Pulmonary Physiology and Pathophysiology in Obesity

0.132 l/cmH2O). We conclude that many severely obese supine
subjects at relaxation volume have positive Ppl throughout the chest.

Obesity is a known cause of restrictive respiratory physiology and low lung volumes. Morbidly obese individuals [body mass index (BMI) ≥ 40 kg/m²] have reduced total lung capacity (TLC), functional residual capacity (FRC), and vital capacity (VC) (6, 26). These subjects often have FRC reduced to near residual volume (RV); the reduction of FRC is even greater in the supine position (26). Such reductions in lung volume suggest elevation of pleural pressure (Ppl) in morbid obesity.

To date, the studies of respiratory restriction in the obese have focused on changes in Ppl that determine chest wall and lung compliance (Ccw, Cl) rather than estimating Ppl itself. Naimark and Cherniack (11) and later Sharp et al. (16) reported

that chest wall compliance was significantly reduced in obesity while lung compliance was normal. Subsequent studies by Hedenstierna and Santesson (5) and Suratt et al. (20) reported contrary findings of normal Ccw and decreased Cl in the obese. More recently, Pelosi et al. (13) found both Ccw and Cl to be reduced in morbidly obese subjects.

All the aforementioned studies reported changes in esophageal pressures (Pes); none reported actual values of Pes, presumably due to concern about the validity of esophageal manometry in estimating Ppl in the obese. Although esophageal balloon catheters have been used to estimate Ppl in normal subjects (3), their use in the obese has not been validated.

In this study we report values of Ppl as estimated independently by esophageal balloon and by using the relation between the airway pressure (PAO) and lung volume (Vl) during passive inflation of the lungs. We studied severely obese subjects and normal-weight controls, anesthetized and paralyzed, and tested the hypotheses that our severely obese subjects had higher Ppl than normal subjects and that Pes is a useful indicator of Ppl in obese subjects. We also related Pes to estimated Ppl, gastric pressure (Pga), and BMI and studied the compliance of the respiratory system (Crs), Ccw, and Cl.

Subjects and Methods

Subjects. Fifty morbidly obese subjects and one moderately obese subject, which we will collectively call “severely obese subjects,” and 10 nonobese subjects (BMI < 30), all with healthy lungs, were studied immediately after induction of general anesthesia for elective surgery at Beth Israel Deaconess Medical Center. The severely obese subjects had BMI ranging from 38.0 to 80.7 kg/m² (48.5 ± 8.9, mean ± SD) and were aged 20 to 69 yr (43.8 ± 11.9 yr), and 33 were female (see Supplement available with the online version of this article). Ten control subjects had BMI ranging from 19.2 to 29 kg/m² (25.2 ± 2.8 kg/m²) and were aged 21–61 yr (44.7 ± 11.4 yr), and 8 were female. Two additional subjects originally recruited as controls were not included in the analysis but are shown in the figures with distinct symbols. The research was approved by the Committee on Clinical Investigations, and subjects gave informed written consent before study.

Measurements. Subjects were studied before surgical incision and immediately after induction of general anesthesia including complete muscle relaxation using vecuronium with or without succinylcholine. Subjects were supine and mechanically ventilated with 100% O₂ with tidal volumes of 0.64 ± 0.11 liters (Supplemental Table S-1, available with the online version of this article) and no preset positive end-expiratory pressure (PEEP), although a small PEEP was present in all subjects due to ventilator characteristics. Pes and Ppl were measured using an adult esophageal balloon catheter (Ackrad Laboratories), passed by mouth or nose to position the balloon’s tip at 60 cm from

Address for reprint requests and other correspondence: S. H. Loring, Dept. of Anesthesia, Critical Care and Pain Medicine, Dana 715, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, MA 02215 (e-mail sloring@bidmc.harvard.edu).

Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

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the incisors to measure $P_{ga}$ and then withdrawn to 40 cm to measure $P_{es}$. (In 25 subjects in whom it was not possible to advance the balloon into the stomach, $P_{ga}$ was not measured.) The 10-cm-long balloon was inflated with 0.5–1.0 ml of air. $P_{ao}$ was measured at the endotracheal tube, and airflow was measured with a pneumotachometer (Fleisch pneumotachograph type 1, Metabo SA). Signals were digitized, displayed, and recorded using Windaq software and hardware (Datalab Instruments, Akron, OH).

**Threshold inflation airway pressure, $P_{ao-thr}$.** A major aim of this study was to estimate the distribution of pleural pressure surrounding the lungs. To do this, we inferred $P_{th}$ from the airway pressure needed to cause lung inflation. We reasoned that in a relaxed intubated subject with open airways, if the highest $P_{th}$ to be found in the chest is subatmospheric, then inflation should begin immediately as the airway pressure ($P_{ao}$) is raised above atmospheric pressure. By contrast, if the lowest $P_{th}$ to be found in the chest is above atmospheric pressure, the lungs would not begin to inflate until $P_{ao}$ is raised above that lowest $P_{th}$ (where the local transpulmonary pressure would first become positive). Therefore, the $P_{ao}$ at which the lung volume first begins to increase is an approximate indicator of the lowest $P_{th}$ to be found in the chest at $V_{rel}$. To estimate how much $P_{ao-thr}$ would be increased above atmospheric pressure even with all the balloons inflated, $P_{ga}$ was not measured. In all subjects in whom it was possible to pass the incisors to measure $PGa$ and then withdrawn to 40 cm to measure $P_{es}$. (In 25 subjects in whom it was not possible to advance the balloon into the stomach, $P_{ga}$ was not measured.) The 10-cm-long balloon was inflated with 0.5–1.0 ml of air. $P_{ao}$ was measured at the endotracheal tube, and airflow was measured with a pneumotachometer (Fleisch pneumotachograph type 1, Metabo SA). Signals were digitized, displayed, and recorded using Windaq software and hardware (Datalab Instruments, Akron, OH).

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**Threshold inflation airway pressure, $P_{ao-thr}$** The protocol is illustrated in Fig. 1. We measured $P_{ga}$ and $P_{es}$ during five or more tidal mechanical breaths. Then we disconnected the subject from the ventilator for 10–15 s to allow deflation to $V_{rel}$. We connected an Ambu bag to the endotracheal tube, and increased $P_{ao}$ until $P_{ga}$ was 0.5 at 3 cmH$_2$O (mean = 1.5 cmH$_2$O) until the bag was nearly empty. The deflation to $V_{rel}$ and subsequent quasi-static inflation for determination of $P_{ao-thr}$ were repeated three times with at least one intervening minute of mechanical ventilation (Fig. 1A).

**Analysis.** We measured $P_{ao}$ and $P_{es}$ and $P_{ga}$ at end expiration ($P_{es-ee} \cdot P_{ga-ee}$) and at end inspiration ($P_{es-ei} \cdot P_{ga-ei}$) averaged over five consecutive tidal breaths. We also measured $P_{es}$ at $V_{rel}$ ($P_{es-rel}$). Dynamic compliance of the respiratory system ($C_{res}$) was defined as average tidal volume change ($\Delta V_{L}$, found by integration of flow) divided by the average difference in $P_{ao}$ from end inspiration to end expiration at instants of zero flow: $C_{res} = \Delta V_{L}/\Delta P_{ao}$. Similarly, the dynamic compliance of the lung ($C_{L}$) was defined as $C_{L} = \Delta V_{L}/\Delta P_{L}$, where $P_{L}$ = transpulmonary pressure = $P_{ao} - P_{es}$, and dynamic compliance of the chest wall ($C_{CW}$) as $C_{CW} = \Delta V_{L}/\Delta P_{CW}$.

To explore the mechanism of obesity-related restriction, we compared the elastance of the respiratory system ($E_{RS} = 1/C_{RS}$) with its additive components, lung and chest wall elastance ($E_{L} = 1/C_{L}$ and $E_{CW} = 1/C_{CW}$; $E_{RS} = E_{L} + E_{CW}$).

**Statistics.** We used linear regression with correlation analysis to test the associations between $P_{ao-thr}$, $P_{es-rel}$, BMI, and $P_{ga}$ and Student’s $t$-test to compare the compliance and elastance values between obese and control groups. Statistical significance was assumed for $P < 0.05$. Results are reported as means ± SD.

**RESULTS**

$P_{ao-thr}$ ranged from 0.6 to 14.0 cmH$_2$O (3.1 ± 3.0 cmH$_2$O) in the obese group and from 0.2 to 0.9 cmH$_2$O (0.4 ± 0.2 cmH$_2$O) in the control group ($P < 0.0001$). In most of our obese subjects (22 female and 15 male), $P_{ao-thr}$ was above 1.3 cmH$_2$O indicating that most of the airways were closed and/or $P_{th}$ surrounding most of the lung was above atmospheric pressure at $V_{rel}$. By contrast, all control subjects had $P_{ao-thr}$ below 1.3 cmH$_2$O, indicating that most of the airways were open and $P_{th}$ was subatmospheric surrounding most of the lung at $V_{rel}$.

$P_{es-rel}$ ranged from 3.0 to 25.7 cmH$_2$O (12.5 ± 3.9 cmH$_2$O) in the severely obese group and from 0.7 to 12.2 cmH$_2$O (6.9 ± 3.1 cmH$_2$O) in the control group ($P < 0.0001$). In all subjects, there was a significant correlation between $P_{es-rel}$ and $P_{ao-thr}$ ($R^2 = 0.16, P = 0.0015$, Fig. 2) and a weak correlation in the obese group analyzed separately ($R^2 = 0.086, P = 0.0363$).

In the 30 obese subjects in whom it was possible to pass the balloon into the stomach, $P_{ga-ee}$ ranged from 6.7 to 17.0 cmH$_2$O (11.5 ± 2.8 cmH$_2$O). $P_{ga}$ and $P_{es}$ were well correlated in all subjects at end expiration and end inspiration ($R^2 = 0.44, P < 0.0001$ and $R^2 = 0.39, P < 0.0001$ respectively, Fig. 3) and in the obese group analyzed separately ($R^2 = 0.17, P = 0.0225$ and $R^2 = 0.13, P = 0.0470$).

$C_{RS}$ in the severely obese group was lower than in the controls ($P < 0.0001$, Table 1). $C_{CW}$ in the obese group was not statistically different from values in the control group (Table 1), whereas $C_{L}$ was substantially lower in obese than in controls ($P = 0.0016$, Table 1). Respiratory system elastance ($E_{RS}$), which is the sum of $E_{L}$ and $E_{CW}$, was strongly correlated with $E_{L}$ in all subjects ($R^2 = 0.91, P < 0.0001$, Fig. 4) and in the obese group ($R^2 = 0.90, P < 0.0001$), whereas $E_{RS}$ was not significantly correlated with $E_{CW}$. In all subjects, neither $P_{es-rel}$ nor $P_{ga-ee}$ was correlated with $E_{CW}$. However, both $P_{es-rel}$ and $P_{ga-ee}$ were positively correlated with both $E_{L}$ and $E_{RS}$ ($R^2 = 0.17, P = 0.0092$).

In all subjects, BMI was positively correlated with $E_{RS}$ ($R^2 = 0.23, P < 0.0001$) and $E_{L}$ ($R^2 = 0.20, P < 0.0003$) but not with $E_{CW}$. In the obese subjects, neither $P_{ao-thr}$ (Fig. 5) nor $P_{es-rel}$ was correlated with BMI. When the BMI range was expanded to include the controls, a weak correlation was found for $P_{ao-thr}$ ($R^2 = 0.068, P = 0.0425$) and a stronger correlation for $P_{es-rel}$ ($R^2 = 0.26, P < 0.0001$).

To explore the mechanism leading to high $P_{ao-thr}$, we analyzed data obtained during inflation of the lung with the Ambu bag. We reasoned that in subjects with low $P_{ao-thr}$ the
inflation would begin with open airways, and the quasi-static inflation $P_{AO}-V_L$ curve would be relatively linear, whereas in those obese subjects with high $P_{AO}$-Thr, inflation would begin with many airways closed, and the quasi-static inflation $P_{AO}-V_L$ curve would exhibit the effects of recruitment after prior airway closure. Comparing the quasi-static inflation $P_{AO}-V_L$ curves from the obese subjects with the five highest and five lowest $P_{AO}$-Thr values, we found that in the lowest $P_{AO}$-Thr group (Fig. 6A), the inflation $P_{AO}-V_L$ curves appear almost linear above $V_{Rel}$, consistent with open airways in a

Fig. 1. A: typical data from one experiment, illustrating the protocol (see text for explanation), showing airway pressure ($P_{AO}$), gastric pressure ($P_{Ga}$), and esophageal pressure ($P_{Es}$). Note the pressure rise when the balloon is withdrawn from stomach into the lower esophagus. B: third quasi-static inflation in A with expanded time scale and volume channel added. The gradual rise in $P_{AO}$ above the threshold airway pressure ($P_{AO}$-Thr) causes lung inflation. $P_{AO}$-Thr is 7.3 cmH2O in this example. (The threshold volume change of 10 ml is not visible at this scale.)

Expanded in Fig. B
pleural pressure in supine subjects have ignored the resting “baseline” values of PEs, reporting only changes in PEs.

This is also the first study to estimate PPl in obese subjects by a method independent of PEs. The correlation between PEs-Rel and PAO-Thr suggests that both measurements can be used to estimate the likelihood of high effective PPl in obese supine subjects. However, although PEs and PAO-Thr are correlated, they differ substantially and variably. What could explain this difference? First, PAO-Thr is thought to be higher than PPl in the supine posture (7, 25). The esophagus is roughly midway between the ventral and dorsal boundaries of the thoracic cavity, and in the supine posture, there is a hydrostatic increase in pressure within the mediastinum due to the weight of the heart and mediastinal tissues above. Therefore, PAO-Thr is probably higher than PPl surrounding the lung at the same height in thorax, a discrepancy estimated to be ~5 cmH2O (25). Second, the hydrostatic pressure gradient in the pleural space could cause PAO-Thr (i.e., the lowest pleural pressure surrounding a substantial portion of the lung at VRel plus any opening pressure. In summary, PAO-Thr and PEs-Rel are correlated, although hydrostatic pressure gradients in the mediastinum and pleural space and the opening pressure of the collapsed airways weaken the correlation.

The second major finding is that, compared with control subjects, our severely obese subjects are characterized by lower CRS and CL, whereas CCW is usually normal. This finding differs from those of Naimark and Cherniak (11) and Sharp et al. (16), who measured compliance while subjects breathed spontaneously or relaxed respiratory muscles voluntarily. Both studies had reported normal CI with low CCW in obesity. However, more recent studies during muscle paralysis (5) or with confirmed diaphragm relaxation (20) reported normal CCW in obesity, suggesting that differences in CCW were due to the experimental method. Van Lith et al. (23) investigated this possibility by comparing elastance in six healthy obese subjects both during voluntary muscle relaxation and during anesthesia with paralysis. They found higher ERS and ECW during voluntary relaxation than during paralysis, suggesting that incomplete relaxation in early studies could have contributed to lower CCW in the obese (23). By exception, Pelosi et al. (13) found both CCW and ECW during voluntary relaxation than during paralysis, suggesting that incomplete relaxation in early studies could have contributed to lower CCW in the obese (23). By exception, Pelosi et al. (13) found both CCW and ECW during voluntary relaxation than during paralysis, suggesting that incomplete relaxation in early studies could have contributed to lower CCW in the obese (23). By exception, Pelosi et al. (13) found both CCW and ECW during voluntary relaxation than during paralysis, suggesting that incomplete relaxation in early studies could have contributed to lower CCW in the obese (23).

It is possible that ventilation with 100% oxygen in our study could have contributed to development of atelectasis. A recently completed study suggested that atelectasis is due to the weight of the heart and mediastinal tissues above, and not due to the weight of the abdomen. This finding differs from those of Naimark and Cherniak (11) and Sharp et al. (16), who measured compliance while subjects breathed spontaneously or relaxed respiratory muscles voluntarily. Both studies had reported normal CI with low CCW in obesity. However, more recent studies during muscle paralysis (5) or with confirmed diaphragm relaxation (20) reported normal CCW in obesity, suggesting that differences in CCW were due to the experimental method. Van Lith et al. (23) investigated this possibility by comparing elastance in six healthy obese subjects both during voluntary muscle relaxation and during anesthesia with paralysis. They found higher ERS and ECW during voluntary relaxation than during paralysis, suggesting that incomplete relaxation in early studies could have contributed to lower CCW in the obese (23). By exception, Pelosi et al. (13) found both CCW and ECW during voluntary relaxation than during paralysis, suggesting that incomplete relaxation in early studies could have contributed to lower CCW in the obese (23). By exception, Pelosi et al. (13) found both CCW and ECW during voluntary relaxation than during paralysis, suggesting that incomplete relaxation in early studies could have contributed to lower CCW in the obese (23).
on 100% oxygen (~10 min) argues against the primary role of atelectasis in reducing CL in the obese.

Another possibility is that CL is lower in obese subjects because the positional artifact that increases PEs in supine subjects is volume dependent (7). The importance of this artifact is said to decrease during inflation because upward movement of the ventral thorax lifts the heart and mediastinal contents, which no longer rest as heavily on the esophagus and balloon (7). However, the artifactual reduction in PEs during inflation would cause the apparent elastance of the lung to increase and that of the chest wall to decrease by the same amount, so the sum of these elastances, which is ERS, would not be altered. Therefore, the strong correlation of respiratory system elastance, which is independent of PEs, with lung elastance (R² = 0.8962) argues against this explanation and suggests that the increase in ERS is caused by a real increase in EL. In addition, the above artifact could cause a downward concavity of the PEs-VL curve as the positive pressure artifact in PEs decreased during inflation (see rationale and depiction in Ref. 7). We examined the quasi-static inflation curves of chest wall (PEs-VL) curves) in those subjects pictured in Fig. 6B and found no hint of the decreasing compliance that might be predicted by this mechanism (7).

The fact that CCW is normal in obese subjects is consistent with “mass loading” of the chest wall rather than “stiffening of the chest” by elastic loading, as demonstrated experimentally by Sharp et al. (15).

Model of P-V curves in obesity. Another mechanism whereby high Pp could cause low compliance of the lung and respiratory system is shown schematically in Fig. 7. In Fig. 7A, pressure-volume (P-V) curves are drawn for a normal lung and chest wall, and the respiratory system P-V curve was constructed by adding the pressures across lung and chest wall. FRC (taken as equal to VRel) is the volume at which lung and chest wall recoil pressures are equal and opposite. In this depiction, the normal lung is shown as having a region of low compliance and stiffening at low volumes where airway closure occurs at negative transpulmonary pressures. This region of the inflation P-V curve of normal lungs is seldom observed in vivo, because normally transpulmonary pressures are not statically negative, especially in upright subjects (14). However, this behavior is observed routinely in experimental preparations, for example when excised lungs are exposed to sustained negative PAO (24). Stiffening of the lungs at very low volumes has also been demonstrated in healthy breath-hold divers after they empty their lungs below residual volume by employing glossopharyngeal exsufflation (8).

Figure 7B illustrates the possible effects of an increase in extrapulmonary volume, for example fat, within the chest wall or “mass loading” (15). The chest wall P-V curve as drawn exhibits higher pressures at any lung volume without being stiffer (i.e., without a decrease in slope), consistent with our observations of normal CCW and high PEs in many obese subjects. The volumes of intra-abdominal and mediastinal fat increase in obesity (9), which could cause the chest wall to contain more volume and the lung to be smaller than normal at VRel, making the pleural pressure more positive. Since the normal chest wall curve stiffens at low volumes, largely due to developing tension in the diaphragm (17), the chest wall curve becomes more compliant as chest wall volume increases. Thus increasing the volume of fat within the chest wall could...
actually increase its compliance over much of the vital capacity.

In the resulting respiratory system P-V curve in Fig. 7B, FRC has decreased to a lung volume near the former RV, where the lung’s P-V curve is stiffened by small airway closure, a phenomenon that causes the respiratory P-V curve to exhibit a downward convexity (24) similar to that observed by Pelosi et al. (13) in anesthetized obese subjects.

This theoretical analysis is consistent with the quasi-static inflation PAO-VL curves of the obese subjects with the five highest and five lowest PAO-Thr values (Fig. 6). In the lowest PAO-Thr group, the inflation PAO-VL curves were nearly linear above VRel, consistent with most of the airways being open and PPl surrounding most of the lung being at or below atmospheric pressure (Fig. 6A). Increasing airway pressure caused inflation. By contrast, in the group with highest PAO-Thr, the PAO-VL curves have a “knee” or region of downward convexity above VRel, consistent with pleural pressure surrounding most of the lung being above atmospheric pressure, causing closure of most small airways at VRel. As PAO increased, initially there was little inflation until the airways opened and positive pleural pressure was exceeded, enabling progressive recruitment of lung regions until the PAO-VL curve followed a linear trajectory similar to those in the low PAO-Thr group.

During spontaneous breathing, positive end-expiratory alveolar pressure, known as intrinsic PEEP (PEEPi), is greater in obese subjects and is increased by the supine posture (12). PEEPi constitutes a threshold load for inspiration, increasing the work of breathing and increasing the dynamic elastance of the lung during tidal ventilation. Our findings that dynamic Ei and ERS were positively correlated with PEs-Rel and PGa-EE suggest that high pleural pressures in the obese reduce the FRC, lowering expiratory flow rates, increasing PEEPi, and reducing the measured dynamic lung compliance.

As expected, Pgas was elevated in most of our obese subjects. Assuming the equivalence of Pgas and bladder pressure in assessing intra-abdominal pressure (IAP) (1), and using reference values of the World Congress on Abdominal Compartment Syndrome (10), we found 23 of 30 obese subjects (76%) had IAP greater than normal (Pgas ≥ 10 cmH2O), and three of them (all female) had IAP in the range of abdominal hypertension (Pgas ≥ 16.3 cmH2O).

PGas and PEs were correlated at end expiration and end inspiration in all subjects (Fig. 3) and in the obese group, as was reported in ventilated patients by Talmor et al. (21). However, the correlation is not very strong for several reasons. The distal esophagus is lower than the gastric fundus in supine subjects, causing a gravitational pressure gradient that raises...
P_Es relative to P_Ga to differing degrees among subjects. In addition, there may be passive tension in the diaphragm in some subjects reducing P_Es relative to P_Ga. Finally, the aforementioned effects of the mediastinal contents pressing on the esophagus contribute variability and weaken the correlation between P_Es and P_Ga.

In obese and control subjects combined, there was a weak correlation of P_AO-Thr with BMI and a stronger correlation of P_Es with BMI. However, contrary to expectation, we found no correlation between BMI and P_AO-Thr (Fig. 5) or P_Es in our severely obese subjects, suggesting that obesity, per se, is not predictive of high pleural pressure. The question whether the pattern of obesity (abdominal vs. peripheral) might affect the levels of PAO-Thr and/or PEs-Rel in obese subjects.

elevation of PPl was tested in the final 13 obese subjects in pattern of obesity (abdominal vs. peripheral) might affect the

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None of the authors has any financial interest that could be affected by the subject of this report. No conflicts of interest are declared by the authors.

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