Introduction

Atherosclerosis is a highly prevalent cardiovascular disease characterized by localized vascular inflammation and deposition of fatty lipids leading to the development and build-up of intravascular plaques (Ross 1999). Whilst plaques obstruct localized blood flow, severe or even fatal cardiovascular events are common in the case of a ruptured plaque, where plaque deposits cause thrombus blockage in downstream vasculatures. As such, atherosclerosis is one of the main causes of death in the world, with approximately 70% of fatal myocardial infarctions (Naghavi et al. 2003) and up to 30% of all ischemic strokes (Kolominsky-Rabas 2001, Henry et al. 2007) estimated to have been caused by ruptured plaques.

However, the development of atherosclerotic plaques is a very heterogeneous process, with several different plaque types identified (Stary et al. 1995) and with a range of different risk-factors deemed influential in the establishment of the disease (Libby 2001). Keeping this in mind, the key clinical question of plaque risk stratification—separating vulnerable rupture prone plaques from more stable plaque formations—is a highly complex task. Clinical protocols still largely rely on analysing the degree of obstructing stenosis in classifying plaque risk, where a stenosis degree of >60%–75% generally leads to endarterectomy (Biller et al. 1998). However, such
simplified analysis does not take into account any information on the degree of inflammation, plaque morphology, or plaque constitutive behaviour, all shown to correlate to plaque stability in vivo (Hodgson et al 1993, Takano et al 2001, Libby et al 2002). In particular, the structure and composition of atherosclerotic plaques have shown to be of specific importance when predicting plaque stability, where thin-cap fibroatheromas have been identified as particularly prone to rupture (Kolodgie et al 2001, Moreno 2009).

Several methods have been developed to assess plaque composition in vivo. Among those proposed, ultrasound-based elastography has shown particular potential following a series of recent clinical studies (Schaar et al 2003, Naim et al 2013, Mahmoud et al 2016). Using ultrasound elastography, plaque constituitive behaviour and regional morphological differences can be assessed by analysing the displacement field imposed by either external (focused acoustic radiation) or internal (hemodynamic pressure pulses) means. In an early work, de Korte et al (2000) showed that the displacement fields obtained by intravascular elastography could successfully identify both lipid-rich and macrophage-prevalent areas in plaques in vivo. Similarly, non-invasive ultrasound elastography has been shown to correlate well with magnetic resonance imaging data of carotid plaques in several studies (Naim et al 2013, Doherty et al 2015, Huang et al 2016, Roy Cardinal et al 2017). Acoustic radiation force impulse (ARFI) imaging—an elastographic image technique based on assessing relative tissue displacements following external mechanical stress—has also been applied for plaque characterization (Dumont et al 2006), where quantitative of fibrous cap thickness (Czernuszewicz et al 2017) and even the relation between elastography-based metrics and standardized plaque classification scales (Czernuszewicz et al 2015) has been attempted. Shear wave elastography (SWE) is another variation on ultrasound elastography, where an acoustic radiation force push is used to induce the propagation of mechanical shear waves. By subsequently tracking the wave propagation by means of ultrafast ultrasound plane wave imaging, the mechanical properties of the tissue can be quantitatively mapped. For plaque characterization, SWE has been applied in vivo showing correlation to both histological evaluations (Garrard et al 2015) as well as assessed neurological symptoms (Ramnarine et al 2014b). Recently, attempts to correlate SWE results to intraplaque neovascularization also showed promising results (Huang et al 2017), further underlining the potential for refined plaque analysis using elastography based techniques.

Despite the increasing amount of clinical studies performed using ultrasound elastography for plaque characterization, the clinical potential of the method is still uncertain. Regarding intravascular techniques, a defined limitation exists in the method’s invasiveness (Segal et al 2001, Tavakol et al 2012), especially considering the reported high incidence of plaque debris in catheterized patients (Keeley and Grines 1998). The heterogeneity and confined geometry of atherosclerotic plaques also affects the accuracy of ultrasound elastography. It has been shown in several studies that using infinite media assumptions in confined geometries renders inaccurate estimations (Makstuti et al 2016, 2017a, Caenen et al 2017). Such assumptions have however still been used in several clinical studies on plaque ultrasound elastography (Ramnarine et al 2014b, Garrard et al 2015, Liu et al 2015), maintaining the potential to distinguish plaques of different stiffness. To this end, a wide range of imaging specifications have been used, where vascular elastography has been performed in both longitudinal (Schmitt et al 2007, Naim et al 2013) and transverse (Hansen et al 2010, He et al 2017) imaging planes, as well as using varying positioning, levels, and sources of the imposed acoustic radiation force or internal displacement (Czernuszewicz et al 2015, Huang et al 2017, Roy Cardinal et al 2017). With varying levels of accuracy reported (Widman et al 2016, Czernuszewicz et al 2017, Roy Cardinal et al 2017) even between different imaging planes of the same plaque type (Urban et al 2017), no clear consensus exists on the optimal setup for plaque differentiation using ultrasound elastography.

Therefore, the aim of this study was to assess the accuracy and the ability to differentiate plaques of different stiffness using SWE as a function of varying plaque geometry, acoustic radiation force push location, and imaging plane. To evaluate this in a parametric fashion, a refined experimental setup was constructed, taking the complexity of the arterial wall into account whilst still allowing for control and variation of plaque geometry and stiffness by using sets of in vitro phantom plaques. To the above, the accuracy and the ability to differentiate plaques of different stiffness was also evaluated using both global and frequency based wave speed metrics, all in order to unveil the optimal parameter settings for refined plaque characterization by SWE.

Method

The following section provides a description of the experimental phantom plaque setup, along with details of image acquisition settings, data analysis and post-processing schemes.

Phantom plaque construction

To mimic the overall geometry and stiffness of intraluminal carotid plaque, phantom plaques were created out of poly(vinyl alcohol) (PVA) cryogel. Specifically, a solution in mass percentage of 87% deionized water, 10% fully hydrolysed PVA (molecular weight: 56.140 g mol⁻¹, density: 1.269 g cm⁻³, Sigma-Aldrich, St. Louis, MO)
and 3% graphite powder (molecular weight: 12.01 g mol$^{-1}$, density: 5 g cm$^{-3}$, particle size ≤ 50 µm, Meck KGaA, Darmstadt, Germany) was used. The solution was mixed and heated to approximately 65 °C during continuous stirring, before being poured into specifically manufactured phantom plaque moulds. The plaque moulds consisted of two complementary plastic mould parts with a surrounding poly(methyl methacrylate) cylinder, such that when mounted the confined inner hollow compartment resembled that of a tapered plaque (for an overview of the phantom plaques and plaque moulds used, see figure 1). The created phantom plaque had a longitudinal length of 20 mm, an outer diameter of 14 mm (corresponding to the intraluminal vessel cross-section diameter) along with a tapered intraluminal opening. To generate different sets of phantom plaques, plaque moulds with intraluminal diameter openings of 3.5, 5, and 7 mm were used, respectively. Additionally, each plaque mould was generated with the intraluminal cavity being either centred inside the moulded phantom plaque, or off-centred such that the intraluminal cavity was positioned 2 mm from the centre of the phantom plaque (representing a shift of 1:3), generating one centred and one off-centred setup for each intraluminal cavity opening, respectively. In total, this generated a set of six different plaque moulds (intraluminal cavity opening: 3.5/5/7 mm, off-centred and centred, respectively). All plaque moulds were manufactured with a 3D printer (Formlabs, Form 2, Somerville, MA).

Once poured into the moulds, the mixture was stirred with a needle to ensure that no air bubbles were trapped inside the hollow mould cavity and the moulds were subsequently closed shut. The phantoms then underwent a series of freeze-thaw (FT) cycles, where each FT-cycle consisted of a freezing phase of 24 h at approximately −23 °C, and a subsequent thawing phase of 24 h at approximately 23 °C. Four series of phantom plaques with different stiffness were created by applying 2, 3, 4, and 5 FT-cycles, respectively, because PVA-stiffness can be controlled by varying the number of performed FT-cycles (Fromageau et al 2003). With each set comprising six different geometries (variations of intraluminal diameter and cavity position, respectively), this generated a total of 24 phantom plaques. For a summarized overview, table 1 gives details of the entire set of phantom plaques generated.

In addition to the above mentioned phantom plaques, with each batch of PVA and FT-cycle, a large cylindrical phantom (diameter: 50 mm, length: 100 mm) was created as reference for the generated plaque phantom stiffness.

![Figure 1](https://example.com/figure1.jpg)

**Figure 1.** Moulds used to generate phantom plaques. (a) Complementary mould parts for centred (upper row) and off-centred (bottom row) phantom plaques (note that three sets of phantom plaques were manufactured with intraluminal cavity opening of 3.5, 5, and 7 mm, respectively); (b) Mounted phantom plaque moulds with surrounding poly(methyl methacrylate) cylinder for centred (upper row) and off-centred (lower row) phantom plaques. The phantom plaque consisted of the hollow inner compartment of the phantom plaque mould. (c) One batch of phantom plaques with three different intraluminal cavity openings, in centred and off-centred configuration (six plaques in total). Three centred phantom plaque moulds are also shown. All dimensions are given in mm.

| Intraluminal cavity diameter [mm] | Intraluminal cavity position | FT-cycles |
|---------------------------------|-----------------------------|-----------|
| 3.5/5/7                        | Centred/off-centred         | 2/3/4/5   |

Table 1. Geometry of created phantom plaques. In total 24 phantom plaques were created.
Experimental setup

A porcine aorta (female Swedish Yorkshire pig, weight: 32 kg) was used to simulate the human carotid artery (approximate dimensions, length: 100 mm, intraluminal diameter: 14 mm). The artery had been surgically removed during medical training, and was stored frozen at −23 °C in a 0.9% saline solution. Prior to the experiments, the porcine aorta was thawed in cold water. Once fully thawed, surrounding fascia was removed and intercostal arterioles closed by hybrid glue (Loctite, Düsseldorf, Germany). A phantom plaque was inserted and slid into the middle of the artery, and the artery was mounted onto customized end fixtures in a designed closed experimental compartment, see figure 2. Common fishing line was used to fixate the aorta to the end fixtures, and if necessary the aorta was slightly stretched to avoid exaggerated sagging. When an off-centred phantom plaque was used, the plaque was positioned such that the thicker plaque wall was facing the anterior wall of the aorta with respect to the transducer (facing upwards in the experimental setup), and the thinner plaque wall was facing the posterior wall of the aorta.

The artery with intraluminal phantom plaque was rinsed and filled with deionized water. This was performed to (1) detect potential leakage from non-closed intercostal arterioles, (2) remove air bubbles inside the intraluminal space, and (3) fill up the intraluminal cavity to avoid gravitational collapse of the mounted aorta. The end fixtures were then closed to keep a constant water pressure inside the aorta (note however that no additional intraluminal pressurization was imposed).

A 5 mm thick attenuating rubber plate was placed at the bottom of the experimental compartment, and the side walls of the compartment were mounted. To avoid leakage out of the designated compartment, petroleum jelly was applied on the sides of the end fixtures before the compartment walls were mounted.

Figure 2. Experimental setup. (a) Porcine aorta mounted on customized end fixture (note that one side plate is removed for insight). (b) Set surrounding agar block (one side plate removed) with linear array ultrasound transducer positioned for longitudinal acquisition. (c) Longitudinal B-mode view of a phantom plaque inside the porcine aorta, with surrounding agar material. (d) Transverse view of plaque shown in (c). Note that the B-mode images were acquired using an Aixplorer system (SuperSonic Imagine, Aix-en-Provence, France) with a SuperLinear SL15-4 transducer.

Figure 3. Illustration of performed ARF push locations. (a) Longitudinal push locations (1.–5.). (b) Transverse push locations (6.–7.). The numbering corresponds to the description in the section Data acquisition. Also, an approximate depiction of the manually adjusted ROI is given by the red rectangles (note that when pushing at locations 4., or 5., the ROI was positioned in the posterior part of the phantom plaque).
The aorta and phantom plaque were then fixated inside a box in which mimicked surrounding tissue was moulded (approximate mould dimensions, length: 130 mm, width: 40 mm height: 40 mm, aorta positioned in the cross-sectional mid-point). For the surrounding tissue, a solution in mass percentage of 1% agar (Merck, KGaA, Darmstadt, Germany), 3% graphite powder (molecular weight: 12.01 g mol$^{-1}$, density: 5 g cm$^{-3}$, particle size $\leq 50$ µm, Meck KGaA, Darmstadt, Germany), and 96% deionized water was used (the defined composition was based on preliminary tests where a 1% agar mixture resulted in an approximate group velocity shear wave speed of 3.25 m s$^{-1}$). Whilst being continuously stirred, the solution was heated to approximately 65 °C. The mixture was then cooled down to 37 °C before being poured into the experimental compartment, surrounding the now submerged porcine aorta with inserted phantom plaque fully. The agar solution was then allowed to set in room temperature for approximately 2 h, such that the solution fully solidified. An ultrasound transducer was then mounted on top of the agar block for the subsequent SWE image acquisition. For completeness, figure 2 gives an overview of the mounted artery, set agar block with mounted ultrasound transducer, and a corresponding longitudinal and transverse B-mode image of the porcine aorta with inserted phantom plaque and surrounding agar.

When the image acquisition had been performed for a single phantom plaque, surrounding agar was removed and the porcine aorta unmounted from the customized end fixtures. Once the imaged phantom plaque had been removed and the porcine aorta had been cleaned from surrounding agar material, the aorta was reused for subsequent phantom plaques in order to keep arterial mechanical properties identical between different plaque sessions.

Note that any potential change in constitutive behaviour of the porcine artery over time was not monitored. However, post-measurement assessment of group velocity indicated no significant change between the very first and the very last measurement session separated by several weeks.

Data acquisition
A L7-4 linear array transducer (Philips Healthcare, Andover, MA) was mounted on the upper part of the block phantom, providing either longitudinal or transverse views (see figure 2). Ultrasound gel (Aquasonic 100, Parker Laboratories, Fairfield, NJ) was used to provide contact between transducer elements and block phantom. The transducer was mounted such that full contact was made with the phantom without imposing any significant external pressure on the block.

SWE acquisitions were performed using a Verasonics V1 system (Verasonics, Kirkland, WA, USA). The ARF push frequency was set to 4.09 MHz with push duration of 196 µs, which was then switched to ultrafast plane wave acquisition tracking the shear wave at 6.43 MHz with a single cycle pulse (pulse repetition interval = 85 µs with 1 full cycle used for the transmitted tracking pulse. Note that the short push length was chosen following previous studies indicating maximized bandwidth at short pushes (Widman et al 2016)). No harmonic tracking was used. All 128 transducer elements were activated during plane wave imaging, whereas 40 and 52 elements were activated at the anterior and posterior push locations, respectively (this to maintain a $f$-number = 1 for all pushed, see below for further details). From each measurement, demodulated in-phase quadrature (IQ) data was collected with a resolution of approximately 0.12 mm$^2$.

For each phantom plaque, ARF pushes at a series of different push locations were performed in order to evaluate optimal image acquisition for mechanical plaque characterization using SWE. Specifically, ARF pushing was performed:

1. In the longitudinal view in the anterior wall of the porcine aorta, approximately 20 mm longitudinally from the anterior plaque boundary.
2. In the longitudinal view in the anterior wall of the porcine aorta, at the anterior plaque boundary
3. In the longitudinal view in the anterior wall/in the middle of the anterior plaque
4. In the longitudinal view in the posterior wall of the porcine aorta, approximately 20 mm longitudinally from the posterior plaque boundary
5. In the longitudinal view in the posterior wall of the porcine aorta, at the posterior plaque boundary
6. In the transverse view through a mid-cut of the plaque, approximately 20 mm laterally from the side of the porcine aorta, at the same depth as the plaque lumen
7. In the transverse view through a mid-cut of the plaque, at the boundary of the porcine aorta

The push locations are illustrated in figure 3.

For each push location, three consecutive SWE measurements were performed. Note also that for each push location, the SWE was generated by the left-most elements of the ultrasound transducer ($f$-number = 1), allowing for the propagating shear waves to be tracked from left to right through the field-of-view.
As reference, SWE acquisitions were also performed on the large cylindrical phantoms (one per FT-cycle batch). The ARF push was positioned approximately 20 mm into the sample, with push parameters being identical to the ones used in the plaque experiments.

**Data post processing**

For the acquired in-phase/quadrature (IQ) data, axial particle velocities were estimated in the entire acquired field-of-view using a 2D autocorrelation algorithm (Loupas et al 1995) commonly deployed for elastographic motion estimation. After autocorrelation, median filtering using a $3 \times 3$ kernel was applied on each temporal frame. Additionally, a zero-phase bandpass filter with a passband of 50–950 Hz was employed on the retrieved signal. For each acquisition view, a rectangular region-of-interest (ROI) was manually adjusted to cover the investigated phantom plaque (see figure 3). Within this selected ROI, axial velocities were averaged in depth over the entire ROI, and used to generate axial velocity maps. Using the ROI and corresponding axial velocity maps, a set of quantitative parameters were retrieved:

**Group velocity**

Shear wave group velocity, $c_g$, was estimated using the time-to-peak method (TTP) (McLaughlin and Renzi 2006), identifying the global wave front of the travelling shear wave in the axial velocity maps. To improve the linear regression fit, a random sample consensus (RANSAC) filter (Wang et al 2010) was employed for the TTP estimation.

**Phase velocity**

Shear wave phase velocity, $c_p$, was estimated by employing a 2D fast Fourier transform (FFT) on the axial velocity maps (Bernal et al 2011), generating a $k$-space representation of the propagating shear wave. The first quadrant of $k$-space was selected and subsequently masked to contain frequencies only within 12 dB relative to the centre frequency (identified as the frequency of peak energy in $k$-space), and subsequently converted to a phase velocity-intensity map representation by relating wave number to phase velocity at a given apparent frequency (Maksuti et al 2016). The phase velocity as a function of frequency (dispersion curve) was then identified as the phase velocity at which the intensity was maximized at a given frequency.

To generate comparable scalar values, as well as considering that dispersion behaviour at different frequencies changes as a function of geometrical confinement (Maksuti et al 2016, 2017b), phase velocity values were retrieved in a defined set of frequency ranges. Specifically, for each plaque ROI, phase velocities within 450–550 Hz, 700–800 Hz, and 950–1050 Hz, were estimated, respectively, by averaging the phase velocity within the defined frequency range. With such, three phase velocity values, $c_p,450$–$550\text{Hz}$, $c_p,700$–$800\text{Hz}$ and $c_p,950$–$1050\text{Hz}$, were obtained for each image acquisition.

**Signal-to-noise ratio**

To quantify the quality of the retrieved shear wave signal, the signal-to-noise ratio (SNR) of the wave front in the axial velocity map was evaluated. Using the TTP-estimation from the group velocity analysis, signal was estimated as being all pixels within 1 mm of the wave front, evaluated through the axial velocity map (entailing in the given setup a wave front travelling for around 4–6 ms). Conversely, noise was estimated as being the same number of pixels however in the lower left corner of the axial velocity map (i.e. the furthest away from the wave push and propagation). With these values, SNR was given as

$$\text{SNR} = \frac{m}{\sigma}$$

with $m$ representing the mean of the signal, and $\sigma$ the standard deviation of the noise. Figure 4 shows an axial velocity map with identified signal and noise region, respectively.

Note that the SNR will have a slight dependence on the size of the manually selected ROI in the original B-mode image (see Data post processing). Specifically, preliminary studies indicated a maximum change of around 1.4 in SNR within ±8 pixels in either width or depth. To take this into account when evaluating potential significance between groups (see Statistical analysis below), the results were controlled within variations in SNR of ± 1.4.

**Maximum particle velocity**

The maximum shear wave particle velocity was retrieved from each ROI by setting it equal to the maximum particle velocity of any given pixel in the ROI at any given time point.

With data collected for all different phantom plaque configurations, the metrics above were compared as a function of different stiffness, plaque geometries, imaging plane, and push location, respectively. For push location, a separate analysis was also performed evaluating longitudinal against transverse views, respectively. For all
estimations, accuracy was evaluated against group velocities from the large reference phantoms, serving as a gold standard metric for all phantom plaques of the same PVA-batch.

**Statistical analysis**

For the different plaque geometries, the ability to statistically differentiate plaques of different stiffness was evaluated using a two-sided Wilcoxon rank sum test with significance level set at $p < 0.05$, comparing phantom plaques of different mechanical stiffness against each other.

For the different push locations, the quality of signal and quality of wave velocity estimation was evaluated in a pooled manner using a one-way analysis of variance (ANOVA) test, with a Tukey’s range test serving as a post-hoc assessment to quantify potential significances between discrete push locations. Again significance was set at $p < 0.05$.

95% confidence intervals (CI) were calculated using

$$\text{CI} = k \pm z^* \cdot \frac{\sigma}{\sqrt{n}}$$

(2)

where $z^*$ is the critical value, set for a confidence level of 95%, $k$ is the mean value, $\sigma$ is the standard deviation and $n$ is the individual group sample size.

All post-processing and statistical analysis was performed using MATLAB R2016a (MathWorks, Natick, MA, USA).

**Results**

Following the outlined experimental procedure, 24 phantom plaques were successfully manufactured. Twenty-three of these were imaged following the defined protocol, whereas one phantom plaque (centred 5 mm lumen) had to be discarded following an incident where it got dissolved in surrounding agar material due to a loose porcine aorta fitting. Figure 5 shows B-mode images of a few sample plaque setups.

Figure 6 also shows a typical depiction of axial velocity map for both the entire selected depth and the ROI, respectively, together with k-space before and after frequency masking, and a final phase velocity intensity map and corresponding dispersion curve.

**Push location**

Figure 7 shows SNR and maximum particle velocity as a function of different push locations. Additionally, numerical values are provided in table 2.
The closer the push location was to the plaque, the higher the SNR and maximum particle velocity. Particularly, push locations 3 and 5 both show significantly higher SNR compared to all other push locations ($p < 0.01$). Similarly, out of the longitudinal push locations, these also experienced significantly higher maximum particle velocity ($p < 0.01$). Comparing to all longitudinal push locations, significantly higher maximum particle velocity could be seen for both the transverse push locations ($p < 0.01$), albeit no significant increase in SNR could be reported for these cases.

With regards to the quality of the wave speed estimate, figure 8 shows the relative error in wave velocity as a function of different push locations and wave speed metrics, respectively. Similarly, numerical mean and standard deviations are provided in table 3. Confidence intervals of the same are provided in supplementary table 1. Note that the references samples had a group wave velocity of 3.47, 4.37, 4.82, and 5.67 m s$^{-1}$ for 2–5 FT-cycles, respectively.

In contrast to the results for SNR and maximum particle velocity, the quality of the estimate does not improve significantly as the push location is moved closer to the plaque (compare e.g. location 1–3, or 4–5, respectively). Instead, the main difference is between longitudinal (1–5) and transverse (6–7) push locations, where pushes in the transverse view show a slightly higher underestimation of shear wave speed compared to those in the longitudinal view.

For the group velocity estimation, a consistent underestimation in wave speed is apparent regardless of push location. For the phase velocity estimation, similar underestimation is apparent at lower frequencies (450–500 Hz), however this effect diminishes with increasing frequency. Particularly, at the highest frequency band (950–1050 Hz) estimates are centred around a relative error of $-2\%$, indicating an improved accuracy. Coupled to the phase velocity estimates, the k-space median frequency was around 1250 Hz for all estimates.

---

**Figure 5.** B-mode examples of the plaque phantoms. (a) Longitudinal view, off-centred 3.5 mm intraluminal cavity diameter. (b) Transverse view, off-centred 3.5 mm intraluminal cavity diameter. (c) Longitudinal view, centred 5 mm intraluminal cavity diameter. (d) Transverse view, centred 5 mm intraluminal cavity diameter. (e) Longitudinal view, centred 7 mm intraluminal cavity diameter. (f) Transverse view, off-centred 7 mm intraluminal cavity diameter. Note a slight sedimentation in the dispersion of the surrounding agar. All B-mode images were acquired using an Aixplorer system (SuperSonic Imagine, Aix-en-Provence, France) with a SuperLinear SL15-4 transducer.
whereas the centre frequency (corresponding to the maximum intensity) ranged from 584–676 Hz when going from phantom plaques of 2–5 FT-cycles. Noteworthy is that despite the underestimation, $c_g$ estimates show the lowest deviation out of the four wave speed metrics, with a standard deviation of approximately 11% over all push locations, compared to 19, 21, and 20% for $c_p, 450–550$ Hz, $c_p, 700–800$ Hz, and $c_p, 950–1850$ Hz, respectively.

Table 2. SNR and particle velocity ($\mu m s^{-1}$) as a function of different push location. Results given as mean ± standard deviation.

| Push location | 1     | 2     | 3     | 4     | 5     | 6     | 7     |
|--------------|-------|-------|-------|-------|-------|-------|-------|
| SNR          | 5.9 ± 4.3 | 13.2 ± 8.8 | 22.4 ± 9.8 | 7.2 ± 5.8 | 19.4 ± 13 | 4.3 ± 4.3 | 7.7 ± 5.4 |
| Max. particle velocity | 0.9 ± 0.8 | 2.6 ± 1.9 | 4.3 ± 2.3 | 1.3 ± 0.8 | 5.8 ± 4.5 | 8.6 ± 6.3 | 8.2 ± 5.5 |

Figure 6. Typical example of the analysed SWE data, given for a centered 5 mm intraluminal cavity, pushing in location 1. (a) B-mode with manually selected ROI (blue rectangle), (b) axial velocity map without restricting the ROI in width, (c) axial velocity map of the ROI, (d) 2DFFT without frequency masking, showing some signs of higher order modes appearing, (e) 2DFFT with dB-masking, and (d) corresponding phase velocity map, with the dispersion curve identified by the red continuous line.

Figure 7. Quality of signal as a function of different push locations (Loc), reported in the form of (a) SNR and (b) maximum phantom plaque particle velocity ($\mu m s^{-1}$). Notice that Loc. 1–5 represents longitudinal views, whereas 6–7 represents transverse views (see figure 3). Based on an ANOVA test with a Tukey post-hoc test for significance, all push locations differed significantly from each other ($p < 0.05$) apart from (1–4/6/7, 3–5, 4–6/7, 6–7) for SNR (with results double checked against ROI-size deviation in SNR), and (1–2/4, 2–3/4, 3–5, 6–7) for maximum particle velocity. Each box represents min, max, median, 25th and 75th percentile, respectively ($N = 72$).
Figure 8. Quality of wave speed estimate as a function of different push locations, reported in the form of relative error (against reference phantoms) for (a) group velocity, \( c_g \), (b) phase velocity, \( c_p \), at 450–550 Hz (c) 700–800 Hz, and (d) 950–1050 Hz. Notice that push locations 1–5 represents longitudinal views, whereas 6–7 represents transverse views. Also, the red dashed line corresponds to the reference value (relative error of 0%). Based on an ANOVA test with a Tukey post-hoc test for significance, all push locations differed significantly from each other (\( p < 0.05 \)) apart from (a) (1–3/4/5, 2–3, 3–4–5–7, 6–7), (b) (1–4, 2–4, 3–5/6/7, 5–6/7, 6–7), (c) (1–2/4, 2–4, 3–3/5/6/7, 5–6/7, 6–7), and (d) (1–3/4/5/6/7, 2–3/4, 3–4/5/6/7, 4/7, 5–6/7, 6–7). Each box represents min, max, median, 25th, and 75th percentile, respectively (\( N = 72 \)).

Table 3. Relative error (%) as a function of different push locations for the four wave speed metrics (group velocity, \( c_g \), and phase velocity, \( c_p \), at 450–550 Hz, 700–800 Hz, and 950–1050 Hz, respectively. Data given as mean ± standard deviation.

| Push location | 1     | 2     | 3     | 4     | 5     | 6     | 7     |
|--------------|-------|-------|-------|-------|-------|-------|-------|
| Rel. error \( c_g \) | \(-12 ± 10\) | \(-3 ± 11\) | \(-7 ± 10\) | \(-10 ± 11\) | \(-14 ± 12\) | \(-23 ± 11\) | \(-19 ± 12\) |
| Rel. error \( c_p, 450–550 \text{ Hz} \) | \(2 ± 21\) | \(-10 ± 24\) | \(-26 ± 16\) | \(-5 ± 25\) | \(-29 ± 18\) | \(-26 ± 13\) | \(-30 ± 12\) |
| Rel. error \( c_p, 700–800 \text{ Hz} \) | \(7 ± 24\) | \(6 ± 27\) | \(-6 ± 20\) | \(6 ± 18\) | \(-13 ± 18\) | \(-13 ± 21\) | \(-12 ± 22\) |
| Rel. error \( c_p, 950–1050 \text{ Hz} \) | \(-3 ± 20\) | \(10 ± 20\) | \(3 ± 17\) | \(5 ± 19\) | \(-6 ± 17\) | \(-7 ± 25\) | \(-2 ± 19\) |

Plaque geometries

The wave speed results for all imaged plaque geometries are summarized in figure 9. \( c_g \), \( c_{p, 450–550 \text{ Hz}} \), \( c_{p, 700–800 \text{ Hz}} \) and \( c_{p, 950–1050 \text{ Hz}} \) are reported, together with corresponding reference values. Note that in all cases, data are reported for all push locations pooled together.

For the varying plaque sizes, results from the push location analysis are evaluated, indicating an underestimation of wave speed for the group velocity analysis, with increasing accuracy achieved using phase velocity at the upper-most frequency band. Also, the underestimation against reference values increased with increasing stiffness levels, where the 2 FT-cycle plaques showed an average underestimation of 0.4 m s\(^{-1}\) or 12%, compared to 1.0 m s\(^{-1}\) or 18% at 5 FT-cycles (data given for group velocity analysis). However, despite the systematic underestimation, the ability to differentiate plaques of different stiffness was strongest using group velocity analysis: out of the 18 group differences evaluated for plaque size (2–5 FT-cycles at 3 different lumen sizes, see upper row of subfigures in figure 9), only 2 could not be statistically differentiated using group velocity analysis. Conversely, weakest differentiation was achieved at the lowest frequency band (7 out of 18) with higher ability to differentiate.
plaque groups reported at higher frequency bands (11 out of 18, and 13 out of 18 at 700–800 and 950–1050 Hz, respectively).

For the varying intraluminal cavity positions, group velocity analysis again rendered the highest number of significantly differentiable stiffness levels (11 out of 12, see middle row of subfigures in figure 9). Comparing centred and off-centred plaques, slightly higher ability to separate plaque groups was seen for the off-centred plaques, albeit these also indicated a slightly increased underestimation using any of the analysed wave speed metrics. As for the varying intraluminal cavity dimensions, weakest ability to separate plaque groups was seen at the lower frequency bands of the phase velocity analysis.

Similarly, the ability to separate phantom plaques of different stiffness was higher using group velocity analysis in both anterior and posterior view. Out of the two, the anterior part of the plaque (representing the thicker part of the off-centred plaques) showed higher differentiation ability, where the difference between 2 FT and 3 FT could not be distinguished using any of the wave speed metrics when pushes were performed in the thinner posterior part of the plaque.

**Imaging plane**

The difference in accuracy and ability to quantify different plaque stiffness levels was also evaluated as a function of different imaging planes, respectively. The results are summarized in figure 10, with relative error compared to reference phantoms given in table 4. Confidence intervals of the same are provided in supplementary table 2.

In table 4, a systematic underestimation of shear wave speed can be seen at all plaque stiffness levels using group velocity analysis. For phase velocity analysis, an underestimation was only present at lower frequencies, whereas the high frequency analysis (950–1050 Hz) indicated no defined underestimation for any of the used imaging planes. However, comparing longitudinal and transverse views, transverse views experienced a slightly pronounced underestimation.

With regards to the ability to statistically differentiate plaque groups from each other, longitudinal imaging planes were superior being able to differentiate 20 out of 24 groups from each other; only the difference between 3 and 4FT-cycle plaques could not be separated. In the transverse view, 14 out of 24 groups could be differentiated, and none of the stiffer plaques could be separated from each other using phase velocity analysis.
Ultrasound elastography has shown the potential for improved atherosclerotic risk stratification, however the accuracy, optimal analysis settings, and specific effects of plaque geometry have remained unexplored. Therefore, the aim of this study was to parametrically evaluate the accuracy and ability to differentiate plaques of different stiffness using SWE—a subset of ultrasound elastography imaging.

The results show that plaque differentiation with respect to variations in mechanical stiffness can be achieved using SWE. However this ability is dependent on the choice of analysed wave speed metric. In particular, results indicate that either group velocity analysis or phase velocity analysis at high frequencies (>1 kHz) is to be preferred, with both metrics showing superior ability to differentiate plaques of different stiffness. Albeit showing a

![Figure 10](image-url)  
Figure 10. SWE results for different longitudinal and transverse imaging planes, respectively. Results are shown for four different wave speed metrics (a) group velocity, $c_g$ and phase velocity in three different frequency bands, (b) $c_p,450–550$ Hz, (c) $c_p,700–800$ Hz, and (d) $c_p,950–1050$ Hz). In each subfigure, results are provided for ranging levels of plaque stiffness (2–5 FT cycles) with reference values given by the horizontal red lines within each box plot. Additionally, differences in stiffness is statistically quantified by a Wilcoxon rank sum test, indicated by the top horizontal bars where the green continuous lines indicate $p < 0.05$, whereas the red dotted lines indicate $p \geq 0.05$. Each box represents min, max, median, 25th and 75th percentile, respectively ($N = 82$ and 45 for longitudinal and transverse view, respectively).

|               | 2     | 3     | 4     | 5     | Total |
|---------------|-------|-------|-------|-------|-------|
| Longitudinal, rel. error | $c_g$ | $-7 \pm 14$ | $-5 \pm 10$ | $-11 \pm 11$ | $-12 \pm 9$ | $-9 \pm 11$ |
| $c_p,450–550$ Hz | $-3 \pm 29$ | $-6 \pm 20$ | $-19 \pm 17$ | $-24 \pm 19$ | $-13 \pm 21$ |
| $c_p,700–800$ Hz | $2 \pm 27$ | $10 \pm 22$ | $-4 \pm 17$ | $-8 \pm 19$ | $0 \pm 21$ |
| $c_p,950–1050$ Hz | $13 \pm 27$ | $8 \pm 19$ | $1 \pm 17$ | $-3 \pm 18$ | $5 \pm 20$ |
| Transverse, rel. error | $c_g$ | $-22 \pm 15$ | $-14 \pm 11$ | $-18 \pm 10$ | $-24 \pm 11$ | $-20 \pm 12$ |
| $c_p,450–550$ Hz | $-21 \pm 15$ | $-26 \pm 9$ | $-30 \pm 13$ | $-39 \pm 10$ | $-29 \pm 12$ |
| $c_p,700–800$ Hz | $-4 \pm 30$ | $-7 \pm 11$ | $-15 \pm 12$ | $-26 \pm 15$ | $-13 \pm 17$ |
| $c_p,950–1050$ Hz | $1 \pm 22$ | $2 \pm 17$ | $-7 \pm 15$ | $-14 \pm 22$ | $-5 \pm 19$ |

Discussion

Ultrasound elastography has shown the potential for improved atherosclerotic risk stratification, however the accuracy, optimal analysis settings, and specific effects of plaque geometry have remained unexplored. Therefore, the aim of this study was to parametrically evaluate the accuracy and ability to differentiate plaques of different stiffness using SWE—a subset of ultrasound elastography imaging.

The results show that plaque differentiation with respect to variations in mechanical stiffness can be achieved using SWE. However this ability is dependent on the choice of analysed wave speed metric. In particular, results indicate that either group velocity analysis or phase velocity analysis at high frequencies (>1 kHz) is to be preferred, with both metrics showing superior ability to differentiate plaques of different stiffness. Albeit showing a
systematic underestimation of acquired wave speed, group velocity analysis showed both highest ability to dif-
ferral plates of different stiffness, and lowest wave speed deviation underlining its potential use as a clinical,
metric, in line with previous feasibility studies (Ramnarine et al 2014b, Garrard et al 2015, Lou et al 2017).
The study also indicates differences in accuracy and differentiability between longitudinal and transverse imaging
plane, as well as posterior and anterior plaque wall analysis. However, the wave speed estimation was invariant to
the elastographic push location, showing promising robustness ahead of any clinical implementation.

Different push locations were evaluated with respect to quality of signal as well as quality of estimate
(figures 7, 8 and tables 2, 3). As reported, different push locations experienced distinct differences in both SNR
and maximum particle velocity, however, the two did not seem directly correlated. In particular, the transverse
push locations experienced highest maximum particle velocity, whilst showing relatively low SNR. The reason
for this discrepancy is difficult to isolate, but could spurt from the difference in fundamental wave propagation
behaviour between transverse and longitudinal imaging planes. For longitudinal imaging, the shear wave propa-
gation follows the preferential direction of the plaque, generating a guided wave (Gazis 1959a, 1959b, Chimenti
and Nayfeh 1985, Mal et al 1989) travelling through the long-axis direction of both the intravascular plaque and
the surrounding arterial wall. In contrast, for transverse imaging, the shear wave propagates seemingly unob-
structed through the surrounding tissue before passing through the plaque and artery as an embedded inclusion
rather than as a guided wave. Note though that circumferential guided waves will appear in the transverse plane,
however the analysis of such requires refined acquisition settings (Hansen et al 2010, He et al 2017). With higher
particle velocities apparent for the transverse push locations, the inclusion based wave propagation transfers a
larger portion of the wave energy into the plaque itself, whereas the guided wave propagation of the longitudinal
view will render typical dispersion behaviour, obstructing optimal energy transfer in the direction of the ana-
lysed wave (Bernal et al 2011, Puthillath et al 2013). Along the same lines, the longitudinal push location generates
guided waves with an interface facing the intraluminal fluid-filled cavity. With such, leaky wave guided behaviour
will occur (Chimenti and Nayfeh 1985, Mal et al 1989) where a portion of the energy of the propagating wave is
transferred into the fluid phase, effectively dampening the wave and weakening the experienced particle velocity.
In contrast, no such leaky wave behaviour is expected in the transverse view.

Despite these apparent differences in quality of signal, the quality of the estimated wave did not vary dis-
tinctly between different push locations, as indicated in figure 8 and table 2. Instead, the main difference is seen
between the different wave speed metrics. Group velocity analysis shows a systematic underestimation of the
retrieved wave speed, whereas the accuracy of the phase velocity shows defined frequency dependence. At low
frequencies a pronounced underestimation in wave speed is apparent, whereas this effect vanishes and converges
towards accurate estimates with increasing frequency. Again, this behaviour could be explained by coupling the
results to the fundamental wave propagation of the travelling shear waves. As described extensively in literature
(Gazis 1959a, 1959b, Chimenti and Nayfeh 1985, Mal et al 1989, Bernal et al 2011, Maksuti et al 2016), wave propa-
gation through confined media generates dispersion behaviour where different frequencies travel at different
velocities. With increasing frequency the phase velocity converges towards an asymptotic phase velocity where
the geometrical confinement no longer influences the wave propagation. However, at low frequencies the simi-
larity in wave length and spatial plaque dimensions causes a variation in phase velocity, where typical fluctuating
behaviour (due to interplay between fundamental zero-order wave modes) becomes apparent. Previous studies
on arterial SWE (Couade et al 2010, Bernal et al 2011, Maksuti et al 2016) have reported such typical fluctuations
as occurring <500 Hz for arteries of <1 cm in thickness, and theoretical work has even shown that the range
of this fluctuating wave propagation behaviour increases with increasing material stiffness (Li et al 2017). With
such, the results of this study conform to wave propagation theory, where the reported underestimation stems
from lower-order frequencies being hampered in its propagation by the confined plaque geometry. Additionally,
the reported underestimation increases with increasing plaque stiffness (see e.g. figure 9), again agreeing with
previous theoretical (Li et al 2017) and numerical findings (Urban et al 2017).

Differences in spread of the acquired wave speed metrics were also found. Albeit the previously discussed
underestimation, group velocity analysis rendered the most stable estimate with an average variation of 11%. In
comparison, phase velocity analysis showed a variation of around 20% regardless of frequency band. Again the
spatial plaque dimensions might influence low frequencies to a higher extent causing pronounced deviation in
results, whereas high frequency phase velocities might be more sensitive to spurious noise signals or decreased
signal strength. The results therefore imply a slight trade-off between accuracy and robustness, where group
velocity analysis renders underestimated but robust results, whereas phase velocity analysis renders accurate but
less robust results. The clinical importance of this trade-off remains to be evaluated with respect to plaque risk
stratification, however previous studies using group velocity analysis have indicated promising results in vivo
(Ramnarine et al 2014b, Garrard et al 2015, Lou et al 2017).

The effect of plaque geometry was also evaluated including variations of intraluminal cavity diameter, position,
and plaque side, all summarized in figure 9. As pointed out, group velocity analysis was most successful in
differentiating plaques where only occasionally the difference between 3 and 4 FT-cycles could not be deter-
mined. For the phase velocity analysis, again increased frequency rendered more favourable results, however still showing difficulties in differentiating the 3 and 4 FT-cycle plaques from one another. In fact, these two batches proved the most difficult for any configuration, spurring from the fact that the difference in reference value was the smallest between these two (0.45 m s$^{-1}$ difference, compared to 0.9 m s$^{-1}$ and 0.85 m s$^{-1}$ between 2–3 and 4–5 FT-cycles, respectively). An effective wave speed resolution is thus apparent for the SWE measurements, being in the range of 0.5 m s$^{-1}$ as indicated by the presented results. However, results also indicate that this resolution and ability depends on plaque geometry: if imaging an off-centred plaque, pushing in the anterior (in this case larger) plaque side renders more favourable differentiation of different plaque groups. Similarly, plaques with higher degrees of stenosis and with smaller intraluminal cavity opening were easier to differentiate compared to smaller plaques. This again can be coupled to wave propagation behaviour, where smaller plaques results in increased wave propagation confinement, and vice versa. Thus, for any clinical implementation, the ability to differentiate and classify plaque groups successfully seem maximized if opting for imaging at the largest possible region of the evaluated plaque.

The implication of the results are interesting when translated to a clinical setting: if striving for improved risk stratification—virtually endeavouring improved differentiation between plaques of different composition—the absolute accuracy is of lesser importance (since the least accurate group renders the highest ability to differentiate plaques of different stiffness). Consequently, group velocity would be a preferred metric, with which plaque differentiability has already been attempted (Ramnarine et al 2014b, Garrard et al 2015, Lou et al 2017). With that said, phase velocity analysis at the highest frequency band also rendered favourable results with respect to differentiability. With dispersion behaviour converging at increased frequencies, improved accuracy and robustness might thus be achieved if going to even higher frequencies (i.e. >1 kHz). This poses challenges on the acquisition side, but as has been shown for arterial SWE (Widman et al 2016), a reduction in push duration typically increases shear wave bandwidth.

In previous studies, SWE output has generally been displayed in the form of an apparent shear modulus (Couade et al 2010, Bernal et al 2011, Ramnarine et al 2014b, Garrard et al 2015, Maksuti et al 2016, Widman et al 2016). However, as discussed the relationship between wave speed and mechanical stiffness is not trivial in highly confined geometries. For this reason, we decided to evaluate the accuracy and differentiability of using direct a wave speed output. Importantly, with the shear modulus generally proportional to the square of the wave speed, any wave speed uncertainties (as unveiled by this study) might amplify errors in any stiffness evaluation. However, if an appropriate constitutive model would be used, taking the geometrical confinement into account, there could be a clinical value in continuing into tissue stiffness, providing a quantitative patient-specific value for further plaque risk stratification. With this in mind, the apparent trade-off between accuracy, robustness, and differentiability seen in this study underlines the complexity of this task.

Our results indicate that push locations further away from the imaged plaque could be used with maintained accuracy but reduced plaque particle velocity. One could even imagine refined push sequences, e.g. multi-sided comb-push excitations (Song et al 2012) where the accumulated particle velocity would still be lower than that of a single push located in the middle of the plaque. This might have some minor implications on the safety aspects of elastographic plaque imaging (in line with the ALARA (as low as reasonably achievable) principle (Barnett et al 2000), albeit previous studies have indicated the safe use of ultrasound elastography for general cardiovascular applications (Doherty et al 2013, Maksuti et al 2017b).

For all of the above, the evaluated phantom plaque velocities were compared to group velocity values from large reference phantoms. The reason for not using reference phantom phase velocities stemmed from the fact that 1. PVA only shows minor viscous dispersion, and 2. the large dimensions of the phantoms minimised any geometrical dispersion. Following this, the wave propagation in the reference phantoms could be likened to wave propagation through infinite, elastic medium where no dispersion behaviour is seen. This can be validated experimentally in table 5, where no significant difference can be reported between group and phase velocity in any of the analysed frequency bands, or for any of the analysed phantom plaque stiffness, in the reference phantoms used within this paper.

| FT-cycles | $\zeta_2$ | $\zeta_{450–550\,\text{Hz}}$ | $\zeta_{700–800\,\text{Hz}}$ | $\zeta_{950–1050\,\text{Hz}}$ |
|-----------|-----------|-----------------|-----------------|-----------------|
| 2         | 3.47      | 3.49            | 3.49            | 3.50            |
| 3         | 4.37      | 4.32            | 4.35            | 4.37            |
| 4         | 4.82      | 4.90            | 4.84            | 4.83            |
| 5         | 5.67      | 5.77            | 5.66            | 5.72            |

There are a number of limitations associated with the present study. In particular, extrapolating results from in vitro experiments to in vivo applications can be challenging, especially considering the relative simplicity of the analysed phantom plaques (even though image parameter optimization in vitro is not uncommon in the field of
medical imaging (Rahim et al 2006, Havre et al 2008)). In comparison to human plaques the analysed specimens had both homogeneous stiffness and morphology, and did not show any difference in internal plaque composition otherwise characteristic for vulnerable plaques. However, the reason for the simplified plaque phantoms was to allow for a controlled and parametric variation of plaque stiffness and geometry, singling out their effect on SWE performance. Also, previous feasibility tests on SWE in ex vivo plaque tissue (Larsson et al 2016) has indicated that shear wave velocities could correlate to localized variations in plaque composition, and the potential of using the metrics evaluated in the present study might thus be applicable even in the case of more complex plaque structures. In addition, care was taken to maintain the complexity of the arterial wall in the created experimental setup, as was the effect of surrounding tissue included (something that has been neglected in some previous phantom studies on cardiovascular ultrasound elastography (Hansen et al 2010, Ramnarine et al 2014a, Widman et al 2016)). Regardless, important aspects of plaque stability such as the degree and development of inflammation or internal plaque morphology would have to be addressed using a more realistic setup. Similarly, any clinical translation of the obtained output and imaging settings would have to be preceded by intermediate in vivo evaluations of their defined impact.

A further limitation in the experimental setup is the lack of any pressurization or pulsatile flow inside the intraluminal cavity. However, with the generated shear wave travelling orders of magnitude faster than the cardiovascular pressure pulse (Couade et al 2010) and with the intravascular dynamic pressurization typically not deforming plaque tissue significantly during such short time scales (Kock et al 2008), its impact on the ability to properly image plaque tissue might be limited. It is worth noting that with both PVA and vascular tissue exhibiting hyperelastic material behaviour at large strains, internal pressurization might increase the apparent stiffness assessed by SWE. Following the findings of our study, this might render an even more pronounced underestimation of wave speed, however the effect on the ability to differentiate plaques of different stiffness from each other remains unknown.

Lastly, albeit some evaluation of anterior versus posterior push location was performed, the direct impact of pushing depth on evaluated stiffness (previously shown to affect shear wave measurements (Wang et al 2014)) remains to be evaluated for plaque tissue analysis. Similarly, the use of directional filtering might improve accuracy or reduce deviation in the acquired elastography data (Lipman et al 2016).

With the development of refined 3D printing techniques, refined phantom plaque samples of high complexity could be generated and tested for medical imaging purposes (Porée et al 2017). However, ex vivo plaque analysis might represent a closer step for translating experimental SWE development into the clinics, where detailed mapping of shear wave propagation in heterogeneous, realistic plaque tissue could be performed. With that, a range of feasibility tests have already been performed in vivo (Ramnarine et al 2014b, Mahmood et al 2016, Lou et al 2017, Roy Cardinal et al 2017), and it is primarily through such controlled clinical studies that the potential of SWE for improved cardiovascular care can be clearly defined. Based on the results of the performed study however, the potential to differentiate plaques of different stiffness were enabled by SWE, and by optimizing imaging and used wave speed metric the ability to differentiate different plaque types might be even further enhanced.

Conclusion

This study has showed that differentiation of simulated plaques with different mechanical stiffness can be achieved using SWE. Importantly, this ability seems directly dependent on used wave speed metric and image specifications, where imaging in a longitudinal plane using either group or phase velocity analysis at sufficiently high frequencies (≥1 kHz) seemed the superior choice. Despite a systematic underestimation of wave speed, group velocity analysis showed lowest variability of all analysed wave speed. With these results also invariant to shear wave push location, this indicates a potential robust use of SWE for future in vivo characterization of intravascular plaques. However, for such a clinical translation detailed studies on shear wave propagation in confined and heterogeneous plaque tissue could be required, especially with the results of this study indicating a tight connection between wave propagation behaviour and SWE output.

Acknowledgment

The authors thank technician Peter Arfert for his invaluable help in creating the experimental equipment. The authors also acknowledge the Jonasson Centre for Medical Imaging for providing the programmable ultrasound equipment, as well as the Mayo Clinic and Karolinska Institutet Collaboration Platform for assisting in the transatlantic collaboration. The study was also financially supported by the Swedish Research Council (VR, 2015-04237).
ORCID iDs

David Marlevi https://orcid.org/0000-0003-1002-2070
Elira Maksuti https://orcid.org/0000-0002-9654-447X

References

Barnett S B, Ter Haar G R, Ziskin M C, Rott H-D, Duck F A and Maeda K 2000 International recommendations and guidelines for the safe use of diagnostic ultrasound in medicine Ultrason. Med. Biol. 26 355–66

Bernal M, Menadic I, Urban M W and Greenleaf J F 2011 Material property estimation for tubes and arteries using ultrasound radiation force and analysis of propagating modes J. Acoust. Soc. Am. 129 1344–54

Biller J, Feinberg W M, Castaldo J E, Whittamore A D, Harbaugh R E, Dempsey R J, Caplan I R, Kresowik T F, Matchar D B and Tooze J F 1998 Guidelines for carotid endarterectomy: a statement for healthcare professionals from a special writing group of the Stroke Committee, American Heart Association Circulation 97 501–9

Caenen A, Pernot M, Shcherbakova D A, Mertens L, Kersemans M, Segers P and Swillens A 2017 Investigating shear wave physics in a generic Phys. Med. Biol. 64 349–61

Chimenti D and Nayfeh A H 1985 Leaky Lamb waves in fibrous composite laminates J. Appl. Phys. 58 4531–8

Coumades M, Pernot M, Prada C, Messas E, Emmerich J, Brunet P, Criton A, Fink M and Tanter M 2010 Quantitative assessment of arterial wall biomechanical properties using shear wave imaging Ultrason. Med. Biol. 36 1662–76

Czernuszewicz T J, Homeister J W, Caughey M C, Farber M A, Fulton J J, Ford P F, Marston W A, Vallabhaneni R, Nichols T C and Gallippi C M 2015 In vivo carotid plaque stiffness measurements with ARFI ultrasound in endarterectomy patients 2015 IEEE Int. Uralons. Symp. (IUS) (2015) IEEE pp 1–4

Czernuszewicz T J, Homeister J W, Caughey M C, Wang Y, Zhu H, Huang B Y, Lee E R, Zamora C A, Farber M A and Fulton J J 2017 Performance of acoustic radiation force impulse imaging for carotid plaque characterization with histologic validation J. Vascular Surg. 66 1749–57

De Korte C L, Painterkamp G, Van Der Steen A E, Woutman H A and Born N 2000 Characterization of plaque components with intravascular ultrasound elastography in human femoral and coronary arteries in vitro Circulation 102 617–23

Doherty J R, Dahl J J, Kranz P G, El Hussein N, Chang H C, Chen N K, Allen J D, Ham K I and Trahey G E 2013 Comparison of acoustic radiation force impulse imaging derived carotid plaque stiffness with spatially registered MRI determined composition IEEE Trans. Med. Imaging 34 2354–65

Doherty J R, Dumont D M, Trahey G E and Palmeri M L 2013 Acoustic radiation force impulse imaging of vulnerable plaques: a finite element method parametric analysis J. Biomech. 46 83–90

Dumont D, Behler R H, Nichols T C, Merricks E P and Gallippi C M 2006 ARFI imaging for noninvasive material characterization of atherosclerosis Ultrason. Med. Biol. 32 1783–11

Fromageau J, Bruseau E, Vray D, Gimenez G and Delacharte P 2003 Characterization of PVA cryogel for intravascular ultrasound elasticity imaging IEEE Trans. Ultrason. Ferroelectr. Freq. Control 50 1318–24

Garrard J, Ummur P, Nduwayo S, Kanber B, Hartshorne T, West K, Moore D, Robinson T and Rammarine K 2015 Shear wave elastography may be superior to greyscale median for the identification of carotid plaque vulnerability: a comparison with histology Ultraschall Med. 36 386–90

Gazis D C 1959a Three-dimensional investigation of the propagation of waves in hollow circular cylinders. I. Analytical foundation J. Acoust. Soc. Am. 31 568–73

Gazis D C 1959b Three-dimensional investigation of the propagation of waves in hollow circular cylinders. II. Numerical results J. Acoust. Soc. Am. 31 373–8

Hansen H H, Lopata R G, Idzenga T and de Korte C L 2010 An angular compounding technique using displacement projection for noninvasive ultrasound strain imaging of vessel cross-sections Ultrason. Med. Biol. 32 1947–56

Havre R F, Elde E, Gilja O H, Ødegaard S, Eide G E, Matre K and Nesje L B 2008 Freehand real-time elastography: impact of scanning parameters on image quality and in vitro intra- and interobserver validations Ultrason. Med. Biol. 34 1638–50

He Q, Li G Y, Lee F F, Zhang Q, Cao Y and Luo J 2017 Novel method for vessel cross-sectional shear wave imaging Ultrason. Med. Biol. 43 1520–32

Henry M, Polydorou A, Klomaris C, Henry I, Polydorou A and Hugel M 2007 Carotid angioplasty and stenting under protection. State of the art Minerva Cardioangiol. 55 19–36

Hodgson J M, Reddy K G, Suneha R, Nair R N, Lesniewski E J and Sheehan H M 1993 Intraocular ultrasound imaging: correlation of plaque morphology with angiography, clinical syndrome and procedural results in patients undergoing coronary angioplasty J. Am. Coll. Cardiol. 21 35–44

Huang C, Pan X, He Q, Huang M, Huang L, Zhao X, Yuan C, Bai J and Luo J 2016 Ultrasound-based carotid elastography for detection of vulnerable atherosclerotic plaques validated by magnetic resonance imaging Ultrason. Med. Biol. 42 365–77

Huang R, Urban M W, DeMarco J K, Brinjikji W, Huston J, Macedo T A, Dailey E J, Hagen M E and Mulvagh S L 2017 Lipoproteins, statin therapy, carotid atherosclerotic plaque vulnerability and stiffness: a study of novel ultrasound methods utilizing microbubble contrast enhancement and shear wave elastography J. Am. Coll. Cardiol. 69 1577

Keeley E and Grimes C J 1998 Scraping of aortic debris by coronary guiding catheters: a prospective evaluation of 1000 cases J. Am. Coll. Cardiol. 32 1861–5

Kock S A, Nygaard J V, Eldrup N, Fründ E-T, Klærke A, Paaske W P, Falk E and Kim W Y 2017 Contrast enhancement and shear wave elastography J. Am. Coll. Cardiol. 69 1577

Kolodgie F D, Burke A P, Farb A, Gold H K, Yuan J, Narula J, Finn A V and Virmani R 2001 The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes Curr. Opin. Cardiol. 16 285–92

Kolominsky-Rabs P L, Weber M, Gefeller O, Neumoerler B and Heuschmann P U 2001 Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study Stroke 32 2735–40
Loupas T, Roy J, Gasser T C, Urban M W, Colaritisti-Tosi M and Larsson M 2016 An ex vivo setup for characterization of atherosclerotic plaque using shear wave elastography and micro-computed tomography 2016 IEEE Int. Ultrasonics Symp. (IUS) (2016) (IEEE) pp 1–4
Li G-Y, He Q, Jia L, He P, Luo J and Cao Y 2017 An inverse method to determine arterial stiffness with guided axial waves Ultrasound Med. Biol. 43 505–16
Libby P 2001 Current concepts of the pathogenesis of the acute coronary syndromes Circulation 104 365–72
Libby P, Ridker P M and Masera A 2002 Inflammation and atherosclerosis Circulation 105 1135–43
Lipman S L, Rouze N C, Palmeri M I and Nightingale K R 2016 Evaluating the improvement in shear wave speed image quality using multidimensional directional filters in the presence of reflection artifacts IEEE Trans. Ultrason. Ferroelectr. Freq. Control 63 1049–63
Liu F, Yong Q, Zhang Q, Liu P and Yang Y 2015 Real-time tissue elastography for the detection of vulnerable carotid plaques in patients undergoing endarterectomy: a pilot study Ultrasound Med. Biol. 41 705–12
Lou Z, Yang J, Tang L, Jin Y, Zhang J, Liu C and Li Q 2017 Shear wave elastography imaging for the features of symptomatic carotid plaques: a feasibility study J. Ultrasound Med. 36 1213–23
Loupas T, Powers J and Gill R W 1995 An axial velocity estimator for ultrasound blood flow imaging, based on a full evaluation of the Maksuti E, Bini F, Fiorentini S, Blasi G, Urban M W, Larsson D, Marinozzi F and Larsson M 2017b Strain and strain rate generated by shear wave elastography in an ex vivo porcine aorta 2017 IEEE Int. Ultrasonics Symp. (IUS) (2017b) (IEEE) pp 1–4
Makutski E, Widman E, Larsson D, Urban M W, Larsson M and Bjallmark A 2016 Arterial stiffness estimation by shear wave elastography: validation in phantoms with mechanical testing Ultrasound Med. Biol. 42 308–21
Mal A, Xu P-C and Bar-Cohen Y 1989 Analysis of leaky Lamb waves in bonded plates Int. J. Eng. Sci. 27 779–91
McLaughlin J and Renzi D 2006 Shear wave speed recovery in transient elastography and supersonic imaging using propagating fronts Inverse Problems 22 6811
Moreno P R 1999 Atherosclerosis— an inflammatory disease New Engl. J. Med. 340 115–26
Naghibi M, Libby P, Fark E, Cascolos SW, Litovsky S, Rumberger J, Badimon J I, Stefanadis C, Moreno P and Pasterkamp G 2003 From vulnerable plaque to vulnerable patient a call for new definitions and risk assessment strategies: part I Circulation 108 1664–72
Naim C, Cloutier G, Mercure E, Destrempes F, Qin Z, El-Abyad W, Lanthier S, Giroix M-F and Soulez G 2013 Characterization of carotid plaques with ultrasound elastography: feasibility and correlation with high-resolution magnetic resonance imaging Eur. Radiol. 23 2030–41
Porée J, Chayer B, Soulez G, Ohayon J and Cloutier G 2017 Noninvasive vascular modulography method for imaging the local elasticity of atherosclerotic plaques: simulation and in vitro vessel phantom study IEEE Trans. Ultrason. Ferroelectr. Freq. Control 64 1805–17
Puthilath P, Galan J M, Ren B, Lissenden C J and Rose J L 2013 Ultrasonic guided wave propagation across waveguide transitions: energy transfer and mode conversion J. Acoust. Soc. Am. 133 2624–33
Rahim A, Taylor S L, Bush N L, ter Haar G R, Bamber J C and Porter C D 2006 Physical parameters affecting ultrasound/microbubble-mediated gene delivery efficiency in vitro Ultrasound Med. Biol. 32 1269–79
Rammarine K V, Garrard J W, Dexter K, Nduwayo S, Panerai R B and Robinson T G 2014a Shear wave elastography assessment of carotid plaque stiffness: in vitro reproducibility study Ultrasound Med. Biol. 40 200–9
Rammarine K V, Garrard J W, Kanber B, Nduwayo S, Hartshorne T C and Robinson T G 2014b Shear wave elastography imaging of carotid plaques: feasible, reproducible and of clinical potential Cardiovasc Ultrason. 12 1
Ross R 1999 Atherosclerosis—an inflammatory disease New Engl. J. Med. 340 115–26
Roy Cardinal M-H, Heusinkveld M H, Qin Z, Lopata R G, Naim C, Soulez G and Cloutier G 2017 Carotid artery plaque vulnerability assessment using noninvasive ultrasound elastography: validation with MRI J. Am. J. Roentgenol. 209 142–51
Schaar J A, de Korte C L, Mastik F, Strijder C, Pasterkamp G, Boerma E, Serruys P FW and van der Steen A F 2003 Characterizing vulnerable plaque features with intravascular elastography Circulation 108 2636–41
Schmitt C, Soulez G, Maurice R L, Giroix M-F and Cloutier G 2007 Noninvasive vascular elastography: toward a complementary characterization tool of atherosclerosis in carotid arteries Ultrasound Med. Biol. 33 1841–58
Segal A, Abernethy W, Palacios I, BeLue R and Rordorf G 2001 Stroke as a complication of cardiac catheterization: risk factors and clinical consequences Neurology 56 975–7
Song P, Zhao H, Manduca A, Urban M W, Greenleaf J F and Chen S 2012 Comb-push ultrasound shear elastography (CUSE): a novel method for two-dimensional shear elasticity imaging of soft tissues IEEE Trans. Med. Imaging 31 1821–32
Stary H C, Chandler A B, Dinuzofor R E, Fuster V, Glagov S, Insull W, Rosenfeld M E, Schwartz C J, Wissler W D and Wissler R W 1995 A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis: a report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association Circulation 92 1355–74
Takano M, Mizuno K, Okamatsu K, Yokoya S, Obha T and Sakai S 2001 Mechanical and structural characteristics of vulnerable plaques: analysis by coronary angiography and intravascular ultrasound J. Am. Coll. Cardiol. 39 99–104
Tavakol M, Ashraf S and Brener S J 2012 Risks and complications of coronary angiography: a comprehensive review Glob. J. Health Sci. 4 65 Urban M, Carlson K and Daescu D D 2017 Finite element models of wave propagation in embedded vessels with simulated plaques 2017 IEEE Int. Ultrasonics Symp. (IUS) (2017) (IEEE) pp 1–4
Wang C-Z, Zheng J, Huang Z-P, Xiao Y, Song D, Zeng J, Zheng H-R and Zheng R-Q 2014 Influence of measurement depth on the stiffness assessment of healthy liver with real-time shear wave elastography Ultrasound Med. Biol. 40 461–9
Wang M H, Palmeri M L, Rotemember V M, Rouze N C and Nightingale K R 2010 Improving the robustness of time–of–flight based shear wave speed reconstruction methods using RANSAC in human liver in vivo Ultrasound Med. Biol. 36 802–13
Widman E, Maksuti E, Arnadottir C, Urban M W, Caidahl K and Larsson M 2016 Shear wave elastography quantifies stiffness in ex vivo porcine artery with stiffened arterial region Ultrasound Med. Biol. 42 2423–35