Anesthesiology 2005; 103:460–9

Kinetics and Extravascular Retention of Acetated Ringer's Solution during Isoflurane or Propofol Anesthesia for Thyroid Surgery

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Background: **In sheep, isoflurane causes extravascular accumulation of infused crystalloid fluid. The current study evaluates whether isoflurane has a greater tendency than propofol to cause extravascular retention in surgical patients.**

Methods: **Thirty patients undergoing thyroid surgery lasting for 143 ± 32 min (mean ± SD) received an intravenous infusion of 25 ml/kg acetated Ringer's solution over 30 min. Anesthesia was randomized to consist of isoflurane or propofol supplemented by fentanyl. The distribution and elimination of the infused fluid was estimated using volume kinetics based on the fractional dilution of blood hemoglobin over 150 min. Extravascular retention of infused fluid was taken as the difference between the model-predicted elimination and the urinary excretion. The sodium and fluid balances were measured.**

Results: **The fractional plasma dilution increased gradually to approximately 30% during the infusion and thereafter remained at 15–20%. Urinary excretion averaged 11% of the infused volume. Mean arterial pressure was 10 mmHg lower in the isoflurane group ($P < 0.001$). The excess fluid volumes in the central and peripheral functional body fluid spaces were virtually identical in the groups. The sum of water losses by evaporation and extravascular fluid retention amounted to 2.0 ± 2.5 ml/min for isoflurane and 2.2 ± 2.1 ml/min for propofol. The sodium balance refuted that major fluid shifts occurred between the extracellular and intracellular spaces.**

Conclusions: **The amount of evaporation and extravascular retention of fluid was small during thyroid surgery, irrespective of whether anesthesia was maintained by isoflurane or propofol.**

INTRAVENOUS administration of crystalloid fluid is a cornerstone of patient treatment during surgery. Much is known about the disposition of such fluids under laboratory conditions,[1–4] whereas technical difficulties explain why less is known about this during surgery.[5,6] There is a relative lack of data regarding the influence of anesthetic techniques on volume kinetics in humans. The kinetics of infusion fluids might actually be changed by anesthesia itself.[7] Recently, a crystalloid fluid load was followed by excessive extravascular retention during isoflurane anesthesia in sheep.[8] Most of the model-predicted elimination of fluid did not appear as urine and was therefore considered to have been sequestrated into body fluid spaces without any functional exchange with the plasma volume. A follow-up study confirmed that these fluid losses were due to isoflurane and not to the mechanical ventilation used during the anesthesia.[9]

Extravascular retention of infused fluid is a concept with similarities to the "third spacing," which has been the subject of much debate since the 1960s.[10,11] This term originally denoted an isotope-verified reduction of the extracellular fluid space during surgery which should be replaced by crystalloid fluid to maintain cardiovascular stability. The term *third space* is sometimes used less strictly today, and therefore, we use the phrase extravascular retention to imply fluid that is functionally unavailable.

In the current study, we use volume kinetics to evaluate whether increased extravascular retention of infused fluid occurs in response to isoflurane anesthesia in patients undergoing surgery in the thyroid region. Because the fluid retention might be a unique feature of isoflurane, the results were compared to those obtained in patients who received propofol-based intravenous anesthesia. The type of surgery was chosen because of small expected evaporation losses and low variability in hemodynamics and surgical bleeding.

This article is accompanied by an Editorial View. Please see: Prough DS: "The proper study of mankind is man"—rather, men and women undergoing anesthesia and surgery. ANESTHESIOLOGY 2005; 103:451–2.

Materials and Methods

Thirty patients with American Society of Anesthesiologists physical status classification of I or II who were scheduled to undergo thyroid or parathyroid surgery gave their informed consent to participate in the study, which had been approved by the Ethics Committee of Southern Stockholm, Sweden. The patients were randomized, *via* sealed envelopes, to receive one of two methods of anesthesia, isoflurane (n = 15) or propofol (n = 15), both supplemented by fentanyl. One patient in the propofol group was excluded because of excessive blood loss (1,700 ml).

Anesthesia

All patients entered the operating room at approximately 8:00 AM after having received premedication with

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Received from the Department of Anesthesiology, South Hospital, Stockholm, Sweden. Submitted for publication December 16, 2004. Accepted for publication April 12, 2005. Supported by department funds and the Swedish Research Council, Stockholm, Sweden.

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Table 1. Demographics and Fluid Balance Data in Patients Undergoing Thyroid Surgery during Isoflurane or Propofol Anesthesia

	Isoflurane	Propofol
Sex, F/M, n	14/1	11/3
Thyroid/parathyroid surgery	13/2	10/4
Age, yr	50 ± 15	57 ± 16
Body weight, kg	68.5 ± 9.0	68.7 ± 12.2
Height, cm	167.4 ± 5.7	167.4 ± 11.4
Operating time, min	144 ± 25	143 ± 39
Total fentanyl dose, μg	390 ± 120	430 ± 80
Ephedrine		
Treated patients, n	8	4
Dose, mg	16 ± 8	9 ± 5
Before induction of anesthesia		
Hemoglobin, g/dl	12.8 ± 1.6	12.8 ± 0.9
Plasma albumin, g/l	39.3 ± 3.6	40.0 ± 2.6
After induction		
Hemoglobin, g/dl	12.3 ± 1.4	12.2 ± 0.7
Plasma albumin, g/l	37.6 ± 3.0	37.6 ± 2.6
Infused fluid volume	1,777 ± 233	1,716 ± 307
Urinary excretion, ml	181 (105–257)	143 (77–359)
Excreted/infused fluid, %	11 (5–15)	7 (5–25)
Urinary sodium concentration, mM	29 (19–39)	48 (29–85)*
Sodium excretion, mM	4.6 (1.9–6.1)	9.8 (4.7–12.9)*
Urine osmolality, mOsmol/kg	193 (176–220)	400 (147–514)*
Blood loss, ml	100 (50–100)	100 (50–200)

Data are presented as mean ± SD or, when distribution is skewed, median (interquartile range).

* The difference was significant at $P < 0.05$.

diazepam by mouth 1 h before. A cannula was placed in each antecubital vein, one for infusion of fluid and one for blood sampling. Induction of anesthesia was accomplished by intravenous injection of 2 mg/kg propofol and 100–150 μg fentanyl. Tracheal intubation was facilitated by injecting 0.5–0.6 mg/kg rocuronium. Nitrous oxide or positive end-expiratory pressure was not used.

In half of the patients, isoflurane (Abbott Laboratories, Chicago, IL) at an end-tidal concentration of 1.2 ± 0.2% (mean ± SD) was used to maintain anesthesia. The others received an intravenous infusion of 9.5 ± 1.7 mg · kg^{-1} · h^{-1} propofol (Propofol-Lipuro; B. Braun, Melsungen, Germany). Analgesia was ensured by boluses of fentanyl up to 300–500 μg (table 1) and rocuronium as required to maintain a train-of-four less than 25%. To increase anesthetic depth, a bolus injection of fentanyl was the primary intervention rather than an adjustment of the isoflurane or propofol dosage.

All patients were ventilated in a low-flow semiclosed anesthesia circuit (ADU Anesthesia Delivery Unit; Datex, Helsinki, Finland). Heart rate and noninvasive mean arterial pressure were displayed on an AS 3-monitor (Datex). The tidal volume of the oxygen–air mixture was adjusted to maintain normocapnia. The inspired oxygen concentration was kept between 45% and 50% to ensure a hemoglobin saturation greater than 96% as measured by pulse oximetry. The flow of fresh gas in both groups was 4 l/min during induction and for the first 5 min of anesthesia and was reduced thereafter to 0.8 l/min. An intravenous bolus of 5 mg ephedrine was given if the mean arterial blood pressure decreased to below 55% of baseline (table 1).

Starting approximately 10 min after intubation, 25 ml/kg acetated Ringer's solution was administered intravenously over 30 min (ion content: 130 mM Na^+, 4 mM K^+, 2 mM Ca^{2+}, 1 mM Mg^{2+}, 110 mM Cl^-, and 30 mM $acetate^-$). No fluid was infused during the induction of anesthesia or after the 30-min infusion of acetated Ringer's solution except for the injected anesthetics, which amounted to approximately 17 ml in the isoflurane group and 32 ml in the propofol group. The study period was 150 min, but the anesthesia was prolonged until the protocol was finished in the event that surgery had been completed earlier. The mean operating time was 143 min (table 1).

Measurements

Two venous blood samples, 2.5 ml each, were collected every 5 min during the first 60 min and every 10 min during the following 90 min. A discard volume of 3 ml was drawn before each blood collection. This blood was then returned and the cannula flushed with 3 ml saline to prevent clotting and to replace the amount of withdrawn plasma.

The hemoglobin concentration in whole blood, the erythrocyte count, and the mean corpuscular volume were measured by a Technicon H2 (Bayer, Tarrytown, NY) using colorimetry at 546 nm for hemoglobin and light dispersion using a helium neon laser for the other two parameters. The serum albumin concentration was analyzed using the bromcresol green method, followed by reflection spectrophotometry (Ektachem 250/950 IRC; Johnson & Johnson, Rochester, MN). The baseline samples were drawn in triplicate, and the mean values were used in the calculations. The serum sodium concentration was measured at baseline and at 150 min on a Hitachi Modular (Hitachi Hi-Tech Corp., Tokyo, Japan).

An indwelling catheter was inserted into the bladder immediately after the induction but before the intravenous infusion was started. Urine was measured and collected every 15 min. The sodium concentration and the osmolality were measured in the total urine volume.

Volume Kinetic Analysis

The distribution of the fluid given by intravenous infusion was analyzed by fitting a two-volume fluid-space model to the hemoglobin-derived plasma dilution and the dilution of the plasma albumin concentration. Details are given in the appendix on how the dilution was calculated.

Fluid infused at the rate k_i is distributed between one central (V_1) and one peripheral (V_2) body fluid space, the sizes of which then increase to v_1 and v_2 at a later time (t). The net rate of fluid exchange between v_1 and v_2 is proportional to the relative difference in deviation from V_1 and V_2 by a constant, k_t (fig. 1). Elimination occurs by virtue of a zero-order parameter, k_b, and a first-order elimination rate constant, k_r. The volume

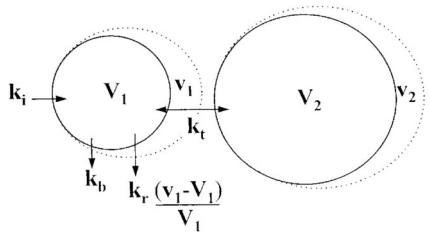

Fig. 1. Schematic drawing of the kinetic model used to analyze the body's handling of infused crystalloid fluid. The fluid is infused at a rate k_i that expands a central body fluid space v_1 and a peripheral space v_2, both of which strive to return to their baseline volumes V_1 and V_2 by acting on the dilution-dependent elimination mechanism, k_r (which can be set to the urinary excretion). The sum of evaporation, bled plasma, and extravascular fluid retention is represented by the zero-order rate parameter k_b.

changes in v_1 and v_2 are described by the following differential equations:

$$\frac{dv_1}{dt} = k_i - k_b - k_r\frac{(v_1(t) - V_1)}{V_1} - k_t\left[\frac{(v_1(t) - V_1)}{V_1} - \frac{(v_2(t) - V_2)}{V_2}\right] \quad (1)$$

$$\frac{dv_2}{dt} = k_t\left[\frac{(v_1(t) - V_1)}{V_1} - \frac{(v_2(t) - V_2)}{V_2}\right]. \quad (2)$$

The solution to the differential equations describing the two-volume kinetic model[2] were fitted to the data from each patient separately by using a nonlinear least-squares regression routine, based on a modified Gauss-Newton method and programmed in the Matlab version 4.2 (The MathWorks, Inc., Natick, MA), which was repeated until no parameter changed by more than 0.001 (0.1%) in each iteration. No weight was applied because the residual errors were constant throughout the range of the studied dilutions. A correction for sampled hemoglobin and surgical losses of hemoglobin was applied (see appendix).

The sum of water loss by evaporation, bleeding, and extravascular retention was estimated for the entire study period (150 min) in the following two ways:

1. By letting these two factors be represented by k_b and estimating this parameter from the kinetic model. In this case, k_r was taken as the total urinary excretion divided by the area under the curve (AUC), as obtained by the linear trapezoid method, for the dilution–time profile as follows:

$$k_r = \frac{\sum \text{urine volume}}{\text{AUC for}\ \dfrac{(v_1(t) - V_1)}{V_1}}. \quad (3)$$

2. From a direct comparison between the measured urinary excretion and the eliminated fluid volume as obtained from the kinetic model.

Table 2. Volume Kinetic Parameters for Curve Fitting based on the Blood Hemoglobin or Serum Albumin Concentration in Patients Undergoing Thyroid Surgery during Isoflurane or Propofol Anesthesia.

	Hemoglobin Marker		Albumin Marker	
	Isoflurane	Propofol	Isoflurane	Propofol
V_1, l	2.46 ± 0.98	2.83 ± 1.42	2.64 ± 0.94	3.04 ± 1.46
SD	0.33 ± 0.13	0.42 ± 0.28	0.55 ± 0.22	0.53 ± 0.32
V_2, l	6.25 ± 2.60	7.68 ± 4.03	9.05 ± 3.70	9.48 ± 3.79
SD	1.13 ± 1.35	1.12 ± 1.29	2.01 ± 1.96	2.50 ± 2.90
k_t, ml/min	174 ± 76	211 ± 64	259 ± 74	252 ± 71
SD	30 ± 17	42 ± 36	52 ± 28	58 ± 47
k_b, ml/min	2.0 ± 2.5	2.2 ± 2.1	1.9 ± 2.4	4.4 ± 3.5
SD	1.2 ± 0.8	1.2 ± 0.9	1.1 ± 0.7	0.9 ± 0.5
k_r, ml/min	9.2 ± 13.4	12.8 ± 14.5	10.1 ± 9.2	17.4 ± 19.2

The first row for each parameter shows the mean ± SD for the optimal estimate in the group. The second row gives the uncertainty associated with the estimation process, which is expressed as an SD different from the group variability.

k_b = elimination (in ml/min) not accounted for by urinary excretion; k_r = elimination rate constant based on urinary excretion; k_t = distribution rate constant; V_1 = central body fluid space; V_2 = peripheral body fluid space.

Simulations of the expected dilution response in V_1 and the fluid volume eliminated from the kinetic model were based on the numerical solutions to equations 1 and 2. The best estimate of the model parameters (table 2) were inserted into the solutions, which had been programmed into the Matlab software.[2] A time-stepping method was then used to generate the predicted dilution–time curve. The volumes of v_1 and v_2 were taken as the product of the simulated dilution and the baseline volume (V_1 or V_2).

The volume kinetics based on albumin was also calculated because a comparison with the reference tracer (hemoglobin) indicates how much albumin that leaves or enters v_1. The translocation of albumin was taken as the product of the albumin concentration at any time t and the simultaneous difference between the volume of v_1 as obtained by the hemoglobin tracer and the volume of v_1 as obtained by the albumin tracer.

Intracellular Fluid Shift

The net translocation of fluid into and out of the cells from 0 to 150 min was calculated by the sodium dilution method,[12,13] which is based on a mass balance equation implying that the number of sodium ions (Na) and the water in the extracellular fluid (ECF) remain constant over time except for additions and losses that can be quantified. Because Na is distributed throughout the ECF space, the plasma Na concentration at time (t) during or after an intravenous infusion of fluid (PNa(t)) equals the amount of Na in the ECF volume divided by the current

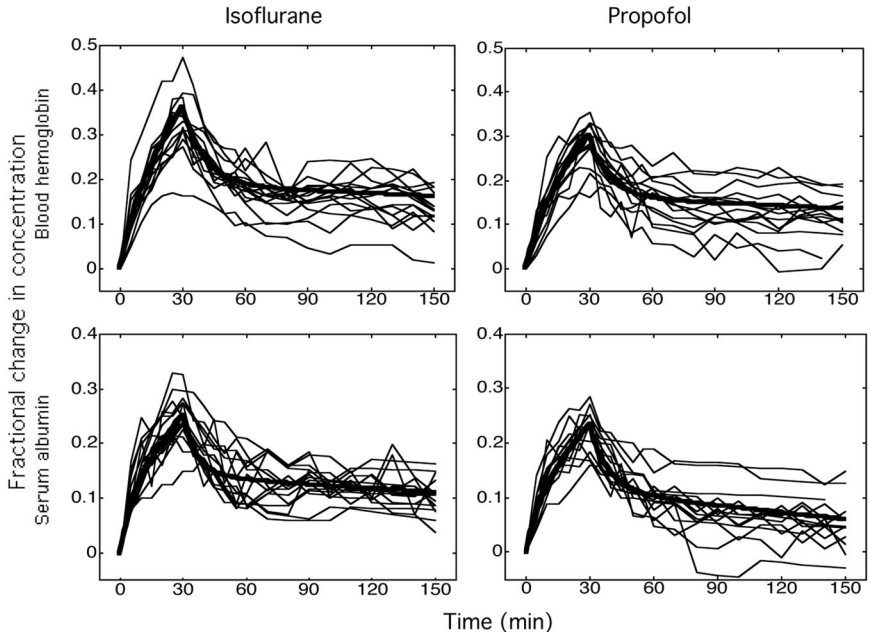

Fig. 2. The fractional plasma dilution based on hemoglobin (top) and albumin (bottom) during intravenous infusion of 25 ml/kg acetated Ringer's solution over 30 min during thyroid surgery under isoflurane (left) or propofol (right) anesthesia. *Fine lines* represent individual patients, and *thick lines* represent simulated dilution–time profiles based on the mean kinetic parameter estimates as shown in table 2.

ECF volume. This relation can be expressed as

$$\mathrm{PNa}(t) = \frac{(\text{infused} - \text{urine})\,\mathrm{Na}\,(t) + (\mathrm{PNa} \cdot \mathrm{ECF})}{(\mathrm{ECF} + (\text{infused} - \text{urine})\text{volume}(t) - \Delta\mathrm{ICF}(t))}, \quad (4)$$

where PNa and ECF are the plasma sodium concentration and the ECF volume at baseline, and $\Delta\mathrm{ICF}(t)$ is the change in the water content of the intracellular fluid compartment from baseline to time (t). Because ECF corresponds to approximately 20% of the body weight,[14] ΔICF could be calculated from the following rearrangement:

$$\Delta\mathrm{ICF}(t) = \mathrm{ECF} + (\text{infused} - \text{urine})\ \text{volume}(t) - \frac{(\text{infused} - \text{urine})\mathrm{Na}(t) + (\mathrm{PNa} \cdot \mathrm{ECF})}{\mathrm{PNa}(t)}. \quad (5)$$

Statistics

The results are presented as the mean ± SD. The study was powered to detect a difference of 3 ml/min in k_b by $P < 0.01$ with 90% confidence,[15] the SD for this estimate being 2 ml/min as obtained for sheep.[9] Changes were evaluated by repeated-measures analysis of variance, and correlations were evaluated by simple and multiple linear regression, where R^2 is the coefficient of determination. The median (interquartile range) was used where distribution was skewed. The Wilcoxon matched-pair test was used for pairwise comparisons, and the Mann–Whitney test was used for nonpairwise comparisons. Incidence data were compared by using the chi-square test. $P < 0.05$ was considered significant.

Results

Age, body weight, height, dose of fentanyl given, and surgical blood loss did not differ significantly between the isoflurane and propofol groups (table 1). More patients in the isoflurane group received ephedrine because of arterial hypotension (eight *vs.* four), but this difference did not reach statistical significance.

Volume Kinetic Analysis

A plasma dilution of 6.5% developed during induction of general anesthesia, despite the fact that only small amounts of anesthetics had been given intravenously (table 1). The fractional plasma dilution further increased by approximately 30% during infusion in both groups and remained half as high for the rest of the study. The scatter between the individual dilution–time profiles was small, and the modeled curve of the fractional dilution was similar for isoflurane and propofol anesthesia (fig. 2).

The kinetic analysis based on hemoglobin showed that the infused fluid expanded a baseline central body fluid space (V_1) of 2.34 l in the isoflurane group and of 2.73 l in the propofol group. The size of V_2 was also slightly larger, and the exponential rate constants (k_t and k_r) were higher in the propofol group, but the differences from the isoflurane group were not statistically significant (table 2). However, the actual volume expansion over time, which is obtained as the product of the measured dilution of v_1 and the calculated dilution of v_2

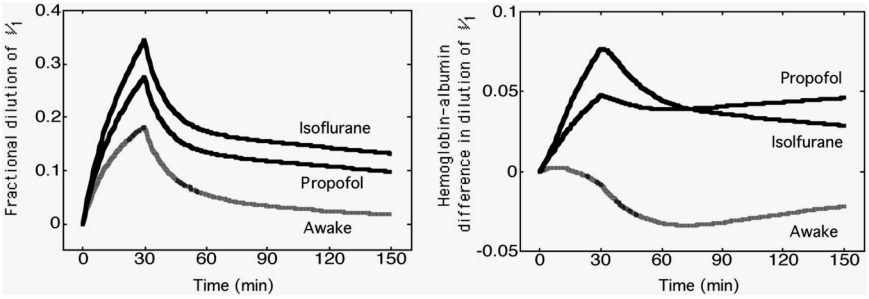

Fig. 3. Fractional dilution of hemoglobin (left) and the difference in fractional dilution between hemoglobin and albumin (right) during and after a 30-min intravenous infusion of acetated Ringer's solution during thyroid surgery performed during isoflurane or propofol anesthesia. The simulations were based on the mean parameter estimates (table 2). Comparison is made with data derived from previous experiments in which awake volunteers received the same fluid regimen.[2] Positive values indicate that albumin enters v_1.

and their corresponding baseline volumes V_1 and V_2, were virtually identical in the isoflurane and propofol groups.

The hemoglobin-derived plasma dilution was greater than the albumin dilution, particularly during the propofol experiments (fig. 3, left). The kinetic analyses based on albumin generally yielded higher parameter values than for hemoglobin, a difference that was significant for V_2 ($P < 0.02$), k_t ($P < 0.001$), and k_r ($P < 0.003$, Wilcoxon test; table 2). This implied that albumin molecules entered v_1 (fig. 3, right). The translocated amount was approximately 5–6 g, which corresponds to the albumin content of 150 ml plasma.

Extravascular Retention

The rate of water loss by evaporation, surgical plasma loss, and extravascular accumulation of fluid was first given as k_b during the curve-fitting procedure. This value averaged 2.0 ml (isoflurane) and 2.2 ml (propofol) per minute (table 2), the point estimate for the difference being 0.2 ml/min (95% confidence interval, −1.5 to +2.0). After accounting for minimal evaporation and bled plasma, approximately 160 ml (9% of the infused fluid) no longer participated in the volume equilibration between v_1 and v_2 at the end of the study and was considered to have been retained extravascularly (fig. 4, top).

The second approach, which was based on a comparison between the model-predicted elimination of fluid and the measured urine, could only be used in 21 patients. This was due to intercorrelations that distorted the estimates of k_r and V_2, typically when the elimination phase lacked an apparent slope (5 in the isoflurane and 3 in the propofol group). The 21 successful analyses showed that elimination amounted to 681 ml (255–869 ml), 39% (21–58%) of which could be accounted for as urine, with no differences between the groups. When calculated in this way, k_b averaged 2.9 ml/min, corresponding to 435 ml during the 150-min study. After accounting for minimal evaporation and bled plasma, approximately 270 ml (15% of the infused fluid) no longer participated in the volume equilibration between v_1 and v_2 at the end of the study (fig. 4, middle). Slightly lower values were obtained on excluding those patients who received ephedrine (fig. 4, bottom).

Hemodynamics, Urine, and Sodium

In the isoflurane group, heart rate was slightly higher at baseline ($P < 0.01$) and during anesthesia (repeated-measures analysis of variance, $P < 0.05$; fig. 5, top). The mean arterial pressure was lower during isoflurane anesthesia ($P < 0.001$; fig. 5, middle).

Only 11% (5–18%) of the infused fluid was excreted during the experiment. The maximum urine flow rate occurred 15 min later with isoflurane than with propofol (fig. 5, bottom), but the total volume did not differ between the groups (table 1). Using multiple regression analysis, the combination of high patient age ($P < 0.001$) and low mean arterial pressure during surgery ($P < 0.002$) accounted for 53% of the interpatient variability

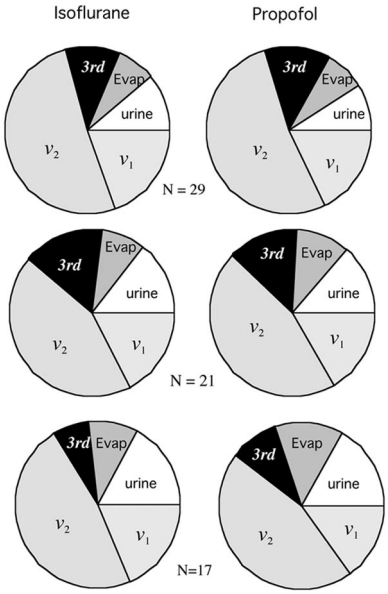

Fig. 4. The distribution of infused fluid after 150 min of thyroid surgery during isoflurane or propofol anesthesia for all patients (top), in those without horizontal elimination curves (middle), and in the patients who were *not* given ephedrine (bottom). 3rd = extravascular fluid retention ("third spacing"); Evap = sum of estimated evaporation and bled plasma; v_1 = central body fluid space; v_2 = peripheral body fluid space.

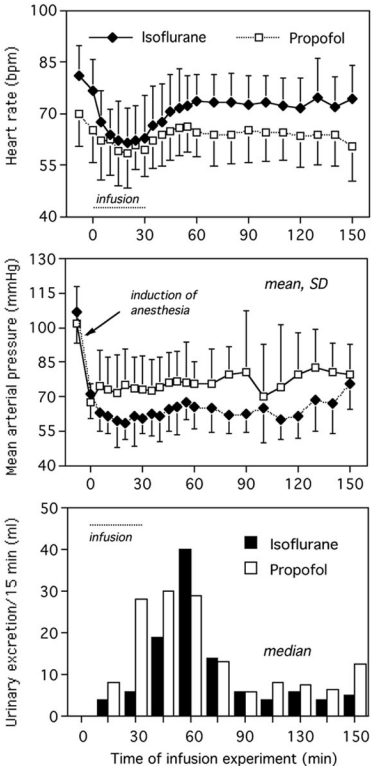

Fig. 5. Heart rate (top), mean arterial pressure (middle), and urinary excretion per 15-min interval (bottom) during thyroid surgery, depending on the form of anesthesia. Heart rate was significantly higher and the arterial pressure was significantly lower ($P < 0.05$) during isoflurane anesthesia. Time zero is when the fluid infusion started.

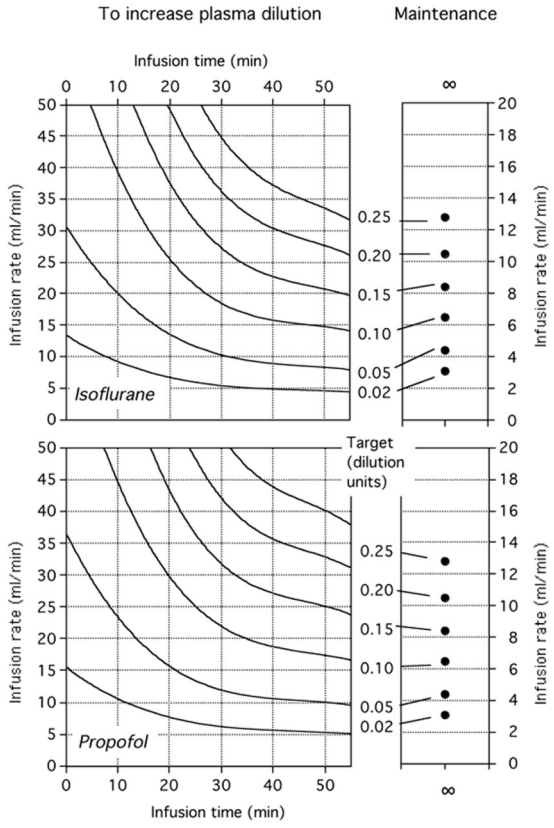

Fig. 6. Nomogram showing the relation between infusion rate and infusion time required to dilute the plasma to a predetermined degree during isoflurane and propofol anesthesia (left) and the infusion rate required thereafter to maintain a steady state dilution at 120 min (right) during thyroid surgery in an average patient weighing almost 70 kg. The mean kinetic data based on hemoglobin shown in table 2 were used for the simulations.

in urinary excretion. Patients with a low arterial pressure also tended to have a lower sodium excretion (R^2 = 0.32, $P < 0.002$). The urinary sodium concentration decreased with the urinary osmolality (R^2 = 0.46, $P < 0.001$); this correlation indicates that isotonic urine corresponded to a sodium concentration of 40 mM.

The sodium balance used to assess the intracellular–extracellular fluid shift implied that isoflurane was associated with accumulation of a negligible amount of excess fluid within the cells, 7 ml (−57 to +64 ml). For propofol, 89 ml (−21 to 197 ml) was translocated from the intracellular to the extracellular fluid space ($P < 0.04$, Mann–Whitney test).

Nomograms

Computer simulations were performed based on the mean kinetic parameters (table 2). As a guideline to intraoperative use, nomograms were created based on the plasma dilution expected to result from infusing acetated Ringer's solution at various rates (fig. 6). They show that propofol anesthesia required a higher rate of infusion of the crystalloid fluid to obtain a predetermined plasma dilution than isoflurane, whereas the rates needed to maintain steady state were quite similar.

Discussion

Thyroid surgery during general anesthesia was associated with enrichment of infused crystalloid fluid in the plasma and a low urinary excretion. Fluid freely communicated with a functional peripheral space (V_2). However, between 300 and 435 ml of the infused volume could not be accounted for. This figure may seem to be small, considering that it includes fluid losses through accumulation in wounded tissue, breathing, and evaporation from surgical wound and body surfaces as well as bled plasma (sampled plasma was replaced).

This estimation is based on a calculation of the distribution and elimination of infused acetated Ringer's solution in 29 patients. Volume kinetics was applied to data on plasma dilution and urinary excretion during and after surgery but before anesthesia was terminated. The calculations accounted for the amount of fluid present in a system of exchange between a functional central (v_1) and a peripheral (v_2) body fluid space. Eliminated fluid that did not appear as urine was considered to have been "lost" from the kinetic system, by evaporation, bleeding,

or sequestration within the body (extravascular retention). By definition, lost fluid was irreversibly removed from v_1, part of which is the sampled plasma.

Several of the sources of fluid loss can be estimated. The bled plasma amounted to 50–60 ml (table 1), and water evaporation from the surgical wound was probably only 5–10 ml.[16] The baseline evaporation in adults is usually taken to be 0.5 ml/min,[17] or 75 ml of water during the present operations, although the low-flow breathing system reduces evaporation losses from the airway because the circulating gases become saturated with humidity within a few minutes of anesthesia.[18] If we assume that exudation into the surgical wound was negligible, between 160 (9%) and 270 ml (15%) of the infused fluid still remains that might be considered to have been retained extravascularly.

Sheep anesthetized with isoflurane have a similar plasma volume expansion in response to crystalloid fluid as awake sheep, but they show a smaller urinary excretion and excessive extravascular accumulation.[8,9] The current study contrasts with these findings by the more intravascular distribution of infused fluid and also less extravascular retention. A factor contributing to this difference might be that that both isoflurane and propofol combined with fentanyl induced arterial hypotension in our patients, whereas the blood pressure was unchanged or slightly increased in the animals.

Isoflurane versus *Propofol*

The main hypothesis in this study was that isoflurane anesthesia would be associated with a greater extravascular retention of infused fluid than propofol anesthesia. Two studies in sheep (weighing 28–42 kg) encouraged testing of this hypothesis in humans. They both show that isoflurane induces a marked difference between the model-predicted fluid elimination and the measured urine, amounting to between 3 and 4 ml/min, whereas this rate was negligible when the sheep were awake.[8,9] If inhaled isoflurane exerts this effect in humans, it would appear as a difference in extravascular fluid retention compared with intravenous (propofol) anesthesia. However, isoflurane was not associated with any greater retention than propofol anesthesia in the current study. When estimated directly as k_b in the kinetic model, the sum of water losses by evaporation and in extravascular fluid retention occurred at a rate of 2.0–2.2 ml/min, or 300–330 ml during the entire study period. The similar results in the groups indicate that isoflurane does not promote extravascular accumulation of fluid in humans undergoing surgery. Slight sequestration of fluid within the body probably occurred as a result of both forms of anesthesia, but even so, it seems to be less pronounced in humans than in sheep.

The plasma dilution response to crystalloid fluid was quite consistent and allowed curve fitting with good confidence despite the fact that the patients had undergone surgery (fig. 2). There were slightly lower estimates of V_1, k_t, and k_r during isoflurane anesthesia, which is the same direction in which these parameters change when spinal or general anesthesia is induced.[7] Anesthesia with isoflurane, using conventional dosing, caused a larger decrease in arterial pressure than propofol, and these patients also tended to receive ephedrine more often. Isoflurane increases the heart rate by stimulating catecholamine release,[19] which might also be relevant. For both forms of anesthesia, however, the plasma dilution was much more pronounced than previously found in awake volunteers (fig. 3, left).

Several factors may serve to explain the difference in fluid distribution between humans and sheep. To be able to follow the surgical patients for as long as possible, the period of hemodynamic equilibration was limited to only 10 min after tracheal intubation. Only the patients underwent surgery, and the anesthesia consistently included fentanyl. Despite a lower minimum alveolar concentration, isoflurane was associated with a decrease of arterial pressure in the patients but not in the animals. There are also slight differences in volume kinetics between the acetated Ringer's solution given to our patients and the isotonic saline that the animals received.[20] These factors make it difficult to directly compare the current results with the previous studies in sheep,[8,9] but isoflurane does not seem to play a unique role as an anesthetic that increases extravasation during clinical anesthesia, at least not during routine thyroid surgery.

Modeling and Fluid Retention

The only modeling problem occurred when the total elimination of fluid was estimated from the kinetic curve without being stabilized by the measured urinary excretion. Strong intercorrelations are known to develop between V_2 and k_r in cases where the terminal part of the elimination curve is close to horizontal. This can be solved by letting k_r be determined by the urinary excretion,[21] but this is not justified when extravascular fluid retention is anticipated, as during surgery, because then the model-predicted elimination of fluid is not the same as the urinary excretion. This became an issue when the sum of evaporation and extravascular fluid retention was estimated by our second approach. Completely horizontal elimination curves were sometimes associated with injections of ephedrine, which might have caused a slight upward shift due to the β-adrenergic properties of this drug.[22] In the patients without horizontal elimination curves, fluid losses occurred at a rate of 2.9 ml/min, or 435 ml during the study, rather than the average of 2.0–2.2 ml/min, which is based on all patients (table 2). Although open to debate, 435 ml, of which 270 ml represents extravascular fluid retention, is probably the most correct figure. Overall, however, there were only

quite limited differences in fluid distribution, depending on how the calculations were made (fig. 4).

The almost horizontal nature of the terminal dilution–time curve is mostly due to the fact that elimination of Ringer's solution,[5] as well as glucose-containing fluid,[6] is quite slow during anesthesia. During the current 2.5-h study period, urinary excretion amounted to 11% of the infused volume. By comparison, healthy volunteers excrete between 43% and 75% of an isotonic fluid load within 3-4 h after starting an infusion.[3,23,24] Despite the fact that additional fluid losses occurred as a result of evaporation and extravascular fluid retention, the poor urine output explains why the patients, even with a small blood loss, attained a long-lasting hemodilution after fluid therapy was completed. From a practical point of view, the slow elimination reduced the need for liberal crystalloid infusion during both forms of anesthesia, and only 7 ml/min would be necessary to maintain a steady state plasma dilution of 10% (fig. 6).

Protein Transport

Hemoglobin is the standard tracer for volume kinetic analysis of infusion fluids because this molecule remains intravascularly. In contrast, the albumin dilution reflects both the kinetics of the infused fluid and transport of albumin in and out of v_1. In the current study, the difference in volume kinetics based on hemoglobin and albumin was used to indicate the direction and possibly also the magnitude of the translocation of albumin.

In animals, crystalloid fluid administration induces transcapillary protein leakage,[25] which might be mediated by the atrial natriuretic peptide.[26,27] Such extravasation of albumin can be indicated as a greater plasma dilution when measured by serum albumin as compared with hemoglobin.[2] During both isoflurane and propofol anesthesia in humans, however, the hemoglobin–albumin gradient was reversed. Our data indicate that, despite a marked dilution of the serum albumin concentration, there was a net transport *from* the interstitial space *to* plasma (fig. 3). Translocation of albumin in this direction is more consistent with the capillary refill after hemorrhage.[28,29] Perioperative blood loss was hardly the cause, however, because bled volumes were small. Furthermore, the albumin–hemoglobin gradient in fractional dilution was much greater in the current study than in experimental hemorrhage in volunteers followed by infusion of acetated Ringer's solution.[24] Increased lymph flow could boost the albumin content of plasma after hemorrhage, but this seems to be a later phenomenon.[30] Anesthesia *per se* and the reduction of the arterial pressure are more likely causes.

The same factors probably translocated albumin to the plasma during induction of general anesthesia, which induces a spontaneous plasma dilution of approximately 5% if the decrease in arterial pressure is approximately 30%.[5] This endogenous plasma dilution was excluded from all further calculations because it may represent an adaptation of the plasma volume to a new baseline due to the hypotension. Interestingly, the percentage reduction of hemoglobin and serum albumin were almost identical from before to after the induction (table 1), but the plasma dilution based on hemoglobin was 40% greater because the percentage reduction should be divided by (1 − hematocrit). This indicates that albumin was translocated to the plasma also during the induction of anesthesia.

Sodium

The sodium balance was used to capture marked fluid shifts between the extracellular and intracellular fluid spaces. This approach was originally developed to study the distribution of the electrolyte-free irrigating fluid used during transurethral surgery.[12] However, the sodium balance has also been applied to nearly isotonic solutions[13] and corroborated volume kinetic results obtained during intravenous administration of glucose solution.[6] The model is based on the assumption that sodium ions are evenly distributed throughout the extracellular space, whereas evaporation losses create a false indication of intracellular volume expansion by increasing serum sodium (see equation 5). The current results show that no significant fluid shifts occurred between the extracellular and intracellular spaces, and the 2–3 ml/min that was detected as the sum of evaporation and extravascular retention of fluid can hardly have accumulated intracellularly.

The urinary flow rate peaked later during isoflurane anesthesia, which might be due to the lower arterial pressure. An interesting detail is the low sodium concentration in the collected urine (table 1). One might expect that infusion of acetated Ringer's solution with a sodium concentration of 130 mM would be followed by excretion of urine of the same sodium concentration, but this is not the case. Such a discrepancy is followed by a translocation of fluid from the intracellular to the extracellular space,[13] but this effect does not become apparent in the current study because of the small urinary excretion. The body normally excretes urine with a much lower sodium concentration than near-isotonic saline, and the linear relation between urinary sodium and urinary osmolality,[13] which was also observed in the current study, suggests that the urine must be quite concentrated before acetated Ringer's solution can be excreted without being coupled with sodium retention. This probably contributes to the protracted difficulties connected to excreting a crystalloid volume load (up to 1 week) that has been reported after colonic surgery.[31]

Conclusion

Extravascular retention of crystalloid fluid was similar in thyroid surgery performed during isoflurane- or propofol-based anesthesia. Infused fluid had a high tendency to remain in the plasma, whereas elimination by urinary excretion was quite slow.

Appendix

Hemoglobin-derived Plasma Dilution

The hemoglobin-derived plasma dilution was used to indicate the dilution of the central body fluid space expanded by the infused fluid, $(v_1(t) - V_1)/V_1$. The reference equation for this relation is

$$\frac{v_1(t) - V_1}{V_1} = \frac{\text{Hb}/\text{Hb}(t) - 1}{1 - \text{Hct}},$$

where v_1 is the size of the expanded central body fluid space, V_1 is the same body fluid space at baseline, Hct is the hematocrit, and Hb is the hemoglobin concentration in whole blood. Symbols without an index denote baseline values, and (t) indicates those obtained at a later point in time.

The need for correction of this expression for blood sampling, surgical blood loss, and alterations in erythrocyte size necessitated performance of the calculations in a slightly different way, which considers the plasma volume expansion instead of the plasma dilution. For this purpose, surgical losses of hemoglobin are assumed to have occurred at the same rate throughout the 150-min procedure. The total hemoglobin mass (MHb) is first obtained, using the blood volume at baseline (BV) according to Nadler *et al.*,[32] from which losses are subtracted, and the expanded blood volume is then obtained at a later time (BV(t)):

$$\text{MHb} = \text{BV} \cdot \text{Hb}$$

$$\text{MHb}(t) = \text{MHb} - [(\text{sampled} + \text{bled})\ \text{volume} \cdot \text{Hb}(t)]$$

$$\text{BV}(t) = \frac{\text{MHb}(t)}{\text{Hb}(t)}.$$

This expression is converted from blood volume to plasma volume (PV) data:

$$\text{PV} = \text{BV} \cdot (1 - \text{Hct})$$

$$\text{PV}(t) = \text{BV}(t) \cdot \left[1 - \text{Hct} \cdot \frac{\text{Hb}(t)}{\text{Hb}}\right].$$

Changes in erythrocyte size are considered by adding a term for the relation between the mean corpuscular volume at baseline (MCV) and at the later time (MCV(t)). Thus, the dilution of V is calculated as

$$\text{PV}(t) = \text{BV}(t) \cdot \left[1 - \text{Hct} \cdot \frac{\text{Hb}(t)}{\text{Hb}} \cdot \frac{\text{MCV}(t)}{\text{MCV}}\right]$$

$$\frac{v_1(t) - V_1}{V_1} = \frac{\text{PV}(t) - \text{PV}}{\text{PV}}.$$

The same calculations are performed for the erythrocyte count over time, and the mean value for the hemoglobin and erythrocyte dilution is then used as the "hemoglobin-derived plasma dilution." The relation between the baseline hemoglobin and a diluted value obtained later is written hemoglobin/hemoglobin(t) in the reference equation, whereas the inverse relation is used when the calculations use an assumed blood volume based on the weight and height of the subjects.

Simulations show that the error introduced by applying too low or too high blood volume is quite small. The error associated with applying an erroneous sampling volume is larger since blood sampling is done frequently in volume kinetic studies.

Albumin Dilution

The corresponding equations for calculating the dilution of V_1 based on the serum albumin concentration between baseline (no index) and time (t) were the following, in which Malbumin is the albumin mass:

$$\text{PV} = \text{BV} \cdot (1 - \text{HCT})$$

$$\text{Malbumin} = \text{PV} \cdot \text{Albumin}$$

$$\text{Malbumin}(t) = \text{Malbumin} - [\text{Sample volume} \cdot \text{Albumin}(t) \cdot (1 - \text{Hct}(t))]$$

$$\frac{v_1(t) - V_1}{V_1} = \frac{\text{Albumin} - \dfrac{\text{Albumin}(t) \cdot \text{Malbumin}}{\text{Malbumin}(t)}}{\text{Albumin}}.$$

Eva-Lena Bergling (Nurse Anesthetist, Department of Anesthesiology, South Hospital, Stockholm, Sweden) assisted during the operations.

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