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Washin and Washout of Isoflurane Administered via *Bubble Oxygenators during Hypothermic Cardiopulmonary Bypass*

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Washin and washout of a volatile anesthetic given through the oxygenator during hypothermic (23.4 ± 2.1° C) cardiopulmonary bypass were studied in nine patients. The authors administered isoflurane and measured its partial pressure in arterial (P_a) and venous (P_v) blood and the gas exhausted from the oxygenator (P_E) at 1, 2, 4, 8, 16, 32, and 48 min during washin. These measurements were repeated during washout, which coincided with rewarming. During washin, P_E, P_a, and P_v progressively rose toward inlet gas partial pressure (P_I). Equilibration of P_a with P_I was 41% after 16 min, 51% after 32 min, and 57% after 48 min of washin. During washout, P_a declined to 24% of its peak after 16 min and to 13% after 32 min. Washin and washout were considerably slower in mixed venous blood. Washin of isoflurane appeared to occur more slowly during cardiopulmonary bypass than during administration *via* the lungs in normothermic patients, presumably because hypothermia increases tissue capacity, compensating for the effect of hemodilution that otherwise would decrease the blood/gas partition coefficient. During rewarming, washout appeared to occur as rapidly as from the lungs of normothermic patients. This may have resulted from the declining blood/gas partition coefficient (due to rewarming) and relatively limited tissue stores of isoflurane. The relationship between exhaust and arterial partial pressures was reasonably consistent; for clinical purposes, measurement of P_E can be used to estimate P_a. (Key words: Anesthetics, volatile: isoflurane. Pharmacokinetics. Surgery, cardiac: cardiopulmonary bypass; oxygenators.)

DURING CARDIOPULMONARY BYPASS (CPB), volatile anesthetics are often added to the oxygen flowing through the oxygenator to provide anesthesia, to regulate systemic vascular resistance, and to attenuate the hormonal response to CPB.[1–5] Because these anesthetics have depressant cardiovascular effects, it is usually desirable to reduce the arterial anesthetic partial pressure before termination of CPB.[5,6] Although the ability of oxygenators to transfer anesthetic gases has been defined,[7] factors other than oxygenator efficiency affect the partial pressure of anesthetic in arterial blood during clinical CPB, *e.g.*, hemodilution, perfusion, and tissue capacity for anesthetic during hypothermia and rewarming.

In this study, we sought to answer the following questions: 1) How rapid are washin and washout of isoflurane during CPB? 2) To what degree do bubble oxygenators limit transfer of isoflurane during washin and washout? 3) What is the tissue uptake in the hypothermic patient, as reflected by the arterial-to-venous partial pressure difference? and 4) Does the partial pressure of anesthetic in oxygenator exhaust gas reflect the partial pressure in arterial blood? To accomplish this, we measured the partial pressure of isoflurane in arterial blood, venous blood, gas entering the oxygenator, and gas exiting the oxygenator during anesthetic washin in patients undergoing hypothermic CPB. We repeated these measurements during washout, which coincided with rewarming during CPB. These data provide a guideline for timing the discontinuation of a volatile anesthetic so that minimal concentrations are present at termination of cardiopulmonary bypass.

Methods

The protocol was approved by the Committee on Human Research at the University of California, San Francisco, and written informed consent was obtained from nine patients scheduled to undergo hypothermic CPB. The components of the CPB circuit included a Bentley Ben-10® bubble oxygenator (Bentley Laboratories, Inc., Irvine, CA), cardiotomy reservoir, arterial tubing filter, and the Tygon® tubing (Norton Co., Akron, OH) connecting these components. Because the circuits were primed with 2000 ml of lactated Ringer's solution, hemodilution occurred with the onset of CPB (hematocrit = 22.9 ± 2.9%, mean ± SD). During hypothermic CPB, temperature was 23.4 ± 2.1° C, oxygen flow rate to the oxygenator was 3.4 ± 0.8 l/min, and pump flow rate was 4.0 ± 0.4 l/min. During rewarming, oxygen flow rate was 4.3 ± 0.7 l/min while pump flow rate was 4.1 ± 0.4 l/min.

Intravenous agents (fentanyl and diazepam or sufentanil and diazepam) were used to induce and maintain anesthesia before CPB; isoflurane was not administered prior to CPB. During the first 15–20 min of CPB, the hypothermic temperature (23.4 ± 2.1° C) was allowed to stabilize; temperature was measured at the arterial outlet

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of the oxygenator using a Yellowsprings® temperature probe calibrated against a National Bureau of Standards mercury thermometer. Then, isoflurane 1% was added *via* a calibrated vaporizer to the oxygen flowing to the oxygenator. Approximately 20 min prior to beginning isoflurane administration, the vaporizer was set at 1% and oxygen was allowed to flow through it at a rate of 3.5 l/min to stabilize vaporizer output prior to beginning the study. The vaporizer output was connected *via* polyvinyl chloride tubing to the hospital scavenging system. A mass spectrometer connected to the gas line exiting the vaporizer verified accurate delivery of isoflurane (1.0 ± 0.08%) during CPB.

Arterial blood samples were drawn from a stopcock in the arterial tubing located just distal to the arterial filter. For each patient, a simultaneous sample was obtained from the radial arterial catheter at least once during CPB; these samples consistently contained anesthetic concentrations that were virtually identical to the corresponding concentrations obtained from the arterial tubing. Mixed venous blood samples were obtained from a stopcock located in the venous tubing just before entry into the oxygenator. Anesthetic partial pressure in gas delivered to the oxygenator was measured in samples obtained from a stopcock in the gas inflow tubing just proximal to the gas inlet of the oxygenator. Anesthetic partial pressure in gas exiting the oxygenator was measured in samples drawn through a stopcock attached to the oxygenator's exhaust port. Blood and gas samples were obtained just before the addition of isoflurane, and at 1, 2, 4, 8, 16, 32, and 48 min after beginning its administration (washin). A final set of samples was obtained just before rewarming (mean elapsed time of isoflurane administration = 43 ± 17 min); these samples contained peak anesthetic concentrations. Isoflurane administration was discontinued as rewarming began and blood and gas samples were withdrawn at 1, 2, 4, 8, 16, and 32 min during washout. The temperature increased to 37° C during washout, while hematocrit was unchanged. The patient's lungs were not inflated or ventilated throughout the study period. The study ended just before pulmonary ventilation recommenced, prior to weaning from CPB.

Anesthetic concentrations in all samples were measured by a gas chromatograph calibrated with a secondary (tank) standard. The chromatograph was a 30-m, fused silica open tubular capillary (0.53-mm internal diameter) column coated with a layer of methylsilicone oil (J & W Scientific DB-1) that was 1.5-μm thick. A nitrogen carrier stream of 6 ml/min was directed through the column with a "make-up" flow of nitrogen of 40 ml/min delivered to the detector. A flame ionization detector at 200° C was supplied by hydrogen at 40 ml/min and by air at 280 ml/min. Samples were injected with a 0.05-ml gas sample loop.

Blood/gas partition coefficients were determined in quintuplicate for each patient.[8] Seven-milliliter samples of blood were placed in 50-ml syringes and equilibrated by tonometry with 21 ml of isoflurane vapor in air. The syringes were maintained at the mean oxygenator temperature that existed during the stable hypothermic period of CPB.[8] Equilibration proceeded for approximately 2 h, during which time the syringes were shaken at 15-min intervals. The gas phase then was analyzed by gas chromatography. An aliquot, approximately 4 ml, of the remaining blood from each syringe was injected into an evacuated flask of known volume, approximately 600 ml. The flask was maintained at the temperature at which the syringe has been equilibrated for 1.5 h or longer and was shaken at 15-min intervals. Midway through this period, the pressure within the flask was brought to ambient pressure by the addition of ambient air. At the end of the period, 10 ml of air was added to the flask. Twenty milliliters of gas from within the flask was withdrawn and analyzed by gas chromatography. The blood/gas partition coefficients (λ) were determined as follows:

$$\lambda = [(V_f + 10\ ml - V_b) \div V_b][C_f \div (C_s - C_f)],$$

where V_f is the volume of 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. Ten milliliters are added to the numerator to account for the 10 ml of air added prior to removal of the sample for analysis. The subtraction of C_f from C_s in the denominator corrects for the anesthetic remaining in blood.

Using the blood/gas partition coefficients determined for each patient, we converted anesthetic concentrations to partial pressures. For each conversion, the blood/gas partition coefficient was corrected to the true temperature of each sample at the time it was obtained.[8]

Linear regression analysis was used to examine the relationship between partial pressure of isoflurane in blood *versus* partial pressure of isoflurane in oxygenator exhaust gas.

Results

The mean blood/gas partition coefficient of isoflurane in this study was 1.39 ± 0.18 with hypothermia (23.4 ± 2.1° C) and hemodilution (hematocrit 22.9 ± 2.9%). This value is similar to the value of 1.46 ± 0.09 for isoflurane previously measured in undiluted blood at normal body temperature.[8] Data from Eger and Eger would give a coefficient of 2.85 ± 0.24 for undiluted blood at 22° C; this differs from our value of 1.39 ± 0.18 because of the condition of hemodilution in our study.[8]

Duration of CPB was 93 ± 25 min and duration of washin was 43 ± 17 min. During washin, the partial pres-

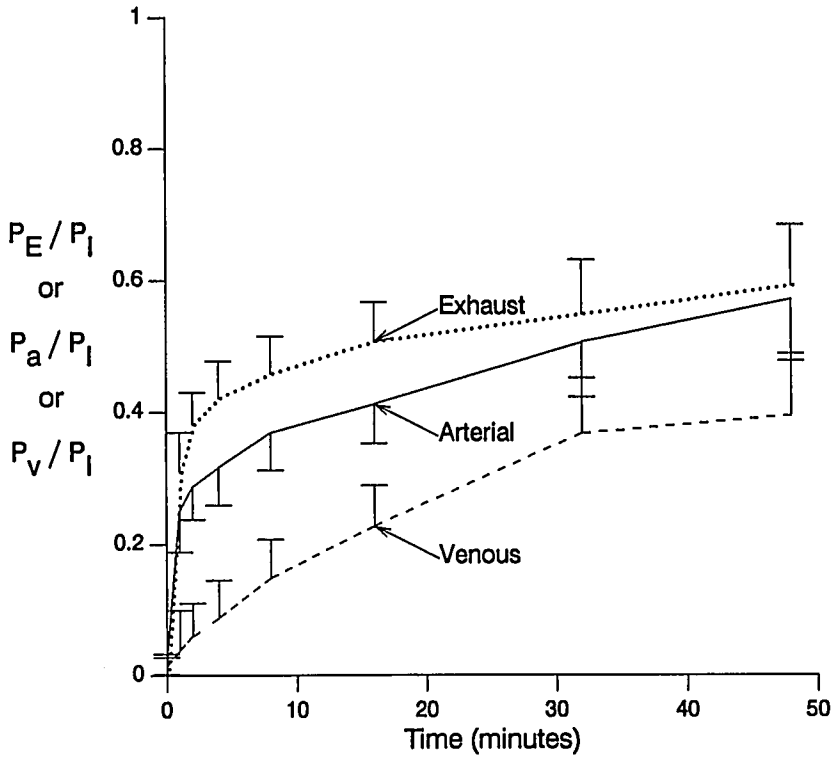

FIG. 1. Ratio of partial pressure of isoflurane in exhaust gas (P_E) and arterial (P_a) and venous (P_v) blood, to partial pressure of inlet gas (P_I) during washin. P_E, P_a, and P_v progressively rise with increasing duration of anesthetic administration. As with data from normothermic, self-perfused patients, there is an initial rise in the arterial (and exhaust) curve to a "knee" at 1–2 min; however, unlike the data from normothermic patients, a second "knee" at 10–15 min is more difficult to discern.

sure of isoflurane in arterial blood (P_a) rose slowly toward inlet gas partial pressure (P_I) (fig. 1). After 16 min of washin, P_a was 41 ± 6% that of P_I. After 32 min, equilibration had reached 51 ± 8%; after 48 min, equilibration was 57 ± 9%. Anesthetic partial pressure in mixed venous blood (P_v) was lower than that in arterial blood throughout washin.

During washout, P_a decreased to 36 ± 15% of its peak partial pressure (P_{a_0}) by 8 min after discontinuing isoflurane administration (fig. 2). After 16 min, P_a had declined

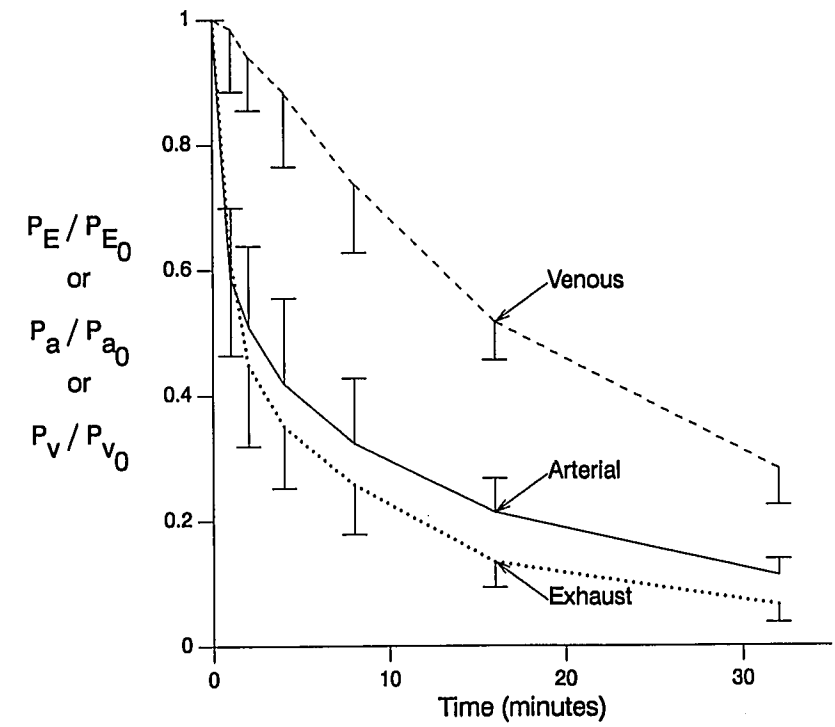

FIG. 2. Ratio of partial pressure of isoflurane in exhaust gas (P_E), and arterial (P_a) and venous (P_v) blood to the partial pressure in gas or blood just before discontinuing anesthetic administration (P_{E_0}, P_{a_0}, or P_{v_0}). Washout curves for P_E and P_a decrease rapidly; P_v decreases more slowly because of the limitation imposed by the increasing temperature (which increases the anesthetic partial pressure in tissues and, therefore, increases the tissue-to-blood anesthetic gradient).

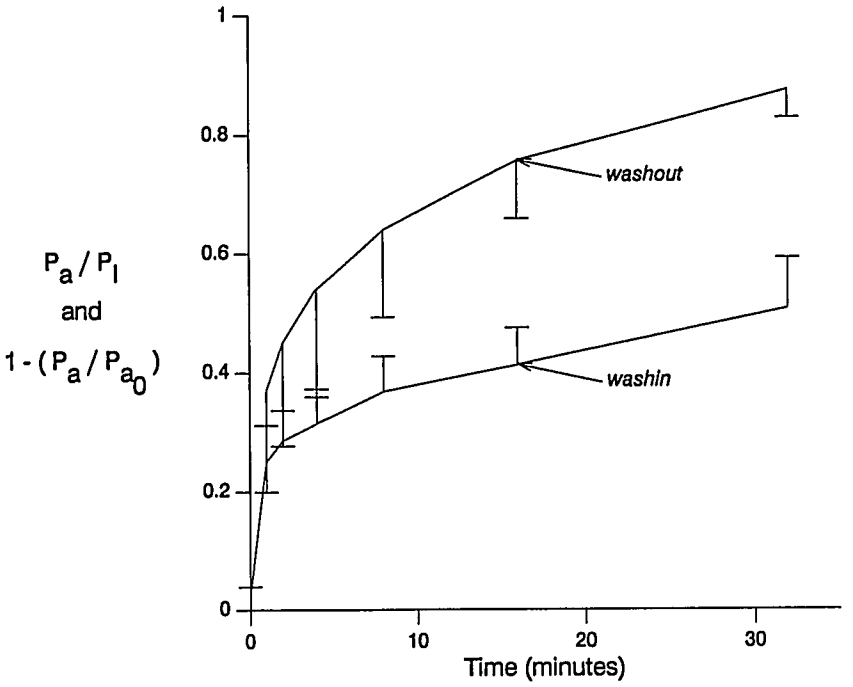

FIG. 3. Ratio of partial pressure of isoflurane in arterial blood (P_a) to partial pressure of inlet gas (P_I) during washin. Distribution of isoflurane to the tissues slows washin. During washout, the ratio of partial pressure of isoflurane remaining in arterial blood to the partial pressure in the arterial blood just before discontinuing anesthetic administration (P_a/P_{a_0}) is subtracted from 1. Partial pressure of isoflurane declines more rapidly during washout than it rises during washin because of redistribution from the vessel-rich group to muscle and fat groups.

to 24 ± 10% and after 32 min, to 13 ± 5% of its peak. Anesthetic partial pressure in mixed venous blood, expressed as a fraction of the peak venous partial pressure (P_v/P_{v_0}), declined more slowly than that in arterial blood during washout. Partial pressure of isoflurane in arterial blood declined during washout more rapidly than it rose during washin (fig. 3).

The partial pressure of isoflurane in exhaust gas (P_E) correlated reasonably well with P_a during both washin and washout (fig. 4).

Discussion

Two factors affect the solubility of anesthetics in blood during CPB. Anesthetics are more soluble in blood at lower temperatures;[8–10] therefore, during hypothermia, there is a slower increase in arterial anesthetic partial pressure with induction of anesthesia and slower decrease during recovery.[11,12] Conversely, hemodilution, produced by addition of crystalloid prime to the patient's blood volume, exerts an opposite effect on anesthetic solubility, because anesthetics are less soluble in saline than blood.[9,10,13] In this study, the blood/gas partition coefficient resulting from the opposing effects of these factors is similar to that in undiluted blood at normal body temperature.[8]

Other factors affecting anesthetic kinetics during CPB are tissue uptake of anesthetic during the hypothermic phase of CPB and release of anesthetic from tissues during the rewarming phase. Hypothermia increases the capacity of both blood and tissues for anesthetic. Since the tissue forms the far greater bulk, it will have the greater effect. Our data indicate that washin of isoflurane during hypothermic CPB was slower than that found in normothermic patients not undergoing CPB.[14] After 45 min, only 50% of the delivered partial pressure of isoflurane was present in arterial blood. The relatively slow increase in P_a/P_I during washin probably resulted, in part, from the greater tissue capacity produced by hypothermia, in the presence of a blood/gas partition coefficient equal to that found in normothermic nonhemodiluted patients, rather than from limitation of anesthetic gas transfer through the oxygenator, as discussed below. An additional factor probably was decreased average tissue perfusion. Although there are minor changes in regional blood flow during CPB,[15] the primary determinant of the distribution of flow is the decrease in temperature, which decreases metabolism. Correspondingly, pump flow (cardiac output) is decreased to about 75% of that which would exist in normothermic adult patients.

Decreased average tissue perfusion and increased tissue solubility (and no change in blood solubility) increase tissue time constants. During hypothermic CPB, at 23.4° C, the tissue solubility would be increased by about 80%[8] or 1.8-fold. Perfusion of our patients was 4.0 l/min, whereas a normal, awake, normothermic adult might have a perfusion of 5.4 l/min. Thus, the time constant might be increased by 2.4-fold [(1.8 · 5.4) ÷ 4.0 = 2.4-fold]. For isoflurane, the vessel-rich tissue group has a tissue/blood partition coefficient of 2.0 at 37° C.[16] The normal time constant, assuming a vessel-rich group perfusion of 4 l/min to 6 l of tissue, would be 3 min [(2 · 6) ÷ 4 = 3 min]. Therefore, the time constant for the vessel-rich group during CPB might be 7.3 min rather than 3 min. This

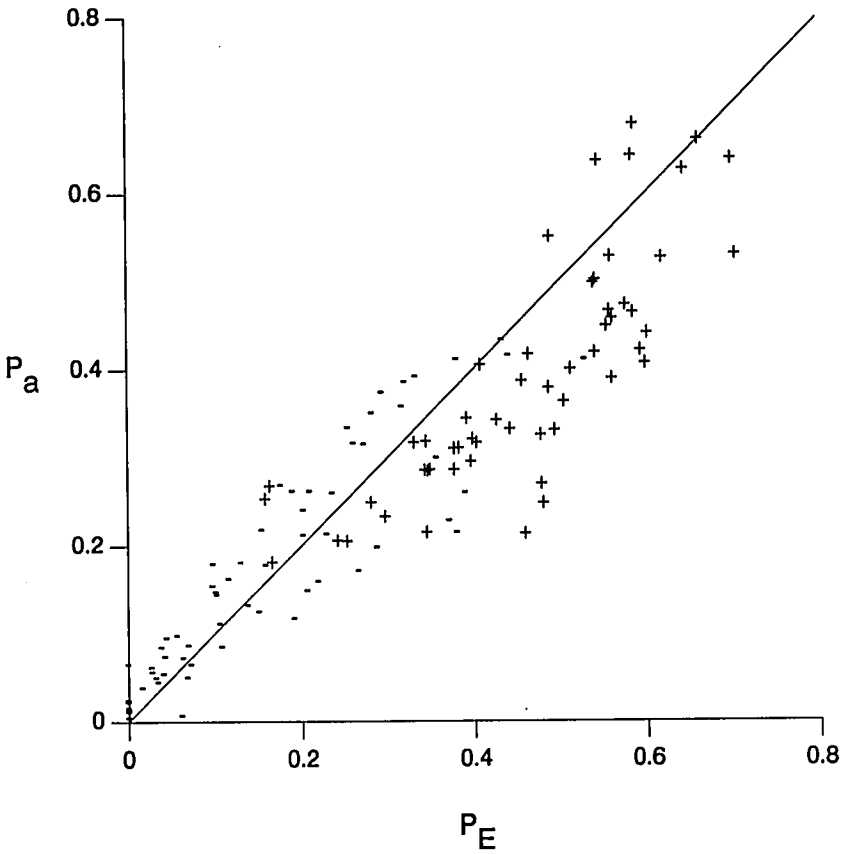

FIG. 4. The partial pressure of isoflurane in the arterial blood (P_a) correlates reasonably well with the partial pressure in the gas leaving the oxygenator (P_E). The solid line is the line of identity. During washin, the slope (±SD) determined by least squares linear regression did not differ from the slope during washout. For washin and washout data combined, slope (±SD) = 0.77 ± 0.03; standard error of the estimate = 0.07 and r^2 = 0.84.

might explain the absence of a second "knee" in the curve depicting washin of isoflurane into arterial blood during CPB (fig. 1); such a knee might have been evident had we been able to double the time of observation for washin.

Washout of isoflurane during CPB, which coincided with rewarming, occurred more rapidly than washin (fig. 3) and was comparable to washout curves measured after pulmonary administration to normothermic patients.[14] This normal decay rate may be the result of two factors: 1) a limited deposition of anesthetic in tissue because of the factors affecting tissue time constants, as discussed above; and 2) a declining blood/gas partition coefficient, due to increasing temperature.

Price *et al.* also found that isoflurane concentrations rapidly decrease during elimination of anesthetic *via* a bubble oxygenator.†† Our results, however, differ in that we found a slower washout. For example, at 4 min, our exhaust partial pressure was 46 ± 19% of the partial pressure immediately prior to cessation of anesthetic administration, while Price *et al.* found a value of 14 ± 6%. This difference may have resulted from modest differences in temperature, pump flow, and fresh gas flow. We had a lower temperature, higher pump flow, and lower fresh gas flow—all of which would have relatively increased our washout values. The equilibration times applied by Price *et al.*, however, were substantially (more than twice) longer than ours and this should have increased their washout concentrations relative to ours. Possibly, their lower values reflect incomplete equilibration or contamination of the gas samples with room air. It is not possible to speculate further because Price *et al.* did not determine arterial anesthetic partial pressures. Without such values, we do not know if a gradient existed.

In order to estimate the disequilibrium of patient tissue uptake of isoflurane at the end of washin, the instantaneous tissue uptake during washin ($[C_a - C_v] \cdot \dot{Q}$) and the instantaneous tissue elimination during washout ($[C_v - C_a] \cdot \dot{Q}$) were calculated at each sampling interval, where C_a is the concentration (at standard temperature) of isoflurane in arterial blood, C_v is the concentration (at standard temperature) of isoflurane in venous blood, and $\dot{Q}$ is the perfusion flow rate (fig. 5). The area under the instantaneous tissue uptake curve was 4.16 ml during the first 32 min of washin, while the area under the instantaneous tissue elimination curve was 0.73 ml during the first 32 min of washout. Therefore, for the same period of time, washout of isoflurane was only 18% that of washin. The difference between the areas under the instantaneous tissue uptake *versus* elimination curves provides an approximate indication of the disequilibrium of

†† Price SL, Brown DL, Carpenter RL, Unadkat JD, Crosby SS: Isoflurane elimination *via* a bubble oxygenator during extracorporeal circulation. J Cardiothoracic Anesth 2:41–44, 1988.

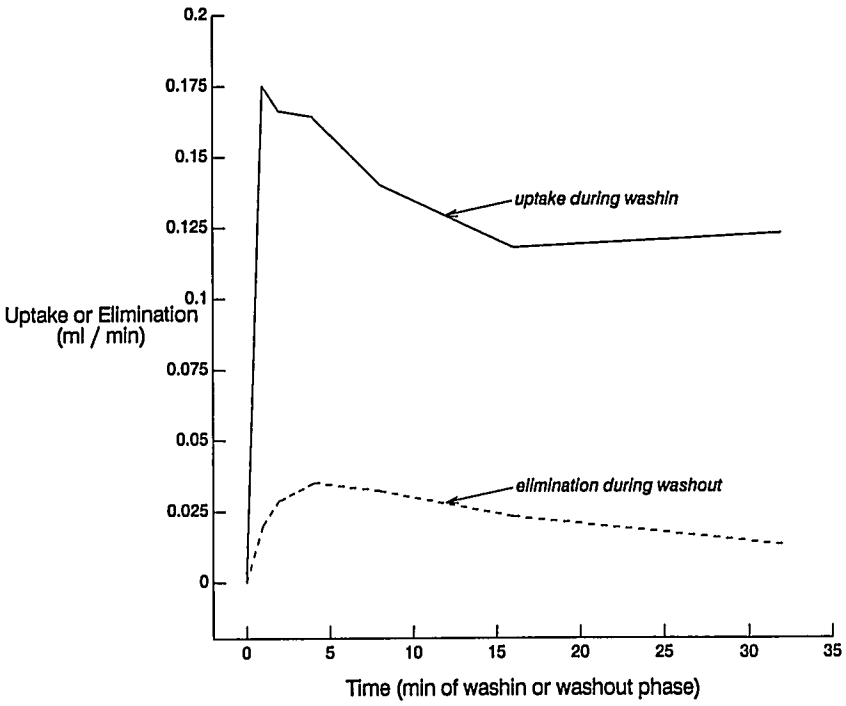

FIG. 5. Instantaneous tissue uptake ($[Ca - Cv]\cdot\dot{Q}$) and elimination ($[C_v - C_a]\cdot\dot{Q}$) of isoflurane during cardiopulmonary bypass, where Ca is the concentration (at standard temperature) of isoflurane in arterial blood, Cv is the concentration (at standard temperature) of isoflurane in venous blood, and $\dot{Q}$ is the perfusion flow rate. The area under the instantaneous tissue uptake curve is 4.16 ml during the first 32 min of washin, while the area under the instantaneous tissue elimination curve is 0.73 ml during the first 32 min of washout.

the tissues at the end of washin. During washout, redistribution of isoflurane (from the vessel-rich group to muscle and fat groups) significantly influences the decline of P_a/P_{a_0}, because P_a continues to exceed partial pressure in fat and muscle during the early period of washout.

We have previously measured the degree to which bubble oxygenators limit transfer of isoflurane to diluted blood in *in vitro* studies (fig. 6).[7] Superimposed on these data in figure 6 are washin and washout curves for isoflurane administered to patients during hypothermic CPB in the current study. The slower rates of isoflurane washin and washout during clinical CPB compared to the rates found *in vitro* display the significant effect of tissue uptake by the hypothermic patient. Washout of isoflurane *via*

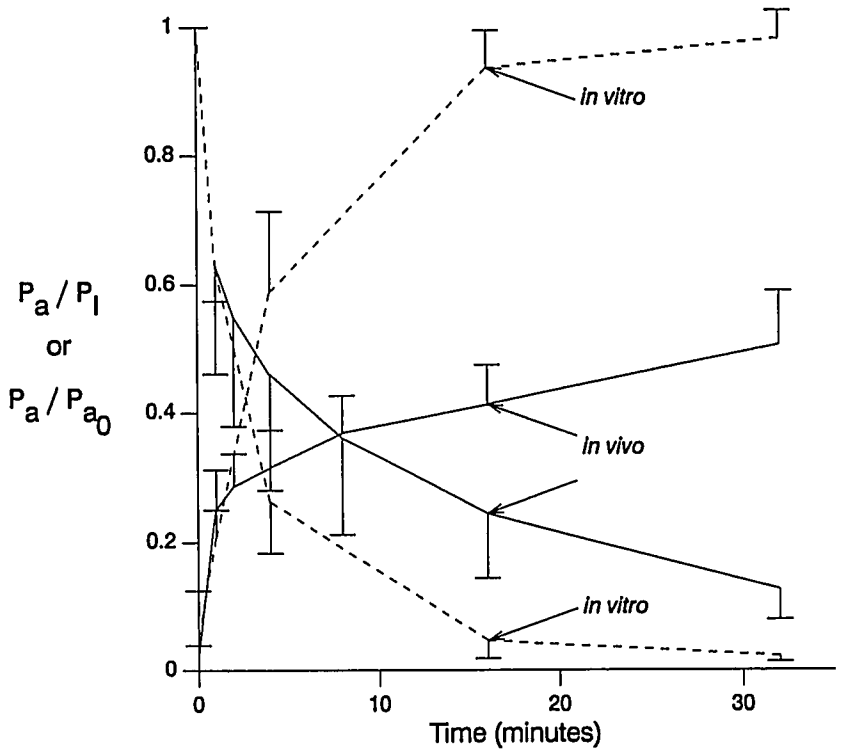

FIG. 6. The washin and washout of isoflurane via bubble oxygenators *in vitro*[7] is more rapid than that obtained in patients during cardiopulmonary bypass in the current study. Parameters and abbreviations as in figures 1 and 2.

bubble oxygenators was as rapid in our patients as in the patients of Loomis *et al.*,[1] who received isoflurane administered *via* membrane oxygenators during cardiopulmonary bypass. Our clinical data, however, have unknown relevance for newer membrane oxygenators, which may have improved efficiency for gas transfer.

Anesthetic partial pressure in mixed venous blood was significantly lower than in arterial blood throughout the hypothermic washin period, due to ongoing uptake of isoflurane by cold patient tissues (fig. 1). Also, during washout, isoflurane partial pressure in mixed venous blood declined more slowly than in arterial blood (fig. 2), because of ongoing transfer of anesthetic from hypothermic patient tissues to the rapidly warming blood perfusing these tissues. Even after 32 min, nearly 30% of the peak venous partial pressure of isoflurane still remained in venous blood. This finding is of interest because mixed venous partial pressure represents the algebraic sum of tissue perfusion and tissue anesthetic partial pressure. If low pulmonary gas flows are administered as pulmonary ventilation is recommenced and CPB is terminated, then arterial, venous, and alveolar partial pressures of isoflurane may be sustained despite the absence of anesthetic administration, because of continued isoflurane release from patient tissues into warmer blood with a lower capacity for anesthetics.

The partial pressure of isoflurane in exhaust gas was similar to the partial pressure in arterial blood during both washin and washout (fig. 4). In addition to analyzing the data by linear regression, we calculated the ratio of P_a/P_E, for data points where both exceeded 0.2% (we decided not to include the lowest values in order to eliminate the potential for experimental variability and calculation errors they may introduce). During washin, the mean ratio was 0.82 ± 0.14; during washout, the mean ratio was 1.03 ± 0.22. These values are consistent with nearly complete equilibrium between blood and gas in the oxygenator; neither ratio was significantly different from 1.0. Therefore, analysis of anesthetic partial pressure in oxygenator exhaust gas (*e.g.*, with a mass spectrometer or infrared device) should be a useful clinical guide for the estimation of anesthetic partial pressure in arterial blood during CPB. Care must be taken in such sampling of exhaust gas to ensure accuracy and avoid risk to the patient. The sampling port attached to the oxygenator's exhaust port must be devised to prevent contamination of the sample by room air and at the same time must allow for unimpeded gas egress, to avoid pressurizing and bursting the oxygenator.

The data we have collected have an important clinical implication. Washin of isoflurane during hypothermic CPB is somewhat slower than in a normal patient, but is rapid in either case. Washout during CPB is not delayed at all. Thus it would appear that the control that can be exerted on anesthetic depth (dose) during normothermia by pulmonary transfer of anesthetic is also possible during hypothermia and CPB.

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