Imaging the Murine Cardiovascular System With Magnetic Resonance

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Evolving imaging technologies are changing the breadth and depth of fundamental and integrated investigations of cardiovascular physiology and pathophysiology. Magnetic resonance (MR) techniques are arguably some of the most rapidly evolving and powerful imaging approaches for studying the cardiovascular system. They provide nondestructive and often unique insights into cardiac and vascular morphology, function, and metabolism in animal models and people. Several sophisticated imaging techniques have been adapted for studies of transgenic mice to characterize the pathophysiological consequences of targeted genetic manipulations.

Despite the importance to molecular biologists and cardiovascular physiologists, imaging the mouse heart under physiological conditions is nontrivial. The mouse heart is small (≈0.1 g) and fast (≈600 beats/min or 10 beats/sec). Therefore, high spatial and temporal resolution are fundamental requirements for murine cardiac imaging. Several imaging techniques are being adapted for mouse studies, including x-ray computed tomography, positron emission tomography, echocardiography, and magnetic resonance imaging (MRI). Echocardiography is presently the most commonly used technology for cardiovascular mouse imaging, and its applications are expanding. Two-dimensionally directed M-mode echocardiography is available in many laboratories and has become a relatively inexpensive, portable imaging technique for rapid phenotypic analysis. Cardiac MRI applications in the mouse have lagged behind those of echocardiography, but they are quickly becoming state of the art.

There are several clear and established strengths of MRI for murine cardiovascular studies, and these include intrinsically high-tissue contrast, tomographic acquisitions, and the ability to study many physiological parameters. High MR tissue contrast greatly enhances delineation of cardiac and vascular structures, even without the need for contrast agents. Unlike echocardiography, the fundamental tomographic nature of MRI eliminates the need for geometric assumptions when calculating ventricular mass and function. MRI is presently the most accurate and reliable method for noninvasively quantifying left ventricular mass in mice. It has been used to characterize the presence and severity of global dysfunction in mouse models. MRI is probably also the leading noninvasive imaging technique for characterizing the structure and function of the irregularly shaped right ventricle in mice, where echocardiographic techniques may require the use of transesophageal probes. The high spatial resolution and tissue contrast of MRI have also been exploited for vascular imaging in mice, and reports identify aortic lesions and coronary arteries. Finally, MR 31P spectroscopy (MRS) techniques can be used with high-resolution imaging to uniquely study regional, cardiac high-energy phosphate metabolism in intact mice and its functional correlates.

The study by Wiesmann et al in this issue of Circulation Research extends the application of high-resolution, rapid MRI to the cardiovascular system in mice. Three aspects are of special interest to cardiovascular physiologists. First, the method was implemented in a regional model of left ventricular dysfunction. Without dependence on geometric assumptions, global left ventricular mass, volumes, and ejection fraction as well as regional thickening were directly measured noninvasively in infarcted mouse hearts with high precision. Second, these measures were obtained before and during inotropic stimulation. Administration of intraperitoneal dobutamine increased heart rate, cardiac output, and ejection fraction at lower diastolic volumes for a sustained period in normal mice. As expected, gross morphological abnormalities were present before dobutamine in infarcted hearts with ventricular dilatation, depressed ejection fractions, and wall thinning. Dobutamine allowed the study of contractile reserve and demonstrated increased systolic wall thickness only in regions remote from infarction. Third, images were acquired with a sufficiently high temporal resolution to allow the separate assessment of systolic and diastolic left ventricular performance with estimation of ventricular ejection and filling rates. With 20 to 30 frames per cardiac cycle from a single midventricular plane, significant reductions in calculated left ventricular ejection and filling rates were confirmed in infarcted hearts. Of special interest, the combination of rapid imaging for ventricular filling was combined with dobutamine stress in hearts overexpressing the β1-adrenergic receptor. These hearts were modestly hypertrophic but had baseline ejection fractions, cardiac outputs, and filling rates that were similar to wild-type animals. During dobutamine stimulation, however, left ventricular filling was significantly lower in transgenic β1-adrenergic overexpressors. These observations demonstrate the feasibility for rapid, high-resolution MRI during inotropic stress to detect abnormalities in filling and early dysfunction in some murine models that are not detectable under nonstressed conditions.
Despite this progress, hurdles remain for murine cardiac MR investigation. Murine cardiac MRI/MRS studies presently require anesthesia and careful attention to experimental detail to avoid cardiac depression. Although the heart rates reported by Wiesmann et al.\textsuperscript{14} are higher than those from some earlier reports, more physiological heart rates are obtainable during MR examinations today.\textsuperscript{12} These new measures of ventricular ejection and filling rates in mice are of potential scientific value in studies of diastolic function. However, their accuracy and reproducibility merit additional study, as suggested by the subtle differences in these measures between wild-type animals under similar experimental conditions.\textsuperscript{14} This may be because of the necessary trade-off between high-temporal resolution and spatial resolution (one ventricular slice) while limiting the total acquisition time to that of inotropic stimulation. However, these limitations are clearly not major barriers to additional efforts. Higher-field magnets, stronger gradient capabilities, and newer coil designs should additionally extend the temporal and spatial capabilities of MR approaches. The major hurdle to widespread implementation of MR for murine cardiac studies today is not a limitation of the technique but the cost and availability of high-resolution MR equipment. As the unique value of cardiac MR technology in small animal models is advanced, the technology will undoubtedly spread.

Cardiovascular MRI technology can be used to noninvasively measure cardiac mass, structure, function, and metabolism as well as vascular anatomy in a single investigation in people and mice. The present study by Wiesmann et al.\textsuperscript{14} extends the capabilities in mice to studies of diastolic function and inotropic stimulation. High-resolution imaging techniques, and especially MRI/MRS, are becoming essential, noninvasive tools to phenotypically characterize the pathophysiological significance and serial consequences of genetic manipulations on the cardiovascular system of murine models.

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**References**

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