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NONINVASIVE INTRACARDIAC PRESSURE MEASUREMENTS USING SUBHARMONIC AIDED PRESSURE ESTIMATION: PROOF OF CONCEPT IN HUMANS

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Abstract

This study evaluated the feasibility of noninvasive intracardiac pressure estimation using subharmonic signals from ultrasound contrast agents in humans. This IRB approved proof-of-concept study included 15 consenting patients scheduled for left and right heart catheterization. During the catheterization procedure, Definity (Lantheus Medical Imaging, N Billerica, MA) was infused intravenously at 4–10 ml/min. Ultrasound scanning was performed with a Sonix RP (BK Ultrasound, Richmond, Canada) 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. 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.

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Keywords

Subharmonic aided pressure estimation; noninvasive pressure estimation; intracardiac pressures; ultrasound contrast agents; cardiac catheterization

Introduction

About 85.6 million Americans suffer from 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 suffering with cardiovascular diseases, particularly for those with heart failure, intracardiac pressure measurements provide essential information for clinical assessment and management. For patients with heart transplants, intracardiac pressure measurements are necessary to monitor for rejection with even moderate to severe episodes of biopsy negative rejections being accompanied by changes in the intracardiac pressures; also serial monitoring of intracardiac 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 advancing these catheters into the cardiac chambers under fluoroscopic guidance are the current standard-of-care (Solomon and Stevenson 2009). Additional parameters such as the ventricular relaxation time constant (τ) and rate of the isovolumic diastolic decline in pressure (peak isovolumic $-dP/dt$), which are beneficial to assess 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 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 noninvasive technique for intracardiac pressure estimation would be very clinically beneficial.

Noninvasive techniques based on Doppler ultrasound, tissue Doppler techniques, 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, Tschöpe and Paulus 2009). Several approaches to utilizing 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 1982, 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 to utilize 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 also, 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 the pressure catheter measurements (within 3.5 mmHg) (Dave et al. 2012b, 2012c). To the best of our knowledge, this is the most accurate noninvasive *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 intracardiac pressures versus 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 procedure and to evaluate if the results from the pre-clinical studies are translatable to a clinical population.

Materials and Methods

The study was approved by the Institutional Review Board. Patients over the age of 21 years, who were scheduled for clinically indicated left and right heart catheterization, were included in the study. Exclusion criteria 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 where 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, N Billerica, MA) microbubbles could traverse as a bolus, females who were pregnant or nursing and patients with known hypersensitivity to Definity. For patients who provided written informed consent, grayscale imaging was performed before the catheterization procedure with a Sonix RP scanner and a PA4-2 transducer (BK Ultrasound, Richmond, 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 set up using a calibrated hydrophone). For the data acquisition in this proof-of-concept study, three incident acoustic outputs corresponding to 0 dB (100% acoustic output; 897 kPa_{peak-to-peak}), -2 dB (79% acoustic output) and -4 dB (63% acoustic output) were selected based on our previous results with these incident acoustic pressures *in vitro* and pre-clinical work (Dave et al. 2011, 2012b, 2012c, Halldorsdottir et al. 2014, Shi et al. 1999).

Definity was the contrast agent selected for this study based on previously proven ambient pressure sensitivity of the subharmonic signals from Definity microbubbles (Halldorsdottir et al. 2011) and given that Definity is already FDA approved for left ventricular opacification studies. Definity consists of a sterile, non-pyrogenic suspension of liposome-encapsulated perfluoropropane microbubbles with the mean diameter ranging from 1.1 µm to 3.3 µm with 98% microspheres having size less than 10 µm. Two vials of activated Definity were mixed with 50 ml of saline for intravenous contrast infusion. This infusion was administered via an existing intravenous line port in the antecubital vein.

As a part of the cardiac catheterization procedure, the interventional cardiologist advanced a standard pressure catheter under fluoroscopic guidance into the cardiac chambers for clinical pressure measurements under conscious sedation. For the right ventricle, the catheters used were 7 Fr (pulmonary wedge catheter, Medtronic, Minneapolis, MN; Swan Ganz catheter, Edwards Lifesciences, Irvine, CA; Berman Swan catheter, Arrow International Inc., Reading, PA) and for the left ventricle, the catheters used ranged from 4 to 6 Fr (Pigtail or coronary catheters, Cordis – Cardinal Health, Fremont, CA). Once the presence of the pressure catheter in a cardiac chamber was confirmed by fluoroscopy, Definity microbubbles were infused at a rate of 4–10 ml/min as per the manufacturer's recommendation. The presence of Definity in the cardiac chambers was visually confirmed and ultrasound data was acquired using a pulsed Doppler gate positioned in the cardiac chamber (Fig. 1). Three acquisitions (5 s per acquisition) were performed synchronously with pressure catheter measurements at each of the three incident acoustic output levels. All other scanning parameters (e.g., pulse repetition frequency, focal zone, depth of pulse gate, gate size, etc.) were optimized for each patient individually. After acquiring the ultrasound and pressure catheter data from the left or the right ventricle, Definity infusion was stopped. The interventional cardiologist repositioned the catheter in the other ventricle, Definity infusion was resumed, and the data were acquired as before. Thus, overall data were acquired from the left and right ventricle at three different acoustic outputs. After ultrasound data acquisition, the catheterization procedure continued as per clinical standard of care.

Data Processing and Statistical Analysis

All the data were processed offline as described previously (Dave et al. 2011, 2012a). Briefly, the subharmonic amplitudes were obtained in a 0.25 MHz bandwidth around the theoretical subharmonic frequency (1.25 MHz). The resulting signal was processed using a

smoothing filter. The subharmonic maximum and minimum amplitudes at each incident acoustic output were compared and the acoustic output level with maximum range was considered to be the optimum acoustic output level for SHAPE in each case. Given that this is a proof-of-concept study for intracardiac SHAPE, the feasibility of obtaining SHAPE specific subharmonic data was assessed. Linear regression analysis was used to compare SHAPE and the pressure catheter data. The equation corresponding to the best-fit line resulting from the linear regression analysis was used to convert the subharmonic signal amplitude (in dB) to pressure values (in mmHg). All statistical analysis was done using IBM SPSS Statistics (Version: 23; IBM Corporation, Armonk, NY).

Results and Discussion

Clinical data

Overall 33 patients were approached for recruitment out of which fifteen patients declined to participate in the study. Eighteen patients provided written informed consent. For three of these patients the catheterization procedure was canceled due to other clinical conditions. Consequently, 15 patients (2 females and 13 males; age range: 49 to 80 years) comprised the study group. Thirteen of the patients in the study had undergone a heart transplant procedure in the past; a detailed list of patients' existing and other known conditions based on their medical history are summarized in Table 1.

For two patients, data from the left ventricle were not obtained because of aggravating conditions during the catheterization procedure (not related to Definity infusion) as noted by the interventional cardiologist. Therefore, left ventricle pressure catheter data was available from 13 patients and right ventricle pressure catheter data was available from 15 patients. Based on data from all patients, the peak systolic and minimum diastolic left ventricle pressures measured with the pressure catheter were 133 ± 19 mmHg (mean $\pm$ standard deviation) and 17 ± 5 mmHg, respectively. Based on data from all patients, for the right ventricle, the peak systolic and minimum diastolic pressures measured with the pressure catheter were 41 ± 12 mmHg and 14 ± 7 mmHg, respectively.

SHAPE data

Overall, no adverse events occurred during Definity infusion, even in this vulnerable population with a large number of existing clinical conditions (cf., Table 1). The overall contrast infusion time across all patients ranged from 8 to 13 minutes. A total of 304 RF data files were acquired and processed.

After processing the RF data files, data from 3 patients showed a low subharmonic signal to noise ratio due to extrinsic factors related to the infusion of contrast. In two cases the intravenous line was changed which led to loss of contrast and in the third case, there was a relatively long wait time between acquisitions because the patient (who was under conscious sedation) was repeatedly talking with the interventional cardiologist during SHAPE data acquisition. Data from these 3 cases were not processed further, because the subharmonic signal to noise ratio was too low (subharmonic signal amplitude close to the noise level). Further, for two additional patients, processed RF data from the left ventricle showed no

subharmonic amplitude dependence on incident acoustic output i.e., for the 3 different incident acoustic output levels, the subharmonic signal amplitude was the same. This indicated either low subharmonic signal generation or subharmonic signal saturation; both conditions in which the subharmonic signal is not sensitive to changes in ambient pressure. Thus overall, data from right ventricle of 12 patients and left ventricle of 8 patients were available for comparisons (Table 2).

Table 2 shows the subharmonic signal range and the corresponding pressure range obtained from the left and right ventricles of the patients. Figure 2 illustrates sample results from the right ventricle of two patients obtained not at and at the optimum incident acoustic output level. Overall the SHAPE data showed moderate correlation with pressure catheter data; for data from the left ventricle the correlation coefficient ranged from -0.3 to -0.6 and for data from the right ventricle the correlation coefficient ranged from -0.3 to -0.9 (Fig. 2). For the best correlation coefficient value of -0.9 the pressure errors between SHAPE and pressure catheter were 2.6 mmHg. On average, the sensitivity of subharmonic signal to changes in ambient pressure was 2.5 mmHg/dB and 10.8 mmHg/dB for data obtained from the right and left ventricles, respectively (Table 2). This relatively low sensitivity of subharmonic signals from the left ventricle as compared to those from the right ventricle in response to pressure changes, presumably contributed to the low correlation noted.

There were a number of challenges encountered in this proof-of-concept study. First, the planned data acquisitions were not obtained from all the patients. This was due to problems with contrast infusion in 3 patients and deteriorating clinical conditions during catheterization in 2 other patients; additionally data from the left ventricle in 2 patients showed no dependence of the subharmonic signal amplitude on the incident acoustic output (implying lack of subharmonic signal generation or subharmonic signal saturation). Second, all the ultrasound data were acquired under challenging conditions i.e., patients lying in the supine position where achieving an optimum acoustic window for cardiac imaging was difficult. Third, there were no additional techniques such as breath-holding that could be used to reduce patient motion and the patients coughed and/or spoke to the cardiologist during the procedure (as they were under conscious sedation). Over a single cardiac cycle, due to heart movements, local incident acoustic pressure variations may also occur and contribute to the correlation seen between the subharmonic signal amplitude and the ambient pressures. Fourth, this study was aimed to evaluate the efficacy of a new intracardiac pressure measurement technique, however it was tested in a group of patients (scheduled for left and right heart catheterization) with a number of different existing clinical conditions; in some cases the catheter pressure values were not periodic based on underlying disease state (cf., Fig. 2a). Fifth, the effect of possible variations in microbubble concentration resulting from placing the pulsed Doppler gate to acquire SHAPE data from different imaging planes, in the same patient in the same cardiac chamber, was not explicitly studied here. However, previous results have suggested that the subharmonic reduction for SHAPE, in response to ambient pressure changes, increased only slightly (< 2 dB) as the microbubble concentration was more than tripled (Shi et al. 1999).

Most importantly, the interventional procedure was on-going and there was limited time available for data acquisition. Therefore, all the possible incident acoustic outputs ranging

from -16 dB to 0 dB were not used for data acquisition; instead, only three incident acoustic output levels were used for data acquisition. The SHAPE technique is sensitive to incident acoustic output levels (Andersen and Jensen 2009, 2010, Dave et al. 2011, 2012b, 2012c, Eisenbrey et al. 2013, Frinking, et al. 2012, Halldorsdottir, et al. 2011, 2014, Shi et al. 1999), and the incident acoustic output level eliciting ambient pressure sensitive signals will vary from patient to patient based on attenuation differences between patients. The results of this study show that incorporating an automated real-time incident acoustic output optimization program may allow SHAPE data acquisition under optimal transmit settings. Our group has implemented an automated incident acoustic output optimization program for cases where the ambient pressure is not changing as much as it changes during a single cardiac cycle (e.g., portal vein pressures vs. cardiac pressures) (Eisenbrey et al. 2013). Varying ambient pressures encountered during a cardiac cycle require a different implementation of the incident acoustic output optimization program as compared to what has been implemented previously and this is the goal of ongoing research efforts (Esposito et al. 2017). The Sonix RP scanner was used in this study, because it provided access to the unprocessed radiofrequency data for subharmonic signal extraction. However, this platform could not be configured for real-time incident acoustic output optimization for cardiac pressure estimation.

Conclusion

This study evaluated the feasibility of noninvasive intracardiac pressure estimation using subharmonic signals from ultrasound contrast agents in humans. The data for this study were acquired under challenging circumstances. No adverse events attributable to the Definity microbubbles were noted even in this vulnerable population with a large number of existing clinical conditions. Overall the results showed correlation coefficients between the subharmonic amplitude and pressure catheters ranging from -0.3 to -0.6 and from -0.3 to -0.9 for data from the left and right ventricles, respectively. For cases in which the data were acquired at optimum incident acoustic outputs higher correlation was noted (e.g., -0.9) with low corresponding errors (e.g., 2.6 mmHg). However, a major limitation of this study was the fixed incident acoustic output levels selected for SHAPE and this highlights the need for automatically determining optimum acoustic output during scanning for each patient; this challenge remains to be addressed before deciding on the ultimate clinical applicability of cardiac SHAPE.

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Figure 1.

A snap-shot of ultrasound data-acquisition for SHAPE. In this case, a 4.5 mm pulsed-Doppler gate (arrow) was placed in the right ventricle of a patient for data acquisition.

Figure 2.

Sample results from right ventricle of 2 patients where SHAPE data were acquired not at (a; $r = -0.3$) and at (b; $r = -0.9$) optimum incident acoustic output. Solid line indicates SHAPE output whereas dotted line indicates the pressure catheter data.

Table 1

Existing and other known conditions of patients recruited in this study

Patient	Heart transplant	Diabetes	A-Fib [*]	By-pass	Obstructive sleep apnea	DVT [†]	Lipid disorders abuse	Substance	Smoker	NI-CM [‡]	CHF ^{**}	CAD [§]	Multiple Stents
1	✓	✓	✓	✓									
2				✓									
3	✓				✓								
4	✓												
5	✓	✓				✓							
6	✓						✓						
7													
8	✓	✓							✓	✓			
9	✓	✓											
10	✓	✓								✓			
11	✓						✓						
12	✓		✓										
13	✓												
14	✓	✓		✓			✓					✓	✓
15	✓												
Total	13	6	1	3	1	1	3	1	1	1	1	1	1

^{*} A-Fib: Atrial fibrillation;[†] DVT: Deep vein thrombosis;[‡] NI-CM: Non-ischemic 431 cardiomyopathy,^{**} CHF: Congestive heart failure;[§] CAD: Coronary artery disease

Table 2

Range of pressures and subharmonic signal amplitude values from the right and left ventricles of the patients in this study

Patient	Right Ventricle		Left Ventricle	
	Pressure (mmHg)	Subharmonic (dB)	Pressure (mmHg)	Subharmonic (dB)
1	35	NA *	132	NA *
2	18	12.5	104	5.5
3	18	18.8	115	13.1
4	18	15.0	NA †	NA †
5	28	NA *	97	NA *
6	35	6.4	91	5.0
7	20	7.0	97	14.9
8	31	8.5	144	6.0
9	39	6.4	138	26.3
10	30	10.3	118	5.8
11	17	12.0	NA †	NA †
12	27	NA *	112	NA *
13	34	12.2	123	NA ‡
14	25	7.8	119	8.9
15	28	10.1	113	NA ‡

* Data not considered in the analysis due to problems during contrast infusion;

† Left ventricle data not acquired due to aggravating conditions during catheterization noted by the attending interventional cardiologist;

‡ No dependence of subharmonic signal amplitude on the incident acoustic output.