Ultrasound in Med. & Biol., Vol. ■, No. ■, pp. 1–13, 2017

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2017.06.019

● *Original Contribution*

REPRODUCIBILITY AND ANGLE INDEPENDENCE OF ELECTROMECHANICAL WAVE IMAGING FOR THE MEASUREMENT OF ELECTROMECHANICAL ACTIVATION DURING SINUS RHYTHM IN HEALTHY HUMANS

LEA MELKI,* ALEXANDRE COSTET,* and ELISA E. KONOFAGOU*†

*Department of Biomedical Engineering, Columbia University, New York, New York, USA; and †Department of Radiology, Columbia University Medical Center, New York, New York, USA

(*Received* 11 *January* 2017; *revised* 13 *May* 2017; *in final form* 19 *June* 2017)

Abstract—Electromechanical wave imaging (EWI) is an ultrasound-based technique that can non-invasively map the transmural electromechanical activation in all four cardiac chambers *in vivo*. The objective of this study was to determine the reproducibility and angle independence of EWI for the assessment of electromechanical activation during normal sinus rhythm (NSR) in healthy humans. Acquisitions were performed transthoracically at 2000 frames/s on seven healthy human hearts in parasternal long-axis, apical four- and two-chamber views. EWI data was collected twice successively in each view in all subjects, while four successive acquisitions were obtained in one case. Activation maps were generated and compared (i) within the same acquisition across consecutive cardiac cycles; (ii) within same view across successive acquisitions; and (iii) within equivalent left-ventricular regions across different views. EWI was capable of characterizing electromechanical activation during NSR and of reliably obtaining similar patterns of activation. For consecutive heart cycles, the average 2-D correlation coefficient between the two isochrones across the seven subjects was 0.9893, with a mean average activation time fluctuation in LV wall segments across acquisitions of 6.19%. A mean activation time variability of 12% was obtained across different views with a measurement bias of only 3.2 ms. These findings indicate that EWI can map the electromechanical activation during NSR in human hearts in transthoracic echocardiography *in vivo* and results in reproducible and angle-independent activation maps. (E-mail: ek2191@columbia.edu) © **2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Electromechanical wave imaging, Reproducibility, Angle independence, Electromechanical activation sequence, Echocardiography.**

INTRODUCTION

Cardiac conduction abnormalities and arrhythmias can often lead to stroke, heart failure and sudden cardiac death (Mehra 2007; Mozaffarian et al. 2016; Zipes and Wellens 1998). These diseases remain a major cause of death worldwide. In fact, although the rate of deaths attributable to cardiovascular diseases has decreased by 28.8% in the last decade, cardiovascular diseases still accounted for 30.8% of all deaths in the United States in 2013—approximately one of every three deaths (Mozaffarian et al. 2016; Zoni-Berisso et al. 2014). Yet, despite this health impact and the urgent need for prevention, the imaging techniques currently available clinically for heart activation sequence mapping are invasive, ionizing, time consuming and costly (Knackstedt et al. 2008; Packer 2004).

Mapping the electrical activation of the heart is necessary for the diagnosis and treatment of arrhythmias. Providing physicians with simpler tools that allow early detection of arrhythmias and more prompt and precise treatment would undoubtedly improve treatment outcomes. Our group has developed a direct and non-invasive ultrasound-based technique to study the electromechanical behavior of the heart: electromechanical wave imaging (EWI) (Konofagou et al. 2010). This ultrasound-based modality, capable of mapping the electromechanical activation in all four cardiac chambers *in vivo* (Provost et al. 2011a), is transmural and has a high temporal resolution (0.5–3 ms), a high spatial resolution and real-time feedback capabilities (Provost et al. 2010, 2011b; Wang et al. 2008).

The heart needs to be electrically activated before it can mechanically contract (Glass et al. 1991).

Address correspondence to: Elisa E. Konofagou, Department of Radiology, Columbia University Medical Center, 630 West 168th Street, Physicians & Surgeons 19-418, New York, NY 10032, USA. E-mail: ek2191@columbia.edu

The electromechanical wave (EW) refers to the propagation of the onset of the cardiac contraction in response to electrical activation of the heart. The EW has been found to be highly correlated with the electrical activation sequence in the left ventricle (LV), in both normal and paced canines *in vivo* (Provost et al. 2011a, 2011b). Furthermore, the electromechanical delay is defined as the lag between the depolarization of the cardiomyocytes, that is, the electrical activation, and the onset of their contraction, that is, the electromechanical activation. Typically, this delay is on the order of tens of milliseconds (Bers 2002; Cordeiro et al. 2004; Provost et al. 2011a).

Electromechanical wave imaging has been previously reported in a variety of applications, such as ischemia and infarct assessment in canines, as well as cardiac resynchronization therapy (CRT) in heart failure patients. EWI was found capable of detecting infarcted regions in the canine hearts and monitoring the formation of myocardial infarction over several days (Costet et al. 2017). In addition, EWI not only was successful in distinguishing between healthy and heart failure patients, but was also capable of mapping the electromechanical activation pattern of the ventricles under CRT and differentiating responders from non-responders (Bunting et al. 2017).

In previous studies, EWI was reported to be reproducible in simulations and canine experiments (Provost et al. 2011c), as well as repeatable within the same acquisition across consecutive cardiac cycles in open-chest dogs (Costet et al. 2014). However, reproducibility in closed-chest humans has yet to be investigated. Furthermore, it is critical for clinical applications to reliably measure the activation sequence independently of the imaging view. Our group recently established that EWI is capable not only of properly identifying the origin of activation of focal rhythms, but also of distinguishing between epicardial and endocardial origins in a focal paced canine heart *in vivo* (Costet et al. 2016). These findings result from an open-chest animal model and still require further investigation in a closed chest.

Initial results on premature ventricular contractions (PVCs) and Wolff–Parkinson–White (WPW) syndrome patients have been reported (Costet 2016) for potential applications in radiofrequency (RF) ablation treatment planning (Bunting et al. 2016; Papadacci et al. 2017b). Accordingly, it is essential that the arrhythmic focus or re-entry pathway locations identified with EWI remain consistent, no matter the position and orientation of the ultrasound probe. Current techniques for localizing the accessory pathways in patients with WPW in the clinic mostly rely mostly on 12-lead electrocardiogram (ECG) interpretation, intracardiac electrophysiology and fluoroscopy. Recently, non-invasive approaches without radiation exposure have emerged, such as tissue Doppler imaging (Esmaeilzadeh et al. 2013) and 3-D speckle tracking echocardiography (STE) (Ishizu et al. 2016). However, strain imaging with STE on B-mode images typically operates at lower frame rates and is less accurate than RF-based cross-correlation (Walker and Trahey 1995), whereas pulsed wave (PW) Doppler estimation is known to be angle dependent. Therefore, assessing the angle independence of our technique is not only crucial for accurate diagnosis and treatment planning of arrhythmias such as PVCs, persistent atrial fibrillation or focal tachycardia, but would also prove the advantage of EWI over tissue Doppler-based techniques.

In this study, our aim was to determine the reproducibility and angle independence of EWI for the assessment of electromechanical activation during normal sinus rhythm (NSR) in healthy humans *in vivo*. To achieve this goal, activation maps of five healthy male volunteers were generated and compared (i) within the same acquisition across consecutive cardiac cycles; (ii) within the same standard echocardiographic view across successive acquisitions; and finally, (iii) within equivalent LV regions across different imaging views.

METHODS

Experimental protocol

The human subject study protocol was approved by the institutional review board of Columbia University, and informed consent was obtained before all procedures described herein. While lying down on their left side in the lateral decubitus position, seven healthy male volunteers (aged 23 to 33 y) were imaged by a trained cardiologist with a Vantage 256 system (Verasonics, Redmond, WA, USA).

Ultrasound acquisition for EWI was performed in three standard echocardiographic views: parasternal long-axis and apical four- and two-chamber. A 2.5-MHz phased array probe (P4-2 ATL/Philips, Andover, MA, USA) was used to emit unfocused circular waves (Provost et al. 2011a), and to achieve frame rates high enough for displacement estimation applications, RF channel data were acquired at 2000 fps at a 20-cm depth. The latter were followed by a standard 64-line B-mode anatomic acquisition of 1.5 s at 30 fps and 20-cm depth, which was later used for precise manual myocardium segmentation. We acquired RF frames up to four successive times for each view during sinus rhythm. The consecutive scans were recorded less than a minute apart, and the probe was repositioned on the subject between acquisitions. The processing was later performed on a separate computer in MATLAB (The MathWorks, Natick, MA, USA) using a graphics processing unit (GPU) (Tesla NVIDIA, Santa Clara, CA, USA) and parallel processing.

Simultaneous recording of the electrical activity was performed with three electrodes placed on the subject's chest and connected to an ECG unit (77804 A, HP, Palo