factors in this group, or on untargeted preventive measures. Whatever the reason, this phenomenon must be monitored and fast changes in lifestyles (diet, smoking, physical activity) should be induced.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (Shewan and Coats 2010;144:1-2).

References

[1] Levi F, Lucchini F, Negri E, La Vecchia C. Trends in mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world. Heart 2002;88(2):119–24.
[2] Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. Circulation 2004;109(9):1101–7.
[3] Vaartjes I, O'Flaherty M, Grobbee DE, Bots ML, Capewell S. Coronary heart disease mortality trends in the Netherlands 1972–2007. Heart 2011;97(7):569–73.
[4] O'Flaherty M, Ford E, Allender S, Scarborough P, Capewell S. Coronary heart disease trends in England and Wales from 1984 to 2004: concealed levelling of mortality rates among young adults. Heart 2008;94(2):178–81.
[5] O'Flaherty M, Bishop J, Redpath A, et al. Coronary heart disease mortality among young adults in Scotland in relation to social inequalities: time trend study. BMJ 2009;339:b2613.
[6] O'Flaherty M, Allender S, Taylor R, Stevenson C, Peeters A, Capewell S. The decline in coronary heart disease mortality is slowing in young adults (Australia 1976–2006): A time trend analysis. Int J Cardiol doi:10.1016/j.ijcard.2011.01.016.
[7] Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. J Am Coll Cardiol 2007;50(22):2128–32.
[8] Allender S, Scarborough P, O'Flaherty M, Capewell S. Patterns of coronary heart disease mortality over the 20th century in England and Wales: Possible plateaus in the rate of decline. BMC Public Health 2008;8:148.
[9] Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988–1994. Diabetes Care 1998;21(4):518–24.
[10] Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006;295(13):1549–55.
[11] Miura K, Daviglus ML, Dyer AR, et al. Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men: the Chicago Heart Association Detection Project in Industry. Arch Intern Med 2001;161(12):1501–8.
[12] Pereira M, Lunet N, Azevedo A, Barros H. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. J Hypertens 2009;27(5):963–75.
[13] Carmo Id, Dos Santos O, Camolas J, et al. Prevalence of obesity in Portugal. Obes Rev 2006;7(3):233–7.
[14] Marques-Vidal P, Dias CM. Trends in overweight and obesity in Portugal: the National Health Surveys 1995–6 and 1998–9. Obes Res 2005;13(7):1141–5.
[15] Padez C, Fernandes T, Mourão I, Moreira P, Rosado V. Prevalence of overweight and obesity in 7–9-year-old Portuguese children: Trends in body mass index from 1970–2002. Am J Hum Biol 2004;16(6):670–8.
[16] Santos AC, Barros H. Smoking patterns in a community sample of Portuguese adults, 1999–2000. Prev Med 2004;38(1):114–9.

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Non-invasive assessment of endothelial shear stress and coronary stiffness using multislice computed tomography

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We present a methodology for a safe, accurate, direct and rapid assessment of coronary stiffness and endothelial shear stress (ESS) with the use of multislice computed tomography. We report a positive correlation between coronary stiffness and ESS, which is a novel finding adding a new perspective to the already known interplay between ESS and plaque progression. High-volume plaques are located in arterial regions with low ESS and are less stiff compared to low-volume plaques, while non-stenotic plaques have lower stiffness than stenotic ones. Also, this is the first study to show that normal regions in the immediate proximity to plaques ($\leq$2 mm) are less stiff and have lower ESS compared to normal segments located elsewhere. Coronary stiffness may potentially be a novel surrogate marker to characterize atherosclerotic plaque progression and vulnerability.

ESS is a major factor affecting atherosclerosis [1,2] as it determines the individual progression rate of any lesion [3]. Its calculation typically requires a three-dimensional (3D) coronary artery reconstruction by fusing intravascular ultrasound and coronary angiography [3–7]. However, these are both invasive procedures and embrace specific patient risks [8]. Novel non-invasive methods for 3D coronary imaging as multislice computed tomography (MSCT) [9] warrant diminished risks of adverse events and may be more widely applicable.

In vascular physiology, stiffness reflects the rigidity of the arterial wall [10]. During atherosclerotic plaque growth, the coronaries sustain qualitative and quantitative changes which result in gradual wall stiffening [11]. Stiffness is an emerging independent risk factor for coronary disease [12,13], as it is proposed to interplay with local ESS accentuating flow conditions which favor atherosclerosis [2].

We non-invasively studied the effects of coronary stiffness on ESS and atherosclerosis in 10 subjects (9 males, mean age 60.6 $\pm$

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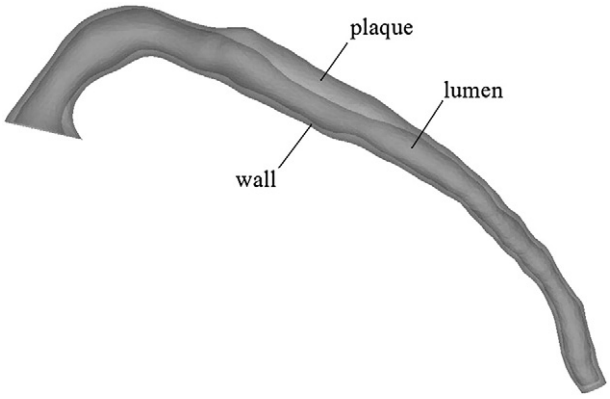

Fig. 1. Three-dimensional left anterior descending artery reconstruction, where both wall and lumen are visible.

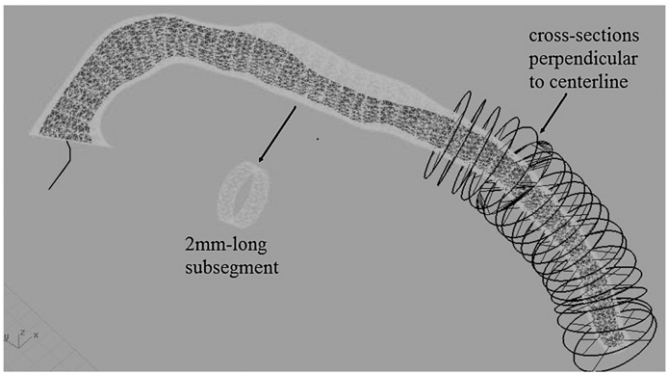

Fig. 3. Division of an artery in 2 mm-long segments.

3.4 years) undergoing cardiac MSCT (128-slice, SIEMENS, SOMATOM Definition AS+) for evaluation of suspected coronary artery disease. Blood pressure was measured with an arm-band sphygmomanometer prior to MSCT. The examination took place in a single breath hold and the images were ECG-gated. All participants provided written informed consent.

The coronary arteries were 3D reconstructed with use of MIMICS® v13.1 (Materialise NV, Leuven, Belgium). The lumen was reconstructed in both systole and diastole based on the ECG, whereas the arterial wall was reconstructed only in diastole (Fig. 1).

A computational grid was applied in each vessel (Gambit®, Fluent Inc Products, Lebanon, NH, USA) and was subsequently imported to computational fluid dynamics software (Fluent®, Fluent Inc Products, Lebanon, NH, USA). ESS and wall pressure were estimated in diastole and systole (Fig. 2). Each artery was divided in 2 mm-long segments (Rhinoceros® v4.0 McNeel and Associates, Seattle, WA, USA) (Fig. 3). Mean ESS and mean wall pressure were calculated in each segment in both cardiac phases using Matlab® (The MathWorks Inc, Natick, MA, USA).

Segments were further classified as diseased (apparent atheromatic lesions or wall thickening) and non-diseased (controls), and also in low- and high-ESS groups, the cut-off being 1 Pascal (Pa) in diastole. Lumen area and wall volume were measured in each segment. We considered the wall volume to represent plaque. Using the median volume (14.08 mm^3) as cut-off, the plaques were assigned to high- and low-volume groups.

Arterial remodeling was assessed by calculating % luminal stenosis (% *Stenosis*) and using the mean of cross-sectional areas at the beginning ($S_{proximal}$) and end (S_{distal}) of each plaque as reference (Fig. 4)

$$\%Stenosis = \frac{S_{reference} - S_{lesion}}{S_{reference}} = \frac{\frac{S_{proximal} + S_{distal}}{2} - S_{lesion}}{\frac{S_{proximal} + S_{distal}}{2}}$$

$$= \frac{S_{proximal} + S_{distal} - 2 \times S_{lesion}}{S_{proximal} + S_{distal}}$$

where $S_{reference}$ is the reference area and S_{lesion} the minimum lumen area in cases where lesion area was smaller than $S_{reference}$ or the maximum lumen area in the cases where lesion area was larger than $S_{reference}$. As of this definition, negative values for % *Stenosis* denote luminal dilatation. Stenotic was considered for plaques causing % *Stenosis* $\geq$25% whereas non-stenotic for those with values <25% or with luminal dilatation.

Coronary stiffness was computed in each segment using the formula

$$Stiffness = \frac{\Delta P \times V}{\Delta V}$$

where ΔP is the mean wall pressure change, ΔV the volume change from diastole to systole, and V the systolic volume [10].

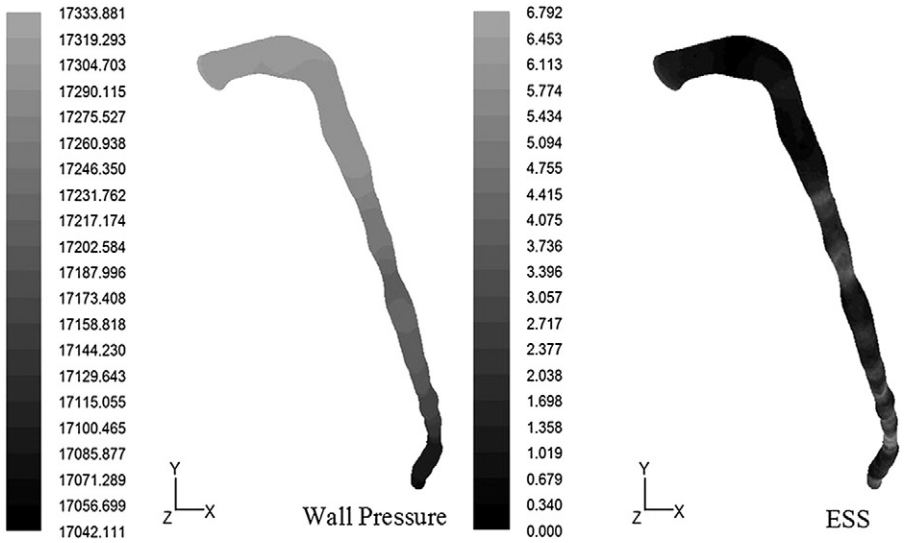

Fig. 2. Wall pressure and endothelial shear stress in the left anterior descending artery, calculated using computational fluid dynamics. Values are in Pascals.

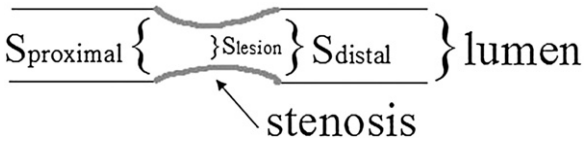

Fig. 4. Methodology for the calculation of luminal stenosis. % luminal stenosis (% *Stenosis*) was assessed using the mean of cross-sectional areas at the beginning ($S_{proximal}$) and end (S_{distal}) of each plaque as reference ($S_{reference}$). S_{lesion} is the minimum lumen area in cases where lesion area was smaller than $S_{reference}$ or the maximum lumen area in the cases where lesion area was larger than $S_{reference}$. $\%Stenosis = \frac{S_{reference} - S_{lesion}}{S_{reference}} = \frac{\frac{S_{proximal} + S_{distal}}{2} - S_{lesion}}{\frac{S_{proximal} + S_{distal}}{2}} = \frac{S_{proximal} + S_{distal} - 2 \times S_{lesion}}{S_{proximal} + S_{distal}}$.

The statistical analyses were performed using SPSS, version 17.0 (SPSS Inc, Chicago, IL, USA).

MSCT was performed in 6 left anterior descending arteries and 4 right coronary arteries. The average arterial length was 64 mm. There were 320 segments identified; 108 diseased and 212 non-diseased (Tables 1 and 2).

The stiffness of low-ESS segments was significantly smaller than that of high-ESS segments [median 57.8 interquartile range (IQR) 36.4 to 93.4 mm Hg vs. median 81.0 IQR 47.9 to 127.5 mm Hg, $p<0.01$]. High-volume plaques were prone to occur in low-ESS regions [odds ratio (OR) 2.29, 95% confidence intervals (CI) from 1.08 to 4.86, $p<0.05$] and were less stiff compared to low-volume plaques (median 52.5 IQR 36.9 to 101.9 mm Hg vs. median 83.1 IQR 38.5 to 166.2 mm Hg, $p<0.01$). Non-stenotic plaques had also reduced stiffness compared to stenotic ones (median 50.2 IQR 32.7 to 90.9 mm Hg vs median 134.6 IQR 79.2 to 218.7 mm Hg, $p<0.001$). Atherosclerosis-free regions immediate ($\leq$2 mm) and proximal to plaques (toward the ostium) tended to be less stiff (median 60.2 IQR 35.7 to 84.4 mm Hg vs median 81.2 IQR 51.5 to 143.3 mm Hg, $p=0.08$) and have lower ESS (median 0.85 IQR 0.60 to 1.44 Pa vs median 1.39 IQR 0.87 to 1.92 Pa, $p=0.06$) compared to the remaining normal segments.

These data show that atheromatic lesions with reduced wall stiffness have lower ESS than areas with increased stiffness. Also, high-volume plaques are located in regions with lower ESS and are less stiff compared to low-volume plaques. Our study suggests that atheromatic lesions characterized by lower ESS and reduced stiffness accommodate high-volume plaques, where lipid-rich core likely prevails, but the lumen is preserved. On the other hand increased stiffness is noted in low-volume but stenotic plaques, where fibrous tissue and/or calcium are probably the major components.

Based on the above findings one could speculate that plaques with decreased stiffness are associated with certain features of vulnerability, these being increased volume, decreased luminal obstruction and low ESS. Decreased stiffness may have a common pathophysiologic basis with plaque vulnerability with extracellular matrix degradation being a common feature in both cases [14–16]. Vulnerable plaques are usually minimally stenotic and associated with expansive remodeling, characterized by a thin fibrous cap and a large necrotic lipid core, while low ESS has been found to be an independent predictor [1].

Normal segments proximal and contiguous to plaques tended to be less stiff and have lower ESS compared to the remaining normal segments, suggesting that regions close to plaques are susceptible to atherosclerosis. This concept may have potential implications in the optimal stent size selection in cases of percutaneous coronary intervention. This finding implies that in an earlier stage of atherosclerosis prior to intimal thickening, the coronary wall already exhibits structural changes reflected in decreased stiffness, and this may be the first marker of vascular pathology in these regions.

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Table 1
Study patient characteristics.

Demographics/clinical characteristics	
Patients (n)	10
Age (years)	60.6 (43–77)
Males	9
Body mass index (kg/m^2)	27.35 (24.6–38.2)
Heart rate (bmp)	59 (44–77)
Medical history (n)	
Myocardial infarction	1 (10%)
Arrhythmia	2 (20%)
Aortic aneurysm	1 (10%)
Peripheral vascular disease	1 (10%)
Risk Factors for coronary artery disease (n)	
Smoking	3 (30%)
Diabetes mellitus	2 (20%)
Hypercholesterolemia (>240 mgr/dl)	7 (70%)
Arterial hypertension	6 (60%)
Positive family history	4 (40%)
Exercise (n)	4 (40%)
Walking	3 (30%)
Teacher of martial arts	1 (10%)
Medication (n)	
Statins	5 (50%)
ω3-fatty acids	2 (20%)
Beta-blockers	2 (20%)
Calcium antagonists	3 (30%)
Angiotensin converting enzyme inhibitors	3 (30%)
Diuretics	4 (40%)
Angiotensin II receptor blockers	1 (10%)

Table 2
Characteristics of the investigated vessels and subsegments.

	Average length (mm)	Vessels			Subsegments		
		Non-diseased	Diseased	Total	Non-diseased	Diseased	Total
LAD	75.01	1	5	6	116	64	180
RCA	84.60	2	2	4	96	44	140
Total	73.92	3	7	10	212	108	320

References

[1] Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J Am Coll Cardiol 2007;49:2379–93.
[2] Chatzizisis YS, Giannoglou GD. Coronary hemodynamics and atherosclerotic wall stiffness: a vicious cycle. Med Hypotheses 2007;69:349–55.
[3] Koskinas KC, Feldman CL, Chatzizisis YS, et al. Natural history of experimental coronary atherosclerosis and vascular remodeling in relation to endothelial shear stress: a serial, in vivo intravascular ultrasound study. Circulation 2010;121:2092–101.
[4] Chatzizisis YS, Giannoglou GD, Matakos A, et al. In-vivo accuracy of geometrically correct three-dimensional reconstruction of human coronary arteries: is it influenced by certain parameters? Coron Artery Dis 2006;17:545–51.
[5] Giannoglou GD, Chatzizisis YS, Koutkias V, et al. A novel active contour model for fully automated segmentation of intravascular ultrasound images: in vivo validation in human coronary arteries. Comput Biol Med 2007;37:1292–302.
[6] Papadogiorgaki M, Mezaris V, Chatzizisis YS, Giannoglou GD, Kompatsiaris I. Image analysis techniques for automated IVUS contour detection. Ultrasound Med Biol 2008;34:1482–98.
[7] Chatzizisis YS, Giannoglou GD, Sianos G, et al. In vivo comparative study of linear versus geometrically correct three-dimensional reconstruction of coronary arteries. Am J Cardiol 2008;101:263–7.
[8] Scanlon PJ, Faxon DP, Audet AM, et al. ACC/AHA guidelines for coronary angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. Circulation 1999;99:2345–57.
[9] Escolar E, Weigold G, Fuisz A, Weissman NJ. New imaging techniques for diagnosing coronary artery disease. CMAJ 2006;174:487–95.
[10] Sakuragi S, Abhayaratna WP. Arterial stiffness: methods of measurement, physiologic determinants and prediction of cardiovascular outcomes. Int J Cardiol 2010;138:112–8.
[11] London GM, Marchais SJ, Guerin AP, Pannier B. Arterial stiffness: pathophysiology and clinical impact. Clin Exp Hypertens 2004;26:689–99.
[12] Laurent S, Boutouyrie P, Lacolley P. Structural and genetic bases of arterial stiffness. Hypertension 2005;45:1050–5.

[13] Cohn JN, Duprez DA, Grandits GA. Arterial elasticity as part of a comprehensive assessment of cardiovascular risk and drug treatment. Hypertension 2005;46: 217–20.
[14] Pasterkamp G, Schoneveld AH, Hijnen DJ, et al. Atherosclerotic arterial remodeling and the localization of macrophages and matrix metalloproteases 1, 2 and 9 in the human coronary artery. Atherosclerosis 2000;150:245–53.
[15] Liu J, Sukhova GK, Yang J-T, et al. Cathepsin L expression and regulation in human abdominal aortic aneurysm, atherosclerosis, and vascular cells. Atherosclerosis 2006;184:302–11.
[16] Dollery CM, Owen CA, Sukhova GK, Krettek A, Shapiro SD, Libby P. Neutrophil elastase in human atherosclerotic plaques: production by macrophages. Circulation 2003;107:2829–36.

0167-5273/$ – see front matter
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