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● *Original Contribution*

# TOWARD 3-D ECHOCARDIOGRAPHIC DETERMINATION OF REGIONAL MYOFIBER STRUCTURE

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**Abstract—As a step toward the goal of relating changes in underlying myocardial structure to observed altered cardiac function in the hearts of individual patients, this study addresses the feasibility of creating echocardiography-derived maps of regional myocardial fiber structure for entire, intact, excised sheep hearts. Backscatter data were obtained from apical echocardiographic images acquired with a clinical ultrasonic imaging system and used to determine local fiber orientations in each of seven hearts. Systematic acquisition across the entire heart volume provided information sufficient to give a complete map for each heart. Results from the echocardiography-derived fiber maps compare favorably with corresponding results derived from diffusion tensor magnetic resonance imaging. The results of this study provide evidence of the feasibility of using echocardiographic methods to generate individualized whole heart fiber maps for patients. (E-mail: mlmilne@smcm.edu)** © **2016 World Federation for Ultrasound in Medicine & Biology.**

***Key Words:*** **Anisotropy, Heart, Echocardiography, Fiber structure, Myocardium.**

## INTRODUCTION

In the heart, function and structure are closely linked (Arts et al. 2003; Buckberg et al. 2008; Sengupta et al. 2006, 2007), and as a consequence, knowledge of the specific myocardial fiber structure throughout the heart of an individual patient could aid in identification of the origin of dysfunction, as well as in evaluation of the potentially beneficial effects of therapy. To this end, the advancement of methods to image intrinsic myocardial structure has been identified as a key area of development in recommendations from the National Heart, Lung and Blood Institute (NHLBI) (Baumgartner et al. 2005; Buckberg et al. 2004; Williams et al. 2006). Alterations in myocardial fiber structure and orientation can also precede cardiac dysfunction and the clinical manifestation (Giglio et al. 2003). Mapping the fiber structure of the whole heart would provide insight into both global and regional function and could potentially permit a better understanding of the role that the underlying myocardial structure is playing in the individual's cardiac function (Arts et al. 2003; Buckberg et al. 2008; Costa et al. 2001; McQueen and Peskin 2000; Peskin and McQueen 1992; Sengupta et al. 2006, 2007). Such information could be useful in identifying subclinical alterations in fiber structure and thus create the opportunity for early intervention for a better outcome. Furthermore, assessment of fiber orientation may provide additional insights into the origin of observed altered global and regional cardiac deformation as currently assessed by advanced methods such as *in vivo* wall motion tracking methods and, hence, provide additional diagnostic information. To this end, efforts have been made to map the fiber structure of the heart using modalities such as diffusion tensor imaging (DTI) and elastic tensor imaging (ETI) (Lee et al. 2012a, 2012b). Therefore, one of the motivations behind this study is to contribute to the development of a method that will permit a better understanding of the role fiber structure plays in overall cardiac function in individual patients.

Ultrasonic imaging is well suited as a modality for generating myocardial fiber maps for the individual patient. Ultrasound is widely available, is used in routine

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clinical practice for decision making and is relatively inexpensive. It does not involve ionizing radiation and thus is well suited for serial evaluations. Although this approach would be useful in observing the undesirable remodeling associated with myocardial infarction, its primary contribution is likely to be in monitoring (constructive) reverse remodeling, such as that seen in resynchronization therapy (Mekkaoui et al. 2012; Yu et al. 2002), or potential reverse remodeling observed in heart failure patients using left ventricular assist devices (LVADs) and, therefore, monitoring the efficacy of therapy (Ambardekar and Buttrick 2011; Hellawell and Margulies 2012). In children born with single ventricle physiology, staged palliation employing the single ventricle to support the systemic circulation has resulted in remarkable survival of children with a heart defect otherwise proving uniformly fatal if not repaired with this palliation (Cetta et al. 1996; Gaynor et al. 2002). However, in many, the palliation fails as a result of single-ventricle failure (Khairy et al. 2008) that arises partly from the abnormal myocardial fiber architecture and fibrous matrix of the ventricular myocardium (Ho et al. 1996). A study of single-ventricle myocardial fiber orientation may help in selection of the appropriate intervention. This is often hampered by the lack of a non-invasive and easy-to-use tool to study the myocardial fiber architecture.

To this end, our laboratory previously reported that, in principle, quantitative measurements of myocardial fiber structure for individual hearts can be derived from analyses of echocardiographic images (Milne et al. 2012). That study, limited to 2-D short-axis reconstructions, found that echocardiography-based measurements of fiber structure in a specific transverse plane qualitatively agreed with the corresponding estimates obtained using diffusion tensor magnetic resonance imaging (MRI) methods. The objective of the present study was to extend the previous work on single planes of the heart by determining the feasibility of creating quantitative myofiber multiplane structure maps over the entire volume of intact hearts based on 3-D echocardiographic information. In addition, our echocardiography-derived estimates are quantitatively compared with published diffusion MRI measurements of fiber structure. Regional differences in fiber structure within the heart are also elucidated for selected regions of interest (ROIs).

## METHODS

Seven sheep hearts were obtained within 1 h of slaughter from a local slaughterhouse using a procedure consistent with the policies of the Animal Studies Committee of Washington University. Sheep hearts were used because they are comparable in size and composition to the human heart (Rudolph 2009). The intact, excised hearts were thoroughly rinsed and fixed in a 10% formalin solution for a minimum of 5 weeks before being imaged. The use of fixed tissue permitted ample time for imaging of the hearts without concerns for structural degradation. (Some limitations arising from the use of fixed tissue are described in the Discussion.)

Methods for data acquisition and analysis were similar to the methods described in a previous article from our laboratory (Milne et al. 2012). In brief, after fixation preparation was completed, each heart was placed base down in a cylindrical water-filled tank in preparation for collection of backscatter data. A series of apical echocardiographic images, in 5° rotational increments about the apex of each heart, were obtained using a General Electric Vivid 7 clinical imaging system (GE Healthcare, Wauwatosa, WI, USA) at a nominal center frequency of 5.0 MHz in fundamental imaging mode (Fig. 1a). A GE Model 7 S phased-array probe was used in fundamental imaging mode at 5.0-MHz nominal frequency. The post-processing settings on the clinical imaging system were configured such that the gray-scale level of the images had a linear relationship to the amount of backscattered energy, to allow quantitative estimates of the level of backscatter from the gray-scale images. The details of this calibration have been previously described by our laboratory (Holland et al. 2006). The time-gain compensation (TGC) settings were adjusted so that the backscatter signal strength was within the useful linear dynamic range for all depths, and a single transmit focus was placed near the center of the left ventricle.

After image acquisition, the backscatter values along individual transverse profile lines corresponding to specific depths from the apex were normalized using the following approach: Myofibers that are perpendicular to the ultrasound beam (typically fibers in the midmyocardium) are known to yield the largest acoustic backscatter values (Hoffmeister et al. 1995; Holland et al. 1997; Yang et al. 2007). Consequently, at a specific distance from the apex, the pixels with the highest values of backscatter along transverse profile lines placed on the left and right walls of the heart in the gray-scale image were identified as arising from locations where the fiber orientation was predominately perpendicular to the ultrasonic beam direction. These brightest pixels were normalized to the maximum gray-scale value, and all other pixels were normalized to their corresponding relative gray-scale value. Normalizing the backscatter in this fashion provided an approach to compensate for the effects of signal attenuation as the acoustic beam traveled through the overlying tissue in a fashion that is analogous to transthoracic apical window imaging in a clinical setting (Fig. 1b). Possible issues arising from the assumption that the brightest pixels