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Effects of Various Anesthetic Protocols on ^{18}F-Flurodeoxyglucose Uptake into the Brains and Hearts of Normal Miniature Pigs (*Sus scrofa domestica*)

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This study used positron emission tomography–computed tomography (PET–CT) to evaluate the effects of 4 anesthetic protocols on 2-deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}F-FDG) accumulation in the brains and hearts of miniature pigs (*Sus scrofa domestica*). The ^{18}F-FDG standard uptake value was quantified by dividing the brain into 6 regions: cerebellum, brainstem, and frontal, parietal, temporal, and occipital lobes. Five (2 female and 3 male) clinically normal miniature pigs were premedicated with medetomidine (200 μg/kg IM) after which the following 4 anesthetic protocols were administered by using a crossover design: 1) propofol (4 mg/kg IV)–isoflurane inhalation; 2) propofol (4 mg/kg IV); 3) ketamine (5 mg/kg IV); 4) tiletamine–zolazepam (4.4 mg/kg IM). Compared with levels after other protocols, brain accumulation of ^{18}F-FDG increased during propofol anesthesia but decreased with tiletamine–zolazepam. Relative to that due to other protocols, heart accumulation of ^{18}F-FDG increased with propofol–isoflurane anesthesia but decreased with tiletamine–zolazepam. Comparing glucose accumulation in the brain and heart of miniature pigs by using PET–CT, we found that glucose accumulation varied according to the anesthetic protocol and between the 2 organs. These results can be used to evaluate how different anesthetic agents affect glucose metabolism in brain and heart of miniature pigs. Furthermore, these data should be considered when selecting an anesthetic agent for miniature pigs that will undergo PET–CT imaging with ^{18}F-FDG.

Abbreviations: CBF, cerebral blood flow; PET–CT, positron emission tomography–computed tomography; SUV, standard uptake value.

In recent years, miniature pigs have been used widely in biomedical research. Their small size relative to that of other large animals facilitates housing and handling, and their ample blood volume permits frequent serial blood collection, which can be problematic in rodents. In addition, miniature pigs are similar to humans in physiologic structure, state, and organ size.

Use of general anesthesia allows procedural ease, efficiency, and minimization of stress to the animal. Many types of anesthesia can be used for pigs during scanning procedures and surgery. To avoid possible side effects of anesthesia on research results, some investigators rely on physical restraint. However, restraint can also induce stress and affect results.[27]

Although imaging techniques do not cause pain, anesthesia is necessary so that animals do not move during the imaging procedure.[2] Therefore, sedation and muscle relaxation are important.[2] However, anesthetic drugs vary in their capacity to interfere with homeostatic mechanisms responsible for glucose metabolism.[15] A glucose analog, 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG), is the most frequently used positron emission tomography (PET) radiotracer. PET coupled with computed tomography (CT) and using ^{18}F-FDG is a valuable tool for detecting abnormal glucose metabolism and is widely applied in animal studies of the brain and heart, 2 major functional organs of glucose metabolism.[17,29] However, the effects of various anesthetics during PET imaging of miniature pigs have not been reported. Furthermore, little is known about anesthetic effects on ^{18}F-FDG accumulation in the brain and heart of miniature pigs. The purpose of the current study was to evaluate the effects of 4 anesthesia regimens on ^{18}F-FDG accumulation in the brains and hearts of miniature pigs to establish baseline conditions for PET imaging of this animal model.

Materials and Methods

Animals. Five (2 female, 3 male) SPF miniature pigs (crossbreds of PWG micropigs and Yucatan, native, pigmy, and miniature potbelly pigs) were obtained from Medi Kinetics (Pyeongtaek, Korea). All pigs were quarantined for 4 wk before use in experiments and were clinically healthy prior to the study. The pigs (age, approximately 6 mo; weight, 9.8 to 17.62 kg) were individually housed in stainless-steel cages (152 × 92 × 102 cm) and fed ad libitum a standard commercial pig diet (Lab Pig Chow, Purina Korea, Gyeonggi, Korea) once daily. Fresh water purified by reverse osmosis was provided ad libitum. Pigs were housed in a barrier facility on a 12:12-h light:dark cycle (lights on at 0800) with a room temperature of 23 ± 1 °C, a relative humidity of 50% ± 5%, and 25 complete changes of filtered air

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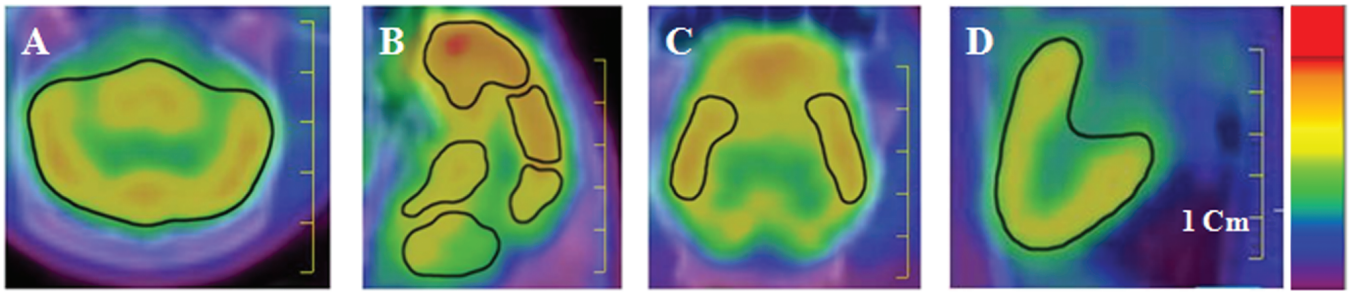

Figure 1. Images from ^{18}F-FDG–PET-CT of miniature pigs. Regions of interest were manually drawn from the (A) transverse (whole brain), (B) midsagittal (frontal, parietal, and occipital lobes; cerebellum; and brainstem), (C) dorsal (temporal lobe), and (D) midsagittal (heart) images. The color indicates the relative ^{18}F-FDG concentration (from red [high] to blue [low]) in the respective image. Scale bar, 1 cm.

hourly. The study protocol was approved by the University of Konkuk IACUC.

Anesthetic protocols. This study used a crossover design, with each pig exposed to each anesthetic protocol and a 2-wk washout period between protocols. All pigs were food-fasted for 6 h prior to administration of anesthesia, with free access to drinking water. All pigs were premedicated with medetomidine (200 µg/kg IM; Domitor, Pfizer Korea, Seoul, Korea), and anesthesia was administered after the pigs became sedated. Local anesthetic cream (lidocaine 2% jelly, Astra, Sodertalje, Sweden) was applied to the pigs' ears 45 min prior to administration of anesthesia to prevent pain during insertion of an ear-vein catheter. The 4 anesthetic protocols evaluated were as follows: 1) propofol (4 mg/kg IV; Provive 1%, Myungmoon Pharm, Hwasung, Korea) to facilitate orotracheal intubation followed by isoflurane (Ifran, Hana Pharm, Seoul, Korea) administered at 1.5 to 2% with 100% oxygen for maintenance; 2) propofol (4 mg/kg IV; Provive 1%, Myungmoon Pharm); 3) ketamine hydrochloride (5 mg/kg IV; Yuhan, Gunpo, Korea); and 4) tiletamine–zolazepam (4.4 mg/kg IM; Virbac, Carros, France). After administration of the anesthetic medication, an endotracheal tube was inserted and a mechanical ventilator connected to provide 100% O_2, because arterial carbon dioxide and oxygen concentration levels need to be maintained throughout brain PET studies.[32] Pigs were monitored until fully recovered from anesthesia.

These protocols and dosages were selected based on those reported previously.[4,38] Blood glucose measured prior to ^{18}F-FDG administration (mean, 104.6 ± 26.9 mg/dL) was within the normal reference range (43 to 133 mg/dL) in all pigs.[4]

^{18}F-FDG–PET scanning. ^{18}F-FDG (148 MBq, 4 mCi) was administered intravenously 1 h prior to PET–CT imaging (Gemini PET–CT, Philips, Eindhoven, The Netherlands) of the brain and heart. A 50- to 60-min interval between ^{18}F-FDG administration and imaging is sufficient obtain a useful tumor:background ratio of the tracer.[5]

The scanning time for PET–CT was 20 min; PET scans were acquired immediately after CT imaging. The PET images were derived from section slices with a thickness of 4 mm, and 170- to 200-section images were obtained. The CT images were derived from section slices with a thickness of 3.2 mm, and 370- to 400-section images were acquired. The PET–CT images were reconstituted by using 3D Row Action Maximum Likelihood Algorithms and fused by using Syntegra software (version 2.1F; Philips). The ^{18}F-FDG standard uptake value (SUV) was quantified by dividing the brain into 6 regions: frontal, parietal, temporal, and occipital lobes; cerebellum; and brainstem. The region of interest within each brain and heart region was determined by consensus among one laboratory animal technician, 2 veterinarians, and one person experienced in human nuclear imaging. Manual drawings of transverse, midsagittal, and dorsal images were made (Figures 1 and 2). The SUV with a region of interest around the focal ^{18}F-FDG accumulation zone was calculated by using a whole-body protocol according to the following formula:

$$\text{SUV} = \frac{\dfrac{\text{decay - corrected activity (kBq)}}{\text{tissue volume (mL)}}}{\dfrac{\text{injected FDG dose (kBq)}}{\text{body weight (g)}}}$$

Statistical analysis. All statistical analyses were performed using GraphPad Prism for Windows (version 4.0; GraphPad Software, San Diego, CA). Data were recorded as mean ± SEM and analyzed by Kruskal–Wallis test; and P values less than 0.05 were considered significant. If significant differences were detected, Dunn multiple comparisons were performed.

Results

Brain. Each of the 6 brain regions showed at least one difference in SUV between the 4 anesthetic protocols used in the miniature pigs (Figures 2 and 3). Kruskal–Wallis tests showed significant ($P < 0.05$) differences between propofol and tiletamine–zolazepam and between ketamine and tiletamine–zolazepam. For all brain regions, the SUV for propofol-anesthetized miniature pigs was significantly ($P < 0.05$) higher than those for all other anesthetic protocols. The lowest ^{18}F-FDG accumulation occurred in the brains of tiletamine–zolazepam-anesthetized pigs, with greater ($P < 0.05$) glucose accumulation in the frontal lobe than other regions. The SUV for the frontal lobe (3.03 ± 1.09 g/mL) of propofol-anesthetized miniature pigs was significantly higher than other regions; the occipital lobe of propofol-anesthetized pigs showed the lowest SUV (2.46 ± 0.53 g/mL). In tiletamine–zolazepam-anesthetized miniature pigs, SUV was significantly higher in the frontal lobe (1.78 ± 0.37 g/mL) than other regions. The lowest SUV in tiletamine–zolazepam-anesthetized miniature pigs occurred in the occipital lobe (1.54 ± 0.10 g/mL) and cerebellum (1.54 ± 0.11 g/mL).

Heart. In all of the miniature pigs, the propofol–isoflurane combination (4.23 ± 0.31 g/mL) yielded the highest coronary glucose accumulation values and tiletamine–zolazepam the lowest (2.10 ± 0.38 g/mL; Figures 4 and 5). In addition, SUV were higher in the pigs anesthetized with ketamine (2.85 ± 0.55 g/mL) compared with propofol (2.43 ± 0.63 g/mL). Kruskal–Wallis tests showed significant differences between propofol–isoflurane and propofol ($P < 0.05$) and between propofol–isoflurane and tiletamine–zolazepam ($P < 0.01$).

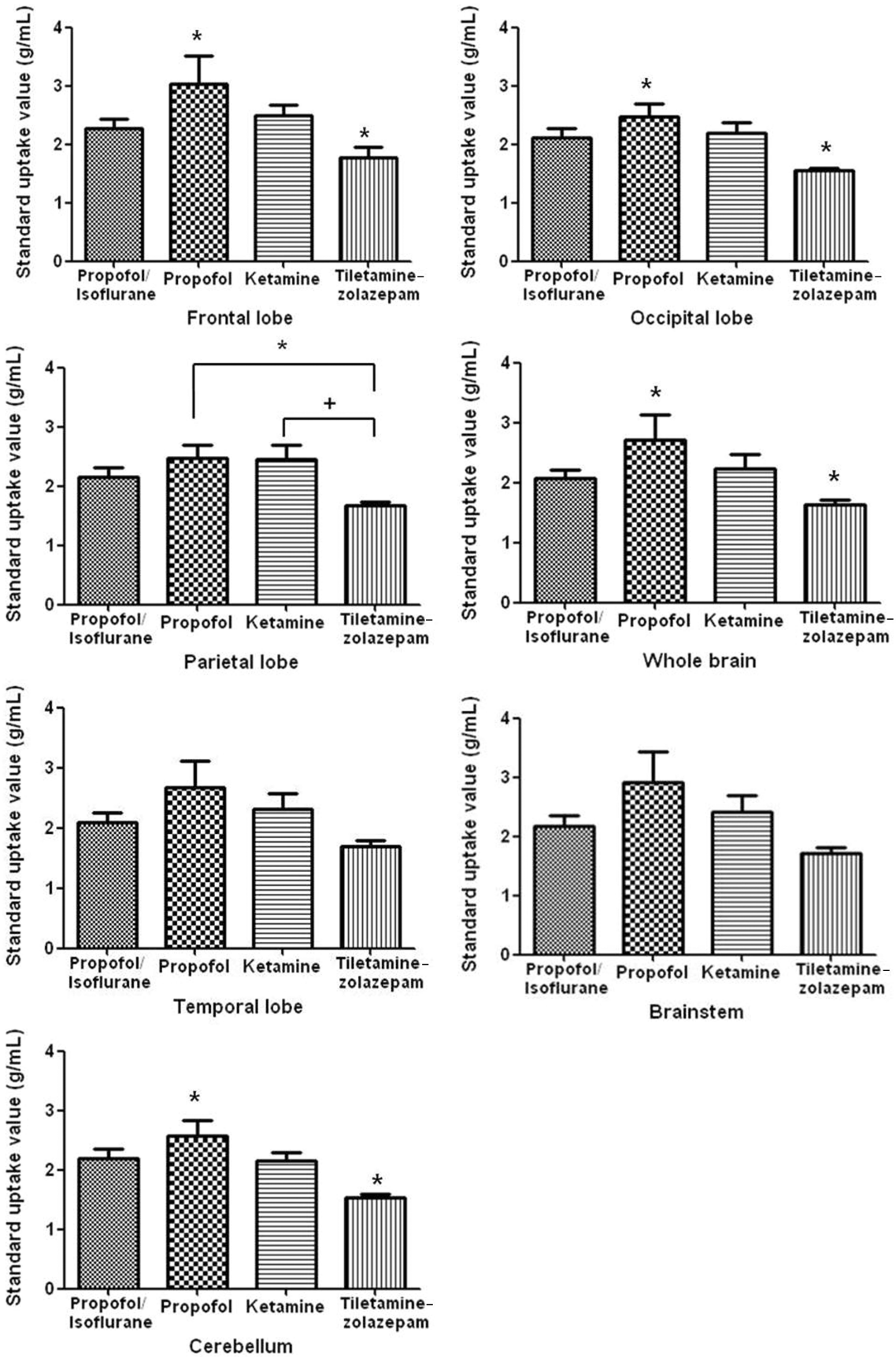

Figure 2. Standard uptake values of ^{18}F-FDG in the frontal, parietal, temporal, and occipital lobes; cerebellum; brainstem; and whole brain of normal miniature pigs (n = 5) anesthetized by using 4 different protocols. Values within a brain region that are indicated by similar symbols (*, +) are significantly ($P < 0.05$) different between anesthetic protocols.

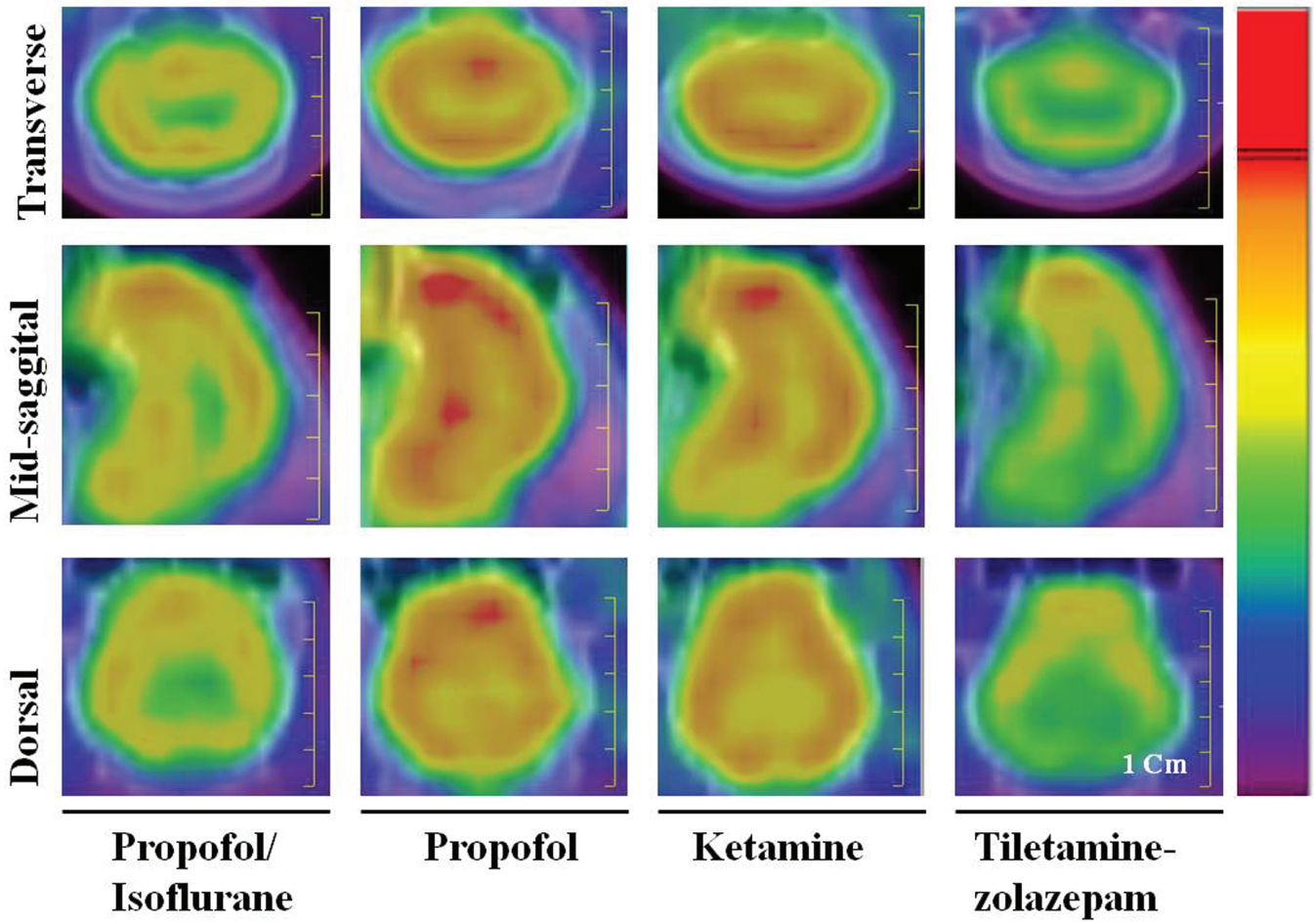

Figure 3. Comparison of features in ^{18}F-FDG–PET images from transverse, midsagittal, and dorsal views between propofol–isoflurane, propofol, ketamine, and tiletamine–zolazepam anesthetic protocols. The color indicates the relative ^{18}F-FDG concentration (from red [high] to blue [low]) in the respective image. Scale bar, 1 cm.

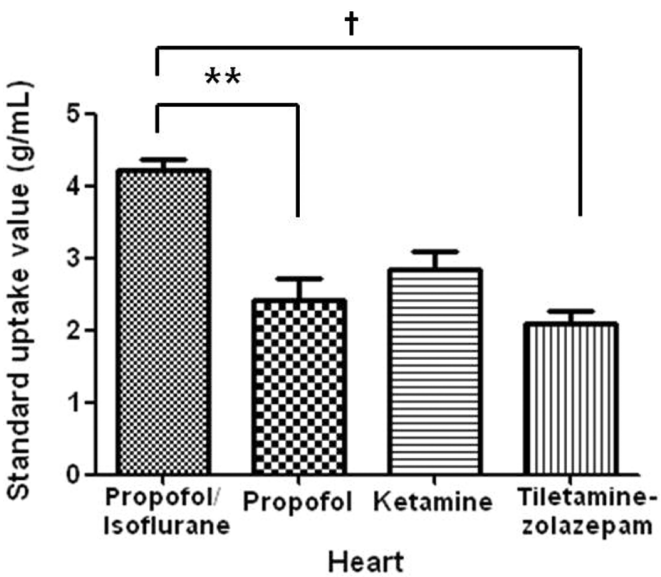

Figure 4. Standard uptake values of ^{18}F-FDG obtained from hearts of normal miniature pigs (n = 5) anesthetized by using different anesthetic protocols. *, Significant ($P < 0.05$) difference between values for propofol–isoflurane and ketamine; †, significant ($P < 0.01$) difference between values for propofol–isoflurane and tiletamine–zolazepam.

Discussion

Anesthesia has significant effects on the central nervous, cardiovascular, and respiratory systems.[43] PET using radiolabeled tracers allows molecular imaging of physiologic events in living subjects.[43] ^{18}F-FDG is an analog of glucose and is taken up and trapped by living cells during the first stages of the normal glucose pathway. The rationale behind the use of ^{18}F-FDG as a tracer for cancer diagnosis is based on the increased glycolytic activity in neoplastic cells.[5] In the present study, we evaluated the effects of 4 different anesthetic protocols on ^{18}F-FDG accumulation in the brains and hearts of miniature pigs. We found that ^{18}F-FDG accumulation varied according to the type of anesthetic agents used and between the brain and heart.

The 4 anesthetic protocols we evaluated had different effects on the hearts of miniature pigs. Specifically, isoflurane increased ^{18}F-FDG accumulation, whereas tiletamine–zolazepam decreased accumulation. Volatile anesthetics have been shown to have cardioprotective[41,42] and vasodilatory effects[11,20,37] that are mediated by activation of ATP-sensitive potassium channels in cardiac myocytes and vascular smooth muscle cells, respectively.[40] Isoflurane currently is recommended as the primary inhalant anesthetic for use in swine[36] and has been shown to increase coronary blood flow (and decrease coronary vascular resistance) in swine.[9] Isoflurane-induced dilation of porcine coronary arterioles is mediated by K–ATP channels.[20,40] Whereas isoflurane causes the mitochondrial K–ATP channels in cardiac myocytes to open, the intravenous anesthetics propofol and

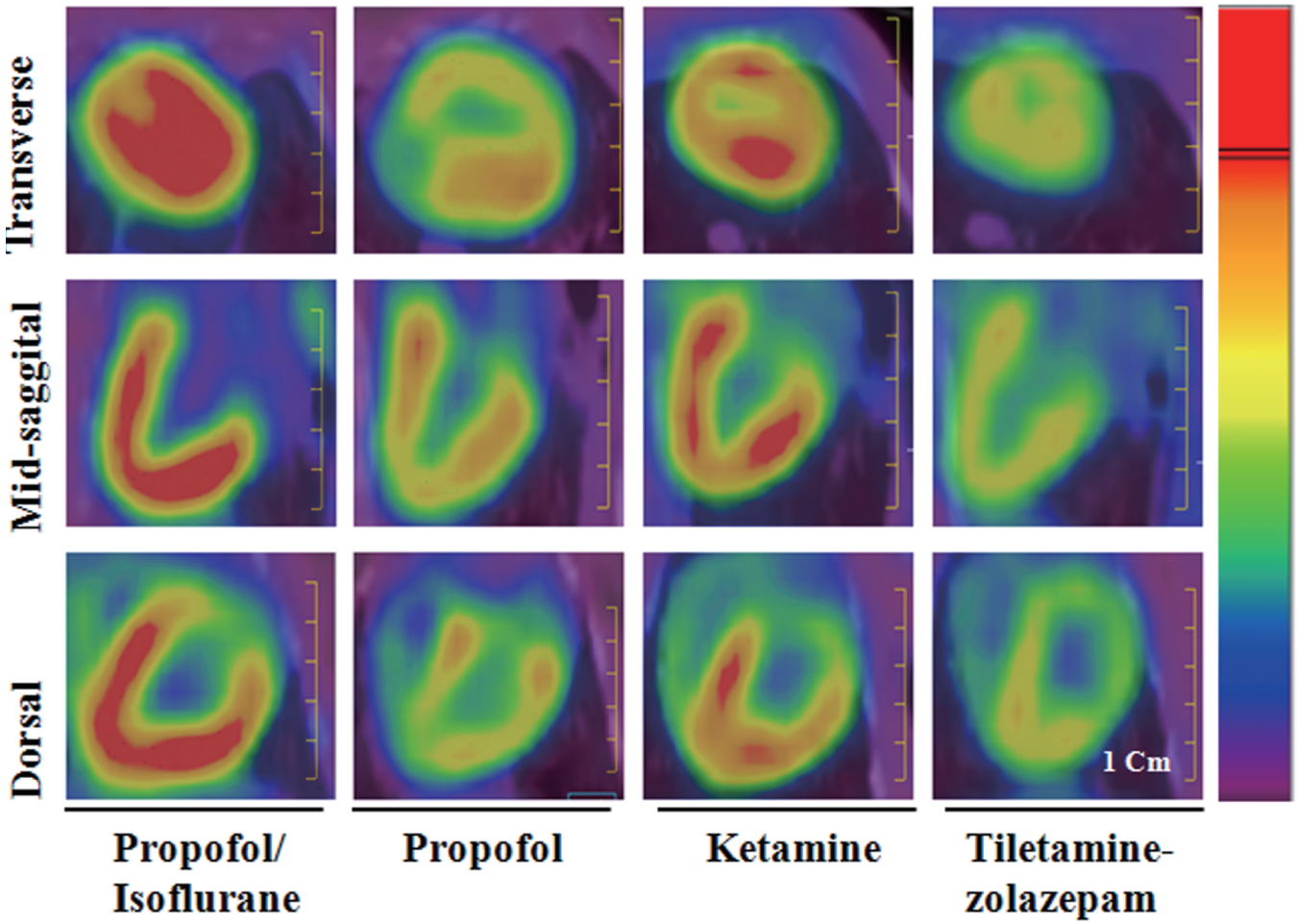

Figure 5. Comparison of features with ^{18}F-FDG–PET images in transverse, midsagittal, and dorsal views between propofol–isoflurane, propofol, ketamine, and tiletamine–zolazepam. The color indicates the relative ^{18}F-FDG concentration (from red [high] to blue [low]) in the respective image. Scale bar, 1 cm.

pentobarbital have been reported to have no direct effect on mitochondrial K–ATP channels.[22] These mitochondrial KATP channel mechanisms may explain why isoflurane, compared with other anesthetic agents, caused ^{18}F-FDG accumulation to increase in the hearts of the pigs in our current study.

As in the heart, the 4 anesthetic regimes we investigated had different effects on the brains of minipigs. Specifically, propofol increased ^{18}F-FDG accumulation whereas tiletamine–zolazepam decreased accumulation compared with that due to other anesthetic protocols. In the brain, glucose is taken up by astrocytes or enters neurons, and PET–CT using ^{18}F-FDG enables visualization of cerebral glucose metabolism. ^{18}F-FDG is phosphorylated by hexokinase; however, unlike glucose, ^{18}F-FDG does not participate further in the glycolysis pathway. Therefore, ^{18}F-FDG is trapped in the cells, mainly in astrocytes.[30,34] Glucose uptake into astrocytes is known to be coupled to astrocytic glutamate uptake.[28] ATP generated from glycolysis is responsible for the cycling of glutamate between neurons and astrocytes.[35] Consequently, glutamate regulates astrocytic glucose metabolism in a concentration-dependent manner.[34,39]

Anesthetics (for example, isoflurane, propofol, ketamine, and tiletamine–zolazepam) are widely recognized to act on glutamatergic and GABAergic neurons.[18] Glutamate is the signal molecule at the glutamatergic neurons and is the precursor of GABA, which is released from GABAergic neurons. Anesthetics might affect the astrocytic glutamate concentration, and concomitantly, cerebral glucose metabolism; however, the mechanisms of action underlying these effects are still unknown. In addition, the transporter system involved in astrocytic glutamate uptake varies and is distributed differentially at the level of neuronal cells and brain regions.[12] These differences in distribution, as well as other factors, may affect regional differences in glucose metabolism as measured by PET–CT.

No information is available on the effects of tiletamine–zolazepam on heart glucose utilization. Tiletamine (2-[ethylamino]-2-[2-thienyl] cyclohexanone hydrochloride) is a dissociative anesthetic agent with pharmacologic properties similar to those of ketamine, but the potency and duration of action of tiletamine are intermediate between those of long-acting phencyclidine and short-acting ketamine.[3] Zolazepam (4-[o-fluorophenyl]-6,8-dihydro-1,3,8-trimethylpyrzolo[3,4-e][1,4]diazepine-7[1H]-1) is a benzodiazepine derivative with pharmacologic properties similar to those of diazepam.[3] Tiletamine–zolazepam is a 1:1 mixture by weight of tiletamine and zolazepam that depresses cardiorespiratory functions.[14,25] These effects may explain the decreased ^{18}F-FDG accumulation in the hearts of pigs that received tiletamine–zolazepam. Many anesthetics cause some degree of cardiovascular alteration in animals;[7,8] however, little is known about the mechanism(s) of action of these drugs at relevant central autonomic sites.[6,7]

Anesthesia can influence brain physiology, including cerebral glucose metabolism and cerebral blood flow (CBF).[32] Ketamine

induces increased CBF and cerebral glucose metabolism in humans.[23] Isoflurane has been reported to decrease regional cerebral glucose metabolism and CBR, leading to decreased cerebral accumulation of ^{18}F-FDG as measured by PET imaging, in humans.[1] We obtained similar results in our pigs. However, the use of isoflurane as an anesthetic in rats has been shown to increase regional brain metabolism.[33] The use of propofol as an anesthetic decreases glucose metabolism and regional CBF in humans.[21] The differences between CBF and ^{18}F-FDG accumulation in response to anesthetics is not known definitively for many different species. Our results were similar to those recently reported from isoflurane-anesthetized mice, in which administration of identical doses of ^{18}F-FDG resulted in lower ^{18}F-FDG accumulation in brain than in heart.[43] In rhesus monkeys, ketamine anesthesia increased ^{18}F-FDG accumulation in brain, as determined by PET–CT.[19] Results from a study in dogs were opposite to our findings in swine. Specifically, the SUV in brain indicated the greatest ^{18}F-FDG accumulation for dogs anesthetized with a combination of medetomidine–tiletamine–zolazepam and the least accumulation in those given propofol–isoflurane. [26] These differences in accumulation may be due to differences in specific brain features, such as CBF, which is known to vary by species,[16] sex,[10] and age.[13]

Pigs must be anesthetized prior to administration of ^{18}F-FDG for PET–CT imaging. We used medetomidine as premedication for all pigs and therefore did not measure the ^{18}F-FDG SUV for this independent anesthetic agent. To our knowledge, no information is available on the effects of a medetomidine mixture on glucose utilization by the brain and heart. One of the limitations of our study was that only a small number of animals was evaluated. More animals should be tested for each anesthetic agent to accurately evaluate ^{18}F-FDG accumulation in miniature pigs by using PET–CT imaging.

The SUV reported for abnormal human cardiac sarcoidosis (2.51 to 14.70 g/mL) were much higher than those in normal human tissue (1.86 to 1.98 g/mL).[31] An SUV greater than 2.5 is considered a malignant characteristic in humans.[24] The differences in heart SUV due to the different anesthetic agents (2.1 to 4.2 g/mL) used in the current study are clinically significant and has the potential to influence experimental outcomes. Therefore, the anesthetic agent for PET imaging procedures with ^{18}F-FDG in miniature pigs should be selected carefully.

In conclusion, by using PET–CT to measuring ^{18}F-FDG SUV, we showed that the SUV varies according to the anesthetic agent used and organ evaluated. We also found that SUV differed between various parts of the brain. These results illustrate how different anesthetic agents affect glucose metabolism in the brains and hearts of miniature pigs. Furthermore, we suggest that the predicted analytic results of each data set are important factors to consider when selecting an anesthetic agent for use during ^{18}F-FDG–PET imaging studies in miniature swine.

Acknowledgments

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