Effect of Bronchodilator Therapy on Exhaled Nitric Oxide Measurement in Chronic Obstructive Pulmonary Disease

-Protocol-

Background and Rationale

Chronic obstructive pulmonary disease (COPD) is a common condition and major health burden in New Zealand, resulting in more than 200,000 GP visits, and over $100 million in direct healthcare costs per annum [1]. It is an airways disease characterised by persistent – and usually progressive – airflow obstruction, which may be partially reversible with bronchodilators, and typically manifests as chronic cough, sputum production and increasing breathlessness that may lead to respiratory failure. The principles of stable COPD management comprise risk factor modification – such as cessation of cigarette smoking – and pharmacological treatment, namely bronchodilator and inhaled corticosteroid (ICS) therapy [2].

The use of ICS in COPD is controversial [3, 4], but this therapy is recommended for patients with severe airflow limitation [2] and is prescribed to around 70% of COPD patients, despite evidence that it is of minimal or no benefit [3]. ICS therapy does not significantly affect the rate of lung function deterioration or mortality compared to placebo [5, 6] or a long-acting β2-agonist [7], and the risk of moderate-severe exacerbations does not increase following stepwise withdrawal [4]. In addition, it has several drawbacks, including hoarseness and oral candidiasis – to which COPD patients are particularly susceptible [6] – and increased risk of pneumonia [8, 9]. Further, the inhalers required to administer ICS are expensive, with the price of an inhaler, typically providing one month of treatment, ranging from $15 to $109 [10]. Thus, it would be advantageous to target ICS therapy to the minority of COPD patients who show objective benefit [11, 12] – as this has the potential to improve patient outcomes, reduce exposure to treatment side-effects and reduce costs – and exhaled nitric oxide (FENO) measurement is a clinical test that may be helpful in this regard [13].

FENO – a non-invasive and relatively inexpensive breath test – is a marker of eosinophilic airway inflammation, which typically occurs in asthma [14], and it is this type of inflammation that is responsive to ICS. FENO is therefore useful for predicting whether or not a
patient with airways disease will respond to ICS, with high levels being associated with greater responsiveness to ICS [15].

Nonetheless, as a clinical tool, $F_{ENO}$ has limitations. One of the reasons for this is that $F_{ENO}$ levels appear to be influenced by airway calibre. A study in asthma patients showed that an acute reduction in airway diameter was associated with a drop in $F_{ENO}$ levels [16]. This is problematic because, at a time of deteriorating asthma control, bronchoconstriction may act to reduce $F_{ENO}$ levels thereby implying minimal airway inflammation, whereas the opposite may be true.

However, little is known about the effect of changes in airway calibre in COPD. There is some evidence to suggest that $F_{ENO}$ levels are reduced in COPD patients with more severe airflow obstruction [17], while other studies have shown that elevated $F_{ENO}$ levels are associated with eosinophilic airway inflammation, with increased sputum eosinophils and a greater degree of reversibility of airway obstruction [18]. Patients with this eosinophilic phenotype are also more likely to respond to steroid [13, 19]. However, to date, there are no studies examining the effect of changes in airway calibre on $F_{ENO}$ levels in individual COPD patients. This is important to investigate because COPD patients with this phenotype are more likely to respond to ICS, but may be difficult to detect if $F_{ENO}$ levels are measured when their airways are constricted, and $F_{ENO}$ is lower than it otherwise might be.

**Hypotheses**

In patients with COPD:

- $F_{ENO}$ levels increase following administration of bronchodilator
- There is an association between the change in $F_{ENO}$ level and the change in forced expiratory volume in 1 second ($FEV_1$) following administration of bronchodilator

**Aims**

- Determine any change in $F_{ENO}$ level following administration of bronchodilator in patients with COPD
- Determine the relationship between the change in $F_{ENO}$ level and $FEV_1$ in these patients
Research Design and Methods
In this study, twenty patients with COPD will complete a single visit at the Otago Respiratory Research Unit. Patients will abstain from bronchodilators for 12-24 hours prior to attendance.

During the visit we will:
1. Provide study information and obtain patient consent
2. Take a focussed history, and record pulse and BP
3. Complete a modified Medical Research Council (mMRC) dyspnoea score [20] and COPD assessment test (CAT) [21]

<table>
<thead>
<tr>
<th>Visit Schedule</th>
<th>est. time</th>
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<tbody>
<tr>
<td>1) Information and consent</td>
<td>15 min</td>
</tr>
<tr>
<td>2) Demographics, history, pulse and BP</td>
<td>15 min</td>
</tr>
<tr>
<td>3) $F_{ENO}$ and $MEF_{ENO}$</td>
<td>30 min</td>
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<tr>
<td>4) Spirometry ($FEV_1$)</td>
<td>10 min</td>
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<td>5) Washout following spirometry – complete mMRC &amp; CAT scores give bronchodilator at 45 min</td>
<td>1 hr</td>
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<tr>
<td>6) Repeat $F_{ENO}$ and $MEF_{ENO}$</td>
<td>30 min</td>
</tr>
<tr>
<td>7) Spirometry ($FEV_1$)</td>
<td>10 min</td>
</tr>
<tr>
<td><strong>Total Participant Time</strong></td>
<td>2 hr 50 min</td>
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4. Measure $F_{ENO}$ and $MEF_{ENO}$ pre- and post-bronchodilator
5. Perform spirometry ($FEV_1$) pre- and post-bronchodilator

Inclusion Criteria
- Males or females aged 45 years and over
- Diagnosis of COPD with post-bronchodilator $FEV_1 < 80\%$
- Smoking history of greater than 10 pack-years

Exclusion Criteria
- Diagnosis of bronchiectasis or lung cancer
- Other co-morbidity likely to affect study participation
- Use of nasal steroid
- Inability to perform $F_{ENO}$ testing
Assessments

Clinical assessment.
History of current and past respiratory symptoms, co-morbidities, medication, and smoking history will be taken. Blood pressure will be assessed once using a manual sphygmomanometer according to the standard technique [22].

$FE_{NO}$ levels.
$FE_{NO}$ measurements will be performed pre- and post-bronchodilator with a chemiluminescence analyser at an expiratory flow rate of 50 mL/s, as per the ATS guidelines [23].

$MEF FE_{NO}$.
Multiple expiratory flow $FE_{NO}$ ($MEF FE_{NO}$) will be assessed pre- and post-bronchodilator using the technique described previously [24].

Spirometry.
Spirometry will be performed after measurements of exhaled nitric oxide before and after administration of 400mcg salbutamol via spacer, according to current standards [25].

Statistical analysis.
Pre- and post-bronchodilator $FE_{NO}$ and $FEV_1$ measurements will be compared using paired t-tests, and the association between the change in $FE_{NO}$ and $FEV_1$ will be evaluated by Spearman’s rank correlation.
References