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Mild hypothermia is associated with altered volume kinetic parameters of an intravenous crystalloid fluid bolus in healthy isoflurane-anesthetized cats

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OBJECTIVE
To assess the impact of mild hypothermia on the distribution and elimination of an IV crystalloid fluid bolus in healthy anesthetized cats using volume kinetic (VK) analysis.

METHODS
10 adult cats were anesthetized and included in a prospective, randomized, cross-over study. The subjects were maintained either normothermic (38.3 ± −16.9 °C) or mildly hypothermic (35 ± −16.9 °C), with a 7-day washout period between anesthetic episodes. All cats received 20 mL/kg of a balanced isotonic solution (Normosol-R) IV over 20 minutes, following the achievement and stabilization of target temperature. Hemoglobin concentration, PCV, and urinary output were measured at established time points and served as input variables for VK analysis.

RESULTS
Hypothermia was associated with a larger central compartment volume (V_c); higher body weights were associated with an increased V_c and a decreased elimination rate; higher end-tidal isoflurane concentration (ETISO) was associated with an increased V_c and a higher distribution rate constant. Heart rate, blood pressure, and ETISO were significantly lower in the hypothermic group. No statistically significant difference was observed in urinary output between groups.

CONCLUSIONS
Body weight, temperature, and ETISO were significant covariates affecting VK parameters. Hypothermia did not induce cold diuresis but was associated with an increase in V_c. The negative relationship between body weight and the elimination rate constant requires further verification. Hypothermia was associated with lower heart rate and blood pressure despite reduced ETISO.

CLINICAL RELEVANCE
Hypothermia was associated with smaller plasma volume expansion from fluid bolus. Fluid dosing based on ideal body weight should be considered to avoid overdosing.

Keywords: volume kinetics, hypothermia, fluid therapy, cats, feline

Despite advancements in veterinary emergency and critical care medicine, treating shock in cats remains challenging due to their distinctive physiological responses and limited scientific evidence. Intravenous fluid resuscitation is a common approach for restoring circulating volume and improving tissue perfusion in shock management. Cats with circulatory shock often present with hypotension, hypothermia, and bradycardia, making their response to IV fluid resuscitation unique.[1] Conservative fluid resuscitation combined with active rewarming is often recommended based on the anecdotal sensitivity of cats to overhydration and the physiological changes associated with hypothermia.[1–2]

In hypothermic cats, hypotension often does not respond well to volume expansion possibly due

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to vasodilation.[3] Additionally, as a cat is rewarmed, fluid stored in capacitance vessels may rapidly reenter active circulation, potentially leading to hypervolemia.[3] In humans, a reduction in arterial blood pressure has been associated with slower elimination of a fluid bolus.[4] Although this phenomenon has not been specifically studied in cats, it raises the possibility that a cat in shock might similarly retain fluids longer due to slower elimination.

Although not well documented in cats, mild to moderate hypothermia in many mammals can lead to increased urine production, a phenomenon known as cold diuresis.[5] This effect is attributed to increased renal blood flow secondary to peripheral vasoconstriction, which occurs early in mild hypothermia, before a noticeable drop in core temperature. As hypothermia progresses, reduced levels of antidiuretic hormone can further enhance diuresis.[6] Therefore, an IV fluid bolus administered to a hypothermic cat might be eliminated faster than the same fluid given to a normothermic cat. Understanding the behavior of a fluid bolus during hypothermia could provide valuable insights into fluid therapy in hypothermic cats, which are crucial for improving our understanding and treatment of shock in this species.

Volume kinetic (VK) analysis is an adaptation of pharmacokinetic (PK) principles that allows the analysis and simulation of IV fluid disposition. Applying a mass balance equation to serial hemoglobin (Hb) measurements allows for the extrapolation and analysis of changes in plasma volume over time using VK techniques.[7,8] Comprehensive reviews on VK are available in the literature.[7–11] Briefly, VK analysis is based on the concept that IV fluid, administered at a specified rate, increases the volume of an expandable space. The volume of this expanded space changes over time as fluid is eliminated from and potentially distributed within the body. Volume kinetic analysis assumes that only the extra volume participates in elimination and distribution, following first-order kinetics. Currently, the most common models are 1-compartment and 2-compartment, though a 3-compartment model has also been proposed.[12] Schematic diagrams of the 1-volume fluid space (1-VOFS) and 2-volume fluid space (2-VOFS) kinetic models are provided **(Figure 1)**.

Although VK has been studied extensively in humans and laboratory animals to explore the distribution and elimination patterns of IV fluids under various physiological and pathological conditions, this concept is relatively novel in companion animal species.[11] A recent study[13] demonstrated the feasibility of VK analysis in healthy conscious cats, providing a better understanding of IV fluids kinetics and body water physiology. Utilizing VK analysis, it has also been demonstrated that anesthetized cats exhibit a bolus rate-dependent distribution and overall slow elimination of additional fluids.[14]

This study aimed to assess whether mild hypothermia affects the VK of a single IV crystalloid fluid bolus in healthy anesthetized cats. We hypothesized that mild hypothermia would result in slower distribution and faster elimination of an IV fluid bolus in these cats.

Methods

This prospective, randomized, cross-over experimental study was conducted at the Scott Ritchey Research Center at Auburn University College of Veterinary Medicine. The study was approved by and adhered to IACUC guidelines (protocol No. 2023-5221). The cats were originally sourced from a colony under protocol No. 2021-3909. Between May and June 2023, 10 healthy, adult, purpose-bred domestic

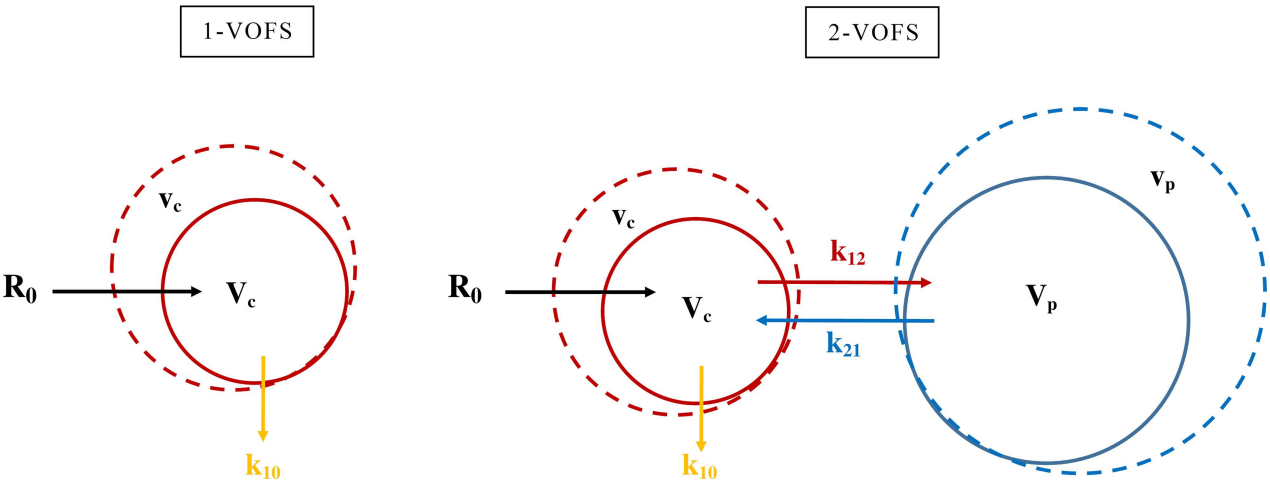

Figure 1—Schematic representation of the 1-volume of fluid space (1-VOFS) and 2-volume of fluid space (2-VOFS) microconstant kinetic models. The 1-VOFS model assumes a single compartment for fluid distribution, while the 2-VOFS model accounts for both central and peripheral compartments. k_{10} = Elimination rate constant. k_{12} = Distribution rate constant from the central to peripheral compartment. k_{21} = Distribution rate constant from the peripheral to central compartment. R_0 = Rate of administered fluid. V_c = Volume of central compartment; v_c = Volume of the expanded central compartment. V_p = Volume of peripheral compartment; v_p = Volume of expanded peripheral compartment.

shorthair cats were enrolled. The cats consisted of 5 intact males and 5 intact females. The median age was 17 months (range, 14 to 81 months), and the mean body weight was 3.80 ± 0.97 kg. Each cat was deemed healthy based on physical examination, CBC, serum biochemistry profile, and N-terminal pro-B-type natriuretic peptide SNAP test. Housing and enrichment were provided to the subjects following approved IACUC protocols.

Study protocol

Food but not water was withheld for at least 12 hours before data collection. Each cat was anesthetized twice and maintained either normothermic (38.3 ± −16.9 °C) or mildly hypothermic (35 ± −16.9 °C), with a minimum of a 7-day washout period between anesthetic episodes. Target body temperature was achieved through surface cooling, forced warm air, or a warming blanket. Surface cooling was performed by placing the subject on a cold metal table.

The experimental treatment order was assigned using a coin toss. After cats achieved and were stable at the target temperature for 30 minutes, they received 20 mL/kg of a balanced isotonic solution (Normosol-R) at room temperature, administered IV over 20 minutes.

Anesthesia

All cats received alfaxalone (2 mg/kg) and midazolam (0.2 mg/kg) IM for premedication. Following sedation, a 22- or 20-gauge over-the-needle catheter was placed in the cephalic vein for fluid and medication administration. After catheter placement, alfaxalone was administered IV for induction (2 mg/kg to effect), followed by orotracheal intubation. General anesthesia was maintained with isoflurane in oxygen using an out-of-circuit precision vaporizer in a nonrebreathing anesthesia circuit. The flow rate was adjusted to prevent rebreathing, as monitored by capnography. Techniques to achieve the target temperature were initiated postinduction. Temperature was continuously monitored with an esophageal probe positioned in the fourth to fifth intercostal space. A 20-gauge over-the-needle catheter was placed in the jugular vein for blood sampling during the resting period after induction. A 3.5-French, 10-inch (25-cm) tomcat urinary catheter was placed for urinary output measurement. After catheter placement, the bladder was emptied immediately before administering the IV fluid bolus using a syringe attached to the urinary catheter. Urinary production was measured by emptying the bladder 60 minutes after the bolus and at the end of data collection using the same method. Point-of-care ultrasound was performed to confirm bladder emptying. A 22- or 24-gauge arterial catheter was used for direct blood pressure monitoring, placed in either the dorsal pedal or coccygeal artery. The cats were then placed in sternal recumbency for the remainder of the data collection. Heart rate (HR), respiratory rate, end-tidal carbon dioxide partial pressure, end-tidal isoflurane concentration (ETISO), esophageal temperature, and arterial blood pressure were monitored with a multiparameter monitor (MP 70; Philips Healthcare) and recorded every 5 minutes. A built-in oscillometric method was used to monitor blood pressure when direct arterial blood pressure could not be measured due to failure to place the arterial catheter. However, systolic (SAP), mean (MAP), and diastolic (DAP) arterial pressure readings from the oscillometric method were not used in data analysis. Isoflurane levels were adjusted to maintain light to moderate stage 3 general anesthesia based on physical assessment by the investigators. The target MAP range was 60 to 80 mm Hg, and end-tidal carbon dioxide partial pressure was maintained between 35 and 50 mm Hg using supplemental mechanical ventilation. In instances of lighter anesthesia, characterized by the return of palpebral reflex, increased jaw tone, spontaneous movement, or sudden increase in HR or blood pressure, 1 mg of alfaxalone was administered IV. This corresponded to a dose range of approximately 0.17 to 0.33 mg/kg for the cats in this study.

Data collection

For each experiment, Hb concentration and PCV were measured at the following time points **(Figure 2)**: after cephalic catheter placement, at the start and end of target temperature stabilization, and immediately before, during, and after the fluid bolus administration. During the fluid bolus, Hb was measured every 5 minutes. Afterward, Hb was measured every 10 minutes for 60 minutes and then every 20 minutes for an additional 80 minutes. Total anesthesia time ranged from 250 to 300 minutes.

For each blood sampling, 0.5 mL of whole blood was collected into a 500-µL EDTA microtainer tube. Blood samples were collected from the jugular catheter using the following technique: aspiration of 1 mL of sample from the jugular catheter, collection of the blood sample (0.5 mL of whole blood), return of the 1-mL initial sample (diluted blood) through the cephalic catheter, followed by a 0.25-mL flush of heparinized saline (2 units/mL) through both the cephalic and jugular catheters.

Hemoglobin was measured with a point-of-care analyzer (Hb 201+; HemoCue) that had been previously validated for use in cats.[11] Duplicate measurements of

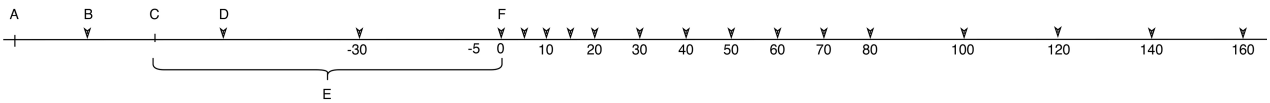

Figure 2—Schematic of the experimental design showing premedication (A), cephalic catheterization (B), induction of anesthesia and initiation of instrumentation (C), jugular catheter placement (D), achievement and stabilization of target temperature (E), and administration of fluid bolus (F). Arrows indicate specific time points for blood sample collection.

Hb and PCV were performed to assess the coefficient of variance and reduce measurement error.

Twenty experimental datasets (10 from the normothermic group and 10 from the hypothermic group) were acquired from 10 cats on 2 separate days, with at least 1 week between sessions.

Recovery

A single dose of SC meloxicam (0.1 mg/kg) was administered before extubation to alleviate potential discomfort from intubation and catheter placement. During the recovery of hypothermic cats, active warming was implemented using a forced-air warming device set to 43 °C to expedite the return to normothermia. After extubation and catheter removal, the cats were transferred to a cage with a blanket and closely monitored until the cats were ambulatory (typically within 10 minutes after extubation). No further temperature monitoring was performed due to temperament. Once fully recovered, they were returned to their housing.

Volume kinetic and covariate analyses

The mean of the duplicate baseline Hb and PCV measurements was used as the initial baseline values for each experiment. Plasma dilution at baseline (time 0) was set to zero. Plasma dilution at each subsequent time point was calculated from serial Hb concentrations using computer software (Excel; Microsoft Corp). The formula used to calculate plasma dilution from uncorrected Hb was $[(Hb_0 - Hb_t)/Hb_t]/(1 - PCV_0)$. Data points from 5 minutes before to 15 minutes after any instances where a light anesthetic plane necessitated alfaxalone administration were excluded from the analysis, based on previous experience and unpublished data, due to the potential for a spike in Hb.

Population maximum likelihood modeling with microconstant parameterization was performed using the naïve pooled algorithm and optimized with the first-order conditional estimation with an extended least squares algorithm in a commercial PK analysis software package (Phoenix 8.4; Certara). Both 1-VOFS and 2-VOFS kinetic models were fitted separately. Input variables included individual plasma dilution values at each time point, crystalloid fluid infusion rate, time, subject ID, and measured cumulative urine output. These variables were used by the models to generate the best parameter estimates for the volume of the central compartment (V_c), the elimination rate constant (k_{10}), the distribution rate constant from the central to the peripheral compartment (k_{12}), and the distribution rate constant from the peripheral to the central compartment (k_{21}). The statistical fit of the 1-VOFS and 2-VOFS models was compared, with the base model for subsequent covariate analysis selected based on the lowest Akaike information criterion value, provided that parameter estimates were realistic and had a coefficient of variation of < 50%.

Potential covariates in the VK base model were identified using correlation ratios (η) and covariate

Table 1—Key physiological parameters under normothermic and hypothermic states.

Parameter	Normothermic (estimated marginal mean and 95% CI)	Hypothermic (estimated marginal mean and 95% CI)	Estimated difference (normothermic-hypothermic; estimated marginal mean and 95% CI)	*P* value
Body temperature (°C)	38.15 (38.08 to 38.22)	35.09 (35.02 to 35.16)	3.06 (3.01 to 3.10)	< .001
HR (bpm)	136.81 (128.80 to 144.82)	104.09 (96.09 to 112.10)	32.71 (30.75 to 34.67)	< .001
ETISO (%)	1.46 (1.40 to 1.52)	1.22 (1.16 to 1.28)	0.24 (0.21 to 0.27)	< .001
SAP (mm Hg)	80.90 (77.14 to 84.66)	78.01 (74.18 to 81.84)	2.89 (0.57 to 5.21)	.015
MAP (mm Hg)	63.67 (61.60 to 65.75)	59.45 (57.31 to 61.59)	4.22 (2.55 to 5.90)	< .001
DAP (mm Hg)	54.02 (52.02 to 56.02)	48.94 (46.88 to 50.99)	5.08 (3.55 to 6.62)	< .001
Urine output (mL/kg/h)	0.71 (0.56 to 0.85)	0.57 (0.43 to 0.72)	0.13 (–0.32 to 0.06)	.155

bpm = Beats per minute. DAP = Diastolic blood pressure. ETISO = End-tidal isoflurane concentration. HR = Heart rate. MAP = Mean arterial pressure. SAP = Systolic arterial pressure.

Table 2—Volume kinetic (VK) parameter estimates from the 2-volume of fluid space kinetic model and representative covariates reflecting interindividual variabilities of VK parameters.

VK parameter	Covariate	Estimate	2.5% CI	97.5% CI	CV (%)
V_c (mL)		216.0	200.6	231.4	3.63
k_{10} (L/min)		0.0013	0.0011	0.0014	6.39
k_{12} (L/min)		0.0312	0.0210	0.0413	16.55
k_{21} (L/min)		0.0109	0.0015	0.0202	43.62
Covariate effect					
V_c (mL)	Body weight	1.143	0.7944	1.491	15.48
V_c (mL)	Hypothermia	0.2122	0.0886	0.3357	29.58
k_{12} (L/min)	ETISO	1.629	0.6606	2.598	30.21
k_{10} (L/min)	Body weight	–1.241	–2.072	–0.4107	–34.00
V_c (mL)	ETISO	0.3907	0.0919	0.6896	38.86

CV = Coefficient of variance. k_{10} = Elimination rate constant. k_{12} = Distribution rate constant from the central to the peripheral compartment. k_{21} = Distribution rate constant from the peripheral to the central compartment. V_c = Volume of central compartment.

box and scatter plots. Variables considered as possible covariates included categorical variables such as sex, body condition score, and treatment group (hypothermia or normothermia), as well as continuous variables such as body weight, HR, SAP, DAP, and MAP, actual body temperature, and ETISO. Covariate analysis was performed using the stepwise covariate search function (forward addition and backward elimination) in the software, with thresholds set at $P = .05$ for adding and $P = .01$ for removing a covariate effect. A covariate effect was added to the model if it reduced the negative 2 log likelihood by > 3.84 ($P < .05$) and was eliminated if it increased the negative 2 log likelihood by < 6.64 ($P < .01$). A covariate effect was considered statistically significant if the 95% CI did not include zero.

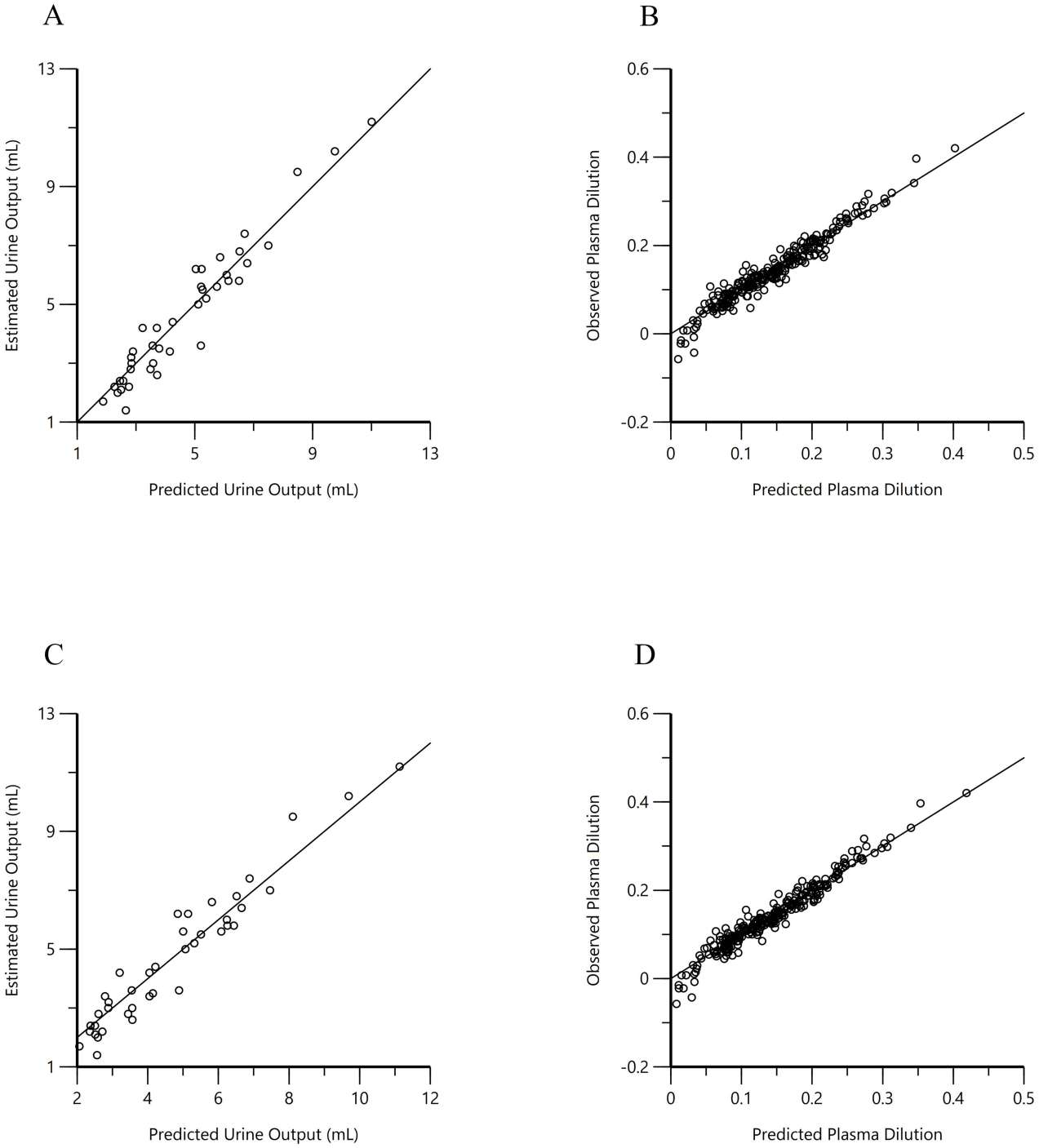

Figure 3—Model-predicted versus observed plasma dilution plots for the 2-volume fluid space kinetic model before (A and B) and after (C and D) accounting for significant covariate effects, including hypothermia, body weight, and end-tidal isoflurane concentration.

Statistics

All analyses were conducted using RStudio (version 2023.06.0 + 421; RStudio Team) and R (version 4.4.0; R Core Team). Age was reported as median and range, while body weight was reported as mean ± SD. A linear mixed-effects model was fitted using the lmer() function from the lmerTest package in R to analyze all physiological parameters, with the subject treated as a random effect and time, treatment, and time X treatment interaction as fixed effects. Similarly, a linear mixed-effects model was fitted to urine output, with the subject treated as a random effect and treatment as a fixed effect. The built-in anova() function in R was used to perform a type III ANOVA to assess the significance of fixed effects. Estimated marginal means (EMMs) and

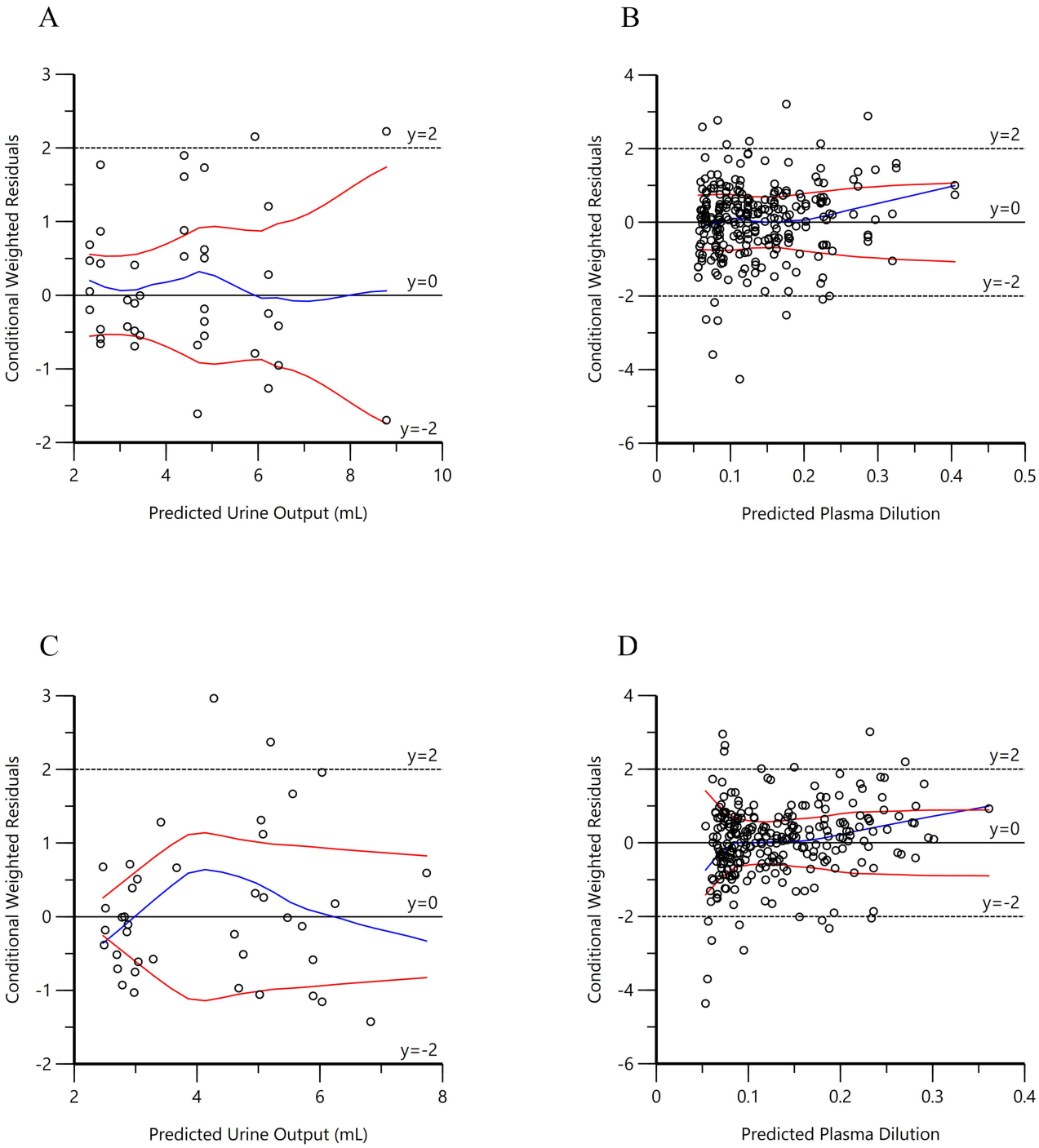

Figure 4—Conditional weighted residuals versus predicted values for the 2-volume fluid space kinetic model before (A and B) and after (C and D) accounting for significant covariate effects, including hypothermia, body weight, and end-tidal isoflurane concentration.

95% CI were obtained using the emmeans package. Multiple comparisons were conducted using the pairs() function from the emmeans package, with the Bonferroni method applied for multiplicity adjustment. Significance was defined as P values < .05.

While a formal power analysis was not conducted, the sample size of 10 cats was chosen based on previous VK studies in cats, which demonstrated reasonable results with similar subject numbers.[12,14] This sample size is also consistent with typical PK modeling studies, which generally include 8 to 15 subjects.

Results

All 10 cats completed the study. Analysis of body temperature, HR, and ETISO showed significant effects of both time (P < .001) and treatment (P < .001). The EMMs and estimated differences for each treatment are summarized **(Table 1)**. For body temperature, pairwise comparisons between time points revealed significant differences for some comparisons; however, these differences were < 0.3 °C and are therefore not reported. Heart rate was significantly higher at 5 and 15 to 30 minutes postinduction compared to 100 minutes and at 30 minutes compared to 120 and 160 minutes. The ETISO was significantly lower from 0 to 40 minutes compared to 160 minutes and at 10 to 20 minutes compared to 120 minutes.

Analysis of direct blood pressure showed significant treatment effects on SAP (P = .014), MAP (P < .001), and DAP (P < .001), with a significant effect of time on DAP (P = .041). The normothermic group had higher EMMs and estimated differences in all cases, and these data are summarized (Table 1). Pairwise comparisons between time points for DAP did not reveal any statistically significant differences after adjusting for multiple comparisons.

Urine output for the cats is summarized (Table 1), with no statistically significant difference found between groups (P = 0.155).

Volume kinetics analysis

Twenty data sets were obtained; however, direct blood pressure measurements were unavailable for 2 cats in the hypothermic group due to failure of arterial catheter placement. A subgroup analysis of the remaining 16 data sets revealed that direct blood pressure was not a significant covariate. Consequently, all 20 data sets were analyzed together, excluding the direct blood pressure values entirely. Of the 600 paired serial Hb concentration measurements, 32 (5.3%) were excluded due to a lighter plane of general anesthesia and the administration of alfaxalone.

Both 1-VOFS and 2-VOFS kinetic models were evaluated to determine the best statistical fit. The 2-VOFS kinetic model had the lowest Akaike information criterion value and was selected as the base model for covariate analysis, which identified several significant covariates. In the final model, body weight was a significant covariate for both V_c and k_{10}, body temperature was a significant covariate for V_c, and ETISO was a covariate for both V_c and k_{12} **(Table 2)**. The goodness-of-fit and residual plots showed slight improvements after incorporating these covariates **(Figures 3 and 4)**.

In summary, the VK parameter estimates for individual cats in the final model can be expressed as follows:

$$
\begin{aligned}
&V_c \text{ individual} \\
&= (V_c \text{ population} \times e^{\text{Group}}) \\
&\times (\text{body weight individual} \\
&\quad \div \text{mean population body weight})^{1.1426} \\
&\times (\text{ETISO individual} \\
&\quad \div \text{mean population ETISO})^{0.3907}
\end{aligned}
$$

$$
\begin{aligned}
&k_{10} \text{ individual} \\
&= k_{10} \text{ population (body weight individual} \\
&\quad \div \text{mean population body weight})^{-1.2413}
\end{aligned}
$$

$$
\begin{aligned}
&k_{12} \text{ individual} = k_{12} \text{ population} \\
&\quad (\text{ETISO} \div \text{mean ETISO})^{1.6293}
\end{aligned}
$$

where the group exponent is 0 for the normothermic group and 0.2122 for the hypothermic group.

Discussion

This study investigated the effects of mild hypothermia on the VK of an IV crystalloid fluid bolus in healthy anesthetized cats. The 2-VFOS kinetic model provided a better fit than 1-VFOS kinetic model. Covariate analysis identified hypothermia, body weight, and ETISO as significant covariates affecting V_c, k_{10}, and k_{12}. Mild hypothermia was associated with a larger V_c. Higher body weight was associated with a larger V_c, as might be expected, and a slower k_{10}, while higher ETISO correlated with both an increased V_c and a faster k_{12}. Furthermore, hypothermia resulted in reduced HR, lower blood pressure, and lower ETISO. Contrary to the initial hypothesis, hypothermia did not significantly affect the k_{10} of the fluid bolus or induce cold diuresis. Additionally, hypothermia was not associated with slower fluid k_{12}.

The superior fit of the 2-VOFS model aligns with the findings of Yiew et al,[14] who used VK modeling to explore fluid disposition in healthy conscious cats. The study of Yiew et al[14] reported a V_c of 139 mL (95% CI, 83 to 195), whereas this study found a higher V_c of 216 mL (95% CI, 201 to 231) in normothermic anesthetized cats. Differences in methodology, cat populations, and the effects of anesthesia likely contributed to these variations. Anesthesia, possibly through mechanisms such as vasodilation and splenomegaly, may lead to larger V_c. It is important to note that in VK modeling, the central compartment represents an apparent or functional volume, similar to the volume of distribution in traditional PK analysis, rather than a fixed anatomical space or actual blood volume. The intercompartmental rate constants (k_{12} and k_{21}) in the study of Yiew et al[14] were 0.753/min (95% CI, 0.199 to 1.308)

and 0.161/min (95% CI, 0.089 to 0.233), respectively. These values indicate a more rapid fluid exchange between compartments in conscious cats compared to the anesthetized subjects in this study, where the values were lower at 0.0312/min (95% CI, 0.0210 to 0.0413) for k_{12} and 0.0109/min (95% CI, 0.0015 to 0.0202) for k_{21}. Additionally, k_{10} was slower in this study, with a value of 0.0013/min (95% CI, 0.0011 to 0.0014), compared to the k_{10} in the study of Yiew et al[14] of 0.007/min (95% CI, 0.004 to 0.010). It should be emphasized that the comparison between this study and the study of Yiew et al[14] involves comparing anesthetized and conscious states. Another study[15] in healthy, normothermic, anesthetized cats found a V_c of 78.8 mL/kg (236 mL for a 3 kg cat) and a k_{12} of 0.0419/min. These findings are consistent with the results of this study, suggesting a level of consistency across different conditions in anesthetized cats. Without data on awake subjects from this study, a direct comparison with the study of Yiew et al[14] cannot be made. Therefore, further research comparing awake and anesthetized states is needed to fully understand these differences.

The lower ETISO observed in hypothermic cats (1.22% vs 1.46%) suggests that hypothermia may reduce anesthetic requirements, consistent with previous studies[16–18] in both humans and animals. Specifically, Liu et al[16] demonstrated a reduction of approximately 5.1% in isoflurane MAC per degree Celsius drop in body temperature in children, which aligns with the findings in hypothermic cats. Contrary to our hypothesis, hypothermia did not significantly affect the elimination rate or increase urine output in anesthetized cats, diverging from reports[5,6,19] of cold diuresis observed in other mammalian species such as rats and humans. Although there is a lack of feline-specific data, this slower elimination and lack of cold diuresis observed in anesthetized cats may be attributed to the effects of anesthesia on renal function and overall fluid distribution, retention, and elimination.[20–23] In conscious humans, mild hypothermia typically triggers sympathetic vasoconstriction and decreases ADH secretion, leading to increased urine output.[6] However, anesthesia appears to significantly alter these responses. Studies[20,21] have shown that anesthesia can increase plasma ADH concentrations, promoting water retention and reducing urine output in humans and dogs. This increase in ADH during anesthesia likely counteracts the diuretic effects usually seen in hypothermia. Furthermore, anesthesia-induced vasodilation can offset the sympathetic vasoconstriction that normally occurs as an initial response to hypothermia, thereby reducing the stimulus for increased urine production.[20] In addition, a previous VK study[22] demonstrated that isoflurane reduces the k_{10} by 50% in anesthetized, spontaneously breathing human subjects compared to when awake. A subsequent study[4] that combined data from several publications in humans attributed the reduction in k_{10} to MAP and age. It has been proposed that decreased MAP due to anesthesia leads to the unloading of baroreceptors, which subsequently activates renal sympathetic nerves. This activation enhances sodium and water reabsorption and induces renal vasoconstriction, decreasing urine output.[23] Although arterial blood pressure was not a significant covariate in this study, the influence of ETISO on V_c and k_{12} suggests that anesthesia-related changes could be relevant in cats.

Covariate analysis in this study demonstrated that hypothermia and higher ETISO were associated with increased V_c. Both inhalant anesthesia and hypothermia can induce vasodilation and splenomegaly, which may partly explain the larger V_c.[24–27] Furthermore, higher ETISO were linked to a faster k_{12}. The dose-dependent vasodilation from isoflurane could contribute to this higher k_{12} by increasing capillary hydrostatic pressure due to the relaxation of arterioles.[24,28]

Cats with higher body weights had a larger V_c and a slower k_{10}. The positive relationship between weight and V_c is consistent with the understanding that body weight correlates with blood volume. This relationship is supported by another study[29] demonstrating a linear correlation between blood volume and body weight in cats up to 4 kg, beyond which the increase in blood volume becomes less apparent. The authors proposed that weight gain above 4 kg is primarily due to an increase in fat, which is metabolically inactive and contains less blood volume. This same mechanism may also explain the negative relationship between body weight and k_{10}. Recent human studies[30,31] suggest that using actual body weight to calculate urine output can lead to an overestimation of acute kidney injury in obese patients, as the additional body fat contributes minimally to metabolic activity. In this study, despite all cats having body condition scores of 4 out of 9, body composition analysis was not performed. Therefore, whether the negative relationship between k_{10} and body weight was due to excessive body fat or represents a spurious finding remains unclear.

In the study by Ahn et al,[32] surface cooling in cats led to a progressive decrease in HR, blood pressure, and myocardial contractility. In that study, both SAP and DAP decreased significantly as body temperature fell, with DAP showing a more pronounced reduction. This study replicated these findings, demonstrating that hypothermia significantly lowered HR and blood pressure, with MAP and DAP showing a greater reduction than SAP.

The reduction in DAP observed during hypothermia may be attributed to several factors. Hypothermia has been shown to reduce norepinephrine release and diminish the effectiveness of catecholamines on organs and vessels.[25–27] Therefore, hypothermia induces vasodilation, which decreases peripheral resistance, directly lowering DAP since it is primarily influenced by arterial resistance.[33,34] Additionally, hypothermia leads to a significant reduction in HR, which extends the diastolic period. This extended diastolic period allows more time for blood to leave the arterial circulation, contributing further to the reduction in DAP.[33,35]

This study offers valuable insights into the effects of mild hypothermia on VK in anesthetized cats;

however, several important limitations should be considered. The small sample size, which consisted only of healthy, purposed-bred, anesthetized adult cats, may limit the generalizability of these findings to a broader feline population, including those of varying ages, health conditions, and body condition scores. Additionally, challenges with arterial catheter placement affected direct blood pressure measurements in 2 cats in the hypothermic group, potentially influencing the results. Despite this, blood pressure was assessed in 8 cats, and no significant covariate effect was found, with similar microconstant parameter estimates for the base model. Another limitation is the lack of cardiac output measurements, which would have provided a more comprehensive understanding of hemodynamic changes during hypothermia and fluid administration. Furthermore, other relevant factors affecting VK may not have been captured. Further studies should explore additional covariates and their interactions to gain a deeper understanding of the complex interplay between hypothermia, anesthesia, and fluid kinetics in cats.

This study investigated the effects of mild hypothermia on the VK of an IV crystalloid fluid bolus in healthy anesthetized cats. A 2-VOFS kinetic model best fits the data. Significant covariates affecting VK parameters included body weight, body temperature, and ETISO. Contrary to our hypothesis, mild hypothermia did not significantly impact urinary output but was associated with an increased V_c. This increase in V_c may represent decreased fluid potency and plasma volume expansion from the fluid bolus compared to normothermic states. The observed negative relationship between body weight and k_{10} suggests the need to base fluid therapy on ideal rather than actual body weight to avoid potential overdosing. Additionally, the dose-dependent increase in V_c and k_{12} with higher isoflurane concentrations suggests that higher isoflurane doses may reduce the potency and duration of the fluid bolus. Further studies are warranted to reproduce these findings and explore their implications.

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