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High Frame Rate Contrast-Enhanced Ultrasound for Velocimetry in the Human Abdominal Aorta

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***Abstract*— Treatment of abdominal aortic (AA) aneurysms and stenotic lesions may be improved by analyzing their associated blood flow patterns. Angle-independent blood flow patterns in the AA can be obtained by combining echo-particle image velocimetry (ePIV) with high frame rate contrast-enhanced ultrasonography. However, ePIV performance is affected by ultrasound contrast agent (UCA) concentration, microbubble stability and tissue clutter. In this study we assessed the influence of acoustic pressure and UCA concentration on image quality for ePIV analysis. We also compared amplitude modulation (AM) and singular value decomposition (SVD) as tissue suppression strategies for ePIV. Fourteen healthy volunteers were imaged in the region of the distal AA. We tested four different UCA bolus volumes (0.25, 0.5, 0.75 and 1.5 ml) and four different acoustic output pressures (mechanical indices: 0.01, 0.03, 0.06 and 0.09). As image quality metrics, we measured contrast-to-background ratio, bubble disruption ratio and maximum normalized cross-correlation value during ePIV. At mechanical indices ≥ 0.06, we detected severe bubble destruction, suggesting that very low acoustic pressures should be used for ePIV. SVD was able to suppress tissue clutter better than AM. The maximum tracking correlation was affected by both UCA concentration and flow rate, where at high flow rates, lower UCA concentrations resulted in slightly higher correlation values but more signal drop-outs during late diastole. High frame rate ePIV was successfully performed in the AA of healthy volunteers and shows promise for future studies in patients.**

Index Terms— **abdominal aorta, echography, echo-particle image velocimetry, ePIV, high frame rate ultrasound, vascular flow, ultrasound contrast agents**

I. INTRODUCTION

Study of abdominal aortic (AA) flow patterns may assist the disease-progression prediction process in patients with AA stenotic lesions and aneurysms. Several studies on stenotic lesions suggest that local flow patterns and their associated flow parameters, such as wall shear stress, have an influence on lesion development and progression [1]–[3]. In AA aneurysms, changes in flow patterns modulate inflammatory mechanisms in the vascular endothelium, causing aneurysm growth [4]. For AA aneurysms and stenotic lesions around the aortic bifurcation, *in vitro* data have shown that different treatment options generate different flow perturbations [5], [6], which can partly explain the different outcomes of these treatments. Post-treatment analysis of AA blood-flow patterns may make the follow-up schemes after endovascular treatment more patient-specific by predicting potential failure.

Investigation of blood flow patterns *in vivo* requires full field, angle independent velocity measurements. Currently, the most widely used method of assessing AA blood flow is Doppler ultrasound. However, conventional Doppler is angle dependent, which complicates imaging blood flow in regions of bifurcation, where blood flows in different directions, and where it can also flow approximately perpendicular to the ultrasound beam (70° to 110°) [7], [8].

Several ultrasonic techniques have been developed to overcome the angle dependency limitations of standard Doppler. *Vector Doppler Imaging* (VDI) splits the transmit aperture, obtaining multiple Doppler measurements at known angles to each other, from which both velocity magnitude and direction can be deduced [9], [10]. However, for imaging of deep structures, the angles between beams, and hence velocity estimates, can become unreliable due to the limited aperture [11]. *Transverse Oscillation* is a technique that also utilizes a split aperture, although usually only synthetically in receive [12]. Although originally limited to linear arrays, this method has recently been expanded to work with curved arrays, being demonstrated in the portal vein of a healthy volunteer [13]. However, the velocities expected in the AA are much higher

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than those in the portal vein. *Blood Speckle Tracking* can obtain angle-independent velocity measurements by tracking the speckle motion of moving red blood cells between frames [14]. It, however, requires sufficient temporal resolution for tracking the range of flows expected in the AA. High frame rate (HFR) imaging, using unfocussed transmissions, allows for the temporal resolution required for tracking high blood flow velocities, but is complicated by strong clutter in the blood-pool from surrounding tissue and reduced penetration depth compared to focused transmissions [15].

Echo-particle imaging velocimetry (ePIV) using ultrasound contrast agent (UCA) can be beneficial for the penetration depths required in AA flow imaging in patients (6-10 cm), since backscattered signal is greatly improved over native blood cells. We have shown previously that HFR ePIV can accurately measure the high velocity flows which are expected in the AA, *in vitro* [16]. Translation to *in vivo*, however, requires further optimization of critical UCA related parameters, such as mechanical index (MI), UCA concentration and the applied tissue suppression strategy.

UCA specific acquisition sequences suppress tissue signal by exploiting the non-linear behavior of UCA, e.g. amplitude modulation (AM) or pulse inversion. However, these sequences incur a cost in frame rate, as multiple transmissions are required to reconstruct a single image. Alternatively, singular value decomposition (SVD) based tissue suppression has been shown to perform equivalently or better than UCA specific acquisition sequences, although only for microvascular flow environments [17]. It is not yet known whether SVD also performs well in large vessels like the abdominal aorta.

The use of UCA also mandates careful tuning of the acoustic pressures used for imaging. Too-low pressures may generate insufficient signal from the bubbles; while overly-high pressures can result in bubble destruction. In both cases, velocity estimation will be compromised. The relationship between acoustic pressure and bubble destruction during HFR imaging has been reported only for *in vitro* studies [18]–[20]. It is well known that bubble stability is affected by physiological conditions. In this study we assess bubble destruction *in vivo.*

Another variable requiring optimization is UCA concentration. Higher concentrations are associated with higher signal power, but may reduce ePIV accuracy if too high [21], [22]. Conversely, low concentrations may leave void regions, occupied only by noise. The effect of UCA concentration has not yet been studied for HFR ePIV.

In this study, we investigate the effect that tissue suppression strategy (AM versus SVD), acoustic pressure and UCA concentration have on image quality metrics for ePIV, in human volunteers.

II. METHODS

A. Study Design

After approval as a pilot study, by the medical ethic committee of the Erasmus Medical Center (NL58025.078.16), 15 healthy volunteers (age 18-35 years, BMI <25) were imaged in the region of the distal aorta with the aortic bifurcation and proximal iliac vessels in a coronal view. Four bolus injections of UCA (0.25, 0.5, 0.75 and 1.5 ml, SonoVue, Bracco S.p.A., Milano, Italy) were administered before acquiring 2.5 s of HFR ultrasound data with a research ultrasound system (Vantage 256, Verasonics Inc., Kirkland WA, USA).

An additional clinical ultrasound system (Epiq 7, Philips Healthcare, Andover, MA, USA) was used to simultaneously record contrast mode image sequences in the left superficial femoral artery (downstream of the AA). HFR recordings in the AA were initiated on the research ultrasound system once the bolus was detected in the femoral artery.

After imaging the first volunteer, some minor adjustments/improvements were made to the acquisition scheme, making the data of this volunteer incomparable with the others. Measurements were performed on the remaining 14 volunteers during four measurement sessions (afternoons) in groups of 3-4.

The first three volunteers were imaged at a transmit voltage of 30V. Due to clearly visible bubble destruction on the clinical system, the transmit voltage on the Verasonics ultrasound system was decreased for subsequent volunteers, after each measurement session. Thus, three volunteers were imaged using a transmit voltage of 30V, three at 20V, four at 10V and four at 5V. The transmit voltages of 30V, 20V, 10V and 5V correspond to MIs of 0.09, 0.06, 0.03 and 0.013, respectively (at a depth of 30-50 mm taking into account a tissue attenuation of -0.3 dB per cm).

Additionally, the volunteers underwent MRI phase contrast imaging and the detected flow was compared to the ePIV results. This part of the study is not further described here, but reported elsewhere [23].

B. Ultrasound Acquisition and Image Reconstruction

RF data were acquired with a curvilinear probe (3 MHz, C5-2, ATL, Bothell WA, USA) connected to the research ultrasound system. The AM sequence consisted of diverging waves (transmit delays all zero, single cycle pulse) transmitted with different apodization schemes (even, full, and odd elements active [24], [25]) at a pulse repetition frequency (PRF) of 3000 Hz. The sum of odd and even apodization transmissions was coherently subtracted from the full transmit to produce AM images at 1000 fps. From the full transmit acquisitions a standard B-mode sequence of 1000 fps was also generated, producing synchronized datasets for comparison. Images were beamformed into the polar domain where further analysis was performed.

C. Singular Value Decomposition (SVD)

SVD based clutter suppression assumes that the tissue, blood and noise components of an image sequence can be separated based on their respective spatiotemporal coherence energy [26]. Tissue signal is typically higher intensity and more spatiotemporally coherent than flowing blood (and bubble) signal. Thus, when an image sequence containing blood flow and surrounding tissue is decomposed using SVD, the tissue signal accumulates more coherence energy than the flowing blood. This causes tissue to collect in the low-rank modes of the system while blood and bubbles are distributed more centrally (Fig 1.). Noise, being relatively incoherent and low intensity, typically resides in the high-order modes. Truncating low and/or high order modes allows for selective removal of tissue and/or noise from the image sequence.

In this study, a low-rank threshold selection algorithm was used to automatically detect the transition between tissue and flowing UCA. Low-rank selection was based on the ratio of successive singular values: $\sigma_n/\sigma_{n-1} > 0.99$ (see Fig. 1). This criterion selects the first mode *n* which decreases less than 1% in energy from its predecessor [27]. A high-rank cutoff was not used in this study.

The number of frames used when performing SVD (ensemble length) is known to affect the separability of slow moving bubbles and tissue [17]. Thus, to assess the effect of SVD ensemble length on contrast-to-background ratio (CBR) four different SVD ensemble lengths were tested: 32, 64, 128 and 1250 frames (all frames). CBR was assessed during periods of slow flow (velocity magnitude < 0.1 m/s) and fast flow (velocity magnitude > 0.4 m/s) separately. Comparison was performed on data with MI = 0.01 only to reduce the influence of bubble disruption on the comparison.

SVD was performed on beamformed IQ data. For ensemble lengths of 32, 64 and 128, individual SVD outputs needed to be combined into a continuous set of frames. Thus, ensembles were overlapped by 87.5%, where overlapping frames from different SVD ensembles were averaged to create the final SVD outputs. This was not required with the 1250 ensemble as only one SVD output was created.

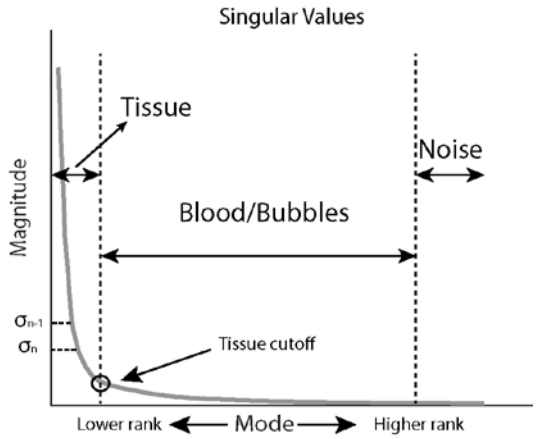

Fig. 1. Illustration of the low-rank threshold selection algorithm used in this study. Tissue cutoff is found by searching for the point in the curve where the slope begins 'flattening out'.

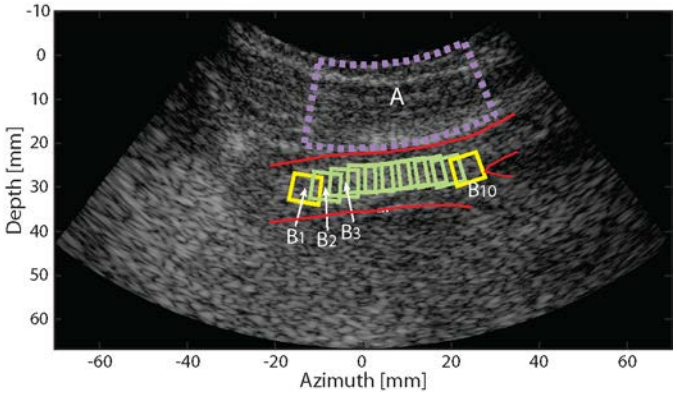

Fig. 2. Regions used for calculating DR and CBR. Red lines indicate outlines of AA and bifurcation to iliac arteries. Purple dotted region A was used for tissue signal strength. Regions B1 to B10 were used for UCA signal strength. B1 and B10 were used for DR. Images displayed at 50dB dynamic range.

D. Tissue Suppression Strategies

AM was compared to SVD (ensemble length = 1250 frames) as a method for suppressing tissue signal without deteriorating the UCA signal. SVD images were computed from the B-mode sequences. Additionally, a 2nd order Chebyshev high-pass filter with a -6dB cut-off at 15 Hz was applied to the AM data, acting as a low-cutoff frequency Doppler wall-filter (AM+Cheby). SVD was also applied to the AM processed data (ensemble length = 1250 frames) as an additional group for comparison (AM+SVD), to investigate the usefulness of a combination of the two techniques.

E. Contrast-to-Background Ratio (CBR)

Tissue suppression efficacy was assessed using contrast-to-background ratio (CBR) [28], defined as $CBR = 10\log_{10}\left(\overline{RMS}_{B_{1-10}}/\overline{RMS}_A\right)^2$, where $\overline{RMS}$ is the time-averaged root-mean-square signal strength in UCA (Fig. 3: $\mathbf{B_{1\text{-}10}}$) and tissue regions (Fig. 3: **A**). Comparison between AM and SVD was performed during periods of slow flow (mean velocity < 0.1 m/s), which is the worst-case scenario for SVD, where bubble coherence between frames is similar to that of slowly moving tissue, increasing the likelihood that bubble signal will be removed along with the tissue signal

F. Disruption Ratio

UCA disruption ratio (DR), a measure of acoustically driven bubble destruction, was calculated as $DR = 1 - \overline{RMS}_{B_{10}}/\overline{RMS}_{B_1}$, where $\overline{RMS}$ is the time-averaged RMS signal in the proximal (Fig. 3:$\mathbf{B_1}$) and distal (Fig. 3:$\mathbf{B_{10}}$) regions inside the AA. DR values range from 0 to 1, implying not any and full bubble destruction, respectively [20]. DR was calculated on the SVD processed datasets during systole only (mean velocity > 0.4 m/s) to ensure that fresh bubbles were being supplied to the region of interest.

G. Bubble Concentration / Velocity Tracking

This section describes how the velocity and correlation values were calculated for comparison between different bolus concentrations. Velocity in the center of the vessel was

estimated using normalized cross-correlation (along slow-time, frequency domain implementation) in ten regions (Fig 3: $\mathbf{B_{1\text{-}10}}$) running along the length of the vessel. Each region was 4.7° by 6 mm in size, resulting in regions sized approximately 6 mm by 6mm, once scan converted. This size was chosen to meet the widely accepted ¼ interrogation window rule for PIV [29]. Normalized cross-correlation was performed on the polar beamformed data after envelope detection. The maximum correlation value was used as a measure of tracking performance for different UCA concentrations. Velocity vectors were determined by finding the location of maximum cross-correlation per region (Fig 3. $\mathbf{B_{1\text{-}10}}$). Subpixel displacement was estimated using the centroid approach [29]. Velocity vectors were scan-converted and then smoothed using a temporal moving median filter (15 ensemble length). Bubble concentrations during diastolic (mean velocity < 0.1 m/s) and systolic (mean velocity > 0.4 m/s) phases were assessed separately, where maximum normalized cross-correlation and CBR were used for comparison.

H. ePIV Measurement

A full ePIV measurement is demonstrated on a volunteer imaged at 0.01 MI with a bolus volume of 1.5 ml, after applying a 1250 ensemble SVD filter. Four cross-correlation iterations were performed with window deformation, using interrogation areas of 9.5° x 6.1 mm and an overlap of 75% [29]. Correlation compounding was performed on three subsequent frame pairs before subpixel displacement estimation using a centroid approximation [29]. Vector fields were processed for display - at peak systole, backflow and diastole - using the dynamic visualization procedure described in [30]. Vessel boundaries were manually segmented.

I. Statistics and Reporting

Significance of differences was statistically tested using a two-tailed Student's t-test, where a p-value < 0.05 implied significance. Results are reported as mean ± standard deviation.

For box plots: circles denote individual data points; whiskers extend to max and min values of non-outliers; boxes start and stop at first and third quartiles; solid lines denote median; and dashed lines denote mean (if present).

III. Results

Ultrasound contrast agent (UCA) was detected in all volunteers using HFR ultrasonography with no adverse events. UCA signal could be detected using all of the tissue suppression strategies tested.

A. SVD Ensemble Length

Increasing SVD ensemble lengths resulted in increasing CBR during periods of slow flow (Fig. 3). However, during periods of fast flow shorter ensembles resulted in higher CBR.

B. Mechanical Index (MI)

For AM processed data, increasing MI resulted in reduced CBR (Fig. 4.a). Larger bolus volumes resulted in higher CBR

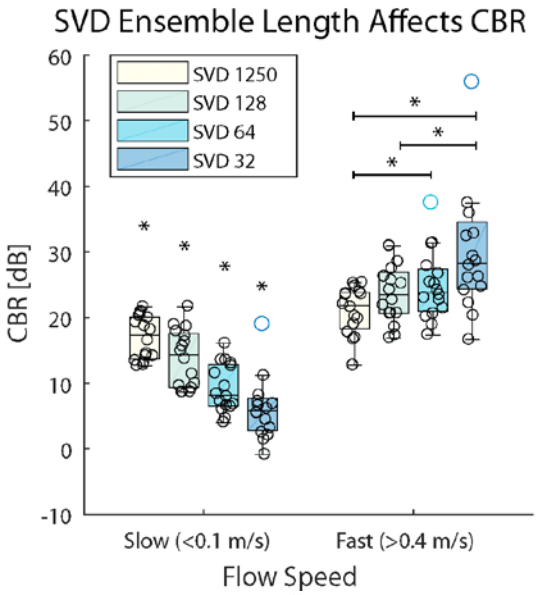

Fig. 3. CBR values obtained with different SVD ensemble lengths during periods of slow and fast flow. Longer ensembles achieve higher CBR during slow flow. During fast flow, the opposite is true. Only 0.01 MI data was used for this comparison. n = 16 (volunteers x bolus volumes). ***** $p < 0.05$

but only for the lower MIs (0.01 and 0.02 - Fig 4.a). The tissue signal after AM processing increased quadratically with increasing MI (Fig 4.b). Higher MIs (0.06 and 0.09) caused considerably more microbubble destruction than lower MIs (Fig. 4.c). Contrast-ultrasound recordings in the femoral artery, downstream from the HFR imaged AA, showed dips in intensity during HFR insonification for the higher MIs but not for the lower MIs (Fig. 5).

C. Tissue Suppression

SVD consistently provided superior CBR values to AM and filtered derivatives of it, for all the MIs tested (Fig. 6). No significant differences were noted between AM+Cheby or AM+SVD, although both resulted in higher CBR than AM alone, even at 0.01 MI, where AM performed at its best. Frames of each filter group at different MIs are shown during slow flow only ($|v| < 0.1$ m/s) in Fig. 7. The average depth to the centerline of the aorta observed in these volunteers was 32±5 mm.

D. Bubble Concentration

Correlation between frames during fast flow (0.3 ± 0.05) was weaker than during slow flow, independent of UCA concentration (0.7 ± 0.1, Fig. 8.a). The 0.25 ml bolus had a lower correlation during slow flow than the 1.5 ml bolus (0.65 ± 0.14 vs. 0.79 ± 0.05, p=0.03) but a higher correlation during fast flow (0.35 ±0.04 vs. 0.30 ± 0.02, p=0.007). Larger bolus volumes increased CBR for both diastolic and systolic flow rates (Fig. 8b), where systolic CBR was higher than diastolic on average (23±5 dB vs 18 ± 5 dB, respectively, $p < 0.001$). For the 0.25 ml bolus volumes, signal 'drop-outs' were observed towards the end of diastole, where bubble signal was

lost in small regions. This was less prominent in higher concentrations.

E. ePIV Measurement

Taking into account the optimization described in previous sections, ePIV vector-fields were derived from a volunteer with an MI of 0.01 and a UCA bolus of 1.5ml. The results are shown in Fig 9.

IV. Discussion

High frame rate contrast enhanced ultrasonography was successfully performed in the abdominal aorta of healthy volunteers. Velocity field information could be determined using ePIV (with the optimization described in this study) which was very similar to 4D phase-contrast magnetic resonance imaging [23].

A. SVD Ensemble Length

Longer ensemble lengths resulted in increased sensitivity to slow moving bubbles. This was expected as using more frames allows for more time for slow-moving bubbles to develop differences in spatial-temporal coherence from the slow-moving tissue. We also observed that shorter ensemble lengths resulted in higher CBR values for fast flow; this may be due to shorter ensembles being able to remove the pulsatile motion of the vessel wall better than long ensembles.

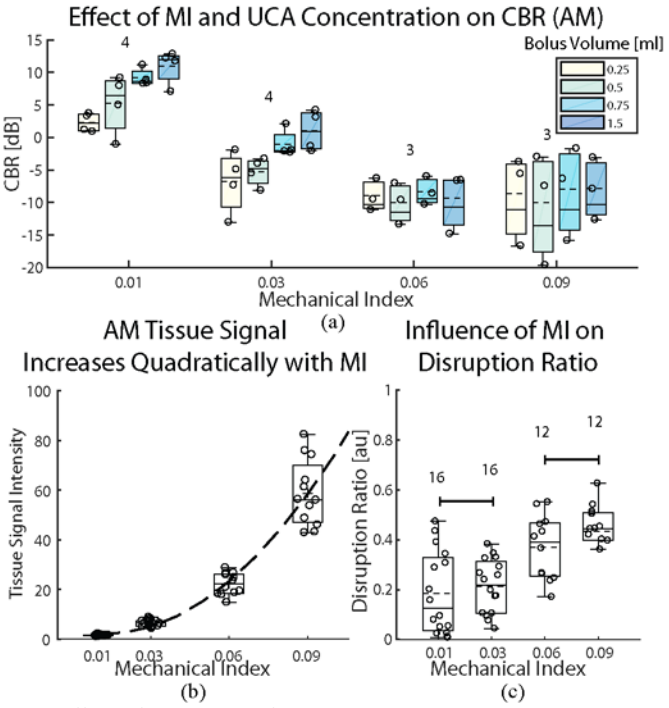

Fig. 4. Effects of MI on CBR of AM images and DR. a) Increasing MI results in lower CBR for AM processing. At MI ≤ 0.03 larger bolus volumes result in more CBR. b) Tissue-signal intensity after AM processing increases quadratically with MI (dashed line indicates quadratic fit). c) Increasing MI results in more bubble destruction, where horizontal bars denote **non**-significant differences between groups. Numbers represent sample size (volunteers x bolus volumes).

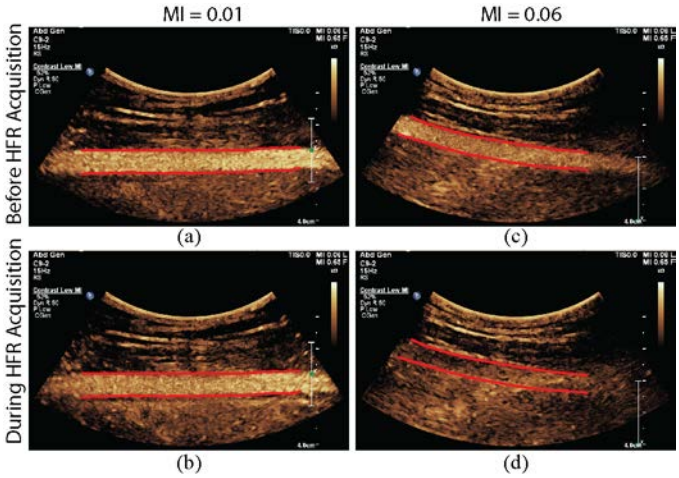

Fig. 5. Contrast mode images recorded downstream from the abdominal aorta, in the left superficial femoral artery with a clinical ultrasound system. Images are recorded a few seconds before (a, c) and during (b, d) the high frame rate (HFR) acquisitions in the abdominal aorta, for MIs of 0.01 (a, b) and 0.06 (c, d). For 0.06 MI, note the dramatic reduction in contrast intensity before (c) and during (d) the HFR acquisition. This is not the case of 0.01 MI, where contrast intensities before (a) and during (b) HFR acquisition are very similar.

However, for AA applications longer ensemble lengths are preferable as their CBR is best during slow flow and sufficient during fast flow.

B. Mechanical Index (MI)

1) Contrast-to-Background Ratio (CBR)

Lower MIs resulted in higher CBR values for AM processing (Fig 4.a). The reason is two-fold: 1) higher MI results in more bubble destruction (Fig. 4.b); and 2) higher MI accompanied higher tissue signal (Fig. 4.c), even after removal of the linear signal component. The reason for the increased tissue intensity is likely non-linear propagation of the pressure wave through tissue, which increases quadratically with the ultrasonic pressure applied [31]. We also observed apparent bubble signal below the AA (Fig. 7), possibly caused by non-linear

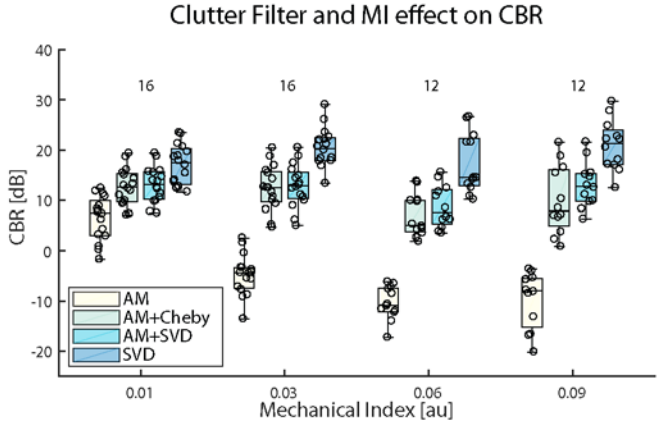

Fig. 6. CBR values for increasing MI and different contrast enhancement schemes (clutter filters). SVD is consistently superior to AM, AM+Cheby and AM+SVD. Note that while AM CBR reduces with increasing MI, AM+Cheby and AM+SVD do not. CBR calculated during periods of slow flow only (velocity < 0.1 m/s). Numbers represent sample sizes (volunteers x bolus volumes).

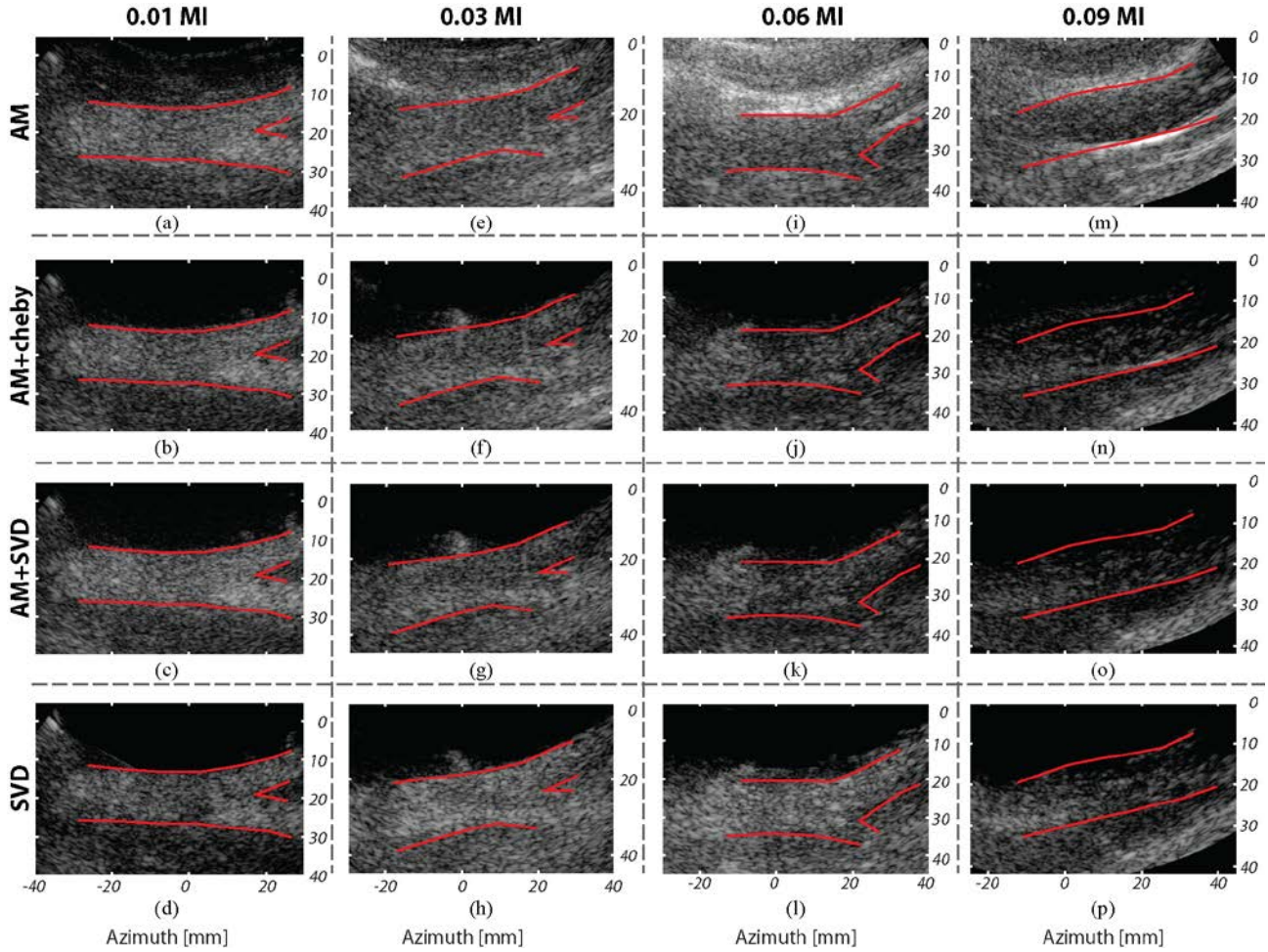

Fig. 7. AM, AM+Cheby, AM+SVD and SVD processed frames during slow diastolic flow (<10 cm/s) for the MIs studied (different volunteers). Bolus volume was 1.5 ml. Red lines indicate vessel boundaries. Higher MI results in higher AM tissue signal power and increased bubble destruction (left column to right column). SVD processing produces higher CBR than AM and its filtered derivatives. Images displayed at 50dB dynamic range and normalized individually.

propagation through the UCA filled AA, as described in [32], [33].

2) Disruption Ratio (DR)

We observed some differences in bubble destruction to those reported by in vitro studies. Couture *et al.* [18] reported more than 75% DR at peak-negative pressures of 0.2 MPa (~MI of 0.01 at 7.5 MHz), whereas we observed ~ 20% DR at a MI of 0.01. However, exposure time to ultrasound (~80 ms here versus 25 s used in their study) and acoustic frequencies used (3 MHz versus 7.5 MHz) were drastically different between our two studies. To the contrary, Toulemonde *et al.* [20] observed negligible bubble destruction at a MI of 0.1. However, their MI values were measured close to the probe, whereas here (and in [18]) MI was measured at the depth of interest (30 mm here and 20mm in [18]). Finally, *in vitro* studies do not typically account for physiological temperatures [34]–[36] and pressures [37], gas exchange between blood and UCA [38], [39] or filtration by the lungs. We found that a maximum MI of 0.03 could be used without severe bubble destruction. However, it is important to note that DR was established during periods of fast flow; during slow flow, the contrast bubbles will be exposed several times longer to ultrasound resulting in more severe bubble destruction in a given region. Therefore, the lowest MI is preferred. In further research, even lower MI values could be tested.

C. Amplitude Modulation vs. Singular Value Decomposition

SVD achieved higher CBR values than AM (Fig. 6 and Fig. 7). Even when combined with a very 'mild' wall filter (AM+Cheby), AM performed worse than SVD. We also tested how applying SVD to AM processed images would compare to SVD on a B-mode image. From Fig. 7c, it appears that AM+SVD provides higher signal intensities. However, Fig. 6 shows that SVD alone provides higher CBR values than AM+SVD. AM processing reduces the signal level and introduces additional noise during the coherent subtraction process of the AM sequence, which both deteriorate CBR.

Although SVD performed well on this data, with small amounts of non-rigid tissue motion, it may not perform so well

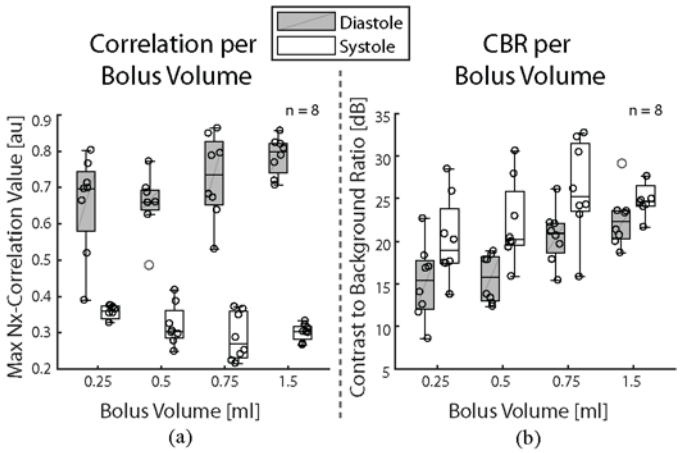

Fig. 8. Effect of increasing UCA concentration (bolus volume) on a) maximum normalized cross-correlation values and b) CBR. During fast flow, low concentrations result in slightly stronger correlation between frames than high concentrations. However, during periods of slow flow the opposite was true. Numbers represent sample sizes (number of volunteers).

where tissue motion is relatively large, e.g. the motion of the heart valves and wall in echocardiography.

CBR is not the only factor worth considering in the comparison between AM and SVD. AM needs at least two transmissions to produce an image; we implemented a commonly used three-transmission sequence which overcomes a limitation in the research ultrasound system to quickly switch between different transmit voltages. SVD can be applied to single transmission sequences, as performed in this study. Thus higher frame rates can be achieved when using SVD alone, or angular compounding can be used to reduce side-lobe levels, increasing both resolution and contrast [40]. However, it should be noted that coherent compounding of angular transmissions in the presence of fast moving scatterers is not straightforward, as decorrelation of the scatterers between different angles causes strong imaging artefacts [41]. Alternatively, for ePIV applications, the compounding of individual angles can be performed in the correlation domain [42], [43].

D. UCA concentration

The mean correlation values obtained during fast flow were much lower than during periods of slow flow, independent of UCA concentration. This was expected as more bubbles will exit (and enter) the interrogation region as the flow rate increases. Additional factors linked to flow speed, such as large flow gradients or out-of-plane flow can also reduce the correlation value obtained. There are methods to account for these effects: including the use of different size interrogation windows between frames; or the use of iterative block-matching schemes with window offset and/or deformation [29] (as was used to obtain the results in Fig. 9).

We found that high UCA concentrations facilitated higher correlation during low flow rates and vice versa. The reason for poor performance of low bubble concentrations during slow flow was likely the lower CBR during slow flow (Fig. 8b). The CBR decrease during slow flow was likely due to more bubble destruction, caused by the increased ultrasound exposure time. Indeed, we observed distinct regions with signal loss, particularly during late diastole, which were more prominent in the 0.25 ml bolus data than in the 1.5 ml bolus data. Thus, for low concentrations, these signal drop-outs during slow flow may outweigh the small correlation improvements during fast flow, as the drop-outs result in significant tracking error.

The small correlation improvement gained by low UCA concentrations during fast flow is in agreement with *in vitro* studies using conventional line-scanning ultrasound for ePIV [21], [22]. Likely caused by less ‘particle-pairs’ being present in an interrogation window which reduces correlation uncertainty in the presence of strong flow gradients.

E. Limitations

This study did not test other non-linear contrast specific tissue suppression strategies, such as pulse inversion or power modulated pulse inversion (PMPI), which may have performed better with a different transducer. However, Desailly *et al.* reported similar results to this study when

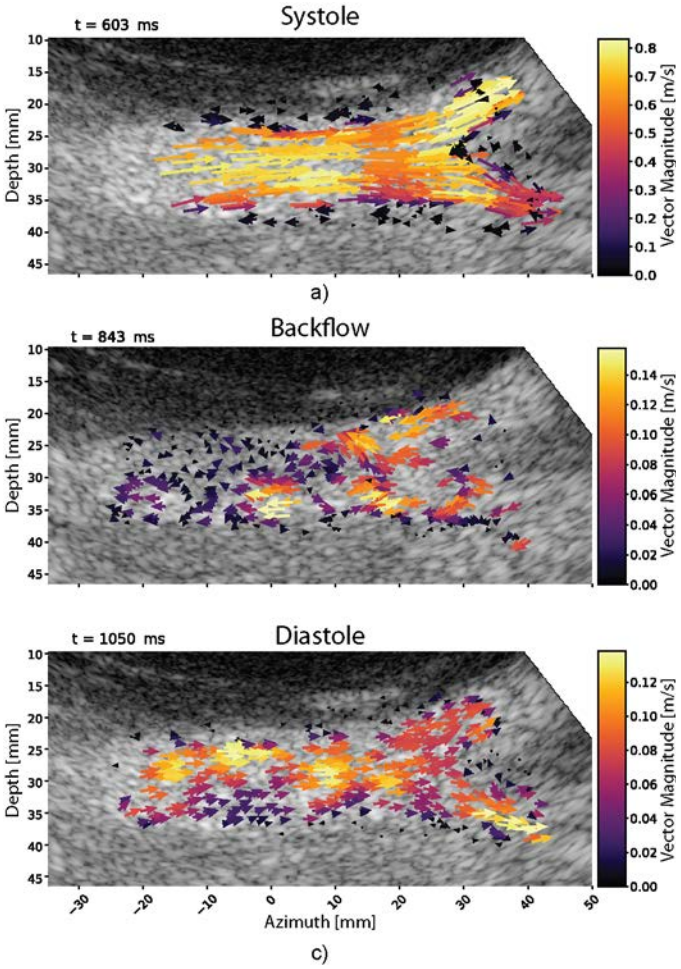

Fig. 9. ePIV derived velocity fields during three phases of the cardiac cycle: a) peak systole, b) backflow, and c) diastole. Results obtained with 0.01 MI, 1250 SVD ensembles and 1.5 ml UCA bolus.

comparing SVD with PMPI in a microvasculature environment [17].

The volunteers in this study had lower BMI than anticipated in the patients of interest, with relatively superficial aortas (32±5 mm) compared with the depths that can be expected in patients (up to 100 mm, sometimes deeper). However, this preliminary study aimed to prove that HFR ePIV was possible in the region of the AA bifurcation, and to gain insight into optimal UCA parameters for future patient studies. The acoustic pressures required to obtain sufficient signal were also very low, thus the transmit power can be increased to obtain similar MIs in deeper regions. How ePIV is affected by the increased attenuation and reduced image quality in patients will be assessed in future studies.

We tested lower MIs only after discovering that the planned MI of 0.09 (derived from previous in-vitro studies) was causing severe bubble destruction *in vivo*. This forced a parameter adjustment for the following batches of volunteers, but allowed us to assess the influence of MI, which was beneficial for the final outcome. For future HFR CEUS studies, *in vivo*, one should be prepared to use very low MI, maybe even lower than the values used here.

The use of the normalized cross-correlation value as a surrogate for tracking performance is also a limitation of this study, although this is not uncommon [21]. This was required as reliable ground truth measurements were not feasible *in vivo*.

Finally, the PRF used in this study was not as high as physically possible, but was limited to keep spatial-peak temporal-average intensity (I_{SPTA}) under the recommended value for abdominal imaging [44]. We performed our I_{SPTA} safety measurements to allow for the maximum MI value tested, resulting in an I_{SPTA} value close to the 94 mW/cm^2 recommended for abdominal imaging. The use of the lower output pressures (MI ≤ 0.01) in this study would allow for a higher PRF in future, possibly up to the physical maximum of ~8000 Hz at a depth of ~10 cm.

V. Conclusion

We have shown that SVD can provide higher CBR than AM in the abdominal aorta, without requiring multiple transmissions per image. We found that lower MIs should be used *in vivo* to prevent bubble destruction, as compared to *in vitro* studies. Finally, we observed that higher UCA concentrations were associated with higher correlation during slow flow conditions and less signal drop-outs, but lower concentrations were associated with slightly higher correlation under fast flow conditions.

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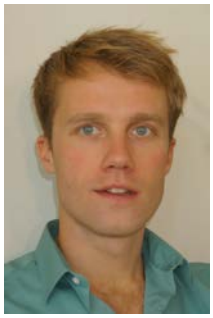

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