % | 1.83 (1.63–2.36) | 1.72 (1.50–2.78) | 2.54 (2.30–2.94) | 2.70 (2.23–2.90) | 0.12    |
| FVC % of predicted, % | 80.7 (76.6–84.9) | 82.5 (78.9–86.8) | 83.8 (76.8–87.2) | 83.9 (83.4–88.2) | 0.87    |
| FEV1% of predicted, % | 85.6 (74.6–94.9) | 83.3 (79.9–105.1) | 113.5 (106.7–118.3) | 96.7 (81.0–102.4) | 0.10    |
| %DLCO /VA, %   | 81.1 (73.9–86.4) | 81.7 (67.7–85.9) | 107.0 (104.9–110.8) | 77.7 (71.2–85.1) | 0.14    |
| Exhaled NO fraction, ppb | 85.7 (68.6–99.9) | 88.2 (77.9–93.8) | 95.7 (89.1–103.2) | 70.3 (64.6–75.7) | 0.30    |
| Alveolar NO concentration, ppb | 48.1 (28.8–61.8) | 17.4 (13.5–30.0) | 12.0 (8.9–15.5) | 20.5 (18.0–22.4) | <0.0005 |
| Neutrophil count in BALF, cells μL⁻¹ | 11.2 (7.7–14.1) | 6.2 (3.9–8.6) | 4.6 (3.5–6.2) | 5.8 (4.5–6.2) | <0.005  |
| Eosinophil count in BALF, cells μL⁻¹ | 16 (3–35) | 12 (2–37) | 33 (10–58) | 17 (10–33) | 0.68    |
| Lymphocyte count in BALF, cells μL⁻¹ | 32 (11–100) | 3 (0–25) | 4 (2–6) | 4 (2–8) | <0.0001 |

The data are presented as median (interquartile range). EP: eosinophilic pneumonia; COP: cryptogenic organizing pneumonia; HP: hypersensitive pneumonitis; DLCO: diffusion lung carbon monoxide; VA: alveolar volume; BALF: bronchoalveolar lavage fluid.

Figure 1. The mean blood eosinophil counts, FeNO and Calv values for the etiologies of acute-onset interstitial lung disease. EP: acute eosinophilic pneumonia (* p < 0.0005; * p < 0.005); COP: acute cryptogenic organizing pneumonia; HP: hypersensitivity pneumonitis (HP).
Second, the Calv levels in the patients with EP were significantly higher than in those with other types of acute-onset ILD. A Calv >10.2 ppb yielded 71% sensitivity and 96% specificity for differentiating patients with EP from other types of acute-onset ILD. We have reported that the Calv levels in patients with EP were significantly higher than in the healthy subjects and in patients with IPF, and had significantly positive correlations with both the inducible type of NOS (iNOS) expression and 3-nitrotyrosine (3-NT) positive cells in BALF [23]. These results suggested that the excessively generated NO in the lung parenchyma induces nitrosative stress in EP. Although the subjects were acute phase in the current study, the FeNO and Calv levels in the patients with EP were nevertheless significantly higher than in the other acute-ILD groups. These results speculate that in EP, eosinophils may infiltrate not only into the lung parenchyma, but also into the airway. Ogawa et al also reported that airway and alveolar inflammation often coexist in patients with EP [24]. Specimens of bronchial biopsy revealed eosinophil infiltration into the bronchial mucosa, and lung biopsy specimens showed eosinophil infiltration into the epithelium of the bronchioles. After all, both airway and lung parenchyma are important as the main site of inflammation in EP.

As shown in table 3, the combination of FeNO and Calv increased the specificity and positive predictive value compared to the separate markers. The complication of asthma in patients with EP is high compared

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**Figure 2.** Receiver operating characteristic curves of blood eosinophil counts, FeNO, and Calv for the diagnosis of acute eosinophilic pneumonia. The solid thin line represents blood eosinophils, the solid thick line represents FeNO and the dotted line represents Calv.

**Figure 3.** The mean FeNO values for eosinophilic pneumonia (EP) and other types of acute-onset ILD (non-EP). The EP group was subdivided by the blood eosinophil levels; high blood eosinophils were defined as $\geq 5 \times 10^2$ cells $\mu l^{-1}$, and low blood eosinophils were defined as $<5 \times 10^2$ cells $\mu l^{-1}$.

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to those with other ILDs [25, 26]. The combination of measuring FeNO and Calv could decrease the risk of overlooking the EP.

FeNO has been proposed as a marker of airway inflammation and a guide for anti-inflammatory therapy in asthma [2–4]. Acute EP is characterized by a rapid response to systemic corticosteroids with few relapses and improvement of radiologic abnormalities without fibrosis [27, 28]. However, there is controversy about the dosing and tapering of corticosteroids [29–31]. We have reported that systemic corticosteroid treatment reduced the Calv and the FeNO levels in patients with EP; therefore Calv and FeNO might serve as a marker of the response by treatment [23]. Park et al reported that the FeNO level might be useful for monitoring eosinophilic parenchymal inflammation and determining the appropriate corticosteroid dose in chronic EP [32]. Although we did not investigate the FeNO levels after corticosteroid therapy in this study, FeNO may be of value for guiding anti-inflammatory therapy in EP.

Figure 4. The receiver operating characteristic curves of FeNO for discriminating eosinophilic pneumonia (EP) from other types of acute-onset ILD (non-EP). The EP group was subdivided by the (A) low (<5 × 10^2 cells μl^-1) or (B) high (≥5 × 10^2 cells μl^-1) levels of blood eosinophil numbers.
Table 3. The sensitivity, specificity, PPVs and NPVs at FeNO > 23.4 ppb, Calv > 10.2 ppb and combined with FeNO > 23.4 ppb and Calv > 10.2 ppb for the diagnosis of acute eosinophilic pneumonia.

| Markers in exhaled air | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|------------------------|-----------------|-----------------|---------|---------|
| FeNO > 23.4 ppb        | 94.1            | 72.7            | 73.9    | 94.1    |
| Calv > 10.2 ppb        | 70.6            | 95.5            | 92.3    | 77.8    |
| FeNO > 23.4 ppb and Calv > 10.2 ppb | 66.7 | 100.0 | 100.0 | 78.6 |

PPV: positive predictive value; NPV: negative predictive value; FeNO: exhaled nitric oxide fraction; Calv: alveolar nitric oxide concentration.

This study had several limitations. First of all, our study population did not include NSIP, DIP, AIP, acute exacerbation of IPF, DAH or drug-induced ILD. During the recruitment period, patients with these diseases came to the hospital. We excluded them in this study because they violated the exclusion criteria, including current smokers or biopsy not available. However, in these diseases, because of the risk of patient deterioration, lung tissue biopsy is rarely possible. Secondly, the acute EP group had a higher proportion of patients with asthma history, but the patients with EP often had complicated asthma [33]. The Calv levels were elevated in patients with alveolitis compared to those in asthmatics [34]. The elevated Calv levels in the patients with EP suggest that the NO production may be useful for differentiating between the causes of ILD. Thirdly, current smokers were excluded in this study since they can demonstrate chronically reduced levels of FeNO. Finally, a few patients were excluded because of clinical severity and/or because of inadequate cooperation to perform technically acceptable and repeatable FeNO measurements as well spirometry.

Conclusion

In this study of patients who fit the definition of acute-onset ILD, we found that FeNO was of value for differentiating EP from other types of acute-onset ILD, regardless of the blood eosinophil levels. The Calv levels in the patients with EP were significantly higher than in the other types of acute-onset ILD. Further studies are needed to assess whether FeNO may be useful for differentiating EP from various causes of acute-onset ILD and for guiding anti-inflammatory therapy in EP.

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