Calculation of body surface area via computed tomography-guided modeling in domestic rabbits (*Oryctolagus cuniculus*)

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Objective—To optimize the use of CT-guided modeling for the calculation of body surface area (BSA) in domestic rabbits (*Oryctolagus cuniculus*).

Animals—12 domestic rabbits.

Procedures—Adult rabbits (body weight, 1 to > 4 kg) that were client-owned animals undergoing CT for disease diagnosis or deceased laboratory animals donated from other research projects were scanned with a CT scanner. Images were transferred to a radiation therapy planning software program. Image slices were captured as contiguous slices at 100 kVp and 100 mA and processed to 0.1-cm-thick sections. The length of each contoured slice was summed to calculate a final BSA measurement. Nonlinear regression analysis was then used to derive an equation for the calculation of BSA in rabbits.

Results—The constant calculated by use of this method was 9.9 (range, 9.59 to 10). The R^2 for the goodness of fit was 0.9332. The equation that best described BSA as a function of body weight for domestic rabbits with this method was as follows: $BSA = (9.9 \times [\text{body weight (in grams)}]^{2/3})/10,000$.

Conclusions and Clinical Relevance—The BSA calculated via the CT-guided method yielded results similar to those obtained with equations for other similarly sized mammals and verified the use of such equations for rabbits. Additionally, this technique can be used for species that lack equations for the accurate calculation of BSA. (*Am J Vet Res* 2012;73:1859–1863)

Body surface area has been used as a basis for calculation of doses for drugs with a narrow therapeutic index in veterinary and human medicine since the early 1950s.¹ Initial studies^{2,3} in humans used various methods, including paper cutouts and plasticized molds, to determine surface areas in patients, and multiple equations were derived from these procedures. The equation that currently is most commonly used in human medicine takes into account height and weight.^{3,4} The veterinary profession has historically determined BSA with an equation that uses body weight and a constant

ABBREVIATIONS

BSA	Body surface area
CI	Confidence interval

(ie, K) that differs among species. This equation was initially published in 1879⁵ and is based on the observation that the surfaces of similar solids are proportional to their volume raised to the two-thirds power. This equation is most accurate for subjects that differ in size but not in shape.³ Values of K have been determined for multiple species.^{6–10} In most of these studies, the skin was removed from animals of known body weight, and the BSA was determined by tracing the skins on paper.^{7,11} Most of the species evaluated have values of K between 8.0 and 10.5, but there are marked differences among species.

Although the K for rabbits has been determined by use of triangulation and skinning,⁶ the equations currently used for rabbits include a K value adapted from dogs, cats, or rats.¹² It is unknown whether these estimates are appropriate for use in rabbits. The objective of the study reported here was to evaluate a novel method for determining surface area in rabbits and to compare the values for this method with those obtained via traditional equations used in small animal medicine for calculation of appropriate doses for chemotherapeutic

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drugs. By establishing a method to accurately determine BSA in rabbits, further studies can be conducted on the application of this method for determining BSA in other species and the appropriateness of the use of BSA for calculating drug doses in those species.

Materials and Methods

Animals—Adult domestic rabbits (*Oryctolagus cuniculus*) of various weight classes (1 to 2 kg, 2 to 3 kg, 3 to 4 kg, and > 4 kg) were included in the study. The body weight (in grams) of each rabbit was recorded. All rabbits had a body condition score between 3.5 and 6.0 (scale of 1 to 9), as determined during examination by an attending veterinarian.

Rabbits included in the study were client-owned animals undergoing CT examination for diagnosis of disease processes or were deceased laboratory animals donated from other research projects. Informed consent was obtained for client-owned animals. Clients were informed of the need for a short additional period of anesthesia and that additional measurements would be obtained only if the rabbit was judged by the attending veterinarian to be stable during anesthesia. No client-owned animals were included that had diseases or conditions (eg, tumors or amputated limbs) that would have substantially altered body shape. Because only client-owned animals and deceased laboratory animals were used, approval by an institutional animal care and use committee was not required for the study.

Procedures—Client-owned rabbits were anesthetized in accordance with protocols selected by the attending veterinarian and anesthesia service at the veterinary medical teaching hospital of the University of California-Davis. Images were obtained with a helical CT scanner.^a Images were obtained in contiguous non-overlapping slices with a pitch of 1 and a tube rotation time of 1 second at 100 kVp and 100 mA. The reconstruction interval was the same as the slice thickness. The slice thickness varied from 3 to 7 mm to obtain approximately 100 slices/scan.

The CT images were transferred to radiation therapy planning software^b for body contouring. The series of images for each rabbit were reformatted into a 3-D image with 0.1-cm slices. The body outline was then contoured by use of a computer via the body contouring function of the software and edited manually in each 2-D plane to include areas that were not included on the initial computer-derived outline and to remove areas where the computer overestimated the body margin. The image was viewed as a 3-D reconstruction to confirm that the body outline was accurate (Figure 1). Two observers (AMZ and MSK) each separately edited the computer body contours so that interobserver variability could be assessed.

The discrete points along the length of each section of the body contour for each 0.1-cm slice were exported from the radiation therapy planning software and imported into a commercially available spreadsheet program.^c The sum of the distances between the discrete points along the contour for each slice was then determined. Total surface area for each rabbit was then calculated by summing the total of all the lengths and

multiplying this value by 0.1 cm to transform the length into an area. For the end slices, an area was calculated and added to the lengths of all the remaining body slices to account for the surface area of the terminal slices. The resulting surface area was then converted from cm² to m² by dividing the total by 10,000.

To confirm the validity of the method, 3 shapes (a cone, a cylinder, and a rectangular prism) were drawn within the radiation therapy software. The surface area of each of these shapes was also calculated by the method described and compared with the known surface areas obtained by geometric calculation.

Statistical analysis—To test for interobserver variation in body outline contouring, a correlation coefficient between the 2 sets of measurements was calculated. The BSA for each observation was plotted against the body weight (in grams). The following equation was used to calculate a nonlinear regression equation to describe the association between BSA and body weight:

$$y = K \bullet (x^a) / 10,000$$

where y is the BSA (in m²), x is the body weight (in grams), and a is the mass coefficient (ie, 2/3). A 95% CI and SEM were calculated for K. Residual values for each data point were calculated and plotted for the BSA measures. All statistical analyses were performed with a commercially available software program.^d

The surface area for each of the 3 shapes was calculated. The expected surface area of a cone was calculated as follows: area = ($\pi \bullet r^2$) + ($\pi \bullet r \bullet s$), where r is the radius of the circular base of the cone, and s is the length of the side of the cone from base to tip. The expected surface area of a cylinder was calculated as follows: area = ($2\pi \bullet r \bullet h$) + ($2\pi \bullet r^2$), where r is the radius and h is the height of the cylinder. The expected surface area of a rectangular prism was calculated as follows: area = $2(l \bullet w) + 2(l \bullet h) + 2(w \bullet h)$, where l is the length, w is the width, and h is the height.

For the 3 shapes, the percentage difference between the observed (ie, calculated) and expected values for BSA was calculated as follows: percentage difference = $(1 - \{BSA_{\text{expected}} - BSA_{\text{calculated}}\} / BSA_{\text{expected}}) \bullet 100$.

Results

Animals—Twelve domestic rabbits were included in the study. Body weight of the 12 rabbits ranged from 1.64 to 6.94 kg (mean, 3.18 kg; median, 3.08 kg). None of the rabbits had external physical abnormalities that distorted the body contour. Breeds represented in the

Figure 1—A 3-D reconstruction of a domestic rabbit (*Oryctolagus cuniculus*) based on CT-guided BSA mapping.

study included New Zealand White (n = 3), Mini-lop (2), Netherland Dwarf (1), Dutch Belted (1), Chinchilla (1), and Flemish Giant (1); the breed of 3 rabbits was unknown.

Interobserver variability—Two observers each manually edited the body outlines of the rabbits created by the radiation therapy planning software. These manual additions were primarily to distal aspects of the extremities, including the ear tips and toes, which apparently could not be automatically outlined by the software. The BSA calculated from the body outlines created by each of the 2 observers as well as the percentage differences between observers for each rabbit were determined (Table 1). The correlation coefficient from these 2 sets of observations was 0.999, which confirmed that there was minimal variation attributable to the 2 observers.

Confirmation of method accuracy—For method confirmation, surface area of 3 shapes (cone [r = 14.52 cm

and s = 23.47 cm], cylinder [r = 8.50 cm and h = 20.69 cm], and rectangular prism [l = 19.54 cm, w = 11.59 cm, and h = 11.68 cm]) were determined via the method. The calculated and measured areas for the cone were 560.33 cm² and 541.23 cm², respectively. The calculated and measured areas for the cylinder were 552.5 cm² and 556.22 cm², respectively. The calculated and measured areas for the rectangular prism were 909.39 cm² and 908.88 cm², respectively. The percentage differences between calculated and measured values were 3.4% (cone), -0.67% (cylinder), and 0.056% (rectangular prism).

Relationship of body weight to BSA—Values for BSA versus body weight were plotted (Figure 2). Additionally, residual plots of the BSA in relation to body weight were also graphed.

Equation for the calculation of BSA—The K obtained via the equation $y = K \cdot (x^{2/3})/10,000$ was 9.9 (95% CI, 9.59 to 10.20). The R² for the goodness of fit was 0.9332.

Discussion

The study reported here provided a novel CT method for calculation of BSA in domestic rabbits. Additionally, this method can be used in other species for which a good approximation of BSA currently does not exist. The availability of accurate BSA calculations may allow for better determination of doses of chemotherapeutic agents, many of which are currently administered on the basis of BSA calculations. This CT method is minimally invasive and subject to little interobserver error, which will allow the technique to be easily applied. The K obtained by use of this technique (9.9) is extremely similar to the K used for other domestic animals with a similar body type (dogs, 10.1; cats, 10.0), which suggests that previous estimates of BSA calculated on the basis of values for similar species were most likely accurate. Additionally, the only reference available on the determination of the K for rabbits via historical methods indicated values ranging from 5.7 to 11.3.⁶ It should be mentioned that the primary references for these values were not available, so the number of rabbits included for these determinations cannot be ascertained, and the

Table 1—Values for BSA calculated from body outlines of 12 domestic rabbits (*Oryctolagus cuniculus*) created by 2 separate observers using CT images and radiation therapy planning software.

Body weight (g)	Surface area (m ²)		Percentage difference
	Observer 1	Observer 2	
1,640	0.1421	0.1429	0.56
1,782	0.1292	0.1284	0.62
1,890	0.1740	0.1737	0.17
2,005	0.1740	0.1778	2.18
2,100	0.1758	0.1831	4.15
2,760	0.1902	0.1899	0.16
3,400	0.2206	0.2251	2.04
3,587	0.2207	0.2205	0.09
3,597	0.2133	0.2146	0.61
3,747	0.2266	0.2275	0.40
4,677	0.2555	0.2563	0.31
6,935	0.3876	0.3871	0.13

Values were calculated by use of the following equation: $BSA = (9.9 \times [\text{body weight (in grams)}]^{2/3})/10,000$. The percentage difference between the observed (ie, calculated) and expected values for BSA was calculated as follows: percentage difference = $(1 - [BSA_{\text{expected}} - BSA_{\text{calculated}}]/BSA_{\text{expected}}) \cdot 100$.

Figure 2—Plot of BSA and body weight for 12 domestic rabbits (*Oryctolagus cuniculus*) in which BSA was calculated by use of CT images and radiation therapy treatment planning software (A) and a plot of residuals for BSA in relation to body weight (B). Each circle represents results for 1 rabbit. In panel A, notice the line of best fit for the data; R² for the goodness of fit was 0.9332. In panel B, error bars indicate the SD for data points at which there was a difference between the 2 observers.

ranges of body weight for the 4 values of K are from 26 to 40 g up to 2,600 g.⁶ However, for rabbits with a body weight in the range of 1,120 to 1,140 g, the K is 10.0 (range, 9.0 to 11.0),⁶ which agrees closely with the calculated value for the present study.

The question of whether the use of BSA is appropriate for calculating the dose of chemotherapeutic drugs for small mammals is one that certainly deserves attention. The rationale for basing drug doses with a small therapeutic ratio on BSA is predicated on the fact that multiple physiologic processes, including renal function and energy metabolism, are proportional to surface area. There are limitations to this assumption because individual and species variations in drug metabolism, distribution, and excretion can lead to variation in the mass exponent or K. Furthermore, individual drugs may work through different mechanisms of action, and there may be differences in protein binding, absorption, metabolism, and excretion, which leads to potential problems when attempting to use BSA equations to determine drug doses.

The literature regarding chemotherapeutic doses in humans suggests that this may not be the best method for determining metabolic activity.^{13–15} Additionally, experiments in dogs suggest that administration of doses determined on the basis of BSA may result in overdosing of smaller animals, whereas milligram per kilogram doses have been recommended for some drugs to decrease the risk of toxic effects.¹⁶ This effect appears to differ depending on the agent involved, and research is needed to determine those agents that can be safely administered to rabbits and whether doses calculated on the basis of body weight are more appropriate than doses calculated on the basis of BSA. Given that rabbits have a relatively small range for body weight, compared with that for other domestic species, these effects may not be as important as in other species.

As mentioned previously, it has been suggested that adding an additional linear variable in the equation for BSA may help improve the equation's accuracy. In humans, height has been used in addition to body weight to improve the accuracy of BSA determinations. Taking into account a linear constant (eg, length) when determining BSA may be less important in rabbits than in other species that have greater variation in body shape.

One variable that may be important in intraindividual variation in rabbit BSA is ear length, given that the surface area will increase more rapidly than will body weight in rabbits with extremely large ears because there is little muscle or fat storage in ears. However, this was not examined in the present study and would require evaluation of rabbits of the same body weight but with different ear conformation to determine the effect of ear size on BSA. To then determine whether this variation is clinically relevant, toxicity and efficacy testing for individual drugs would be needed.

Another limitation of the present study was that CT images were obtained only for rabbits with body condition scores of 3.5 to 6.0. A cachectic or obese animal may not have the same volume of distribution or metabolism of a drug as an animal with the same BSA and a normal body condition score. It is also not known how disease states or age affect the pharmacokinetics

and pharmacodynamics of any drugs in rabbits, and this may affect the use of BSA for predicting the efficacy or toxic effects of drug doses.

Including a larger number of rabbits in the study may have enabled us to further refine the model, decrease the 95% CI, and increase the R^2 goodness of fit. Although the calculated BSA for most of the rabbits correlated closely with the value obtained by use of body weight, the value for 1 rabbit did not. This may have been attributable to the fact that there were more rabbits in the lower weight range in this study and that the model would have been further refined with the addition of rabbits in the upper end of the weight range. This was supported by the graph of the residuals, where the residual in the rabbit weighing 2,100 g is above the line. In this case, the 2 observers measured the BSA as 0.1758 and 0.1831 m², respectively, and used the model to derive a BSA of 0.162 m². This could result in underdosing of agents and poor outcome in this animal. In any biological system, it can be expected that actual values for some individual animals will differ from values predicted by any model, and it is an inherent limitation of modeling any complex system, as seen in the plot of the residuals and individual data points from the nonlinear regression.

The study reported here provides a method for determining BSA in domestic rabbits and will allow investigation by clinicians and researchers on how to best calculate doses of chemotherapeutic and other drugs with a low therapeutic index for use in this species. The CT surface area method described here could also be used to confirm the value of K used for BSA calculations in dogs, cats, and other species and to determine whether K remains constant within a species and across different body shapes and weights.

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- a. Model HiSpeed FX/I, General Electric, Milwaukee, Wis.
 - b. Eclipse treatment planning software 8.0, Varian Medical Systems, Palo Alto, Calif.
 - c. Excel 2008 for Macintosh, Microsoft Corp, Redmond, Wash.
 - d. GraphPad Prism, version 5.0, Graphpad Software Inc, La Jolla, Calif.
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