CARDIOVASCULAR ELASTOGRAPHY

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Abstract

Elastography is a technique that enables assessment of the mechanical or contractile properties of tissue. In cardiovascular medicine, this technique is used for characterisation of plaques and myocardium, and assessment of myocardial function.

An unstable atherosclerotic plaque contains a large lipid pool covered by a thin fibrous cap. Such a plaque may rupture and cause an acute thrombotic reaction. Intravascular ultrasound (IVUS) elastography might be considered an ideal technique to assess the presence of lipid pools and identify proneness for rupture. Validation *in vitro* demonstrated that the strain in the different plaque types is different. Additionally, elastography has a 88% sensitivity and 89% specificity for identifying the unstable plaque. *In vivo,* in an atherosclerotic Yucatan mini-pig animal model also higher strain values in fatty than in fibrous plaques were found. Recently this technique was upgraded to three-dimensions. In vivo 3D elastograms of the aorta of atherosclerotic rabbits revealed high strain in unstable plaques and low strain in stable plaque regions.

The viability of the myocardium can be assessed using the local shortening and lengthening. This information can be obtained by strain and strain-rate imaging. We acquired rf-data in 3 patients using a Vingmed SystemV. The strain can be determined using the following 3 step approach: First, the region of interest has to be segmented. Next the global motion of the tissue has to be determined. Finally, the strain and strain rate are calculated using a cross-correlation based technique. Using this technique, strain values up to 30% were observed in the intraventricular septum

Introduction

In many medical applications, the echogenicity alone is not sufficient to make a proper diagnosis. Assessment of the deformation of tissue using ultrasound provides new information that might be beneficial for clinical decision making. This technique is called elastography and uses multiple ultrasound images, acquired under different levels of deformation, to calculate the strain. This principle was first described and patented in the early 1990's by Ophir and co-workers [1]. Strictly speaking elastography uses a user dependent mechanical load (as described in the patent), but also natural sources that were first considered an error source are nowadays considered useful. The deformation of the tissue is determined using two or more ultrasound datasets of the tissue under investigation that are acquired at different levels of deformation. Using cross-correlation based techniques, the local deformation is determined from the raw rf- or demodulated ultrasound signal. In cardiovascular applications, this technique was first used by O'Donnell and co-workers to characterize atherosclerotic plaques in arteries. The technique was based on a compliant balloon that was inflated in the artery to act as mechanical load.

Other groups are using the pulsatile systemic blood pressure as source for mechanical deformation. Although this technique misses the user adjustable well controllable mechanical load, it prevents possible damage of the arterial wall, and thus increases the clinical applicability. In cardiac applications, the use of a user controllable mechanical device is unlikely. Besides practical limitations, the most interesting parameter of the myocardium is its contractile function. In these applications, assessment of deformation is called strain imaging. An often assessed other parameter called strain-rate stands for the rate, or velocity, of the deformation.

In the first part of this paper, techniques to assess the composition and the stability of atherosclerotic plaques are described and discussed. Identification of different plaque components is of crucial importance to detect the rupture prone plaque. Typical parameters of these plaques are an eccentric plaque with a large lipid pool shielded from the lumen by a thin fibrous cap [2, 3]. Inflammation of the cap by macrophages further increases the vulnerability of these plaques [4]. The mechanical properties of fibrous and fatty plaque components are different [5-7]. Furthermore, fibrous caps with inflammation by macrophages are weaker than caps without inflammation [8]. Because the lipid pool is unable to withstand forces, all the stress that is applied to the plaque by the pulsating blood is concentrated in the cap [9, 10]. The cap will rupture if it is unable to withstand the stress applied to it. This increased circumferential stress will result in an increased radial deformation (strain) of the tissue due to the incompressibility of the material. Therefore, methods

that are capable of measuring the radial strain provide information that are relevant for clinical decision-making.

The second part focuses on strain and strain-rate imaging of the myocardium. Ultrasound strain and strain-rate imaging of the myocardium were proposed in 1998 by Heimdal et al.[11] The method is based on Tissue Doppler Imaging (TDI) [12]. Using the difference between local velocities of the tissue as assessed with TDI, the strain-rate can be determined. This parameter has proven to be highly correlated to myocardial contractility[13]. Temporal integration of the strain-rate results in the local strain of the tissue. The major drawback of this Doppler based technique is that only a one-dimensional estimate of the strain can be made. TDI determines the velocity of tissue along the ultrasound beam and therefore this estimate is also angle dependent. Especially in hearts with complicated geometries, like the mono-ventricular heart, one-dimensional strain and strain-rate imaging based on TDI has limited clinical value. Two-dimensional assessment of the strain appears to be feasible using the similar techniques as used in elastography. This rf-based technique requires higher frame rates than TDI-based strain(-rate) imaging.

Intravascular elastography

In intravascular elastography, the intraluminal pressure difference is in the order of 5 mmHg for frame-rates of 20 per second. The strain, induced by this pressure differential in vascular tissue is in the order of 1%. This means that a block of tissue with an initial size of 100 μm will be deformed to 99μm. To differentiate between strain levels, sub-micron estimation of the deformation is required.

Envelope based methods. Two groups worked on intravascular elastography using the envelope of the ultrasound signal. Talhami *et al* [14] introduced a technique to assess the strain that is based on the Fourier scaling property of the signals and uses the chirp Z-transform. The scaling property directly represents the strain in the tissue. The chirp-Z transform was determined from the envelope signal to overcome decorrelation of the rf-signal due to large deformation of the tissue. The result is displayed as a color-coded ring around the image of the vessel. Initial results on vascular tissue *in vitro* and *in vivo* were described. Although the technique seems relatively easy to implement, it was not further developed and validated.

Ryan and Foster [15] developed a technique based on speckle tracking in video signals. The strain can be determined from these displacement estimates. The technique was tested using vessel-mimicking phantoms. It was shown that in a phantom that was partly made of soft and partly made of hard material the displacement in soft material was larger than the displacement in hard material.

An advantage of envelope-based methods is the fact that the correlation function is smoother than the rf-based correlation function. This prevents 'peak hopping', meaning that the correlation function is maximized around the wrong peak. This makes the method less noise sensitive. Furthermore, the video signal is commonly available from any commercial echo system. A disadvantage is the limited resolution and the low sensitivity of the method for low strain values. Since small tissue strains are expected for intravascular applications, and the arterial wall is relatively thin, it is expected that the use of the high frequency rf signal will greatly improve the resolution. Based on work of Varghese and Ophir [16], a smaller variance of the strain estimate is expected using RF data instead of envelope data.

RF based methods: Shapo *et al* [17, 18] developed a technique based on cross-correlation of scan lines. The group proposes a large deformation to maximize the signal-to-noise ratio of the displacement and strain estimation. Since the deformation that is needed is larger than the deformation that occurs in arteries *in vivo*, the tissue is deformed using a non-compliant balloon that is inflated up to 8 atmospheres. Large displacement will decorrelate the ultrasound signals to such an extent that correlation detection is unreliable. For this reason, the cross-correlation is calculated in several intermediate steps of intraluminal pressure. For detection, they use a phase-sensitive speckle tracking technique. The technique was demonstrated in simulations and tissue mimicking phantoms. Recently this group [19] presented data on a compliant balloon containing an intravascular catheter. The compliant balloon is inflated to 2 atmospheres to obtain strain values up to 40%. This method was tested in phantoms and *in vitro*. The phantom (with one half soft and one half hard material) revealed strains from 20-40% in the soft part and strains lower than 20% in the hard part. These results were corroborated by finite element analysis. *In vitro*, low strain values (7%) were found for fibrous tissue in the human femoral artery and high strain values (35%) were found in thrombus in a rabbit aorta.

De Korte *et al* [20, 21] incorporated the 'classical' way of performing elastography [1] for intravascular purposes. The vascular tissue is strained by different levels of the intraluminal pressure. The local displacement of the tissue is determined using cross-correlation analysis of the gated rf-signals. This technique uses the principle that the peak of the cross-correlation function is found at the position representing the displacement of the tissue. For each scanning angle, the displacement of the tissue at the lumen vessel-wall boundary is determined. Next, the

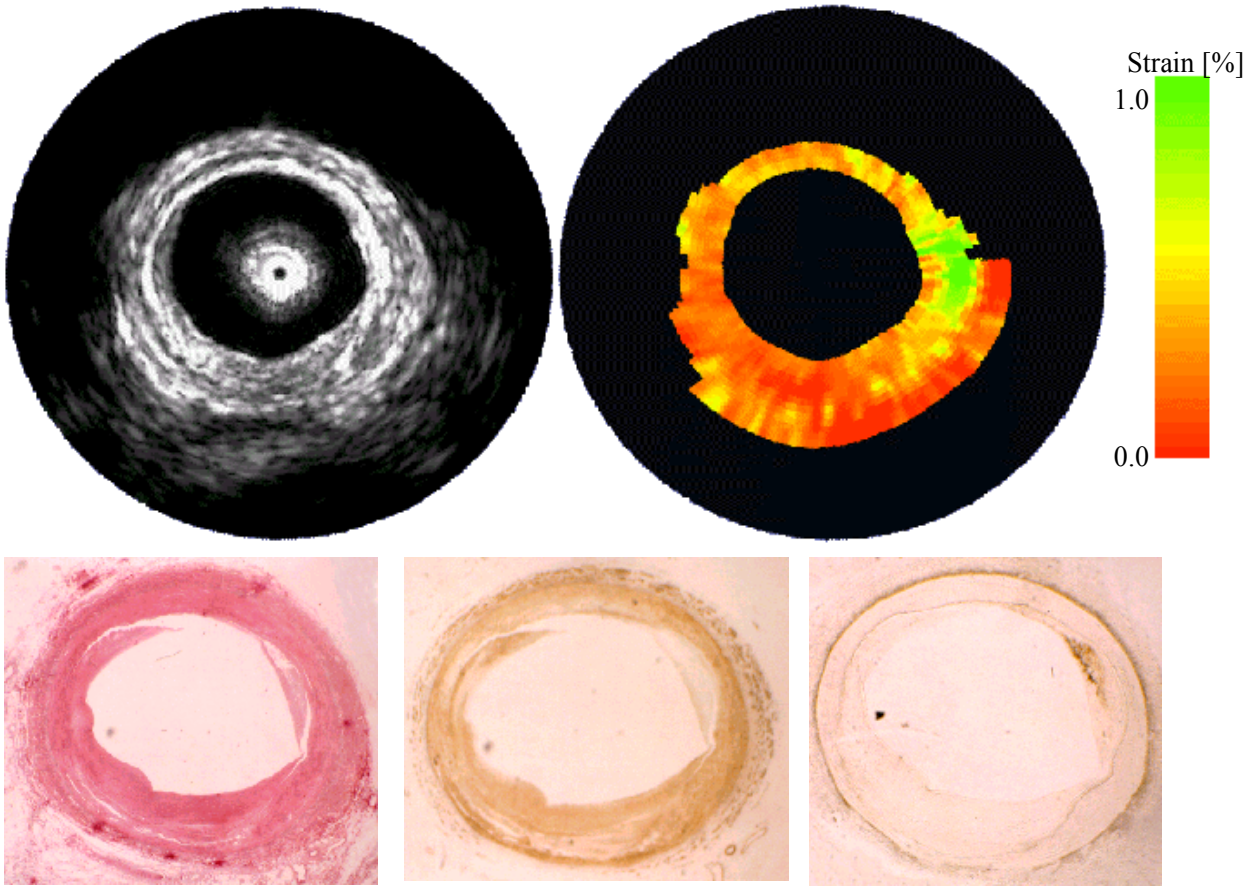

Figure 1: Echogram (upper panel,left), elastogram (upper panel, right) and histologic sections (lower panel) of a human femoral artery with a mixed eccentric plaque. The echogram reveals an eccentric plaque between 2 and 11 o'clock. The elastogram shows that the plaque can be divided into two parts: A low strain part (0.2%) between 4 and 11 o'clock and a high strain part (1%) between 2 and 4 o'clock, both compared to the moderate strain (0.5%) in the normal vessel wall. The histology reveals that the region between 4 and 11 o'clock is fibrous material and the region between 2 and 4 o'clock is fatty material.

displacement of the tissue 300 µm distal from the vessel-wall boundary is determined. The strain of the tissue can be calculated by dividing the differential displacement (displacement of tissue at boundary – displacement of tissue in wall) by the original distance between these two regions (300 µm) The strain for each angle is colour-coded and plotted as a ring (palpogram) at the lumen vessel-wall boundary. [22, 23]. If the strain is determined for multiple regions per angle, a two-dimensional image of the strain can be constructed. This additional image to the IVUS echogram is called elastogram. The method was validated using vessel phantoms with the morphology of an artery with an eccentric soft or hard plaque [24]. The plaque could be clearly identified from the vessel wall using the elastogram, independently of the echogenicity contrast between vessel wall and plaque. The technique was validated *in vitro* and tested in atherosclerotic animal models and during interventions in patients (as discussed further on).

This cross-correlation based technique is especially suited for strain values smaller than 2.5%. These strain values are present during *in vivo* acquisitions when only a part of the heart cycle is used to strain the tissue [25]. The maximum strain that will be present between the systolic and diastolic pressure is in the order of 10 %. For these strain rates, another approach that takes into account the change in shape of the signals can be applied. This 'local scaling factor estimation' technique [26] has been recently described for intravascular purposes [27] and has proven to be more robust to large deformations. The signal after compression is processed as a delayed and scaled replica of the signal before deformation. An adaptive strain estimation method based on the computation of local scaling factors has been applied to compute elastograms of cryogel phantoms mimicking vessels and of a freshly excised human carotid artery using a 30 MHz mechanical rotating single element ultrasound scanner (ClearView, CVIS, Boston Scientific Corp.) [28].

In vitro validation: De Korte *et al* [29] performed a validation study on excised human coronary (n=4) and femoral (n=9) arteries (figure 1). Data were acquired at room temperature at intraluminal

pressures of 80 and 100mmHg. Coronary arteries were measured using a solid state 20 MHz array catheter (EndoSonics, Rancho Cordova, CA, USA). Femoral arteries were investigated using a single element 30 MHz catheter (DuMed/EndoSonics, Rijswijk, The Netherlands) that was connected to a modified motor unit (containing the pulser and receiver and a stepper-motor to rotate the catheter). The rf-data was stored and processed off-line. The visualized segments were stained on the presence of collagen, smooth muscle cells and macrophages. Matching of elastographic data and histology was performed using the IVUS echogram. The cross-sections were segmented in regions (n=125) based on the strain value on the elastogram. The dominant plaque types in these regions (fibrous, fibro-fatty or fatty) were obtained from histology and correlated with the average strain and echo-intensity.

Mean strain values of 0.27%, 0.45% and 0.60% were found for fibrous, fibro/fatty and fatty plaque components. The strain values for the three plaque types as determined by histology differed significantly (p=0.0002). This difference was independent of the type of artery (coronary or femoral) and was mainly evident between fibrous and fatty tissue (p=0.0004). The plaque types did not reveal echo-intensity differences in the IVUS echogram (p=0.992). Conversion of the strain into Young's modulus values was performed by the relation $E=\Delta P/2\varepsilon$. Because the pressure differential and thus the stress are only known at the boundary between lumen and vessel-wall and due to non-linearity of this parameter this gives only a first order approximation of the modulus. Conversion of strain into modulus resulted in values of 493 kPa, 296 kPa and 222 kPa for fibrous, fibro/fatty and fatty plaques. Although these values are higher than values measured by Lee *et al* [7], the ratio between the modulus of fibrous and fatty material is similar. Since fibrous and fatty tissue demonstrated a different strain value and high strain values were often co-localised with increased concentrations of macrophages, these results reveal the potential of identification of the vulnerable plaque.

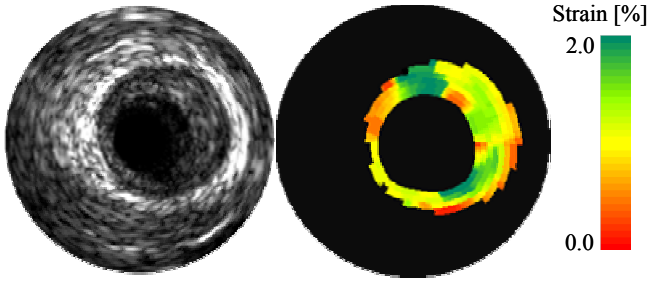

Figure 2: Intracoronary echogram and elastograms obtained in a patient with unstable angina pectoris during an interventional procedure. The High strain regions at the shoulders of this eccentric plaque provide evidence for a mechanically unstable plaque.

Animal studies: Recently, IVUS elastography was validated *in vivo* using an atherosclerotic Yucatan mini-pig [30]. External iliac and femoral arteries were made atherosclerotic by endothelial Fogarty denudation and subsequent atherosclerotic diet for the duration of 7 months. Balloon dilation was performed in the femoral arteries and the diet was discontinued. Before termination, 6 weeks after balloon dilation and discontinuation of the diet, data were acquired in the external iliac and femoral artery in 6 Yucatan pigs. In total, 20 cross-sections were investigated with a 20 MHz Visions® catheter (JOMED, Rancho Cordova, CA). The tissue was strained by the pulsatile blood pressure. Two frames acquired at end diastole with a pressure differential of approximately 4 mmHg were taken to determine the elastograms.

After the ultrasound experiments and before dissection, X-ray imaging was used to identify the arterial segments that had been investigated by ultrasound. The specimens were frozen in liquid nitrogen. The cross-sections (7μm) were stained for collagen (picro Sirius red and polarized light), fat (oil red O) and macrophages (alcalic phosphatase). Plaques were classified as absent, early fibrous lesion, early fatty lesion or advanced fibrous plaque. The mean strain in these plaques and in normal cross-sections was determined.

Strains were similar in the plaque free arterial wall and the early and advanced fibrous plaques (Table 1). Univariate Analysis of Variance revealed significantly higher strain values in cross-sections with early fatty lesions than in fibrous plaques (p=0.02). Although a higher strain value was found in plaques with macrophages than in plaques without macrophages, this difference was not significant after correction for fatty components. The presence of a high strain spot had a high predictive value to identify the presence of macrophages (a sensitivity and specificity of 92%). In case there was no high strain spot present, no fatty plaques were found (Table 2).

Patient studies: Preliminary acquisitions were performed in patients during percutaneous trans-luminal coronary angioplasty (PTCA) procedures [25]. Data were acquired in patients (n=12) with an EndoSonics InVision echo apparatus equipped with an rf-output. For obtaining the rf-data, the machine was working in ChromaFlo mode resulting in images of 64 angles with unfocussed ultrasound data. The systemic pressure was used to strain the tissue. This strain was determined using cross-correlation analysis of sequential frames (frame rate is 20/s). A likelihood function was determined to obtain the frames with minimal motion of the catheter in the

lumen, since motion of the catheter prevents reliable strain estimation. Minimal motion was observed near end-diastole. Reproducible strain estimates were obtained within one pressure cycle and over several pressure cycles. Validation of the results was limited to the information provided by the echogram. Strain in calcified material (0.20%) was lower ($p<0.001$) than in non-calcified tissue (0.51%).

Additionally, high-resolution elastograms were acquired using an EndoSonics InVision echo apparatus [31]. The beam-formed image mode (512 angles) ultrasound data (f_c = 20 MHz) was acquired with a PC based acquisition system. Frames (frame rate is 20/s) acquired at end-diastole with a pressure difference of approx. 5 mmHg were taken to determine the elastograms. Elastograms of soft, calcified and stented plaques were determined. The elastogram of a soft plaque, as identified from the deformation during the pressure cycle, reveals strain values up to 2% with increased strain regions at the shoulders of the plaque (figure 2). Calcified material, as identified from the echogram, shows strain values of 0-0.2%. The elastogram of stented plaques revealed very low strain values, except for two regions: these are between the stent struts and at the shoulders of the plaque.

Three dimensional palpography: In the previous studies, elastograms revealed information of one cross-section. However, the distribution of the strain in the 3 dimensional geometry of an artery is an important tool to identify the presence of high strain spots, the amount and the distribution. Especially, since the correlation between plaque vulnerability and parameters provided by the echogram is low [32, 33] selection of cross-sections based on the IVUS echogram introduces selection bias and dramatically increases the chance to miss the vulnerable spot. Additionally, during longitudinal monitoring of patients it is extremely difficult to find back the same spot after some months. Therefore, it would be a big step forward to have strain information of the full 3D coronary artery. In this approach, the strain in the inner layer of tissue is determined. This layer provides the crucial information if this plaque is mechanically stable or unstable and thus might rupture in the near future. The strain is plotted as a colour coded contour at the lumen vessel-wall boundary and is called palpogram.

In elastography, out of plane motion is considered as one of the main sources for decorrelation of the signals and thus decreasing the quality of the strain estimate [34, 35]. Therefore, for elastographic acquisitions, the position of the transducer is kept as stable as possible and only motion in the direction of the beam is allowed [1, 36]. As a consequence, it is unlikely that valid intravascular strain elastograms can be obtained while performing a continuous pullback of the catheter. However, if the pullback speed is only 1 mm/s and the strain is determined using two subsequent frames, the motion introduced by the pullback is minimal. Furthermore, it is known that the due to the contraction of the heart, in diastole the catheter will move in the distally in the coronary if the catheter is kept at a steady position. Therefore, performing a pullback will decrease out of plane in this phase of the heart cycle. Since 3D palpography uses data acquired in the diastolic phase, performing a pullback and thus obtaining 3D data seems feasible.

Experiments in rabbit aortas reveal that three dimensional palpography is feasible in vivo. Despite the introduction of out-of-plane motion by the continuous pull back of the catheter, the similarity between successive frames acquired in the diastolic phase is high enough to calculate several palpograms per heart cycle. By combining these palpograms, one compound palpogram per heart cycle is determined [22]. Repetitive pull-backs revealed high similarity between the 3D palpograms. Initial experience in humans demonstrate that 3D palpograms of a large part of a coronary artery can be determined (figure 3).

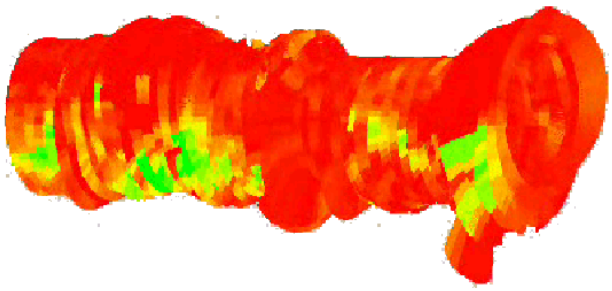

Figure 3: 3D palpogram of 50 mm of a human coronary artery obtained in vivo. High strain spots are present in several regions of this coronary.

Myocardial strain(-rate) imaging

The strain is determined using a cross-correlation based approach. Since this technique is only suitable for small strain values, high frame-rates are required to be able to assess the deformation of the fast contracting myocardium. Using a GE VingMed System V with a built-in rf-data storing option, frame rates up to 130/s are achievable. In this operation mode, only 16 angles per frame can be obtained. Data were stored in IQ format and converted to rf-data using an off-line algorithm. The resulting data was sampled at 20 MHz. Initial experiments were performed on the intra-ventricular septum that can be fully imaged and followed in time over the heart-cycle. Assessment of the strain is performed in three steps. First the septum has to be segmented. The next step is global motion estimation (tracking) to follow the tissue in time. Finally the strain is determined.

Segmentation: Segmentation of the intra-ventricular septum is performed using a gradient based image operator. First the edge was detected using the 'Sobel' algorithm. After a dilation, bridging, closing, and erosion step, the septum was segmented.

Tracking: The septum was followed over the heart-cycle using the Sum of Absolute Differences (SAD) between sequentially acquired frames. A two dimensional matrix of 5 angles and 200 sampling points containing the septum echo-data of a frame was matched to the next frame using the SAD of the envelope signals. This method has a good performance, is relatively fast and has proven to have a good performance in tracking echo-data for strain imaging in other applications [37]

Strain estimation: The time-delay between frames was determined using a window size of 100 sampling points with a 90% overlap. In total 100 time delays were calculated over the septum from apex to the base. The strain is calculated from these time-delays using a finite difference procedure. As can be seen in figure 4, a similar strain pattern is obtained over successive heart cycles. The strain pattern further shows that the base first contracts and the apex follows later in time. Also the strain levels in the base are higher than in the apex.

Discussion and Conclusion

The term elastography was for the first time mentioned in a paper in 1991 by Ophir and co-workers [1]. After a decade in which the technique was developed, fundamentally described and tested using simulations and phantoms, we are now entering a decade in which the strain starts to enter into the clinic and starts to play a role in clinical decision making. The availability of faster computers allows real-time strain estimation strategies and imaging possibilities.

Identification of plaque components and the proneness of a lesion to rupture is a major issue in interventional cardiology. Elastography might be a technique to identify these dangerous plaques. It has been shown by several groups that elastograms of vessel-like phantoms and arteries *in vitro* can be produced. Furthermore, the feasibility of IVUS elastography *in vivo* in animals and patients was demonstrated.

The question still not answered is the relevance of the information given by the elastogram. An elastogram is an image of the strain and is therefore an artifactual representation of the Young's modulus. Using finite element analysis, an image of the Young's modulus can be reconstructed using the strain and/or displacement information (also known as solving the inverse problem) [38, 39]. Analysis of

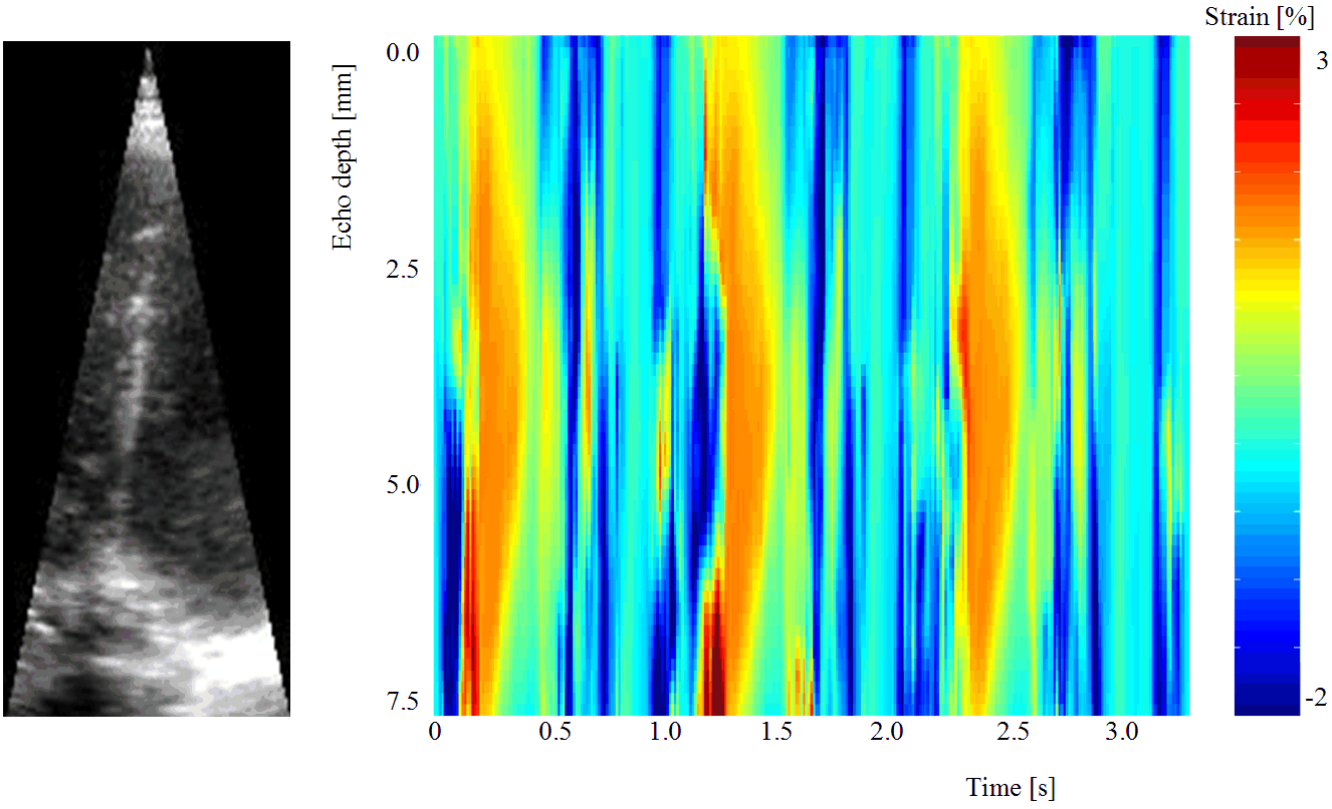

Figure 4: Myocardial strain of the intraventricular septum. The septum is imaged from apex (top of echogram) to the base (bottom of the echogram). The strain is color coded and plotted over 3 heart cycles. Reproducible strain values were observed over the three heart cycles. The septum first contracts at the base. Also higher strain values were found in this region than in the apex of the heart.

more complex geometries has to be performed to identify the differences between, and the similarities of strain and modulus images. Currently, the inverse problem is being solved for strain images acquired from human artery specimen *in vitro*. The resulting Young's modulus images and the strain images will be related to the histology [40].

Currently, there is no clinical technique available which is capable of identifying the rupture prone plaque. Identification of these plaques is of paramount importance to investigate the underlying principle of plaque rupture, the effectiveness of pharmaceutical treatments, and on the long-term, preventing sudden cardiac death. IVUS elastography has proven to be able to identify the rupture prone plaque *in vitro* with high sensitivity and specificity. *In vivo* experiments have demonstrated the power to identify fibrous and fatty plaque components. Therefore, IVUS elastography may be one of the first techniques that can be applied in patients to assess the vulnerability of plaques.

After the introduction of TDI-based strain rate imaging, this technique is now applied in various clinical institutes all over the world. However, the breakthrough of this technique as a reliable clinical tool did not happen until now. Multidimensional strain imaging might increase the clinical applicability. Furthermore, validation studies using animal models, allowing the possibility to relate the strain imaging findings to the golden standard histology, might reveal that myocardial strain imaging is a clinically useful technique that can quantify myocardial function and contractility. Since currently various congenital as well as other heart diseases can not be accurately diagnosed and monitored well, the need for such a technique is high.

References

1. J. Ophir, E. I. Céspedes, H. Ponnekanti, Y. Yazdi, and X. Li, "Elastography: a method for imaging the elasticity in biological tissues," Ultras Imag vol. 13, pp. 111-134, 1991.
2. E. Falk, P. Shah, and V. Fuster, "Coronary plaque disruption," Circulation vol. 92, pp. 657-671, 1995.
3. V. Fuster, B. Stein, J. Ambrose, L. Badimon, J. J. Badimon, and J. H. Chesebro, "Atherosclerotic plaque rupture and thrombosis. Evolving concepts," Circulation vol. 82, pp. II.47-II.59, 1990.
4. P. R. Moreno, E. Falk, I. F. Palacios, J. B. Newell, V. Fuster, and J. T. Fallon, "Macrophage infiltration in acute coronary syndromes: implcations for plaque rupture," Circulation vol. 90, pp. 775-778, 1994.
5. H. M. Loree, B. J. Tobias, L. J. Gibson, R. D. Kamm, D. M. Small, and R. T. Lee, "Mechanical properties of model atherosclerotic lesion lipid pools," Arteriscler Thromb vol. 14, pp. 230-234, 1994.
6. H. M. Loree, A. J. Grodzinsky, S. Y. Park, L. J. Gibson, and R. T. Lee, "Static circumferential tangential modulus of human atherosclerotic tissue," J Biomech vol. 27, pp. 195-204, 1994.
7. R. T. Lee, G. Richardson, H. M. Loree, A. J. Gordzinsky, S. A. Gharib, F. J. Schoen, and N. Pandian, "Prediction of mechanical properties of human atherosclerotic tissue by high-frequency intravascular ultrasound imaging," Arteriscler Thromb vol. 12, pp. 1-5, 1992.
8. C. L. Lendon, M. J. Davies, G. V. R. Born, and P. D. Richardson, "Atherosclerotic plaque caps are locally weakened when macrophage density is increased.," Atherosclerosis vol. 87, pp. 87-90, 1991.
9. H. M. Loree, R. D. Kamm, R. G. Stringfellow, and R. T. Lee, "Effects of fibrous cap thickness on peak circumferential stress in model atherosclerotic vessels," Circ Res vol. 71, pp. 850-858, 1992.
10. P. D. Richardson, M. J. Davies, and G. V. R. Born, "Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques," Lancet vol. 21, pp. 941-944, 1989.
11. A. Heimdal, A. Stoylen, H. Torp, and T. Skaerpe, "Real time strain rate imaging of the left ventricle by ultrasound.," J Am Soc Echocardiogr vol. 11, pp. 1013-1019, 1998.
12. W. McDicken, G. Sutherland, C. Moran, and L. Gordon, "Color Doppler Velocity imaging of the myocardium.," Ultras Med Biol vol. 18, pp. 651-654, 1992.
13. F. Jamal, T. Kukulski, J. D'hooge, I. De Schreuder, and G. Sutherland, "Abnormal postsystolic thickening in acute ischemic myocardium during coronary angioplasty: a velocity, strain and strain rate DMI study.," J Am Soc Echocardiogr vol. 12, pp. 994-996, 1999.
14. H. E. Talhami, L. S. Wilson, and M. L. Neale, "Spectral tissue strain: a new technique for imaging tissue strain using intravascular ultrasound," Ultras Med Biol vol. 20, pp. 759-772, 1994.
15. L. K. Ryan and F. S. Foster, "Ultrasonic measurement of differential displacement and strain in a vascular model," Ultras Imag vol. 19, pp. 19-38, 1997.
16. T. Varghese and J. Ophir, "Characterization of elastographic noise using the envelope of echo signals," Ultrasound Med Biol vol. 24, pp. 543-555., 1998.
17. B. M. Shapo, J. R. Crowe, R. Erkamp, S. Y. Emelianov, M. Eberle, and M. O'Donnell, "Strain imaging of coronary arteries with intraluminal ultrasound: experiments on an inhomogeneous phantom," Ultras Imag vol. 18, pp. 173-191, 1996.
18. B. M. Shapo, J. R. Crowe, A. R. Skovoroda, M. Eberle, N. A. Cohn, and M. O'Donnell, "Displacement and strain imaging of coronary arteries with intraluminal ultrasound," IEEE Trans UFFC vol. 43, pp. 234-246, 1996.
19. C. D. Choi, A. Skovoroda, S. Emelianov, and M. O'Donnell, "Strain imaging of vascular pathologies using a compliant balloon catheter," Proceedings of the IEEE Ultrasonics Symposium, Puerto Rico, USA, 2000.
20. C. L. de Korte, E. I. Céspedes, A. F. W. van der Steen, G. Pasterkamp, and N. Bom, "Intravascular ultrasound elastography: Assessment and imaging of elastic properties of diseased arteries and vulnerable plaque," Eur J Ultras vol. 7, pp. 219-224, 1998.
21. C. de Korte, A. van der Steen, E. I. Céspedes, G. Pasterkamp, S. Carlier, F. Mastik, A. Schooneveld, P. Serruys, and N. Bom, "Characterisation of plaque components and vulnerability with intravascular ultrasound elastography," Phys Med Biol vol. 45, pp. 1465-1475, 2000.
22. M. Doyley, F. Mastik, C. L. de Korte, S. Carlier, E. Cespedes, P. Serruys, N. Bom, and A. F. W. van der Steen, "Advancing intravascular ultrasonic palpation towards clinical applications," Ultras Med Biol vol. 27, pp. 1471-1480, 2001.
23. E. I. Céspedes, C. L. de Korte, and A. F. W. van der Steen, "Intraluminal ultrasonic palpation: assessment of local and cross-sectional tissue stiffness," Ultras Med Biol vol. 26, pp. 385-396, 2000.

24. C. L. de Korte, E. I. Céspedes, A. F. W. van der Steen, and C. T. Lancée, "Intravascular elasticity imaging using ultrasound: feasibility studies in phantoms," Ultras Med Biol vol. 23, pp. 735-746, 1997.
25. C. L. de Korte, S. G. Carlier, F. Mastik, M. M. Doyley, A. F. W. van der Steen, P. W. Serruys, and N. Bom, "Morphological and mechanical information of coronary arteries obtained with Intravascular elastography: *a feasibility study in vivo*.," Eur Heart J vol. 23, pp. 405-413, 2002.
26. S. Alam, J. Ophir, and E. Konofagou, "An adaptive strain estimator for elastography," IEEE trans UFFC vol. 45, pp. 461-472, 1998.
27. E. Brusseau, C. Perrey, P. Delachartre, M. Vogt, D. Vray, and H. Ermert, "Axial strain imaging using a local estimation of the scaling factor from RF ultrasound signals.," Ultras Imag vol. 22, pp. 95-107, 2000.
28. E. Brusseau, J. Fromageau, G. Finet, P. Delachartre, and D. Vray, "Axial strain imaging of intravascular data: results on polyvinyl alcohol cryogel phantoms and carotid artery.," Ultras Med Biol vol. 27, pp. 1631-1642, 2001.
29. C. L. de Korte, G. Pasterkamp, A. F. W. van der Steen, H. A. Woutman, and N. Bom, "Characterization of plaque components using intravascular ultrasound elastography in human femoral and coronary arteries in vitro," Circulation vol. 102, pp. 617-623, 2000.
30. C. L. de Korte, M. Sierevogel, F. Mastik, C. Strijder, E. Velema, G. Pasterkamp, and A. F. W. van der Steen, "Identification of Atherosclerotic Plaque Components with Intravascular Ultrasound Elastography in vivo: a Yucatan pig study," Circulation vol. 105, pp. 1627-1630, 2002.
31. C. L. de Korte, M. M. Doyley, S. G. Carlier, F. Mastik, A. F. W. van der Steen, P. W. Serruys, and N. Bom, "High resolution IVUS elastography in patients," Proceedings of the IEEE Ultrasonics Symposium, Puerto Rico, USA, 2000.
32. F. Prati, E. Arbustini, A. Labellarte, B. D. Bello, L. Sommariva, M. T. Mallus, A. Pagano, and A. Boccanelli, "Correlation between high frequency intravascular ultrasound and histomorphology in human coronary arteries," Heart vol. 85, pp. 567-570, 2001.
33. N. Komiyama, G. Berry, M. Kolz, A. Oshima, J. Metz, P. Preuss, A. Brisken, M. Moore, P. Yock, and P. Fitzgerald, "Tissue characterization of atherosclerotic plaques by intravascular ultrasound radiofrequency signal analysis: An in vitro study of human coronary arteries," Am Heart J vol. 140, pp. 565-574, 2000.
34. E. Konofagou and J. Ophir, "A new elastographic method for estimation and imaging of lateral displacements, lateral strains, corrected axial strains and Poisson's ratios in tissues," Ultras Med Biol vol. 24, pp. 1183-1199., 1998.
35. F. Kallel and J. Ophir, "Three dimensional tissue motion and its effect on image noise in elastography," IEEE trans UFFC vol. 44, pp. 1286-1296, 1997.
36. J. Ophir and Y. Yazdi, "Method and apparatus for measurement and imaging of tissue compressibility or compliance," vol. WO9107657, pp. 1992.
37. C. Janssen, C. L. de Korte, M. van der Heiden, C. Wapenaar, and A. van der Steen, "Angle matching in intravascular elastography," Ultrasonics vol. 38, pp. 417-423, 2000.
38. C. L. de Korte, E. I. Céspedes, A. F. W. van der Steen, and C. T. Lancée, "Image artifacts in intravascular elastography," Proceedings of the IEEE EMBS Symposium, Amsterdam, The Netherlands, 1996.
39. L. Soualmi, M. Bertrand, R. Mongrain, and J. C. Tardif, "Forward and inverse problems in endovascular elastography," in *Acoustical Imaging*, S. Lees and L. A. Ferrari, eds. (Plenum, New York, USA, 1997), pp. 203-209.
40. R. Baldewsing, C. L. de Korte, F. Mastik, J. Schaar, and A. F. W. van der Steen, "Comparison of Finite Element Model elastograms and IVUS elastograms acquired from phantoms and arteries," Proceedings of the IEEE Ultrasonics Symposium, Munich, Germany, 2003.