demonstrated inhibitory effects of glucocorticoids on muscle protein synthesis [19]. The present finding that cortisol administration increased leucine flux and therefore protein breakdown is in accord with the previous observation that 3-methylhistidine excretion increased following glucocorticoid administration to rats [9].

In view of the potency of the pancreatic hormones insulin and glucagon in affecting leucine turnover [25] it appeared to be of importance to maintain plasma insulin and glucagon concentrations unchanged during stress hormone infusion. This was attempted by somatostatin adminstration combined with insulin and glucagon replacements. Surprisingly, plasma insulin concentrations were higher during cortisol administration than with epinephrine alone, suggesting either diminished metabolic clearance of insulin, or a breakdown of the somatostatin blockade during cortisol administration. The higher insulin concentrations argue in favor of the role of cortisol in increasing leucine flux since insulin would exert an opposite effect [25].

Thus, the interaction of epinephrine and cortisol in regulating leucine flux demonstrated in the present study suggests that acute hypercortisolemia exerts protein catabolic effects by increasing protein breakdown. These effects are blunted when there is a simultaneous increase in plasma epinephrine. Whether this interaction is equally operative in clinical conditions of severe stress has to be examined in further studies.

Acknowledgments. This work was supported by a grant No. 3.898.83 of the Swiss National Science Foundation. The superb technical assistance of A. Keller is gratefully acknowledged.

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0014-4754/88/020176-03$1.50 + 0.20/0

Influence of ventilatory and circulatory changes on the pharmacokinetics of halothane and isoflurane

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Summary. In two groups of dogs, uptake and elimination of halothane and isoflurane were studied using a closed-loop anesthesia system which automatically controlled end-tidal halothane or isoflurane partial pressure at minimal alveolar concentration (MAC) equivalent levels. Hemodynamic and respiratory variables were recorded and the anesthetic partial pressure was measured in the inspired and expired air, as well as in the arterial, cerebrovenous and mixed venous blood. Data were recorded during wash-in, hyperventilation, hypercirculation, hypotension and wash-out. For halothane, the controller delivered a higher inspired partial pressure than for isoflurane to compensate for the higher blood/gas partition coefficient. This was especially pronounced during the wash-in and the hypercirculation periods. Smaller differences between halothane and isoflurane partial pressures occurred during hyperventilation, hypotension and the wash-out period and could be explained by the lower solubility of isoflurane. These results show that even under unstable ventilatory and hemodynamic conditions, the inspired concentration of isoflurane has to be adjusted less often and to a smaller degree than that of halothane if end-tidal concentrations are to be maintained constant.
Key words. Dog anesthesia; halothane; isoflurane; hemodynamic variables; respiratory variables.

The goal of inhalational anesthesia should be to obtain rapidly and safely an adequate partial pressure of the volatile anesthetic in the brain. Isoflurane, because of its reportedly lower partition coefficients (blood/gas and tissue/blood), is considered to have a more favorable pharmacokinetic profile than halothane [4, 7]. Although brain tissue partial pres-

sure cannot be measured directly in patients, the end-tidal partial pressure can be continuously monitored and can, within certain limitations, be related to the brain tissue partial pressure. However, with conventional anesthesia systems, the anesthetist can only control the inflow partial pressure by adjusting the vaporizer setting. An unpredictable difference exists between the partial pressure set at the vaporizer and the end-tidal partial pressure, as many factors such as absorption by system components, circulation and ventilation influence the rate of uptake and elimination of volatile anesthetics. Even if the end-tidal partial pressure in such a system can be continuously measured, its accurate adjustment – especially at the beginning of anesthesia – is difficult due to the delay times between changes in halothane input to the system and changes in the end-tidal concentration. The longer this delay, the greater the danger of overshooting the desired arterial partial pressure with the risk of untoward effects on organs other than the brain. A feedback system [11] can be used to automatically adjust inflow of the anesthetic agent into the system to maintain a constant end-tidal partial pressure. This set-up can be used to follow the uptake and elimination of halothane and isoflurane from the lung to the blood and from the blood to the brain tissue assuming that the partial pressure of halothane and isoflurane in cerebral venous blood represents cerebral tissue partial pressure. The aim of this study was to investigate whether there are significant differences in pharmacokinetics between halothane and isoflurane in dogs and to see if changes in ventilation and circulation had any impact on the uptake and elimination of the two agents.

Methods. Twelve mongrel dogs (24–39 kg) were premedicated with 40 µg/kg fentanyl and 2 mg/kg droperidol i.m. 1 h prior to instrumentation. Anesthesia was induced with pentobarbital 12–15 mg/kg i.v. and the trachea intubated. The dogs were placed supine and ventilated with 100% oxygen at 12 breaths per minute. Tidal volume was adjusted to maintain arterial carbon dioxide ($PaCO_2$) at 40 mm Hg. To provide basal anesthesia during the preparation, a bolus of droperidol (30 mg) and fentanyl (600 µg) was given followed by a continuous infusion of fentanyl (15 µg/kg/h) and pancuronium (60 µg/kg/h). Fluid volume was maintained with an infusion of 0.9% sodium chloride (2 ml/kg/h). The dogs were heparinized with 500 IU/kg heparin. Temperature was maintained at 37 °C using a heated, operating table which was thermostatically controlled. Hemodynamic monitoring consisted of electrocardiogram (ECG) and arterial pressure via a femoral artery catheter, as well as central venous, pulmonary artery and pulmonary capillary wedge pressures using a thermistor-tipped Swan-Ganz catheter inserted into the internal jugular vein. 5-ml iced injectate was used to measure cardiac output in triplicate with an Edwards 520 cardiac output computer. The retroglenoid vein was isolated, all branches were ligated except the one coming from the brain, and a 1-mm diameter catheter was advanced into the transverse sinus for sampling cerebral venous blood.

The feedback-controlled anesthesia delivery system which was used had been developed earlier in our laboratory [11]. The system includes a 2-l water-sealed bellows, a circulating pump and a soda lime canister. Feedback controllers maintain end-tidal anesthetic partial pressure and circuit volume at the desired level by regulating anesthetic and oxygen inflow into the circuit. As leaks from the circuit are negligible, oxygen and anesthetic uptake of the subject equals that supplied to the system.

The volatile anesthetic partial pressure in the arterial, cerebral venous and mixed venous samples was determined using a head space gas chromatography (GC) method [13]. A tonometer was used to create blood with a well-defined partial pressure of the volatile anesthetics for each dog before and after the experiment. An individual average standard curve was plotted relating GC counts to partial pressure. A Beckman LB-2 infrared analyzer, the accuracy of which had previously been verified [14], was used for determination of the partial pressure both in the inspired and expired gas and at the outlet of the tonometer, thereby relating partial pressure in the gas phase to partial pressure in the blood phase. The blood/gas partition coefficient was determined for each dog individually.

Following surgical preparation and after baseline hemodynamic measurements, six dogs received halothane at a feedback controlled end-tidal partial pressure of 6.44 mm Hg halothane and another six dogs were given isoflurane at 9.47 mm Hg. These concentrations have been shown to be equipotent and are defined as the minimal alveolar concentrations (MAC) of the anesthetic required to keep a dog from responding by gross purposeful movement to a painful stimulus [10]. Measurements of anesthetic concentrations, and hemodynamic and respiratory variables were made 1, 2, 3, 6, 9, 20, 40 and 57 min after the start of wash-in. At 60 min, ventilation was increased in order to lower end-tidal pCO_2 from 40 mm Hg to 30 mm Hg. The measurements were repeated at 61, 62, 63, 66, 69 and 77 min. Normoventilation was then reestablished. In order to increase cardiac output by about 100%, an epinephrine infusion was given at a dosage of 2 µg/kg/min which is at the lowest margin to produce arrhythmias [6, 9]. Measurements were again performed at 101, 102, 103, 106, 109 and 117 min. After a further control period, a nitroprusside infusion was used to lower mean arterial blood pressure by about 30%. Measurements were taken at 141, 142, 143, 146, 149 and 157 min, after which the nitroprusside infusion was stopped, which resulted in a rapid rise of arterial blood pressure. The anesthetic was then removed from the circuit by switching a 1-l activated charcoal absorber into the breathing circuit. Wash-out continued for a further 60 min, and the standard measurements were performed at 161, 162, 163, 166, 169, 180, 200 and 217 min.

To compare the rate of uptake and elimination for halothane and isoflurane, the partial pressure values of isoflurane were scaled by the factor 0.87/1.28 to obtain partial pressures which were equipotent relative to MAC for comparison with halothane. For each dog and for each experimental period, the area under the resulting partial pressure curve of the inspired, end-tidal, arterial, cerebral venous and mixed venous compartment was calculated and divided by the time interval considered to yield a value which represents the average partial pressure. The mean and standard deviation of this average partial pressure was calculated for each compartment and for each agent.

The differences of the means between the halothane and the isoflurane group and the standard errors of these differences were then obtained using the error propagating law:

$$SE_{(\bar{x}-\bar{y})} = \sqrt{SE_{(\bar{x})^2} + SE_{(\bar{y})}}$$

where:

$SE_{(\bar{x})}$ = standard error of the average partial pressure of halothane during a time period

$SE_{(\bar{y})}$ = standard error of the average partial pressure of isoflurane during a time period

$SE_{(\bar{x}-\bar{y})}$ = standard error of the difference of the average partial pressures of the volatile agents.

In figure 3, the vertical bars represent differences of mean partial pressures between the two groups during each experimental period.

Results. Figures 1 and 2 display the uptake and elimination curves for halothane and isoflurane. For both agents inspired partial pressure increased rapidly during the wash-in period, decreased slightly during hyperventilation, but increased dramatically during hypercirculation and increased slightly during hypotension. Approximately 3 min after the start of wash-in, the preset end-tidal partial pressures were reached and remained constant during the first 160 min. Ar-

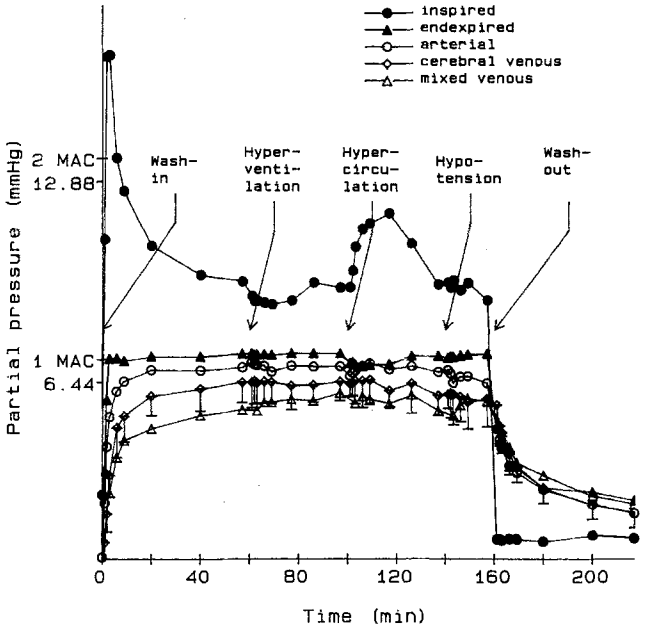

Figure 1. Partial pressure for halothane in the inspired, end-tidal, arterial, cerebral venous, and mixed venous blood. Partial pressure is given as mmHg and as MAC equivalents (0.87 vol.% for dogs). The average barometric pressure is taken as 740 mmHg.

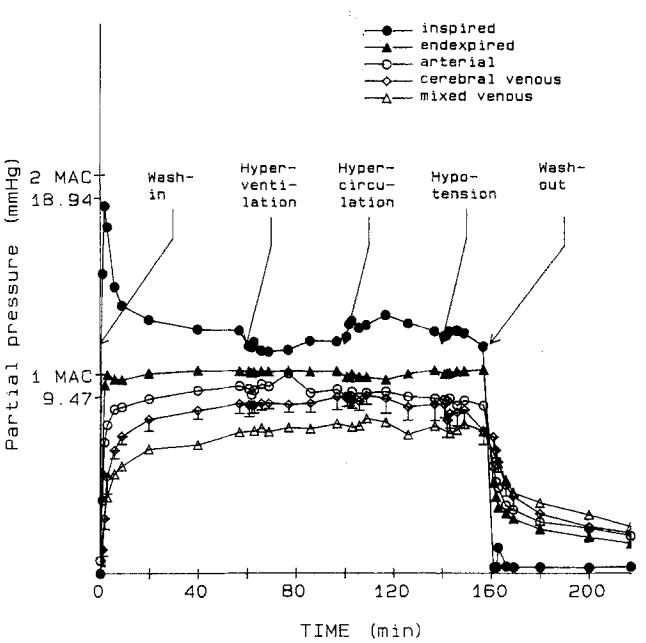

Figure 2. Partial pressure for isoflurane in the inspired, end-tidal, arterial, cerebral venous, and mixed venous blood. Partial pressure is given as mmHg and as MAC equivalents (1.28 vol.% for dogs). The average barometric pressure is taken as 740 mmHg.

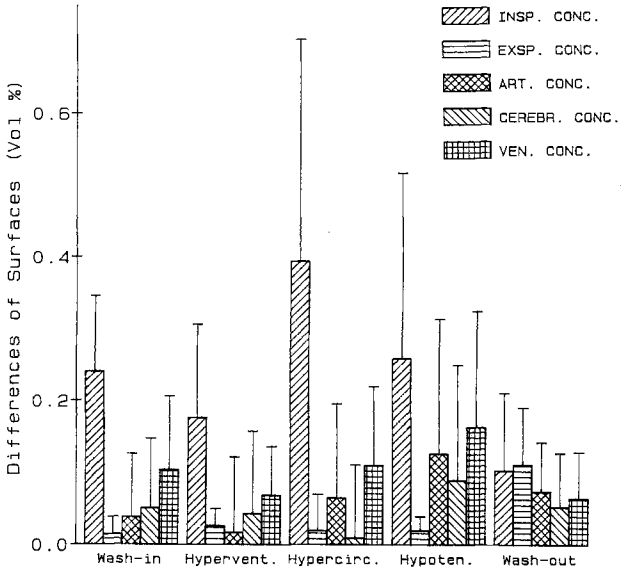

Figure 3. Difference of the areas under the concentration curves. The error bars are computed using the error propagating law from the standard deviation of the areas of the two groups.

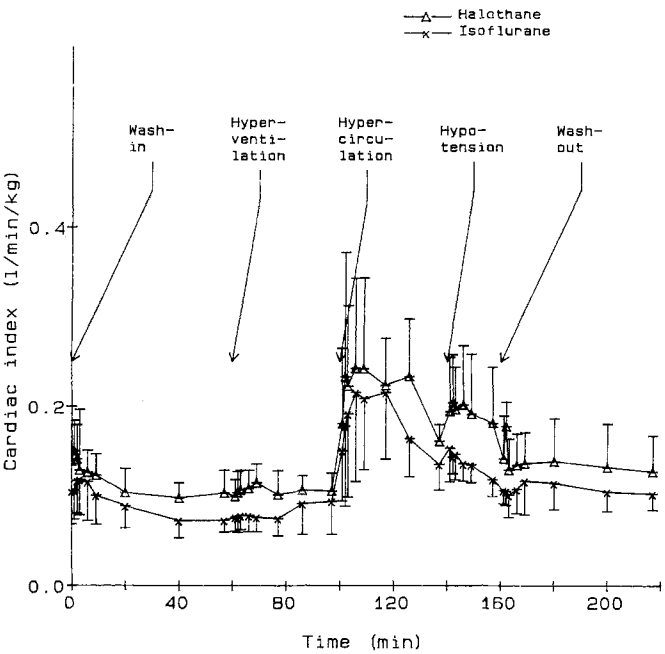

Figure 4. Cardiac index in l/min/kg/ for halothane and isoflurane during different periods.

terial, cerebral venous and mixed venous partial pressure approached the end-tidal partial pressure gradually but an equilibration was not yet obtained. Interestingly, the arterial partial pressure decreased during the hypotensive period with both agents. During elimination there was an identical exponential decline in partial pressure for both agents and for all compartments.

Figure 3 shows the difference of the areas under the partial pressure curves in each period between halothane and isoflurane. The inspired partial pressures were larger in the halothane group during all periods. The difference in expired partial pressures was almost zero, which shows that the feedback system worked satisfactorily. Arterial, cerebral venous and mixed venous partial pressures all showed slight positive differences, thus signifying that the corresponding value for halothane was always higher than that for isoflurane.

Figure 4 shows the uptake in ml liquid of anesthetic/min. Increased uptake occurred during three periods of the experiment: at the beginning of wash-in, hypercirculation and hypotension. This was true for both agents. No change oc-

curred during the hyperventilation period. Except for the early wash-in period, these changes are related to the increase in cardiac index.

Hemodynamic data (heart, blood pressure, cardiac output) of the halothane group were compared to those of the isoflurane group with a Mann Whitney test with a significance level of 0.05. No significant difference could be found between halothane and isoflurane in any of the periods and in any of the parameters tested.

Additional physiological values (arterial blood gases, temperature, pulmonary or shunt, pulmonary dead space, and weight) were determined at the beginning and end (240 min) of the experiment. No significant differences between the two groups were present.

Discussion. This study measured the rate of uptake and elimination of halothane or isoflurane from the alveolar space to the blood and from the blood to the brain tissue using a new feedback control technique [11]. This allowed end-tidal anesthetic partial pressure to be held constant [14]. Even when changes in respiratory or hemodynamic parameters were introduced, the inspired partial pressure was adequately adjusted by the controller independent of which agent was being used. In contrast, when using clinical methods (open or semi-closed systems), the inspired partial pressure is kept more or less constant and the end-tidal partial pressure changes in an unpredictable way.

The protocol employed simulates the clinical sitiuation in which premedicated patients receive a baseline anesthetic with fentanyl and droperidol during ongoing surgery to which isofluane or halothane is added. Four important parameters may influence the pharmacokinetics of volatile anesthetics; solubility, metabolism, cardiac output, and ventilation. A change in solubility of isoflurane and halothane in blood or tissue caused by the baseline anestethics seems to be very unlikely, because the baseline drugs were present in the ng range. The saturation of enzmyes responsible for the metabolism of volatile anesthetics occurs at very low concentrations of these agents, thus metabolism of other drugs per se can hardly alter the pharmokinetics of the inhalational anesthetics[8]. Droperidol, fentanyl, pancuronium, and pentobarbital all influence hemodynamics and ventilation, however, these parameters were controlled in our study and no initial differences could be found between the two groups.

The blood-gas partition coefficient in man is 1.4 for isoflurane [1] and 2.3 for halothane [4] and in this study could be determined as 1.3 ± 0.1 and 2.6 ± 0.3, respectively. This difference in solubility explains most of the observed changes in pharmacokinetics of the two agents.

During the whole wash-in period, inspired concentrations were always higher with halothane compared to isoflurane. This can be explained by the higher partition coefficient of halothane. It is well known that hyperventilation increases the rate of rise of the end-tidal partial pressure (ratio of end-tidal to inspired partial pressure P_{et}/P_i is increased) [4]. However, when constant end-tidal partial pressures are automatically achieved, as in this study, lower inspired partial pressures are needed (figs 1 and 2). The change of the ratio P_{et}/P_i during hyperventilation is expected to be smaller with a less soluble agent [12]. We could document an increase of this ratio of 9.59% with halothane and 8.37% with isoflurane. Increased cardiac output will increase the uptake of volatile anethetics. The results in a decrease of the P_{et}/P_i ratio [4] which is more pronounced with more soluble agents. Thus, when end-tidal concentrations are automatically kept constant, a higher inspired partial pressure would be expected with halothane (fig. 3).

Induced hypotension results in an increased cardiac output (fig. 4). This results in the same changes (although to a minor degree) which occurred during the hypercirculation period.

The difference between end-tidal and arterial partial pressure (P_{et}-P_a) is due to ventilation/perfusion inequalities which are always present during anesthesia [5]. For halothane it has been shown that this difference is related to the difference between inspired and end-tidal partial pressure (P_i-P_{et}), the ratio (P_{et}-P_a)/(P_i-P_{et}) being 0.2 [3]. Because ventilation/perfusion inequalities have a larger influence on the difference between end-tidal and arterial partial pressure with a less soluble agent, this ratio should, theoretically, be smaller with isoflurane [2]. In fact, our data showed that both the inspired and arterial partial pressures are always higher with halothane compared to isoflurane. Together with constant end-tidal partial pressures this results in low ratios (P_i-P_{et})/(P_{et}-P_a) for isoflurane. The differences between partial pressures of halothane compared with those of isoflurane in the arterial, cerebral venous and mixed venous blood are small and probably not relevant compared with the differences in the inspired gas.

In summary our data suggest that when isoflurane is used clinically instead of halothane, the inspired concentration has to be adjusted less frequently and to a smaller extent in order to compensate for changes in ventilation and circulation.

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