Contribution of multiple inert gas elimination technique to pulmonary medicine · 6

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Ventilation-perfusion relationships during anaesthesia

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Anaesthesia is given on approximately 60 000–70 000 occasions per million inhabitants in Western Europe and Scandinavia with more than half of these being general anaesthetics.

It has been well known for about a century that the oxygenation of arterial blood is impaired during anaesthesia; as early as 1943 Maier and Cournand[1] found that the oxygen saturation of arterial blood was reduced after thoracotomy. In 1958, after the introduction of the blood gas electrodes, Campbell and coworkers[2] showed that anaesthesia was often associated with an increased alveolar-arterial oxygen tension difference. Sometimes life threatening hypoxaemia can develop. It is generally held that the impairment of arterial oxygenation during anaesthesia is more severe in older subjects.[3] Obesity is associated with a decrease in the oxygenation of blood,[4] and smokers show more gas exchange impairment than non-smokers.[5] The impairment in arterial oxygenation has made it routine to increase the inspired oxygen fraction during anaesthesia to 0·3–0·4 during an uncomplicated procedure, and even higher during anaesthesia in obese, bronchitic, or elderly patients. Despite numerous studies the causes of impaired gas exchange during anaesthesia have remained unclear; it is not until the last decade that a better understanding of the underlying mechanisms have been elucidated. The application of two advanced techniques in anaesthesia accounts for most of our new insight into gas exchange impairment in the anaesthetised subject – the multiple inert gas elimination technique (MIGET) and computed tomographic scanning (CT). However, before proceeding with the findings made with these techniques a short review of proposed mechanisms for impaired gas exchange during anaesthesia is presented.

ABSORPTION ATELECTASIS

Bendixen and coworkers[6] published their "concept of atelectasis" 30 years ago. They noticed successive decreases in lung compliance and arterial oxygen tension (Pa_{O_2}) which returned towards normal after deep inflation of the lungs. The authors proposed slow development of absorption atelectasis. Other groups were unable to reproduce their results, however, but found a rapid decrease in compliance and arterial oxygen tension on induction of anaesthesia.[3 7 8] Moreover, atelectasis could not be shown on conventional chest radiographs. Atelectasis was therefore considered to be an unlikely cause of impaired oxygenation during anaesthesia.

AIRWAY CLOSURE

In 1966 Milic-Emili and coworkers[9] demonstrated airway closure in dependent lung regions during a deep expiration in awake, healthy volunteers. In view of the reduced functional residual capacity (FRC) during anaesthesia[10] the question arose as to whether airway closure was the cause of impaired gas exchange. Don *et al*[11] found that gas was trapped in the lungs during anaesthesia and that it could be released only by deep inflations. A few years later direct evidence of airway closure was shown.[12 13] Conflicting reports have, however, been presented and varying correlations between the magnitude of airway closure and the degree of impaired arterial oxygenation have been reported.[12 14 15] Airway closure is therefore unlikely to be a major contributor to the impaired gas exchange during anaesthesia although it may be a factor.

HYPOXIC PULMONARY VASOCONSTRICTION

In 1946 von Euler and Liljestrand[16] observed that hypoxia produced pulmonary vasoconstriction and some 20 years later Thilenius[17] showed that inhalational anaesthetics attenuated hypoxic vasoconstriction. In later studies Sykes and coworkers showed that most inhalational anaesthetics attenuate hypoxic vasoconstriction.[18] Bjertnaes, on the other hand, found that intravenous barbiturates did not reduce hypoxic vasoconstriction.[19] Results vary, however, presumably because of confounding factors obscuring the hypoxic vasoconstriction response.[20] It should also be stressed that attenuation of hypoxic vasoconstriction does not cause impairment of the gas exchange unless an underlying disturbance of lung function causing a lowered Pa_{O_2}

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is present. Thus, release of hypoxic vasoconstriction by the anaesthetic agent augments an already existing impairment of gas exchange, but does not lead to disturbances in an otherwise normally functioning lung.

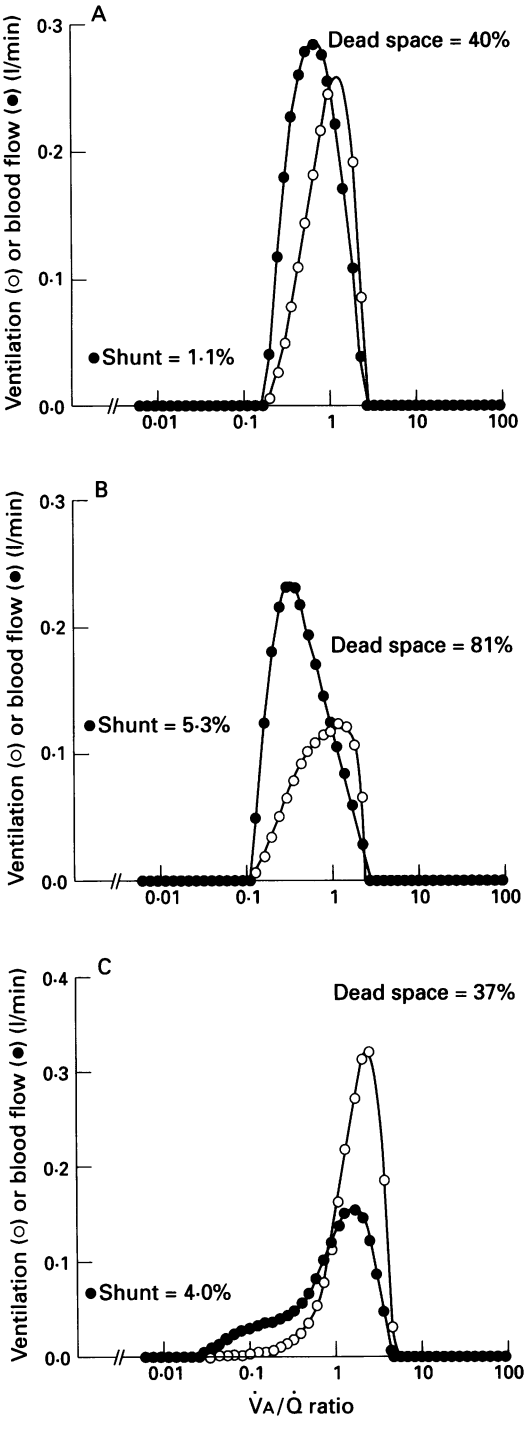

Figure 1 Distributions of $\dot{V}A/\dot{Q}$ in a 43 year old man with no cardiopulmonary disease before elective surgery (A) when awake, (B) during enflurane anaesthesia spontaneously breathing through a face mask (non-intubated, non-paralysed), and (C) after endotracheal intubation and muscle paralysis with mechanical ventilation. Inspired oxygen fraction was 0·21 during the awake recording and 0·40 during anaesthesia. Note the good matching of ventilation and blood flow in the awake situation and the presence of only a small shunt. Anaesthesia and spontaneous breathing caused some widening of the $\dot{V}A/\dot{Q}$ distribution, an increase in shunt and dead space ventilation. Intubation and muscle paralysis caused a slight widening of the $\dot{V}A/\dot{Q}$ distribution and reduced dead space ventilation to about the same level as when awake. From Tokics et al,[44] previously unpublished figure.

GAS DISTRIBUTION

Hulands *et al*[21] and Rehder *et al*,[22 23] using either an isotope technique or nitrogen washout, found decreased ventilation of the dependent lung regions in anaesthetised spontaneously breathing individuals, and during muscle paralysis and mechanical ventilation. Hulands *et al*[21] also found a small increase in perfusion of dependent lung regions with a subsequent

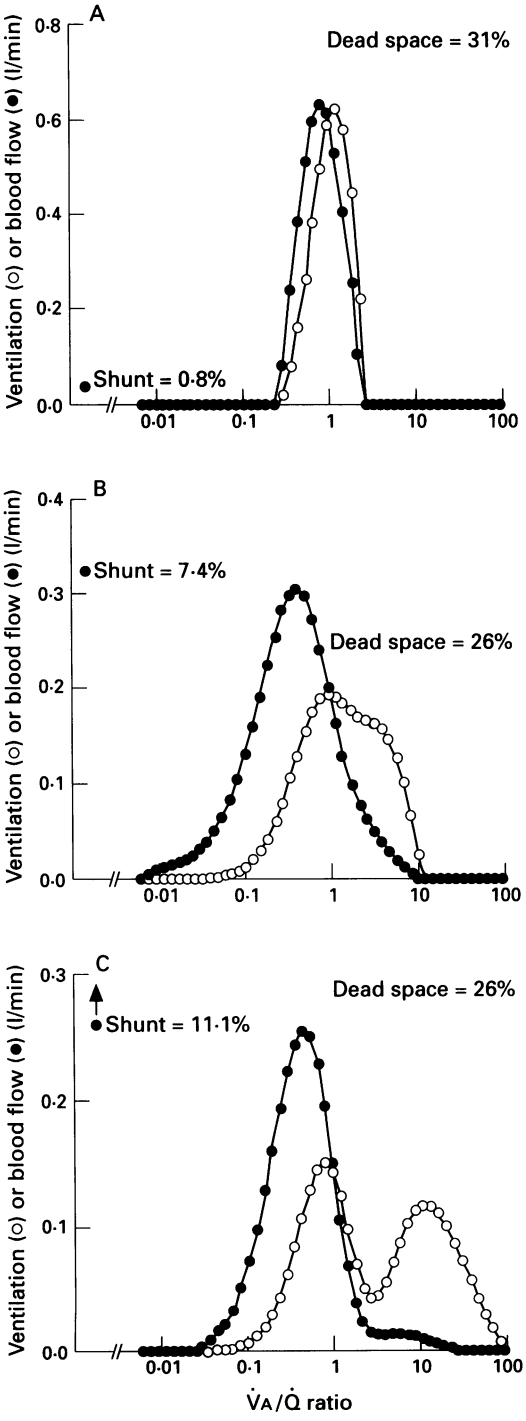

Figure 2 Distribution of $\dot{V}A/\dot{Q}$ in a 62 year old woman with no cardiopulmonary disease before cholecystectomy (A) when awake, (B) during anaesthesia and paralysis with mechanical ventilation, and (C) after addition of a PEEP of 10 cm H_2O. Note the good matching of ventilation and blood flow when awake with almost no shunt, and the considerable $\dot{V}A/\dot{Q}$ mismatch during anaesthesia as well as appearance of shunt. With PEEP, further widening of the $\dot{V}A/\dot{Q}$ distribution was seen with the appearance of high $\dot{V}A/\dot{Q}$ mode and an increased shunt. From Tokics et al,[44] previously unpublished figure.

Mean (SD) ventilation-perfusion relationships in subjects with no cardiopulmonary disease (normal, n = 45)[48] and patients with severe chronic obstructive pulmonary disease (COPD, n = 10),[50] awake and during general anaesthesia and muscle paralysis

	QMEAN	log SDQ	VMEAN	log SDV	Shunt (% $\dot{Q}_T$)	Dead space (% $\dot{V}_T$)	PaO_2 (kPa)
Normal							
Awake	0·76 (0·33)	0·68 (0·28)	1·11 (0·52)	0·52 (0·15)	0·5 (1·0)	34·8 (14·2)	12·5 (1·7)
Anaesthesia	0·65 (0·34)	1·04 (0·36)	1·38 (0·76)	0·76 (0·31)	4·8 (4·1)	35·0 (9·9)	21·4 (6·4)
COPD							
Awake	0·64 (0·29)	0·94 (0·23)	1·37 (0·66)	0·80 (0·26)	0·7 (0·9)	43·0 (7·5)	9·6 (1·3)
Anaesthesia	0·61 (0·18)	1·30 (0·33)	2·41 (0·84)	1·03 (0·33)	1·0 (1·1)	32·9 (7·5)	16·8 (6·1)

QMEAN, VMEAN = mean $\dot{V}_A/\dot{Q}$ of the perfusion and ventilation distribution; log SDQ, log SDV = logarithmic standard deviation of the perfusion and ventilation distributions. Inspired oxygen fraction: awake 0·21, anaesthesia 0·40.

increase in the scatter of ventilation-perfusion ratios. However, no clear quantitative analysis was possible and the mechanism behind the increased scatter remained unknown.

Ventilation-perfusion relationships

Severinghaus and Stupfel[24] showed that anaesthesia caused impaired elimination of carbon dioxide. Using a single breath washout technique, Nunn and Hill[25] found that the anatomical (or series) dead space (mainly airways) was unchanged during anaesthesia, indicating that the alveolar (or parallel) dead space (ventilated but unperfused alveoli) was increased. Venous admixture, as calculated according to the standard oxygen "shunt" equation, is also increased during anaesthesia to approximately 10% of cardiac output.[26] However, the elimination of carbon dioxide and oxygenation of blood allow no detailed analysis of the ventilation-perfusion relationships ($\dot{V}_A/\dot{Q}$), and do not enable a clear separation of dead space and lung regions ventilated in excess of their perfusion (high $\dot{V}_A/\dot{Q}$ regions). Similarly, venous admixture includes not just perfusion of non-ventilated lung tissue (true shunt), but also regions which are poorly ventilated or perfused in excess of their ventilation ("low $\dot{V}_A/\dot{Q}$ regions"). The MIGET method, introduced in 1974,[27] makes the construction of a virtually continuous distribution of ventilation-perfusion ratios possible. In young healthy volunteers studied by MIGET during anaesthesia with thiopentone and methoxyflurane both ventilation and perfusion were distributed to wider ranges of $\dot{V}_A/\dot{Q}$ ratios after induction of anaesthesia and muscle paralysis.[28] Shunt, on the other hand, was little affected with a mean value of approximately 1%. This contrasted with the larger shunt found in subjects of the same age during halothane an-

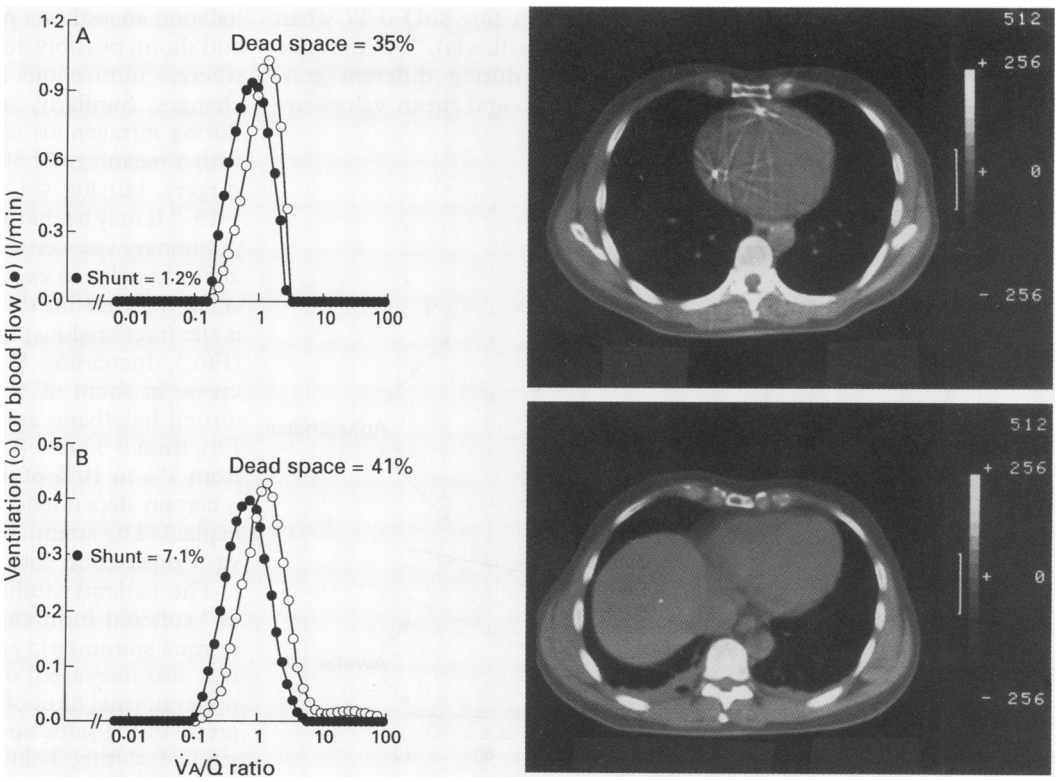

Figure 3 Transverse computed tomographic (CT) scans of the chest and $\dot{V}_A/\dot{Q}$ distributions in a patient who was to undergo cholecystectomy (A) when awake, and (B) during anaesthesia and paralysis prior to surgery. When awake there were no densities in dependent lung regions on the CT scan and the $\dot{V}_A/\dot{Q}$ distribution was normal. During inhalational (enflurane) anaesthesia and paralysis dense regions are seen in dependent lung regions on the CT scan. Shunt increased with widening of the $\dot{V}_A/\dot{Q}$ distribution (increased log SDQ). From Gunnarsson et al.[50]

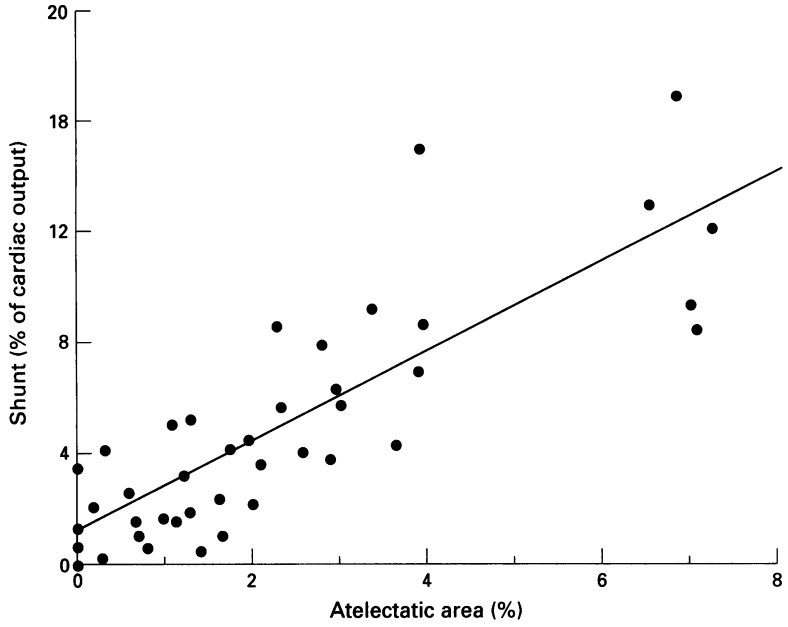

Figure 4 Atelectatic area (% of intrathoracic area) and shunt (% of cardiac output) during anaesthesia. Regression equation: Shunt = 1·6 × atelectatic area + 1·7; r = 0·81, p <0·001. From Gunnarsson et al.[48]

aesthesia and muscle paralysis.[29] A mean shunt of 8% was present with a range from 0% to 23%, as well as an increase in the scatter of $\dot{V}A/\dot{Q}$ ratios, expressed as the logarithmic standard deviation of the perfusion distribution (log SDQ) which almost doubled from 0·43 when awake to 0·80 during anaesthesia.[29]

An increase in shunt from 1·6% when awake to a mean of 8·6% during anaesthesia was recorded in other studies on older (37–64 years) surgical patients, and there was a widening of the $\dot{V}A/\dot{Q}$ distribution (log SDQ 0·47 when awake, 1·01 during anaesthesia).[30] An example of $\dot{V}A/\dot{Q}$ distributions during different conditions is given in fig 1 and mean values are given in the table.

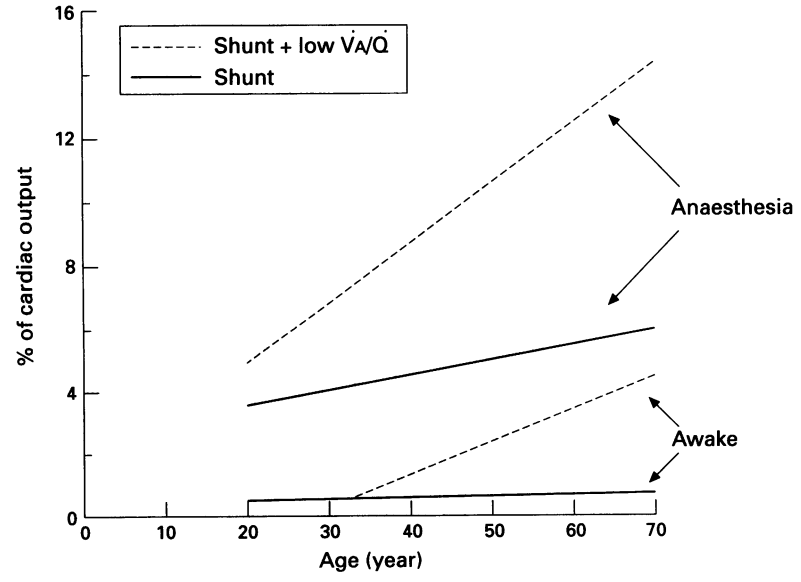

Figure 5 Schematic drawing of shunt and the sum of shunt and perfusion of regions with low $\dot{V}A/\dot{Q}$ against age when awake and during anaesthesia. Note the appearance or increase of shunt during anaesthesia and the increasing perfusion of low $\dot{V}A/\dot{Q}$ regions with age both when awake and during anaesthesia. From Gunnarsson et al.[48]

In elderly patients with more severe impairment of lung function, halothane anaesthesia with muscle paralysis, with or without nitrous oxide, caused considerable widening of the $\dot{V}A/\dot{Q}$ distribution with log SDQ increasing from 0·87 when awake to 1·73 during anaesthesia.[31] In addition, shunt increased to a mean of 15% but with a large range (0–30%). Thus, the most consistent findings during anaesthesia are an increased $\dot{V}A/\dot{Q}$ mismatch, expressed as an increased log SDQ, and an increase in shunt.

During anaesthesia and mechanical ventilation regions with high $\dot{V}A/\dot{Q}$ ratios develop, and the ratios further increase during ventilation with greater levels of PEEP (fig 2).[30] The additional high $\dot{V}A/\dot{Q}$ mode may be explained by the tiny perfusion of corner vessels in the interalveolar septa of lung tissue in upper lung regions where alveolar pressure may exceed pulmonary vascular pressure (zone I). Support for this hypothesis comes from a study on excised dog lungs, both artificially ventilated and perfused, so that a zone I was produced.[32]

In the studies referred to above, anaesthesia was maintained with inhalational agents. Dueck and coworkers compared intravenous (pentobarbitone) and inhalational (halothane and nitrous oxide) anaesthesias in a sheep model[33] and found no significant changes during intravenous anaesthesia in $\dot{V}A/\dot{Q}$ relationships, blood gases, or in FRC. However, inhalational anaesthesia increased shunt from 1% when awake to 11% and 14% during anaesthesia with spontaneous and mechanical ventilation, respectively. FRC was reduced during inhalation anaesthesia and more so after muscle paralysis. In the sheep, therefore, inhalation anaesthesia produced $\dot{V}A/\dot{Q}$ mismatch and shunt, possibly due to the decrease in FRC, whereas intravenous anaesthesia produced no changes. Similarly, small shunts were found during intravenous anaesthesia in 14 patients with a mean age of 59 years before pulmonary surgery, but log SDQ increased from 0·77 to 1·13.[34] It may be that a better preserved hypoxic pulmonary vasoconstriction during barbiturate anaesthesia[19] can explain the absence of, or the small increase in, shunt. An additional factor is the fractional inspired oxygen concentration (F_{IO_2}). Increasing F_{IO_2} to 0·5 caused an increase in shunt of 3–4%.[34] In elderly patients during halothane anaesthesia[35] an increase in F_{IO_2} from 0·53 to 0·85 caused shunt to increase from 7% to 10% of the cardiac output. Thus, a certain dependence on F_{IO_2} exists, possibly explained by attenuation of hypoxic pulmonary vasoconstriction with increasing F_{IO_2}.

The patients studied by Anjou-Lindskog *et al*[34] suffered from chronic bronchitis with abnormal spirometric parameters. Their log SDQ was also increased, on average well above the upper normal limit of 0·6.[36] In a similar patient group of the same age with chronic bronchitis, studied during halothane anaesthesia before vascular reconstructive surgery on their legs, there was only a small increase in shunt during anaesthesia but an increased scatter of $\dot{V}A/\dot{Q}$ ratios.[37] These findings suggest that abnormal preoperative respiratory function may mod-

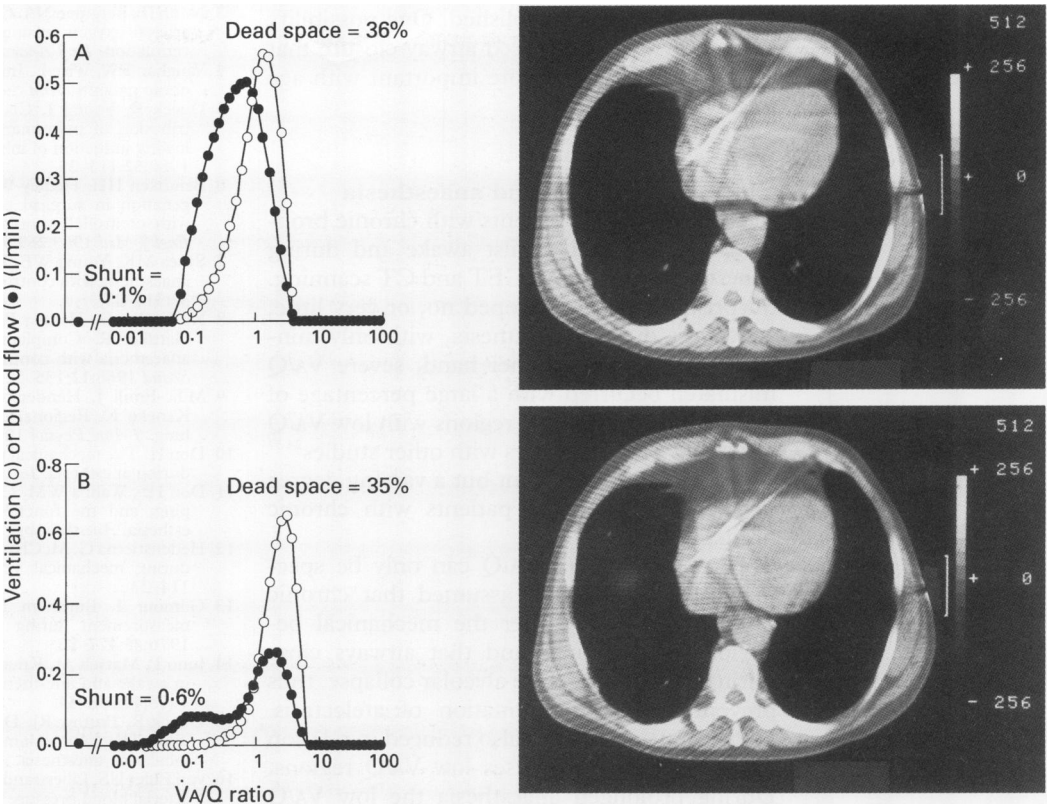

Figure 6 Ventilation-perfusion distributions and computed tomographic (CT) scans in a patient with severe COPD (A) when awake and (B) during inhalational anaesthesia. Note the large transverse lung area on the CT scan when awake which is unchanged during anaesthesia (compare with fig 3). There is no atelectasis and practically no shunt either when awake or anaesthetised. "Low" V̇A/Q̇ regions (0·005<V̇A/Q̇<0·1) appear during anaesthesia. From Gunnarsson et al.[50]

ulate the anaesthesia-induced effects on the V̇A/Q̇ distribution with less formation of shunt. This will be discussed further below.

Atelectasis formation

Prompt development of densities in dependent regions of both lungs has been demonstrated during anaesthesia by computed tomographic scanning,[38] and similar densities have been seen in anaesthetised infants.[39] The densities appear both during spontaneous breathing and after muscle paralysis, and during both inhalational and intravenous (barbiturate) anaesthesia.[40] In anaesthetised sheep and horses similar densities in dependent lung regions were seen, and subsequent morphological analysis showed them to be atelectasis with little or no interstitial oedema or vascular congestion.[41,42] If these findings are extrapolated to humans it can be concluded that anaesthesia causes atelectasis. The rapid appearance of the densities following induction of anaesthesia and after discontinuation of PEEP of 10 cm H_2O is against slow resorption of gas as a cause of atelectasis,[38] and another as yet unidentified mechanism remains to be found. This may be relaxation of the respiratory muscles, in particular the diaphragm, permitting the transmission of the higher intra-abdominal pressure into the intrathoracic cavity. Preliminary findings during phrenic nerve stimulation during anaesthesia show reduction of the atelectasis.

More recently, the V̇A/Q̇ distribution has been correlated with CT findings during anaesthesia. The major V̇A/Q̇ disturbance was once again shunt and very little low V̇A/Q̇[43,44] (fig 3), and a good correlation between the magnitude of shunt and the size of atelectasis was seen (fig 4). PEEP can reduce the atelectatic area but the effect on shunt varies; in some patients it falls and in others it increases.[44,45] The continuing shunt despite PEEP can probably be explained by a redistribution of blood flow towards dependent, atelectatic regions.[46] The intravenous anaesthetic agent ketamine, which does not reduce muscle tone, did not produce atelectasis or shunt as assessed by MIGET, whereas both were seen when the same patient was paralysed with a muscle relaxant.[47]

Atelectasis and shunt did not increase with age of the patients when data from several studies were pooled.[48] Thus, the worsening of arterial oxygenation in the elderly[3,48] needs another explanation. Figure 5 shows the dependence of shunt (probably caused by atelectasis) and perfusion of low V̇A/Q̇ regions on age. In the awake state shunt is negligible and perfusion of low V̇A/Q̇ regions is also small, although it increases with age. During anaesthesia shunt is much larger, but still essentially independent of age. Perfusion of low V̇A/Q̇ regions increases both with anaesthesia and age.[48] It can be said that anaesthesia worsens the match of ventilation and blood flow by as much as 20 years of aging. Why the V̇A/Q̇ match deteriorates during anaesthesia

still remains to be established. One possibility is the previously discussed airway closure that is known to become more important with age in the awake subject.[49]

Chronic bronchitis and anaesthesia

In a recent study[50] patients with chronic bronchitis were studied whilst awake and during anaesthesia by both MIGET and CT scanning. Surprisingly, they developed no, or very little, atelectasis during anaesthesia, with only minimal shunt. On the other hand, severe $\dot{V}A/\dot{Q}$ mismatch occurred with a large percentage of perfusion going to lung regions with low $\dot{V}A/\dot{Q}$ ratios (fig 6). This agrees with other studies[34 37] which found minor shunt but a varying degree of $\dot{V}A/\dot{Q}$ mismatch in patients with chronic bronchitis (table).

The cause of low $\dot{V}A/\dot{Q}$ can only be speculated upon, but it is assumed that chronic hyperinflation may alter the mechanical behaviour of the lungs and that airways close during expiration before alveolar collapse, thus preventing prompt formation of atelectasis. However, ventilation is also reduced in relation to perfusion which causes low $\dot{V}A/\dot{Q}$ regions. During prolonged anaesthesia the low $\dot{V}A/\dot{Q}$ regions may become atelectatic and shunt develops due to a faster uptake of gases by the blood than is delivered to alveoli via the airways.

Conclusion

Calculations from carbon dioxide elimination and oxygenation of blood have demonstrated increased dead space and venous admixture during anaesthesia. With the use of MIGET, a more detailed insight into the impairment of gas exchange during anaesthesia has emerged. Thus, dead space is unchanged or increased modestly, whereas regions with high $\dot{V}A/\dot{Q}$ ratios develop, usually in upper non-dependent lung regions with poor perfusion of alveoli. Shunt – that is, perfusion of regions with $\dot{V}A/\dot{Q}$ ratios <0·005 – is increased in most patients and correlates with the formation of atelectasis as assessed by CT scanning. In addition, anaesthesia increases or causes $\dot{V}A/\dot{Q}$ mismatch with increased dispersion of $\dot{V}A/\dot{Q}$ ratios by a mechanism that has not yet been fully established, but may be airway closure. Shunt and perfusion of "low $\dot{V}A/\dot{Q}$ regions" correlate well with the amount of venous admixture as determined by the standard oxygen shunt equation. Atelectasis and shunt are independent of age, whereas the $\dot{V}A/\dot{Q}$ mismatch increases with age, explaining the worsening of oxygenation of blood that occurs in the elderly. Finally, the abnormal gas exchange in patients with obstructive lung disease during anaesthesia appears to be explained mainly by increased $\dot{V}A/\dot{Q}$ mismatch, whereas shunt and atelectasis formation is minimal.

1 Maier HC, Cournand A. Studies of the arterial oxygenation saturation in the postoperative period after pulmonary resection. *Surgery* 1943;**13**:199–213.
2 Campbell EJM, Nunn JF, Peckett BW. A comparison of artificial ventilation and spontaneous respiration with particular reference to ventilation-blood-flow relationships. *Br J Anaesth* 1958;**30**:166–75.
3 Nunn JF, Bergman NA, Coleman AJ. Factors influencing the arterial oxygen tension during anaesthesia with artificial ventilation. *Br J Anaesth* 1965;**37**:898–914.
4 Vaughan RW, Wise L. Intraoperative arterial oxygenation in obese patients. *Ann Surg* 1976;**184**:35–42.
5 Dueck R, Young I, Clausen J, Wagner PD. Altered distribution of pulmonary ventilation and blood flow following induction of inhalational anesthesia. *Anesthesiology* 1980;**52**:113–25.
6 Bendixen HH, Hedley-Whyte J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation: a concept of atelectasis. *N Engl J Med* 1963;**269**:991–6.
7 Sykes MK, Young WE, Robinson BE. Oxygenation during anaesthesia with controlled ventilation. *Br J Anaesth* 1965; **37**:314–25.
8 Norlander O, Herzog P, Nordén I, Hossli G, Schaer H, Gattiker R. Compliance and airway resistance during anaesthesia with controlled ventilation. *Acta Anaesthesiol Scand* 1968;**12**:135–52.
9 Milic-Emili J, Henderson JAM, Dolovich MB, Trop D, Kaneko K. Regional distribution of inspired gas in the lung. *J Appl Physiol* 1966;**21**:749–759.
10 Don H. The mechanical properties of the respiratory system during anesthesia. *Int Anesthesiol Clin* 1977;**15**:113–36.
11 Don HF, Wahba WM, Craig DB. Airway closure, gas trapping, and the functional residual capacity during anesthesia. *Anesthesiology* 1972;**36**:533–9.
12 Hedenstierna G, McCharty G, Bergström M. Airway closure during mechanical ventilation. *Anesthesiology* 1976;**44**: 114–23.
13 Gilmour I, Burnham M, Craig DB. Closing capacity measurement during general anesthesia. *Anesthesiology* 1976;**45**:477–82.
14 Juno P, Marsch M, Knopp TJ, Rehder K. Closing capacity in awake and anesthetized-paralyzed man. *J Appl Physiol* 1978;**44**:238–44.
15 Dueck R, Prutow RJ, Davies NJH, Clausen JL, Davidson TM. The lung volume at which shunting occurs with inhalation anesthesia. *Anesthesiology* 1988;**69**:854–61.
16 von Euler US, Liljestrand G. Observations on the pulmonary arterial blood pressure in cat. *Acta Physiol Scand* 1946;**12**: 310–20.
17 Thilenius OG. Effect of anesthesia on response of pulmonary circulation of dogs to acute hypoxia. *J Appl Physiol* 1966; **21**:901–4.
18 Sykes MK, Loh L, Seed RF, Kafer ER, Chakrabarti NK. The effects of inhalational anaesthetics on hypoxic pulmonary vasoconstriction and pulmonary vascular resistance in the perfused lungs of the dog and cat. *Br J Anaesth* 1972;**44**: 776–88.
19 Bjertnaes LJ. Hypoxia induced vasoconstriction in isolated perfused lungs exposed to injectable or inhalation anaesthetics. *Acta Anaesthesiol Scand* 1977;**21**:133–47.
20 Marshall BE. Regulation of the pulmonary circulation. In: Stanly TH, Sperry RJ, eds. *Anesthesia and the lung*. 1st edn. London: Kluver Academic Publishers, 1989.
21 Hulands GH, Greene R, Iliff LD, Nunn JF. Influence of anaesthesia on the regional distribution of perfusion and ventilation in the lung. *Clin Sci* 1970;**38**:451–60.
22 Rehder K, Hatch DJ, Sessler A, Fowler WS. The function of each lung of anesthetized and paralysed man during mechanical ventilation. *Anesthesiology* 1972;**37**:16–26.
23 Rehder K, Sessler AD, Rodarte JR. Regional intrapulmonary gas distribution in awake and anesthetized-paralyzed man. *J Appl Physiol* 1977;**42**:391–402.
24 Severinghaus JW, Stupfel M. Alveolar dead space as an index of distribution of blood flow in pulmonary capillaries. *J Appl Physiol* 1957;**10**:335–48.
25 Nunn JF, Hill DW. Respiratory dead space and arterial to end-tidal CO_2 tension difference in anesthetized man. *J Appl Physiol* 1960;**15**:383–9.
26 Nunn JF. *Applied respiratory physiology*. 3rd edn. London: Butterworths, 1987:370–1.
27 Wagner PD, Salzman HA, West JB. Continuous distribution of ventilation-perfusion ratios:theory. *J Appl Physiol* 1974; **36**:588–99.
28 Rehder K, Knopp TH, Sessler AD, Didier EP. Ventilation-perfusion relationships in young healthy awake and anesthetized-paralyzed man. *J Appl Physiol* 1979;**47**:745–53.
29 Prutow RJ, Dueck R, Davies NJH, Clausen J. Shund development in young adult surgical patients due to inhalational anesthesia. *Anesthesiology* 1982;**57**:A477.
30 Bindslev L, Hedenstierna G, Santesson J, Gotlieb I, Carvallhas A. Ventilation-perfusion distribution during inhalation anaesthesia. Effect of spontaneous breathing, mechanical ventilation and positive end-expiratory pressure. *Acta Anaesthesiol Scand* 1981;**25**:360–71.
31 Dueck R, Young I, Clausen J, Wagner PD. Altered distribution of pulmonary ventilation and blood flow following induction of inhalational anesthesia. *Anesthesiology* 1980;**52**:113–25.
32 Hedenstierna G, White FC, Mazzone R, Wagner PD. Redistribution of pulmonary blood flow in the dog with positive end-expiratory pressure ventilation. *J Appl Physiol* 1979;**46**:278–97.
33 Dueck R, Rathbun M, Greenburg AG. Lung volume and $\dot{V}A/\dot{Q}$ distribution response to intravenous versus inhalation anesthesia in sheep. *Anesthesiology* 1984;**61**:55–65.
34 Anjou-Lindskog E, Broman L, Broman M, Holmgren A, Settergren G, Öhqvist G. Effects of intravenous anesthesia on $\dot{V}A/\dot{Q}$ distribution: a study performed during ventilation with air and with 50% oxygen, supine and in the lateral position. *Anesthesiology* 1985;**62**:485–92.

35 Lundh R, Hedenstierna G. Ventilation-perfusion relationships during halothane anesthesia and mechanical ventilation. Effect of varying inspired oxygen concentrations. *Acta Anaesthesiol Scand* 1984;**28**:191–8.
36 Wagner PD, Hedenstierna G, Bylin G. Ventilation-perfusion inequality on chronic asthma. *Am Rev Respir Dis* 1987; **136**:605–12.
37 Hedenstierna G, Lundh R, Johansson H. Alveolar stability during anaesthesia for reconstructive vascular surgery in the leg. *Acta Anaesthesiol Scand* 1983;**27**:26–34.
38 Brismar RB, Hedenstierna G, Lundqvist H, Strandberg Å, Svensson L, Tokics L. Pulmonary densities during anesthesia with muscular relaxation – a proposal of atelectasis. *Anesthesiology* 1985;**62**:422–8.
39 Damgaard-Pedersen K, Qvist T. Pediatric pulmonary CT-scanning. *Pediatr Radiol* 1080;**9**:145–8.
40 Strandberg Å, Tokics L, Brismar B, Lundqvist H, Hedenstierna G. Constitutional factors promoting development of atelectasis during anesthesia. *Acta Anaesthesiol Scand* 1987;**31**:21–4.
41 Hedenstierna G, Tokics L, Lundh B, Strandberg Å, Brismar B, Lundquist H, *et al.* Pulmonary densities during anaesthesia. An experimental study on lung histology and gas exchange. *Eur Respir* 1989;**2**:528–35.
42 Nyman G, Frostell C, Hedenstierna G, Tokics L, Strandberg Å, Kvart C, *et al.* Atelectasis causes gas exchange impairment in the anaesthetized horse. *Equine Vet J* 1991; **22**:317–24.
43 Hedenstierna G, Strandberg Å, Tokics L, Lundqvist H, Brismar B. Correlation of gas exchange impairment to development of atelectasis during anaesthesia and muscle paralysis. *Acta Anaesthesiol Scand* 1986;**30**:183–91.
44 Tokics L, Hedenstierna G, Strandberg Å, Brismar B, Lundqvist H. Lung collapse and gas exchange during general anesthesia: effects of spontaneous breathing, muscle paralysis and positive end-expiratory pressure. *Anesthesiology* 1987;**66**:157–67.
45 Hewlett AM, Hulands GH, Nunn JF, Milledge JS. Functional residual capacity during anesthesia. III: Artificial ventilation. *Br J Anaesth* 1974;**46**:495–503.
46 West JB, Dollery CT, Naimark A. Distribution of blood flow in isolated lung: relations to vascular and alveolar pressure. *J Appl Physiol* 1964;**19**:713–24.
47 Tokics L, Strandberg Å, Brismar B, Lundqvist H, Hedenstierna G. Computerized tomography of the chest and gas exchange measurements during ketamine anaesthesia. *Acta Anaesthesiol Scand* 1987;**32**:684–92.
48 Gunnarsson L, Tokics L, Gustavsson H, Hedenstierna G. Influence of age on atelectasis formation and gas exchange impairment during general anaesthesia. *Br J Anaesth* 1991; **66**:423–32.
49 Leblanc P, Ruff F, Milic-Emili J. Effects of age and body position on airway closure in man. *J Appl Physiol* 1970; **28**:448–51.
50 Gunnarson L, Tokics L, Lundqvist H, Brismar B, Strandberg Å, Berg B, *et al.* Chronic obstructive pulmonary disease and anaesthesia: formation of atelectasis and gas exchange impairment. *Eur Respir J* 1991;**4**:1106–16.