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SEMINAL STUDY

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The effects of anesthesia and muscle paralysis on the respiratory system

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Abstract *Background:* Oxygenation is impaired in almost all subjects during anesthesia, and hypoxemia for shorter or longer periods is a common finding. Moreover, postoperative lung complications occur in 3–10% after elective abdominal surgery and more in emergency operations. *Discussion:* Rapid collapse of alveoli on induction of anesthesia and more widespread closure of airways seem to explain the oxygenation impairment and may also contribute to postoperative pulmonary infection. Causative mechanisms to atelectasis and airway closure seem to be loss of respiratory muscle tone and gas resorption. *Conclusion:* Avoiding high inspired oxygen fractions during both induction and maintenance of anesthesia prevents or reduces atelectasis, while intermittent "vital capacity" maneuvers recruit atelectatic lung regions.

Keywords Anesthesia · Mechanical ventilation · Atelectasis · Airway closure · Shunt

Introduction

Anesthesia during mechanical ventilation is administered to 10–15 million patients per year in the countries of the European Union. A frequent finding is impaired oxygenation, despite the administration of 30–40% oxygen in the inspired gas. Increased alveolar-arterial oxygen tension difference ($P_{A\text{-}a}O_2$) is therefore seen in 90% or more of anesthetized patients [1]. This holds true for all anesthetic regimes, whether intravenous or inhalational agents are used, and whether the patient is breathing spontaneously or is ventilated mechanically [2]. Moreover, postoperative pulmonary complications occur in 3–10% of patients undergoing elective abdominal surgery [3, 4], and more in emergency surgery. To what extent postoperative complications are caused by a respiratory dysfunction during anesthesia is not clear. However, atelectasis that develops during anesthesia remains in the postoperative period, and impairment in arterial oxygenation and decrease in forced spirometry are correlated with the size of the atelectasis [5]. Moreover, in view of the large number of anesthesias that are given in the Western world even a moderate complication rate will have considerable social and economic consequences.

This review examines the morphological and functional causes of impaired oxygenation that is regularly seen during anesthesia and mechanical ventilation.

Gas exchange

Shunt, as calculated from arterial, mixed venous, and alveolar PO_2 [6], increases from 1–2% in the waking subject to 8–10% in the anesthetized patient [1]. The standard shunt equation is based on the assumption of two populations of alveoli, those that are "ideally" perfused in proportion to their ventilation and those that are perfused but not at all ventilated (the shunt). However, the lung does not contain two populations of alveoli only. There are a number of units with less ventilation than perfusion, with low ventilation-perfusion ratios ("low V_A/Q regions"), as well as units that are ventilated in excess of

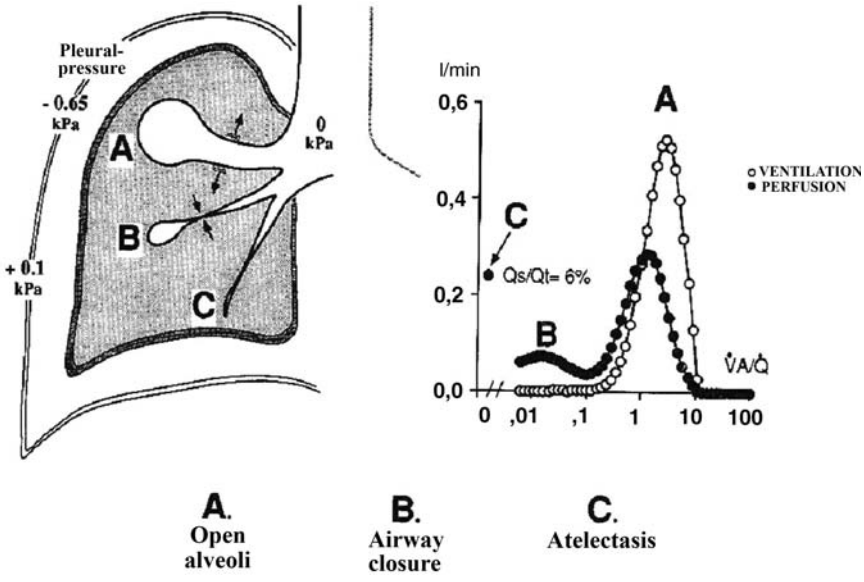

Fig. 1 *Right* Ventilation-perfusion matching (V_A/Q) in an anesthetized subject. Note the large normal mode centered on a V_A/Q ratio of 1, as well as a low V_A/Q mode with V_A/Q ratios between 0.01 and 0.1, and finally shunt ($V_A/Q=0$). *Left* The morphological and functional correlates with intermittent airway closure explaining low V_A/Q and atelectasis explaining the shunt

their perfusion ("high V_A/Q regions"). Perfusion of low V_A/Q regions also impedes the oxygenation of blood and to a varying extent is included in the calculated "shunt." The shunt, as measured by the standard oxygen technique, should therefore rather be called "venous admixture" [1]. A good correlation between venous admixture and the sum of "true" shunt and perfusion of "low V_A/Q regions" was seen in a study of 45 anesthetized subjects [7].

The extent by which venous admixture includes low V_A/Q regions depends on the inspired oxygen fraction (FIO_2). The higher it is, the less of low V_A/Q is included. However, with high FIO_2 the regions with low V_A/Q collapse because of gas adsorption and be transformed to shunt regions [8, 9].

A more detailed picture of the distribution of V_A/Q ratios with no need to change FIO_2 can be obtained by the multiple inert gas elimination technique [10]. This technique is based on the infusion of a number of inert gases (usually six) in a vein and the calculations of the retention (arterial/mixed venous concentration ratio) and excretion (mixed expired/mixed venous concentration ratio) of each gas. The ratios, together with the measured solubilities of the inert gases, enable the construction of a virtually continuous distribution of ventilation and perfusion against V_A/Q ratios.

When this technique is applied to the anesthesia setting, a major finding is increased dispersion of V_A/Q with the appearance of low V_A/Q ratios. Thus there is impaired matching of ventilation and perfusion during anesthesia with regions that are poorly ventilated in relation to their perfusion. Another major observation is the appearance of true shunt of around 8%, but frequently exceeding 20% [11, 12, 13]. Figure 1 presents an example of a V_A/Q distribution. Thus there seem to be at least two major functional causes of impaired oxygenation during anesthesia, low V_A/Q and true shunt. The morphological correlates are be discussed below.

Hypoxic pulmonary vasoconstriction

Attenuation of hypoxic pulmonary vasoconstriction (HPV) is frequently considered a mechanism of impaired gas exchange during anesthesia. Most inhalational anesthetics inhibit HPV in isolated lung preparations [14]. However, no such effect has been seen with intravenous anesthetics (barbiturates) [15]. Results from human studies vary, reasonably explained by the complexity of the experiment that causes several variables to change at the same time. In studies with no gross changes in cardiac output the inhalational anesthetics isoflurane and halothane depress the HPV response by 50% at twice the minimum alveolar concentration [16]. The HPV response acts efficiently both in the atelectatic lung (where HPV seems to be more important than mechanical kinking of vessels) and during ventilation with hypoxic gases [17].

The breathing of pure oxygen may increase the shunt by promoting alveolar collapse [18]. High FIO_2 may also increase shunt by increasing alveolar PO_2 and thus attenuate the HPV response [16]. Similarly, pulmonary hypertension counters HPV, presumably by requiring higher muscle force to constrict a vessel.

It should also be emphasized that attenuation of the HPV response cannot be the only disturbance during anesthesia to cause gas exchange impairment. If there were no corresponding ventilatory impediment, loss of pulmonary vascular tone would be of no significance since adequate gas exchange would still occur. Loss of HPV can only aggravate an existing V_A/Q mismatch.

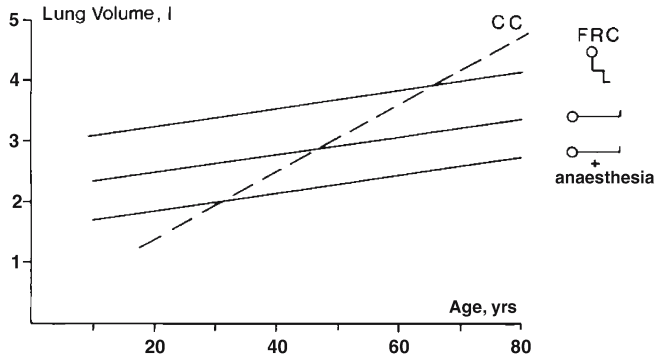

Fig. 2 Functional residual capacity (*FRC*) and closing capacity (*CC*, the lung volume at which airways begin to close during expiration). Note the decrease in FRC from sitting or standing to supine and the further decrease with anesthesia. Note also the slight increase in volumes with age, an effect of loss of elastic tissue in the lung (as well as elsewhere in the body). Note also the much faster increase in CC with age, making airway closure more common in elderly. Airway closure during a breath occurs at ages of 30 years and more in the supine anesthetized subject

Lung volume and respiratory mechanics

The resting lung volume (functional residual capacity, FRC) is reduced by 0.8–1.0 l by changing body position from upright to supine, and there is another decrease by 0.4–0.5 l when anesthesia is induced [19]. The end-expiratory lung volume is thus reduced from approx. 3.5 to 2 l, the latter being close or equal to residual volume. When one tries to breathe voluntarily at that level, one realizes the difficulty in doing so! The decrease seems to be related to loss of respiratory muscle tone, shifting the balance between the elastic recoil force of the lung and the outward forces of the chest wall to a lower chest and lung volume [20, 21]. Maintenance of muscle tone, such as during ketamine anesthesia, does not reduce FRC [22]. The effect of body position and anesthesia on FRC is shown in Fig. 2. As seen here, FRC increases with age. This is dealt with below.

Compliance of the respiratory system (lungs and chest wall) is also reduced during anesthesia, from a mean of 95 to 60 ml/cmH_2O [23]. This may be due mainly to decreased lung compliance [23]. Rehder and coworkers [24] ruled out direct effects of the anesthetic on the lung tissue, and it is more likely that the fall in compliance is a consequence of the reduced FRC. This promotes airway closure and atelectasis, as is discussed below.

The resistance of the respiratory system and of the lungs has also been measured, showing considerable increase during both spontaneous breathing and mechanical ventilation [23, 24]. However, studies on resistance during anesthesia have been hampered by different experimental conditions during the awake and the anesthetized conditions. Thus studies that enables comparison of resistance under both isovolume and isoflow conditions are still lacking. It is rather likely that the increased lung resistance merely reflects the reduced FRC.

Atelectasis

In their classical study in 1963 Bendixen and coworkers [25] proposed "a concept of atelectasis" as a cause of impaired oxygenation during anesthesia. They had observed a subsequent decrease in compliance of the respiratory system and a similar subsequent decrease in arterial oxygenation in both anesthetized humans and experimental animals. This was interpreted as the formation of atelectasis. However, other research groups who were unable to reproduce their findings noted a more rapid fall in compliance and PaO_2 on induction of anesthesia. Moreover, atelectasis could not be shown by conventional chest radiography.

In the middle 1980s new observations were made that may explain the altered function of the lung during anesthesia. Using computed tomography (CT) with transverse exposures of the chest Brismar and coworkers [26] demonstrated prompt development of densities in dependent regions of both lungs during anesthesia. Similar densities had previously been seen in anesthetized infants [27]. Morphological studies of these densities in various animals supported the diagnosis of atelectasis [28]. An example of atelectasis as shown by CT is shown in Fig. 3.

Atelectasis appears in around 90% of patients who are anesthetized [7]. It occurs both during spontaneous breathing and after muscle paralysis and regardless of whether intravenous or inhalational anesthetics are used [2]. The atelectatic area on CT slice near the diaphragm is generally approx. 5–6% of the total lung area but can easily exceed 15–20%. It should also be remembered that the amount of tissue that is collapsed is even larger, the atelectatic area comprising mainly lung tissue whereas the aerated lung consists only of 20–40% tissue, the rest being air. Thus 15–20% of the lung is regularly collapsed at the base of the lung during uneventful anesthesia—before any surgery has been done! Abdominal surgery adds only little to the atelectasis, but it can remain for several days in the postoperative period [5]. It is likely to be a focus of infection and may contribute to pulmonary complications [29]. One should also note that after thoracic surgery and cardiopulmonary bypass more than 50% of the lung can remain collapsed even several hours after surgery [30]. The amount of atelectasis decreases towards the apex, which is mostly spared (fully aerated).

There is a weak correlation between the size of the atelectasis and body weight or body mass index [31], obese patients showing larger atelectatic areas than lean ones. While this was expected, it came as a surprise that the atelectasis is independent of age, with children and young persons showing as much atelectasis as elderly patients [7]. Another unexpected observation was that

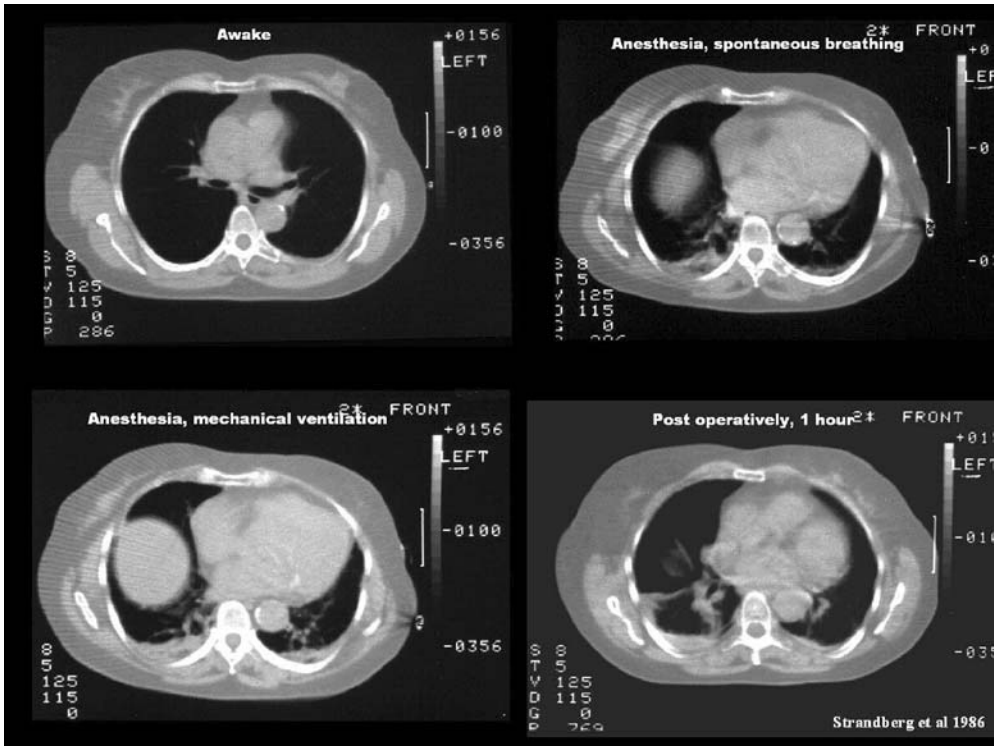

Fig. 3 Computed tomography in a subject when awake (*upper left*), during anesthesia with spontaneous breathing (*upper right*), after muscle paralysis (*lower left*), and 1 h postoperatively (*lower right*). Note the appearance of atelectasis already during spontaneous breathing during anesthesia with a slight further increase with mechanical ventilation (mainly explained by the end-expiratory exposure in the paralyzed subject whereas during spontaneous breathing the exposure covers most of the breath). Note also that the anesthesia-induced atelectasis remains for some time in the postoperative period. The *large gray area* in the middle of the right lung field (to the left in the CT image) is the diaphragm and liver that have been moved cranially during anesthesia. (Redrawn from [23])

patients with chronic obstructive lung disease show less, or even no, atelectasis during the 45 min of anesthesia of study [32]. The mechanism that prevents the lung from collapsing is not clear, but it may be airway closure occurring before alveolar collapse takes place or an altered balance between the chest wall and the lung that counters a decrease in the lung dimensions.

There is a good correlation between the amount of atelectasis and pulmonary shunt as measured by the multiple inert gas elimination technique. The regression equation based on 45 patients studied during inhalational anesthesia has been calculated as: shunt=0.8 ×atelectasis +1.7 (r=0.81, p<0.01), with atelectasis as a percentage of the lung area just above the diaphragm on CT and shunt as a percentage of cardiac output. Interestingly, shunt did not increase with age [7]. Combining CT and single photon emission computed tomography confirms the distribution of shunt and its location within the atelectatic area [33] (Fig. 4).

Airway closure

In addition to atelectasis, intermittent closure of airways can be expected to reduce the ventilation of dependent lung regions. Such lung regions may then become "low V_A/Q" units if perfusion is maintained or not reduced to the same extent as ventilation. Airway closure increases with age [34] (see also Fig. 2) as does the perfusion to "low V_A/Q" regions [7]. Since anesthesia causes an FRC reduction by 0.4–0.5 l [35], it may be anticipated that airway closure becomes even more prominent in the anesthetized subject. There is accumulating evidence that this is indeed the case [36, 37, 38]. The reduced ventilation in the lower half of the lung just above the atelectasis that can be seen in Fig. 4 is thus reasonably explained by airway closure. It can also be seen that ventilation is smaller than perfusion, causing "low V_A/Q" regions. These contribute to impaired oxygenation during the anesthesia.

As much as 74% of the impaired arterial oxygenation can be explained by atelectasis and airway closure taken together, according to the equation [39]: P_aO_2 (mmHg)= 218–22 ×ln atelectasis (cm^2)–0.06 (CV–ERV) (ml)

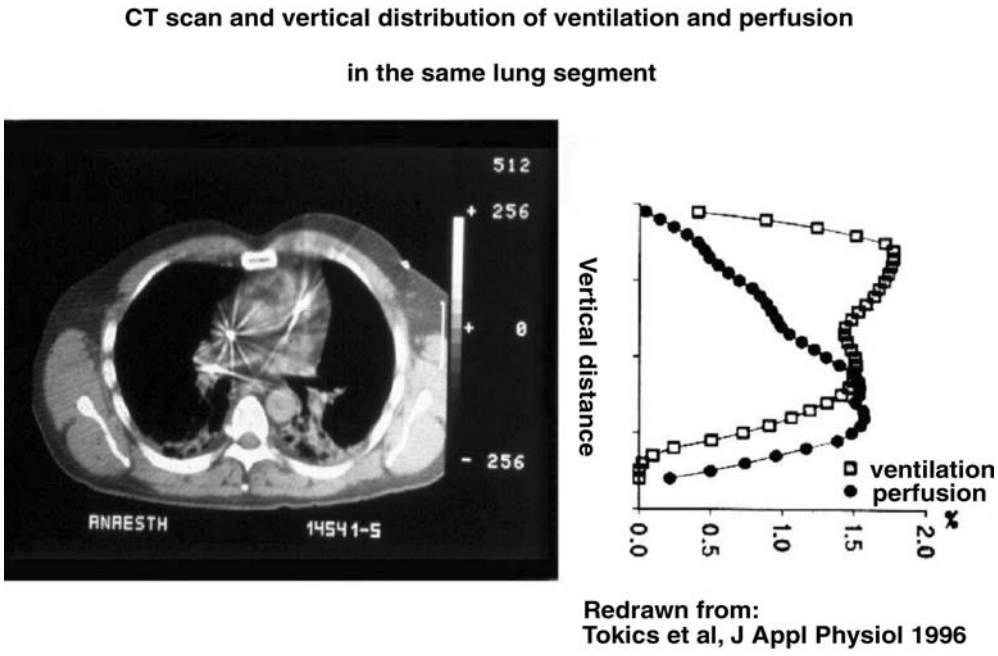

Fig. 4 Transverse computed tomography with atelectasis visible in the dependent parts of both lungs (*left*) and corresponding vertical distributions of ventilation and lung blood flow by isotope technique (single photon emission computed tomography, *right*) in an anesthetized subject. Note that ventilation is distributed preferentially to upper lung regions, contrary to what is normally seen in the waking subject. Note also the decreasing ventilation in the lower part and the complete cessation of ventilation in the bottom, corresponding to the atelectatic area. Perfusion, on the other hand, increases down the lung, except for the bottom-most region where a decrease is seen (so-called "zone IV"). (Redrawn from [28])

(r=0.86, p<0.001) where (CV−ERV) indicates the amount of airway closure occurring above FRC, CV is closing volume, and ERV is expiratory reserve volume. A simple three-compartment lung model can thus be constructed to explain oxygenation impairment during anesthesia. The model consists of one compartment with "normal" ventilation and perfusion, one with airway closure that impedes ventilation, and one of collapsed lung with no ventilation at all. This is shown in Fig. 1 together with the subsequent impact on the V_A/Q distribution.

Anesthesia vs. muscle paralysis

How much of the lung function impairment is produced by the anesthetic and how much by the muscle paralysis? Interestingly, the anesthetic per se causes a fall in FRC despite the maintenance of spontaneous breathing [20, 40]. The addition of muscle paralysis does not produce a further drop in FRC. Since airway closure and atelectasis depends on the lung volume the findings suggest that most of the impairment is caused by the anesthesia per se [2]. Figure 3 shows the appearance of atelectasis during spontaneous breathing with no significant increase with muscle paralysis. However, there may be a difference between spontaneous and mechanical ventilation; that is, the spontaneous breath may have a different effect on the aeration of the lung than the mechanically delivered. The diaphragm during the active respiration moves with the dorsal, dependent part making the largest excursions whereas during passive ventilation the anterior, nondependent part is pushed away more than other regions [41]. The spontaneous breath may therefore recruit collapsed tissue in the bottom of the lung better than the mechanical breath. The CT sequence in Fig. 3 does not provide substantial support to this, and it may be that any positive effect is that recruited tissue stays open with spontaneous breathing whereas slow derecruitment occurs with mechanical breaths. This remains to be tested.

Anesthesia vs. acute respiratory distress syndrome

Hallmarks of acute respiratory failure and its most severe form, acute respiratory distress syndrome (ARDS), are hypoxemia, reduced respiratory compliance, and atelectasis/consolidation as seen on CT of the lung [42, 43]. There are indeed qualitative similarities between anesthesia and ARDS, however with much more severe changes in ARDS. Widespread but mainly dependent lung regions collapse under their own weight, causing atelectasis. In addition, alveoli may become fluid filled. However, can it be that the treatment of ARDS per se adds to the atelectasis? This is indeed rather likely. Loss of

muscle tone, as caused by muscle relaxants, anesthetics, and sedatives, and the use of high oxygen concentration in inspired gas are the prerequisites to produce atelectasis in the lung healthy subject during anesthesia. This is common treatment in ARDS and certainly adds to the collapse and consolidation caused by the disease itself. Maintenance of muscle tone and modest use of supplemental oxygen may be a better approach to treatment than abuse of muscle depressants and oxygen. There is hardly any confirmation of beneficial effects of supranormal oxygen tension in blood, but it is frequently seen in the treatment of ARDS!

Prevention of atelectasis during anesthesia

There are several interventions that can help prevent atelectasis or even reopen collapsed tissue. These are discussed below.

PEEP

The application of 10 cmH_2O positive end-expiratory pressure (PEEP) has been tested in several studies and been shown consistently to reopen collapsed lung tissue. This is more likely an effect of increased inspiratory airway pressure than of PEEP per se [26, 44]. However, some atelectasis persists in most patients. Whether further increase in the PEEP level reopens this tissue was not analyzed in these studies. PEEP, however, appears not to be the ideal procedure. First, shunt is not reduced proportionately, and arterial oxygenation may not improve significantly. Hewlett and coworkers [45] warned as early as 1974 of the "indiscriminate use of PEEP in routine anesthesia." The persistence of shunt may be explained by a redistribution of blood flow towards more dependent parts of the lungs when intrathoracic pressure is increased by PEEP. Under such circumstances any persisting atelectasis in the bottom of the lung receives a larger share of the pulmonary blood flow than without PEEP [46]. Also, increased intrathoracic pressure impedes venous return and decreases cardiac output. This results in a lower venous oxygen tension for a given oxygen uptake and reduces arterial oxygen tension [8]. Second, the lung recollapses rapidly after discontinuation of PEEP. Within 1 min after cessation of PEEP the collapse is as large as it was before the application of PEEP [26].

Maintenance of muscle tone

The use of an anesthetic that allows maintenance of respiratory muscle tone prevents the formation of atelectasis. Ketamine does not impair muscle tone and does not cause atelectasis. This is the only anesthetic so far tested that does not cause collapse. However, if muscle relaxation is required, atelectasis appears as with other anesthetics [22]. Another attempt is to restore respiratory muscle tone by pacing of the diaphragm. This was tested by applying phrenic nerve stimulation, which did reduce the atelectatic area [47]. The effect, however, was small, and this technique is certainly too complicated to be used as a routine during anesthesia and surgery.

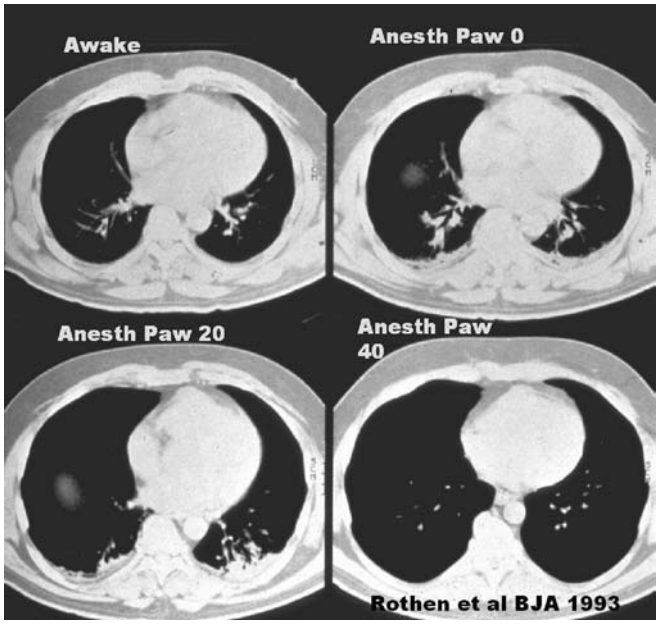

Fig. 5 Computed tomography in a patient awake (*left upper*) during anesthesia at zero airway pressure (*Paw*), i.e., after a normal expiration (*right upper*), after an inflation to Paw 20 (*left lower*) and 40 cmH_2O (*right lower*) and a breath hold of 15 s. Note the appearance of atelectasis in the dorsal part of the lungs during anesthesia and the persistence of the atelecatsis even with inflation to 20 cmH_2O. Not until Paw was increased to 30 cmH2O did some of the atelectasis reopen. A Paw of 40 cmH_2O was required to open up all atelectasis (From [48] with permission from the publisher)

Recruitment maneuvers

The use of a sigh maneuver, or a double tidal volume, has been advocated to reopen any collapsed lung tissue [48]. However, the atelectasis is not decreased by tidal volume or by a sigh up to an airway pressure of 20 cmH_2O. Not until an airway pressure of 30 cmH_2O is reached does the atelectasis decrease to approximately one-half the initial size. Complete reopening of all collapsed lung tissue requires an inflation pressure of 40 cmH_2O (Fig. 5) [48]. Such a large inflation corresponds to a maximum spontaneous inspiration and can thus be called a vital capacity maneuver.

Because the vital capacity maneuver may result in adverse cardiovascular events, the dynamics in resolving atelectasis during such a procedure was analyzed [49]. It

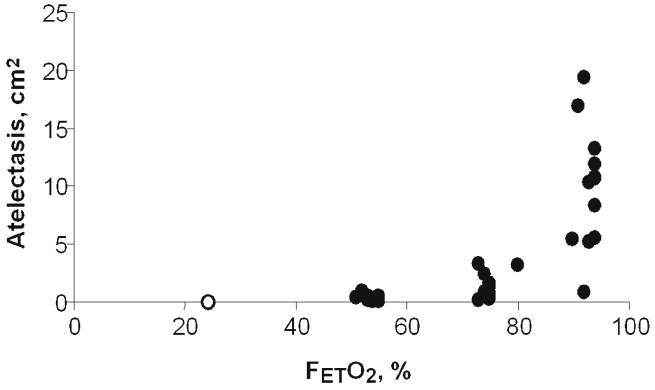

Fig. 6 Atelectasis near the diaphragm in individual patients (*filled circles*) after induction of anesthesia and a period of apnea in relation to their endtidal O_2 concentration ($F_{ET}O_2$) just before the period of apnea. The results are compared with data (*open circle*) [51] in which subjects were ventilated with 30% oxygen in nitrogen (From [52] with permission from the publisher)

was found that in adults with healthy lungs inflation of the lungs to +40 cmH_2O maintained for no more than 7–8 s may reexpand all previously collapsed lung tissue.

Minimizing gas resorption

Ventilation of the lungs with pure oxygen after a vital capacity maneuver that had reopened previously collapsed lung tissue has been shown to result in a rapid reappearance of the atelectasis [50]. If, on the other hand, 40% O_2 in nitrogen is used for ventilation of the lungs, atelectasis reappears slowly, and 40 min after the vital capacity maneuver only 20% of the initial atelectasis has reappeared. Thus ventilation during anesthesia should be carried out with a moderate FIO_2, for example., 0.3–0.4, and be increased only if arterial oxygenation is compromised.

The striking effects of oxygen during anesthesia raised the question of whether the preoxygenation during induction of anesthesia affects atelectasis formation. The breathing of 100% O_2 for only a few minutes before and during the commencement of anesthesia increases the safety margin in the event of a difficult intubation of the airway with prolonged apnea. However, there proves to be a prize for this. Avoidance of the preoxygenation procedure (ventilation with 30% O_2) eliminates atelectasis formation during the induction and subsequent anesthesia [51]. In a recent study, 12 patients breathed 100% O_2 during the induction of anesthesia, 12 80% O_2, and 12 60% O_2 [52]. Atelectasis appeared in all patients on 100% O_2 and was much less in the 80% O_2 group and almost absent in the 60% O_2 group (Fig. 6).

Preliminary data from our own experiments show that with induction of anesthesia during 100% preoxygenation atelectasis occurs within 7 min and continues to increase in extent for at least another 7 min. Very little was seen after 4 min, suggesting that there is a narrow time window after the induction and the intubation of the airway when no collapse yet has occurred, and that might be prevented by a deep breath with more modest oxygen concentration, the make-up gas being nitrogen. That rather subtle changes in the preoxygenation procedure and anesthesia regime can prevent substantial atelectasis formation with potential decrease in postoperative lung complications is likely but requires further study.

In summary, rapid collapse of alveoli on induction of anesthesia and more widespread closure of airways seem to explain oxygenation impairment during anesthesia. They may also contribute to postoperative pulmonary infection. Causative mechanisms seem to be a loss of respiratory muscle tone and gas resorption. Avoiding high inspired oxygen fractions during both induction and maintenance of anesthesia prevents or reduces atelectasis, while intermittent "vital capacity" maneuvers recruit atelectatic lung regions.

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