ANESTHESIOLOGY

Oxygenation Impairment during Anesthesia

Influence of Age and Body Weight

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ABSTRACT

Background: Anesthesia is increasingly common in elderly and overweight patients and prompted the current study to explore mechanisms of age- and weight-dependent worsening of arterial oxygen tension (Pa_{O_2}).

Methods: This is a primary analysis of pooled data in patients with (1) American Society of Anesthesiologists (ASA) classification of 1; (2) normal forced vital capacity; (3) preoxygenation with an inspired oxygen fraction (Fi_{O_2}) more than 0.8 and ventilated with Fi_{O_2} 0.3 to 0.4; (4) measurements done during anesthesia before surgery. Eighty patients (21 women and 59 men, aged 19 to 69 yr, body mass index up to 30 kg/m^2) were studied with multiple inert gas elimination technique to assess shunt and perfusion of poorly ventilated regions (low ventilation/perfusion ratio [$\dot{V}_A/\dot{Q}$]) and computed tomography to assess atelectasis.

Results: Pa_{O_2}/Fi_{O_2} was lower during anesthesia than awake (368; 291 to 470 [median; quartiles] *vs.* 441; 397 to 462 mm Hg; $P = 0.003$) and fell with increasing age and body mass index. Log shunt was best related to a quadratic function of age with largest shunt at 45 yr ($r^2 = 0.17$, $P = 0.001$). Log shunt was linearly related to body mass index ($r^2 = 0.15$, $P < 0.001$). A multiple regression analysis including age, age^2, and body mass index strengthened the association further ($r^2 = 0.27$). Shunt was highly associated to atelectasis ($r^2 = 0.58$, $P < 0.001$). Log low $\dot{V}_A/\dot{Q}$ showed a linear relation to age ($r^2 = 0.14$, $P = 0.001$).

Conclusions: Pa_{O_2}/Fi_{O_2} ratio was impaired during anesthesia, and the impairment increased with age and body mass index. Shunt was related to atelectasis and was a more important cause of oxygenation impairment in middle-aged patients, whereas low $\dot{V}_A/\dot{Q}$, likely caused by airway closure, was more important in elderly patients. Shunt but not low $\dot{V}_A/\dot{Q}$ increased with increasing body mass index. Thus, increasing age and body mass index impaired gas exchange by different mechanisms during anesthesia.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic:

- During anesthesia oxygenation is impaired, especially in the elderly or obese, but the mechanisms are uncertain.

What This Article Tells Us That Is New:

- Pooled data were examined from 80 patients studied with multiple inert gas elimination technique and computed tomography. Oxygenation was impaired by anesthesia, more so with greater age or body mass index. The key contributors were low ventilation/perfusion ratio (likely airway closure) in the elderly and shunt (atelectasis) in the obese.

Arterial oxygenation is impaired during anesthesia, and this has made it a rule to ventilate the patient with oxygen-enriched gas with an inspired oxygen fraction (Fi_{O_2}) of 0.3 to 0.4 instead of the 0.21 of air.[1] A major cause of the impairment seems to be atelectasis formation, *i.e.*, lung collapse, as suggested more than 50 yr ago[1] but not demonstrated until computed tomography was available.[2–8] Arterial oxygen tension (Pa_{O_2}) is more reduced in elderly patients and in overweight patients during anesthesia than in younger and leaner ones.[9,10] Because of the increasing number of elderly and overweight patients undergoing anesthesia,[10–12] oxygenation impairment may become a more common concern, prompting a better understanding of its causes.

The purpose of the current study was to explore the mechanisms of the age- and weight-dependent worsening of arterial oxygenation during anesthesia. The main hypothesis was that the oxygenation impairment in elderly and overweight patients is related to shunt, mainly caused by atelectasis, and to regions with low alveolar ventilation/perfusion ratios (low $\dot{V}_A/\dot{Q}$), caused mainly by airway closure. This hypothesis was tested by pooling previously collected data from all patients studied by our group (studies listed in the appendix) in which the multiple inert gas elimination technique had been used to discriminate between perfusion of nonventilated lung regions (shunt) and perfusion of poorly ventilated regions (low $\dot{V}_A/\dot{Q}$). A secondary hypothesis was an additional influence on arterial oxygenation by a reduced cardiac output in relation

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to the metabolic demand. This hypothesis was tested in a subgroup of patients where necessary data were available (see Gas Exchange section below).

Materials and Methods

Data from eight previous studies from our group were pooled, the studies having been performed in two different hospitals (Huddinge University Hospital, Huddinge, Sweden, and Uppsala University Hospital, Uppsala, Sweden). All patients had given their consent to participate in the initial studies. We included patients (1) who belonged to American Society of Anesthesiologists (ASA) class 1 and thus were clinically free from cardiopulmonary disease without previous or ongoing treatment of chest disease; (2) who had normal forced vital capacity (± 2 SD of predicted reference values[13,14]; including current and former smokers); (3) whose anesthesia was induced during preoxygenation with an FIO_2 higher than 0.8 and were then ventilated mechanically with an FIO_2 0.3 to 0.4, nitrogen being the makeup gas; and (4) who were studied before elective neurosurgical or abdominal surgery had been performed. Using these criteria, 80 patients (21 women and 59 men, aged 19 to 69 yr) were identified in whom the multiple inert gas elimination technique had been used to assess shunt and low $\dot{V}_A/\dot{Q}$ (further details in Gas Exchange section below). No obese patients according to the World Health Organization classification (body mass index greater than 30 kg/m^2; see also the article by Hedenstierna *et al.*[15]) had been studied with multiple inert gas elimination technique during anesthesia. Moreover, no power analysis was conducted before the study because all patients who had been investigated by using the multiple inert gas elimination technique during anesthesia were included. The studies are listed in the appendix. Patient characteristics are given in table 1.

Table 1. Baseline Patient Characteristics

	Study site		
	Huddinge	Uppsala	*P*
Women/men	15/44	11/10	0.024
Age, yr	48 (20–69)	48 (19–66)	0.644
Height, cm	176 (172–181)	179 (166–180)	0.118
Weight, kg	75 (70–81)	76 (65–86)	0.754
BMI, kg/m^2	24 (22–26)	25 (23–27)	0.206
FVC, % predicted	96 (91–105)	94 (84–105)	0.191
Smoking –/+	25/29	21/5	0.004
Anesthesia			
inh/IV	48/6	0/26	< 0.001
VT/IBW, mL/kg	8.6 (7.2–9.2)	10.2 (9.7–11.9)	< 0.001
RR, breaths/min	12 (9–15)	10 (10–10)*	< 0.001

Continuous variables are presented as median and categorical variables as numbers. Values within parentheses are the range of age and respiratory rate, and the interquartile range of the other variables. BMI, body mass index; FVC, forced vital capacity; inh/IV, inhaled/intravenous; RR, respiratory rate; Smoking –/+, never/previous and current; VT/IBW, tidal volume/ideal body weight.

*All patients had a respiratory rate of 10 per min.

Shunt in the lung-healthy anesthetized patient can be expected to be caused by atelectasis, which in our study was quantified by computed tomography.[15] Similarly, low $\dot{V}_A/\dot{Q}$ can be expected to be caused by airway narrowing and airway closure,[16] and any gas exchange impairment not explained by atelectasis was attributed to airway closure (after having considered hypokinetic circulation). Thus, in 51 of these 80 patients, the arterial-mixed venous oxygen content difference($C(a\text{-}v')O_2$), another factor that can influence arterial oxygenation, could be retrieved to test global circulatory adaptation to anesthesia.

Anesthesia

The patient received premedication with 0.25 to 0.5 mg atropine IV to avoid bradycardia during induction of anesthesia. Preoxygenation (FIO_2 greater than 0.8) was given for 1 to 3 min, without any continuous positive airway pressure.

Anesthesia was induced using an opioid and a hypnotic agent (thiopentone, 3 to 5 mg/kg, or propofol, 2 to 3 mg/kg). In some patients, according to clinical routines, diazepam, 2.3 to 7.5 mg was administered during induction. Tracheal intubation was achieved using IV suxamethonium 75 to 100 mg or a nondepolarizing muscle relaxant and sustained by a nondepolarizing muscle relaxant. Anesthesia was maintained by halogenated inhalational agents or by IV infusion of propofol. After initial manual ventilation, the patient was connected to a ventilator equipped with a carbon dioxide analyzer (equipment from several manufacturers). The ventilation frequency was between 9 and 15 breaths per min. The tidal volume was adjusted to maintain an end-tidal carbon dioxide concentration of approximately 4%. The patient was ventilated without any positive end-expiratory pressure (PEEP).

Gas Exchange

FIO_2 was measured in all patients. Arterial blood gases were analyzed in blood taken from the radial artery while patients were awake during air breathing (FIO_2: 0.21) and during anesthesia (FIO_2: 0.31 to 0.43). By dividing the arterial oxygen tension with FIO_2, a PaO_2/ FIO_2 ratio was created to enable comparison between air breathing under waking conditions and ventilation with higher FIO_2 during anesthesia (fig. 2, table 2). The multiple inert gas elimination technique is based on the infusion of inert gases with different solubilities in blood and, during steady state conditions, blood sampling from a systemic artery and pulmonary artery, and collection of mixed expired gas for measurement of the inert gas concentrations. The infused gases were, from lowest to highest solubility, sulfur hexafluoride, ethane, cyclopropane, halothane (or enflurane), ether, and acetone. Shunt was defined as perfusion of regions with a $\dot{V}_A/\dot{Q}$ ratio lower than 0.005, and low $\dot{V}_A/\dot{Q}$ as regions

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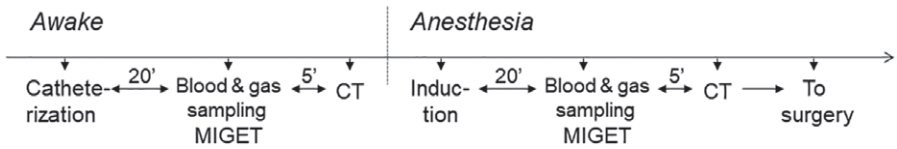

Fig. 1. Study protocol.

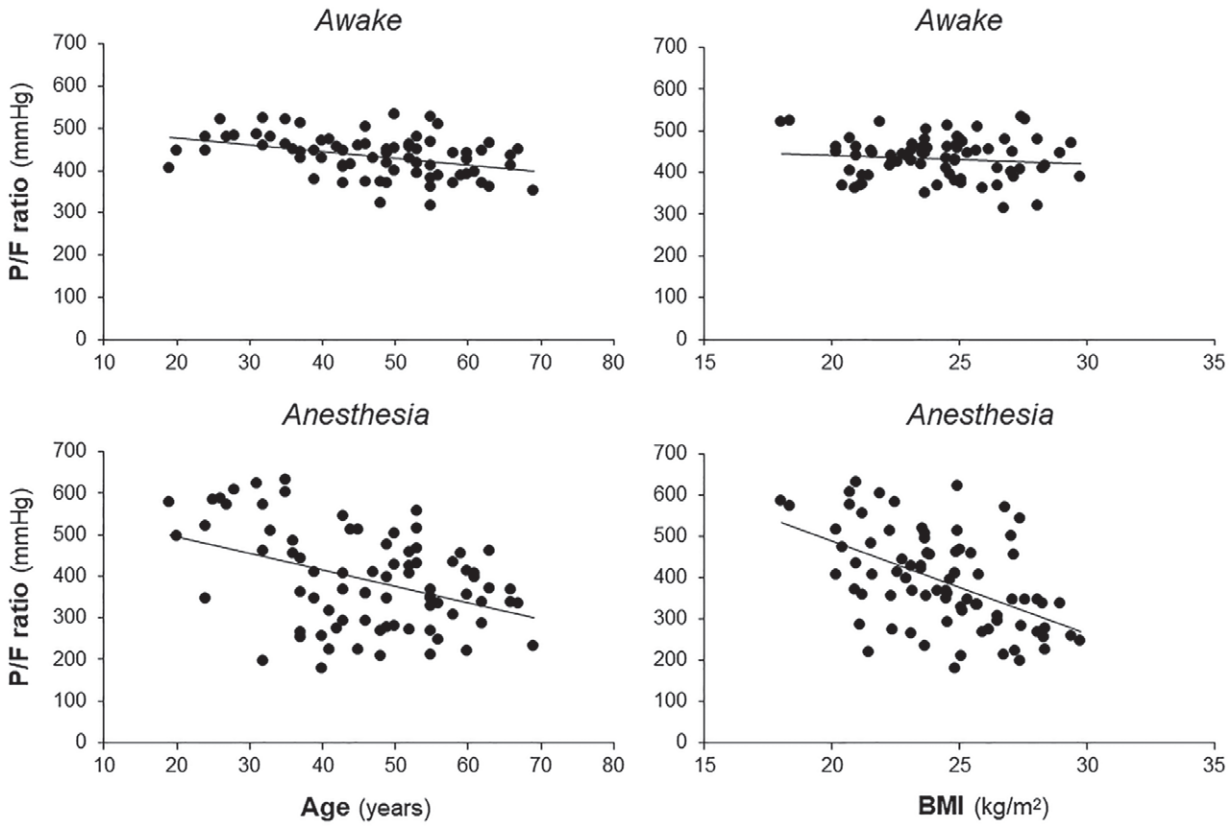

Fig. 2. Arterial oxygen tension (PaO_2)/inspired oxygen fraction (FIO_2) ratio during air breathing awake (*upper panels*), and during anesthesia with mechanical ventilation with an FIO_2 ranging from 0.31 to 0.43 (*lower panels*). Dependence on age is shown to the left, and dependence on body mass index (BMI) is shown to the right. Age: PaO_2/FIO_2 ratio awake, $y = -1.59x + 509$, $P = 0.001$; PaO_2/FIO_2ratio anesthetized, $y = -3.99x + 576$, $P < 0.001$; x, age in years; y, PaO_2/FIO_2 ratio in mm Hg. Body mass index: PaO_2/FIO_2 ratio awake, $y = -2.03x + 483$, $P = 0.363$; PaO_2/FIO_2 ratio anesthetized, $y = -22.4x + 937$, $P < 0.001$; x, body mass index in kg/m^2; y, PaO_2/FIO_2 ratio in mm Hg.

with $0.005 \leq \dot{V}_A/\dot{Q} < 0.1$. For further details, see Roca and Wagner.[17]

An altered arterial-mixed venous oxygen content difference reflects an altered balance between cardiac output and the metabolic demand. An increase in arterial-mixed venous oxygen content difference causes a decrease in Pa_{O_2}, other conditions being kept constant.[18] Accordingly, we tested, in a limited number of patients in whom we had available data (n = 51), for any dependency of arterial-mixed venous oxygen content difference on anesthesia and on patient age and body mass index as a potential cause of impaired arterial oxygenation.

Computed Tomography

The patient was placed in the supine position. With the patient awake and later during anesthesia, a frontal scout view covering the chest was obtained at end-expiration. The exposure time was 1 to 5 s at 115 to 255 mAs, voltage from 125 to 137 kV. Slice thickness was 4 to 8 mm. Scans

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Table 2. Gas Exchange Data and Atelectasis

	Awake		Anesthesia		
	n	Median (Q_{25} to Q_{75})	n	Median (Q_{25} to Q_{75})	*P*
Pa_{O_2}, mm Hg	72*	92.6 (83.4–97.2)	80	147.3 (117.0–190.9)	< 0.001
$PaCO_2$, mm Hg	74*	39.1 (33.8–40.6)	80	35.3 (33.8–38.6)	0.19
Pa_{O_2}/Fi_{O_2} ratio	72*	441 (397–462)	80	368 (291–470)	0.003
Shunt, %	77†	0.0 (0.0–0.4)	80	4.1 (1.5–8.3)	< 0.001
Low $\dot{V}_A/\dot{Q}$, %	77†	0.0 (0.0–2.4)	79[2]	3.7 (1.0–7.3)	< 0.001
$C(a\text{-}\bar{v})O_2$, ml/l	48‡	41.7 (37.5–46.7)	51[3]	37.2 (30.3–42.0)	< 0.001
Atelectasis, cm^2	80	0.0 (0.0–0.0)	80	4.4 (1.8–10.1)	< 0.001

Arterial oxygen and carbon dioxide tensions, Pa_{O_2}/Fi_{O_2} ratio, perfusion of poorly ventilated (low $\dot{V}_A/\dot{Q}$) or nonventilated (shunt) regions in percent of cardiac output, $C(a\text{-}\bar{v})O_2$, and atelectasis.

Data are shown as median and interquartile values (Q_{25} to Q_{75}). $C(a\text{-}\bar{v})O_2$, arterial-mixed venous oxygen content difference; FIO_2, inspired oxygen fraction; PaO_2, arterial oxygen tension; $\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio.

*Blood gas data not available in six to eight patients awake. †Shunt and low ventilation/perfusion ratios (low $\dot{V}_A/\dot{Q}$) data missing in three patients awake and low $\dot{V}_A/\dot{Q}$ data in one patient during anesthesia (but no missing data in awake condition). ‡Measurements limited to 48 to 51 patients.

in the transverse plane were done at end-expiration, 1 cm above the top of the right diaphragm (lung base). To identify atelectasis, the dorsal border between the thoracic wall and the dense areas was drawn manually, and the ventral border between inflated lung tissue and atelectasis was identified by the region-of-interest program after exclusion of any visible vessels. All pixels with attenuation values between −100 and +100 Hounsfield units in the region of interest were taken to represent atelectatic lung tissue. The total area of pixels within this range was calculated, and the atelectatic area presented in cm.[2,19]

Study Protocol

In the catheterization laboratory a radial artery and peripheral venous catheters were inserted and a balloon-tipped thermistor catheter advanced to the pulmonary artery under fluoroscopy. The patient was then moved to the radiology department and positioned on a computed tomography scan table. The inert gas infusion had been started before transfer to the radiology department, and after 40 min of rest (including transport) blood was sampled from systemic and pulmonary arteries, and mixed expired gas was collected *via* a heated mixing box for the assessment of shunt and low $\dot{V}_A/\dot{Q}$ (multiple inert gas elimination technique). Within 5 min, a lung computed tomography was taken. The patient was anesthetized on the computed tomography scan table, the trachea was intubated, and mechanical ventilation was commenced. Twenty minutes later, new blood sampling and expired gas collection were performed for the multiple inert gas elimination technique and blood gas analysis, followed by computed tomography. Finally, the patient, still anesthetized, was moved to the operating theater for the planned surgery. The study protocol is shown in figure 1. Throughout the study, the patient was supervised by both a medical doctor and a nurse who had no part in the study.

Statistics

Continuous variables were summarized by medians and interquartile range. Categorical variables were summarized by frequency counts. The Wilcoxon Mann–Whitney rank sum test was used to compare continuous variables between hospitals and the Wilcoxon sign-rank test to compare continuous variables before and during anesthesia in the same patients. The Fisher exact test was used to compare categorical variables between hospitals. Monotone associations were assessed by using Spearman's rank correlation.

Univariable regression analysis was used to assess the crude relation between gas exchange variables and predictors and confounders. Because distributions were skewed, the outcome measures shunt and low $\dot{V}_A/\dot{Q}$ were log-transformed before the regression analysis. A possible quadratic relation between certain gas exchange variables and age was tested by adding age^2 to the model, after first having mean-centered age to eliminate the collinearity between age and age^2. To evaluate the models with and without age^2 we used the Akaike information criterion defined as Akaike information criterion $= -2\max_\theta \{\log[L(\theta \mid x)]\} + 2k$, where $L(\theta \mid x)$ is the likelihood function and k the number of estimated parameters. The penalty $2k$ discourages overfitting.

Multiple regression analysis using the awake measure of the outcome as a covariate was used to assess the relation between age and body mass index and the gas exchange measures during anesthesia: (1) Pa_{O_2}/Fi_{O_2} ratio; (2) log shunt, and (3) log low $\dot{V}_A/\dot{Q}$. Both unadjusted and multi-adjusted models were assessed. The latter were adjusted for hospital, sex, smoking (ever or never), forced vital capacity in percent of predicted, and tidal volume divided by ideal body

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weight during anesthesia. The assumptions for the multiple regression analysis were checked visually by normal probability plots of the (n − 1)-fold cross-validated residuals. The variance inflation factor, which is the ratio of variance in a model with multiple terms and the variance of a model with one term, was used to quantify the degree of collinearity in the multiple regression analysis. It provides a measure of how much the variance of an estimated regression coefficient is increased as a result of collinearity. Ideally the variance inflation factor should be close to 1, but values less than 5 are considered acceptable.

We also considered including the interactions between age and hospital and body mass index and hospital in the multi-adjusted models, but this did not improve the models, instead they began to deteriorate, probably because of the limited number of patients.

SPSS version 24.0 (IBM, USA) was used for all analyses, except the multiple regression analyses, which were run in Minitab version 16.2.4 (Minitab Inc., USA), and the Akaike information criterion assessments, which were run in SAS version 9.4 (SAS Institute Inc., USA). A two-sided *p* value less than 0.05 was considered as statistically significant.

Results

Patient Baseline Characteristics and Differences between Study Sites

Table 1 gives summarized measures of sex, age, height, weight, body mass index, smoking habits, forced vital capacity, anesthesia type, and tidal volume during anesthesia categorized by study site. There was a larger number of patients from one hospital (Huddinge) than from the other (Uppsala). During anesthesia, the respiratory rate was set at a median of 12 breaths/min in Huddinge and 10 breaths/min in Uppsala, and tidal volume was adjusted to result in normoventilation (table 1). Thus, the tidal volume, divided by ideal body weight,[20] was slightly smaller in Huddinge, 8.6 *versus* 10.2 ml/kg (table 1). The resulting alveolar ventilation was essentially the same, as expressed by $PaCO_2$ (Huddinge: 36.0 [33.8 to 39.8], Uppsala: 34.5 [33.3 to 36.4]; $P = 0.074$).

Arterial oxygenation was normal at both study sites in awake patients, with no difference between sites in the Pa_{O_2}/F_{IO_2} ratio or low $\dot{V}_A/\dot{Q}$ (tables 2 and 3). However, shunt was larger in a few patients at Huddinge during measurements in awake patients, but no differences were seen during anesthesia (table 3).

Age and Arterial Oxygenation

In the awake patient, the Pa_{O_2}/F_{IO_2} ratio decreased with increasing age, similar to findings in previous studies on larger numbers of patients (fig. 2, table 3).[21]

During anesthesia, the Pa_{O_2}/F_{IO_2} ratio also decreased with increasing age, and more rapidly than it did in awake patients (regression coefficient for delta Pa_{O_2}/F_{IO_2} ratio, −2.98; $P = 0.003$; 95% CI, −4.95 to −1.02). However, the variation was large, and the squared correlation (r^2) was no greater than 0.17. No difference was seen between inhalational or intravenous anesthesia.

Influence of Body Mass Index and Other Factors on Arterial Oxygenation

The Pa_{O_2}/F_{IO_2} ratio was unaffected by body mass index in the waking state but fell with increasing body mass index during anesthesia (fig. 2, table 3). The r^2 between the Pa_{O_2}/F_{IO_2} ratio and body mass index was 0.26, and when both age and body mass index were included in the regression analysis, r^2 was 0.37. The other tested factors (study site, gender, smoking habits, and forced vital capacity) had no significant effect in single regression analysis (table 3).

Mechanisms of Impaired Oxygenation during Anesthesia: Shunt and Low $\dot{V}_A/\dot{Q}$

Log shunt as measured by multiple inert gas elimination technique showed a linear relation to age ($r^2 = 0.08$, $P = 0.010$). A quadratic function (age + age^2) resulted in a better fit with almost twice as high r^2 (0.17) and a clearly lower *p* value (0.001). Furthermore, the Akaike information criterion decreased from −165.4 to −171.1 when age^2 was added to the model. Thus, shunt increased when age increased from the youngest studied, 19 yr old, up to 45 yr, and then decreased up to the oldest patients, 69 yr old (fig. 3, table 3). Log low $\dot{V}_A/\dot{Q}$, on the other hand, showed a linear relation to age, with continuous increase from the youngest to the oldest patients (log low $\dot{V}_A/\dot{Q}$: $r^2 = 0.20$, $P < 0.001$) with a slope that was significant also after adjusting for awake state (table 3). There was no improvement by including age^2; r^2: 0.20 and 0.21 respectively, and $P = 0.001$ for both models. Here Akaike information criterion increased from −157.1 to −155.4 when age^2 was added to the model indicating that adding age^2 failed to improve model fit. The better fit with a quadratic relation between age and log shunt compared to a linear relation, but not between age and log low $\dot{V}_A/\dot{Q}$, is shown in figure 4.

Log shunt was linearly related to body mass index ($r^2 = 0.15$, $P < 0.001$; fig. 3, table 3). No association was seen between body mass index and log low $\dot{V}_A/\dot{Q}$ ($r^2 = 0.01$, $P = 0.360$; fig. 5, table 3).

Adding body mass index in a multiple regression analysis of log shunt *versus* age + age^2 showed a further strengthening of the relation ($r^2 = 0.27$, $P < 0.001$ and Akaike information criterion = −179.3 *vs.* $r^2 = 0.17$, $P = 0.001$ and Akaike information criterion = −171.1 compared with age + age^2 alone). A multiple regression analysis was also performed adjusting for hospital, sex, smoking (ever or never), forced vital capacity in percent of reference, and tidal volume divided by ideal body weight during anesthesia. However, in no case did these potential confounders alter the results on log shunt or log low $\dot{V}_A/\dot{Q}$ (table 4). The assumptions

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Table 3. Univariable Regression Analysis of Factors (Site, Sex, Smoking, Age, BMI, FVC%) That May Influence Pao_2/FIO_2 Ratio, Shunt, or Low $\dot{V}_A/\dot{Q}$.

	Awake					Anesthesia					Anesthesia Adjusted for Awake				
	n	r^2	*B*	95% CI	*p*	n	r^2	*B*	95% CI	*p*	n	r^2	*B*	95% CI	*p*
PaO_2/FIO_2 ratio															
Site	72	0.00	−1.44	−26.16 to 23.27	0.908	80	0.01	−25.54	−80.90 to 29.90	0.362	72	0.15	−12.93	−65.92 to 40.07	0.628
Gender	72	0.04	21.33	−3.80 to 46.45	0.095	80	0.01	24.26	−34.80 to 83.30	0.416	72	0.14	0.31	−55.85 to 56.47	0.991
Smoking	72	0.01	−11.77	−35.24 to 11.70	0.321	80	0.03	−38.50	−90.50 to 13.50	0.145	72	0.14	−3.52	−30.21 to 23.16	0.793
Age	72	0.15	−1.59	−2.49 to −0.69	0.001	80	0.17	−3.99	−5.99 to −2.00	<0.001	72	0.28	−3.76	−5.86 to −1.67	0.001
BMI	72	0.01	−2.03	−6.44 to 2.39	0.363	80	0.26	−22.39	−31.00 to −13.90	<0.001	72	0.32	−18.17	−26.71 to −9.64	<0.001
$FVC_{\%}$	70	0.00	0.24	−0.69 to 1.16	0.610	76	0.02	1.34	−0.75 to 3.42	0.206	70	0.14	0.48	−1.51 to 2.46	0.633
Log shunt															
Site	77	0.09	−0.11	−0.19 to −0.03	0.008	80	0.01	0.07	−0.10 to 0.25	0.415	77	0.09	0.15	−0.23 to 0.33	0.087
Gender	77	0.02	−0.31	−0.75 to 0.14	0.176	80	0.00	0.02	−0.17 to 0.20	0.846	77	0.06	0.06	−0.12 to 0.24	0.505
Smoking	77	0.00	0.004	−0.09 to 0.08	0.930	80	0.01	0.09	−0.08 to 0.25	0.307	77	0.05	0.03	−0.06 to 0.11	0.562
Age*	77	0.02	0.002	0.00 to 0.01	0.245	80	0.08	0.009	0.000 to 0.02	0.010	77	0.14	0.009	0.003 to 0.020	0.007
Age**						80		0.007	0.000 to 0.013	0.036	77		0.007	−0.001 to 0.000	0.031
Age^2**						80	0.17	−0.001	−0.001 to 0.000	0.007	77	0.21	−0.001	−0.001 to 0.000	0.010
BMI	77	0.01	0.01	−0.01 to 0.02	0.309	80	0.15	0.05	0.03 to 0.08	<0.001	77	0.17	0.05	0.02 to 0.08	0.002
$FVC_{\%}$	74	0.05	0.003	0.00 to 0.01	0.048	76	0.02	−0.004	−0.01 to 0.00	0.284	74	0.10	−0.006	−0.01 to 0.001	0.084
Log low $\dot{V}_A/\dot{Q}$															
Site	77	0.04	0.14	−0.03 to 0.30	0.101	79	0.01	−0.09	−0.29 to 0.11	0.368	76	0.09	−0.14	−0.34 to −0.05	0.152
Gender	77	0.02	−0.11	−0.28 to 0.07	0.231	79	0.01	−0.11	−0.32 to 0.10	0.309	76	0.08	−0.08	−0.29 to 0.13	0.445
Smoking	77	0.01	−0.08	−0.24 to 0.08	0.327	79	0.02	0.13	−0.06 to 0.31	0.177	76	0.09	0.06	−0.03 to 0.16	0.186
Age	77	0.13	0.010	0.00 to 0.02	0.001	79	0.20	0.015	0.01 to 0.02	<0.001	76	0.21	0.01	0.01 to 0.02	<0.001
BMI	77	0.00	0.004	−0.03 to 0.04	0.779	79	0.01	0.016	−0.02 to 0.05	0.360	76	0.08	0.02	−0.02 to 0.05	0.365
$FVC_{\%}$	74	0.00	0.002	−0.01 to 0.01	0.607	75	0.00	0.000	−0.01 to 0.01	0.781	73	0.06	0.00	−0.01 to 0.01	0.898

Note that for log shunt the regression analysis is based on (*): age, and (**): age + age^2, where r^2 denotes the value for the total model. BMI, body mass index; FIO_2, inspired oxygen fraction; $FVC_{\%}$, forced vital capacity in percent of predicted; PaO_2, arterial oxygen tension; $\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio.

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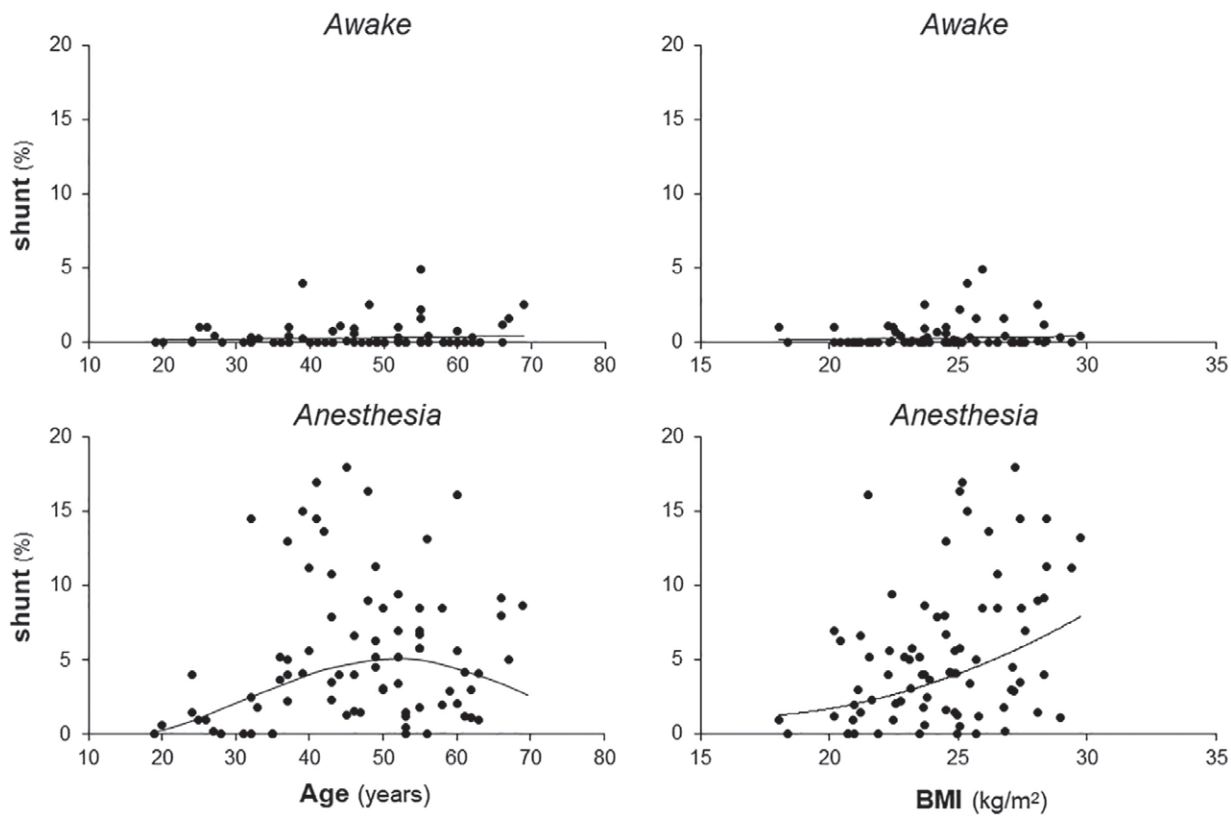

Fig. 3. Shunt during air breathing awake (*upper panels*), and during anesthesia with mechanical ventilation (*lower panels*). Dependence on age is shown to the left, and dependence on body mass index (BMI) is shown to the right. For visual clarity, shunt values are presented on a linear scale (*y* axis). Regression equations have been performed on log shunt, explaining the more or less curved appearance in the panels. Age: Log shunt awake, $y = 0.002x + 0.011$, $P = 0.245$; Log shunt anesthetized, $y = -0.0006x^2 + 0.0069x + 0.761$, $P = 0.001$; *x*, age in years; *y*, log shunt in percent of cardiac output. Body mass index: Log shunt awake, $y = 0.008x - 0.091$, $P = 0.309$; Log shunt anesthetized, $y = 0.054x - 0.638$; $P < 0.001$; *x*, body mass index in kg/m²' *y*, log shunt in percent of cardiac output.

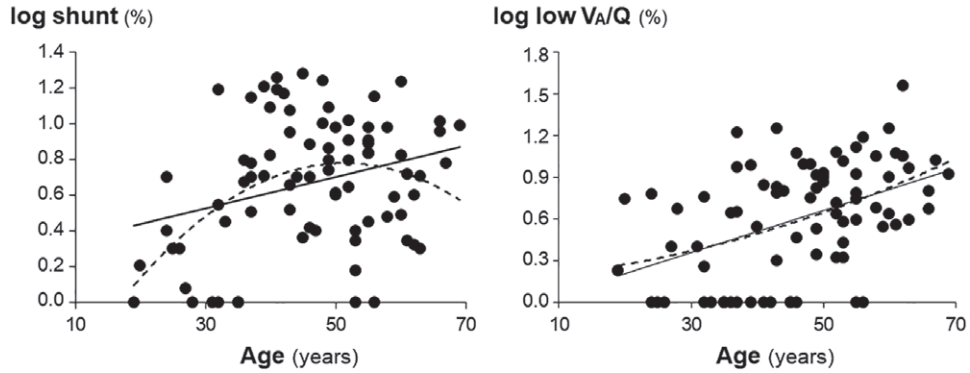

Fig. 4. Log shunt (left panel) and log low $\dot{V}_A/\dot{Q}$ (right panel) during anesthesia plotted against age including both a linear and a quadratic function. Note the clear quadratic relations on log shunt but not on log low $\dot{V}_A/\dot{Q}$, where the quadratic and linear relations almost coincide. Equations for log shunt: Linear function, $y = 0.0087x + 0.667$, $r^2 = 0.082$, $P = 0.010$; quadratic function, $y = -0.0006x^2 + 0.0069x + 0.761$, $r^2 = 0.166$, $P = 0.001$; where x = age in years and y = log shunt in percent of cardiac output. Equations for log low $\dot{V}_A/\dot{Q}$: Linear function, $y = 0.0152x + 0.604$; $r^2 = 0.202$, $P < 0.001$; quadratic function, $y = 0.0001x^2 + 0.016x + 0.584$; $r^2 = 0.205$, $P < 0.001$; where x = age in years and y = log low $\dot{V}_A/\dot{Q}$ in percent of cardiac output.

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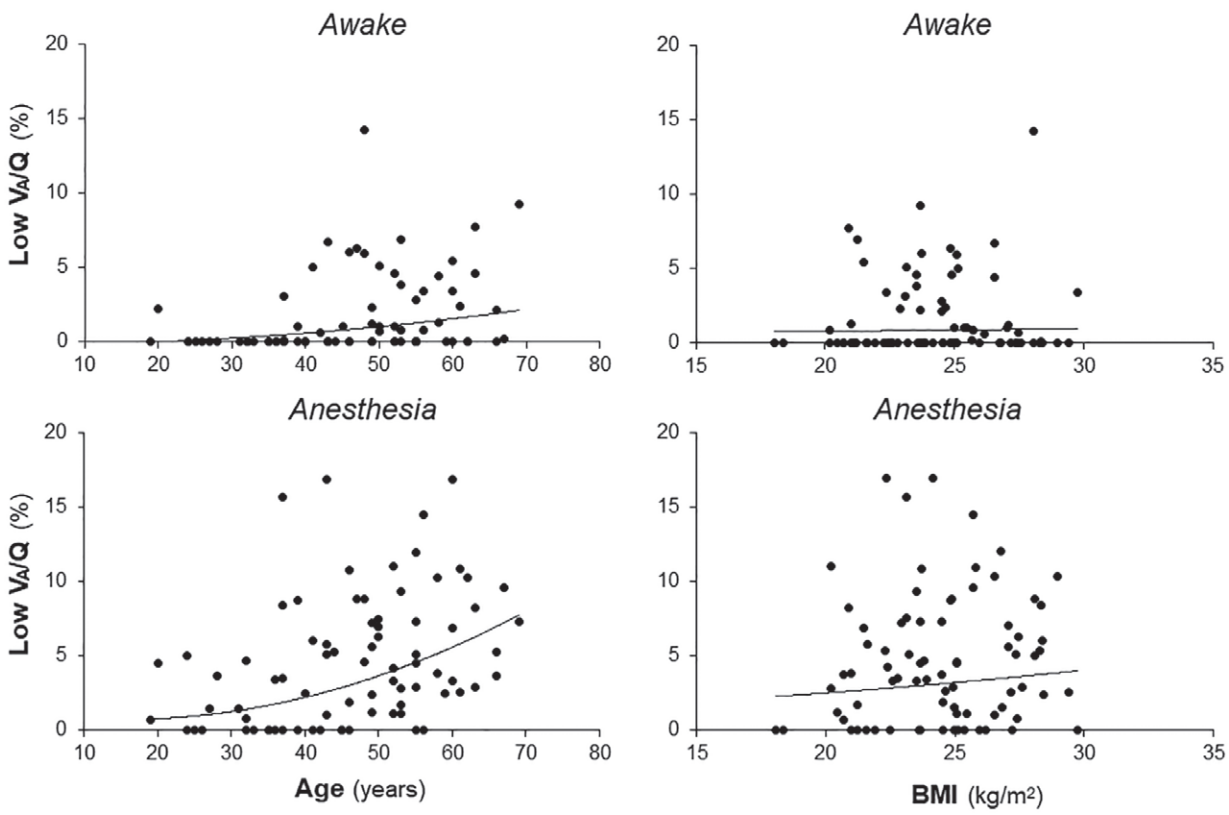

Fig. 5. Low $\dot{V}_A/\dot{Q}$ during air breathing awake (*upper panels*) and during anesthesia with mechanical ventilation (*lower panels*). Dependence on age is shown to the left, and dependence on body mass index (BMI) is shown to the right. For visual clarity, low $\dot{V}_A/\dot{Q}$ values are presented on a linear scale (*y* axis). Regression equations have been performed on log low $\dot{V}_A/\dot{Q}$, explaining the more or less curved appearance in the panels. The exclusion of an outlier with a low $\dot{V}_A/\dot{Q}$ of 35% did not significantly change the slope of the regression line, and the equations below include the outlier. Age: Log low $\dot{V}_A/\dot{Q}$ awake, $y = 0.010x - 0.217$, $P = 0.001$; Log low $\dot{V}_A/\dot{Q}$ anesthetized, $y = 0.015x - 0.093$, $P < 0.001$; *x*, age in years; *y*, log low $\dot{V}_A/\dot{Q}$ in percent of cardiac output. Body mass index: Log low $\dot{V}_A/\dot{Q}$ awake, $y = 0.004x + 0.159$, $P = 0.779$; Log low $\dot{V}_A/\dot{Q}$ anesthetized, $y = -0.016x + 0.224$, $P = 0.360$; *x*, body mass index in kg/m²; *y*, log low $\dot{V}_A/\dot{Q}$ in percent of cardiac output.

for the multiple regression analysis were checked visually by normal probability plots of the (n − 1)-fold cross-validated residuals (see Supplemental Digital Content 1, http://links.lww.com/ALN/B919). These plots show that the residuals are approximately normally distributed. The shunt was related to atelectasis, as assessed by computed tomography ($r^2 = 0.58$, $P < 0.001$; fig. 6).

Influence of Cardiac Output in Relation to Metabolic Demand

Finally, a test was made of whether cardiac output in relation to the metabolic demand, expressed as arterial-mixed venous oxygen content difference, was affected by anesthesia. Median arterial-mixed venous oxygen content difference was significantly lower during anesthesia than awake (table 2), with no significant influence owing to age or body mass index ($P = 0.337$ and 0.071, respectively). Thus, any worsening of arterial oxygenation during anesthesia could not be explained by a decrease in cardiac output in relation to the metabolic demand.

Discussion

In the present study, a retrospective analysis of pooled data from two different hospitals was done in awake nonobese (body mass index less than 30 kg/m²) patients, free from cardio-pulmonary disease and subsequently during anesthesia and mechanical ventilation without PEEP, before surgery. During anesthesia, the Pa_{O_2}/F_{IO_2} ratio decreased continuously with increasing age and also with increasing body mass index, despite no obese patients being included. Shunt, on the other hand, increased in patients up to around the age of 45 yr and then decreased with further increase in age. Low $\dot{V}_A/\dot{Q}$ increased linearly with age and became a more important cause of oxygenation impairment than shunt in

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Table 4. Unadjusted and Multi-adjusted Regression Analyses of Pa_{O_2}/F_{IO_2} Ratio, Shunt, and Low $\dot{V}_A/\dot{Q}$ during Anesthesia *versus* Age and BMI, Using the Awake State Measure as Covariate

Outcome	Predictor	Regression Coefficient	95% Confidence Interval	*P* Value	VIF
PaO_2/FIO_2 ratio an, n = 72	PaO_2/FIO_2 ratio aw	0.475	0.011 to 0.939	0.045	1.18
	Age	−3.15	−5.08 to −1.23	0.002	1.21
	BMI	−16.1	−24.1 to −8.0	< 0.001	1.04
PaO_2/FIO_2 ratio an*, n = 69	PaO_2/FIO_2 ratio aw	0.564	0.084 to 1.044	0.022	1.23
	Age	−3.45	−5.32 to −1.59	< 0.001	1.20
	BMI	−11.2	−20.1 to −2.3	0.022	1.21
Log shunt an, n = 77	log_Shunt aw	0.360	−0.047 to 0.767	0.082	1.04
	Age	0.006	−0.000 to 0.012	0.054	1.09
	Age^2	−0.0005	−0.0010 to −0.0001	0.018	1.08
	BMI	0.038	0.010 to 0.066	0.008	1.05
Log shunt an*, n = 73	log_Shunt aw	0.641	0.190 to 1.091	0.006	1.25
	Age	0.006	−0.001 to 0.012	0.070	1.13
	Age^2	−0.0006	−0.0011 to −0.0008	0.007	1.14
	BMI	0.039	0.007 to 0.071	0.017	1.25
Log low $\dot{V}_A/\dot{Q}$ an, n = 76	log_low $\dot{V}_A/\dot{Q}$ aw	0.134	−0.125 to 0.393	0.307	1.15
	Age	0.013	0.006 to 0.021	0.001	1.18
	BMI	0.007	−0.026 to 0.039	0.690	1.03
Log low $\dot{V}_A/\dot{Q}$ an*, n = 72	log_low $\dot{V}_A/\dot{Q}$ aw	0.192	−0.097 to 0.482	0.189	1.33
	Age	0.012	0.004 to 0.020	0.005	1.27
	BMI	0.007	−0.031 to 0.046	0.708	1.22

*Regression coefficients adjusted for hospital, sex, smoking (ever or never), forced vital capacity in percent of predicted, and tidal volume divided by ideal body weight during anesthesia. The latter was adjusted for hospital because the respiratory rate was set at a different target in the two hospitals. an, anesthesia; aw, awake; BMI, body mass index; F_{IO_2}, inspired oxygen fraction; FVC%, forced vital capacity in percent of predicted; Pa_{O_2}, arterial oxygen tension; $\dot{V}_A/\dot{Q}$, ventilation/perfusion ratio; VIF, variance inflation factor.

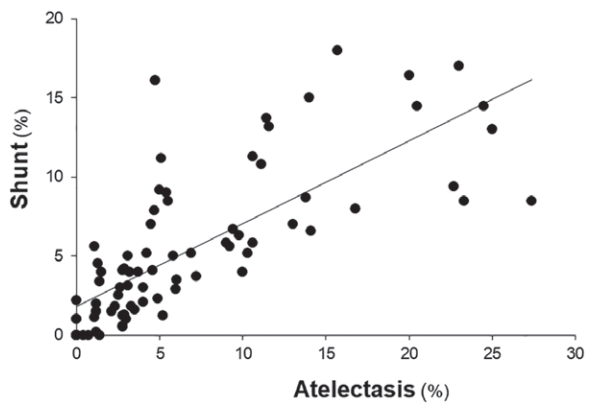

Fig. 6. Shunt during anesthesia and mechanical ventilation plotted against atelectasis. Equation: $y = 0.52x + 1.82$, $r^2 = 0.58$, $P = 0.001$, where x = atelectasis in cm^2 and y = shunt in percent of cardiac output.

elderly patients. We also found that shunt increased linearly with increasing body mass index. However, body mass index had no influence on low $\dot{V}_A/\dot{Q}$. Thus, the main hypothesis that shunt and low $\dot{V}_A/\dot{Q}$ are major causes of impaired oxygenation during anesthesia was supported by our data, but their relative contributions in relation to age and to body mass index are different, as will be discussed below. The secondary hypothesis, that reduced cardiac output caused additional impairment of oxygenation, could not be proven.

Although it seems easy to explain the worsened oxygenation when body mass index increases (*i.e.*, by atelectasis-induced shunt), the age-dependent worsening is more difficult to explain. However, we suggest the following mechanism. Cyclic airway closure (opening and closing during a breath) is a normal phenomenon in the waking state and increases with age.[22] The amount of airway closure increases during anesthesia as a result of the fall in resting lung volume (functional residual capacity),[23] and the closure may be continuous throughout the breath. Gas, especially oxygen, behind closed airways will be absorbed, eventually resulting in atelectasis formation, and the higher the oxygen concentration, the more rapid the formation of atelectasis.[24] Thus, it seems reasonable to explain the increased shunt up to around age 45 by increasing amount of atelectasis. But why do we see a decrease of shunt in the older patients? A possible explanation is that preoxygenation during the induction of anesthesia is less successful or requires more time in elderly patients because of more airway closure in these patients, both when awake and during anesthesia. Thus, if preoxygenation is given for the same period of time in elderly patients as in younger ones, the result is a lower alveolar oxygen concentration and more remaining nitrogen in the elderly patients.[25] Nitrogen acts as a scaffold and counters atelectasis. We have previously shown this probable mechanism using preoxygenation with 60% or 80% O_2,

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which causes much less atelectasis than preoxygenation with 100% O_2.[26] If only 30% O_2 is given during the induction, essentially no atelectasis is produced.[27] Thus, in one sense, the slower and mostly incomplete oxygenation of alveoli during the induction of anesthesia in elderly patients prevents them from developing more atelectasis than would otherwise be expected. If the preoxygenation had lasted longer than 1 to 3 min (the time used in the present study), then alveolar oxygen tension might have been as high in the elderly patients as it was in younger patients, and atelectasis would have been larger.[28] However, Pa_{O_2} continued to fall during anesthesia in relation to increasing patient age, despite decreasing shunt, because of an increasing amount of low $\dot{V}_A/\dot{Q}$. The latter can be explained by cyclic airway closure, creating regions with poor ventilation in relation to blood flow.[16]

The different age-dependent behaviors of shunt and low $\dot{V}_A/\dot{Q}$ can be illustrated by calculating the magnitude of shunt and of low $\dot{V}_A/\dot{Q}$ in three hypothetical patients, 25, 45, and 65 yr old. The resulting shunt and low $\dot{V}_A/\dot{Q}$ are 2.0% and 1.2% of cardiac output in the young patient, 5.8% and 4.6% in the middle-aged, and 2.4% and 8.0% in the elderly patient. Thus, the young patient had a minor shunt and almost no low $\dot{V}_A/\dot{Q}$. The middle-aged patient had considerable shunt and a low $\dot{V}_A/\dot{Q}$. The elderly patient had less shunt, but twice as much low $\dot{V}_A/\dot{Q}$ as the middle-aged patient. Low $\dot{V}_A/\dot{Q}$ was almost eight times higher in the elderly patient than in the younger patients.

The individual effect of shunt and low $\dot{V}_A/\dot{Q}$ on Pa_{O_2} is difficult to estimate since the impact of $\dot{V}_A/\dot{Q}$ will depend on the scatter of $\dot{V}_A/\dot{Q}$ ratios and their median values and on the F_{IO_2}.[29] No analysis of the separate effect on Pa_{O_2} of shunt and low $\dot{V}_A/\dot{Q}$ was therefore made. However, the finding of an increased amount of low $\dot{V}_A/\dot{Q}$ in anesthetized elderly patients suggests that it could be advantageous to modify the ventilatory regime in these patients compared with what is considered appropriate in younger patients. Thus, a recruitment maneuver, commonly recommended during anesthesia,[30,31] will be less useful in elderly patients because there is less shunt and presumably atelectasis to be opened up. Stabilizing airways to prevent them from closing seems to be important in elderly patients to maintain sufficient arterial oxygenation. Airway closure is a cause of lung impairment, also during mechanical ventilation in the intensive care unit.[32] An age-dependent low $\dot{V}_A/\dot{Q}$ can thus be an additional cause of respiratory problems in intensive care patients, and this should be taken into consideration to assure optimal treatment.

Airway closure can be prevented in several ways. Increase in lung volume will widen airways and can be achieved by PEEP. Because PEEP in itself will counter atelectasis,[33] it seems to be a first choice that may reduce both shunt and low $\dot{V}_A/\dot{Q}$. However, the hemodynamic effects of PEEP may limit its use, especially in low cardiac output states or in patients with diastolic heart dysfunction.[34] Another approach is to decrease expiratory flow, because it will prevent or delay the appearance of airway closure,[35] a procedure that can be compared with the pursed-lips breathing taught to patients with chronic obstructive lung disease. A technique with intentional decrease of expiratory flow during mechanical ventilation has also been tested, but the influence of age was not evaluated.[36]

There are limitations to the study, mainly related to the use of a complicated technique, the multiple inert gas elimination technique, in anesthetized patients. The main reason for using this technique rests on the fact that no other technique enables similar discrimination between different causes of oxygenation impairment. However, the multiple inert gas elimination technique has no spatial resolution, so if shunt or low $\dot{V}_A/\dot{Q}$ is present, additional techniques are needed to demonstrate what causes them. In the present study, the amount of multiple inert gas elimination technique shunt was related to the amount of atelectasis as assessed by computed tomography. This suggests that shunt is occurring primarily in atelectatic regions of the lung. Another limitation of this study was that no obese patients were studied with multiple inert gas elimination technique; however, a linear relation was seen between body mass index and shunt. Whether such a relation is seen in severely obese patients remains to be determined. Another uncertainty is that data were obtained in two different hospitals. However, median values for Pa_{O_2}/F_{IO_2} ratio, shunt, and low $\dot{V}_A/\dot{Q}$ were similar in these hospitals, and adding interactions between age and hospitals and body mass index and hospitals revealed no differences between them. Finally, only 80 patients have been studied, but use of an advanced technique under experimental conditions will always limit the number of patients studied.

In conclusion, arterial oxygenation during anesthesia is impaired more in elderly and overweight patients than in younger and leaner ones, but the causes are to some extent different. Thus, in the overweight patient, atelectasis-induced shunt can explain the oxygenation impairment. In the elderly patient, the additional oxygenation impairment is explained mainly by an increasing amount of low $\dot{V}_A/\dot{Q}$, likely caused by airway narrowing and airway closure. In addition to efforts to reduce atelectasis during anesthesia, attention should also be directed toward prevention of airway closure in elderly patients. The development of techniques to stabilize airways may be an interesting new target in anesthesia.

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Competing Interests

The authors declare no competing interests.

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Appendix: Studies included in this study

The authors pooled previously collected data from all patients studied by our group. Studies included are:

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