Alveolar-to-Arterial-to-Venous Anesthetic Partial Pressure Differences in Humans

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To determine the correlation between the partial pressures of anesthetics in venous and arterial blood (Pv and Pa), and to assess whether this correlation was better than that between the partial pressure of anesthetic in alveolar gas (Pd) and Pa, isoflurane (n = 4) or halothane (n = 4) was administered to eight patients undergoing surgery, and Pd, Pa, and Pv were measured. Pa correlated with Pd better than did Pa (R = 0.960 vs. 0.878), and there was less variability in the data. Differences between Pd and Pa increased as the relative blood flow to the hand decreased [indicated by an increasing arterial-to-venous (a-v) O2 content difference]. The difference between Pa and Pd was approximately 20% of the difference between inspired gas (Pd) and Pa. The differences between Pa and Pd appear to be due primarily to contamination of alveolar gas by physiologic dead space gas. (Key words: Anesthetics, volatile: halothane; isoflurane. Pharmacokinetics: alveolar-to-arterial anesthetic gradients; arterial-to-venous anesthetic gradients. Solubility; blood–gas partition coefficients.)

The partial pressure of inhaled anesthetic in arterial blood (Pa) is considered to directly correlate with the effects of the anesthetic. However, accurate measurement of Pa can provide valuable information, Pd is rarely measured for three reasons: 1) analysis is complicated because it requires determination of blood concentration and anesthetic solubility in blood; 2) arterial sampling is thought to impose a significant risk; and 3) the partial pressure of anesthetic in alveolar gas (Pd), which is in equilibrium with arterial blood, is widely accepted as an accurate estimate of Pa.

Because Pa cannot be directly measured, the partial pressure of anesthetic in end-tidal gas samples is assumed to represent the true Pa. However, this assumption may not be warranted. Differences between Pa and Pd of up to 20% have been reported. This difference is thought to result from two factors: contamination of true alveolar gas with physiologic dead space gas and intrapulmonary shunting of blood. The difference between Pa and Pd increases as the difference between Pa and the partial pressure of inspired gas (Pd) increases. When Pd–Pa differences are large (e.g., induction, emergence), Pa becomes a less reliable indicator of Pd. Despite these limitations, measurement of Pa as a reflection of Pd has remained popular, primarily because it is noninvasive and easy to perform.

Any alternative to end-tidal gas or arterial blood sampling would have to be less invasive than arterial blood sampling and more accurate than end-tidal sampling. We speculated that sampling venous blood from the hand might satisfy both criteria. First, venous blood can be sampled through existing iv catheters inserted during most anesthetics. Second, cutaneous blood flow is greatly increased during anesthesia, and direct arteriovenous shunts open in the hand, such that venous blood in the forearm and hand is "arterIALIZED" and the PCO2 is nearly identical to that in arterial blood. Furthermore, this increase in cutaneous blood flow occurs during normal operating room conditions under general anesthesia and persists at least until esophageal temperature declines below approximately 35°C. Consequently, we speculate that the anesthetic partial pressure of arterialized venous blood may be close to that in arterial blood during general anesthesia. If so, Pa may correlate better with Pd than does Pa. Accordingly, we measured Pa, Pd, and Pw, then correlated Pa and Pa with Pd to determine the stronger correlation.

Methods

With approval from the Committee on Human Research at the University of California, San Francisco, we studied eight healthy patients 21–65 yr of age (52 ± 16 yr, mean ± SD), of average height (173 ± 8 cm) and weight (73 ± 12 kg). All were undergoing surgery for which anesthetic management required arterial and venous catheterization and tracheal intubation. None had a history of pulmonary disease or smoking. Patients were randomly divided into two groups of four: one group was given isoflurane and the other halothane, at doses necessary to meet surgical demands (Pd = 0.8–1.6% for isoflurane and 0.5–1.3% for halothane). The choice of anesthetic agent was determined by the attending anesthesiologist. The lungs of all patients were mechanically ventilated via a nonbreathing circuit.

Samples of arterial and venous blood and end-tidal and inspired gases were collected simultaneously and analyzed for partial pressure of anesthetic. Arterial and venous
blood samples were collected through indwelling catheters located in the radial artery and in veins on the back of the hand or distal forearm. These blood samples were also analyzed for pH, PO₂, PCO₂, and hemoglobin. End-tidal gas samples were collected through a catheter the tip of which was placed near the tracheal end of the endotracheal tube, and inspired samples collected proximal to the nonbreathing valve. All samples were drawn either during the first 15 min of anesthesia or after the inspired concentration had been held constant for at least 15 min. As early as 6 and as late as 470 min after induction of anesthesia (the maximum duration of surgery), 2-5 sets of samples were collected from each patient. Anesthetic partial pressures in end-tidal and inspired gases were continuously measured by mass spectrometry. The mass spectrometer automatically calibrates every hour, is checked for accuracy every 15 min, and, if inaccurate, is recalibrated. Core temperature was measured using an esophageal temperature probe, and minute ventilation was recorded with a water seal spirometer.

The anesthetic blood-gas partition coefficient was determined in duplicate for each patient using the following method. Ten milliliters of blood was drawn into a 30-ml glass syringe sealed with a thin layer of silicone grease. Approximately 15 ml of gas containing isoflurane at 1.3% or halothane at 1% concentration was added to the syringe, which was then shaken vigorously and immersed in a water bath at 37° C. At 15-min intervals, the syringe was removed from the bath, shaken again, and replaced in the bath. The latter procedure was repeated for 1.5 h, at the end of which the anesthetic concentrations in the gas and blood phases were determined. The concentration of anesthetic in gas was analyzed by direct injection into a gas chromatograph (Tracer® Model 550). The concentration of anesthetic in blood was measured by extraction of isoflurane or halothane from an aliquot of known volume (approximately 4 ml) of the equilibrated blood that was injected into an evacuated flask of known volume (approximately 500 ml). The flask was shaken vigorously for 30 s, then immersed into a water bath at 37° C. After 15 min the flask was removed from the bath and the pressure within the flask brought to ambient pressure by the addition of room air. The flask was then removed from the bath, shaken vigorously, and returned to the bath every 15 min for 1.5 h. At the end of the 1.5-h equilibration period, 15 ml of room air was added to and mixed with the flask contents, 15 ml of gas was then withdrawn, and the anesthetic concentration was determined by gas chromatography.

The blood-gas partition coefficients (λ) were determined using the formula:

\[ \left[ \frac{(V_t + V_a - V_h)}{V_h} \right] \cdot \left[ \frac{C_r}{(C_a - C_t)} \right] \]

where \( V_t \) is the volume of the flask, \( V_a \) is the 15 ml added to the flask, \( V_h \) is the volume of blood, \( C_r \) is the concentration of anesthetic in the gas phase of the flask, and \( C_a \) is the concentration of anesthetic in the gas phase of the syringe.

The partial pressures of anesthetic in blood were determined by collecting arterial or venous blood in a glass syringe of known volume (approximately 4 ml) and injecting this blood into a flask of known volume (approximately 500 ml). The flask contained a small amount of EDTA crystals for anticoagulation. The anesthetic was extracted and measured by gas chromatography as described for determination of blood-gas partition coefficients. Anesthetic partial pressure in arterial or venous blood was determined using the formula:

\[ \frac{C_r \cdot (V_t + \lambda \cdot V_h)}{(\lambda \cdot V_h)} \]

where the blood gas partition coefficient (λ) was adjusted to the patient’s core temperature at the time the sample was collected using a correction factor previously reported.7

We used a gas chromatograph to detect isoflurane or halothane. The column was composed of 10% SF 96 on Chromasorb WHP, 68/80-mesh, 0.32 cm by 6.1 m, and was kept at 65–70° C. A nitrogen carrier stream was delivered at 45 ml/min through the column to a flame ionization detector at 200° C, which was supplied by hydrogen at 40 ml/min and air at 280 ml/min. Peak chromatograph heights were proportional to anesthetic concentration over the entire range of concentrations studied. Calibration standards prepared as described previously9 were injected at intervals during each study.

Arterial and venous blood gases were measured in a Radiometer® America (ABL2 Model D) respiratory blood-gas machine. Three-point calibration was performed manually each day and two point calibration was performed automatically every 105 min. Oxygen (O₂) content was calculated as (Hgb . 1.34 . Sat) + (P0₂ . 0.003), where Hgb is the patient’s hemoglobin, and Sat is the fractional oxygen saturation. Arterial-to-venous (a-v) O2 content differences were calculated from these data.

To determine the correlation of venous, end-tidal, and inspired partial pressures of anesthetic with the arterial partial pressure, \( P_v \), \( P_a \), and \( P_t \) values were individually compared with the corresponding (simultaneously determined) \( P_a \) values. To assess the correlation between \( P_v \) and \( P_a \) when venous blood was highlyarterialized, we compared \( P_v \) samples collected when the difference in a-v O₂ content was less than 1 vol % with corresponding \( P_a \) samples. We also compared the \( P_a - P_t \) difference with that for \( P_t - P_v \) to determine the relationship of these differences. We compared the normalized \( P_a - P_t \) difference \[ (P_a - P_t)/P_a \] with the tidal volume (in ml/kg) at the
time of sampling to assess the relationship between tidal volume and the $P_A-P_s$ difference. Finally, to determine the correlation of the differences between $P_s$ and $P_a$ and a-v O$_2$ content, we normalized the $P_v-P_s$ difference [(P$_s$ - P$_v$)/P$_s$] and compared that with the a-v O$_2$ content difference. The correlation of all data pairs was determined using linear regression analysis. To assess the degree of arterialization of venous blood produced by halothane and isoflurane, a-v O$_2$ content differences were calculated and compared by unpaired t test. To assess differences in the correlation of $P_A$ with $P_s$, $P_A/P_s$ ratios for halothane and isoflurane were compared by unpaired t test. Statistical significance was defined as $P < 0.05$.

Results

$P_v$ and $P_s$ values correlated closely for isoflurane ($R = 0.892$), for halothane ($R = 0.885$), and for combined data ($R = 0.878$, fig. 1). $P_v$ was consistently lower than the corresponding $P_s$. Although $P_v-P_s$ differences frequently decreased during the course of anesthesia, this trend was not consistent, and these differences often increased. The increase in the difference between a-v anesthetic partial pressures appeared to parallel an increase in the a-v O$_2$ content difference. The correlation between the normalized $P_v-P_s$ difference ($P_v - P_s/P_s$) and the a-v O$_2$ content difference ($R = 0.717, P < 0.001$) supports this parallel. The correlation between $P_v$ and $P_s$ can be improved by eliminating pairs of values collected when the venous blood is not highly arterialized, i.e., when $P_v-P_s$ differences are greatest. For example, if all values collected when the a-v O$_2$ content difference is greater than 1 vol% are eliminated, $P_v$ and $P_s$ correlate well and the scatter in the data decreases ($R = 0.945$, fig. 2). Isoflurane and halothane reduced a-v O$_2$ content differences to a similar extent (1.9 ± 2.2 vs. 1.6 ± 1.7 vol%, mean ± SD, $P = 0.7$), indicating that the effect on cutaneous blood flow and shunting was similar for isoflurane and halothane.

$P_A$ correlated well with $P_s$ for isoflurane ($R = 0.932$), for halothane ($R = 0.972$), and for the combined data ($R = 0.960$, fig. 1). $P_A$ values were consistently higher than those for $P_s$, but this difference decreased during the course of anesthesia (fig. 3). $P_A-P_s$ ratios were greater for halothane than isoflurane (1.23 ± 0.13 vs. 1.11 ± 0.09, $P = 0.09$), indicating that $P_A-P_s$ differences were greater for halothane than isoflurane.

Although there is much scatter in the data, $P_A-P_s$ differences significantly correlated with $P_s-P_r$ differences for isoflurane ($P < 0.004$), for halothane ($P < 0.04$), and for the combined data ($P < 0.001$, fig. 4). The linear regression equation for these differences is: ($P_A-P_s$) = 0.22($P_r-P_s$) + 0.02. There was no correlation between the tidal volume (ml/kg) and the normalized $P_v-P_s$ difference.

![Diagram](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931365/)
Discussion

Pv correlates well with Pa during anesthesia, and this correlation can be improved if comparisons are limited to highly arterialized venous blood samples (figs. 1 and 2). However, even if comparisons are limited to these highly arterialized samples, the correlation between Pv with Pa is not as close as that between PA with Pa (figs. 1 and 2). There was no difference between halothane and isoflurane in these correlations or in the ability of either anesthetic to "arterialize" venous blood in the hand (as assessed by a-v O2 content differences).

There are at least two reasons for differences between Pv and Pa. First, anesthetic is lost to cutaneous tissues until the tissues (in the hand) equilibrate with the partial pressure of anesthetic in arterial blood. This loss occurred each time the attending anesthesiologist increased the inspired anesthetic partial pressure, as necessary to maintain the desired depth of anesthesia. Although samples were collected after at least 15 min at a constant inspired partial pressure, this 15-min period may not have provided enough time for arterial blood and the tissues of the hand to equilibrate.

Second, total blood flow to cutaneous tissues of the hand (or distribution of blood flow within the hand) varied during some of the studies, as indicated by changes in the a-v O2 content difference. The effect of changing blood flow may be explained as follows. The extraction of anesthetic by the tissues is not constant. Initially, extraction is high, but as tissues equilibrate with arterial blood, the extraction of anesthetic should decrease. Consequently, Pp-Pa differences should decrease during the course of the anesthetic if the tissues of the hand behave as a single compartment (i.e., perfusion is equally distributed throughout the tissue and the tissue-blood partition coefficient is constant). If true, changes in blood flow could only change the rate at which the tissues equilibrate with Pa. Thus, an increase in blood flow (as occurs in cutaneous tissues during anesthesia) should increase the rate of equilibration, resulting in a more rapid decrease in the amount of anesthetic extracted from the blood and, therefore, a more rapid approach of Pp-Pa. A subsequent decrease in tissue blood flow (demonstrated by an increased a-v O2 content difference) should decrease the rate of equilibration and slow the approach of Pp-Pa: a decrease in flow should not increase the difference between Pp and Pa.

Our results were not entirely consistent with these predictions. The deviations are illustrated in the values obtained for one patient anesthetized with isoflurane (fig. 5). These data are unique because the alveolar concentration was maintained between 0.80% and 0.86% for the duration of anesthesia. Because in this case Pa was relatively constant, equilibration of the hand tissues should be reflected by the temporal changes in Pv. Although Pv initially approached Pa, Pa later diverged as illustrated by the decrease in the ratio of Pp/Pa (i.e., away from 1). This occurred at the same time that the a-v O2 content difference increased, as indicated by the decreased a-v O2 con-

![Fig. 3. The Pa/Pa ratio for halothane (Δ) and isoflurane (□) versus the duration of inhalational anesthesia. The more accurately Pa reflects Pv, the closer this ratio approaches 1.0. When Pa overestimates Pv, the Pa/Pa ratio is greater than 1.0, and as this difference increases, the ratio also increases. Pa in general is more accurate for isoflurane and improves in accuracy with longer durations of anesthesia.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931365/)

![Fig. 4. Pp-Pa differences are compared with Pp-Pa differences (isoflurane = □; halothane = Δ). Pa-Pa differences increase as Pp-Pa differences increase (P < 0.001). This correlation indicates that part of the Pp-Pa difference can be explained by the concurrent Pp-Pa difference.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931365/)
P_v–P_a differences were positively correlated with the a-v O_2 content differences. As a-v O_2 content differences increased (and blood flow likely decreased), the P_v–P_a differences increased. When venous blood was not highly arterialized, P_a was up to 260% greater than P_v. Errors of this magnitude are possible whenever P_v is used to estimate P_a and a-v O_2 content differences are not known. Thus, to have confidence in the validity of P_v measurement of both arterial and venous blood gases is necessary, and the advantage of sampling P_v is lost. The large errors observed when venous blood is not sufficiently arterialized, makes P_v an unsatisfactory method for estimating P_a.

P_A correlates closely with P_a. The difference between P_A and P_a is largely, but not completely, explained by the concurrent P_t–P_a difference (fig. 4). A similar correlation was demonstrated by Eger and Bahlman who estimated that end-tidal gas samples are composed of approximately 80% true alveolar gas and 20% physiologic dead space gas. Because physiologic dead space gas is composed of unchanged inspired gas, the error this 20% contamination introduces increases as the P_t–P_a difference increases. Consequently, end-tidal values are least accurate when inspired-to-end-tidal partial pressure differences are the greatest, such as during induction and emergence. The correlation between P_t–P_a and P_A–P_a differences supports this conclusion (fig. 4). The slope of this correlation (0.22) indicates that our end-tidal samples also are contaminated by approximately 20% with physiologic dead space gas. Finally, end-tidal-to-arterial anesthetic partial pressure differences should be greater with anesthetics having higher blood solubility. Indeed, P_A–P_a differences were greater for halothane than for isoflurane (fig. 3).

Differences between P_A and P_a also could be caused by pulmonary shunting of blood. Our method does not allow us to distinguish between shunt and physiologic dead space. However, the percent of pulmonary shunt can be roughly estimated at 7.2 ± 2.6% (mean ± SD) if we assume an arterial-to-mixed venous O_2 content difference of 5 ml/100 ml and compare the measured arterial P_O_2 with the P_O_2 predicted by the inspired oxygen concentration. This estimate indicates that pulmonary shunting of blood accounts for only a small fraction of the P_A–P_a difference.

In conclusion, both P_A and P_v correlated well with P_a; however, P_A was found to be most accurate. Consequently, we recommend that P_A continue to be used as an estimate of P_a when direct measurement of P_v is not feasible. We would like to emphasize, however, that the correlation between P_A and P_a is not perfect. Differences in these values are consistently found, especially during times of large P_t–P_A gradients (e.g., during induction and emer-
P_{A} - P_{E}. ANESTHETIC DIFFERENCES

Because the brain (and all tissues of the body) equilibrates with arterial blood and not with end-tidal gas, truly accurate measurement of P_{a} requires arterial sampling and direct measurement.

References

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