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Review Article

Applications of Micro-CT in Imaging Heart Diseases of the Murine Models

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Abstract

Objective: This non-systematic review discusses the feasibility and advancements on the application of micro-Computed Tomography (micro-CT) in the experimental scope of murine cardiac models.

Methods: Medline and Elsevier were searched for inclusion of relevant studies. A total of 69 articles were downloaded by using 'micro-CT', 'murine', and 'heart' as the keywords including synonyms like 'mouse', 'rat', 'rodent', and 47 of them were retained after review. No limitations in time were considered.

Results: The major application of micro-CT in murine heart research included the following disease models: Atherosclerosis (AS), Myocardial Infarction (MI), Coronary Artery Disease (CAD), Congenital Heart Defects (CHD) and Ischemia/Reperfusion (I/R). Experimental advancements in recent years of micro-CT are listed, while limitations and challenges of micro-CT are briefly discussed. Future trends of the imaging technology are also mentioned in the following part.

Conclusion: A number of years of preclinical practices have proven the feasibility and efficacy of micro-CT. However, new studies based on multimodality are still in demand to help strengthen our understanding of the mechanisms that give rise to the progression of cardiac diseases.

Keywords: Micro-CT; Small animal modeling; *In vivo*; *Ex vivo*; Heart disease

Abbreviations

Micro-CT: Micro-Computed Tomography; AS: Atherosclerosis; MI: Myocardial Infarction; CAD: Coronary Artery Disease; CHD: Congenital Heart Defects; I/R: Ischemia/Reperfusion; CNT: Carbon Nano Tube; Micro-CTA: Micro-Computed Tomography Angiography; DM: Diabetes Mellitus; ApoE: ApolipoproteinE; LF: Left Ventricle; CO: Cardiac Output; SV: Stroke Volume; MRI: Magnetic Resonance Imaging; DOB: Dobutamine; Micro-PET: Micro Positron Emission Tomography; Micro-SPECT: Micro Single-Photon Emission Computed Tomography.

Introduction

Over the past 20 years, technical advances in picture acquisition and imaging capabilities have vastly increased the quality and quantity of anatomical and physiopathologic data. Micro-Computed tomography (Micro-CT) is a relatively new modality that rapidly improves high spatial resolution imaging of subtle structures. Due to its high density resolution, relatively low cost and scanning efficiency, micro-CT imaging has been improved over the last decades and has shown its utility in many preclinical practices. Micro-CT, suitable for either *ex vivo* or *in vivo* imaging, has evolved from custom-made to commercially available scanner. The purpose of this paper is to provide an overview of applications of micro-CT on murine models with a focus on the diagnostic accuracy and preclinical value in heart disease. Experimental advancements in recent years of micro-CT are listed, while limitations and challenges of micro-CT are briefly discussed. Future trends of the imaging technology are also mentioned in the following section.

CT imaging in clinical use

CT scanner has rapidly evolved from single slice to multi-slice which started from 4-slice systems in 1998 to the latest 256-slice and even 320-slice CT systems [1]. Becker H-C [2] from reviewing the literature and clinical results concluded that cardiac CT could accurately diagnose heart disease or other sources of chest pain, markedly decrease health care expenditure, and reliably predict clinical outcomes with appropriate patient selection.

Cardiac imaging with coronary CT angiography provide indications about: (1) evaluation of coronary arteries for atherosclerosis or anomalies; (2) evaluation of noncoronary pathology including the great vessels, chambers, myocardium, valves, or pericardium; (3) evaluation of cardiac chamber function, including ejection fraction and chamber volumes; (4) evaluation of low-to-intermediate risk symptomatic patients presenting with symptoms of stable angina or acute chest pain; and (5) discordant or inconclusive stress tests [3]. In a recent study [4], it was reported that the sensitivity and specificity of 320-slice Computed Tomography Angiography (CTA) were 100% and 87% to detect significant Coronary Artery Disease (CAD) in patients with acute chest pain in the Emergency Department.

For the cardiac surgeons, the main benefits of Multi-Detector-Row CT (MDCT) lie in the combination of large scan-volume coverage, high spatial resolution, decent identification of calcifications, and the record other thoracic structures simultaneously. Preoperative applications may include the assessment of heart valves, noninvasive

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Table 1: The checklist of applications of cardiac micro-CT in murine.

Authors	Publication Year	Animal Models	Objective	Contrast Agents	Type
Detombe S A, et al [22]	2008	MI mice model	Cardiac Function	Fenestra VC(ART, Qc, Canada	*in Vivo*
Martinez H G, et al [17]	2009	ApoE Knockout mouse	Atherosclerotic plagues	without	*ex vivo*
Sebastian J, et al [19]	2010	C57BL/6 mice	Cerebral, thoracic and abdominal vasculature	Imeron300(INN,Latin) and Fenestra VC	*in Vivo*
Badea C T, et al [25]	2011	DOB-induced cardiac stress rats	Cardiac Function	liposomal-based blood pool contrast agent	*in Vivo*
Pai V M, et al [18]	2012	CAD mouse model	coronary artery wall and lipid deposition	OsO_4	*ex vivo*
Detombe S A, et al [47]	2012	C57BL6/ and BALB/c mice	enhancement-time curves of different tissues	eXIA160(Binitio Biomedical, Ottawa, Canada)	*in vivo*
Sangaralingham S, et al [20]	2012	Fisher rats	myocardial volume of intramyocardial and epicardial vessels	microfil(Ladd Research, Williston,USA)	*ex vivo*
Vandoorne K, et al [23]	2013	MI mouse model	cardiac function and angiogenesis	microfil MV120	*ex vivo*
Detombe S A [47]	2013	C57BL/6 mice	lung volume, lung density, left ventricular volume and ejection fraction	without	*ex vivo*
Kim A J, et al [21]	2013	CHD mouse model	identifying a wide spectrum of CHD	iodine contrast-enhanced agents	*in vivo*
Wait J M, et al [15]	2013	ApoE-null mice	calcification volume and plaque areas	without	*in vivo*
Le Quang K, et l [16]	2014	a mouse model of combined dyslipidemia and type 2 diabetes mellitus	calcification in the aortic valves	without	*in vivo*
Lee C L, et al [13]	2014	mice after partial-heart irradiation	permeability of myocardial vessels and cardiac physiology indexes	AuNp	*in vivo*
Burk L M, et al [24]	2015	I/R mice model	delayed contrast enhancement in the LV wall and cardiac function Omnipaque	300(GE Healthcare, Cork, Ireland) and Fenestra VC	*in vivo*

MI: Myocardial Infarction; apoE: ApolipoproteinE; DOB: Dobutamine; CAD: Coronary Artery Disease; CHD: Congenital Heart Defects; I/R: Ischemia Reperfusion

evaluation of large thoracic vessels, staging of cardiac tumors, and programming of minimally invasive surgical procedures. After surgery, MDCT examinations particularly facilitate an early identification of severe postoperative complications [5]. MDCT may also be used to assess coronary artery bypass graft patency and to detect transplant-related complications in heart transplant recipients at an early stage. For instance, CT is the modality of choice in patients with aortic stenosis arranged for planning of aortic valve implantation. A multicenter trial of 1038 European patients enrolled at 32 centers (SOURCE-registry) showed overall survival of 76.1% after one year [6,7]. A two-year follow-up of patients in the placement of aortic transcatheter valves (PARTNER) trial supported it as an alternative to surgery in high risk patients with the death rate of 33.9% [8].

Applications of micro-CT in murine heart

Apart from integrative murine modeling of normal physiological function, micro-CT has been successfully used for detecting diseases of bone fracture [9,10], lung fibrosis [11], nonalcoholic fatty liver disease [12] and cardiac injury [13], and understanding mechanisms of pathological conditions. This paper summarized the applications of micro-CT in murine with a focus on the heart. Calcifications, atherosclerosis plagues, shape of vessel and cardiac structure were detected with or without contrast material. Cardiac functional metrics can be computed by 4D cardiac micro-CT data sets. All of the concerned articles were listed in (Table 1) chronologically.

Calcifications

Because of its enchanting characteristics such as fast switching, electronic programmability, distributed source, and multiplexing, Carbon Nano Tube (CNT) based field emission x-ray source technology has newly been investigated for diagnostic imaging applications. The feasibility for prospective-gated cardiac micro-CT imaging of free-breathing mice under their natural position was demonstrated [14]. Calcification volume and plaque areas were measured using CNT-based x-ray source in the aortic arch of ApolipoproteinE (ApoE)–null mice [15]. Last year, calcification in the aortic valves was detected in a mouse model of combined dyslipidemia and type 2 Diabetes Mellitus (DM) [16]. It demonstrated that the dysmetabolic state of type 2 DM impelled early mineralization of the aortic valve and calcified aortic valve disease pathogenesis.

Atherosclerosis plagues

When stained with a pre-commercial staining solution, excised hearts from an apoE knockout mouse showed atherosclerotic plaques in the aortic leaflet and ascending aorta [17]. Furthermore, freely available software tools exist for the visualization of natural edge boundary features of 3-dimensional tissues as well as volume quantification of atherosclerotic lesions at multiple foci to microliter accuracy. Vinay M Pai et al [18]. Demonstrated that a combination of OsO_4 (osmium tetroxide) and micro-CT permitted the visualization of the coronary artery wall in intact apoE knockout mouse hearts. Additionally, since OsO_4 preferentially attaches to lipids, it highlighted lipid deposition in the artery wall. This imaging protocol could potentially be a very useful implement for detecting plaques in the coronary arteries of mouse Coronary Artery Disease (CAD) models.

Morphology of vessels and heart chambers

Schambach and coworkers described a protocol for *in vivo* micro-CTA (micro-computed tomography angiography) in mice using both a bolus technique with a conventional contrast agent, Imeron 300 (INN, Latin) and angiography with a blood-pool contrast agent,

Table 2: Comparison between micro-CT and other imaging modalities.

	Advantages	Disadvantages
Ultrasound	measure the size of organ, volume and blood flow velocities	Inexpensive
	repeatedly and dynamically inexpensive without radiation	low specificity
Micro-PET	high sensitivity	low signal to noise ratio
	high specificity	expensive
	security guaranteed	low spatial resolution contrast agents needed
Micro-SPECT	simultaneous anatomic	low accuracy and resolution
	functional	low contrast to noise ratio
	molecular imaging	contrast agents needed
MRI	no radioactive damage	long acquisition time
	multi-parameter imaging and high contrast to noise	more costly
	ratio and signal to noise ratio	Technically complicated
Micro-CT	high spatial resolution high density resolution time-saving cost-effective	effect of radiation

Fenestra VC (ART, QC, Canada). The contrasts of vascular structures of brain, thorax and abdomen with these two agents were compared. From this initial experiment we learned, that using a blood-pool contrast agent the vessels were well detected [19].

To figure up the myocardial volume of intramyocardial and epicardial vessels, the isolated microfilm (Ladd Research, Williston, USA) injected into the rat hearts were harvested and prepared for scanning on a high resolution, volumetric custom build micro-CT scanner. Fischer rats of different ages separated into two groups underwent cardiac micro-CT imaging as well as echocardiography, blood pressure and fibrosis analysis. The results illustrated the reduction in normalized intramyocardial vessel volume of the aged hearts, in association with increased epicardial vessel volume, in the setting of increased Left Ventricle (LV) fibrosis and mild LV dysfunction [20].

Kim A J et al. [21] investigated the efficacy of micro-CT to screen Congenital Heart Defects (CHD) in stillborn/fetal mice. Analysis of 2105 fetal/newborn mice by iodine contrast-enhanced micro-CT showed this imaging modality was highly effective in identifying a wide spectrum of CHD. Overall, they observed an accuracy of 89.8% for diagnosing ventricular septal defects. Outflow tract anomalies were diagnosed with 97.4% accuracy. Accuracy of detecting aortic arch anomalies was 99.6%.

Cardiac function

Nowadays, global cardiac functional metrics such as Cardiac Output (CO), Stroke Volume (SV), ejection fraction, and myocardial mass as well as dynamic metrics such as wall motion can be computed by 4D cardiac micro-CT data sets.

Equipped with retrospective gating, cardiac function in sham and the infracted mice could be evaluated longitudinally. Significant differences in the systolic volumes, diastolic volumes and EF, between the sham and the Myocardial Infarction (MI) groups were detected [22].

Similarly, excised hearts filling with microfil MV120, a radio-opaque silicone rubber, in the cardiac arteries were used to investigate

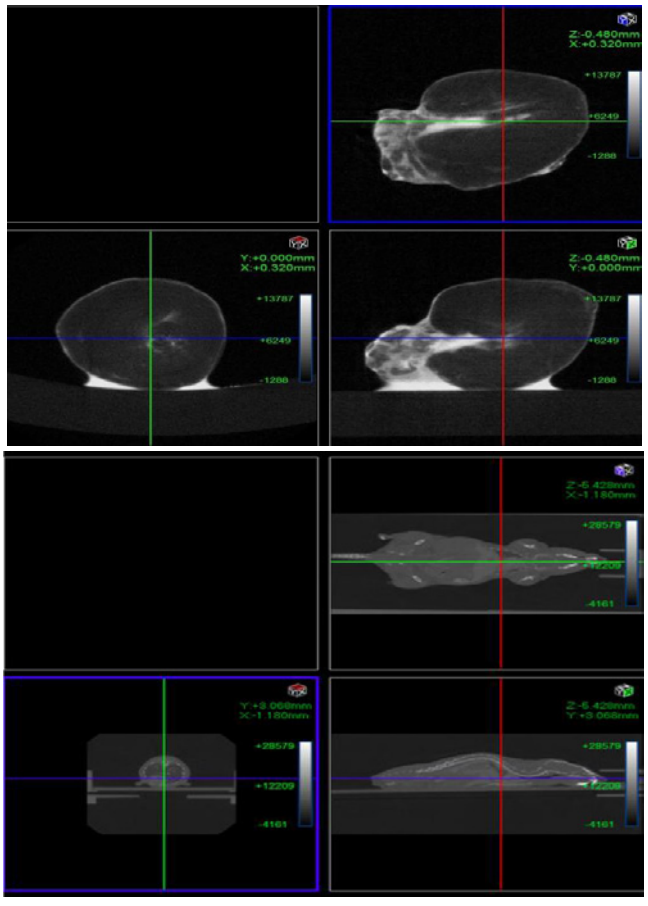

Figure 1: 3D CT imaging of mouse heart, the upper one *ex vivo*, the lower one *in vivo*.

the impact of systemic Akt1 deficiency on cardiac function and angiogenesis before and after MI. Magnetic Resonance Imaging (MRI) revealed mildly decreased baseline cardiac function in Akt1 null mice, whereas *ex vivo* stereomicroscopy and micro-CT revealed substantially the reduced coronary macrovasculature [23]. This

longitudinal study provided clear evidence that mice with chronic loss of Akt1 exhibited improved heart function and reduced LV remodeling after experimental MI. Long-term inhibition of Akt1 might offer an alternative therapeutic strategy aimed to reduce secondary damage caused by cardiac remodeling.

Choi and coworkers found that the AuNp contrast agent and delayed DE micro-CT could be utilized to non-invasively assess the change in permeability of myocardial vessels after partial-heart irradiation [13]. They also measured a number of clinically important endpoints of cardiac physiology, including the LV end-diastolic volume, end-systolic volume, SV, EF, and CO.

Burk L M, et al [24] demonstrated the ability to identify areas of myocardial infarct consistently in mice and provided functional cardiac information using a delayed contrast enhancement technique.

Drug safety

Cardiovascular safety is an important concern in contemporary drug development and a significant contributor to safety-related attrition of novel drugs in development. Micro-CT has also been used for the evaluation of drug effects, such as shown in a study on assessment of Dobutamine (DOB) induced cardiac stress in rats [25]. In order to assess normal response to DOB stress in rats, SV, EF and correlative peripheral arterial pressures associated with the significant increases in CO were measured. Accordingly, the impact of such an enabling technology can be tremendous in evaluating cardiotoxic effects of various test drugs.

Technical limitations of micro-CT

Not only micro-CT, but also several other imaging modalities have been adapted from their clinical counterparts for animal experiments, such as high-frequency ultrasound, micro Positron Emission Tomography (micro-PET), micro Single-Photon Emission Computed Tomography (micro-SPECT) and MRI. Compared to other imaging modalities, micro-CT has its technical merits and drawbacks (Table 2).

First, radiation dose associated with micro-CT methods is not negligible. X-ray exposure can be harmful since it can disrupt chemical bonds and create free radicals in the body. Typically, the whole-body radiation dose for a 3D micro-CT scan reported in the literature ranges from 0.017Gy to 0.78Gy, depending on the diagnostic demand and the contrast resolution required [26]. On the opposite, ultrasound, echocardiography and micro-PET, remaining the cornerstone for diagnosing and monitoring heart disease, are not interfered with radioactive damage [27-30]. So there has been a continuing effort to improve security guarantee of this condition with micro-CT.

Second, the low X-ray absorption of non-mineralized tissues is one of the major challenges for micro-CT imaging so that contrast agents are commonly involved to increase the lesion-to-tissue ratio. Kinds of contrast materials have emerged in need. Iodine-based, low molecular weight contrast agents designed for clinical CT imaging applications (e.g. Omnipaque from GE Healthcare, Isovue from Bracco Diagnostic) can also be used for preclinical micro-CT imaging in animals even though they clear from mouse vasculature within seconds [31]. Iodine-based, blood pool contrast materials (e.g. Fenestra from ART, eXIA from Binitio Biomedical) provide stable enhancement over the course of minutes to an hour [32]. In addition, dose of contrast agents and the way of injection have an effect on the practice concerned with soft tissues [33].

Future trends of the imaging technology

CT imaging will continue to make progress in multiple sources, multiple-slice, multi-domain and multi-function, so that the improvements in scan speed, coverage, image quality and application value could be achieved. On the other hand, multimodality cardiovascular imaging which involves combination of at least two cardiovascular imaging techniques is a certain tendency in both clinical and experimental fields. They are typically combined in a side-by-side or fusion mode in order to present functional and morphological data to better delineate heart disease, most frequently used as PET/CT and SPECT/CT [34], with more proven efficacy than the modality used separately. Furthermore, the integration of vessel anatomy and myocardial perfusion imaging is admitted to provide better diagnostic and prognostic information that could be translated into improved level of experiments [35].

Discussion

Generally speaking, micro-CT is an imaging scanner allowing the virtual reconstruction of objects with pixel size in the micrometer range. X-rays generated by the X-ray tube emit toward the sample and the detector measures the intensity of the transmitted X-rays on the opposite side. Users get different attenuated X-ray shadow images depending on the length traveled in the absorbing material, the material composition and its density (i.e. attenuation coefficient). The 2D gray images projections, also referred to as slice plans, are reconstructed using mathematical (e.g. Filtered Back Projection FBP [36]) and iterative algorithms (e.g. Algebraic Reconstruction Technique ART [37]). For example, cone-beam source uses the Feldkamp algorithm as a tomographic reconstruction algorithm [38]. Finally, the reconstructed 2D radiographs are gathered and stacked together. As a result, the complete 3D map of the sample is computed and available for further processing [39]. Reconstructing isotropic voxels allows visualization in any orientation as 2D slices or a rendered 3D volume.

As we know, the contrast properties of CT significantly depend on the X-ray energy spectrum used to measure the object. Conventional CT uses a single energy spectrum and suffers from ambiguity at times so that two different materials that share similar grayscale intensity values as in the case of bone and iodine can appear identical. Dual energy CT yields precise anatomic and functional images by using two different energy spectra that can remove this ambiguity [40]. A two-tube/detector system ensures simultaneous acquisition of two projections, thus reducing scanning time and the doses of contrast injections in studies. The additional metallic beam filters are placed between the source and the specimen, like 1-2 mm of aluminum or copper. These metallic beam filters can be used to preferentially remove low energy photons and to improve spectral separation between polychromatic scans [41]. Various dual energy micro-CT sampling strategies are feasible, such as single source sequential scanning at two different kVps, simultaneous dual source acquisition and single source with kVp switching [42].

The proposed method produces 5D volumetric images that distinguish different materials at different points in time, and can be used to segment regions containing iodinated blood and calculate cardiac function [43]. Projection interpolation and 5D bilateral filtration (three spatial dimensions + time + energy) help to reduce noise and artifacts associated with retrospective gating. With cardiac MRI as standard of reference, double-source CT was confirmed to offer the possibility to quantify left ventricular function from coronary CT angiography datasets with sufficient diagnostic accuracy, adding to the value of the modality in a comprehensive cardiac assessment [44].

Micro-CT can provide versatile, high-contrast, quantitative *in vivo* or *ex vivo* images of small animals. The radiation dose and low x-ray contrast of soft tissues are widely recognized; however, newly developed contrast agents and novel acquisition and reconstruction strategies show extraordinary potential in overcoming these limitations and challenges. We just summarize the applications of micro-CT on heart diseases of murine, but actually it can be used on a variety of animal specimens. The breadth of possible applications has been illustrated with kinds of micro-CT images of model and non-model animals, including volume and section images of vertebrates, insects, embryos, and other invertebrates [45]. Chinese medicine is another field that waiting for micro-CT to realize its value. Although comprehensive micro-CT protocols rapidly provide convincing result for the diagnosis of heart diseases, the appropriate usage should be balanced against the implied exposure to radiation and contrast material, therapeutically effects and associated costs.

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