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● *Original Contribution*

ECHOCARDIOGRAPHIC ANALYSIS OF CARDIAC FUNCTION AFTER INFARCTION IN MICE: VALIDATION OF SINGLE-PLANE LONG-AXIS VIEW MEASUREMENTS AND THE BI-PLANE SIMPSON METHOD

Andre Heinen,* Annika Raupach,† Friederike Behmenburg,† Nina Hölscher,† Ulrich Flögel,‡ Malte Kelm,§ Wolfgang Kaisers,† Rianne Nederlof,* Ragnar Huhn,† and Axel Gödecke*

* Institute of Cardiovascular Physiology, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany; † Department of Anesthesiology, University Hospital Düsseldorf, Düsseldorf, Germany; ‡ Department of Molecular Cardiology, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany; and § Department of Cardiology, University Hospital Düsseldorf, Düsseldorf, Germany

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Abstract—Although echocardiography is commonly used to analyze cardiac function in small animal models of cardiac remodeling after myocardial infarction, the different echocardiographic methods are validated poorly. End-diastolic volume, end-systolic volume and ejection fraction were analyzed using either standard single-plane analysis from parasternal long-axis B-mode views (PSLAX) or the bi-plane Simpson method (using PSLAX and three short-axis views) and validated using magnetic resonance imaging as standard. Ejection fraction measured by PSLAX was moderately correlated with a coefficient of $R^2 = 0.49$. The standard deviation of residuals was 9.91. Simpson analysis revealed an improved correlation coefficient of $R^2 = 0.77$ and a reduction in standard deviation of residuals by 45% (5.45 vs. 9.92, $p = 0.014$). Subgroup analysis revealed that the high variation in PSLAX is due to changes in ventricular geometry after myocardial infarction. Our results indicate that the bi-plane Simpson method is advantageous for the assessment of cardiac function after myocardial infarction. (E-mail: heinen@hhu.de) **© 2018 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

Key Words: **Myocardial infarction, Cardiac remodeling, Echocardiography, Method validation, Mouse.**

INTRODUCTION

Small animal models have become invaluable tools in preclinical cardiovascular research, in part because of the availability of transgenic mouse lines and the improvement in surgical techniques for the induction of pathologic disease models, for example, transverse aortic constriction and coronary artery occlusion. Therefore, a great need exists for methods that assess cardiac function for phenotyping and longitudinal disease development. Echocardiography in small rodents requires high temporal and spatial resolution because of the small anatomic structures and the high heart rate. Since the development of new echocardiographic systems, the assessment of cardiac function by high-frequency echocardiography has also become more common in small animals (Ram et al. 2011; Stypmann et al. 2009). However, the procedures and analysis tools are less standardized compared with methods used in patients. The analysis of left ventricular volumes and ejection fraction, which are important parameters for cardiac function, requires geometric assumptions of the left ventricular shape (Picard et al. 2008). Therefore, the accuracy of the analyses might be limited when the left ventricle develops an irregular shape, for example, by the occurrence of aneurysms or regional wall motion defects after myocardial infarction. In the most common murine model used to study cardiac remodeling after myocardial ischemia and reperfusion, the left anterior descending (LAD) coronary artery is ligated temporarily, causing permanent regional wall motion defects. The left ventricular contraction is characterized by hypokinetic or akinetic areas within the apex and the free wall, whereas the remote myocardium, for example, the septum, has normal contraction. A consequence of these regional contraction abnormalities is an irregular shape of the left ventricle, especially during systole (Fig. 1). This deformation might affect the

Address correspondence to: Andre Heinen, Institute of Cardiovascular Physiology, Heinrich-Heine-University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany. E-mail: heinen@hhu.de

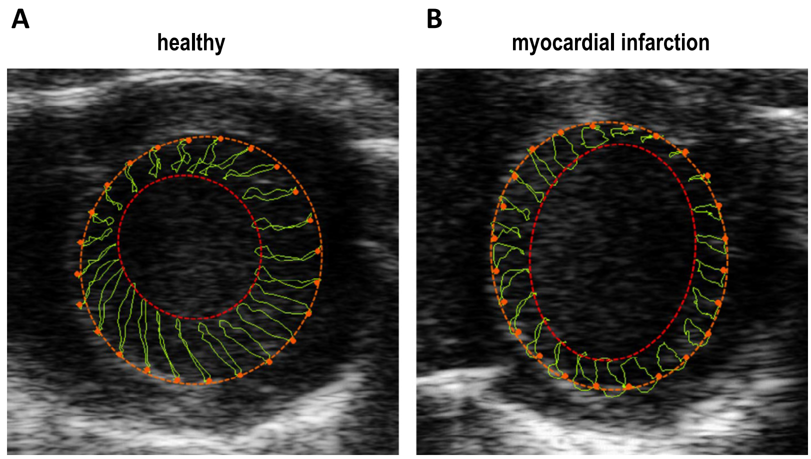

Fig. 1. Myocardial infarction and left ventricular shape. An automatic speckle-tracking method was used to visualize the myocardial contraction of one heart cycle in a healthy mouse heart (A) and that in a mouse heart after myocardial infarction (B). The endocardium was manually traced (*orange dots*), and the endocardial displacement during the heart cycle is visualized by the *green lines*. In healthy animals, the left ventricle has a round shape during both systole (*red*) and diastole (*orange*). In contrast, myocardial infarction caused regional wall motion defects resulting in an elliptical shape of the ventricle, especially during systole.

accuracy of volume determinations by echocardiographic methods that use calculations based on a regular circular shape of the ventricle. Therefore, the optimal strategy for volume analysis would be the use of a real-time volumetric 3-D imaging that detects all regions of the ventricular wall and would be more robust against shape changes. Although it was reported more than a decade ago that echocardiographic 3-D reconstructions of both the rat heart and the mouse heart are possible (Dawson et al. 2004; Scherrer-Crosbie et al. 1999), these methods are not routinely used in pre-clinical cardiovascular research, because they are extremely time consuming compared with other echocardiographic analysis procedures. Although the problem of irregular ventricular shapes and the potential influence on echocardiographic analysis methods is known, the left ventricular function of either permanent or transient occlusion of the LAD coronary artery is assessed in the majority of (also recent and high ranking) publications by the analysis of only single-plane views (Inserte et al. 2016; Reboll et al. 2017; Shi et al. 2017; Yan et al. 2017). The most commonly applied method is the single-plane parasternal long-axis B-mode view (PSLAX) analysis (Fig. 2A). Therefore, there is great need for validation of alternative echocardiographic methods in small animal models with irregular ventricular shapes. An alternative method for echocardiographic volume analysis is the bi-plane modified Simpson method (Fig. 2B). As illustrated in Figure 2, the underlying calculation of the modified Simpson method is based on measurements from all three dimensions: the ventricular length from PSLAX and the

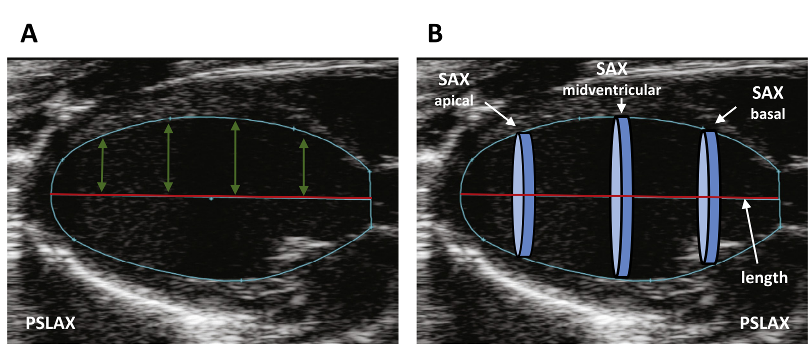

Fig. 2. Volume determination with PSLAX left ventricular trace and modified Simpson method. (A) PSLAX analysis uses a traced single-plane parasternal long axis view. The left ventricular volume is calculated as the rotational volume of the endocardial tracing (*blue*) around the long-axis line of the spline (*red*) by using the distances between spline and endocardial tracing (*green*). (B) Volume calculations with the bi-plane modified Simpson method requires the length of the ventricle (*red*) obtained from a PSLAX view (endocardial tracing is *blue*), and the left ventricular areas from three orthogonal SAX (midventricular, apical, basal) views (*blue disks*). PSLAX = parasternal long-axis; SAX = short-axis.