

## Reduction of total lung capacity in obese men: comparison of total intrathoracic and gas volumes

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**Watson RA, Pride NB, Thomas EL, Fitzpatrick J, Durighel G, McCarthy J, Morin SX, Ind PW, Bell JD.** Reduction of total lung capacity in obese men: comparison of total intrathoracic and gas volumes. *J Appl Physiol* 108: 1605–1612, 2010. First published March 18, 2010; doi:10.1152/jappphysiol.01267.2009.—Restriction of total lung capacity (TLC) is found in some obese subjects, but the mechanism is unclear. Two hypotheses are as follows: 1) increased abdominal volume prevents full descent of the diaphragm; and 2) increased intrathoracic fat reduces space for full lung expansion. We have measured total intrathoracic volume at full inflation using magnetic resonance imaging (MRI) in 14 asymptomatic obese men [mean age 52 yr, body mass index (BMI) 35–45 kg/m<sup>2</sup>] and 7 control men (mean age 50 yr, BMI 22–27 kg/m<sup>2</sup>). MRI volumes were compared with gas volumes at TLC. All measurements were made with subjects supine. Obese men had smaller functional residual capacity (FRC) and FRC-to-TLC ratio than control men. There was a 12% predicted difference in mean TLC between obese (84% predicted) and control men (96% predicted). In contrast, differences in total intrathoracic volume (MRI) at full inflation were only 4% predicted TLC (obese 116% predicted TLC, control 120% predicted TLC), because mediastinal volume was larger in obese than in control [heart and major vessels (obese 1.10 liter, control 0.87 liter,  $P = 0.016$ ) and intrathoracic fat (obese 0.68 liter, control 0.23 liter,  $P < 0.0001$ )]. As a consequence of increased mediastinal volume, intrathoracic volume at FRC in obese men was considerably larger than indicated by the gas volume at FRC. The difference in gas volume at TLC between the six obese men with restriction, TLC < 80% predicted (OR), and the eight obese men with TLC > 80% predicted (ON) was 26% predicted TLC. Mediastinal volume was similar in OR (1.84 liter) and ON (1.73 liter), but total intrathoracic volume was 19% predicted TLC smaller in OR than in ON. We conclude that the major factor restricting TLC in some obese men was reduced thoracic expansion at full inflation.

magnetic resonance imaging; restricted total lung capacity; mediastinal volume

ABOUT 50 YEARS AGO, IT WAS established that functional residual capacity (FRC) and expiratory reserve volume (ERV) are reduced in most seated obese subjects (14, 32). More recently, reduction in total lung capacity (TLC), formerly thought only to occur in massively obese subjects (28), has been found in some subjects with less severe obesity (17). Consistent with the development of a restrictive pattern of lung function in some obese subjects, prospective studies have shown that weight gain is associated with loss of vital capacity (VC) (6, 7, 34), while weight loss is associated with increase in VC (22, 28, 29, 31).

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The mechanical factors reducing VC and TLC in obesity are uncertain, but it has been speculated that increased abdominal volume in some way reduces inspiratory descent of the diaphragm and consequent expansion of the thorax. Recent studies of induced ascites in dogs have shown that, at FRC, the lung-expanding action of the diaphragm was reduced. The mechanism was an increase in abdominal elastance combined with an expansion of the ring of insertion of the diaphragm to the lower rib cage (19, 20). A further possible cause of reduction in TLC is an increase in intrathoracic fat competing for space with the lungs within the intrathoracic cavity. This mechanism would be analogous to that proposed for the restrictive pattern associated with chronic heart failure, which is much improved after cardiac transplantation (16, 23).

We are not aware of studies measuring total intrathoracic volume and its major compartments at full inflation in either normal weight or obese subjects. Such measurements would define the contribution of any increase in intrathoracic fat to the restrictive pattern in obesity and also allow an estimate of intrathoracic volume at all other gas volumes, including FRC.

In the present exploratory study, we have measured total intrathoracic volume at full inflation using magnetic resonance imaging (MRI) and compared these results with measurements of TLC and subdivisions in 7 control and 14 obese men. Both measurements were made in the supine position. These measurements were made as part of a study that also measured abdominal volumes and visceral and subcutaneous fat in all the subjects; these results will be the subject of a separate report.

### METHODS

#### Subjects

All subjects were healthy, middle-aged men without significant symptoms, in particular, no history of cardiac or respiratory disease, sleep disturbance, breathlessness, or reduced effort tolerance. Control men were normal weight or slightly overweight, with the highest body mass index (BMI) being 27.5 kg/m<sup>2</sup>. Obese subjects were seen on a preliminary occasion to establish that their BMI was between 35 and 45 kg/m<sup>2</sup> (grade 2 or 3 obesity) and that spirometry showed no obstructive features.

Written, informed consent was obtained from all subjects, and the protocol was approved by the Hammersmith Research Ethics Committee.

#### Anthropometry

Height without shoes and weight wearing light clothing were measured on a stadiometer. Hip circumference was taken at the level of the trochanters. Waist circumference (standing with arrested normal breathing) was measured at the midlevel between lowest rib and iliac crest. Four skinfold thicknesses (triceps, biceps, subscapular,



suprailiac) were measured, as recommended by Cotes et al. (8) and Durnin and Womersley (9). In some men with a large amount of subcutaneous fat, it was not possible to measure a skinfold with the skin calliper, which was then recorded as 45 mm.

### Lung Function

Spirometry was measured seated using a portable Vitalograph flowhead (Vitalograph Maids Moreton, Bucks, UK). Subjects were asked to perform slow vital capacities (SVC) and then forced expirations to obtain forced expiratory volume in 1 s ( $FEV_1$ ). The best of at least three readings of each was taken.

TLC and subdivisions were measured in duplicate in the supine position using the multibreath helium dilution (MBHe) technique (Morgan Benchmark) (4). Subjects were positioned comfortably on the mouthpiece and, when relaxed and breathing regularly, were turned into the circuit at the end of a tidal expiration. Occasional deep inhalations were made by the subject, and helium equilibrium was reached in  $\approx 3$  min. The subject was then asked to take a full inspiration [inspiratory capacity (IC)] to TLC, followed by a SVC. TLC was taken as the sum of the gas volume at which the subject was turned into the circuit (FRC) and IC. The residual volume (RV) was TLC-SVC. Two repeatable measurements of FRC were obtained and averaged. European reference values (27) were used for spirometry, TLC, VC, and RV.

After these measurements and while attached to a recording spirometer and remaining supine, the subjects were trained to take a repeatable full inspiration followed by breath holding for 17 s; this maneuver would be used and repeated several times during the (immediately subsequent) MRI scans.

### MRI Acquisition

With the use of a Philips Achieva 1.5-T MRI scanner with a Q-Body Coil (Philips Medical System, Best, NL) a T1-weighted turbo spin echo sequence, which covered the entire thoracic cavity, was acquired. Subjects lay supine with arms by their side and hips and knees slightly flexed and were instructed to make a full inflation and then breath hold for 17 s while images were acquired in the coronal plane. Typical parameters: field of view 530 X 300 mm; repetition time 400 ms; echo time 17 ms; number of slices 50/stack; slice thickness 6 mm; interslice gap 1 mm; reconstructed voxel 1.56 X 1.56 mm; and 5 breath holds.

During scanning, a marker was placed on the midsternum to indicate sternal displacement and monitored during the breath hold to ensure inspired volume was maintained. In addition, the definition of the lung border was checked visually to ensure that there was no motion artifact during a breath hold. Total MRI scan time was 20 min.

### Analysis and Identification of Fat, Lungs, Heart, and Main Vessels

Each coronal slice was segmented into six tissue types on the basis of pixel density using commercial imaging software (Slicomatic 4.2; Tomovision, Montreal, Canada). Adipose tissue has a high signal intensity compared with most other tissues, but an experienced oper-

ator (VardisGroup, London, UK), who was unaware of the objectives of the study, coded tissue compartments using expert anatomical knowledge, as previously reported (30).

### Calculation of Intrathoracic Volumes

See Fig. 1. The intrathoracic cavity at full inflation was well defined by the pleural border of the lungs over almost all of its surface. The cavity was bounded by the rib cage, anteriorly by the sternum, posteriorly by the vertebral column, caudally by the diaphragm, and cranially at the level of the lung apices.

The total intrathoracic cavity volume was subdivided into three volumes. 1) The first is total lung volume (TLV). In addition to gas volume, TLV includes the volume of intrapulmonary tissue, blood, and fluid. Because the cranial boundary of TLV was at the apex of the lungs, air in the intrathoracic trachea was included. When comparing TLV with TLC measured by MBHe, 0.07 liter was deducted from TLC to allow for the volume of air in the extrathoracic airway (TLC\*) (24). 2) The second volume is intrathoracic fat. 3) The third volume is heart and major blood vessels (aorta, superior vena cava, and major hilar extrapulmonary vessels) and other mediastinal structures (e.g., esophagus).

We refer to the sum of the second and third volumes as mediastinal volume.

To estimate intrathoracic volume at FRC or RV, IC or VC was subtracted from the measured value of total intrathoracic volume at full inflation. The difference between gas volume and intrathoracic volume at any level of lung inflation then equals (mediastinal volume plus lung tissue volume). This ignores any change in intrathoracic blood volume (heart, major extrapulmonary vessels, intrapulmonary blood vessels) that may occur with lung deflation.

All lung gas volumes and all MRI volumes were measured as liters. To allow for differences in height between individuals, we also expressed gas volumes (TLC and subdivisions) as a percentage of predicted values (%pred) (27). Because we required a height-corrected unit of volume to compare gas and MRI volumes, we also empirically expressed all MRI volumes as a percentage of predicted TLC. We are not aware of any data relating heart and/or mediastinal volume to height or to TLC.

## RESULTS

### Anthropometry

See Table 1. Control and obese men were well matched for age, but control men were, on average, 5 cm taller than the obese men ( $P = 0.07$ ). Obese men had highly significant increases in BMI and standard markers of obesity.

### Lung Function Results: Spirometry

See Table 2. The obese men had some reduction in seated  $FEV_1$  and VC (both as absolute volumes and %pred), but  $FEV_1/VC$  was normal.

Fig. 1. Coronal section of magnetic resonance imaging (MRI) scan of thorax in an obese man, shaded to show lungs, heart, and intrathoracic fat (mainly pericardial). For clarity, this scan was acquired with the subject supine, but with his arms extended above his head. sc, Subcutaneous.

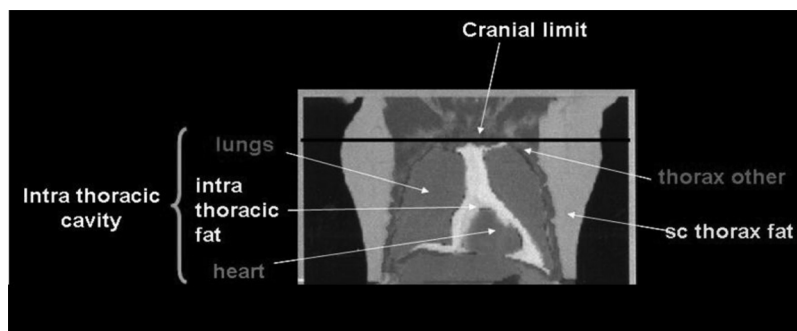


Table 1. *Anthropometry of subjects*

	Controls	Obese	P	Obese Subdivisions	
				>80%predicted TLC (ON)	<80%predicted TLC (OR)
n	7	14		8	6
Age, yr	50.1 ± 9.3	52.4 ± 6.3	NS	53.1 ± 6.3	51.3 ± 6.9
Height, m	1.82 ± 0.04	1.77 ± 0.07	0.07	1.77 ± 0.1	1.76 ± 0.1
Weight, kg	82.4 ± 8.0	121.0 ± 11.2	<0.0001	122.2 ± 11.5	119.3 ± 11.7
Body mass index, kg/m <sup>2</sup>	25.0 ± 2.2	38.8 ± 2.2	<0.0001	38.9 ± 2.2	38.7 ± 2.4
Waist circumference, cm	92.2 ± 4	127.3 ± 8.4	<0.001	128.3 ± 9.4	126.0 ± 7.6
Waist/hip	0.93 ± 0.05	1.02 ± 0.05	0.002	1.03 ± 0.06	1.00 ± 0.03
ISkinfolds, mm	53.2 ± 22.0	119.7 ± 13.2	<0.001	115.8 ± 15.1	124.3 ± 9.7

Values are means ± SD; n, no. of subjects. TLC, total lung capacity; ON, obese nonrestrictive; OR, obese restrictive; waist/hip, ratio of waist to hip. P values: controls vs. obese. Nonsignificant (NS) =  $P > 0.2$ .

### Supine TLC and Subdivisions

The most striking and consistent abnormalities in the obese men were a small FRC and FRC-to-TLC ratio (FRC/TLC), leading to a small ERV. As a further consequence of the low FRC/TLC, mean IC was identical in the obese and control men. Differences in mean TLC, VC, RV, and FEV<sub>1</sub> between obese and control men were not statistically significant. There was no relation between FRC or FRC/TLC and BMI within either group.

A principal objective of this study was to examine factors that might be responsible for a reduced TLC, so we have subdivided the obese men into those with a restrictive disorder (TLC < 80%pred; group OR; n = 6) and those with TLC > 80%pred (group ON; n = 8). This arbitrary but commonly used subdivision (2 men in the ON subgroup had TLC 82%pred) is used to facilitate presentation of the results in Tables 2 and 3. In Figs. 2–4, individual results for all 21 men that we studied are shown with ON and OR subgroups identified by different symbols.

### Comparison of Obese Men With TLC < 80%pred (OR) and With TLC > 80%pred (ON)

There were no differences in mean values of any of the anthropometric features between the two obese subgroups (Table 1).

The OR subgroup with TLC < 80%pred also had smaller mean values of all subdivisions of TLC (VC, RV, FRC, IC;  $P < 0.03$  in all cases), except ERV ( $P = 0.51$ ).

The ON subgroup had similar values of TLC, VC, RV, and FEV<sub>1</sub> as the control men ( $P$  values > 0.15 in all cases), but differed from the control men in having a smaller FRC ( $P = 0.036$ ) and ERV ( $P = 0.014$ ).

### Intrathoracic Volumes at Full Inflation Measured by MRI

See Table 3. Total intrathoracic volume at full inflation was, on average, 0.71 liter larger in control than obese men; expressing total intrathoracic volume as %pred TLC, mean control and obese values were 120 and 116%pred TLC, respec-

Table 2. *Spirometry and lung volumes*

	Controls	Obese	P	Obese Subdivisions	
				>80%predicted TLC (ON)	<80%predicted TLC (OR)
n	7	14		8	6
<i>Seated</i>					
FEV <sub>1</sub>					
Liters	4.12 ± 0.8	3.45 ± 0.8	0.07	3.81 ± 0.8	2.97 ± 0.4
%Predicted	106 ± 14	96 ± 15	0.155	105.5 ± 12.9	83.2 ± 4.8
FEV <sub>1</sub> /VC, %	76 ± 7	81 ± 6	NS	80 ± 7	82 ± 4
<i>Supine</i>					
TLC					
Liters	7.15 ± 0.8	5.96 ± 1.3	0.04	6.83 ± 0.9	4.81 ± 0.6
%Predicted*	96 ± 8	84 ± 15	0.08	95 ± 10	69 ± 4
VC					
Liters	5.23 ± 0.8	4.43 ± 0.9	0.063	4.98 ± 0.7	3.71 ± 0.6
%Predicted*	108.1 ± 11.8	99.3 ± 17.1	NS	111.1 ± 0.5	83.6 ± 9.3
RV					
Liters	1.91 ± 0.5	1.53 ± 0.6	NS	1.85 ± 0.7	1.11 ± 0.2
%Predicted*	84 ± 17	68 ± 25	NS	81 ± 26	50 ± 8
FRC, liters	3.32 ± 0.5	2.13 ± 0.7	0.001	2.51 ± 0.8	1.61 ± 0.3
FRC/TLC, %	46.4 ± 6.1	35.0 ± 5.9	0.0005	36.1 ± 7.2	33.5 ± 3.3
ERV, liters	1.40 ± 0.5	0.60 ± 0.4	0.006	0.66 ± 0.5	0.51 ± 0.3
IC, liters	3.84 ± 0.69	3.84 ± 0.69	NS	4.32 ± 0.4	3.20 ± 0.4

Values are means  $\pm$  SD; *n*, no. of subjects. FEV<sub>1</sub>, forced expiratory volume in 1 s; VC, vital capacity; RV, residual volume; FRC, functional residual capacity; ERV, expiratory reserve volume; IC, inspiratory capacity. Predicted values are for upright TLC and subdivisions. *P* values: controls vs. obese. NS = *P* > 0.2.

Table 3. Total intrathoracic volumes at full inflation measured by magnetic resonance imaging

	Control	Obese	P	Obese Subdivisions	
				>80%predicted TLC (ON)	<80%predicted TLC (OR)
n	7	14		8	6
Total intrathoracic volume					
Liters	8.92 ± 0.9	8.21 ± 1.3	NS	8.87 ± 1.0	7.32 ± 1.1
%Predicted TLC	120 ± 8	116 ± 13	NS	124 ± 10	105 ± 11
Heart and vessels, liters	0.87 ± 0.2	1.10 ± 0.2	0.016	1.04 ± 0.2	1.18 ± 0.2
Fat, liters	0.23 ± 0.1	0.68 ± 0.2	<0.0001	0.69 ± 0.2	0.66 ± 0.3
Lungs (TLV)					
Liters	7.82 ± 0.8	6.43 ± 1.3	0.004	7.14 ± 0.8	5.48 ± 0.8
%Predicted TLC	105 ± 7	90.8 ± 13	0.016	99.9 ± 8	78.6 ± 8
Lungs (TLV)/total intrathoracic volume, %	88 ± 1.5	78 ± 4.2	<0.0001	80 ± 1.81	75 ± 4.5

Values are means ± SD; n, no. of subjects. P values: controls vs. obese. NS = P > 0.2.

tively (Table 3). This 4% difference compared with a 12% difference in TLC %pred measured by MBHe dilution (Table 2). These mean results conceal great between-individual variability within both groups (Figs. 2–4).

Each of the three compartments of total intrathoracic volume differed between control and obese men. By far, the largest compartment was TLV, which occupied, on average, 88% of the total intrathoracic volume in control men. Mean TLV (%pred TLC) was smaller in the obese men than in the control men (P = 0.016).

Mean values of both mediastinal components of intrathoracic volume were larger in the obese men than in the control men (Fig. 2): mean heart and major blood vessel volume was 1.10 liter in obese vs. 0.87 liter in control men (P = 0.016), while mean volume of intrathoracic fat (mainly pericardiac and mediastinal, but sometimes also extending over the adjacent pleural surface of the diaphragm, Fig. 1) was 0.68 liter in obese and 0.23 liter in control men (P < 0.0001). Because of the increased mediastinal volume, the inflated lungs only occupied, on average, 78% of the total intrathoracic cavity volume in obese men.

Thus increased mediastinal volume might contribute to reduction in TLC in some of the obese men. However, mean mediastinal volume was similar in the obese subgroups with

(OR 1.84 liter) and without (ON 1.73 liter) reduced TLC (P = 0.56). The relation between TLV and total intrathoracic volume in all 21 men is shown in Fig. 3. In the ON men, whose values of TLV overlapped those of the control men, mean total intrathoracic volume was actually slightly greater (124%pred TLC) than in the control group (120%pred TLC). In contrast, total intrathoracic volume was only 105%pred TLC in the OR subgroup. This 19%pred TLC difference in mean total intrathoracic volume between ON and OR (P = 0.005) was the major factor accounting for the smaller TLC MBHe in the OR subgroup.

Comparison of Lung Volume at Full Inflation Measured by MRI and MBHe Dilution

Individual values of TLV measured by MRI were closely related to, but slightly greater than, TLC\* measured by MBHe

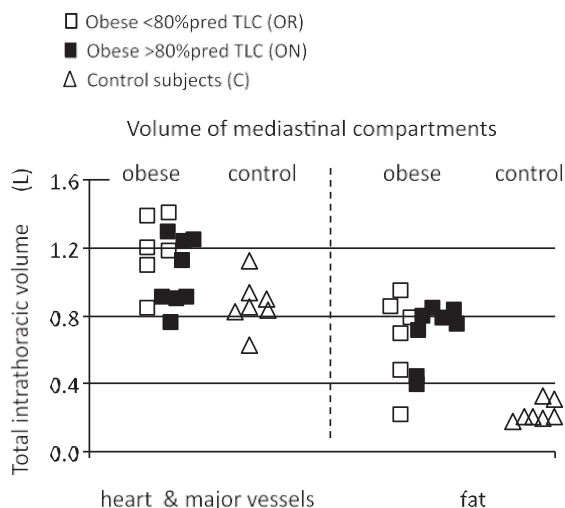


Fig. 2. Contributions of volumes of heart and major blood vessels (left) and intrathoracic fat (right) to total intrathoracic volume in control and obese men. Symbols distinguish control men from obese restrictive (OR) and obese nonrestrictive (ON) subgroups. TLC, total lung capacity.

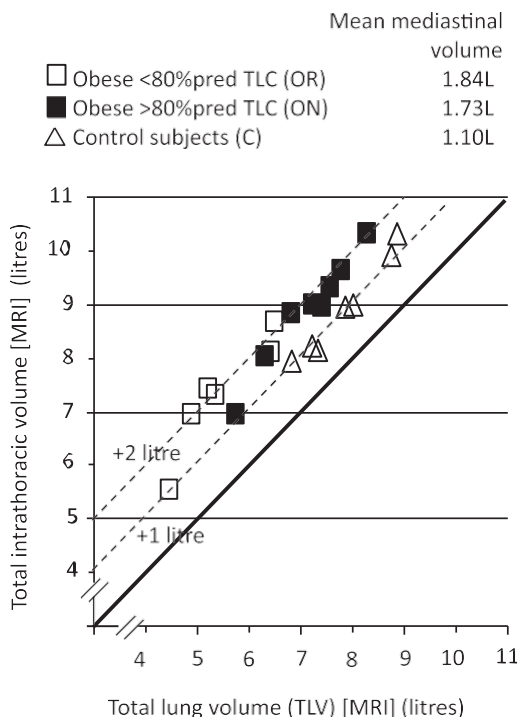


Fig. 3. Total lung volume (TLV) at full inflation plotted against total intrathoracic volume in control and obese men. The thick diagonal line is the line of identity, and the dashed lines indicate when the total intrathoracic volume is 1 or 2 liters greater than TLV. Note that many values of TLV in ON subgroup and in control men overlap.

dilution (Fig. 4). The mean volume difference (TLV-TLC\*), which reflects the volume of intrapulmonary tissue and fluid, was 0.74 liter in control and 0.54 liter in obese men (difference nonsignificant,  $P = 0.61$ ).

#### Comparison of Gas Volumes and Estimates of Intrathoracic Volumes When the Lungs Are Deflated

Because mediastinal volume was, on average, 0.68 liter larger in obese than control men, differences between control and obese men in all intrathoracic volumes were smaller than the difference in corresponding gas volumes. For example,

while mean FRC gas volume was 45%pred TLC in control and 30%pred TLC in obese men, mean intrathoracic volume at FRC was 69%pred TLC in control and 62%pred TLC in obese men (Fig. 5).

#### DISCUSSION

In this exploratory study, in obese middle-aged men, we measured total intrathoracic volume and its components at full inflation to investigate the features of restrictive lung disease (TLC <80%pred). A restrictive pattern was found in 6 of the 14 men and was associated with a smaller total intrathoracic volume. Mediastinal volume was 0.68 liter larger in obese than control men due to increase in volumes occupied by the heart and major blood vessels and by intrathoracic fat, but was similar in obese men with and without restrictive lung disease.

#### Methodology

**Subjects.** We chose men for this exploratory study of restrictive lung disease associated with obesity, because two prospective studies (6, 34) have shown that loss of VC with increase in weight is greater in men than in women. Possibly this is because men have a more central pattern of obesity than women; in our department, visceral abdominal fat measured by MRI averages 14.8% of total body fat in obese men and 8.9% in obese women (E. L. Thomas, unpublished observations).

**MRI scanning technique.** The pleural edges of the lungs were well defined during breath holding, allowing an accurate measurement of TLV. Intrathoracic fat was also clearly visu-

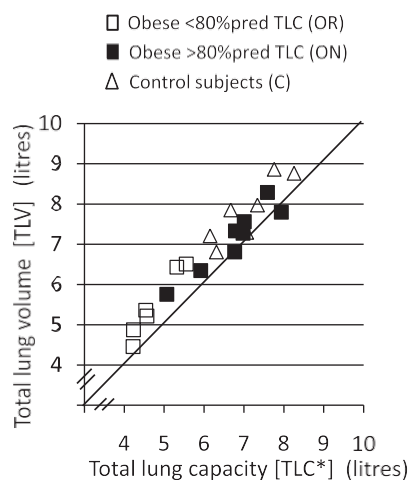


Fig. 4. Comparison of TLC measured by multibreath helium dilution (TLC\*) and TLV measured by MRI in control men. The diagonal line is the line of identity. In this comparison, measured TLC has been reduced by the estimated volume of the extrathoracic airway (see METHODS).

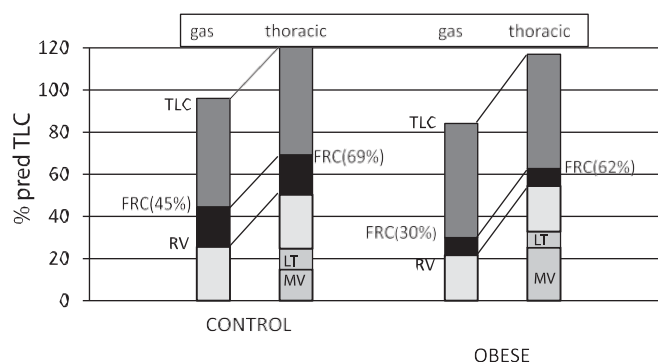


Fig. 5. Comparison of mean gas volumes and estimates of mean intrathoracic volumes (all expressed as %predicted TLC) in control and obese men. LT, lung tissue volume; MV, mediastinal volume; FRC, functional residual capacity; RV, residual volume. Increased mediastinal volume in the obese men results in the differences in intrathoracic volumes between obese and control men being smaller than the corresponding differences in gas volumes.

alized by its characteristic density. The heart and major blood vessels, including the extrapulmonary hilar vessels, were the major contributors to the remaining mediastinal compartment, which includes organs such as the esophagus. This nonvascular volume should be small and similar in control and obese men. The close correspondence between values of TLV and TLC (Fig. 4) in an individual supports the effectiveness of the "training" in breath holding at full inflation; furthermore, it suggests that helium equilibrated with true total gas volume in the obese men, even though they were supine with a very low FRC/TLC, and so probably had some airway closure during tidal breathing (15). Frequent deep inspirations were made during helium equilibration so as to allow access of helium to lung beyond any closed airways. TLV measured by imaging includes intrapulmonary tissue, fluid, and blood, as well as gas, so (TLV-TLC\*) potentially estimates lung tissue and fluid volume, albeit with limited accuracy because of the following. 1) TLV and TLC were measured in separate maneuvers, during which esophageal pressure was not measured. Hence we do not know if a comparable lung recoil pressure was achieved in all full-inflation maneuvers, nor whether glottal closure occurred during breath holding. 2) These estimates depend on the difference between two volumes, which are 8–10 times larger. Nevertheless, our mean estimate of lung tissue and fluid volume for the 21 men of 0.61 liter (0.74 liter in control men, 0.54 liter in obese men) is similar to previous estimates in healthy subjects using gas uptake of 0.61 liter (5), or by comparing volumes measured by chest radiographs at full inflation with body plethysmography of 0.72 liter (26). We had expected lung tissue volume to be larger in the obese than the control men, because, in obesity, intrapulmonary blood volume is probably larger (2, 18, 29), particularly when supine.

**Differences between supine and seated gas volumes.** There is no consistent supine change in RV, but supine values of TLC and VC in normal subjects are, on average, slightly lower (200 ml or less) than seated values (3, 21, 32, 33, 35), with the reduction being attributed to an increase in central blood volume when supine. Similar small reductions in supine TLC and VC have been shown in obese subjects (3, 32, 33, 35); indeed, previously our laboratory found that supine TLC in obese subjects, some of whom had lung restriction, was, on average, only 80 ml smaller than seated values (33). Hence we believe our results for TLC, VC, and RV also apply to seated

subjects. This is not the case for FRC. Whereas in normal subjects, FRC falls by 700–800 ml on going from the seated to the supine position (3, 21, 32, 33, 35), in severely obese subjects our laboratory (33, 35) and others (3, 32) have shown that supine falls in FRC are much smaller and may even be absent. The difference in values of FRC, FRC/TLC, and ERV between control and obese subjects shown in Table 2, therefore, would be even larger if the subjects were seated.

#### *Comparison of Supine Lung Gas Volumes in Obese Men With and Without Restriction*

Obese men had highly significant reductions in supine FRC, FRC/TLC, and ERV compared with control men. Reduction in TLC in the obese men was more variable and, when results were corrected for height differences between control and obese men, did not quite reach statistical significance vs. control subjects.

In early studies of individual patients with “morbid” obesity with hypercapnia (“Pickwickian”, or obesity hypoventilation syndrome), reduction in TLC was a prominent feature (14, 29), but was often not found in later, less selected studies of obesity (28). Recently, the relation of BMI to seated TLC and subdivisions has been clarified by Jones and Nzekwu (17), who studied 373 men and women (their results were not distinguished) whose BMI ranged from 20 to 58 kg/m<sup>2</sup>. Mean values of seated TLC, FRC, VC, ERV, and RV all declined progressively with increasing BMI, but at very different rates and with a wide scatter of results, especially for ERV and RV. The largest and most consistent reductions were in FRC and, consequently, also in ERV, which were found in mild obesity. At a BMI of 30–35 kg/m<sup>2</sup>, mean FRC was 75% and mean ERV 47% of values at BMI of 20 kg/m<sup>2</sup>; values of ERV as small as 20%pred or less were common, limiting the possibility of any further reduction at higher BMI. As a result, an exponential curve was fitted to these data. In contrast mean reductions in TLC, VC, and RV with increase in BMI were much smaller, so that group mean values remained within the normal range (TLC and VC both 88%pred, RV 90%pred), even in subjects with BMI >40 kg/m<sup>2</sup>. Our finding that obese men had large reductions in FRC, whether or not they were in the ON or the OR group, is, therefore, consistent with Jones and Nzekwu’s findings.

*Total intrathoracic volume in obesity.* In control men, the fully inflated lungs occupied, on average, 88% of the total intrathoracic volume, but in obese men only 78% because of their larger mediastinal volume, which, in the obese men, averaged 1.78 liter (25.2%pred TLC) compared with 1.10 liter (14.8%pred TLC) in the control men. We are not aware of earlier measurements of intrathoracic fat, but an increase in central blood volume was consistently noted in early studies of obesity hypoventilation syndrome, even in the absence of overt heart failure (18, 29), and has been confirmed more recently in obese subjects without any symptoms to suggest clinical heart disease (2). The mean 10% pred TLC increase of mediastinal volume in the obese compared with the control men hardly contributed to the large difference in TLC between the ON and OR groups, because mean mediastinal volume was only 0.11 liter larger in the OR than in the ON subgroup. Indeed, Fig. 3 shows that, whereas individual values of TLV largely overlap in the ON and control groups, total intrathoracic volume at a

given TLV tends to be larger in the ON individuals, perhaps suggesting the thoracic wall has “accommodated” to the larger mediastinal volume.

The major contributor to restriction of TLC in the OR group was that, while the eight ON men had a mean total intrathoracic volume at full inflation slightly larger (124%pred TLC) than the control men (120%pred), in the six OR men, mean total intrathoracic volume at full inflation was 105%pred TLC. Possibly, therefore, in some obese men, the large abdomen limits caudal movement of the diaphragm at full inflation. Recent experiments inducing acute ascites in dogs have shown that the load on the diaphragm was increased by an increase in abdominal elastance, but, in addition, the lung-expanding action of the diaphragm was impaired by reduction in its pressure-generating ability (19, 20). We are not aware of comparable studies of diaphragm function and load in human obesity.

The immediate cause of reduction in TLC is a reduction in VC (changes in RV are small and inconsistent). Reductions in VC with increase in weight have been shown in men in three prospective studies over 5–7 yr, with mean losses of forced VC (FVC) of 26 ml (6), 21 ml (7) and 17 ml (34) for each kg of weight gained. Two of these studies also studied women (6, 34) in whom losses of FVC per kg weight gain were considerably smaller. Conversely, rises in VC following reductions in weight were first reported in small studies many years ago (29, 31). In the last decade gastric surgery has become a popular method to induce large and rapid reductions in weight; so far only a few studies have reported the effects on spirometry, but in them mean FVC has consistently increased 6 mo or more after operation (22). The precise mechanism by which VC is reduced by increase in weight, why this loss of VC is larger in men than in women, and why reduction in TLC is very variable among obese men of similar age and BMI all remain uncertain.

*Reduction in FRC and RV.* The reduction in FRC and ERV in healthy subjects when lying supine is attributed to a rightward displacement of the PV curve of the relaxed chest wall, increasing its pressure at a given gas volume, and reducing relaxation volume ( $V_r$ ) (1). A comparable supine decrease in  $V_r$  would be expected in obesity. In practice, in severe obesity when supine FRC hardly falls below seated values, FRC is probably maintained above  $V_r$  as a response to expiratory flow limitation (25, 35).

Our finding of an increase in mediastinal volume in obesity potentially alters the interaction between elasticity of the chest wall and of the lungs. Classically, this interaction is related to a common volume, defined by the volume of gas contained in the lungs. When considering the pleural cavities, this convention obscures the normal difference between the volume enclosed by the parietal pleura and intrapulmonary gas volume, which arises from the tissue and fluid content (including blood) within the lungs. In intrathoracic disease, the difference between total intrapleural volume and intrapulmonary gas volume may be increased, as originally analyzed by Fenn (11) for pneumothorax, or for both pleural cavities with increase in intrapulmonary fluid, blood, or tissue volume in conditions such as interstitial lung fibrosis (12). FRC, TLC, and RV all are partly determined by active or passive characteristics of the chest wall and respiratory muscles, so their values in thoracic diseases can be fully interpreted only if chest wall volume is known or can be inferred (13).



Previously, two papers have suggested that restriction of TLC may be partially reversed by heart transplantation, due to the effects of increased heart volume in chronic heart failure (16, 23); one of these studies (16) estimated the change in heart volume following heart transplantation from chest radiographs.

In the present study, we have measured mediastinal volume in a few healthy middle-aged men. This volume, when combined with lung tissue and fluid volume, is responsible for the "normal" difference between total intrathoracic volume and total gas volume. So far, despite the wide availability of three-dimensional imaging techniques that could measure simultaneously total intrathoracic volume and TLV, we have not found any published estimates of mediastinal volume to check against our value of 1.10 liter.

The acquired increase in mediastinal volume in obesity implies that the difference between intrathoracic volume and the corresponding gas volume has increased on average by 0.68 liter in adult life. In middle-aged healthy men, chest wall compliance in the operating tidal range close to FRC averages 1.176 l/cmH<sub>2</sub>O seated and 0.161 l/cmH<sub>2</sub>O supine (10). Hence an acute increase of 0.68 liter in mediastinal volume could increase pressure exerted by the relaxed chest wall by as much as 4 cmH<sub>2</sub>O, which would have a large effect on V<sub>r</sub>. However, with a chronic increase in mediastinal volume, the elastic properties of the chest wall may show partial or even complete adaptation.

Increase in mediastinal volume may also influence the value of RV, at least in younger obese adults in whom RV is determined by a static balance between the maximum muscle pressure and the outward recoil of the passive structures of the chest wall as its volume is reduced (1). The minimum gas volume of the lung at RV may be reduced, if there is an increase in indistensible volume within the thoracic cavity. This may explain that, while gas volume at RV was smaller in the obese men than in the control men, intrathoracic volume at RV was slightly larger in the obese men than in the control men (see Fig. 5). Thus it seems possible that increase in mediastinal volume may influence the values of FRC and RV in obesity, even if it is not important in restricting TLC in obesity.

In conclusion, we found that reduction in TLC in obese men was associated with reduced expansion of the thoracic cage. Both intrathoracic fat volume and the volume of heart and major blood vessels were larger in the obese than the control men, but these volumes did not differ between obese men with and without lung restriction. Further studies are required to determine the factors impairing full expansion of the thorax in some obese men.

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#### DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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## Reduction of total lung capacity in obese men: comparison of total intrathoracic and gas volumes

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**Watson RA, Pride NB, Thomas EL, Fitzpatrick J, Durighel G, McCarthy J, Morin SX, Ind PW, Bell JD.** Reduction of total lung capacity in obese men: comparison of total intrathoracic and gas volumes. *J Appl Physiol* 108: 1605–1612, 2010. First published March 18, 2010; doi:10.1152/jappphysiol.01267.2009.—Restriction of total lung capacity (TLC) is found in some obese subjects, but the mechanism is unclear. Two hypotheses are as follows: 1) increased abdominal volume prevents full descent of the diaphragm; and 2) increased intrathoracic fat reduces space for full lung expansion. We have measured total intrathoracic volume at full inflation using magnetic resonance imaging (MRI) in 14 asymptomatic obese men [mean age 52 yr, body mass index (BMI) 35–45 kg/m<sup>2</sup>] and 7 control men (mean age 50 yr, BMI 22–27 kg/m<sup>2</sup>). MRI volumes were compared with gas volumes at TLC. All measurements were made with subjects supine. Obese men had smaller functional residual capacity (FRC) and FRC-to-TLC ratio than control men. There was a 12% predicted difference in mean TLC between obese (84% predicted) and control men (96% predicted). In contrast, differences in total intrathoracic volume (MRI) at full inflation were only 4% predicted TLC (obese 116% predicted TLC, control 120% predicted TLC), because mediastinal volume was larger in obese than in control [heart and major vessels (obese 1.10 liter, control 0.87 liter,  $P = 0.016$ ) and intrathoracic fat (obese 0.68 liter, control 0.23 liter,  $P < 0.0001$ )]. As a consequence of increased mediastinal volume, intrathoracic volume at FRC in obese men was considerably larger than indicated by the gas volume at FRC. The difference in gas volume at TLC between the six obese men with restriction, TLC < 80% predicted (OR), and the eight obese men with TLC > 80% predicted (ON) was 26% predicted TLC. Mediastinal volume was similar in OR (1.84 liter) and ON (1.73 liter), but total intrathoracic volume was 19% predicted TLC smaller in OR than in ON. We conclude that the major factor restricting TLC in some obese men was reduced thoracic expansion at full inflation.

magnetic resonance imaging; restricted total lung capacity; mediastinal volume

ABOUT 50 YEARS AGO, IT WAS established that functional residual capacity (FRC) and expiratory reserve volume (ERV) are reduced in most seated obese subjects (14, 32). More recently, reduction in total lung capacity (TLC), formerly thought only to occur in massively obese subjects (28), has been found in some subjects with less severe obesity (17). Consistent with the development of a restrictive pattern of lung function in some obese subjects, prospective studies have shown that weight gain is associated with loss of vital capacity (VC) (6, 7, 34), while weight loss is associated with increase in VC (22, 28, 29, 31).

The mechanical factors reducing VC and TLC in obesity are uncertain, but it has been speculated that increased abdominal volume in some way reduces inspiratory descent of the diaphragm and consequent expansion of the thorax. Recent studies of induced ascites in dogs have shown that, at FRC, the lung-expanding action of the diaphragm was reduced. The mechanism was an increase in abdominal elastance combined with an expansion of the ring of insertion of the diaphragm to the lower rib cage (19, 20). A further possible cause of reduction in TLC is an increase in intrathoracic fat competing for space with the lungs within the intrathoracic cavity. This mechanism would be analogous to that proposed for the restrictive pattern associated with chronic heart failure, which is much improved after cardiac transplantation (16, 23).

We are not aware of studies measuring total intrathoracic volume and its major compartments at full inflation in either normal weight or obese subjects. Such measurements would define the contribution of any increase in intrathoracic fat to the restrictive pattern in obesity and also allow an estimate of intrathoracic volume at all other gas volumes, including FRC. In the present exploratory study, we have measured total intrathoracic volume at full inflation using magnetic resonance imaging (MRI) and

compared these results with measurements of TLC and subdivisions in 7 control and 14 obese men. Both measurements were made in the supine position. These measurements were made as part of a study that also measured abdominal volumes and visceral and subcutaneous fat in all the subjects; these results will be the subject of a separate report.

## METHODS

### *Subjects*

All subjects were healthy, middle-aged men without significant symptoms, in particular, no history of cardiac or respiratory disease, sleep disturbance, breathlessness, or reduced effort tolerance. Control men were normal weight or slightly overweight, with the highest body mass index (BMI) being 27.5 kg/m<sup>2</sup>. Obese subjects were seen on a preliminary occasion to establish that their BMI was between 35 and 45 kg/m<sup>2</sup> (grade 2 or 3 obesity) and that spirometry showed no obstructive features.

Written, informed consent was obtained from all subjects, and the protocol was approved by the Hammersmith Research Ethics Committee.

### *Anthropometry*

Height without shoes and weight wearing light clothing were measured on a stadiometer. Hip circumference was taken at the level of the trochanters. Waist circumference (standing with arrested normal breathing) was measured at the midlevel between lowest rib and iliac crest. Four skinfold thicknesses (triceps, biceps, subscapular,

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suprailiac) were measured, as recommended by Cotes et al. (8) and Durnin and Womersley (9). In some men with a large amount of subcutaneous fat, it was not possible to measure a skinfold with the skin calliper, which was then recorded as 45 mm.

### Lung Function

Spirometry was measured seated using a portable Vitalograph flowhead (Vitalograph Maids Moreton, Bucks, UK). Subjects were asked to perform slow vital capacities (SVC) and then forced expirations to obtain forced expiratory volume in 1 s ( $FEV_1$ ). The best of at least three readings of each was taken.

TLC and subdivisions were measured in duplicate in the supine position using the multibreath helium dilution (MBHe) technique (Morgan Benchmark) (4). Subjects were positioned comfortably on the mouthpiece and, when relaxed and breathing regularly, were turned into the circuit at the end of a tidal expiration. Occasional deep inhalations were made by the subject, and helium equilibrium was reached in  $\approx 3$  min. The subject was then asked to take a full inspiration [inspiratory capacity (IC)] to TLC, followed by a SVC. TLC was taken as the sum of the gas volume at which the subject was turned into the circuit (FRC) and IC. The residual volume (RV) was TLC-SVC. Two repeatable measurements of FRC were obtained and averaged. European reference values (27) were used for spirometry, TLC, VC, and RV.

After these measurements and while attached to a recording spirometer and remaining supine, the subjects were trained to take a repeatable full inspiration followed by breath holding for 17 s; this maneuver would be used and repeated several times during the (immediately subsequent) MRI scans.

### MRI Acquisition

With the use of a Philips Achieva 1.5-T MRI scanner with a Q-Body Coil (Philips Medical System, Best, NL) a T1-weighted turbo spin echo sequence, which covered the entire thoracic cavity, was acquired. Subjects lay supine with arms by their side and hips and knees slightly flexed and were instructed to make a full inflation and then breath hold for 17 s while images were acquired in the coronal plane. Typical parameters: field of view 530 X 300 mm; repetition time 400 ms; echo time 17 ms; number of slices 50/stack; slice thickness 6 mm; interslice gap 1 mm; reconstructed voxel 1.56 X 1.56 mm; and 5 breath holds.

During scanning, a marker was placed on the midsternum to indicate sternal displacement and monitored during the breath hold to ensure inspired volume was maintained. In addition, the definition of the lung border was checked visually to ensure that there was no motion artifact during a breath hold. Total MRI scan time was 20 min.

### Analysis and Identification of Fat, Lungs, Heart, and Main Vessels

Each coronal slice was segmented into six tissue types on the basis of pixel density using commercial imaging software (Slicomatic 4.2; Tomovision, Montreal, Canada). Adipose tissue has a high signal intensity compared with most other tissues, but an experienced oper-

ator (VardisGroup, London, UK), who was unaware of the objectives of the study, coded tissue compartments using expert anatomical knowledge, as previously reported (30).

### Calculation of Intrathoracic Volumes

See Fig. 1. The intrathoracic cavity at full inflation was well defined by the pleural border of the lungs over almost all of its surface. The cavity was bounded by the rib cage, anteriorly by the sternum, posteriorly by the vertebral column, caudally by the diaphragm, and cranially at the level of the lung apices.

The total intrathoracic cavity volume was subdivided into three volumes. 1) The first is total lung volume (TLV). In addition to gas volume, TLV includes the volume of intrapulmonary tissue, blood, and fluid. Because the cranial boundary of TLV was at the apex of the lungs, air in the intrathoracic trachea was included. When comparing TLV with TLC measured by MBHe, 0.07 liter was deducted from TLC to allow for the volume of air in the extrathoracic airway (TLC\*) (24). 2) The second volume is intrathoracic fat. 3) The third volume is heart and major blood vessels (aorta, superior vena cava, and major hilar extrapulmonary vessels) and other mediastinal structures (e.g., esophagus).

We refer to the sum of the second and third volumes as mediastinal volume.

To estimate intrathoracic volume at FRC or RV, IC or VC was subtracted from the measured value of total intrathoracic volume at full inflation. The difference between gas volume and intrathoracic volume at any level of lung inflation then equals (mediastinal volume plus lung tissue volume). This ignores any change in intrathoracic blood volume (heart, major extrapulmonary vessels, intrapulmonary blood vessels) that may occur with lung deflation.

All lung gas volumes and all MRI volumes were measured as liters. To allow for differences in height between individuals, we also expressed gas volumes (TLC and subdivisions) as a percentage of predicted values (%pred) (27). Because we required a height-corrected unit of volume to compare gas and MRI volumes, we also empirically expressed all MRI volumes as a percentage of predicted TLC. We are not aware of any data relating heart and/or mediastinal volume to height or to TLC.

## RESULTS

### Anthropometry

See Table 1. Control and obese men were well matched for age, but control men were, on average, 5 cm taller than the obese men ( $P = 0.07$ ). Obese men had highly significant increases in BMI and standard markers of obesity.

### Lung Function Results: Spirometry

See Table 2. The obese men had some reduction in seated  $FEV_1$  and VC (both as absolute volumes and %pred), but  $FEV_1/VC$  was normal.

Fig. 1. Coronal section of magnetic resonance imaging (MRI) scan of thorax in an obese man, shaded to show lungs, heart, and intrathoracic fat (mainly pericardial). For clarity, this scan was acquired with the subject supine, but with his arms extended above his head. sc, Subcutaneous.

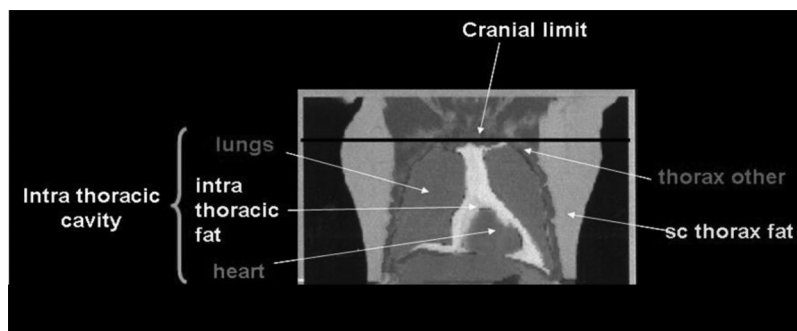


Table 1. *Anthropometry of subjects*

	Controls	Obese	P	Obese Subdivisions	
				>80%predicted TLC (ON)	<80%predicted TLC (OR)
<i>n</i>	7	14		8	6
Age, yr	50.1 ± 9.3	52.4 ± 6.3	NS	53.1 ± 6.3	51.3 ± 6.9
Height, m	1.82 ± 0.04	1.77 ± 0.07	0.07	1.77 ± 0.1	1.76 ± 0.1
Weight, kg	82.4 ± 8.0	121.0 ± 11.2	<0.0001	122.2 ± 11.5	119.3 ± 11.7
Body mass index, kg/m <sup>2</sup>	25.0 ± 2.2	38.8 ± 2.2	<0.0001	38.9 ± 2.2	38.7 ± 2.4
Waist circumference, cm	92.2 ± 4	127.3 ± 8.4	<0.001	128.3 ± 9.4	126.0 ± 7.6
Waist/hip	0.93 ± 0.05	1.02 ± 0.05	0.002	1.03 ± 0.06	1.00 ± 0.03
ISkinfolds, mm	53.2 ± 22.0	119.7 ± 13.2	<0.001	115.8 ± 15.1	124.3 ± 9.7

Values are means ± SD; *n*, no. of subjects. TLC, total lung capacity; ON, obese nonrestrictive; OR, obese restrictive; waist/hip, ratio of waist to hip. *P* values: controls vs. obese. Nonsignificant (NS) = *P* > 0.2.

### Supine TLC and Subdivisions

The most striking and consistent abnormalities in the obese men were a small FRC and FRC-to-TLC ratio (FRC/TLC), leading to a small ERV. As a further consequence of the low FRC/TLC, mean IC was identical in the obese and control men. Differences in mean TLC, VC, RV, and FEV<sub>1</sub> between obese and control men were not statistically significant. There was no relation between FRC or FRC/TLC and BMI within either group.

A principal objective of this study was to examine factors that might be responsible for a reduced TLC, so we have subdivided the obese men into those with a restrictive disorder (TLC < 80%pred; group OR; *n* = 6) and those with TLC > 80%pred (group ON; *n* = 8). This arbitrary but commonly used subdivision (2 men in the ON subgroup had TLC 82%pred) is used to facilitate presentation of the results in Tables 2 and 3. In Figs. 2–4, individual results for all 21 men that we studied are shown with ON and OR subgroups identified by different symbols.

### Comparison of Obese Men With TLC < 80%pred (OR) and With TLC > 80%pred (ON)

There were no differences in mean values of any of the anthropometric features between the two obese subgroups (Table 1).

The OR subgroup with TLC < 80%pred also had smaller mean values of all subdivisions of TLC (VC, RV, FRC, IC; *P* < 0.03 in all cases), except ERV (*P* = 0.51).

The ON subgroup had similar values of TLC, VC, RV, and FEV<sub>1</sub> as the control men (*P* values > 0.15 in all cases), but differed from the control men in having a smaller FRC (*P* = 0.036) and ERV (*P* = 0.014).

### Intrathoracic Volumes at Full Inflation Measured by MRI

See Table 3. Total intrathoracic volume at full inflation was, on average, 0.71 liter larger in control than obese men; expressing total intrathoracic volume as %pred TLC, mean control and obese values were 120 and 116%pred TLC, respec-

Table 2. *Spirometry and lung volumes*

	Controls	Obese	P	Obese Subdivisions	
				>80%predicted TLC (ON)	<80%predicted TLC (OR)
<i>n</i>	7	14		8	6
<i>Seated</i>					
FEV <sub>1</sub>					
Liters	4.12 ± 0.8	3.45 ± 0.8	0.07	3.81 ± 0.8	2.97 ± 0.4
%Predicted	106 ± 14	96 ± 15	0.155	105.5 ± 12.9	83.2 ± 4.8
FEV <sub>1</sub> /VC, %	76 ± 7	81 ± 6	NS	80 ± 7	82 ± 4
<i>Supine</i>					
TLC					
Liters	7.15 ± 0.8	5.96 ± 1.3	0.04	6.83 ± 0.9	4.81 ± 0.6
%Predicted*	96 ± 8	84 ± 15	0.08	95 ± 10	69 ± 4
VC					
Liters	5.23 ± 0.8	4.43 ± 0.9	0.063	4.98 ± 0.7	3.71 ± 0.6
%Predicted*	108.1 ± 11.8	99.3 ± 17.1	NS	111.1 ± 0.5	83.6 ± 9.3
RV					
Liters	1.91 ± 0.5	1.53 ± 0.6	NS	1.85 ± 0.7	1.11 ± 0.2
%Predicted*	84 ± 17	68 ± 25	NS	81 ± 26	50 ± 8
FRC, liters	3.32 ± 0.5	2.13 ± 0.7	0.001	2.51 ± 0.8	1.61 ± 0.3
FRC/TLC, %	46.4 ± 6.1	35.0 ± 5.9	0.0005	36.1 ± 7.2	33.5 ± 3.3
ERV, liters	1.40 ± 0.5	0.60 ± 0.4	0.006	0.66 ± 0.5	0.51 ± 0.3
IC, liters	3.84 ± 0.69	3.84 ± 0.69	NS	4.32 ± 0.4	3.20 ± 0.4

Values are means  $\pm$  SD; *n*, no. of subjects. FEV<sub>1</sub>, forced expiratory volume in 1 s; VC, vital capacity; RV, residual volume; FRC, functional residual capacity; ERV, expiratory reserve volume; IC, inspiratory capacity. Predicted values are for upright TLC and subdivisions. *P* values: controls vs. obese. NS = *P* > 0.2.

Table 3. Total intrathoracic volumes at full inflation measured by magnetic resonance imaging

	Control	Obese	P	Obese Subdivisions	
				>80%predicted TLC (ON)	<80%predicted TLC (OR)
n	7	14		8	6
Total intrathoracic volume					
Liters	8.92 ± 0.9	8.21 ± 1.3	NS	8.87 ± 1.0	7.32 ± 1.1
%Predicted TLC	120 ± 8	116 ± 13	NS	124 ± 10	105 ± 11
Heart and vessels, liters	0.87 ± 0.2	1.10 ± 0.2	0.016	1.04 ± 0.2	1.18 ± 0.2
Fat, liters	0.23 ± 0.1	0.68 ± 0.2	<0.0001	0.69 ± 0.2	0.66 ± 0.3
Lungs (TLV)					
Liters	7.82 ± 0.8	6.43 ± 1.3	0.004	7.14 ± 0.8	5.48 ± 0.8
%Predicted TLC	105 ± 7	90.8 ± 13	0.016	99.9 ± 8	78.6 ± 8
Lungs (TLV)/total intrathoracic volume, %	88 ± 1.5	78 ± 4.2	<0.0001	80 ± 1.81	75 ± 4.5

Values are means ± SD; n, no. of subjects. P values: controls vs. obese. NS =  $P > 0.2$ .

tively (Table 3). This 4% difference compared with a 12% difference in TLC %pred measured by MBHe dilution (Table 2). These mean results conceal great between-individual variability within both groups (Figs. 2–4).

Each of the three compartments of total intrathoracic volume differed between control and obese men. By far, the largest compartment was TLV, which occupied, on average, 88% of the total intrathoracic volume in control men. Mean TLV (%pred TLC) was smaller in the obese men than in the control men ( $P = 0.016$ ).

Mean values of both mediastinal components of intrathoracic volume were larger in the obese men than in the control men (Fig. 2): mean heart and major blood vessel volume was 1.10 liter in obese vs. 0.87 liter in control men ( $P = 0.016$ ), while mean volume of intrathoracic fat (mainly pericardiac and mediastinal, but sometimes also extending over the adjacent pleural surface of the diaphragm, Fig. 1) was 0.68 liter in obese and 0.23 liter in control men ( $P < 0.0001$ ). Because of the increased mediastinal volume, the inflated lungs only occupied, on average, 78% of the total intrathoracic cavity volume in obese men.

Thus increased mediastinal volume might contribute to reduction in TLC in some of the obese men. However, mean mediastinal volume was similar in the obese subgroups with

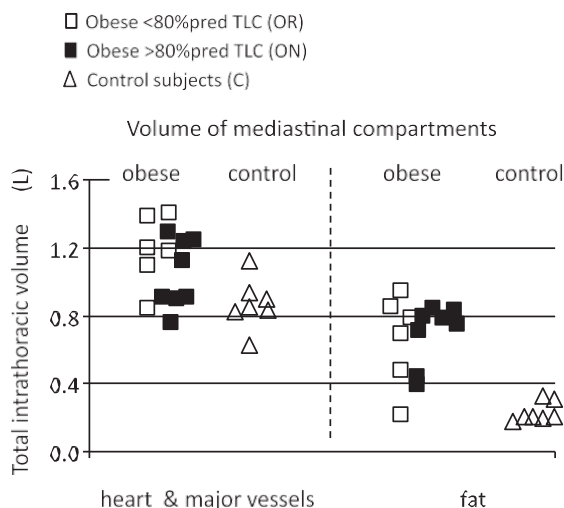


Fig. 2. Contributions of volumes of heart and major blood vessels (left) and intrathoracic fat (right) to total intrathoracic volume in control and obese men. Symbols distinguish control men from obese restrictive (OR) and obese nonrestrictive (ON) subgroups. TLC, total lung capacity.

(OR 1.84 liter) and without (ON 1.73 liter) reduced TLC ( $P = 0.56$ ). The relation between TLV and total intrathoracic volume in all 21 men is shown in Fig. 3. In the ON men, whose values of TLV overlapped those of the control men, mean total intrathoracic volume was actually slightly greater (124%pred TLC) than in the control group (120%pred TLC). In contrast, total intrathoracic volume was only 105%pred TLC in the OR subgroup. This 19%pred TLC difference in mean total intrathoracic volume between ON and OR ( $P = 0.005$ ) was the major factor accounting for the smaller TLC MBHe in the OR subgroup.

#### Comparison of Lung Volume at Full Inflation Measured by MRI and MBHe Dilution

Individual values of TLV measured by MRI were closely related to, but slightly greater than, TLC\* measured by MBHe

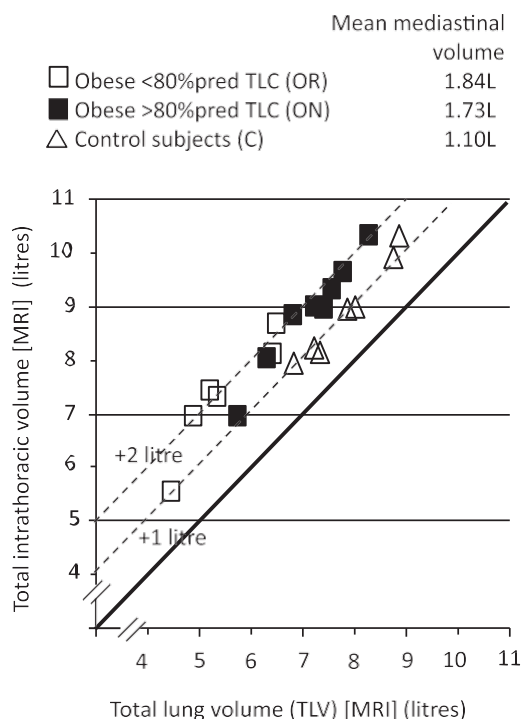


Fig. 3. Total lung volume (TLV) at full inflation plotted against total intrathoracic volume in control and obese men. The thick diagonal line is the line of identity, and the dashed lines indicate when the total intrathoracic volume is 1 or 2 liters greater than TLV. Note that many values of TLV in ON subgroup and in control men overlap.



dilution (Fig. 4). The mean volume difference (TLV-TLC\*), which reflects the volume of intrapulmonary tissue and fluid, was 0.74 liter in control and 0.54 liter in obese men (difference nonsignificant,  $P = 0.61$ ).

#### Comparison of Gas Volumes and Estimates of Intrathoracic Volumes When the Lungs Are Deflated

Because mediastinal volume was, on average, 0.68 liter larger in obese than control men, differences between control and obese men in all intrathoracic volumes were smaller than the difference in corresponding gas volumes. For example,

while mean FRC gas volume was 45%pred TLC in control and 30%pred TLC in obese men, mean intrathoracic volume at FRC was 69%pred TLC in control and 62%pred TLC in obese men (Fig. 5).

#### DISCUSSION

In this exploratory study, in obese middle-aged men, we measured total intrathoracic volume and its components at full inflation to investigate the features of restrictive lung disease (TLC <80%pred). A restrictive pattern was found in 6 of the 14 men and was associated with a smaller total intrathoracic volume. Mediastinal volume was 0.68 liter larger in obese than control men due to increase in volumes occupied by the heart and major blood vessels and by intrathoracic fat, but was similar in obese men with and without restrictive lung disease.

#### Methodology

**Subjects.** We chose men for this exploratory study of restrictive lung disease associated with obesity, because two prospective studies (6, 34) have shown that loss of VC with increase in weight is greater in men than in women. Possibly this is because men have a more central pattern of obesity than women; in our department, visceral abdominal fat measured by MRI averages 14.8% of total body fat in obese men and 8.9% in obese women (E. L. Thomas, unpublished observations).

**MRI scanning technique.** The pleural edges of the lungs were well defined during breath holding, allowing an accurate measurement of TLV. Intrathoracic fat was also clearly visu-

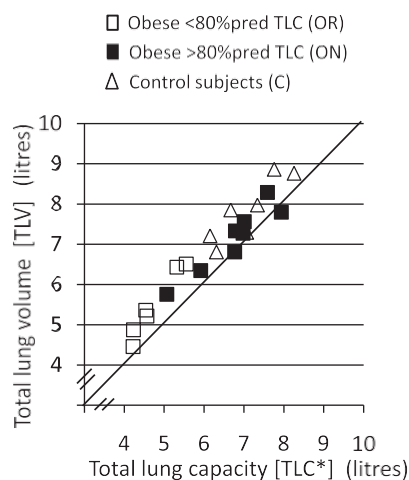


Fig. 4. Comparison of TLC measured by multibreath helium dilution (TLC\*) and TLV measured by MRI in control men. The diagonal line is the line of identity. In this comparison, measured TLC has been reduced by the estimated volume of the extrathoracic airway (see METHODS).

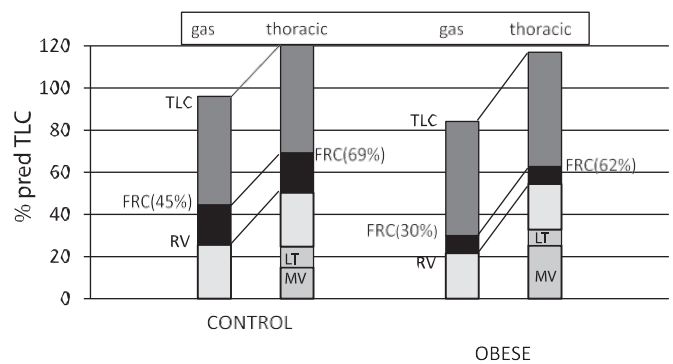


Fig. 5. Comparison of mean gas volumes and estimates of mean intrathoracic volumes (all expressed as %predicted TLC) in control and obese men. LT, lung tissue volume; MV, mediastinal volume; FRC, functional residual capacity; RV, residual volume. Increased mediastinal volume in the obese men results in the differences in intrathoracic volumes between obese and control men being smaller than the corresponding differences in gas volumes.

alized by its characteristic density. The heart and major blood vessels, including the extrapulmonary hilar vessels, were the major contributors to the remaining mediastinal compartment, which includes organs such as the esophagus. This nonvascular volume should be small and similar in control and obese men. The close correspondence between values of TLV and TLC (Fig. 4) in an individual supports the effectiveness of the "training" in breath holding at full inflation; furthermore, it suggests that helium equilibrated with true total gas volume in the obese men, even though they were supine with a very low FRC/TLC, and so probably had some airway closure during tidal breathing (15). Frequent deep inspirations were made during helium equilibration so as to allow access of helium to lung beyond any closed airways. TLV measured by imaging includes intrapulmonary tissue, fluid, and blood, as well as gas, so (TLV-TLC\*) potentially estimates lung tissue and fluid volume, albeit with limited accuracy because of the following. 1) TLV and TLC were measured in separate maneuvers, during which esophageal pressure was not measured. Hence we do not know if a comparable lung recoil pressure was achieved in all full-inflation maneuvers, nor whether glottal closure occurred during breath holding. 2) These estimates depend on the difference between two volumes, which are 8–10 times larger. Nevertheless, our mean estimate of lung tissue and fluid volume for the 21 men of 0.61 liter (0.74 liter in control men, 0.54 liter in obese men) is similar to previous estimates in healthy subjects using gas uptake of 0.61 liter (5), or by comparing volumes measured by chest radiographs at full inflation with body plethysmography of 0.72 liter (26). We had expected lung tissue volume to be larger in the obese than the control men, because, in obesity, intrapulmonary blood volume is probably larger (2, 18, 29), particularly when supine.

**Differences between supine and seated gas volumes.** There is no consistent supine change in RV, but supine values of TLC and VC in normal subjects are, on average, slightly lower (200 ml or less) than seated values (3, 21, 32, 33, 35), with the reduction being attributed to an increase in central blood volume when supine. Similar small reductions in supine TLC and VC have been shown in obese subjects (3, 32, 33, 35); indeed, previously our laboratory found that supine TLC in obese subjects, some of whom had lung restriction, was, on average, only 80 ml smaller than seated values (33). Hence we believe our results for TLC, VC, and RV also apply to seated

subjects. This is not the case for FRC. Whereas in normal subjects, FRC falls by 700–800 ml on going from the seated to the supine position (3, 21, 32, 33, 35), in severely obese subjects our laboratory (33, 35) and others (3, 32) have shown that supine falls in FRC are much smaller and may even be absent. The difference in values of FRC, FRC/TLC, and ERV between control and obese subjects shown in Table 2, therefore, would be even larger if the subjects were seated.

#### *Comparison of Supine Lung Gas Volumes in Obese Men With and Without Restriction*

Obese men had highly significant reductions in supine FRC, FRC/TLC, and ERV compared with control men. Reduction in TLC in the obese men was more variable and, when results were corrected for height differences between control and obese men, did not quite reach statistical significance vs. control subjects.

In early studies of individual patients with “morbid” obesity with hypercapnia (“Pickwickian”, or obesity hypoventilation syndrome), reduction in TLC was a prominent feature (14, 29), but was often not found in later, less selected studies of obesity (28). Recently, the relation of BMI to seated TLC and subdivisions has been clarified by Jones and Nzekwu (17), who studied 373 men and women (their results were not distinguished) whose BMI ranged from 20 to 58 kg/m<sup>2</sup>. Mean values of seated TLC, FRC, VC, ERV, and RV all declined progressively with increasing BMI, but at very different rates and with a wide scatter of results, especially for ERV and RV. The largest and most consistent reductions were in FRC and, consequently, also in ERV, which were found in mild obesity. At a BMI of 30–35 kg/m<sup>2</sup>, mean FRC was 75% and mean ERV 47% of values at BMI of 20 kg/m<sup>2</sup>; values of ERV as small as 20%pred or less were common, limiting the possibility of any further reduction at higher BMI. As a result, an exponential curve was fitted to these data. In contrast mean reductions in TLC, VC, and RV with increase in BMI were much smaller, so that group mean values remained within the normal range (TLC and VC both 88%pred, RV 90%pred), even in subjects with BMI >40 kg/m<sup>2</sup>. Our finding that obese men had large reductions in FRC, whether or not they were in the ON or the OR group, is, therefore, consistent with Jones and Nzekwu’s findings.

*Total intrathoracic volume in obesity.* In control men, the fully inflated lungs occupied, on average, 88% of the total intrathoracic volume, but in obese men only 78% because of their larger mediastinal volume, which, in the obese men, averaged 1.78 liter (25.2%pred TLC) compared with 1.10 liter (14.8%pred TLC) in the control men. We are not aware of earlier measurements of intrathoracic fat, but an increase in central blood volume was consistently noted in early studies of obesity hypoventilation syndrome, even in the absence of overt heart failure (18, 29), and has been confirmed more recently in obese subjects without any symptoms to suggest clinical heart disease (2). The mean 10% pred TLC increase of mediastinal volume in the obese compared with the control men hardly contributed to the large difference in TLC between the ON and OR groups, because mean mediastinal volume was only 0.11 liter larger in the OR than in the ON subgroup. Indeed, Fig. 3 shows that, whereas individual values of TLV largely overlap in the ON and control groups, total intrathoracic volume at a

given TLV tends to be larger in the ON individuals, perhaps suggesting the thoracic wall has “accommodated” to the larger mediastinal volume.

The major contributor to restriction of TLC in the OR group was that, while the eight ON men had a mean total intrathoracic volume at full inflation slightly larger (124%pred TLC) than the control men (120%pred), in the six OR men, mean total intrathoracic volume at full inflation was 105%pred TLC. Possibly, therefore, in some obese men, the large abdomen limits caudal movement of the diaphragm at full inflation. Recent experiments inducing acute ascites in dogs have shown that the load on the diaphragm was increased by an increase in abdominal elastance, but, in addition, the lung-expanding action of the diaphragm was impaired by reduction in its pressure-generating ability (19, 20). We are not aware of comparable studies of diaphragm function and load in human obesity.

The immediate cause of reduction in TLC is a reduction in VC (changes in RV are small and inconsistent). Reductions in VC with increase in weight have been shown in men in three prospective studies over 5–7 yr, with mean losses of forced VC (FVC) of 26 ml (6), 21 ml (7) and 17 ml (34) for each kg of weight gained. Two of these studies also studied women (6, 34) in whom losses of FVC per kg weight gain were considerably smaller. Conversely, rises in VC following reductions in weight were first reported in small studies many years ago (29, 31). In the last decade gastric surgery has become a popular method to induce large and rapid reductions in weight; so far only a few studies have reported the effects on spirometry, but in them mean FVC has consistently increased 6 mo or more after operation (22). The precise mechanism by which VC is reduced by increase in weight, why this loss of VC is larger in men than in women, and why reduction in TLC is very variable among obese men of similar age and BMI all remain uncertain.

*Reduction in FRC and RV.* The reduction in FRC and ERV in healthy subjects when lying supine is attributed to a rightward displacement of the PV curve of the relaxed chest wall, increasing its pressure at a given gas volume, and reducing relaxation volume ( $V_r$ ) (1). A comparable supine decrease in  $V_r$  would be expected in obesity. In practice, in severe obesity when supine FRC hardly falls below seated values, FRC is probably maintained above  $V_r$  as a response to expiratory flow limitation (25, 35).

Our finding of an increase in mediastinal volume in obesity potentially alters the interaction between elasticity of the chest wall and of the lungs. Classically, this interaction is related to a common volume, defined by the volume of gas contained in the lungs. When considering the pleural cavities, this convention obscures the normal difference between the volume enclosed by the parietal pleura and intrapulmonary gas volume, which arises from the tissue and fluid content (including blood) within the lungs. In intrathoracic disease, the difference between total intrapleural volume and intrapulmonary gas volume may be increased, as originally analyzed by Fenn (11) for pneumothorax, or for both pleural cavities with increase in intrapulmonary fluid, blood, or tissue volume in conditions such as interstitial lung fibrosis (12). FRC, TLC, and RV all are partly determined by active or passive characteristics of the chest wall and respiratory muscles, so their values in thoracic diseases can be fully interpreted only if chest wall volume is known or can be inferred (13).

Previously, two papers have suggested that restriction of TLC may be partially reversed by heart transplantation, due to the effects of increased heart volume in chronic heart failure (16, 23); one of these studies (16) estimated the change in heart volume following heart transplantation from chest radiographs.

In the present study, we have measured mediastinal volume in a few healthy middle-aged men. This volume, when combined with lung tissue and fluid volume, is responsible for the "normal" difference between total intrathoracic volume and total gas volume. So far, despite the wide availability of three-dimensional imaging techniques that could measure simultaneously total intrathoracic volume and TLV, we have not found any published estimates of mediastinal volume to check against our value of 1.10 liter.

The acquired increase in mediastinal volume in obesity implies that the difference between intrathoracic volume and the corresponding gas volume has increased on average by 0.68 liter in adult life. In middle-aged healthy men, chest wall compliance in the operating tidal range close to FRC averages 1.177 l/cmH<sub>2</sub>O seated and 0.161 l/cmH<sub>2</sub>O supine (10). Hence an acute increase of 0.68 liter in mediastinal volume could increase pressure exerted by the relaxed chest wall by as much as 4 cmH<sub>2</sub>O, which would have a large effect on V<sub>r</sub>. However, with a chronic increase in mediastinal volume, the elastic properties of the chest wall may show partial or even complete adaptation.

Increase in mediastinal volume may also influence the value of RV, at least in younger obese adults in whom RV is determined by a static balance between the maximum muscle pressure and the outward recoil of the passive structures of the chest wall as its volume is reduced (1). The minimum gas volume of the lung at RV may be reduced, if there is an increase in indistensible volume within the thoracic cavity. This may explain that, while gas volume at RV was smaller in the obese men than in the control men, intrathoracic volume at RV was slightly larger in the obese men than in the control men (see Fig. 5). Thus it seems possible that increase in mediastinal volume may influence the values of FRC and RV in obesity, even if it is not important in restricting TLC in obesity.

In conclusion, we found that reduction in TLC in obese men was associated with reduced expansion of the thoracic cage. Both intrathoracic fat volume and the volume of heart and major blood vessels were larger in the obese than the control men, but these volumes did not differ between obese men with and without lung restriction. Further studies are required to determine the factors impairing full expansion of the thorax in some obese men.

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#### DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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