THE INTRAVASCULAR ULTRASOUND ELASTICITY-PALPOGRAPHY TECHNIQUE REVISITED: A RELIABLE TOOL FOR THE IN VIVO DETECTION OF VULNERABLE CORONARY ATHEROSCLEROTIC PLAQUES

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Abstract—Critical to the detection of vulnerable plaques (VPs) is quantification of their mechanical properties. On the basis of intravascular ultrasound (IVUS) echograms and strain images, E. I. C. Cespedes, C. L. de Korte CL and A. F. van der Steen (Ultrasound Med Biol 2000;26:385–396) proposed an elasticity-palpography technique (E-PT) to estimate the apparent stress-strain modulus palpogram of the thick endoluminal layer of the arterial wall. However, this approach suffers from major limitations because it was developed for homogeneous, circular and concentric VPs. The present study was therefore designed to improve the E-PT by considering the anatomic shape of the VP. This improved E-PT was successfully applied to six coronary lesions of patients imaged in vivo with IVUS. Our results indicate that the mean relative error of the stress-strain modulus decreased from 61.02 ± 9.01% to 15.12 ± 12.57% when the IE-PT was used instead of the E-PT. The accuracy of the stress-strain modulus palpograms computed using the improved theoretical framework was also investigated with respect to noise, which may affect prediction of plaque vulnerability. (E-mail: jacques.ohayon@imag.fr)

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INTRODUCTION

Vulnerable atherosclerotic plaque (VP) rupture is the leading cause of acute coronary syndrome, myocardial infarction and stroke in the Western world (Lloyd-Jones et al. 2010). Morphologically, an unstable vulnerable coronary lesion consists of a relatively large extracellular necrotic core with a thin fibrous cap (<65 μm) infiltrated by macrophages (Virmani et al. 2000). The thin-cap fibroatheroma is the precursor lesion, which, once ruptured, may lead to the formation of a thrombus causing an acute syndrome and possibly death (Virmani et al.

2006). Several intravascular (IV) techniques are used to detect coronary VPs in clinics (Vancraeynest et al. 2011), including ultrasound (IVUS) (Carlier and Tanaka 2006; Rioufol et al. 2002), optical coherence tomography (OCT) (Jang et al. 2002; Tearney et al. 2008) and magnetic resonance imaging (IVMRI) (Briley-Saebo et al. 2007; Larose et al. 2005). Diagnosing unstable VPs, on the other hand, is still imprecise, as the thickness of the fibrous cap alone is not a sufficient predictor of plaque stability (Fleg et al. 2012; Maldonado et al. 2012; Ohayon et al. 2008; Virmani et al. 2000). Biomechanical studies have identified peak cap stress amplitude as an additional key predictor of vulnerability to rupture (Finet et al. 2004; Loree et al. 1992; Ohayon et al. 2001).

Quantifying intraplaque stress distribution, to predict plaque rupture, has been a challenge. To overcome this hurdle, the local deformation (strain) of a tissue can be
calculated and can then be directly related to the intraplaque stress and its mechanical properties. Ophir and colleagues (Ophir et al. 1991; Céspedes et al. 1993) were the pioneers in developing imaging techniques based on the strain field. On the basis of their work, several elegant IVUS methods were developed to highlight spatial strain distribution (i.e., strain elastogram) over the entire vessel wall (Maurice et al. 2007) or over a restricted thick endoluminal region (De Korte et al. 2002; Doyley et al. 2001). Such IVUS techniques based on optical flow (Maurice et al. 2004) or time-delay correlation estimation (De Korte et al. 2002) allowed calculations of intraplaque strain images during the cardiac cycle.

These methods did not, however, overcome a main limitation related to the complex geometries of atherosclerotic plaques, which alter intraplaque strain fields and inhibit direct translation into plaque mechanical properties. Therefore, to complement the characterization of an atherosclerotic lesion from an IVUS echogram and strain images, Céspedes et al. (2000) developed an elegant one-dimensional elasticity-palpography technique (E-PT) to estimate and display an apparent local stiffness (called the stress-strain modulus [S-SM] palpogram) of the thick endoluminal layer of the arterial wall (called the palpography domain). Although such work presents promising concepts for the identification of atherosclerotic lesions, current E-PT suffers from major limitations. First, the mechanical solution used to extract the S-SM palpogram was obtained by assuming a cylindrical concentric arterial wall made of a homogeneous isotropic incompressible medium and submitted to a uniform outer radial stress distribution (Timoshenko and Goodier 1987). Second, with such a simplified model, it is difficult to correlate the resulting S-SM to the real Young’s modulus distribution in the palpography domain. Such a solution is too restrictive and must be used with caution in atherosclerotic lesions with high eccentricity and non-uniform wall thickness.

The present biomechanical study was designed to improve the theoretical framework of the E-PT by considering the anatomic shape of the atherosclerotic coronary artery. This improved elasticity-palpography technique (IE-PT), based on the continuum mechanics theory prescribing the strain field in the palpography region, was successfully applied to six coronary lesions of patients imaged in vivo with IVUS. The robustness and performance of the new IE-PT were investigated with respect to noise, which may affect prediction of plaque vulnerability.

**METHODS**

Six patients underwent coronary IVUS, and the extracted plaque geometries were used to simulate strain fields for which the performance of the improved elasticity-palpography technique was tested. Moreover, one idealized eccentric and circular non-vulnerable plaque geometry with a homogeneous lesion was designed to highlight the main limitations of the original E-PT.

**Intravascular ultrasound study and plaque geometries**

**Patient population.** Arteries of patients referred for percutaneous coronary intervention at the Lyon Cardiology Hospital (Hôpital Cardiologique et Pneumologique de Lyon, France) after a first acute coronary syndrome with troponin I elevation were explored. Investigations were approved by the institutional board of the hospital’s cardiology department, and consent was obtained from the patients.

**IVUS imaging.** Non-ruptured VP geometries were obtained from IVUS scans of the coronary arteries using the protocol described by Rioufol et al. (2002). To avoid vasospasms, IVUS exploration was performed after intracoronary administration of 200 μg of nitroglycerine. The acquired cross-sectional IVUS image of the VP corresponded to the site exhibiting the thinner fibroatheroma cap. IVUS scans were performed with the iLab platform (Boston Scientific, Watertown, MA, USA) equipped with 40-MHz catheters (Atlantis SR Pro 3.6F, Boston Scientific). The spatial resolution of the ultrasound images acquired with the IVUS system was approximately 90 μm in the radial direction (Chopard et al. 2010).

**IVUS image analysis.** IVUS echogenicity aspects were used to characterize VP components: (i) highly hypoechogenic components (or anechoic zones), suggestive of quasi-cellular tissues (lipid or cellular deposition); (ii) homogeneous reflective components, suggestive of organized or disorganized fibrosis; or (iii) hyperechogenic components (or bright zones), suggestive of calcified regions (Di Mario et al. 1998). A manual segmentation procedure using ImageJ software (ImageJ, NIH, Bethesda, MD, USA) was performed by a cardiologist to extract the contours of each plaque component.

**IVUS measurements and definitions.** Each cross-sectional IVUS image of a lesion was quantitatively analyzed. Plaque area (Plaarea, mm²); lumen area (Luarea, mm²); necrotic core area (Corearea, mm²); calcified area (Calarea, mm²); degree of stenosis (Stenos(deg, %)), which is $100 \times \frac{\text{Plaarea}}{\text{Plaarea} + \text{Luarea}}$; and cap thickness (Capthick, mm), which is defined as the shortest distance between the lumen and the necrotic core, were measured.

**Forward problem: Strain field distributions**

The files of the digitized contours obtained with ImageJ were imported into MATLAB and then transferred in Comsol (Structural Mechanics Module, Version 3.5,
Comsol, France) via the LiveLink MATLAB/Comsol toolbox. Radial strain elastograms were obtained by performing static finite-element (FE) computations on all VP geometries using Comsol software. Entire plaque geometries were meshed with approximately 15,000 six-node triangular elements. The center of gravity of the lumen, which was numerically determined as the barycenter (i.e., the center of mass) of the lumen area, was used as the origin of the cylindrical coordinate system \((r, \theta)\). The strain fields were interpolated on a regular polar mesh with a given radial step resolution of 36 \(\mu\)m and an angular step resolution corresponding to 256 radial directions, which is the resolution that can be expected from endovascular elastography (Maurice et al. 2007).

**Boundary conditions and material properties.** The FE simulations were conducted under the assumption of plane strain. Because instantaneous pressure was not recorded during IVUS scans of the coronary arteries, we assumed a blood pressure differential, \(\Delta P\), of 1 kPa (or 7.5 mm Hg), which corresponds to a realistic pressure gradient occurring between two successive IVUS images recorded during the cardiac cycle. Free boundary condition was assumed at the external diameter of the artery. The mechanical properties of the fibrosis, calcified area and soft necrotic core were modeled as isotropic and quasi-incompressible media (Poisson ratio \(\nu = 0.49\)) with Young’s moduli \(E_{\text{fibrosic}} = 800\) kPa, \(E_{\text{calcified}} = 5000\) kPa and \(E_{\text{core}} = 5\) kPa, respectively (Finet et al. 2004).

**Sensitivity study of effect of noise on input radial strain data.** To investigate the influence of noise on the performance of the improved elasticity-palpography technique, white noise was added to each FE simulated radial strain field used as input. For the noise model, we used a normal distribution of noise with zero mean and a standard deviation of \(\sigma_{\varepsilon} = a \varepsilon_s + b \beta\), where \(a = 0.2\%\), \(b = 0.04\%\) and \(\varepsilon_s\) is the local value of the radial strain (Baldewsing et al. 2005; Le Floc’h et al. 2009). The noise field was significantly amplified by increasing \(\beta\) from 1 to 6. For each level of noise \(\beta\), 10 computations in which the noise was spatially randomly distributed were performed, and the averaged Young’s modulus of each plaque constituent (± standard deviation) was presented.

**Inverse problem: Stress-strain modulus palpogram**

**Stress-strain modulus palpogram of Céspedes et al. (2000).** The S-SM (called \(E_{\text{palpo}}\)) was defined by Céspedes et al. (2000) as the local radial stiffness of the thick endoluminal layer of the arterial wall (i.e., of the palpography domain). Inspired by the expression of the S-SM obtained for a thick-walled isotropic cylindrical vessel with a specific concentric cylindrical palpography domain, Céspedes et al. (2000) proposed the S-SM approximation (all details are presented in Appendix I)

\[
E_{\text{palpo}}^{\text{Céspedes}}(\theta) = \frac{\Delta P/2}{\varepsilon(\theta)} \tag{1a}
\]

\[
\varepsilon(\theta) = \int_{R_i(\theta)}^{R_o(\theta)} \varepsilon_{\sigma}(r, \theta) dr \tag{1b}
\]

where \(R_i(\theta)\) and \(R_o(\theta)\) are the inner and outer radii of the palpography domain, respectively.

**Stress-strain modulus palpogram revisited.** We revisited the S-SM formulation of Céspedes et al. (2000) to account for both the anatomic shapes of the atherosclerosis plaque and the palpography domain. On the basis of the relationship between the deviatoric radial stress \(\sigma_{\sigma}^{\text{dev}}(r, \theta)\), the Young’s modulus \(E(r, \theta)\) and the radial strain component \(\varepsilon_r(r, \theta)\) for a heterogeneous, isotropic, incompressible and linear elastic continuum medium (Timoshenko and Goodier 1987),

\[
\sigma_{\sigma}^{\text{dev}}(r, \theta) = \frac{2}{3} E(r, \theta) \varepsilon_r(r, \theta) \tag{2}
\]

we redefined the S-SM as the ratio of the average deviatoric radial stress to the average radial strain along the radial axis

\[
E_{\text{palpo}}^{\text{new}}(\theta) = \frac{3}{2} \int_{R_i(\theta)}^{R_o(\theta)} \frac{\sigma_{\sigma}^{\text{dev}}(r, \theta) dr}{\varepsilon(\theta)} \tag{3}
\]

where \(\varepsilon(\theta)\) is given by Eq. (1b).

Moreover, knowing that the radial strain \(\varepsilon_r(r, \theta)\) is proportional to the imposed change in pressure, \(\Delta P\), and inversely proportional to the amplitude of the Young’s modulus, \(E(r, \theta)\),

\[
\varepsilon_r(r, \theta) = \frac{3}{2} \frac{\Delta P}{E(r, \theta)} h(r, \theta) \tag{4}
\]

(where the constant \(3/2\) is introduced for mathematical convenience only), the expression of the deviatoric radial stress given by Eq. (2) can be rewritten as

\[
\sigma_{\sigma}^{\text{dev}}(r, \theta) = \frac{3}{2} \frac{\Delta P}{E(r, \theta)} h(r, \theta) \tag{5}
\]

where \(h(r, \theta)\) is a new correcting shape function that accounts for the entire plaque morphology, including the geometries of all plaque heterogeneities. Taking advantage of such an expression for the deviatoric radial stress, the new S-SM (Eq. [3]) becomes
Because $h(r, \theta)$ is an unknown function that escapes to direct measurements, we computed an approximated correcting shape function, $h^\text{approx}(r, \theta)$, that accounts for anatomic cross-sectional plaque geometry.

$$E_{\text{palpo}}(\theta) = \frac{\Delta P \int_{R_i(\theta)}^{R_o(\theta)} h(r, \theta) dr}{e(\theta)}$$  \hspace{1cm} (6)

Such an approximated correcting function was obtained by using a FE analysis and by assuming the plaque homogeneous, isotropic and quasi incompressible with the Young’s modulus $E$. This FE simulation was performed in linear elasticity with a loading blood pressure amplitude $\Delta P$. From Eq. (4) and with the knowledge of the spatial radial strain distribution, we extracted the approximated shape function, $h^\text{approx}(r, \theta)$, which was used to revisit the S-SM formulation for complex plaque geometries.

**Table 1. IVUS-detected and modeled atherosclerotic plaque characteristics**

<table>
<thead>
<tr>
<th>Plaque no.</th>
<th>Origin of geometry</th>
<th>Cap thickness (µm)</th>
<th>Necrotic core</th>
<th>Calcium</th>
<th>Plaque</th>
<th>Lumen</th>
<th>Stenosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Model</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>25.13</td>
<td>3.14</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>IVUS</td>
<td>93</td>
<td>1.36</td>
<td>—</td>
<td>8.74</td>
<td>2.789</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>IVUS</td>
<td>100</td>
<td>5.39</td>
<td>—</td>
<td>16.70</td>
<td>3.24</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>IVUS</td>
<td>162</td>
<td>1.200.51</td>
<td>—</td>
<td>17.85</td>
<td>6.75</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>IVUS</td>
<td>193</td>
<td>2.11</td>
<td>0.40</td>
<td>17.53</td>
<td>3.60</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>IVUS</td>
<td>62</td>
<td>3.54</td>
<td>1.60</td>
<td>15.64</td>
<td>4.52</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>IVUS</td>
<td>220</td>
<td>2.15/0.70</td>
<td>0.89</td>
<td>16.88</td>
<td>3.62</td>
<td>82</td>
</tr>
</tbody>
</table>

IVUS = intravascular ultrasound.

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**Fig. 1.** Performance of the improved elasticity-palpography technique. (a) Contours (in red) of an idealized eccentric and circular plaque model (called plaque 1) in which the lesion is homogeneous. The palpography domain, $\Omega_{\text{palpo}}$, is also given (blue contours). (b) Radial strain elastogram computed in the palpography domain. (c) Computed original (Céspedes et al. 2000) stress-strain modulus (S-SM) palpogram. (d) Comparisons between original S-SM, improved (Revisited) S-SM and averaged Young’s modulus (AYM) palpograms.
Interestingly, this original revisited S-SM formulation (Eq. [7]) allows us to find the real Young’s modulus amplitude $E$ when considering a homogeneous isotropic plaque (i.e., $E_{\text{palpo}}(\theta) = E$), whatever their geometries and the palpography domains considered $Q_{\text{palpo}}$, where $R_l(\theta) \leq r \leq R_p(\theta)$.

The Young’s modulus palpogram. To discuss the physical meaning of the original and revisited S-SM formulations given by Eqs. (1) and (7), respectively, we compared them with the circumferential distribution of the averaged Young’s modulus along the radial axis (AYM):

$$E_{\text{palpo}}(\theta) = \frac{\Delta P \int_{R_l(\theta)}^{R_p(\theta)} h^*(r, \theta) dr}{e(\theta)}$$

(7)

where $E(r, \theta)$ is the spatial distribution of the Young’s modulus.

Moreover, to quantify the accuracy of the reconstructed S-SM palpograms we computed the mean relative stress-strain modulus error ($MR_{\text{error}}$):

$$MR_{\text{error}} = 100 \int_0^{2\pi} \frac{E_{\text{palpo}}(\theta) - AYM(\theta)}{AYM(\theta)} d\theta$$

(9)

RESULTS

Intravascular ultrasound study

Six non-ruptured VPs with necrotic cores and calcified areas were identified after extensive IVUS scanning. The geometric characteristics of the six non-ruptured VPs scanned in vivo (plaques 2–7) and the eccentric circular idealized homogeneous plaque (plaque 1) are summarized in Table 1. All results presented in our figures were obtained from simulations performed without white noise (i.e., $\beta = 0$) and with a blood pressure differential, $\Delta P$, of 1 kPa, unless otherwise stated.
Performance of improved elasticity-palpography technique

Importance of considering the correcting stress function. To highlight the importance of using the revisited S-SM formulation for non-concentric lesions with arbitrary palpography domains, we first conducted our simulations on the idealized eccentric plaque geometry (see plaque 1, Fig. 1). This idealized homogeneous plaque was assumed to be isotropic ($E = 800$ kPa) and quasi-incompressible (Poisson ratio $\nu = 0.49$). The improved S-SM palpogram appears to be less sensitive to the geometries of the arterial plaque and palpography domain than that derived with the E-PT. The S-SM palpogram computed with the IE-PT remains almost constant and close to 800 kPa—which is also the value of the real averaged Young’s modulus—even in the free-plaque arc length, which is the thinnest region of the palpography domain (Fig. 1d).

Detection of soft inclusions. Improved S-SM palpograms obtained for VPs with one (plaques 2 and 3, Figs. 2 and 3) and two (plaque 4, Fig. 4) necrotic cores are illustrated. Necrotic core sites were accurately detected using the IE-PT. The amplitude of the revisited S-SM was found to be close to the Young’s modulus of the fibrosis (i.e., close to 800 kPa) excepted at a soft inclusion locations, for which the S-SM amplitudes were found to be lower. Compared with the AYM, the S-SM values at the necrotic core locations were underestimated.

Detection of vulnerable plaques with calcified inclusions. For two VP morphologies (plaques 5 and 6) with isolated necrotic cores and calcified inclusions (Figs. 5 and 6), the IE-PT detected and differentiated the soft and hard inclusions. Compared with the AYM, the S-SM amplitudes at the calcified inclusion locations were underestimated by almost a factor of 2. Figure 7 illustrates the abilities of the proposed IE-PT to detect a complex VP (plaque 7) with adjacent soft and hard inclusions located between 7 and 9 o’clock and one isolated large necrotic core located between 2 and 6 o’clock. The IE-PT successfully detected the isolated soft inclusion adjacent to the calcified area.

Comparison between original and improved elasticity-palpography techniques. Our quantitative results indicated that the mean relative error of the stress-strain modulus decreased from $61.02 \pm 9.01\%$ to $15.12 \pm 12.57\%$ when using the improved rather than the original elasticity-palpography technique (see...
Table 2). Simulations performed on plaque 4 (Fig. 4) using the original palpography approach did not differentiate the geometric effects induced by the shape of the VP from those generated by the mechanical properties of heterogeneous plaque (Fig. 4d). When the E-PT of Céspedes et al. (2000) was used, the S-SM amplitudes computed along the plaque-free segment (i.e., between angular positions 180° and 300°, Fig. 4a, d) were found to be similar to those computed at the plaque segment with necrotic cores (i.e., between 0° and 90°, Fig. 4a, d). The IE-PT corrected for such geometric effects because the improved S-SM palpogram highlighted the soft inclusion site only. Similar results were found for all VPs considered in this study (see Figs. 2, 3 and 5).

Influence of white noise on stress-strain modulus palpogram. The influence of noise was studied on vulnerable plaque 2 (Fig. 8 and Table 2). Based on the definition of the signal-to-noise ratio, we converted our white noise amplitude on the decibel scale (see Appendix II). By applying such an approach to plaque 2, we found that $\beta = 2, 4$ and 6 corresponds to noise levels of 13, 7 and 3.4 dB, respectively. The robustness of the IE-PT with increasing white noise level is illustrated in Figure 8. According to the simulations performed, even on introduction of significant white noise ($\beta = 6$), the IE-PT was still able to detect the soft inclusion site (Fig. 8c). We found that the mean relative error of the stress-strain modulus $MR_{error}$ increased from $4.70 \pm 4.90\%$ at a white noise level of $\beta = 2$ to $26.18 \pm 16.24\%$ at triple the white noise ($\beta = 6$) (Table 2).

DISCUSSION

Critical to the detection of VPs is accurate quantification of both the morphology and the mechanical properties of the diseased arteries (Cheng et al. 1993; Finet et al. 2004). Such knowledge could lead to development of a specific therapy for prevention of acute thrombotic events (Libby 2001). Although several endovascular approaches have been implemented to approximate mechanical strain in vivo (de Korte et al. 2002; Doyley 2012; Kim et al. 2004; Maurice et al. 2007; Wan et al. 2001), the spatial plaque Young’s modulus has not yet been determined for “real-time” clinical use. Such an elasticity map remains difficult to assess because the full inverse problem needs to be solved in continuum mechanics using sophisticated non-linear mathematical optimization tools and complex procedures (Doyley...
Céspedes et al. (2000) proposed the E-PT, which allows rapid quantification of wall stiffness on the basis of arterial strain and blood pressure measurements. However, this technique suffers from major limitations because it was developed for homogeneous, isotropic, quasi incompressible, circular and concentric atherosclerotic plaques only. Therefore, in the present study, the original palpography technique was successfully revisited and improved to account for complex plaque and arbitrary palpography domain geometries.

Our results clearly indicate that the performance of the revisited S-SM formulation not only significantly improved the accuracy of the original S-SM palpogram, but, more importantly, gave physical meaning to the amplitude of the improved S-SM palpogram.

Has the revisited stress-strain modulus formulation significantly improved the palpography technique?

The original S-SM palpogram neglected the geometric effects induced by the anatomic shape of the atherosclerotic plaque and was derived on the assumption of a circular palpography domain. When the E-PT was used, the resulting S-SM values along the plaque-free segment of the atherosclerotic coronary artery were found to be lower than the averaged Young’s modulus amplitudes of the arterial wall. The original S-SM palpogram of plaque 2 (Fig. 2d) shows such sites with low S-SM amplitudes located between angular positions 50° and 150° (Fig. 2a and c). The IE-PT corrects for this limitation as it accounts for real plaque and palpography domain geometries. Moreover, simulations performed on the idealized homogeneous lesion (plaque 1) (Fig. 1) clearly illustrate the advantage of considering the new approach. Indeed, the exact solution was reached when using the revisited technique, whereas the mean relative error was close to 49% when the original technique was used (Table 2). The IE-PT is less sensitive to geometric effects and can differentiate between plaque elasticity and apparent stiffness, which is dependent on arterial wall thickness (Fig. 1).

Is the stress-strain modulus palpogram sufficient to detect vulnerable plaques?

The IE-PT is sufficient to detect and identify all VPs without calcified inclusions (see Figs. 2, 3 and 4). More interestingly, the IE-PT appears to be reliable enough to detect complex VPs with calcified inclusions (Figs. 5, 6 and 7). Let us point out that although both S-SM palpograms for plaque 7 (Fig. 7c), correctly identified the presence of the necrotic core, even though a soft
inclusion was adjacent to the calcified inclusion and
increased the amplitude of the AYM at this site (i.e.,
between angular positions 180°/C14 and 240°/C14) (Figs. 7 a, d),
only the IE-PT was able to correct for the elasticity ampli-
tudes at the plaque-free segment (i.e., between angular
positions 30°/C14 and 180°/C14) (Fig. 7 a, d).

Is the revisited stress-strain modulus palpogram
sufficient to diagnose the degree of stability of
vulnerable plaques?

Fibrous cap thickness is often used by interventional
cardiologists to diagnose the degree of VP instability.
Recent studies (Cilla et al. 2012; Ohayon et al. 2008)
have shown that other emergent biomechanical factors
such as necrotic core thickness (rather than necrotic
core area) and arterial remodeling index are also critical
in determining plaque instability. The palpography tech-
nique does not permit direct measurements of such key
morphologic determinants. Therefore, although the IE-
PT is reliable in detecting VPs, this approach is not suffi-
cient to diagnose the degree of stability of VPs.

Is there an optimal size for the palpography domain?

As mentioned previously, the main limitation of the
palpography technique is that an optimal circular palpog-
raphy domain is necessary to obtain accurate and reliable
S-SM palpograms. Thus, the original S-SM appears to be
more adaptable to the detection of vulnerable concentric
atherosclerotic lesions, because its formulation was based
on the assumption of a cylindrical concentric plaque. The
IE-PT may be viewed as an extension of the original
formulation allowing the detection of eccentric VPs,
which are very common (Glagov et al. 1987). Furthermore,
the cardiologist has the flexibility to choose any
arbitrary endoluminal thick layer size and shape as the
palpography domain.

Study limitations

A major limitation of this study was that our anal-
ysis was performed in the absence of residual strain.
The effects of such residual strain have been investi-
gated in an *ex vivo* study performed by Ohayon
et al. (2007) with several human vulnerable coronary
plaque samples. We found that residual strain was
not negligible and affects mainly the peak cap stress
amplitude in the thin fibrous cap. Therefore, on the
basis of our previous findings, the absence of residual
strain should not alter the characterization of the
mechanical properties presented in this study, which
was the ultimate goal.
A second study limitation was that our study was performed on a relatively small number of cases \((n = 7)\). Such atherosclerotic lesions were chosen to be representative of a larger population. Indeed, different necrotic core and calcified inclusion shapes were used to take into account a large variety of clinical cases. Nevertheless, further studies are needed to extend and strengthen the present findings.

Potential clinical implication

Stabilization of vulnerable plaque remains a significant clinical problem (Abela et al. 2011; Ylää-Herttuala et al. 2011). Studies conducted to analyze the structural variation in the fibrous cap and necrotic core with specific drug treatments \((\text{e.g., all statins, angiotensin-converting enzyme inhibitors})\) revealed an enhancement of plaque stability (Libby et al. 2002; Nozue et al. 2012). As shown

Table 2. Mean relative errors (MR\textsubscript{error}) obtained from palpograms when using either the original or improved elasticity-palpography technique

<table>
<thead>
<tr>
<th>Plaque no.</th>
<th>Original MR\textsubscript{error} (%) without noise</th>
<th>Without noise ((\beta = 0))</th>
<th>(\beta = 2)</th>
<th>(\beta = 4)</th>
<th>(\beta = 6)</th>
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<tbody>
<tr>
<td>1</td>
<td>48.97</td>
<td>0.00</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>60.82</td>
<td>11.43</td>
<td>4.70 ± 4.90</td>
<td>14.52 ± 12.46</td>
<td>26.18 ± 16.24</td>
</tr>
<tr>
<td>3</td>
<td>61.70</td>
<td>17.30</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>71.26</td>
<td>10.89</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>55.49</td>
<td>8.21</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>6</td>
<td>73.97</td>
<td>40.18</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>54.89</td>
<td>17.85</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>61.02 ± 9.01</td>
<td>15.12 ± 12.57</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* The influence of white noise was studied using vulnerable plaque 2.
in one of our previous studies (Finet et al. 2004), a very slight increase in the mechanical properties of plaque constituents, namely, hardening of the lipidic necrotic core, can tilt a VP from instability to stability. The proposed improved elasticity-palpography imaging technique is promising because it provides a non-invasive approach to analyze the evolution of the mechanical properties of atherosclerotic plaques during drug therapies.

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REFERENCES


FORMULATION OF THE ORIGINAL STRESS-STRAIN MODULUS PALPOGRAM

Céspedes et al. (2000) defined the S-SM modulus as the ratio of the average radial stress to the average radial strain along the radial axis.

\[
\frac{\sigma_{r}(r)}{\epsilon_{r}(r)} = \frac{1}{R_{o}} \int_{R_{i}}^{R_{o}} \sigma_{r}(r,\theta)dr
\]

where \(\epsilon_{r}(\theta)\) is the average radial strain (given by Eq. (1b)); \(\sigma_{r}(r,\theta)\) is the radial stress component; and \(R_{i}(\theta)\) and \(R_{o}(\theta)\) are the non-constant inner and outer radii of the palography domain \(\Omega_{palpo}\), respectively.

Let us assume that the artery is a thick-walled cylinder (with inner and outer radii \(R_{i}\) and \(R_{o}\), respectively), isotropic, homogeneous, incompressible, linearly elastic (with Young's modulus \(E\)), submitted to uniform pressure \(\Delta P\) on the inner boundary \(r = R_{i}\) and zero pressure on the outer boundary \(r = R_{o}\). By assuming plane strain condition and by considering a concentric circular palography domain \(\Omega_{palpo}\) (with \(R_{i} \leq r \leq R_{o}\)), the spatial distribution of the local S-SM (given by Eq. (A1)) becomes constant through \(\Omega_{palpo}\) and equal to...
\[ E_{\text{cylinder}} = \frac{\Delta P}{6} \int_0^{R_0} g(r) dr \]  
(A2)

with

\[ \varepsilon = \frac{3}{2E} \frac{\alpha_o^2 - \alpha_p^2}{\alpha_p (\alpha_o^2 - 1)} \Delta P \]  
(A3a)

\[ \int_0^{R_0} g(r) dr = \frac{(\alpha_o^2 - \alpha_p^2)}{\alpha_p (\alpha_o^2 - 1)} \]  
(A3b)

where the constant \( \varepsilon \) is the absolute value of the compressive average radial strain (with amplitude given by Eq. [A3a]); and \( \alpha_o \) and \( \alpha_p \) are the relative thicknesses of the arterial wall and palpography domain \( \Omega_{\text{palpo}} \), respectively (i.e., when \( R_p = |2\alpha_o^2/(\alpha^2_0 + 1)|R_i \), the amplitude of the uniform local S-SM becomes:

\[ E_{\text{cylinder}}^{\text{palpo}} = \frac{\Delta P/2}{6} \varepsilon \]  
(A4)

It is interesting to note that this S-SM (i.e., \( E_{\text{cylinder}}^{\text{palpo}} \)) is not the Young’s modulus \( E \) of the isotropic concentric plaque, because by substituting Eq. (A3a) into Eq. (A4) we obtain the relationship

\[ E_{\text{cylinder}}^{\text{palpo}} = \frac{1}{3} \frac{\alpha_o^2 - 1}{\alpha_o^2} E \]  
(A5)

An exact analytical S-SM formula is difficult to derive for heterogeneous, eccentric and complex plaque geometries. Céspedes et al. (2000) were inspired by the simplified S-SM solution obtained for a thick-walled cylindrical vessel (Eq. [A4]) to propose their S-SM approximation given by Eq. (1a).

**APPENDIX II**

**CONVERTING OUR WHITE NOISE INTO DECIBELS**

To find correspondence between the imposed white noise and the signal-to-noise ratio (SNR, in dB), we used the relationship

\[ \text{SNR} = 10 \log_{10} \left( \frac{A_{\text{signal}}}{A_{\text{noise}}} \right) \]  
(A6)

where \( A_{\text{signal}} \) and \( A_{\text{noise}} \) are the signal and noise amplitudes, respectively. We identified the signal amplitude \( A_{\text{signal}} \) to the mean spatial strain amplitude free of noise. Moreover, in our study, we used the following normal distribution of noise \( A_{\text{noise}} \) with zero mean and standard deviation \( \sigma(r, \theta) = (a \sigma_p(r, \theta) + b) \beta \) where \( a = 0.2 \%, b = 0.04 \% \) and \( \beta \) varies from 2 to 6 (Baldewsing et al. 2005; Le Floc’h et al. 2009):

\[ A_{\text{noise}}(r, \theta) = \text{Normal}[0, \sigma(r, \theta)^2] \]  
(A7)

By considering these two expressions of \( A_{\text{signal}} \) and \( A_{\text{noise}} \), we found that

\[ \text{SNR} = 10 \log_{10} \left( \sum_{\Omega} \frac{|x_n(r, \theta)|^2}{\sum_{\Omega} |A_{\text{noise}}(r, \theta)|^2} \right) \]  
(A8)