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On Acquiring Intra-Cardiac Pressures Noninvasively in Real-Time Using Subharmonic Aided Pressure Estimation (SHAPE)

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Abstract—**Subharmonic aided pressure estimation (SHAPE) measures ambient pressure dependent subharmonic signals from contrast microbubbles. This study evaluated if Definity® (Lantheus Medical Imaging, N Billerica, MA, USA) or Sonazoid (GE Healthcare, Oslo, Norway) microbubbles are useful for real-time noninvasive intra-cardiac pressure estimation using SHAPE. Patients scheduled for a right and/or left heart catheterization procedure were approached to participate in this IRB approved study and provided written consent. During the standard-of-care catheterization procedure, a pressure catheter was advanced into the cardiac chambers or the aorta to obtain clinically relevant systolic and diastolic pressures. After catheter placement, the patients received either an infusion of Definity (40 patients; 2 vials in 50 mL of saline; infusion rate: 4-10 mL/min) or Sonazoid (41 patients; rate (mL/hour) = 0.18 x weight in kg co-infused with saline at 120 mL/hour). A customized interface on a SonixTablet scanner (Analogic Corporation, Peabody, MA, USA) was used to acquire SHAPE data synchronously with the pressure catheter data. Previously determined optimal transmit parameters were used for data acquisition with Definity ($f_{transmit}$: 3.0 MHz; chirp down pulse) and Sonazoid ($f_{transmit}$: 2.5 MHz; square wave pulse) microbubbles. An algorithm to determine optimum incident acoustic output was initiated for each patient (to account for attenuation differences). Then, SHAPE data were acquired at the optimum incident acoustic output. Linear correlation between the SHAPE and pressure catheter data were computed using MATLAB (Mathworks, Natick, MA, USA). The correlation coefficient between SHAPE and pressure catheter data obtained using Definity was -0.86 ± 0.06 (n=15) and -0.87 ± 0.06 (n=18) for data obtained from the left and right ventricles, respectively. In two cases, adverse events were observed post Definity infusion. Both events were resolved with return to baseline conditions. Using Sonazoid, the correlation coefficient between the SHAPE and pressure catheter data was -0.83± 0.05 (n=10) and -0.82 ± 0.06 (n=7) for data obtained from left and right ventricles, respectively. These results indicate that SHAPE is a useful technique to noninvasively obtain intra-cardiac pressures in real-time.**

Keywords— subharmonic signals, subharmonic aided pressure estimation, ultrasound contrast agents, incident acoustic output optimization, real-time noninvasive pressure estimation

I. Introduction

There are currently 92.1 million Americans suffering from multiple cardiovascular diseases or the after-effects of stroke [1]. Pressure measurements within chambers of the heart provide critical information for the diagnosis and management of these diseases. Currently, the only way to obtain intra-cardiac pressures is an invasive cardiac catheterization procedure. This procedure is not only invasive but also expensive and therefore, precludes frequent pressure monitoring. Hence, a noninvasive, accurate, and cost-effective approach for measuring intra-cardiac pressure is an unmet, clinical necessity for patients suffering from cardiovascular diseases.

A. Ultrasound Contrast Agents

Ultrasound contrast agents are gas-filled microbubbles (mean diameter < 8μm) with a lipid, protein, or polymer shell that traverse the entire vasculature [2-6]. When ultrasound contrast agents are insonated at acoustic pressures greater than 100 kPa, they act as nonlinear oscillators [5-6]. Energy components in the received echo signals at frequencies ranging from the subharmonic (half of transmit frequency) to higher harmonics are generated from these nonlinear oscillations [5-6]. The subharmonic signal has shown sensitivity to ambient pressures [7]. Therefore, a technique known as subharmonic aided pressure estimation (SHAPE) was developed to exploit this sensitivity [2-4, 7-9].

B. SHAPE - In Vitro

One of the first experiments investigating the pressure dependence of the backscattered fundamental, second harmonic, and subharmonic signals from contrast microbubbles was performed in 1999 by Shi et al. [7]. This study found that the subharmonic generation can be divided into three stages (occurrence, growth, and saturation) [7]. During the growth stage, the subharmonic component increases with acoustic pressure [7]. This stage is where Shi and co-workers found an excellent linear correlation (r = -0.98) between subharmonic amplitude and hydrostatic pressure [7]. The relationship between subharmonic amplitude variations and hydrostatic pressure variation found in this study forms the basis for SHAPE.

Halldorsdottir et al. also investigated the relationship between subharmonic signals and hydrostatic pressures using five ultrasound contrast agents [8]. Exceptional linear regressions (r^2 ranging from 0.97 to 0.99) between changes in the subharmonic signal and ambient pressure variations were reported [8]. The relationship between subharmonic amplitude variations and ambient pressure variations from different contrast agents provides additional evidence for SHAPE.

C. SHAPE - Preclinical and Clinical Studies

Using SHAPE for *in vivo* cardiac applications was initially examined in canines using the contrast agent Sonazoid (GE Healthcare, Oslo, Norway) [2, 3]. Systolic and diastolic pressures from the left and right ventricles in canines were obtained using a pressure catheter and the SHAPE technique [2, 3]. Errors between the techniques ranged from 0.0 to 3.4 mmHg for these systolic and diastolic pressures, and from -2.3 to 2.9 mmHg, for waveform derived indices such as the isovolumic relaxation rate.

Following the canine studies, a pilot study was performed in patients using Definity (Lantheus Medical Imaging, N Billerica, MA, USA), to compare intra-cardiac pressures acquired during cardiac catheterization with pressures estimated using SHAPE. Fifteen consenting adults scheduled for left and/or right heart catheterization were enrolled [4]. SHAPE data were acquired using a Sonix RP scanner (Ultrasonix Corp, Richmond, BC, Canada) at three incident acoustic output levels (0 dB or 100% acoustic output i.e., maximum output; -2 dB or 79% of the maximum value and -4 dB or 63% of the maximum value) [4]. Estimation errors between the SHAPE technique and the pressure catheter data were as low as 2.6 mmHg at the optimal incident acoustic output [4].

These studies were successful in that low errors (< 5 mmHg) were found between SHAPE data and pressure catheter data, but faced increased scanning time (> 5 minutes) and inability to determine optimal incident acoustic output for scanning in real-time. These limitations resulted in only 3 incident acoustic output levels being used for acquiring data in the pilot study [4]. Some patients were not scanned at the optimal incident acoustic output, due to these limitations.

We have developed, implemented, and tested an interface for real-time intra-cardiac SHAPE using a SonixTablet scanner (Ultrasonix Corp, Richmond, BC, Canada) [9]. This interface was tested in an *in vitro* study using a closed-loop flow system (0.1 mL Definity, 750 ml isotonic diluent, and a pressure catheter) [9]. Linear correlation between the simultaneously acquired catheter and subharmonic data revealed a higher range of correlation coefficient values between the catheter and subharmonic data at the optimal incident acoustic output level (-0.6 to -0.9), than below and above the optimal incident acoustic output level (-0.4 to -0.8 and -0.6 to -0.8, respectively) [9]. This *in vitro* study concluded that the customized interface addressed the limitations in the pilot study [9]. Therefore, the purpose of this work was to evaluate the efficacy of the SHAPE technique for real-time determination of intra-cardiac pressures using this customized interface that addresses the limitations of previous studies.

II. MATERIALS AND METHODS

In this IRB approved study, patients over the age of 21 who were scheduled for left and/or right heart catheterization were screened as per inclusion and exclusion criteria for Definity and Sonazoid provided by the contrast agent manufacturers. Study-eligible patients were approached for consent. In a previous study, Definity was found to be the most sensitive to changes in ambient pressure, among the FDA approved ultrasound contrast agents [8]. Of all the contrast agents investigated in our previous study, Sonazoid was found to be the most sensitive to changes in ambient pressure [8]. Thus, both Definity and Sonazoid were used in this study.

For consenting patients, grayscale imaging was performed before the catheterization procedure using a SonixTablet scanner and a PA4-2 transducer (Analogic Corporation, Peabody, MA, USA) to determine an optimum acoustic window for SHAPE data acquisition during cardiac catheterization (when the patient would be in the supine position).

A. Data Acquisition for SHAPE

Using the SHAPE algorithm (Fig. 1), a customized interface was developed and implemented on a SonixTablet scanner for real-time intra-cardiac SHAPE (Fig. 2). Each patient was scanned using this customized interface. Briefly, this interface enables each patient to be scanned at all 16 incident acoustic outputs available on the ultrasound scanner and performs a real-time determination of the optimal incident acoustic output. For patients scanned using Definity, a transmit frequency of 3.0 MHz and a chirp down pulse were used. For patients scanned using Sonazoid, a transmit frequency of 2.5 MHz and a square wave pulse were used. These settings were the optimal parameters for real-time intra-cardiac SHAPE as determined in a previous study [10]. A PA4-2 transducer was used for data acquisition along with a pulse inversion technique.

During the cardiac catheterization procedure, an interventional cardiologist advanced the pressure catheter (femoral/radial/carotid access) into the cardiac chambers or the aorta using fluoroscopic guidance to obtain clinically relevant cardiac pressures. Once the placement of the pressure catheter in the cardiac chamber was confirmed, Definity or Sonazoid microbubbles were infused into the patient. Patients that were scanned using Definity received a continuous infusion at a rate of 4-10 mL/min from two vials of activated Definity mixed in 50 mL of saline. Patients that were scanned using Sonazoid received a continuous infusion of Sonazoid at a rate equivalent to 0.18 ml/hour/kg x patient-weight (in kg) co-infused with saline at 120 mL/hour. For both sets of subjects, the contrast infusion was administered using an existing intravenous line.

The SHAPE algorithm (flowchart shown in Fig. 1) was initiated using the customized interface. Briefly, raw RF data were acquired at each of the 16 incident acoustic output levels (10 seconds of data at each incident acoustic output level) [9].

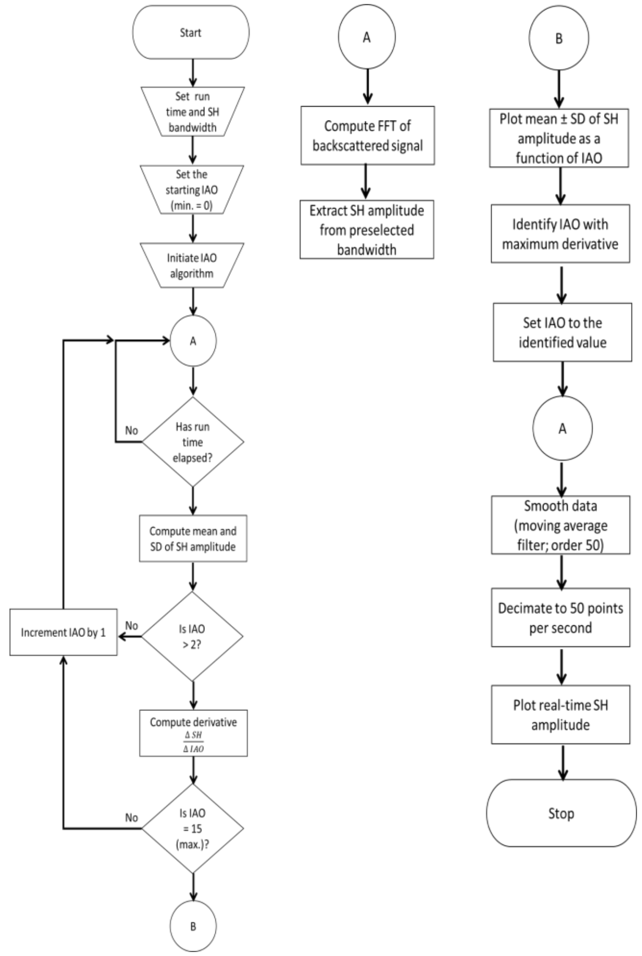

Fig. 1: Flowchart of the SHAPE algorithm implemented on the SonixTablet scanner. This backend SHAPE algorithm is accessed via a customized interface that allowed configuration of transmit and receive parameters, and real-time display of imaging as well as SHAPE data. (IAO – incident acoustic (acquired for 10 seconds for each patient) output; FFT – fast Fourier transform; SD – standard deviation; SH – subharmonic amplitude; min. – minimum and max. – maximum).

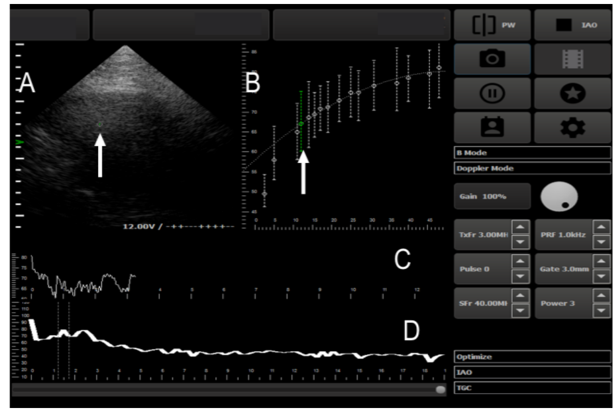

Fig. 2: An example of the customized interface after the incident acoustic output optimization algorithm has been executed. (A) depicts the grayscale image in real-time (arrow shows the PW gate within the right ventricle of a patient scanned using Definity microbubbles). (B) depicts the mean subharmonic amplitude ± standard deviation as a function of incident acoustic output levels along with the third order polynomial fit. The green marker (arrow) represents the optimal incident acoustic output level. (C) shows the real-time subharmonic amplitude as a function of time at the selected IAO level from (B). (D) depicts the average FFT of the received pulses in real-time and the dotted lines represent the 0.5MHz bandwidth around the subharmonic frequency.

The optimal incident acoustic output was determined in real-time by the customized interface. The SHAPE data was processed, and the subharmonic amplitudes were obtained, via the customized interface, using a 0.5 MHz bandwidth around the theoretical subharmonic frequency (1.5 MHz for Definity and 1.25 MHz for Sonazoid microbubbles). Then the subharmonic signal was processed using a median filter, order 250. This data was compared to the simultaneously acquired pressure catheter data. After SHAPE data acquisition, the cardiac catheterization continued as per clinical standard of care.

B. Data and Statistical Analysis

A linear regression analysis was used to compare SHAPE and pressure catheter data. All processing/statistical analysis was done using MATLAB (Mathworks, Natick, MA, USA).

III. Results and Discussion

A total of 81 patients provided written informed consent (41 patients received Sonazoid infusion and 40 patients received Definity infusion). For Definity, 55% of the patients recruited were male and 45% were female. The average age for patients scanned using Definity was 64 years (range: 40 to 81 years). An example of the relationship between pressure catheter and SHAPE data using Definity microbubbles is shown in Fig. 3. The mean value (± standard deviation) of the correlation coefficient between SHAPE and pressure catheter data obtained using Definity was -0.86 ± 0.06 (n = 15) and -0.87 ± 0.06 (n = 18) for data obtained from the left and right ventricles, respectively.

For Sonazoid, 65% of the patients recruited were male and 35% were female. The average age for patients scanned using Sonazoid was 62 years (range: 32 to 81 years). An example of the relationship between pressure catheter and SHAPE data for patients scanned using Sonazoid microbubbles is shown in Fig. 4. For Sonazoid, the mean value (± standard deviation) of the correlation coefficient between SHAPE and pressure catheter data was -0.83 ± 0.05 (n = 10) and -0.82 ± 0.06 (n =7) for the left and right ventricle, respectively.

In two cases, adverse events were observed using Definity. Each of these events were resolved with a return to baseline conditions. There were no adverse events observed during infusion of Sonazoid.

The negative correlation for both Sonazoid and Definity data matches the inverse linear relationship between SHAPE and hydrostatic pressure previously noted [2-4, 7,8]. The range of correlation coefficient values from data acquired from the left ventricle were -0.71 to -0.93 and -0.72 to -0.88 for Definity and Sonazoid, respectively. For data acquired from the right ventricle, the correlation coefficient values were -0.72 to -0.93 and -0.72 to -0.91 for Definity and Sonazoid, respectively. Both of these data sets had a smaller range and higher correlation coefficient values than what was found in the pilot study (-0.3

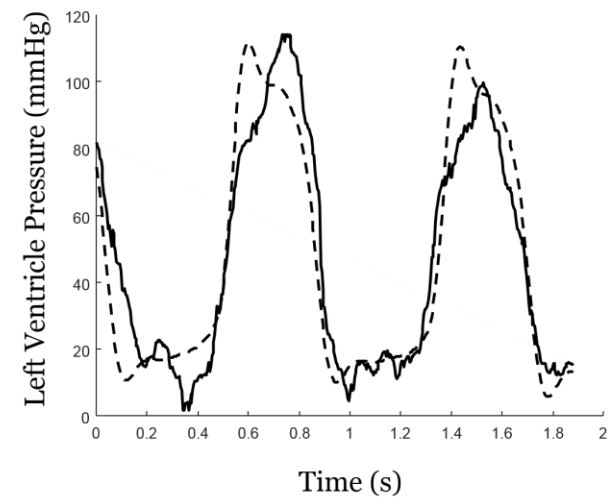

Fig. 3: Catheter (dotted line) and SHAPE (solid line) data from a 64 year old female with non-rheumatic mitral regurgitation scheduled for a left and right heart catheterization. Relationship between SHAPE and pressure catheter data at the optimal incident acoustic output using Definity microbubbles. The linear correlation between the SHAPE and pressure catheter data depicted above is -0.93.

to -0.6 and -0.3 to -0.9 for data acquired from the left and right ventricle respectively) [4]. While this is an ongoing study, these preliminary results indicate that the utilization of this customized interface addresses the inability to determine the optimal incident acoustic output for intra-cardiac SHAPE in real-time, which was a major limitation of the pilot study [4].

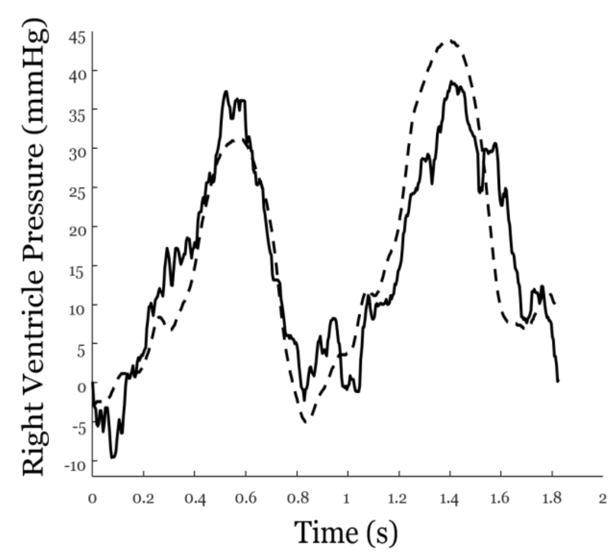

Fig. 4: Catheter (dotted line) and SHAPE (solid line) data from a 60 year old male with a left ventricular assist device and awaiting organ transplant that was scheduled for a right heart catheterization. Relationship between SHAPE and pressure catheter data at the optimal incident acoustic output using Sonazoid microbubbles. The linear correlation between the SHAPE and pressure catheter data depicted above is -0.90.

Overcoming this limitation places us one-step closer to using SHAPE to monitor intra-cardiac pressures in the clinic.

IV. Conclusion

The use of the SHAPE technique as a noninvasive method to gain real-time intra-cardiac pressures was investigated in patients. Results indicate that SHAPE may be used to monitor intra-cardiac pressures in real-time.

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