High frame rate contrast enhanced echocardiography: Microbubbles stability and contrast evaluation

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***Abstract*— Contrast Echocardiography (CE) with microbubble contrast agents have significantly advanced our capability in assessing cardiac function, including myocardium perfusion imaging and quantification. However in conventional CE techniques with line by line scanning, the frame rate is limited to tens of frames per second and image quality is low. Recent works in high frame-rate (HFR) ultrasound have shown significant improvement of the frame rate. The aim of this work is to investigate the MBs stability and the contrast improvement using HFR CE compared to CE transmission at an echocardiography relevant frequency for different mechanical indices (MIs). Our results show that the contrast and bubble destruction of HFR CE and standard CEUS varies differently as a function of space and MIs. At low MIs, HFR CE shows a similar behavior as focused CE with little MB destruction, and generates better CTR (up to 3 folds). As MI increases, the MB destruction is more significant for HFR CE with a reduction of the CTR.**

***Keywords*—** *Echocardiography, High frame rate / ultrafast contrast enhanced ultrasound, bubble disruption / stability, Contrast-to tissue ratio*

I. Introduction

Ultrasound contrast agents (UCA), or microbubbles, for contrast enhanced ultrasound (CEUS) imaging is revolutionalising the role of ultrasound that can play in clinical practice research [1]. These bubbles are highly sensitive to ultrasound, and once introduced into blood stream intravenously, they can generate significant signal enhancement. Various signal processing techniques have been developed in order to achieve highly sensitive, specific and quantitative imaging of the bubbles for flow and perfusion imaging [2], [3].

Another significant advance in biomedical ultrasound is the development of high frame-rate (HFR) ultrasound imaging techniques for various clinical applications [4]. More specifically different approaches have been proposed in order to improve the frame rate for cardiac acquisition: multi-line acquisition, multi-line transmission and diverging wave transmission [5-11]. The benefit of imaging with diverging waves has been shown for 3D cardiac Doppler [8] and cardiac elastography [9]. The first combination of HFR cardiac imaging using pulse inversion (PI) and diverging waves for contrast echocardiography (CE) ultrasound, named HFR CE, for *in-vivo* myocardium perfusion experiments was shown recently [11]. The contrast between the heart chamber full of ultrasound contrast agents and the myocardium was improved by a factor of 2 compared to standard focused transmission, even with a peak negative pressure for HFR CE that was 4 times lower than conventional focused CE transmission. While it has great potential for improved quantification of myocardium perfusion, it is not clear as whether the stability of microbubbles is reduced under HFR ultrasound.

Indeed during HFR CE, microbubbles are exposed to much more frequent ultrasound excitation than that of the conventional approach, potentially causing more bubble destruction. This may affect myocardium perfusion quantification. Existing studies on ultrasound contrast agent stability and contrast improvement only have evaluated HFR plane wave versus conventional CEUS transmission at high clinical frequencies where commercial MBs' behavior is very different from that at lower clinical ultrasound frequency used in cardiac imaging. In [12-13], plane wave transmission was evaluated for B-Mode images and CPS transmission. In [14] plane wave and focus amplitude modulation transmissions have been evaluated for different PNP (70 – 110 – 140 kPa). It was shown that plane wave transmission resulted in less destruction of UCAs compared to focused transmission as well as better contrast. However, plane wave transmission was at high clinical frequency (3.5 MHz and 7.5 MHz) and the destruction was only evaluated at a few centimetres (2.5 cm). In a previous conference [15], we have presented preliminary results of the acoustic stability of microbubbles and resolution improvement for cardiac HFR CE applications but in a free beaker.

The aim of this work is to investigate the MBs stability and the contrast improvement using HFR CE compared to conventional CE transmission at an echocardiography relevant frequency for different mechanical indices (MIs).

II. Materials and Methods

A HFR CE system based on a 128-Verasonics platform (Verasonics Inc., Redmond, WA) mounted with a 96 element P4-1 phased-array transducer was used during in-vitro experiments. In order to obtain a diverging wave, a virtual point source was created behind the probe creating a diverging beam which enlarge the region illuminated (Figure 1) [15].

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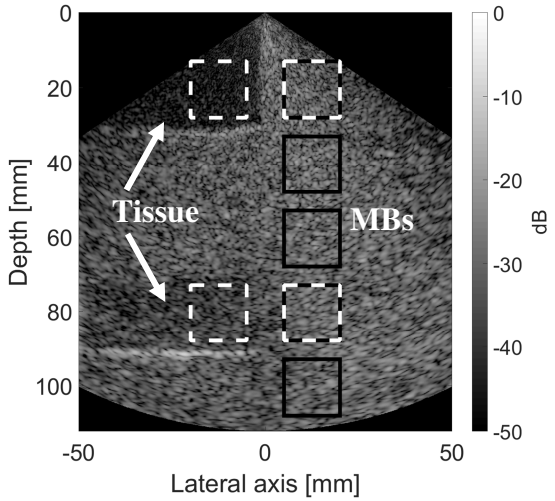

Fig. 1. Tissue phantom submerges in a diluted Sonovue suspension with the ROIs, 15 x 15 mm (depth x lateral), for disruption (black) and CTR (white) evaluation.

Similar to plane wave imaging, a single diverging wave has a low contrast and resolution. So a coherent diverging compounded image is obtained by varying the position (steering) of the virtual point source and by coherently averaging the echoes of the diverging transmissions. Moreover, for each steering angle, two successive pulses of opposite phase were transmitted and combined in post-processing to form the PI image. The transmission parameters are show in Table I. Several values of mechanical index (MI) were used. In the case of diverging transmission, the MI is obtained by using the spatial peak acoustic pressure close to the probe while for the focus, it is at the focal depth set at 80 mm.

TABLE I
TRANSMISSIONS PARAMETERS

	HFR-CE	CE
Frequency (Cycles)	1.25 / 1.50 / 1.75 MHz (3)	
Angle range	60	90
Number of angles/lines	7 (x2 PI)	82 (x2 PI)
Focus	---	80 mm
Frames (seconds)	1000 (2.86s)	80 (2.67s)
PRF	5000 Hz	5000 Hz
Frame rate	350 Hz	30 Hz
MI	0.05 / 0.10 / 0.15 / 0.20 / 0.25	

A tissue mimicking phantom, consisting of agar, was developed for evaluating the HFR CE method. The tissue mimicking phantom was composed of (percentage of the total weight): Agar 4%, water 95% and glass beads 1% (45 – 90 µm). The phantom was cut in order to have an F-shape. The phantom was set in a water tank filled with water (24°C) and a 1/40000 time's diluted solution of Sonovue ultrasound contrast agent. The solution is mixed by a magnetic stirrer and the stirring was stopped 50s before each acquisition in order to avoid flow during measurements. The P4-1 probe was held by a clamp and half of the transducer was in contact with the phantom.

The acoustic stability of UCAs and the contrast improvement were evaluated on 4 acquisitions as a function of

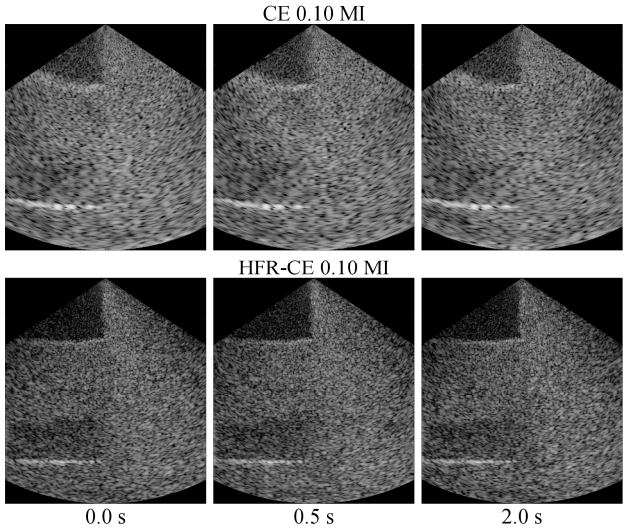

Fig. 2. Tissue phantom submerges in a diluted Sonovue suspension with CE (Top) and HFR-CE (Bottom) frames at 0.0, 0.5 and 2.0 s for 0.10 MI. The frames are normalized by the maximum intensity frame of the full sequence and displayed with a dynamic range of 50 dB.

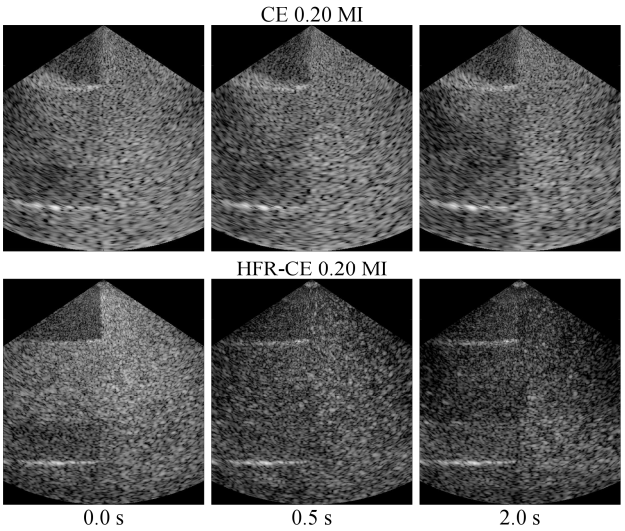

Fig. 3. Tissue phantom submerges in a diluted Sonovue suspension with CE (Top) and HFR-CE (Bottom) frames at 0.0, 0.5 and 2.0 s for 0.20 MI. The frames are normalized by the maximum intensity frame of the full sequence and displayed with a dynamic range of 50 dB.

MI and at several depths. The squares in Figure 1 show the different regions-of-interest (ROIs) where the acoustic stability (black squares) and the contrast improvement (white squares) are evaluated. The acoustic stability is defined as the disruption ratio. The disruption ratio at any time point for an ROI is calculated by normalizing the intensity of the microbubbles in the ROI at that time point against that at time zero [12]. The image quality improvement is evaluated by measuring the contrast between the agar tissue and the microbubbles. The contrast evaluation is based on the contrast-to-tissue (CTR) ratio defined as [13-14]:

$$CTR = 20 \log_{10}\left(\frac{\mu_{UCA}}{\mu_{Tissue}}\right) \quad (1)$$

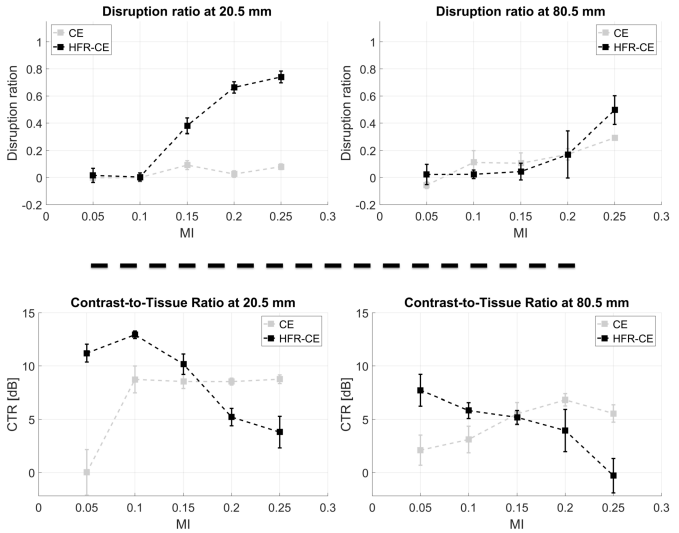

Fig. 4. Mean and standard deviation of HFR CE and CE (Top) disruption ratio and (Bottom) CTR as a function of MIs (Right) close to the probe and (Right) at the focus depth at 0.5s.

where in (1) μ_{UCA} and μ_{Tissue} are the mean in a ROI of the UCAs and tissue, respectively.

III. Results

Figure 2 and Figure 3 show three frames of CE (Top) and HFR CE (Bottom) at 0.0, 0.5, and 2.0 seconds for two MIs, 0.10 and 0.20, respectively. With 0.10 MI, for both transmission, there is visually no disruption of microbubbles (Figure 2). While at 0.2 MI, there are already some image intensity changes at 0.5s for HFR CE and apparent disruption for both techniques at 2.0s (Figure 3).

The Top of Figure 4 gives the disruption of UCAs as a function of MI at 20.5 mm and 80.5 mm. The Bottom of Figure 4 gives the CTR for the same depths and MIs. The values in the graphic are obtained after 0.5s of transmission of both technics. For both positions, the disruption of UCAs increases with the MI. The disruption of UCAs close to the probe is more significant for HFR CE for MIs superior to 0.1. However, at the focus depth, the disruption of both transmission types is similar. The CTR obtained close to the probe shows a higher CTR for HFR CE until 0.15 MI. At the focus depth, HFR CE CTR is better until 0.10 MI. The optimal contrast close to the probe is obtained with 0.10 MI while at the focus depth, it is with 0.05 MI.

Figure 5 shows the HFR CE disruption ratio and CTR as a function of time for 0.10, 0.15 and 0.20 MI close to the probe. For disruption and for all MI shown, there is a small negative bump quickly after the beginning of the transmission. Then for 0.10 MI, there is no disruption while for the other MI, the disruption increases until it reaches a plateau. For CTR, at 0.10 MI, the contrast is invariant. However for higher MI, the contrast decreases as a function of time. As disruption, after few milliseconds, there is a small bump for higher MI.

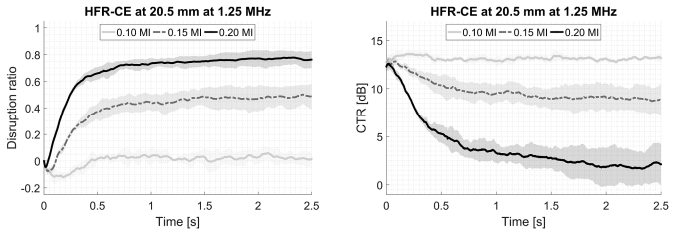

Fig. 5. Mean and standard deviation of HFR CE (Left) disruption ratio and (Right) CTR close to the probe as a function of time for 0.10, 0.15 and 0.20 MI.

IV. Discussion and Conclusion

This work presents the acoustic stability of ultrasound contrast agent, or microbubbles, as well as the contrast improvement for cardiac applications using high-frame-rate (HFR) pulse inversion (PI) diverging waves and standard contrast echocardiography (CE) ultrasound transmission. Previous research studies have highlighted the impact of the HFR acquisition on microbubbles stabilities but they were less relevant to cardiac applications because of their high frequencies transmission, and small imaging depth [12-14].

In this work, it can be seen that for a low frequency transmission, the bubble destruction of HFR CE and standard CE varies differently as a function of space and MI. At low MIs, HFR CE shows a similar behaviour as conventional CE with little microbubble destruction, and generates better CTR, up to 3 folds. As MI increases, the microbubbles destruction is more significant for HFR CE with a reduction of the CTR. The time comparison is also an important factor as it has been shown. Few milliseconds after the beginning of the transmission, the disruption decreases and then increase. For CTR it is the opposite, an increases after a decay. A similar effect has been observed in [12] where after a disruption pulse, the intensity of the microbubbles increases and decays. This phenomenon appears when, an emission higher than the disruption threshold is transmitted, microbubble's gas is freed from its shell and left to dissolve.

These results highlight the importance of this study in order to optimise the transmission parameters of HFR CE for myocardium perfusion. Currently the guidelines for conventional CE acquisition allow to use a MI until 0.30 for myocardium perfusion and as it was reported, most of microbbules inside the myocardium may be destroyed if the same amount of energy is transmitted [16]. A better contrast, as well as an increase of the time resolution can be achieved with HFR CE compared to the conventional CE with a careful consideration of the MI.

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