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● *Technical Note*

NON-INVASIVE INTRA-CARDIAC PRESSURE MEASUREMENTS USING SUBHARMONIC-AIDED PRESSURE ESTIMATION: PROOF OF CONCEPT IN HUMANS

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Abstract—This study evaluated the feasibility of employing non-invasive intra-cardiac pressure estimation using subharmonic signals from ultrasound contrast agents in humans. This institutional review board–approved proof-of-concept study included 15 consenting patients scheduled for left and right heart catheterization. During the catheterization procedure, Definity was infused intra-venously at 4–10 mL/min. Ultrasound scanning was performed with a Sonix RP using pulse inversion, three incident acoustic output levels and 2.5-MHz transmit frequency. Radiofrequency data were processed and subharmonic amplitudes were compared with the pressure catheter data. The correlation coefficient between subharmonic signals and pressure catheter data ranged from −0.3 to −0.9. For acquisitions with optimum acoustic output, pressure errors between the subharmonic technique and catheter were as low as 2.6 mmHg. However, automatically determining optimum acoustic output during scanning for each patient remains to be addressed before clinical applicability can be decided. (E-mail: jaydev.dave@jefferson.edu) © **2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Subharmonic-aided pressure estimation, Non-invasive pressure estimation, Intra-cardiac pressures, Ultrasound contrast agents, Cardiac catheterization.**

INTRODUCTION

About 85.6 million Americans have more than one type of cardiovascular disease, with 80 million Americans having high blood pressure (Mozaffarian et al. 2016). It is estimated that by 2030, the total annual cost associated with all cardiovascular diseases will be about $918 billion (Mozaffarian et al. 2016). For patients with cardiovascular diseases, particularly for those with heart failure, intra-cardiac pressure measurements provide essential information for clinical assessment and management. For patients with heart transplants, intra-cardiac pressure measurements are necessary to monitor for rejection, with even moderate to severe episodes of biopsy negative rejections being accompanied by changes in intra-cardiac pressures; furthermore, serial monitoring of intra-cardiac pressures for heart transplant patients is recommended (Fishbein and Kobashigawa 2004). Invasive pressure measurements obtained after insertion of pressure-sensing catheters into blood vessels and advancement of these catheters into the cardiac chambers under fluoroscopic guidance constitute the current standard-of-care (Solomon and Stevenson 2009). Additional parameters such as the ventricular relaxation time constant (tau or τ) and rate of the isovolumic diastolic decline in pressure (peak isovolumic $-dP/dt$), which are beneficial in assessing ventricular diastolic function, require use of calibrated high-fidelity micromanometer-tipped catheters (Ommen et al. 2000; Starling et al. 1987) and, therefore, are not performed during routine catheterization procedures. Overall the invasiveness, cost

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and use of ionizing radiation during cardiac catheterization restrict the frequency with which such procedures are performed on patients (Connors et al. 1996; Shah et al. 2005; Solomon and Stevenson 2009). Frequent monitoring of central cardiac pressures is beneficial, especially because of varied patient responses to different vasoactive medications (Papaioannou et al. 2009; Solomon and Stevenson 2009). Therefore, a non-invasive technique for intra-cardiac pressure estimation would be very clinically beneficial.

Non-invasive techniques based on Doppler ultrasound, tissue Doppler techniques and tonometric and plethysmographic principles have failed to quantify absolute pressures in the cardiac ventricles (Baicu et al. 2005; Baumgartner et al. 1993; Geske et al. 2007; Kidawa et al. 2005; Papaioannou et al. 2009; Strauss et al. 1993; Tschope and Paulus 2009). Several approaches to the use of ultrasound contrast agents for ambient pressure estimation have been proposed, but high errors (as much as 50 mmHg or 30% relative to the reference standard) associated with these techniques have prevented pre-clinical or clinical applications (Bouakaz et al. 1999; Fairbank and Scully 1977; Hök 1981; Miwa 1984; Shankar et al. 1986); clinical applications would require errors on the order of 5 mmHg with the reference standard (Pickering et al. 2005). One of the other approaches that uses microbubble based ultrasound contrast agents for ambient pressure estimation is based on the subharmonic signal amplitude, and this approach has been tested and used extensively by our group and others (Adam et al. 2005; Andersen and Jensen 2009, 2010; Dave et al. 2011, 2012a, 2012b, 2012c; Eisenbrey et al. 2013; Forsberg et al. 2005; Frinking et al. 2012; Halldorsdottir et al. 2011, 2014; Shi et al. 1999). Briefly, this approach relies on eliciting ambient pressure-sensitive subharmonic signals, extracting the subharmonic signal amplitude (which is at half the transmit frequency) and then estimating ambient pressure based on a linear relationship between the subharmonic signal amplitude and the ambient pressure. This technique is referred to as subharmonic-aided pressure estimation (SHAPE).

The SHAPE technique has been tested *in vitro* (Dave et al. 2011, 2012a; Halldorsdottir et al. 2011; Shi et al. 1999), in pre-clinical studies (Dave et al. 2012b, 2012c; Forsberg et al. 2005; Halldorsdottir et al. 2014) and in humans for portal hypertension assessment (Eisenbrey et al. 2013). The cardiac applications of the SHAPE technique have been limited to pre-clinical studies to date. Encouragingly low errors were observed in the left and right ventricles of canines between the SHAPE technique and pressure catheter measurements (within 3.5 mmHg) (Dave et al. 2012b, 2012c). To the best of our knowledge, this is the most accurate non-invasive *in vivo* cardiac pressure estimation reported to date. A major difference between testing the SHAPE technique for human cardiac applications and our previous study in patients with portal hypertension arises from the nature of the underlying pressure signal (constantly changing pressure amplitude during a cardiac cycle for intra-cardiac pressures vs. relatively constant pressure amplitude in portal veins). Therefore, the purpose of this work was to conduct a proof-of-concept study to evaluate the feasibility of cardiac SHAPE in patients undergoing left and right heart catheterization procedures and to evaluate whether the results from the pre-clinical studies are translatable to a clinical population.

METHODS

The study was approved by the institutional review board. Patients over the age of 21 y who were scheduled for clinically indicated left and right heart catheterization were included in the study. Excluded from this study were clinically unstable patients (patients who were clinically in decompensated heart failure, patients presenting for admission with an acute coronary syndrome); patients in whom introduction of a catheter into the left ventricle was contraindicated or would potentially be dangerous (*e.g.,* patients with active ventricular arrhythmias or with significant aortic valve stenosis in whom crossing the aortic valve might be difficult and not clinically necessary); patients with anatomic right-to-left, bi-directional or transient right-to-left cardiac shunts where Definity (Lantheus Medical Imaging, North Billerica, MA, USA) microbubbles could traverse as a bolus; female patients who were pregnant or nursing; and patients with known hypersensitivity to Definity. For patients who provided written informed consent, gray-scale imaging was performed before the catheterization procedure with a Sonix RP scanner and a PA4-2 transducer (BK Ultrasound, Richmond, BC, Canada) to mark optimum acoustic windows for cardiac imaging in supine position because the patient would be in supine position during the cardiac catheterization procedure.

Data acquisition for SHAPE

A Sonix RP scanner was configured for pulse inversion imaging. In this mode, two transmit pulses with a phase difference of 180° were transmitted, and the received signal was summed. A PA4-2 transducer was used for data acquisition with a transmit frequency of 2.5 MHz (based on our previous work [Dave et al. 2012b, 2012c]). The incident acoustic output on the Sonix RP scanner is coded in 2-dB decrements from 0 dB (0 dB is the maximum incident acoustic output, and the corresponding mechanical index was less than 0.38, as measured in a water tank setup using a calibrated hydrophone). For the data acquisition in this proof-of-concept study, three incident acoustic outputs