Evaluation of cardiac function by nuclear imaging in preclinical studies

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Rodent models of heart diseases have provided valuable insights into the mechanisms that occur in response to a variety of pathologies and provide a means to examine the effects of translational therapeutic interventions.[1] Induction of myocardial infarction (MI) by surgical ligation of the left coronary artery is a well-established model to study left ventricle (LV) remodeling and heart failure following MI.[1] Early work done on this model has been crucial in understanding the process of LV remodeling and determinants of systolic dysfunction after MI as well as demonstrating that inhibition of angiotensin-converting enzyme (ACE), when initiated soon after the induced MI, attenuates the remodeling process.[2]

The measurement of cardiac contractile function is the basis for assessing changes in cardiac anatomy and physiology caused by diseases and therapeutic interventions. Currently, non-invasive imaging techniques offer excellent alternatives to invasive measurement of hemodynamics using pressure-volume catheters for monitoring cardiac function over time in small animals.[1] Challenges for cardiac imaging in small animals include small size of the heart (5-8 mm in length) coupled with high heart rate (> 400 beats·minute^{-1}). After MI, a particular challenge is that the LV remodeling is non-uniform including thinning of the LV free wall and thickening of the non-infarcted LV wall. Therefore, volume calculations based on geometrical assumptions may provide incorrect results compared to absolute volume measurements.

Echocardiography is a widely used and effective non-invasive imaging technique to assess cardiac structure and function in mice.[1] Dedicated small animal devices enable accurate assessment of LV volumes and function at very high temporal (up to several hundred frames per second) and spatial resolution (< 0.1 μm). The main limitations of echocardiography are operator dependent image acquisition and the need for geometrical models instead of absolute volume measurements.

Cardiac magnetic resonance (CMR) imaging systems developed for small rodents (mice and rats) have ultra-high magnetic fields providing high spatial resolution (0.1-0.2 mm) and an unlimited regional access to the myocardium.[1] In continuous stacks of electrocardiography (ECG)-gated images covering the entire LV, accurate and reproducible measurement of absolute ventricular volumes and EF are possible.[1] Furthermore, CMR is a versatile tool enabling assessment of perfusion and viability in the same study. More recently, dedicated micro-computed tomography (CT) scanners that permit ECG-gated cardiac imaging analogous to CMR have become available.[3]

In this issue, Hess et al report their study on the accuracy of ECG-gated radionuclide perfusion imaging with small animal positron emission tomography (PET) and pinhole single-photon emission computed tomography (SPECT) to assess LV volumes and function in healthy mice and mice with MI induced by coronary ligation.[4] Small animal contrast-enhanced CT was used as an anatomical reference for [^{13}N]ammonia PET and small animal 7T CMR for [^{99m}Tc]Sestamibi SPECT. The main finding is that diastolic and systolic LV volumes are consistently underestimated by PET and SPECT, whereas EF shows relatively good agreement with CMR or CT. Importantly, in the study by Hess et al,

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heart rate of mice was in the physiological range (on average 477 beats·minute^{-1}) as recommended in the guidelines.[1]

Nuclear imaging in small animal models of ischemic heart disease is appealing, because it enables accurate measurement of MI size,[5-9] evaluation of myocardial perfusion,[10,11] and molecular imaging of metabolism such as oxygen consumption combined with substrate metabolism.[12,13] However, previous studies evaluating nuclear imaging for the assessment of cardiac volumes and function have been mainly focused on other conditions than MI.[14-17] Therefore, the study of Hess et al provides valuable information by validating nuclear imaging with anatomical imaging modalities in mice after MI. Delineation of myocardial contours is difficult in the presence of low tracer uptake in the MI region and automatic software dedicated for small animal experiments is currently not available. However, Hess et al demonstrate that functional evaluation with manual contour delineation is feasible with a relatively good reproducibility in repeated measurements.[4] Compared with the anatomical imaging methods, the spatial resolution of nuclear imaging is limited, which is the most likely explanation for systematic underestimation of ventricular volumes. However, as discussed by Hess et al, spatial resolution of PET/CT imaging is at best when using perfusion tracers labeled with ^{18}F due to shorter positron range than that of [^{13}N] ammonia.

The study indicates that functional measures obtained with different methods in small animals are not interchangeable, which should be considered when comparing results obtained with different modalities. For example, average EF values varied from 27% with CMR to 37% with SPECT and from 40% with CT to 55% with PET in the same mice after MI.[4] Regardless of differences in absolute values, nuclear imaging may be proven to be useful for monitoring changes in LV function, although the test–retest reproducibility remains to be studied. Such an approach does not require additional scans with another modality, which reduces the time of anesthesia and animal stress, and does not contain any toxic contrast agent enabling longitudinal studies in the same animal. Given the concerns over reproducibility and accuracy of cardiac functional evaluation in small animal studies,[1] prospective and careful planning of experimental conditions, especially anesthetic conditions, is important for reproducibility of experiments between laboratories.

The study by Hess et al provides important information on the evolution of nuclear imaging techniques in small animals that may offer feasible alternatives to anatomic imaging modalities for the evaluation of LV function in experimental models of MI and ischemic myocardial injury in mice. Furthermore, this non-invasive methodology might be useful in longitudinal studies to monitor changes in LV functional parameters in combination with various molecular imaging approaches offered by SPECT or PET.

Disclosures

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