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Fluid flow measurement for diagnosis of ventricular shunt malfunction using nonlinear responses of microbubbles in the contrast-enhanced ultrasound imaging

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Abstract

Contrast-enhanced ultrasound imaging utilizing the nonlinear responses of microbubbles is proposed for identifying ventricular shunt malfunction. The developed method suppresses the signal from walls of a shunt catheter and background tissues, and allows accurate measurements of the cerebrospinal fluid flow within the shunt catheter using a relatively small concentration of microbubbles. The flow rates estimated in the linear mode were significantly underestimated (65% at 0.1 ml/min and 5.0% microbubble concentration) while estimates using the nonlinear mode were not. Overall, the nonlinear responses of microbubbles improve the estimation of flow rates in a shunt catheter at low concentrations of microbubbles.

Hydrocephalus is a condition with an excessive accumulation of cerebrospinal fluid (CSF) in the brain and may occur in both children and adults (1,2). It can be caused by improper drainage of CSF from the ventricles and subarachnoid space. The estimated prevalence of the hydrocephalus in children is 1-2 in 1000, and the excessive intracranial pressure (ICP) can significantly impair mental development and often cause cranial bulging in infants (2). A common treatment for hydrocephalus is placing a drainage tube, such as a ventricularperitoneal (VP) shunt, between the brain ventricles and the peritoneal cavity (3). However, complications including block-age, breakage, and leakage are associated with malfunctions of ventricular shunts (hereinafter referred to as shunt) (3–5).

When the shunt malfunctions, most patients experience symptoms (e.g., headache, vomiting, and papilledema) due to increased ICP. In 20% of cases, the symptoms can be misinterpreted, which lead to fatal circumstances (6). The nuclear medicine shuntograms have been recommended for the diagnosis of shunt malfunctions (5–7). However, this test has shown 2-36% false negative rates and requires injection of radioactive contrast agents

(6). Quantitative measurement of CSF flow in a shunt can help accurately diagnose shunt malfunctions and identify the need for further screening. Doppler ultrasound imaging, proposed previously for monitoring the flow, has limited sensitivity at low flow rates and has high angle dependency (8,9). In our recent study (10) we demonstrated that contrast-enhanced ultrasound speckle tracking imaging has potential use for diagnosing shunt malfunctions even at low flow rates.

Contrast-enhanced ultrasound imaging utilizes gas micro-bubbles that act as acoustic scatterers with a strong nonlinear response (11–13). Although microbubbles are FDA-approved contrast agents for cardiac ultrasound imaging, they are intended for intravenous (IV) administration. Hence, there can be safety concerns associated with injected microbubbles. Although injecting microbubbles for ultrasound imaging should be a safer option compared to injecting radioactive materials for shuntograms; it is desired to use lower doses of microbubbles to avoid any possible complications. Generally, nonlinear responses from gas microbubbles are stronger than the responses from the surrounding tissues (11,13). Thus, the nonlinear response helps differentiate between the microbubbles, the shunt catheter and the surrounding tissues. In this study, we utilize the nonlinear response of microbubbles to estimate fluid flow rate in a shunt, and investigate the influence of bubble concentration on the accuracy of fluid velocity estimation.

The experimental setup used to simulate fluid flow in a shunt catheter (Medtronic) is shown in Fig. 1. The catheter (inner diameter 1.2 mm and outer diameter 2.4 mm) in a water tank was submerged in water parallel to the surface of the ultrasound imaging transducer in the lateral direction of the imaging plane. The flow within the shunt catheter was controlled by a syringe pump (Cole Parmer) operating a 20 ml syringe. A microbubble solution (GE Healthcare Optison) was diluted to 5.0, 1.0, and 0.1% of the original concentration, and a 0.5 ml aliquot was injected into the shunt valve. The input flow rates (Q_{in}) of the fluid were set to 0.01, 0.05, and 0.1 ml/min to mimic low CSF flow rates. Given that the syringe pump flow rate was calibrated, the input flow rates were assumed to be the actual flow rates that were compared with the measured values.

For the imaging of microbubbles in the shunt catheter, pulse-inversion imaging technique (13,14) was implemented using an ultrasound imaging system (Verasonics V1). A linear array transducer (L7-4, 128 elements) was used to transmit a pulse at 3.75 MHz center frequency and the received signals (IQ data) were sampled at 22.5 MHz. The acoustic power was set to 6% during imaging to avoid bubble disruption (e.g., bubble motion and destruction) caused by the high susceptibility of microbubbles. Linear (i.e., B-mode) data were obtained from the received signals of the first pulse, and nonlinear (i.e., contrast-mode) data were generated by summation of the responses from the first and the second pulses, where the second pulse was an inverted replica of the first pulse. The shunt catheter was placed at a depth of 25 mm where the elevational focus of the transducer was located. The frame rate was 30 frames per second. For each flow rate and concentration of microbubbles, 30 frames of linear and nonlinear data were acquired. When the bubbles appeared and filled the shunt catheter within the imaged area, the time was set to 0 and data collection was initiated.

The displacements of the bubbles in the shunt catheter were estimated by a crosscorrelation based speckle tracking algorithm (15). Kernel sizes were 1.8 mm in lateral and 0.167 mm in axial directions. The geometry of the shunt catheter and the flow pattern are shown in Fig. 2. The velocities in the lateral direction [x-direction in Fig. 2(a)] were calculated from the two-dimensional estimates of the displacements for both the linear and nonlinear responses. Owing to beam width variation in the elevational direction, as shown in Fig. 2(b), the velocity estimates were averaged across the inner tube of the catheter affected by the ultrasound beam (10). Thus, the estimated velocity is the mean velocity of the bubbles within the elevational direction of the beam. To calculate the correction factor to compensate for the velocity averaging, the velocity profile was assumed to be a fully developed laminar flow. The estimated velocities in the catheter were compensated by the correction factor. Since the elevational beam width of the L7-4 array probe was 1.2 mm at the 25 mm depth, the correction factor was 1.33.

Spectral analysis of signals received from the catheter tube (for fundamental frequency) and from microbubbles in the linear and nonlinear modes was performed using Fourier transform. Also, mean values and standard deviations of velocity profiles were calculated from 30 frames of estimated velocities in the z-direction (-0.6 to 0.6 mm) of the inner tube of the catheter (Fig. 2). The velocity profiles from the linear and nonlinear responses were compared with the velocity profile of the laminar flow.

To quantitatively analyze the relationship of flow rate with bubble concentration, linear and nonlinear data were acquired at three different bubble concentrations (5.0, 1.0, and 0.1%) and varying CSF flow rates (0.01, 0.05, and 0.1 ml/min). Using the velocity estimates, the mean and standard deviation of flow rates were calculated for each input flow rate.

Ultrasound images of the shunt catheter in the linear and nonlinear modes are shown in Fig. 3. Linear mode images of the catheter without microbubbles and with 5% microbubbles in the flow are shown in Figs. 3(a) and 3(b), respectively, while a nonlinear mode image of the catheter with 5% microbubbles in the flow is presented in Fig. 3(c). In the linear mode image, the inner and outer tube walls were clearly visualized [Fig. 3(a)] and the received signal from the tube was observed to be stronger than that from the microbubbles inside the tube [Fig. 3(b)]. In contrast, the nonlinear signal from the microbubbles was dominant in the nonlinear mode whereas the tube wall was vaguely seen in the nonlinear mode image [Fig. 3(c)].

Frequency responses of microbubbles within the shunt catheter are shown in Fig. 4. The fundamental response from the tube wall confirmed that the pulse echo response of the transducer has a fundamental frequency at 3.75 MHz. Once the microbubbles were injected into the shunt valve, the fundamental frequency was dominant in the linear mode and nonlinear components in the second-harmonic (near 7.5 MHz) were also observed. In the nonlinear mode, nonlinear fundamental and harmonics from bubbles were obtained. The second harmonic response near 7.5 MHz in the nonlinear mode was approximately 18 dB higher than that in the linear mode.

Velocity profiles in the shunt catheter for known concentrations (5.0, 1.0, and 0.1%) are shown in Fig. 5. The laminar velocity profile at a flow rate of 0.1 ml/min is presented for comparison. As expected, the estimated velocity near the center of the catheter was high and that far from the center of the inner tube was low. It was clearly seen that the velocities estimated from nonlinear responses [Fig. 5(b)] were more accurate (i.e., less underestimated) than those estimated from linear responses [Fig. 5(a)].

In Table I, the measured flow rates at varying concentrations of microbubbles (5.0, 1.0, and 0.1%) compared with the input flow rates (0.01, 0.05, and 0.1 ml/min) were summarized. When the input flow rates were 0.1 and 0.05 ml/min with 5% microbubbles, the estimated flow rates in the nonlinear mode (0.0985 and 0.0504 ml/min) were close to the input flow rates (0.1 and 0.05 ml/min). However, the estimated flow rates in linear mode with 5.0% micro-bubbles were 65 and 42% underestimated at input flow rates of 0.1 and 0.05 ml/min, respectively. When the microbubble concentration was 1.0%, the estimated flow rates were 71.4% (0.10 ml/min) and 58.8% (0.05 ml/min) underestimated in the linear mode, and 13% (0.10 ml/min) and 9% (0.05 ml/min) underestimated in the nonlinear mode. However, when the flow rate was down to 0.01 ml/min, the estimated flow rates were significantly (more than 78%) underestimated in the linear mode.

This study shows that the estimation of flow rate in shunt catheters is sensitive to the concentration of microbubbles. Our results (Fig. 5, and Table I) prove that the nonlinear imaging of microbubbles can improve the accuracy of the estimation of flow rate. From Table I, we can see that the threshold of the concentration of microbubbles is related to the flow rate of the bubbles. Hence, injection of a high concentration of bubbles may be needed if the flow rate is low.

Underestimation of flow rate was mainly due to the signals produced by the wall of the shunt catheter. The shunt wall is a strong acoustic reflector and, therefore, produces reverberations. The signals from the wall were more prominent in the linear mode than in the nonlinear mode, as shown in Fig. 3. Pre-processing can be used to exclude the signals reflected from the walls of the catheter, but the reverberations may be difficult to remove in a clinical study. Thus, the nonlinear mode has an advantage owing the weak nonlinear signals generated from the wall of the catheter. In addition, the kernel size selected for calculation of cross-correlation can cause errors in velocity estimation, so optimization of the motion tracking algorithm including kernel size will be further investigated.

While a received signal in the linear mode is mainly composed of fundamental frequency, a received signal in the nonlinear mode contains additional frequency components (i.e., harmonics), as shown in Fig. 4. Thus, in the nonlinear mode, the quality of the crosscorrelation based speckle tracking method can be compromised when the displacements are estimated from IQ data. The velocity profiles were skewed such that the upper portion of the catheter located closer to the ultrasound transducer (near -0.6 mm position of the catheter in Fig. 5) showed lower velocities than the lower portion of the catheter (near 0.6 mm position of the catheter). This was mainly due to the adhesion of the bubbles to the catheter walls and the buoyancy forcing bubbles into the upper portion of the catheter. Although the effect was more noticeable in the nonlinear mode [Fig. 5(b)] since the

estimation was more accurate than that in the linear mode, our previous study (10) has shown that the linear mode clearly presented asymmetric velocity profiles when using a higher frequency (15 MHz) probe. The measurements can be optimized to reduce the asymmetry error by controlling the transmission power and bubble concentration.

In this study, we chose the concentration of microbubbles that could be used to reliably measure the expected flow rate (i.e., 0.10 ml/min at 5% microbubble concentration in the nonlinear mode). Although a low concentration of micro-bubbles can lead to the underestimation of flow rate, a high concentration of microbubbles can prevent fluid flowing due to the adhesion of the microbubbles to the catheter walls. To apply this technique in a clinical environment, a low dose of microbubbles should be used in order to avoid any medical complications. In addition, we need to consider other factors that can cause additional errors in the estimation of flow rate, such as the buoyancy forcing the bubbles to the upper wall of the catheter when the flow rate is low, and the high acoustic power that can push the bubbles to the lower wall of the catheter.

In this study, we demonstrated that the nonlinear responses from microbubbles can be utilized to improve detection of flow in a shunt system using a reduced concentration of bubbles.

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Fig. 1.
Experimental setup to image the flow in a shunt catheter using an ultrasound imaging system.

Fig. 2.

Geometry of the shunt catheter (a) in lateral direction, (b) in elevational direction. x : lateral direction (direction of flow), y : elevational direction, z : depth, R : inner radius of the catheter, $2r_0$: elevational beam width.

Fig. 3.

Ultrasound images of the shunt catheter, (a) Linear mode (B-mode) image of shunt without microbubbles, (b) linear mode (B-mode) image of shunt with microbubbles (5% of concentration), and (c) nonlinear mode (contrast mode) image of shunt with microbubbles (5% of concentration).

Fig. 4. Frequency responses from microbubbles in linear (Bubble-Linear) and nonlinear modes (Bubble-Nonlinear). Fundamental response is a pulse-echo response from transducer in the frequency domain.

Fig. 5.

Velocity profiles (at flow rate of 0.1 ml/min) for laminar flow, and mean values and standard deviations of velocity estimates for known concentrations (5.0%, 1.0%, and 0.1%) in the shunt catheter in (a) linear and (b) nonlinear modes.

Table I

Estimated flow rates for varying bubble concentrations in linear and nonlinear modes.

Flow rate [ml/min]	Bubble conc. [%]	Estimated flow rate (mean std) [ml/min]	
		Linear mode	Nonlinear mode
0.10	5.0	0.0348 ± 0.0026	0.0985 0.0115
0.10	1.0	0.0286 ± 0.0021	0.0870 ± 0.0075
0.10	0.1	0.0206 ± 0.0009	0.0373 ± 0.0045
0.05	5.0	0.0291 ± 0.0013	0.0504 ± 0.0053
0.05	1.0	0.0206 ± 0.0009	0.0456 0.0035
0.05	0.1	0.0003 ± 0.0001	0.0050 0.0018
0.01	5.0	0.0022 ± 0.0001	0.0072 0.0009
0.01	1.0	0.0010 ± 0.0002	0.0037 0.0009
0.01	0.1	0.0003 ± 0.0001	0.0031 0.0015