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Contribution of the Closure of Pulmonary Units to Impaired Oxygenation during Anesthesia

Norman A. Bergman, M.D., and Ying K. Tien, M.D.†*

Associations between airway closure, alveolar-arterial oxygen tension difference ($A\text{-}aD_{O_2}$), and positive end-expiratory pressure (PEEP) were investigated in anesthetized, paralyzed, artifically ventilated patients. The difference between closing capacity (CC) and functional residual capacity (FRC) was measured with a modified standard technique using a bolus of N_2 to detect airway closure in denitrogenated patients. At $F_{I_{O_2}} = 0.4$ during anesthesia before application of PEEP, $A\text{-}aD_{O_2}$ was larger than expected in comparable conscious subjects and increased at about 1 mmHg/yr of age. CC was below FRC in young subjects but above FRC in older subjects, the two coinciding at about age 43 yr. Thus, during anesthesia both $A\text{-}aD_{O_2}$ and CC-FRC increased with age. The proximity and point of coincidence of CC and FRC suggested that CC is reduced during anesthesia.

In patients whose CC exceeded FRC, imposition of PEEP estimated to be sufficient to elevate FRC above CC decreased $A\text{-}aD_{O_2}$ to a level comparable to that in patients exhibiting airway closure below FRC without PEEP. Patients in whom CC was initially below FRC failed to improve oxygenation with PEEP. At least half of the decrease in $A\text{-}aD_{O_2}$ associated with application of PEEP persisted for 20–30 min after the withdrawal of PEEP, although the withdrawal resulted in an immediate recurrence of airway closure above FRC. The authors conclude that closure of pulmonary units operates in some circumstances to contribute to pulmonary dysfunction in anesthetized patients but is neither the only nor necessarily the most important such mechanism. (Key words: Lung: airway closure; closing capacity; closing volume. Oxygen: gradients. Ventilation: Positive end-expiratory pressure.)

CLOSURE OF PULMONARY UNITS as a consequence of changes in the balance of elastic forces acting on the lung or dynamic compression of conducting air passages has been suggested as an important mechanism contributing to decreasing Pa_{O_2} with advancing age and in lung disease.[1,2] In any individual, the relative contribution of this mechanism to genesis of arterial hypoxemia is determined by the relation between the lung volume at which closure of pulmonary units begins (closing capacity [CC]) and the resting end-expiratory lung volume (functional residual capacity [FRC]). Craig and associates nicely illustrate how hypoxemia might appear and intensify as tidal volume and FRC descend from above to around to below CC.[3] Reduction in FRC has been documented repeatedly as an almost inescapable consequence of induction of general anesthesia in the supine patient.[4,5] Increased alveolar-arterial oxygen tension difference ($A\text{-}aD_{O_2}$) with lower than expected Pa_{O_2} also characterizes the anesthetized state.[6,7] The obvious possibility that the pulmonary dysfunction observed during anesthesia might be attributed to a change in the relationship of CC and FRC has been investigated previously with conflicting results.[8–11] Also, attempts to elevate Pa_{O_2} during anesthesia by increasing end expiratory lung volume to eliminate this mechanism using positive end-expiratory pressure (PEEP) have been disappointing and inconsistent.[10,12]

In an earlier preliminary study of airway closure and anesthesia, we demonstrated an age-related relationship between CC and FRC.[13] We reported that the age at which CC and FRC coincided in supine anesthetized patients was identical to that reported by others in conscious subjects.[1] In the present study, examination of airway closure during anesthesia has been extended in a larger series of patients in an attempt to clarify the relationship between age, CC-FRC relationship and Pa_{O_2} during anesthesia. The hypothesis that improvement in oxygenation of patients during anesthesia with use of PEEP should occur primarily in those in whom closure of lung units occurs within or above tidal breathing (*i.e.*, CC > FRC) also was tested.

Methods

Subjects of this study were 36 consenting patients scheduled for elective surgery under general anesthesia who were free from or had minimal cardiopulmonary disease but without associated physical or radiographic stigmata. The study was approved by our institutional Human Research Committee. Premedication, selection, and administration of anesthesia were done by anesthesiologists not involved in the study and varied among patients in accord with accepted clinical practices at our institution. Common relevant features of anesthesia in all subjects included presence of a tightly fitting cuffed

* Professor of Anesthesiology.

† Assistant Professor of Anesthesiology.

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Dr. Tien's present address is the Department of Anesthesiology, University of California at Irvine, Irvine, California.

Address reprint requests to Dr. Bergman: Department of Anesthesiology, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, Oregon 97201.

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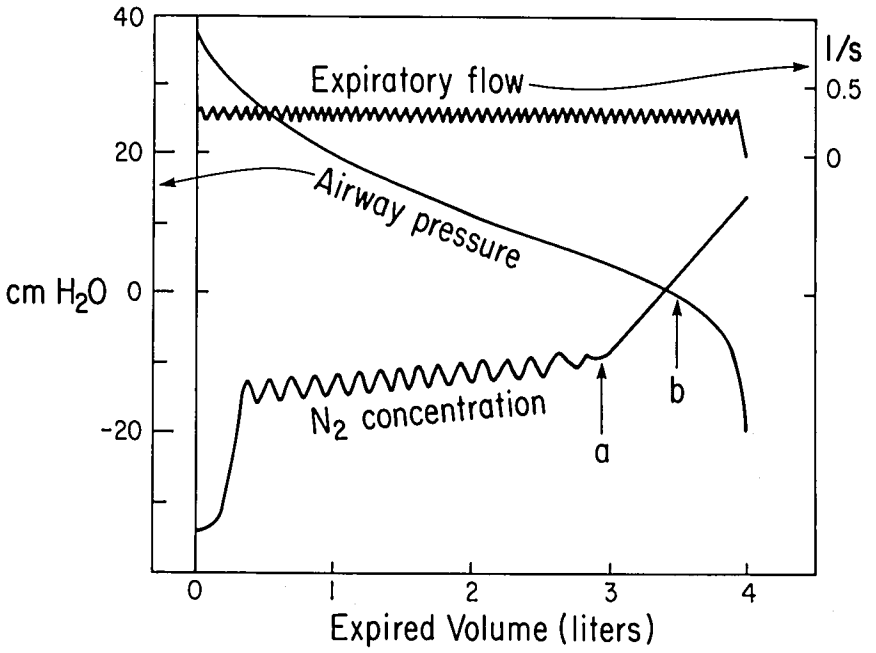

FIG. 1. A schematic representation of the oscilloscopic tracings, showing airway pressure, expiratory flow rate, and N_2 concentration as functions of expired volume during a slow lung deflation. *Arrow a* points to the volume location where a sudden rise in N_2 concentration occurred (*i.e.*, CC) and, *arrow b*, where airway (transrespiratory) pressure passed through zero (*i.e.*, FRC). CC-FRC therefore can be estimated readily without separate measurements of CC and FRC. The airway pressure at *arrow a*, about 5 cmH_2O in this example, represents the minimum PEEP estimated to bring FRC above CC. Absolute nitrogen concentrations are not indicated because of the uncertainty of these values in the presence of halogenated anesthetics.

endotracheal tube, complete neuromuscular paralysis with pancuronium, the supine position, and a continuously monitored $F_{I_{O_2}}$ of 0.40 ± 0.005 (balance nitrous oxide, nitrous oxide and halothane, or nitrous oxide and enflurane). All were artifically ventilated at a tidal volume of 10 ml/kg at a rate of 10/min, and all measurements were made during surgery.

Following 30–40 min of anesthesia, a control arterial blood specimen was obtained and analyzed immediately for $P_{a_{O_2}}$, $P_{a_{CO_2}}$, and pH_a with a Corning model 165 blood–gas analyzer. Then two or three determinations of closing volume were done using a bolus technique with nitrogen as the foreign tracer gas, as previously described.[13] Subjects were disconnected from the anesthesia system and connected to the measuring circuit. Subjects' lungs initially were evacuated to a transrespiratory pressure of −20 cmH_2O (which in this study was arbitrarily considered residual volume [RV]). At this point, 150–200 ml air was introduced into the lung. Rotation of a fourway tap placed the lungs in continuity with an oxygen-filled 7-l syringe (Research Instrument Services, Oregon Health Sciences University), whose piston was moved by rotation of a linear actuator (Model 3-012, Barry Controls, Watertown, Massachusetts). The cylinder on both sides of the piston was gas tight, and the compartment of the syringe not connected to the patient was connected to a 10-l waterless spirometer (Wedge® Spirometer, Model 270, Med-Science Electronics, St. Louis, Missouri). Thus volume change and flows in and out of lungs produced by motion of the piston could be reproduced and determined from the output of the volume and flow transducers of the spirometer.

After introduction of the air bolus, the subjects' lungs were inflated slowly with oxygen from the giant syringe to a transrespiratory pressure of +40 cmH_2O (which, in this study, arbitrarily was considered total lung capacity [TLC]). We then deflated the lungs to RV at a flow rate of 0.25–0.4 l/s. In addition to volume and flow measured with the Wedge Spirometer, transrespiratory pressure and nitrogen concentration at the endotracheal tube were measured by a pressure transducer and Nitrogen Analyzer (Nitralyzer®, Model 505, Med-Science Electronics). During the controlled exhalation, transrespiratory pressure, expiratory flow rate, and exhaled nitrogen concentration were recorded continuously as a function of exhaled volume using a storage oscilloscope (Model 5103N, Tektronix, Beaverton, Oregon), and the image on the oscilloscope screen was photographed and retained as the experimental record (fig. 1). In addition, the image was inspected to determine the relationship between onset of airway closure and FRC. Point of airway closure was identified as the first convincing departure of the exhaled nitrogen recording from the "alveolar plateau."[2] FRC was identified as the point where transrespiratory pressure was zero. Thus, CC-FRC relationship could be determined directly from the recording, and if onset of airway closure occurred above FRC, the amount of pressure at the airway opening required to raise FRC above CV also could be estimated, since the pressure-volume curve of the respiratory system had been inscribed during the deflation. Measured gas volumes were corrected to BTPS.

Artificial ventilation then was resumed at the previous frequency, tidal volume, and $F_{I_{O_2}}$. Patients in whom airway closure occurred above FRC received PEEP of suf-

ficient magnitude estimated to be capable of raising FRC above CC, using either 5, 7.5, or 10 cm H_2O Boehringer PEEP valves (Boehringer Laboratories, Inc., Wynnewood, Pennsylvania) in the expiratory limb of the anesthesia circuit. Patients in whom airway closure occurred below FRC received 5 cmH_2O PEEP. After 20–30 min of ventilation employing PEEP, arterial blood gases again were obtained and PEEP was discontinued. In some patients, if time permitted, closing volume determinations were repeated immediately after termination of PEEP. Also, if time permitted, an additional arterial blood gas specimen was obtained 20–30 min after discontinuation of PEEP.

Alveolar oxygen tension (PA_{O_2}) was calculated using a simplified alveolar gas equation with an assumed respiratory exchange ratio of 0.8:

$$PA_{O_2} = PI_{O_2} - Pa_{CO_2}/0.8$$

and A-aD_{O_2} was calculated. All oscilloscopic photographs were copied xerographically in random sequence without patient identification and were analyzed "blindly" and independently by four individuals experienced in interpretation of closing volume measurements. Each CC-FRC result is the mean of a duplicate or triplicate measurement as interpreted by the four analysts. CC-FRC data from 15 additional patients (ages 17–73 yr) from an earlier study done under identical circumstances[13] were included in the analysis of (CC-FRC) as a function of age, but information on blood gases and effects of PEEP were not available for these subjects.

Relationships between groups of data were evaluated and tested for statistical significance using Student's *t* test, paired or independent as appropriate, and also least-squares linear regression. A *P* value less than 0.05 was designated as the level of significance, and 95% confidence limits are given for appropriate derived parameters.[14] Apparent unreasonably extreme values were examined using a test for outlying observations and were discarded if the probability was greater than 95% that they were derived from different populations than the other values under consideration.‡

Results

Data derived from study of 51 patients are presented. Numbers of observations available for the different comparisons to be made varied for several reasons. As mentioned previously, 15 patients from an earlier series lacked blood–gas data. In others, surgery was completed sooner than anticipated, so a complete set of observations was not possible. One study was aborted prematurely because of a clinically unacceptable 30 mmHg drop in arterial pressure associated with initiation of PEEP. Two values for CC-FRC and one value for change in A-aD_{O_2} with PEEP were discarded after statistical evaluation as outlying values.

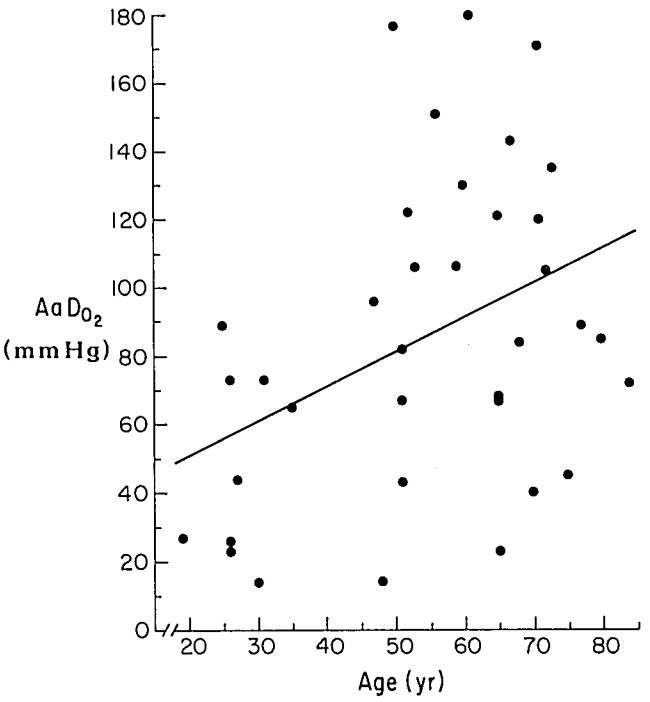

FIG. 2. A-aD_{O_2} in 36 subjects at FI_{O_2} of 0.40 prior to the measurement of airway closure and application of PEEP as a function of age. Equation relating the variables was: A-aD_{O_2} = 1.0 × age + 30.5 mmHg. The association between the variables was weak (r = 0.399) but significant ($P < 0.05$).

Alveolar ventilation remained essentially constant throughout all phases of the study. In 17 patients in whom blood gases were measured before, during, and after application of PEEP, Pa_{CO_2} was 30.6 ± 1.3, 30.6 ± 1.3, and 31.3 ± 1.6 mmHg respectively.

There was a significant association between advancing age and A-aD_{O_2} at FI_{O_2} = 0.40 ± 0.005, such that in the 36 subjects from whom control blood samples were obtained:

$$A\text{-}aD_{O_2} = 1.0 \times \text{age (yr)} + 30.5 \text{ mmHg}$$

$$(r = 0.339 \quad P < 0.05) \qquad (1)$$

See figure 2. Upper and lower 95% confidence limits for the coefficient of age were 1.8 and 0.2.

In 49 subjects the difference between the lung volume at which closure of pulmonary units was first detectable (closing capacity or CC) and resting end-expiratory position of the lung (FRC) increased with advancing age (fig. 3). The relationship between the two variables was:

‡ Grubbs FE: Sample criterion for testing outlying observations. Annals of Mathematical Statistics 21:27–58, 1950 (Discussed in Statistics Pac for Hewlett Packard Calculator, model 9810A.HP part #9810-70800).

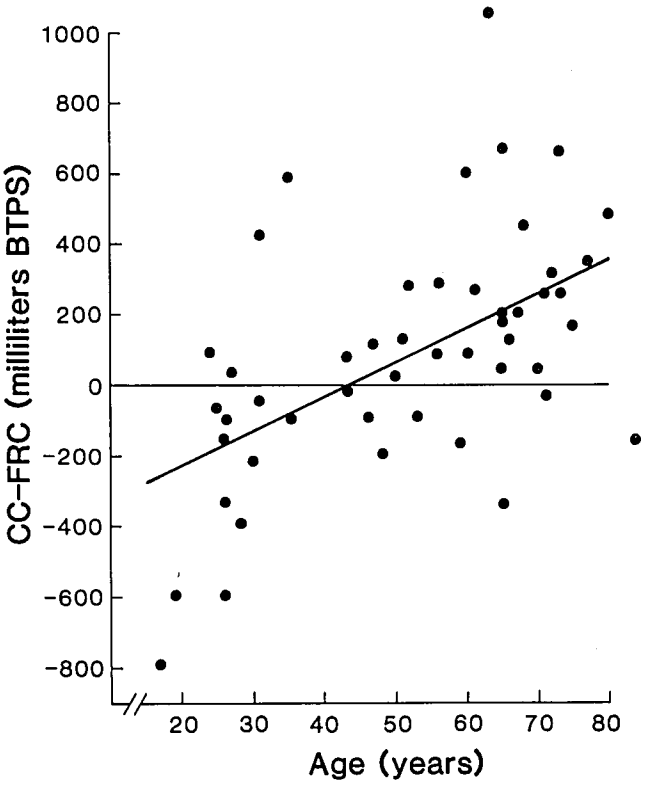

FIG. 3. CC-FRC as a function of age. Of the 51 patients, 36 are from the present study and 15 from a previous study using identical techniques. The regression equation is: CC-FRC = 9.9 × age − 430 ml. Again, there is a weak (r = 0.54) but highly significant ($P < 0.005$) association between the variables.

$$\text{CC-FRC} = 9.9 \times \text{age (yr)} - 430 \text{ ml}$$
$$(r = 0.54 \quad P < 0.005) \qquad (2)$$

The upper and lower 95% confidence limits for the coefficient of age were 15.0 and 5.4. Statistically, closing capacity and FRC would be expected to coincide at age 43.4 yr in this group of anesthetized patients.

$A\text{-}aD_{O_2}$ during anesthesia increased as CC-FRC became larger. The observed relationship in 34 patients when CC-FRC is expressed in milliliters was:

$$A\text{-}aD_{O_2} = 0.1 \times \text{CC-FRC} + 82 \text{ mmHg}$$
$$(r = 0.52 \quad P < 0.005) \qquad (3)$$

See figure 4. (A virtually identical equation could be obtained by simultaneous algebraic solution of equations [1] and [2] above). Ninety five per cent confidence limits for the coefficient of CC-FRC lay between 0.16 and 0.04. Mean $A\text{-}aD_{O_2}$ during the initial control period at ZEEP for all patients in this series whose closing capacity was below FRC (n = 14) was 65.1 mmHg (SD = 43.8). In patients whose closing capacity was above FRC (n = 20), mean $A\text{-}aD_{O_2}$ was 103.5 mmHg (SD = 42.1). The difference between the means of these two groups were statistically significant ($P < 0.02$).

The change in $A\text{-}aD_{O_2}$ during imposition of the prescribed standardized amount of PEEP was significantly related to CC-FRC:

$$\Delta\ A\text{-}aD_{O_2} = -0.031 \times \text{CC-FRC} - 13.5 \text{ mmHg}$$
$$(r = -0.48 \quad P < 0.01) \qquad (4)$$

See figure 5. Upper and lower 95% confidence limits for the coefficient of CC-FRC in this equation were −0.008 and −0.055, respectively. Imposition of 5 cmH_2O PEEP in 10 patients whose closing capacity was below FRC caused $A\text{-}aD_{O_2}$ to decline from a mean of 58 mmHg to 43 mmHg, and this decrease was not statistically significant. In 19 patients whose closing capacity was above FRC, application of the indicated amount of PEEP lowered mean $A\text{-}aD_{O_2}$ from 101 to 81 mmHg, a significant decrease ($P < 0.01$).

Patients whose closing capacity was below FRC had a mean $A\text{-}aD_{O_2}$ of 65 (SD 43.7) mmHg when breathing at ZEEP. When patients who had initial closing capacities above FRC were made to breathe at their prescribed levels of PEEP, their mean $A\text{-}aD_{O_2}$ was 82 (SD 37.9)

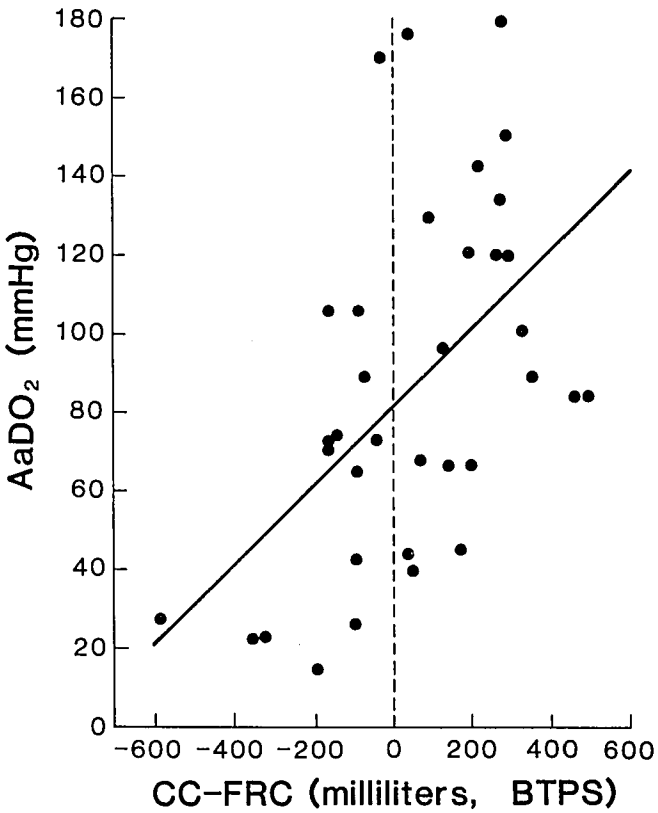

FIG. 4. $A\text{-}aD_{O_2}$ as a function of CC-FRC in 34 subjects at FI_{O_2} = 0.40. The variables were related by the equation: $A\text{-}aD_{O_2}$ = 0.1 × CC-FRC + 82 mmHg. r = 0.52, $P < 0.005$.

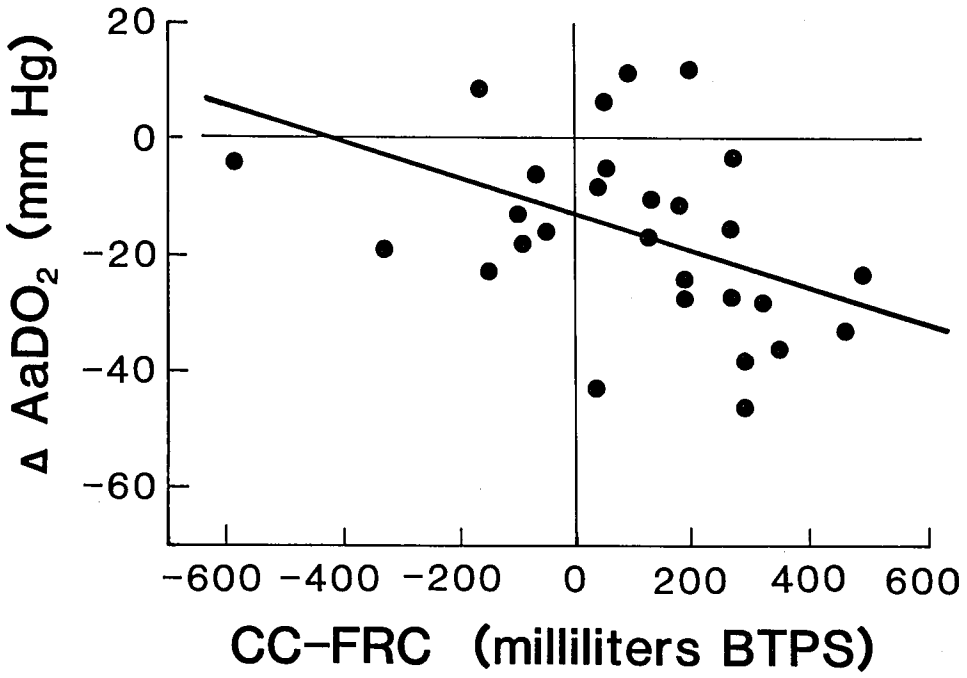

FIG. 5. Reduction in A-aD_{O_2} with PEEP as a function of CC-FRC. In 31 subjects at $F_{I_{O_2}}$ = 0.40, the relevant regression equation was: Δ A-aD_{O_2} = −0.031 × CC-FRC − 13.5 mmHg. r = −0.48, $P < 0.01$.

mmHg. There was no significant difference in A-aD_{O_2} between the two groups of patients under these specified conditions when both groups were presumably breathing above closing capacity.

In 17 patients (six in whom CC < FRC; 11 in whom CC > FRC) an additional arterial blood gas specimen was obtained 20–30 min after PEEP had been discontinued. A-aD_{O_2} was significantly smaller than control at the stated time after discontinuation of PEEP. In 12 of these 17 patients (CC-FRC) measurements were repeated immediately after discontinuation of PEEP. Mean value was virtually identical with that measured in the control period.

Discussion

Data of the present study confirm that, during anesthesia, as in the conscious state, A-aD_{O_2} increases with advancing age. This finding is in agreement with that of Roberts *et al.*[15] Other previous authors, on the basis of a survey of the literature, had concluded that anesthesia causes both young and old lungs to function as if aged to the same extent, so that Pa_{O_2} during anesthesia was not age dependent.[16]

The changing closing capacity (CC) to functional residual capacity (FRC) relationship with advancing age and its relation to efficiency of pulmonary gas exchange in conscious subjects has been discussed extensively.[1–3,11]

Juno *et al.* have demonstrated that both FRC and CC decreased with anesthesia, but the same general types of relationships reported between the two lung capacities in conscious subjects also occurred in anesthetized patients.[11] CC-FRC increased with age, and was zero at about age 45 yr. A small difference from the awake state noted in the Juno *et al.* study was a tendency for CC-FRC to increase more slowly with age during anesthesia than in the conscious state. If this observation is of physiological significance, it would be expected to exaggerate closure of pulmonary units in younger anesthetized subjects and ameliorate this effect in the more elderly anesthetized patients. Other investigators have been unable to demonstrate a decrease in CC with anesthesia.[10]

Results of our measurements of the CC-FRC relationship in anesthetized patients in the present study are in accord with those of Juno *et al.* We could not measure absolute lung volumes. Presence of halogenated anesthetic agents influences reading of the nitrogen analyzer.[17] Therefore, our use of this device was confined to the qualitative detection of the abrupt change in slope of exhaled nitrogen concentration identifying closing volume. Preliminary studies confirmed the validity of this application (N. Bergman, unpublished observations). We presume that all patients sustained the significant decrease in FRC repeatedly demonstrated in association with the anesthetized state.

Closure of pulmonary units in dependent areas of the lungs has been invoked as a possible contributory cause for the increased A-aD_{O_2} repeatedly demonstrated by many investigators during anesthesia. In the present study there was a significant association between A-aD_{O_2} and CC-FRC. Others also have demonstrated similar relationships in anesthetized patients.[9,10] We postulated that

opening some or all of these closed units by application of PEEP might improve oxygenation. Although PEEP is of proved value for improving oxygenation in many situations involving respiratory failure, its role in anesthesia remains controversial. Frumin and associates reported improved oxygenation during anesthesia when 5 cmH_2O of PEEP was compared with 5 cmH_2O NEEP but not with ZEEP.[18] Wyche and associates found a modest increase in Pa_{O_2} with PEEP most prominent in elderly patients and those with initially low Pa_{O_2}.[12] McCarthy and Hedenstierna, however, observed no decrease in $A\text{-}aD_{O_2}$ with 4–10 cmH_2O PEEP applied to increase FRC to the level of CC in seven supine anesthetized patients.[10] This failure to improve oxygenation was attributed to circulatory impairment manifested by hypotension associated with PEEP. The present study was designed, in part, to determine whether beneficial effects of PEEP on oxygenation during anesthesia occurs only in patients with demonstrable closure of pulmonary units in or above the tidal volume range. Several features of the techniques for measurement and interpretation used in the present study could have influenced reported results. Among these are failure to approach actual extremes of lung volume, designation of lung volume at which transrespiratory pressure was zero as FRC without correcting for the small pressure difference required to sustain the expiratory flow rate of 0.25–0.4 l/s, neglecting effects of respiratory pressure-volume hysteresis, and the arbitrary use of 5 cmH_2O PEEP in patients exhibiting closure of respiratory units below FRC. Our data systematically may be slightly in error, but we believe that the derived relationships and their interpretations are valid. Also, it would be unduly optimistic to believe that levels of PEEP prescribed on the basis of the pressure-volume relationship of patients' respiratory systems would completely and exactly accomplish the intended purpose. Such PEEP would be just as likely to overdistend already-functioning pulmonary units as to reopen closed ones. Also, circulatory effects of PEEP were likely to have modified any favorable effect on pulmonary gas exchange. The method of prescribing PEEP employed was devised as a reasonable way of matching magnitudes of CC-FRC and PEEP.

All of our anesthetized patients had an $A\text{-}aD_{O_2}$ in excess of what would be anticipated at $F_{I_{O_2}} = 0.4$. At this inspired oxygen concentration, young, healthy subjects are expected to have an $A\text{-}aD_{O_2}$ of about 25–40 mmHg, with a modest increase with age to perhaps 55 mmHg in patients over the age of 60 yr[19–21] Measurement of CC-FRC permitted identification of two groups among our subjects. In the first were younger patients in whom, during anesthesia, closure of pulmonary units occurred below FRC, who had a mean control $A\text{-}aD_{O_2}$ of 65 mmHg, 1.5 to two times that anticipated in comparable conscious subjects. These subjects had a small, nonsignificant decrease in $A\text{-}aD_{O_2}$, with application of 5 cm H_2O PEEP. In the second group were older subjects whose CC was above FRC. These patients had a control $A\text{-}aD_{O_2}$ of 101 mmHg, again, twice that expected when conscious. With imposition of their prescribed level of PEEP, there was a significant decrease in mean $A\text{-}aD_{O_2}$. Measured mean value for $A\text{-}aD_{O_2}$ on PEEP in this second group was not significantly different from that in the first group breathing at ZEEP. Beneficial effects of PEEP on oxygenation persisted in part long after discontinuation of PEEP. CC-FRC relationship was identical immediately after termination of PEEP to that measured before imposition of PEEP.

Several observations in the present study support the contention that impaired oxygenation during anesthesia is related, at least in part, to closure of pulmonary units in dependent portions of the lung under some circumstances in healthy patients. In anesthetized patients $A\text{-}aD_{O_2}$ is related significantly to CC-FRC (Fig. 4). The efficacy of PEEP in decreasing $A\text{-}aD_{O_2}$ also is correlated significantly with CC-FRC (Fig. 5). A significant reduction in $A\text{-}aD_{O_2}$ by PEEP was confined to subjects in whom CC was greater than FRC. When FRC was increased artificially toward or above CC in these subjects with PEEP, their $A\text{-}aD_{O_2}$ was not significantly different from patients in whom FRC never dropped below CC breathing at ZEEP. It is concluded that closure of pulmonary units in dependent lung regions occurs in the same qualitative manner in anesthetized patients as it is postulated to occur in conscious subjects. This airway closure appears to have the same physiologic impact during anesthesia as in the conscious state and is responsible for the increasing $A\text{-}aD_{O_2}$ with advancing age.[3]

There must be causes in addition to closure of pulmonary units involved in impairment of pulmonary efficiency during anesthesia. Heneghan and Bergman have shown that there was no improvement in oxygenation when lung volume was increased significantly in anesthetized patients by tilting them 30° head up, even when attendant changes in cardiac output were considered.[22] In the present study, imposition of expiratory pressure, a proved method of increasing lung volume, was either ineffective or only partially effective in reducing abnormal $A\text{-}aD_{O_2}$ values toward those expected in comparable conscious subjects. All or most of the $A\text{-}aD_{O_2}$ during anesthesia seems resistant to change by manipulation of lung volume. Improvement in that portion of the $A\text{-}aD_{O_2}$ that did decrease with PEEP persisted for a considerable period after return to ZEEP. CC and FRC probably return to their original relationship almost immediately after discontinuation of PEEP in anesthetized patients. Changes in lung volume both with imposition and withdrawal of PEEP are virtually complete within 1 min in patients with respiratory failure.[23] Thus, it is apparent that mechanisms

in addition to and probably more important than closure of pulmonary units are major contributors to pulmonary dysfunction during anesthesia. The nature of these mechanisms remains speculative.

Finally, one might speculate how findings and conclusions of the present study might be related to clinical practice of anesthesia. Frequent use of PEEP during "routine" anesthesia cannot be recommended because of the circulatory and other associated problems of this modality. Increasing $F_{I_{O_2}}$ remains the method of choice for provision of an acceptable Pa_{O_2} in anesthetized patients. However in the occasional situations where constraints on $F_{I_{O_2}}$ exist, for example, a commitment to obtain maximum analgesia and amnesia from nitrous oxide in an elderly patient, judicious application of PEEP to increase Pa_{O_2} at a fixed $F_{I_{O_2}}$ might be a useful clinical maneuver.

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References

1. Leblanc P, Ruff F, Milic Emili J: Effects of age and body position on "airway closure" in man. J Appl Physiol 28:448–451, 1970
2. Buist AS: Early detection of airways obstruction by the closing volume technique. Chest 64:495–499, 1973
3. Craig DB, Wahba WM, Don HF, Couture HF, Becklake MR: "Closing volume" and its relationship to gas exchange in seated and supine positions. J Appl Physiol 31:717–721, 1971
4. Hewlett AM, Hulands GH, Nunn JF, Heath JR: Functional residual capacity during anaesthesia II: Spontaneous respiration. Br J Anaesth 46:486–494, 1974
5. Hewlett AM, Hulands GH, Nunn JF, Milledge JS: Functional residual capacity during anaesthesia III: Artificial ventilation. Br J Anaesth 46:495–503, 1974
6. Nunn, JF: Factors influencing the arterial oxygen tension during halothane anaethesia with spontaneous respiration. Br J Anaesth 36:327–341, 1964
7. Nunn JF, Bergman NA, Coleman AJ: Factors influencing the arterial oxygen tension during anaesthesia with artificial ventilation. Br J Anaesth 37:898–914, 1965
8. Weenig CS, Pietak S, Hickey RF, Fairley HB: Relationship of preoperative closing volume to functional residual capacity and alveolar-arterial oxygen differences during anesthesia with controlled ventilation. ANESTHESIOLOGY 41:3–7, 1974
9. Hedenstierna G, McCarthy G, Bergstrom M: Airway closure during mechanical ventilation. ANESTHESIOLOGY 44:114–123, 1976
10. McCarthy GS, Hedenstierna G: Arterial oxygenation during artificial ventilation. The effect of airway closure and of its prevention by positive end-expiratory pressure. Acta Anaesthesiol Scand 22:563–569, 1978
11. Juno P, Marsh HM, Knopp TJ, Rehder K: Closing capacity in awake and anesthetized-paralyzed man. J Appl Physiol 44:238–244, 1978
12. Wyche MO, Teichner RL, Kallos T, Marshall BE, Smith TC: Effects of continous positive pressure breathing on functional residual capacity and arterial oxygenation during intra-abdominal operations. ANESTHESIOLOGY 38:68–74, 1973
13. Waltemath CL, Bergman NA: Measurement of closing volume in apneic subjects. Crit Care Med 4:139–141, 1976
14. Snedecor GW, Cochran WG: Statistical Methods. Ames, Iowa, Iowa State University Press, 1972, pp 91–119, 135–171
15. Roberts JG, Prys-Roberts C, Moore MA, Fraser ANL: CardioPulmonary function during ether/air/relaxant anaesthesia. Anaesthesia 29:4–16, 1974
16. Marshall BE, Wyche MO Jr: Hypoxemia during and after anesthesia. ANESTHESIOLOGY 37:178–209, 1972
17. Gilmour IJ, Holland R Craig DB: Nitrogen analyzer adaptation for use in the presence of halogenated anesthetics. ANESTHESIOLOGY 43:674–676, 1975
18. Frumin MJ, Bergman NA, Holaday DA, Rackow H, Salanitre E: Alveolar-arterial O_2 differences during artificial respiration in man. J Appl Physiol 14:694–700, 1959
19. Karetzky MS, Keighley JF, Mithoefer JC: The effect of oxygen administration on gas exchange and cardiopulmonary function in normal subjects. Respir Physiol 12:361–370, 1971
20. Lenfant C: Measurement of ventilation/perfusion distribution with alveolar-arterial differences. J Appl Physiol 18:1090–1094, 1963
21. Harris EA, Kenyon AM, Nisbet HD, Seelye ER, Whitlock RML: The normal alveolar-arterial oxygen tension gradient in man. Clin Sci Mol Med 46:89–104, 1974
22. Heneghan CPH, Bergman NA: Changes in (PA_{O_2}–PaO_2) are unrelated to changes in lung volume during anaesthesia. Br J Anaesth 54:1139, 1982
23. Katz JA, Ozanne GM, Zinn SE, Fairley HB: Time course and mechanisms of lung volume increase with PEEP in acute respiratory failure. ANESTHESIOLOGY 54:9–16, 1981