Distribution of 2-deoxy-2-fluoro-D-glucose in the coelom of healthy bald eagles (*Haliaeetus leucocephalus*)

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Objective—To determine 2-deoxy-2-fluoro (fluorine 18)-D-glucose (^{18}FDG) biodistribution in the coelom of bald eagles (*Haliaeetus leucocephalus*).

Animals—8 healthy adult bald eagles.

Procedures—For each eagle, whole-body transmission noncontrast CT, 60-minute dynamic positron emission tomography (PET) of the celomic cavity (immediately after ^{18}FDG injection), whole-body static PET 60 minutes after ^{18}FDG injection, and whole-body contrast CT with iohexol were performed. After reconstruction, images were analyzed. Regions of interest were drawn over the ventricular myocardium, liver, spleen, proventriculus, cloaca, kidneys, and lungs on dynamic and static PET images. Standardized uptake values were calculated.

Results—Kidneys had the most intense ^{18}FDG uptake, followed by cloaca and intestinal tract; liver activity was mild and slightly more intense than that of the spleen; proventricular activity was always present, whereas little to no activity was identified in the wall of the ventriculus. Activity in the myocardium was present in all birds but varied in intensity among birds. The lungs had no visibly discernible activity. Mean ± SD standardized uptake values calculated with representative regions of interest at 60 minutes were as follows: myocardium, 1.6 ± 0.2 (transverse plane) and 1.3 ± 0.3 (sagittal plane); liver, 1.1 ± 0.1; spleen, 0.9 ± 0.1; proventriculus, 1.0 ± 0.1; cloaca, 4.4 ± 2.7; right kidney, 17.3 ± 1.0; left kidney, 17.6 ± 0.3; and right and left lungs (each), 0.3 ± 0.02.

Conclusions and Clinical Relevance—The study established the biodistribution of ^{18}FDG in adult eagles, providing a baseline for clinical investigation and future research. (*Am J Vet Res* 2013;74:426–432)

Positron emission tomography is a noninvasive functional imaging modality that is widely used in human medicine, primarily to detect and monitor neoplastic diseases, and it is becoming increasingly available for use in veterinary medicine. The most common positron-emitting radionuclide is ^{18}FDG, a glucose analog in which the positron-emitting isotope ^{18}F is substituted for the hydroxyl group at the 2' position. Once taken into the cell, ^{18}FDG is phosphorylated by hexokinase during the first step of glycolysis; however, it cannot be further metabolized and becomes trapped in the cell, where it accumulates and reaches steady state. In the body, ^{18}FDG is used to characterize physiologic and metabolic processes on the basis of the expression of GLUTs and hexokinase activity associated with glucose uptake and metabolism, with increased uptake indicative of inflamed or neoplastic tissues.[1]

The SUV is often used in PET imaging to provide a semiquantitative measurement of radiotracer accumulation in a specific tissue or ROI, allowing monitoring of changes in tissue uptake over time. In veterinary species, PET studies establishing the ^{18}FDG distribution in healthy animals have been performed in cats,[2] dogs,[3,4] and Hispaniolan Amazon parrots (*Amazona ventralis*).[5]

Abbreviations

^{18}FDG	2-deoxy-2-fluoro [fluorine 18]-D-glucose
GLUT	Glucose transporter
PET	Positron emission tomography
ROI	Region of interest
SUV	Standardized uptake value

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Presently, PET scanners are becoming increasingly accessible to veterinarians; therefore, an understanding of the distribution of ^{18}FDG in healthy birds is necessary for accurate assessment of inflammatory and neoplastic diseases in avian species. The prevalence of neoplastic diseases in avian species is not completely understood; however, neoplastic diseases have been documented in long-lived species such as companion birds[6] and captive or free-ranging raptors.[7] Captive raptor species often have longer life spans than their wild conspecifics, and various species of eagles, including bald eagles (*Haliaeetus leucocephalus*), have been reported to live for 30 to 40 years or longer.[8] Although a previous study[5] describing the distribution of ^{18}FDG in healthy Hispaniolan Amazon parrots (*Amazona ventralis*) has been performed, the numerous anatomic and physiologic variations within and among avian taxonomic groups underscore the importance of determining ^{18}FDG distribution in individual species before use of this imaging modality for the diagnosis of disease in all avian species. The purpose of the study reported here was to describe the biodistribution of ^{18}FDG in healthy adult bald eagles.

Materials and Methods

Eight bald eagles maintained in a sanctuary were used. The eagles were nonreleasable because of orthopedic conditions but were otherwise healthy. In the sanctuary, they were housed in social groups in a wooded outdoor enclosure all year, monitored via daily observation, and received an annual wellness examination that included CBC, serum biochemical panel, and a physical examination. Four males and 4 females, aged (mean ± SD) 17 ± 6.72 years (range, 10 to 24 years) and weighing 3,935 ± 476 g, were used. Food was withheld from the eagles for 12 to 24 hours prior to anesthesia, and they were transported to the PET-CT imaging facility on the day of the scan. Access to water was provided until approximately 2 hours prior to the scan. Prior to the study, the eagles were kept in a darkened carrier for 1 to 2 hours to limit muscle exertion. Anesthesia was performed via mask induction with 3% isoflurane. The birds were intubated with a 6.0-mm (males) or 6.5-mm (females) uncuffed endotracheal tube, and anesthesia was maintained with 2% isoflurane. An IV catheter was placed in the right or left basilic vein for blood collection to determine prescan glucose concentration and for administration of ^{18}FDG and iodinated contrast medium. Positive pressure ventilation was provided, and anesthetic monitoring consisted of ECG, pulse oximetry, use of an ultrasonic Doppler flow detector, and measurement of end-tidal CO_2 concentration.

PET and CT—The eagles were imaged in dorsal recumbency with a 64-slice PET and CT scanner.[a] Scans included a noncontrast, whole-body CT scan performed with collimation of 1.2 mm, pitch of 1.5, 120 kV, 50 mA,[b] and rotation time of 0.5 seconds with images reconstructed at 3-mm collimation with a medium smooth algorithm; a 60-minute list mode dynamic PET scan of the coelomic cavity started simultaneously with IV administration of (mean ± SD) 128.5 ± 20.2 MBq (3.5 ± 0.5 mCi) of ^{18}FDG, in which data were reconstructed with appropriate binning to determine the kinetic redistribution of radiotracer with time; a whole-body PET scan at steady state started immediately after the dynamic scan, by use of 5 bed positions at 2 min/position, TrueX reconstruction method,[c] an all-pass filter, and 3 iterations/24 subsets; and a post-contrast, whole-body CT (iodinated non-ionic contrast medium[d] [528 mg of I/kg, IV) by means of the same parameters as for the noncontrast scan.

All studies were reconstructed, viewed, and analyzed with dedicated software[e] by a board-certified veterinary radiologist with experience in the interpretation of PET images. First, ^{18}FDG distribution in coelomic organs was evaluated subjectively by use of both

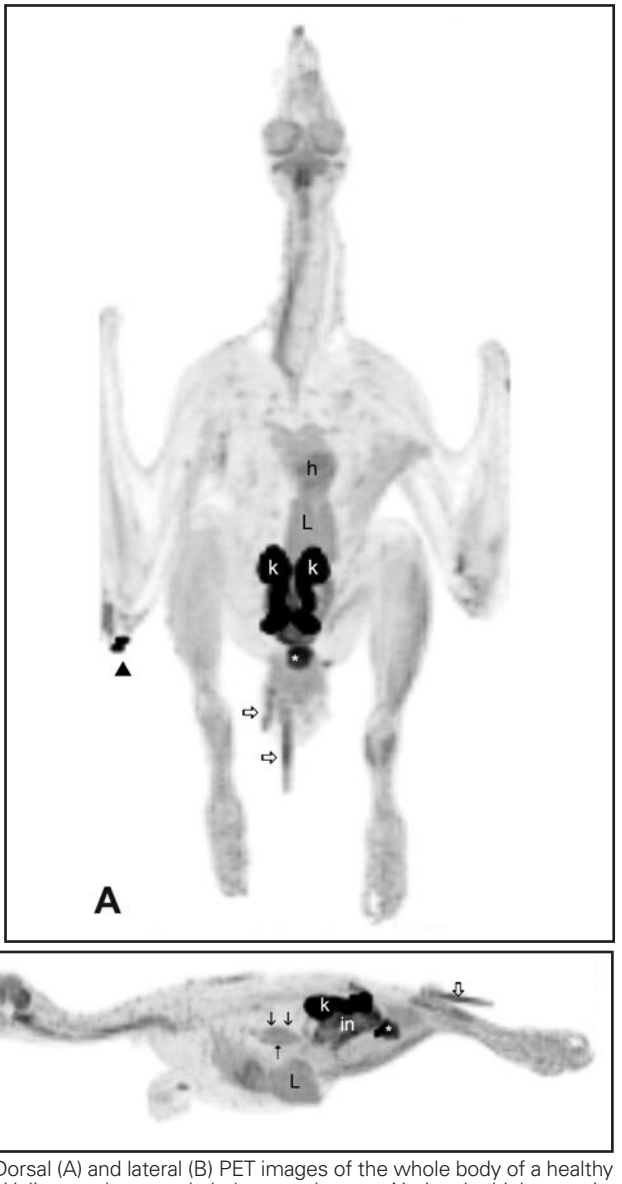

Figure 1—Dorsal (A) and lateral (B) PET images of the whole body of a healthy bald eagle (*Haliaeetus leucocephalus*) at steady state. Notice the highest activity in the kidneys (k) and cloaca (asterisk) and the homogeneous pattern of uptake in the kidneys. High intensity activity is also present in the intestinal tract (in). The liver (L) and proventriculus (black arrows) have intermediate activity, which is slightly less than that of the myocardium (h). There is a focal area of tracer retention in the catheter at the level of the right wing (arrowhead). Blood feathers are also seen, with high intensity activity (white arrows).

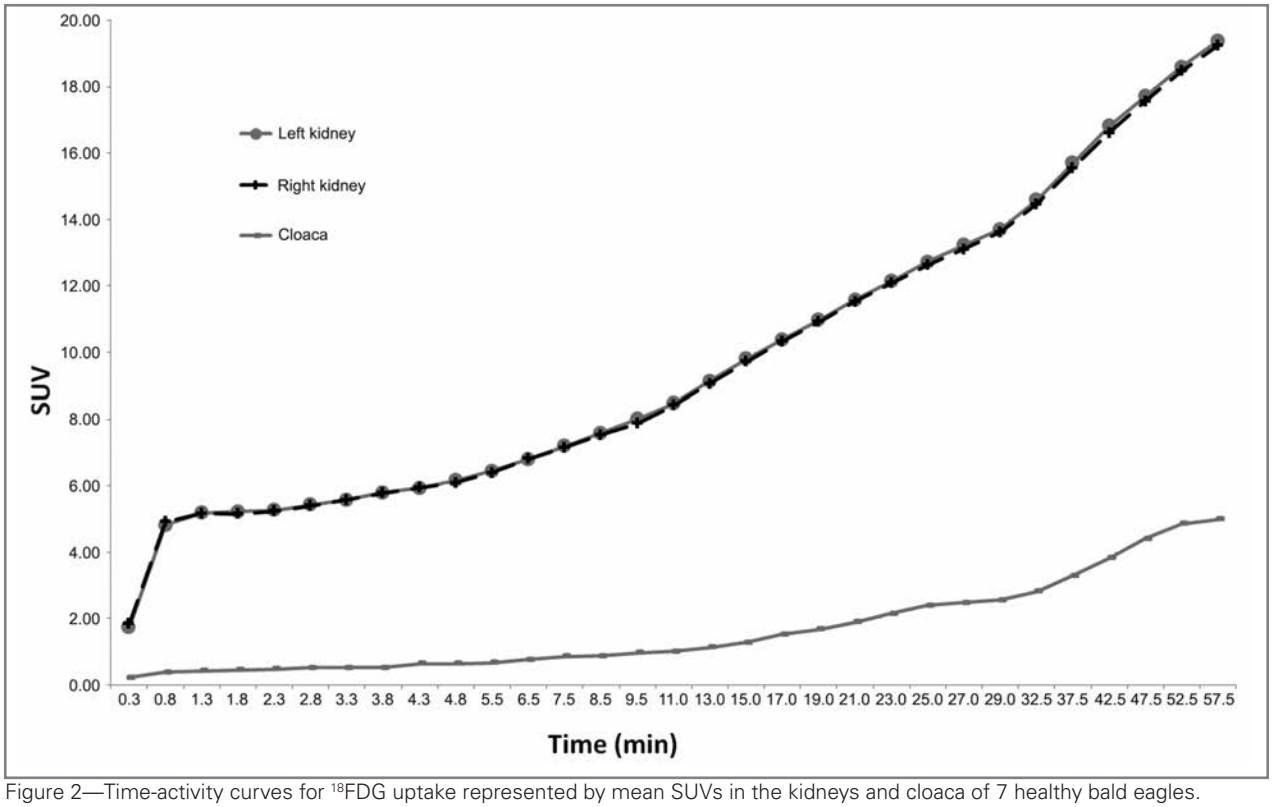

Figure 2—Time-activity curves for ^{18}FDG uptake represented by mean SUVs in the kidneys and cloaca of 7 healthy bald eagles.

PET data and fused PET-CT data. Second, quantitative analysis was performed by calculating SUV in various celomic organs with established formula following decay correction as follows:

SUV = decay-corrected activity concentration in tissue/(injected activity/body weight)

where activity concentration in tissue is in kBq/mL (decayed-corrected to the time of injection), injected activity is in kBq, and body weight is in grams.[9]

The SUVs were calculated via ROIs that were drawn over target coelomic organs by use of the postcontrast CT scan fused to the dynamic PET data with freehand technique; the CT data were used to delineate the organs' margins. Two techniques were used: a single ROI was drawn over the image that best represented the organ in question (representative ROI); for all organs other than the lungs, a volumetric ROI was also created from several individual ROIs that were drawn then interpolated. Multiplanar evaluation of the images was used to ensure accurate placement of the ROIs, and in the case of volumetric ROIs, modifications were made as needed to ensure exclusion of nonpertinent tissue, such as the collection system for the kidneys and luminal content for the proventriculus. Representative renal ROIs were drawn on transverse images at the level of the cranial pole of the kidneys, with special care to exclude the collection system. Representative ROIs for the cloaca were drawn in the mid portion of the organ; both representative and volumetric cloaca ROIs included both the wall and the lumen and excluded the most distal aspect of the ureters. Splenic ROIs were drawn on transverse images, as were hepatic ROIs. To ensure similar placement of the representative hepatic ROIs among the different birds, the ROIs were drawn 1.5 cm caudal to the cardiac apex as seen on sagittal views. Similarly, representative lung ROIs were drawn on transverse images obtained 3 cm caudal to the cranial aspect of the tracheal bifurcation, as seen on dorsal images; ROIs were drawn in the caudodorsal aspect of the right and left lungs, avoiding large vessels and bronchi. Proventricular ROIs were drawn in the dorsal plane, with special care to exclude luminal content. The ROIs for the left ventricular myocardium were drawn on 2 image planes, sagittal and transverse, with special care to exclude the ventricular lumen. The ROIs drawn on the fused contrast CT-dynamic PET images were then imported into the static PET data sets, to ensure consistent placement.

Statistical analysis—The SUVs calculated by means of representative or volumetric ROIs were compared via the Student *t* test or Mann-Whitney rank sum test, depending on whether the data were normally distributed. Representative and volumetric myocardial SUVs calculated in the sagittal and transverse planes and representative and volumetric SUVs calculated for the right and left kidneys were also compared via 1-way ANOVA. Significance was set at $P < 0.05$ for all tests.

Results

Prescan plasma glucose concentrations were measured in all birds except the first bird imaged; mean ± SD blood glucose concentration was 295.7 ± 25.1 mg/dL. One bird was excluded from the analysis because of uncorrectable misregistration (misalignment between the CT and PET data sets). One bird did not receive

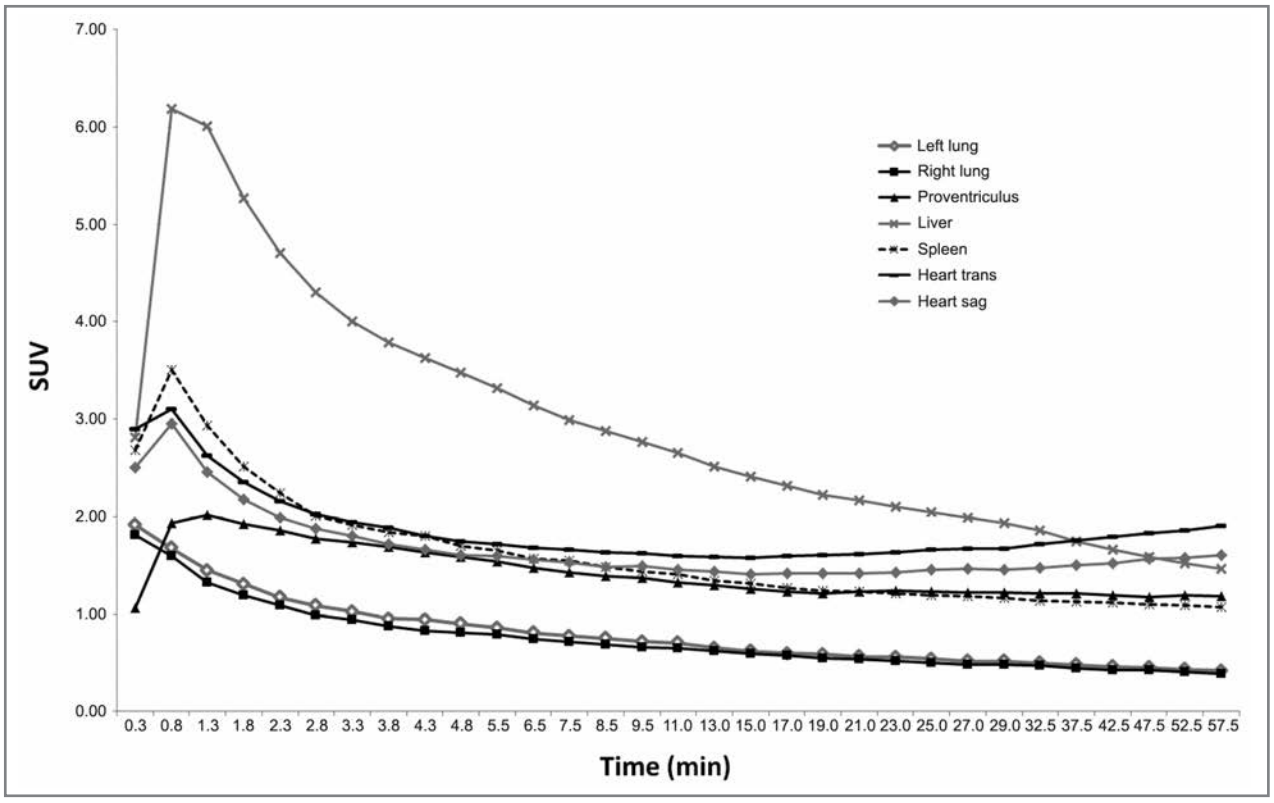

Figure 3—Time-activity curves for ^{18}FDG uptake represented by mean SUVs in the lungs, proventriculus, liver, spleen, and ventricular myocardium (heart) of 7 healthy bald eagles. trans = Transverse. sag = Sagittal.

iodinated contrast medium IV. All birds recovered without complications from anesthesia.

In all birds, the highest ^{18}FDG activity was associated with the kidneys, followed by the cloaca and the intestinal tract. The distribution of activity in the kidneys at equilibrium (ie, 60 minutes after injection) was homogeneous in all birds. Proventricular activity was variable but always present, whereas little to no activity was identified at the level of the wall of the ventriculus. Although mean proventricular activity was less than myocardial activity, when comparing the relative uptake in these 2 organs in individual birds, proventricular activity was less than myocardial activity in 4 birds and greater in the remaining 3 birds. Myocardial activity was also always present and variable among birds. Liver activity was mild, uniform, and slightly higher than splenic activity, both in mean values and in individual birds (**Figure 1**). No discernible lung activity was identified in any of the birds, and gonadal tissue was not identified in any of the birds.

Dynamic data did not reveal any evidence of reflux from the cloaca into the colon. Time-activity curves for all organ studies were determined (**Figures 2** and **3**). Standard uptake values (mean ± SD) obtained at the steady state from representative ROIs were determined (**Table 1**).

There were no significant differences between SUVs calculated by means of representative and volumetric ROIs for all organs. Although it was subjectively easier to draw the myocardial ROI on sagittal images, there was no difference between cardiac SUVs calculated from sagittal versus transverse images. There was also no significant difference between SUVs at the level of the right and left kidney.

Table 1—Summary of the SUVs (mean ± SD) for ^{18}FDG obtained at steady state from representative and volumetric ROIs in 7 healthy bald eagles (*Haliaeetus leucocephalus*).

ROI	Representative SUV	Volumetric SUV
Myocardium (transverse plane)	2.4 ± 0.3	2.1 ± 0.5
Myocardium (sagittal plane)	1.9 ± 0.4	2.0 ± 0.5
Liver	1.7 ± 0.1	1.7 ± 0.1
Spleen	1.4 ± 0.1	1.3 ± 0.2
Proventriculus	1.5 ± 0.1	1.3 ± 0.1
Cloaca	6.6 ± 4.2	4.9 ± 3.3
Left kidney	26.5 ± 0.5	24.0 ± 1.4
Right kidney	25.9 ± 1.6	24.8 ± 1.2
Left lung	0.5 ± 0.02	NA
Right lung	0.5 ± 0.04	NA

NA = Not applicable.

Discussion

The PET image data revealed that eagles had both similarities and differences when compared with humans, dogs, and cats in regard to ^{18}FDG uptake, which were likely the result of anatomic and physiologic differences between birds and mammals. When compared to the only reported study[5] in birds (Amazon parrots), there were also differences between carnivorous and granivorous-omnivorous avian species and taxa groups.

The highest ^{18}FDG activity was detected in the kid-

neys. Renal activity in eagles was comparatively much higher than that of dogs,[3] cats,[2] and humans.[10] Avian species typically maintain a plasma glucose concentration that is much higher than that of mammalian species. Because the kidneys are the only organs other than the liver that have gluconeogenic activity, it is feasible that the gluconeogenic activity of the kidneys in birds may be greater than that of mammals. To maintain the high plasma glucose, birds have developed effective glucose transport in the renal tissue to prevent the loss of glucose through excretion in the urine.[11] Thus, birds possess many of the same GLUTs and sodium-glucose cotransporters as mammals. One study[f] revealed that the maximum transport capacity (tubular maximum for glucose transport) of the kidneys of birds is 4 to 5 times that of human kidneys. In mammals, the kidneys provide up to 30% of glucose by gluconeogenesis (by use of lactate, amino acids, pyruvate, and glycerol as substrates). Similarly, the kidneys of domestic chicks are able to produce 30% of circulating glucose during periods of starvation, presumably through the metabolism of fatty acids.[12] In small passerine species, glycogen reserves are used up quickly during the evening (a period without food intake), and free fatty acids become the primary energy source to spare the use of glucose as well as catabolism of muscle protein for gluconeogenesis.[13] Interestingly, carnivorous species are able to maintain plasma glucose concentrations during periods of both unfed and fed states.[14]

A potentially confounding factor affecting renal uptake and excretion of ^{18}FDG in birds is the presence of the renal portal valve, which is located in the lumen of the common iliac vein, leading toward the caudal vena cava.[15] The smooth muscle of this valve is under both adrenergic (stimulatory, resulting in valve closure) and cholinergic (inhibitory, causing opening of the valve) innervation causing blood to flow directly into the vena cava when the valve is open or into the renal portal vein when the valve is closed.[16,17] The exact mechanisms associated with opening and closure of the valve are not completely understood. Furthermore, the effects on renal blood flow and, ultimately, uptake of ^{18}FDG in an excited or anesthetized bird are not known.

The second-most intense ^{18}FDG uptake occurred in the cloaca and intestinal tract. Presence of ^{18}FDG in the cloaca is the result of excretion of the radionuclide by the kidneys through the ureters and into the urodeum portion of the cloaca. In many avian species, urine is refluxed (retropulsed) back into the coprodeum, colon (rectum), and ceca as a mechanism to conserve water, electrolytes, nitrogen, glucose, and amino acids[16,18] that would be excreted in the urine; this occurs especially in xerophilic avian species.[17] Reflux of urine from the cloaca into the distal portion of the intestine was documented in a study[5] in Amazon parrots, indicating that a dynamic PET scan is necessary to differentiate between increased metabolism or reflux of urine and ^{18}FDG in the intestine.[5] We did not observe reflux of urine from the cloaca into the lower intestine in any of the eagles during the course of the present study; absence of such reflux may be explained by the distinct differences in anatomy and physiology between parrots and eagles. First, water resorption in the ceca (a sodium-dependent process) of most raptor species is considered low because most raptors (including eagles) have small or rudimentary ceca (with the exception of the barn owl [*Tyto alba*], great-horned owl [*Bubo virginianus*], and possibly other species).[17,18] Secondly, raptors are believed to have functional salt glands, and therefore may not have a strong functional capacity to absorb water from the rectum and ceca.[15,19] The small intestine is the primary site of water resorption in birds of prey. Lastly, reflux of urine into the distal portion of the intestine is not necessary in raptors due to the quantity of water (50% to 80%) in the prey they consume, which is enough to satisfy their water requirements if they are healthy.[18]

The ^{18}FDG activity in the eagles' small intestine was considered higher than that reported in Amazon parrots; however, quantitative evaluation was not performed because it was not possible to draw reproducible ROIs over the small intestines. Glucose is the primary carbohydrate absorbed by the small intestine in birds, and this absorption occurs through carrier-mediated transport (GLUTs and sodium-glucose cotransporters) and paracellular diffusion through intercellular spaces.[11] The exact reason for the difference between eagles and parrots is unknown but may be associated with increased efficiency of digestion and absorption of specific nutrients (proteins, lipids, and carbohydrates) in carnivorous species that consume a low-fiber diet,[18] compared with granivorous and omnivorous species. Alternatively, insulin may be the primary mediator of carbohydrate metabolism in carnivorous avian species[20] in which carbohydrates make up only a small percentage (2%) of the diet[21] versus glucagon in granivorous species.[22] In mammals, the predominate insulin responsive GLUT is GLUT-4.[11] Although GLUT-4 may not be expressed in tissues of domestic chickens, mourning doves, ducks, pigeons, and canaries,[23] it is possible that GLUT-4 may be present in tissues in carnivorous species such as raptors. However, the extent to which GLUT-4 is present in raptors is presently unknown.

The stomach of birds is divided into the proventriculus, which is the glandular portion of the stomach, and the ventriculus, which is used for physical breakdown of ingested foods. The ventriculus is more developed and muscular in granivorous species such as poultry, while that of carnivorous species is less muscular and functions more as a storage area for chemical digestion. In birds of prey, the ventriculus also functions as the site of accumulation of undigested food items and formation of a pellet or casting that is egested (regurgitated). In the eagles in this study, activity was always present in the proventriculus, whereas little to no activity was identified in the wall of the ventriculus. Because food was withheld from these eagles, it is unclear why there was activity in the proventriculus and not the ventriculus, which usually forms a pellet within 24 hours after feeding.[24] However, variably high uptake of ^{18}FDG in the proventriculus, with little activity in the ventricular wall, was also described in Amazon parrots[5]; it is possible that the uptake in the stomach compartments of birds is predominantly affected by gastrointestinal motility, which is, in turn, affected by withholding of food and anesthesia, rather than by type of diet.

Hepatic activity in the eagles was mild, although slightly more intense than activity in the spleen. Hepatic activity was less than that described in humans and slightly higher than that reported in cats[2]; in comparison with dogs,[3,4] liver activity in the eagles was either slightly higher or slightly lower than reported values. The exact reason for this was unclear, considering that GLUT-1 and GLUT-2 have been identified in the liver of avian species (chickens), and the avian liver contributes substantially to circulating blood glucose concentration.[18,25] The GLUTs are not found in the liver of chicks,[26] suggesting that there may be differences between age groups. Glucokinase (hexokinase IV), which is found only in hepatocytes, regulates the uptake of glucose into the liver to be converted to glycogen and stored there. However, the lesser hepatic activity of ^{18}FDG, compared with that of dogs and humans, may be explained by differences between taxonomic groups and the presence or effectiveness of glucokinase to clear glucose from the blood. Previous studies suggest that hexokinase in birds is physiochemically similar to that in lizards and snakes but different from the enzymes found in mammals[27] and that glucokinase is all but absent in birds.[18]

In the eagles in this study, activity in the myocardium was always present but variable among the subjects. Myocardial SUVs were similar to values reported in dogs but less than those reported in cats. In humans, myocardial uptake varies depending on the substrate used: in the postprandial state, a physiologic increase of glycolysis results in increased ^{18}FDG uptake by the myocardium; in the fasted state, high free fatty acid concentrations and low plasma insulin concentrations reduce ^{18}FDG uptake. Glucose metabolism in avian cardiac tissue is likely similar to that of humans in that the heart relies heavily on free fatty acids and lactate for energy, thereby sparing carbohydrate reserves (glycogen) in heart muscle.[22]

The lack of significant lung uptake of ^{18}FDG in eagles of the present study was expected and similar to that in humans, dogs, cats, and Amazon parrots. It is interesting to note that there was no ^{18}FDG uptake in the gonads; in fact, gonadal tissue was difficult to identify in all eagles. Although the eagles used in the study were adult, and in some cases, breeding eagles, we postulate that the time of the year (fall and winter) when the scans were done coincided with little to no reproductive activity in this group.

In addition to subjective evaluation, SUV calculation was used to determine the intensity of ^{18}FDG uptake in specific organs. For the purpose of SUV calculation, 2-D (representative) and volumetric ROIs were used. Volumetric ROIs encompass the entire organ of interest; however, they are more time consuming to draw. Results indicated no significant difference in the SUVs calculated with both techniques and indicated that representative ROIs are acceptable for the purpose of SUV calculation.

Although measurement of SUV is standard in clinical practice, SUVs can be affected by several factors that may cause substantial variability.[28] Biological factors, such as blood glucose concentration, uptake time, and respiratory motion, can have substantial effects on SUV. High blood glucose concentrations can substantially decrease SUV, which is why routine measurement of blood glucose concentrations was performed immediately prior to image acquisition. Technical factors, such as scanner type, image acquisition protocol, reconstruction parameters, and interobserver variability (ROI placement), may also affect SUV; however, in this study, all imaging studies were performed with the same scanner and same acquisition and reconstruction protocol, and data were evaluated by the same individual. Body composition may affect SUV; however, in this study, physical examination of the birds revealed that they were of typical body weights and not considered obese or to have high percentages of body fat. Although the number of eagles imaged in the course of this study was small, the low variability in the calculated SUV (as evidenced by the SD) suggested that a representative population was sampled and provided clinically relevant results for ^{18}FDG in this species.

The study reported here determined the biodistribution of ^{18}FDG in bald eagles. Although similarities in results may exist within an order of birds, differences were evident between Amazon parrots and bald eagles, which suggests the need for evaluation of different avian taxa and the establishment of species-specific reference ranges to improve the diagnostic accuracy of PET in avian species. The best use of quantitative SUV measurements remains the comparison of follow-up studies to baseline studies in the same patient by means of the same platform and acquisition protocol.

a. Siemens MCT, Siemens Medical Solutions USA Inc, Knoxville, Tenn.
b. Care Dose, Siemens Medical Solutions, Forchheim, Germany.
c. TrueX, Siemens Medical Solutions, Forchheim, Germany.
d. Ominpaque, Iohexol 240, GE Healthcare Inc. Princeton, NJ.
e. Inveon Research Workplace, Siemens Preclinical Solutions USA, Hoffman Estates, Ill.
f. Morgan C, Braun EJ. Glucose handling by the kidney of the domestic fowl (abstr). *FASEB J* 2001;15:A854.

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