Ultrasonics 53 (2013) 880–888

Contents lists available at SciVerse ScienceDirect

Ultrasonics

journal homepage: www.elsevier.com/locate/ultras

On the implementation of an automated acoustic output optimization algorithm for subharmonic aided pressure estimation

J.K. Dave [a,b], V.G. Halldorsdottir [a,b], J.R. Eisenbrey [a], D.A. Merton [a], J.B. Liu [a], P. Machado [a], H. Zhao [a,1], S. Park [c,2], S. Dianis [c,3], C.L. Chalek [c], K.E. Thomenius [c], D.B. Brown [a], F. Forsberg [a,*]

[a] Department of Radiology, Thomas Jefferson University, Philadelphia, PA 19107, USA
[b] School of Biomedical Engineering, Science and Health Systems, Drexel University, Philadelphia, PA 19104, USA
[c] GE Global Research, Niskayuna, NY 12309, USA

ARTICLE INFO

Article history:
Received 31 October 2012
Received in revised form 20 December 2012
Accepted 20 December 2012
Available online 2 January 2013

Keywords:
Noninvasive pressure estimation
Ultrasound contrast agents
Incident acoustic output optimization
Portal hypertension
Subharmonic ultrasound signals

ABSTRACT

Incident acoustic output (IAO) dependent subharmonic signal amplitudes from ultrasound contrast agents can be categorized into occurrence, growth or saturation stages. Subharmonic aided pressure estimation (SHAPE) is a technique that utilizes growth stage subharmonic signal amplitudes for hydrostatic pressure estimation. In this study, we developed an automated IAO optimization algorithm to identify the IAO level eliciting growth stage subharmonic signals and also studied the effect of pulse length on SHAPE. This approach may help eliminate the problems of acquiring and analyzing the data offline at all IAO levels as was done in previous studies and thus, pave the way for real-time clinical pressure monitoring applications. The IAO optimization algorithm was implemented on a Logiq 9 (GE Healthcare, Milwaukee, WI) scanner interfaced with a computer. The optimization algorithm stepped the ultrasound scanner from 0% to 100% IAO. A logistic equation fitting function was applied with the criterion of minimum least squared error between the fitted subharmonic amplitudes and the measured subharmonic amplitudes as a function of the IAO levels and the optimum IAO level was chosen corresponding to the inflection point calculated from the fitted data. The efficacy of the optimum IAO level was investigated for *in vivo* SHAPE to monitor portal vein (PV) pressures in 5 canines and was compared with the performance of IAO levels, below and above the optimum IAO level, for 4, 8 and 16 transmit cycles. The canines received a continuous infusion of Sonazoid microbubbles (1.5 μl/kg/min; GE Healthcare, Oslo, Norway). PV pressures were obtained using a surgically introduced pressure catheter (Millar Instruments, Inc., Houston, TX) and were recorded before and after increasing PV pressures. The experiments showed that optimum IAO levels for SHAPE in the canines ranged from 6% to 40%. The best correlation between changes in PV pressures and in subharmonic amplitudes ($r = -0.76$; $p = 0.24$), and between the absolute PV pressures and the subharmonic amplitudes ($r = -0.89$; $p < 0.01$) were obtained for the optimized IAO and 4 transmit cycles. Only for the optimized IAO and 4 transmit cycles did the subharmonic amplitudes differ significantly ($p < 0.01$) before and after increasing PV pressures. A new algorithm to identify optimum IAO levels for SHAPE has been developed and validated with the best results being obtained for 4 transmit cycles. The work presented in this study may pave the way for real-time clinical applications of estimating pressures using the subharmonic signals from ultrasound contrast agents.

1. Introduction

The goal of this study was to develop, implement and validate an algorithm to automatically determine optimum incident acoustic output (IAO; i.e., the acoustic output from an ultrasound transducer incident on a region of interest) for subharmonic aided pressure estimation (SHAPE). A secondary goal of this study was to compare SHAPE's performance with 4, 8 and 16 transmit cycles. The clinical relevance and *in vivo* applications of SHAPE have been documented [1–4]. The current study builds on previous *in vitro* and *in vivo* SHAPE studies [1–7] and solves the problem of determining optimum IAO levels to insonate the ultrasound contrast agents (UCAs) for SHAPE applications. If successful, this approach may help eliminate the problems of acquiring and analyzing the data offline at all IAO levels as was done previously [1–3,6] and, thus, pave the way for real-time clinical pressure monitoring applications.

* Corresponding author. Address: 7 Main, Suite 763J, 132 South 10th Street, Philadelphia, PA 19107, USA. Tel.: +1 215 955 4870; fax: +1 215 955 8549.
E-mail address: flemming.forsberg@jefferson.edu (F. Forsberg).
[1] Present address: Department of Ultrasound, The Second People's Hospital of Fujian, Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian 350003, China.
[2] Present address: Samsung Advanced Institute of Technology, Yongin-si, Gyeonggi-do 446-712, South Korea.
[3] Present address: Philips Healthcare, Andover, MA 01810, USA.

0041-624X/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ultras.2012.12.010

1.1. Ambient pressure estimation using ultrasound contrast agents

A review of techniques to estimate ambient pressures using microbubbles has been provided in this section. Techniques to estimate ambient hydrostatic pressures using UCAs have been proposed [8–13]. Amongst these, techniques based on utilizing a shift in resonance frequency [9], amplitude of single bubble echoes [10], dual frequency excitations to calculate ambient pressure modulated size changes [12] and onset of ambient pressure modulated cavitations [11] have been tested with free microbubbles (mostly comprising of air) and errors in the range of 10–15 mmHg with respect to true pressure values were reported.

Modern UCAs are encapsulated microbubbles containing gases such as C_4F_{10} or SF_6 that have relatively low diffusivity relative to air (coefficient of diffusivity of air, C_4F_{10} and SF_6 in water are 2.05×10^{-9} m^2/s, 0.69×10^{-9} m^2/s and 1.20×10^{-9} m^2/s, respectively [14]) [15]. These UCAs have diameters less than 8 μm and can traverse the entire vasculature including the capillaries [15]. *In vivo* the UCAs provide a source of acoustic impedance mismatch relative to blood and a difference in compressibility between the gas contained within these microbubbles and the blood resulting in relatively strong backscattered signals (about 10–30 dB enhancement) [15]. Apart from a backscattered signal at the insonation frequency (f_0), these UCAs also backscatter signals at the subharmonic ($f_0/2$), harmonic ($n * f_0$; $n \in$ N) and ultraharmonic ($((2n-1)/2) * f_0$; $n \in$ N & $n > 1$) frequencies [15].

Two techniques to utilize these modern UCAs for ambient pressure estimation have been proposed; one based on dissolution time of free microbubbles following rupture of encapsulated microbubbles [8] and the second one based on ambient pressure modulated subharmonic signal amplitude referred to as SHAPE [13]. However, techniques based on dissolution time of free microbubbles yielded errors as high as 50 mmHg [8], which are not clinically practical. In clinical practice errors less than 5 mmHg are desirable for most applications.

1.2. Subharmonic aided pressure estimation (SHAPE)

In this section, the theory and previous studies of SHAPE have been summarized. The subharmonic signal amplitude from UCAs exhibits a sigmoidal relationship with IAO showing three distinct stages – occurrence, growth and saturation [13,16,17]. The growth stage subharmonic signal amplitudes were shown to be sensitive to ambient pressures and the subharmonic signal amplitudes in the growth stage decreased linearly with an increase in ambient pressures [13]. Other independent studies have also reported on ambient pressure modulated subharmonic amplitudes [18–23].

A proof-of-concept *in vivo* study showed that SHAPE predicted canine aortic pressures with a maximum standard error of 5.4 mmHg compared to pressure catheter measurements (the reference standard), but the experimental setup used in that study was not suitable for clinical implementation [4]. Subsequently, another *in vitro* study undertaken to compare the performance of different UCAs for SHAPE showed that subharmonic signals from Sonazoid microbubbles (GE Healthcare, Oslo, Norway) were most sensitive to ambient pressure changes; the sensitivity of Sonazoid microbubbles to ambient pressure changes peaked at an insonation frequency of 2.5 MHz and 0.35 MPa IAO [7]. Sonazoid microbubbles contain a perfluorobutane gas encapsulated in a membrane of hydrogenated egg phosphatidyl serine, have a volume median diameter of 2.6 ± 0.1 μm and contain about 1.2×10^9 microbubbles per ml [24]. Sonazoid microbubbles are commercially available, have a proven safety profile [25] and are approved for clinical use [26]. *In vivo* SHAPE documented errors in the range of 0.0–3.5 mmHg when estimating cardiac pressures in canines [2,3]. Further, data obtained from a previous *in vivo* study geared towards tracking portal vein (PV) pressures in canines using SHAPE, indicated that out of 2, 3 and 4 transmit cycles, SHAPE worked best with 4 transmit cycles [1].

A major limitation in the above studies [1–4,7] impeding real-time clinical applications is the lack of knowledge of the IAO levels on the Sonazoid microbubbles *in vivo*. The IAO levels may be known at the transducer focal point based on *in vitro* measurements using a hydrophone, but these IAO levels will differ *in vivo* based on the scanned anatomy and patient body habitus. The IAO levels determine the stage of the subharmonic signal amplitude including the growth stage in which the subharmonic signal amplitudes are sensitive to ambient pressures. Hence, a failure to elicit subharmonic signals in the growth stage will result in erroneous pressure estimation when using SHAPE.

2. Materials and methods

2.1. Animal preparation

This research study was approved by the Institutional Animal Care and Use Committee of Thomas Jefferson University and conducted in accordance with the guidelines provided by the National Institutes of Health. Five canines were used in this study (mean weight: 22.4 ± 1.72 kg). Proof of the value offered by the SHAPE technique for PV pressure monitoring was already provided elsewhere [1]. In this study, the efficacy and function of the automated IAO optimization algorithm was evaluated and thus, only five canines were used. The canines were fasted for a period of 12 h prior to the experiments, to reduce post-prandial effects on the flow and, thus, the pressures in the PV [27]. An intravenous injection of Propofol (Abbott Laboratories, Chicago, IL; dose 7 ml/kg) was used as the initial anesthetic. During the course of the experiments, the animals were intubated and anesthesia was maintained with 0.5–2.0% Isoflurane (Iso-thesia; Abbott Laboratories) via an endotracheal tube. The canines were placed on a warming blanket to maintain normal body temperature. An 18 gauge catheter was placed in a forelimb vein for Sonazoid infusion (1.5 μl/kg/min with 0.9% saline administered at 2 ml/min). The canines' respiration, ventilation, oxygenation, electrocardiogram, temperature and anesthesia were monitored by certified veterinary technicians throughout the study.

A midline abdominal incision was created to provide access to the main PV. A 5F pressure catheter (SPR 350S/SPR 350, Millar Instruments, Inc., Houston, TX) was surgically introduced into the main PV to provide the reference PV pressures. An additional surgical inlet to the main PV was also created to induce portal hypertension (PH; increase in PV pressures). Pathophysiologically, an increase in intra-hepatic vascular resistance contributes to PH [28–30]. Gelfoam (Ethicon, Somerville, NJ) was used for embolization of liver circulation; it has been used previously in canines with no inflammatory response or foreign body reactions [31,32]. Also, an acute model of PH induced with Gelfoam was used previously and this model was relatively straightforward to implement with a success rate greater than 90% in canines [1,33]. Thus, Gelfoam was selected to induce PH in canines.

A sterile sheet of Gelfoam (100 cm^2) was cut into small pieces and diluted with saline. The resulting mixture was introduced into the PV via the additional surgical inlet to induce PH. The PV pressures were continuously monitored via the Millar pressure catheter. Following the experiments, the canines were sacrificed by intravenous injection of Beuthanasia (0.25 mg/kg).

2.2. Ultrasound scanner operation

The experimental setup is shown in Fig. 1. A Logiq 9 scanner (GE Healthcare, Milwaukee, WI) with a curved array 4C probe was