2.7 Ultra Sound Sensors

3D Intravascular Ultrasound Palpography for Vulnerable Plaque Detection

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Abstract
When a lesion is unstable, it may rupture and cause an acute thrombotic reaction. A rupture prone plaque contains a large lipid pool covered by a thin fibrous cap. Intravascular ultrasound (IVUS) elastography can assess the presence of lipid pools and identify high stress regions. The deformation of the tissue is determined using ultrasound. For intravascular purposes, the intraluminal pressure is used as the excitation force. The radial strain in the tissue is obtained by cross-correlation techniques on the radio frequency (rf) signal. The strain is colour-coded and plotted as a complimentary image to the IVUS echogram, or, in case of palpography, as a ring on the lumen vessel boundary.

Introduction
IntraVascular UltraSound (IVUS) is the only commercially available clinical technique providing real-time cross-sectional images of the coronary artery in patients [1]. IVUS provides information on the severity of the stenosis and the remaining free luminal area. Furthermore, calcified and non-calcified plaque components can be identified. Although many investigators studied the value of IVUS to identify the plaque composition, identification of fibrous and fatty plaque components remains limited [2, 3]. Although recent rf-based tissue identification strategies appear to have better performance [3, 4], these techniques require a substantial window-length and the resolution of these approaches is in the order of 200 µm or worse. As a consequence, identification of a thin fibrous cap is difficult.

Identification of different plaque components is of crucial importance to detect the vulnerable plaque since these are characterised by an eccentric plaque with a large lipid pool shielded from the lumen by a thin fibrous cap [5, 6]. Inflammation of the cap by macrophages further increases the vulnerability of these plaques [7]. The mechanical properties of fibrous and fatty plaque components are different [8, 9]. The cap will rupture if it is unable to withstand the stress applied on 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 may influence clinical decision-making. In 1991, Ophir et al. [10] proposed a method to measure the strain in tissue using ultrasound. The tissue was strained by applying an external force on it. Different strain values were found in tissues with different mechanical properties. Implementing this method for intravascular purposes has potential to identify the vulnerable plaque by:
1. Identification of different plaque components.
2. Detection of high strain regions.

**Underlying Principle**
An ultrasound image of an artery is acquired at a low pressure. A second acquisition at a higher intraluminal pressure (pressure differential is approximately 5 mmHg) is performed. The elastogram (image of the radial strain) is plotted as a complimentary image to the IVUS echogram. The different strategies to perform intravascular elastography (i.e. assess the local deformation of the tissue) are in the way of detecting the strain and the source of deforming the vascular tissue[11].

**Implementation of the Technique**
Typically in intravascular elastography, intraluminal pressure differences in the order of 5 mmHg are used. 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-micrometer estimation of the deformation is required. Talhami et al [12] and Ryan and Foster [13] introduced strain estimation techniques based on the envelope of the ultrasound data. Although robust, these techniques do not provide sufficient resolution and signal to noise ratio for clinical practice. Based on work of Varghese and Ophir [14], a smaller variance of the strain estimate is expected using RF data instead of envelope data. Shapo et al [15, 16] developed a technique based on cross-correlation of A-lines. This group primarily reports on high strain obtained from high deformations. 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 inside the vessels. Sofar this technique has not been developed towards clinical applications. We incorporated ‘correlation based’ elastography [10] for intravascular purposes [17, 18]. 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. A cross-correlation function between two signals will have its maximum if the signals are not shifted with respect to each other. If a shift between the signals is present, the peak of the cross-correlation function is found at the position representing the displacement of the tissue. For each angle, the displacement of the tissue at the lumen vessel-wall boundary is determined.
Next, the displacement of the tissue in the plaque (350 µm from the lumen 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 plaque) by the distance between these two regions (350 µm). The strain for each angle is colour-coded and plotted as a ring (palpogram) at the lumen vessel-wall boundary. [19-21]. 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. The maximum strain that will be present between the systolic and diastolic pressure is in the order of 10 %.

**In vitro validation**

De Korte et al [22] performed a validation study on excised human coronary (n=4) and femoral (n=9) arteries at room temperature. The IVUS rf-data were acquired at two intraluminal pressures and processed off-line. The visualized segments were stained on the presence of collagen, smooth muscle cells and macrophages. 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 for the three plaque types as determined by histology differed significantly (p=0.0002). This difference was independent on 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). Although plaque vulnerability is associated with the plaque composition, detection of a lipid or fibrous composition does not directly warrant
identification of the vulnerable plaque. Therefore, a study to evaluate the predictive power of elastography to identify the vulnerable plaque was performed. In histology, a vulnerable plaque was defined as a lesion with a large atheroma (>40%), a thin fibrous cap with moderate to heavy infiltration of macrophages. A plaque was considered vulnerable in elastography when a high strain region was present at the lumen-plaque boundary that was surrounded by low strain values. This in vitro in 54 diseased coronary arteries revealed that elastography has 88% sensitivity and 89% specificity to identify plaques with a typical rupture prone morphology [23].

3D palpography
Our experience with Elastography has taught us that the strain information that we expect to be clinical relevant is all present in the first layer of a few hundred micrometer starting at the lumen/vessel wall interface. For that reason we developed a technique called intravascular ultrasound palpography [19-21]. It is a similar technique to Elastography, only the strain is just calculated in one window at the intraluminal boundary. The strain is color coded and depicted as a ring on the boundary. This technique is less computational intensive and more robust than elastography. Palpograms can be acquired while pulling back the IVUS catheter. In this way the whole artery can be examined in 3D. [24, 25] (Fig 1). Since 3D palpography allows interrogation of a whole vessel it is well suited for establishing the condition at baseline and in follow up. In this way pharmaceutical treatment can studied.

![Fig. 2: Intravascular echogram and elastogram of a coronary artery obtained in vivo in a patient. The echogram suggests a calcified region between 12 and 3 o'clock. The elastogram reveals low strain values in this region corroborating this finding. High strain values were found at the shoulders of this eccentric plaque.](image)

Patient Results
Elastograms and palpograms are acquired in patients during percutaneous transluminal coronary angioplasty (PTCA) procedures [26]. For this goal a JOMED InVision echo apparatus was equipped with an rf-output. Intravascular rf-ultrasound data are acquired with a PC based acquisition system. Frames acquired at end-diastole
with a pressure difference of approx. 5 mmHg are taken to determine the elastograms. The systemic pressure is used to strain the tissue. This strain is determined using cross-correlation analysis of sequential frames. A likelihood function is 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 is observed near end-diastole.

An elastogram of an eccentric plaque with calcification in the central part, reveals low strain values in this part of the plaque. However, increased strain values were found at the shoulders of this plaque (fig 2). Reproducible strain estimates were obtained within one pressure cycle and over several pressure cycles. A study in which 55 patients were studied revealed that the number of high strain spots was directly related to the instability of the patient[27].

Discussion
Identification of plaque components and the proneness of a lesion to rupture is a major issue in interventional cardiology. Intravascular ultrasound echography is a real-time, clinical available technique capable of providing cross-sectional images and identifying calcified plaque components. Since elastography only requires ultrasound data sets that are acquired at different levels of intraluminal pressure, it can be realised using conventional catheters. 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.

Currently, there is no clinical available technique 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 deaths. IVUS elastography has proven to be able to identify the rupture prone plaque in vitro with high sensitivity and specificity and in vivo experiments demonstrate 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. Since IVUS palpography is a faster and more robust technique, introduction of this technique in the catheterisation laboratory may be easier. Although palpography reveals no information on the composition of material deeper in the plaque, it may be a powerful technique to identify the weak spots in an artery. If a plaque will rupture, this rupture will start at the lumen vessel wall boundary and this region is imaged by palpography. A natural history study is a prerequisite to assess the predictive value of intravascular palpography to identify the rupture prone plaque in the vulnerable patient.

Conclusion
Intravascular elastography has proven to be a technique capable of providing information on the plaque composition. IVUS elastography was tested in vitro in several institutes using different IVUS systems, different sources of mechanical stimulus and different processing techniques. Experiments in vivo in animals and patients demonstrate that IVUS palpography may develop into a clinical available tool to identify the rupture prone plaque.
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References


