Imaging Techniques in Large Animals

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Summary
Imaging techniques in large animals bridges the gap between preclinical and clinical research.
The same scanners can be used for large laboratory animals and for human beings and, with few modifications, the same scanning protocols can also be used. Therefore, knowledge obtained from imaging techniques in animal research can readily be used in humans. Similarly, medical hypotheses and problems from clinical experience with humans can often be tested and studied in large animals. Imaging techniques create either anatomical images (Computerized Tomography, CT or Magnetic Resonance Imaging, MRI) or functional images of the body (Positron Emission Tomography, PET). While X-ray radiation is used to get a cross-sectional CT image of the body, MRI involves the use of a magnetic field that forces the hydrogen cellular nuclei to align in different positions. PET utilizes radiation emitted from the animal after injection of radioactive tracers. The most commonly used large animals in imaging research are dogs, sheep, goats, pigs and nonhuman primates. These laboratory animals have large organs and blood volumes that allow repeated blood sampling, which is needed in most PET studies, while blood sampling is unnecessary for CT and MRI imaging. Large animals are outbreed, and so many animals are typically needed in each study, due to marked individual variation. That situation is unfavourable, because imaging studies of large animals are expensive and time consuming. Except for nonhuman primates, large animals must be anaesthetised for scanning procedures, and this may influence the experiments.

Introduction
Imaging techniques play a major role in modern biomedical research (*Olsen et al., 2007*). Especially, imaging of mice and rats in small-animal scanners is currently in focus, because such studies of transgenic animals and other rodent disease models are particularly fruitful (*Colby and Morenko, 2004*). This has produced fundamentally new knowledge over the past 10 years about genetic human diseases, and provided unique insight into how single genes affect the body (*Fossella and Casey, 2006*). During the same period, other unique research has been performed by imaging large animals, bridging the gap between preclinical and clinical research. Results obtained in large animal experimentation can instantly be applied to human protocols. Similarly, questions raised in the human clinic can be tested in laboratory animals by using the same protocols, scanners and equipment (*Olsen et al., 2007*). This close relationship between preclinical and clinical research has been very profitable for research groups that are able to perform imaging studies of both large animals and human beings. This work has been used, for example, for testing new tissue implants, for establishing dosimetry, and for developing new imaging procedures for heart diseases. Also, the medical industry has discovered the potential of using large animal imaging in drug development. Some companies have established their own preclinical and clinical Positron Emission Tomography (PET) research centers, while others collaborate with public research laboratories, such as our cooperation at Aarhus PET Center with GlaxoSmithKline. PET imaging of large animals

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can be used for testing new drug candidates. In the following we will focus on imaging techniques used for large animals. After that we will discuss the usefulness of the most used large animals in imaging studies.

Imaging techniques

Imaging of large animals, as well as of humans, is concerned with the interaction of radiation with tissue and the development of technologies to extract useful information from observations, spatial as well as temporal, of these interactions. This section deals with the three main methods used in imaging of large animals: computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). Depending on the imaging methods and application, the data acquired can be interpreted to yield information not only about anatomy and structures, but also many physiological processes such as glucose metabolism, oxygen utilization, blood volume, perfusion, and receptor binding (*Haacke, 1999; Prokop, 2002; Baailey, 2005*). This information is usually displayed as images. However, it is important to keep in mind that the images produced are pictures of tissue characteristics that influence the way energy is emitted, transmitted, reflected, etc by the imaged tissue. These characteristics are related to, but not the same as, the actual structure (anatomy), composition (biology and chemistry), and function (physiology and metabolism) of the imaged tissues. In many cases extensive data processing has been applied after the actual imaging process. Traditionally, CT and MRI have been coincided structural modalities, where PET mainly has provided functional information. However, today a large number of functional protocols are eversible for mainly MRI but to some extent also for CT (*Haacke, 1999; Prokop, 2002*). Utilizing anatomical landmarks to superimpose images, the functional information from PET images can be combined with anatomical information in CT or MRI images in a process called co-registration. With the advent of combined PET/CT scanners, generating combined structural and functional images has become possible without the time-consuming process of co-registration. Figure 1 illustrates how merging PET and CT images into a single image provides useful information about the precise location of a PET-tracer in the liver.

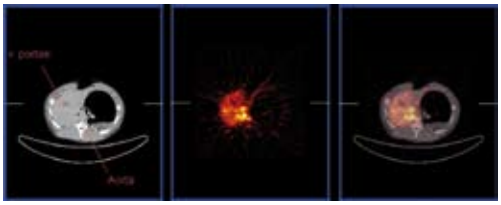

Figure 1. CT (left), $C^{15}O$-PET (middle), and fused PET/CT (right) images of the porcine liver region. Without the CT image it is difficult to localize the anatomy of the liver and its supplying vessels.

Computed tomography (CT), through its high spatial resolution and moderate differentiation of tissue contrast, is a fast and exceptionally useful technique for visualizing general anatomy (*Prokop, 2002*). The basic principle of CT imaging involves X-ray generation, detection, and computer image reconstruction. An X-ray tube and X-ray detectors are positioned on opposite sides of a rotating ring. X-rays passing through a body placed inside the ring are attenuated at different rates by different tissues. Computer processing is used to generate a three-dimensional image of the inside of the body from the large series of two-dimensional X-ray images taken around the axis of rotation (*Prokop, 2002*). CT uses ionizing radiation, however, doses are relatively small and even when working with surviving experimental animals, no further consideration is required.

Magnetic resonance imaging (MRI) provides, like CT, detailed images with millimetre spatial resolution (Table 1). However, MRI has a much greater soft tissue contrast than CT, making it especially useful in neurological imaging. The principles of MRI involve the use of a powerful magnetic field to align the nuclear magnetization of hydrogen atoms in the water in the body (*Haacke, 1999*). Radiofrequency fields are used to systematically alter the alignment

Table 1. Advantages and disadvantages using CT, MRI and PET techniques:

Imaging technique	Advantages	Disadvantages
CT	High spatial resolution (1 mm) Available in most hospitals Cheap and easy to operate	Ionizing radiation Low soft tissue contrast Little functional information
MRI	No X-rays or radioactive tracers High spatial resolution (1 mm) Excellent soft tissue contrast Characterization of the biochemistry through spectroscopy Some functional protocols	Few and expensive scanners Special equipment needed
PET	True functional imaging Many tracers are available Physiological modelling	Few and expensive scanners Low spatial resolution (4–5mm) Use of radioactive tracers Little anatomical information

of this magnetization, causing the hydrogen nuclei to produce a rotating magnetic field detectable by the scanner. This signal can be manipulated by additional magnetic fields to build up enough information to reconstruct an image of an animal placed in the scanner. Special MRI-safe surgical equipment, implants etc. are needed, due to the strong magnetic fields.

Positron emission tomography (PET) can record biological processes in three dimensions following administration of radiolabelled tracers by intravenous injection or inhalation (Table 1). Specific PET tracers can be synthesized for studies of specific metabolic processes by radiolabelling naturally occurring substances and analogues thereof (e.g. 18F-deoxy-2-glucose, FDG), pharmaceuticals, etc (*Baailey, 2005*). During and following tracer administration, the time course of the concentration of radioactivity in the tissue is recorded by the PET scanner, and the time course of the concentration of radioactivity in the blood is measured in successive blood samples. The resulting data are then analyzed using kinetic models. PET isotopes must generally be produced on-site, as their radioactive half-life is short, limiting the availability of PET imaging. Compared to other imaging modalities, contemporary PET has a lower spatial resolution. The use of combined PET/CT further provides the anatomical location (CT) of the biological processes (PET) in merged images (Figure 1). No high attenuation objects, e.g. metal heating mats, may be added or removed during the experiment.

Table 1 summarizes some of the properties of the presented imaging techniques. Each imaging method, individually and in combination, provides information essential to modern animal research.

Bridging the gap between preclinical and clinical research

An advantage for imaging large animals is that protocols used in preclinical research can be modified and used for clinical research in humans. Imaging of large animals has produced a fruitful milieu, in which preclinical research can be used in the clinical research and vice versa. We have experienced the close interaction between pig and human research in the field of brain, liver and bone diseases at Aarhus PET Center. Furthermore, they have an organ size

that is similar to human organs, allowing human equipment such as surgical instruments, catheters and medical devices to be used (*Tai and Afforest, 2005*). Often, the same scanners can be used for patients and human volunteers as for imaging of large animals. Human imaging centers already have experts in all aspects of imaging techniques, and they often have state-of-the-art equipment for managing human patients. As a result, animal experiments can be performed in the best and most updated ways. It is the experience from our PET Center that the staff often prefer to work with laboratory animals, because it can be a welcome break in a routine work with clinical imaging of patients. But it is of importance to remind that handling and imaging of humans and animals may differ in some aspects, and work with animals may require special training. As an example, animals cannot be anaesthetised by the same protocols as human (*Wolfensohn and Lloyd, 2003*). Therefore, it is necessary to have animal specialists working together with the imaging specialists, and the staff must be trained and educated in the field of laboratory animal science. This is also part of the European legislation that demands basis courses for employees working with laboratory animals (*van der Valk and van Zutphen, 2004*). Without a thorough knowledge of laboratory animals, researchers cannot expect to get useful results from the experiments, and the welfare of the animals can be threatened. In addition, there must be enough equipment, personnel, and scanners available for scanning of both human patients and laboratory animals, so the animal experiments will not be performed at the expense of human patients. Due to risk of offensive smells and zoonoses, animal studies should be performed on days without imaging of patients, or they should be performed after ending of clinical imaging. In some cases, a single scanner can be dedicated to animal research. Obnoxious smells can be prevented by cleaning the animals prior to scanning, and anaesthetised animals may be covered with blankets and plastic sheets to prevent contamination. Bladder catheters can be installed before long-term imaging studies to help prevent urinary contamination (*Olsen et al., 2007*). For some animals, such as male pigs, bladder catheters cannot be placed, but instead nappies can be used to prevent urinary contamination. The use of human scanners for animal experiments requires that the scanners are cleaned and sanitized after use. The procedures for sanitizing should be cleared by the hospital infection control department and the institutional veterinarian to prevent infections and allergies (*Olsen et al., 2007*). Standard Operation Procedures for cleaning of scanners are recommended.

The large body size

The blood volume of larger animals makes it possible to collect repeated blood samples while performing the imaging studies. Repeated blood sampling is performed during PET imaging for establishing time-activity curves that are used to estimate the precise uptake of the tracers (*Meyer et al., 2006*). In survival studies, a maximum of 10 % of the total blood volume can be sampled during a three-week period (*Joint Working Group on Refinement, 1993*). Note that the blood volume of small laboratory animals such as mice and rats is insufficient for repeated blood sampling in survival studies (*Sossi and Ruth, 2005*), while it is possible to collect up to a total volume of 300 ml blood from a 40 kg pig during a period of three weeks (Table 2). Furthermore, a large blood volume makes it possible to collect blood samples during PET scans with different tracers in each animal on one day. It is an advantage that the PET tracer doses (MBq kg^{-1}) are lower in large animals, while microPET scanners used for mice and rats require higher tracer doses to obtain images with high resolution (*Sossi and Ruth, 2005*). Also, the requirements for specific activity (MBq mol^{-1}) of PET tracers are less demanding in large animals compared to rodents due to the lower tracer doses used (*Hume et al., 1998*). A disadvantage of large body weight is, however, related to strain on the staff when handling the animal. This may increase the risk of getting back injury, and special equipment for transporting

Table 2. Biological data, monitoring parameters and examples of anaesthesia protocols for large animals used for imaging studies:

	Dog	**Sheep**	**Goat**	**Pig[1]**	**Nonhuman primate[2]**
Biological data					
Adult body weight (kg)	10-15	70-100	70-90	220-250	4-11
Blood volume (mL kg^{-1})	76-107	58-64	57-90	56-69	55-80
Monitoring parameters					
Body temperature (^oC)	37.9-39.9	39.0	38.5	38.7-39.7	36-40
Heart rate (min^{-1})	70-160	60-120	70-135	50-100	120-180
S.Blood pressure (mmHg)	95-136	-	-	150	125
Respiration rate (min^{-1})	22	12-20	15-25	10-16	32-50
Example of anaesthesia protocols					
Fasting (hours)	12	12	12	12	8
Premedication	Metadone + Diazepam	Diazepam	Diazepam	Ketamine + Midazolam	Ketamine Diazepam
Induction	Propofol	Propofol	Propofol	Propofol	Propofol
Maintain, injection	Propofol	Propofol	Propofol	Propofol	Ketamine
Maintain, inhalation	Isoflourane	Isoflurane	Isofluorane	Isoflurane	Isoflurane

[1]Domestic pigs. [2]Rhesus macaque. All data from: Wolfensohn & Lloyd (2003).

and handling of large animals is recommended. The staff should be trained in handling large animals prior to the work.

Large animals are outbred

A major disadvantage of using large animals for imaging is that they are outbred (Table 3). A few inbred strains exist, like the Banna minipig (*Cheng et al., 2001*), but they are only rarely used. On the other hand, inbred strains of mice and rats are commonly used in research, and they are commercially available for imaging studies. A major consequence of using outbred animals is larger variation between the animals, and therefore more animals must be included in each study (*Festing, 2003*). This is especially problematic for expensive imaging studies, such as protocols involving PET. It is the authors' opinion that, in too many imaging studies, too few animals have been used, and this may have increased the risk of type 2 errors (i.e. missing a real difference between groups). One way to avoid problems of using outbred animals is to use a crossover design. By including baseline scans in the design, each animal can be used as its own control, and this will reduce the number of animals needed.

Limited knowledge about biology of large animals

It is a disadvantage that knowledge about the biology of large animals is limited compared to what we know about mice and rats. This is especially a problem for sheep, goats and other large animals that are rarely used as laboratory animals in imaging research. However, knowledge about large animal

Table 3. Advantages and disadvantages of small animals (mice and rats) versus large animals (pigs etc) for imaging studies.

Species	Advantages	Disadvantages
Small animals	Easy to handle	Small size of organs
	Cheap	Small blood volume
	Inbred strains	Difficult for anaesthetize
	Transgenic strains	
	Knowledge of biology	
Large animals	Large size of organs	Not easy to handle
	Large blood volume	Large genetic variation
	Easy to anaesthetize	Expensive
	Use of human protocols	No/few transgenic strains

biology is increasing day-by-day. For example, knowledge about the biology of the Göttingen minipig has increased markedly in recent years, and an MRI-based brain atlas is available (*Watanabe et al., 2001*).

Anaesthesia

Before larger animals are scanned, they must be anaesthetized. Although imaging techniques do not cause pain, it is necessary to anesthetize the animals so that they do not move during the imaging procedure. Therefore, good sedation and muscle relaxation are important. Both injection/infusion and inhalations anaesthetics are widely used, but nonmagnetic equipment must be utilized for MRI studies or else the equipment must be shielded adequately from the magnetic field (*Olsen et al., 2007*). In some studies, anaesthetized animals have been fixated during the imaging procedure (*Momosaki et al., 2004; Hosoi et al., 2005*), in order to avoid the possible side effect of anaesthesia on research results. But fixating animals may also affect the results, because fixation seems to induce stress (*Madrigal et al., 2006*). Furthermore, there are welfare problems concerning fixation of laboratory animals. As an alternative, the laboratory animals can be trained to be scanned while awake. This is possible in nonhuman primates (*Blaizot et al., 2000*), but the success of the training depends on for how long a time the primates must be scanned, and this is different for each imaging type: CT (approximately one minute), MRI (few minutes) and PET (from few minutes to several hours). The advantages of using awake primates are obvious, and studies in awake and anaesthetized primates have documented that anaesthesia can influenza the results. For example, the effect of cocaine on the synaptic concentration of dopamine differs in awake and isofluorane-anaesthetized Rhesus monkeys (*Tsukada et al., 1999*). Also, cerebral blood flow is decreased by propofol, benzodiazepine, barbiturate and opioid anaesthesia and increased by isofluorane and dissociative anaesthesia (*Swindley, 2007*). While some information on the effects of anaesthesia on imaging studies is already available, much more information and research are needed.

Installing catheters in vessels

In PET studies intraveneous radiotracer injections are always needed, and intravenous contrast agent injections are often needed for CT and MRI imaging. Venous catheters are used for infusion of anaesthetics, test drugs and saline. Superficial veins can be canniculated in most species, such as the cephalic vein in dogs and nonhuman primates and an ear vein in pigs (*Wolfensohn and Lloyd, 2003*),

whereas no superficial veins exist in sheep and goats. Surgically placed central venous catheters are therefore needed in sheep and goats, and sometimes also in pigs, and this may include the jugular vein or the femoral vein (mostly used in pigs) (*Olsen et al., 2007*). For dynamic PET studies, arterial blood sampling is needed, and it may also be used for monitoring of blood gases and blood pressure. Arterial catheters are often surgically installed in the femoral or carotid artery. Catheters can be placed in the femoral artery and vein in pigs, and this site is ideal for brain studies, because of the long distance from the brain to the vessel access (*Olsen et al., 2007*).

The importance of monitoring

In many papers dealing with imaging of large animals, no information is given about monitoring of physiological variables and parameters. However, such information is of crucial importance for the validity of the results. The animals must also be monitored to ensure that they are adequately anaesthetized. Papers should always deal with basic information about monitoring, especially if the animals are scanned for several hours or if they are used for functional imaging such as functional MRI or PET. The importance of monitoring in functional imaging is emphasized by the fact that changes in the arterial carbon dioxide concentration markedly affects cerebral blood flow and cerebral blood volume, as shown by $H_2{}^{15}O$- and $C^{15}O$-PET in pigs (*Olsen et al., 2006*). Detailed information on the importance of each monitoring variable and parameter of large animals in imaging studies is, however, lacking today. It is advisable to monitor the following variables and parameters during functional imaging of large animals: electrocardiogram, heart rate, respiration rate, body temperature, pulse goniometry and reflexes (interdigital, corneal and palpebral) (*Danielsen et al., 1997; Olsen et al., 2006*). When arterial catheters are placed, monitoring may also include blood pressure, blood glucose and blood gases (*Olsen et al., 2006*). To prevent hypothermia, animals are to be placed on an electric blanket with thermostatic feedback to the temperature monitor during imaging procedures.

Dogs

Dogs are used for imaging studies of bones (*Carrera et al., 2008*), joints (*Boileau et al., 2007*), heart (*Ibrahim et al., 2007*), prostate (*Shetty et al., 2007*) and cancer (*Black et al., 2008*). Dogs are generally easy to train for new procedures, but to our knowledge, they have never been trained for imaging in the awake state. Therefore, imaging is carried out on anaesthetised dogs (*Boileau et al., 2007; Ibrahim et al., 2007; Shetty et al., 2007; Carrera et al., 2008*). Dogs must be fasted for 12 hours prior to premedication. A mixture of methadone, diazepam and atropine is useful for premedication of dogs. A catheter is placed in the cephalic vein for induction of anaesthesia and for infusion of test drugs, saline, anaesthetics, tracers and contrast agents. Anaesthesia can be induced and maintained with protocol, but isofluorane can also be used to maintain anaesthesia during imaging studies (*Black et al., 2008*). It is relatively easy to keep dogs anaesthetised for many hours.

Sheep and goats

Sheep and goats are often used in imaging studies of lungs (*Schroeder et al., 2007*), bones (*Stroh et al., 2008*) and fetus (*Ward et al., 2006)*. Because of the large body weight of ruminants, and problems in training them for imaging procedures, they are difficult to handle and to induce the required level of anaesthesia (*Ward et al., 2006*). Sheep and goats must be fasted at least 12 hours prior to anaesthesia to prevent tympani is. Withholding food for more than 12 hours has little effect on the volume of food in the rumen, but may reduce the production of gases and reduce the risk for tympanitis (*Wolfensohn and Lloyd, 2003)*. Sheep and goats can be premedicated with midazolam and ketamine. Atropine must be avoided or only given in small doses, as it renders salivary and bronchial secretions more viscous and harder to clear (*Wolfensohn and Lloyd, 2003*). Often anaesthesia is maintained with propofol or

isofluorane (*Ward et al., 2006*). Sheep and goats must be placed with the left side down, because this enables produced gases to leave the rumen. Catheters can be placed in the jugular vein. If the scannings have to be repeated on several days, a vascular loop or a vascular access port can surgically be put in prior to the imaging study.

Pigs

Pigs are often used in heart (*Chareonthaitawee et al., 2006*), liver (*Sørensen et al., 2008*), brain (*Cumming et al., 2007*), bone (*Foldager et al., 2008*) and lung (*Hong et al., 2005*) studies. In acute studies and short-term survival studies, domestic pigs are very often used, while several types of minipigs are used in long-term surviving studies, because domestic pigs grow too fast for long-term studies. The Göttingen minipig had the advantages of being well-characterized genetically and microbiologically. It is, however, more expensive than most other pigs for research (*Swindle, 2007*). Typically, pigs are fasted 12 hours and premedicated prior to placing an ear vein catheter (*Danielsen et al., 1997*). A mixture of ketamine and midazolam is useful for inducing anaesthesia in pigs (Table 4) (*Danielsen et al., 1997*; *Olsen et al., 2007*). Anaesthesia can also be induced by intravenous injection of propofol or thiopentone (*Wolfensohn and Lloyd, 2003; Swindle 2007*). It is relatively difficult to intubate pigs, so some researchers prefer to place the tube by tracheatomy. However, that procedure is not recommended in survival studies. In the first few hours after induction of anaesthesia, pigs can respirate spontaneously, but it is recommended to artificially ventilate the pigs in long-term studies or if the arterial carbon dioxide and oxygen concentration must be stable as in most brain PET studies (*Olsen et al., 2006*). The anaesthesia can be maintained with either infusion

Table 4. The preparation and anaesthesia of domestic pigs (Danish Landrace x Yorkshire, 40 kg, females) prior, under and after PET scanning at the Aarhus PET Center:

Premedication		10 ml s-ketamine (25 mg/ml) IM
		10 ml midazolam (5 mg/ml) IM
Ear vein catheter		21 G Venflon
Induction of anaesthesia		4-6 ml s-ketamine IV
		10 ml midazolam IV
Intubation		Tubus size 7.0
Maintain	alternative # 1	Propofol (infusion rate depends on reflexes) IV
	alternative # 2	Isoflurane (1.5-2.5 %) in 1 O_2 + 2 N_2O
Catheters		Cortex catheter in femoral artery
		Cortex catheter in femoral vein
		Bladder catheter
Monitoring		Heart Rate / Puls
		Invasive Blood Pressure
		$SatO_2$
		Body temperature
		End tital carbondioxide ($ETCO_2$)
		Blood gases ($PaCO_2$, PaO_2)
		Plasma glucose
		Reflexes
Euthanasia		Pentobarbitone (100 mg/kg) IV

anaesthetics such as propofol or by inhalation anaesthetics such as isofluorane. Bolus injections of neuromuscular-blocking agens are often needed to prevent spontaneous respiration under isoflurourane anaesthesia; however, care must be taken to ensure the pig is under adequate anaesthesia before these agents are used (*Olsen et al., 2007*). Intraveneous access is always needed for PET imaging and also for contrast CT and MRI imaging, and the ear vein can be used for this. Alternatively, catheters can be placed in the jugular or femoral vein. The femoral vein is often used when imaging the porcine brain, because the test drugs, contrast agents and tracers can be injected at a site far from the tomograph, to minimize effects of the procedure on the imaging. Head holders have been designed for pig studies (Figure 2).

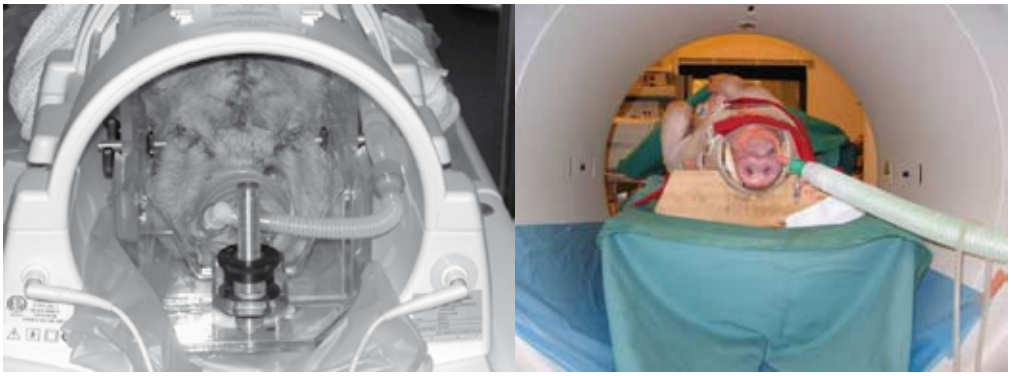

Figure 2. Left: A Göttingen minipig placed in a MRI head holder. The pig is ventilated and kept anaesthetized by use of isofluorane. Note the stereotaxtic frame that gives excact coordinates for the position of the minipig brain. Right: A head holder used for PET scannings of domestic pig brains. The pig is ventilated and kept anaesthetized by isoflurane. Note the dorsal position of the pig - it makes blood sampling from femoral artery more easy.

Nonhuman primates

Imaging of nonhuman primates is mainly performed in drug abuse studies and brain research of aging (*Doudet et al., 2006; Seneca et al., 2007; Liu et al., 2008; Nader and Czoty, 2008*). Imaging is performed in human scanners or in microPET scanners specially built for nonhuman primates (*Machado et al., 2008*). Imaging of primates is very popular, because it is a noninvasive technique and may allow these very expensive animals to survive from study-to-study. There is always a risk that treatments from previous studies can affect the results of ongoing studies, and therefore imaging papers in nonhuman primates often include a section describing the history of the animals. Another risk by using primates is zoonoses (*Wolfensohn and Lloyd, 2003*). However, screening programs for monitoring of primate pathogenes exist, and this may reduce the risk for the staff when handling the animals (*Wolfensohn and Lloyd, 2003*). The primates are most often anaesthetised (*Doudet et al., 2006*), but they can also be trained for imaging while awake (*Blaizot et al., 2000*). In this situation, imaging of nonhuman primates can be performed under conditions that closely resemble those used for imaging of humans. Awake primates are rarely monitored in imaging studies, and this is similar to imaging of humans. When primate imaging is performed under anaesthesia, ketamine is often used for premedication and induction, and isofluorane for maintaining of anaesthesia (*Doudet et al., 2006; Chen et al., 2007; Seneca et al., 2007; Sullivan et al., 2007; Zhang et al., 2007*). Intravenous catheters for anaesthetics, tracers, contrast agents and

saline infusion are often placed in a cephalic vein (*Machado et al., 2008*).

Conclusions

Imaging techniques in large animals bridge the gap between preclinical and clinical research.

It is possible to use the same scanners to image large laboratory animals and humans, and with few modifications the same scanning protocols can also be used. Therefore, knowledge obtained in animal experiments can readily be used in humans. Moreover, medical hypotheses and problems addressed in the human clinic or in human investigations can be tested and studied in imaging studies of large animals. Dogs, sheep, goats, pigs and nonhuman primates have large organs and blood volumes that allow collecting of repeated blood samples. Large animals are outbred, and due to their increased variation, many animals are needed in each study. Imaging studies of large animals are, therefore, expensive and time-consuming. Except for nonhuman primates, large animals must be anaesthetised for scanning, and this may influence results. Careful monitoring of physiological functions in large animals is required during imaging so that appropriate adjustments can be made to assure stable and replicable findings.

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