Editorial Commentary

Advocating for the implementation of SonoVue microbubbles as pressure sensors: a call to action for clinical noninvasive pressure estimation

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Pressure measurement within the body is of pivotal significance in the diagnosis of vascular and organ-related diseases associated with hydrostatic pressure. At present, the most commonly used clinical method is to insert a catheter along with a pressure sensor and then guide it to the area of interest through vessels such as central venous pressure (CVP). However, the presence of sensors within the vessel of interest will inevitably cause alterations to the circulation and thus affect blood pressure. Moreover, the use of invasive methods does not allow monitoring of every area inside the body.

Ultrasound contrast agents (UCAs), which are microbubbles, comprise a core of gas encased within a membrane made of lipids, proteins, or polymers. These agents are employed in contrast-enhanced ultrasonography (CEUS). UCA microbubbles can induce nonlinear oscillatory behaviors in the acoustic pressure field generated by ultrasound pulses (1). The nonlinear scattering signals of UCAs span a broad spectrum of frequencies, encompassing subharmonic frequencies (1/2*f*). And the subharmonic amplitude of the subharmonic scattering signal at a frequency $1/2f_{\text{transmit}}$ shows better ambient pressure sensitivity compared to fundamental harmonic amplitude (2). Additionally, these signals can be distinguished from those of tissue, improving the signal-to-noise ratio and facilitating the development of contrast-specific imaging modalities (3). Given that the acoustic properties of these gas-filled UCA microbubbles are closely correlated with the ambient pressure, they can serve as pressure sensors upon exposure to appropriate ultrasound stimulation (4). Allowing for a clinically acceptable level of sensitivity, the variation in subharmonic amplitude of the echo scattered by microbubbles has emerged as the most promising and suitable approach for clinical application. Presently, various studies have established a linear relationship between ambient pressure and the subharmonic signaling components emitted by various UCAs (5-7).

The team, directed by Prof. Forsberg, pioneered the revelation that UCAs could serve as noninvasive tools for pressure measurement, functioning as pressure sensors,

Table 1 Differences between Sonazoid and SonoVue contrast microbubbles

Contrast agent microbubbles	Physical structure and acoustic properties				
	Shell material	Core gas	Average diameter (μm)	Duration *in vivo* (min)	Frequency of resonance (MHz)
SonoVue™	Phospholipid	Sulfur hexafluoride	2.6	5	2.0
Sonazoid™	Hydrogenated egg phosphatidyl serine	Perfluorobutane	2. 1	30	4.4

through the observation of variations in the amplitude of subharmonic contrast bubble signals (2). This groundbreaking and innovative approach, termed subharmonic-aided pressure estimation (SHAPE), is predicated on the inverse linear relationship (r^2>0.90) between the amplitude of subharmonic signals and the ambient hydrostatic pressure. It is advocated for noninvasive pressure determination (2,8,9). The emergence of SHAPE enables the noninvasive measurement of absolute pressures and pressure gradients throughout the body. To date, extensive clinical trials have concentrated on the utilization of SHAPE in conjunction with Sonazoid for the diagnosis of clinically significant portal hypertension (PH) (9,10). PH represents a significant complication of cirrhosis and is deemed pivotal in the success of liver transplantation. However, validated non-invasive techniques for its measurement are currently lacking (11,12). In a 2013 study, Eisenbrey *et al.* (9) examined the relationship between SHAPE data and the hepatic venous pressure gradient (HVPG). The gradient derived from the SHAPE from the portal to hepatic veins demonstrated a strong concordance with the HVPG (R=0.82). Patients identified as having an elevated risk for variceal hemorrhage (HVPG ≥12 mmHg) had a significantly greater mean subharmonic gradient than patients with lower HVPGs (1.93±0.61 *vs.* −1.47±0.29 dB, P<0.001), accompanied by 100% sensitivity and 81% specificity, suggesting the potential of the SHAPE as an effective screening instrument for the diagnosis and prediction of PH in patients undergoing trans-jugular liver biopsy. A prospective, multicenter trial conducted by Gupta *et al.* (10) reported that participants diagnosed with PH (n=21), characterized by an HVPG of 10 mmHg or greater, exhibited a greater SHAPE gradient than those with lower HVPGs (n=91) (0.27±2.13 *vs.* −5.34±3.29 dB; P<0.001), and the SHAPE achieved a sensitivity of 91% [95% confidence interval (CI): 88–93%] and a specificity of 82% (95% CI: 75–85%), corroborating that the SHAPE correlates well with the HVPG and allows the identification of participants with PH and those at elevated risk of variceal bleeding. In addition, despite limited sample sizes, SHAPE and three-dimensional subharmonic imaging have demonstrated their potential for estimating imaging responses and outcomes to neoadjuvant chemotherapy in patients with breast cancer as early as after the completion of 10% of neoadjuvant therapy (13).

To date, some research has also made essential contributions to the application of SHAPE under other ambient pressures. Esposito *et al.* (14) extended the SHAPE with Definity microbubbles to detect intracardiac pressures noninvasively and accurately and found that the root mean square, mean, and median errors across data acquired from the right ventricle and left ventricle were <5 mmHg. Kalayeh *et al.* (15) demonstrated the applicability of the SHAPE in measuring bladder pressure based on the strong relationship between the SHAPE data and bladder phantom pressure. Li *et al.* (16) reported that the SHAPE technique can estimate alterations in pressure within the vascular system and has the potential to introduce a novel approach for monitoring the biomechanical properties of the carotid artery, as well as evaluating the vulnerability of carotid plaque. Qiao *et al.* (17) utilized SHAPE in conjunction with plane wave transmission to noninvasively assess the pressure distribution and fractional flow within the middle cerebral artery in an *in vitro* setting and found that the fractional flow value was highly consistent with the value measured by a sensor.

In the second generation of UCAs, both SonoVue and Sonazoid microbubbles exhibit greater stability but have structural differences from each other (18). As shown in *Table 1*, Sonazoid is characterized by hydrogenated

egg phosphatidyl serine and a perfluorobutane core, whereas SonoVue consists of a single phospholipid shell encapsulating an inert sulfur hexafluoride gas core. The above factors determine the potential difference in functional properties between the two in SHAPE. The function of SonoVue, which is mainly marketed and widely used in clinical diagnostics in China, as a pressure sensor in SHAPE technology has been less studied, and the conclusion is still unclear (7,19,20). Consequently, a series of experiments were undertaken by our research group with commercially accessible SonoVue microbubbles. These experiments explored the effect of acoustic parameters on the sensitivity of these microbubbles to pressure, as well as their potential for noninvasive pressure assessment. The outcomes garnered from these investigations were substantial and noteworthy. A previous experiment was carried out at ambient pressures in the range of 8–180 mmHg with an average gradient of change of 43 mmHg (19). The results indicated that SonoVue microbubbles under medium mechanical index (0.25–0.4) excitation exhibited high sensitivity and linearity for ambient pressure estimation based on subharmonic amplitude. Our *in vitro* experimental study carried out in a closed-loop dynamic flow experimental system demonstrated that the subharmonic amplitude of SonoVue microbubbles occurred in three stages with different incident acoustic pressures at 10 and 40 mmHg ambient pressure: the first growth stage (40–300 kPa), the saturation stage (300–400 kPa), and the second growth stage (400–540 kPa). In the first growth stage, the subharmonic amplitude increased with increasing ambient pressure (17). In the second growth stage, the subharmonic amplitude decreases with increasing ambient pressure and has the best correlation at an incident sound pressure of 520 kPa (r^2=0.99), possibly originating from microbubble destruction during the second growth stage (21). Similar experiments by Nio *et al.* reported that the subharmonic amplitude of SonoVue microbubbles increased as the ambient pressure increased. In their study, within the acoustic pressure range of 20–500 kPa at a frequency of 4 MHz, the subharmonic amplitude of SonoVue microbubbles increased with increasing ambient pressure, reaching its peak at 50 mmHg (7). However, they only observed one growth phase, which is different from our study. In the second growth stage, we observed that the amplitude of subharmonics decreased significantly when the sound pressure was between 450 and 500 kPa (19). These results are consistent with the subharmonic amplitude increase in the sound pressure curve of another experimental phospholipid-coated microbubble (Bracco Research S.A., Geneva, Switzerland) explored by Frinking *et al.* (22). Based on the conclusion that the subharmonic amplitude of the second growth phase of SonoVue correlates more strongly with ambient pressure and root mean square error than that of the first growth phase, Lu *et al.* established animal models of PH to carry out *in vivo* experiments (23). The findings revealed a linear association between the subharmonic amplitude of SonoVue microbubbles and portal venous pressure (PVP) (<20 mmHg) at an incident sound pressure of 453 kPa. Subsequent validation of this discovery was conducted through *in vivo* experimentation utilizing a canine model of pulmonary hypertension by Xu *et al.* (24). When the incident sound pressure was set to 563 kPa, the diagnostic performance for PH was 93.3%, the specificity was 91.7%, and the overall accuracy was 92.6%. These experimental results show that the subharmonic scattering of SonoVue provides a promising noninvasive method for evaluating PVP.

Currently, numerous clinical trials involving diverse ambient pressures and types of UCAs are underway investigating various applications of SHAPE in Asia, Europe, and North America (*Table 2*). Building upon the substantial evidence provided by existing studies (21,23,24), which suggest that subharmonic scattering signals derived from SonoVue microbubbles are a viable noninvasive alternative for assessing PVP *in vivo*, forthcoming research endeavors aim to evaluate the practical applicability of this methodology in a clinical setting. Moreover, the subharmonic scattering signal from SonoVue microbubbles has the highest sensitivity, accuracy, and specificity under specific conditions and can be extended to pressure measurements at other ambient pressures, such as ventricular pressure, carotid artery pressure, and bladder pressure. Although the results of the clinical trials are still pending, this nevertheless suggests that we may soon witness the integration of SHAPE into standard clinical practice.

Table 2 Clinical trials investigating various applications of SHAPE with diverse ambient pressures and types of UCA

Manometry environment	Type of UCA	Status	Phase	Country	Interventional Model	Study start date	ID
Portal vein pressures	Sonazoid	Completed	Phase 4	US	Single group assignment	2015-04-06	NCT02489045
	Sonazoid/Definity	Recruiting	Phase 3	US/ Switzerland	Parallel assignment	2022-11-28	NCT05470205
	Sonazoid/Lumison (SonoVue)	Recruiting	Phase 2	US	Parallel assignment	2021-11-03	NCT04720456
Intracardiac pressure	Sonazoid	Completed	Phase 2	US	Single center study/single group assignment	2017-12-04	NCT03245255
	Definity	Completed	Phase 2	US	Single group assignment	2017-06-01	NCT03243942
Pressure in the cancer	Definity	Recruiting	Phase 2 Phase 3	US	Single group assignment	2020-12-07	NCT04715958
	Definity	Recruiting	Early phase 2	US	Single group assignment	2020-11-24	NCT04721886
	Unknown	unknown	Phase 0	China	Unknown	2020-06-01	ChiCTR2000032911
Pressure gradient across the carotid plaque cap	Definity	Active, not recruiting	Phase 4	US	Single group assignment	2020-12-01	NCT04643431
	Sonazoid	Completed	Unknown	China	Unknown	2021-05	ChiCTR1900027295
Others	Definity	Completed	Phase 2 Phase 3	US	Parallel assignment	2020-07-01	NCT05247541

SHAPE, subharmonic-aided pressure estimation; UCA, ultrasound contrast agent; US, United States.

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Footnote

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