Anorexia Nervosa and Emphysema

To the Editor:

The conclusion of Dr. Coxson and colleagues in their recent article that “emphysema-like” or “early emphysema” changes in their patients were induced by anorexia nervosa is based on correlations between body mass index (BMI) and lung diffusing capacity (DL) and between BMI and DL and computed tomography (CT) scans of the lung. Because CT lung measurements were only recently described, and have not yet been validated by other studies, we limit our remarks to lung function results. Although the authors describe their control group as normal, the BMI of these subjects, according to NIH guidelines, place them in the overweight category, thus spuriously amplifying the difference between patients and “normal subjects.” In agreement with our own results in subjects with anorexia, both spirometry and DL values were within normal limits in their patients and comparable to the values recorded in a control group, practically excluding the presence of emphysema. The authors report a significant correlation between BMI and predicted values of DL, but not between the absolute figures of DL and BMI. However, the r value was rather low (0.5), explaining only about a quarter of the variance. It is not clear why the authors consider that a rather weak correlation between BMI and DL is an argument for malnutrition-induced emphysema, but normal values for both spirometry and DL are not an argument against this hypothesis. Confounding factors can influence this correlation. For example, the authors also report, but without comment, a negative correlation between BMI and FEV1/FVC—that is, that curiously enough, an increase in BMI would be associated with a low FEV1/FVC. It must also be stressed that DL is not an indicator of early emphysema (3). The report by the authors of a single case of anorexia nervosa associated with bullae and a low DL cannot be considered an argument for their hypothesis. We have found (2), like others (4), decreased values for maximal inspiratory and expiratory pressure in our patients, a rather direct reflection of malnutrition. Coxson and coworkers report normal values for these indices (1). However, predicted values were not reported (there is a wide range of predicted values), and maximal pressures were not measured in their control group.

Finally, the study (5) done in subjects who died in the Warsaw Ghetto during World War II, suggesting that death from starvation was associated with emphysema, should be considered with caution because it was done before criteria for pathologic diagnosis of emphysema were available.

Conflict of Interest Statement: D.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter; T.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter.

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References


From the Authors:

We thank Drs. Stanescu and Pieters for their interest in our article (1). We agree that the Warsaw Ghetto studies and case reports should be interpreted with caution. However, the Warsaw Ghetto studies have inspired many animal model studies and investigations in humans. The animal studies have demonstrated a relationship between starvation and the development of an “emphysema-like” condition. Replication of these studies in humans is difficult because tissue samples are not available for pathologic analysis.

We also agree that the pulmonary function tests alone do not show significant differences between groups. In our study we only found evidence of a reduction in lung mass in patients with a very low body mass index (BMI). This suggests why average values were not abnormal and the correlation between BMI and lung mass for all subjects was not greater. It has been shown that in anorexia nervosa there is a reduction in maximal inspiratory and expiratory pressure that is presumably due to a concomitant decrease in diaphragmatic muscle mass without a change in lung structure (2). We chose to present the maximal inspiratory and expiratory values as absolute values because we did not have control values to compare against, although they were both within the normal range (100 ± 23% and 88 ± 39%, respectively). We chose to present the diffusing capacity as percent predicted, corrected for both hemoglobin and alveolar volume, to allow comparison to normal and to the control group. Thurlbeck concludes in his paper that the diffusing capacity has the best correlation with emphysema observed at necropsy, but suggests that a combination of functional tests must be used to infer the presence of emphysema (3).

Finally, these observations have led us to the main aim of the study, which was to attempt to measure the structure of the lung in subjects with anorexia nervosa. We disagree that CT studies have not been validated, as there have been numerous careful investigations (4–6) that have demonstrated a correlation between quantitative pathology and the structure of the lung measured using CT.

There is still much work that needs to be done to clarify a relationship between malnutrition and emphysema. However, we stand by the conclusion of our paper that there is a correlation between BMI and diffusing capacity and CT measurements of lung structure. A causal mechanism and the potential reversibility of lung pathology await elucidation. Importantly, the CT scan does provide us with a tool to help answer these questions longitudinally.

Conflict of Interest Statement: H.O.C. received $2,500 in 2002 and £1,500 in 2003 for serving on an advisory board for GlaxoSmithKline (GSK) and in addition is the coinvestigator on two multicenter studies sponsored by GSK and has received travel expenses to attend meetings related to the project, and a percentage of salary between 2003 and 2006 ($15,000/year) derives from contract funds provided to a colleague, Peter D. Pare, by GSK for the development of validated methods to measure emphysema and airway disease using computed tomography; C.L.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.R.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.
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References

Testosterone Supplementation during Respiratory Rehabilitation

To the Editor:

Casaburi and colleagues recently reported a randomized controlled trial exploring the effect of testosterone supplementation in men with COPD with or without additional resistance training during respiratory rehabilitation (1). While conducting a systematic review that included this question (2), we noted a few issues for which readers would require clarification.

A “screening” criterion was serum testosterone of < 400 ng/dl. However, the mean serum testosterone level was 408 ng/dl in patients randomized to testosterone + resistance training and between 277 and 302 ng/dl in the other three groups. In addition, standard deviations varied greatly between the four groups (from 89 to 154). It is also stated that 44% of all patients had levels above 400 ng/dl at baseline. Thus it seems that the “screening” and actual inclusion criteria were not identical. An explanation why this was not the case and what the actual inclusion criteria could help to answer our concerns. Another explanation for differences between the testosterone levels at screening and baseline would be that testosterone measurements had poor reproducibility. In that case, repeated testosterone levels may have prevented enrolment of patients for whom this intervention was not intended. The high baseline levels in one group and the lower levels in the other groups also complicate drawing conclusions about patient profiles to which the results apply.

Important baseline imbalances in FEV1, peak work rate, and constant work rate existed between patient groups. These problems are likely to originate from the small sample sizes that limit the likelihood of successful randomization. It is inappropriate to test baseline imbalances for statistical significance in a randomized controlled trial (3). Statistical adjustment for baseline imbalances in clinical trials is in order when randomization fails to achieve balanced groups (4). Because randomization did not result in similar distributions for important variables in this trial, the authors should have corrected statistically for these baseline imbalances.

Casaburi and coworkers state they are the first to report on the combined effect of androgenic steroid supplementation and rehabilitation in patients with COPD. We would like to alert readers to the trial by Creutzberg and colleagues (5) that assessed the supplemental benefit of nandrolone during respiratory rehabilitation. The authors found no significant differences in improvement between groups in terms of muscle function, exercise capacity, and health status. The latter study included an outcome that is important to patients.

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References

From the Authors:
We are pleased to respond to Drs. Puhan and Schünemann regarding our study (1).

It deserves to be stressed that our trial studied short-term effectiveness of testosterone, strength training, and their combination in improving muscle mass and strength. It was a single-center trial; this facilitated standardizing interventions and outcome measurements but limited sample size. We emphasized that our results, though quite encouraging, deserve further investigation in larger studies of longer duration.

In this initial investigation of testosterone administration to men with COPD, we focused on men whose testosterone level was somewhat low (though normal ranges are difficult to define). However, recent work has shown that the dose–response relationship to testosterone supplementation is linear (2), raising the
We present 45 baseline descriptors of this study population. Drs. Puhan and Schülemann focus on three variables that they feel exhibit “important baseline imbalances” among the four groups. They suggest statistical adjustment for these imbalances. However, the paper they cite (3) as supporting such adjustments deals with clinical trials with, on average, 10 times our study population. Further, in this paper unadjusted analyses are recommended unless baseline factors for covariate adjustment are predeclared on the basis of their strong relation to outcome. We believe that the modest differences among groups in these three variables (that in no case reaches statistical significance) would not be expected to influence change in either body composition or muscle strength with these interventions. We reassert that our randomization procedures resulted in well-balanced study groups.

We correctly stated that ours was the first demonstration that strength increases accompany androgenic steroid supplementation in COPD. The work of Creutzberg and coworkers (4) deserves citation, but it was published while our paper was under review. That study confirms our finding that androgenic steroids increase lean body mass, but it fails to detect enhanced muscle strength, perhaps because a group receiving anabolic steroids without exercise training was not included.

**Conflict of Interest Statement:** R.C. has been an investigator in a multicentered trial of Oxandrolone (an oral steroid) in COPD sponsored by Biotechnology General Corporation (total payments to site of approximately $75,000); L.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter; J.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter; M.I.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter; M.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter; T.W.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this letter.

**References**


**Endoscopic Ultrasound Staging of Lung Cancer**

**To the Editor:**

I wish to congratulate Dr. LeBlanc and colleagues on their recent article published in *AJRCCM* (1), but I would like to point out several key differences about their work relative to other published studies. Our group has published a nearly identical study in the area of endoscopic ultrasound staging (EUS) staging of lung cancer patients without evidence of enlarged mediastinal lymph nodes on CT (2). Both are prospective, controlled studies in similar populations comparing EUS to pathological staging. Both studies came to similar conclusions. In our study, the “yield” of EUS for detection of metastatic or unresectable disease was nearly identical (17/69 [25%] patients in our study, 18/72 [25%] patients in LeBlanc and coworkers’ study). Both studies detected malignant mediastinal lymph nodes as well as extrathoracic metastases (left adrenal, celiac lymph nodes).

The main difference between the studies was the overall accuracy of EUS. For both, the sensitivity was low, which is not surprising given the challenging group of patients (all with lymph nodes < 1 cm on CT). In our study the sensitivity was 61% and specificity 98%. In LeBlanc and colleagues’ study the sensitivity was only 25% with specificity 100%. Why the difference in sensitivity? In my view, the key difference is the fact that LeBlanc and coworkers only sampled (by fine needle aspiration) lymph nodes which appeared malignant based on the EUS image. In our study, we sampled all visible lymph node stations including completely normal appearing ones. Other work by our group has suggested that the EUS image of a lymph node and tumor location (relative to the lymph node location) are poor predictors of nodal metastases (3). Even normal appearing lymph nodes can harbor metastatic disease and should be sampled at the time of EUS staging.

Based on these two large prospective studies, EUS clearly can detect metastatic disease and avoid surgical staging in ~25% of lung cancer patients with “normal” mediastinal CT. Is this good enough to routinely recommend EUS in these patients? Given the alternatives of mediastinoscopy, or other surgical methods, I feel the answer is “yes,” but we can and should still strive for better results.

The future of lung cancer staging indeed looks very bright with increasingly sensitive and decreasingly invasive methods of detecting and staging disease. Much work is to be done, but studies such as those by LeBlanc and colleagues are clearly on the “right track.”

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**From the Authors:**

We would like to thank Dr. Wallace for his insightful comments regarding our study (1). The aim of our study was to determine the role of EUS and EUS-guided fine needle aspiration (EUS-FNA) in patients with non–small-cell lung cancer (NSCLC) without mediastinal lymphadenopathy who would otherwise proceed directly to surgery. We learned that mediastinal lymph node echocoecharacteristics are poor predictors of malignancy. In mediastinal lymph node regions accessible to EUS our sensitivity was 42%. We agree that tissue sampling of all mediastinal lymph nodes (malignant-appearing and benign-appearing) would likely result in a higher sensitivity of EUS in staging the mediastinum, as benign-appearing lymph nodes may harbor malignancy. Sampling of all mediastinal lymph nodes, however, increases procedure time, and we question the cost effectiveness as separate needles (approximately $200 each) would be required. It is interesting that despite differences in sensitivity, the detection rate of unresectable disease was 25% in both of our studies (1, 2). Further, metastases were found in regions that are not routinely interrogated during thoractomy (adrenal gland and celiac lymph nodes).

We feel that recommendations on the utility of EUS in staging NSCLC with respect to tumor location are still premature, as tumor location may be a predictor of nodal metastases that can be sampled with EUS-FNA. Unlike Wallace and coworkers’ recent study, we found that lower lobe and hilar tumors (versus left upper lobe tumors) were more likely to have metastases to mediastinal lymph nodes accessible to EUS. This is similar to unpublished data from the University of Alabama, Birmingham group, which showed that lower lobe tumors were six times more likely to have malignant mediastinal lymph nodes accessible to EUS-FNA compared with upper lobes (M.A. Eloubeidi, personal communication). It is our hypothesis that EUS-FNA could be directed toward patients with primary tumors in the lower and hilar lobes, and thus ultimately be cost effective in staging NSCLC. The standard of care in NSCLC staging is evolving, and certainly further studies examining the clinical and economic impact of EUS in staging NSCLC are needed so that management of patients with NSCLC is optimized.

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