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MINIREVIEWS

Pancreatic imaging: Current status of clinical practices and small animal studies

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Abstract

Different causative factors acting on the pancreas can result in diseases such as pancreatitis, diabetes and pancreatic tumors. The high incidence and mortality of pancreatic diseases have placed diagnostic imaging in a crucial position in daily clinical practice. In this mini-review article different pancreatic imaging techniques are discussed, from the standard clinical imaging modalities and state of the art clinical magnetic resonance imaging techniques to current situations in pre-clinical pancreatic imaging studies. In particular, the challenges of pre-clinical rodent pancreatic imaging are addressed, with both the image acquisition techniques and the post-processing methods for rodent pancreatic imaging elaborated.

Key words: Pancreatic imaging; Rats; State of the art clinical magnetic resonance imaging; 3.0T scanner; Quantitative magnetic resonance imaging

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Core tip: In this minireview, the challenges of pre-clinical rodent pancreatic imaging are addressed, basic clinical magnetic resonance imaging techniques and post-processing methods for rodent pancreatic imaging are also elaborated.

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INTRODUCTION

The pancreas is an important visceral organ performing both endocrine and exocrine functions. Abnormalities

of the pancreas result in diseases such as pancreatitis, diabetes, and pancreatic tumors[1,2]. The onset of diabetes is usually long after beta cell dysfunction and insulin resistance[3,4]; pancreatic cancer is generally asymptomatic and frequently diagnosed at a late stage[5]; acute pancreatitis is a painful inflammatory condition often with severe complications and high mortality despite treatment[6], while chronic pancreatitis can mimic the symptoms of pancreatic cancer and lead to misdiagnosis[7]. The high incidence of pancreatitis and diabetes, and poor survival rate of pancreatic cancers have increased the demand for new diagnostic and therapeutic strategies[8,9] Herein multimodality multi-parametric imaging plays an indispensable role in disease detection, therapy guidance and patient follow-up. In this mini-review, current situations of common clinical practices and recent development of pre-clinical rodent studies in pancreatic imaging are inspected and discussed with the emphasis on basic magnetic resonance imaging (MRI) techniques and post-processing methods for rodent pancreatic studies.

OVERVIEW OF CLINICAL IMAGING MODALITIES

Ultrasound

As an initial step, abdominal ultrasound is most commonly used in screening for biliary stones and tumors, as this equipment is widely available at relatively low costs[10]. However, the quality of ultrasound images and diagnostic accuracy are highly user-dependent, and the retroperitoneal location of the pancreas may impose image artifacts and hamper the ultrasound diagnosis[11]. For further confirmation and staging of pancreatic diseases, imaging modalities with higher quality and sensitivity are needed.

Computed tomography

Contrast-enhanced multi-detector computed tomography (MDCT) remains the standard modality in clinic for the assessment of pancreatitis and pancreatic cancer[12,13]. Due to its high spatial resolution and fast image acquisition, MDCT combined with contrast agents injection, has shown its powerful capacity in the staging of pancreatitis and pancreatic cancer with high sensitivity and specificity[7,12].

MRI

MRI as a non-ionizing imaging modality has been increasingly utilized in clinic due to its multi-parametric capability[14]. With the constant improvement of the new MRI hardware and imaging reconstruction algorithms, MRI is currently capable of acquiring images of spatial resolution approaching to that of CT. Meanwhile, with the application of accelerated parallel imaging techniques, most MRI protocols have the feasibility to be accomplished in one or a few breath-holds[14,15].

Traditionally, T2-weighted MRI sequences are commonly used to provide structural information on the anatomy of the pancreatic ductal system and lesions[14]. MR cholangiopancreatography (MRCP) using heavily T2-weighted sequences has been widely applied as non-invasive alternative to endoscopic retrograde cholangiopancreatography (ERCP) for biliopancreatic duct system evaluation[16]. The combination of dual-echo (in/opposed-phase) T1-weighted MRI sequences is useful for hemorrhage and fat content assessment[14]. Dynamic contrast-enhanced (DCE) MRI scans are performed for differential diagnosis and grading of solid pancreatic lesions and pancreatitis by analyzing the pharmacokinetic parameters or contrast concentration curves[17,18]. In addition, diffusion-weighted MRI (DWI) protocols have also shown a great potential to depict and characterize pancreatic diseases including acute/chronic pancreatitis and benign or malignant tumors[19] without a need to use contrast agents.

Other more advanced but less popular pancreatic imaging modalities, often with a certain invasiveness or radiation exposure, include endoscopic and contrast enhanced US (EUS and CEUS), positron emission computed tomography and single-photon emission computed tomography incorporated with X-ray based CT (PET/CT and SPECT/CT) for improved spatial resolution and co-localization of imaging findings, *etc*. For a more comprehensive overview, a recent review article about imaging pancreatic diseases is recommended[5].

CURRENT STATUS OF RODENT PANCREATIC IMAGING

Challenges in rodent pancreatic imaging

In order to develop new diagnostic and therapeutic strategies against pancreatic diseases, rodent models are commonly used in preclinical studies. However, imaging the pancreas in rodents proves to be extremely challenging due to motion artifacts and uncertain anatomy. The pancreas in humans represents a retroperitoneal solid organ, which can be identified by imaging modalities even without contrast enhancement, as stated above. However, unlike the human pancreas, the rodent pancreas appears as a soft, diffuse and irregularly lobulated organ, which is very difficult to discern from surrounding tissues[19-22], even during open abdominal surgery (Figure 1). Pancreas-specific contrast agents would facilitate pancreas visualization, but currently those pancreatic specific markers are unavailable yet. Without specific labeling, rodent caudate liver lobes and abdominal fat tissue are frequently identified as pancreas by mistake. In some animal studies, pancreas associated injuries in other solid organs, instead of the pancreas itself, were investigated using contrast-enhanced protocols and MR spectroscopy (MRS)[23,24].

Three dimensional pancreatic imaging

To avoid the misdiagnosis and to have a detailed

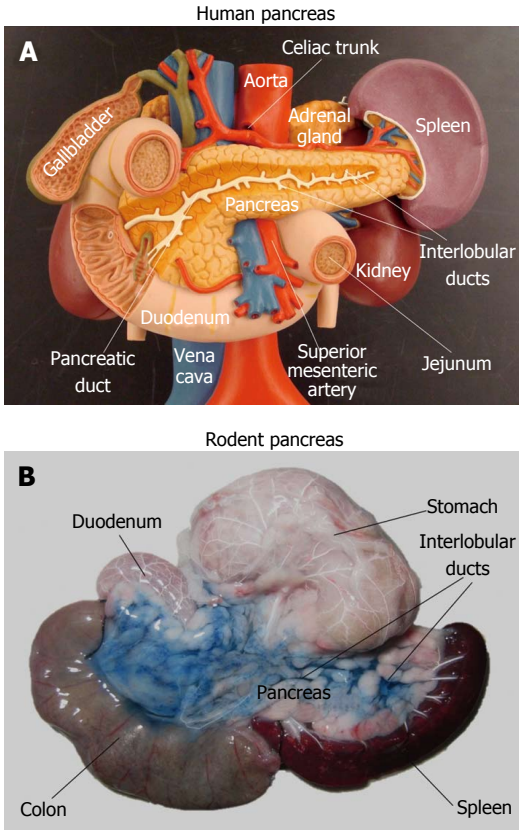

Figure 1 Anatomical difference between human and rodent pancreas. Unlike the human pancreas which is a well-defined solid organ (A), the rat pancreas appears as a soft, diffuse and irregularly lobulated organ (B), which is very difficult to discern from surrounding tissues even at open abdominal surgery. To better visualize it, the pancreatic ductal system was infused with Evans blue dye while the arterial system was injected with a barium sulphate suspension.

overview of the pancreas anatomy, two pancreatic imaging studies were performed using contrast-enhanced high-resolution three dimensional (3D) modalities to provide more precise anatomical information of the rodent pancreas[20,22]. In a micro-CT study[20], the *in vivo* rat pancreatic tail portion could be identified after a two-step contrast injection. Unlike the human pancreas that can be readily depicted by MRI even without using any contrast agent (Figure 2), detailed 3D rodent pancreatic anatomy and surrounding landmarks could only be demonstrated (Figure 2) by biliopancreatic local infusion of mixed contrast media in a post-mortem model[22].

Diabetes imaging

In order to achieve early diagnosis in diabetes, the development of pancreatic specific contrast agents became a hot topic. Among others, some contrast agents were used to target pancreatic beta cells for diabetes related research subjects, for instance, glucagon-like peptide-1 (GLP1) receptor and GLP1 analogues have been frequently studied in rodent diabetes imaging[25,26]. The micro-vascular changes in case of diabetes and pancreatic inflammation were also investigated[27,28].

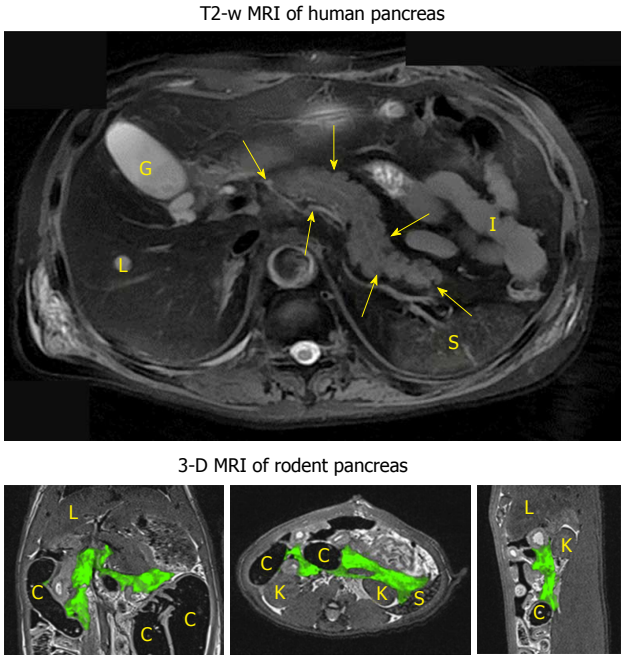

Figure 2 Typical human pancreatic magnetic resonance imaging *vs* rodent pancreatic magnetic resonance imaging. The upper transverse image shows the human pancreas (contoured by arrowheads) as a solid organ adjacent to the liver (L), gallbladder (G), spleen (S), kidney (K) and small intestines (I). The lower 3-D images display the coronal (left), transverse (mid) and sagittal (right) views of the contrast-infused rat pancreas with green color coding, adjacent to the liver (L), spleen (S), kidney (K) and colon (C). MRI: Magnetic resonance imaging.

Pancreatitis imaging

The first attempt of rodent pancreatitis imaging started during the 1980's, conducted by Paajanen *et al*[29], in which Gd-DTPA was applied as a contrast agent for T2/T1 relaxation measurements in an acute hemorrhagic pancreatitis model. In 1989, Kushnir *et al*[30] performed several MRS experiments to identify imaging biomarkers in an acute pancreatitis model. More recently, specific nanoparticles were developed for pancreatitis imaging, with lipase as the target[31]. Imaging of acute edematous pancreatitis can also be performed with MRCP, T2 relaxation measurement and non-specific contrast enhancement using modified protocols on a state of the art clinical MRI scanner[32].

Pancreatic tumor imaging

The direct visualization of rodent pancreas and corresponding pancreatic landmarks could facilitate more precise diagnosis of a pancreatic tumor in the early stages. As a tumor grows to a certain volume, the identification of the solid tumor mass is much easier to perform than imaging other pancreatic disorders. Quantitative T2 and T1 relaxation measurements, DWI parameters and perfusion information can be obtained using multi-parametric MRI[33]. Currently, rodent pancreatic tumor models are increasingly used

to investigate new therapeutic strategies in longitudinal follow-up studies by non-invasive MRI.

RODENT PANCREATIC IMAGING USING A CLINICAL MRI SCANNER

Rationale behind the use of a clinical MRI scanner for rodent pancreatic research

Due to the small size of the rodent pancreas, it is necessary to use high resolution 3D anatomical images for precise pancreas localization. Misdiagnosis could be avoided by carefully tracking the anatomy of the surrounding organs or tissues in 3D mode. Unfortunately, 3D anatomical MRI in the abdominal region is extremely challenging in commonly used high-field pre-clinical scanners, due to their high sensitivity to motion artifacts at high magnetic field and unavoidable long scanning durations. Alternatively, by the combined use of dedicated multi-channel coils and accelerated parallel imaging, clinical MR scanners have shown the feasibility and flexibility for rodent abdominal imaging[22,32,33].

Limits and benefits of clinical scanners

The biggest problem using clinical scanners for small animal studies is the limited gradient strength[34]. Most clinical MRI scanners have a gradient amplitude of 40 mT/m and slew rates up to 200 T/m per second. Although the maximum gradient amplitude in the recent 3T Siemens Prisma scanner has been increased to 80 mT/m, the gradient strengths are still up to 10 times lower than that of the current state of the art pre-clinical scanners. Consequently, the minimum slice thickness and minimal field of view (FOV) in the clinical systems are more restricted. In our studies, to maintain enough signal-to-noise-ratio (SNR), most 2D scans were performed with a slice thickness of 2 mm, which is identical to those acquired from small animal scanners. However, the minimal FOV is usually limited to around 70 mm. The limited gradient strengths also hamper the use of echo planar imaging (EPI) due to the prolonged readout, which leads to severe image distortions.

On the other hand, current state of the art clinical MRI scanners provide an excellent hardware stability, higher field homogeneity and a dedicated user interface, and are more widely accessible compared to small animal scanners. With the combination of dedicated clinical multi-channel surface coils and the self-calibrated parallel imaging techniques GRAPPA (GeneRalized Autocalibrating Partial Parallel Acquisition), it is possible to acquire high SNR images in rodent heterogeneous abdominal region with a sufficiently short scan duration. Moreover, lower magnetic field and application of GRAPPA provide a higher feasibility to rodent abdominal imaging.

Basic clinical MRI techniques for rodent pancreatic imaging

In our serial studies[22,32,33], clinical scanners were used for pancreatic imaging: The Magnetom Tim Trio (Siemens, Erlangen, 45 mT/m, 200 T/m per second) combined with an 8-channel wrist coil; and the Magnetom Prisma (Siemens, Erlangen, 80 mT/m, 200 T/m per second) together with a 16-channel wrist coil. There are several standard clinical protocols which can be directly translated to pre-clinical research, including T2-weighted 3D turbo spin-echo (TSE) based SPACE (3D TSE with variable-flip-angle refocusing RF pulses) imaging and MRCP protocols, standard 2D multi-echo spin-echo sequences for T2 relaxation, as well as diffusion and perfusion sequences. The animal models introduced in these studies[22,32,33] are a rat acute pancreatitis model and a rat orthotopic pancreatic tumor model, in which we intended to characterize pathological changes including edema, hemorrhage and necrosis by those modified MRI methods.

Three-dimensional volumetric images: As mentioned above, 3D imaging would facilitate the localization of rodent pancreas. The other benefit is the possibility of volumetric measurements in 3D. In case of edematous pancreatitis, edema volume is a biomarker for pancreatitis. Meanwhile, 3D views could also provide a more accurate measurement for irregularly shaped abdominal tumors (Figure 2). The volume of the target tissue can be obtained from post-process image segmentation. The most important 3D imaging protocols used here are T2-weighted SPACE and MRCP, which are also widely used in clinical MRI abdominal examinations.

Quantitative MRI measurements: Quantitative MRI relaxation measurements are useful in organ/tissue characterization. T2 mapping is helpful in the assessment of fluid content and hemorrhage; and native T1 mapping is essential for the calculation of the tissue concentration time curve (CTC) in DCE protocols. In these studies, mono-exponential T2 mapping and inversion recovery based T1 mapping were performed.

Measurements of Gaussian and non-Gaussian diffusion for water in biological tissues can be accomplished using DWI with different combinations of diffusion weightings. Mean diffusivity and diffusion kurtosis were obtained from 3-trace diffusion images.

Moreover, tissue perfusion can be characterized using DCE protocols, after the injection of a gadolinium based MRI contrast agent. After the signal conversion to gadolinium concentration using pre-contrast native T1 relaxation information, either semi-quantitative information or quantitative parameters from the pharmacokinetic Tofts model were extracted. Detailed MRI protocol parameters are elaborated in the different serial studies[22,32,33].

Data processing

In these studies, open-source software and in-house built programs were used for data processing. This includes image segmentation, registration and 3D image visualization in open-source software ITK-SNAP (www.itksnap.org) and MeVisLab (MeVis Medical Solutions, Bremen, Germany); DICOM process, MRI mathematical modeling and quantitative analysis in Matlab programs (MathWorks, Natick, Massachusetts); and statistical analysis and data visualization using programs combining both Matlab and R (https://cran.r-project.org). Detailed image processing equations are included in the next section.

SOME OF THE ONGOING RESEARCH IN RODENT PANCREATIC MRI STUDIES

Identified objectives

Present research project aims at providing practical solutions to rodent pancreatic imaging using clinical facilities, from *ex vivo* to noninvasive *in vivo* imaging with the following systematic objectives identified: (1) To overcome the limitations of clinical MRI scanner for small rodent imaging studies; (2) detailed visualization of a complete pancreas and topographic landmarks through contrast enhanced CT and MR imaging in a rat postmortem model; (3) to explore noninvasive MR imaging methods for characterization of the Caerulein induced acute pancreatitis in rats; (4) to estimate the reliability of 3D isotropic MRI and quantitative multi-parametric MRI for characterization of an orthotopic pancreatic head tumor model in rats; and (5) to investigate therapeutic response of a vascular disruption agent in rat pancreatic tumor models with further modified quantitative multi-parametric methods.

Processing for quantitative parameters in rodent pancreatic MRI

MRI quantitative parameters can be obtained from advanced image processing methods using machine learning algorithms[35-37]. For practical considerations, quantitative parameters are re-generated from in-house built Matlab programs using non-linear least square methods with CPU (Central Processing Unit) acceleration.

T2 mapping: Traditionally, the transverse relaxation time T2 is obtained using multi-echo spin-echo pulse sequences, by sampling signals at several different echo-times (TE), and fitted to either multi- or single-exponential decay functions[38]. Fast T2 mapping can be obtained using balanced steady-state free precession (SSFP) readout[39].

T1 mapping: On a clinical scanner, fast T1 mapping can be measured using inversion recovery methods or from variable flip angles experiments[39,40]. Since the MRI acquisition has to be synchronized with animal respiration, the effective repetition time (TR) is usually longer than 1 s. Thus, inversion recovery based protocols would be suggested for T1 mapping in rodent pancreatic imaging. Typically, the equation for measured signal in the inversion recovery T1 mapping experiment is a three-parameter function: $SI_{(t)} = a + b \times \exp(-t/T1^{*})$, where $SI_{(t)}$ is the signal intensity after each inversion time t, and $T1^{*}$ is the effective longitudinal relaxation time. The actual T1 relaxation time can be obtained after correction for the flip angles[41], or the Look-Locker readout[42].

Diffusion-weighted model: In DWI experiments, the simple Gaussian diffusion can be assumed using a mono-exponential model. The two-compartment intravoxel incoherent motion model on the other hand is currently widely used in clinical pancreatitis and pancreatic tumor studies[43,44], and separates diffusion into the true-diffusion and the pseudo-diffusion fraction. Alternatively, sampling with high b-values above 1000 s/mm^2 can be applied for non-Gaussian diffusion estimation using a diffusion kurtosis model[45].

Post-processing for DCE model: The first step in DCE data post-processing is the conversion of the raw MRI signal to the tissue concentration time curve (CTC). The tissue concentration C_t of contrast agent (CA) during the DCE perfusion experiment is solved as: $1/T1_{(t)} = 1/T1_0 + r1 \times C_{t(t)}$, where $T1_0$ is the T1 value before contrast injection, obtained from inversion recovery T1 mapping, and r1 is the longitudinal relativity of the applied CA. In a high temporal resolution DCE experiment, the T1 relaxation $T1_{(t)}$ after CA injection can be converted from the signal intensity (SI) time curve as described previously[33]. Alternatively, CTC information can be directly extracted from the dynamic T1 mapping.

The vascular input function (VIF) C_p is determined by the CA concentration in blood C_b: $C_p = C_b/(1 - Hct)$, which is obtained from CTC of the aorta or a major vein, and the hematocrit level Hct which is set to 42% in our studies. VIF is usually fitted into a bi-exponential function for further kinetic modeling. Perfusion indices, the transfer coefficient *Ktrans* and the rate constant *kep*, can be obtained from the standard or the modified Tofts model[46]. In practice, the discrete convolution can be constructed as a matrix multiplication. The fraction volume *ve* of extravascular extracellular space is calculated as: ve = Ktrans/kep.

CONCLUSION

The diagnosis of pancreatic diseases and their management have been largely facilitated by ever advancing multimodal and multi-parametric imaging technologies in clinical settings. Likewise, thanks to the above-mentioned efforts, preclinical research on rodent models of pancreatic pathologies are also rapidly progressing in terms of visual identification

of rodent pancreas on 2D and 3D images, imaging characterization of common pancreatic disorders such as pancreatitis and pancreatic malignancies, and noninvasive imaging follow-up of investigative therapies for new drug development. Eventually clinical practices in patients suffering from those often deadly diseases on this complex visceral organ of pancreas will benefit from all these translational studies.

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