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*Review Article*

# Imaging the Gastrointestinal Tract of Small Animals

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**Abstract** Animal models of human diseases are increasingly available and are invaluable for studies of organ pathophysiology. Megacolon, abnormal dilatation of the colon not caused by mechanical obstruction, involves the destruction of the autonomic nervous system innervating the colon. Animal models of megacolon include mouse models of Chagas disease and Hirschprung's disease. Small animal imaging has become an important research tool and recent advances in preclinical imaging modalities have enhanced the information content available from longitudinal studies of animal models of human diseases. While numerous applications of imaging technologies have been reported to study the brain and heart of mouse models, fewer studies of the gastrointestinal system have been undertaken due to technical limitations caused by peristaltic and respiratory motion. Various imaging modalities relevant to study of the gastrointestinal tract of intact live animals are reviewed herein.

**Keywords** gastrointestinal tract, small animal imaging, megacolon, MRI, CT, PET, US

## 1 Introduction

Megacolon, abnormal dilatation of the colon not caused by mechanical obstruction, involves the absence (in congenital Hirschprung's disease) or destruction (in Chagas disease caused by infection with the parasite *Trypanosom cruzi*) of ganglion cells. Whereas Hirschprung's disease specifically affects the ganglia in the rectum and colon, Chagas disease can result in the destruction of ganglia throughout the bowel, with some patients exhibiting megaesophagus in addition to megacolon [15,21,23,33]. This destruction of the autonomic nervous system innervation of the bowel in Chagas disease leads to a loss of smooth muscle tone of the bowel wall and subsequent dilation, affecting peristaltic motion that can result in severe constipation, difficulty swallowing, and malnutrition. Animal models of human diseases are increasingly available and are invaluable for studies of organ pathophysiology. Mouse models of Chagas disease have been used extensively by our laboratory for studying both cardiac and gastrointestinal pathology [11,13, 14,19,27,28,31]. Mouse models of Hirschprung's disease have been developed; however, noninvasive imaging studies of those mice have not yet been reported [7,25,36,37].

Small animal imaging has become an important research tool and recent advances in preclinical imaging modalities have enhanced the information content available from longitudinal studies of animal models of human diseases. The use of small animal imaging modalities for phenotyping genetically engineered mice and the imaging of neurogastroenterology in humans have recently been reviewed [3,5]. Fewer studies of the gastrointestinal (GI) system have been undertaken in mice due to technical limitations. Factors confounding the acquisition and interpretation of images of the intestines of mice include excessive motion artefacts due to peristalsis, cardiovascular pulsation, and respiration. There is also a lack of suitable oral contrast agents for delineation of the entire intestinal tract using various imaging modalities. Nonetheless, small animal imaging is attractive, particularly with the potential for multiple modality imaging since the noninvasive nature of the technologies permits longitudinal studies of the same animal over an extended period of time. Furthermore, the development of imaging applications in animal models using magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), optical, and ultrasound (US) methods can quickly move from the basic research arena to the clinical setting. These methods are briefly reviewed below.

## 2 Magnetic resonance imaging

MRI is a noninvasive imaging modality with high resolution ($\sim$50–100 $\mu$m for small animal studies) and excellent soft tissue contrast. MRI can be used to image anatomic structures, blood flow, and diffusion. While magnetic resonance spectroscopy measurements can be used to

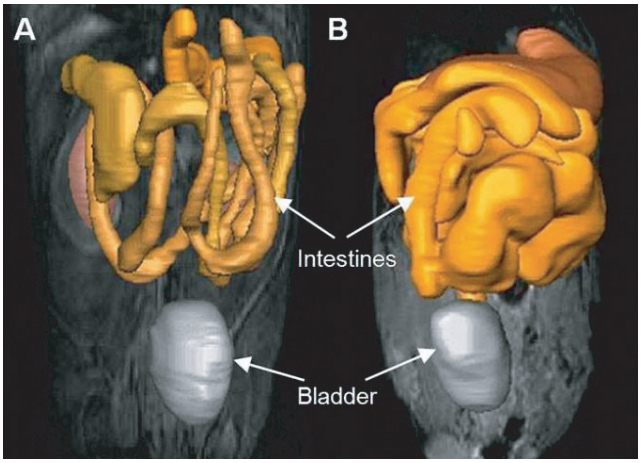


**Figure 1:** MRI images in grey scale with a color overlay indicating the intestines and (in yellow) and the bladder in grey. Panel A shows an uninfected normal mouse and panel B shows an infected mouse. Note the enlargement of the intestine in the infected mouse.

evaluate bioenergetics and measure specific metabolites, it is an insensitive technique requiring submillimolar concentrations of metabolites. However, a number of magnetic resonance methods have been introduced for the study of the GI tract of small animals. These include $^{1}$H and $^{19}$F MRI methods and even electron paramagnetic resonance (EPR) imaging. MRI has emerged as a diagnostic modality for the evaluation of patients with inflammatory bowel disease and contrast-enhanced imaging permits the identification of healthy and inflamed colon tissue in mouse models of human bowel diseases [24]. Real-time MRI has also been applied to measure GI tract motility, recently in patients with Parkinson's disease [34]. Colon wall thickness can also be evaluated. These parameters are useful for the evaluation of therapeutics in longitudinal studies in both research and clinical studies.

Although the megasyndrome as it pertains to the GI tract is a common feature of human *T. cruzi* infection, there had been no detailed description in a mouse model. We recently applied MRI to study the GI tract in a mouse model of *T. cruzi* infection [11,27]. Figure 1 shows the GI tract of an infected mouse with enlarged GI tract (right panel) and the GI tract of a normal mouse (left panel). In that study, we used MRI to monitor intestinal dilatation in *T. cruzi*-infected mice that lacked nitric oxide synthase (NOS) isoforms 1, 2, or 3 in an effort to understand the role of nitric oxide (NO) in progression of GI complications in Chagas disease [27]. We were able to measure average lumen diameters and use average intestine lumen diameter as a parameter to evaluate dilatation. Although both NOS2 and NOS3 levels were elevated in infected wild-type mice, we demonstrated increased lumen diameter, inflammation, and ganglionitis in all infected mice, regardless of the presence or absence of NOS. The study demonstrated the utility of MRI for longitudinal monitoring of intestinal dilation in mice. In the more recent study, we evaluated the effect of selenium supplementation on the degree of intestinal dilatation caused by infection with *T. cruzi* [11]. In that longitudinal study, we found that selenium limited the increase in intestine lumen diameter when administered in the drinking water as sodium selenate or in food as methylselenocysteine.

Confounding factors in imaging the GI tract of mice include the presence of signal from food in the intestines and artefacts caused by peristaltic motion. These factors can make it difficult to accurately delineate polyps and tumors and to measure the intestinal wall thickness. Kiryu et al. recently reported that feeding mice potato (or sweet potato) for 24 h before the MRI session reduced the signal from food and motion artefacts while intestinal cleansing (laxative administration and fasting similar to that used for preparation of patients) was ineffective in reducing artefacts in the mouse [22]. The results suggest that appropriate dietary preparation may be more useful than fasting for evaluation of mouse GI tract images.

A novel MRI imaging method for studying the GI tract employs $^{19}$F MRI and perfluorononane [32]. The $^{19}$F MRI approach is attractive as a selective imaging method since there is no background signal. Perfluorononane is insoluble in water, has low viscosity, and can be administered by gavage. Since the resonance frequency of $^{19}$F is close to that of $^{1}$H, the coils designed to image $^{19}$F can usually detect $^{1}$H as well, thus permitting the selective $^{19}$F imaging of the GI tract and the anatomic $^{1}$H imaging of the entire mouse abdomen.

Electron paramagnetic (EPR) imaging has also introduced as a tool for imaging the GI tract of mice by spatial mapping of spectra. The method of spectral-spatial EPR imaging in combination with a charcoal probe has been used to map oxygenation in the normal mouse intestine, see Figure 2 [18]. In that study, an oxygen gradient from the proximal to the distal GI tract was detected. The method has promise for noninvasive mapping of oxygenation in animal models of disease and possibly for clinical use in humans.

## 3 Ultrasound

Ultrasound (US) has high spatial resolution ($\sim$50 $\mu$m) and contrast in soft tissue. In additional to being portable, US is a fast and economical technique. US has been extensively used for echocardiography studies of small animals. Transabdominal US methods have been used to evaluate the GI tract in patients for several decades, and recent advances in technology and in contrast agent development have improved resolution such that US studies of the GI tract of small animals is possible. Encapsulated gaseous microbubbles targeted to mucosal addressin cellular

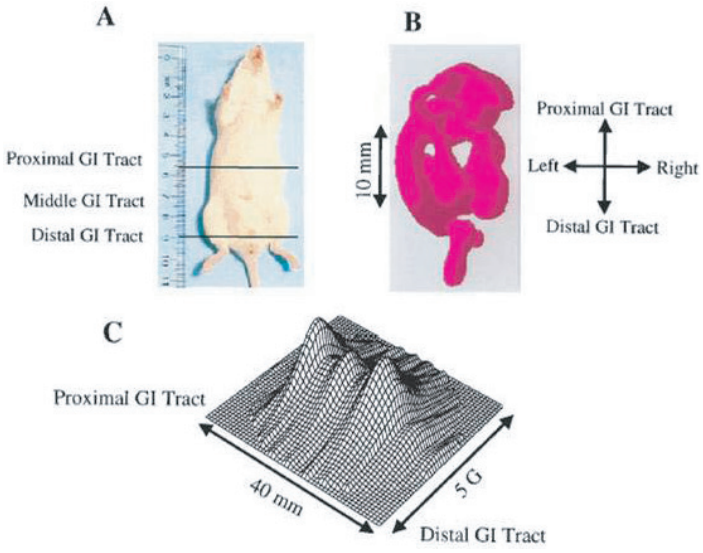


**Figure 2:** Photograph of the mouse studied with demarcation of the region imaged and corresponding 3D spatial and 2D spectral-spatial image data. (A) A photograph of the mouse with a ruler for scale. The area imaged is shown between black lines. The mouse was fed with the charcoal probe for 1 day. (B) Spatial EPR 3D image visualizing the location of the charcoal probe in the GI tract. (C) Spectral-spatial 2D image data along the longitudinal axis from the proximal to the distal GI tract. From G. He, R. A. Shankar, M. Chzhan, A. Samouilov, P. Kuppusamy, and J. L. Zweier, *Noninvasive measurement of anatomic structure and intraluminal oxygenation in the gastrointestinal tract of living mice with spatial and spectral EPR imaging*, Proc Natl Acad Sci USA, 96(1999), pp. 4586–4591. "Copyright (1999) National Academy of Sciences, USA."

adhesion molecule-1 were recently employed to detect and quantify intestinal inflammation in an experimental model of ileitis relevant to inflammatory bowel disease [2]. Such applications provide methods to diagnose and monitor therapeutics in patients.

## 4 Optical coherence tomography

Optical coherence tomography (OCT) is a highly sensitive, minimally invasive, nondestructive imaging technique. It uses backscattered near infrared light to create high-resolution images. The contrast in OCT images is generated by the intrinsic properties of tissue obviating the need for exogenous agents. OCT can be adapted for fiber-based endoscopic applications with relative ease, including miniaturization for small diameter applications, such as in mice. Ultrahigh resolution (UHR) OCT has been used to detect colorectal tumors in mice [17]. OCT can also be combined with other optical techniques such as fluorescence molecular imaging [35]. The combination of the two techniques can permit evaluation of both structural and molecular information simultaneously and holds promise for translation to the clinic where it can be used for diagnosis and for monitoring response to therapeutics.

## 5 Computed tomography

Computed tomography (CT) has been used to monitor human inflammatory bowel disease (IBD) and has also been applied to study malformations of the intestines and colon tumors in mouse models [10,29]. Figure 3 shows the improvement in the CT image with bowel prepping [29]. While microCT is the gold standard for imaging bone in mice, contrast agents are used to enhance soft tissues. CT provides a means to monitor anatomic

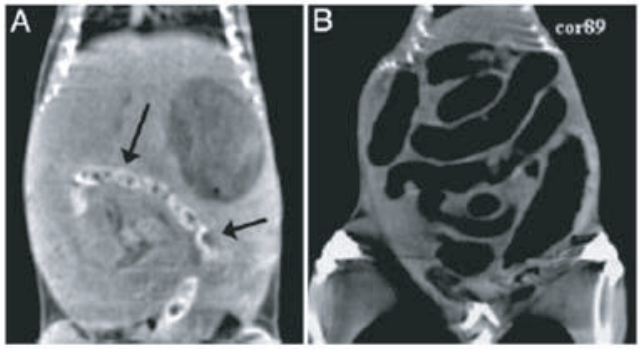


**Figure 3:** Ungated coronal microCT images of normal chow-fed (A) and low-density, bowel-prepped (B) mice. Although fecal pellets (A, arrows) are distinguishable by virtue of their relatively high density, the lumen of the Intestinal tract is much easier to map after low-density bowel preparation (B). From P. J. Pickhardt, R. B. Halberg, A. J. Taylor, B. Y. Durkee, J. Fine, F. T. Lee, Jr., and J. P. Weichert, *Microcomputed tomography colonography for polyp detection in an in vivo mouse tumor model.* Proc Natl Acad Sci USA, 102(2005), pp. 3419–3422. "Copyright (2005) National Academy of Sciences, USA."

structures longitudinally and can be used to monitor colon wall thickness [16]. It is a high-resolution ($> 50\,\mu$M), fast (minutes), X-ray-based technique. Single photon emission computed tomography (SPECT-CT) has also been applied to studies of the GI tract in mice. SPECT-CT utilizes radioisotopes that are used to collect specific physiological information, such as blood flow, or to measure biodistribution of a radiolabeled molecule or cell. The radioisotopes used are typically longer lived than those used for positron emission tomography. Indium-111 (111In) labeled anti-CD4+ antibodies were used in a study of a mouse colitis model and SPECT-CT imaging visualization of the labeled CD4+ cells in the colon. A concern with CT, particularly with longitudinal studies, is the radiation dose, which may be high enough to induce changes in the biological pathways being studied and the need for contrast agents for soft tissue imaging.

## 6 Positron emission tomography

Positron emission tomography (PET) is a highly sensitive (pM) molecular imaging technique that can be used to visualize a variety of in vivo biological processes. The resolution of microPET (1–2 mm) is not as high as CT or MRI but is adequate for small animal imaging. The molecule 2-deoxy-2-[$^{18}$F]fluoro-D-glucose (FDG) is routinely used in the clinical setting for the detection of cancer, based on increased uptake of glucose by malignant cells. It is also a biomarker for inflammation and has been employed in studies of bowel inflammation in humans and in mice [4,26,30]. In addition to $^{18}$F-FDG, other radioisotopes can be employed in microPET studies. Recently, Dearling et al. reported the use of a $^{64}$Cu-labeled anti-b7 integrin antibody to study intestinal inflammation in mice [12]. In the study, mice were imaged at 1, 24, and 48 h postinjection. Higher uptake of $^{64}$Cu was observed in mice with colitis compared with controls suggesting that integrin b7 may be a diagnostic and therapeutic target for the disease. MicroPET can also be used to track radiolabeled cells. Adonai et al. recently reported a study using rat glioma C6 cells and lymphocytes that were labeled ex vivo with $^{18}$F-FDG or $^{64}$Cu-pyruvaldehyde-bis(N4-methylthiosemicarbazone) and tracked in vivo by microPET, see Figure 4 [1]. While not focused on the GI tract, their study demonstrates the potential for labeling cells and tracking inflammation.

We recently acquired MRI, US (echocardiography), and microPET images of the hearts of mice infected with Chagas Disease [31]. In that study, we detected alterations in cardiac glucose uptake using microPET that appeared before morphological and functional changes could be observed by MRI or US, thus the microPET technique should also be valuable for assessing inflammation of the GI tract of mice infected with *T. cruzi*.

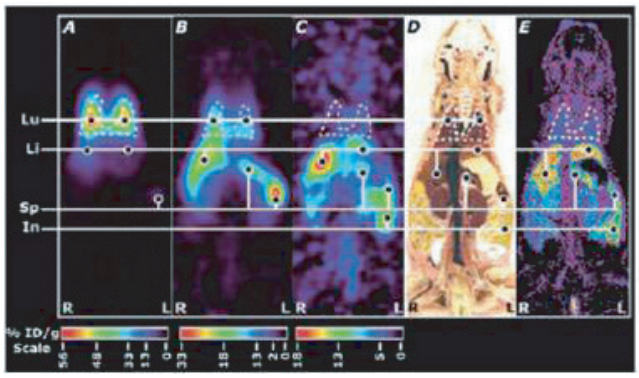


**Figure 4:** In vivo microPET imaging of $^{64}$Cu-PTSM-labeled lymphocytes post i.v. injection into a mouse. The mouse was microPET-scanned 0.12 h (A. 11.2 $\mu$Ci), 3.12 h (B, 9.48 $\mu$Ci), and 18.9 h (C, 4.01 $\mu$Ci) postinjection of lymphocytes. Each microPET image shown here (A–C) is an average of 5–6 coronal slices. After the last microPET scan, this mouse was killed for DWBA (20.7 h). The location of activity In the last microPET image (C) clearly correlates with the DWBA image (E). The photo (D) provides the anatomic map necessary to resolve the source of activity in the microPET image from the DWBA section. Note that splenic lymphocytes initially traffic through lungs (A) and then accumulate in liver and spleen (B and C). The %ID/g scale quantifies the magnitude of signal observed in each microPET image, Lu, lungs; Li, liver; Sp, spleen; In, intestine. From N. Adonai, K. N. Nguyen, J. Walsh, M. Iyer, T. Toyokuni, M. E. Phelps, T. McCarthy, D. W. McCarthy and S. S. Gambhir, *Ex vivo cell labeling with 64Cu-pyruvaldehyde-bis(N4-methylthiosemicarbazone) for imaging cell trafficking in mice with positron-emission tomography.* Proc Natl Acad Sci USA, 99(2002), pp. 3030–3035. "Copyright (2002) National Academy of Sciences, USA."

## 7 Multimodality molecular imaging approaches

The imaging techniques appropriate for study of the GI tract are complementary and advances in nanotechnology and molecular imaging that may be applied in multiple imaging modalities present unique opportunities for combined imaging approaches. For example, coregistration of images from PET with MRI or CT provides complementary information on metabolism and anatomic detail with high spatial resolution. Interpreting microPET images of the intestines of small animals is challenging since it is a large, mobile organ with many turns and overlapping regions. By combining microPET with CT, Brewer et al. were able to improve quantitation of $^{18}$F-FDG uptake in the intestine of the mouse to assess inflammation and immune colitis in mice [4].

Combined PET/CT systems are used clinically, although radiation exposure and limited soft tissue contrast remain limitations. Preclinical small animal imaging systems that combine PET and/or SPECT with CT are also commercially available. PET/MRI systems are currently being designed [6,8,9,20]. These systems would reduce the problems associated with the increased radiation exposure of PET/CT and would provide the excellent soft tissue contrast inherent to

MRI. In addition to the development of hardware, the integration of multiple imaging modalities requires optimization of software tools for coregistration and visualization of the images from multiple modalities. The introduction of new molecular imaging probes that can be targeted to distinct populations of sensory neurons involved in peristalsis would permit the direct observation of nerve cells in the GI tract and further increases the wealth of information available from small animal imaging studies.

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