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Original paper

In vivo quantification of renal function in mice using clinical gamma cameras

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ABSTRACT

Introduction: In preclinical research, the growing number of transgenic models has led to the need for renal-function studies in mice. Many efforts have been made to develop dedicated SPECT systems for rodents, but their availability is limited due to high capital costs. The aim of this work is to demonstrate the feasibility of mouse renal imaging by using an inexpensive alternative based on clinical gamma-cameras.

Methods: A healthy mouse was scanned 3 h after injection of 6 mCi of Dimercaptosuccinic acid (DMSA) labeled with 99mTc by using a single-head gamma-camera in conjunction with a dedicated pinhole collimator. List-mode data were binned to emulate multiple injections of 1 mCi, 0.1 mCi and 0.01 mCi of 99mTc-DMSA and 6-min ventral and dorsal planar images were acquired and SPECT imaging (60 projection images acquired over 60 min) was performed. An optimization of the protocols in terms of injected activity, time scan, renal cortex uniformity and cortex-to-pelvis contrast was carried out.

Results: The appropriate protocols were an injected activity of 0.6 mCi, combined with duration of scanning of 1 min for planar and 60 min for SPECT imaging. Our results were validated through the relative quantification of renal function, which showed that both kidneys contributed equally to the total function. They showed that functional structures of the mouse kidneys can be visually distinguished as easily as in human studies.

Conclusions: Our findings showed the feasibility of conducting quantitative DMSA SPECT studies of anesthetized mice on clinical gamma cameras.

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Introduction

Dimercaptosuccinic acid (DMSA) labeled with 99mTc is a major renal cortical imaging agent used in the diagnosis of renal parenchymal disorders and the evaluation of renal function, based on its capacity to provide functional imaging of the proximal renal tubular mass [1,2]. This agent is taken up by the renal tubular cells and then accumulated in the renal cortex. After 6 h, approximately half of the administered activity will end up in the tubular cells and excellent visualization of the renal cortex is obtained with the background activity having largely cleared. In clinical practice, DMSA scintigraphy is the technique of choice for estimating renal function and to visually assess cortical integrity of the kidneys [3]. For example, it is an excellent imaging tool for the detection of renal cortical lesions. Nevertheless, due to limitations such as the distribution of background counts, DMSA SPECT imaging has been reported as a more appropriate tool for the renal uptake quantification [4].

In preclinical research, many DMSA studies have been performed in different animal models to investigate human renal disorders. Although these studies were initially performed in

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medium-sized animals, the growing number of transgenic mouse models has led to the need for functional imaging studies also in mice. The major drawback of these studies in animals as small as mice is the spatial resolution required to detect small structures. In last decade, a number of SPECT systems for rodents have been developed, and nowadays several such scanners are commercially available [5–7]. It is expected that, as in other research areas, dedicated SPECT scanners can be highly beneficial in research with mice models of renal diseases. At present, the use of dedicated SPECT scanners for imaging rodents has been spread to many research centers. Although dedicated small-animal SPECT scanners may be available in large academic research centers, their high cost is prohibitive for more widespread installations in hospitals and smaller research facilities.

An inexpensive alternative to dedicated small-animal systems is the use of a clinical gamma camera, and many such studies of DMSA in animals have been reported [8–12]. Nevertheless, they so far have been limited to medium-sized animals, such as rabbits, due to the relatively coarse spatial resolution of clinical gamma cameras, which prevents clear visualization of renal cortex of mouse kidneys. Some technical solutions have been proposed to circumvent the poor spatial resolution, such as to keep static the gamma-camera and rotate the animal [13] or using triple-head scanners [14], thus minimizing the mechanical misalignments. It has been also demonstrated that the use of high-performance tomographic reconstruction can lead to higher resolution images [15]. In recent years, some DMSA imaging studies in mice were performed by using clinical gamma cameras [16,17], but these have been limited to planar studies. The feasibility of using clinical gamma cameras for SPECT-based investigation of mouse kidneys is still unclear and more data are required.

The aim of this work is the in vivo quantification assessment of the proximal tube renal function in anesthetized mice using DMSA SPECT imaging. Specifically, our objective was to perform a high-resolution DMSA imaging study of mouse kidneys on a clinical gamma camera with a dedicated pinhole collimator (as proposed and described in an earlier work [18]), mechanical pre-calibration, high-performance reconstruction methods, and optimization of the injected activity, scan time and reconstruction parameters.

Material and methods

Clinical gamma-camera and dedicated pinhole collimator

We investigated the feasibility of conducting small animal SPECT studies using a single head Siemens Orbiter gamma-camera (*Siemens Medical Solutions*, *USA*, *Inc*). This gamma-camera is a general-purpose scintillation camera with a circular 39 cm diameter NaI(Tl) crystal coupled to 37 photomultiplier tubes.

Data were acquired in list-mode format keeping static the gamma-camera by using a portable device containing an animal holder, a motorized positioning system with a rotation stage and a dedicated pinhole collimator [18,19]. The collimator is a single pinhole of 2-mm diameter with an opening angle of 60°, made of a stack of five 1-mm thick tungsten sheets. Tomographic projections are acquired by rotating the animal with the rotation stage, by using a focal length of 33 cm, radius of rotation of 34.5 cm (aperture-to-object distance of 1.5 cm), and diameter of the field of view of 3 cm.

Acquisition

a) *DMSA planar study:* A healthy mouse was scanned 3 h after injection of 1 mCi of 99mTc-DMSA in the tail vein. Two planar opposed (ventral and dorsal) 6-min images were acquired. Planar images were generated from list-mode data by binning all acquired data (100%) and using only 10% and 1% of the detected counts, thus emulating injected activities of 1 mCi, 0.1 mCi and 0.01 mCi, respectively. Mouse was anesthetized with ketamine (100 mg/kg).

b) *DMSA SPECT study:* A healthy mouse was scanned 3 h after injection of 6 mCi of 99mTc-DMSA in the tail vein. With the kidney region centered in the field of view, 60 projections images were acquired over 60 min (i.e., at 1 min per projection image). List-mode data were binned into the sinograms by using all of the acquired data (100%) and using only 50%, 17%, 10%, 5% and 1% of the detected counts. This allows us to emulate injected activities of 6 mCi, 3 mCi, 1 mCi, 0.6 mCi, 0.3 mCi and 0.06 mCi, respectively. Mouse was anesthetized with ketamine (100 mg/kg).

High-performance reconstruction

a) *Mechanical pre-calibration:* A mechanical calibration was performed to estimate acquisition parameters such as focal distance, shifts between the center of the image and the center of the projections, radius of rotation, mechanical offset (displacement of the camera axis with respect to the rotation axis) and detector tilt and twist angles [20]. This calibration was performed using a three-point phantom filled with 99mTc, with a total activity of 0.5 mCi.

b) *High-performance reconstruction algorithm:* Data were reconstructed using an iterative algorithm based on the Ordered Subsets Expectation Maximization algorithm and a pre-computed system response matrix. This reconstruction algorithm was previously validated and adapted to our system [21].

Injected activity optimization

The injected activity (or alternatively the scan time) is a key parameter in order to study the feasibility of using clinical gamma cameras for renal studies with mice. In human DMSA studies the injected activities can range between 4 mCi and 10 mCi. For pre-clinical imaging in mice, the injected activity has to be significantly reduced, preferably below 1 mCi, to at least approach a comparable body mass-normalized activity. To this end, both planar and SPECT DMSA reconstructed images were visually and quantitatively evaluated in order to find an optimal injected activity with the lowest activity which maintains image quality in terms of different quantitative parameters.

Reconstruction optimization

For iterative reconstruction algorithms, it is well-known that the image noise increases with the number of iterations. It is considered as an undesired effect of convergence, because the image contrast also increases with the number of iterations and therefore the optimal number of iterations depends on the statistics of the data, and should be estimated for each study. To this end, list-mode data from DMSA acquisitions were reconstructed by using 1-16 iterations in order to obtain the signal-to-noise ratio (SNR) and the image contrast for each number of iteration. The SNR was estimated in a region of interest (ROI) placed in the renal cortex. It is obtained as ratio between the mean value (signal) and the standard deviation (noise) on the ROI. The contrast was defined as the ratio between the mean value on the renal cortex ROI and the mean value on other ROI placed in the renal pelvis.

Quantitative renal function

The renal function can be expressed in terms of a semi-quantitative parameter called differential renal function (DRF). It is defined as the relative contribution of each kidney to the total function. It is commonly accepted that the normal range for DRF is

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