Early Emphysema in Patients with Anorexia Nervosa

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Postmortem studies of patients who died in the Warsaw Ghetto during World War II suggested that death from starvation was associated with pulmonary emphysema. This study re-examines this hypothesis in patients who are chronically malnourished because of anorexia nervosa. Age, smoking history, body mass index, and pulmonary function were measured in 21 subjects with anorexia nervosa and 16 control subjects. Computed tomography (CT) scans were obtained from three regions of the lung (at the level of the aortic arch, the carina, and the posterior position of the eighth rib) using a multislice scanner. The CT measurements of lung density, emphysema, and surface area-to-volume ratio were obtained using the X-ray attenuation values. CT measurements of emphysema were greater in the group that was anorexic than in historical control subjects ($p < 0.001$). Furthermore, there were significant correlations between the body mass index and the CT measures of emphysema for all the patients and between diffusing capacity and the CT measurements in the patients who were anorexic. A multiple linear regression analysis showed the diffusing capacity was predicted best by the percentage of lung voxels within the large emphysematous changes category. These data demonstrate that emphysema-like changes are present in the lungs of patients who are chronically malnourished.

Keywords: anorexia nervosa; chronic obstructive pulmonary disease; computed tomography; emphysema; malnutrition

The pathogenesis of emphysema is thought to be a complex interaction between environmental factors, for example, tobacco smoke and genetic susceptibility (1). There has also been an association suggested between malnutrition and emphysema. A study conducted in the Warsaw Ghetto during World War II (2) showed that a surprisingly high percentage of the people who died of starvation had emphysema (autopsy findings 50/370 [13.5%]); 34 of these 50 were less than 40 years old. Furthermore, studies on rats whose caloric intake had been severely restricted for a few weeks showed changes in pulmonary mechanics and lung structure that were described as "emphysema-like" (3–9).

Anorexia nervosa is the purest form of human malnutrition. It occurs as a result of a voluntary restriction of caloric intake and is independent of other diseases or environmental causes. Although abnormalities in pulmonary function have been demonstrated in people who have anorexia nervosa, an association with emphysema has not been reported (10).

This study examines the hypothesis that long-term malnutrition results in emphysematous changes in the lung. Lung structure was measured using computed tomography (CT) scans obtained from a group of subjects with anorexia nervosa and a well-nourished control group. Some of the results of this study have been presented in abstract form (11, 12).

METHODS

Twenty-one subjects who had anorexia nervosa were recruited from the Eating Disorders Program at St. Paul's Hospital and were matched for age and sex with a group of 16 normal subjects. All of the subjects gave informed consent to take part in the study. The study was approved by the University of British Columbia Clinical Ethics Review Board.

Baseline anthropometric data were collected, including sex, age, body mass index (BMI), and smoking history. Blood was drawn to measure hemoglobin, differential cell count, and serum α1-antitrypsin.

Spirometry was measured using a computerized spirometer (P. K. Morgan, Boston, MA). Total lung capacity, FRC, and residual volume (RV) were measured using the helium dilution technique on a P. K. Morgan Transfertest Pulmonary Function System (P. K. Morgan Ltd, Chatham, Kent, UK). The diffusing capacity for carbon monoxide (D_{LCO}) was measured by the single-breath method of Miller and colleagues (13). The results were corrected for both V_A and hemoglobin.

CT scans were acquired from three regions of the lung using a stacked multislice acquisition protocol on either a GE "Lightspeed-Ultra," an 8 detector row (General Electric Medical Systems, Milwaukee, WI), or a Siemens "Sensation 16," a 16 detector row (Siemens AG Medical Solutions, Erlangen, Germany) CT scanner. Using this protocol, a series of either eight 1.25-mm and two 5-mm thick images (GE) or ten 1.0- and two 5-mm (Siemens) thick images were obtained at the level of the aortic arch, the tracheal carina, and posterior aspect of the eighth rib. Images were reconstructed using an intermediate (standard) and a high (edge-enhancing) spatial frequency reconstruction algorithm. A radiologist, using the 1- and 1.25-mm thick images, assessed any clinical abnormalities. The lung anatomy was analyzed on the 5-mm thick images (standard reconstruction algorithm only). CT images from one control patient (BMI = 19 kg/m^2) and one patient who was anorexic (BMI = 12 kg/m^2) are shown in Figure 1.

The extent of emphysematous changes between groups was compared by subdividing the frequency distribution of the volume of gas per weight of lung tissue, calculated from the CT scans, into three categories that have been shown to correlate with lung pathology (14): (*1*) normal lung (0- to 6.0-ml gas/g tissue, more than −855 Hounsfield units [HU]), (*2*) small emphysematous changes (6.0- to 10.2-ml gas/g tissue, −855 HU to −910 HU), and (*3*) large emphysematous changes (> 10.2-ml gas/g tissue, less than −910 HU). The surface area-to-volume ratio of the lung was estimated as previously described (14).

The correlation of clinical, anthropometric, and pulmonary function values with the CT measurements was summarized using the Pearson correlation coefficient. Multiple linear regression analysis was employed to assess simultaneous predictive value of the variables for BMI and D_{LCO}. Only variables that correlate with the outcome or those of special clinical interest were entered in the prediction model. Clinical, anthropometric, pulmonary function, and CT measurements were compared between groups using a two-tailed student's *t* test. Variables that were not normally distributed (smoking history and hemoglobin levels) were compared using a nonparametric test, the Wilcoxon W-test.

RESULTS

Anthropometric and Clinical Data

The anthropometric and clinical data are shown in Table 1. As expected, the BMI (kg/m^2) of the two groups was very different

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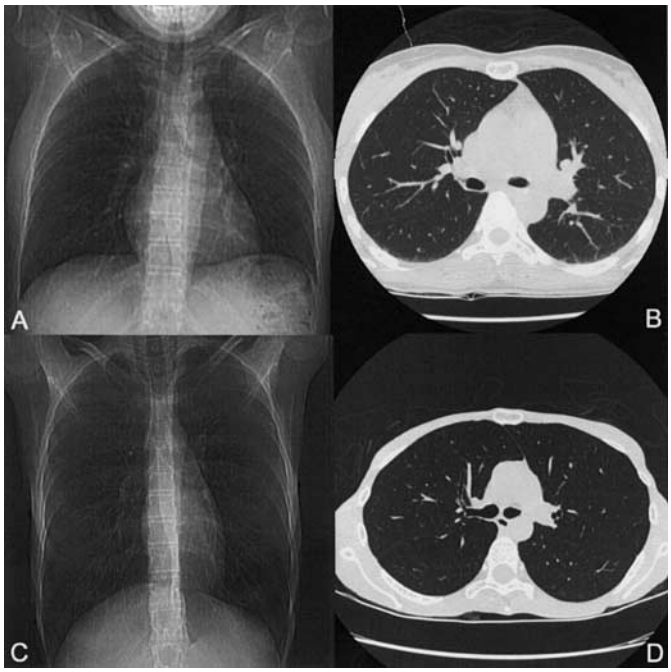

Figure 1. Representative posterior–anterior computed tomography (CT) "locating scout" and thin-slice CT image from a control patient (*A* and *B*) with a body mass index (BMI) of 19 kg/m^2 and the patient who was anorexic (*C* and *D*) with a BMI of 12 kg/m^2. CT images are 1.25-mm thick images reconstructed using an edge-enhancing algorithm (window width = 1,500, window level = −600). The quantitative analysis was performed using thick slice images (5 mm) and an intermediate spatial frequency reconstruction algorithm.

($p < 0.001$), with seven of the BMIs for patients who were anorexic below the World Health Organization cut-off for starvation (BMI = 17.5 kg/m^2) (15) and the control groups' BMI within the obese range (25.0–29.9 kg/m^2) (16). The tobacco use was less for the group that was anorexic ($p = 0.004$); only four of the anorexic subjects were active or ex-smokers. The average length of disease in the subjects who were anorexic was 16 years (range, 1 to 36 years). There was no difference between the groups in age, sex, or pulmonary function. The group that was anorexic did have significantly lower hemoglobin levels than the control group ($p = 0.04$), but the serum α1-antitrypsin levels were normal (0.93 to 1.77 g/L). The maximal inspiratory pressure and maximal expiratory pressure for the subjects who were anorexic were normal.

CT Measurements of Lung Structure

The lung density, volume of gas per weight of lung tissue, and surface area-to-volume data are different ($p < 0.001$) between the subjects who were anorexic and the control subjects (Table 2). The frequency distribution of the volume of gas per weight of lung tissue divided into the three emphysema categories is shown in Figure 2 (normal: 0- to 6.0-ml gas/g tissue; small emphysematous changes: 6.0- to 10.2-ml gas/g tissue; large emphysematous changes: > 10.2-ml gas/g tissue). There is a marked difference between groups in the percentage of the lung volume in all three categories: normal lung ($p < 0.001$), small emphysematous changes ($p = 0.006$), and large emphysematous changes ($p < 0.001$).

There are significant correlations between the CT measurements of lung structure and the clinical measurement of BMI.

TABLE 1. ANTHROPOMETRIC AND CLINICAL DATA

	Subjects Who Were Anorexic	Control Subjects	p Value
Anthropometric			
Number	21	16	
Age, yr (range)	36 (21–54)	40 (28–50)	0.15
Sex	Female	Female	
BMI ± SD, kg/m^2	18 ± 3	27 ± 6	< 0.001
Smoking history ± SD, pack-yr	4 ± 9	19 ± 17	0.004
Length of disease, yr (range)	16 (1–36)	NA	
Pulmonary function, % of predicted			
FEV_1 ± SD	106 ± 13	110 ± 15	0.32
FVC ± SD	109 ± 17	115 ± 14	0.27
FEV_1/FVC ± SD	83 ± 7	81 ± 6	0.24
RV ± SD	88 ± 29	87 ± 24	0.97
FRC ± SD	88 ± 14	93 ± 14	0.30
TLC ± SD	96 ± 13	103 ± 11	0.11
D_{LCO} ± SD	88 ± 13	89 ± 18	0.87
D_{LCO}/V_A ± SD (corrected for Hgb)	81 ± 15	89 ± 17	0.12
MIP ± SD, cm H_2O	75 ± 25	NA	
MEP ± SD, cm H_2O	83 ± 37	NA	
Hemoglobin ± SD, g/L	127 ± 11	135 ± 8	0.04
Serum α1-antitrypsin ± SD, g/L	1.45 ± 0.34	NA	

Definition of abbreviations: BMI = body mass index; D_{LCO} = diffusing capacity for carbon monoxide; MEP = maximum expiratory pressure; MIP = maximum inspiratory pressure; NA = not applicable; RV = residual volume; TLC = total lung capacity.

There are also additional correlations between the CT density and the volume of gas per weight of lung tissue and the FEV_1/FVC ratio (Table 3). There are significant correlations, only in the group that was anorexic, between the D_{LCO} percentage predicted and CT density ($r = 0.20$, $p = 0.03$), volume of gas per weight of lung tissue ($r = -0.52$, $p = 0.02$), and surface area-to-volume ratio ($r = 0.44$, $p = 0.05$). There are also significant correlations between the BMI and the D_{LCO} percentage predicted in the group that was anorexic ($r = 0.54$, $p = 0.01$) and between the BMI and FEV_1/FVC ratio in all the patients ($r = -0.41$, $p = 0.01$). The multiple regression analysis showed that the volume of gas per weight of lung tissue is a predictor of BMI ($r = -0.59$, $p < 0.001$), and the D_{LCO} percentage is predicted by the percentage of lung in the large emphysematous changes category (> 10.2-ml gas/g tissue, $r = -0.39$, $p = 0.02$). There was no significant correlation between pulmonary function or CT parameters and the length of disease.

DISCUSSION

These results show that long-term caloric malnutrition is associated with a loss of lung tissue, which is consistent with the presence

TABLE 2. COMPUTED TOMOGRAPHY MEASUREMENTS OF LUNG DENSITY, LUNG EXPANSION INDEX, AND SURFACE AREA TO VOLUME

	Subjects Who Were Anorexic	Control Subjects	p Value
Mean CT density, g/ml	0.17 ± 0.03	0.22 ± 0.03	< 0.001
Mean volume of gas per weight of lung tissue, ml gas/g tissue	5.3 ± 1.1	3.7 ± 0.7	< 0.001
Surface area/volume, m^2/L	12 ± 6	25 ± 7	< 0.001

Definition of abbreviation: CT = computed tomography.

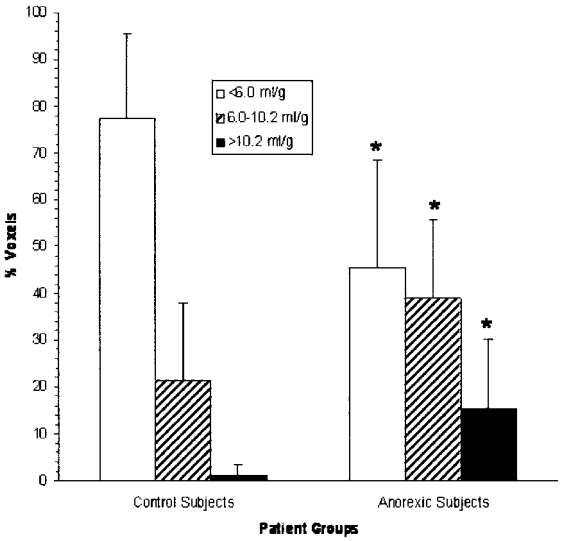

Figure 2. Graph showing the percentage of the lung voxels within the three volume of gas per weight of lung tissue categories: (*open bars*) normal lung (0- to 6.0-ml/g tissue, greater than −855 Hounsfield units [HU]), (*hatched bars*) small emphysematous changes (6.0- to 10.2-ml gas/g tissue, −855 to −910 HU), and (*solid bars*) large emphysematous changes (greater than 10.2-ml gas/g tissue, less than −910 HU). *Lung categories in the anorexic subjects are different from the control subjects: normal lung ($p < 0.001$), small emphysematous changes ($p = 0.006$), and large emphysematous changes ($p < 0.001$).

of emphysema. As the BMI decreases in subjects who were anorexic, there is a decrease in the D_{LCO}, as well as an increase in both the mean volume of gas per weight of lung tissue and the percentage of the lung that is expanded beyond the normal range.

The hypothesis that malnutrition causes emphysema is not a novel concept. Emphysema was first described in malnourished subjects in a remarkable study conducted in the Warsaw Ghetto by Jewish physicians during the Nazi occupation (2). These provocative results have led to many animal studies, which have shown that severe caloric restriction in rats induces decreased production of surfactant (4, 5), a reduction in the number of alveoli, and a corresponding increase in the alveolar volume and decrease in the surface area (6–9, 17). Although these findings are suggestive of emphysema, they do not identify tissue destruction and are usually considered "emphysema-like."

Anorexia nervosa is the purest form of human malnutrition in that it is independent of other diseases or environmental causes. Abnormalities in pulmonary function, including low to normal VC as well as a decrease in FEV_1 have been demonstrated in malnourished patients who have anorexia nervosa (18–20). Pieters and colleagues (10) investigated patients who were anorexic to determine whether malnutrition was associated with emphysematous changes, as determined by pulmonary function testing and D_{LCO}. Results of their study showed that although the D_{LCO} of the patients who were anorexic was more variable, it was not different from the control group. This led them to conclude that there was no evidence of starvation-induced emphysema in patients who had anorexia, even in those patients who smoked. However, in a recent study, we reported a patient with a long history of anorexia nervosa who had a low diffusing capacity, localized bullae, a reduced overall lung density, and a reduced surface area-to-volume ratio, as measured by quantitative CT (21). This patient had a much longer history of anorexia nervosa than those reported by Pieters and colleagues (10).

Emphysema is defined as abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls, without obvious fibrosis (22). Until recently, the study of emphysema in humans has been restricted to examining postmortem specimens of lung obtained from individuals who were at least 50 years old and had a very significant smoking history. This precluded the study of other contributing factors, for example, malnutrition.

The advent of the CT scan has allowed researchers to obtain anatomic information without having to remove the organ from the body. The extent of emphysema, measured pathologically, has been correlated with the frequency distribution of X-ray attenuation values (14, 23–26) obtained from a CT scan. We have also shown that the volume of gas per weight of lung tissue can be estimated from the inverse of the X-ray attenuation values and that the percentage of lung voxels expanded beyond 10.2-ml gas/g tissue (< −910 HU) represented large emphysematous lesions (> 5-mm diameter) and that CT voxels within the range of 6.0- to 10.2-ml gas/g tissue (−855 HU to −910 HU) represented small emphysematous (< 5-mm diameter) lesions (14). Therefore, in this study, the extent of emphysematous changes was quantified by subdividing the CT measurements of gas per weight of lung tissue into three categories: (*1*) normal lung (0- to 6.0-ml gas/g tissue, > −855 HU), (*2*) small emphysematous changes (6.0- to 10.2-ml gas/g tissue, −855 HU to −910 HU), and (*3*) large emphysematous changes (> 10.2-ml gas/g tissue, < −910 HU).

The results of this study confirm and extend those of Pieters and colleagues (10) in that there was no difference between the group who was anorexic and control group in any of the clinical measurements except BMI, smoking history, and hemoglobin values. However, there is a correlation between the D_{LCO} levels and BMI in the subjects who were anorexic, suggesting that the lower the body weight the lower the diffusing capacity. This decrease in diffusing capacity is similar to data reported by

TABLE 3. REGRESSION ANALYSIS FOR ALL SUBJECTS

	Mean CT Density (*g/ml*)		Volume of Gas Per Weight of Lung Tissue (*ml gas/g tissue*)		Surface Area/Volume (m^2/L)	
	r	p	*r*	p	*r*	p
BMI, kg/m^2	0.59	< 0.001	−0.60	< 0.001	0.60	< 0.001
D_{LCO}/V_A, %P corrHGB	0.20	0.24	−0.27	0.11	0.17	0.33
FEV_1, %P	0.22	0.20	−0.19	0.26	0.22	0.19
FVC, %P	0.32	0.06	−0.31	0.06	0.32	0.06
FEV_1/FVC	−0.32	0.05	0.36	0.03	−0.30	0.07
TLC, %P	0.21	0.21	−0.20	0.25	0.23	0.18

Definition of abbreviations: BMI = body mass index; corrHGB = corrected for hemoglobin; CT = computed tomography; D_{LCO} = diffusing capacity for carbon monoxide; TLC = total lung capacity.

Harkema and colleagues who showed a low diffusing capacity without change in expiratory flow rates in starved rats (17). Furthermore, these data show that there is a correlation between the BMI and lung structure (Table 3) and an increase in the percentage of the lung expanded to levels that correlate with mild to severe emphysema (14, 27) (Figure 2). As there is no indication of increased residual volume or total lung capacity in these subjects, we conclude that the CT findings indicate early emphysematous or "emphysema-like" changes in the lung. It has been shown by quantitative histology (28, 29) and CT (30) that as the lung ages the airspace size increases. Some aging individuals show a disproportionately large airspace size, which has been characterized as "senile lung" (29, 31). Functionally, senile lungs are considered to be intermediate between normal and emphysematous (31), whereas structurally they show signs of abnormal enlargement without the destruction associated with emphysema (29). This process may be similar to our findings in the lungs of those who were anorexic. There is no evidence that CT differences are due to the hemoglobin content because only one subject was anemic and a multiple regression analysis indicated that only the mean volume of gas per weight of lung tissue is a significant predictor of BMI, and the percentage of lung expanded into the large emphysematous changes category (> 10.2 ml/g, < -910 HU) is the only significant predictor of diffusing capacity. There was no significant correlation between pulmonary function and CT parameters and length of disease. These data show that malnutrition may play a role in the development of emphysema, which may have implications for the treatment of emphysema and for the counseling of patients who have anorexia nervosa.

An alternative hypothesis for the emphysematous changes measured in this study could be related to the body's need for oxygen (32). Studies have shown that the surface area of the lung is directly correlated to body size and linked to oxygen consumption in mammals across all body sizes (33). Oxygen uptake falls during calorie restriction in rats. (34). Therefore, the reduction of lung surface area could be a survival mechanism whereby tissue is removed to provide substrate for other vital organs such as the brain and muscle (32). This hypothesis would explain the lung regrowth that occurs in the animal models of calorie restriction.

This study has several limitations. First, a diagnosis of emphysema cannot be made without the pathologic examination of lung tissue. However, CT scans can quantify the extent of emphysema and the amount of tissue and airspace within the lung (14, 24, 26, 27, 35). Therefore, although we cannot "see" the presence of emphysema on our CT studies, we are confident that we can measure the early changes that lead to the later obvious visual changes. Second, the effects of malnutrition cannot be separated from those of tobacco smoke, which is known to be the greatest environmental risk factor for emphysema. It is worth noting that although the control group has a significantly longer smoking history than the subjects who were anorexic, the control subjects do not exhibit the same degree of emphysematous change in their lung structure. Nevertheless, the mechanism by which malnutrition affects the inflammatory response in the lung and whether there is an interaction between malnutrition and smoking history are unknown. The serum levels of α1-antitrypsin are within the normal range, suggesting that it is not merely a protease–antiprotease imbalance interacting with tobacco smoke. Third, to reduce the radiation exposure to this group of young women, CT images were acquired from only three regions of the lung. However, Mishima and colleagues have shown that obtaining images of three regions of the lung provides a reliable estimate of the extent of emphysema in the whole lung (36). Finally, we have used the helium dilution technique to measure the subdivisions of lung volume. Helium dilution underestimates lung volumes because of poor ventilation in regions of obstruction. However, our subjects who were anorexic did not show signs of serious airway obstruction by standard spirometry, and the control group were measured using the same technique. Therefore, we think that the lung volume results are valid and comparable between the two study groups.

In conclusion, there is a correlation between BMI and the diffusing capacity of the lung in subjects who were anorexic. Furthermore, there are correlations between both BMI and diffusing capacity and the CT measurements of emphysema for both groups. These data suggest that there are "emphysematous-like" changes in the lungs of subjects who are malnourished. It remains to be seen whether these changes are reversible, as they are in animal studies (37, 38).

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

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