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Morphological and mechanical information of coronary arteries obtained with intravascular elastography

Feasibility study in vivo

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Aims Plaque composition is a major determinant of coronary related clinical syndromes. In vitro experiments on human coronary and femoral arteries have demonstrated that different plaque types were detectable with intravascular ultrasound elastography. The aim of this study was to investigate the feasibility of applying intravascular elastography during interventional catheterization procedures.

Methods and Results Data were acquired in patients (n=12) during PTCA procedures with an EndoSonics InVision echoapparatus equipped with radiofrequency output. The systemic pressure was used to strain the tissue, and the strain was determined using cross-correlation analysis of sequential frames. 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 ($0{\cdot}20\% \pm 0{\cdot}07$) was lower ($P<0{\cdot}001$) than in non-calcified tissue ($0{\cdot}51\% \pm 0{\cdot}20$).

Conclusion In vivo intravascular elastography is feasible. Significantly higher strain values were found in non-calcified plaques than in calcified plaques.
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Introduction

There is a great variation in the stability of coronary atherosclerotic plaques. When coronary flow is limited by plaque, patients develop angina, which can be stable for years. However, disruption of coronary plaques with superimposed thrombosis is the main cause of acute events, such as unstable angina pectoris, sudden coronary death and acute myocardial infarction[1–3]. There are two major mechanisms underlying plaque disruption[4,5]: rupture of a fibrous cap of a lipid-rich plaque[6] and denudation and erosion of the endothelial surface[7].

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It is now widely accepted that the propensity of a lesion to rupture is poorly predicted by coronary angiography[6,8]. A major problem is that vulnerability of plaque is not directly related to plaque size[7,9] but that the plaque composition is a major determinant[8]. Using intravascular ultrasound, the geometry of lumen, plaque and vessel wall can be obtained and is closely correlated to clinical angina[10]. However, identification of the different plaque components is still limited[11,12] although some promising ultrasound based techniques are currently being developed[13–15].

A wide range of techniques have the potential to visualize or characterize the plaque. Using scintigraphy, detection of plaque instability remained confined[16–18]. Other potential techniques may be magnetic resonance imaging[19,20] or optical coherence tomography[21]. With spectroscopy[22], as well as with angioscopy[23] and

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Raman spectroscopy[24,25] certain plaque components may be detectable. Promising new techniques are electrical impedance imaging[26] and thermal examination[27,28] of plaque surfaces, since a positive correlation between plaque vulnerability and parameters obtained using these techniques were found.

The main disadvantage of the techniques described above is that plaque vulnerability is associated with indirect parameters, such as plaque geometry, content, colour or temperature, although plaque vulnerability is mainly a mechanical phenomenon: using computer simulations, concentrations of circumferential tensile stress were more frequently found in unstable than in stable plaques[29,30]. For example, a thin fibrous cap shielding a lipid core from the blood may rupture since it is unable to bear the high circumferential stress due to the pulsating blood pressure. These high stress regions can be caused by the geometry of the plaque[30,31] or by local weakening of the plaque due to macrophage infiltration[32].

In 1991, a new technique was proposed, called elastography, which directly measures mechanical properties of tissue by ultrasound[33]. This technique was developed using phantom studies[34] and evaluated in vivo[35]. The underlying principle is that tissue is strained and that the strain rate is related to the local mechanical properties. The local strain of the material is obtained by comparing several ultrasound images. Currently, this technique is developed for intravascular purposes[36–38] and was recently applied in human coronary and femoral arteries in vitro[39,40]. These experiments revealed that the local strain, as measured with intravascular elastography is significantly different for fibrous and fatty plaque components. Furthermore, this technique had the potential to identify plaque vulnerability. Since the radial strain can be obtained, the technique may detect regions with elevated stress: increased circumferential stress is associated with an increased radial strain of the material.

In this study, the feasibility of obtaining elastographic images in vivo has been investigated. Elastograms were determined, using data obtained from arteries, where a PTCA procedure was planned. The pulsatile intracoronary pressure was used to obtain different levels of strain in the arterial wall. Since the catheter was moving in the lumen due to the contraction of the heart, an algorithm to determine the echo frames with minimal motion artefacts was applied on the data. The elastographic results were compared with echographic results.

Methods

Patient description and intravascular ultrasound examination

Intravascular ultrasound data was obtained in patients (n=12) referred for percutaneous intervention (Table 1). All the patients signed an informed consent. The culprit lesion to be treated was situated in the left anterior descending artery (n=3), the circumflex (n=3) and the right coronary artery (n=4). The left main coronary artery was investigated in another patient and the renal artery in the final patient. After intravenous administration of 10 000 IU heparin and 250 mg acetylsalicylic acid, a 6 Fr guiding catheter was advanced up to the ostium of the involved artery. After injection of a bolus of 3 mg isosorbide dinitrate, pre-intervention intravascular ultrasound assessment of the lesion was performed with a 3·5 Fr 64F/X intravascular ultrasound catheter (n=5) or a MegaSonics© (EndoSonics, Rijswijk, The Netherlands), a combination device consisting of an angioplasty balloon (3–3·5 mm diameter, length 20·0 mm) and a 64 F/X array intravascular ultrasound transducer proximal to the balloon (n=7). Lesions were crossed and imaged without complication. With the catheter crossing the lesions without inducing symptomatic ischaemia, a stable position was sought for the transducer in the centre of the lumen, offering visualization of significant plaque. The radiofrequency data were acquired as described below. The pressure was measured at the level of the extremity of the guiding catheter connected to a standard fluid-line system (Ohmeda, Bilthoven, The Netherlands).

Table 1 Baseline clinical and intravascular ultrasound characteristics

Patients, n	12
Age, years	56 ± 12 [36–75]
Male, %	7 (58%)
Systolic blood pressure (mmHg)	132 ± 18 [98–156]
Diastolic blood pressure (mmHg)	79 ± 14 [57–107]
Stable angina, %	5 (42%)
Unstable angina, %	7 (58%)
Prior MI, %	4 (33%)
Risk factors, %	
Diabetes mellitus	1 (8%)
Hypercholesterolaemia	7 (58%)
Hypertension	4 (33%)
Smoking history	4 (33%)
Artery, %	
Left main	1 (8%)
Left anterior descending	3 (25%)
Circumflex	3 (25%)
Right coronary	4 (33%)
Renal artery	1 (8%)
Lesion characteristics, %	
De novo	10 (83%)
Restenotic	2 (17%)
Concentric	7 (58%)
Eccentric	5 (42%)

Data acquisition and analysis

The 64-element phased array catheter was connected to an EndoSonics InVision system. The system is equipped with analog radiofrequency data output. This output provides the data for a ChromaFlo™ flow mode image[41]. In this mode, the catheter operates in linear

instead of phase array mode, thus providing low-resolution images[42]. Each frame contains 64 angles, including a radiofrequency signal of 10 μs (corresponding to 7·5 mm). These data were digitized in a custom-made acquisition system, containing a Pentium computer with an acquisition board (Signatec, Corona, CA, U.S.A.) with 128 Mbyte to store the radiofrequency data at a sampling rate of 200 MHz in 8 bits.

Ten frames per second were acquired at cross-sections where the intravascular ultrasound echogram revealed diseased vessel wall with significant plaque. For determination of the strain, cross-correlation techniques were applied to the data[39]. First the movement of the tissue along the ultrasound beam was determined. The local strain was obtained from this displacement. Due to the contraction of the heart, the catheter was moving in the lumen[43]. For in-plane motion (catheter moving in the imaging plane), correction algorithms were developed[44]. For large longitudinal motion (i.e. motion along the catheter), the frames acquired at the different intraluminal pressures may image different tissue. In this case, the echo signals are not correlated, thus hindering adequate displacement estimates.

An algorithm to determine the similarity between sequential echo frames was used as a figure of merit for the motion of the catheter in the lumen. The normalized absolute difference between two sequential echo frames was determined using the likelihood between the frames: 0% corresponding to no similarity between the frames and 100% was obtained when both frames were exactly the same. Sequential frames with a high likelihood and a pressure differential large enough (5 mmHg on average) to result in strain levels between 0 and 1% were taken to calculate the elastograms. The determined strain values were tested on validity, using the relation between strain and peak-value of the cross-correlation function[39,45]. Erroneous strain estimates were replaced by the median value of the surrounding strain estimates. The typical number of erroneous strain estimates was 10%. Elastograms with more than 35% erroneous strain estimates were considered unreliable.

Since validation of the experimental results using histology was not available, the elastographic experiments could only be partially validated using the echogram. Strain values for calcified material, accurately and specifically identified using the echogram by the bright echo and the distal shadowing, were compared to the values corresponding to plaque accumulation and normal coronary segments. Low strain values were expected in the calcified segments.

Statistical analysis

Values are reported as means ± SD. Analyses were accomplished using a standard software package (SPSS 9.0, SPSS Inc. Chicago, IL, U.S.A.). Differences in strain between calcified and non-calcified regions were evaluated by an unpaired Student's t-test. Comparison between groups of patients was evaluated by one way analysis of variance.

Results

Intra-cardiac cycle reproducibility

The acquisition of intravascular elastograms in vivo is illustrated in Fig. 1. The pressure curve (in blue) shows a diastolic pressure of 105 mmHg and a systolic pressure of 135 mmHg. The curve representing the resemblance between the sequential echo frames is in green. Relating this likelihood curve to the pressure curve reveals that the sequential frames have the best match near end-diastole. The maximum likelihood is present just before the P wave of the ECG (in red). The minimal motion of the catheter in this phase corresponds well to the absence of movement and contraction in this phase of the heart cycle. As can be appreciated, the pressure differential between frames at this point in the pressure curve is in the order of 4 mmHg.

The intravascular ultrasound echogram (upper right corner) reveals a concentric plaque in this artery. The echogenicity of the plaque is lower than the echogenicity of the wall. A strong reflection of the lumen–plaque boundary is observed between 4 and 8 o'clock. Between 11 and 1 o'clock the echogenicity is low and the thickness of the plaque is small.

Three frames near end-diastole were taken to determine two elastograms. The pressure differential of 4 mmHg is large enough to strain the vessel wall and plaque between 0 and 1% (colour coded from red to green). Both images indicate that the region between 11 and 2 o'clock has high strain values indicating soft tissue. The region at 3 o'clock is relatively hard. The region between 3 and 6 o'clock has intermediate strain values at the lumen vessel wall boundary and high strain levels distal to this region. The region between 6 and 11 o'clock has low strain values. The similarity between the two frames is high, indicating that the determination of the strain values in one pressure cycle is reproducible.

Inter-cardiac cycles reproducibility

Data from another patient is presented in Fig. 2. Blood pressure was between 100 and 150 mmHg. The likelihood curve (in green) again demonstrates that during systole the resemblance between the frames is small but that near end-diastole the similarity between frames is high. The pressure differential between sequential frames near end-diastole is approximately 5 mmHg.

The echogram of this cross-section shows an eccentric plaque between 3 and 9 o'clock. At 8 o'clock, a calcified deposit is visible in the plaque. In all the elastograms, low strain values are observed in the corresponding region. The arterial wall between 9 and 3 o'clock has moderate to high strain levels. The plaque area between 3 and 7 o'clock has low strain estimates. It can be

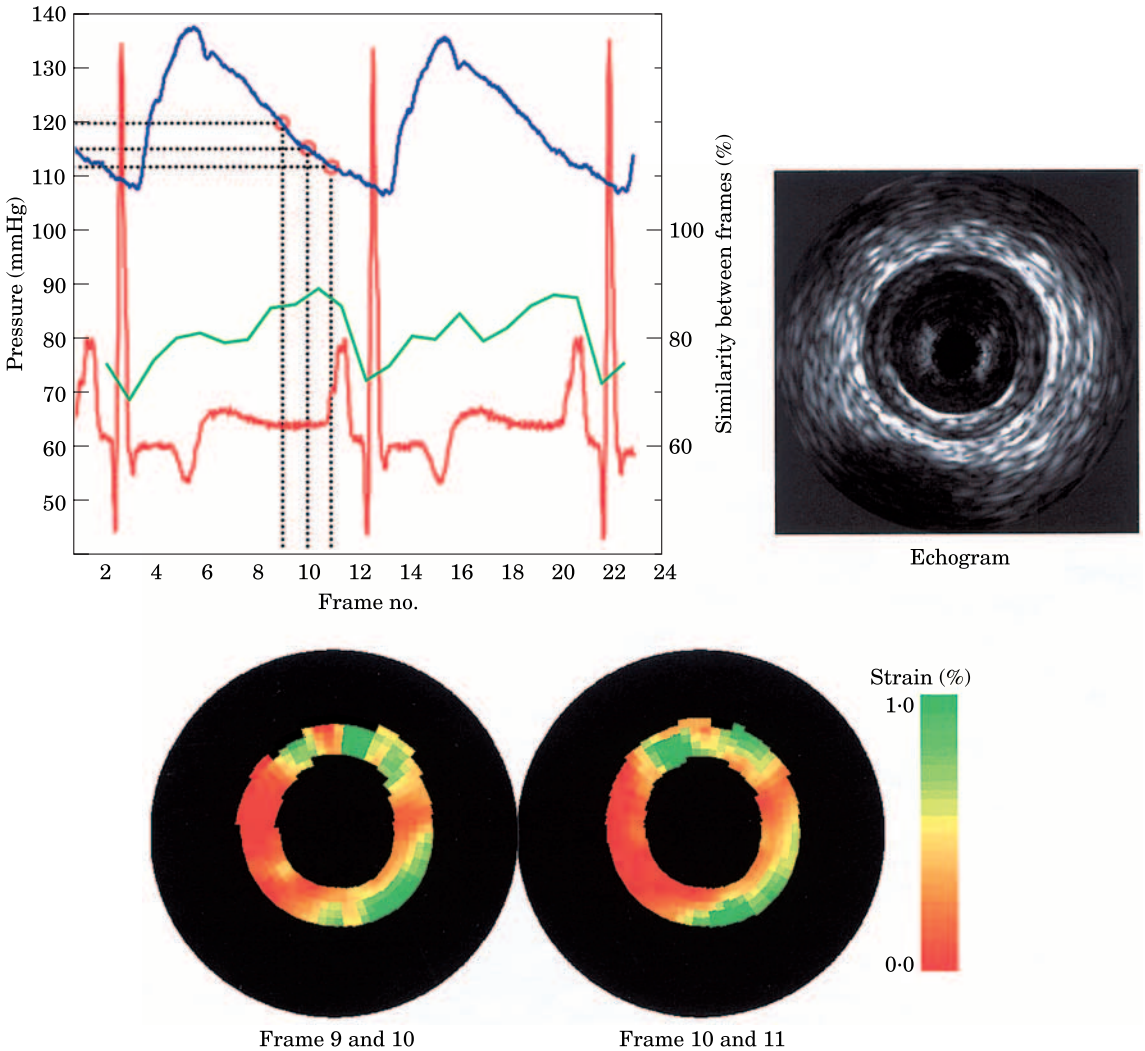

Figure 1 **The principle of acquiring an intravascular elastogram in vivo. The likelihood curve (green line) reveals a maximum near end-diastole. Three echoframes (9, 10 and 11) were taken to determine two elastograms. Both reveal soft material between 10 and 2 o'clock, hard material between 7 and 10 o'clock and mixed (soft material distal to hard material) between 2 and 7 o'clock.**

appreciated that the elastograms have a similar appearance over the sequential pressure cycles. At 3 o'clock, erroneous strain estimates can be observed caused by not properly working transducer elements. This artefact was also visible when the ChromaFlo™ mode was activated.

The mean strain profile with error bars is shown in Fig. 3. Errorbars increase with increasing mean strain value. For low strain values (<0·4%), a standard deviation of 0·08% is present. The standard deviation increases to 0·25% for strain values of 1%.

Strain estimates in function of plaque morphology

In Fig. 4, two echograms and an elastogram are presented. The data for determining the elastogram were acquired near end-diastole. The left echogram is the original echogram, as produced using the EndoSonics InVision system. The echogram reveals a highly calcified wall between 1 and 9 o'clock with distal shadowing. The region between 9 and 1 o'clock contains no calcified material. The low-resolution echogram in the middle is the echogram determined directly from the radiofrequency data. Since the radiofrequency data is acquired in ChromaFlo™ mode, only 64 angles are available at low resolution. The elastogram (Fig. 4left) shows very low strain values (average=0·15%) between 2 and 9 o'clock corresponding to the calcified area. The region between 9 and 2 o'clock has high strain levels (average = 0.76%), indicating soft material in this region.

Among the 12 intravascular ultrasound cross-sections acquired in the 12 patients investigated, three demonstrated similar calcified regions ($104 \pm 70°$). The corresponding average strain values was $0{\cdot}20 \pm 0{\cdot}07$.

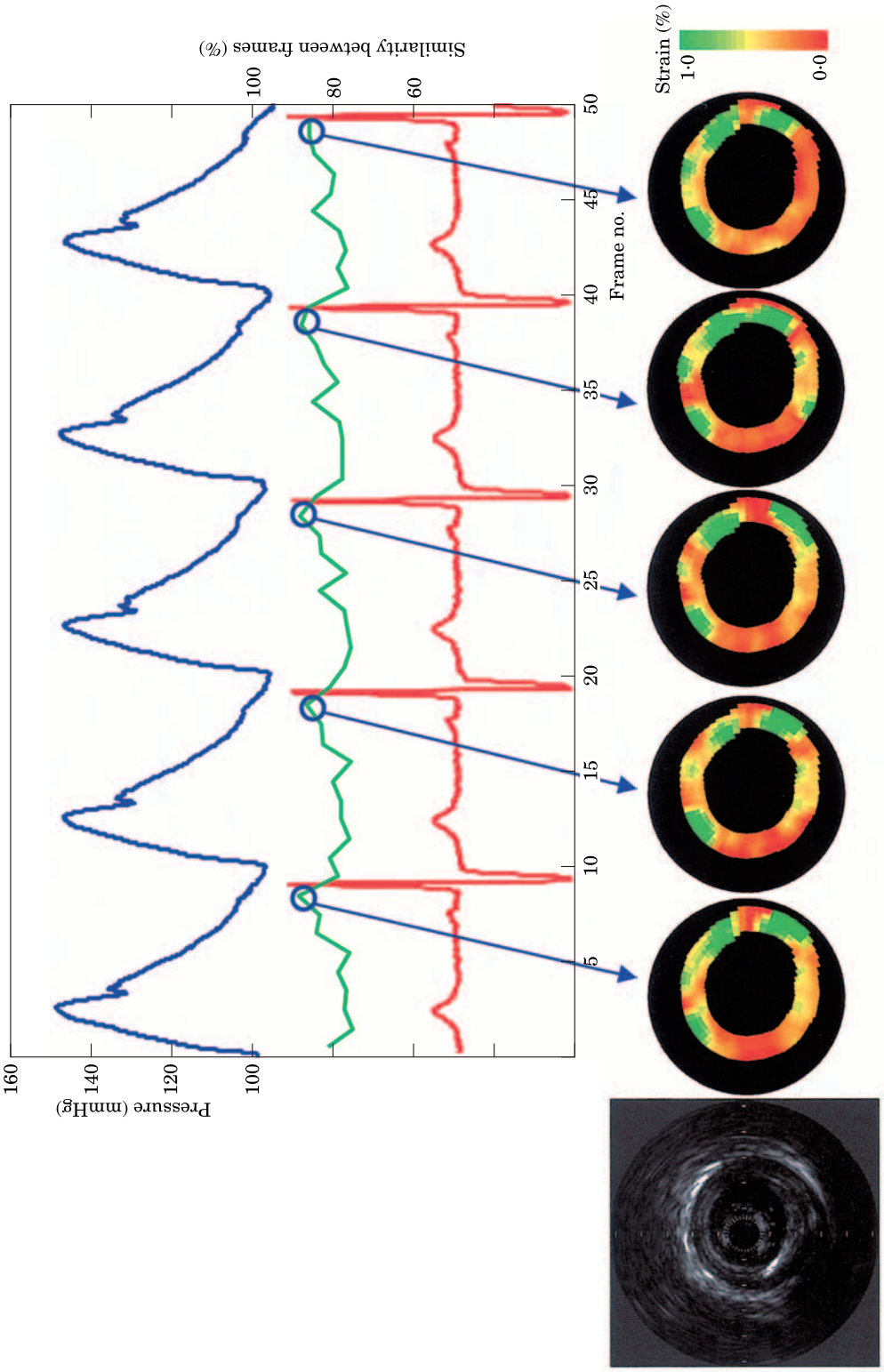

Figure 2 **Reproducibility of the elastographic acquisition over several pulsations. Five elastograms are acquired at end-diastole in sequential heart cycles. The elastograms show similar features in all the elastograms.**

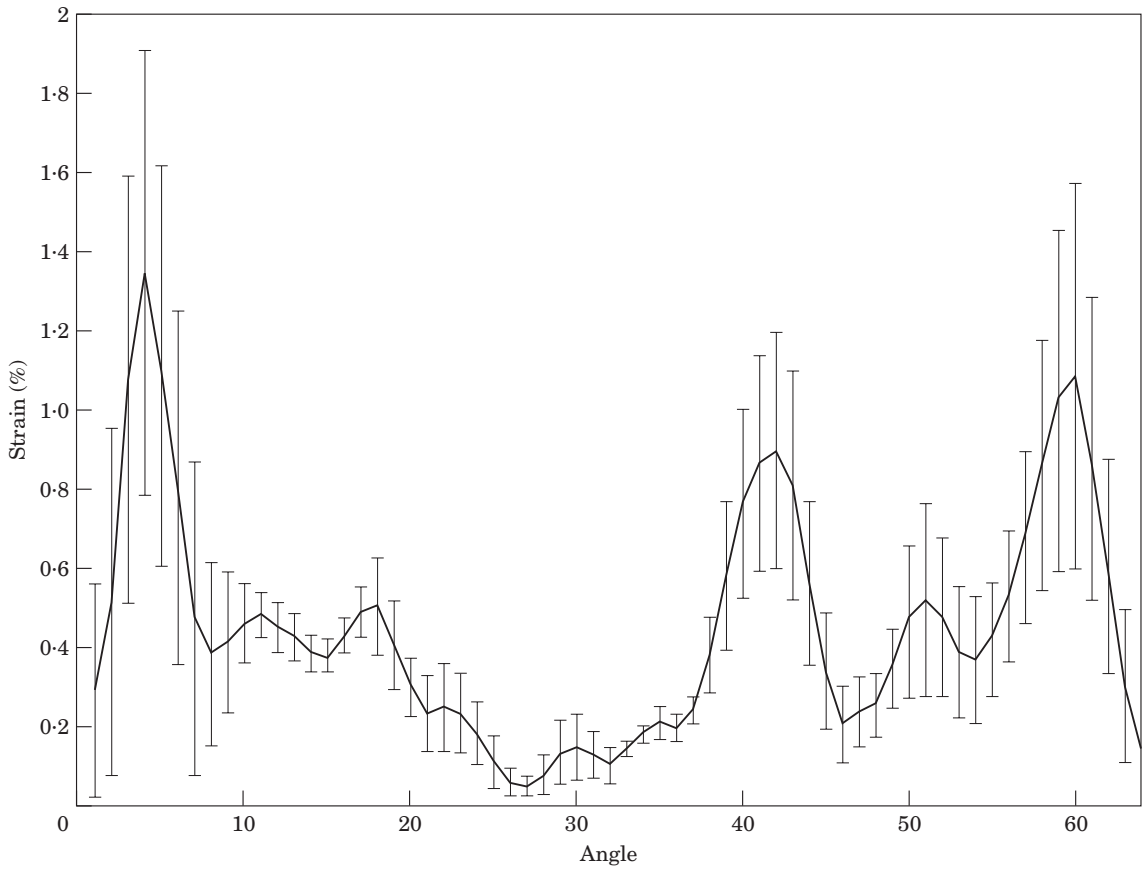

Figure 3 **Mean strain and standard deviation of five elastograms acquired over five sequential pulsations (Fig. 2). The standard deviation increases for higher mean strain values. The high standard deviation near elements 1 and 64 can be explained by the poor sensitivity of the elements at this side of the catheter.**

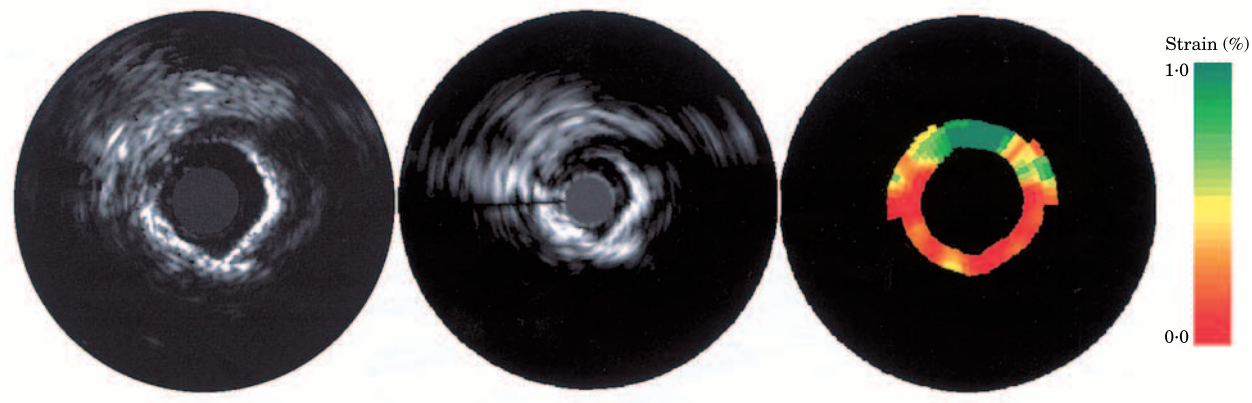

Figure 4 **Echogram (acquired in image and ChromaFlo mode) and elastogram of a cross-section in the LAD. The echogram (left) reveals calcified material between 12 and 9 o'clock. The echogram acquired in ChromaFlo™ (middle) reveals the decreased resolution of this acquisition mode. The elastogram shows low compression in this area and high compression in the remaining region (between 9 and 12 o'clock).**

Conversely, the average strain value in all non-calcified regions was $0{\cdot}51 \pm 0{\cdot}20$ ($P<0{\cdot}001$).

Patients' characteristics are given in Table 1. No statistical differences in average strain value over each cross-section were found in function of these characteristics (concentric/eccentric, stable/unstable angina, etc.).

Discussion

Identification of plaque vulnerability is crucial. Currently, there is no clinically available tool for reliably detecting vulnerable plaque. Elastography is a promising technique, capable of assessing the local mechanical

properties of the vessel wall and plaque[40]: in vitro experiments demonstrated that strain values obtained with intravascular elastography differ significantly for fibrous and fatty plaque components. It was also shown that fatty regions with an increased macrophage content were co-localized with high strain values.

In this study, in vivo elastograms of diseased human coronary arteries are presented. Contrary to a previous in vitro study[40], a dynamic instead of static pressure differential is used to strain the tissue. The advantage is that this excitation source is already present in the arterial system. Using gated acquisition, different levels of intravascular pressure were obtained. These preliminary results indicate that reproducible elastograms can be obtained using this acquisition scheme.

Compared to the in vitro study, the pressure differential between the two frames is smaller: 4–5 mmHg instead of 20 mmHg. A smaller pressure differential will immediately result in lower strain values. However, the strain values found in this in vivo study were in the same range as the strain values found in the in vitro study indicating that the tissue in this study is softer. A possible explanation is that the elastic moduli of tissue will be elevated after the tissue is excised[46] and may even further increase after cold storage. Additionally, since the in vitro study was performed at room temperature, fatty tissues will be harder than at body temperature[47] resulting in decreased strain values.

Another way to strain the tissue is to use a compliant angioplasty type of balloon with the transducer in the balloon, as proposed by Shapo *et al.*[38]. Although the motion artefacts due to the contraction of the heart are minimized, this technique has several disadvantages (interruption of the blood flow, non-radial expansion of the artery when the lumen is not circular, movement of the transducer in the balloon due to inflation of the balloon, balloon dilatation in an artery segment which may not require an angioplasty).

Contrary to the in vitro validation study, a phased array transducer, used every day in our catheterization laboratory for clinical purposes, was used for the data acquisition. This monorail catheter presents better trackability and pushability than single element catheters and there is no artefact from the guidewire. Moreover, the use of an array catheter removes the artefacts due to non-uniform rotation. Therefore, two-dimensional instead of one-dimensional cross-correlation techniques might be applied to determine the strain values. These techniques are currently being implemented. In principle, two-dimensional cross-correlation techniques are more robust and should lead to more reliable strain estimates[48].

Limitations

A major problem of advancing intravascular elastography to cardiac in vivo applications is the acquisition of data in a pulsating artery located in a contracting heart. The catheter will move in the lumen and this will result in a mismatch of the data acquired at the low and high pressure. Correct strain estimates are only obtained when the two echoframes (at low and high pressure) image the same cross-section. This study revealed that the motion of the catheter is minimal near end-diastole in the relaxed phase of the cardiac cycle. Figure 3 shows that the standard deviation of the strain estimate increases with increasing mean strain. This increased standard deviation is caused by decorrelation effects at higher strain rates[45]. The use of the high resolution beam-formed data will improve the signal to noise ratio and thus decrease the standard deviation.

Useful data were not obtained during all measurements. In four other patients, the motion was still too large even near end-diastole. This large motion resulted in an increased number of erroneous strain estimates (more than 35%). Currently, improved signal processing tools are being developed to increase the robustness of the method[48]. Another possible solution to this problem is to obtain data during inflation of the angioplasty balloon of the Megasonics catheter: by inflating the balloon, the position of the transducer is fixed in the artery.

In this study, the pressure is measured in the ostium using a fluid filled line. Therefore, the pressure at the cross-section of interest may have a delay and may deviate from this pressure. For reconstruction of Young's modulus images and to investigate the influence of a severe stenosis between the measured cross-section and the ostium, the pressure would have to be measured using a high fidelity pressure wire.

The elastograms presented in this study could not be validated using histology. Therefore, the elastographic findings were compared with the echographic findings. Intravascular ultrasound echograms have proven to be a useful tool for the detection of calcified regions and assessment of the morphology of the plaque and vessel wall[49–51]. However recent intravascular ultrasound studies revealed that the correlation between echogenicity and fibrous, fibro-fatty or fatty plaque components is low[11,12,40]. Additionally, intravascular ultrasound echograms present limited information for the detection of microcalcification accumulation[52]. Therefore, no validation of the high strain regions in the elastograms was performed. Currently, the technique is validated using an atherosclerotic yucatan minipig animal model. Validation of the elastographic findings in humans could be performed using a directional atherectomy device. However, the correlation of the excised plaque with the intravascular ultrasound image in a radial and longitudinal direction will be extremely difficult. Validation of small spots would need a system that is able to determine the tissue type with a higher resolution. The current developments in optical coherence tomography[21] and Raman spectroscopy[53] may allow performing such validation of intravascular elastography in vivo in the near future[54]. Plaque unstability detected by elastography will be compared in the future with thermographic recordings, recently demonstrated as a potential useful method[28].

The resolution of the described system is 200 μm in a radial direction. This resolution is above the thickness of caps of rupture prone plaques that are typically thinner than 100 μm. Therefore, the thickness of the fibrous cap will be over-estimated. However, a cap that is rupture prone will have increased circumferential stress values[55]. The resulting increased radial strain is obtained using elastography. The power of elastography is that the actual strain is measured and is not based on assumptions[55,56].

We could demonstrate a significantly lower strain value in the calcified regions of the cross-sections recorded among these 12 patients than in the rest of the vessel wall, as expected. However, no further differentiation among these segmented regions in function of the plaque composition (normal/neointimal thickening, soft/fibrous plaque)[11] could be performed because of the poor resolution of the acquired cross-sections in the 64 angles ChromaFlo™ mode, as illustrated on Fig. 4. This is being currently improved on the new high-speed digital interface available for the EndoSonics In-Vision platform. It was also not possible to demonstrate strain differences in function of the clinical presentation. This will be investigated in the future among a more important study population.

Conclusions

It is feasible to apply intravascular elastography in vivo. Using the pulsatile pressure as a mechanical stimulus, different strain levels were measured for different tissue components. The strain in non-calcified material is significantly higher than in calcified material.

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