Frequency dependence of compliance in the evaluation of patients with unexplained respiratory symptoms


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Frequency dependence of compliance (FDC) reflects non-homogeneous ventilatory distribution and, in the presence of a normal measured airway resistance, suggests peripheral airways dysfunction. This study evaluated peripheral airway function and bronchial reactivity in irritant exposed or non-exposed individuals with normal routine pulmonary function tests (PFTs) who had persistent unexplained lower respiratory symptoms.

Twenty-two patients were identified with persistent respiratory symptoms and with normal chest X-ray and PFTs. Twenty were non-smokers; two had stopped smoking more than 10 years before evaluation. Twelve patients had been exposed to irritants in their workplaces or at home. Non-specific bronchial hyper-reactivity (nsBHR) and FDC, pre- and post-bronchodilator, were measured in all patients. Studies were repeated in 6/12 irritant-exposed subjects after exposure removal and inhaled corticosteroid treatment.

Whereas 12/22 patients had nsBHR, all 22 subjects demonstrated FDC [dynamic lung compliance/static lung compliance \( C_{\text{dyn,1}} / C_{\text{st,1}} \) at respiratory frequency \( 60 \text{ min}^{-1} \) (f60), mean 46%, range 27–67%]. After bronchodilator administration, a 15% improvement \( C_{\text{dyn,1}} \) was observed most consistently at f60 (mean% improvement 26%, 95% CI 14–38%) and in subjects without nsBHR. However, \( C_{\text{dyn,1}} \) at f60 did not return to normal after inhaled bronchodilator. Irritant-exposed and unexposed individuals appeared similar in results of testing for FDC and nsBHR.

FDC and its response to bronchodilators provide objective physiological measures of an airway abnormality which may provide a basis for clinical symptoms in patients with normal routine pulmonary function studies. The presence of persistently abnormal FDC after bronchodilator (BD) and on follow up studies may reflect chronic inflammatory and/or structural changes in the airways in addition to bronchoconstriction.

Key words: bronchial reactivity; lung compliance; lung diseases, obstructive; irritants; respiratory function tests; asthma; adrenergic beta-agonists.

Introduction

Abnormal peripheral airways resistance may not be apparent on routine pulmonary function tests (spirometry and plethysmography). Frequency dependence of compliance (FDC) reflects non-homogeneous ventilatory distribution and, in the presence of a normal measured airway resistance, suggests peripheral airways dysfunction (1–3). FDC has been reported in smokers, the elderly and patients with chronic obstructive lung disease (including asthma) (2,4–9). Inhalation of respiratory toxicants can cause a spectrum of lesions and dysfunction at different levels of the respiratory tract, which depends on the severity of the exposure and on individual factors (10,11). It has been demonstrated histologically that small airway damage can result from such exposures (12–14) and abnormal FDC has been reported in radiographically evident coal workers’ pneumoconiosis (15), short-term exposure to asbestos (16) and isolated case reports of inhalation injury caused by nitrogen dioxide (17) and ammonia (18,19). Despite these considerations, the requirement for esophageal manometry has limited the use of this test. In addition, while FDC has been absent in the asymptomatic non-smoking individuals of several studies (1,5,7,9,15,20), it has been observed in selected asymptomatic individuals of other studies and its role in clinical diagnosis of lung diseases remains unclear.

The primary aim of this study was to evaluate peripheral airway function and non-specific bronchial hyper-reactivity (nsBHR) in irritant-exposed or non-exposed, non-smoking, previously healthy individuals with normal pulmonary
function tests who had persistent, unexplained respiratory symptoms. Secondary aims included: 1. to assess the acute response of FDC to inhaled bronchodilator and 2. to evaluate the response of FDC to exposure removal and inhaled corticosteroid treatment in irritant-exposed patients.

**Methods**

The protocol for this study was approved by our institution’s ethics committee and informed consent was obtained for participation in the study.

**SUBJECTS**

Subjects were recruited from referrals to the Chest Service at Bellevue Hospital from December, 1993 to January, 1997. Of all patients referred from the Occupational Medicine and Primary Care Asthma Clinics, 32 patients were identified with persistent and unexplained respiratory symptoms (cough, exertional dyspnoea, chest tightness and/or wheezing) whose chest radiographs spirometry, lung volumes and specific conductance were within normal limits. Premorbid medical records were reviewed in every patient to exclude subjects with diagnoses of lung disease predating irritant exposure or current symptoms. Subjects were limited to those who were lifetime non-smokers or who had stopped smoking more than 10 years before evaluation. Based on the above criteria, the study group consisted of 22 of these 32 patients.

Table 1 summarizes several demographic and clinical characteristics of the 22 subjects. Although symptoms were frequently disruptive, most patients were able to continue their normal daily activities. Twelve patients had been exposed to irritants in the workplace (n = 10) or at home (n = 2), but the intensity and duration of the exposures varied widely. Clinical histories of all 12 irritant exposed patients suggested that their symptoms were related to the irritant exposures. Three of the patients met criteria for a diagnosis of reactive airways dysfunction syndrome (RADS) (21). Their single-episode high-level exposure had taken place 2–24 months before our evaluation. In contrast, for those who were exposed at home (n = 2), the exposures had taken place for several years at low levels. The irritants included ammonia, acetic acid, glutaraldehyde, perchloroethylene and other organic solvents, sodium hypochlorite and other cleaning agents, and triethylene tetramine.

**PULMONARY FUNCTION TESTING**

Spirometry, lung volumes and specific airway conductance were measured with a plethysmograph (P.K. Morgan, Andover, MA, U.S.A.). Measured parameters were referenced to previously published prediction equations (22–26).

Non-specific bronchial hyperreactivity (nsBHR) was assessed by methacholine challenge (27) (19/22 patients) or cold-air and exercise challenge (28) (3/22). A 20% decrease in FEV₁ with a nebulized methacholine concentration (PC₂₀) of 8 mg/dl or less, or after cold air breathing and exercise challenge, was considered a positive test.

Static and dynamic compliance of the lung were measured with a plethysmograph (P.K. Morgan). Esophageal manometry was performed utilizing an esophageal balloon (Ackrad Laboratories; Cranford, NJ, U.S.A.) positioned in the distal third of the esophagus. Elastic recoil of the lung (Pel) was assessed at TLC using a quasi-static technique. Static compliance (Cst₁) was measured with an interrupter technique after three vital capacity maneuvers (2). Dynamic compliance (Cdyn₁) was determined at increasing respiratory rates including the patient’s baseline frequency, 40 breaths min⁻¹ and 60 breaths min⁻¹ (fBL, f₄₀ and f₆₀, respectively). Tidal volume was monitored at all frequencies and did not vary by more than ± 50 ml. Prior to measurements at each respiratory frequency, patients were instructed to relax and exhale to their resting lung volume. Constancy of Cdyn₁ during successive breaths at each frequency provided evidence that changes in FRC did not affect the results. Albuterol was administered by metered-dose inhaler to 19/22 patients and measurements of Cdyn₁ were repeated over the full range of frequencies. For all measures of elastic recoil pressure and lung compliance, data are presented as the mean value from three reproducible maneuvers.

In order to assess the response of the physiological abnormalities to treatment, follow-up evaluation was performed in 6/12 irritant exposed subjects at least 6 months after complete removal (5/6) from or significant reduction (1/6) of exposure. Treatment consisted of an inhaled corticosteroid (triamcinolone acetonide 0.8 mg day⁻¹) with or without inhaled β₂-agonist.

**STATISTICAL ANALYSIS**

Data were stored and analysed using an SPSS statistical program (29). Fisher’s exact test was performed for bivariate analysis of categorical variables. Unpaired t-tests or, when data distribution was not normal, Mann–Whitney U-tests were used to compare group means of continuous variables. Paired t-tests or, where appropriate, Wilcoxon signed ranks tests were used to compare within-individual lung compliance measurements. Two-tailed tests were performed using an α level of 0.05 to determine statistical significance. The Bonferroni procedure was used to adjust

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**Table 1. Characteristics of the 22 study patients**

<table>
<thead>
<tr>
<th>Age, years</th>
<th>38 ± 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/Male, n</td>
<td>15/7</td>
</tr>
<tr>
<td>Symptoms, n</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14</td>
</tr>
<tr>
<td>Cough</td>
<td>13</td>
</tr>
<tr>
<td>Wheezing</td>
<td>2</td>
</tr>
<tr>
<td>Symptom duration, months</td>
<td>22 ± 16</td>
</tr>
<tr>
<td>Smoking status, n</td>
<td></td>
</tr>
<tr>
<td>Lifetime non-smoker</td>
<td>20</td>
</tr>
<tr>
<td>Former smoker (&gt;10 yr)</td>
<td>2</td>
</tr>
</tbody>
</table>

*Data are provided as counts (n) or means ± 1sd.
for multiple comparisons (30). The FDC response to bronchodilator is calculated for each respiratory frequency as the % change in \( C_{dyn,1} = (C_{dyn,1 \ post-bronchodilator} - C_{dyn,1 \ pre-bronchodilator})/C_{dyn,1 \ pre-bronchodilator} \). Response of FDC to bronchodilator was analysed by two methods: 1. as a continuous variable, by paired comparison of pre- and post-BD values; and 2. as a categorical variable, by utilizing an a priori cutoff point of 15% improvement to define a positive response (31).

**Results**

Table 2 presents the pulmonary function data obtained in the 22 patients studied. By design, lung volumes, flow rates and specific conductance were within normal limits for all subjects. Elastic recoil (Pel) at TLC and \( C_{st,1} \) were also normal in all subjects.

Whereas 12/22 patients had nsBHR (including the three subjects with RADS), all 22 subjects demonstrated frequency dependence of compliance (Fig. 1). FDC expressed itself at respiratory rates ranging from the baseline rate (fBL, mean 22 min\(^{-1}\)) to f60 (Fig. 1). Paired testing confirmed that the compliance changed significantly with frequency (\( C_{dyn,1} \) at fBL, f40 and f60 compared with \( C_{st,1} \), \( P < 0.001 \) for each). \( C_{dyn,1}/C_{st,1} \) at f60 was less than 67% in all subjects with a mean value of 46% ± 21% (mean ± SD).

Figure 2 illustrates the mean values (± st) for \( C_{dyn,1} \) pre and post-bronchodilator at each respiratory frequency studied in 19 of the 22 patients. There was a post-bronchodilator improvement in \( C_{dyn,1} \) at each frequency. Paired analyses revealed that the change in \( C_{dyn,1} \) post-bronchodilator for the group was statistically significant at f40 (mean 25%, 95% CI 9–41%, \( P < 0.001 \)) and at f60 (mean 26%, 95% CI 14–38%, \( P < 0.001 \)), but not at fBL (mean 11%, 95% CI –2%–24%, \( P = 0.26 \)). A 15% improvement in \( C_{dyn,1} \) after bronchodilator was observed in 6/19 at fBL, 10/19 at f40 and 11/19 at f60. Values for \( C_{dyn,1} \) at f60 remained abnormal post-bronchodilator in all subjects (Fig. 2). Of note, 5/19 subjects demonstrated a paradoxical decrease in \( C_{dyn,1} \) after bronchodilator at fBL (range of % change –6% to –14%).

Response of \( C_{dyn,1} \) to bronchodilator was assessed in 10 of the 12 subjects with nsBHR, and nine of the 10 subjects without nsBHR. A statistically significant inverse association was observed between nsBHR and the magnitude of the FDC response to bronchodilator at f60. Mean bronchodilator response of \( C_{dyn,1}/C_{st,1} \) at f60 was 14.5% for the group with nsBHR and 37.4% for the group without nsBHR (\( P = 0.02 \). Using the cutpoint of 15% improvement, FDC response to bronchodilator at f60 was present in 30% of subjects with nsBHR and 89% of those without nsBHR (Fisher’s exact \( P = 0.02 \)).

Irritant-exposed and non-exposed groups appeared similar on measures of \( C_{st,1}, C_{dyn,1}/C_{st,1} \) at all three respiratory frequencies, and proportion of subjects with nsBHR (Table 3 and Fig. 1). No difference was apparent between individuals with RADS and those who were exposed to relatively lower levels of irritants.

Six of the 12 irritant-exposed patients returned for follow-up studies 7–34 months after complete elimination or reduction of their exposure and treatment with inhaled steroids. This group included two of the patients with RADS, who were evaluated 21 and 34 months after their index exposure episode. All six patients reported partial resolution of their symptoms over time. Follow-up nonspecific bronchoprovocation demonstrated reversal of nsBHR in four (including two of the subjects with RADS),...
Discussion

This study demonstrated abnormal airway function, as assessed by FDC, in all 22 subjects. Since nsBHR was demonstrated in only 12 of these subjects, FDC was the only detectable physiological abnormality in the remaining 10. Partial reversal of FDC in response to an inhaled bronchodilator was more evident at the highest frequency (f60) and in subjects without nsBHR. Comparisons between irritant-exposed and non-exposed subjects revealed similar FDC, FDC response to bronchodilator, and nsBHR. Although the sample size limited the statistical power to detect differences between these two groups, the overlap in their test results (and with those of the three individuals who met current criteria for RADS) suggests that they are functionally similar. FDC has been recognized as a feature of non-specific obstructive airway disease. These data suggest that peripheral airway dysfunction may be a frequently overlooked feature in individuals who have persistent and unexplained respiratory symptoms, or who have been exposed to irritants over a wide range of concentrations.

Some methodological aspects deserve comment. The study design was best suited for a comparison of the findings of a widely used test (non-specific bronchoprovocation) with those of a technically demanding test (FDC) with limited availability. Despite some suggestion that FDC may be the more sensitive test of small airway function (7,32), controlled studies are warranted using measurements derived from single-breath nitrogen washout or helium–oxygen flow–volume curves, or frequency dependence of resistance (33). Using a maximal expiratory maneuver to assess nsBHR, although in widespread clinical use, may have underestimated the presence of nsBHR in our subjects (34,35), particularly since study entry criteria in all likelihood selected individuals with less severe airway obstruction (36).

For subjects in the current study, FDC was manifest over a range of respiratory frequencies from fBL to f60. The effects of peripheral airway obstruction on Cdyn,1 manifest

**Table 3.** Comparison of irritant-exposed (n=12) and unexposed (n=10) patients in the study*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Irritant exposure</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>+</td>
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<tr>
<td>Cst,1, cm⁻¹ H₂O</td>
<td>0.177±0.036</td>
</tr>
<tr>
<td>Cdyn,1/Cst,1 at fBL (%)</td>
<td>79±14</td>
</tr>
<tr>
<td>Cdyn,1/Cst,1 at f40 (%)</td>
<td>61±13</td>
</tr>
<tr>
<td>Cdyn,1/Cst,1 at f60 (%)</td>
<td>47±11</td>
</tr>
<tr>
<td>Cdyn,1/Cst,1 at fBL, post-BD (%)</td>
<td>81±15</td>
</tr>
<tr>
<td>Cdyn,1/Cst,1 at f40, post-BD (%)</td>
<td>71±17</td>
</tr>
<tr>
<td>Cdyn,1/Cst,1 at f60, post-BD (%)</td>
<td>58±12</td>
</tr>
<tr>
<td>Bronchial hyper-reactivity (n)</td>
<td>7/12</td>
</tr>
</tbody>
</table>

*Data are provided as means ±1sd.
predominantly but not exclusively at high respiratory frequencies (2,3,6,7). A decrease of C_{dyn,1} at baseline respiratory rate has been observed occasionally in chronic bronchitis (2), in asthma early during recovery from an acute attack of bronchospasm (37), in nitrogen dioxide inhalation injury (17), as well as other lung diseases (38). The observed variability of FDC and its response to bronchodilator likely reflects a spectrum of airway abnormality ranging in severity and anatomic location.

The response of FDC to inhaled bronchodilator was variable across subjects and manifested at varying respiratory frequencies. Although some subjects demonstrated a post-bronchodilator improvement in C_{dyn,1} at fBL, the improvement was more marked and consistent at f40 and f60. This improvement of FDC after inhaled bronchodilator is compatible with the observation that peripheral airways, including those with a diameter of less than 2 mm, have smooth muscle (39), which responds to histamine and isoproterenol (40), and that FDC can be induced in response to intravenous histamine (20).

Inhaled bronchodilator paradoxically worsened FDC in approximately 25% of subjects at fBL, but not at higher frequencies. These data are in accord with the observations of Woolcock et al., who postulated that smooth muscle tone in the peripheral airways may act to reduce variations in time constants between lung units (2). Accordingly, administration of a bronchodilator may interfere with this adaptive phenomenon and lead to increased FDC.

The observed inverse association between nsBHR and the magnitude of the FDC response to BD was an unexpected finding. One possible explanation is a more effective deposition of inhaled BD in the peripheral airways of individuals with lesser degrees (or lack) of nsBHR. In a recent study, Wagner et al. (40) directly measured peripheral airway resistance and inhaled bronchodilator response in asthmatic (all with nsBHR) and non-asthmatic (all without nsBHR) subjects. They observed that inhaled BD reverted a histamine induced increase in peripheral airway resistance in their asthmatic (nsBHR) and non-asthmatic (nsBHR−) subjects. These observations may suggest that the predominant site of airway hyper-responsiveness differs among patients with intermittent obstructive disease and underline the limitations of nsBHR as a predictor of peripheral airway physiologic changes and responses. These observations clearly deserve further investigation.

Asymptomatic cigarette smokers may demonstrate FDC or other markers of peripheral airway dysfunction (2,6,7,9,41). These physiological abnormalities have been shown to correlate with peripheral airways changes in some (41), and to be reversible after smoking cessation in others (6). In contrast, clinical symptoms and bronchial hyper-reactivity may persist in individuals with occupational asthma despite exposure removal with or without inhaled steroid treatment (42). In the current study, follow-up evaluation of irritant-exposed subjects revealed persistent FDC despite elimination or reduction of irritant exposure, inhaled corticosteroid treatment, partial improvement of symptoms and improvement in nsBHR. This finding, as well as that of persistent FDC after bronchodilator in all subjects, may reflect chronic inflammatory and/or structural changes in the airways (2,6,39). This could be consistent with the morphological changes described in individuals with obstructive airway disease of diverse etiologies (13,14,39,41,43).

Normal asymptomatic subjects may occasionally demonstrate FDC. Although FDC may reflect a more complex model, any physiological system with a resistance and elastance in series will demonstrate frequency dependence beyond a critical point. This has confounded the definition of an abnormal FDC. Whereas the majority of studies have indicated that values of C_{dyn,1}/C_{st,1} at f60<80% are abnormal and define small airways dysfunction (2,6–9,15,20,44), other studies have reported greater degrees of FDC in a minority of asymptomatic subjects (4,45). This finding may be attributable to several factors. Small airways disease may occur in the absence of clinical symptoms. Some studies have included current or prior smokers as normal subjects (4). In addition, Begin et al. demonstrated an age-related mechanism for FDC in normal subjects, attributable to an increase in C_{st,1} without concomitant change in C_{dyn,1} (45). For subjects in the current study it is likely that the observed FDC does reflect abnormality. Subjects in the present study uniformly

![Fig. 3. The observed values for C_{dyn,1}/C_{st,1} at f60 for all study subjects are plotted as a function of age. The shaded area represents the 95% tolerance interval reported by Begin et al. (40). 20/22 subjects had values for C_{dyn,1}/C_{st,1} at f60 that were below the 95% tolerance interval reported by Begin et al. Note, since two subjects had identical values, only 21 data points are illustrated.](image-url)
demonstrated greater FDC than has been observed in our laboratory or reported in studies of normal subjects (2,4,6–9,15,20,44,45). In addition, following bronchodilator administration, $C_{dyn,1}/C_{st,1}$ at f60 improved an average of 26% indicating at least partial reversibility of FDC. Lastly, in most subjects $C_{dyn,1}/C_{st,1}$ at f60 was below the age-adjusted normal range reported by Begin et al. (45). This is graphically presented in Fig. 3 which illustrates that 20/22 subjects had values for $C_{dyn,1}/C_{st,1}$ at f60 that were below the 95% tolerance interval reported by Begin et al. (indicated by the shaded area). Future studies to corroborate normative data for FDC and/or with control groups are warranted.

Despite some remaining uncertainty as to the exact location of its underlying abnormalities (20,37), FDC clearly provides information about a segment of the airways that is not sufficiently explored by routine PFT measurements or non-specific bronchoprovocation.

In conclusion, FDC and its response to bronchodilator provide objective physiological measures of an airway abnormality which may provide a basis for clinical symptoms. In the occupational setting, FDC may contribute to the early detection, physiological characterization and evaluation of impairment in cases of irritant-induced airway injury (especially at relatively low exposure levels) and asthma (44,46,47). In the primary care setting, the concept of asthma as an inflammatory disorder which includes structural and physiological abnormalities in the peripheral airways suggests that tests of peripheral airway function, such as FDC and its response to bronchodilator, may have an important diagnostic and therapeutic role.

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