NONINVASIVE VASCULAR ULTRASOUND ELASTOGRAPHY

H.H.G. Hansen
NONINVASIVE VASCULAR ULTRASOUND ELASTOGRAPHY

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,
volgens het besluit van het college van decanen
in het openbaar te verdedigen op vrijdag 16 november 2012
om 12.00 uur precies

door

Hendrik Hubertus Gertrudis Hansen
geboren op 11 februari 1982
te Roermond
This research was financially supported by the Dutch Technology Foundation STW (project number 07589).

Financial support by the Dutch Heart Foundation and Stichting Kindergeneeskunde for the publication of this thesis is gratefully acknowledged.

<table>
<thead>
<tr>
<th>TABLE OF CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. General Introduction 1</td>
</tr>
<tr>
<td><strong>PART I: NONINVASIVE VASCULAR ELASTOGRAPHY METHODS</strong></td>
</tr>
<tr>
<td>2. Segment Based Compounding of Axial Strains 25</td>
</tr>
<tr>
<td>3. Segment Based Compounding of Axial Displacements 43</td>
</tr>
<tr>
<td>4. Nonsegment Based Compounding of Axial Displacements 57</td>
</tr>
<tr>
<td><strong>PART II: STRAIN ESTIMATION IMPROVEMENTS</strong></td>
</tr>
<tr>
<td>5. Optimizing Grating Lobe Filtering for Strain Estimation 79</td>
</tr>
<tr>
<td>6. Strain Imaging in Shearing and Rotating Tissue 93</td>
</tr>
<tr>
<td><strong>PART III: APPLICATION OF NONINVASIVE VASCULAR ELASTOGRAPHY</strong></td>
</tr>
<tr>
<td>7. Noninvasive Compound Elastography in Pulsating Vessels 111</td>
</tr>
<tr>
<td>8. In Patient Validation of Noninvasive Compound Elastography 121</td>
</tr>
<tr>
<td><strong>PART IV: RECENT DEVELOPMENTS</strong></td>
</tr>
<tr>
<td>9. Plane Wave Noninvasive Compound Elastography 141</td>
</tr>
<tr>
<td>10. Noninvasive Vascular Shear Strain Imaging 149</td>
</tr>
<tr>
<td>11. Elastic Modulus Reconstructions using Compound Elastography 163</td>
</tr>
<tr>
<td><strong>PART V: GENERAL DISCUSSION</strong></td>
</tr>
<tr>
<td>12. General Discussion 175</td>
</tr>
<tr>
<td>13. Summary 181</td>
</tr>
<tr>
<td>14. Samenvatting 187</td>
</tr>
<tr>
<td>15. Bibliography 193</td>
</tr>
<tr>
<td>List of Publications and Presentations 209</td>
</tr>
<tr>
<td>Dankwoord 217</td>
</tr>
<tr>
<td>About the Author 223</td>
</tr>
</tbody>
</table>
Cardiovascular diseases are responsible for many deaths in Western society. A substantial part of all strokes are caused by the rupture of atherosclerotic plaques in the carotid artery. The rupture proneness of a plaque is related to its geometry and composition. To determine both geometry and composition of a plaque ultrasound elastography can be used. This chapter will provide background information on atherosclerosis and the vulnerable plaque first. Next, the basics of ultrasound and the use of ultrasound for vascular imaging will be discussed. At the end of the chapter an overview of ultrasound elastography methods and their application for vulnerable plaque detection will be given.


CHAPTER 1

The cardiovascular system and cardiovascular disease

The cells of the human body require the supply of nutrients and oxygen in order to function properly. These supplies are delivered by the cardiovascular system which consists of the heart and the blood vessels. The heart is a muscle which contracts on average once per second. The heart consists of two halves that are each made up of an atrium and a ventricle. In a closed loop the blood is pumped through the human body. Contraction of the right ventricle causes deoxygenated blood to be pumped into the lungs, where carbon dioxide molecules are exchanged for oxygen molecules. The oxygen-rich blood returns to the heart via the left atrium. Opening of the tricuspid valve between the left atrium and the left ventricle allows the blood to enter the left ventricle. When the left ventricle contracts the blood is propelled into the aorta that supplies all organs and muscles from oxygen and nutrients. The oxygen-poor blood then returns to the heart through the right atrium and the cycle is repeated. In this way four to six liters of blood are pumped through a healthy human body every minute. Failure of the cardiovascular system is often lethal. In 2006 29-2% of all worldwide deaths was due to cardiovascular disease (CVD) [2]. In Europe even 42% of all deaths was due to CVD in 2008 [2]. The two main forms of CVD are coronary heart disease and stroke. The first is responsible for about half of the cardiovascular deaths and is a disease of the blood vessels supplying the heart muscle, the latter is a disease of the blood vessels supplying the brain and is responsible for one third of all cardiovascular deaths in Europe. This explains the importance of developing methods for diagnosis of the health of the vasculature.

Atherosclerosis and the vulnerable plaque

Both for coronary heart disease and stroke the decline in the quality of the vessel wall is caused by atherosclerosis. Atherosclerosis is a systemic disease which means that it affects the status of the entire vascular tree [3]. The healthy arterial wall consists of three layers: the intima (inner layer), media (middle layer) and the adventitia (outer) layer, Fig. 1-1. Each layer is separated from the next layer by an elastic lamina. The intima is formed by a single layer of endothelial cells and enables the uptake and release of materials from the blood stream into the tissue and vice versa. The media consists of circumferentially arranged smooth muscle cells and elastin fibers. These muscle cells can actively contract or relax causing active constriction or dilation of the vessel. This layer gives the artery its mechanical strength. The adventitia is composed of collagen and elastin fibers and is responsible for the connection of the vessel to the surrounding tissue.

Atherosclerosis usually starts with the uptake of excess low density lipoproteins (LDL) from the circulation in the vessel wall [4-6]. These LDL molecules can then oxidize and cause a series of inflammatory reactions that result in an accumulation of lipoproteins, macrophages and white blood cells in the intima. Initially these accumulations are small and referred to as fatty streaks. Over time these fatty streaks can disappear, or develop into a so-called stable or vulnerable plaque. The differences in composition and geometry of stable and vulnerable plaques are illustrated in Fig. 1-2. A stable plaque has a small lipid pool that contains few macrophages and is separated from the blood by a thick fibrous cap. Vulnerable plaques are characterized by a large lipid pool rich that is covered by a thin fibrous cap which is infiltrated by macrophages and lymphocytes (white blood cells) and has a decreased amount of smooth muscle cells [4,7,8]. These plaques are also named Thin Cap Fibroatheroma’s (TCFAs). A coronary artery cap is considered as thin when it is less than 65 μm thick [4]. For a carotid artery this threshold has been set at 165 μm [9]. However, the exact thickness is debatable since these measures are only based on autopsy studies and do not take into account the composition and structure of the cap. Another difference between both plaque types is that stable plaques slowly tend to grow into the luminal area, whereas most of the luminal area is maintained for vulnerable plaques due to positive remodeling of the vessel wall [10,11]. The slow decrease in luminal area during growth of stable plaques, which decreases oxygen supply to tissue is often recognized from clinical symptoms like stable angina pectoris and overall fatigue. Although severe occlusion of arteries will eventually result in ischemia and tissue necrosis, the aforementioned clinical symptoms can often be used as a warming and give a surgeon time to perform catheterization, endarterectomy, stenting or bypass surgery before it is too late. Vulnerable
plagues are less symptomatic since the luminal area is not reduced initially. However, forces exerted by the pulsating blood flow can lead to rupture of the thin cap, leading to exposure of the lipid pool content to the blood flow. When this happens a thrombus (blood clot) is formed [12,21]. Sometimes when this happens the plaque stabilizes again. However, the thrombus can also break loose and cause a complete occlusion of a smaller artery downstream. This sudden occlusion of arteries without preceding clinical symptoms is exactly what happens during a myocardial infarction or stroke. Due to the insufficient supply of oxygen and nutrition to the tissue beneath cell death occurs. The majority of myocardial infarctions and strokes is caused by rupture of plaques in the coronary and carotid arteries respectively [14-16]. This explains why early identification of vulnerable plaques is of crucial importance to prevent morbidity and mortality and why it is a well addressed topic in literature [5,17-20].

Atherosclerosis imaging

It is possible to investigate the stage of atherosclerosis with a variety of imaging modalities. When a patient presents with the symptoms of a stroke often a computer tomography (CT) angiography scan is carried out to visualize the position of the atherosclerotic plaque and the degree of luminal occlusion. To visualize the blood in the vessels a iodine based contrast liquid is injected into the blood stream which becomes visible when exposed to ionizing radiation. Contrast enhanced CT angiography can also be used to visualize the density of calcifications in a plaque [21]. Also, the degree of vascular remodelling can be assessed. Recently, a contrast fluid (N1177) has been described which allows visualization of macrophages by means of CT [22]. Macrophages can also be visualised by combining CT with positron emission tomography (PET). To identify the macrophages with PET a tracer called 18F-labeled fluorodeoxyglucose (FDG) is used which enables the detection of macrophages [23,24]. The detection of lipid content is not possible with CT. It is also not possible to assess the thickness of the fibrous cap, because currently a multi-detector CT has a spatial resolution of 400-600 μm [23]. At the moment these incapabilities make it impossible to identify vulnerable plaques using CT. Next to that, due to the aforementioned positive remodelling of the vessel wall, patients with vulnerable plaques often do not present with any clinical symptoms before the actual event of rupture, which would ask for a technique which can be applied to screen for atherosclerosis in patients with a high risk profile. It is unlikely that CT will be used for this kind of screening, because of the exposure to ionizing radiation. Furthermore, people can be allergic to iodine-based contrast fluids which reduces the applicability of CT.

A different imaging modality which can be utilized for imaging of atherosclerosis is magnetic resonance imaging (MRI). MRI scanning sequences have been developed to visualize the various plaque components, like lipids, calcifications, fibrous tissue and intra-plaque thrombus with high sensitivity and specificity [5,20,25-27]. MRI also allows assessment of plaque area and positive remodelling. Using magnetic resonance angiography (MRA) the luminal area can be visualized and thus the percentage of luminal narrowing can be determined. It is also possible to perform targeted molecular imaging with MRI. Several studies describe the use of iron oxide nano-particles (USPIO) for the detection of inflammation [28,29]. Altogether this makes MRI very useful for the detection of vulnerable plaques. However, for screening purposes of subclinical patients MRI is less suitable, because it is contraindicated in patients with severe claustrophobia and implanted electronic devices. Furthermore, it is expensive and time consuming.

Ultrasound has a higher temporal and spatial resolution than CT or MRI, can be applied to anybody, is fast and relatively cheap and does not require ionizing radiation. This makes it one of the most promising modalities for scanning of the vascular tree in high risk populations. The principles of ultrasound and more specifically ultrasound strain imaging and their application for identification of the vulnerable plaque will be addressed in the remainder of this chapter.

Ultrasound

Ultrasound is a cyclic acoustical vibration with a frequency of over 20 kHz, the upper limit of human hearing. Medical ultrasound typically operates at frequencies in the range of 1 to 50 MHz. Medical ultrasound imaging is based on the transmission and reception of ultrasound by means of an ultrasound transducer. An ultrasound wave is transmitted into a tissue, where inhomogeneities in the tissue cause part of the wave to be returned towards the transducer. Since ultrasonic waves travel at the speed of sound, which is around 1540 m/s for soft biological tissues, the distance to each inhomogeneity can be determined based on the time between transmission and reception. The amplitude of the received signal provides information about the different media and inhomogeneities that are present in the imaged tissue. Each medium has an acoustic impedance $Z$ which is equal to the product of the density of the tissue $p$ and the speed of sound $c$. When an ultrasonic wave crosses the interface between two media with different acoustic impedances, part of the wave is reflected and part of the wave is transmitted. The relations between incident $p_i$ reflected $p_r$ and transmitted pressures $p_t$ are:

$$p_r = Z_2 \cos \theta \left( -Z_1 \cos \theta - Z_2 \cos \theta \right)$$  \hspace{1cm} (1-1)

$$p_t = \frac{2Z_1 \cos \theta - Z_2 \cos \theta}{Z_1 \cos \theta + Z_2 \cos \theta}$$  \hspace{1cm} (1-2)

where $\theta$ is the angle of incidence and the indices 1 and 2 refer to medium 1 and 2, respectively. These reflections appear as amplitude peaks in an ultrasound signal. The larger the difference in acoustic impedance between two media, the stronger the reflection and thus the less energy left to image the tissue distal to that interface. When there is no difference in acoustic impedance, the wave will continue to travel in the same direction without loss of energy, because no reflection will occur. Inhomogeneities smaller or similar to the wavelength of the ultrasound can absorb part of the energy of the ultrasound signal and scatter it in all directions. These inhomogeneities are therefore called scatterers. Usually the density of scatterers is high. All scatterers interact which leads to a complex interference pattern. When the amount of scatterers per volume exceeds a certain limit, known as the Rayleigh distribution limit, the interference pattern does not change anymore [30]. The typical interference pattern that is generated in that case is called a (fully developed) speckle pattern. Speckles are visible as low amplitude peaks in an ultrasound signal. As the ultrasound wave travels further into the tissue scattering and reflection cause the ultrasound signal to attenuate. An additional source of attenuation of the ultrasound signal is absorption. When tissue is exposed to the ultrasound signal it converts part of the acoustical energy into heat. For soft biological tissue the average decay is $-0.5 \mathrm{dB/cm/MHz}$. Thus, the attenuation is frequency dependent: for high frequencies the signal attenuates faster and the imaging depth is reduced. Of course the penetration can be increased by raising the output power, although this can only be done to a level at which
the tissue is not damaged due to overheating. Since the resolution of the ultrasound images improves with the transmission frequency, the highest possible frequencies and powers are used that are still within a certain safety margin for a certain tissue at a given imaging depth. To compensate for the depth dependent attenuation often the signal is amplified at reception as a function of travelling time, the so-called time gain compensation (TGC).

Piezoelectric materials are used to generate the ultrasonic pulses. Piezoelectric materials are materials that deform when an electrical voltage is applied to them [31]. Electrical excitation causes these materials to vibrate and generate ultrasonic waves in the adjacent tissue. The frequency of the generated wave depends on the thickness of the piezoelectric material. The materials also function the other way around: when an ultrasound wave strikes a piezoelectric material it starts to vibrate and generates an alternating electrical voltage. Thus, the same material can be used both as a transmitter and as a receptor of ultrasound.

Most ultrasound transducers consist of multiple piezoelectric elements, small blocks of piezoelectric material. The spatial positioning, the excitation frequency and the order of electronic activation of these elements makes a certain transducer more suited for a specific imaging application. The most common types of transducers are the linear array transducer, phased array transducer, the matrix array transducer and the curved array transducer, see Fig. 1-3. To obtain ultrasound images at high resolutions it is also possible to perform ultrasound registrations from within the body using either intravascular, transrectal or transoesophagal probes. An overview of the frequency ranges and applications is presented in Table 1-1.

To obtain a line of an ultrasound image a group of adjacent piezoelectric elements is excited, the transducer aperture (Fig. 1-4A). The ultrasonic pulses of all the individual elements interfere and this results in an ultrasound beam with a certain shape. The shape of the ultrasound beam can be altered by apodization and focusing (Fig. 1-4B&D). Apodization is the application of additional attenuation to some of the activated elements. It is often performed to reduce the intensity of the ultrasound signal on the sides of the ultrasound beam and with that to limit the signal of side lobes, regions of increased intensity in a different direction than the main beam. Focusing can be performed by posing different short transmittal delays to the individual elements. The application of delays can also be used to steer the ultrasound beam in a different direction (Fig. 1-4C). For a phased array transducer the principle of beam steering is used to obtain the various image lines. For a linear array transducer subgroups of elements are activated to generate each new image line (Fig. 1-4A). Often dynamic focusing is performed in receive for linear array transducers. Dynamic focusing means that instead of a single focus, focusing is performed for all depths by applying time variant delays to the signals received by the various transducer elements. Dynamic focusing is mainly important for obtaining maximum intensity at each imaging depth and a good spatial resolution in the direction perpendicular to the ultrasound beam, the lateral direction. The lateral resolution in a focal point depends on the ratio between the effective transducer aperture and focal distance (the F-number) and on the central transmit frequency of the transducer. Higher F-numbers and higher frequencies result in a higher lateral resolution. The spatial resolution in the axial direction, along the ultrasound beam, depends on the length of the transmitted echo-pulse. A large bandwidth results in a short echo-pulse and a high axial resolution.

Table 1-1. Transducer types, applications and frequencies of operation

<table>
<thead>
<tr>
<th>Transducer</th>
<th>Application</th>
<th>Frequency range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear array transducer</td>
<td>2D vascular imaging</td>
<td>3-20 MHz</td>
</tr>
<tr>
<td>Phased array transducer</td>
<td>2D cardiac/fetal imaging</td>
<td>2-11 MHz</td>
</tr>
<tr>
<td>Curved array transducer</td>
<td>2D abdominal/vascular imaging</td>
<td>2-15 MHz</td>
</tr>
<tr>
<td>Matrix array transducer</td>
<td>3D cardiac/fetal imaging</td>
<td>2-7 MHz</td>
</tr>
<tr>
<td>Intravascular transducer</td>
<td>2D&amp;3D intravascular imaging</td>
<td>20-50 MHz</td>
</tr>
<tr>
<td>Transrectal transducer</td>
<td>2D prostate/bladder imaging</td>
<td>3-15 MHz</td>
</tr>
<tr>
<td>Transoesophageal transducer</td>
<td>2D&amp;3D cardiac imaging</td>
<td>2-7 MHz</td>
</tr>
</tbody>
</table>

Fig. 1-3. Schematic representation of the most commonly used types of ultrasound transducers. A: linear array transducer, B: phased array transducer, C: matrix array transducer, D: curved array transducer.

Fig. 1-4. Schematic overviews of A: the formation of the image lines for a linear array transducer, B: the application of apodization, C: the principle of electronically steering of the ultrasound beams, and D: the principle of focusing by adjustment of the delays of the individual elements.
Before display on a commercial ultrasound device the received raw radio frequency (RF) signals are processed in several steps. To remove high- and low-frequency artifacts band-pass filtering is applied. Next, overall gain compensation, like TGC, is performed. After that, the envelope signal of the RF data is calculated by amplitude demodulation. Phase information is discarded in this processing step. Throughout this thesis amplitude demodulation is achieved by Hilbert transformation. Finally the signal is rectified and log compressed. Log compression takes place to allow visualization of both low and high intensity echo’s on the same color scale. Sometimes more sophisticated processing steps are added, however the described steps are always performed.

The resulting amplitude data can be displayed in several imaging modes (Fig. 1-5). An A-mode image (A = amplitude) is a graph of the ultrasound amplitude for a single image line as a function of depth. A B-mode image (B = brightness) displays the amplitude data of several adjacent ultrasound lines as a grayscale coded image. Large amplitudes are displayed as bright spots, whereas low amplitudes appear darker. The advantage of this mode over A-mode is that it allows a 2-D view of the imaged tissue. M-mode (M = motion) is similar to B-mode, instead of displaying the data of adjacent echo lines, data of a single line are plotted in time. M-mode is very useful for studying tissue in motion.

Vascular ultrasound

Ultrasound is the most applied imaging modality for investigation of the condition of the vascular tree. Not only the anatomy of the vascular tree can be investigated, but also the geometry and size of the plaque, the blood flow, blood velocity and distensibility of the arterial wall can be determined.

Blood flow and velocity can be measured using Doppler techniques. Doppler imaging is based on the fact that a shift in frequency occurs when the transmitted ultrasonic pulse is reflected by tissue in motion, like the flowing red blood cells. This shift in frequency can be determined upon receiving and translated into an absolute velocity using a Fourier transformation. The higher the blood velocity, the larger the Doppler shift. It is important to measure blood velocities in case of stenosis to grade the severity of the occlusion. Just like B-mode, several Doppler modes are available for assessment of velocities in the vascular system. The most often used modes for diagnosis are pulsed Doppler, color Doppler and power Doppler mode. Examples of these modes are shown in Fig. 1-6. Each of these Doppler modes has a dedicated application. These applications are listed in Table 1-2.

Geometry and size of the plaque are often quantified by measuring the thickness of the two innermost layers of the vessel (the intima-media thickness (IMT)) in a longitudinal view of the carotid artery [32-34]. The intima-media thickness can be determined quite easily from an ultrasound image when ultrasound strikes the vessel layers perpendicularly: the lumen-intima interface produces a bright reflection, which is followed by low echo levels corresponding to the media, and then followed again by brighter echoes from the advential layer (see also Fig. 1-5B&C). Luminal area reduction and degree of outward remodeling are usually derived from B-mode recordings of the vessel wall in a transverse imaging plane.

Several measures for stiffness have been developed based on ultrasound data. A value for the global and also local stiffness can be derived from the velocity by which the arterial pulse wave travels over the arterial wall. The pulse wave will travel at a greater speed when the arterial wall is stiffer. The Pulse Wave Velocity (PWS) can be estimated by dividing the known distance between two measurement sites by the time it takes the wave to travel that distance. Specific features of the pressure waveform are used to determine the transit time accurately [35-37]. A different measure for local stiffness that can be obtained from M-mode recordings of the arterial wall is the so called distensibility: i.e. the relative change of the luminal diameter over the pressure cycle. The distensibility can be determined by tracking the change in distance between the lumen-intima reflections at the anterior (near) and posterior (far) wall [38].

### Table 1-2. Doppler modes and their main purpose

<table>
<thead>
<tr>
<th>Doppler mode</th>
<th>Visualizes</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color Doppler</td>
<td>Direction and intensity of mean velocity component visualized as color in a large volume</td>
<td>Overall impression of velocities + detection of occlusions</td>
</tr>
<tr>
<td>Power Doppler</td>
<td>Intensity of main velocity component</td>
<td>Detection of occlusions in low flow regions</td>
</tr>
<tr>
<td>Pulsed Doppler</td>
<td>Detailed velocity visualized as intensity profile in a small volume over the cardiac cycle</td>
<td>Grading the impact of an occlusion</td>
</tr>
</tbody>
</table>

Examples of A: A-mode, B: B-mode, and C: M-mode ultrasonic representations of a carotid artery. A and C were constructed using data obtained along the image line indicated by the dotted line in B.
Although all of the aforementioned techniques provide information about the degree of atherosclerosis, none of these techniques provides information about the composition of the plaque. As stated before, plaque composition is a very important parameter in determining the rupture proneness of a plaque and thus in determining the risk at cardiovascular events. Several ultrasound based techniques exist that focus on the measurement of plaque composition. One category of methods are the spectral techniques, like virtual histology and integrated back-scatter analysis. These techniques examine as well the amplitude as the frequency content of the reflected RF signal for small plaque regions of tissue. Based on the amplitude and frequency distribution these plaque regions are for instance classified as being lipidic, fibrotic or calcified [5,39-41].

A different technique for the detection of vulnerable plaques focuses on a property of plaques that was not discussed in the preceding text: the vasa vasorum. Vasa vasorum are small blood vessels that infiltrate the plaque from the adventitia in response to the lack of oxygen that arises in the plaque due to the growth of the plaque and the activity of inflammatory macrophages [42]. To image the vaso vasorum, echo contrast agents are injected into the blood stream which travel into the vasa vasorum where they can be imaged [43]. The development of broad-band transducers which allow the reception of higher harmonics or subharmonics of the ultrasound frequency transmitted improve the visualization of the vasa vasorum further [44,45]. Contrast enhanced vasa vasorum imaging has been shown to successfully differentiate between carotid artery plaques with a large density of microvessels and a small density of microvessels [46]. A drawback of the technique is the required injection of the contrast agent.

The final series of techniques to gain information about plaque vulnerability are strain imaging/elastography techniques. These are the group of techniques this thesis focuses on. In the remainder of this chapter the principles of strain imaging/elastography and more advanced methods for vascular strain imaging/elastography and their results will be described.
CHAPTER 1

A major drawback of the technique is its invasiveness, which means that it can only be applied representing a weak (rupture prone) spot. Although the intravascular results were convincing, plaques were identified by a high strain spot at the boundary between lumen and vessel wall with a sensitivity of 88% and a specificity of 89% [54]. These vulnerable plaques were identified with a sensitivity of 88% and a specificity of 89% [54]. Several vulnerable plaques in the carotid artery are a strong indicator that vulnerable plaques are also present in other arteries, like the coronary artery [55]. Several studies have investigated this hypothesis, and the majority of them also confirm this hypothesis [25,56-58].

There are two challenges for noninvasive elastography compared to intravascular elastography. The first challenge is that the center frequency of the used ultrasound signal cannot be as high as the frequencies used intravascularly. IVUS elastography typically uses a center frequency of about 20-40 MHz. The attenuation of the ultrasound signal at these frequencies is high resulting in a penetration in the order of a centimeter. For noninvasive application, the ultrasound signal has to travel through the skin, fat and muscle tissue that surround the artery. Consequently center frequencies around 7-15 MHz are used. As a consequence the spatial resolution of the ultrasound signal and the strain images is less which asks for more sophisticated strain imaging algorithms. The second challenge of noninvasive vascular elastography is that the ultrasound beams are in general not aligned with the radial direction in a transverse imaging plane, as shown in Fig. 1-9. Instead of measuring radial strains directly, first all components of the strain tensor need to be estimated and converted into radial strains afterwards. This is not as straightforward as it seems, because the strain component perpendicular to the ultrasound beam axis (lateral) can usually not be estimated as precise as the along the beam component (axial), due to the lower resolution and the unavailability of phase information in that direction [59-63]. It is also possible to change the imaging plane from transverse to longitudinal, i.e. in the direction of the vessel axis. In that situation the axial and radial component are usually aligned.

Noninvasive vascular elastography

Doppler based methods

The first attempt at noninvasive elastography for assessing vascular atherosclerosis comes from Bonnefous and coworkers [64]. The described method originated from the field of Doppler based blood flow velocity imaging. Cross-correlation was used to calculate the radial motion and radial strains in longitudinal recordings of arteries. The radial strains were calculated by straightaway differentiation of the axial displacements in the axial direction. Next, a strain image was constructed which had strong intensities in the regions where high strains and low and high strains. At patients that already go to the cath-lab. For preventive screening of a population at risk, a noninvasive variant of the technique is required. The coronary artery is too small and is at a too large imaging depth to image noninvasively. Therefore, noninvasive vascular elastography focuses on the larger and more superficially located arteries, like carotid arteries and femoral arteries. Since atherosclerosis affects the entire vascular system, it is likely that the presence of vulnerable plaques in the carotid artery is a strong indicator that vulnerable plaques are also present in other arteries, like the coronary artery [55]. Several studies have investigated this hypothesis, and the majority of them also confirm this hypothesis [25,56-58].

In most applications strain provides indirect measures of a tissue’s elastic properties. In that case strain imaging is also often called elastography in literature. The measurement of the active contraction (strains) of muscles is an example of strain imaging that can not be referred to as elastography, because the strains are not related to the tissue’s intrinsic elastic properties.

Two parameters that describe the elastic characteristics of a tissue are the Young’s modulus and the Poisson’s ratio. The Poisson’s ratio describes how a tissue, when it is compressed in one direction, extends or compresses in a perpendicular direction. Consequently, this parameter directly provides information on volume change when a tissue is compressed in a certain direction. Many biological tissues are nearly incompressible, which means that the tissue volume does not change when deformed in any direction. In that case the Poisson’s ratio is = 0.5. The Young’s modulus of a tissue describes the degree of strain in a direction that is generated in response to an applied stress in the same direction. The Young’s modulus is a direct indicator of the stiffness of the tissue. However, the local stress is required for converting strain into Young’s modulus images. It is possible to derive Young’s modulus images from strain images using modulography techniques, such a technique is presented in chapter 11.

Intravascular elastography

Initially vascular elastography was applied to detect vulnerable plaques in coronary arteries [49-51]. An intravascular ultrasound (IVUS) catheter was inserted into a coronary artery and radio frequency (RF) ultrasound data were recorded for the full circumference of the arterial wall. From multiple acquisitions at various intraluminal pressures radial strains were calculated. It was shown that IVUS elastography enabled differentiation between fibrous, fatty and fibro-fatty plaques based on their strain values [52]. Later, IVUS elastography also proved to be successful in differentiating between fibrous and fatty materials in vivo using data from atherosclerotic iliac and femoral arteries of Yucatan minipigs [53]. The technique also showed to be successful in detecting vulnerable plaques in excised human coronary arteries: vulnerable plaques were identified with a sensitivity of 88% and a specificity of 89% [54]. These vulnerable plaques were identified by a high strain spot at the boundary between lumen and vessel wall representing a weak (rupture prone) spot. Although the intravascular results were convincing, a major drawback of the technique is its invasiveness, which means that it can only be applied to patients that already go to the cath-lab. For preventive screening of a population at risk, a noninvasive variant of the technique is required. The coronary artery is too small and is at a too large imaging depth to image noninvasively. Therefore, noninvasive vascular elastography focuses on the larger and more superficially located arteries, like carotid arteries and femoral arteries. Since atherosclerosis affects the entire vascular system, it is likely that the presence of vulnerable plaques in the carotid artery is a strong indicator that vulnerable plaques are also present in other arteries, like the coronary artery [55]. Several studies have investigated this hypothesis, and the majority of them also confirm this hypothesis [25,56-58].

In most applications strain provides indirect measures of a tissue’s elastic properties. In that case strain imaging is also often called elastography in literature. The measurement of the active contraction (strains) of muscles is an example of strain imaging that can not be referred to as elastography, because the strains are not related to the tissue’s intrinsic elastic properties. Two parameters that describe the elastic characteristics of a tissue are the Young’s modulus and the Poisson’s ratio. The Poisson’s ratio describes how a tissue, when it is compressed in one direction, extends or compresses in a perpendicular direction. Consequently, this parameter directly provides information on volume change when a tissue is compressed in a certain direction. Many biological tissues are nearly incompressible, which means that the tissue volume does not change when deformed in any direction. In that case the Poisson’s ratio is = 0.5. The Young’s modulus of a tissue describes the degree of strain in a direction that is generated in response to an applied stress in the same direction. The Young’s modulus is a direct indicator of the stiffness of the tissue. However, the local stress is required for converting strain into Young’s modulus images. It is possible to derive Young’s modulus images from strain images using modulography techniques, such a technique is presented in chapter 11.
Another early method for noninvasive vascular elastography that also came from the field of Doppler imaging is the method developed by Kanai and coworkers [65,66]. They developed a phase tracking method. The technique is based on the principle that tissue displacement between a predeformation and postdeformation situation induces a change in the phase of the echo signal. The phase change $\Delta \phi_d(n)$ that occurs due to tissue motion between frame $n$ and the next frame $n+1$ is calculated using the complex cross-correlation of the complex quadrature demodulated predeformation and postdeformation RF signals. This phase change can be translated into displacements in the direction of the ultrasound beam by:

$$\Delta x_d(n) = \frac{c \Delta \phi_d(n)}{4\pi fc},$$

where $\Delta x_d(n)$ corresponds to the displacement along the ultrasound beam of a point at a depth $d$ that occurred between frames $n$ and $n+1$. $c$ and $f_c$ are the speed of sound and the center frequency, respectively. The technique can be very successful in finding subsample displacements, although an exact value for the center frequency is required. As the authors correctly state the center frequency does not remain equal for the entire tissue, due to frequency dependent attenuation and due to variations in the interference pattern caused by interframe strain of the tissue [67]. Therefore, the authors also developed a method to estimate the center frequency locally [68-71]. The center frequency correction method was experimentally validated using a homogeneous circle symmetric vessel phantom. The errors of the theoretical strain profile and the standard deviation in radial strain reduced from 23.7% and 46.2% without the center frequency correction to 12.0% and 14.1% with the correction, respectively. The technique was also applied to in vitro recordings of a femoral artery. Low strain regions were observed in calcified regions and higher strains were found for regions that contained a lot of smooth muscle cells and collagen. Also, four studies were reported in which strains were calculated for in vivo data of carotid arteries [70]. In [68,69] the phase tracking method was applied to 242 individuals with type 2 diabetes. Also, IMT values and risk factors for atherosclerosis were determined for each patient. It was observed that elasticity and max IMT correlated with the number of risk factors. The risk factors were hypertension, hyperlipidemia and smoking, in addition to diabetes. An important finding was that in subjects with IMT $<1.1$ mm, who are classified as not having atherosclerosis as defined by IMT criteria, carotid artery elasticity did significantly correlate with the number of risk factors. Fig. 1-10 shows examples of in vivo results in the posterior wall of a carotid artery for a plaque-rich region and a nonplaque region. As can be observed, strains are more inhomogeneous in the two plaques of the plaque-rich region. Furthermore, the left plaque shows lower strains than the right plaque which is less echogenic. Next to the strain images, Fig. 1-10 also shows elasticity images. These images of the elastic modulus were derived by combining the estimated strain data with knowledge of changes in the blood pressure. In [72] such elasticity images revealed lower elastic moduli for lipid rich regions compared to regions that mainly contained collagen and smooth muscle cells. A drawback of this method is that lateral motion is not taken into account, which implies that the method will perform suboptimal when large lateral motion occurs between frames. Recently however, the authors also introduced a similar phase sensitive method for lateral motion detection [72]. To generate the lateral phase component a Hilbert transform was performed using the complex cross-correlation of the complex quadrature demodulated RF signals.
carried out on the RF data in lateral direction (after correction for axial motion) resulting in a real and an imaginary signal. Again, the phase shift which occurs between predeformation and postdeformation state corresponds to a displacement. A possible advantage of that technique is that it has a lower computational load compared to other lateral estimation methods that perform interpolation of RF lines. A drawback of the technique might be that it heavily depends on a correct guess of the axial displacements. The lateral motion estimation method has not been applied to human tissue yet, although the technique enabled estimating lateral displacements in a phantom experiment with a concentric homogeneous phantom that expanded radially and translated longitudinally with respect to the transducer [72].

**Advanced cross-correlation based methods**

The next group of methods that will be discussed are more advanced 2-D variants of the original cross-correlation concept. Instead of a single 1-D cross-correlation of predeformation and postdeformation data for fixed window sizes, cross-correlation is repeated iteratively with decreasing 2-D window sizes [59,73,74]. These algorithms are referred to as coarse-to-fine or multi-level cross-correlation based approaches. The coarse-to-fine approach is performed for at least three reasons. First of all, to avoid peak hopping: i.e., the detection of a peak in the cross-correlation function which does not correspond to the actual displacements. This is taken care of in the initial ‘coarse’ iteration. The selection of larger data windows increases the chance of finding the correct peak. Especially when large translational motion occurs, data windows need to be large to ensure that both the predeformation data and the corresponding shifted segment of postdeformation data are compared in the cross-correlation procedure. Usually the coarse displacement estimates from this iteration are used to guide the algorithm in following iterations in order to find the correct cross-correlation peak on a finer scale. Often the first iteration is carried out on the B-mode/envelope signal, whereas in following iterations RF data is used. In Fig. 1-8 it can be observed that the peak of the envelope signal is much broader than the peak of the RF based cross-correlation function. As a consequence, envelope based cross-correlation is more robust for finding the correct peak and also works better when large translational motion occurs. However, because the peak is broader, the peak’s location is also less precisely defined. This is why RF data are used in the subsequent iterations. A second reason for performing coarse-to-fine strain estimation is to be able to detect small displacements. As the window sizes decrease, the cross-correlation function becomes more sensitive for small displacements. A third reason for the coarse-to-fine approach is, that it allows the detection of large deformations/high strains. When high strains are present, signal decorrelation occurs very fast. Short windows are required to be able to find the correct peak when decorrelation is present. Céspedes described this phenomenon in 1995 and theoretically derived an upper bound for window size for a certain maximum level of strain [75].

Another improvement compared to the original method of Ophir et al. [47] is related to the fact that RF data are digitally sampled and stored. Because of this digitization, originally the location of the cross-correlation peak and consequently the displacement estimates were rounded to an integer number of sample points. This rounding introduces errors in displacement estimation. However, because the cross-correlation function is a periodic signal this implies that the exact peak of the cross-correlation function can be fairly guessed at subsample level by ‘around the peak’ interpolation of the discrete cross-correlation function. This is illustrated in Fig. 1-11. Multiple analytical functions have been proposed for the interpolation: a spline function, a cosine function and a parabolic function [59,61,76]. To reduce computational load usually only the values closest to the peak are used for the interpolation. A different approach for finding the displacements at subsample level is by using the zero-phase crossing method as proposed in [77]. The phase of the demodulated cross-correlation signal is equal to zero exactly when the peak of the normalized cross-correlation function equals 1, as is also shown in Fig. 1-11. Furthermore, the phase has a linear relationship with time. By fitting a linear interpolation through the cross-correlation phase function, the zero-phase crossing point can be derived and the subsample displacement is known.

The zero-phase crossing method was applied to in vivo images of a healthy volunteer and a diseased subject in work by Kim et al. [98]. For both subjects images of a brachial artery were acquired in a transverse plane. The axial strains that were estimated for two points on the arterial wall were presented. The acquisition frame rate was 107 Hz and strains were shown for a period of 5 seconds. A nice cyclic pattern was observed. For the healthy vessel a peak strain rate of 100 %/s was reported during diastole and -250 %/s during systole, which was three times higher than that for the diseased vessel. Recently, the same method was applied to examine peripheral artery-vein bypass grafts [79]. Two subjects that had had a femoral to popliteal artery in situ bypass were examined. One of the subjects developed a stenosis. This subject was measured before and after the development of the stenosis. The strain values in the stenotic region were significantly lower than the strain values in the adjacent normal tissue even before the stenosis developed. Furthermore, the strain values were about four times lower than those in the nonstenotic patient. In another recent study [80] the zero phase crossing technique was applied to evaluate dialysis fistula stenosis in two subjects. Images were acquired at a frame rate of 180 Hz. Again, higher strain values were observed for the nonstenotic tissue compared to the stenotic tissue.

![Fig. 1-11. The peak of the cross-correlation function can be estimated at subsample level by interpolation of the amplitude values closest to the peak, or by finding the zero-phase crossing of the cross-correlation phase plot.](image-url)
Several publications in which a 2-D single- or multi-level cross-correlation based strain estimation method is applied to vascular data can be found. In a study by Larson et al. a single-level 2-D cross-correlation method was applied to estimate radial and longitudinal strains in longitudinal recordings of vessels. To increase the number of points in lateral direction linear interpolation was applied to generate four additional lines of RF data in between the original data. Spline interpolation of the cross-correlation function was used to obtain displacements at subsample level. The method was validated using simulated ultrasound images of a pulsating vessel. Additionally, it was shown that the method allowed estimation of longitudinal and radial strain in a healthy subject and a subject known with coronary artery disease. The strains for the healthy subject were higher than those for the diseased subject. Furthermore, strains were reproducibly measured for two subsequent pressure cycles [81].

In another study by Weitzel et al. [82], sixteen atherosclerotic carotid artery plaques were imaged in the longitudinal plane using a multi-level 2-D cross-correlation based approach and classified as being soft or calcified based on their echo intensity and percentage of stenosis. Maximum axial strains were calculated for a certain region within each plaque and cumulated over time for three or more subsequent heartbeats. Lateral motion of a region of interest (ROI) in the plaque with respect to a ROI in the vessel wall was also calculated. It was observed that calcified plaques deformed less than soft plaques and also the lateral motion of the plaque with respect to the vessel wall was less for the calcified plaques. Ribbers et al. [83] applied a 2-D coarse-to-fine algorithm to derive axial and lateral strains for in vivo recordings in longitudinal and transverse cross sections of 12 carotid arteries. Based on the strain values a soft and a hard plaque were identified. With the ability to track both axial and lateral displacements it is theoretically possible to construct radial and also circumferential strains for transverse cross sections. In the same study radial and circumferential strains for a homogeneous vessel phantom with a concentric lumen were presented. As expected, a quadratic radial strain decay was observed from the inside to the outside of the vessel wall. The constructed radial and circumferential strain images were severely distorted by the contribution of the lateral strain component.

**Lagrangian speckle motion estimator**

An alternative to the aforementioned cross-correlation based techniques is the Lagrangian Speckle Motion Estimator [62,84], which is an image registration method. Basically, the method functions as follows: a predeformation image is deformed in multiple iterations until it matches a postdeformation image best. The translations and deformations of the predeformation image that are required to find the optimal match correspond to the 2-D displacements and strains that occurred between predeformation and postdeformation situation. A difference with the cross-correlation based techniques is that this method allows taking into account changes in the ultrasonic speckle morphology that occur when the tissue deforms. Furthermore, it directly provides strain estimates, whereas spatial derivation is required in the latter case. The technique also allows a simultaneous estimation of all 2-D components of the strain tensor. To speed up the iterative process and to remove large translational motion often a cross-correlation step is performed before applying the LSME. Analogous to the validation of most of the other techniques, the Lagrangian speckle motion estimator (LSME) was also first tested on RF data of a radially expanding homogeneous circle-symmetric vessel-mimicking phantom [62]. Additionally, phantoms with soft and hard regions were simulated. The results demonstrated the potential of the technique to differentiate between hard and soft tissue. Since the technique also allows estimation of all 2-D components of the strain tensor, also strain components in other directions can be derived. The authors use the 2-D information to determine Von Mises strains for the various vessel phantoms. The Von Mises strain expresses the magnitude of strain in a certain point regardless of its direction. The LSME has also been applied in human tissue. For instance, intravascularly in an excised human carotid artery using an IVUS catheter [85]. The strain images revealed a low strain region that corresponded well with a collagen rich region observed from histology. Furthermore, the technique has been applied in vivo [86, 87]. In the first study the carotid arteries of four subjects were imaged during 5 to 7 heart cycles in a longitudinal plane. Two of the subjects were young and healthy, the other two subjects were 75-year-old asymptomatic patients with severe carotid stenosis. An adapted version of the LSME was used and it showed to enable a periodically reproducible measurement of axial strains for the healthy subjects. The maximum interframe strain (measured at a frame rate of about 20 Hz and a heartbeat of approximately 65 BPM) was between 4% and 6% for the healthy subjects. To compare strains of normal tissue with strains of stenotic tissue cumulated axial strain curves for ROIs in a stenotic region and an ROI in the normal wall region were determined. It was illustrated that the hard calcified stenotic tissue strained less than the wall tissue. Furthermore, it was found that the strain pattern in the stenotic region was much more heterogeneous than the strain pattern for the vessel walls of the healthy subjects. In a second study the LSME was applied to measure axial strains for healthy female and male subjects in four age categories [88]. In total, data of 8 males and 7 females were reported. Two different radiologists acquired data of their left and right common and internal carotid arteries in a longitudinal plane. It seemed that axial strains in common carotid arteries were lower for male subjects than for female subjects of the same age, although it should be kept in mind that the number of subjects per age group was very small. Furthermore, the authors reported a good correlation between the measurements of both radiologists for the strain measurements for the common carotid arteries. The correlation was less for the internal common carotid arteries. Likewise, the correlation of the measured strain for the left and the right common carotid arteries was larger than that for the left and right internal carotid artery.

**Dedicated methods for transverse plane elastography**

Methods for radial and circumferential ultrasound strain imaging in transverse carotid cross sections are scarcely reported, due to the aforementioned problems with the assessment of lateral strain. Only one dedicated method for radial strain imaging in a transverse plane has been described previously [88]. Adjacent ultrasound beams are all steered through the center of the lumen by changing the time delays of the transducer elements, Fig. 1-12. In this way, the ultrasound beams become aligned with the radial direction and regular axial 1-D displacement tracking and strain derivation can be performed to obtain radial strains. An advantage of the method is that a larger part of the intima becomes visible on the echo. Furthermore, the method is computationally efficient, since no conversions from axial and lateral strains to radial strains are required. A disadvantage of the technique is that only a partial strain image of the artery can be obtained since it is impossible to steer the ultrasound beam through the center for all 360 degrees. This beam steering method [89] was applied to a pressurized rubber tube and in vivo ultrasound registrations of a carotid artery. Despite promising initial results, a more recent publication on this technique could not be found.
Transducer

**Fig. 1-12.** Beam steering can be used to steer adjacent ultrasound beams through the center of a lumen. In this way radial strains can be calculated for a small segment of the cross-section.

---

**Short summary and thesis outline**

Ultrasound and especially ultrasound elastography seems to be a very promising method for the noninvasive assessment of atherosclerotic plaques in carotid arteries of asymptomatic and symptomatic patients for several reasons: (1) Intravascular ultrasound elastography studies have demonstrated a high correlation between high strain and vulnerable plaque features, both *ex vivo* and *in vivo*; (2) the potential of most noninvasive elastographic methods to detect vulnerable plaques has been shown using simulations, phantom experiments and also several promising results have been reported *in vitro*; (3) ultrasound is patient friendly, of relatively low cost, fast, nonionizing, does not require the injection of contrast fluids and has a higher temporal and spatial resolution than MRI and CT. A proper *in vivo* validation in which noninvasive strain images are compared with histology data however is lacking. Furthermore, no strain imaging method dedicated to radial strain estimation in transverse cross-sectional views of the artery existed that enabled radial strain estimation with high accuracy for the full circumference. Therefore, the goal of this thesis was to develop and validate noninvasive elastography for vulnerable plaque detection in transverse vessel cross sections.

In chapter 2 to 4 three distinct methods are described which were developed specifically for the estimation of radial strain in a transverse imaging plane. The methods are tested using simulated and experimental data of quasi-static vessel-mimicking phantoms with simple geometries. In chapter 5 and 6 methods to improve the accuracy of strain estimation are discussed. Chapter 5 focuses on the optimization of strain estimation accuracy when using beam steered RF acquisitions. Chapter 6 introduces a novel concept for 2-D cross-correlation based strain estimation which enables more accurate strain estimation when rotation or shearing is present in a tissue. In chapter 7 the most advanced method will be applied to a pulsating phantom, an *in vivo* recording of a healthy carotid artery and a simulation of a vulnerable plaque based on finite element modeling. Chapter 8 is addressed to the validation of the method in atherosclerotic patients. The method is applied to *in vivo* recordings of patients scheduled for endarterectomy and the strain results are validated using histological data. Chapter 9, 10 and 11 discuss recently developed techniques for assessing the severity of atherosclerosis that are based on noninvasive ultrasound elastography and offer new opportunities for assessing atherosclerosis. Chapter 12 consists of a general discussion and chapter 13 and 14 consist of a summary in English and Dutch, respectively.
PART I: NONINVASIVE VASCULAR ELASTOGRAPHY METHODS
In this chapter a method for noninvasive elastography in transverse carotid artery cross sections is introduced. It is shown that high quality radial and circumferential strains can be obtained by combining segments of radially or circumferentially projected axial strain estimates acquired at multiple beam steering angles. The performance of the proposed segment based multi-angle elastography is compared to single-angle acquisition elastography using experiments with a pressurized homogeneous vessel mimicking phantom with a concentric lumen. Additionally, adaptive techniques to correct for grating lobe interference and other artifacts that occur when performing beam steering at large angles are introduced.

CHAPTER 2

Abstract

Stoke and myocardial infarction are initiated by rupturing vulnerable atherosclerotic plaques. With noninvasive ultrasound elastography, these plaques might be detected in carotid arteries. However, since the ultrasound beam is generally not aligned with the radial direction in which the artery pulsates, radial and circumferential strains need to be derived from axial and lateral data. Conventional techniques to perform this conversion have the disadvantage that lateral strain is required. Since the lateral strain has relatively poor accuracy, the quality of the radial and circumferential strains is reduced.

In this study, the radial and circumferential strain estimates are improved by combining axial strain data acquired at multiple insonification angles. Adaptive techniques to correct for grating lobe interference and other artifacts that occur when performing beam steering at large angles are introduced. Acquisitions at multiple angles are performed with a beam steered linear array. For each beam steered angle, there are two spatially restricted regions of the circular vessel cross section where the axial strain is closely aligned with the radial strain and two spatially restricted regions (different from the radial strain regions) where the axial strain is closely aligned with the circumferential strain. These segments with high quality strain estimates are compounded to form radial or circumferential strain images.

Compound radial and circumferential strain images were constructed for a homogeneous vessel phantom with a concentric lumen subjected to different intraluminal pressures. Comparison of the elastographic signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) revealed that compounding increases the image quality considerably compared to images from 0° information only. SNR and CNR increase up to 2.7 and 6.6 dB, respectively. The highest image quality was achieved by projecting axial data, completed with a small segment determined by either principal component analysis or by application of a rotation matrix.

Introduction

Strain imaging is a well-known ultrasound technique for estimating the elastic properties of tissue [90]. One of the fields in strain imaging research that gained a lot of interest during the last decade is vascular strain imaging, with a focus on atherosclerosis [91,92]. Atherosclerosis is a systemic disease that causes arteries to thicken, due to the deposition of atherogenic lipoproteins in the vessel wall. Most people in Western society suffer from atherosclerosis when they age, however, atherosclerosis in itself is not dangerous [7]. Atherosclerosis becomes life-threatening when a plaque ruptures, and a blood clot is formed as part of the body’s healing process. In most of the cases this blood clot does not occlude the artery at the site of rupture, but is transported distally by the blood flow towards the heart, or brain, where it might occlude a smaller artery, resulting in a cardiac infarct, or in a stroke, respectively. Therefore, the vulnerability of a plaque is a measure for the risk caused by atherosclerosis. Vulnerable plaques are characterized by a large lipid pool, that often contains large amounts of macrophages, surrounded by a thin fibrous cap [8]. The pulsating blood pressure exerts forces on the thin cap, which can lead to rupture. This usually happens at the spots of highest strain [93], which makes ultrasound elastography a very promising candidate for detection of the vulnerable plaque.

Carotid atherosclerosis is strongly related to coronary and cerebrovascular disease [94]. Previous studies, in which an intravascular catheter is used to perform strain imaging, have confirmed the high sensitivity and specificity of ultrasound elastography for detecting vulnerable plaques in vitro [95] and in vivo [53]. However, the intravascular approach however has some large practical drawbacks: it is invasive, and can only be applied to patients that already undergo surgical intervention. If it was possible to convert this technique into a non-invasive technique, all of these disadvantages would be overcome, allowing the technique to be applied on a broad scale, perhaps even for screening purposes. Hence, a noninvasive technique for detection of vulnerable plaques in the carotids will have a high clinical impact.

In recent studies [62,83,86], the feasibility of transcutaneous ultrasound strain imaging of the carotids has been investigated. It was shown [62,83] that noninvasive strain imaging of the carotids is feasible. However, in contrast to intravascular strain imaging, in the noninvasive case the ultrasound beam is generally not aligned with the radial strain for the complete vessel cross section. Therefore, firstly the axial and lateral strains need to be estimated, which are converted into radial and circumferential strains afterwards. Axial and lateral strains can be estimated in a number of ways; by cross-correlation of precompression and postcompression data [83], or by application of a Lagrangian speckle motion model estimator [52,84]. In both approaches, the relatively poor quality of the lateral estimates, due to the lower lateral resolution and the lack of phase information in this direction, restricts the image quality of the reconstructed radial and circumferential strains.

This study investigates a new approach to obtain radial and circumferential strain images of higher quality by combining strain data noninvasively obtained at large beam steered angles. The approach is based on the fact that there are regions (circle segments) of a vessel cross section in which the radial strain and the ultrasound beam, or the circumferential strain and the ultrasound beam, are closely aligned. In those regions the radial or circumferential strain estimates are mainly dependent on axial strain input. In other words, the distortion caused by lateral strain input in these circle segments is small. With beam steering techniques [96], it is possible to change the ultrasound beam direction and thereby the segments in which the ultrasound beam and radial or circumferential strain estimates are aligned. By combining these circle segments of high quality strain estimates, obtained at different angles, it should be possible to construct radial and circumferential images of high quality for the entire vessel cross section. A number of studies can be found that also perform angular compounding to improve the signal-to-noise ratio as well as the contrast-to-noise ratio of ultrasound images [97] as well as of strain images [96,98]. However, usually only small angles up to 15° of steering are used to construct compound strain images, whereas the proposed approach uses beam steering at larger angles up to 45°. Furthermore, the proposed compounding technique consists of combining different regions of strain data acquired at multiple angles, whereas the aforementioned studies image a single region from multiple angles and combine the data to improve the image quality in that region. One of the major difficulties that arises when performing beam steering at large angles, are artifacts caused by grating lobes. Grating lobes are secondary ultrasound beams caused by diffraction of the array transducer, when the element pitch of the array is larger than half the wavelength. The reflection and scattering generated by the secondary beam is interpreted as if it originated from the main beam, which causes the generation of artifacts on the ultrasound image. In clinical images the artifact is present in the entire image, whereas in a simple phantom experiment the artifact appears local.
This paper describes and compares various methods to construct full 360° radial and circumferential strain images from noninvasively obtained radio frequency (RF) data at large insonification angles by means of a vessel phantom experiment. Furthermore, the techniques to correct for grating lobe interference and other artifacts, that occur when performing beam steering at large angles, are described.

Materials & Methods

Materials

A homogeneous vessel phantom was made of a 8% gelatin (Dr. Oetker, Ede, The Netherlands) solution with 3% Agar (Agar Agar CMN, Boom, Meppel, The Netherlands), and 1% SiC scatterers (9-15 μm, E. Merck, Darmstadt, Germany). To create the solution, water was heated to 60 °C, and 8 g of gelatin, 3 g of Agar, and 1 g of scatterers were added. The mixture was boiled and stirred until a homogeneous solution of 100 grams remained. During cooling to room temperature, the resulting solution was degassed by a vacuum pump and poured into a cylindrical mold with an outer radius of 6.5 mm. The “lumen” was created by central placement of a metal rod with a radius of 1.5 mm. The resulting wall thickness of 5 mm is equal to the wall thickness of the vessel phantom used in intravascular experiments performed earlier by our group [99]. The mould with solution was placed in a refrigerator at 6 °C for one night.

The next day, the phantom was placed in a tank filled with a 2.95% saline solution. The lumen of the phantom was attached to a pressure column filled with the same saline solution on one side, and to a closed valve on the other side as illustrated previously [83]. Remaining air bubbles in the lumen were removed by opening of the valve and flushing with the solution. The pressure column was used to impose different intraluminal pressures on the phantom. The room temperature was 21.6 °C during the experiment. The saline solution was used to reduce previously reported artifacts [83] caused by refraction of the ultrasound beam at the liquid-phantom transition areas due to speed of sound differences between the two media [100]. The speed of sound in gelatin at 21.6 °C is about 1520 m/s [101], which also is the speed of sound in a saline solution of 2.95% at 21.6 °C [102].

Data acquisition

RF data of the phantom were obtained with a Philips Sonos 7500 ultrasound machine equipped with an RF interface (Bothell, WA, USA). Measurements were performed with a linear array transducer (Philips, 11-3L) with a central transmit frequency of 7 MHz and a bandwidth of 3-11 MHz. The RF data were sampled at 39 MHz. Cross-sectional data were obtained with the transducer mounted facing downwards to the phantom. Measurements were carried out starting on an intraluminal overpressure of 10 mmHg. At this intraluminal pressure, RF data were recorded at the following insonification angles: 45°, 30°, 15°, 0°, -15°, -30°, and -45°. Next, the pressure difference was increased with 4 mmHg and postcompression images were recorded at the mentioned beam steered angles. This procedure was repeated for eight different cross sections of the vessel phantom, resulting in eight datasets with a pressure difference of 4 mmHg between precompression and postcompression. A pressure difference of 4 mmHg was applied, since it results in strains ranging from -1.5% to +1.5%, which corresponds to the interframe strain range measured in vivo in a carotid artery [86]. Furthermore, the pressure step applied and the strain range achieved also correspond to those applied and observed in the aforementioned intravascular vessel phantom experiments [99]. This enables us to compare the current noninvasive experiments with the previous intravascular experiments. The whole procedure took approximately 16 min (~2 min for each cross section).

Data processing: speed of sound correction

Before the strain algorithm was applied to the precompression and postcompression datasets a number of corrections were carried out on the RF data. In general, in ultrasound imaging an average speed of sound in tissue of 1540 m/s is assumed. This has several consequences, especially when compounding images obtained at various insonification angles. When the speed of sound in the examined tissue is lower than 1540 m/s, as is the case for this phantom material, each RF pulse will have a longer traveling time, which will be interpreted as an echo coming from a larger depth. The ultrasound image will therefore be an elongated version of the real tissue. The depth of a point in the image d_{image} is related to the depth of the same point in reality d_{real}, by the ratio of the assumed speed of sound c_{image} and the real speed of sound, c_{real} [103].

\[ d_{image} = \frac{c_{image}}{c_{real}} d_{real} \]  

(2-1)

Overestimation or underestimation of the speed of sound also gives rise to another artifact that appears when beam steering is performed. To transmit the ultrasound beam at a certain angle, a specific delay is calculated for each transducer element. This delay is inversely proportional to the assumed speed of sound. Overestimation of the speed of sound, i.e., a lower speed of sound in reality, results in an underestimation of the time delays. This means, that the ultrasound beam will be transmitted at a smaller angle in reality \( \alpha_{real} \) (Fig. 2-1), than the imposed angle \( \alpha_{image} \). The larger the angle, the larger the mismatch caused by the speed of sound difference [103].

\[ \sin \alpha_{real} = \frac{c_{image}}{c_{real}} \sin \alpha_{image} \]  

(2-2)

Since the real sound speed is known for the used setup, the data were scaled accordingly, and the angle was corrected. The difference between \( \alpha_{image} \) and \( \alpha_{real} \) was never larger than one integer value corresponding to \( \alpha_{image} \) will be used.

Data processing: adaptive grating lobe correction

Grating lobes are secondary ultrasound beams emitted in directions other than the electronically steered direction. The angle of appearance of grating lobe artifacts, \( \beta \) (Fig. 2-2), depends on the ratio of the pitch of the transducer elements \( \Delta x \), the transmitted wavelength \( \lambda_{real} \), and the angle of the ultrasound beam \( \alpha_{real} \) [104].

\[ \beta = \arcsin(\frac{m\alpha_{real}}{\Delta x} + \sin \alpha_{real}) \]  

(2-3)

with \( \lambda_{real} = c_{real} f \) and \( m = \text{order of the grating lobe} (m = \pm 1, \pm 2, \ldots) \).

The scattering caused by this secondary beam is received by the transducer and interpreted as originating from the main beam, which gives rise to the appearance of artifacts. An example
of a grating lobe artifact for the used setup is shown in Fig. 2-2A. The blurred part on the left of the image is the grating lobe artifact. Fig. 2-2A&B schematically explains how the misinterpretation of the reflections and scattering caused by a first order grating lobe gives rise to artifacts, like the one shown in Fig. 2-2A, for a high and a low (approximately three times lower) transmit frequency, respectively. As can be noticed, also from the \( \lambda_{real} \) term in (2-3), the grating lobe appearance and the corresponding artifact are frequency dependent. The artifact becomes stretched and moves out of the image plane when the transmit frequency is lowered, due to the corresponding increase of \( \beta \). When \( \beta \) equals 90° the artifact is no longer present. In other words there is a certain frequency \( f_{\text{cutoff}} \) below which the grating lobes disappear.

\[
\text{f}_{\text{cutoff}} = \frac{c_{\text{real}}}{(1 + \sin \beta)Dx}
\]  
(2-4)

This equation can be derived from (2-3) by setting \( m \) and \( \sin \beta \) to 1, or to –1, for negative and positive beam steering angles, respectively, and solving for \( f \).

Each line of RF data of the phantom measurements was low-pass filtered with this angle dependent cutoff frequency, of course at the cost of spatial resolution. The larger the insonification angle, the lower the cutoff frequency of the applied low-pass filter. Since \( Dx \) of the used transducer is 35 μm, the cutoff frequency when beam steering at 45° is 6.6 MHz. The effect of low-pass filtering for the removal of the grating lobe artifacts at 45° beam steering can be appreciated from Fig. 2-2B.

**Data processing: skewed mesh correction**

Now that the grating lobes have been filtered and the real beam angle and speed of sound are known, an additional processing step is required before strain estimation techniques are applicable. This processing step only applies to the RF data acquired at nonzero beam angles. Normally, when measuring without beam steering, the sample points of each RF line form a rectangular grid with the sample points of the next RF line. However, due to the beam steering, the RF data is stored in a rectangular grid, while it contains sample points acquired at an angle. This causes the image to be a skewed representation of reality, as can be observed in Fig. 2-2A&B. To reshape the skewed data to right-angled data, each RF line is shifted by a certain number of points, defined by “shift”, compared to the next RF line.

![Schematic explanation for the appearance of grating lobe artifacts when performing beam steering](image)

Before applying the strain algorithm, a region of interest (ROI) is selected with the same inner radius as the phantom, but with a slightly smaller outer radius, to avoid possible boundary artifacts. This ROI is rotated for each insonification angle to make sure that the same region is selected for the data measured at all insonification angles. The lateral and axial displacement measurements are calculated in an iterative coarse-to-fine process, as described in [59]. Per iteration, the displacements are globally estimated by 2-D cross-correlation of windows of the precompression and postcompression data. The “coarsest” precompression window length used was 128 points and the “finest” 16 points. Each window had an overlap with the next window of 50%. For a window length of 16 points this results in a resolution of approximately 250 μm. By fitting a 2-D parabola through the cross-correlation peak value and its nearest neighbors, the displacements can be more precisely estimated. In an additional iteration the displacement estimates are used to align the precompression and postcompression windows at subsample and subpixel level to obtain even better displacement estimates. The lateral displacements resulting from each iteration were filtered with a 2-D median filter of 7x7 data points. Displacement values in the axial direction were filtered with a median filter of 5x5 points. Lateral and axial strain values were obtained using a 1-D least-squares strain estimator (LSQSE) [48] with a window length of nine samples. In a final step, local temporal stretching is applied [105,106]: RF signals of the “finest” postcompression windows are rescaled according to the previously determined strain values and then the displacement and strain estimation is repeated. Due to the stretching of the postcompression windows, the cross-correlation peak can be detected more accurately, and as a consequence, the accuracy of the displacements and strains also increases.

**Data processing: radial and circumferential strain**

Lateral and axial strains need to be converted to radial and circumferential strains since the latter two are rotationally symmetric for a cylindrical structure: for a certain distance to the
lumen centre the radial strain will be equal for all angles, whereas the axial and lateral strain values change from positive to negative or vice versa for each quarter of the cross section [83]. Three methods for calculating radial and circumferential strains from axial and lateral strains are investigated. The first method is principal component analysis [107]. Principal strains are defined as normal strains along the axes of deformation, where shear strains are zero. For a concentrically deforming isotropic homogeneous cylinder, these axes are in the radial and circumferential direction. To obtain the principal strains, the estimated strain tensor is transformed into a symmetrical tensor. The positive and negative eigen values of this symmetrical tensor represent the circumferential and radial strain, respectively.

The second method [108] makes use of a rotation matrix to rotate the symmetrical strain tensor $E_n$ into the polar strain tensor $E_{\theta}$.

$$E_{\theta} = M E_n M^T, \text{ where } M = \begin{bmatrix} \cos \theta & -\sin \theta \\ \sin \theta & \cos \theta \end{bmatrix}$$

where $\theta$ is the angle between the ultrasound beam and the radial strain, which is calculated with respect to a manually selected reference point that corresponds to the center of the lumen. The diagonal values of $E_{\theta}$ represent the radial and circumferential strains.

The third method estimates the radial and circumferential strain by projection of the axial and lateral strains. A plane strain condition is assumed, which was shown to be a valid assumption for a concentric homogeneous vessel phantom and seems to be a reasonable assumption for the in vivo case, regarding the low strains measured in vivo in the direction of the vessel axis [83]. In regions I and III (Fig. 2-3), the radial strain is closely aligned with the ultrasound beam and, therefore, the axial strain is a fair approximation of the radial strain. In these regions the lateral strain is equivalent to the circumferential strain. In regions II and IV it is exactly the opposite. The projection results in an underestimation of the actual radial and circumferential strains, which can be corrected for [109].

**Regions I and III:**

$$\varepsilon_{rad,xx} = \frac{\varepsilon_{xx}}{2 \cos^2 \theta - 1}, \text{ and } \varepsilon_{circ,yy} = \frac{\varepsilon_{yy}}{2 \cos^2 \theta - 1}$$

**Regions II and IV:**

$$\varepsilon_{circ,xx} = \frac{\varepsilon_{xx}}{2 \sin^2 \theta - 1}, \text{ and } \varepsilon_{rad,yy} = \frac{\varepsilon_{yy}}{2 \sin^2 \theta - 1}$$

where $\theta$ is again the angle between the ultrasound beam and the radial strain, and $\varepsilon_\cdot$ are the estimated strains. The first index of $\varepsilon$ indicates whether the radial or circumferential strain is estimated, the second index explains whether the axial $\varepsilon_{xx} = \varepsilon_{xx}$ or the lateral strain $\varepsilon_{yy} = \varepsilon_{yy}$ was used for the projection.

**Data processing: compounding**

Once the circumferential and radial strains are determined, compound images of the radial and circumferential strains obtained at multiple insonification angles are constructed. The compounding method for a radial strain image is visualized in Fig. 2-4. For each insonification angle, the radial strain data in circle segments of $-30^\circ$ to $+30^\circ$ with respect to the insonification direction are selected for contribution, as illustrated in Fig. 2-4A. As pointed out in the previous section, the radial strain closely resembles the axial strain in these segments and is, therefore, more accurately approximated than in segments which require more lateral strain input to construct radial strains. The segments acquired at the multiple angles are all reoriented as if they were obtained at a $0^\circ$ insonification angle. For instance, the segments selected at the maximum insonification angle of $+45^\circ$ will contribute data from $+15^\circ$ to $+75^\circ$ to the compound image, and the segments selected at $+30^\circ$ will contribute from $+0^\circ$ to $+60^\circ$. In the regions where the segments overlap, the strain values are averaged. Fig. 2-4B shows the compounding schematically. Fig. 2-4B also shows that it is not possible to construct a full $360^\circ$ compound image from the described segments. The compound image is completed by adding two smaller segments ($40^\circ$ opening angle) of radial strain estimates determined from $0^\circ$ data. It should be remarked that the radial strain estimates in these segments are of poorer quality because they are mainly determined by the lateral strain. For the construction of the compound circumferential strain images, segments perpendicular to the segments chosen for the radial strain image are selected.

For each dataset a reference radial and circumferential strain image is constructed from data acquired at the $0^\circ$ insonification angle only. Principal component analysis is used to obtain these images, since it was also used by Ribbers et al. [83], thus enabling a comparison between the present multi-angle and previous single-angle approach. For each dataset also five compound radial and circumferential strain images are constructed using different methods. Compound images are constructed from segments calculated by: principal component analysis, the rotation formula, projection of axial and lateral strains, a combination of projection of axial strains and principal component analysis, and a combination of projection of axial strains and the rotation formula.

Due to the cylindrical geometry and homogeneity of the phantom, theoretically the radial strain values are negative and equal at equal distances $r$ from the centre of the lumen. The
circumferential strain values are positive and equal at equal distances r. Furthermore, the absolute strain decays proportionally to 1/r^2, as described by [99]. Due to this circle symmetric decay it is possible to calculate elastographic signal-to-noise, SNR_e, and contrast-to-noise ratios, CNR_e, in decibels for the reference and compound images, using points located on circles around the lumen centre:

Here, μ_1 and μ_2 are the mean, and σ_1 and σ_2 are the standard deviations of the strain values located on circles positioned around the lumen centre:

$$\text{SNR}_e = 20 \log_{10} \frac{\mu_1}{\sigma_1}$$

$$\text{CNR}_e = 20 \log_{10} \frac{2(\mu_1 - \mu_2)^2}{(\sigma_1^2 + \sigma_2^2)}$$

The SNR_e and CNR_e values of the various compounding methods were compared with one another, with the reference images and with the previous intravascular experiments [101]. Paired t-tests were performed to confirm the difference and statistical significance was defined as P < 0.05.

CNR_e is usually used to quantify target detectability in elastography [98]. A more general definition of CNR_e is used in this study: the ability of a technique to distinguish two homogeneous regions with different levels of strain, in this case a circle with high strain values close to the lumen, and a circle with lower strain values more distal to the lumen.

**Results**

The constructed radial and circumferential strain images for the first dataset are shown in Fig. 2-5. In Fig. 2-5A the reference images are shown. On the right of the colour bar are the compounded images. Fig. 2-5B represents the compound images estimated by combining segments of principal strain data. The other subplots are constructed by using the rotation matrix (C), by projecting axial and lateral strain (D), and by projecting axial strain and adding a segment of principal strain (E), or rotational strain (F). It should be recalled that projecting strain is only an option for small projection angles and is, therefore, useful only when constructing a compound image. As can be observed, the radial strain is negative and the circumferential strain is positive, corresponding to compression and expansion of the tissue in these regions, respectively. The increase in intraluminal pressure causes the phantom to be compressed from the inside to the outside, in other words, negative strain values will be resulting in the radial direction. The diameter is increasing by the increased intraluminal pressure, causing extension of the material in circumferential direction. Due to the plane strain assumption, the circumferential strain has to be the opposite of the radial strain.

The circular symmetry, as predicted by theory, is also clearly visible. Although a small area with unexpected strain values is present between 5 and 7 o'clock in the circumferential strain im-

![Fig. 2-4. Schematic overview of the construction of a compound radial strain image from radial strain data obtained at multiple insonification angles. From all insonification angles the radial strain in the region between -30° and +30° with respect to the ultrasound beam is used for the construction of the compound image. Because it is not possible to construct a full 360° compound image from this information, smaller segments calculated from mainly lateral strain data obtained at 0° steering are added.](image)

**Fig. 2-4.** Schematic overview of the construction of a compound radial strain image from radial strain data obtained at multiple insonification angles. From all insonification angles the radial strain in the region between -30° and +30° with respect to the ultrasound beam is used for the construction of the compound image. Because it is not possible to construct a full 360° compound image from this information, smaller segments calculated from mainly lateral strain data obtained at 0° steering are added.

![Fig. 2-5. Radial (top row) and circumferential (bottom row) strain images for a concentric homogeneous vessel phantom. A: radial, and circumferential strain images calculated by principal component analysis from 0° data only. B-F: compound radial and circumferential strain images constructed by; principal component analysis, application of the rotation matrices, projection of axial and lateral strain, projection of axial strain completed with a segment of principal component analysis, projection of axial strain completed with a segment obtained from the rotation matrices.](image)
CHAPTER 2

ages. It should be noticed that the size of this erroneous compound area is smaller for the compound images. The three rightmost radial and circumferential compound images that were constructed by projection of mainly axial data, show a much better circular symmetry than the reference images.

Mean and standard deviations of the SNR and CNR values for the reference images calculated from the eight datasets using 0° data only, are shown in Table 2-1. The mean and standard deviations of the SNR and CNR values of the compound strain images are also shown in Table 2-1. Improvements or reductions in SNR or CNR of the compound images compared to the reference images that were found to be significant are marked with an asterisk.

In general, the images of highest quality are obtained when the projection formula is used to construct the major part of the image. Significant contrast- and signal-to-noise ratio increases up to 2.7 dB, and 6.6 dB are observed, respectively. SNR and CNR increase significantly when instead of projecting lateral strains, principal component analysis, or the rotation method is used to complete the compound radial strain image (paired t-test, P < 0.05). The differences in SNR and CNR between the images completed with principal component analysis and the rotation method, are not significant (paired t-test, P > 0.05). The compound images constructed by the rotation matrix and by principal component analysis are of poorer quality than the reference images.

Discussion

Compounding allows the construction of radial strain images with higher quality than can be determined from zero degree information only. Primarily, the higher quality is obtained because the images are mainly based on axial strain, instead of on axial and lateral strain. The lateral strain estimate has a lower SNR than the axial strain estimate [89, 210]. Furthermore, in this circular geometry, erroneous lateral strain values are found in some regions (at 5 and 7 o'clock in this phantom) due to the aforementioned refraction artifact [100]. The ultrasound lines are redistributed in space due to this effect, and this redistribution changes when the inhomogeneous lateral strain fields are redistributed in space due to this effect, and this redistribution changes when the reference images.

Table 2-1. SNR and CNR values for the reference images and the compound strain images constructed with the five methods.

<table>
<thead>
<tr>
<th>Method</th>
<th>SNR (dB)</th>
<th>CNR (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± sd</td>
<td>Mean ± sd</td>
</tr>
<tr>
<td>Radial strain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref. principal</td>
<td>7.7 ± 1.8</td>
<td>6.6 ± 4.2</td>
</tr>
<tr>
<td>Principal strain</td>
<td>*5.2 ± 3.5</td>
<td>*4.1 ± 3.6</td>
</tr>
<tr>
<td>Rotation matrix</td>
<td>*4.9 ± 2.8</td>
<td>6.7 ± 5.2</td>
</tr>
<tr>
<td>Projection only</td>
<td>8.4 ± 3.9</td>
<td>*32.0 ± 4.3</td>
</tr>
<tr>
<td>Projection &amp; principal</td>
<td>*8.9 ± 1.8</td>
<td>*13.1 ± 1.2</td>
</tr>
<tr>
<td>Projection &amp; rotation</td>
<td>*8.8 ± 1.9</td>
<td>*32.1 ± 1.0</td>
</tr>
<tr>
<td>Circumferential strain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref. principal</td>
<td>7.0 ± 1.7</td>
<td>6.4 ± 2.2</td>
</tr>
<tr>
<td>Principal strain</td>
<td>*5.9 ± 1.8</td>
<td>*8.4 ± 5.9</td>
</tr>
<tr>
<td>Rotation matrix</td>
<td>*3.4 ± 2.0</td>
<td>*4.1 ± 3.1</td>
</tr>
<tr>
<td>Projection only</td>
<td>*9.1 ± 1.7</td>
<td>*10.0 ± 4.0</td>
</tr>
<tr>
<td>Projection &amp; principal</td>
<td>*9.7 ± 1.4</td>
<td>*11.6 ± 3.4</td>
</tr>
<tr>
<td>Projection &amp; rotation</td>
<td>*9.6 ± 1.4</td>
<td>*11.6 ± 3.5</td>
</tr>
</tbody>
</table>

*Outcome of paired t-test <0.05 when compared to reference image

SEGMENT BASED COMPOUNDING OF AXIAL STRAINS

The increase in SNR and CNR when principal component analysis or the rotation method is used to complete the compound radial strain image, instead of projecting lateral strains (Table 2-1), might be explained by the fact that in the latter case pure lateral information is used, whereas in the other cases also axial information is added to estimate the radial strains. It is disputable whether principal component analysis or the rotation method should be used to complete the compound image. The rotational method requires the selection of a center of reference with respect to which a rotation is carried out, which is not required for principal component analysis. Therefore, the use of the rotational formula certifies that the calculated radial strain is really the strain in the radial direction with respect to the chosen center. The minimum eigen value obtained by the principal component analysis does however not necessarily represent the strain in the (exact) radial direction. An artifactuous negative strain value in circumferential direction could easily be regarded as radial strain by the principal component analysis. This incorrect “attenuation” of artifacts is probably the reason why the SNR and CNR are higher for the images that were completed by principal component analysis.
For in vivo application, which implies that mainly inhomogeneous and asymmetrical structures are investigated, the use of principal strains is discouraged. The principal strain directions would then also differ from the radial and circumferential directions.

Rao et al. [96] described angular compounding of axial strain data obtained at various beam steered angles for a cylindrical inclusion phantom, and reported increases in SNR and CNR of 3 and 10 dB, respectively. Although smaller increases were found in the current study, the value of the comparison is to be doubted, because of essential differences between both techniques, and because different phantoms were used in the studies. Rao et al. uses angular compounding to improve the quality of the axial strain image for one part of the phantom, whereas the current study combines radial or circumferential strain estimates in different phantom regions, calculated from acquisitions at different angles, to construct a compound radial or circumferential strain image of high quality for a larger region. The image quality does not improve further when performing beam steering at angles larger than 10° when using the first technique [96], due to increasing decorrelation of the precompression and postcompression RF data. Because the regions of interest in the current study are chosen in such a way that the investigated strain rotates with the beam steering angle, the decorrelation effect is counteracted, and it is possible to increase image quality by adding data obtained at beam steering angles of more than 10°.

Using an intravascular transducer de Korte et al. found SNR and CNR values of +6.3 dB and -2.3 dB, respectively. These values were calculated from Fig. 1 in [99]. Thus, the current multiple angle approach even outperforms the intravascular approach that was performed with a transducer with a center frequency of 20 MHz. The large increase in CNR of about 9 dB, when comparing the intravascular results to our results, can probably be ascribed to the more sophisticated strain algorithm and the improved quality of the ultrasonic equipment. The strain algorithm has been improved by implementing a 2-D instead of 1-D cross-correlation, a coarse-to-fine approach, an aligning procedure, and local temporal stretching. Finally, it should be noticed that although the current phantom contained more Agar than the phantom used intravascularly, the measured strains were in the same range. The Young's modulus of the phantom was also similar to that of the intravascular experiments. By fitting a 1 over r curve through the strain data and then solving the theoretical relation for the strain as function of the radius [90] a Young's modulus of 32 kPa was found. The Young's modulus of the intravascular phantom was reported to be about 30 kPa. The agreement of the Young's moduli despite of the differences in Agar content is probably due to differences in preparation and the used measurement method.

The compounding of segments is now performed by straightforward averaging in the regions of overlap. Making use of the fact that the strain estimate quality diminishes when the angle increases, due to the increased amount of filtering applied, the application of weight functions to the various contributions will probably increase the quality of the compound strain images further. The reduction in frequency band for larger angles could also be taken into account by adapting window sizes of the 1-D LSQSE, and the median filters.

For the compounding technique to be applicable in vivo, it would be ideal if the same cross section could be measured at the multiple insonification angles before and after compression. However, since the carotid is moving and pulsating this is probably not possible. ECG or blood pressure triggering to obtain images of the cross section at similar moments at different angles during subsequent heartbeats would be required. Tracking of the deforming tissue might also be useful to reduce movement errors. Of course, it can be expected that not all motion artifacts can be corrected for, which will result in less improvement in SNR and CNR than observed in the current in vitro study. However, it is likely that the reduction in improvement is rather small, since IVUS elastography has shown that it is possible to construct strain images of a cross section of a pulsating artery with an ultrasound probe that was mounted on a freely moving catheter [53].

The selection of the region of interest and of the point of reference, with respect to which the projections are carried out, was currently performed manually. However, automated segmentation of the boundary between lumen and arterial wall seems feasible [111]. Segmentation of the peri-adventitia might be performed using this method, or using similar approaches such as currently developed for cardiac imaging [112]. Automatic calculation of the center of gravity from this segmented luminal contour [51] could then serve as point of reference for the projections.

Recently, we could show [113], that the quality of the strain images increased, when more angles were added to the compounding. Due to the nonstationarity in vivo, it will only be possible to perform the acquisitions for one angle per heartbeat. Investigation of the minimum selection of angles that enables the construction of compound strain images with acceptable quality and whether the radial strain profile remains reproducible during those acquisitions is required. Furthermore, due to the different imaging depth of the carotid artery in vivo, there will probably be a limit on the maximum beam steering angle that can be used. The maximum angle will have to be determined, and if required segment sizes will have to be increased. Additionally, dedicated transducers might be developed for imaging deeper arteries.

The speed of sound was homogeneous in the used setup. However, in vivo this will not be the case. Presumably, this will necessitate assuming (based on anatomy) or determining regions of equal sound speed within the tissue, which might even be possible in an automated manner [114]. The RF corrections for skewness, grating lobes, and speed of sound, would then have to be carried out separately for all different regions. Dividing the image in two regions of homogeneous sound speed: one corresponding to the fat layer between skin and artery, and one corresponding to the vessel wall and lumen, might perhaps be sufficient to deal with most of the speed of sound problems.

Finally, it should be noticed, that with IVUS elastography it is only possible to estimate circumferential strains by deriving them from lateral information (i.e., perpendicular to the ultrasound beam), since the ultrasound beams are transmitted in the radial direction. With the noninvasive compounding approach, radial as well as circumferential strains can be reconstructed from mainly axial data. A proper estimation of radial as well as circumferential strain is expected to enable a more correct reconstruction of elastic moduli [115,116].
Conclusion

It is possible to construct compound radial and circumferential strain images from RF data obtained at multiple large beam steered angles ranging from -45° to 45°. Compounding increased image quality with approximately 2 dB in SNR, and 6 dB in CNR, compared to the radial and circumferential strain images obtained without beam steering. The compound images of highest quality are constructed when mainly axial strain that is projected in radial or circumferential direction is used.

Acknowledgment

The authors would like to thank McKee Poland of Philips Medical Systems in Andover for the adjustments made to the Sonos 7500 to enable beam steering up to 45°.
In this chapter an alternative segment based method for noninvasive radial strain estimation in transverse cross sections of superficial arteries is introduced. Opposed to the projection of axial strains in the radial direction as presented in chapter 2, now axial displacements are projected in the radial direction. It is shown that this allows the construction of radial strain images of higher quality using fewer acquisitions and smaller beam steering angles.


Segment Based Compounding of Axial Displacements
CHAPTER 3

Abstract

Strain is considered to be a useful indicator of atherosclerotic plaque vulnerability. This study introduces an alternative for a recently introduced strain imaging method that combined beam steered ultrasound acquisitions to construct radial strain images of superficial arteries. In that study, axial strains were projected in the radial direction. Using the alternative method introduced in this study, axial displacements are projected radially, followed by a least squares estimation of radial strains. This enables the use of a larger projection angle. Consequently, fewer acquisitions at smaller beam steering angles are required to construct radial strain images. Simulated and experimentally obtained radiofrequency data of radially expanding vessel phantoms were used to compare the two methods. Using only three beam steering angles (-30°, 0° and 30°), the new method outperformed the older method that used seven different angles and up to 45° of beam steering; the root mean squared error was reduced by 38% and the elastographic signal- and contrast-to-noise ratios increased by 1.8 dB and 4.9 dB, respectively. The new method was also superior for homogeneous and heterogeneous phantoms with eccentric lumens. To conclude, an improved noninvasive method was developed for radial strain imaging in transverse cross sections of superficial arteries.

Introduction

Most strokes and myocardial infarctions are considered to be initiated by the rupture of an atherosclerotic plaque [14-16]. Therefore, a method to detect the vulnerable plaque before a rupture occurs is of paramount importance. The vulnerability of a plaque is mainly determined by its geometry and composition [17-19]. Ultrasound strain imaging provides detailed information about the geometry and indirect information about the composition of a plaque. Both in transcutaneous and in intravascular studies, it has been shown that strain values significantly differ for various plaque components [52,53,67,78,82,86]. Because ultrasound strain imaging is noninvasive, relatively cheap and able to be applied noninvasively, it is a promising technique for the identification of vulnerable plaques.

Noninvasive vascular ultrasound strain imaging has been shown to be feasible in the longitudinal and transverse directions [68,83,86,87]. Usually, axial strains in longitudinal recordings of the vessel are investigated [68,86,87]. This is probably because the axial direction of the ultrasound beam is aligned with the vessel’s radial direction, which is one of the main directions of motion for a pulsating vessel. However, transverse imaging is also important; plaques, and especially the vulnerable spots of plaques, are not always located in the field of view when imaged longitudinally and 2-D longitudinal imaging does not enable measurement of circumferential strain. Simultaneous imaging in the transverse plane is not as straightforward as strain imaging in the longitudinal direction because the radial (and circumferential) deformations of the artery are not always aligned with the direction of the transmitted ultrasound beams [83,88, Ch. 2]. Then, a conversion of axial and lateral information is required to calculate radial (and circumferential) strains. In the most straightforward implementation, axial and lateral data contribute equally to the radial strain image [83]. However, the lateral strain estimates (which are derived from the lateral displacements) are less accurate than the axial strain estimates (which are derived from the axial displacements) due to a lack of phase information and a lower resolution in that direction. Consequently, the lateral component causes deterioration of the constructed radial (and circumferential) strain images.

SEGMENT BASED COMPOUNDING OF AXIAL DISPLACEMENTS

Recently, we introduced a method to minimise the contribution of lateral strain required to construct a radial strain image [Ch. 2]. A linear array transducer was beam steered to image the blood vessel from multiple angles. For each beam steered acquisition, radial strains were calculated for segments of the cross section by radial projection of mainly axial strain data [109]:

$$\varepsilon_{rad} = \frac{\varepsilon_{ax} \cos^2 \theta}{2 \cos \theta - 1} \tag{3-1}$$

where $\theta$ corresponded to the angle between the radial and axial direction and $\varepsilon_{ax}$ and $\varepsilon_{cor}$ corresponded to the radial and axial strains, respectively. The segments obtained at the various beam steering angles were combined to form a compound radial strain image for the entire vessel cross section. In phantom experiments, the image quality improved compared with the approach in which no beam steering was applied. The segments used were only 60° wide (-30° ≤ $\theta ≤ +30°$, with respect to the beam steered angle) so a large number of beam steered acquisitions were required. Even more importantly, lateral data from a 0° acquisition and axial data from beam steering angles of up to 45° were necessary to construct a radial strain image that covered the entire cross section. The quality of data acquired at beam steering angles of 45° is rather poor due to grating lobe artefacts and lower signal intensity that is inherent to the directional sensitivity of the transducer elements. Furthermore, because data from successive acquisitions are combined and the artery is pulsating, the number of acquisition angles should be limited as much as possible to reduce motion artefacts. Therefore, it would be ideal to have a method that enables the construction of a radial strain image for the entire cross section using fewer acquisitions at smaller beam steering angles and does not require any lateral input.

This study presents a method that has all of these advantages. Instead of axial strains, axial displacements for each segment are projected radially:

$$u_{rad} = \frac{u_{ax}}{\cos \theta} \tag{3-2}$$

where $u_{ax}$ and $u_{rad}$ correspond to the radial and axial displacements, respectively. Subsequently, radial strains are derived from the radial displacements. The denominators of (3-1) and (3-2) describe to which extend the axial information contributes to the radial displacement/strain. The axial contribution decreases twice as fast when the projection angle increases for the strain projection method compared to the displacement projection method. This implies that twice as large projection angles can be used for the displacement projection method as for the strain projection method, while having the same contribution of the axial component. Thus, instead of using 60° wide segments, now 120° wide segments (-60° ≤ $\theta ≤ +60°$, with respect to the beam steered angle) are used, while the measured axial component is still 50% of the radial component. Consequently, fewer acquisitions at smaller beam steering angles are required to construct a radial strain image for the entire cross section. In addition, lateral input is no longer required when using beam steering angles of 30° or more. In Fig. 3-1 the percentage of contribution of the axial information to the radial displacement/strain is shown as a function of the projection angle. It should be noticed that strain projection does not allow projection angles larger than 45°, because the denominator of (3-1) equals zero then.

This study starts by determining and comparing the performances of the displacement projection method, the strain projection method and a 0° reference method using simulated radio
frequency (RF) data of a pressurised homogeneous vessel phantom with a concentric lumen. Then, the comparison is repeated for experimental data of a similar phantom made of gelatine. Finally, the effect of circumferential motion on the performance of all methods is studied using strain images of a homogeneous and a “soft plaque” vessel phantom with an eccentric lumen. The strain images of the eccentric phantoms are compared with theoretical radial strain images obtained by finite element modelling (FEM).

Materials and methods

Concentric homogeneous vessel simulations

RF data from a transverse cross section of a homogeneous vessel with a concentric lumen were simulated in an uncompressed and a compressed state using the Field II simulation program [120,121]. The simulated vessel had an outer radius of 6.5 mm, a lumen radius of 1.5 mm and an elevational width of 4 mm. The lumen centre was positioned at 9 mm depth. A beam steered linear array transducer was simulated with a centre frequency \( f_0 \) of 8.7 MHz, an element pitch of 135 µm, and an element height of 6 mm. The transducer consisted of 288 physical elements. Each element was subdivided into 10-by-10 mathematical elements. In transmit mode, four elements were activated without apodization. A single focus was set at a depth of 2.5 mm, corresponding to the focal depth used in the experiments. In receive mode, dynamic focusing was simulated with an F number of 0.875. The number of simultaneously active elements was restricted to 128. Hamming and Hanning windows were used for apodization in the lateral and elevational directions, respectively. The elevational focus was set to 2.5 cm. RF data were simulated at a sampling rate of 39 MHz to match the sampling frequency of the transducer used in the experiments.

The vessel was made up of 1 million randomly positioned point-like scatterers. Plane strain was assumed. The radial position \( R_i \) of each scatterer, after compression, was calculated using [99]:

\[
R_i = r_i + \frac{a^2 \Delta p}{E(b^2 - a^2)} \left( b^2 (1 + \nu) \left( 1 + \nu \right) (1 - 2\nu) r_i + 1\right)
\]

where \( r_i \) is the radial position of a scatterer \( i \) before compression, \( \Delta p \) is the intraluminal pressure change, \( \nu \) is Poisson’s ratio, \( E \) is the Young’s modulus, \( a \) is the lumen radius and \( b \) is the vessel radius. The pressure change was set to 0.532 kPa (4 mmHg). \( \nu \) and \( E \) were chosen to be 0.495 and 50 kPa, respectively. A Young’s modulus of 50 kPa is close to the Young’s modulus for nonfibrotic vascular tissue [122].

RF data from the vessel were simulated in precompression and postcompression states for beam steering angles ranging from -45° to 45° in angular increments of 15°. Fig. 3-2A shows the simulated Hilbert transformed 0° RF data from the vessel before compression.

Vessel phantom experiments

In analogy with the simulations, a concentric homogeneous vessel phantom was created from an 8% gelatine (Dr. Oetker, Ede, The Netherlands) – 3% agar (Agar Powder CMN, Boom, Melle, The Netherlands) solution. Furthermore, two phantoms with eccentric lumens were con- structed: a homogeneous phantom and a “soft plaque” phantom. A 12% gelatine – 1% agar solution was used to create the homogeneous phantom. The “soft plaque” phantom consisted of a soft layer (soft plaque), made of a 12% gelatine – 0% agar solution, surrounded by a stiff layer (vessel wall) made of a 12% gelatine – 4% agar solution. 1% by weight SiC particles (9 to 15 µm, E. Merck, Darmstadt, Germany) were added for ultrasonic scattering. The phantoms were created according to the production procedures described by [99]. All phantoms had an inner radius of 1.5 mm and an outer radius of 6.5 mm.

After construction, the phantoms were placed in a water tank. The lumens were attached to a closed valve on one side and a water column on the other side. By varying the water level in the column, the intraluminal pressure was controlled. A SONOS 7500 ultrasound system (Philips Medical Systems, Bothell, WA, USA) equipped with a linear array transducer (11-3L, \( f_0 = 8.7 \) MHz, element pitch = 135 µm) and an RF interface was used to acquire RF data, which were recorded in pre- and postcompression states (\( \Delta p = 4 \) mmHg) for beam steering angles ranging from -45° to 45° in angular increments of 15°. Eight different transverse cross sections of

![Fig. 3-2. Precompression envelope images of A: a simulated and B: an experimental homogeneous vessel lumen obtained without beam steering. C shows the selected region-of-interest (ROI) and geometry of the concentric phantom.](image-url)
the homogeneous concentric phantom were imaged to assess reproducibility. Only one cross section was imaged for the other phantoms. Fig. 3-2B shows the 0° precompression Hilbert transformed RF data from the concentric phantom before compression at 0° of beam steering.

Radial strain imaging methods: general steps

Regardless of the strain estimation method used, all RF data were preprocessed. The preprocessing consisted of correcting for grating lobe interference and data grid skewness as described in detail in chapter 2. Subsequently, regions-of-interest (ROIs) were selected in the 0° images of each phantom. For the simulations, the position of the ROI was known exactly (Fig. 3-2C). For the experiments, the ROIs were selected manually. To make sure that the same tissue region was selected for all acquisition angles, the positions of the 0° ROIs were recalculated with respect to the beam steered data grids. Next, axial and lateral displacements were estimated for the data within the ROIs using a 2-D cross-correlation based iterative coarse-to-fine algorithm [59]. All settings of the algorithm were equal to those described in chapter 2. The algorithm provided displacement values for each 155 x 135 μm² of tissue. The various methods for converting axial and lateral displacements into radial strains are described below.

Radial strain imaging methods: reference method

The reference method used only data from a 0° acquisition. The axial and the less precise lateral estimates were converted into radial displacements, by [63]:

\[ u_{\text{rad}} = u_{\text{ax}} \cos \theta + u_{\text{lat}} \sin \theta \quad (3-4) \]

Subsequently, radial strains were derived from the radial displacements by applying a nine-point least squares strain estimator (LSQSE) in the radial direction [48]. The radial displacement data were interpolated on a polar grid using bilinear interpolation to enable the application of an LSQSE in the radial direction (Fig. 3-3A&B). All settings of the algorithm were equal to those described in chapter 2. The algorithm provided displacement values for each 155 x 135 μm² of tissue. The obtained radial strain values were converted back to a Cartesian grid (Fig. 3-3C&D). It should be noted that no assumptions about circumferential motion or incompressibility have been made for the reference method.

Radial strain imaging methods: strain projection

For this method, radial strains were derived by projection of axial strains in the radial direction (3-1). To obtain the axial strains, a nine-point 1-D LSQSE was applied to the axial displacements. Fig. 3-3A illustrates how the data from the various beam steering angles were compounded. Strain values were averaged in the regions where segments overlapped. As these segments did not cover the entire cross section, radial strains estimated by the reference technique were added for the remainder of the cross section. The strain projection method assumes tissue incompressibility to roughly compensate for circumferential strain.

Radial strain imaging methods: displacement projection

For the displacement projection method, radial displacements were calculated according to (3-2). Next, radial strains were derived by applying a LSQSE in the radial direction, as described

Fig. 3-4. Flowchart for the two compounding methods. A: represents the previously developed strain projection method, and B: describes the steps for the displacement projection method. The example images were obtained experimentally for a pressurised homogeneous concentric vessel phantom. *Data calculated with the reference method using 0° data.
for the reference method. Fig. 3-4B illustrates the compounding process. Using this method, the axial information based segments covered the entire cross section when the steering angle was ±30°. No incompressibility was assumed and no circumferential motion was taken into account by this method, as will be discussed below.

Comparison of methods

For each cross section, eight compound radial strain images were constructed by using the displacement projection method and another eight by using the strain projection method. Data from different combinations of beam steering angles were used to construct the eight images for each method. The investigated combinations are shown in the left column of Table 3-1. In addition, for each cross section a radial strain image was derived using the reference method.

For the simulated data, where the exact input strains were known, the performance of the various methods was compared by calculating the root mean squared error, RMSE:

\[ \text{RMSE} = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (e_{\text{rad,meas}}^{i} - e_{\text{rad,true}}^{i})^2} \]  
(3-5)

where \( e_{\text{rad,meas}}^{i} \) and \( e_{\text{rad,true}}^{i} \) are the estimated and the input radial strains for the \( i \)th pixel within the ROI, respectively. N is the total number of strain pixels within an ROI. Additionally, elastographic signal- and contrast-to-noise ratios, SNR, and CNR, were calculated. This calculation was performed according to the procedure described in chapter 2. SNR and CNR values were also calculated for the experimental data from the concentric phantom. The values were averaged over all cross sections (n=8). The RMSE could not be calculated for the experiments because the input strains were not known exactly.

With respect to the applicability of the displacement method, it has to be noted that for a concentric homogeneous vessel the radial displacement vector \( (u_{\text{rad,true}}) \) is aligned with the resultant displacement vector \( (u_{\text{true}}) \) and, therefore, (3-2) is correct. However, if this is not the case, a small error \( (u_{\text{err}}) \) is introduced during the projection procedure (Fig. 3-5). Consequently, the measured radial displacement vector \( (u_{\text{rad,meas}}) \) deviates from the true radial displacement vector \( (u_{\text{rad,true}}) \). In general, this is the case when circumferential motion occurs. Two configuration differences, which lead to circumferential motion, are 1) an eccentric lumen and 2) heterogeneity of the tissue. As such, the eccentric phantoms were constructed to compare the performance of the methods in the presence of circumferential motion. Radial strain images were estimated for both phantoms using each of the three methods. The estimated radial strain images were visually compared with theoretical radial strain images because it was not possible to calculate RMSE, SNR, or CNR, values for these phantoms due to the irregular strain fields and the lack of knowledge about the exact input. The theoretical radial strain images were determined by finite element modelling (Appendix A).

Results & Discussion

Examples of constructed radial strain images for the concentric phantom are presented in Fig. 3-6. From the left to the right, the images became more circularly symmetric and the 3 and 9 o'clock regions, in particular, became less noisy due to the decreased contribution (strain projection) and finally omission (displacement projection) of lateral information. This was observed for the simulated (Fig. 3-6A-C) as well as the experimental data (Fig. 3-6D-F). The RMSE values (Table 3-1) support these observations: the lowest RMSE was observed for the displacement projection method, followed by the strain projection method and finally the reference method. For seven angles, the strain projection method enabled the construction of a radial strain image that had a 25% lower RMSE than the image constructed with the reference method. Compared to this seven-angle image, the displacement projection method enabled the construction of a radial strain image with an even 38% lower RMSE using data from only

<table>
<thead>
<tr>
<th>Beam steering angles (°)</th>
<th>RMSE (1e-3 %)</th>
<th>SNR (dB)</th>
<th>CNR (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strain</td>
<td>Displ.</td>
<td>Strain</td>
</tr>
<tr>
<td>0</td>
<td>2.7</td>
<td>2.3</td>
<td>7.0</td>
</tr>
<tr>
<td>-15, 0, 15</td>
<td>2.7</td>
<td>1.8</td>
<td>7.0</td>
</tr>
<tr>
<td>-30, 0, 30</td>
<td>2.5</td>
<td>1.3</td>
<td>6.3</td>
</tr>
<tr>
<td>-45, 0, 45</td>
<td>2.2</td>
<td>1.5</td>
<td>7.2</td>
</tr>
<tr>
<td>-30, -15, 0, 15, 30</td>
<td>2.4</td>
<td>1.3</td>
<td>6.3</td>
</tr>
<tr>
<td>-45, -15, 0, 15, 45</td>
<td>2.1</td>
<td>1.4</td>
<td>7.3</td>
</tr>
<tr>
<td>-45, -30, 0, 30, 45</td>
<td>2.1</td>
<td>1.4</td>
<td>7.3</td>
</tr>
<tr>
<td>-45, -30, -15, 0, 15, 30</td>
<td>2.1</td>
<td>1.3</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Table 3-1. RMSE, SNR, and CNR values of radial strain images constructed from simulated data of a homogeneous vessel with a concentric lumen. Compound radial strain images constructed with the strain and displacement projection techniques and the 0° no beam steering reference method are compared with the theoretical strain image.
In terms of SNR and CNR, the displacement projection method also outperformed the other methods. Slightly higher SNR and CNR values were observed when data from the intermediate angles (-35° and 15°) were added. This suggests that data from intermediate angles can be added to further increase the image quality, assuming that the frame rate is sufficiently high.

Contrary to the results obtained by the RMSE analysis, SNR and CNR were lower for the displacement projection method than for the reference method when using 0° information only. Furthermore, the strain projection method did not perform better than the reference method in terms of SNR and CNR. These contradicting observations can be explained by the fact that additional data were required to complete the compound images in some cases. These additional radial strains were derived mainly from lateral 0° data and thus were more erroneous. This disturbed the outcome of the SNR and CNR analyses. If we recalculated the SNR and CNR for the cross section without additional data (-60° ≤ θ ≤ 60°), values of 10.2 dB and 12.9 dB were found for the reference method, versus values of 17.5 dB and 29.6 dB for the displacement projection method. The SNR and CNR values for the strain projection method were also higher than those for the reference method when the additional segments were not taken into account. The SNR and CNR values for the displacement projection method were not influenced as long as beam steering angles of 30° or more were used; in that case, no lateral data were needed to complete the radial strain image.

Table 3-2 shows the means and standard deviations of the SNR and CNR values for the eight cross sections of the concentric homogeneous phantom. Again, the image quality was highest for the compound images constructed with the displacement projection method. The radial strain images constructed with the displacement projection method, from data acquired at -30°, 0° and 30°, had average SNR and CNR values that were 1.8 dB and 4.9 dB higher than those for the radial strain images constructed with the strain projection method using data from seven beam steering angles. Compared with the reference method, increases of 2.2 dB in SNR and 7.6 dB in CNR were observed.

Based on the values reported in Table 3-1 and Table 3-2, it is likely that the maximum beam steering angle can be reduced from 45° to 30° for the displacement projection method without a considerable loss of image quality. The ability to use smaller beam steering angles has the benefit that the tissue of interest can be at a larger imaging depth for a certain fixed transducer size.

Fig. 3-7 shows the radial strain images for the eccentric phantoms. The beam steering angles and the techniques used to construct the images were equal to those used for the images in Fig. 3-6. Again, the strain pattern in the 3 and 9 o'clock regions became less noisy. Also, from the left to the right, the images more and more resemble the theoretical strain images (Fig. 3-7B&I). The strain patterns for both phantoms differed. For the homogeneous phantom (Fig. 3-7A&E) the highest strains were found at the thinnest part of the wall. This is corroborated theoretically by the Laplace theory: because the pressure gradient is largest at that spot [123], the highest stresses, and, consequently, the highest strains, are expected there. For the heterogeneous phantom (Fig. 3-7F-J) the highest strains were observed on the opposite side of the lumen, where the soft layer was situated. The “plaque region” was clearly visible for both the constructed and the theoretical strain images. The performance of the displacement projection method does not seem to be hampered by the eccentricity of the lumen nor by the soft region (Fig. 3-7). In fact, the image quality seems to improve. However, further investigations are required to determine the exact impact of heterogeneity and lumen eccentricity on the performance of the displacement compounding method. Another configuration difference

![Fig. 3-6. Estimated radial strain images for a homogeneous vessel phantom with a concentric lumen. Top row: simulations, bottom row: experiments. A and D were constructed with the reference method from 0° data. B and E were constructed by strain projection using data from beam steering angles of -45°, -30°, -15°, 0°, 15°, 30°, and 45°. C and F were obtained by displacement projection using data from beam steering angles of -30°, 0°, and 30°.](image-url)
that would generate circumferential motion is noncircularity of the lumen. This was not investigated because most in vivo observations of lumen shapes for vulnerable plaques do not deviate notably from circular, due to remodelling of the vessel wall [124,125]. Furthermore, it should be noted that the error introduced by one beam steering angle's contribution is often partially compensated by contributions from other beam steering angles in the regions of overlap.

The quality of the compound images might be further increased by adjusting the ratios at which the data from the various beam steering angles contribute. Because data from larger beam steering angles are of lower quality, it makes sense to reduce their contributions in regions where the data is overlapped by data from smaller beam steering angles. This can be achieved by introducing a weighting factor that decreases as the projection and/or beam steering angle increases. The principle of weighting for multi-angle compounding has been described by [126]. Weighting might also reduce the stitching artefacts at the segment transitions of the compound images (Fig. 3-6 and Fig. 3-7).

A limitation of the study is that the experiments were quasi-static. The amount of stitching artefacts would likely increase if the vessel moved between the frames needed for constructing a compound strain image. Before in vivo application of the proposed technique, the effect of motion should be investigated. This was beyond the scope of the current study.

Another point of discussion is the applicability of the method when the tissue has no homogeneous sound speed, which is probably the case in vivo. For large variations in the sound speed, the coordinate transformations become difficult and it will be harder to combine data from the various beam steering angles. Sophisticated techniques for local determination of sound speed, like [114], succeeded by pathlength corrections would then be required to properly combine the data from the various angles. However, because most of the sound speed problems are probably caused by the fat layer surrounding the artery, the in vivo situation might be sufficiently approximated by assuming only two layers (fat and vessel) with a different speed of sound.

### Table 3-2. Mean and standard deviations of SNR, and CNR, values of radial strain images constructed from experimental data of a homogenous vessel with a concentric lumen. Compound radial strain images constructed with the strain and displacement projection techniques are compared with the reference method.

<table>
<thead>
<tr>
<th>Beam steering angles (°)</th>
<th>Mean ± sd SNR, (dB)</th>
<th>Mean ± sd CNR, (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strain</td>
<td>Displ.</td>
</tr>
<tr>
<td>0</td>
<td>8.2 ± 1.7</td>
<td>9.7 ± 2.1</td>
</tr>
<tr>
<td>-30, 0, 15</td>
<td>8.2 ± 2.0</td>
<td>11.0 ± 2.3</td>
</tr>
<tr>
<td>-30, 30</td>
<td>9.1 ± 2.3</td>
<td>10.5 ± 0.9</td>
</tr>
<tr>
<td>-45, 0, 45</td>
<td>8.1 ± 1.5</td>
<td>10.8 ± 1.3</td>
</tr>
<tr>
<td>-30, -15, 0, 15, 30</td>
<td>9.2 ± 2.3</td>
<td>11.3 ± 0.7</td>
</tr>
<tr>
<td>-45, -15, 0, 15, 45</td>
<td>8.4 ± 1.7</td>
<td>11.9 ± 1.0</td>
</tr>
<tr>
<td>-45, -30, 0, 30, 45</td>
<td>8.6 ± 1.6</td>
<td>11.5 ± 1.3</td>
</tr>
<tr>
<td>-65, -30, -15, 0, 15, 30, 45</td>
<td>8.7 ± 1.7</td>
<td>12.2 ± 1.0</td>
</tr>
<tr>
<td>Reference: no beam steering</td>
<td>8.3 ± 1.7</td>
<td>10.9 ± 4.0</td>
</tr>
</tbody>
</table>

## Conclusions

A displacement projection based compounding procedure was developed for the construction of radial strain images for transverse cross sections of superficial arteries. With simulations and phantom experiments, it was shown that the novel method outperformed a previously developed strain projection compounding technique. Fewer acquisitions at smaller beam steering angles were required to construct radial strain images of higher quality. Initial results for homogeneous and "soft plaque" vessel phantoms with eccentric lumens showed that the new method also outperformed the older method for more challenging geometries.

## Acknowledgements

The authors acknowledge Philips Medical Systems for their support. The authors also thank Stichting Nationale Computerfaciliteiten (National Computing Facilities Foundation, NCF) for the use of supercomputer facilities, with financial support from the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (Netherlands Organization for Scientific Research, NWO).

## Appendix A: finite element modelling

To obtain theoretical radial strain images of the eccentric phantoms, finite element models (FEMs) were constructed using the partial differential equation toolbox of Matlab 2007a. The geometries of the modelled phantoms were equal to that shown in Fig. 3-6E&J. Poisson’s ratio for each layer was set to 0.495. The Young’s moduli were derived using the experimental method reported in Appendix B. To prevent rigid body translation and to obtain unique FEM solutions, a highly compressible and soft surrounding layer (ν = 0.001, E = 1 Pa) with a fixed outer boundary was added to the FEMs. FEM solutions were calculated under the assumption of plane strain for an intraluminal pressure increase of 4 mmHg.

## Appendix B: Young’s modulus estimation

To determine the Young’s moduli of the layers of the eccentric phantoms, additional homogeneous concentric phantoms were created from the various mixtures of gelatine and agar content that were used to create the eccentric phantoms. All phantoms were placed in a water tank and RF data were acquired at intraluminal pressure levels ranging from 0 to 25 mmHg in steps of 5 mmHg. At each pressure p, the inner diameter of the vessel r, was determined from the RF data. The Young’s moduli E were estimated from the slope of a linear fit (dp/dr) of the internal radii as function of the intraluminal pressures:

$$ E = \frac{dp}{dr} \left( \frac{a^2}{b^2 - a^2} \right) \left( \frac{b^2(1 + \nu)}{a} + (1 + \nu)(1 - 2\nu)a \right) $$

where ν is the Poisson’s ratio, a and b are the lumen and wall radii at 0 mmHg intraluminal pressure, respectively. ν was assumed to be 0.495. The Young’s modulus for the 12% gelatine – 0% agar solution, the 12% gelatine – 1% agar and the 12% gelatine – 4% agar solutions were found to be 11.1 kPa, 23.4 kPa and 118 kPa, respectively, which is in the same range measured previously with a dynamic mechanical analyser [101].
In this chapter a nonsegment based method is presented for noninvasive ultrasound strain imaging/elastography in superficial tissues, like arteries. It is shown that by projection of axial displacement estimates obtained at only three beam steering angles it is possible to accurately determine the full 2-D displacement vector and strain tensor. For each point in the image the combination of data from a nonsteered acquisition and acquisitions at a large positive and an equally large but negative steering angle enabled the most precise estimation of the strain components.

CHAPTER 4

Abstract

Ultrasound strain imaging is used to measure local tissue deformations. Usually, only strains along the ultrasound beam are estimated, because those estimates are most precise, due to the availability of phase information. For estimating strain in other directions we propose to steer the ultrasound beam at an angle, which allows estimating different projections of the 2-D strain tensor, while phase information remains available. This study investigates beam steering at maximally three different angles to determine the full 2-D strain tensor. The method was tested on simulated and experimental data of an inclusion phantom and a vessel phantom. The combination of data from a nonsteered acquisition and acquisitions at a large positive and an equally large but negative steering angle enabled the most precise estimation of the strain components. The method outperforms conventional methods that do not use beam steering.

Introduction

Physicians often use their tactile senses to distinguish malignant from benign tissue. The physician presses on tissue and perceives information about the stiffness and mobility of the tissue. This manual palpation technique can also be performed objectively using strain imaging techniques [90,127,128]. Strain imaging is based on exactly the same principle as palpation, i.e., hard tissue deforms/strains less than soft tissue when a certain force is applied to it. Strain imaging using ultrasound data was first described by [90]. In general, ultrasound data are acquired of tissue in two different states of deformation. The transition from the initial “predeformation” state to the subsequent “postdeformation” state can be mathematically described by a displacement vector field. Local estimates of the displacement vectors can be obtained by image registration techniques, like the Lagrangian speckle motion estimator [84], or by cross-correlating windows of the radio frequency data (or envelope data) acquired in the different states of deformation [59,73,90,129]. Strain is estimated by taking first-order spatial derivatives of the displacement estimates. For two dimensions the strain tensor equals [130]:

\[
\varepsilon_{ij} = \frac{1}{2} \left( \frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right), \quad \text{for instance } \varepsilon_{11} = \frac{1}{2} \left( \frac{\partial u_1}{\partial x_1} + \frac{\partial u_1}{\partial x_1} \right) \quad (4-1)
\]

where \(x\) are the coordinates, \(u\) are the estimated displacements, and \(\varepsilon\) are the various strain components. The indices \(i\) and \(j\) represent the measurement directions: along the beam (axial direction = 2), or perpendicular to the beam (lateral direction = 1). Usually, only the axial displacement \((u = u_2 = u)\) and strain components \((\varepsilon = \varepsilon_{11} = \varepsilon)\) are estimated from ultrasound acquisitions, because of the availability of phase information and the high resolution in the beam direction, which increase the performance of the strain estimation techniques. However, tissue often is anisotropic and the main axis of deformation does not always correspond to the axis direction (for instance, when trying to assess radial or circumferential strains in a carotid artery noninvasively [82, Ch. 2]). An accurate assessment of the lateral strain component \(\varepsilon_{12} = \varepsilon_{21} = \varepsilon_{xy}\) and shear strain components \((\varepsilon_{12} = \varepsilon_{21} = \varepsilon_{xy} = \varepsilon)\) is also desired in that case. As can be deduced from equation (4-1), all 2-D strain components can be derived when both axial displacements \((u_1 = u = u)\) and lateral displacements \((u_{12} = u = u)\) are known. However, the quality of the lateral displacement estimate is lower than that of the axial displacement estimate [59-63, Ch. 2]. This explains why many studies investigate approaches for improving lateral displacement estimates. Some authors propose interpolation of RF lines in-between the measured RF lines [61], or interpolation of the 2-D cross-correlation function [59,76], others assume tissue incompressibility [60].

Another interesting way to improve the lateral displacement and strain components as well as the axial components is by means of spatial compounding, as described by Varghese and co-workers [96,125,121,122]. This approach makes use of the possibility of deriving displacement components in any direction from axial displacements estimated using at least two different beam steering angles. Since displacements are estimated more accurately in the axial direction, the lateral displacements estimated by spatial compounding can also be more accurate. Our ultimate goal is to perform noninvasive radial and circumferential strain imaging for transverse cross sections of carotid arteries. This requires an accurate estimation of both displacement components. Therefore, we propose to use a similar technique. Since the carotid artery tissue moves, the frame rate should be kept as high as possible. For that reason, we only investigate the possibilities of beam steering for a maximum of three different beam steering angles. Three angles, because noninvasive strain imaging of carotid arteries has been shown to be feasible at a frame rate of about 30 Hz [82,67] and commercially available ultrasound systems are capable of single-angle imaging at about 100 Hz (10 x 33 Hz). As will be shown later on, the contribution of the axial and lateral displacement component to the angular component as a function of the beam steering angle is described by a cosine and a sine term, respectively. This implies that the estimation precision of the axial component decreases when the beam steering angle increases, whereas the precision of the lateral component increases. Theoretically, a beam steering angle of 90° would be most optimal for the lateral component. The theoretical advantage of using large beam steering angles for lateral strain estimation is however counteracted by a decrease in echo signal quality, due to increased grating lobe interference and reduced sensitivity of the transducer elements when the beam steering angle increases. Furthermore, larger beam steering angles result in a reduced imaging depth. In their most recent study, Rao and Varghese found an optimum at 15° of beam steering [131]. In that study the interference caused by grating lobes was not corrected for. Grating lobes are more pronounced at larger beam steering angles and inevitably cause problems in displacement estimation when not corrected for. Since grating lobes are frequency dependent, the interfering signal that is caused by grating lobes can be removed by adaptive low pass filtering [Ch. 2]. It can be expected that with such filtering, beam steering angles larger than 15° provide even better lateral displacement and strain estimates. Furthermore, Rao and Varghese [131] chose a fixed incremental angle of 1° and then increased the maximum angle. In that case a maximum beam steering angle of 20° implies that data from 41 different but smaller angles are contributing (-20°, -19°, …, 0°, …, 19°, 20°). In this way, the small angle contributions dominate (and perhaps deteriorate) the large angle contribution and thus the theoretical advantage of the large angle data is not fully exploited. To circumvent this, we started by using data from only two beam steering angles. Afterward, data from a third intermediate beam steering angle can be added.

This study investigates in which manner data from a maximum of three beam steering angles can be combined to obtain the most precise estimation of both displacement components and the full 2-D strain tensor for various types of superficial tissue. The analysis was performed for simulated and experimental data of an inclusion model and a vessel model using a commercially available ultrasound system with a radio frequency output and a linear array transducer. Beam steering angles of up to 45° were investigated and adaptive low pass filtering was applied to remove the interference caused by grating lobes.
CHAPTER 4

Methods

Simulations

Radio frequency (RF) data of a rectangular block with a stiff cylindrical inclusion and a homogeneous vessel with a concentric lumen were simulated before and after deformation using the Field II simulation program [120,121]. Field II requires the user to define a transducer, a scanning sequence and a matrix which contains the three-dimensional coordinates of scatterers with respect to the transducer surface. First, the definition of the "scatterer" matrices for the inclusion phantom and the vessel phantom will be described, followed by a description of the transducer and other imaging settings.

Inclusion phantom

Inclusion models are commonly used to assess the performance of strain estimation methods [59,96,127,133]. To create the pre- and postdeformation matrices of the inclusion phantom, first a finite element model (FEM) of a block of 4x4x4 cm³ was constructed. Over 20000 three-dimensional linear-elastic finite elements were defined and distributed over the block volume. All elements were assumed to be nearly incompressible (Poisson’s ratio, ν = 0.495) and isotropic. Their Young’s modulus was set to 15 kPa. To simulate the presence of a cylindrical inclusion (diameter of 1 cm) centered in the block, the Young’s modulus of the elements within the inclusion was set to 60 kPa. Next, the three-dimensional displacement field of the block after two % of vertical (axial) compression was calculated using the finite element software package SEPRAN (Sepra BV, The Hague, The Netherlands).

The predeformation scatterer matrix of the inclusion phantom was created by random distribution of two and a half million scatterers within a slice of 4x4x2 cm³ in the middle of the FEM block. The slice thickness of 1 cm was sufficient, because it exceeded the -16 dB elevational width of the ultrasound beam, which was 6 mm wide. The postdeformation position of each scatterer was defined as its predeformation position plus the axial and lateral displacement components as obtained from the FEM. Elevational motion was assumed to be zero.

Vessel phantom

The vessel phantom consisted of a homogeneous tube with a concentric lumen, an inner diameter of 3 mm and an outer diameter of 13 mm. The lumen center was located at an imaging depth of 0.9 cm. Because of the smaller volume of this model, for this phantom approximately 1 million scatterers were randomly distributed to obtain the predeformation scatterer positions. The postdeformation radial positions (Rᵢ) of each scatterer i with respect to the vessel axis, were calculated using the plane strain equation for a homogeneous tube with a concentric lumen [59,99,130]:

\[ R_i = r_i + \frac{\alpha i (p_i - p_0)}{E (b_i^2 - a_i^2)} \left( \frac{b_i^2 (1 + \nu)}{2} + (1 + \nu) (1 - 2\nu) r_i \right) \]

where \( p_i - p_0 \) is the intraluminal pressure change, \( r_i \) are the predeformation radial positions of a certain scatterer i with respect to the vessel axis, and \( a_i \) and \( b_i \) are the inner and outer radius of the tube, respectively. Poisson’s ratio \( \nu \) and Young’s modulus \( E \) were set to 0.495 and 50 kPa, respectively. These values are similar to those for nonfibrotic vascular tissue [122]. The pressure change was set to 0.532 kPa (4 mmHg). For these settings radial strains of about -1.5% occur at the lumen-vessel interface. These correspond well to the inter-frame strain values reported for a common carotid artery in vivo [86].

Ultrasound scanning settings

All transducer properties were maintained for both deformation states. A linear array transducer was simulated with a center frequency (f) of 8.7 MHz and 288 physical elements. The element pitch was 135 µm and the element height 6 mm. Each physical element was subdivided into 10 by 10 mathematical elements. During the simulations the sampling frequency was set to 117 MHz. Afterward, the simulated RF data were down sampled to 39 MHz to match the sampling frequency used in the experiments: each sample with a sample number that was not a multiple of three was deleted. The three times higher sampling rate during the simulations was chosen, because Field II uses digitally sampled versions of the excitation and impulse responses, which are continuous signals in reality. For a higher sampling frequency the discrepancy between Field II and reality is smaller, and thus, more realistic ultrasound signals were simulated. In the axial-elevational direction, a fixed focus of 2.5 cm was set and Hanning apodization was used in both transmit and receive. In the axial-lateral direction, fixed transmit foci of 2.5 mm and 1.6 cm were set for the vessel and the inclusion model, respectively. In transmit, no apodization was applied; in receive, dynamic focusing was applied with an F-number of 0.875. The maximum number of simultaneously active elements was restricted to 128. Lateral apodization with a Hamming window was applied in receive. Toward the edges of the transducer less elements were active in receive and transmission resembling a real transducer.

RF data of the cylindrical inclusion model were simulated in pre- and postdeformation state for beam steering angles ranging from -30° to +30° with an angular increment of 5°. The beam steering angle was restricted to 30° because this was the largest angle at which the inclusion remained entirely in the field of view. RF data of the vessel model were simulated for angles ranging from -45° to +45°, also with an angular increment of 5°. At a beam steering angle of 45° the vessel remained almost entirely in the field of view. Fig. 4.1 shows examples of the simulated ultrasound data and the field of view at maximum beam steered angle for both models. The strains that were used as input for the simulations are also presented. To investigate the performance of the displacement estimation techniques in the presence of noise, band-limited noise (3-11 MHz) was added to the simulated data of the block and vessel. Datasets with signal-to-noise ratios (SNR) of 5 dB, 10 dB, 20 dB and 50 dB were investigated.

Experiments

In analogy with the simulations, an inclusion model was constructed from polyvinyl alcohol (PVA) solutions [134,135]. A solution of 10% by weight PVA (Boom, Meppel, The Netherlands) was freeze-thawed twice to form a cube of 4x4x4 cm³ (Young’s modulus ~40 kPa [136]) and a 15% by weight solution of PVA was freeze-thawed three times to construct a stiff cylindrical inclusion with a diameter of 1 cm centered in the cube (Young’s modulus ~130 kPa [137]). 1% by weight SiC particles (9-15 µm, E. Merck, Darmstadt, Germany) were added to provide ultrasonic scattering. The freeze temperature was -19°C. After creation, the phantom was placed at room temperature to acclimatize. Once acclimatized, the phantom was positioned underneath a compressor plate. The top and bottom of the phantom were lubricated with ultrasound gel.
sonic gel to provide a slip free boundary condition. A Philips SONOS 7500 ultrasound machine equipped with a linear array transducer (11-3L, f₀ = 8.7 MHz, pitch = 135 µm) and an RF interface was used to collect RF data of the phantom through a hole in the compression plate. A preload was applied to the phantom by moving the compressor plate 4 mm down to make sure that the contact with the ultrasound gel was maintained. This preload situation was defined as the predeformation state. RF data were recorded in this state and after applying an additional 0.5%, 1%, 2% and 4% vertical deformation for beam steering angles ranging from -30° to 30° with an angular increment of 5°. The total imaging sequence was repeated seven times to be able to assess reproducibility. The multiple levels of deformation were applied to investigate the performance of the displacement estimation technique for various levels of strain. Data were digitized at a sampling rate of 39 MHz.

Also in analogy with the simulations, a homogeneous vessel phantom with a concentric lumen was constructed as described in chapter 2. The phantom was placed in a water tank and connected to a water column. Again, a pressure step of 4 mmHg was applied to deform the tissue, which also resulted in radial strains of about -1.5% at the lumen-vessel interface. RF data were recorded for beam steering angles ranging from -45° to +45° with an angular increment of 15° using the same ultrasound system and transducer as used in the inclusion phantom experiments. RF data of eight different transverse cross sections were acquired to assess reproducibility. RF data of eight different transverse cross sections were acquired to assess reproducibility.

Displacement estimation

Before performing displacement estimation, all RF data were preprocessed (Ch. 2): first, the data were filtered with an adaptive low-pass filter to remove artifacts caused by grating lobes. Second, the skewness of the data grid was corrected for. Angular axial and lateral displacements for all sets of pre- and postdeformation RF data were calculated by 2-D cross-correlation of windows of RF data in an iterative procedure. Six iterative steps were performed to improve the accuracy of the cross-correlation procedure. The first four iterations consisted of a coarse-to-fine method [59,72]. Initially, “coarse” displacements were estimated by cross-correlating large windows of envelope data (inclusion model) or RF data (vessel model). In the subsequent iterations, window sizes were halved such that “finer” displacements were obtained. RF data were used for both the inclusion model and the vessel model for these “finer” iterations.

![Fig. 4-1. A: Simulated B-mode image and B: “true” vertical strain image of the block model with inclusion. C: Simulated B-mode image and D: “true” radial strain image of the vessel model. The dashed lines denote the borders of the region that was within the field of view for all beam steering angles.](image)

“Rounded” displacement estimates of preceding “coarser” iterations were used to guide the cross-correlation function to the correct peak in each new iteration. The window sizes and the percentages of window overlap that were used for the inclusion model and the vessel model are shown in Table 4-1. The fifth iteration consisted of subsample “aligning” of the postdeformation data. The peak of the cross-correlation functions found during the fourth iteration was interpolated using a 2-D parabolic function to obtain subsample displacements [59,76]. These subsample displacements were used to align the postdeformation data with the predeformation data on the subsample scale after which 2-D cross-correlation was repeated. In the final iteration, local temporal stretching of the postdeformation data was performed in the axial direction to further enhance the cross-correlation procedure [59,138]. The axial stretch factors were obtained by applying a 1-D nine-point least squares strain estimator (LSQSE) to the displacement estimates obtained in the fifth iteration [48]. After each iteration, the axial and lateral displacement estimates were median filtered to remove outliers. The window size of the median filter was 9 by 9 displacement estimate values.

Strain tensor estimation

From now on the α lateral displacement component will be referred to as the horizontal displacement component and the o α axial displacement component will be referred to as the vertical displacement component. We first focused on improving the horizontal estimates. Since we only want to use a maximum of three different beam steering angles, we have three options for estimation of the horizontal displacement components: 1) from data at a single beam steering angle; 2) from data of two different beam steering angles; 3) from data obtained at α° and two other beam steering angles.

When data from only one beam steering angle are used, horizontal displacements (u, α) and vertical displacements (u, o) can be derived by rotating the angular axial and lateral displacement estimates to the α° grid:

\[
\begin{bmatrix}
    u_{ax}
    \\
    u_{lat}
\end{bmatrix}
= \begin{bmatrix}
    \cos \alpha & \sin \alpha \\
    -\sin \alpha & \cos \alpha
\end{bmatrix}
\begin{bmatrix}
    u_{ax,\alpha}
    \\
    u_{lat,\alpha}
\end{bmatrix}
\]

where u, ax,α, and u, lat,α are the axial and lateral displacement estimates determined at a certain beam steering angle α, as illustrated in Fig. 4-2A.

![Table 4-1. Pre- and postdeformation window settings for the displacement estimation algorithm for the inclusion model and the vessel model.](image)
CHAPTER 4

NONSEGMENT BASED COMPOUNDING OF AXIAL DISPLACEMENTS

Horizontal displacements were calculated for every possible one-, two- and 0° plus two-angle combination using the aforementioned equations. Subsequently, root mean squared errors (RMSE) of the horizontal displacement estimates were calculated for each combination:

\[
RMSE = \sqrt{\frac{\sum_{i=1}^{N} (\hat{u}_i - u_i)^2}{N}} \tag{4-5}
\]

where \(\hat{u}_i\) are the displacements that were used as input for the simulations and \(u_i\) are the estimated displacements. \(N\) is the number of points taken into account. RMSE was calculated for the simulated data of both the inclusion model and the vessel model for all four SNR levels. RMSE was calculated only for the region which was in the field of view for all beam steering angles (Fig. 4-3).

RMSE values cannot be obtained for experimental data, because the exact local displacement inputs are unknown. However, a commonly used approach to quantify image quality for experimental data of an inclusion model is by determining elastographic signal-to-noise ratios (SNR) and elastographic contrast-to-noise ratios (CNR) for regions with homogeneous strains [98]. To obtain the horizontal strains, a 25-point 1-D LSQSE [48] was applied horizontally to the estimated horizontal displacement field. Horizontal SNR and CNR were calculated for all deformation levels and for each repeated measurement. The regions of homogeneous strain that were used to calculate the SNR (region 1) and CNR (region 1 and 2) are indicated in Fig. 4-3A. For the vessel phantom experiments it is not possible to calculate SNR and CNR based on horizontal information only, since there are no large regions with homogeneous horizontal strain values (Fig. 4-3B).

The RMSE and SNR and CNR analysis will reveal which combination of beam steering angles results in the best horizontal displacement and strain estimates. With respect to imaging of the full strain tensor, also the vertical displacement component needs to be estimated. The horizontal component measured at \(0^\circ\) already is very precise. However, the precision might be increased further by adding information from the beam steering angles used in the estimation of the horizontal displacements. Only a select number of possibilities for vertical displacement estimation were investigated. For instance, if beam steering angles \(\alpha_1\) and \(\alpha_2\) resulted in the most precise horizontal displacement estimates, then three combinations of angles for vertical displacement estimation were investigated: 1) using data from \(0^\circ\) only; 2) using data from \(\alpha_1\) and \(\alpha_2\) and 3) using data from \(\alpha_1\), \(0^\circ\) and \(\alpha_2\). All options were compared by calculating vertical displacement RMSE values (4-6). This was performed for the simulated data of both phantoms. It should be noticed that the combinations of data from \(\alpha_1\) and \(0^\circ\) beam steering, and \(\alpha_2\) and \(0^\circ\) beam steering do not require an investigation, since they provide exactly the same vertical displacements as a single \(0^\circ\) acquisition.

For the angle combination that resulted in the most precise horizontal and vertical displacement estimates, all components of the strain tensor were calculated and strain images were constructed. These images were compared with strain images constructed from a single \(0^\circ\) acquisition. For the vessel model, 9-point 1-D LSQSEs were applied horizontally and vertically to obtain the horizontal, vertical and shear strain components [Ch. 2]. For the inclusion model, 9-point 1-D LSQSEs were applied vertically and 25-point 1-D LSQSEs were applied horizontally. For the inclusion model, a larger LSQSE size in the horizontal direction was chosen, because

---

**Fig. 4-2.** Consider a certain point in tissue which displaces along the vector named “Total displacement” during deformation, then the horizontal and vertical displacement components can be determined either from A: the axial and lateral displacement components measured at a single beam steering angle, or from B: the axial displacement components measured at multiple beam steering angles.

For two or more beam steering angles, both the horizontal and vertical component can be derived from only axial displacements estimated at different beam steering angles without using lateral displacement estimates [132]:

\[
\begin{bmatrix}
\hat{u}_{ax,1} \\
\hat{u}_{ax,2} \\
\end{bmatrix}
= \begin{bmatrix}
\cos \alpha_1 & \sin \alpha_1 \\
\cos \alpha_2 & \sin \alpha_2 \\
\vdots & \vdots \\
\cos \alpha_n & \sin \alpha_n \\
\end{bmatrix}
\begin{bmatrix}
\hat{q}_{1} \\
\hat{q}_{2} \\
\vdots \\
\hat{q}_{n} \\
\end{bmatrix}

\text{where } A = \begin{bmatrix}
\cos \alpha_1 & \sin \alpha_1 \\
\cos \alpha_2 & \sin \alpha_2 \\
\vdots & \vdots \\
\cos \alpha_n & \sin \alpha_n \\
\end{bmatrix}
\]

where \(A^T\) is the transposed version of matrix \(A\), and \(\alpha_i\) to \(\alpha_n\) are the various beam steering angles. For two beam steering angles, this equation reduces to:

\[
\begin{align*}
\hat{u}_{ax,1} &= \frac{\hat{u}_{ax,1} \sin \alpha_2 - \hat{u}_{ax,2} \sin \alpha_1}{\sin (\alpha_2 - \alpha_1)} \\
\hat{u}_{ax,2} &= \frac{\hat{u}_{ax,1} \cos \alpha_2 - \hat{u}_{ax,2} \cos \alpha_1}{\sin (\alpha_2 - \alpha_1)} \\
\end{align*} \tag{4-5}
\]

Fig. 4-2B illustrates the axial displacement based reconstruction for two beam steering angles.
of the noisier estimates in that direction. This was not performed for the vessel phantom given its smaller dimensions.

Until now, the precision analysis was performed separately for the horizontal and vertical component. To assess the performance of the beam steering method for a combination of the two components, radial and circumferential strains were calculated from the experimental vessel data. These radial and circumferential strains were obtained by rotating the 2-D strain tensor using rotation matrices \([139]\). Multiples measures to assess the precision of the strain components were defined and calculated. First of all, radial and circumferential SNR\(_e\) and CNR\(_e\) were calculated using strain values located at circles with radii of 3 mm and 5 mm with respect to the lumen center (Fig. 4-3C) according to the method described in chapter 2. Additionally, two other measures for estimation precision were introduced and calculated. The first one was based on the fact that the radial and circumferential strains decay quadratic as a function of the vessel radius. A quadratic function is fitted through the strain values and the deviation (RMSE) of the strain values from the fit is calculated using equation (4-6) with \(\hat{u}_i\) the radial/ circumferential strains according to the fit, and \(u_i\) the estimated radial/circumferential strains. The second measure was based on the fact that the shear strain (according to \(u_i\) should be equal zero for every point of the cross section in a plane strain situation. Again, (4-6) was used to calculate an RMSE value, with \(\hat{u}_i\) equal to zero, and \(u_i\) the estimated shear strains. All quality measures were calculated for each of the eight vessel cross sections.

Results

Fig. 4-4 partially shows the results of the root mean squares analysis for horizontal displacement estimation. The left plot shows results for the simulations of the inclusion model with a SNR of 10 dB. The right plot shows results for the simulations of the vessel model with a SNR of 10 dB. The RMSE analysis was carried out for every possible one-, two- and 0°+two-angle combination. The values on the diagonal from top left to bottom right correspond to the RMSE analysis for single-angle acquisitions. All other values represent the two-angle combinations.

The results for the 2 angles + 0° combinations are not shown, but the pattern is similar. In general the addition of the 0° contribution leads to higher RMSE values, and thus less accurate horizontal displacement estimates. As can be observed in Fig. 4-4 the best results are obtained for positive and negative angles that are exactly opposite in sign. In other words, horizontal displacements are estimated most accurately for symmetric angle combinations, for example -15° and 15°. From a mathematical point of view it should be noted that the 0° acquisition does not contribute to the estimation of the horizontal displacement component when two symmetric beam steering angles are used, (4-6) is exactly equal to Fig. 4-5B in that case.

Fig. 4-5 illustrates the performance of the technique at the various noise levels. Only the results for symmetric angle combinations are shown. The values at 0° correspond to the lateral displacement estimates obtained in a conventional way from a single 0° acquisition. As can be observed the performance increases as the beam steering angle increases for the inclusion model as well as for the vessel model. The beam steering approach remains successful at low signal-to-noise levels. The RMSE reduction achieved by beam steering with respect to the 0° single-angle acquisition increases when the signal-to-noise level decreases. It should be noted that the y-axes are logarithmic.

Fig. 4-6 shows the mean SNR\(_e\) and CNR\(_e\) values for the repeated inclusion model experiments \((n = 7)\) at vertical deformation levels of 0.5%, 1%, 2% and 4% for all symmetric angle combinations. As can be observed, the shape of the curves is similar for all levels of deformation. In general, the precision of the horizontal displacement estimation increases with increasing beam steering angle, after a short decrease in precision at 5° of beam steering. Compared to the 0° acquisitions beam steering improves the SNR\(_e\) of the horizontal estimates at all deformation levels with at least 1.9 dB. The CNR\(_e\) is improved with at least 8.3 dB. The estimates improve most at low strain levels: increases of 8.0 dB in SNR\(_e\) and 22.7 dB in CNR\(_e\) at a vertical compression level of 0.5%.
The increase in the precision of the horizontal displacement estimation with increasing beam steering angle was also observed in the RMSE analysis of the vessel phantom. For the vessel application it should however be noted that although the RMSE keeps on decreasing when the beam steering angle increases, angles of -45° and 45° are not very realistic in practice. A real carotid artery has a radius of about 1 cm with a lumen center that is positioned at a depth of about 2 cm. A linear array transducer with an imaging width of 3.5 cm would imply that the maximum beam steering angle at which the vessel cross section remains completely in the field of view is ~30°, see Appendix A. Therefore to investigate which option is best for vertical displacement estimation, all options were compared for simulated data from beam steering angles of -30°, 30°, and 0° for both the inclusion and the vessel model. The results of the corresponding RMSE analysis for the vessel and the inclusion phantom are shown in Table 4-2 and Table 4-3, respectively.

Both Table 4-2 and Table 4-3 show that the use of data that were obtained at large positive and negative beam steering angles does not lead to an improvement in vertical displacement estimation accuracy. In fact, using only data from the two beam steered acquisitions almost doubles the error in displacement estimation. The combination of estimates from all three angles gives intermediate results, due to the 0° component.

Fig. 4-7 shows strain images that were constructed with and without beam steering for the simulated as well as the experimental data of the inclusion model. Furthermore, the FEM input strain images are shown on the left. As can be observed the proposed beam steering technique improves all horizontal displacement based strain tensor images in the simulations and in the experiments. The inclusion is much better delineated in the horizontal strain images constructed with beam steering and also the shear strain pattern becomes much clearer in those images.

Fig. 4-8 shows examples of radial, circumferential and shear strain images that were derived with and without beam steering for the vessel phantom. Again, it is clearly visible that the accuracy of the strain estimates increases when beam steering is applied. The resemblance with the theoretical images, which are shown on the left, is much better. The shear strain image is probably the most illustrative. As explained, the shear strain should be equal to zero for every point of the cross section in a plane strain situation. As can be observed the shear strain values of the images estimated without beam steering are less close to zero.

Table 4-4 shows the results of the performance analysis of the beam steering method for the experimental vessel data. The values of the various precision measures averaged over the eight cross sections are presented in this table. All measures reflect the increase in image quality that was observed in Fig. 4-8. Again the image quality increases with increasing beam steering angles, although slightly lower values can be observed for the beam steering combination with positive and negative angles. This also clearly shows the intermediate results that were expected from Table 4-3.

Discussion

From the Results section it becomes clear that combination of three beam steering angles allows a more precise assessment of the full 2-D strain tensor than that can be obtained from a single angle.

Table 4-2. Root mean squared errors (RMSE) of vertical displacements that were estimated from simulated data of an inclusion model. Various ways to combine data from beam steering angles of -30°, 0° and 30° were investigated. The RMSE analysis was repeated for signal-to-noise levels of 5, 10, 20 and 50 dB.

<table>
<thead>
<tr>
<th>Angles</th>
<th>SNR = 50 dB</th>
<th>SNR = 20 dB</th>
<th>SNR = 10 dB</th>
<th>SNR = 5 dB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0°</td>
<td>0.77 μm</td>
<td>0.78 μm</td>
<td>0.87 μm</td>
<td>1.05 μm</td>
</tr>
<tr>
<td>-30°, 0°, 30°</td>
<td>2.59 μm</td>
<td>2.57 μm</td>
<td>2.64 μm</td>
<td>2.88 μm</td>
</tr>
<tr>
<td>-30°, 0°, 30°</td>
<td>1.44 μm</td>
<td>1.43 μm</td>
<td>1.48 μm</td>
<td>1.65 μm</td>
</tr>
</tbody>
</table>
Table 4-3. Root mean squared errors (RMSE) of vertical displacements that were estimated from simulated data of a vessel model. Various ways to combine data from beam steering angles of -30°, 0° and 30° were investigated. The RMSE analysis was repeated for signal-to-noise levels of 5, 10, 20 and 50 dB.

<table>
<thead>
<tr>
<th>Angles</th>
<th>Vert. RMSE SNR = 50 dB</th>
<th>Vert. RMSE SNR = 20 dB</th>
<th>Vert. RMSE SNR = 10 dB</th>
<th>Vert. RMSE SNR = 5 dB</th>
</tr>
</thead>
<tbody>
<tr>
<td>0°</td>
<td>0.63 μm</td>
<td>0.69 μm</td>
<td>0.73 μm</td>
<td></td>
</tr>
<tr>
<td>-30°, 30°</td>
<td>1.02 μm</td>
<td>1.04 μm</td>
<td>1.17 μm</td>
<td></td>
</tr>
<tr>
<td>-30°, 0°, 30°</td>
<td>0.77 μm</td>
<td>0.77 μm</td>
<td>0.87 μm</td>
<td></td>
</tr>
</tbody>
</table>

conventional 0° acquisition only. RMSE improvements of up to 27% and 55% were found for the horizontal displacement estimates of the inclusion and vessel simulations at an SNR of 10 dB, respectively (Fig. 4-5). Also, for experimental data beam steering leads to an improvement of all horizontal displacement based strain components. The radial SNR\(_r\) and CNR\(_r\) and the circumferential SNR\(_c\) and CNR\(_c\) increased by 4.0 dB, 9.8 dB, 6.4 dB and 14.0 dB, respectively. These increases were larger than the 1.1 dB, 6.6 dB, 2.6 dB and 5.2 dB increases reported with the beam steering technique of chapter 2. Moreover, in the study of that chapter acquisitions at seven different beam steering angles were required to achieve the increase in image quality, whereas only three beam steered acquisitions are required in the present study. Furthermore, a large advantage of the present technique is that no assumptions about tissue compressibility or isotropy are made, whereas incompressibility was assumed in the former study. Finally, it should be noted that the current method can be applied to all kinds of tissues as shown by the inclusion phantom, whereas the previously developed method was applicable only to circular structures.

The finding that the precision of vertical displacements did not improve when data from large beam steering angles were added is not surprising. As mentioned in the introduction, theoretically the contribution of the vertical component to the angular axial displacements decreases when the beam steering angle increases. Furthermore, the image quality decreases for larger beam steering angles, due to decreased sensitivity of the transducer and due to the larger amount of filtering that is required to remove grating lobes. The only way to improve the accuracy of the vertical displacement component is to add information from small beam steering angles. It has been reported earlier that vertical displacement estimates can be improved in this way as long as the maximum beam steering does not exceed 10° [131]. The addition of data from such small beam steering angles was however not an option due to our choice to use only three beam steering angles. Furthermore, the vertical displacement estimates are already of better quality than the horizontal displacement estimate.

With regard to Fig. 4-5, it was noted that the beam steering technique improved the estimation precision for horizontal displacements especially for low signal-to-noise ratios with respect to the results obtained by conventional 0° horizontal (lateral) displacement estimation. A plausible explanation for this observation is that although high amounts of noise were added to the signal, phase information can still be used for displacement estimation when perform-
CHAPTER 4

simulations and experiments. Furthermore, out of plane motion was not present in the simulation precision above 30° are not very large, it is probably more useful to choose beam steering angles of 30° and 45° of beam steering for the used transducer. Since the increases or decreases in estimation precision are small but positive beam steering angle enables a more precise estimation of the full 2-D strain tensor than that can be obtained with a single 0° acquisition. For beam steering angles up to 45° it appears that the larger the angle the more accurate the derived horizontal (lateral) displacements, provided that the interfering signal of grating lobes is removed. For the commercial linear array transducer used in this study the best performance was observed for steering angles close to 30°. The maximum steering angle was mainly determined by the depth of the tissue to image. The method can be applied for all types of superficial tissue and showed to function correctly for strains ranging from 0 to 2% horizontally and 0 to 4% vertically. The beam steering approach outperformed conventional nonsteered strain imaging even at very low signal-to-noise levels of 5 dB.

Conclusions

The combination of RF data from beam steering angles of 0°, a large negative and an equally large but positive beam steering angle enables a more precise estimation of the full 2-D strain tensor than that can be obtained with a single 0° acquisition. For beam steering angles up to 45° it appears that the larger the angle the more accurate the derived horizontal (lateral) displacements, provided that the interfering signal of grating lobes is removed. For the commercial linear array transducer used in this study the best performance was observed for steering angles close to 30°. The maximum steering angle was mainly determined by the depth of the tissue to image. The method can be applied for all types of superficial tissue and showed to function correctly for strains ranging from 0 to 2% horizontally and 0 to 4% vertically. The beam steering approach outperformed conventional nonsteered strain imaging even at very low signal-to-noise levels of 5 dB.

Acknowledgments

This work is supported by the Dutch Technology Foundation (STW), project NKG 07589.

Table 4-4. Results of the precision analysis for radial, circumferential and shear strain images constructed without and with beam steering for experimental data of a homogeneous concentric vessel phantom. Mean and standard deviations of various precision measures are presented.

<table>
<thead>
<tr>
<th>Quality measure</th>
<th>0°</th>
<th>-15° &amp; 15°</th>
<th>-30° &amp; 30°</th>
<th>-45° &amp; 45°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial RMSE (e-4 %)</td>
<td>17.5 ± 1.8</td>
<td>10.2 ± 0.7</td>
<td>9.5 ± 0.7</td>
<td>9.8 ± 0.7</td>
</tr>
<tr>
<td>Radial CNR (dB)</td>
<td>10.4 ± 1.6</td>
<td>12.8 ± 1.2</td>
<td>14.4 ± 1.5</td>
<td>14.1 ± 1.9</td>
</tr>
<tr>
<td>Circ RMSE (e-4 %)</td>
<td>20.1 ± 1.3</td>
<td>9.8 ± 1.0</td>
<td>7.9 ± 0.9</td>
<td>8.0 ± 0.8</td>
</tr>
<tr>
<td>Circ CNR (dB)</td>
<td>8.0 ± 0.9</td>
<td>11.9 ± 1.0</td>
<td>14.4 ± 1.1</td>
<td>13.9 ± 0.8</td>
</tr>
<tr>
<td>Shear RMSE (e-4 %)</td>
<td>10.0 ± 1.7</td>
<td>19.1 ± 1.8</td>
<td>24.0 ± 1.8</td>
<td>23.7 ± 1.5</td>
</tr>
</tbody>
</table>

In general, Fig. 4-4, Fig. 4-5, Fig. 4-6 and Table 4-4 show that the accuracy of the horizontal displacement estimates keeps on improving for larger beam steering angles, although Table 4-4 shows that there is a slight decrease in estimation accuracy when increasing the beam steering angle over 30°. There also seems to be a slight increase in the RMSE values of the inclusion phantom at SNR levels above 10 dB when going from 25° to 30° of beam steering.

The combination of RF data from beam steering angles of 0°, a large negative and an equally large but positive beam steering angle enables a more precise estimation of the full 2-D strain tensor than that can be obtained with a single 0° acquisition. For beam steering angles up to 45° it appears that the larger the angle the more accurate the derived horizontal (lateral) displacements, provided that the interfering signal of grating lobes is removed. For the commercial linear array transducer used in this study the best performance was observed for steering angles close to 30°. The maximum steering angle was mainly determined by the depth of the tissue to image. The method can be applied for all types of superficial tissue and showed to function correctly for strains ranging from 0 to 2% horizontally and 0 to 4% vertically. The beam steering approach outperformed conventional nonsteered strain imaging even at very low signal-to-noise levels of 5 dB.

Acknowledgments

This work is supported by the Dutch Technology Foundation (STW), project NKG 07589.
Appendix A: field of view for a beam steered linear array transducer

Fig. 4-9 schematically shows the field of view for a linear array transducer that is beam steered to image a vessel cross section from a positive and an equally large but negative beam steering angle, $\alpha$. The maximum angle $\alpha$ for which the entire vessel cross section remains in the field of view can be calculated. From basic goniometry on the dark gray thick-lined triangle and successively on the light gray triangle it follows that:

$$
\tan \alpha = \frac{1/2A - x}{D + y} = \frac{1/2A - r \cos \alpha}{D + r \sin \alpha}
$$

(4-7)

where $A$ is the image width, $D$ is the distance from the transducer to the vessel center and $r$ is the radius of the vessel. $x$ and $y$ correspond to the distances that are shown in Fig. 4-9. $x$ and $y$ were introduced to simplify the equations. Rewriting gives:

$$
1/2A \cos \alpha - D \sin \alpha - r = 0
$$

(4-8)

By solving this equation for $\alpha$, the maximum applicable beam steering angle can be determined. For our 11-3 transducer which had an imaging width of 3.5 cm ($A$) and a vessel centered at a depth of 2 cm ($D$) with a radius of 0.5 cm, this resulted in a maximum beam steering angle of $\sim 30^\circ$.

![Diagram](image)

**Fig. 4-9. Schematic overview of a vessel that is imaged from two beam steering angles that are opposite in sign. The maximum beam steering angle ($\alpha$), for which the vessel remains entirely in the field of view, depends on the imaging width of the transducer ($A$), the depth at which the vessel is located ($D$), and the radius of the vessel ($r$).**
PART II: STRAIN ESTIMATION IMPROVEMENTS
All noninvasive vascular elastography methods described in the previous chapters make use of linear array data obtained at beam steering angles of ~30°. It is generally known that the use of large beam steering angles leads to the generation of grating lobe artifacts. Grating lobes are higher order ultrasound beams in a direction other than the main beam which signal is interpreted as originating from the main beam. In chapter 2 it was shown that grating lobes and the corresponding artifacts can be removed entirely by low-pass filtering. In this chapter the influence of grating lobe filtering on strain estimation is investigated more thoroughly. It is shown that for optimal strain estimation accuracy it is better not to set the frequency cutoff of the low-pass filter too low. The optimal low-pass filtering frequency is a tradeoff between minimal grating lobe signal and maximal main lobe signal.

Abstract

Ultrasound displacement estimation accuracy can be improved by compounding of displacements estimated at multiple beam steering angles. However, with increasing angle and ultrasound frequency grating lobe artifacts increase. Grating lobes can be fully removed by low-pass filtering. However, this also removes part of the main lobe signal. In this study it was observed that for optimal displacement estimation accuracy it is beneficial not to remove the grating lobe signal entirely by low-pass filtering before displacement estimation. The optimal low-pass filtering frequency is a tradeoff between minimal grating lobe signal and maximal main lobe signal.

Introduction

Ultrasound strain imaging is a technique that is used to measure active or passive deformations of tissue [90]. Multiple methods have been developed to estimate local strains in the tissue [59,140,144]. The method exploited in this paper is a cross-correlation based method [59]. The cross-correlation function between kernels of ultrasound data acquired before and after the deformation of the tissue is calculated. The location of the peak of the cross-correlation function with respect to the center coordinate of this function corresponds to the local displacement of the tissue in the kernel. By repeating this procedure for several kernels representing subsequent regions in depth and width, a 2-D displacement field of the tissue is obtained. First-order spatial derivation can be applied to these fields to obtain the strain tensor [48].

To improve the estimation precision of the displacement and subsequent strain estimation a technique called angular compounding can be used [96,126,332,144,143,Ch. 4]. Angular compounding is a method which combines displacement estimates obtained at several insonification angles to improve the displacement component in a certain direction. The vertical displacement component (perpendicular to the transducer footprint) can be most optimally improved by combining axial (along the beam direction) displacements estimated from small angle insonifications. Combining axial displacements from angles up to a maximum angle of around 10° to 15° results in the most accurate vertical displacement estimate [96,131]. The largest improvement in horizontal (direction parallel to the transducer footprint) displacement accuracy is achieved by combining data from large insonification angles of more than 20° [Ch. 4]. RMSE improvements of up to 55% were found for the horizontal displacement estimates in that study.

To generate an insonification at a nonzero angle for a linear array transducer, a technique called beam steering is applied. Beam steering implies adjusting the electronic delays of the transducer elements. To generate an insonification at a nonzero angle for a linear array transducer, a technique called beam steering is applied. Beam steering implies adjusting the electronic delays of the transducer elements. For a transducer which has an element pitch larger than half the wavelength interference of the signal of the individual elements, travels at an angle other than perpendicular to the transducer footprint. For a transducer which has an element pitch larger than half the wavelength interference of the signal of the individual elements, travels at an angle other than perpendicular to the transducer footprint. For a transducer which has an element pitch larger than half the wavelength interference of the signal of the individual elements, travels at an angle other than perpendicular to the transducer footprint. For a transducer which has an element pitch larger than half the wavelength interference of the signal of the individual elements, travels at an angle other than perpendicular to the transducer footprint. For a transducer which has an element pitch larger than half the wavelength interference of the signal of the individual elements, travels at an angle other than perpendicular to the transducer footprint. For a transducer which has an element pitch larger than half the wavelength interference of the signal of the individual elements, travels at an angle other than perpendicular to the transducer footprint. For a transducer which has an element pitch larger than half the wavelength interference of the signal of the individual elements, travels at an angle other than perpendicular to the transducer footprint. The element sensitivity, $D_{\text{element}}$, as a function of the angle of incidence $\theta$, is described by [68,144]:

$$D_{\text{element}}(\theta) = \sin(c \frac{w}{\lambda} \sin \theta)$$  \hspace{1cm} (5-2)

where $w$ is the width of the element. Secondly, the angle of appearance of the grating lobe artifact is smaller with respect to the $0^\circ$ beam direction when the beam steering angle increases, as can be derived from (5-1). This smaller angle of appearance combined with (5-2) leads to an increased intensity of the grating lobe signal. Furthermore, the portion of the ultrasound beam spectrum that adds to the grating lobe signal also increases when the beam steering angle increases. As can be appreciated from (5-1) the angle of appearance of the grating lobe is frequency dependent. For lower frequencies the grating lobe signal appears at a larger angle. Fig. 5-18 illustrates the frequency dependence of the grating lobes generated for a beam steered angle of 45 degrees for the same phantom.

In a previous study we determined that the frequency component in the spectrum $f_{\text{cutoff}}$ below which no grating lobe signal exists can be calculated using [Ch. 2]:

$$f_{\text{cutoff}} = \frac{c}{(1 + \sin(\alpha))Dx}$$  \hspace{1cm} (5-3)

In that study all data were low-pass filtered before displacement and strain estimation using this cutoff frequency. Filtering removed all grating lobe signal. However, the transducer used in that study had a very small pitch of only 135 $\mu$m. Usually commercial transducers have a pitch of 200 to 300 $\mu$m. Table 5-1 shows the cutoff frequencies for different pitches and different beam steering angles calculated using (5-3). This information combined with the fact that linear array transducers often have center frequencies around 7 MHz suggests that it is not possible to use information from beam steering angles of more than 15°, because otherwise the center frequency of the ultrasound beam is filtered out.

**Fig. 5-1.** A: Log compressed envelope images of a homogeneous vessel-mimicking phantom obtained at beam steering angles of 15°, 30° and 45°. B: Log compressed envelope images of the same phantom at a beam steering angle of 45° after low-pass filtering with filters with high-end cutoff points of 6.5 MHz, 8.5 MHz and 10.5 MHz.
Table 5-1. Frequencies (MHz) below which no grating lobes exist as a function of transducer element pitch and beam steering angle. A speed of sound of 1540 m/s was assumed.

<table>
<thead>
<tr>
<th>Pitch (μm)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>235</td>
<td>11.4</td>
<td>10.5</td>
<td>9.7</td>
<td>9.1</td>
<td>8.5</td>
<td>8.0</td>
<td>7.6</td>
<td>7.2</td>
<td>6.9</td>
<td>6.7</td>
</tr>
<tr>
<td>250</td>
<td>10.3</td>
<td>9.4</td>
<td>8.7</td>
<td>8.2</td>
<td>7.7</td>
<td>7.2</td>
<td>6.8</td>
<td>6.5</td>
<td>6.2</td>
<td>6.0</td>
</tr>
<tr>
<td>200</td>
<td>7.7</td>
<td>7.1</td>
<td>6.6</td>
<td>6.1</td>
<td>5.7</td>
<td>5.4</td>
<td>5.1</td>
<td>4.9</td>
<td>4.7</td>
<td>4.5</td>
</tr>
<tr>
<td>245</td>
<td>6.3</td>
<td>5.8</td>
<td>5.4</td>
<td>5.0</td>
<td>4.7</td>
<td>4.4</td>
<td>4.2</td>
<td>4.0</td>
<td>3.8</td>
<td>3.7</td>
</tr>
<tr>
<td>250</td>
<td>6.2</td>
<td>5.7</td>
<td>5.2</td>
<td>4.9</td>
<td>4.6</td>
<td>4.3</td>
<td>4.1</td>
<td>3.9</td>
<td>3.7</td>
<td>3.6</td>
</tr>
<tr>
<td>300</td>
<td>5.1</td>
<td>4.7</td>
<td>4.4</td>
<td>4.1</td>
<td>3.8</td>
<td>3.6</td>
<td>3.4</td>
<td>3.3</td>
<td>3.1</td>
<td>3.0</td>
</tr>
</tbody>
</table>

However, the question is whether it is really necessary to filter the entire grating lobe signal before performing displacement or strain estimation. Perhaps the filter frequency can be set a little higher such that the signal over a larger band of frequencies can be used for the displacement estimation. This study investigates the accuracy of displacement estimation using ultrasound data filtered at various cutoff frequencies. The goal is to determine the frequency cutoff point above which the increase in displacement estimation accuracy due to the addition of main lobe signal is overshadowed by grating lobe distortion. To this end, simulations and experiments were performed for transducers with various element pitches.

Materials & Methods

Simulations

A homogeneous block phantom (10 cm width, 0.5 cm elevational thickness, 4 cm height) was simulated before and after 400 μm vertical displacement using the ultrasound simulation software package Field II [120,121]. Field II requires the user to define: the position of scatterers that make up the ultrasonicographic tissue, the physical transducer properties, and an imaging sequence.

To "create" the block phantom in its initial position 2.1 million scatterers were randomly distributed over a volume of 10 by 4 by 0.5 cm³. The block was centered at a depth of 2.5 cm. The position of the scatterers after 400 μm displacement was achieved by subtracting 400 μm from the z-coordinate of each scatterer. Since there were more than 10 scatterers per sampling volume, fully developed speckle was generated, [30].

Three linear array transducers were simulated. Each transducer was approximately 3.8 cm wide, however with different number of elements and pitches: 282 elements and a pitch of 135 μm, 190 elements and a pitch of 200 μm, and 156 elements and a pitch of 245 μm. The elements were 0.875 μm pitch wide and 4 mm in height. Each physical element was subdivided into 10 x 10 mathematical elements. The sampling frequency (f \_s) was set to 88 MHz and the transmit frequency (f \_t) was set to 8.8 MHz for all transducers, (-20 dB bandwidth: 4 - 12 MHz, Fig. 5-2A). In transmit, a fixed focus was set at 1.6 cm with an F-number of 2.9. In receive, dynamic focusing was applied with a constant F-number of 0.875. The maximum aperture used for transmission and reception was 2.56 cm. In transmission no apodization was applied in the axial-lateral plane, in receive a Hamming window was applied. In the axial-elevational plane an elevational focus was set at 1.6 cm and Hanning apodization was applied in both transmit and receive. Toward the edges of the transducer less elements were active in receive and transmission resembling a real transducer. Radio frequency (RF) data for both phantom positions and all three transducers were simulated for beam steering angles ranging from 0° to +30° in steps of 10°. Band-limited noise (3 - 13 MHz) was added to the simulated data of the block to make realistic simulations resembling a signal-to-noise ratio (SNR) of 15 dB [Ch. 3].

Experiments

A homogeneous block phantom of 10x10x4 cm³ was created by freeze thawing a solution of 1% SiC scatterers (15 to 40 μm, E. Merck, Darmstadt, Germany), 20% of polyvinyl alcohol (Boom, Meppel, The Netherlands), 20% cooling liquid (Koolvloeistof Basic Safe, Halfords, The Netherlands), and water. The solution was created by dissolving 5 g of scatterers, 50 g of PVA and 100 g of cooling liquid in 345 ml of water that was heated to ~90 degrees Celsius in a closed cylinder. The cooling liquid was added to the solution to reduce the generation of tissue inhomogeneities caused by the increased pressure that is usually generated by inward freezing of the water. Two ultrasound systems with transducers were used to acquire RF data of the phantom before and after 400 μm displacement in vertical direction with respect to the transducer. The first ultrasound system used was a Philips SONOS 7500 ultrasound system equipped with a linear array transducer L11-3 (pitch 135 μm, f \_c = 7.5 MHz, f \_t = 39 MHz, -20 dB bandwidth: 3 - 11 MHz, Fig. 5-2A). The second ultrasound system used was a Samsung Medison Accuvix V10 ultrasound system equipped with a linear array transducer L5-13 (pitch 200 μm, f \_c = 8 MHz, f \_t = 61.6 MHz, -20 dB bandwidth: 4 - 13 MHz, Fig. 5-2A). RF data were acquired at beam steering angles of -30° to +30° in steps of 10°. Measurements with the SONOS 7500 were repeated nineteen times, measurements with the Accuvix V10 were repeated fifteen times. To obtain data of the phantom before and after displacement the phantom was placed inside a water reservoir. The reservoir was placed on a plate that could be moved in vertical direction using a micromanipulator. The transducers were placed in a static holder above the reservoir, facing towards the phantom and were partially submerged in the water to enable ultrasound to travel from the transducer into the phantom and back. The speed of sound in the phantom c was 1505 m/s and was determined from the distance in sample points N between the top and bottom of the phantom in the RF data, the sampling frequency f \_s and the thickness of the phantom measured in reality D\_real:

$$c = \frac{2f_s D_{\text{real}}}{N}$$  \hspace{1cm} (5.4)

Postprocessing

The RF data of each dataset were filtered using band-pass filters with varying upper frequency cutoff points and a fixed lower frequency cutoff point (Fig. 5-2B). The lower frequency cutoff point was kept fixed at 2.5 MHz. The high-end frequency cutoff was increased from 3.5 MHz to 13.5 MHz in steps of 1 MHz. In this way all data between 3 MHz and the upper frequency cutoff minus 0.5 MHz passed unaltered. Before displacement estimation was performed, the RF data for all nonzero beam steering angles were unskewed: each RF line was shifted with respect to the edges of the transducer. Radio frequency (RF) data for both phantom positions and all three transducers were simulated for beam steering angles ranging from 0° to +30° in steps of 10°. Band-limited noise (3 - 13 MHz) was added to the simulated data of the block to make realistic simulations resembling a signal-to-noise ratio (SNR) of 15 dB [Ch. 3].

This, to correct for the fact that RF data are stored in a rectangular grid for beam steered acquisitions, while the sample points form a skewed grid in reality.
Displacement estimation

Axial displacements for each dataset were estimated in two iterations using a coarse-to-fine 2-D cross-correlation based algorithm [59]. In the first iteration tissue displacements between successive frames were estimated by calculating the 2-D shift of the peak of the 2-D cross-correlation function obtained by cross-correlating windows of RF data of ~1 mm (axially) times ~1 mm (laterally) of the initial frame with windows of RF data of ~2 mm (axially) times ~2 mm (laterally) in the frame corresponding to the displaced phantom (the search frame). In the second iteration the procedure was repeated with window sizes that were twice as small in axial direction. The “coarse” 2-D displacements obtained in the first iteration were used as offset for the RF data of the search frame in the second iteration. No filtering of the displacements was performed in between the iterations. At the end, the displacements were filtered with a 5x5 median filter. In order to estimate the location of the cross-correlation peak at subsample and subline level, a 2-D parabolic function was fitted through the peak of the cross-correlation function [59,76,145]. Displacements were estimated for every ~250 μm axially and for every separate lateral line.

Displacements were only estimated for a certain region of interest (ROI). For each transducer the ROI corresponded to the region of tissue which remained inside the image view for all acquisition angles both before and after displacement, minus a margin of 2 mm thickness to avoid boundary problems. The ROI used for the recordings with the L5-13 transducer is shown in Fig. 5-3A. The ROI was diamond-shaped for this transducer, because only half of the aperture was used for transmission at each beam steering angle. For the other transducer the ROI was triangular, because the full aperture was used. The obtained 2-D angular axial displacement fields were projected in the vertical direction to obtain the vertical displacement fields:

\[ u_{ax} = \frac{u_{ax,0}}{\cos(\alpha + \gamma)} \]  

(5.5)

where \( u_{ax} \) is the axial displacement and \( u_{ax,0} \) is the axial displacement estimated at a beam steering angle equal to \( \alpha \). The parameter \( \gamma \) is the angle between the applied displacement and the main axis of the transducer (Fig. 5-3B). For the simulations this angle was equal to zero. For the experiments this angle was calculated using the median values of the \( \alpha \) axial and lateral displacements, \( \hat{u}_{ax,0} \) and \( \hat{u}_{lat,0} \) estimated without beam steering at the high-end cutoff frequency of 13.5 MHz.

**OPTIMIZING GRATING LOBE FILTERING FOR STRAIN ESTIMATION**

Fig. 5-2. A: The frequency content of the various transducers used in this study as determined from the same region in the homogeneous block phantom. B: The frequency characteristics of some of the band-pass filters employed in this study.

Fig. 5-3. A: A compound ultrasound image of the log compressed envelope ultrasound data of the phantom acquired at beam steering angles of -30° to 30°. The diamond-shaped ROI that was used for analysis of the L5-13 data is indicated. B: A schematic overview of the applied displacement component and the various angles involved.

\[ \gamma = \arctan\left( \frac{u_{lat,0}}{u_{ax,0}} \right) \]

(5.6)

Performance evaluation

To determine which cutoff frequency resulted in the most accurate displacement estimates, the root mean squared error (RMSE) of the vertical displacement estimates in the ROI was calculated after exclusion of the 5% highest and 5% lowest values. For the experimental data the RMSE was averaged over all measurement series. The exclusion of the 5% highest and 5% lowest values was performed to reduce distortion of the RMSE analysis due to outliers.

Results

The results for beam steering angles of 0°, 10°, 20° and 30° after band-pass filtering at various cutoff frequencies for the simulations with the various transducers are shown in Fig. 5-4, Fig. 5-5 and Fig. 5-6. As can be observed, the results clearly differ for the transducers with the various pitches. The transducer with the smallest pitch of 135 µm (Fig. 5-4A and Fig. 5-5A) has the lowest RMSE values. Furthermore, the shape of the RMSE curve is independent of the beam steering angle. It is best to set the cutoff frequency as high as possible for all beam steering angles, because the RMSE keeps on decreasing. For the transducer with the intermediate pitch of 200 µm (Fig. 5-4B and Fig. 5-5B) again it is best to set the cutoff frequency as high as possible for the beam steering angles of 0°, and 10°. However, for the 30° acquisition an optimum is observed around 5 to 6 MHz. With including more frequency content or less frequency content the estimation accuracy degrades fast. The accuracy in terms of RMSE for the 20° acquisition angle does not improve nor decrease above a cutoff of 5 MHz. The transducer with the largest pitch of 245 µm Fig. 5-6 performs worst, the RMSE values are higher than for the other two transducers. Furthermore, already at 20° a clear optimum around 5 to 6 MHz is visible in the RMSE curve. Although the RMSE curve again reveals an optimum at 5 MHz for beam steering at 30°, the displacement image shown in Fig. 5-6A shows that it is hardly possible to estimate correct displacements for this transducer at this large beam steering angles.
OPTIMIZING GRATING LOBE FILTERING FOR STRAIN ESTIMATION

For 0° beam steering, again the best results are obtained while using the full bandwidth of the transducer. The RMSE of the displacement estimates at 10° of beam steering does not further reduce or increase above a cutoff frequency of 8 MHz.

The results for the experimental data are shown in Fig. 5-7 and Fig. 5-8. Again, the lowest RMSE values are found for the transducer with the smallest pitch, the L11-3 transducer (Fig. 5-7A and Fig. 5-8A). In accordance with the results for the simulations the most accurate displacements for this transducer are obtained when setting the high-end frequency cutoff at the maximum value of 13.5 MHz independent of the beam steering angle applied. The results for the L5-13 transducer (Fig. 5-7B and Fig. 5-8B) are also similar to those of the simulated transducer with a pitch of 200 \(\mu\)m. Again, no intermediate optimum is observed for beam steering angles of 0°, 10° and 20°, whereas it is observed for a beam steering angle of 30°. The optimum is now found at 6 to 7 MHz, whereas it was found at 5 to 6 MHz in the simulations.

The results for the experimental data are shown in Fig. 5-7 and Fig. 5-8. Again, the lowest RMSE values are found for the transducer with the smallest pitch, the L11-3 transducer (Fig. 5-7A and Fig. 5-8A). In accordance with the results for the simulations the most accurate displacements for this transducer are obtained when setting the high-end frequency cutoff at the maximum value of 13.5 MHz independent of the beam steering angle applied. The results for the L5-13 transducer (Fig. 5-7B and Fig. 5-8B) are also similar to those of the simulated transducer with a pitch of 200 \(\mu\)m. Again, no intermediate optimum is observed for beam steering angles of 0°, 10° and 20°, whereas it is observed for a beam steering angle of 30°. The optimum is now found at 6 to 7 MHz, whereas it was found at 5 to 6 MHz in the simulations.

Discussion

It was observed both in the simulations and the experiments that transducers with smaller pitches in general enable a more accurate estimation of displacements when using different beam steering angles. This improvement is most obvious for the RMSE curves that were found for beam steering angles of 20° and 30°. This is mainly, due to the aforementioned facts that grating lobes interfere more when the ratio between pitch and transmit frequency increases, and also interfere more for larger beam steering angles.

No clear optima were found in the RMSE curves for the transducer with the pitch of 135 \(\mu\)m both in the simulations and in the experiments. Furthermore, the optimal cutoff values for the
other transducers all exceed the "no grating-lobe" frequencies reported in Table 5-1. Therefore, it can be concluded that to obtain the most optimal displacement estimates for a certain transducer, it is best not to remove the grating lobe signal entirely by low-pass filtering, because it also removes part of the main lobe signal still beneficial for displacement estimation.

The reason for finding higher cutoff points might be due to two phenomena. First, the main lobe signal moves in the same direction over the entire frequency band, whereas the grating lobe signal moves in distinct directions for every separate frequency. This is because the angle of appearance of the grating lobe changes with frequency as stated in (5-1). The uniformity of motion for the main lobe versus the nonuniform motion of the grating lobe makes it more likely that the cross-correlation-based displacement estimation algorithm is dominated by the motion of the main lobe signal. Secondly, the ratio of the magnitude of the main lobe signal and the grating lobe signal changes with frequency. For lower frequencies the grating lobe is weak in comparison with the main lobe. For higher frequencies vice versa. The ratio can be calculated as follows:

\[ \text{ratio} = 20 \log_{10} \frac{D_{\text{main}}(\alpha)}{D_{\text{main}}(\beta)} \]  

(5-7)

where \( \alpha \) is the beam steering angle and \( \beta \) is the corresponding grating lobe angle for a certain frequency as calculated from (5-1). The ratio is plotted as a function of beam steering angle and frequency in Fig. 5-9.

Using this graph it is possible to define cutoff frequencies for which a certain ratio between grating lobe and main lobe magnitude exists. In Table 5-2 the cutoff frequencies for several ratios are presented. The cutoff frequencies were determined to be the most optimal for 0°, 10°, 20° and 30° of steering which are somewhere between those observed for the 3 dB and the 0 dB ratio cutoff point. It is very hard to determine the optimal cutoff setting solely based on Table 5-2. It does however provide a general guidance. For instance when performing steering with a transducer with a certain pitch at a specific beam steering angle that corresponds to a 3 dB ratio cutoff that is close to the lowest frequency contained in the -20 dB bandwidth is not advisable. The simulated transducer with the pitch of 245 μm that was steered at 30° resulting in the lowest frequency component close to 4 MHz is an example of this situation. As can be observed, no accurate displacement image could be determined (Fig. 5-6). Based on the small optimum in cutoff frequency observed at 30° for the L5-13 transducer (Fig. 5-9B) it is recommended for future research with beam steered linear array transducers having a pitch/frequency ratio larger than that for the L5-13 transducer to determine the exact optimum for steering angles over 20° by performing a similar experiment as presented in this study.

The fact that the optimum frequency cutoff observed for the experimental transducer of 300 μm is 1 MHz higher than that observed for the simulated transducer with an equal pitch at a beam steering angle of 30° is probably due to some remaining small differences in the imaging settings between the simulations and the experiments. For instance the shape of the pulse and the settings for the apodization were not exactly known to us, although Fig. 5-2 shows that the frequency content of experiments and simulations matched fairly well.

All results presented here focused solely on the estimation of the axial displacement component along various beam steering directions. The displacements were subsequently projected in the vertical direction with respect to the micromanipulator. Of course the axial displacement from the various beam steering angles can also be compounded to derive lateral/horizontal displacement components using previously published approaches [126, 142, 143, Ch. 4]. Since these are all processing steps based on axial displacement estimates it is expected that the optimum filter cutoffs found here will also provide the most accurate estimates of these components. The same expectation is for strain estimation, which is usually also an additional step that requires the displacement estimates as input [48].

This study has at least one limitation, namely that tissue with homogeneous echogenicity was examined only. It can be expected that in a situation in which a hard reflector is located close to the transducer surface which is not struck by the main lobe, but only by the grating lobe, the settings for the apodization were not exactly known to us, although Fig. 5-2 shows that the frequency content of experiments and simulations matched fairly well.

Table 5-2. Cutoff frequencies (MHz) below which the ratio of the magnitude of the main lobe to the grating lobe is less than the indicated ratio for transducers with pitches similar to those simulated in this study. A speed of sound of 1540 m/s was assumed.

<table>
<thead>
<tr>
<th>Pitch (μm)</th>
<th>Beam steering angle (°)</th>
<th>Main lobe / grating lobe (dB)</th>
<th>3 6 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>135</td>
<td>30</td>
<td>7.60 MHz</td>
<td>7.60 MHz</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>8.50 MHz</td>
<td>9.11 MHz</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>9.80 MHz</td>
<td>&gt;15 MHz</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>&gt;15 MHz</td>
<td>&gt;15 MHz</td>
</tr>
<tr>
<td>200</td>
<td>30</td>
<td>5.13 MHz</td>
<td>5.13 MHz</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>5.74 MHz</td>
<td>6.15 MHz</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>6.61 MHz</td>
<td>12.11 MHz</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>&gt;15 MHz</td>
<td>&gt;15 MHz</td>
</tr>
<tr>
<td>245</td>
<td>30</td>
<td>4.19 MHz</td>
<td>4.19 MHz</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>4.68 MHz</td>
<td>4.68 MHz</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>5.36 MHz</td>
<td>5.36 MHz</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>6.29 MHz</td>
<td>6.29 MHz</td>
</tr>
</tbody>
</table>
displacement estimation is more difficult to perform and perhaps impossible to carry out properly. However, this situation is so specific, that thorough investigation was not performed in this study.

Conclusions

Grating lobes disturb displacement estimation. For higher transmit frequencies and larger beam steering angles the grating lobe signal increases. Based on the displacement estimates obtained for two commercial transducers and three simulated transducers we were able to show that for optimal displacement estimation it can be better not to remove the grating lobe signal entirely by low-pass filtering, because it also removes part of the main lobe which can be vital for accurate displacement estimation.

Acknowledgements

The authors like to acknowledge Donkuk Shin, Jong-Sik Kim, Jongho Yu and Wim van de Voo- ren of Samsung Medison for the implementation of the radial zone scanning mode on the Medison Accuvix V10 ultrasound system. The authors also acknowledge Stichting Nationale Computerfaciliteiten (National Computing Facilities Foundation, NCF) for the use of supercomputer facilities, with financial support from the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (Netherlands Organization for Scientific Research, NWO).

Fig. 5-9. Ratio of the magnitude of the main lobe to that of the grating lobe plotted as a function of beam steering angle and transmit frequency for a transducer with a pitch of 200 μm and an element width of 175 μm.
In this chapter a modification to the 2-D coarse-to-fine strain imaging method of the previous chapters is introduced which is dedicated to strain estimation in the presence of shear strain and rotation. The performance of the new “free-shape” method is compared to 1-D and 2-D coarse-to-fine imaging using simulated ultrasound data of a deforming and rotating block. It is shown that the “free-shape” method outperforms the other two methods by producing more accurate displacement and strain estimates. Furthermore, rotations up to 4.0 - 5.0° can be measured and are more accurately estimated when the “free-shape” 2-D method is used instead of the other methods.

CHAPTER 6

STRAIN IMAGING IN SHEARING AND ROTATING TISSUE

Abstract

This simulation study is concerned with: 1) the feasibility of measuring rotation and 2) the assessment of the performance of strain estimation in shearing and rotating structures. The performance of three different radio frequency (RF) based methods is investigated. Linear array ultrasound data of a deforming block were simulated (axial shear strain = 2.0, 4.0, and 6.0%, vertical strain = 0.0, 1.0, and 2.0%). Furthermore, data of a rotating block were simulated over an angular range of 0° to 10°. Local displacements were estimated using a coarse-to-fine algorithm using 1-D and 2-D predeformation kernels. A new estimation method was developed in which axial displacements were used to correct the search area for local axial motion.

The study revealed that this so-called “free-shape” 2-D method outperformed the other two methods and produced more accurate displacement images. For higher axial shear strains, the variance of the axial strain and the axial shear strain reduced by a factor of four to five. Rotations could be accurately measured up to 4.0° to 5.0°. Again, the free-shape 2-D method yielded the most accurate results. After reconstruction of the rotation angle, the mean angles were slightly underestimated. The precision of the strain estimates decreased with increasing rotation angles.

In conclusion, the proposed “free-shape” 2-D method enhances the measurement of (axial shear) strains and rotation. Experimental validation of this method has still to be performed.

Introduction

Ultrasound strain imaging, or elastography, is a technique that measures local strain in biological tissue and organs [90,128,146,147]. The strain data might be used to reconstruct the elastic properties of the tissue [148,149]. Originally, the displacements and strains were estimated using one-dimensional (1-D) time delay estimation [90,128,150,151]. In the last decade, two-dimensional (2-D) estimation techniques have been developed, using both B-mode data [152,153] and raw, radio frequency (RF) data [154,155]. These 1-D and 2-D strain imaging techniques are being used primarily for cardiovascular applications [144,156,157] and breast and prostate tumor research [158,159].

Several groups have been investigating the opportunity of shear strain imaging and its possible applications [89,126,160]. For instance, shear strain imaging has been of interest for characterization of breast tumors [161,162] and cardiovascular applications [163-167]. Rotation and, especially, torsion, are of great interest in cardiovascular research [164,165,167]. Besides clinical relevance, a practical issue is the negative effect of shearing or rotation on strain image quality during free-hand palpation [168,169].

Axial shear strain has been measured using RF data [89,160]. However, rotation and torsion measurements have been performed solely with 2-D B-mode speckle tracking techniques [170-172] and optical flow techniques [84,173,174]. RF data have the advantage of providing raw, radio frequency (RF) data [154,155]. These 1-D and 2-D strain imaging techniques are being used primarily for cardiovascular applications [144,156,157] and breast and prostate tumor research [158,159].

The results of these conventional algorithms were compared with those obtained with the so-called “free-shape” 2-D strain method. The limits on rotation angle measurements were investigated as well as the influence of axial shearing and rotation on strain accuracy and vice versa.

Materials

A block containing 3.5 million randomly positioned point scatterers (5 cm x 5 cm x 1 cm) was generated using MATLAB® (The Mathworks Inc., Natick, MA, USA). This block was used to simulate predeformation RF data using Field II© (Fig. 6-1A). Next, the block of point scatterers was deformed to generate the “postdeformation” scatter configurations for axial deformation, shearing or rotation. First, the scatterers were translated to simulate an axial shear strain of ε_y = 2.0, 4.0, and 6.0%, without any vertical or horizontal strain present (see also Fig. 6-1B) by simply translating the scatter points in the axial direction, using the center as the reference point:

\[
y' = y - \varepsilon_y (x - x_{\text{avg}}) / (x_{\text{avg}} - x_{\text{min}})
\]  

(6-1)

To examine the influence of strain on axial shear strain measurements, a vertical load corresponding to ε_y = 1.0% and 2.0% deformation was applied to the block for all cases of axial shearing. The blocks were assumed to be linearly elastic and nearly incompressible. Consequently, the Poisson’s ratio was set to 0.495. For a vertical deformation of 1.0% and 2.0%, the resulting horizontal strains were ε_x = 0.5 and 0.99%, respectively.

\[
x' = (1 + \varepsilon_x) x
\]  

(6-2)

\[
y' = (1 - \varepsilon_y) y
\]  

(6-3)

Second, simulations were performed of blocks of scatterers that were rotated over 0.5°, 1.0° to 5.0°, and 10.0° (see Fig. 6-1C). The center of the scatter matrix was used as axis of rotation.
The rotation simulations were repeated while applying a vertical deformation \((c_y = 1.0\) and \(2.0\%))\). These modified, “postdeformation’, scatterer configurations were again convolved (Field II©) with an ultrasound RF pulse to simulate the postdeformation ultrasound data.

Field II© was used to simulate linear 2-D ultrasound images [121]. A linear array transducer was simulated with a center frequency \(f_c = 8.73\) MHz. The linear array consisted of a total number of 288 elements, of which 128 were used in transmit and receive mode. The pitch was set to \(35\) μm and the element height was \(6\) mm. The fixed lateral and elevational focus of the transducer was positioned in the middle of the block, \(i.e.,\) at \(35\) mm (the top of the volume lies at \(10\) mm depth). Dynamic focusing was used with focal zones every \(2.0\) mm to obtain a uniform beam profile [59]. Pre- and postdeformation RF data were simulated using the simulated volumes of scatterers and were sampled at \(39\) MHz. The simulation was performed for 225 RF lines, resulting in a rectangular image with a depth of \(70\) mm and a width of \(30.4\) mm. The number of scatterers per smallest sampling volume was \(10\), which is sufficient to ensure that the speckle of the ultrasound images is fully developed [30].

Methods

Two-dimensional displacement and strain estimation can be performed by cross-correlating 1-D or 2-D windows of predeformation RF data with a larger 2-D postdeformation window (Fig. 6-1A&B). Using a larger 2-D postdeformation window allows for the estimation of lateral displacements, regardless whether a 1-D or 2-D predeformation window is used [59,155]. Consequently, the windows of RF data have a rectangular shape. However, in case of axial shearing (and rotation), a lateral gradient is found in the axial displacement of the scatterers. Neighboring RF lines are shifted relatively to each other in the axial direction, and the speckle tracking can estimate the global displacements despite the large axial shearing or rotation.

The simulated data were processed using a coarse-to-fine 2-D displacement estimation algorithm using 2-D parabolic interpolation and additional recorrelation techniques [59]. For the three coarse-to-fine iterations, the axial window size was set to \(4.0, 2.0,\) and \(1.0\) mm with an overlap of \(75\%\). The lateral predeformation window was set to \(1\) line for \(1\)-D and \(5\) lines (\(0.68\) mm) for 2-D window matching for all iterations [59,155]. For the first iteration (coarse scale search), the lateral postdeformation window was set to \(43\) lines (\(5.80\) mm), defining a large search area. The signal envelope was used during the first iteration, because 2-D B-mode speckle tracking can estimate the global displacements despite the large axial shearing or rotation that is present. The lateral postdeformation window was cropped to \(11\) lines (\(1.5\) mm) for all subsequent iterations. All window sizes used for aligning and stretching were equal to the settings of the last coarse-to-fine iteration. The axial and lateral displacement data were smoothed using a median filter of \(2.8\) mm \(\times\) \(1.5\) mm (axial \(\times\) lateral). The axial and lateral strains were calculated using a 1-D LSQSE with a kernel length of \(2.8\) mm [48]. It is noted that the vertical strain \((c_y)\) corresponds to the axial strain and the horizontal strain \((c_x)\) is equivalent to the lateral strain, because linear array data were used in this study.

The three algorithms were applied to the simulated RF data. The conventional 1-D and 2-D strain estimation using rectangular, rigid 2-D kernels of postdeformation RF data are in this paper referred to as “rigid 1-D” and “rigid 2-D”, respectively, whereas “free 2-D” is used for the proposed “free-shape” method. The free 2-D method differed from the conventional approaches after the first, coarse iteration. The displacement estimates were now used to deform

\[
x' = x \cos \theta + y \sin \theta
\]

\[
y' = -x \sin \theta + y \cos \theta
\]

Fig. 6-1. Example of a small segment of normal B-mode image data (A), after shearing (B), and after rotation (C). The position of the measured RF lines relative to the scatter movement is also illustrated (lower row).
the postdeformation 2-D window of RF data for all subsequent iterations. The displacements and strains were estimated, as well as the axial shear strains and rotation angle in the corresponding simulations. The root mean squared error (RMSE) and maximum cross-correlation ($CCF_{max}$) for a square region in the middle of the image ($34 \text{ mm} \times 21 \text{ mm}$) were also calculated to facilitate comparison of the different methods. The differences in RMSE were tested using a two-sample $t$-test (95% confidence interval). The strain results were normally distributed. Therefore, the mean and standard deviation were computed and the significance of the differences in variance was tested using the F-test for variances (99% confidence interval). For the rotation data, a circular region around the axis of rotation was omitted from analysis, because large artifacts occurred due to noise in the small displacement estimates near the axis of rotation (see Discussion).

**Results**

**Axial shearing**

Fig. 6-3 shows the estimated, unfiltered, axial displacement images for the three different applied axial shear loads and the three estimation methods. The displacement images revealed more noise for larger axial shear strain. At first glance, the “free-shape” 2-D method yielded less noisy displacement images. The accuracy of the three methods can be assessed using Fig. 6-4. For all methods, the RMSE increases with increasing axial shear strain. The rigid 1-D method showed the highest RMSE in both axial and lateral direction for all applied axial shear strains ($p < 0.001$). The axial RMSE curves revealed a significantly smaller error using the free 2-D method compared with the rigid 2-D technique for 6% axial shear strain ($p < 0.001$), whereas the lateral RMSE curves decreased significantly for 4 and 6% axial shear strain ($p < 0.03$). The lateral displacements were lower and the lateral RMSE seems lower than the axial RMSE. However, both the axial and lateral RMSE of free 2-D decreased with 50% and 33% compared with rigid 1-D and rigid 2-D, respectively (Fig. 6-4A-F). Furthermore, the application of a vertical load on the block seemed to have little influence on the RMSE. An increase in maximum cross-correlation was observed for free 2-D as compared with rigid 2-D (Fig. 6-4G-I) and approached the 1-D curves. Still, the cross-correlation values for rigid 1-D seemed slightly higher (see Discussion).

Axial shear strain images and axial strain images are shown in Fig. 6-5 for rigid 2-D and free 2-D. The figures corroborate the RMSE results that the free 2-D technique is especially beneficial for higher axial shear strains and both the axial ($e_{yy}$) and axial shear strain ($e_{yx}$) images were less noisy. The mean values and standard deviations of the axial, lateral and axial shear

![Fig. 6-3. The measured, unfiltered, axial displacements using A: rigid 1-D and B: 2-D kernel matching and C: “free-shape” 2-D kernel matching for an applied axial shear strain of 2.0% (top row), 4.0% (middle row), and 6.0% (lower row).](image)

![Fig. 6-4. The root mean squared error (RMSE) between the measured and “true” axial displacements (top row), lateral displacements (middle row) and the measured maximum cross-correlation values as a function of shear load ($\epsilon_{yx}$) for all three methods. The results are shown for an applied axial load ($\epsilon_{yy}$) of 0.0% (left column), 1.0% (middle column), and 2.0% (right column).](image)
Table 6-1. Measured mean strain ± standard deviation for all shearing simulations (N = 21039)

<table>
<thead>
<tr>
<th></th>
<th>Applied load: ε_{yy} = 1.0%</th>
<th>Applied load: ε_{yy} = 2.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rigid 2-D</td>
<td>Free 2-D</td>
</tr>
<tr>
<td>Axial strain (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε_{yy} = 2.0%</td>
<td>1.00 ± 0.04</td>
<td>-1.00 ± 0.04</td>
</tr>
<tr>
<td>ε_{yy} = 4.0%</td>
<td>-0.99 ± 0.12</td>
<td>-0.99 ± 0.11</td>
</tr>
<tr>
<td>ε_{yy} = 6.0%</td>
<td>-0.99 ± 0.30</td>
<td>-0.97 ± 0.34</td>
</tr>
<tr>
<td>Lateral strain (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε_{yy} = 2.0%</td>
<td>0.52 ± 0.27</td>
<td>0.51 ± 0.24</td>
</tr>
<tr>
<td>ε_{yy} = 4.0%</td>
<td>0.52 ± 0.44</td>
<td>0.52 ± 0.44</td>
</tr>
<tr>
<td>ε_{yy} = 6.0%</td>
<td>0.53 ± 0.76</td>
<td>0.54 ± 0.80</td>
</tr>
<tr>
<td>Shear strain (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε_{yy} = 2.0%</td>
<td>2.00 ± 0.07</td>
<td>2.00 ± 0.08</td>
</tr>
<tr>
<td>ε_{yy} = 4.0%</td>
<td>-3.99 ± 0.21</td>
<td>-3.99 ± 0.18</td>
</tr>
<tr>
<td>ε_{yy} = 6.0%</td>
<td>-3.99 ± 0.61</td>
<td>-3.99 ± 0.65</td>
</tr>
</tbody>
</table>

Fig. 6-5. The resulting axial (ε_{xx}) images for A: the rigid 2-D and B: “free-shape” 2-D method for an applied vertical strain of 1.0% and an applied shear strain of 2.0% (top row), 4.0% (middle row), and 6.0% (bottom row). The resulting shear strain images (ε_{yy}) for C: the rigid 2-D and D: the “free-shape” 2-D method for an applied vertical strain of 1.0% and an applied shear strain of 2.0% (top row), 4.0% (middle row), and 6.0% (bottom row).

Fig. 6-6. The measured, unfiltered, axial displacements using A: the rigid 2-D and B: “free-shape” 2-D method for increasing applied rotation (0.5° - 10°) and the measured, unfiltered, lateral, displacements using C: the rigid 2-D and D: “free-shape” 2-D methods.

Rotation measurements

The measured, unfiltered, axial and lateral displacement images obtained with rigid 2-D and free 2-D are shown in Fig. 6-6. The displacement images revealed that rotation can be measured up to 4.0° without any deterioration. As before, the free 2-D method appeared to be able to handle the rotational movement better, considering the smoother (unfiltered) displacement images. However, both algorithms failed at 5.0° degrees in the regions with large lateral displacements and no accurate displacements were measured at 10.0°. The axial and lateral RMSE showed an increase for larger rotation angles for all three methods (Fig. 6-7). The differences in terms of RMSE and maximum cross-correlation are similar to those obtained in the study on axial shearing (Fig. 6-4). The axial RMSE seemed to decrease by 90% and 80% for 4.0° and 5.0°, respectively, when using free 2-D instead of rigid 2-D (p < 0.001), whereas the lateral RMSE decreased by 40 to 90% (p < 0.001). The cross-correlation of free 2-D increased...
by 0 to 0.17 compared to rigid 2-D, but was again slightly outperformed by the rigid 1-D algorithm (see Discussion).

Fig. 6-8 shows the measured rotation angle and accuracy for the three methods. The variance on the measured angle decreased with respect to the rigid 1-D method using 2-D techniques and improved for the free 2-D method at larger angles. For the last method, the rotation angle images are shown for the cylindrical region-of-interest (Fig. 6-8D-I). The images revealed that the angle is underestimated in the lower part of the images below the focus. This can also be noticed from the mean rotation angle curves in Fig. 6-8A-C. For larger angles, artifacts were found in the lowest part of the image, which can also be seen in the displacement images (Fig. 6-6).

The rotation was also measured in rotating structures after deformation. In general, the variance of the measured rotation angles increased when 1.0% and 2.0% strain was applied (Fig. 6-9). The curves showed a slightly larger underestimation and larger error bars with increasing applied strain. The strain values were reconstructed [177] and the mean axial and lateral strain values and the corresponding standard deviations are listed in Table 2. The free 2-D method resulted in less bias and variance of both the axial and lateral strain estimates, especially at larger rotation angles (> 3°, p < 0.001). For 4° rotation, the axial variance was six times lower, and the lateral variance decreased by 40%. The method was able to measure axial strain properly and accurately up to 4° rotation angle. For 5°, the axial variance increased tenfold. However, the axial and lateral variances were five to nine times lower, compared with the rigid techniques. Obviously, the variance of the lateral strain estimates was higher as compared as the axial strain, but the improvement in bias is still evident. Similar to the (axial) shearing simulations, the lateral variance was lower when using the free 2-D method, and the improvement, if present, was still significant (p < 0.001).

Table 6-2. Measured mean strain ± standard deviation for all rotation simulation (N = 15228)

<table>
<thead>
<tr>
<th>Applied load : εyy = 1.0%</th>
<th>Applied load : εyy = 2.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle</td>
<td>Rigid 1-D</td>
</tr>
<tr>
<td>0.5°</td>
<td>-1.00 ± 0.02</td>
</tr>
<tr>
<td>1.0°</td>
<td>-1.01 ± 0.03</td>
</tr>
<tr>
<td>Axial strain(%)</td>
<td>-1.01 ± 0.07</td>
</tr>
<tr>
<td>4.0°</td>
<td>-1.14 ± 0.41</td>
</tr>
<tr>
<td>5.0°</td>
<td>-1.19 ± 1.88</td>
</tr>
<tr>
<td>Lateral strain(%)</td>
<td>0.5°</td>
</tr>
<tr>
<td>1.0°</td>
<td>0.48 ± 0.23</td>
</tr>
<tr>
<td>2.0°</td>
<td>0.45 ± 0.37</td>
</tr>
<tr>
<td>3.0°</td>
<td>0.42 ± 0.59</td>
</tr>
<tr>
<td>4.0°</td>
<td>0.36 ± 1.01</td>
</tr>
<tr>
<td>5.0°</td>
<td>0.36 ± 7.55</td>
</tr>
</tbody>
</table>
CHAPTER 6

It must be noted that the performance of the free 2-D method was also investigated (results not shown) for a range of axial window sizes (0.2 – 2.0 mm) and revealed a constant performance independent of the axial window size in terms of axial and lateral RMSE.

The variance of the axial strain and shear strain decreased significantly when using 2-D strain estimators. However, the bias increased (Table 6-2). The improvement of axial displacement and strain estimates in terms of strain variance is larger compared with the lateral results. For instance, the variance of the axial strain and the axial shear strain decreased by a factor of 3 to 5, but the variance of the lateral strain decreased less (-20%). In fact, it is trivial that lateral strain estimates seem less affected by the use of free 2-D. Only the axial translation is corrected for, not the lateral. Furthermore, the variance of the lateral strain remains higher due to a lower lateral resolution and the absence of phase information. However, the bias of the lateral strain estimates increased significantly for higher rotation angles (Table 6-2) and increased more compared to the axial strain results.

The use of RMSE and strain results analysis for comparison of the different methods is favored over the well-known elastographic signal-to-noise and contrast-to-noise ratios (SNR, and CNR, respectively). The RMSE is calculated using the displacements, avoiding the effects of median filtering or LSQ smoothing on strain accuracy. However, RMSE assessment is only possible when the exact displacement is known and that forms a major limitation for phantom experiments. The maximum cross-correlation values were also considered. Apparently, the rigid 1-D method yielded the highest CCF\text{max} values. The cross-correlation of the rigid 1-D strain estimator outperformed the 2-D methods. However, using 2-D kernels is more robust and results in less noisy displacement data and less outliers [59]. This can also be deduced from the RMSE results and Table 1. The strain results reveal that the variability is reduced especially by using the free 2-D technique. However, the bias increased when using the 2-D methods (Table 1). Hence, the CCF\text{max} seemed to be a bad measure for comparison of the three methods. This can be explained by the fact that the 1-D technique is less influenced by the axial motion caused by the axial shear strain. The rigid 2-D method will fail and the free 2-D method will introduce errors caused by the interpolation and recorrelation. Hence, 2-D windows will outperform 1-D windows in terms of robustness and precision (i.e. variance), but might introduce bias and therefore reduce accuracy. This algorithm is a sliding window technique and the motion compensation is performed for each window. However, motion compensated postdeformation RF data are not generated. In such data, the cross-correlation would be a good measure and should show similar results as the RMSE-curves.

It must be noted that, especially in case of bias, the SNR, would have been a bad measure for precision. Overestimation of strain would have led to higher SNR\text{e} or would possibly disguise the fact that the variance had increased, whereas underestimation could imply that the noise increased.

The rotation results seem promising, especially when considering the fact that rotation might be considered as a combination of axial and lateral shearing and translational motion [178], and the RF data cannot be corrected line-by-line for lateral motion. It appears that for angles > 4.0°, the axial gradient in the lateral displacements prevents accurate displacement measurements. Furthermore, the displacement and strain results show large artifacts at the lower part of the images. Again, lateral correction is not possible using RF data, which limits the applicability of this method. B-mode data could be used in combination with nonrigid registra-

Discussion

In this study, an assessment of strain imaging in axial shearing or rotating structures was performed using three different methods and simulated data using only one (state-of-the-art) linear array transducer configuration. The following are the principal findings of this study:

- The “free-shape” 2-D displacement estimation method outperformed conventional 1-D and 2-D algorithms, especially when large axial shearing or rotation is present.
- Axial shear strain can be measured accurately using the aforementioned technique and has little influence on the axial and lateral strain estimates.
- Rotation can be measured in nondeformed tissue up to 4° to 5°.

In deforming tissue, the presence of rotational movement decreases the accuracy of strain estimates dramatically.

It is not surprising that the free 2-D method outperforms the other algorithms in case of severe axial shearing. The applied axial shear strain results in a large lateral gradient of the axial displacements, and the proposed method corrects exactly for this phenomenon. Free 2-D method is a straightforward way to overcome problems caused by large axial shearing and rotational movement. In the coarse-to-fine algorithm, the axial correction was performed using rounded axial displacement values, i.e., integers only, to maintain computational efficiency. Interpolated reshaping of the postdeformation RF data during the recorrelation phase of the algorithm enhanced the cross-correlation even more, but at the cost of a large computational load. The 1-D and 2-D strain estimators, when using an axial window size of 1.0 mm take up 8 to 12 min for five iterations (coarse-to-fine (x3), aligning, stretching). An additional 6 min were required when using the “free-shape” 2-D method, roughly increasing the computation time with 50%. This was consistent for other window sizes. Hence, the proposed method may not be a real-time application in its current form, but efficient coding and implementation in C-code would obviously decrease the computational load.

Fig. 6-9. The measured mean rotation angle (using the “free-shape” 2-D method) for an applied load of A: 0.0%, B: 1.0%, and C: 2.0% axial strain (εy). The variance is shown (error bars) as well as the true rotations (grey dashed lines).

It is not surprising that the free 2-D method outperforms the other algorithms in case of severe axial shearing. The applied axial shear strain results in a large lateral gradient of the axial displacements, and the proposed method corrects exactly for this phenomenon. Free 2-D method is a straightforward way to overcome problems caused by large axial shearing and rotational movement. In the coarse-to-fine algorithm, the axial correction was performed using rounded axial displacement values, i.e., integers only, to maintain computational efficiency. Interpolated reshaping of the postdeformation RF data during the recorrelation phase of the algorithm enhanced the cross-correlation even more, but at the cost of a large computational load. The 1-D and 2-D strain estimators, when using an axial window size of 1.0 mm take up 8 to 12 min for five iterations (coarse-to-fine (x3), aligning, stretching). An additional 6 min were required when using the “free-shape” 2-D method, roughly increasing the computation time with 50%. This was consistent for other window sizes. Hence, the proposed method may not be a real-time application in its current form, but efficient coding and implementation in C-code would obviously decrease the computational load.
tion techniques, although further research is required. It must be noted that displacement and rotation precision will be spatially depended, since the 3 and 9 o’clock region of the phantom consist of axial motion and the top and bottom motion is largely lateral [179]. The influence of rotation on strain estimates is large and increasing rotation has a negative effect on strain accuracy and vice versa. For both 1-D and 2-D strain imaging methods using fixed kernels, the axial and lateral strain were underestimated. In particular the lateral strain accuracy increased when using the free 2-D method. The variances increased for all methods when applying a vertical load. No explanation for the underestimation of the rotation angle beyond the acoustic focus can be given. Other artifacts were found near the axis of rotation. The displacements in this area are relatively small but can still be subject to noise. Hence, the two-argument atan2 function that is used for rotation angle calculation may corrupt rotation estimates around the center of rotation.

This study has several limitations. First of all, this is a methodical study using simulation data generated with only one transducer configuration. However, the authors are aware that experimental work and in vivo validation should be the next, obvious step. Especially in vivo, a comparison with B-mode speckle tracking techniques should be made. Furthermore, the methodology of this study could be adapted to enable an investigation of the ability to measure torsion, which is of great interest for cardiovascular applications. The ultrasound data were simulated using a single type of linear array transducer, for only one center frequency with a fixed bandwidth, a large number of elements, relatively small pitch, and infinite signal-to-noise ratio. The simulated transducer was based on a commercially available system [59]. The influence of transducer characteristics like beam diffraction/focusing on the performance of RF-based strain, axial shearing, and rotation measurements is beyond the scope of this study. Furthermore, these simulations are predefined theoretical deformations and are not based on finite element models. This gives the advantage that there are no boundary effects present in the displacement and strain fields. Lesion detectability and spatial resolution were not assessed in this study. It must also be noted that only the case of axial shearing was examined. Lateral shearing cannot be corrected for using the free 2-D method and was therefore omitted.

Coarse-to-fine displacement algorithms are sensitive to the accuracy of the initial displacement estimates. If the rough displacement cannot be estimated, the algorithm will fail in all consecutive steps. This is also a drawback of the free 2-D method, where each separate RF line within the 2-D search area is shifted according to the measured displacements. This is also illustrated by the displacement results of 5.0° and 10.0° rotation angles. Hence, the first global assessment is crucial for the final result.

Conclusions

In conclusion, a “free-shape”, RF-based 2-D displacement algorithm improves 2-D strain estimation in case of significantly axial shearing and rotating structures. Rotation can be measured using RF data up to 4° to 5°. Normally, strain accuracy deteriorates significantly for larger rotation angles, but this can be overcome using the proposed method.
PART III: APPLICATION OF NONINVASIVE VASCULAR ELASTOGRAPHY
In the previous chapters methods for accurate noninvasive strain estimation in transverse vascular cross sections were developed. The methods were tested for simple vascular geometries in quasi-static situations. In this chapter the nonsegment based method of chapter 4 is challenged in more realistic situations. The performance of the method is investigated using simulated ultrasound data of a vulnerable plaque model, using ultrasound recordings of a periodically pulsating vessel-mimicking vessel phantom and using in vivo recordings of a healthy carotid artery. It is shown that also in these challenging situations the developed nonsegment based method outperforms conventional single-angle elastography.

CHAPTER 7

Abstract

Strain in the arterial wall can be estimated by cross-correlation of radio frequency ultrasound data recorded at various blood pressure levels. Intravascular studies revealed a high correlation between high radial strain regions and plaque vulnerability in coronary arteries. A non-invasive variant of the technique is desired, because it will enable early screening for rupture prone plaques, also in asymptomatic populations. Recently, we have shown that it is possible to obtain more precise radial (and circumferential) strain estimates by combining data from multiple beam steered ultrasound acquisitions in phantoms. However, the multi-angle method was tested using quasi-static data only, thus no motion artifacts were present. This study investigates the performance of the multi-angle method for pulsating vessels. Results are presented for a periodically pulsating vessel-mimicking phantom and in vivo recordings of a healthy carotid artery. It is shown that the multi-angle technique also outperforms conventional single-angle strain imaging for pulsating vessels.

Introduction

Atherosclerotic plaque rupture is considered to be the trigger of myocardial infarction and stroke [15]. For coronary arteries it has been shown that rupture proneness of a plaque is highly correlated with increased radial strain [52,54]. In those studies, strain was estimated by cross-correlation of radio frequency (RF) ultrasound data recorded at various blood pressure levels using an intravascular ultrasound probe. Despite its promising results, its invasiveness restricted the method to patients that already had severe clinical symptoms. Plaques often rupture without preceding clinical symptoms [10]. Therefore, a noninvasive version of the technique is desired.

The carotid artery is the most suitable and interesting artery for noninvasive vulnerable plaque detection, because it is easily accessible by ultrasound and is responsible for most stroke causing plaque ruptures. A challenge for noninvasive strain imaging is that the ultrasound data are not recorded in the radial direction [Ch. 2]. Therefore, radial strains cannot be determined directly, but need to be derived from separately estimated axial (along the ultrasound beam) and lateral (perpendicular to the beam) data. From conventional linear array ultrasound acquisitions, axial displacement and strain can be estimated accurately. However, the lateral counterpart is less accurate, due to the lower resolution and the lack of phase information in that direction. Recently, we showed that more accurate lateral displacements can be obtained by combining axial information from acquisitions at two large beam steering angles [Ch. 4]. In that study the beam steering approach was only tested for quasi-static experimental and simulated ultrasound data of simple phantoms. Quasi-static means that data were acquired for all beam steering angles in an initial state of deformation, after which the level of deformation was changed and another series of data was recorded. Thus, no tissue motion occurred during the change of steering angle and there was no misalignment of the angle information.

In this study the performance of the beam steering method for more realistic cases is investigated. We apply the technique to simulations of a carotid artery with a vulnerable plaque, a periodically pulsating vessel phantom with a soft layer and a carotid artery of a healthy volunteer. The strain estimation performance of the multi-angle method is compared to that of conventional single-angle imaging.

Materials & Methods

Vulnerable plaque simulation

A finite element model (FEM) of a carotid artery with a vulnerable plaque was constructed using the partial differential equation toolbox of Matlab R2007a (The MathWorks, USA). The geometry and the Young’s modulus distribution of the model are presented in Fig. 7-1. The model is an upscaled version of a FEM model for coronary artery atherosclerosis [116]. Two thousand triangular, linearly elastic, isotropic and incompressible (ν = 0.495) finite elements were defined to calculate the motion of the vessel for an intraluminal pressure increase of 4 mmHg under the assumption of plane strain. To avoid rigid body translation during the calculation of the displacement field, a very soft (E = 1 Pa) compressible (ν = 0.001) layer of 2 mm thickness with a fixed outer boundary was temporally added.

For both states of deformation ultrasound RF data for beam steering angles of -30°, 0° and 30° were generated using Field II [120,121]. To perform the simulations, the 3-D pre- and post-deformation positions of one million scatterers were defined with respect to the transducer surface using the FEM solution of the displacement field. Scanning was simulated for a linear array transducer consisting of 192 elements. The element pitch, width and height were 200 μm, 175 μm and 4 mm, respectively. The center frequency (f0) was 8.8 MHz and the RF data were acquired at a sample frequency of 61.6 MHz. In transmission, the focus was at 16 mm (corresponding to the lumen center). In receive, dynamic focusing was applied (F-number of 0.875).

Pulsating vessel phantom experiment

To test the technique for tissue in motion, a two-layered vessel-mimicking phantom was created (Fig. 7-2A) by freeze–thawing a 10% polyvinyl–alcohol water based solution (Boom, Mepel, The Netherlands) with 2% silica-carbon particles (15-40 μm, E. Merck, Darmstadt, Germany). The outer layer was freeze–thawed four times, the softer inner layer (plaque) once. Freezing lasted 16 hours at a temperature of -19°C, thawing lasted 8 hours at 22°C. The 16 cm long phantom was placed in a water tank and connected to a pump that provided a pulsating (1

Fig. 7-1.A: Young’s modulus distribution and geometry. B: simulated B-mode image without beam steering.
Hz) water flow (Fig. 7-2B). RF data of the phantom were recorded for 3 seconds using a Medison Accuvix V10 (Seoul, South Korea) that sequentially stored data from beam steering angles of -26°, 0° and 26°. The data were acquired at a frame rate of 129 Hz (43 Hz/beam steered angle) using an L5–13 linear transducer \( f_c = 8.5 \) MHz, \( f_s = 61.6 \) MHz). Simultaneously, the pressures of the water before and after the phantom were recorded. The pressures varied between 2 and 19 mmHg. The average flow was 400 ml/min.

In vivo carotid artery measurement

Finally, 3 seconds of RF data for a humane carotid artery of a 28-year-old volunteer were acquired in vivo using the aforementioned ultrasonic equipment. An example of a multi-angle B-mode image is shown in Fig. 7-3A.

Displacement and strain estimation

Beam steering at large angles results in distortions caused by grating lobes. The signal caused by grating lobes is mainly present in the upper part of the ultrasound frequency band and was removed by adaptive low-pass filtering [Ch. 5] before performing displacement and strain estimation. For the simulated data band-limited noise (5-13 MHz) was added until a signal-to-noise ratio of 20 dB was reached [Ch. 3]. This was performed to simulate electronic noise.

After this RF postprocessing, 2-D displacements were estimated iteratively using a coarse-to-fine 2-D cross-correlation method [59]. Displacement values were obtained for each 150 \( \mu \)m axially and each 200 \( \mu \)m laterally. Displacement estimation was carried out separately for each beam steering angle. As aforementioned, axial and lateral displacements are required to derive the radial and circumferential components. The axial component was estimated directly from the nonsteered 0° acquisitions both for the multi-angle and for the conventional single-angle acquisition method. The lateral component was either estimated from the nonsteered 0° acquisitions (single-angle imaging) or indirectly, by projecting the axial displacement estimates from the acquisitions at the positive and negative beam steering angles (multi-angle imaging) using

\[
\frac{u_{\text{lat},0}}{2 \sin \alpha} = \frac{u_{\text{ax},+\alpha} - u_{\text{ax},-\alpha}}{2} \tag{7-1}
\]

Here \( u_{\text{ax},0} \) and \( u_{\text{ax},\alpha} \) are the axial displacements estimated at the positive and negative beam steering angle, respectively. \( u_{\text{lat},0} \) is the lateral displacement component with respect to the nonsteered ultrasound beam. The calculated displacements of each frame were used to update the ROI for each new frame. In this way, the tissue was followed throughout the pressure cycles.

To calculate the radial and circumferential displacements a center point was defined which corresponded to the lumen center. The center point for each new frame was derived using the coordinates of the ROI of the vessel-lumen boundary. An ellipsoid was fitted through these coordinates, and the center of this ellipsoid was considered as the origin with respect to which radial and circumferential displacements were calculated. Radial and circumferential strain components were derived using 9-point 1-D least squares strain estimators [Ch. 3].

Analysis

For the vulnerable plaque simulation, the estimation precision of the multi-angle method versus the single-angle method was compared by determining the absolute difference of the radial and circumferential strain estimates with respect to the finite element solution strains. A Wilcoxon signed rank sum test was used to detect significant differences in estimation precision.

Fig. 7-2. A: Cross-sectional view of the physical phantom. B: B-mode image of the same cross-section. C: The computer controlled pump system.

Fig. 7-3. A: Multi-angle B-mode acquisition of the in vivo carotid artery. B: M-mode of the same carotid artery. The diastolic phases are marked.
For the pulsating vessel experiment, the two estimation methods were compared by constructing cumulative radial and circumferential strain images for a pressure increase of 17 mmHg (2 mmHg \( \rightarrow \) 19 mmHg). The cumulative strain (\( E_f \)) for a frame \( f \) was calculated by:

\[
E_f = -1 + \sum_{i=1}^{f} (\varepsilon_i + 1)
\]  

(7-2)

where \( \varepsilon_i \) is the interframe strain. Interframe strain is the relative change in length of tissue in frame \( i \) with respect to its length in the previous frame \( i-1 \).

For the *in vivo* acquisition cumulative radial and circumferential strain images were derived for each separate diastolic phase (Fig. 7-3B) to allow an assessment of reproducibility. Again, cumulative strain images were constructed for both methods and compared visually.

**Results & Discussion**

**Vulnerable plaque simulation**

Fig. 7-4 shows estimated radial and circumferential strain images for the vulnerable plaque simulation. The strain images constructed with multi-angle acquisition resemble the finite element strains better than those obtained with a conventional single-angle acquisition.

The visual improvement in estimation precision was also confirmed quantitatively. The absolute differences of the strain values with respect to the finite element strains were significantly (\( p<0.01 \)) smaller for the multi-angle method compared to the conventional single-angle method. Radially, the median absolute difference and inter-quartile range decreased from 0.39 (0.16-0.80)% to 0.27 (0.12-0.52)% for the circumferential strain this is at 12 and 6 o'clock. Since there was an intraluminal pressure increase, radial compression and circumferential expansion are expected. This is also observed in the strain images by multi-angle imaging. For the radial strain this is at 3 and 9 o'clock, for the circumferential strain this is positive. Furthermore, due to the presence of a soft layer inside a hard layer, the highest strain values are expected in the region which corresponds to the soft layer. This is also observed in the strain images. Unfortunately, the exact Young's moduli of the two layers of the phantom were not known, which makes it impossible to quantify the error of the strain estimates.

**Pulsating vessel phantom experiment**

Fig. 7-5 presents the cumulated strain images for the pulsating vessel phantom. It can be observed that despite the pulsations the multi-angle method outperforms the single-angle method. In those parts of the cross section, where lateral information dominates, a noisy strain pattern is observed in the images obtained by conventional imaging. This disappears in the images by multi-angle imaging. For the radial strain this is at 3 and 9 o'clock, for the circumferential strain this is at 12 and 6 o'clock. Since there was an intraluminal pressure increase, radial compression and circumferential expansion are expected.

**In vivo carotid artery**

Fig. 7-6 shows the constructed cumulative strain images for three successive diastolic phases.

*Fig. 7-4. Radial (top) and circumferential (bottom) strain images of a vulnerable plaque model. A: FEM solution. B: Strain images obtained with conventional single-angle imaging. C: Strain images constructed using multi-angle imaging.*

*Fig. 7-5. Cumulative radial (A&B) and circumferential (C&D) strain images of the pulsating vessel phantom for an intraluminal pressure increase of 17 mmHg. A&C were obtained with conventional single-angle imaging. B&D were constructed using multi-angle imaging.*

*Fig. 7-6. Cumulative radial (A&B) and circumferential (C&D) strain images of a carotid artery in successive diastolic phases. A&C were obtained with conventional single-angle imaging. B&D were constructed using multi-angle imaging.*
As can be observed the strain images are reproducible for both methods. Thus, the intra-recording reproducibility is high. In future it would also be useful to investigate inter-recording reproducibility.

As expected, due to a decrease in intraluminal pressure in the diastolic phase, expansion in radial direction and compression in circumferential direction is observed. Next to this, for a healthy volunteer circle symmetric strain images are expected. The strain images obtained with the multi-angle method are more circularly symmetric than those obtained without beam steering. Therefore, we conclude that the multi-angle method again outperforms the single-angle method also for these in vivo recordings.

**Conclusions**

In transverse vessel cross sections multi-angle strain imaging enables a more accurate estimation of radial and circumferential strains than conventional single-angle imaging. This was shown in simulations of a carotid artery with a vulnerable plaque, in a pulsating two-layered vessel phantom, and in vivo in recordings of a human carotid artery. Furthermore, the in vivo measured strains were reproducible for several pressure cycles.

**Acknowledgments**

This research is supported by the Dutch Technology Foundation STW (NKG 07589), Applied Science Division of NWO and the Technology Program of the Ministry of Economic Affairs. The authors would also like to thank Jongsik Kim, Dongkuk Shin and Jongho Yu of Medison for implementing the multi-angle acquisition mode on their Accuvix V10 system.
In this chapter the step toward the clinical application is taken. After fine-tuning according to the findings in chapters 5 and 6 the nonsegment based elastography method of chapter 4 is applied to acquire radial strain estimates for transverse cross section of 18 carotid arteries of patients that were scheduled for endarterectomy surgery. The strain results are compared with features related to plaque vulnerability that are derived from histologically stained slices of the excised plaques. Two strain parameters are defined which show to have a positive correlation with plaque vulnerability related features: an increased amount of lipids, a thin fibrous cap, superficially located macrophages, and a decreased amount of SMCs. Based on the promising results presented in this chapter, it is expected that the developed elastography method will become the first easily applicable and noninvasive method for detecting carotid artery plaque vulnerability.

CHAPTER 8

Abstract

Severe stenotic carotid artery plaque is one of the main underlying causes of stroke. Plaque rupture may release emboli resulting in occlusion of the outflow vessels and subsequent cerebral ischemia. Atheromatous inflammatory plaques with a thin fibrous cap and a reduced amount of smooth muscle cells (vulnerable plaques) have a higher risk to rupture than fibrous plaques (stable plaques). Vulnerable plaques are expected to deform (strain) more than stable plaques during the pressure cycle. Previously, a technique was developed for the estimation of radial strains in the plaque noninvasively and accurately by combining raw ultrasound radio frequency (RF) data obtained at three insonification angles (α, +20 and -20°). In the present study we investigate the relation between histological plaque vulnerability features and the radial strain estimates cumulated from the moment of maximum pressure till the moment of minimum pressure. Stage imaging was applied in vivo to 18 severely stenotic carotid arteries of symptomatic patients before carotid endarterectomy (CEA). After CEA, segments of the imaged plaque cross section were cut and histologically stained. An expert blinded from the strain results scored the presence of histological features related to plaque vulnerability. He categorized the phenotype of each plaque as being either fibrous, fibro-atheromatous, or atheromatous and also determined the thickness of the fibrous cap, the amount of smooth muscle cells (SMCs) and macrophages, and whether these macrophages were close to or far from the lumen. Two strain parameters were defined and calculated to characterize the strain map by a single value: (1) the percentile strain parameter, the xth-percentile of the strain values of a plaque in ascending order, and (2) the "percent of high strain"-area parameter, the percentage of plaque area with strain values above y percent. To investigate the performance of both parameters in differentiating the various categories of the five histology parameters, receiver operator curves (ROC) were constructed for various threshold settings and the mean area under the curve (AUC) was determined. Next, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at the optimal threshold setting were defined. Finally, the radial strain maps were visually compared with the local histology-based tissue composition. Threshold value x and y were optimal at 87% (mean AUC = 0.72) and 1.5% (mean AUC = 0.75), respectively. With these threshold settings, good differentiation was possible between atheromatous plaques and fibrocalcific plaques, between plaques with thick and thin fibrous caps, plaques with many or few SMCs, and plaques with shallow or deep macrophages. Values for sensitivity, specificity, PPV and NPV were between 60% and 100%. Macrophage quantity was difficult to determine. The performance of both strain parameters was similar. Strain maps revealed that higher strain values were observed for atheromatous regions, whereas lower strain values were observed for fibrous, collagen-rich regions. The compound strain imaging technique proposed seems promising for noninvasive detection of atherosclerotic carotid artery plaque vulnerability. A study on a larger patient population will have to be performed to strengthen the presented findings.

Introduction

Atherosclerotic carotid plaque rupture is a major underlying cause of cardiovascular death. The proneness of a plaque to rupture is mainly related to its composition and geometry [6,14,15]. Plaque development starts with the formation of fatty streaks, accumulations of lipids and intracellular debris inside the vessel wall. Progression of fatty streaks may lead to a plaque that is prone to rupture. These plaques are referred to as vulnerable plaques and are predomi-

nantly composed of thin-cap fibro-atheroma’s (TCFA) [4,6,8]. The main feature of the TCFA as compared to a relatively stable plaque is a medium to large necrotic/lipid-rich core which is separated from the blood in the lumen by a thin fibrous cap (FC), whereas the stable plaque has a much thicker cap and in many cases no necrotic core or lipid pool. Furthermore, the vulnerable plaque often presents with intraplaque hemorrhage (IPH), an increased amount of macrophages, and a decreased number of smooth muscle cells (SMC).

Detection of local plaque features of vulnerability indicates an increased risk of future cardiovascular events [27,55,180]. Thus, assessment of plaque composition at one location may serve as a surrogate marker for other vascular beds. Because vulnerable plaques are initially non-flow-limiting and, as a consequence clinically asymptomatic, a method to assess plaque composition which is noninvasive and has a low patient burden would be ideal. Carotid plaque characteristic identification has been studied by ultrasound, CT, MRI, and PET imaging. However, because ultrasound is nonionizing, fast, and relatively cheap compared to CT, MRI and PET, it seems to be the ideal imaging modality for assessment of plaque vulnerability. Duplex ultrasound is often used to investigate the luminal area reduction, plaque burden, and intima-media thickness of arterial walls in a noninvasive manner. However, using standard B-mode ultrasound images, the ratio and distribution of lipids, collagen and fibrous tissue throughout the plaque cannot be determined directly.

A relatively new ultrasound based technique is ultrasound strain imaging, which is often referred to as ultrasound elastography [90]. Vascular ultrasound strain imaging estimates the deformations/strains in the plaque and the arterial wall that arise due to the forces generated by the pulsating blood [40]. The strains are estimated by comparison of subsequently acquired ultrasound frames using cross-correlation procedures [40,59]. Because the various plaque components have different elastic properties, the components are expected to deform differently during a cardiac cycle. To determine the strains more accurately, usually the raw radio frequency (RF) ultrasound signal instead of the B-mode signal is utilized [59]. Previous intravascular ultrasound (IVUS) strain imaging studies in coronary arteries have shown that strain values differ significantly for fibrous, fibro-atheromatous and atheromatous plaques [53,54,95,181]. Furthermore, it was shown that the presence of high strain spots increased significantly for plaques of postmyocardial infarction patients compared to patients with unstable angina, and for patients with unstable angina versus patient with stable angina [182]. Recently, noninvasive variants of the technique were introduced [72,82,83,86,87,183,Ch. 2&3]. While techniques of other research groups perform strain imaging in a longitudinal imaging plane, our group recently developed a noninvasive technique allowing the estimation of radial strains for full transverse cross sections of carotid arteries using RF ultrasound data acquired at three insonification angles [Ch. 4]. The method was validated using phantom experiments and simulations. The main advantage of imaging in a transverse plane is, that it is possible to visualize the entire plaque cross section. Another advantage is that the technique is easier to extend to 3-D.

The goal of this study was to validate noninvasive three-angle strain imaging technique in vivo by showing that the measured strains are closely related to the typical features of a vulnerable plaque derived from carotid endarterectomy.
CHAPTER 8

Materials & Methods

In this pilot study, in vivo strain data of severely stenotic carotid arteries of eighteen patients were noninvasively obtained using the three-angle technique. Successive to the ultrasound strain estimation, all patients underwent a carotid endarterectomy (CEA). During this surgical intervention, the plaque together with the two innermost layers of the carotid artery was excised. After that, the true histological composition of the plaque was determined according to the protocol of an already 10-year ongoing biobank called the Athero-Express [184,185]. The plaque composition based on the histological staining was correlated with the estimated strains.

Study Population

Characteristics of the eighteen patients that underwent the CEA and preceding ultrasonic examination are presented in Table 8-1. The selection for CEA was discussed in a multidisciplinary team using international guidelines for symptomatic and asymptomatic carotid stenosis [186,187]. All patients agreed to participate in this study and written informed consent was obtained.

Table 8-1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient nr.</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Systolic pressure (mmHg)</th>
<th>Diastolic pressure (mmHg)</th>
<th>Heart rate (BpM)</th>
<th>CEA Side</th>
<th>Sympt. Status**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>M (male)</td>
<td>153</td>
<td>88</td>
<td>74</td>
<td>Left</td>
<td>ASYMP</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>M</td>
<td>161</td>
<td>88</td>
<td>56</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>M</td>
<td>132</td>
<td>76</td>
<td>64</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>M</td>
<td>119</td>
<td>81</td>
<td>57</td>
<td>Right</td>
<td>TIA</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>M</td>
<td>123</td>
<td>74</td>
<td>59</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>6</td>
<td>85</td>
<td>F (female)</td>
<td>158</td>
<td>70</td>
<td>71</td>
<td>Left</td>
<td>ASYMP</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>M</td>
<td>150</td>
<td>72</td>
<td>55</td>
<td>Left</td>
<td>TIA &amp; CI</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>F</td>
<td>124</td>
<td>63</td>
<td>99</td>
<td>Right</td>
<td>CI</td>
</tr>
<tr>
<td>9</td>
<td>72</td>
<td>F</td>
<td>78</td>
<td>43</td>
<td>65</td>
<td>Right</td>
<td>OC</td>
</tr>
<tr>
<td>10</td>
<td>74</td>
<td>M</td>
<td>139</td>
<td>87</td>
<td>68</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>11</td>
<td>84</td>
<td>F</td>
<td>150</td>
<td>72</td>
<td>55</td>
<td>Left</td>
<td>CI</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>F</td>
<td>157</td>
<td>70</td>
<td>76</td>
<td>Left</td>
<td>OC</td>
</tr>
<tr>
<td>13</td>
<td>61</td>
<td>M</td>
<td>121</td>
<td>63</td>
<td>63</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>14</td>
<td>83</td>
<td>F</td>
<td>134</td>
<td>68</td>
<td>91</td>
<td>Left</td>
<td>CI</td>
</tr>
<tr>
<td>15</td>
<td>85</td>
<td>M</td>
<td>153</td>
<td>85</td>
<td>88</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>16</td>
<td>52</td>
<td>M</td>
<td>138</td>
<td>80</td>
<td>61</td>
<td>Left</td>
<td>OC</td>
</tr>
<tr>
<td>17</td>
<td>66</td>
<td>M</td>
<td>166</td>
<td>101</td>
<td>56</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>18</td>
<td>52</td>
<td>M</td>
<td>120</td>
<td>76</td>
<td>76</td>
<td>Right</td>
<td>OC</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>69</strong></td>
<td><strong>65</strong></td>
<td><strong>65</strong></td>
<td><strong>14</strong></td>
<td></td>
</tr>
</tbody>
</table>

* median value and interquartile values
** Symptomatic status: ASYMP = asymptomatic, OC = ocular symptoms, TIA = transient ischemic attack, CI = cerebral infarction

Endarterectomy and histological analysis

During CEA the vascular surgeon excised the plaque together with the two innermost layers of the arterial wall by making a longitudinal incision in the carotid artery wall. In this way, the plaque remained completely intact except for an incision in the longitudinal direction on the ventral side of the plaque. In the laboratory for Experimental Cardiology of the University Medical Center Utrecht the histological analysis was carried out: the culprit lesion segment was identified, cut and stained according to the Athero-Express procedures published before [184,188]. The Athero-Express methods have been extensively validated [185,189]. Before and after cutting, photographs were taken of the plaque and the culprit lesion. Five different stainings were applied which enabled visualization of the following plaque components: macrophages (CD68), smooth muscle cells (alpha actin), collagen (picro-sirius red), calcifications (hematoxylin and eosin (H&E)), luminal thrombus and intraplaque bleeding (H&E, Elastin von Gieson) and lipid core size (H&E, picro-sirius red). Based on the stained slices, parameters

Materials & Methods

In this pilot study, in vivo strain data of severely stenotic carotid arteries of eighteen patients were noninvasively obtained using the three-angle technique. Successive to the ultrasound strain estimation, all patients underwent a carotid endarterectomy (CEA). During this surgical intervention, the plaque together with the two innermost layers of the carotid artery was excised. After that, the true histological composition of the plaque was determined according to the protocol of an already 10-year ongoing biobank called the Athero-Express [184,185]. The plaque composition based on the histological staining was correlated with the estimated strains.

Study Population

Characteristics of the eighteen patients that underwent the CEA and preceding ultrasonic examination are presented in Table 8-1. The selection for CEA was discussed in a multidisciplinary team using international guidelines for symptomatic and asymptomatic carotid stenosis [186,187]. All patients agreed to participate in this study and written informed consent was obtained.

Table 8-1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient nr.</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Systolic pressure (mmHg)</th>
<th>Diastolic pressure (mmHg)</th>
<th>Heart rate (BpM)</th>
<th>CEA Side</th>
<th>Sympt. Status**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>M (male)</td>
<td>153</td>
<td>88</td>
<td>74</td>
<td>Left</td>
<td>ASYMP</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>M</td>
<td>161</td>
<td>88</td>
<td>56</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>M</td>
<td>132</td>
<td>76</td>
<td>64</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>M</td>
<td>119</td>
<td>81</td>
<td>57</td>
<td>Right</td>
<td>TIA</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>M</td>
<td>123</td>
<td>74</td>
<td>59</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>6</td>
<td>85</td>
<td>F (female)</td>
<td>158</td>
<td>70</td>
<td>71</td>
<td>Left</td>
<td>ASYMP</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>M</td>
<td>150</td>
<td>72</td>
<td>55</td>
<td>Left</td>
<td>TIA &amp; CI</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>F</td>
<td>124</td>
<td>63</td>
<td>99</td>
<td>Right</td>
<td>CI</td>
</tr>
<tr>
<td>9</td>
<td>72</td>
<td>F</td>
<td>78</td>
<td>43</td>
<td>65</td>
<td>Right</td>
<td>OC</td>
</tr>
<tr>
<td>10</td>
<td>74</td>
<td>M</td>
<td>139</td>
<td>87</td>
<td>68</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>11</td>
<td>84</td>
<td>F</td>
<td>150</td>
<td>72</td>
<td>55</td>
<td>Left</td>
<td>CI</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>F</td>
<td>157</td>
<td>70</td>
<td>76</td>
<td>Left</td>
<td>OC</td>
</tr>
<tr>
<td>13</td>
<td>61</td>
<td>M</td>
<td>121</td>
<td>63</td>
<td>63</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>14</td>
<td>83</td>
<td>F</td>
<td>134</td>
<td>68</td>
<td>91</td>
<td>Left</td>
<td>CI</td>
</tr>
<tr>
<td>15</td>
<td>85</td>
<td>M</td>
<td>153</td>
<td>85</td>
<td>88</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>16</td>
<td>52</td>
<td>M</td>
<td>138</td>
<td>80</td>
<td>61</td>
<td>Left</td>
<td>OC</td>
</tr>
<tr>
<td>17</td>
<td>66</td>
<td>M</td>
<td>166</td>
<td>101</td>
<td>56</td>
<td>Left</td>
<td>TIA</td>
</tr>
<tr>
<td>18</td>
<td>52</td>
<td>M</td>
<td>120</td>
<td>76</td>
<td>76</td>
<td>Right</td>
<td>OC</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>69</strong></td>
<td><strong>65</strong></td>
<td><strong>65</strong></td>
<td><strong>14</strong></td>
<td></td>
</tr>
</tbody>
</table>

* median value and interquartile values
** Symptomatic status: ASYMP = asymptomatic, OC = ocular symptoms, TIA = transient ischemic attack, CI = cerebral infarction

Endarterectomy and histological analysis

During CEA the vascular surgeon excised the plaque together with the two innermost layers of the arterial wall by making a longitudinal incision in the carotid artery wall. In this way, the plaque remained completely intact except for an incision in the longitudinal direction on the ventral side of the plaque. In the laboratory for Experimental Cardiology of the University Medical Center Utrecht the histological analysis was carried out: the culprit lesion segment was identified, cut and stained according to the Athero-Express procedures published before [184,188]. The Athero-Express methods have been extensively validated [185,189]. Before and after cutting, photographs were taken of the plaque and the culprit lesion. Five different stainings were applied which enabled visualization of the following plaque components: macrophages (CD68), smooth muscle cells (alpha actin), collagen (picro-sirius red), calcifications (hematoxylin and eosin (H&E)), luminal thrombus and intraplaque bleeding (H&E, Elastin von Gieson) and lipid core size (H&E, picro-sirius red). Based on the stained slices, parameters
were defined that characterized the plaque composition. An expert, who was blinded from the strain results, scored the plaques as being fibrotic, fibro-atheromatous, or atheromatous based on the amount of lipid content and collagen observed. This parameter will be referred to as the phenotype of the plaque. The expert also determined whether a plaque had none to minor or moderate to major amounts of smooth muscle cells. The amount of macrophages was also quantified in this way. The position of the macrophages, if present, was also determined and defined as either being shallow or deep with respect to the lumen. The thickness of the fibrous cap was classified as being either thick, thin or intermediate. In total this resulted in five distinct parameters: (1) plaque phenotype, (2) smooth muscle cell quantity, (3) macrophage quantity, (4) macrophage position, (5) cap-thickness. Although thrombus, intra-plaque bleeding and calcifications were often observed in the plaques, these components were not used for further analysis, because it was questionable whether these components were still intact after the preparation procedure followed for the histological staining.

To determine the orientation and rotation of the slices with respect to the ultrasound recordings before strain estimation, the photographs taken during the plaque preparation process were used together with echograms (calculated from the ultrasound RF data after log compression, rectification and Hilbert transformation). The upside of the plaque was roughly determined based on the location of the surgeon’s incision in the excised plaque before cutting as observed on the photograph. The position of the bifurcation enabled us to differentiate between the downstream and upstream side of the slice. By examination of the position of the ICA with respect to the ECA on the photographs and comparing it to the anatomy observed on the constructed ultrasound image, the exact rotation of the plaque was more precisely determined. Sometimes the location of calcifications, which appear brightly on the ultrasound image, were also used to determine the orientation of the slice with respect to the strain image.

**Displacement and radial strain estimation**

The estimation of the radial strains in the vessel wall and plaque due to the pulsating blood flow was carried out in six steps. A flowchart of these steps is presented in Fig. 8-1C. Step one consisted of preprocessing of the RF data. The RF data were band-pass filtered to remove grating lobe artifacts using the adaptive band-pass filter which was described in chapter 5. Also, the beam steered data were re-aligned in lateral direction according to previously described procedures [Ch. 2]. In step 2 the ultrasonic frames were identified that corresponded to the moments of maximum and minimum vessel diameter during each pressure cycle. These frames were determined visually by constructing an M-mode view of the ultrasound line which crossed the center of the lumen using custom made software written in Matlab 2010b (MATLAB, the Mathworks, Natick, MA, USA). After this procedure, the pressure cycle (maximum till next maximum diameter) with the lowest amount of out of plane motion was selected for each patient. This was performed objectively by using the method described in Appendix A. In step 4, a region of interest (ROI) was defined in the first frame of the selected pressure cycle that corresponded to the vessel wall with plaque. This was performed by manually drawing the inner and outer vessel wall border after inspection of the vessel motion throughout the pressure cycle. The ROI was drawn in the 0° direction image and projected onto the beam steered data. In step 5, the displacement estimates for every 12.5 μm in the vertical direction and every 200 μm in the horizontal direction were estimated by using the coarse-to-fine 2-D cross-correlation displacement estimation techniques and displacement compounding methods that were described in [59] and in chapter 4, respectively. A more elaborate description and the exact settings of the displacement estimation is given in Appendix B. The algorithm determines horizontal and vertical displacement estimates for every 12.5 μm in the vertical direction and every 200 μm in the horizontal direction. Displacements for the ROI were cumulated over the entire pressure cycle. In the final step the cumulative radial displacements and strains were estimated. The radial displacements were obtained by combining the horizontal and vertical displacements and projecting them in the radial direction. The center coordinates of an ellipse fitted through the coordinates of the vessel-lumen boundary points of the ROI was considered as lumen center with respect to which the projection was carried out. To derive the radial strains, the cumulative radial displacements were interpolated onto a polar grid using bilinear interpolation, see also chapter 3. The sampling distance of the polar grid was 1° in the circumferential direction and 100 μm in the radial direction. A 2-D least squares estimator of 9 points in radial direction and 5 points in circumferential direction was applied to derive the radial strain [190].
CHAPTER 8

Analysis

From the strain analysis a series of strain images were obtained. We chose to use the cumulative strain image obtained over the period from maximum to minimum diameter for further analyses, because the strain contrast is largest over this diastolic period and because the inter-frame motion is less than when tracking from minimum to maximum diameter (systolic period) would be performed [46]. The moments of maximum and minimum diameter correspond to the systolic and diastolic pressures in the pressure cycle and therefore allow to correct for inter-patient differences in blood pressure. The normalization for blood pressure was carried out according to:

\[ \varepsilon_{\text{norm}} = \frac{40}{p_{\text{sys}} - p_{\text{dias}}} \varepsilon_{\text{ meas}} \]  
(8-1)

where \( \varepsilon_{\text{norm}} \) is the normalized strain, \( \varepsilon_{\text{meas}} \) is the estimated strain, and \( p_{\text{sys}} \) and \( p_{\text{dias}} \) are the systolic and diastolic pressures in mmHg for a certain patient.

To quantify the strain results, two strain parameters were defined. The first one was the percentile strain parameter: the \( y\text{-th} \) percentile of the strain values of a patient’s normalized cumulative strain image in ascending order. The second parameter was the percent of “high strain”-area parameter: the percentage of strain values of a patient’s normalized cumulative strain image with values above threshold value \( y \). In other words, this second parameter describes the percentage of plaque area where strains above \( y\% \) strain are estimated. To determine the values for the threshold-parameters \( x \) and \( y \) that allowed the best overall differentiation between the lowest and highest categories of the five parameters, receiver operating characteristic (ROC) curves were constructed for varying settings of parameter \( x \) and \( y \). \( x \) was varied between 1\% and 100\% using increments of 1\%, and \( y \) was varied between 0\%-strain and 20\%-strain in steps of 0.5\% strain. The area under the curve (AUC) for each ROC curve was determined and a mean AUC curve was constructed by averaging the AUC values of the individual parameters. The threshold settings for \( x \) and \( y \) that resulted in the highest mean AUC values were considered as the most optimal settings. From the ROC curves corresponding to these optimal settings, values for sensitivity and specificity were derived and additionally the positive predictive value (PPV) and negative predictive value (NPV) were calculated. In this study, sensitivity describes which percentage of the plaques that has a “high vulnerability” value for a certain histological parameter is also classified as “highly vulnerable” based on the strain parameter. Specificity is defined as the percentage of the plaques that are considered to have a “low vulnerability” for a particular histological parameter based on the strain parameter which also have a “low vulnerability” based on the histological analysis. The definition of NPV is equal to that for sensitivity, however then for features of low vulnerability. Likewise, PPV is similar to the definition of specificity, however then for features of high vulnerability. In case a histological parameter was categorized in three levels of vulnerability, as was the case for the parameters phenotype and cap-thickness, only the lowest and highest level were taken into account for the ROC analysis. Additional boxplots were constructed to investigate the relation between strain and histology for these three-level parameters. To conclude the analysis, visual matches between cumulative strain images with the histological composition of plaques were determined.

Results

Histological results

The amounts of plaques with histological parameters in each category of vulnerability are presented in Table 8-2. In one case the amount of smooth muscle cells could not be clearly estimated from the staining, for two other cases the thickness of the cap could not be determined with certainty. These cases are indicated as “Other” values in Table 8-2. For “macrophage position” only 8 plaques were considered, because no macrophages were present in the other 10 plaque specimen.

Technical applicability

Ultrasound RF acquisitions could be obtained successfully in all patients. In eight of the eighteen arteries color Doppler mode was required to discriminate between the lumen and the plaque burden.

Strain results

The AUC graphs from which the optimal threshold settings for the strain parameters were determined are presented in Fig. 8-2. As can be observed the maximum mean AUC for the percentile strain parameter was 0.72 and it was found when the 87%-percentile of the strain values for each patient was considered. For the “percent of high strain”-area the optimal threshold was found at 1.5\% strain with a mean AUC of 0.75 (Fig. 8-2B). The sensitivity, specificity, PPV and NPV values found when the strain parameters were set at these threshold values are presented in Table 8-3 and Table 8-4. In general the performance of both strain parameters in terms of sensitivity, specificity and PPV and NPV is good for all parameters, except the macrophage quantity parameter: all values were between 60\% and 100\%. The performance of both strain parameters was similar: the values for sensitivity, specificity, PPV and NPV were exactly the same for phenotype, amount of SMCs and macrophage position. For the other two histological parameters the values were close, although the performance of the percent high strain parameter was slightly better for the determination of macrophage quantity and slightly less for cap thickness than for the percentile strain parameter.

Both strain parameters allowed a perfect classification of the macrophage position. However, as can be observed in Table 8-2 only two of the 8 plaques with macrophages were considered as plaques with “deep” macrophages, thus overinterpretation of the results is possible. A boxplot which gives additional information on macrophages and their impact on the strain

<table>
<thead>
<tr>
<th>Vulnerability grade</th>
<th>Phenotype</th>
<th>SMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>8 (44%)</td>
<td>7 (39%)</td>
</tr>
<tr>
<td>Medium</td>
<td>5 (28%)</td>
<td>10 (52%)</td>
</tr>
<tr>
<td>High</td>
<td>5 (28%)</td>
<td>10 (52%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cap thickness</th>
<th>Macrophages quantity</th>
<th>Macrophages position</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 (39%)</td>
<td>6 (30%)</td>
<td></td>
</tr>
<tr>
<td>10 (56%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>2 (11%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>6 (33%)</td>
<td>10 (56%)</td>
<td></td>
</tr>
</tbody>
</table>
parameters is shown in Fig. 8-3A. The left and center columns show the strain parameter values as a function of macrophage position. It can be observed that macrophages far from the lumen have lower strain parameter values than macrophages close to the lumen, which also is according to what is expected, because macrophages weaken the fibrous cap by destroying the collagen structure. The right columns show the strain parameter values for those cases in which no macrophages were present. As can be observed these had values that were in the range of plaques with both shallow and deep macrophages.

The performance of the strain parameters for the differentiation in phenotype for all three categories is visualized in the boxplot of Fig. 8-3B. As can be observed there is a global increase for the value of both strain parameters when the plaque becomes more atheromatous. This makes sense, because in fibrotic plaque, collagen makes the plaque stiff and therefore the plaque can hardly deform. An example of a fibrotic plaque and the corresponding histological and strain results is shown in Fig. 8-4. As can be observed the strain image reveals much lower strains than for the atheromatous plaque shown in Fig. 8-5. In that plaque strains over 10% were observed in the top left region, due to the softness of the lipids and thrombus. Furthermore, a lot of macrophages are present in the region surrounding the lipid pool, which probably made the plaque very vulnerable. The thrombus is probably the result of a previous rupture of the thin fibrous cap, which can still be observed in the histology images as an interruption in the collagen structure. As expected based on Fig. 8-3B fibro-atheromatous plaques reveal strain values that are in between those for atheromatous and fibrous plaques. For instance in the fibro-atheromatous plaque of Fig. 8-6, higher strains were observed for the lipid-rich region on the bottom left (yellowish on the photograph) than for the collagen rich region on bottom right (reddish on the photograph). Note that the sign of the radial strain was positive relating to measurement of wall expansion during the intraluminal pressure drop from systole to diastole.

Only one plaque was categorized as a plaque with intermediate cap thickness (Table 8-2), therefore no additional boxplot was constructed, although the value for both strain parameters for that plaque was in between that of the plaques with thin and thick caps.

### Table 8-3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>80%</td>
<td>75%</td>
<td>67%</td>
<td>86%</td>
</tr>
<tr>
<td>SMCs</td>
<td>70%</td>
<td>71%</td>
<td>78%</td>
<td>63%</td>
</tr>
<tr>
<td>Cap thickness</td>
<td>80%</td>
<td>60%</td>
<td>82%</td>
<td>75%</td>
</tr>
<tr>
<td>Macro quantity</td>
<td>71%</td>
<td>55%</td>
<td>50%</td>
<td>75%</td>
</tr>
<tr>
<td>Macro position</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

of the thin fibrous cap, which can still be observed in the histology images as an interruption in the collagen structure. As expected based on Fig. 8-3B fibro-atheromatous plaques reveal strain values that are in between those for atheromatous and fibrous plaques. For instance in the fibro-atheromatous plaque of Fig. 8-6, higher strains were observed for the lipid-rich region on the bottom left (yellowish on the photograph) than for the collagen rich region on bottom right (reddish on the photograph). Note that the sign of the radial strain was positive relating to measurement of wall expansion during the intraluminal pressure drop from systole to diastole.

Only one plaque was categorized as a plaque with intermediate cap thickness (Table 8-2), therefore no additional boxplot was constructed, although the value for both strain parameters for that plaque was in between that of the plaques with thin and thick caps.

### Table 8-4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotype</td>
<td>80%</td>
<td>75%</td>
<td>67%</td>
<td>86%</td>
</tr>
<tr>
<td>SMCs</td>
<td>70%</td>
<td>71%</td>
<td>78%</td>
<td>63%</td>
</tr>
<tr>
<td>Cap thickness</td>
<td>80%</td>
<td>60%</td>
<td>82%</td>
<td>75%</td>
</tr>
<tr>
<td>Macro quantity</td>
<td>71%</td>
<td>64%</td>
<td>56%</td>
<td>78%</td>
</tr>
<tr>
<td>Macro position</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

of the thin fibrous cap, which can still be observed in the histology images as an interruption in the collagen structure. As expected based on Fig. 8-3B fibro-atheromatous plaques reveal strain values that are in between those for atheromatous and fibrous plaques. For instance in the fibro-atheromatous plaque of Fig. 8-6, higher strains were observed for the lipid-rich region on the bottom left (yellowish on the photograph) than for the collagen rich region on bottom right (reddish on the photograph). Note that the sign of the radial strain was positive relating to measurement of wall expansion during the intraluminal pressure drop from systole to diastole.

Only one plaque was categorized as a plaque with intermediate cap thickness (Table 8-2), therefore no additional boxplot was constructed, although the value for both strain parameters for that plaque was in between that of the plaques with thin and thick caps.
**Discussion**

With respect to the quantitative analysis of the global plaque, promising results were obtained. It was shown that the value of both strain parameters increased when a plaque had increased features of vulnerability: an increased amount of lipids, an increased amount of macrophages close to the lumen, a thinned fibrous cap, and a decreased amount of smooth muscle cells. All these histological vulnerable features could be detected with a sensitivity, specificity, PPV, and NPV of at least 71%, 60%, 67%, and 60%, respectively. Although other imaging modalities, like MRI and PET-CT have shown similar or in some cases higher sensitivity and specificity values, none of these techniques has all of the advantages ultrasound has: easy applicability, non-ionizing radiation, relatively low cost, fast and no contra-indications for certain patients [5]. If we compare these results to the results obtained for IVUS strain imaging then we see that the sensitivity, specificity, PPV and NPV are lower.

*In vitro* vulnerable coronary artery plaques were detected using IVUS with a sensitivity and a positive predictive value of 88% each, and a specificity and negative predictive value of 89% [95]. In an *in vivo* validation study in which iliac and femoral arteries of Yucatan pigs were examined sensitivities and specificities of 100% and 80% were reported for the detection of atheromatous versus fibrous plaques [53]. However, the plaques in the latter study were not advanced and only contained fibrous and fatty material. Therefore, these results cannot be compared directly to the findings in this study. Furthermore, some differences between the intravascular and noninvasive approach are present. Firstly, intravascularly radial strain maps were estimated from two successively acquired ultrasound frames. To be able to correct for inter-patient differences in blood pressure levels, in this study strains were tracked from the moment of maximum diameter (maximum pressure) till the moment of minimum diameter (minimum pressure), which is a time period of 20 to 25 frames. When cumulating strains for each of these individual images, it is more likely that errors also cumulate. Secondly, intravascularly the ultrasound beams are transmitted radially, which is not the case for the noninvasive situation. Strain estimation is most accurate in the
direction of the ultrasound beam, because in that direction the phase information of the ultrasound signal can be used to enhance the estimation accuracy. Therefore, the situation for measuring radial strain is ideal intravascularly, whereas it is suboptimal noninvasively. However, using the linear array transducer, the ultrasound beam can be better focused especially in receive, resulting in improved image quality. Nevertheless, despite the lower sensitivities and specificities, the observed trends in the relation between strain and the various histological features of vulnerability are similar as in the IVUS studies: strains increase with an increase in fat content, fibrous cap thinning, a decrease in SMC concentration and an increase in macrophage concentration. The real potential of this technique can only be assessed when the number of patients is increased.

If we compare the performance of both strain parameters then we find that both parameters perform similarly, although thin fibrous caps can be determined slightly better with the percentile strain parameter, whereas macrophage quantity can be determined slightly better with the percentile “high strain”-area parameter. Because of this finding it was also investigated if a combination of the two parameters leads to a better overall sensitivity and specificity. All possible combinations of the x- and y- threshold values were investigated. The maximum overall AUC that was achieved was 0.75, which was equal to the mean AUC reached with the percentile “high strain”-area parameter. Therefore, it was concluded that a combination of both parameters did not lead to an improved overall detection of vulnerable plaque features. In this study, the threshold value that resulted in the best overall differentiation of all five histological plaque features was determined. However, it is also possible to optimize the threshold for each separate histological plaque feature, which results in similar or higher sensitivity and specificity values for each parameter. Because this would make the analysis more complex and because the optimal AUC was found at approximately the same thresholds for each individual plaque feature, it was decided not to perform the analysis separately for each parameter.

The observation that plaques without macrophages are in the same strain range as plaques with either deep or shallow macrophages (Fig. 8-3A) might be surprising, because plaques without macrophages are usually found to be more stable than plaques with macrophages. However, a plaque without macrophages can have other features of vulnerability, like a thin cap and a lipid pool, as was shown for instance in the plaque of Fig. 8-5. The opposite can also be the case, a plaque with macrophages can also be rather stable, as was the case for the plaque shown in Fig. 8-4.

As shown in Fig. 8-4, Fig. 8-5 and Fig. 8-6 strain patterns match locally with plaque composition, regions with high lipid concentration deformed more than regions that consisted mainly of collagen. This was however all based on visual inspection, quantification of the degree of local matching was not carried out. Quantification was not performed, because it was nearly impossible for at least two reasons. Firstly, because it was difficult to determine the exact rotation of the histological subslices with respect to the ultrasound recordings for some plaques. This was either because there were no differences in echogeneity between the various plaque regions, or because the plaque was no longer in intact shape after the CEA and the histological preparation. Secondly, strain is a parameter which does not only relate to tissue composition, but also to tissue geometry. For instance, regions distal from the lumen usually deform less than regions close to the lumen, because the force applied per unit area is smaller. It might be possible to deal with this issue by constructing a relative Young’s modulus image instead of a strain image, thus reconstruction of the true elastic modulus of the tissue instead of the deformation in the tissue [69,191-193]. These methods do however not only require accurate strain estimates as input, but also an accurate knowledge of the applied stresses and geometry of the tissue, which makes them rather difficult to apply.

A limitation of this study is the number of patients included. Only 18 patients were considered now. This made it impossible to draw statistically significant conclusions. For instance in the analysis of the strain values in relation to macrophage position, the category of deep macrophages was represented by two plaques only. Therefore, more patients will have to be included to solidify the findings of the present study.

Another limitation of the study is the fact that the amount of thrombus and calcifications could not always be reliably determined from the histology specimen. In the surgical procedure, the arterial wall is longitudinally dissected which specifically may affect the size of pre-existent luminal thrombus. In addition, calcified plaques first underwent a decalcification step to allow the microdissection. Calcium could be visualized but not quantified for that reason.

Finally we would like to remark that the strain findings in this study might be suboptimal, because there is still room of improvement for the ultrasound strain imaging method applied. For instance, motion of the vessel in the longitudinal direction was considered to be negligible in this study. This is of course not entirely correct, because longitudinal motion of the vessel does occur during the cardiac cycle as measured in other studies [82,129, Ch. 10]. To cope with this out of plane motion, a 3-D version of the compounding technique would have to be developed. Although methods for 3-D strain estimation exist, they are usually applied for cardiac imaging and therefore use a lower frequent matrix array probe [194]. For 3-D vascular compound strain imaging a dedicated probe and imaging sequence would have to be developed. Methods for faster acquisition of ultrasound data, like plane wave imaging [144, Ch. 9], would also be very useful to reduce artifacts that arise due to motion in between the acquisition at the various beam steering angles.

**Conclusions**

Noninvasive ultrasound strain imaging/elastography using compounding of ultrasound RF data from three beam steering angles allows in vivo estimation of cumulative radial strains in transverse cross sections of human carotid artery plaques. Local matches were observed between the strain patterns and the actual plaque composition as determined by histological staining. Furthermore, two strain parameters were defined which showed a positive correlation with plaque vulnerability related features, like an increased amount of lipids, a thin fibrous cap, superficially located macrophages and a decreased amount of SMCs. This makes the investigated strain imaging method very promising for assessment of carotid artery plaque vulnerability.

**Acknowledgements**

The authors like to acknowledge Donkuk Shin, Jong-Sik Kim, Jongho Yu and Wim van de Voo- ren of Samsung Medison for the implementation of the radial zone scanning mode on the
Appendix A: Method for determining the optimal pressure cycle

For each patient a number of frames was selected that corresponded to the moments that the vessel was maximally dilated. A pressure cycle was defined as the period between two successive moments of maximum dilation. To find the pressure cycle in which the lowest amount of out of plane motion appeared for a certain patient, we looked at image correlation during a pressure cycle. Since the image correlation between successive frames decreases when out of plane motion intensifies, the pressure cycle that had the highest median cross-correlation value over the entire pressure cycle was selected as optimal pressure cycle for a certain patient.

To calculate the cross-correlation values for each image frame, first the RF data were transformed into "envelope" data by applying a Hilbert transform followed by rectification. Next, a small rectangular region-of-interest (ROI) was manually drawn which enclosed the cross section of the artery with plaque. The "envelope" data within this ROI for each frame (reference frame) were cross-correlated with the "envelope" data in a larger "search" region of the four subsequent frames, which resulted in four cross-correlation functions. The lowest value of the peaks of these cross-correlation functions was used as a value for the degree of correlation for the reference frame.

Appendix B: Horizontal and vertical displacement estimation

First axial and lateral displacements were estimated for every separate beam steering angle. This was performed in four iterative steps. In each iteration the 2-D cross-correlation function for windows of ultrasound data of one frame (predeformation frame) and larger windows of ultrasound data in the subsequent frame were calculated (postdeformation frame). The axial position and lateral positions of the maximum of each 2-D cross-correlation function were determined. The axial position was translated into an axial displacement estimate given the axial sampling frequency, the speed of sound (1540 m/s). The lateral position was translated into a lateral displacement using the information that the transducer's pitch was 200 μm. The predeformation windows overlapped 80% in the axial direction and 67% in the lateral direction. In the first iteration envelope data (rectified RF data after Hilbert transform) were used for the cross-correlation. In the other iterations the raw RF data were used. In iteration 1 predeformation windows of 100 axial points by 3 lateral lines were cross-correlated with postdeformation windows of 150 axial points by 9 lateral lines to find "coarse" displacement estimates. In iterations 2 and 3 window sizes were halved in axial direction such that "finer" displacements were obtained. Estimates of preceding "coarser" iterations were used to guide the cross-correlation function to the correct peak in each new iteration. In the final iteration, the accuracy of the displacements was improved further by subsample "aligning" of the postdeformation data in axial direction before cross-correlating. To this end, the peaks of the cross-correlation functions found during iteration 3 were interpolated in axial direction by fitting a parabolic function to obtain subsample displacement estimates [99,76]. These subsample displacements were used to align the postdeformation window centers with the centers of the predeformation windows by interpolating and shifting the postdeformation data in axial direction. In chapter 6 it was shown for shearing and rotating tissues improved displacement estimates can be obtained when free-shape windows instead of rectangular postdeformation windows. Because we know that there are regions of axial and lateral shearing in the plaque, due to the radial motion of the tissue [195], iterations 2 to 4 were repeated twice: once using rectangular windows and once using free-shape windows. To determine which of the two window shapes provided the most reliable displacement estimate the height of the peaks of the cross-correlation functions for both methods were compared. The displacement estimate that resulted in the highest peak was considered as most accurate and used for the following iterations. In between iterations displacement were filtered using a median filter with a size of 9 by 9 displacement points to reduce the number of outliers. In total these iterations resulted in axial and lateral displacements for each separate beam steering angle.

To obtain accurate horizontal and vertical displacement estimates for the ROI over the entire pressure cycle only the axial displacements estimates of the various beam steering angles were used. The lateral displacements were not considered, because these are usually less accurate. The 0° axial displacement estimate is aligned with the vertical direction and was therefore used as vertical displacement estimate. The horizontal displacements were obtained by projection of the axial displacement estimates from the other two insonification angles according to the methods described in chapter 4. Additional filtering was performed for all horizontal and vertical displacement estimates that were detected to be outliers. Outliers were defined as displacement values that exceeded the median value of its 9x9 neighbours by more than 10 μm. The outliers of the still more noisy horizontal displacement estimates were filtered with a median filter of 15x13 displacement points; the vertical displacement outliers were filtered with a median filter of 9x3 displacement points. The displacements derived for each frame were used to update the ROI for each new frame. In this way, the tissue was tracked over the pressure cycle.
PART IV: RECENT DEVELOPMENTS
The transmission of unfocused plane wave ultrasound, instead of line-wise focused ultrasound, enables ultrasound image formation and strain estimation at much higher frame rates. In this chapter beam steered plane wave transmission is applied to derive strain images of a simulated vulnerable plaque and the results are compared to those obtained with conventional 0° line-wise focused ultrasound transmission and beam steered focused ultrasound transmission. It is found that beam steered plane wave transmission allows more accurate strain estimation than conventional 0° line-wise focused ultrasound transmission at frame rates that are 150 times higher. Compared to beam steered focused transmission, strain estimation is slightly less accurate with plane wave transmission. However, frame rates are still at least a factor 50 higher. Therefore, plane wave imaging might be very useful to extend the developed nonsegment based technique to three dimensions.

Abstract

Ultrasound strain imaging can be used to assess local mechanical properties of tissue. From conventional nonsteered 2-D ultrasound data, the axial (along the beam) displacements and strains can be estimated precisely, whereas lateral (perpendicular to the ultrasound beam) displacements and corresponding strains are more complicated to estimate. The lateral displacements/strains can be estimated more precisely by adding data from acquisitions at various large beam steering angles, although frame rates are reduced. Plane wave ultrasound transmission enables ultrasound acquisition at high frame rates. This study investigated beam steered plane wave ultrasound transmission for full strain tensor estimation at high frame rates. Using finite element modeling (FEM) and Field II, ultrasound radio frequency data of a vessel with a vulnerable plaque were generated before and after the vessel underwent an intraluminal pressure increase of 4 mmHg. RF data were simulated for a linear array transducer (3-11 MHz, f₀ = 39 MHz, pitch = 335 μm) that either transmitted focused pulses or plane waves at beam steering angles of -30°, 0°, and 30°. In receive dynamic focusing was applied. Band limited noise was added to obtain a signal-to-noise ratio of 20 dB. Displacements were iteratively estimated using 2-D cross-correlation. Next, principal strains were derived using 1-D least squares strain estimators. The absolute differences between the estimated principal strains and the FEM principal strains were determined to compare the transmission methods. It was found that plane wave beam steering enabled a fast and more precise estimation (Wilcoxon, P < 0.001) of the full strain tensor than conventional 0° strain imaging. Although focused beam steering provided slightly more precise estimates, the main advantage of the plane wave approach is that it suffers less from motion artifacts when imaging tissue in vivo, due to its at least 50 times higher frame rate.

Introduction

Ultrasound strain imaging is a technique that was first reported by Ophir et al. [90] and was developed to differentiate between malignant and benign tissue based on the deformation pattern of the tissue in reaction to a force. Cross-correlation of raw radio frequency (RF) ultrasound data acquired before and after deformation yields the displacement field that occurs in the tissue and the corresponding strains can be derived by spatial derivation. From conventional nonsteered ultrasound acquisitions, the axial (along the beam) displacement and strain can be estimated precisely. Lateral (perpendicular to the beam) displacements are more difficult to estimate due to the lower resolution and the lack of phase information. However, we have shown that beam steering (electrical steering of the ultrasound beam) also allows an improved estimation of the lateral displacements by combining axial data from acquisitions at two large beam steering angles [Ch. 4]. For the study of tissue in motion this method might give rise to motion artifacts, because the time between the subsequently acquired frames with different beam steering angles is substantial.

Traditionally, ultrasound is acquired line-by-line, which means that the echo pulse transmitted for one echo-line has to be returned before the echo pulse for the next line is transmitted. More recent ultrasound systems, like the Philips IE33 also transmit two or more echo-lines simultaneously, which increases frame rates. With recent advances in computational capacity/speed it has become possible to transmit an unfocussed plane wave and reconstruct all echo-lines in receive at once by software processing, enabling 100 times higher frame rates [68,142].

Strain imaging with plane wave transmission has been reported in several studies [68,142,196,197]. It was found that plane wave transmission only slightly reduced strain estimation precision compared to conventional imaging [197]. This study investigates beam steered plane wave ultrasound transmission for full strain tensor estimation using 2-D cross-correlations. To our knowledge, the use of beam steered plane waves has only been applied before to assess shear wave propagation [142,196].

Materials & Methods

Finite Element Modelling

A finite element model (FEM) of a carotid artery with a vulnerable plaque was constructed, because we are interested in noninvasive strain imaging of carotid arteries for early identification of vulnerable plaques and prevention of stroke [83, Ch. 3&4]. The geometry of the vessel with plaque was an upscaled version of a previously published FEM model for coronary artery atherosclerosis [116]. A vulnerable plaque is characterized by a large lipid pool that is separated from the lumen by a thin fibrous cap [8,198]. The geometry and the Young’s modulus distribution of the model are presented in Fig. 9-1. The lumen center was located at a depth of 16 mm.

The vessel area was divided into over 20000 triangular finite elements using the partial differential equation toolbox of Matlab R2007a (The MathWorks, USA). All elements were assumed to be nearly incompressible (Poisson’s ratio, \( \nu = 0.495 \)) and isotropic. A very soft (\( E = 1 \) Pa) compressible (\( \nu = 0.001 \)) layer of 2 mm thickness was added to avoid rigid body translation during the FEM calculation. This layer was not considered during the strain analysis. Finally, the 2-D displacement field of the vessel was calculated for an intraluminal pressure increase of 4 mmHg under the assumption of plain strain using the same toolbox.

Simulations

RF ultrasound data of the vessel pre- and postdeformation were simulated using Field II [120,121]. Field II requires the user to define a transducer, a scanning sequence and a matrix which contains the three-dimensional coordinates of scatterers with respect to the transducer surface.

Strains and the FEM principal strains were determined to compare the transmission methods. It was found that plane wave beam steering enabled a fast and more precise estimation (Wilcoxon, \( P < 0.001 \)) of the full strain tensor than conventional 0° strain imaging. Although focused beam steering provided slightly more precise estimates, the main advantage of the plane wave approach is that it suffers less from motion artifacts when imaging tissue in vivo, due to its at least 50 times higher frame rate.

**Fig. 9-1. Vulnerable plaque geometry and Young’s modulus distribution.**
A linear array transducer was defined with 288 elements. The element pitch, width and height were 135 μm, 121.5 μm and 6 mm, respectively. The frequency band of the transducer was 3 to 11 MHz and the RF sampling frequency was 39 MHz. The transducer transmitted either focused pulses (conventional imaging) or plane waves at beam steering angles of -30°, 0° and 30° (Fig. 9-2). In focused mode, a maximum of 128 elements was simultaneously activated and the focus was at 16 mm (corresponding to the lumen center). To generate the plane waves, in plane wave mode the focus was set to 100 m and the number of simultaneously active elements was set to 228. In receive dynamic focusing was applied (F-number of 0.875).

The scatterer matrix of the vessel before deformation was created by random distribution of one million scatterers within the vessel area. The postdeformation position of each scatterer was defined as its predeformation position plus the axial and lateral displacement component as obtained from the FEM. Elevational motion was set to zero.

**RF data postprocessing**

Beam steering at large angles results in distortions caused by grating lobes [104]. Grating lobes are a frequency dependent phenomenon and can be removed by low-pass filtering [Ch. 2&5]. Band-pass filtering with cutoff frequencies of 2.5 MHz and 7.6 MHz was applied to the data sets acquired at -30° and 30° of beam steering. The 0° RF data were also band-pass filtered, however with cutoff frequencies of 2.5 MHz and 11.5 MHz. To make sure that the simulations were more realistic, band limited noise was added to obtain a signal-to-noise ratio of 20 dB. The procedure for adding noise is described in chapter 3.

**Displacement estimation**

2-D displacements were iteratively estimated using a coarse-to-fine 2-D cross-correlation method as described in [59]. Displacement estimation was carried out separately for each beam steering angle and for both transmission methods. Displacement values were obtained for every 20 μm axially by 135 μm laterally. The lateral displacement component was either obtained directly, without beam steering (Fig. 9-3A) or indirectly, by projecting the axial displacement estimates from beam steered acquisitions at angles of +30° and -30° (Fig. 9-3B) using

\[
 u_{lat,0} = \frac{u_{ax,1} \cos \alpha_2 - u_{ax,2} \cos \alpha_1}{\sin(\alpha_1 - \alpha_2)}
\]  

(9-1)

Here \( u_{ax,1} \) and \( u_{ax,2} \) are the axial displacements estimated at beam steering angles \( \alpha_1 \) and \( \alpha_2 \), respectively, and \( u_{lat,0} \) is the lateral displacement component as obtained in a conventional nonsteered acquisition.

**Strain estimation**

The corresponding axial, lateral and shear strain components were derived using 1-D least squares strain estimators [48] with a kernel size of 9 displacement values. Once the full strain tensor was estimated, principal strains were calculated by principal component analysis [107].

**Statistics**

The absolute differences (\( \Delta e \)) between the estimated strains and the FEM principal strains were determined to compare the strain estimation precision for the various transmission methods both with and without beam steering. Wilcoxon rank sum tests were performed to detect significant improvements in estimation precision.

---

**Fig. 9-2.** A schematic representation of the various simulated ultrasound transmission methods.

**Fig. 9-3.** The axial and lateral displacement component can either be estimated A: directly from an acquisition without beam steering, or B: by projection of axial displacement components measured at two different beam steering angles.
Results & Discussion

Fig. 9-4 shows the first and second principal component strains that were obtained for the various ultrasound transmission methods. As can be observed, the best estimates were obtained for the methods that used beam steering. The strain images obtained with plane wave transmission were similar to those obtained using conventional ultrasound transmission. Table 9-1 presents the Δe values that were found for the various methods. In agreement with the study by Park et al. [197], plane wave imaging resulted in less precise strain estimates than conventional imaging, although the differences were small. The lowest errors were observed when using beam steering, which supported the findings from Fig. 9-4. Compared to conventional 0° imaging, Δe was significantly lower when using beam steered plane wave acquisitions (Wilcoxon, P<.005). Thus, the new approach enables a more precise estimation of the full strain tensor than conventional 0° imaging at frame rates that are approximately 50 times higher (for an image composed of ~150 lines).

Although conventional beam steering provided slightly, but significantly more precise estimates, this lower precision can probably be compensated by averaging of several successively acquired interleaved strain images in plane wave mode or by addition of information from more than three beam steering angles [96]. For a three-angle acquisition, frame rates can be up to 150 times higher (3 plane wave transmissions versus 3 times 150 line-wise transmissions in focused mode). This frame rate advantage will lead to less motion artifacts when imaging tissue in vivo and might also compensate for the reduction in strain estimation precision.

There is one limitation of the beam steering method. It can only be used for superficial tissue, because the tissue needs to remain in the field of view for all beam steering angles. However, this limitation is present in both conventional as well as plane wave beam steering approaches.

Table 9-1. Strain estimation precision for the various transmission methods calculated with respect to the FEM solution

<table>
<thead>
<tr>
<th>Principal Strain</th>
<th>Absolute difference with FEM (mean ± sd) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional 0°</td>
</tr>
<tr>
<td>1</td>
<td>0.9 ± 0.9</td>
</tr>
<tr>
<td>2</td>
<td>0.8 ± 0.8</td>
</tr>
</tbody>
</table>

Conclusions

Plane wave beam steering enables a more precise estimation of the full strain tensor than can be obtained by conventional 0° strain imaging at a 50 times higher frame rate. This makes it a very promising method for strain estimation in vivo, where tissue is in motion.

Fig. 9-4. Reconstructed principal component strain images obtained for the various simulated ultrasound transmission method and the numerical strain fields obtained by finite element modeling. A: the FEM input, B: conventional 0° transmission, C: plane wave 0° transmission, D: conventional beam steering, E: plane wave beam steering
Opposed to most of the previous chapters, in this chapter the focus is on shear strain estimation in the longitudinal vessel direction. The presence of high levels of longitudinal shear strain in the adventitial layer might initiate and/or stimulate development of atherosclerotic plaques into vulnerable plaques. The study in this chapter shows that noninvasive estimation of the longitudinal shear strain in the adventitial layer of the carotid artery wall is feasible using the 2-D coarse-to-fine method described in previous chapters. Furthermore, it is shown that more accurate strain estimation is possible when using radio frequency data instead of envelope data.

CHAPTER 10

NONINVASIVE VASCULAR SHEAR STRAIN IMAGING

Abstract

The primary trigger for myocardial infarction and stroke is destabilization of atherosclerotic plaques. It is hypothesized that shear strain in the adventitia initiates and/or stimulates development of these plaques into rupture-prone, vulnerable plaques. Therefore, assessment of shear strain might yield a prognosis for the development of vulnerable plaques. In simulations and phantom experiments, longitudinal shear strain was estimated using RF- and envelope-based methods and compared to the applied values. Additionally, longitudinal shear strain estimates in the adventitia of six healthy volunteers were determined. In both experiments, the variance of the RF-based estimates was significantly smaller than that of the envelope-based estimates (Wilcoxon, p < 0.05). The periodicity of the shear strain estimates in volunteers corresponded well with the cardiac cycle. The estimated values were found to be similar to previously published data. Furthermore, the signal-to-noise ratio of the shear strain estimate in the posterior wall based on RF data was significantly higher (Wilcoxon, p < 0.05) than that based on envelope data. In conclusion, noninvasive ultrasound strain imaging using radio frequency signals appeared to allow adequate estimation of longitudinal shear strain in the adventitial layer of the carotid artery wall.

Introduction

Myocardial infarction and stroke are two leading causes of mortality [199, 200]. The primary trigger for these clinical events is destabilization of atherosclerotic plaques. In a study of 72 sudden coronary death cases, 76% of the myocardial infarctions and strokes were caused by rupture of plaques with superimposed thrombus formation [201]. Although atherosclerosis is a systemic disease, plaques usually develop in the conducting arteries (e.g. the coronary, carotid and femoral artery). They start off as so called "fatty streaks" on the intima of the arterial wall and may develop into vulnerable plaques that are prone to rupture. The latter mostly consist of a large pool of lipids and thrombogenic material covered by a thin fibrous cap (known as thin cap fibroatheroma). When the fibrous cap ruptures, the blood comes in contact with the surrounding tissue, leading to thrombus formation. Such a thrombus may cause a myocardial infarction or stroke by blocking a coronary or cerebral artery, respectively.

Major efforts are devoted to identify rupture-prone plaques using invasive [91, 202] and non-invasive ultrasound-based [83, 203, Ch. 2] strain imaging techniques. It has been hypothesized by our group [204] that longitudinal shear strain in the adventitia layer could be related to development of vulnerable plaques. Longitudinal shear strain initiates and/or stimulates neovascularization of the vasa vasorum [63, 205-208] which accelerates plaque progression by intra-plaque neovascularisation, inflammation [209] and bleeding [210]: all determinants of a rupture-prone vulnerable plaque. Stress is exerted on the intima by the pulsating blood flow [211, 212] and, in combination with the pulse wave, this induces displacement of the intima-media complex. The displacement of the intima-media complex results in longitudinal shear strain in the adventitia. Longitudinal shear strain is the first order spatial derivative of longitudinal displacement in the radial direction.

Cintio et al. [129, 213-216] have already presented measurements of longitudinal displacement and shear strain in layers of the carotid arterial wall using ultrasound data. They used an echo-tracking technique based on block matching to estimate the longitudinal displacements.

The tracking was performed using conventional B-mode images (i.e., a log compression of the envelope of the raw, radio frequency (RF) signals). Regions-of-interest (ROI) containing distinct anatomical structures, e.g., in the adventitia layer and in the surrounding tissue, were selected. The selected ROIs were tracked using the envelope data and the shear strain was calculated as the difference in longitudinal displacement divided by the distance between the ROIs. However, for this method to be applicable, distinct echoes need to be present in both ROIs during the full cardiac cycle [215]. Shi et al. [82] used the same approach to calculate the relative lateral shift between a plaque and the arterial wall, but only calculated the difference in longitudinal displacement. A similar technique is the one used by Golemati et al. [217]. They selected an ROI in the B-mode image and cross-correlated the speckle patterns in this ROI with the pattern in a sequential B-mode image, based on the assumption that movement of image patterns is related to movement of speckle patterns. Although this method had limitations with respect to temporal and spatial resolution, the estimated displacements showed a periodicity that was suggestive of the cardiac cycle.

In the current study, we investigate the estimation of longitudinal shear strain using a coarse-to-fine strain algorithm [59] based on RF data and compare the results to a benchmark based on envelope data. The purpose of this study is to develop a method for longitudinal shear strain estimation and to evaluate it in a limited number of volunteers. Longitudinal shear strain is hypothesized to be a parameter for vulnerable plaque risk assessment [204]. The raw RF signals provide echo level as well as phase information, which the envelope does not. This makes it possible to obtain a more precise estimate of displacements [59, 155]. Furthermore, the use of 2-D signal windows in the coarse-to-fine strain algorithm [59, 140, 218] allows a 2-D estimation of displacements, and the various strains. In simulations and phantom experiments we compared this RF-based technique to the envelope-based results using exact knowledge of applied displacement and strain. Finally, in vivo data were acquired in 6 volunteers without symptoms of atherosclerosis and shear strain in the posterior carotid arterial wall was estimated based on RF and envelope data.

Fig. 10.1. Simulated echo-image of the carotid artery. The selected ROI (“0.7 x 0.7 mm”) is used to calculate the mean shear strain. The thickness of the adventitia is 1 mm and the thicknesses of the media and the intima are 0.25 mm.
CHAPTER 10

NONINVASIVE VASCULAR SHEAR STRAIN IMAGING

Materials & Methods

Simulation experiments

Ultrasound RF signals of a carotid artery phantom were simulated using Field II® [219]. The surrounding tissue had a thickness of 10 mm, the adventitia a thickness of 1 mm and the media and intima were each 0.25 mm thick (Fig. 10-1). The dimensions of the simulated phantom are based on experimental thickness measurements of carotid arteries [220]. The RF signals of the simulated carotid artery were acquired in pre- and postshearing states using a simulated linear array transducer (11-3L, f_c = 8.7 MHz, pitch = 135 µm). In the latter state, the intima-media complex and the lumen were shifted in the longitudinal direction over distances of 10, 20, 50, 100, 200, and 500 µm with respect to the surrounding tissue. This resulted in a linear displacement gradient in the adventitia. From the estimated displacements, the applied shear strain (\(\varepsilon_{xy}\)) in the adventitia and intima was derived. This shear strain is defined as the derivative in the radial direction of the longitudinal displacement. It is calculated as follows (Fig. 10-2):

\[\varepsilon_{xy} = \frac{(x_{m+1,n+1} - x_{m,n}) - (x_{m+1,n+1} - x_{m,n+1})}{y_{n+1} - y_n} \times 100\% \]  

(10-1)

The resulting shear strains were 0.75, 1.875, 3.75, 7.5, 18.75, and 37.5%. Shear strain values of up to 30% in the adventitia of the human carotid artery have been previously reported by Cinthio et al. [214].

Phantom experiments

Construction of the phantom

A three-layered phantom was created from an aqueous solution (15 wt% and 10 wt%) of polyvinyl alcohol (PVA) [134,135]. To make the 15 wt% (10 wt%) PVA solution we added 400 ml of water to 70.6 (44.4) g of PVA granules. This mixture was heated in a water bath to approximately 90° Celsius for a maximum of six hours to dissolve the PVA granules in the water. After dissolution, we added SiC as scattering particles to the solution in a concentration of 2 wt%.

The mold for constructing the phantom consisted of a plastic square container (55 mm x 55 mm x 100 mm) with a copper cylinder (inner diameter: 20 mm, outer diameter: 22 mm) in the centre. Along the cylindrical core, a hard plastic tube (outer diameter: 5 mm) with indentations on the outside was concentrically placed. The phantom was constructed in a two-step-process.

Step 1: The mold was filled with 15 wt% PVA solution and kept at room temperature for 2 hours to allow air bubbles to escape. The mold was then placed at -19° Celsius for 16 hours followed by thawing at room temperature for 8 hours. This completed one freeze-thaw cycle. This cycle was repeated six times.

Step 2: The copper cylinder was removed from the mold and the remaining void was filled with the 10 wt% PVA solution (also with 2 wt% SiC scattering particles added). The mold with the added solution was kept at room temperature again for 2 hours to allow air bubbles to escape and the freeze-thaw cycle was repeated once more.

Finally, the phantom was removed from the mold. This resulted in a three-layered phantom: a stiff cylindrical core (diameter: 18 mm) that is attached to the stiff surrounding tissue (thickness: 17.5 mm) by a connecting layer of softer tissue (representing the adventitia, thickness: 1 mm). A schematic drawing of the phantom is shown in Fig. 10-3. Due to practical limitations, it was not possible to construct a phantom with realistic dimensions for all layers. However, the adventitia layer has realistic dimensions, and since the shear strain is calculated in this layer, the phantom is considered adequate to investigate the performance of the RF-based technique in physical phantom experiments. Furthermore, the diameter of the cylindrical core was decreased after freezing-thawing due to shrinkage of the PVA during the freezing-thawing process [134].

Experiments

The phantom was placed in a mechanical setup (Fig. 10-4) with one side placed against one wall of the container. On the other side of the phantom, the plastic tube inside the core was in contact with a metal rod, connected in turn to a micromanipulator (resolution: 10 µm, Fig. 10-4A). The ultrasound probe (a linear array transducer, 11-3L, f_c = 8.7 MHz, f_s = 39 MHz,

Fig. 10-2. Schematic representation of longitudinal shear strain in the adventitial layer. The position \(p\) of particles are depicted in frame \(n\) as grey and in frame \(n+1\) as black at axial depth \(m\) and \(m+1\).

Fig. 10-3. Schematic drawing of the PVA phantom.
CHAPTER 10  NONINVASIVE VASCULAR SHEAR STRAIN IMAGING

Fig. 10-4. A: Measurement setup for the phantom experiments and B: an echo-image of the longitudinal cross section with the three layers marked as cylindrical cylinder, connecting layer and surrounding tissue. In the ROI’s with a dotted line the general displacement in the surrounding tissue and the cylinder are estimated. The ROI with a straight line is used for the coarse-to-fine estimation of shear strain in the connecting layer. The bright lines between the layers are a result of the boundary between the layers.

In vivo experiments

In 6 volunteers without symptoms of atherosclerosis (3 female and 3 male, age: 20-48 yrs., all volunteers gave their informed consent) RF signals of the common carotid artery in the longitudinal direction were acquired during 2 or more cardiac cycles. Simultaneously the ECG-signal was recorded. For each volunteer we used the linear array transducer L11-3 (f. = 8.7 MHz, pitch = 135 µm; Philips SONOS 7500 ultrasound system) with a frame rate of 35 Hz. The focus of the transducer was set at the posterior wall. Before and after the acquisition of the ultrasound data the blood pressure was measured in the upper arm using a sphygmomanometer. As a verification of the applied displacement we selected large ROIs in the surrounding tissue and the core (Fig. 10-4B), and estimated longitudinal displacement in these two ROIs using normalized cross-correlation of the envelope data.

Shear strain estimation

At each applied displacement, the shear strain (and in the phantom experiments also the longitudinal displacement) between pre- and postshearing state were estimated based on the raw RF signals and on the envelope of these signals. The envelope signals were calculated by demodulation of the RF signals, i.e., the absolute value of the Hilbert-transform of the RF signals. Both the displacement and shear strain were estimated using a coarse-to-fine strain algorithm [59] with a fine predeformation window size of 8 pixels by 9 lines (0.16x1.22 mm²) for both the simulations and the phantom experiments. The postshearing window was twice these sizes in both experiments. The overlap between successive windows was 75% in axial direction and 89% in lateral direction. The estimated axial and lateral displacements were median-filtered (axial: 0.52x0.42 mm² and lateral: 0.12x0.76 mm²) and the strain was calculated using 2-D Least squares strain estimators (LSOSE) [48]. The LSOSEs were of the same size as the median filters. To improve the final displacement estimates, local aligning and stretching were applied [59,138]. In the resulting 2-D displacement/strain image, eleven ROIs (~0.7 x ~0.7 mm²) were selected at various equally spaced sites along the adventitial layer in simulated and along the connecting layer in the experimental phantom. In these ROIs the mean shear strain were calculated. In the simulations the root mean squared error (RMSE) for the shear strains was also calculated.

In the in vivo experiments, we selected two large ROIs containing the anterior and posterior wall. In these ROIs we calculated the displacement and strain distributions using the coarse-to-fine algorithm (fine window: 0.32x1.22 mm², overlap in axial and lateral direction of 75% and 89%), the displacements were median-filtered (axial: 0.52x0.95 mm², lateral: 0.28x1.22 mm²) and the strains were calculated using 2-D LSOSEs (axial: 0.52x0.42 mm², lateral: 0.28x1.22 mm²). During the cardiac cycle the selected ROIs were corrected for the radial and longitudinal movement of the tissue using a tracking algorithm based on the estimated axial and lateral displacements [221]. After these postprocessing steps, a smaller region was selected in the adventitia (~0.5 x ~0.5 mm²). For this region, the mean (cumulative) shear strain was calculated during the cardiac cycles.

Statistical analysis

The estimated shear strain from the simulation and phantom experiments were correlated to the applied values using the Spearman’s correlation coefficient (Spearman’s Rho). For each comparison of results in the simulations and the phantom experiments, the Wilcoxon’s signed rank test was used. The SNR of the shear strain estimates from RF- and envelope-based analysis in volunteers was also compared using the Wilcoxon’s signed rank test.

Results

Simulation results

The simulated phantom of the carotid artery is shown in Fig. 10-1. Examples of the estimated displacement and shear strain elastograms (RF- and envelope-based) are presented in Fig. 10-5. The estimated values for the shear strain (mean ± sem) are plotted in Fig. 10-6. Both the RF- and envelope-based estimates were linearly related to the applied shear strain (Spearman’s rho = 0.99 ± 0.00, p < 0.05).

The variance of the RF-based shear strain estimates was significantly smaller than that of the envelope-based estimates (Wilcoxon’s signed rank test, p < 0.05). The RMSE of the RF-based estimates (interquartile range: 0.9 – 1.6%), was also significantly smaller (Wilcoxon’s signed rank test, p < 0.05) than that of the envelope-based estimates (interquartile range: 5.6 – 10.0%).
10
NONINVASIVE VASCULAR SHEAR STRAIN IMAGING

Phantom results

Examples of estimated shear strain distributions in the PVA phantom are displayed in Fig. 10-7. Fig. 10-8A shows displacements in the cylindrical core and the surrounding tissue estimated from the envelope data in the top and bottom ROI as indicated in Fig. 10-4B. This revealed that the displacement in the core was lower than the applied displacement, but also that there was displacement in the surrounding tissue. This results in an actual applied shear strain that was lower than the presumed shear strain. The shear strain estimates based on RF and envelope data, with the actual applied strain as a reference, are plotted in Fig. 10-8B. This actual applied shear strain will be used in further analysis.

The RF- and envelope-based estimated shear strains were both linearly related to the applied shear strain (Spearman’s rho = 0.996 (p < 0.05) and 0.985 (p < 0.05) for the RF- and envelope-based data, respectively). The variance of the RF-based shear strain estimates was significantly smaller than that of the envelope-based estimates (Wilcoxon’s signed rank test, p < 0.001).

Human carotid artery

In Fig. 10-9 an example of the estimated longitudinal shear strain, averaged over the selected ROI, in the adventitia (A) is plotted vs. time during several cardiac cycles with and without the tracking algorithm (B and C, respectively). A simultaneously recorded ECG is shown in Fig. 10-9D.

Without the tracking of axial and lateral displacement and adaptation of the ROI, there was a general long-term trend (decreasing or increasing) in the longitudinal displacement and shear strain. When the tracking between sequential images was included, both the displacement and shear strain were quite reproducible during several cardiac cycles. Fig. 10-10 shows an example of shear strain in the adventitia of the posterior carotid arterial wall and the simultaneously recorded ECG during two cardiac cycles in a volunteer. The cumulated shear strain increased during systole, whereas it decreased and returned to the initial value during diastole. The shear strain curves estimated in the adventitia were cyclic and synchronous to the ECG signal. The SNR of the shear strain estimates based on RF analysis (mean SNR: 5.6 dB) was significantly higher (Wilcoxon’s signed rank, p < 0.05) than that based on envelope analysis (mean SNR: 1.3 dB).

Fig. 10-5. Selected example of displacement and shear strain estimations in the simulated phantom at an applied displacement of 500 µm. The envelope- and RF-based displacements and the true applied displacements are shown in A through C, respectively. The corresponding shear strains are shown in D through F, respectively.

Fig. 10-6. Estimated shear strain (mean ± SEM) in simulated phantoms plotted versus the applied shear strain based on RF (black) and envelope data (grey).

Fig. 10-7. Shear strain estimations at applied displacements of 140 µm (A and C) and 420 µm (B and D) estimated using the envelope (A and B) and RF data (C and D).
Discussion

The pulsating blood flow induces shear stress on the arterial wall in the longitudinal direction. It was hypothesized that the hereby induced shear strain in the adventitial layer of the arterial wall is related to the progression of plaque to a vulnerable plaque [204]. However, to be able to test this hypothesis, a technique to reliably and accurately assess this shear strain is needed. In simulations and phantom experiments, we have shown that the shear strain in the adventitia can be assessed using a noninvasive ultrasound technique based on RF signals and that it outperformed envelope based shear strain estimation.

In simulations, the shear strain estimates (RF-based as well as envelope-based) increased linearly with the applied displacement. Furthermore, the RMSE and the variance of the RF-based estimates were significantly smaller than for the envelope-based estimates. This indicates that the RF-based shear strain estimates were closer to the applied value and more accurate than the envelope-based estimates. Similar results were found in the phantom experiments, although the estimated values for shear strain (RF- as well as envelope-based) underestimated the presumed applied shear strain. The accuracy of the simulation RF-based results in estimating the applied strain suggests that the estimated “effective” applied shear strain is more realistic and lower than the presumed shear strain. This suggestion is also supported by the results from the general displacement estimates in the surrounding tissue and cylinder. The applied shear strain is lower than the presumed shear strain partly because there is displacement of the surrounding tissue. This displacement is possibly due to the construction of the phantom. The cylindrical core and the outer layer are connected (through the middle layer). Pushing the core with a rod on one end displaces it and, through the connecting layer, also the outer layer (as demonstrated by the estimates in Fig. 10-8A). On the opposite end, displacement of the outer layer was prevented. Due to the compressibility of the PVA this might, however, result in deformation in the longitudinal direction of the outer layer. The applied shear strain in the connecting layer would then be less than presumed. This assumption can be substantiated with the results in Fig. 10-8A). The estimated displacement of the core is lower than presumed and the estimated displacement in the surrounding tissue is higher than the presumed zero displacement. This means that the applied shear strain must be lower than the presumed shear strain.

From the simulations and the phantom experiments, it can be concluded that the RF-based estimates had less variation around the mean and were closer to the true effective shear strain than the envelope-based estimates. Therefore, the RF-based estimates can be considered more accurate than those based on the envelope.

In examples in human carotid arteries it is shown that the shear strain in the adventitia of the carotid artery wall varies periodically with the cardiac cycle. Cinthio et al. have also shown...
that the longitudinal displacement of a distinct echo in the intima of the arterial wall varies periodically with the cardiac cycle [213–216]. One of their hypotheses was that the longitudinal displacement of the intima was caused by the shear stress induced by the pulsating blood flow. However, only longitudinal displacement can be estimated at different locations with a distinct echo with the method Cinthio et al. used. With the currently developed method, longitudinal displacement and shear strain can be estimated at any location. They also estimated the shear strain between the intima-media complex and the adventitia and between the adventitia and the surrounding tissue. This was done by estimating the longitudinal displacement in two selected regions (in different layers) and by dividing the difference in longitudinal movement by the radial distance between the selected regions. The use of ROIs in both layers results in poor radial resolution of the shear strain estimation. With the coarse-to-fine algorithm based on RF data, the shear strain distribution in a selected ROI can be estimated accurately. From this distribution an area of interest can be selected and in this area the displacement and strain can be traced during the cardiac cycle. The shear strain curves in the volunteers in the current study showed patterns similar to those found in two subjects by Cinthio et al. [214], an increase in systole followed by a decrease in diastole. We also found curves that showed a small negative shear strain during diastole. These findings support the bidirectional movement pattern that was found by Cinthio et al. [214]. Finally, the SNR of the shear strain estimate was significantly higher when the estimates were based on RF analysis than for envelope-based analysis. This confirms in vivo the results from the simulation and phantom experiments, i.e., shear strain analysis based on RF data is more accurate than analysis based on envelope data.

The SNR analysis is based on the assumption that the shear strain will have a homogeneous distribution in these healthy volunteers. This assumption is likely to be valid in the horizontal direction (parallel to the vessel axis) but not in the vertical direction. However, considering the size of the selected ROI, it is also likely that the assumption is valid in the vertical direction. Furthermore, the parameters for the coarse-to-fine method, including the filter sizes, are identical. Therefore, a possible inhomogeneous shear strain distribution would have the same effect on the SNR when the analysis is based on RF data as when based on envelope data.

For the measurement of longitudinal shear strain in the coronary arteries, deformations of the arteries due to size changes of the heart during the cardiac cycle must be taken into account. The in vivo application of the proposed technique does not take into account deformation of the common carotid artery induced by head and/or neck movement. For the evaluation of the technique, the volunteers were asked to remain stationary, i.e., no head/neck movement.

Conclusion

Based on the measurements presented in this paper, estimation of longitudinal shear strain in the adventitia of the carotid artery using ultrasound radio frequency signals is feasible. RF-based methods outperform envelope-based methods as validated with simulations, phantom experiments and in vivo experiments. Therefore, noninvasive ultrasound imaging could be used as a tool to test the hypothesis that longitudinal shear strain accelerates plaque progression to a rupture-prone, vulnerable plaque.

Acknowledgement

This research is supported by the Dutch Technology Foundation STW, Applied Science Division of NWO and the Technology Program of the Ministry of Economic Affairs. We like to thank prof. dr. ir. Johan M Thijssen for his valuable insights and the critical review of this manuscript.
The elastic Young’s modulus for lipids, fibrous tissue and calcifications differs. Young’s modulus images can be derived from displacement and strain maps. This study investigated if the Young’s modulus for transverse cross sections of vascular structures can be determined using displacement estimates obtained by coarse-to-fine displacement estimation. Furthermore, it is researched if the nonsegment based strain estimation method of chapter 4 enhances the reconstruction accuracy of Young’s modulus images when compared to that based on conventional 0° angle imaging. It is shown for simulated and experimentally obtained RF data of vessel-mimicking phantoms that a modulus reconstruction is feasible. Furthermore, modulus reconstruction based on nonsegment based compound elastography outperforms modulus reconstruction based on 0° acquisitions.


CHAPTER 11

Abstract

Atherosclerotic plaque rupture can initiate stroke or myocardial infarction. Lipid-rich plaques with a thin fibrous cap are more prone to rupture than fibrotic plaques. The elastic Young’s modulus differs for the various plaque components. The goals of this study were 1) to reconstruct Young’s modulus images for transverse vessel cross sections based on 2-D displacement fields of the vessel wall obtained noninvasively with a linear array transducer and 2) to investigate if the reconstruction is improved when using multi-angle displacement compounding instead of single-angle displacement estimation. Simulated and experimental radiofrequency echo data were generated for beam steering angles of -30°, 0° and 30° for three vessel-mimicking phantoms: a homogeneous phantom with a concentric lumen, a homogeneous phantom with an eccentric lumen and a two-layered phantom with a soft layer inside and an eccentric lumen. Displacement fields were estimated using a coarse-to-fine 2-D cross-correlation based algorithm. Relative Young’s modulus images were reconstructed using either compounded displacement fields or 0°-angle displacement fields. To determine the performance of the modulus reconstruction the median absolute differences between the measured and model predicted axial and lateral displacements were calculated. Furthermore, the median and inter-quartile range (IQR) of the relative modulus estimates for each separate phantom layer were calculated and compared to the real values. The median difference between lateral displacements used as input for the reconstruction and those corresponding to the reconstructed modulus image reduced twofold to threefold when using multi-angle compounding instead of single-angle imaging. This also resulted in improved Young’s modulus images: the IQR of the relative Young’s modulus reduced approximately a factor 2 when using compounding. The errors in relative Young’s modulus with compounding were maximally ~10%. Thus, more accurate modulus reconstructions for transverse cross sections of vascular structures can be obtained with compounding than without compounding. Furthermore, evaluation using in vivo data is required to demonstrate the clinical benefit of this technology for vulnerable plaque detection.

Introduction

Rupture of atherosclerotic plaques and the successive formation of thrombus is regarded as one of the major causes of stroke and myocardial infarction [4]. The rupture proneness of a plaque is determined by its geometry and composition, and also to the amount of force the pulsating blood exerts on the plaque [4,117,118]. 60 to 80% of strokes and myocardial infarctions are caused by the rupture of a plaque that has a large inflammatory lipid core which is covered by a thin fibrous cap that separates the lipid content from the blood in the lumen [4]. Due to the fact that the elastic properties of lipid rich, fibrous and calcified tissue differ [122], quantification of the elastic moduli inside the plaque and vessel wall could facilitate the identification of plaques with a high probability of rupture.

Elastic modulus reconstructions have been performed for coronary arteries based on displacement fields that were derived from intravascular ultrasound radio frequency (RF) data obtained using a catheter-mounted ultrasound device [115,222]. Recently, noninvasive methods for assessment of strains and displacements in the carotid artery wall and plaque have been developed [68,83,87,Ch. 4]. Noninvasively, the ultrasound data are usually acquired with a linear array transducer. To our knowledge all existing studies examine the artery in a longitudinal imaging plane, because in that configuration the ultrasound beams are aligned with the radial displacement for the entire cross section. This study focuses on elastic modulus reconstruction for vascular structures in a transverse imaging plane. To perform reconstructions in this imaging plane, accurate estimates are required of the displacements in the direction of the ultrasound beam (axial) as well as in the perpendicular (lateral) direction. Conventional, single-angle ultrasound acquisitions enable accurate estimation of the axial displacements only. Lateral displacement are less accurate, due to the lack of phase information. Compounding of axial displacements estimated at multiple acquisition angles [142,223,Ch. 4] enables a more accurate assessment of lateral displacements. Recently, we proposed a method for estimation of the full 2-D displacement vector by compounding axial displacement estimates obtained at three different acquisition angles [Ch. 4]. A reduction in the root mean squared error of the lateral displacements was observed of up to 55%. Compound frame rates of approximately 30 Hz were achieved with the proposed method, which makes it suitable for strain estimation in pulsating vessels.

The main goal of this study is to examine if the displacements resulting from the previously developed three-angle approach also allow a better reconstruction of the elastic moduli than can be obtained through conventional single-angle imaging.

Materials & Methods

Our reconstruction method was tested for vessels with three different configurations (see Fig. 11-1, the Young’s’s moduli of the vessel layers are shown in blue). The Young’s’s moduli of the inner and outer layer of the rightmost vessel resemble that for soft necrotic core tissue [222] in an artery [122]. The performance of the reconstruction with and without compounded displacement estimates was compared for each vessel using 2-D displacement fields of the vessels. The displacements were obtained in three ways: 1) by finite element modeling, 2) by coarse-to-fine cross-correlation based displacement estimation applied to simulated ultrasound data of the vessels, and 3) by coarse-to-fine cross-correlation based displacement estimation applied to experimentally obtained ultrasound data of vessel-mimicking phantoms made of gelatin-agar solutions.

---

**Fig. 11-1.** The geometries and Young’s moduli of the vessels investigated: (A) a concentric homogenous vessel, (B) an eccentric homogeneous vessel, and (C) an eccentric vessel consisting of two layers with different stiffness.
CHAPTER 11

Finite Element Modeling

Finite element models (FEMs) of the three vessel geometries were constructed using the Partial Differential Equation Toolbox of Matlab 2007a (The Mathworks, Natick, MA, USA). Over 60,000 three-dimensional linear-elastic finite elements were defined and distributed over the vessel volume. All elements were assumed to be nearly incompressible (Poisson’s ratio, \( v = 0.495 \)) and isotropic. Displacement fields were calculated for an intra-luminal pressure increase of 4 mmHg under the assumption of plane strain. To prevent rigid body translation and to obtain unique FEM solutions, a highly compressible (\( v = 0.005 \)) and soft (\( E = 1 \) Pa) surrounding circular layer of 1 cm thickness with a fixed outer boundary was added to the FEMs during the calculation of the displacement fields. The FEM displacement fields were output on a triangular grid and were interpolated on a rectangular grid using bilinear interpolation. The spacing of this grid was 158 \( \mu \)m x 135 \( \mu \)m, equal to the displacement grid spacing obtained in the simulations and experiments.

Simulations

RF data of each vessel were simulated before and after the intraluminal pressure increase for beam steering angles of -30°, 0° and +30° using the ultrasound simulation software package Field II [121]. One million scatterers were defined that moved according to the finite element displacement field. The simulated transducer and imaging settings were equal to those reported previously [Ch. 3&4], and are similar to those used in the experiments (next sub-paragraph). Band-limited noise (3-11 MHz) was added to create a signal-to-noise ratio of 10 dB [Ch. 3].

Experiments

Vessel-mimicking phantoms with geometries and Young’s’s moduli as shown in Fig. 11-1 were constructed from various gelatin-agar solutions. Both the production procedure and the estimation of the Young’s’s moduli were described in chapter 3. The phantoms were placed in a water tank and connected to a water column. A pressure step of 4 mmHg was applied to simulate the vascular elastography [191,193,224]. The algorithm iteratively searches for an elastic modulus distribution which results in axial and lateral displacement fields \( \hat{u}_x(\mu) \) and \( \hat{u}_y(\mu) \) that best match the input displacement fields \( (u_x, u_y) \) by minimizing a penalty function:

\[
\pi(\mu, \mu_0) = \frac{1}{2} \pi_{ax} + \frac{1}{2} \pi_{lat} + \frac{\alpha}{2} \pi_{smooth},
\]

where \( \pi_{ax} \) and \( \pi_{lat} \) are the displacement matching terms and \( \pi_{smooth} \) is a smoothness term that restricts the amount of variation in the modulus field. \( \alpha \) is a weighting factor that determines the amount the smoothness term contributes to the penalty function. \( \alpha \) was set to 1e-9. \( \mu_0 \) is the shear modulus (\( \mu = E/2(1+\nu) \)). \( \mu \) is a background shear modulus value with respect to which the smoothness function was normalized:

\[
\mu_0 = \exp(\frac{\int_{\Omega} \ln(\mu) d\Omega}{\int_{\Omega} d\Omega})
\]

For the heterogeneous case with two layers, the constant \( \mu_0 \) was separately set for each layer. This is called a soft prior reconstruction. A single normalizing constant for both layers would flatten out the contrast in modulus between the two layers, as demonstrated previously [224].

Reconstruction mesh for vessel geometry

To create the finite mesh for the modulus reconstruction, the inner and outer vessel boundaries were segmented, populated with regularly spaced nodes and meshed in a regular fashion, both radially and angularly, with respect to the lumen center (Fig. 11-2) to avoid element discontinuities at the vessel boundaries. In addition, the reconstruction algorithm applied the pressure as a surface traction, normal to the element edges on the inner border to minimize shear artifacts that may exist at the inner border when applying a surface traction to elements on a regular Cartesian mesh. The angular grid spacing was 1°. Radially nodes were maximally 110 \( \mu \)m apart.
Analysis

To determine the performance of the modulus reconstruction the median absolute differences between the axial and lateral displacement input to and output by the reconstruction method were calculated. Furthermore, the median and interquartile range (IQR) of the relative modulus estimates for each separate phantom layer were calculated and compared to the real values. For the heterogeneous case the modulus values were scaled such that the median modulus of the outer layer equaled 1.

Results

Table 11-1 shows the median and IQR values for the relative Young’s modulus reconstructions. Table 11-2 shows the absolute differences between the axial and lateral displacements used as input for the reconstruction and those corresponding to the reconstructed modulus images are presented. As expected, the modulus reconstruction based on the finite element output is

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Relative Modulus (FEM)</th>
<th>Relative Modulus (SIM)</th>
<th>Relative Modulus (EXP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>A0</td>
<td>1.000 (0.997-1.003)</td>
<td>1.000 (0.996-1.004)</td>
<td>1.000 (0.994-1.004)</td>
</tr>
<tr>
<td>A</td>
<td>1.000 (0.997-1.002)</td>
<td>1.000 (0.997-1.002)</td>
<td>1.000 (0.997-1.002)</td>
</tr>
<tr>
<td>B0</td>
<td>1.000 (0.995-1.006)</td>
<td>1.000 (0.982-1.030)</td>
<td>1.000 (0.988-1.008)</td>
</tr>
<tr>
<td>B</td>
<td>1.000 (0.991-1.025)</td>
<td>1.000 (0.995-1.008)</td>
<td>1.000 (0.995-1.008)</td>
</tr>
<tr>
<td>C_{in}</td>
<td>0.105 (0.105-0.105)</td>
<td>0.236 (0.228-0.252)</td>
<td>0.214 (0.208-0.220)</td>
</tr>
<tr>
<td>C_{out}</td>
<td>1.000 (0.996-1.006)</td>
<td>1.000 (0.984-1.015)</td>
<td>1.000 (0.992-1.009)</td>
</tr>
<tr>
<td>C_{out}</td>
<td>1.000 (0.993-1.000)</td>
<td>1.000 (0.995-1.008)</td>
<td>1.000 (0.995-1.008)</td>
</tr>
</tbody>
</table>

A = concentric homogeneous vessel, B = eccentric homogeneous vessel, C_{in} = heterogeneous vessel inner layer, C_{out} = heterogeneous vessel outer layer, A0 = without beam steering, A = with beam steering.

Fig. 11-2. A: The rectangular displacement grid as obtained from a linear array transducer. B: The grid used for the modulus reconstruction.

Fig. 11-3. Relative modulus images obtained for the simulated data without (A-C) and with (D-F) beam steering.

Fig. 11-4. Relative modulus images obtained for the experimental data without (A-C) and with (D-F) beam steering.
close to perfect, although the contrast between the inner and outer layer is slightly lower than expected: theoretically moduli of 0.094 and 1 were expected. This underestimation is probably due to the interpolation onto the finite mesh.

Fig. 11-3 shows the modulus images for the simulations. For all three configurations the modulus images visually improved. The errors close to the lumen-vessel interface reduced and the contrast between the soft and the stiff layer increased for the heterogeneous vessel. This is also reflected in terms of IQR. The modulus IQR decreased by at least a factor 2 for all three vessels when using the three-angle method. Also, the absolute difference between input and output lateral displacements reduced a factor 2 to 3 with the three-angle method. In axial direction displacements were also slightly better matched.

Fig. 11-4 presents the relative modulus images for the experimental phantom data. Again, a visual as well as quantitative improvement in reconstruction accuracy was observed for the homogeneous cases when applying the three-angle method. The lateral displacements were again a factor 2 to 3 better matched and the IQR of the modulus reduced two-fold with respect to the single-angle acquisition. For the two layers of the heterogeneous vessel a better match was found in lateral direction (factor 1.8), although the modulus IQR was similar with and without beam steering.

Table 11-2. The median and interquartile ranges (IQR) of the absolute differences between the input and output displacement fields for the simulations and experiments.

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Ax diff (μm) (SIM)</th>
<th>Ax diff (μm) (EXP)</th>
<th>Lat diff (μm) (SIM)</th>
<th>Lat diff (μm) (EXP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0</td>
<td>0.7 (0.3-1.3)</td>
<td>1.0 (0.5-1.9)</td>
<td>4.8 (2.3-8.3)</td>
<td>3.4 (1.6-5.7)</td>
</tr>
<tr>
<td>A</td>
<td>0.5 (0.2-0.8)</td>
<td>0.8 (0.3-1.5)</td>
<td>1.3 (0.6-2.4)</td>
<td>1.0 (0.5-1.7)</td>
</tr>
<tr>
<td>B0</td>
<td>1.5 (0.7-2.8)</td>
<td>1.0 (0.4-2.6)</td>
<td>8.0 (3.9-13.6)</td>
<td>4.1 (2.0-7.0)</td>
</tr>
<tr>
<td>B</td>
<td>1.3 (0.6-2.3)</td>
<td>1.1 (0.5-2.1)</td>
<td>3.1 (1.4-5.7)</td>
<td>1.6 (0.8-2.8)</td>
</tr>
<tr>
<td>Cin0</td>
<td>2.4 (1.0-4.4)</td>
<td>3.1 (1.5-5.3)</td>
<td>3.3 (1.8-5.4)</td>
<td>3.6 (1.7-6.1)</td>
</tr>
<tr>
<td>Cin</td>
<td>1.2 (0.5-2.0)</td>
<td>2.6 (1.2-5.5)</td>
<td>3.4 (1.6-5.9)</td>
<td>2.0 (1.0-3.5)</td>
</tr>
<tr>
<td>Cout0</td>
<td>2.4 (1.0-4.4)</td>
<td>3.1 (1.5-5.3)</td>
<td>3.3 (1.8-5.4)</td>
<td>3.6 (1.7-6.1)</td>
</tr>
<tr>
<td>Cout</td>
<td>1.2 (0.5-2.0)</td>
<td>2.6 (1.2-5.5)</td>
<td>3.4 (1.6-5.9)</td>
<td>2.0 (1.0-3.5)</td>
</tr>
</tbody>
</table>

1 = No differentiation was made for the two layers of the heterogeneous vessel.
A = concentric homogeneous vessel, B = eccentric homogeneous vessel, Cin = heterogeneous vessel inner layer, Cout = heterogeneous vessel outer layer, A0 = without beam steering, A = with beam steering.

match in the axial direction is probably due to the coupling of the axial and lateral data in the reconstruction algorithm. The improved match in both directions allowed more accurate modulus reconstructions: the variation in relative modulus for homogeneous regions was smaller, as illustrated by the decrease in the modulus interquartile ranges. Therefore, it is concluded that beam steering allows a more accurate elastic modulus reconstruction than single-angle imaging.

Most errors in the reconstructed images are observed at the lumen-vessel interface. The errors are ~10% when performing beam steering and larger without beam steering. The main components we want to distinguish are lipids, fibrous, and healthy vascular tissue, which have Young’s values of ~10, ~600 and ~100 kPa [52,122,222]. With respect to the modulus contrast between these components 10% error is acceptable. However, the performance of the algorithm was tested only for relatively simple and static situations in this study. The errors might increase when applying the methods in vivo. Therefore, further in vivo evaluation is required to demonstrate the clinical benefit of this method for vulnerable plaque detection.

Discussion & Conclusions

The results illustrate that an accurate reconstruction of Young’s’s moduli based on linear array ultrasound data is possible. As can be expected, because the lateral displacements improve with three-angle imaging [Ch. 4], the match between the lateral displacements input to the reconstruction algorithm and those output by the reconstruction algorithm improved when using the three-angle method instead of single-angle imaging. Overall, a better match was found in the axial direction, although the improvements were less pronounced. The better
PART V: GENERAL DISCUSSION
In this chapter the developed techniques will be discussed together with their clinical applicability.
Developed methods

One of the main underlying causes of stroke is the rupture of atherosclerotic plaques. Plaques with a high risk at rupture, vulnerable plaques, have a different composition than stable plaques. Due to this difference in composition, it can be expected that the deformation (strain) due to the pulsating blood in these vulnerable plaques differs from that in stable plaques. Thus, based on these strains it should also be possible to differentiate between a stable and a vulnerable plaque. The noninvasive measurement of radial strain in transverse cross sections of the carotid artery wall was investigated.

Three beam steering approaches for ultrasound based strain estimation in transverse cross sections of arteries were developed. Method one [Ch. 2] and method two [Ch. 3] both were segment based methods. Axial displacements or strains were estimated for circular segments of the cross section in which the radial and axial, or circumferential and axial direction were closely aligned. The axial data was then projected into radial or circumferential direction for that circle segment. The various segments of radial strain obtained at the multiple beam steering angles were added together to form a radial strain image for the entire vessel cross section. The last method [Ch. 4] was not segment based, but combined the entire axial displacement fields measured at three different angles to derive the radial and circumferential strain images.

Chapters 2 to 4 demonstrated that the developed methods outperformed strain estimation methods that used nonbeam steered recordings only. Each of the three methods had some advantages over the other ones. The first method had the drawback that it could not be used to completely circumvent the use of the less accurate lateral derived strain estimates for radial strain estimation in the full carotid cross section. Both other methods allowed radial strain estimation without this lateral distortion. As illustrated in chapter 3, this was also the reason why method one was outperformed by method two. Additionally, method one assumed incompressibility and isotropy of the tissue, which seems reasonable for vascular tissue, although thrombotic tissue can be compressible due to its porosity. These assumptions might however be less erroneous than the assumption posed by method number two. Method two assumed circumferential motion to be negligible. Although this did not seem to hamper strain estimation in experiments with vessel-mimicking phantoms with concentric and eccentric lumens, it might be an issue for in vivo application in complex atherosclerotic arteries. Method 3 did not pose any assumptions on tissue properties, while the strain estimation accuracy was comparable to that of method 2: the root mean square error for simulated data and the elastographic signal-contrast-to-noise ratio’s for experimental data were 54%, 2.2 dB and 8.6 dB for method 2, and 46% and 4.0 dB and 9.8 dB for method 3, respectively. Therefore, method 3 was chosen to be applied in vivo in chapter 7 and 8. Nevertheless, this nonsegment based method does also have several drawbacks. It is the only method that requires the simultaneous input from all three beam steering angles and combines it to derive the desired strain components. Therefore, tissue motion should be negligible between the acquisition of the frames for beam steering angle one, two and three, because otherwise data from the three angles is combined in an incorrect way. However, as shown in chapter 7 in which the method was tested in a pulsating phantom and a healthy carotid artery at a compound frame rate of 43 Hz, inter frame motion did not seem to cause large errors. Another drawback of the method is that the images for each of the angles should be free of artifacts for all regions of the vessel cross section. This can be difficult in vivo, due to shadowing of the vessel wall, which sometimes occurs behind calcifications. For such regions it might be better to use one of the segment based approaches. Thus, a combination of the nonsegment based and the segment based methods is worth investigating, because it will probably improve radial strain estimation for certain regions of the vessel cross section.

A way to reduce and perhaps fully eliminate possible motion artifacts of the segment based approach was presented in chapter 9. By means of plane wave transmission and software based image reconstruction in receive, frame rates were increased by more than a factor of 50 compared to conventional line wise focused imaging, which implies that motion artifacts are also reduced by the same factor. Plane wave imaging might even enable full elimination of motion artifacts, because it is theoretically possible to reconstruct images for any arbitrary receive angle from a single zero angle plane wave transmission. Thus, compound strain imaging/elastography based on data from single plane wave transmits would be within reach, and it would be theoretically possible to perform it for an unlimited number of receive angles. Another advantage of the high frame rates reached with plane wave imaging is that it also brings 3-D vascular ultrasound elastography within reach. Longitudinal displacements and strains are present, but are usually smaller than the displacements in the other directions. It can be expected that strain estimation in 3-D also enables improved estimation of the displacement components in the radial and circumferential direction, because out of plane motion can be taken into account. Out-of-plane motion was considered negligible in the studies presented in this thesis.

For the development of the methods, a transducer with a small pitch, like that of the L11-3 linear array transducer [Ch. 2-5,10&11], is recommended for the compounding approach. Beam steering at large angles for transducers with a larger pitch and a similar transmit frequency results in more artifacts caused by grating lobes [Ch. 2&5]. Although the decrease in strain estimation accuracy due to grating lobe artifacts can be reduced by adequate filtering [Ch. 5], the accuracy of the estimates for a large pitch transducer is less than that for a small pitch transducer.

An important question to raise is how to quantify strain estimates and what strain tensor component should be used. Arteries mainly deform in the radial and circumferential direction. Because of the promising intravascular results for radial strain we have chosen to first focus on strains in this direction in the in vivo validation study. However, as shown in chapter 4 and 7 the nonsegment based technique also enables the measurement of the circumferential strain. It will be very valuable to repeat the study for the circumferential strain in future. Next to that, there are also other strain components that could also be used, for instance the principal strain components [Ch. 2&9]. Other possibilities are the use of a global strain component like the Von Mises strain component [62], which provides a value for strain magnitude without providing information on the direction of the strain. The advantage of the radial and circumferential strain components is that the direction of the strain is well defined. The disadvantage of these strain components is that they require the definition of a lumen center point, which cannot be defined completely accurately, because especially in the presence of plaque the shape of the lumen-wall boundary can be irregular. For the derivation of principal strains or the Von Mises strain component it is not required to define a lumen center point. However, for these components the strain for each point in the tissue can correspond to strain in a different direction, which might be very hard to interpret.
CHAPTER 12

In chapter 8 we defined two strain parameters for the characterization of a strain image: the 87-percentile of the cumulative radial strain image and the percentage of this radial strain image with strains over 1.5%. Of course, other parameters can be defined and might provide a better differentiation of the vulnerable plaque features. An example of a different parameter is used in intravascular palpography, a technique based on intravascular elastography in which only the strain values in the first layer of tissue closest to the lumen border are considered. The mean of these strain values was intravascularly used as a parameter of vulnerability [54, 182, 203].

Strain is not an intrinsic tissue property. Strain is a result of the applied stress and the tissue composition. To determine the composition of a plaque, elastic modulus images can be determined. These can be derived from the strain images for instance by using an inverse problem solver [Ch. 11]. Derivation of the modulus images is rather difficult, because it requires accurate knowledge of the plaque and vessel geometry, knowledge of the pressure distribution at the boundaries and accurate strain estimates as input. For advanced and complex plaques these criteria are very hard to fulfill.

In chapter 10 it has been shown that longitudinal shear strain estimation for the adventitial layer of the carotid artery is more accurate when RF data instead of envelope data are used. It can however be expected that the quality of the estimates is even more accurate when applying the nonsegment based method of chapter 4, because the longitudinal shear strain is derived from the lateral displacement field. Next to application in the longitudinal direction, the nonsegment based compounding method might also be used to detect vulnerable plaques in other superficially located arteries like the femoral artery. Moreover, the method is not restricted to vascular application, but might also be applied to other superficially located tissue, like breast, or thyroid gland tumors.

Clinical discussion

In chapter 8 it was shown that the nonsegment based compounding method allows the derivation of strain parameters that are closely related to histological parameters characterizing plaque vulnerability. Furthermore, local matches between strain and plaque content were observed in a fibrous, a fibro-atheromatous and an atheromatous plaque. Despite the small population of patients studied, these results were very promising. Therefore, the study is currently continued to include more patients and to fully validate that the proposed method provides a way of measuring plaque vulnerability. After proven effectiveness, other studies will be performed. A comparison with plaque vulnerability measures estimated with other imaging modalities, like MRI would allow to include patient with less severe obstructions. Since vulnerable plaques are typically not severely stenotic, this study might be even more interesting than the currently performed study. It is also valuable to investigate the differences in strain for asymptomatic and symptomatic patients and to determine the relations between strain and known risk factors, like male gender, age, smoking, and physical inactivity. Therefore, a study in which several hundred of volunteers are being imaged is currently enrolled. A large number of clinical risk factors is determined and also the intima-media thickness (IMT) is measured for each volunteer. This study will provide us insight when strain values change as a function of each of these clinical risk factors and will also allow us to determine if strain is a more patient specific plaque rupture indicator than IMT.

Before the technique can really be applied clinically as a preventive screening method for atherosclerotic cardiovascular events: an age of above 60, a male gender, smoking, diabetes, high levels of blood cholesterol, an elevated systolic blood pressure, high levels of low density lipo-proteins in blood, and a passive lifestyle. Several systematic approaches have been developed to express the combined risk of these factors by a single score, like the Framingham risk score and the Systematic Coronary Risk Evaluation system [227, 228]. For people below 60 years no reliable method to score the risk at cardiovascular events currently exists. With respect to the second question, several options for treatment are currently available: administration of drugs, endarterectomy surgery, stent placement, etc. It is however questionable which method is the most effective in which patient. Long term effects of the various types of treatment on the health of the vessel wall are also hard to determine. If successful, the developed method would be the first to clarify these issues, because it would enable us to determine direct and long-term effects of various types of treatment on plaque vulnerability in vivo.
Summary

This chapter summarizes the developed techniques for noninvasive vascular elastography and their application for vulnerable atherosclerotic plaque detection in carotid arteries.
Summary

The majority of people in Western society develop atherosclerosis. Atherosclerosis is a systemic disease which usually slowly progresses with age and mainly affects the conducting arteries. Atherosclerosis starts with the formation of lipid-rich accumulations in the vessel wall, named fatty streaks. These fatty streaks can grow and mature into plaques. The majority of these plaques will be stable over years, some can become unstable. These unstable vulnerable plaques can easily rupture which might lead to the generation of a thrombus. This thrombus can suddenly limit the blood flow and with that reduce the supply of oxygen and nutrients to the distal tissue. The resulting effect is cell necrosis, and when this happens in the brain or heart this is called a stroke or myocardial infarction, respectively. More than 60% of all strokes and myocardial infarctions are caused by rupture of a vulnerable plaque and the successive formation of a thrombus. As already stated, not every plaque develops into a vulnerable plaque. The geometry and composition of a plaque are major determinants of vulnerability. Vulnerable plaques typically have a large inflammatory lipid-rich core which is separated from the blood in the lumen by a thin fibrous cap, whereas the stable plaque has a much thicker cap and in many cases no lipid pool. Because vulnerable plaques are responsible for so many sudden deaths, the detection of vulnerable plaques before rupture is the goal of many research studies. In this thesis, noninvasive ultrasound based strain imaging/elastography techniques for the identification of plaque vulnerability were developed and their feasibility for clinical application was investigated.

Strain imaging techniques estimate the deformations (strain) of tissue by cross-correlating ultrasound data from the tissue at different states of deformation. In this way a displacement map of the tissue is obtained which can be transformed into a strain image by spatial derivation. In case of vascular strain imaging/elastography, the strains are generated by the pulsating blood in the lumen. Vascular elastography was initially applied intravascularly by transmitting and receiving ultrasound from a rotating transducer mounted on the tip of a catheter. It has been shown that intravascular ultrasound (IVUS) elastography allows differentiation between vulnerable plaques and stable plaques in vitro and furthermore a relation between the strain values and clinical symptoms was observed in an in vivo patient study. However, a major drawback of IVUS elastography will always remain that it is invasive and therefore cannot be applied to asymptomatic populations. Therefore, a noninvasive variant is desired.

As described in chapter 1 several research groups have been developing noninvasive vascular elastography methods. Almost all of these methods use the raw radiofrequency (RF) ultrasound signal to estimate the strains in the vessel wall instead of the postprocessed B-mode ultrasound image data as currently presented by commercial ultrasound systems. RF data contain the phase information of the transmitted ultrasound, which enables a more accurate estimation of strain. This also explains why usually only the strain component in the ultrasound beam direction (the axial direction) is used for strain estimation, because the phase information is only present in that direction. Estimation of strains in the other directions perpendicular to the ultrasound beams (the lateral and elevational directions) is less accurate. When imaging a vessel noninvasively in transverse direction the vessel’s natural directions of deformation, the radial and circumferential direction, are not aligned with the ultrasound beam direction for the entire cross section. Moreover, at the 3 and 9 o’clock regions of the vessel wall the radial direction is completely aligned with the lateral direction. Due to the reduced accuracy of the lateral component, it is also not possible to derive accurate radial strain estimates for the entire vessel cross section with conventional nonsteered ultrasound acquisitions.

In chapters 2 to 4 strain estimation methods were introduced that combined RF-derived strain estimates acquired at multiple insonification angles to increase the quality of the radial and circumferential strain estimates for transverse vessel cross sections by reducing the amount of required lateral information. To achieve the different steering angles electronic steering of the ultrasound beam was performed which enables the acquisition of ultrasound at different angles without rotation of the transducer. The methods presented in chapter 2 and 3 were both segment based methods which means that strains were estimated for circular segments of the cross section that varied with the beam steering angle. The segments were chosen such that the radial or circumferential direction and the axial direction were closely aligned. The various segments were combined to form a strain image for the entire cross section. To minimize the contribution of the lateral information the method of chapter 2 assumed incompressibility and isotropy; the method of chapter 3 assumed the absence of circumferential motion. The method presented in chapter 4 was not segment based and did not require any of these assumptions. Axial displacement fields measured at three different beam steering angles were combined by means of projection to derive the radial or circumferential strain image. The use of a large positive (+30°), an equally large negative (-30°) and a 0° beam steering angle resulted in the most accurate radial and circumferential strain images. The performance of all methods was demonstrated for simulated and experimental data of vessel phantoms with different geometries. The performance of the methods was expressed as root mean square error (RMSE) for the simulations and as elastographic signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) for the experimental data. With respect to conventional 0° radial strain images the methods of chapter 2, 3 and 4 improved RMSE by 11%, 54%, and 46%, respectively when using beam steering angles of -30°, 0°, and 30°. SNR and CNR improved by 0.8 dB and 3.4 dB, 2.2 dB and 8.6 dB, and 4.0 dB and 9.8 dB, respectively. Circumferential strain images for the same three angles are reported only in chapter 4 and improved the RMSE by 62%, the SNR by 6.4 dB and the CNR by 24.0 dB compared to conventional 0° circumferential strain images. Based on these results and because of the lack of assumptions, the nonsegment based compounding method gained the highest preference.

An often questioned issue is the use of large beam steering angles of ±30°. It is generally known that the use of large beam steering angles leads to the generation of grating lobe artifacts. Grating lobes are higher order ultrasound beams in a direction other than the main beam which signal is interpreted as originating from the main beam. In chapter 2 it was however shown that these artifacts can be removed entirely by low-pass filtering without a tremendous loss of main lobe signal, thus still allowing an adequate estimation of strains. In chapter 3 the influence of grating lobe filtering on strain estimation was investigated more thoroughly. It became clear that for improved strain estimation accuracy it was better to set the cutoff frequency a little higher, such that a larger part of the main lobe remained intact. The improvement in accuracy due to the availability of a larger part of main lobe signal overcompensated the reduction in accuracy caused by the small amount of grating lobe signal present.

As aforementioned the deformations (strain) of tissue can be determined by cross-correlating ultrasound data from the tissue at different states of deformation. Conventionally, rigid rectangular kernels of data are used for calculation of the cross-correlation functions. However, in case of tissue shearing, the use of rectangular kernels might not be optimal. In chapter 6 the strain estimation performance of a new method in which the kernels were allowed to
shear axially was compared with conventional cross-correlation using rectangular kernels. The axial shear was based on previous guesses of the axial displacement for each image line. It was shown that this “free-shape method” outperformed the conventional method in the presence of axial tissue shear. The method also showed to be superior in the estimation of tissue rotation. Because, axial shear strain also occurs in transverse cross sections of vascular structures, the free-shape method was also applied in the in vivo validation study of chapter 8.

In chapters 2 to 4 the compounding methods were only tested using quasi-static data, which means that no motion occurred in between the change of beam steering angle. The presence of such motion might lead to substantial artifacts in the compounding process. To test the performance of the compounding method of chapter 4 in pulsating vessels, a dedicated imaging sequence was implemented on a Medison Accuvix V10 ultrasound system that allowed automatic sequential storage of RF data from various beam steering angles. It was shown in chapter 7 that also in a periodically pulsating vessel-mimicking phantom and in vivo in recordings of a healthy carotid artery the three-angle nonsegment based technique outperformed conventional single-angle elastography. There were less errors in the 3 and 9 o’clock regions of the cumulative strain images for both cases. Furthermore, strain values for subsequent pressure cycles were reproducible.

To validate that the compounding method of chapter 4 allowed the detection of vulnerable plaques in vivo a patient study was carried out (chapter 8). Multi-angle RF data of transverse cross sections of atherosclerotic carotid arteries of patients were recorded the day before the plaque was surgically excised. Cumulative strain values were estimated from end-systole to end-diastole and correlated with plaque composition determined using histological staining. Local matches between plaque composition and strain images were observed. Furthermore, two strain parameters were defined that showed to increase with plaque vulnerability related features, like an increased amount of lipids, a thin fibrous cap, superficially located macrophages and a reduced concentration of smooth muscle cells. Although the correlations did not reach significance due to the limited amount of patients included (n = 18), a clear relation between vulnerable plaque features and strain values was observed.

Chapters 9 to 11 described recent developments closely related to noninvasive carotid elastography. In chapter 9 the possibilities of plane wave ultrasound transmission for compound elastography were researched. Because carotid arteries move in three dimensions during the pressure cycle it would be very valuable to estimate strain in three dimensions. However, assessing strain in three dimensions also asks for higher frame rates. Plane wave imaging enables imaging at higher frame rates than conventional ultrasound imaging, because a single plane wave transmit is used to reconstruct the entire image view, instead of focussed transmissions for every separate image line as used in conventional ultrasound imaging. It was shown for simulated 2-D data that compound elastography based on plane wave transmissions outperformed conventional 0° elastography (Wilcoxon, P<0.001). Due to the unfocussed transmission, the estimates were slightly less accurate than those acquired with focussed multi-angle elastography, however the frame rate was increased by more than a factor of 50. In chapter 10 0° strain estimation was used to assess the longitudinal shear strain in the adventitial layer of carotid arteries. The hypothesis is that longitudinal shear strain accelerates the development of atherosclerotic plaques towards a vulnerable plaque. It was shown that estimation of longitudinal shear strain in the adventitia of the carotid artery was feasible using RF data even without compounding. The RF-based strain estimation outperformed envelope-based (RF after absolute Hilbert transform) strain estimation in simulations, phantom experiments and in vivo experiments. Future studies will have to proof the validity of the hypothesis. Chapter 11 was related to the fact that strain is not a tissue parameter. Strain does however provide indirect information of the elastic properties of a tissue. For instance, it is possible to derive a relative Young modulus image from a strain image by solving what is called the inverse problem: given the tissue geometry, strain image and some boundary conditions a modulus image is reconstructed that would best match the estimated strain image. Chapter 11 showed that compound strain images are a better basis for modulus reconstruction than conventional single-angle strain images, although validation in in vivo atherosclerotic carotid arteries is still to be performed.

To conclude: A multi-angle ultrasound elastography technique was developed for estimation of radial strains in transverse vascular cross sections. Initial results in carotid arteries of a small patient group revealed a positive correlation between the estimated strains and features of plaque vulnerability. Therefore, the developed vascular elastography technique has great potential to become the first noninvasive patient friendly technique able to detect vulnerable plaques in vivo.
Samenvatting

In dit hoofdstuk wordt een samenvatting gegeven van de ontwikkelde technieken voor niet-invasieve elastografie van arteriën en hun toepassing voor het detecteren van instabiele atherosclerotische plaques in de halsslagader.
**Samenvatting**

Het overgrote deel van de westere populatie ontwikkelt atherosclerose. Atherosclerose is een systemische ziekte, die zich meestal langzaam ontwikkelt tijdens het ouder worden en vooral de grote arteriën aantast. Atherosclerose begint met de opstapelning van vetten en andere stoffen in de vaatwand. Zo’n opstapelning wordt een “fatty streak” genoemd. Fatty streaks kunnen groeien en zich doorontwikkelen tot een plaque. De meeste van deze plaques zijn jarenlang stabiel. Echter plaques kunnen ook instabil en kwetsbaar worden, hetgeen betekent dat ze een groot risico op scheuren hebben. Wanneer zo’n instabile plaque scheurt, reageert het lichaam hierop met het vormen van een bloedstolsel. Dit bloedstolsel zorgt dan plotseling voor een belemmering van de bloedstroom en veroorzaakt daarmee een afname in de toevoer van zuurstof en voedingsstoffen naar het achterliggende weefsel. Dit gebrek aan stoffen kan leiden tot celsterfte. Wanneer dit gebeurt in het hart of de hersenen spreken we respectievelijk van een hart- of herseninfarct. In meer dan 60% van de gevallen zijn scheurende instabile plaques de oorzaak van hart- en herseninfarcten. Zoals gezegd ontwikkelt niet elke plaque zich tot een instabile plaque. De geometrie en samenstelling van een plaque bepalen of hij stabiel of instabil is. Instabile plaques worden gekenmerkt door een grote ontstekingsrijke vette kern, die van de bloedstroom gescheiden wordt door een dun fibreus kapij. Stabile plaques hebben daarentegen een veel dikkere kapi en vaak geen vetachtige korn. Omdat instabile plaques verantwoordelijk zijn voor zo’n groot aantal plotselinge sterfdagen is detectie van deze plaques voordat ze scheuren het doel van vele onderzoeksstudies. In dit proefschrift werden niet-invasieve strain imaging/elastografische technieken voor detectie van plaque instabiliteit ontwikkeld en daarnaast werd hun klinische toepasbaarheid onderzocht.

Strain imaging technieken schatten de vervormingen (strains) in een weefsel door echo-ultrageluid-jonamen van het weefsel in verschillende vervormingstoestanden met elkaar te vergelijken. Meestal gebeurt dat doordemiddel van kruiscorrelatie. Eerst wordt een verplaatsingsveld bepaald waaraan de eerste orde spatiale afgeleide de strain afbeelding oplevert. Bij vasculaire toepassing worden die strains die veroorzaakt worden ten gevolge van de pulserende bloedstroom bepaald. Vasculaire strain imaging/elastografie werd initieel ontwikkeld voor intravasculaire toepassingen, waarbij het ultrageluid vanaf de tip van een kather uitgezonden en ontvangen werd. *In vitro* werd met deze intravasculaire techniek aangetoond dat op basis van strain het onderscheid gemaakt kan worden tussen instabile en stabiele plaques. Daarnaast bleken de gemeten strain waarden ook te correleren met klinische symptomen in een patiënten studie. Een groot nadeel van intravasculaire toepassing zal echter altijd blijven dat de methode invasief is en dus niet toepasbaar op asymptomatische populaties. Een niet invasieve variant van deze methode zou dit nadeel kunnen ondervangen.

Zoals in hoofdstuk 1 beschreven staat, wordt er in verschillende onderzoeksgruppen gewerkt aan de ontwikkeling van niet invasieve vasculaire elastografie. Nagenoeg alle methoden gebruiken de ruwe radiofrequente (RF) ultrageluidssignalen voor het bepalen van de strains in de vaatwand in plaats van het nabewerkte B-mode signaal dat standaard uit commerciële echoapparatuur komt. Het gebruik van de RF signalet maakt een nauwkeurigere schatting mogelijk van de strains, omdat het signaal ook de fase-informatie van het uitgezonden ultrageluid bevat. Dit verklaart ook waarom normaliseren alleen de strain component in de richting van de geluids bundel (axiale richting) geschat wordt aangezien de fase informatie alleen in die richting aanwezig is. Strain schattingen in de twee richtingen loodrecht op de richting van de geluids bundel (lateraal en elevationeel) leveren daarom ook minder nauwkeurige resultaten op. Wanneer we een transversale dwarsdoorsnede van een bloedvat in beeld brengen zijn de dominante vervormingrichtingen de radiale en circumferentiële richting. Echter deze richtingen komen niet voor de volledige doorsnede overeen met de richting van de geluids bundel. Sterker nog, er zijn bijvoorbeeld gebieden waar de radiale component volledig in de laterale richting staat. Gezien de geringe nauwkeurigheid van de strain schatting in die richting is het dan ook niet mogelijk om de radiale strain voor de hele doorsnede nauwkeurig te bepalen op basis van conventionele ultrageluidsregistraties.

In hoofdstuk 2 tot en met 4 worden methodes beschreven die het mogelijk maken om een nauwkeurigere radiale en circumferentiële strain afbeelding te schatten door het reduceren van de bijdrage van de laterale component. Om dit te bereiken werden strain afbeeldingen van verschillende geluidstransmissiehoeven gecombineerd. De verschillende zonden kunnen verkregen zonder rotatie van de transducer door aanpassing van de elektronische vertragingen op de verschillende transducerellemen. De methoden van hoofdstuk 2 en 3 waren segment gebaseerde methoden, hetgeen betekent dat strains geschat werden voor cirkelsegmenten van de doorsnede. De positie van die segmenten verschillde per zondehoek en werd zo gekozen dat de radiale of circumferentiële richting nagenoeg gelijkgerecht waren met de axiale richting. De onder de verschillende hoeken verkregen segmenten werden vervolgens samengevoegd om een strain plaatje te vormen voor de volledige doorsnede. Om het gebruik van de laterale bijdrage te reduceren werd bij de methode van hoofdstuk 2 aangenomen dat het weefsel niet samendrukkbaar was en isotroop. De methode van hoofdstuk 3 deed de aanname dat er geen verplaatsingen optraden in de circumferentiële richting. In hoofdstuk 4 werd een niet segment gebaseerde methode gepresenteerd die geen van bovenstaande aannames nodig had. Om de radiale en circumferentiële strain te bepalen voor de volledige doorsnede werden de volledige axiale verplaatsingsvelden van drie hoeken gecombineerd door middel van projectie. De combinatie van een grote positieve (+30°) zondehoek, een even grote negatieve (-30°) zondehoek en een 0° acquisitie resulteerde in de meest nauwkeurige radiale en circumferentiële strain afbeelding. De nauwkeurigheid van alle methoden werd vergeleken aan de hand van simulaties en experimenten met artificiële bloedvaten. Voor de simulaties werd de root mean squared error (RMSE) als maat voor nauwkeurigheid genomen. Voor de experimenten waren dit de elastografische signaal-ruis verhouding (SNR) en contrast-ruis verhouding (CNR). Ten opzichte van de conventionele 0° radiale strain afbeeldingen verbeterden de methoden van hoofdstuk 2, 3 en 4 de RMSE met respectievelijk 11%, 54%, en 46%. SNR en CNR verbeterden respectievelijk met 0.8 dB en 3.4 dB, 2.2 dB en 8.6 dB, en 4.0 dB en 9.8 dB. Circumferentiële strain schattingen voor dezelfde drie zondenhoeken werden alleen beschreven in hoofdstuk 4 en lieten een verbetering zien ten opzichte van de nul graden schattingen van 61% in RMSE, 6.4 dB in SNR en 14.0 in CNR. Op basis van deze resultaten en het niet nodig hebben van aannames, heeft de niet segment gebaseerde methode de voorkeur gekregen.

Het gebruik van zondenhoeken van –30° wordt vaak ter discussie gesteld. Het is algemeen bekend dat zulke grote zondenhoeken leiden tot het ontstaan van artefacten veroorzaakt door grating lobes. Grating lobes zijn hogere orde geluids bundels in een andere richting dan die van de hoofdbundel. Het echosignaal van die bundels wordt geïnterpreteerd alsof het van de hoofdbundel afkomstig, hetgeen tot artefacten leidt. In hoofdstuk 2 werd echter aangetoond dat deze artefacten volledig weg gefilterd konden worden met een low-pass filter. Hierbij bleef het signaal van de hoofdbundel grotendeels intact zodat nog steeds betrouwbare strain bepalings gedaan konden worden. In hoofdstuk 5 werd de invloed van grating lobe filtering nog verder
validatie studie van hoofdstuk 8

CHAPTER 14

parameters en de kenmerken van een instabiele plaque waargenomen. Ondanks dat de correlaties nog niet statistisch significant waren, waarschijnlijk vanwege het nog beperkte aantal geïncludeerde patiënten, werd duidelijk een relatie tussen de strain en de plaque samenstelling. Lokale overeenkomsten in het strain image en de plaque samenstelling werden gevonden. Transversale dwarsdoorsneden van atherosclerotische halsslagaders van patiënten onder de eind diastole en gecorreleerd met de op histologie gebaseerde plaque samenstelling. Cumulatieve strain waarden werden bepaald over de periode van eind systole tot eind diastole en gecorreleerd met de op histologie gebaseerde plaque samenstelling. Verschillende zendhoeken werden de dag voor het chirurgisch verwijderen van een plaque toegepast. Om te bewijzen dat de methode van hoofdstuk 4 detectie van instabiele plaques mogelijk was, werd een nieuwe methode waarin strain als een vrije vorm methode ook in de niet segment gebaseerde methode van hoofdstuk 4 te testen in pulserende bloedvaten werd een speciale imaging sequentie geïmplementeerd op een Medison Accuvix V10 echoapparaat, die om de longitudinale shear-strain in de adventitia van halsslagaders. De hypothese is dat een hoge longitudinale shear strain de ontwikkeling van plaques naar instabiele plaques versnelt. Het werd aangetoond dat het mogelijk was, zelfs zonder toepassing van de niet segment gebaseerde methode, om de longitudinale shear strain in de adventitia te bepalen op basis van RF signalen. De RF-gebaseerde strain schatting resulteerde in betere strain resultaten voor simulaties, fantoom experimenten en in vivo gemeten vrijwilligers, dan bereikt kon worden met een identieke methode toegepast op de omhullende van de RF signalen. Toekomstig onderzoek zal moeten uitwijken of de gestelde hypothese correct is. De methode van hoofdstuk 11 had te maken met het feit dat strain geen intrinsieke weefseleigenschap is. Strain verschilt echter wel indirect inzicht in de elastische eigenschappen van een weefsel. Het is mogelijk om op basis van de strainwaarden, de geometrie en enkele randvoorwaarden terug te redeneren wat de Young's modulus van het gemeten weefsel was, het zogenoemde oplossen van het inverse probleem. Er werd aangetoond dat de strain images die verkregen werden met de niet segment gebaseerde methode een betere oplossing van het inverse probleem mogelijk maakten dan op basis van oö acquisities verkregen kon worden.

Om te bewijzen dat de methode van hoofdstuk 4, detectie van instabiele plaques mogelijk maakt, werd een in vivo patiënt studie uitgevoerd (Hoofdstuk 8). RF signalen van transversale dwarsdoorsneden van atherosclerotische halsslagaders van patiënten onder de verschillende in vivo tijdens de dag voor het chirurgisch verwijderen van een plaque gemeten. Cumulatieve strain waarden werden bepaald over de periode van eind systole tot eind diastole en gecorreleerd met de op histologie gebaseerde plaque samenstelling. Lokale overeenkomsten in het strain image en de plaque samenstelling werden gevonden. Daarnaast werden twee strain parameters gedefinieerd die representatief konden zijn voor de instabiliteit. Deze parameters bleken toe te nemen zodra een plaque meer eigenschappen had van een instabiele plaque, zoals de aanwezigheid van veel vetten, een dun fibreescherm, ontstekingstecellen dicht bij het lumen en het (nagenoeg) ontbreken van gladde spiercellen. Ondanks dat de correlaties nog niet statistisch significant waren, waarschijnlijk vanwege het nog beperkte aantal geïncludeerde patiënten, werd duidelijk een relatie tussen de strain parameters en de kenmerken van een instabiele plaque waargenomen.

In hoofdstuk 9 en met 11 werden enkele nieuwe ontwikkelingen die ofwel voortborduren ofwel nauw verwant zijn aan de gepresenteerde elastografie methoden beschreven. In hoofdstuk 9 werden de mogelijkheden voor elastografie na het uitzenden van een een gefocussed deel van het signaal van de hoofdbundel was namelijk groter, dan de afname in nauwkeurigheid door het nul gering aanwezige deel grating loze signaal.

Zoals eerder genoemd worden strains in een weefsel geschat door het kruiscorreleren van ultrageluiddata van weefsel in verschillende vervormingstoestanden. Conventioneel worden rigide rechthoekige vensters gebruikt voor de kruis-correlaties. In het geval er afschuwfrekken in het weefsel optreden, zou het gebruik van rechthoekige vensters echter niet optimaal kunnen zijn. Dit werd in hoofdstuk 6 onderzocht. De nauwkeurigheid van de strain bepaling op basis van een nieuwe methode waarin vensters niet langer rechthoekig waren, maar in axiale richting beeld en vervormingen op basis van eerdere bepalingen van het axiale verplaatsingsveld, werd vergeleken met de nauwkeurigheid op basis van rechthoekige rechthoekige vensters. Het werd gemonstreerd dat de “vrije vorm methode” nauwkeurigere strain schattingen opleverde dan de conventionele methode in het geval er axiale afschuwfrekken in het weefsel aanwezig waren. De methode was ook superieur in het bepalen van rotaties in weefsel. Vanwege het feit dat axiale afschuwfrekken ook aanwezig zijn in transversale doorsneden van vasculaire structuren, werd de vrije vorm methode ook in de in vivo validatie studie van hoofdstuk 8 toegepast.

In hoofdstuk 2 tot en met 4 werden de zojuist genoemde methoden alleen getest in quasistatische situaties, hetgeen betekent dat er geen beweging plaats vond tijdens de verandering van zenuwacio. De aanwezigheid van zulke beweging zou echter tot substantiële artefacten kunnen leiden bij het samenvoegen van de hoekinformatie. Om de niet segment gebaseerde methode te testen in pulserende bloedvaten werd een speciale imaging sequentie geïmplementeerd op een Medison Accuvix V10 echoapparaat, die het mogelijk maakte automatisch achtereenvolgens RF signalen van drie verschillende zenuwatoeslagen op te nemen. Gebruikmakend van deze imaging sequentie werd in hoofdstuk 7 simulaties, fantoom experimenten en in vivo gemeten vrijwilligers, dan bereikt kon worden met een identieke methode toegepast op de omhullende van de RF signalen. Toekomstig onderzoek zal moeten uitwijken of de gestelde hypothese correct is. De methode van hoofdstuk 11 had te maken met het feit dat strain geen intrinsieke weefseleigenschap is. Strain verschilt echter wel indirect inzicht in de elastische eigenschappen van een weefsel. Het is mogelijk om op basis van de strainwaarden, de geometrie en enkele randvoorwaarden terug te redeneren wat de Young's modulus van het gemeten weefsel was, het zogenoemde oplossen van het inverse probleem. Er werd aangetoond dat de strain images die verkregen werden met de niet segment gebaseerde methode een betere oplossing van het inverse probleem mogelijk maakten dan op basis van oö acquisities verkregen kon worden.
Bibliography

A detailed list of the referenced publications and proceedings
References


CHAPTER 15


CHAPTER 15


204


CHAPTER 15

BIBLIOGRAPHY


List of Publications and Presentations

An overview of the publications and presentations (co)authored by the author


Book chapters


Awards


Proceedings


Conference Presentations


Dankwoord

Een woord van dank aan iedereen die heeft bijgedragen aan de totstandkoming van dit proefschrift.
Dankwoord

Alhoewel er veel mensen zijn die ik graag wil bedanken en die later nog aan bod zullen komen, wil ik beginnen met mijn dank uit te spreken naar mijn copromotor dr. ir. Chris de Korte. Zonder Chris was dit proefschrift niet tot stand gekomen. Daarnaast heeft Chris ook een grote bijdrage geleverd aan mijn persoonlijke ontwikkeling als onderzoeker en als persoon.

Beste Chris, ik heb enorme bewondering voor de manier waarop jij in het leven staat, altijd optimistisch, vol van vertrouwen en ontzettend toegewijd aan alles wat je lieft. Met die houding en je enorme steun heb je me door heel wat moeilijke situaties heen weten te leiden. Ik kan en kon werkelijk alles met je bespreken. Wetenschappelijk gezien heb ik ook veel van je geleerd. Naast je kennis van (vasculair) ultrageluid en elastografie, is jouw manier van samenwerken en onderhandelen met technische, klinische en industriële partners erg boeiend en leerzaam. Daarnaast heb je nog iets anders weten te bereiken. Het heeft nogal wat kopzorgen aan mijn en volgens mij ook aan jouw kant gekost, maar je hebt ervoor gezorgd dat mijn twijfels over een toekomst in de academische onderzoeksworld plaats hebben gemaakt voor een “we gaan er lekker tegenaan en zien wel waar het schip strandt” houding. Voorlopig werkt dat in ieder geval weer vijf jaar de tijd heb om lekker onderzoek te doen in “ons” lab.

Ik wil hierbij ook mijn promotor prof. dr. Mathias Prokop bedanken. Ook al kennen we elkaar nog maar kort, jouw visie op wetenschap en het enthousiasme waarmee je dat overbrengt, spreekt me erg aan. Daarnaast kan ik het erg waarderen dat je ondanks je enorm drukke agenda toch de moeite nam om een feestje van ons lab bij Chris thuis te bezoeken en even kort met iedereen een praatje te maken. Ik ben dan ook blij dat je mijn promotor wilt zijn.


Prof. dr. Gerard Pasterkamp, dr. Gert de Borst, prof. dr. Michiel Bots, Wim van de Vooren en dr. Suzanne Holewijn wil ik ook hartelijk bedanken voor hun enthousiasme en support voor het NWO VIDI project “Vulnerable Plaque Detection in Carotid Arteries using Non-Invasive Ultrasound Elastography” waar dit promotieonderzoek deel van uit maakt. Suzanne, jij stond altijd klaar voor me als er patiënten dan wel collega’s gemeten moesten worden en hebt me zelfs nog een spoedcursus echografie van de halsslagader gegeven. Naast het feit dat het plezierig samenwerken is met jou, heb ik ook veel waardering voor jouw doorzettingsvermogen en manier van onderzoek doen. Wim, jij hebt een essentiële bijdrage geleverd aan dit project door er met jouw overtuigingskracht voor te zorgen dat de team steering acquisitie geimplementeerd werd in een van de Samsung Medison echoapparaten zodat we de ontwikkelde methode daadwerkelijk hebben kunnen toepassen bij patiënten. Hartelijk dank hiervoor. Michiel, jou heb ik ook veel dank verschuldigd. Een projectvergadering met jou aan tafel is erg aangenaam. Jouw pure enthousiasme heeft me keer op keer weer gemoed te om het onderste uit de kan te blijven halen. Daarnaast ben ik je ook erg dankbaar vanwege de twee maanden die ik voor je heb mogen werken. Gert Jan, zonder jouw steun en die van prof. dr. Frans Moll hadden we nooit zo’n mooie patiëntensstudie kunnen realiseren. Daarnaast heb jij er met jouw kritische blik vanuit de vaatchirurgie voor gezorgd dat het in vivo hoofdstuk een geweldig verhaal is geworden. Tenslotte Gerard, jij was blijkbaar al enthousiast over dit project nog voordat ik er überhaupt van gehoord had. Ik ben erg blij dat je dit ook altijd gebleven bent. Eén moment van onze samenwerking zal ik niet gauw vergeten, dat was toen je nog een keer als vanouds plaatsnam achter een microscoop en me de histologie van een typische instabiel plaque liet zien. Je fascinatie voor deze plaque en de manier waarop je dit overbracht sprak boekdelen. Ik hoop dat ik nog vaak met ieder van jullie mag samenwerken.

Jan en Richard jullie zijn natuurlijk extra speciaal als paranimfen. Richard, jij hebt het goede voorbeeld gegeven in een heleboel dingen. Je had niet alleen een geweldig mooi strijd algoritme voor me klaar staan toen ik Nijmegen arriveerde, je hebt me ook laten zien hoe je het maximale uit een congresreis haalt (niet alleen qua presenteren). Ik ben dan ook blij dat onze band verder reikt dan werk alleen en dat we samen deel uitmaken van de “beste band” van de wereld. Jan, jij bent iemand die altijd klaar staat voor iedereen en heel belangrijk is voor de sfeer op de afdeling. Je hebt altijd iets interessants te vertellen en bent heel creatief als er een act op te voeren is. Nogmaals, ik ben erg blij dat jullie paranimf willen zijn. En Jan, als jij gaat promoveren, staan Richard en ik voor je klaar...

Natuurlijk wil ik ook mijn directe collega’s van het Medical UltraSound Imaging Centre (MUSIC, voorheen Klinisch Fysisch Laboratorium) bedanken voor het altijd plezierige werkklimaat waarin iedereen voor elkaar klaar staat. Dit werkt echt geweldig en we moeten dat zo blijven vasthouden. Tim, jij als directe collega op het carotisproject hebt me laten zien dat je gewoon moet volhouden, dan komt het altijd wel een keer goed. Maartje en Annie, jullie waren in het verleden natuurlijk al collega’s, maar de laatste maanden is onze samenwerking nog een stukje versterd. Ik ben erg blij dat ik met zulke goede onderzoekers verder mag aan het nieuwe project. Sonja, natuurlijk ook hartstikke bedankt voor alle administratieve ondersteuning. Je hebt me vele malen een dienst bewezen. Gert, Marianne, Jeroen en Han, jullie ook hartstikke bedankt voor jullie hulp en voor het delen van jullie kennis en kunde. Tot slot wil ik ook de vele studenten, Bart, Annette, Vincent, Michiel, Ellen, Bram, Emma en Dave bedanken voor hun bijdragen aan dit proefschrift en dan nog een stukje verstevigd. Ik ben erg blij dat ik met zulke goede onderzoekers verder mag aan het nieuwe project. Sonja, natuurlijk ook hartstikke bedankt voor alle administratieve ondersteuning. Je hebt me vele malen een dienst bewezen. Gert, Marianne, Jeroen en Han, jullie ook hartstikke bedankt voor jullie hulp en voor het delen van jullie kennis en kunde. Tot slot wil ik ook de vele studenten, Bart, Annette, Vincent, Michiel, Ellen, Bram, Emma en Dave bedanken voor hun bijdragen aan dit proefschrift en daarnaast ook voor de plezierige tijd samen.

Mijn indirecte collega’s in Utrecht wil ik ook van harte bedanken. Erik, Loes, Mourad en Wouter van de afdeling Radiologie bedankt voor de vele middagen die we samen echo’s gemaakt hebben. Sander van de Experimentele Cardiologie, hartstikke bedankt voor het prepareren van de uitgenomen plaques en het maken van de mooie foto’s ervan. Daarnaast verdienen de secretaires van de vaatchirurgie, Cobie en Susan, ook een eervolle vermelding voor de hulp om elke week weer patiënten te kunnen includeren in de studie. Een bijzonder woord van dank gaat ook naar prof. Bleyen en Willem en Simon van de afdeling Anatomie. Het was een bijzonder en uniek onderzoek waar ik veel van geleerd heb. En last but definitely not least wil ik ook de mensen van het Julius Centrum, Lizeth, Lydeke en Manon bedanken voor hun enthousiasme, voor het zoeken naar een oplossing voor de logistieke problemen die je krijgt als je met een apparaat op meerdere locaties wilt en voor het opnemen van beelden voor de longitudinale studie.

Mijn dank gaat ook uit naar de patiënten die geheel zonder eigen belang deel hebben genomen aan de in vivo validatiestudie tussen de spanningen van de endarteriectomie operatie door.
Frank en Tatjana, jullie wil ik ook bedanken voor het prachtige en originele ontwerp van de omslag van dit proefschrift. Het ontwerpen hiervan was, denk ik voor ons allemaal, een leuke nieuwe ervaring.

Natuurlijk heb ik niet alleen gewerkt. Rens, Ruud en Richard hartelijk dank voor de gezellige avonden en de hoognodige en veelal muzikale ontspanning. Joyce en Chris, jullie ook bedankt voor de gezellige etentjes en feesten. Verder wil ik ook alle vrienden die ik via Pauline heb leren kennen hartelijk danken voor de getoonde interesse en de gezellige momenten die we met elkaar door hebben gebracht.

Tevens wil ik ook mijn familie bedanken voor de altijd aanwezige interesse. Ik ben heel blij dat ik uit zo’n fijne gezellige en knusse familie kom en hoop dat we ook nog lang op zo’n plezierige manier met elkaar om kunnen blijven gaan. Ik heb ook veel bewondering voor opa en oma, die aan de basis staan van deze familie en ondanks hun hoge leeftijd nog altijd belangstelling hebben voor de zaken die hun kinderen en kleinkinderen bezig houden.

Papa en mama en Inge en Dave, bij jullie kan ik mijn hele leven al terecht. Door jullie ben ik geworden wie ik ben en heb ik zo ver kunnen komen. Bedankt voor jullie onvoorwaardelijke steun in alle fases van mijn leven. Ook mijn schoonfamilie, Har, Els, Suzette en Geert, wil ik bedanken voor de warme ontvangst telkens weer. Ook met jullie kan ik alles delen en jullie weten me altijd te helpen in moeilijke tijden.

Tenslotte wil ik nog de belangrijkste persoon in mijn leven in het zonnetje zetten. Pauline, aan jou ben ik meer dank verschuldigd dan aan wie dan ook. Zo’n promotieperiode brengt niet alleen ups met zich mee, maar ook downs. Jij was er altijd voor me en wist me altijd weer op te peppen, ondanks mijn humeur op dat soort momenten. Hiervoor kan ik je niet vaak genoeg bedanken. Ik ben enorm trots op je en verheug me meer dan ooit op onze toekomst samen!
About the Author

Curriculum vitae of the author
About the Author

Hendrik (Rik) Hubertus Gertrudis Hansen was born in Roermond, The Netherlands, on 11-02-1982. He successfully graduated in 2000 at the Bisschoppelijk College Schöndeln in Roermond, where he obtained his Gymnasium diploma. Because of his preference for engineering subjects, he chose to study Applied Physics at the Eindhoven University of Technology. During this study Rik also became interested in the medical and clinical applications of Physics. In 2005 he received a M.Sc. degree in Applied Physics after finishing his Master thesis at the Maxima Medical Center in Veldhoven under supervision of dr. ir. Chris Peters, and prof. dr. ir. Pieter F. F. Wijn. During the Master Thesis project, Rik developed a tool for analysis of neonatal brain activity using electro-encephalography signals. In 2006 Rik got his first real job and was employed by Enter Technology Eindhoven, who positioned him as a software/system test engineer at a company called Assembléon BV in Veldhoven. After this experience outside the world of medical physics, Rik started working at the Clinical Physics Laboratory of the Radboud University Nijmegen Medical Center as a PhD student in 2007. This PhD study was performed as part of a VIDI grant project granted to dr. ir. C.L. de Korte titled “Vulnerable Plaque Detection in Carotid Arteries using Non-Invasive Ultrasound Elastography”. As part of the project Rik (co-)authored over ten peer-reviewed papers and two book chapters. Furthermore, he presented his work at many national and international conferences and received two awards for oral presentations. Because of the very fruitful and pleasant collaboration at the Clinical Physics Laboratory (nowadays called the Medical UltraSound Imaging Center) and the interesting research opportunities, Rik has decided to stay with his colleagues in Nijmegen for at least five years. Since May 2012 he has been employed as a post-doctoral researcher on the VICI project titled: “Ultrafast 3-D Ultrasound Imaging: the next level for cardiovascular diagnosis”. As part of this project Rik will further explore the possibilities of plane wave imaging for fast ultrasound strain imaging in a variety of applications, but of course mainly for the assessment of atherosclerosis.