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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 (P_v and P_a), and to assess whether this correlation was better than that between the partial pressure of anesthetic in alveolar gas (P_A) and P_a, isoflurane (n = 4) or halothane (n = 4) was administered to eight patients undergoing surgery, and P_v, P_A, and P_a were measured. P_A correlated with P_a better than did P_v ($R = 0.960$ *vs.* 0.878), and there was less variability in the data. Differences between P_v and P_a increased as the relative blood flow to the hand decreased [indicated by an increasing arterial-to-venous (a-v) O_2 content difference]. The difference between P_A and P_a was approximately 20% of the difference between inspired gas (P_I) and P_a. The differences between P_A and P_a 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 (P_a) is considered to directly correlate with the effects of the anesthetic.[1] Although accurate measurement of P_a can provide valuable information, P_a 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 (P_A), which is in equilibrium with arterial blood, is widely accepted as an accurate estimate of P_a.

Because P_A cannot be directly measured, the partial pressure of anesthetic in end-tidal gas samples is assumed to represent the true P_A. However, this assumption may not be warranted. Differences between P_A and P_a of up to 20% have been reported.[2,3] 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 P_A and P_a increases as the difference between P_A and the partial pressure of inspired gas (P_I) increases. When P_I–P_A differences are large (*e.g.*, induction, emergence), P_A becomes a less reliable indicator of P_a. Despite these limitations, measurement of P_A as a reflection of P_a 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 P_{CO_2} is nearly identical to that in arterial blood.[4,5] 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.[6] 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, P_v may correlate better with P_a than does P_A. Accordingly, we measured P_A, P_a, and P_v, then correlated P_v and P_A with P_a 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 (P_I = 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 nonrebreathing 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

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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 *p*H, P_{O_2}, P_{CO_2}, 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 nonrebreathing 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 (Tracor® 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:

$$[(V_f + V_a - V_b)/V_b] \cdot [C_f/(C_s - C_f)]$$

where V_f is the volume of the flask, V_a is the 15 ml added to the flask, V_b is the volume of blood, C_f is the concentration of anesthetic in the gas phase of the flask, and C_s 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:

$$[C_f \cdot (V_f + \lambda \cdot V_b)]/(\lambda \cdot V_b)$$

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 previously[8] 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 (O_2) content was calculated as $(Hgb \cdot 1.34 \cdot Sat) + (P_{O_2} \cdot 0.003)$, where Hgb is the patient's hemoglobin, and Sat is the fractional oxygen saturation. Arterial-to-venous (a-v) O_2 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_I 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 highly arterialized, we compared P_v samples collected when the difference in a-v O_2 content was less than 1 vol % with corresponding P_a samples. We also compared the P_A–P_a difference with that for P_I–P_a to determine the relationship of these differences. We compared the normalized P_A–P_a difference $[(P_A - P_a)/P_A]$ with the tidal volume (in ml/kg) at the

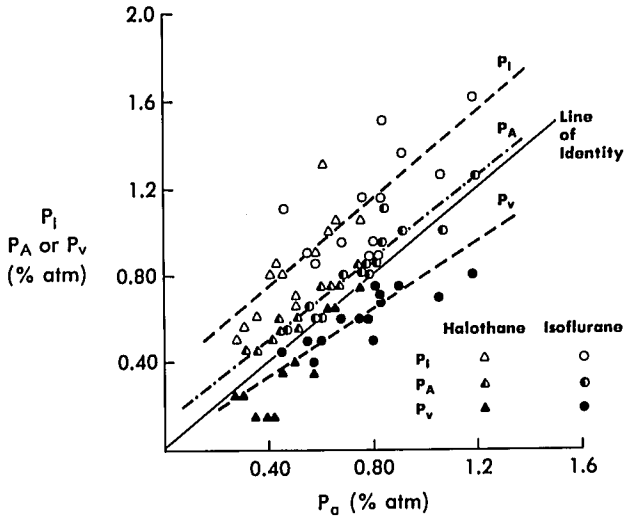

FIG. 1. Inspired (P_I), end-tidal (P_A), and venous (P_v) anesthetic partial pressures are compared with simultaneously obtained arterial partial pressure (P_a) in humans. Although both P_A and P_v correlated with P_a, the correlation for P_A was better (R = 0.960 *vs.* 0.878), and there was less scatter in the P_A data. The P_A–P_a difference increased as the P_I–P_a difference increased.

time of sampling to assess the relationship between tidal volume and the P_A–P_a difference. Finally, to determine the correlation of the differences between P_v and P_a and a-v O_2 content, we normalized the P_v–P_a difference [($P_a - P_v$)/P_a] 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_a, P_A/P_a ratios for halothane and isoflurane were compared by unpaired t test. Statistical significance was defined as $P < 0.05$.

Results

P_v and P_a values correlated closely for isoflurane (R = 0.832), for halothane (R = 0.885), and for combined data (R = 0.878, fig. 1). P_v was consistently lower than the corresponding P_a. Although P_v–P_a 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_a difference ($P_v - P_a/P_a$) and the a-v O_2 content difference (R = 0.717, $P < 0.001$) supports this parallel. The correlation between P_v and P_a can be improved by eliminating pairs of values collected when the venous blood is not highly arterialized, *i.e.*, when P_v–P_a 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_a 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_a 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_a, but this difference decreased during the course of anesthesia (fig. 3). P_A–P_a ratios were greater for halothane than isoflurane (1.23 ± 0.13 *vs.* 1.11 ± 0.09, P = .009), indicating that P_A–P_a differences were greater for halothane than isoflurane.

Although there is much scatter in the data, P_A–P_a differences significantly correlated with P_I–P_a 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: ($P_A - P_a$) = 0.22($P_I - P_a$) + 0.02. There was no correlation between the tidal volume (ml/kg) and the normalized P_v–P_a difference.

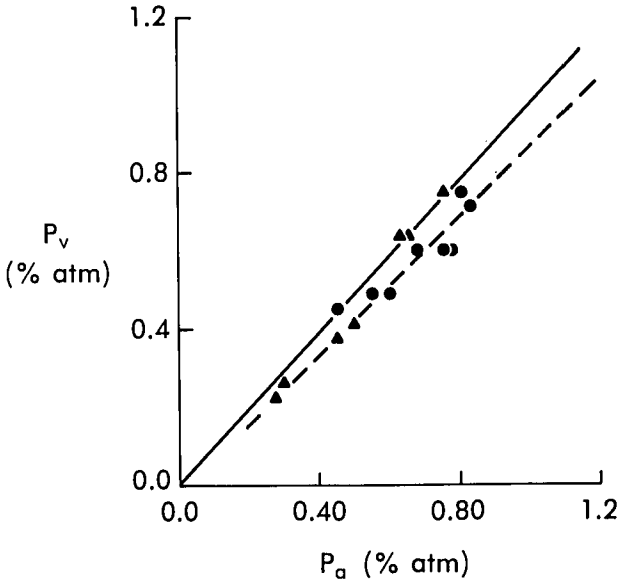

FIG. 2. Venous anesthetic partial pressures (P_v) are compared with simultaneously determined arterial partial pressures (P_a) for samples having an a-v O_2 content difference of less than 1 vol % (isoflurane = ●; halothane = ▲). When only highly arterialized venous samples are compared, the correlation improves (R = 0.945) and the scatter decreases.

Discussion

P_v correlates well with P_a 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 P_v with P_a is not as close as that between P_A with P_a (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 O_2 content differences).

There are at least two reasons for differences between P_v and P_a. 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 O_2 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, P_v–P_a 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 P_a. 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 P_v–P_a. A subsequent decrease in tissue blood flow (demonstrated by an increased a-v O_2 content difference) should decrease the rate of equilibration and slow the approach of P_v–P_a: a decrease in flow should not increase the difference between P_v and P_a.

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 P_A was relatively constant, equilibration of the hand tissues should be reflected by the temporal changes in P_v. Although P_v initially approached P_a, P_v later diverged as illustrated by the decrease in the ratio of P_v/P_a (*i.e.*, away from 1). This occurred at the same time that the a-v O_2 content difference increased, as indicated by the decreased v-a O_2 con-

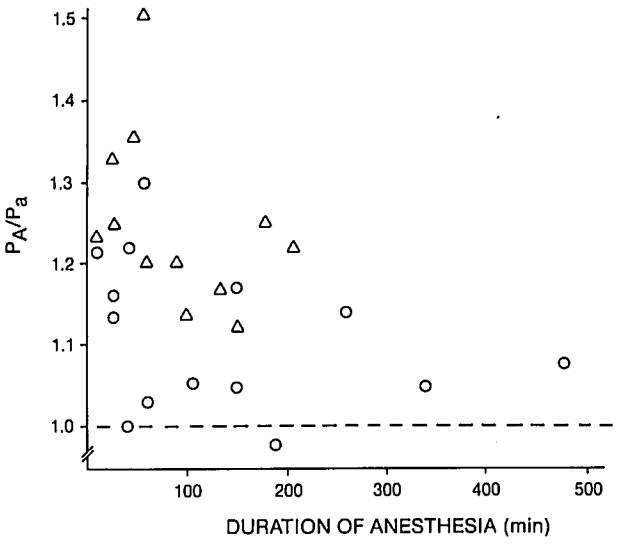

FIG. 3. The P_A/P_a ratio for halothane (Δ) and isoflurane (O) *versus* the duration of inhalational anesthesia. The more accurately P_A reflects P_a, the closer this ratio approaches 1.0. When P_A overestimates P_a, the P_A/P_a ratio is greater than 1.0, and as this difference increases, the ratio also increases. P_A in general is more accurate for isoflurane and improves in accuracy with longer durations of anesthesia.

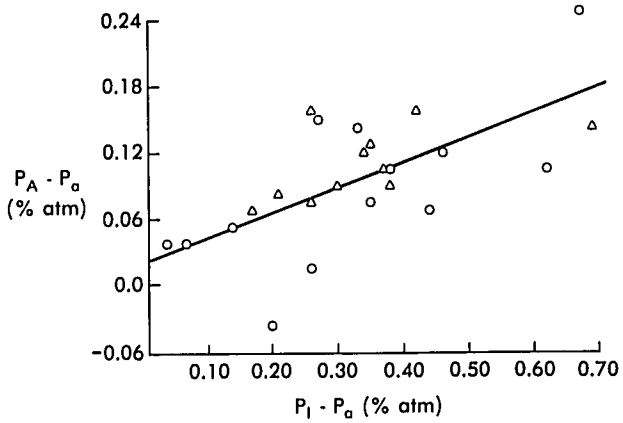

FIG. 4. P_A–P_a differences are compared with P_I–P_a differences (isoflurane = O; halothane = Δ). P_A–P_a differences increase as P_I–P_a differences increase ($P < 0.001$). This correlation indicates that part of the P_A–P_a difference can be explained by the concurrent P_I–P_a difference.

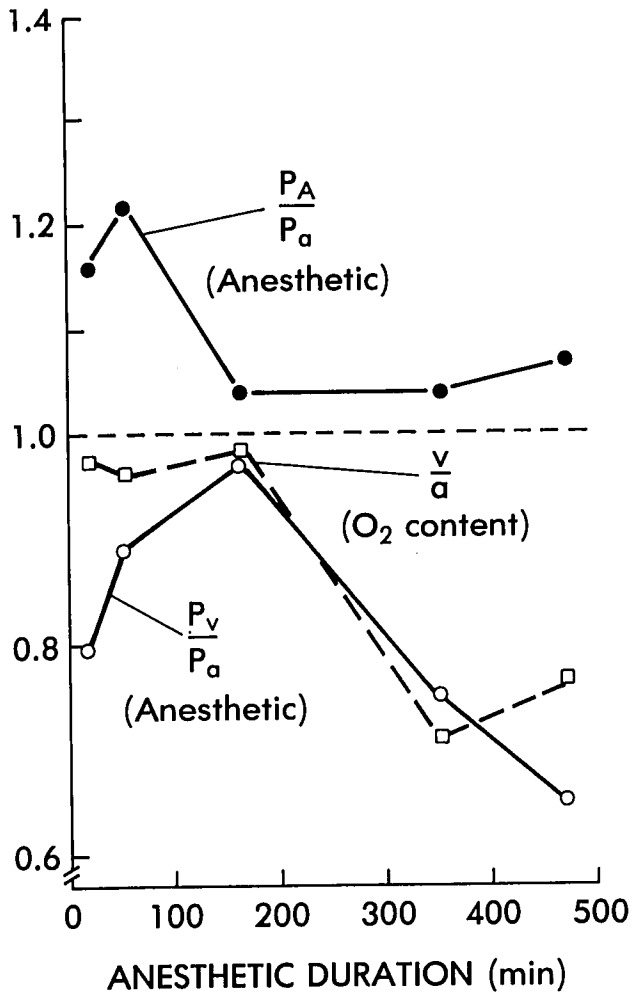

FIG. 5. The ratios of P_A and P_a, venous and arterial O_2 content, and P_v and P_a are plotted against anesthetic duration to illustrate the temporal changes in one patient whose inspired partial pressure of isoflurane was purposefully manipulated to maintain a constant P_A. With longer anesthetic duration, P_A–P_a differences decrease, while P_v–P_a and O_2 content differences initially decrease, then increase. The increase in P_v–P_a difference appears to parallel that in a-v O_2 content difference.

tent ratio (fig. 5). Decreasing blood flow increased the P_v–P_a difference, rather than slowing the rate of equilibration of P_v with P_a. This increase indicates that the cutaneous tissues of the hand do not act as a single compartment: at least two compartments must be present to explain this observation. A two-compartment model for the skin has been previously suggested to explain a similar phenomenon observed during xenon washout from cutaneous tissues, and this second compartment likely represents subcutaneous fat.[9] This divergence is the apparent cause of the greatest differences between P_v and P_a.

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_I–P_a difference (fig. 4). A similar correlation also 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.[3] Because physiologic dead space gas is composed of unchanged inspired gas, the error this 20% contamination introduces increases as the P_I–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_I–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.[10] 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_a 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_I–P_A gradients (*e.g.*, during induction and emer-

gence of anesthesia). 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.

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