SYSTEMATIC REVIEW

Association of coronary wall shear stress with atheromatous plaque vulnerability: a systematic review

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Conflicts of interests

Nothing to declare

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Abstract

Acute coronary syndromes are usually triggered by the erosion or rupture of a vulnerable coronary plaque. A vulnerable plaque (VP) is an atheromatous plaque which, after suffering different transformations, is prone to rupture causing an acute coronary event. Such a VP carries inside several biomarkers considered as “signatures of vulnerability”, which, if identified, can prompt timely initiation of therapeutic measures in order to prevent the development of an acute myocardial infarction. The most

frequently used techniques for identification of vulnerability markers are computed tomographic angiography (CTA), intravascular ultrasound and optical coherence tomography. Endothelial shear stress (ESS) represents a new promising biomarker associated with plaque vulnerability. Determination of ESS is nowadays possible using noninvasive imaging techniques, based on complex computational post-processing of multiple datasets extracted from CTA images and advanced computational fluid dynamics technologies. The aim of this systematic review was to evaluate the role of the coronary ESS, determined using advanced computational techniques for image post-processing, as a feature

associated with CTA-derived biomarkers of atheromatous plaque vulnerability, underlining the conceptual differences between high ESS and low ESS as promoters of vulnerability.

Core tip

A vulnerable plaque is an atheromatous plaque prone to rupture triggering an acute coronary event. Vulnerable plaques carry inside several biomarkers considered as “signatures of vulnerability”, which can be identified using computed tomography or intracoronary imaging. Endothelial shear stress (ESS) represents a new promising biomarker associated with plaque vulnerability, which can be easily determined using computational post-processing of image data and advanced computational fluid dynamics technologies. The aim of this systematic review was to evaluate the role of the coronary ESS as a feature associated with CTA-derived biomarkers of atheromatous plaque vulnerability.

Introduction

Acute coronary syndromes (ACS) are usually triggered by the erosion or rupture of a vulnerable coronary plaque. A vulnerable plaque (VP) is an atheromatous plaque which, after suffering different transformations, is prone to rupture causing an acute coronary event. The concept of VP is based on the premise that certain coronary plaques are more prone to disruption or thrombosis than others, leading to a symptomatic acute coronary event.

Such a VP carries inside several biomarkers considered as “signatures of vulnerability”, which, if identified, can prompt timely initiation of therapeutic measures in order to prevent the development of an acute myocardial infarction (AMI) [1,2]. Therefore, image-based identification of the VPs represented a “holy grail” for many years in interventional cardiology and in related imaging specialities.

The most sensitive biomarkers associated with plaque vulnerability differ largely according to the imaging technique used for assessment of VP. While computed tomographic angiography (CTA) imaging has a definite role in visualization of several vulnerability features such as positive remodeling, napkin ring sign, spotty calcifications or very low density plaques appearing as dark spots on CTA images, its value remains low in assessing the thickness of the fibrous cap, mainly due to the insufficient resolution [3]. Intravascular imaging techniques,

namely intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have been proposed to represent efficient alternatives to CTA imaging for detecting thin cap fibroatheroma as well as for quantification of plaque components [4].

Ten years ago, Motoyama demonstrated that ACSs are more frequently produced by plaques with vulnerability features. However, not all the VPs produce an acute coronary event. In this study of Motoyama, from the total of 72 coronary plaques with at least one vulnerability feature only 11 resulted in an ACS, while the rest of 61 did not produce any coronary event [5]. Therefore one open question remains: why some vulnerable plaque do rupture while others of the same patient do not? The answer to this question may be represented by the local forces acting inside the coronary lumen, that could determine plaque rupture. The major representative of the interaction between these forces is the endothelial shear stress (ESS), which has been recently proposed as a new marker of plaque vulnerability and plaque progression.

ESS represents a new promising biomarker associated with plaque vulnerability. Determination of ESS is nowadays possible using noninvasive imaging techniques, based on complex computational post-processing of multiple datasets extracted from CTA images. Advanced computational fluid dynamics technologies made possible to calculate the shear stress inside the coronary lumen, at any location in the coronary tree and at any site along the coronary arteries.

It has been widely recognized that atheromatous plaques have the tendency to develop in areas exposed to increased friction forces such as bifurcations. Their localization is not randomly distributed within the coronary tree, being more frequently identified in areas where haemorheologic forces are higher. Therefore, new theories explained the development and progression of coronary lesions as a result of altered ESS acting at different magnitudes in different coronary artery locations.

The aim of this systematic review was to evaluate the role of the coronary ESS, determined using advanced computational techniques for image post-processing, as a feature associated with CTA-derived biomarkers of atheromatous plaque vulnerability.

Material and methods

Search strategy

The study was conducted in accordance with the PRISMA methodology (Preferred Reporting

Items for Systematic Reviews and Meta-Analyses) together with Cochrane Collaboration and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) recommendations.

The literature search was centered on all published articles related to coronary shear stress determination, either based on invasive image datasets (IVUS, OCT, coronary angiography) or on non-invasive image datasets (collected by extraction of CTA images).

Two investigators searched Pubmed/Medline, Scopus and Thomson Reuters ClarivateAnalytics databases. The comprehensive search strategy comprised the following medical subject headings (MeSH) terms: “shear stress AND acute coronary syndromes”, “shear stress AND plaque vulnerability”, “shear stress AND vulnerable plaque”.

Study selection and eligibility criteria

This systematic review included all the published studies that addressed the correlation between atheromatous plaque characteristics and ESS in human population. Studies that enrolled only subjects with stable CAD or populations with healthy coronary arteries in the absence of atheromatous plaques were excluded from this analysis. Case reports, case series, reviews, editorials, letters, as well as manuscripts that were not available in a full text form or published in other languages than English have been also excluded from the present systematic review. Furthermore, studies not providing relevant

data, those related to non-coronary vulnerable plaques, virtual studies using only computer data processing or various techniques for development of fused images reflecting shear stress, as well as animal or only ex-vivo studies were also excluded from this analysis.

Data extraction and analysis

The two investigators extracted the subsequent data from the selected manuscripts: number of subjects included in the study, age, gender, plaque morphology and plaque composition at baseline and follow-up, follow-up period, plaque progression, primary and secondary end-points, method for ESS determination, mean values of the ESS, as well as the presence of cardiovascular risk factors such as diabetes, smoking, hypertension history, obesity.

Data extraction included also the odds ratios (OR) and hazard ratios (HR) for the end-points of each study whenever available.

Plaque features analyzed

The following plaque features and their progression in time were searched in each published manuscript and analyzed in relation to ESS:

- a) Plaque morphology
 - presence of positive remodeling
 - thickness of the fibrous cap
 - presence of thin cap fibroatheroma
 - remodeling index

Figure 1. Diagram of the search protocol and results of manuscript selection.

- presence of spotty calcification
- napkin ring signs
- plaque rupture;
- presence of thrombus
- b) Plaque composition**
- plaque burden
- area and volumetric percentage of necrotic core;
- fibrotic tissue;
- fibro-fatty tissue
- calcific tissue
- lipid arch;
- lipid length;
- presence and extent of microvessels;
- macrophages;
- calcifications;
- c) Intraluminal shear stress**

Statistical analysis

The normally distributed reported variables are presented as the mean (SD), as reported in the original sources. Categorical variables are presented as absolute frequencies and percentages.

Results

A total number of 195 studies were identified, out of which 183 through database searching and 12 through manual searching. After 14 duplicate studies had been removed, 181 studies were screened for assessment of shear stress in relation to plaque vulnerability. After further exclusion of 25 studies available in abstract-only form, 156 were checked for eligibility criteria and only 10 fulfilled the eligibility criteria and were included in the analysis (Figure 1). The 10 studies analyzed included a total number of 692 subjects in whom ESS was assessed in parallel with a complex imaging-based assessment of plaque vulnerability markers.

The systematic review was further divided into 3 parts:

Part 1 of the systematic review addressed the topic of CTA assessment of plaque vulnerability in plaques with high ESS versus those with low ESS. It consisted of the analysis of 3 studies including 180 patients in whom vulnerability markers were assessed using CTA.

Part 2 of the systematic review compared high ESS versus low ESS in vulnerable plaques assessed using OCT in a total of 41 patients.

Part 3 of the systematic review consisted in the analysis of 3 studies on 140 subjects in whom assessment of plaque vulnerability was performed using IVUS and IVUS-derived vulnerable features were correlated with ESS

levels.

In the rest of the studies a combined approach was used (CTA and OCT and/or IVUS) for assessment of plaque vulnerability in 406 patients.

Characteristics of the patients and the studies included in the analysis

In total, a number of 692 patients were included in the 10 studies analyzed. Baseline overall characteristics of the subjects analyzed, inclusion/exclusion criteria, study aims and endpoints for each study included in this systematic review are listed in Table 1 [6,7,8,9,10,11,12,13,14,15].

ESS and CTA-derived vulnerability markers

Both studies assessing the CTA features of vulnerability in relation to shear stress identified presence of vulnerability markers in a significantly higher extent in the region exposed to a high ESS as compared to those exposed to a low ESS (Table 2) [14,15]. Coronary regions exhibiting a high ESS presented significantly plaque lower density ($p=0.05$), a higher remodelling index ($p=0.025$) a higher proportion of low attenuation plaque ($p=0.003$) and napkin ring sign ($p<0.0001$). Furthermore, presence of at least one feature of vulnerable plaque was encountered in 29.4% to 51.9% in low-to-intermediate ESS areas versus 38.2% to 76.9% in high ESS area ($p=0.018$), while presence of at least 2 features of vulnerability was encountered in 23.3% in low-to-intermediate ESS areas versus 53.5% in high ESS areas ($p=0.006$) [14,15].

ESS and OCT-derived vulnerability markers

OCT studies showed opposite results, indicating that areas with low ESS exhibit vulnerability features in a significantly higher extent than areas with high ESS (Table 3). In two OCT studies, the mean thickness of the fibrous cap varied from 115 μm to 128.2 μm in low ESS areas and from 165 μm to 170 μm $\pm$ 12.3 in high ESS areas ($p=0.003$ and $p=0.0004$) [6,9]. Furthermore, a follow-up study indicated that in regions with low ESS the fibrous cap thickness remained practically unchanged after statin therapy while in regions with high ESS the thickness of the fibrous cap increased from 165.0 $\pm$ 12.0 to 182.2 $\pm$ 14.1 μm ($p=0.003$) [6]. Another argument supporting the hypothesis that low ESS areas are more vulnerable results

from the observation that the density in macrophages was significantly higher in low ESS areas ($p=0.017$) [9].

Interestingly, in one study the percent of lipid reach plaque was higher in low ESS regions (37.5% vs 20.0%, $p=0.01$) [9], contrary to the observations of CTA studies, however in another study this difference was not statistically significant ($p=0.1$) [6]. At the same time, the incidence of spotty calcifications, coronary calcifications and neovascularisation was not significantly different between the regions with high versus low ESS [9].

ESS and IVUS-derived vulnerability markers

IVUS-compared studies failed to identify significant differences between high and low ESS regions in terms of plaque composition (Table 4) [8,10,13]. However, it is difficult to generalize their conclusions, as they were performed in a low number of cases, and in almost all the cases in one single coronary artery, which was the left anterior descending artery. However, IVUS studies were follow-up studies and they succeeded to demonstrate that the percentage in necrotic core reduction following statin therapy was significantly higher in the regions exposed to high ESS compared to low ESS regions (0.035 vs 0.007 and 0.56 vs 0.47, $p<0.0001$ for plaque area; 0.015 vs 0.008 and 0.17 vs 0.07, $p<0.05$ and $p<0.0001$ for necrotic core) [8,10,13].

Discussions

Coronary plaque vulnerabilisation – more than a localized process

VPs are coronary plaques exposed to a particular risk for rupture, triggering an ACS. Therefore, many efforts have been oriented towards identification of the most reliable biomarkers associated with increased atheromatous coronary plaque vulnerability. In the complex process of coronary plaque vulnerabilisation, once this has been initiated, active inflammation in the sub-endothelial layer, intraplaque haemorrhage and endothelial dysfunction can further contribute to plaque vulnerabilization [16]. It became obvious that besides of the local plaque composition, there should be other factors involved in the complex mechanism of plaque rupture. According to this theory, rupture of a VP occurs as a result of a complex interaction between local factors and haemorheological factors at the level of the coronary tree, on top of

which systemic inflammation plays a major role in entertaining plaque inflammation [17]. Therefore recent types of vulnerability have been described, such as “vulnerable blood” meaning the vulnerability of the systemic blood resulting from an augmented systemic inflammation, or “vulnerable hemodynamic flow” around the plaque [18,19], which is largely related to ESS.

Imaging-based vulnerability markers – an integrative approach

Various imaging-based vulnerability markers have been described in the literature together with their prognostic role. The content in very low density atheroma was found to be significantly higher in culprit lesions as compared to non-culprit ones in patients with ACS [20]. In a study published several years ago, this CTA-derived sign showed a very close correlation with the necrotic core identified by IVUS [21]. Positive remodeling and presence of spotty calcifications inside the plaque have also been encountered in a significantly larger extent in culprit VPs.

In the PROSPECT trial, a plaque burden $>70\%$ was the strongest indicator of MACE rates, predicting worse outcomes with a substantially higher power as compared to all other biomarkers including minimal luminal area [22]. At the same time, the association between a thin fibrous cap, a minimal luminal area $<4.0 \text{ mm}^2$ and a plaque burden $>70\%$ has been shown to have a positive predictive value of 18% for predicting a major cardiac event triggered by that lesion, according to PROSPECT investigators [22]. Yamamoto *et al* also demonstrated that positive remodeling and presence of a low attenuation plaque provide additional prognostic information of coronary artery stenosis [23].

Our results indicate that different imaging techniques can lead to contradictory data related to the influence of shear stress on plaque vulnerability. While CTA seems to indicate high ESS areas as the most vulnerable ones, OCT seems to indicate low ESS areas as more exposed to plaque rupture. Therefore an integrative approach, using more than one single imaging technology, could provide additional information in favor of any of these two hypothesis: the low ESS or the high ESS as promoters of plaque vulnerability. Fusion imaging has been proposed to represent an emerging tool for generating image data sets that will serve for such an integrative approach. Fusion imaging allows assessment of plaque vulnerability using more than one imaging technique and holds many promises to be also applied for ESS calcula-

Table 1. Summary of the included studies

Authors	Year	N*	Inclusion criteria	Exclusion criteria	Study aim/hypothesis	Modality of coronary imaging	Follow-up	Study end-points
Vergallo R <i>et al.</i>	2014	21	ACS patients who underwent FD-OCT imaging before PCI No history of stent implantation in the studied artery	Improper OCT or CA images (decreased image quality, inadequate projection for 3D reconstruction) Incomplete demographic and clinical data Previous stent implantation in the studied arteries	The relationship between local ESS and coronary plaque characteristics	- Invasive CA - FD-OCT	nr	nr
Papafakis MI <i>et al.</i>	2015	324	ACS patients undergoing PCI for the culprit lesion, who underwent complete vascular profiling (IVUS and CA) at baseline and during follow-up from the PREDICTION study cohort	Patients from the PREDICTION study COHORT with vascular profiling only at baseline	The role of ESS in the development of de novo coronary lesions and progression of plaque eccentricity	- Invasive CA - IVUS	6-10 months	- De novo eccentric plaque formation in unaffected arteries - Increased plaque eccentricity and worsening lumen obstruction in affected arteries
Hung O <i>et al.</i>	2016	24	Patients with stable, symptomatic non-obstructive CAD** (AP, NSTEMI) who underwent CA	Cardiogenic shock LVEF<30% Significant hepatic, renal, hematologic impairment History of CABG Contraindication to beta-blocker therapy With coronary lesions that required revascularization of with significant collateralization	The role of nebulivol in improving endothelial dysfunction and ESS, compared to atenolol	- Invasive CA - IVUS	12 months	- Primary: the change in the number of TCFA per vessel - Secondary: inflammatory and oxidative stress biomarkers, endothelial function, microvascular function, arterial remodeling, IVUS plaque area and composition
Yamamoto E <i>et al.</i>	2017	20	Patients with CAD with non-culprit lesion imaging by CA and OCT	History of previous stent implantation in the studied artery follow-up <3 months imaging of the culprit artery alone improper OCT or CA images	The role of ESS at baseline in predicting local changes to plaque phenotype	- Invasive CA - OCT	6 months	- Changes in plaque characteristics (FCT and lipid arc) according to the local ESS
Timminis LH <i>et al.</i>	2017	20	Patients with abnormal non-invasive stress test, stable angina, with determined non-obstructed CAD	nr	Low and oscillatory ESS leads to progression towards plaque vulnerability, and low non-oscillatory ESS to progression towards more stable plaques	- Invasive CA - IVUS	6 months	- Changes in VH-IVUS plaque characteristics (total plaque area, fibrous, fibro-fatty, necrotic core, dense calcium) according to local ESS (high, low, oscillatory, non-oscillatory)

Liu X <i>et al.</i>	2017	12	Patients >18 years old, with ACS (UA, MI) and RCA un-planned for PCI	Previous PCI of the RCA, CABG, renal failures, significant hematological disease	The role of local bio-mechanics factors and vascular characteristics in coronary plaque progression and arterial remodeling	- CCTA	15±8 months	- Minimal lumen area - Plaque burden - Plaque volume - Coronary remodeling (negative and positive)
Fukumoto Y <i>et al.</i>	2008	20	Patients with ACS with a distinct ulcerative coronary lesion on a straight segment of the vessel	Tortuous lesions Lesions with significant mass of thrombus on the plaque surface	The relationship between ESS distribution and coronary plaque rupture	- Invasive CA - IVUS	nr	nr
Corban MT <i>et al.</i>	2014	20	Patients with abnormal non-invasive stress test, stable angina, with determined non-obstructed CAD	nr	The role of plaque burden, ESS and plaque phenotype in predicting coronary plaque progression and vulnerability	- Invasive CA - IVUS	6 months	- Increased plaque vulnerability (increased NC, decreased fibrous and fibro-fatty tissue, positive remodeling) - Plaque burden - Pathological intimal thickening
Park JB <i>et al.</i>	2016	80	Patients with suspected or known CAD	History of MI Previous coronary revascularization Complete occlusion of a coronary artery	The role of pressure distribution and ESS acting on atherosclerotic plaques and their association with plaque characteristics assessed by CCTA	- Invasive CA - FFR - CCTA	nr	nr
Han D <i>et al.</i>	2016	100	Patients with suspected CAD	History of CABG or PCI with suspected in-stent restenosis Contraindications to adenosine Recent ACS or suspicion of ACS Complex congenital heart disease Pacemaker or defibrillator Prosthetic heart valve Significant arrhythmia Creatinine >1.5 mg/dl Allergy to iodinated contrast agent Pregnant state BMI >35 Evidence of instability or life-threatening disease Inability to adhere to study procedures	The relationship between ESS, coronary ischemia evaluated by FFR and coronary plaque characteristics	- Invasive CA - FFR - CCTA	nr	nr

* N – number of patients enrolled in the study; nr – not reported; CA – coronary angiography; FD-OCT – frequency domain optical coherence tomography; IVUS – intravascular ultrasound; CAD – coronary artery disease; AP – angina pectoris; NTSEMI – non-ST segment elevation myocardial infarction; UA – unstable angina; MI – myocardial infarction; CABG – coronary by-pass graft; RCA – right coronary artery; ACS – acute coronary syndrome; CCTA – coronary computed tomography angiography; FFR – fractional flow reserve;

**non-significant CAD includes coronary stenoses <50% by CA, or <70% with FFR >0.8.

Table 2. The relationship between ESS, FFR and plaque vulnerability markers assessed via CCTA

	Han D <i>et al.</i>				Park JB <i>et al.</i>				Liu X <i>et al.</i>			
	Low ESS	Intermediate ESS	High ESS	p value	Lowest ESS	Middle ESS	Highest ESS	p value	Low ESS	Moderate ESS	High ESS	p value
Mean ESS (dyne/cm ²)	89.2±36.1	188.9±31.0	408.7±132.7	<0.0001	-	-	-	-	-	-	-	-
Invasive FFR	0.86±0.13	-	0.79±0.13	0.011	-	0.78±0.12	-	-	-	-	-	-
FFR _{CT}	-	-	-	-	-	0.79±0.11	-	-	-	-	-	-
Lesion length (mm)	23.2±12.9	24.9±12.1	24.3±10.4	0.740	-	14.4±7.9	-	-	-	-	-	-
Minimal lumen diameter (mm)	3.7±2.1	2.7±1.4	2.5±1.4	<0.001	-	1.4±0.5	-	-	-	-	-	-
Minimal lumen area (mm ²)	3.7±2.1	2.7±1.4	2.5±1.4	<0.001	-	2.1±1.0	-	-	-0.79±0.16	0.09±0.12	1.01±0.38	<0.001
CA stenosis (%)	43.4±18.3	47.6±12.2	55±13.4	<0.001	-	52.3±14.4	-	-	-	-	-	-
CCTA findings												
Plaque density (HU)	-	-	-	-	443.5±496.4	421.9±424.6	194.4±273.2	0.057	-	-	-	-
Plaque burden increase at follow-up (%)	-	-	-	-	-	-	-	-	6.28±0.96	-1.12±0.57	-2.32±2.53	<0.001
Plaque volume (mm ³)	-	-	-	-	-	-	-	-	1.02±0.48	-0.88±0.45	0.83±1.86	<0.001
Remodeling index	-	-	-	-	1.11±0.13	1.12±0.12	1.20±0.14	0.025	-	-	-	-
Positive remodeling (%)	32.7	37.0	61.1	0.006	38.5	44.4	69.2	0.062	25	25	31	0.234
Negative remodeling (%)	-	-	-	-	-	-	-	-	51	40	17	-
Low attenuation plaque (%)	14.6	14.8	38.9	0.002	15.4	18.5	53.8	0.003	-	-	-	-
Spotty calcifications (%)	10.9	9.3	18.5	0.309	0.0	18.5	19.2	0.060	-	-	-	-
Napkin ring sign (%)	-	-	-	-	7.7	14.8	53.8	<0.001	-	-	-	-
APC ≥2 (%)	23.3	23.3	53.5	0.006	-	-	-	-	-	-	-	-
APC ≥1 (%)	29.4	32.4	38.2	-	38.5	51.9	76.9	0.018	-	-	-	-

*FFR – Invasive fractional flow reserve; FFR_{CT} – fractional flow reserve assessed via CCTA imaging; CA stenosis – stenosis depicted on invasive coronary angiography; CCTA – coronary CT angiography; HU – Hounsfield units; APC – atherosclerotic plaque characteristics;

Table 3. The relationship between ESS and plaque vulnerability markers assessed via Optical Coherence Tomography

	Yamamoto E <i>et al.</i>		Vergallo R <i>et al.</i>	
Mean age, median (range)	58 (53-66) years		58 (53-69) years	
Patients (n)	20		21	
Analyzed coronary arteries (n)	25		24	
Analyzed coronary segments (n)	145		146	
ESS at baseline, median (range)	1.51 (1.08-2.09) Pa		0.74 (0.44-1.23)	
	Low ESS (<1Pa)	High ESS (≥1Pa)	P value	
Number of coronary segments, n (%)	29 (20%)	(116 (80%))	-	
Lipid rich plaque (%)				
Baseline	37.9	23.3	0.11	37.5
Follow-up	31.0	25.9	0.54	-
TCFA (%)				
Baseline	17.2	3.4	0.001	12.5
Follow-up	10.3	0.9	0.03	-
Lumen area (mm ²)				
Baseline	10.9±3.2	6.4±2.5	<0.001	
Follow-up	10.4±3.1	6.2±2.7	<0.001	-
FCT (µm)				
Baseline	128.2±12.3	165.0±12.0	0.03	
Follow-up	129.1±10.9	182.2±14.1	0.003	-
Lipid arc (µm)				
Baseline	126.4±15.2	131.7±5.6	0.73	
Follow-up	141.1±14.0	128.7±5.2	0.37	-
Thinn fibrous cap (µm)				
	-	-	-	115 (63-166)
Macrophage Density (%)				170 (107-219)
Coronary calcifications (%)				
	-	-	-	8.4 (4.8-12.6)
Spotty calcifications (%)				
	-	-	-	37.5
Neovascularization (%)				
	-	-	-	26.0
				12.0
				0.076
				0.170

*ESS – endothelial shear stress; TCFA – thin cap fibro-atheroma; FCT – Fibrous cap thickness.

Table 4. The relationship between ESS and plaque vulnerability markers assessed via Intravascular Ultrasound

	Timmins LH <i>et al.</i>	Hung O <i>et al.</i>	Corban MT <i>et al.</i>										
Patients (n)	20	24	20										
Mean age (range/SD)	54 (46-68)	52.5±10.3	54 (46-68)										
Analyzed coronary arteries (n)	20 (20 LAD)	24 (23 LAD+1 CXA)	-										
Analyzed VH-IVUS segments (n)	1840	1843	2249										
Follow-up period (months)	6	12	6										
	Low ESS (<10 dynes cm ⁻²)	Intermediate ESS (10-25 dynes cm ⁻²)	High ESS (>25 dynes cm ⁻²)	p value	Low ESS (<1 Pa)	Intermediate ESS (≤1-2.5 Pa)	High ESS (≥2Pa)	p value	PB >40% alone	Low ESS alone (<10 dynes cm ⁻²)	PB >40% with low ESS (<10 dynes cm ⁻²)	PB >60%	p value
Analyzed segments (%)	-	-	-	-	23%	50%	27%	-	43%	9%	1%	-	-
ESS magnitude (dynes cm ⁻²)	6.59±2.00	16.67±4.21	45.24±20.55	<0.0001	-	-	-	-	-	-	-	-	-
Oscillatory ESS (°)	56.14±56.99	23.12±33.18	11.65±17.66	<0.0001	-	-	-	-	-	-	-	-	-
Plaque area (mm ²)	0.40±0.53	0.43±0.58	0.49±0.66	0.11	-	-	-	-	-	-	-	-	-
Fibrous area (mm ²)	0.25±0.34	0.26±0.36	0.28±0.38	0.52	-	-	-	-	-	-	-	-	-
Fibrofatty area (mm ²)	0.05±0.11	0.04±0.01	0.06±0.14	0.02	-	-	-	-	-	-	-	-	-
Necrotic core (mm ²)	0.07±0.15	0.09±0.17	0.11±0.18	0.08	-	-	-	-	-	-	-	-	-

Dense calcium (mm ²)	0.03±0.11	0.04±0.01	0.05±0.12	0.13	-	-	-	-	-	-	-	-
Δ Lumen area after follow-up period (mm ²)	-	-	-	-	-1.17±1.24	-0.64±1.61	0.61±2.15	<0.0001	-	-	-	-
Δ EEM area after follow-up period (mm ²)	-	-	-	-	-0.70±1.32	-0.37±1.29	0.05±1.82	0.400	-	-	-	-
Δ Plaque area after follow-up period (mm ²)	0.007±0.010	-0.032-0.006	-0.028±0.007	<0.001	0.47±1.37	0.27±1.82	-0.56±2.77	<0.0001	-0.28±1.32	0.05±0.71	0.068±1.05	-0.53±1.41
Δ Fibrous area after follow-up period (mm ²)	-0.031±0.006	-	-0.002±0.007	<0.001	0.21±0.76	0.02±1.08	-0.47±1.64	<0.0001	-	-	-	-0.60±1.05
Δ Fibrofatty area after follow-up period (mm ²)	-	-	-	-	0.04±0.30	-0.01±0.24	-0.05±0.35	<0.0001	-	-	-	-0.35±0.59
Δ Necrotic core area after follow-up period (mm ²)	0.008±0.004	-	0.015±0.004	<0.05	-0.07±0.71	-0.01±0.66	-0.17±0.88	<0.0001	-	-	-	0.21±0.65
Δ Dense calcium area after follow-up period (mm ²)	-	-	-	-	-0.01±0.22	0.04±0.22	0.04±0.26	<0.0001	-	-	-	0.20±0.48
Constrictive remodeling at follow-up (%)	-	-	-	-	77	67	51	0.04	-	-	-	-
Compensatory remodeling at follow-up (%)	-	-	-	-	13	13	12	0.04	-	-	-	-
Excessive expansive remodeling (%)	-	-	-	-	10	20	38	0.04	-	-	-	-

*LAD – left anterior descending coronary artery; CXA – Circumflex artery; VH-IVUS – Virtual histology intravascular ultrasound; ESS – endothelial shear stress; EEM – external elastic membrane; Δ – difference between baseline values and follow-up values of the parameter of interest; PB – plaque burden;

tions. This new imaging technology is based on co-registration of at least two different imaging techniques, able to provide in one single image complementary information which are normally separately provided by the two techniques. For instance, CTA-IVUS fusion imaging has been proved feasible, allowing similar visualization of the plaque composition by CTA and assessment of fibrous cap thickness by IVUS. In this way, fusion imaging can successfully integrate two complementary parameters, both reliable biomarkers with complementary added value for characterization of unstable plaques [2]. Fused OCT/IVUS images have also been developed but their role is still under investigation.

Computational flow dynamics for calculation of ESS

Adding computational flow dynamics (CFD) postprocessing to CTA allows calculation of ESS and can offer the possibility to add functional data to the morphologic ones.

Integration of CFD into CTA algorithm led to development of an emerging tool for characterization of the functional significance of a coronary artery stenosis. Fractional flow reserve (FFR) is a valuable parameter for detecting functional significance of a coronary lesion, and its non-invasive brother – CT-FFR, has been largely recognized in the recent years as perfectly comparable to the invasive one. FFR-CT is calculated from standard CTA datasets being able to provide relevant information of functional relevance of a plaque. Several recent studies suggested that FFR is significantly lower in unstable plaques as compared to stable ones with the same anatomical severity [3]. In a retrospective analysis of the images scanned with 1 year prior to an AMI, FFR-CT was lowest and APS was highest in the segments located upstream of the maximum stenosis [24,25].

CFD has been proposed as a valid tool for coronary artery segmentation, generating 3D meshes of the coronary arteries which can allow calculation of the ESS by computing arterial flow [26]. Among the imaging techniques proposed for generating the underlying image datasets for CFD, CTA represents the most frequently used, due to its low cost and high accuracy in comparison with intravascular imaging, representing a more cost-effective technique. In this application, axial CT datasets are digitally processed to extract the geometric contours of the coronary tree and the corresponding segments with atheromatous plaques [27].

One major advantage of CFD analysis is the possibility to provide reliable information

about the hemodynamic changes occurring in the blood vessels even before atherosclerotic plaques are well constituted [28].

ESS is largely influenced by coronary artery blood flow, blood viscosity and arterial geometry [29]. At the downstream and upstream levels of coronary obstructions, flow becomes disturbed and ESS is altered in the sense that it becomes either high or low. Important, low and oscillatory ESS is characterized by bidirectional flow (including reverse flow) and represents a major factor promoting atherosclerosis [29]. Using CFD, Sun *et al.*, demonstrated that wall pressure was decreased at the site of the maximum stenosis in significant stenotic lesions, while post-stenotic sites exhibited increased flow velocities and flow turbulence [30].

In a larger study on 81 patients, CFD was applied on 114 lesions in order to calculate axial plaque stress (APS) and correlate it with lesion geometry. The authors found that APS, a different kind of stress than the ESS, has a close relationship with lesion geometry, being higher in the upstream segment of the upstream dominant lesions ($11.3 \pm 5.5 \text{ dyne/cm}^3$ vs $6.8 \pm 4.3 \text{ dyne/cm}^3$, $p < 0.0001$) and in the downstream segment of the downstream dominant lesions ($7.6 \pm 4.5 \text{ dyne/cm}^3$ vs $11.9 \pm 5.5 \text{ dyne/cm}^3$, $p < 0.0001$), even in the absence of any difference between upstream and downstream lesions in terms of CT-FFR or percentage of stenosis [24].

However, as computational fluid dynamics techniques are time consuming, they cannot serve as efficient clinical decision tools in clinical settings.

ESS and plaque vulnerability

The favorite places for development of atheromatous plaques are represented by bifurcations and the regions of entrance in the segments originating from bifurcations [31].

Several recent studies identified areas with low ESS in the close vicinity of unstable coronary plaques [32]. At the same time, other studies suggested that rather than the low ESS, the high ESS could represent the factor triggering plaque vulnerability. However, conceptually speaking, while the conclusions of these studies are divergent in relation to what kind of alteration (high or low SS) is detrimental for the coronary plaque, all of them recognize the role of alteration of intracoronary mechanical forces in development and progression of a VP.

One possible explanation for the differences recorded in different studies on ESS is that high ESS is considered to have atheropro-

protective effects in healthy arteries, however high ESS associated with atherosclerotic lesions can accentuate plaque vulnerability. The fact that the rupture of a coronary plaque usually occurs at the shoulders of the plaques, an area where the perturbation of haemodynamic forces is highest, proves the role of local elevations of ESS in triggering plaque rupture. At the same time, the areas characterised by an abrupt transition from high ESS to low ESS or opposite could be in fact the most vulnerable zones where plaque rupture occurs. Even if there is a large debate on the role of low versus high ESS in driving plaque vulnerability, a large set of evidence suggests now that ESS represents a major instigator to endothelial injury which in turn triggers plaque rupture [13,33,34,35].

In an experimental study on ApoE^{-/-} mice, in whom a cuff was placed around the carotid artery, regions located upstream of the cuff exhibited significant changes in ESS whereas segments located in the downstream area of the cuff exhibited changes in both ESS and direction [36]. Exposure of endothelial cells to low ESS lead to cell misalignment, allowing penetration by inflammatory mediators [37,38,39]. At the same time, mechanotransduction of ESS stimulated the release of bioactive mediators and micro-RNA synthesis [40].

In a study on 146 non-culprit lesions, Vergallo *et al* showed that compared with segments with higher ESS, those with low ESS had a higher prevalence of lipid-rich plaques, a thinner fibrous cap, a higher prevalence of thin-cap fibroatheroma and a higher content in macrophages [6]. At the same time, in a study by Hetterich *et al.*, a small number of 7 patients underwent CTA followed by IVUS analysis and CFD calculation of ESS. Similarly to the results of our study, the authors showed that areas exposed to low ESS as well as in those exposed to high ESS plaque prevalence was significantly higher than in the areas exposed to low-to-intermediate ESS, demonstrating a close association between ESS pattern and atheromatous plaque distribution within the coronary tree [27].

CTA seems to indicate the role of high ESS in driving plaque vulnerability while intracoronary imaging seems to support the hypothesis of low ESS as determinant of plaque vulnerability. However, we should not forget that CTA studies were carried out on a significantly higher number of patients than IVUS or OCT studies, in which the study lots were extremely low (cca 20 patients in each study). Therefore we should interpret with cautions the results of IVUS/OCT study and we should wait for data on larger number of patients.

Prognostic value of ESS

The idea that ESS can play a role in plaque vulnerability has been very nicely demonstrated by Stone *et al*, who showed that plaque progression occurred almost exclusively in areas of low ESS and can be associated with positive or negative remodeling [41,42].

In a substudy of the PROSPECT trial, Stone *et al* showed that lesions which did not exhibit local low ESS at baseline were not associated with any CV event in the follow-up, demonstrating that ESS added to other morphologic characteristics provides substantial incremental value for characterisation of atheromatous plaques and associated risks [43]. PREDICTION study was another landmark trial which demonstrated that an association between a low ESS and a large plaque burden at baseline predicted significant plaque progression in 10 months [35]. Both studies were IVUS based studies which included population with stable coronary artery disease, therefore they were not included in this analysis. In the light of these two landmark trials corroborated with the results of this systematic review, it would be interesting to study whether low ESS, rather than being associated with simple presence of vulnerability features in an unstable plaque, is associated with progression of plaques with a stable phenotype, leading to plaque transformation, change of plaque phenotype and vulnerability, which in turn augments the ESS.

Conclusions

In conclusion, coronary ESS plays a significant role in atheromatous plaque vulnerability and alteration of the ESS, easily depicted by imaging techniques and CFD, can indicate the risk to suffer an acute coronary event in a close future. However, the exact mechanisms by which ESS acts and the exact role played by the high ESS or low ESS at different areas surrounding the plaque, in triggering plaque rupture, requires further investigations.

References

1. Benedek T. The Link between Periodontal Disease, Inflammation and Atherosclerosis-an Interdisciplinary Approach. *Journal of Interdisciplinary Medicine* 2017;2:11-16
2. Zahnd G, Schrauwen J, Karanasos A, Regar E, Niessen W, Walsum T, et al. Fusion of fibrous cap thickness and wall shear stress to assess plaque vulnerability in cor-

- onary arteries: a pilot study. *Int J Comput Assist Radiol Surg* 2016;11:1779–1790
3. Nyulas T, Chițu M, Mester A, Jáni L, Condea S, Opincariu D, et al. Computed Tomography Biomarkers of Vulnerable Coronary Plaques. *Journal of Interdisciplinary Medicine* 2016;1:263-266
4. Benedek T, Mester A, Benedek A, Rat N, Opincariu D, Chițu M. Assessment of Coronary Plaque Vulnerability in Acute Coronary Syndromes using Optical Coherence Tomography and Intravascular Ultrasound. A Systematic Review. *Journal of Cardiovascular Emergencies* 2016;2:173-184
5. Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol* 2007;50:319-326
6. Vergallo R, Papafaklis MI, Yonetsu T, Bourantas CV, Andreou I, Wang Z, et al. Endothelial shear stress and coronary plaque characteristics in humans: combined frequency-domain optical coherence tomography and computational fluid dynamics study. *Circ Cardiovasc Imaging* 2014;7:905-911
7. Papafaklis MI, Takahashi S, Antoniadis AP, Coskun AU, Tsuda M, Mizuno S, et al. Effect of the local hemodynamic environment on the de novo development and progression of eccentric coronary atherosclerosis in humans: insights from PREDICTION. *Atherosclerosis* 2015;240:205-211
8. Hung O, Molony D, Corban MT, Rasoul Arzumly E, Maynard C, Eshtehardi P, et al. Comprehensive Assessment of Coronary Plaque Progression With Advanced Intravascular Imaging, Physiological Measures, and Wall Shear Stress: A Pilot Double Blinded Randomized Controlled Clinical Trial of Nebivolol Versus Atenolol in Non-obstructive Coronary Artery Disease. *J Am Heart Assoc* 2016;5:e002764
9. Yamamoto E, Siasos G, Zaromytidou M, Coskun AU, Xing L, Bryniarski K, et al. Low Endothelial Shear Stress Predicts Evolution to High-Risk Coronary Plaque Phenotype in the Future: A Serial Optical Coherence Tomography and Computational Fluid Dynamics Study. *Circ Cardiovasc Interv* 2017;10:e005455
10. Timmins LH, Molony DS, Eshtehardi P, McDaniel MC, Oshinski JN, Giddens DP, et al. Oscillatory wall shear stress is a dominant flow characteristic affecting lesion progression patterns and plaque vulnerability in patients with coronary artery disease. *J R Soc Interface* 2017;14:20160972
11. Liu X, Wu G, Xu C, He Y, Shu L, Liu Y, et al. Prediction of coronary plaque progression using biomechanical factors and vascular characteristics based on computed tomography angiography. *Comput Assist Surg (Abingdon)* 2017;22:286-294
12. Fukumoto Y, Hiro T, Fujii T, Hashimoto G, Fujimura T, Yamada J, et al. Localized elevation of shear stress is related to coronary plaque rupture: a 3-dimensional intravascular ultrasound study with in-vivo color mapping of shear stress distribution. *J Am Coll Cardiol* 2008;51:645-650
13. Corban MT, Eshtehardi P, Suo J, McDaniel MC, Timmins LH, Rassoul-Arzumly E, et al. Combination of plaque burden, wall shear stress, and plaque phenotype has incremental value for prediction of coronary atherosclerotic plaque progression and vulnerability. *Atherosclerosis* 2014;232:271-276
14. Park JB, Choi G, Chun EJ, Kim HJ, Park J, Jung JH, et al. Computational fluid dynamic measures of wall shear stress are related to coronary lesion characteristics. *Heart* 2016;102:1655–1661
15. Han D, Starikov A, Ó Hartaigh B, Gransar H, Kolli KK, Lee JH, et al. Relationship Between Endothelial Wall Shear Stress and High-Risk Atherosclerotic Plaque Characteristics for Identification of Coronary Lesions That Cause Ischemia: A Direct Comparison With Fractional Flow Reserve. *J Am Heart Assoc* 2016;5:e004186
16. Stefanadis C, Antoniou CK, Tsiachris D, Pietri P. Coronary Atherosclerotic Vulnerable Plaque: Current Perspectives. *J Am Heart Assoc* 2017;6:e005543
17. Martu S, Nicolaiciuc O, Solomon S, Sufaru I, Scutariu, M, Rezus C, et al. The Evaluation of the C Reactive Protein Levels in the Context of the Periodontal Pathogens Presence in Cardiovascular Risk Patients. *Revista de Chimie* 2017;68:1081-1084
18. Ueda Y, Ogasawara N, Matsuo K, Hirotani S, Kashiwase K, Hirata, et al. Acute coronary syndrome: insight from angioscopy. *Circ J* 2010;74:411-417
19. Park JB, Choi G, Chun EJ, Kim HJ, Park J, Jung JH. Computational fluid dynamic measures of wall shear stress are related to coronary lesion characteristics. *Heart* 2016;102:1655-1661
20. Benedek T, Gyöngyösi M, Benedek I. Multislice computed tomographic coronary angiography for quantitative assessment of culprit lesions in acute coronary syn-

- dromes. *Can J Cardiol* 2013;29:364-371
21. Benedek T, Jako B, Benedek I. Plaque quantification by coronary CT and intravascular ultrasound identifies a low CT density core as a marker of plaque instability in acute coronary syndromes. *Int Heart J* 2014;55:22-28
22. Stone, GW, Maehara A, Lansky AJ. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011;364:226-235
23. Yamamoto H, Kitagawa T, Ohashi N, Utsunomiya H, Kunita E, Oka T, et al. Noncalcified atherosclerotic lesions with vulnerable characteristics detected by coronary CT angiography and future coronary events. *J Cardiovasc Comput Tomogr* 2013;7:192-199
24. Choi G, Lee JM, Kim HJ, Park JB, Sankaran S, Otake H, et al. Coronary Artery Axial Plaque Stress and its Relationship With Lesion Geometry: Application of Computational Fluid Dynamics to Coronary CT Angiography. *JACC Cardiovasc Imaging* 2015;8:1156-1166
25. Nørgaard BL, Leipsic J, Koo BK, Zarins CK, Jensen JM, Sand NP, et al. Coronary Computed Tomography Angiography Derived Fractional Flow Reserve and Plaque Stress. *Curr Cardiovasc Imaging Rep* 2016;9:2
26. Szilágyi SM, Popovici MM, Szilágyi L. Automatic Segmentation Techniques of the Coronary Artery Using CT Images in Acute Coronary Syndromes. *Journal of Cardiovascular Emergencies* 2017;3:9-17
27. Hetterich H, Jaber A, Gehring M, Curta A, Bamberg F, Filipovic N, et al. Coronary computed tomography angiography based assessment of endothelial shear stress and its association with atherosclerotic plaque distribution in-vivo. *PLoS One* 2015;10:e0115408
28. Sun Z. Coronary CT angiography: Beyond morphological stenosis analysis. *World J Cardiol* 2013;5:444-452
29. Zaromytidou M, Siasos G, Coskun AU, Lucier M, Antoniadis AP, Papafaklis MI, et al. Intravascular hemodynamics and coronary artery disease: New insights and clinical implications. *Hellenic J Cardiol* 2016;57:389-400
30. Sun Z, Chaichana T. Computational fluid dynamic analysis of calcified coronary plaques: correlation between hemodynamic changes and cardiac image analysis based on left coronary bifurcation angle and lumen assessments. *Interv Cardiol* 2016;8:713-719
31. Jin S, Yang Y, Oshinski J, Tannenbaum A, Gruden J, Giddens D. Flow patterns and wall shear stress distributions at atherosclerotic-prone sites in a human left coronary artery-an exploration using combined methods of CT and computational fluid dynamics. *Conf Proc IEEE Eng Med Biol Soc* 2004;5:3789-3791
32. Benedek A. Intracoronary Shear Stress and CT Characteristics of Vulnerable Coronary Plaques. *Journal of Interdisciplinary Medicine* 2017;2:242-244
33. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA* 1999;282:2035-2042
34. Gimbrone MA Jr, Topper JN, Nagel T, Anderson KR, Garcia-Cardena G. Endothelial dysfunction, hemodynamic forces, and atherogenesis. *Ann N Y Acad Sci* 2000;902:230-239
35. Stone PH, Saito S, Takahashi S, Makita Y, Nakamura S, Kawasaki T, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION Study. *Circulation* 2012;126:172-181
36. Pedrigi RM, Mehta VV, Bovens SM, Mohri Z, Poulsen CB, Gsell W, et al. Influence of shear stress magnitude and direction on atherosclerotic plaque composition. *R Soc Open Sci* 2016; 3:160588
37. Staughton TJ, Lever MJ, Weinberg PD. Effect of altered flow on the pattern of permeability around rabbit aortic branches. *Am J Physiol Heart Circ Physiol* 2001;281:H53-H59
38. Cancel LM, Tarbell JM. The role of apoptosis in LDL transport through cultured endothelial cell monolayers. *Atherosclerosis* 2010;208:335-341
39. Kang H, Cancel LM, Tarbell JM. Effect of shear stress on water and LDL transport through cultured endothelial cell monolayers. *Atherosclerosis* 2014;233:682-690
40. Thondapu V, Bourantas CV, Foin N, Jang IK, Serruys PW, Barlis P. Biomechanical stress in coronary atherosclerosis: emerging insights from computational modelling. *Eur Heart J* 2017;38:81-92
41. Stone PH, Coskun AU, Kinlay S, Popma JJ, Sonka M, Wahle A, et al. Regions of low endothelial shear stress are the sites where coronary plaque progresses and vascular remodelling occurs in humans: an in vivo serial study. *Eur Heart J* 2007;28:705-710
42. Stone PH, Coskun AU, Kinlay S, Clark ME, Sonka M, Wahle A, et al. Effect of endo-

- thelial shear stress on the progression of coronary artery disease, vascular remodeling, and in-stent restenosis in humans: in vivo 6-month follow-up study. *Circulation* 2003;108:438-444
43. Stone PHMA, Coskun AU, Maynard C, Andreou I, Siasos G. Local Low Endothelial Shear Stress (ESS) Provides Incremental Prediction of Non-culprit MACE in Addition to Plaque Burden, Minimal Lumen Area, and Plaque Morphology: The PROSPECT Study. *J Am Coll Cardiol* 2015;66