CEREBRAL PERFUSION IMAGING OF LIVE MICE BY FLUORESCENT X-RAY CT

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Abstract—Fluorescent X-ray CT (FXCT), which has high-contrast and high-spatial resolution, is being developed for in-vivo biomedical research. Since FXCT could depict the specific heavy atomic number elements in the order of picogram, the functional imaging resembling to single photon emission CT can be obtained. We have applied this technique for in-vivo and ex-vivo biomedical imaging. FXCT system consists of a silicon (111) double crystal monochromator, an x-ray slit system, a scanning table for object positioning, fluorescent x-ray detectors, and pin-diode detectors. Using non-radioactive iodine labeled IMP, cerebral perfusion of a live mouse was clearly demonstrated at a 1 mm spatial resolution and a 0.1 mm slice thickness. In addition, the structure of extracted mouse brain fixed by formalin was depicted much clearly at 0.5 mm spatial resolution due to the availability of long data acquisition time. Thus, the success of in-vivo FXCT imaging with high resolution allows starting to new approach of bio-imaging research.

Keywords—Fluorescent X-ray CT, Synchrotron Radiation, In-vivo imaging, Mouse, Cerebral perfusion, cerebral blood flow

I. INTRODUCTION

In current basic in-vivo biomedical research, functional imaging techniques such as micro positron emission tomography (µPET) and micro single photon emission CT (µSPECT), are important tools to investigate the cause, diagnosis and therapy of disease. However, these techniques essentially require radionuclide agent for imaging, and the spatial resolution is limited to 1 mm in PET and 0.5 mm in µSPECT [1, 2]. Thus, the innovation of the new imaging techniques with high-contrast and high-spatial resolution is required for functional imaging.

Fluorescent x-ray technique with planar mode is one of the most sensitive techniques for detecting the trace elements of medium or large atomic number, however the specimen must be cut into thin slices and be scanned with a beam perpendicular to its surface [3]. Fluorescent x-ray CT (FXCT) that can reveal the cross-sectional distribution of specific elements in biomedical objects, was theoretically considered by Hogan [4], and was developed to detect the iodine within a phantom by us [5]. In the first ex-vivo biomedical application, FXCT depicted the endogenous iodine distribution within thyroid gland at the spatial resolution of 1 mm [6, 7]. Micro FXCT at the spatial resolution of less than 0.2 mm could image the thyroid gland [8, 9] and rat myocardium labeled with non-radioactive iodine BMIPP [10, 11]. In European Synchrotron Radiation Facility or Hamburg Acceleration Synchrotron Laboratory, super-micro FXCT imaging of plants and phantoms was performed at less than 0.01 mm spatial resolution [12, 13].

Since the FXCT technique can be capable to combine the sensitivity of fluorescence x-ray technique and the cross-sectional description of CT [14-16], we examine the feasibility of this technique for in-vivo functional imaging. Firstly the feasibility of FXCT was examined by preliminary phantom experiment [17], and FXCT system with short data acquisition was constructed [18]. Using this FXCT system, cerebral perfusion imaging of a live mouse was succeeded after the injection of non-radioactive iodine labeled cerebral perfusion agent. Here, we describe the in-vivo FXCT imaging and related experimental results.
II. METHODS AND MATERIALS

A. Fluorescent x-ray CT system

FXCT system consists of a silicon (111) double crystal monochromator, an x-ray slit system, a scanning table for object positioning, two fluorescent x-ray detectors with their x-ray collimator, and a pin-diode detectors for incident x-ray and transmission x-ray data (Fig.1). Fluorescent x-rays were detected in a high purity germanium (HPGe) detector [18]. To reduce the scattered radiation, HPGe detector was positioned perpendicular to the incident monochromatic x-ray beam. The distance between the object and the detector was 90 mm. The experiment was carried out at the bending-magnet beam line BLNE-5A of the Tristan accumulation ring (6.5 GeV, 30-55 mA) in Tsukuba, Japan.

B. Fluorescent x-ray CT imaging

Monochromatic x-ray energy was set 37 keV, and the photon flux in front of the object was about 10^8 photons/mm^2/s at beam current of 40 mA. For the live objects, the incident monochromatic x-ray was collimated into a 1 x 0.1 mm^2 pencil beam, and the object was scanned in 1-mm translation and 6-degree rotation over the range of 180 degrees. For the pathological specimens fixed by formalin, collimation was changed to a 0.5 x 0.2 mm^2, and the object was scanned in 0.5-mm translation and 3-degree rotation, respectively. The data acquisition time of the HPGe detector was set 5 sec for each scanning step.

The net counts under the characteristic fluorescent Kα spectral line at each projection were used to reconstruct a FXCT image. The x-ray fluorescent data were corrected for the attenuation of the incident beam and the emitted fluorescent x-ray in the object, using the attenuation information from the absorption x-ray CT image. Finally, the FXCT image was reconstructed by the modified algebraic reconstruction algorithm including the attenuation process [19].

C. Observation targets

Under the anesthesia, the brain of a mouse was imaged by FXCT after the injection of non-radioactive iodine labeled I-127 IMP (N-isopropyl-p-[127I] iodoamphetamine). After then, the excised brain of the mouse was also imaged at high spatial resolution. In addition, the 20 mm in diameter acrylic phantom filled with various concentration of iodine solution was imaged to determine the absolute iodine content within the brain. The present experiment was approved by the Medical Committee for the Use of Animals in Research of the University of Tsukuba.

III. RESULTS AND DISCUSSIONS

A. FXCT image of phantom filled with iodine

To obtain the calibration data of iodine content, 20 mm in-diameter phantom filled with various concentration of iodine was imaged by FXCT at a 1 mm in-plane spatial resolution and a 0.1 mm slice thickness. Iodine in phantom was clearly demonstrated. Since the excellent linear correlation was observed from 0.003 mg/ml to 1 mg/ml between the fluorescent x-ray counts and the iodine concentration (r=0.99), so the method is capable to determine the absolute contents of iodine in tissue from the fluorescent Kα counts.

B. FXCT image of a mouse brain fixed by formalin

The cerebral perfusion in gray matter and basal ganglion of cerebrum, and cerebellum fixed by formalin, which mapped to the degree of I-127 IMP uptake, was clearly shown at a 0.5 mm spatial resolution and a 0.2 mm slice thickness by FXCT image (Fig.2). Its image quality is quite similar to that of autoradiogram with radionuclide agents. The content of iodine in brain was estimated to be about 0.01 mg/g.
C. Fluorescent x-ray CT image of cerebral perfusion in a live mouse

I-127 IMP in the brain of a live mouse was clearly imaged for the first time in the world by FXCT with a 1 mm spatial resolution and a 0.1 mm slice thickness (Fig. 3). I-127 IMP was accumulated in cerebrum, and reduced perfusion was observed at left cortical gray matter. Voxel resolution of this image was 0.1 mm³. The poor spatial resolution of 1 mm was caused by limited data acquisition time of live mouse under the anesthesia. In our present FXCT system, the data acquisition time still required long time about 2 hours and was inadequate the practice in-vivo biomedical imaging. Therefore, we are improving the mechanical scanning system (50% faster by optimized scanning method) and HPGe detector with higher counts rate capability.

IV. CONCLUSION

In-vivo cerebral perfusion images of mouse have succeeded for the first time by FXCT. Further improvement of imaging system with high-speed data acquisition and much higher spatial resolution will promise us new biological information.

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