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IS THE END-TIDAL PARTIAL PRESSURE OF ISOFLURANE A GOOD PREDICTOR OF ITS ARTERIAL PARTIAL PRESSURE?

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SUMMARY

End-tidal partial pressure of isoflurane (PE'_{iso}) may be used as a measure of anaesthetic depth. During uptake, an arterial partial pressure (Pa_{iso}) which is considerably less than PE'_{iso} ($Pa_{iso}/PE'_{iso} \ll 1$) leads to underestimation of depth of anaesthesia and, during elimination, $PE'_{iso}/Pa_{iso} \ll 1$ will lead to an overestimation of anaesthetic depth. We measured Pa_{iso}/PE'_{iso} during a 60-min uptake period of 1% isoflurane and PE'_{iso}/Pa_{iso} during the subsequent 60-min elimination period in 26 patients (age 13–88 yr, ASA I–III) undergoing various surgical procedures. After 15 min of isoflurane uptake, Pa_{iso}/PE'_{iso} of 26 patients was mean 0.78 (SD 0.10) and this increased only marginally at 60 min (0.79 (0.09)), whereas during elimination, PE'_{iso}/Pa_{iso} was in the range 0.79 (0.14)–0.83 (0.11). Predictability of Pa_{iso} in a given patient is hindered by the high SD of Pa_{iso}/PE'_{iso} and PE'_{iso}/Pa_{iso}, but it may be improved by taking into account age, ASA physical status category, vital capacity, inspired minus end-tidal isoflurane partial pressure and arterial minus end-tidal carbon dioxide partial pressure during uptake; and obesity, end-tidal isoflurane partial pressure and arterial minus end-tidal carbon dioxide partial pressure during elimination. However, even with multiple regression analysis (to account for the various possible variables), clinically useful prediction of Pa_{iso}/PE'_{iso} and PE'_{iso}/Pa_{iso} in a particular patient is not possible (residual SD 0.084 and 0.113, respectively).

KEY WORDS

Anaesthetics, volatile: isoflurane. Pharmacokinetics: uptake, recovery.

The pharmacokinetics of isoflurane have been studied in animals [1] and healthy human volunteers [2]. In the latter, no significant alveolar–arterial partial pressure difference was evident. This may be explained by the fact that the usual changes in pulmonary gas exchange observed after induction of anaesthesia [3,4] did not occur in the volunteers, as they inhaled only subanaesthetic concentrations of isoflurane. In another study, in which volunteers inhaled anaesthetic concentrations of halothane, a significant alveolar–arterial partial pressure difference was found [5] and, consequently, a similar difference should be expected for isoflurane. Such data have been published in a study of healthy patients under isoflurane anaesthesia [6]. However, in a heterogeneous patient population this difference might be larger and related to specific patient characteristics.

The present study was performed to investigate differences between arterial and end-tidal partial pressures of isoflurane during uptake and elimination of isoflurane in a mixed patient population undergoing surgery. The relationship between this difference and age, ASA physical status category, obesity, vital capacity (VC), forced expiratory volume in the first 1 s (FEV_1), history of smoking habits, physical examination, chest x-ray and position of the patient on the operating table was also investigated. In addition, isoflurane partial pressure differences were compared with those of carbon dioxide.

PATIENTS AND METHODS

We studied 26 patients (16 female, 10 male; aged 13–88 yr (mean 53 yr)) undergoing elective plastic, orthopaedic, abdominal, or urological surgery

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of at least 3 h duration, requiring invasive arterial pressure monitoring. All patients gave written informed consent and the study was approved by the local Ethics Committee.

Patients undergoing neuro- and cardiopulmonary surgery, and those with known coronary heart disease were excluded.

The patient's gender and any history of productive cough, wheezing and smoking habits were noted. Physical examination and a chest x-ray were performed. Lung function was tested by measuring vital capacity (VC) and forced expired volume in the first 1 s (FEV_1) using a computer pneumotachograph (Pneumoscreen, Jaeger, elektromagnetische Gerätefabrik, Würzburg, Germany). Position on the operating table was noted (supine or lateral).

In patients younger than 60 yr, premedication consisted of morphine 0.1 mg kg^{-1} and hyoscine 0.005 mg kg^{-1}. Premedication was not given to patients older than 60 yr. Anaesthesia was induced with propofol 2 mg kg^{-1}, pancuronium 0.1 mg kg^{-1} and alfentanil 0.5 mg, followed by tracheal intubation and ventilation of the lungs with 100% oxygen. Anaesthesia was maintained by a continuous infusion of propofol 6 mg kg^{-1} h^{-1}. Clinical signs of light anaesthesia were treated with alfentanil in bolus doses of 0.5–1.0 mg. Ventilation of the lungs was performed using a Siemens 900C ventilator at a rate of 6 b.p.m. and a tidal volume of 8–12 ml kg^{-1} body weight to maintain end-tidal P_{CO_2} at 4.2–4.8 kPa. Arterial pressure was monitored via a 20-gauge catheter in the radial artery and recorded every 5 min. ECG, nasopharyngeal temperature, degree of muscle relaxation (train-of-four) and inhaled oxygen concentration were monitored. After a minimum of 30 min following the initial bolus of propofol, surgery was started.

Five to 10 minutes later, isoflurane was introduced into the system at a constant inspired concentration of 1.0%. It was discontinued after 60 min and elimination was studied during the following 60 min. Arterial blood samples were taken for measurement of carbon dioxide and isoflurane partial pressures 5 min before and 1, 3, 5, 10, 15, 20, 30, 45 and 60 min after the start of isoflurane administration, and 1, 3, 5, 10, 15, 20, 30, 45 and 60 min after discontinuing isoflurane.

End-tidal carbon dioxide partial pressure ($P_{E'CO_2}$), inspired and end-tidal isoflurane partial pressures ($P_{I_{iso}}$, $P_{E'_{iso}}$) were measured with Beckman LB2 analysers by aspirating gas (flow rate of 500 ml min^{-1} each) from the connection between the tracheal tube and the Y-piece of the breathing system. The instruments were calibrated before each experiment. End-tidal partial pressures were determined using peak detection. Data were recorded continuously on a three-channel recorder (YEV3056 pen recorder, Yokogawa Hokushin Electric, Japan).

The blood samples were placed on ice, and Pa_{CO_2} was analysed within 45 min after blood collection with an IL System 1302 blood-gas analyser; the values were corrected for the patient's temperature [7].

A slight modification of the method described by Zbinden and colleagues [8] was used for measuring the partial pressure of isoflurane in arterial blood (Pa_{iso}). As it was not always possible to withdraw the exact quantity of 0.5 ml of blood during rapid blood sampling, the weight of the vials was determined before and after sampling to ensure that the exact amount of blood withdrawn was known, so that all gas chromatographic measurements could be corrected to 0.5 ml of blood. All measurements of isoflurane partial pressure were made at 37 °C ($P37_{iso}$). Because temperatures of some of the patients decreased considerably, temperature correction of the values was necessary. A separate study to determine the temperature correction factor was performed.

Blood from five volunteers was tonometered with 1% isoflurane. Equilibration for at least 15 min was allowed at temperatures of 33, 35, 37 and 39 °C. Two blood samples of 0.5 ml each were withdrawn from the tonometer at each temperature, placed into a 5-ml vial and equilibrated with the headspace at the corresponding temperature. Headspace samples were measured in duplicate by gas chromatography. The coefficient of variation was 2.8%. The temperature correction for isoflurane partial pressure was shown to follow an exponential course:

$$Pa_{iso} = P37_{iso} \cdot 10^{0.0135\,(t-37)}$$

where Pa_{iso} is the partial pressure at the patient's temperature, t °C. This temperature coefficient (−3.16 per cent/°C between 37 and 36 °C) agrees with that predicted for isoflurane in water from values for other agents (−3.10 per cent/°C) [9] or with directly measured values (−4.36 per cent/°C) [10].

Definitions and data analysis

Abnormal weight was defined as more than

120% of the ideal weight for each patient [11]. The lower limits of normal VC and FEV_1 were defined as a point located 1.64 RSD (= residual standard deviation = standard error of the estimate) below the mean value for subjects of the same height, sex and age on the regression line [12–14]. The history was defined as either normal or abnormal (= recent history of productive cough, wheezing or smoking of more than 5 cigarettes per day). Physical examination was defined as either normal or abnormal (= wheezing or rales). Chest x-ray was defined as either normal or abnormal (= definitive lung pathology such as emphysema, atelectasis, etc.).

The ratio and the difference between $P_{E'CO_2}$ and Pa_{CO_2} were calculated ($P_{E'CO_2}/Pa_{CO_2}$ and $Pa_{CO_2} - P_{E'CO_2}$, respectively). During isoflurane uptake, the following calculations of isoflurane partial pressure were performed: end-tidal to inspired ($P_{E'iso}/P_{Iiso}$), arterial to inspired (Pa_{iso}/P_{Iiso}), inspired minus end-tidal ($P_{Iiso} - P_{E'iso}$), arterial to end-tidal ($Pa_{iso}/P_{E'iso}$) and end-tidal minus arterial ($P_{E'iso} - Pa_{iso}$). End-tidal to arterial and arterial minus end-tidal partial pressures of isoflurane ($P_{E'iso}/Pa_{iso}$ and $Pa_{iso} - P_{E'iso}$, respectively) were calculated during elimination. $Pa_{iso}/P_{E'iso}$, $P_{E'iso} - Pa_{iso}$, $P_{E'iso}/Pa_{iso}$ and $Pa_{iso} - P_{E'iso}$ are referred to as "estimates of Pa_{iso}" in the text.

In order to analyse the effect of patient characteristics on isoflurane partial pressure, it was necessary to have only one value for the uptake or elimination period for each patient. Because the ratio $Pa_{iso}/P_{E'iso}$ was constant between 20 and 60 min of uptake and between 61 and 120 min of elimination (fig. 2), the mean value for each patient was calculated during the two periods ($(Pa_{iso}/P_{E'iso})_{20-60}$ and $(P_{E'iso}/Pa_{iso})_{61-120}$, respectively). The influence of age (continuous scale data) on these two variables was studied by linear regression. All the other patient characteristics are expressed on an ordinal scale, therefore analysis of variance was used to study the effect on $(Pa_{iso}/P_{E'iso})_{20-60}$ and $(P_{E'iso}/Pa_{iso})_{61-120}$.

Linear regression analysis was used first to study the relation between the estimates of Pa_{iso} and each of the various independent variables ($P_{Iiso} - P_{E'iso}$ during uptake, $P_{E'iso}$ during elimination and $Pa_{CO_2} - P_{E'CO_2}$ and $P_{E'CO_2}/Pa_{CO_2}$ during both time periods). Multiple regression analysis was then tried to improve prediction of each estimate of Pa_{iso} during uptake and elimination. All independent variables which could contribute to a better prediction were included and a stepwise elimination of the most insignificant variables was performed. Patient characteristics were computed as either a continuous variable (age) or "dummy variables" (with two dummy variables for ASA classification, because there are three levels of the nominal scale, and one dummy variable for all the other patient characteristics (normal *vs* abnormal and supine *vs* lateral)) [15]. There are 18 measurements for each patient but only one value for a specific patient characteristic. We solved this problem by attributing the specific patient characteristic to each of the nine measurements during the respective time period.

RESULTS

During isoflurane uptake a rapid increase in Pa_{iso}/P_{Iiso} and $P_{E'iso}/P_{Iiso}$ was observed (fig. 1); after 10 min, more than 80% of the values present at 60 min were reached. However, even after 60 min of isoflurane uptake, a significant difference between $P_{E'iso}$ and P_{Iiso}, and between $P_{E'iso}$ and Pa_{iso} persisted.

During elimination, both $P_{E'iso}$ and Pa_{iso} decreased rapidly and reached 20% of P_{Iiso} at the end of the uptake period after approximately 10 min. As expected, $P_{E'iso}$ was always smaller than Pa_{iso} and there was a persistent difference between $P_{E'iso}$ and P_{Iiso} and between Pa_{iso} and $P_{E'iso}$ after 60 min. Figure 2 shows the mean ratios $Pa_{iso}/P_{E'iso}$ (during uptake) and $P_{E'iso}/Pa_{iso}$ (during elimination).

After 20 min of isoflurane uptake, $Pa_{iso}/P_{E'iso}$ reached the value of 0.78 and remained constant during the rest of the uptake period. Throughout elimination, the mean value of all $P_{E'iso}/Pa_{iso}$ was 0.80, with only small deviations from this value at each particular sampling time. However, the SD of these ratios increased as time progressed, possibly because of an increased error in isoflurane measurement at very small partial pressures and, therefore, a larger fluctuation of the $P_{E'iso}/Pa_{iso}$ ratio.

The heterogeneity of the patient population in terms of age, ASA physical status category, weight, etc., is depicted in table I.

During the uptake period there was a significant correlation between the age of the patient and $(Pa_{iso}/P_{E'iso})_{20-60}$ (table II). The ASA physical status category was related also to small values of $(Pa_{iso}/P_{E'iso})_{20-60}$, with a significant difference between the first and second and the first

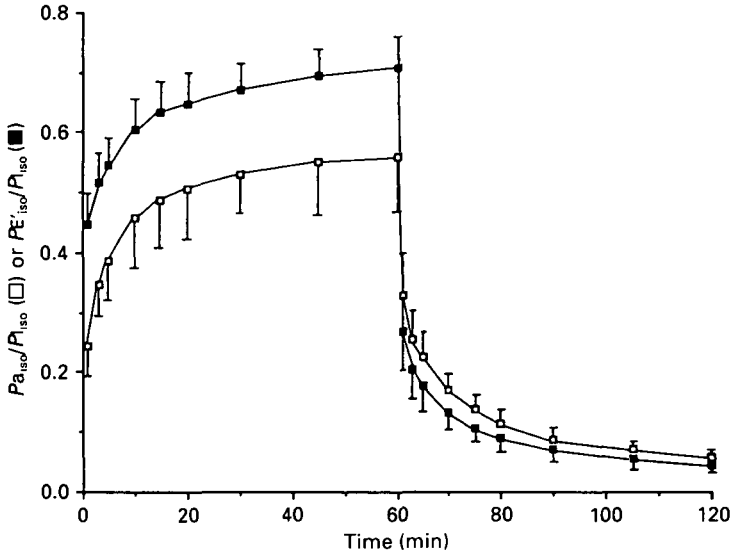

FIG. 1. Uptake and elimination of isoflurane shown as mean (SD) values of the ratios arterial to inspired (Pa_{iso}/PI_{iso}) and end-tidal to inspired (PE'_{iso}/PI_{iso}) isoflurane partial pressures of isoflurane of 26 patients.

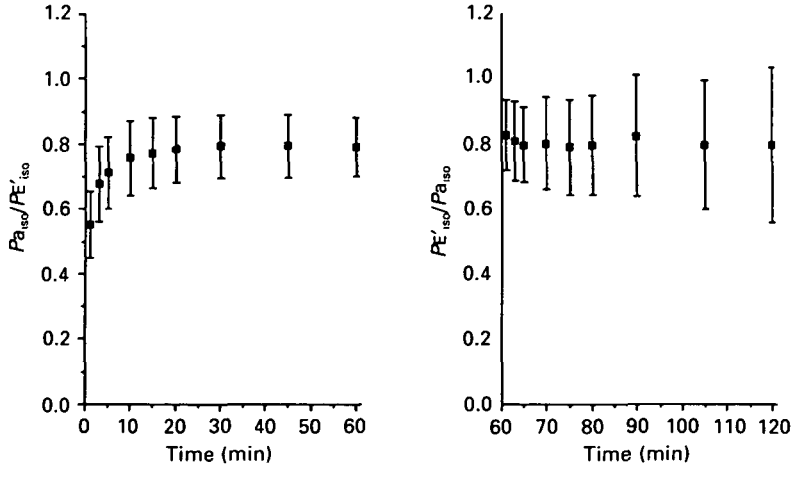

FIG. 2. The means (SD) of the ratios Pa_{iso}/PE'_{iso} (during uptake, left) and PE'_{iso}/Pa_{iso} (during elimination, right) plotted against time. Except during the first 10 min of the uptake period, the values remain relatively constant, although the SD values indicate considerable interindividual variation.

TABLE I. *Patient characteristics. F = female; M = male; N = normal; A = abnormal; S = supine; L = lateral*

Patient No.	Sex	Age (yr)	ASA	% Ideal weight	VC	FEV_1	History	Physical examination	x-Ray	Position	Surgery
1	F	23	II	93	N	N	A	N	N	S	Mammoplasty
2	F	51	I	105	N	N	N	N	N	S	Mammoplasty
3	F	60	II	108	N	N	N	N	N	S	Pancreatic cyst
4	F	33	II	115	N	N	N	N	N	S	Cholecystectomy
5	M	72	II	90	A	N	N	N	N	S	Hip prosthesis
6	F	21	II	112	A	A	N	N	N	L	Internal fixation of pelvis
7	F	83	II	137	A	N	A	N	N	L	Nephrectomy
8	M	67	II	108	A	A	A	N	N	S	Urethral sphincteroplasty
9	M	13	I	74	A	N	N	N	N	L	Abdominal lymphadenectomy
10	M	50	III	127	A	A	A	A	A	L	Nephrectomy
11	F	69	II	97	A	N	N	N	N	S	Internal fixation of tibia
12	M	46	I	134	N	N	A	A	A	S	Hip prosthesis
13	F	31	I	113	N	A	N	N	N	S	Mammoplasty
14	M	56	II	141	A	A	N	N	N	S	Hip prosthesis
15	F	53	II	126	N	N	A	A	A	L	Fundoplication
16	M	63	II	156	A	A	A	A	A	S	Hemicolectomy
17	F	79	II	95	A	N	N	N	N	S	Cholecystectomy
18	F	88	III	114	N	N	N	A	A	S	Hip prosthesis
19	M	32	I	112	N	N	N	N	N	S	Internal fixation of calcaneus
20	F	46	II	106	N	A	N	N	N	S	Anterior resection (rectum)
21	F	80	II	96	A	N	N	N	N	S	Hemicolectomy
22	F	36	II	148	N	N	N	N	N	S	Fundoplication
23	F	26	I	93	N	N	A	N	N	S	Mammoplasty
24	M	61	II	128	A	A	N	N	N	S	Hemicolectomy
25	M	52	II	122	N	N	A	N	N	L	Ureterolithotomy
26	F	78	II	89	A	N	N	N	N	S	Thrombectomy (iliac artery)

TABLE II. *Predictive values of patient characteristics on isoflurane partial pressure ratios (mean values during steady state). No significant (ns) differences could be found for the patient characteristics sex (M vs F), position (S vs L), FEV_1 (N vs A), patient's history (N vs A), physical examination (N vs A) and chest x-ray (N vs A). F = female; M = male; S = supine; L = lateral; N = normal; A = abnormal; α = intercept; β = slope. RSD = Residual standard deviation; ANOVA = analysis of variance.* n = 26

Patient characteristic	Uptake $(Pa_{iso}/PE'_{iso})_{20-60}$		Elimination $(PE'_{iso}/Pa_{iso})_{61-120}$		Statistical method
Age (continuous scale)	$\alpha = 0.916$, $\beta = -0.0023$ ($P < 0.01$) $r^2 = 0.262$, RSD = 0.084		ns		Regression analysis
ASA					
I	0.880 (0.065)	$P < 0.01$	ns		ANOVA
II	0.766 (0.080)				
III	0.696 (0.143)				
Weight	(N *vs* A)				
N	ns		N = 0.874 (0.109)	$P < 0.01$	ANOVA
A			A = 0.671 (0.115)		
Vital capacity					
N	0.840 (0.072)	$P < 0.001$	ns		ANOVA
A	0.735 (0.088)				

TABLE III. *Linear regression between each of the estimates of* Pa_{iso} *and the independent variable* $PI_{iso}-PE'_{iso}$ *(during uptake) or* PE'_{iso} *(during elimination).* n = 234. α = *Intercept*; β = *slope.* RSD = *Residual standard deviation*

	Y	X	α	β	r^2	P	RSD
Uptake	$PE'_{iso}-Pa_{iso}$	$PI_{iso}-PE'_{iso}$	0.756	0.143	0.042	0.0017	0.536
	Pa_{iso}/PE'_{iso}	$PI_{iso}-PE'_{iso}$	1.003	−0.086	0.278	< 0.0001	0.110
Elimination	$Pa_{iso}-PE'_{iso}$	PE'_{iso}	0.12	0.125	0.127	< 0.0001	0.202
	PE'_{iso}/Pa_{iso}	PE'_{iso}	0.742	0.061	0.056	< 0.0005	0.155

TABLE IV. *Linear regression between each of the estimates of* Pa_{iso} *and an independent variable* X. n = 234. α = *Intercept*; β = *slope.* RSD = *Residual standard deviation. All possible equations with* X *being either* $Pa_{CO_2}-PE'_{CO_2}$ *or* Pa_{CO_2}/PE'_{CO_2} *were computed (eight equations), but only those with the smallest* RSD *are shown*

	Y	X	α	β	r^2	P	RSD
Uptake	$PE'_{iso}-Pa_{iso}$	$Pa_{CO_2}-PE'_{CO_2}$	0.591	0.134	0.357	< 0.0001	0.439
	Pa_{iso}/PE'_{iso}	$Pa_{CO_2}-PE'_{CO_2}$	0.852	−0.025	0.235	< 0.0001	0.114
Elimination	$Pa_{iso}-PE'_{iso}$	PE'_{CO_2}/Pa_{CO_2}	1.449	−1.38	0.190	< 0.0001	0.195
	PE'_{iso}/Pa_{iso}	PE'_{CO_2}/Pa_{CO_2}	−0.234	1.19	0.263	< 0.0001	0.138

TABLE V. *Multiple regression analysis between each of the estimates of* Pa_{iso} *and two independent variables* X_1 *and* X_2. n = 234. α = *Intercept*; β = *slope.* RSD = *Residual standard deviation. All possible equations with the second independent variable* (X_2) *either* Pa_{CO_2}/PE'_{CO_2} *or* $PE'_{CO_2}-Pa_{CO_2}$ *were computed (eight equations), but only those with the smallest* RSD *are shown*

	Y	X_1	X_2	α	β_1	β_2	r^2	$P(X_1)$	$P(X_2)$	RSD
Uptake	$PE'_{iso}-Pa_{iso}$	$PI_{iso}-PE'_{iso}$	$PE'_{CO_2}-Pa_{CO_2}$	0.011	0.181	0.139	0.424	< 0.0001	< 0.0001	0.416
	Pa_{iso}/PE'_{iso}	$PI_{iso}-PE'_{iso}$	$PE'_{CO_2}-Pa_{CO_2}$	1.153	−0.094	−0.028	0.562	< 0.0001	< 0.0001	0.085
Elimination	$Pa_{iso}-PE'_{iso}$	PE'_{iso}	Pa_{CO_2}/PE'_{CO_2}	1.474	−1.582	0.151	0.371	< 0.0001	< 0.0001	0.173
	PE'_{iso}/Pa_{iso}	PE'_{iso}	Pa_{CO_2}/PE'_{CO_2}	−0.227	0.042	1.133	0.289	< 0.0001	< 0.0001	0.134

and third categories. An abnormal VC was associated with significantly smaller values of $(Pa_{iso}/PE'_{iso})_{20-60}$. During elimination, only overweight was related significantly to small $(PE'_{iso}/Pa_{iso})_{61-120}$.

The regression equations and the RSD for each estimate of Pa_{iso} and for $PI_{iso}-PE'_{iso}$ during uptake and PE'_{iso} during elimination are shown in table III. All equations are highly significant. The best correlation was found between the ratio Pa_{iso}/PE'_{iso} and $PI_{iso}-PE'_{iso}$ during uptake and between $Pa_{iso}-PE'_{iso}$ and PE'_{iso} during elimination. However, a wide scatter was present in both periods.

There is a significant correlation between the estimates of Pa_{iso} and the differences and the ratio of the partial pressure of carbon dioxide (table IV). The correlation coefficients and the RSD were in the same range as those shown in table III. Multiple regression analyses show that patient characteristics did not contribute to the overall predictability of any of the estimates of Pa_{iso}.

The best correlation was found using the independent variables $PI_{iso}-PE'_{iso}$ and $PE'_{iso}-Pa_{CO_2}$ as predictors for Pa_{iso}/PE'_{iso} during uptake, and PE'_{iso} and Pa_{iso}/PE'_{CO_2} as predictors for $Pa_{iso}-PE'_{iso}$ during elimination (table V). Compared with single regression analysis, prediction was improved (smaller RSD).

DISCUSSION

When administering inhalation anaesthetics, most clinicians use clinical signs as a guide to depth of anaesthesia [16]. The introduction of inhalation anaesthetic gas analysers into clinical practice [17] should enable the anaesthetist to control the anaesthetic depth by following the end-tidal partial pressure assuming this reflects arterial partial pressure. If, however, the difference between arterial and end-tidal partial pressure is large, measurement of the end-tidal partial pressure may lead to overestimation of the "depth of

anaesthesia" during uptake and underestimation during elimination of an inhalation anaesthetic.

In this study, a rapid increase in both $P_{E'iso}$ and Pa_{iso} was found initially. There was a significant and persistent difference between P_{Iiso} and $P_{E'iso}$, and between $P_{E'iso}$ and Pa_{iso} throughout the 1-h uptake period (figs 1, 2). Elimination was characterized by rapid decrease in Pa_{iso} and $P_{E'iso}$ during the first 10 min. Thereafter, Pa_{iso} and $P_{E'iso}$ decreased slowly with a variable difference between the two, the ratio $P_{E'iso}/Pa_{iso}$ being < 1 in most instances.

It is unlikely that the differences observed are caused by anaesthetic technique or the result of a methodological or technical error. The baseline anaesthesia consisted of propofol, alfentanil, pancuronium and ventilation of the lungs with 100% oxygen. This regimen guarantees hypnosis [18], analgesia and neuromuscular block, and allows controlled uptake and elimination of isoflurane without interference by nitrous oxide. Accurate measurement of the partial pressure of isoflurane in blood and alveolar air is critical. The coefficient of variation of the gas chromatographic method used is 4.8% [8] and it can be assumed that weighing the vials before and after sampling further improved accuracy.

Hypothermia causes an increase in blood solubility of isoflurane [10]. Because the body temperature of some of our patients decreased considerably, the measured partial pressure was corrected by a factor which was determined in a separate study with five healthy volunteers. The measured data showed a coefficient of variation of 2.8%, which is within acceptable limits and should not cause erroneous measurements of partial pressure, although the influence of factors such as age and PCV on the temperature correction factor cannot be excluded.

Alfentanil or pancuronium are assumed to be present in blood in concentrations in the nanogram range, and thus unlikely to influence the measurement of isoflurane in blood. Propofol is dissolved in a soyabean fat emulsion and continuous administration of 6 mg kg^{-1} h^{-1} (= fat 0.06 g kg^{-1} h^{-1}) could, theoretically, increase the solubility of isoflurane in blood. The rate of removal of soyabean fat (Intralipid) is governed by a first order reaction in the range 5–10% min^{-1} [19]. Even at an infusion rate of up to 25 g h^{-1} in a 70-kg adult, it does not exceed the elimination limits [20], therefore a constant blood concentration may be assumed in this study. The partition coefficient was measured separately before and after administration of propofol in three patients, and was unchanged.

In healthy awake volunteers breathing subanaesthetic concentrations of isoflurane, $Pa_{iso}/P_{E'iso}$ is close to 1 [2]. It may be expected that anaesthesia (causing an increase in $\dot{V}_A/\dot{Q}$ distribution [3, 4]) would lead to a decrease in $Pa_{iso}/P_{E'iso}$ [21]. Even young, healthy volunteers showed a decrease in the ratio between arterial and end-tidal partial pressures of nitrous oxide [22] and halothane at anaesthetic concentrations [5]. In a more recent investigation, four healthy patients underwent anaesthesia with isoflurane [6]; end-tidal partial pressures were consistently greater than those for arterial blood, the difference being related to the difference between inspired and arterial partial pressures. Unfortunately, no quantitative analysis is provided for this relationship, but visual inspection of figure 4 of that study suggests that there is considerable variability. It was our objective first to quantify the variability of the gradient between $P_{E'iso}$ and Pa_{iso} and second to investigate the usefulness and limits of different variables (patient characteristics, difference between inspired and end-tidal partial pressures of isoflurane and difference between Pa_{CO_2} and $P_{E'CO_2}$) in predicting arterial partial pressure.

Not surprisingly, age correlated significantly with $(Pa_{iso}/P_{E'iso})_{20-60}$. Compared with younger individuals, in the elderly, ventilation distribution is less uniform and, therefore, gas exchange less efficient [23]. Airway closure tends to occur above FRC in older patients [24]. Patients with abnormally small VC have significantly smaller $(Pa_{iso}/P_{E'iso})_{20-60}$. Dueck and colleagues [25] studied patients (age > 50 yr, wide range of abnormal pulmonary function) before induction of anaesthesia and found modest increases in pulmonary $\dot{V}_A/\dot{Q}$ distribution with a small shunt fraction (mean 1.3%) before induction. After induction of halothane anaesthesia, severe gas exchange impairment occurred. This was mainly a result of increased shunt (up to 30% of cardiac output), an increase in low $\dot{V}_A/\dot{Q}$ units (up to 47% of cardiac output), or an increased deadspace ventilation (V_D/V_T up to 0.58), or any combination of these. $\dot{V}_A/\dot{Q}$ distribution was not measured in the present study, but we can assume similar changes in some of our patients, which may partly explain the small values of $(Pa_{iso}/P_{E'iso})_{20-60}$.

The mean $(Pa_{iso}/P_{E'iso})_{20-60}$ of 0.88 for ASA I patients are almost identical with values reported

in a study of healthy patients undergoing isoflurane anaesthesia [6]. The significantly smaller values in patients in higher ASA categories probably reflect some degree of impairment of lung function.

The reason for the significantly small values of $(P_{E'_{iso}}/Pa_{iso})_{61-120}$ in obese patients during elimination is not known. After 1 h of 1% isoflurane administration, the degree of saturation of the adipose tissue is still very small and therefore does not contribute to an increased gradient. It is more likely that the $\dot{V}_A/\dot{Q}$ mismatch induced by anaesthesia takes longer to resolve in obese patients compared with patients of normal weight.

$P_{I_{iso}}-P_{E'_{iso}}$ (during uptake) and $P_{E'_{iso}}$ (during elimination) correlated significantly with the estimates of Pa_{iso} (table III). However, only 4.2–27.8% of the dependent variable are explained by the gradient between inspired and end-tidal partial pressures. The RSD are high and do not allow prediction of Pa_{iso} with a clinically useful probability.

During routine anaesthesia, the gradient between Pa_{CO_2} and $P_{E'_{CO_2}}$ is often known to the anaesthetist. Both carbon dioxide and isoflurane have a low blood/gas solubility and cross the alveolar–capillary membrane easily; therefore, we postulated that estimates of Pa_{iso} could be predicted from $P_{E'_{CO_2}}/Pa_{CO_2}$ or $P_{E'_{CO_2}}-Pa_{CO_2}$. The relatively large RSD (table IV) suggest that $\dot{V}_A/\dot{Q}$ mismatch has a different effect on gas exchange of these two compounds. Isoflurane is an inert gas and equilibration across the alveolar–capillary membrane is almost instantaneous, whereas carbon dioxide equilibration is significantly retarded by the nature of transport of that gas in blood (i.e. the slope of the carbon dioxide dissociation curve and the rate at which carbon dioxide participates in various chemical reactions with blood) [26]. This behaviour of carbon dioxide does not influence gas exchange in young healthy, awake men, but may affect gas exchange in areas of high $\dot{V}_A/\dot{Q}$, where isoflurane may be fully equilibrated, in contrast with carbon dioxide. On the other hand, isoflurane has a much greater molecular weight than carbon dioxide, and this causes increased diffusion limitation in the gas phase [27–29]. This may retard equilibration of isoflurane between alveoli and blood compared with carbon dioxide.

The results in table V show a definitive improvement in the predictability of the estimates of Pa_{iso}. However, it is not certain if it is clinically useful to predict the ratio $Pa_{iso}/P_{E'_{iso}}$ within a 95% range of ± 0.17 (which is approximately 2RSD).

There is no doubt that $P_{E'_{iso}}$ may considerably overestimate Pa_{iso} (and, therefore, anaesthetic depth) during isoflurane uptake. This error is particularly likely in elderly patients, in patients with low VC, and in patients with high $Pa_{CO_2}-P_{E'_{CO_2}}$ and high $P_{I_{iso}}-P_{E'_{iso}}$ differences. During elimination, $P_{E'_{iso}}$ may overestimate Pa_{iso} (and, therefore, recovery), especially in obese patients and in patients with a small $Pa_{CO_2}/P_{E'_{CO_2}}$ ratio.

REFERENCES

1. Zbinden AM, Thomson DA, Westenskow DR, Frei F, Maertens J. Anaesthetic uptake and elimination: is there a difference between halothane and isoflurane in the dog? *British Journal of Anaesthesia* 1988; **60**: 395–401.
2. Cromwell TH, Eger EI, Stevens WC, Dolan WM. Forane uptake, excretion, and blood solubility in man. *Anesthesiology* 1971; **35**: 401–408.
3. Rehder K, Sessler AD, Marsh HM. General anesthesia and the lung. *American Review of Respiratory Disease* 1975; **112**: 541–563.
4. Tokics L, Hedenstierna G, Strandberg A, Brismar B, Lundquist H. Lung collapse and gas exchange during general anesthesia: effects of spontaneous breathing, muscle paralysis, and positive end-expiratory pressure. *Anesthesiology* 1987; **66**: 157–167.
5. Eger EI, Bahlman SH. Is the end-tidal anesthetic pressure an accurate measure of the arterial anesthetic partial pressure? *Anesthesiology* 1971; **35**: 301–303.
6. Carpenter RL, Eger EI. Alveolar to arterial to venous anesthetic partial pressure differences in humans. *Anesthesiology* 1989; **70**: 630–635.
7. Gabel RA. Algorhythms for calculating and correcting blood gas and acid–base variables. *Respiration Physiology* 1980; **42**: 211–232.
8. Zbinden AM, Frei FJ, Funk B, Thomson DA. Determination of the partial pressure of halothane (or isoflurane) in blood. *British Journal of Anaesthesia* 1985; **57**: 796–802.
9. Allott PR, Steward A, Flook V, Mapleson WW. Variation with temperature of the solubilities of inhaled anaesthetics in water, oil and biological media. *British Journal of Anaesthesia* 1973; **45**: 294–300.
10. Eger RR, Eger EI II. Effect of temperature and age on the solubility of enflurane, halothane, isoflurane, and methoxyflurane in human blood. *Anesthesia and Analgesia* 1985; **64**: 640–642.
11. Bierman EL. Obesity. In: Wyngaarden JB, Smith LH, eds. *Cecil Textbook of Medicine*. London, Philadelphia: W. B. Saunders Company, 1982; 1373.
12. Zamel N, Altose MD, Speir WA jr. Statement on spirometry—a report on the section on respiratory pathophysiology. *Chest* 1983; **83**: 547–550.
13. Morris JF, Koski A, Johnson LC. Spirometric standards for healthy nonsmoking adults. *American Review of Respiratory Disease* 1971; **103**: 57–67.

14. Grimby G, Söderholm B. Spirometric studies in normal subjects. *Acta Medica Scandinavica* 1963; **173**: 199–206.
15. Zar JH. *Biostatistical Analysis*, 2nd Edn. Englewood Cliffs, New Jersey: Prentice-Hall, Inc., 1984; 346–347.
16. Sykes MK, Chir B. Continuous monitoring of alveolar and inspiratory concentrations of anesthetic and respiratory gases is difficult and potentially unsafe. *Journal of Clinical Monitoring* 1987; **3**: 116–122.
17. Severinghaus JW. Continuous monitoring of alveolar and inspiratory concentrations of anesthetic and respiratory gases is safe, simple, and cost effective. *Journal of Clinical Monitoring* 1987; **3**: 123.
18. Gepts E, Jonckheer K, Maes V, Sonck W, Camu F. Disposition kinetics of propofol during alfentanil anaesthesia. *Anaesthesia* 1988; **43**: 8–13.
19. Hallberg D. Studies on the elimination of exogenous lipids from the blood stream. *Acta Physiologica Scandinavia* 1965; **64**: 299–305.
20. Lindholm M, Rössner S. Rate of elimination of the Intralipid fat emulsion from the circulation in ICU patients. *Critical Care Medicine* 1982; **10**: 740–746.
21. Eger EI, Severinghaus JW. Effect of uneven pulmonary distribution of blood and gas on induction with inhalation anesthetics. *Anesthesiology* 1964; **25**: 620–626.
22. Eger EI II, Babad AA, Regan MJ, Larson CP, Shargel R, Severinghaus JW. Delayed approach of arterial to alveolar nitrous oxide partial pressures in dog and in man. *Anesthesiology* 1966; **27**: 288–297.
23. Edelman NH, Mittman C, Norris AH, Shock NW. Effects of respiratory pattern on age differences in ventilation uniformity. *Journal of Applied Physiology* 1968; **24**: 49–53.
24. Anthonisen NR, Danson J, Robertson PC, Ross WRD. Airway closure as a function of age. *Respiration Physiology* 1970; **8**: 58–65.
25. Dueck R, Young I, Clausen J, Wagner P. Altered distribution of pulmonary ventilation and blood flow following induction of inhalational anesthesia. *Anesthesiology* 1980; **52**: 113–125.
26. Wagner PD. Diffusion and chemical reaction in pulmonary gas exchange. *Physiological Reviews* 1977; **57**: 257–312.
27. Georg J, Lassen NA. Diffusion in the gas phase of the lungs in normal and emphysematous patients. *Clinical Science* 1965; **29**: 525–531.
28. Scherer PW, Gobran S, Aukburg SJ, Baumgardner JE, Bartkowski R, Neufeld GR. Numerical and experimental study of steady-state CO_2 and inert gas washout. *Journal of Applied Physiology* 1988; **64**: 1022–1029.
29. Paiva M, Verbank S, Van Muylem A. Diffusion-dependent contribution to the slope of the alveolar plateau. *Respiration Physiology* 1988; **72**: 257–270.