Author's response to reviews

Title: Perseverant, non-indicated treatment of obese patients for obstructive lung disease

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Author's response to reviews: see over
Author's covering letter for initial submission

Title: Perseverant, non-indicated treatment of obese patients for obstructive lung disease

Authors:

Version: 1 Date: 27 March 2013

Comments: see over
February 5, 2013

Editor-in-Chief
BMC Pulmonary

Dear Sirs,

Please find our revised manuscript “Perseverant, non-indicated treatment of obese patients for obstructive lung disease” and point-by-point responses/corrections for consideration for publication in BMC Pulmonary. The reviewers have provided many valuable suggestions and we’ve clarified and repaired the manuscript in almost every instance, thus substantially improving the paper. We stand ready to make additional improvements as the reviewers require.

Respectfully,

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Reviewer #1

We are very grateful for the level of attention and detail brought by the reviewer to improve our manuscript.

Major compulsory revisions

1) It is not clear whether the authors used the LLN or the 0.7 fixed value of FEV1/FVC as a cut-off for lung obstruction. This must be cleared because, if fixed value was eventually used, this could have been underestimate the diagnosis of obstruction, considering the young mean age of patients (52 yo). Authors should motivate and discuss their choice.

We have clarified the criteria used – essentially a description of the ATS/ERS standards for PFT interpretations. See page 3-4:

Interpretations of pulmonary function tests (PFTs) were performed by board board-certified pulmonologists who applied ATS-ERS standards and guidelines [8]. Obstruction was defined as reduced forced expired volume:forced vital capacity (FEV1:FVC) ratio below the 5th percentile of the predicted value. Asthma was defined as an obstruction and increase in FEV1 and/or FVC of ≥12% from baseline in response to bronchodilator or a positive metacholine challenge test. A restrictive defect was defined as total lung capacity (TLC) below the 5th percentile of the predicted value or, in absence of lung volumes, when FVC was reduced, the FEV1/FVC was simultaneously increased (85–90%) and the flow–volume curve showed a convex pattern. A “mixed pattern” was defined as both FEV1/FVC ratio and TLC below the 5th percentiles of their predicted values. Inconclusive was defined as abnormal PFTs that we could not be classified in any of the above categories.

2) Authors should also clarify whether all tests were conducted with patients observing wash out from medications.

Patients were instructed not use the bronchodilators the day of the exam and the night before. The exact time for medications to wash out is unknown. See page 3 and listed in limitations page:

Page 3: Spirometry was performed according American Thoracic and European Respiratory Society (ATS-ERS) guidelines [5-7] and patients were instructed to hold taking bronchodilators from the night prior to study.

Page 9: In addition, although patients were instructed not to use bronchodilators for >12 hours, we did not ascertain the rate of compliance.

3) 5 studies (3.2%) were defined as inconclusive. It is unclear what is meant and which criteria have been used to define an unconclusive spirometry. Please add.
Inconclusive tests were defined all the abnormal PFT that did not fall into any of other categories (e.g. PFTs did not include lung volumes and their spirometries showed decreased volumes but normal FEV1/FVC ratio). This is now stated explicitly as described in response to #1 above.

4) Was dyspnea measured? did you apply any score? As known, Obesity correlates positively with dyspnea but not with lung obstruction. for this reason a correlation should be attempted in order to motivate your findings.

Dyspnea was not measured but it was reported by the PCP as the reason for the referral to the pulmonary function test. This is stated in the methods.

*Minor comments*

Please add pneumonia to the potential side effects of inhaled corticosteroids (page 7, line 3).

Done.

*Discretionary revisions*

1) This paper has some strength because it underlines how a large number of patients receiving inhalers still continue the therapy despite the normal results at pulmonary function tests. I am not aware of similar results in literature. For this reason, I would suggest the authors to address the discussion into this direction.

We agree completely. The important finding in our study is that not only are patients perseverantly misclassified, even after PFT evidence to the contrary, but will continue to receive potentially toxic therapies with no benefits (since they have no evidence of obstruction). We’ve emphasized this in the discussion:

See page 8: Mislabeled or misdiagnosis is not without risks and costs, especially when (these) patients receive medications that can cause complications but provide no proven benefit (since they did not have obstruction). In addition to tremor, tachycardia and hypokalemia, beta-agonists have been associated with increased mortality in asthmatic patients, especially African Americans[23]. Anticholinergic medications may also increase the risk of cardiovascular death[24]. Inhaled and systemic corticosteroids are associated with diabetes, hypertension, infection, pneumonia, glaucoma, adrenal insufficiency, thrush, dysphonia, myopathy, and cardiovascular events[25]. While we can find no suggestion that obese patients are more vulnerable to complications from these therapies, they could
exacerbate some diseases (e.g. hypertension, diabetes) that are more common in the obese population.

In figure 3 is shown that the rate of treatment for obstruction reduces after spirometry in the normal and restrictive group. Authors stress this concept in both results and discussion. However, they also should underline that, surprisingly, the rate of treatment reduces amongst asthmatics and does not increases in the 22% of patients with COPD not receiving inhalers. This finding should be discussed and the underuse, but also the lack of interpretation of spirometric results in orienting the management of patients with obstruction focused.

Clarified: see page 7:

Interestingly, the rate of bronchodilator use before and after PFTs remained the same in patients with COPD but decreased in those with asthma. We suspect this is a statistical artifact related to small sample size, nonetheless, it is a perseverant treatment. However, it could suggest bronchodilator prescription driven inappropriately by symptoms (i.e. dyspnea) rather than objective physiologic abnormalities.
**Reviewer #2**

**Major Compulsory Revisions**

We are very grateful to the reviewer for pointing out major omissions/oversights in our first draft and attempted to address every point to the extent possible.

1. The manuscript lacks an appropriate background. Studies on prevalence of airways obstruction and/or restriction, respiratory diagnosis (e.g. COPD, asthma) and use of respiratory medicines in obese patients are not quoted.

We agree and have clarified/elaborated in the first two paragraphs of the discussion:

This observational cohort study demonstrates that half of all obese patients referred for spirometry were treated empirically with bronchodilators before testing, and that even after spirometry demonstrated the absence of airflow obstruction 40% (39 of 97) continued to be prescribed therapies directed at obstructive lung disease 6 or more months after testing. Misdiagnosis of obstructive lung disease is not uncommon. Lindesmith and colleagues reported that many Canadian community clinicians diagnosed obstructive lung disease on clinical grounds; 41% of (37 of 90) patients were labeled as asthmatic but failed to meet diagnostic criteria[2]. As in our study, 62% of these misdiagnosed patients continued to receive inhaled beta-agonists, while 43% received inhaled glucocorticoids. In two separate studies, 30% of patients diagnosed with asthma on clinical grounds did not satisfy pulmonary function test criteria for obstruction[3, 9]. In another study, 10-41% of patients in primary care offices used inhaled steroids for a clinical diagnosis of asthma or COPD without spirometric evidence to support the diagnoses[1].

We are unaware of a previous study that has focused on obese patients receiving spirometric testing. We focused on this population because they comprise a large demographic who commonly present with respiratory complaints[4], most often related to restrictive respiratory mechanics[10] and increased oxygen cost of breathing [4], and who might be – at least in theory – more vulnerable to complications of unnecessary polypharmacy. While some studies have suggested an inverse relationship of BMI and FEV1[11, 12] and an association of obesity and obstructive lung diseases[13, 14], the frequency with which dyspnea is caused by obstructive vs. restrictive physiology in obese patients has not been well-studied. Obese patients are more likely to report respiratory symptoms – especially dyspnea -more than non-obese patients [4]. Truncal obesity can reduce chest wall compliance, and respiratory muscle strength and function [15]. Accordingly, we hypothesized that obese patients with respiratory complaints prompting pulmonary function tests would be at risk of mischaracterization and persistent, non-indicated treatment of obstructive lung disease. Our results supported the hypothesis, but most surprising, treatments with medications for obstruction were continued without clinical or spirometric indications. Clearly such patients are exposed to complications and...
costs of these therapies without proven or plausible clinical benefits. Interestingly, the rate of bronchodilator use before and after PFTs remained the same in patients with COPD but decreased in those with asthma. We suspect this is a statistical artifact related to small sample size, nonetheless, it is a perseverant treatment. However, it could suggest bronchodilator prescription driven inappropriately by symptoms (i.e. dyspnea) rather than objective physiologic abnormalities.

2. The study design is not described in the Methods section. The authors should demonstrate how the use of inhaled bronchodilators changes before and after the results of a single spirometric measurement performed in a group of obese patients consecutively assessed in a hospital lung function laboratory. Confounding factors are not taken into account, for example: possible recent episodes of acute bronchitis or further spirometric measurements performed between the baseline and follow-up evaluation, which may have prompted the prescription of inhaled bronchodilators; respiratory misdiagnosis at baseline (e.g. asthmatic patients in clinical remission); etc.

The change in bronchodilator use is described in the Results:

Prior to testing, 45.5% (28 of 62) of patients with normal spirometry were being treated with medications for obstructive lung diseases; 15 (53.6%) and 13 (46.4%) of these 28 individuals were misdiagnosed with asthma and COPD, respectively. 33.9% (21 of 62) of these patients continued treatments with medications for obstructive lung diseases despite absence of airflow obstruction on spirometry. 60% (21 of 35) of patients with a restrictive pattern in their spirometry received treatment for obstruction prior to spirometry; 10 (47.6%) and 6 (25.6%) of these patients were misdiagnosed as asthma and COPD, respectively. And 86% continued bronchodilator therapy despite spirometry results that did not demonstrate airway obstruction (Figure 3).

And in Figure 3:
We agree that confounding factors were not considered because we did not have access to outpatient records. However, please note that there was no evidence that bronchodilators were EVER stopped after the PFTs that were negative for obstruction. We nonetheless add this as a major limitation as improbable as it may be:

**We cannot assert with certainty that bronchodilators were administered daily in all patients without indications (i.e. in some the medications could have been stopped and later restarted for a bronchospastic episode that was not documented in our medical records).**

3. The criteria and reference values used to define airways obstruction and/or restriction are not specified. For example, according to the ATS-ERS criteria (quoted as reference no. 9 in the manuscript), a restrictive ventilatory defect is defined by a reduction in TLC below the 5th percentile of the predicted value, and a normal FEV1/VC. However, the authors state that only 57 patients (37% of the whole study sample) had measurements of lung volumes. (see Results, first paragraph).

We have clarified the criteria used – essentially a description of the ATS/ERS standards for PFT interpretations. See page 3-4:

**Interpretations of pulmonary function tests (PFTs) were performed by board board-certified pulmonologists who applied ATS-ERS standards and guidelines [8].** Obstruction was defined as reduced forced expired volume:forced vital capacity (FEV1:FVC) ratio below the 5th percentile of the predicted value. Asthma was defined as an obstruction and increase in FEV1 and/or FVC of ≥12% from baseline in response to bronchodilator or a positive metacholine challenge test. A restrictive defect was defined as total lung capacity (TLC) below the 5th percentile of the predicted value or, in absence of lung volumes, when FVC was reduced, the FEV1/FVC was simultaneously increased (85–90%) and the flow–volume curve showed a convex pattern. A “mixed pattern” was defined as both FEV1/FVC ratio and TLC below the 5th percentiles of their predicted values. Inconclusive was defined as abnormal PFTs that we could not be classified in any of the above categories.
4. Descriptive statistics of lung function measurements of the study subjects are not reported. 

Now added. See page 4:

Patients demonstrated a mean FEV1 of 66.6 ±1.4% and mean FVC of 65.9±1.3% with an average FEV1/FVC ratio of 77.8% (table 2). Please refer to table 2 for lung function statistics for each group.

5. The study does not assess statistical differences between the proportion of the same subjects who continue to use inhaled bronchodilators before and after spirometry, stratified by baseline respiratory diagnosis.

An excellent idea, but the sample was too small to permit reliable stratified analysis. Any conclusions would be quite suspect.

6. The logistic regression model is not described (second paragraph in the Methods section) in term of independent variables analyzed, and the obtained results are not presented.

Now clarified: page 3

Independent variables were chosen for modeling based on biological plausibility and/or if they demonstrated an association with inappropriate bronchodilator treatment in univariate analyses.

7. The authors do not discuss possible explanations of misuse of bronchodilators in obese patients (second paragraph of Discussion section). For example: the proportion of study subjects that was referred for spirometry by a pulmonologist is not considered; the physicians who prescribed medications after the spirometry (as reported in table 2) are not characterized.

Unfortunately, our referral forms don’t permit that analysis. Therefore, we cannot investigate whether the referral from a pulmonologist is associated with lower rate of inappropriate bronchodilator use.

8. The authors do not report if the study was approved by the Ethical Committee.

This is now stated in the first line of the Methods:

The study protocol was exempted from review as set forth in the Code of Federal Regulations, 45 CFR 46.101(b) by the Bridgeport Hospital Institutional Review Board.

Minor essential revisions

1. Abstract. Background. Bronchodilators are a mainstay of treatment also for COPD, which is defined by not reversible or partially reversible airflow obstruction.

We agree and have omitted the word “reversible” as you suggest.
2. Figure 1. It is not quoted in the text of the manuscript. The text in the box should be completed with: “53 individuals were excluded because there were no records 6 months after testing”. Part of figure 1 reports the same results reported in Figure 2B.

Corrected. Thank you.

3. Figure 2A and B. It lacks of a legend for abbreviations.

Corrected. Thank you.

4. Table 2 is not quoted in the text of the manuscript.

Corrected. Thank you.

Minor issues not for publication

1. Figure 2B. Correct “incocclusive”.
   Figure 2B is now omitted per your recommendations above.
Reviewer #3

Recommendations for further research - Although this was not the topic of this manuscript, I consider it might be interesting to compare spirometry results for these patients after 6-month period following the first spirometry and to assess the distribution of bronchodilator medications in relation to the pattern of spirometry result/diagnosis.

This is a brilliant idea that we’ll pass on to those who remain at Bridgeport for follow-up. Thank you.