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Coronary artery plaque rupture and erosion: Role of wall shear stress profiling and biological patterns in acute coronary syndromes

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ABSTRACT

Aims: Wall shear stress (WSS) is involved in coronary artery plaque pathological mechanisms and modulation of gene expression. This study aims to provide a comprehensive haemodynamic and biological description of unstable (intact-fibrous-cap, IFC, and ruptured-fibrous-cap, RFC) and stable (chronic coronary syndrome, CCS) plaques and investigate any correlation between WSS and molecular pathways.

Methods and results: We enrolled 24 CCS and 25 Non-ST Elevation Myocardial Infarction-ACS patients with IFC ($n = 11$) and RFC ($n = 14$) culprit lesions according to optical coherence tomography analysis. A real-time PCR primer array was performed on peripheral blood mononuclear cells for 17 different molecules whose expression is linked to WSS. Computational fluid dynamics simulations were performed in high-fidelity 3D-coronary artery anatomical models for three patients per group.

A total of nine genes were significantly overexpressed in the unstable patients as compared to CCS patients, with no differences between IFC and RFC groups (GPX1, MMP1, MMP9, NOS3, PLA2G7, PI16, SOD1, TIMP1, and TFRC) while four displayed different levels between IFC and RFC groups (TNFα, ADAMTS13, EDN1, and LGALS8). A significantly higher WSS was observed in the RFC group ($p < 0.001$) compared to the two other

Abbreviations: ACS, Acute Coronary Syndrome; ADAMTS13, a disintegrin and metallopeptidase with thrombospondin type 1 motif 13; CCS, Chronic Coronary Syndrome; CFD, Computational Fluid Dynamics; EDN1, Endotelin-1; GPX1, Glutathione peroxidase 1; Hs CRP, High-Sensitive C-Reactive Protein; ICAM, Intercellular Adhesion Molecule; IFC, Intact Fibrous Cap; LGALS8, Galectin 8; MMPs, Matrix metalloproteases; NO, Nitric oxide; NOS3, Nitric oxide synthase3; NSTEMI, Non-ST Elevation Myocardial Infarction; OCT, Optical Coherence Tomography; PBMCs, Peripheral Blood Mononuclear Cells; PI16, Peptidase inhibitor 16; PLA1G7, Phospholipase A2 Group VII; RFC, Ruptured Fibrous Cap; SOD1, Superoxide dismutase 1; TFRC, Transferrin Receptor; TIMP, Tissue inhibitor of metalloproteinases 1; TNFα, Tumor necrosis factor α; VEGFA, Vascular Endothelial Growth Factor A; WSS, Wall Shear Stress.

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groups. A significant correlation was observed between TNFα ($p < 0.001$), EDN1 ($p = 0.036$), and MMP9 ($p = 0.005$) and WSS values in the RFC group.
Conclusions: Our data demonstrate that IFC and RFC plaques are subject to different WSS conditions and gene expressions, suggesting that WSS profiling may play an essential role in the plaque instability characterization with relevant diagnostic and therapeutic implications in the era of precision medicine.

1. Introduction

Pathophysiologic mechanisms underlying acute coronary syndromes (ACS) have not been fully identified, yet [1,2]. Frequently, ACS represents the final clinical presentation via alternative mechanisms leading to different culprit plaque morphologies: plaque rupture, plaque erosion, and calcified nodules [3–5],. Plaque rupture is the most common aetiology for ACS, followed by plaque erosion, accounting for at least one-third of ACS cases, while calcified nodules account for only 5–8%. Meanwhile, pharmacologic interventions, such as intensive lipid-lowering strategy, might alter the features of unstable plaques, from plaque rupture to erosion [6,7]. So far, cross-sectional histopathology studies and, more recently, optical coherence tomography (OCT) have provided a detailed description of coronary artery plaques, thus allowing differentiation of plaque phenotypes and a definition of vulnerable plaques [8,9].

Alongside morphological features of plaques prone to rupture, different biological signatures for plaque erosion and plaque rupture have been described [10]. Such data suggested that 1) similar clinical presentations in ACS might have not only different morphological features as shown by OCT, but also different molecular mechanisms, and that 2) some molecules might represent useful tools for the differential diagnosis between eroded and ruptured plaques. However, the triggers underpinning the evolution of the different fates of coronary plaques are not well defined, yet. Molecular mediators are only responsible for the sequence of events leading to different culprit plaque phenotypes, and other factors might be involved. Local alteration of wall shear stress (WSS) has been proposed as a biomechanical trigger predisposing to endothelial cell damage and detachment in plaque erosion [7]. *Post-mortem* and in vivo studies suggested that both erosions and ruptures occur more frequently in the proximal and mid segments of the coronary arteries, with a prevalence of erosion in the left anterior descending artery and coronary bifurcation and a prevalence of rupture in the right coronary artery [11,12]. These differences were ascribed to regional flow disturbances, which might precede and/or influence the progression and fate of atherosclerotic plaques.

In this perspective, image-based computational fluid dynamics (CFD) has enriched the available tools for intracoronary analysis over the last few years. The addition of WSS data has contributed to a better understanding of some pathophysiological mechanisms underlying early and advanced phases of atherosclerosis [13,14]. Indeed, several studies have suggested the role of WSS in plaque progression, composition and destabilisation in coronary arteries [15–17]. Regional haemodynamics changes of WSS may affect cell morphology, metabolism and inflammatory phenotype through signal transduction and endothelium-dependant gene and protein expression [18]. Moreover, several blood-circulating molecules have been demonstrated to be tightly regulated by WSS conditions including mediators of inflammation, cellular adhesion, thrombus formation, immunomodulation, and vasomotility (references for Table 2 in Supplementary Materials).

To date, only a few studies have investigated the relationship between WSS and different plaque phenotypes. Furthermore WSS and biological characteristics have been mainly described with in vitro or animal models (references for Table 2 in Supplementary Materials). Currently, in vivo combined description of haemodynamic and biological features in human eroded (intact fibrous cap, IFC) and ruptured (ruptured fibrous cap, RFC) plaques are lacking. Therefore, this study aims to describe the WSS and molecular patterns of stable (chronic coronary syndromes, CCS) and unstable (IFC and RFC) human coronary artery plaques, and to investigate whether any relationship between coronary WSS and biological data is present in the context of Non-ST Elevation Myocardial Infarction (NSTEMI-ACS).

2. Methods

2.1. Study design and population

This is a single-centre, prospective study (Fig. 1). Two groups of patients were consecutively enrolled: 1) patients with CCS defined by symptoms of stable effort angina lasting >12 months, angiographically confirmed coronary artery disease, no previous acute coronary events, and no overt ischaemic episodes during the previous 48 h ($n = 24$); 2) patients admitted to our Intensive Coronary Care Unit with the first diagnosis of ACS presenting with NSTEMI confirmed at coronary angiography ($n = 25$) [19,20]. The main exclusion criteria are listed in Supplementary Materials.

Table 1 summarizes the baseline characteristics, cardiovascular risk factors, angiographic features, echocardiographic findings, and medications at the time of enrolment. All patients underwent biological analysis of selected gene expression, Table 2. Nine patients underwent high-fidelity three-dimensional (3D) geometrical models of coronary artery reconstruction by using angiographic and OCT data (Supplementary Fig. 1). Methods are detailed in Methods Supplementary Material.

The study complies with the Declaration of Helsinki. All patients gave their written informed consent. The Ethics Committee of the *Fondazione Policlinico Universitario "A. Gemelli" IRCCS - Catholic University of Sacred Heart of Rome* approved the study.

3. Results

3.1. Study population

A total of 49 patients were included in the study, as shown in Fig. 1. None of the patients included in the study had prior coronary artery events. Medications reported in Table 1 refer to those at time of blood samples. In the CCS group a significantly higher number of patients took aspirin, beta-blockers and statins for primary prevention while no differences were observed for the remaining drugs. With regards to baseline laboratory values, only erythrocyte sedimentation rate and C-reactive protein were higher in the NSTEMI-ACS groups.

3.2. Biological analysis

Target gene validation showed significantly different expressions across the three groups for the following 13 molecules: ADAMTS13, EDN1, GPX1, LGALS8, MMP1, MMP9, NOS3, PLA2G7, PI16, SOD1, TFRC, TIMP1, TNFα. No significant difference was observed for CD31, CD44, ICAM1, and VEGF gene expression (Supplementary Table 2).

A total of nine genes were significantly overexpressed in the unstable patients as compared to CCS patients, with no differences between IFC and RFC group: GPX1 ($p = 0.001$ for three groups comparison), MMP1 ($p = 0.019$), MMP9 ($p = 0.001$), NOS3 ($p < 0.001$), PLA2G7 ($p = 0.003$), PI16 ($p < 0.001$), SOD1 ($p < 0.001$), TIMP1 ($p < 0.001$), and TFRC ($p = 0.009$) (Fig. 2, panels A-I).

IFC patients showed the highest gene levels of LGALS8 if compared

to both CCS ($p < 0.001$) and RFC ($p = 0.032$), with RFC also expressing higher gene levels of the molecule if compared to CCS ($p < 0.001$) (p < 0.001 for three groups comparison) (Fig. 3A). Moreover, IFC expressed significantly higher levels of EDN1 if compared to both CCS ($p = 0.002$) and RFC ($p = 0.05$), with no differences between CCS and RFC (p = 0.002 for three groups comparison) (Fig. 3B). Regarding RFC, we found a significantly higher gene expression of ADAMTS13 compared to both CCS ($p < 0.001$) (Fig. 3C) and IFC ($p = 0.04$) (p < 0.001 for three groups comparison), and a significantly lower gene expression of TNFα compared to both CCS ($p = 0.016$) and IFC (p = 0.05), with no difference between CCS and IFC (p = 0.002 for three groups comparison) (Fig. 3D).

3.3. Wall shear stress profiling

The WSS distribution assessed on the entire lesion segment was significantly different among the three plaque categories ($p < 0.001$, Fig. 4A and Supplementary Fig. 5). In particular, the RFC group presented a higher WSS median value as compared to the other two groups (3.3 Pa for the RFC lesions versus 1.9 Pa and 2.5 Pa for the CCS and IFC lesions, respectively, p < 0.001 in the pairwise analysis) (Fig. 4A). Furthermore, the RFC group exhibited a larger WSS IQR (7.6 Pa for the RFC lesions versus 2.4 Pa and 3.0 Pa for the CCS and IFC lesions, respectively), suggesting that the lumen was locally exposed to a wider and more heterogeneous distribution of WSS values (Fig. 4A).

At the segmental level (Figs. 4B-F), the RFC group presented WSS values higher than CCS and IFC groups in the lesion's mid, distal, and downstream segments. Marked differences were observed at the mid segment of the lesion, where the RFC cases presented the highest WSS median value and the largest IQR with respect to the other two categories (7.4 Pa (IQR: 16.5 Pa) for the RFC lesions versus 4.0 Pa (IQR: 4.2 Pa) and 3.3 Pa (IQR: 2.4 Pa) for the CCS and IFC lesions, respectively, $p < 0.001$). Furthermore, the RFC cases were characterized by the maximum WSS value as compared to CCS and IFC groups (539.3 Pa versus 94.4 Pa and 36.0 Pa, respectively).

Although plaque morphology was different among the three groups, not significantly different area stenosis and minimum lumen area was observed (Supplementary Figure and Supplementary Table 3).

Differences between the three plaque morphologies also emerged from the analysis of the lumen areas exposed to low or high WSS (Figs. 5.1 and 5.2, respectively). At a global level, the RFC lesions presented a larger lumen area exposed to low WSS compared to the other lesion categories, with a value of 5.8 ± 1.4% for the RFC lesions versus 1.9 ± 1.4% and 3.9 ± 3.0% for the CCS and IFC lesions, respectively (Fig. 5.1 A). A similar trend emerged at the segmental level (Figs. 5.1 B—F), except for the segment downstream of the lesion, which presented similar values for all lesion categories (Fig. 5.1 E). Of note, the RFC lesions also presented a higher percentage of area exposed to high WSS (22.4% ± 10.3%) compared to the other lesion categories (10.3% ± 15.5% and 5.5% ± 8.0% for the CCS and IFC lesions, respectively, as reported in Fig. 5.2 A). This trend was also confirmed at the segmental level, particularly in the mid, distal and downstream segments (Figs. 5.2 D—F).

3.4. Link between biology and wall shear stress profiling

The trends emerging from the analysis of biological and WSS patterns suggest that some genes are differently expressed in patients with unstable and CCS plaques, depending on different (high or low) WSS distributions at the luminal surface (Figs. 2 and 3). Within unstable patients (IFC and RFC), biological results hint at an overexpression of ADAMTS13 under higher WSS conditions (RFC), while LGALS8, EDN1, and TNFα expression is higher under lower WSS values, as observed in the IFC group. Such qualitative observations might be limited by: 1) the lack of univocal definition of low and high WSS cut-off; 2) the susceptibility of some molecules to both low and high WSS. Bearing in mind the limited number of patients with CFD data available ($n = 9$), a significant correlation was found in the RFC group between WSS and TNFα ($p < 0.001$, $R = 0.9$), EDN1 ($p = 0.036$, $R = -0.4$) and MMP9 ($p = 0.005$, $R = 0.7$). In contrast, no correlation was found in the CCS and IFC groups, thus suggesting a possible role of coronary patterns of WSS in the molecular pathways of ACS patients presenting with plaque rupture.

4. Discussion

This is the first study investigating: 1) WSS and molecular patterns among stable patients and unstable (NSTEMI-ACS) patients with different plaque morphologies (IFC and RFC); 2) a possible link between coronary WSS and molecular patterns in patients with three different plaque phenotypes (CCS, IFC, RFC).

The findings of this study indicate that WSS is different among the CCS, IFC, and RFC plaques, with the latter showing higher levels of WSS and with IFC plaques having an intermediate WSS value between CCS

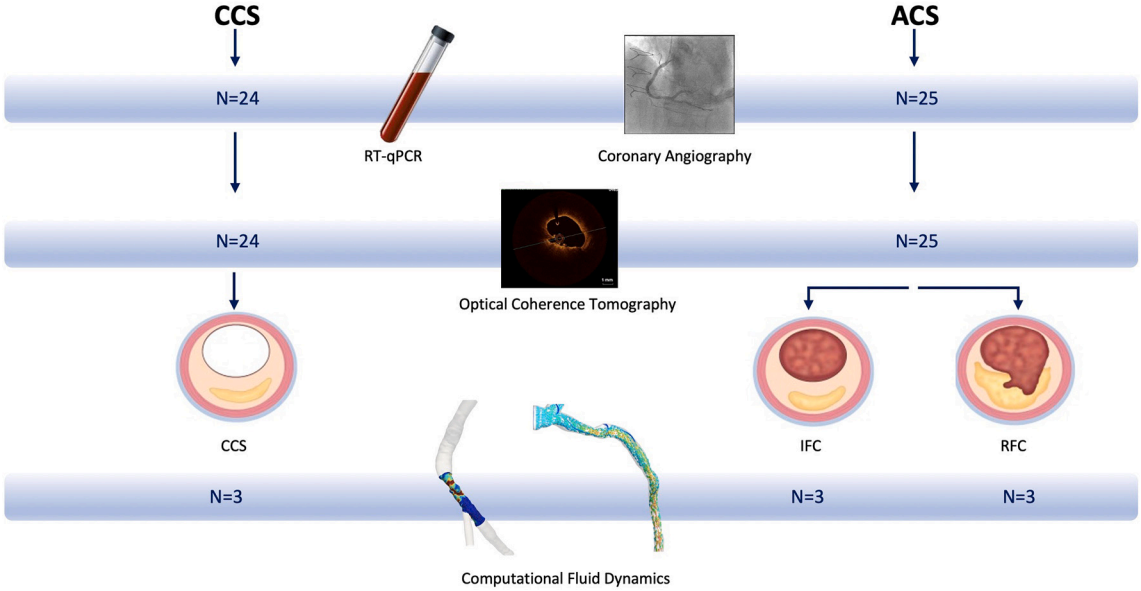


Fig. 1. Study design. CCS: chronic coronary syndrome; IFC: intact fibrous cap; RFC: ruptured fibrous cap.

Table 1
Baseline characteristics of the study population.

	CCS N = 24	IFC N = 11	RFC N = 14	*p* Value
Age, mean ± SD	69 ± 9	59 ± 11	58 ± 13	0.005*,°
Gender, M/F	20/4	9/2	12/2	0.964
CV Risk Factors, n (%)				
Smoke	10 (42)	8 (73)	5 (36)	0.141
Diabetes	5 (21)	0 (0)	5 (36)	0.089
Hypertension	21 (88)	6 (55)	10 (71)	0.100
Dyslipidaemia	18 (75)	5 (46)	6 (43)	0.087
Family history	10 (42)	3 (27)	6 (43)	0.672
Medical Therapy, n (%)				
DAPT	9 (39)	5 (55)	5 (36)	0.602
ASA	22 (96)	5 (55)	7 (50)	0.003*,°
Clopidogrel	7 (30)	3 (27)	1 (7)	0.243
Prasugrel	1 (4)	1 (9)	1 (7)	0.855
Ticagrelor	1 (4)	4 (36)	3 (21)	0.055
Anticoagulants	1 (4)	1 (9)	1 (7)	0.855
Beta-Blockers	18 (78)	5 (46)	4 (29)	0.009
Diuretics	6 (26)	2 (18)	2 (14)	0.672
ACE-I	6 (26)	2 (18)	4 (29)	0.826
ARBs	11 (48)	3 (27)	6 (43)	0.521
Statins	20 (87)	5 (46)	5 (36)	0.003*,°
Ca-antagonists	2 (9)	3 (27)	2 (14)	0.356
Nitrates	3 (13)	0 (0)	0 (0)	0.176
Insulin	2 (9)	0 (0)	0 (0)	0.322
Oral antidiabetic	2 (9)	0 (0)	2 (14)	0.438
Lab Values, mean ± SD				
Tn I, ng/ml	0.02 ± 0.06	787 ± 1970	511 ± 1062	0.134
Hb, g/dl	14.2 ± 1.6	13.9 ± 1.5	14.5 ± 1.9	0.651
WBC, x10^3/ml	7.1 ± 2.0	8.7 ± 4.2	8.4 ± 3.6	0.247
Platelet, x10^3/ml	217 ± 49	222 ± 47	227 ± 43	0.409
Lymphocytes, x10^9/l	2.3 ± 2.0	1.9 ± 1.0	2.0 ± 1.3	0.814
Glycemia, mg/dl	106 ± 26	104 ± 26	117 ± 32	0.447
Creatinine, mg/dl	0.9 ± 0.1	0.9 ± 0.4	0.7 ± 0.3	0.205
Cholesterol, mg/dl	153 ± 33	160 ± 30	167 ± 60	0.642
LDL, mg/dl	82 ± 28	103 ± 28	108 ± 45	0.122
HDL, mg/dl	48 ± 16	36 ± 11	37 ± 8	0.06
Triglycerides, mg/dl	114 ± 46	135 ± 25	143 ± 40	0.174
ESR, mm/h	10 ± 8	10 ± 8	35 ± 25	0.003
hs-CRP, mg/l	1.9 ± 3.0	10.0 ± 7.4	9.7 ± 5.2	0.001*,°

Data refer to the time of patient enrollment and blood withdrawal.
CCS: chronic coronary syndrome; IFC: intact fibrous cap; RFC: ruptured fibrous cap; CV: cardiovascular; DAPT: dual antiplatelet therapy; ASA: aspirin; ACE—I: ACE inhibitors; ARBs: angiotensin II receptor blockers; WBC: white blood cell; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.
* SA vs IFC: $p \leq 0.05$.
° SA vs RFC: $p \leq 0.05$.

Table 2
Function and WSS effect on expression of investigated genes.

GENE	Specific Function	Effect of WSS on expression/function
ADAMTS13	Cleavage of vWF; regulation of blood clotting	Up-regulated under high and very high WSS [1]
CD31	Leukocyte migration, angiogenesis, immunomodulation, mechano-transduction	Activated by WSS [2]
CD44	Cell-cell interactions, cell adhesion and migration, hyaluronan receptor	Increased hyaluronan binding under WSS [3]
EDN1	Vasomotility, vasoconstriction	Down-regulated under high WSS [4,5]
GPX1	Antioxidant enzyme; redox-balancer	Up-regulated under high WSS [6]
ICAM1	Cell proliferation, differentiation, trafficking, apoptosis and tissue architecture	Up-regulated under high WSS [7]
LGALS8	Cell adhesion, cell-matrix interaction, growth, apoptosis, and RNA splicing	Activated under high WSS [8]
MMP1	ECM and molecule degradation	Up-regulated under high WSS [9,10]
MMP9	ECM and molecule degradation; leukocyte migration; inflammation	Up-regulated under high WSS [11,12]
NOS3	Vascular smooth muscle relaxation	Up-regulated under high WSS [13–15]
PI16	Inhibition of cardiomyocyte growth, MMP inhibition	Up-regulated under high WSS [16]
PLA2G7	Modulation of platelet-activating factor (PAF) activity	Up-regulated under high WSS [17,18]
SOD1	Destruction of superoxide anion radicals	Down-regulated under oscillatory SS [19]
TFRC	Erythropoiesis and neurologic development	n.a.
TIMP1	Cell proliferation and potential an anti-apoptotic function, MMP inhibition	Up-regulated under high WSS [9]
TNFα	Inflammation, apoptosis, proliferation, differentiation, lipid metabolism	Up/down-regulated under high WSS [20–22]
VEGF	Proliferation and migration of vascular endothelial cells, angiogenesis	Up-regulated under low WSS [23,24]

ADAM metallopeptidase with thrombospondin type 1 motif 13, ADAMTS13; Cluster of differentiation, CD; Extracellular matrix, ECM; Endotelin-1, EDN1; Glutathione peroxidase 1, GPX1; Intercellular Adhesion Molecule 1, ICAM1; Galectin 8, LGALS8; Matrix metalloprotease, MMP; Nitric oxide synthase3, NOS3; Peptidase inhibitor 16, PI16; Phospholipase A2 Group VII, PLA2G7; Superoxide dismutase 1, SOD1; Transferrin Receptor, TFRC; Tissue inhibitor of metalloproteinases 1, TIMP1; Tumor necrosis factor α, TNFα; Vascular Cell Adhesion Molecule 1; VEGF; von-Willebrand Factor, vWF. See References for Table 2 in Supplementary Materials.

and RFC. The segmental analysis confirms such results. Although the most significant differences are concentrated at the mid-segment (corresponding to the minimum lumen area), the distal and the downstream segments show higher WSS in the RFC plaques compared to CCS and IFC.

Of interest, considering the plaque area exposed to low and high WSS, the patients belonging to RFC are the most subject to both low and high WSS with the widest, heterogeneous range of values as compared to IFC and CCS plaques. Indeed, >50% of the RFC plaque area is exposed to high WSS in the mid-segment, compared to <20% of CCS and IFC plaque areas.

The effect of WSS on coronary artery plaques has been widely investigated over the last years, and the attention has mainly focused on low WSS. The low WSS has been associated to plaque thickening, progression, increase in plaque and necrotic core area, thinner fibrous cap, endothelial dysfunction, negative remodelling and pro-inflammatory state [16,21–27].

Less well-defined is the role of high WSS. However, it has recently gained interest and has been investigated in several pathological mechanisms, including plaque erosion and rupture [28–31]. Multiple factors may be responsible for plaque rupture, including blood pressure and local geometry. Moreover, plaque tissue composition is another key determinant for cap strength and plaque resistance. Indeed, the thinnest areas of the fibrous cap are strictly correlated with the highest WSS areas and co-localise with macrophages infiltration, lipid accumulation, intraplaque hemorrhage and microcalcifications [32–35]. In this perspective, high WSS might be closely involved in plaque rupture as an active actor playing two different roles: directly as a biomechanical stressor "against" the plaque and indirectly making the plaque more vulnerable by changing its composition. Accordingly, our data suggest that detecting high WSS over a plaque might improve its identification as a vulnerable plaque before its rupture. Therefore, independently from WSS thresholds, the co-localization of high WSS and low plaque strength might be considered as a novel marker for the identification of vulnerable plaques. Consequently, WSS profiling, in addition to commonly used intracoronary imaging techniques, might play a crucial role in the differential diagnosis of culprit lesions and in the guidance of therapeutic strategies [36,37]. These results expand the recent EROSION III trial, showing the important clinical implications of different therapeutic strategies for IFC and RFC plaques [38].

In addition to describing WSS among different coronary artery plaques, this study moves a step forward in investigating molecular pathways and trying to find a possible link between WSS and gene expression in patients [39]. Indeed, this is the first in vivo study suggesting that different values of WSS correspond to different gene expressions (13

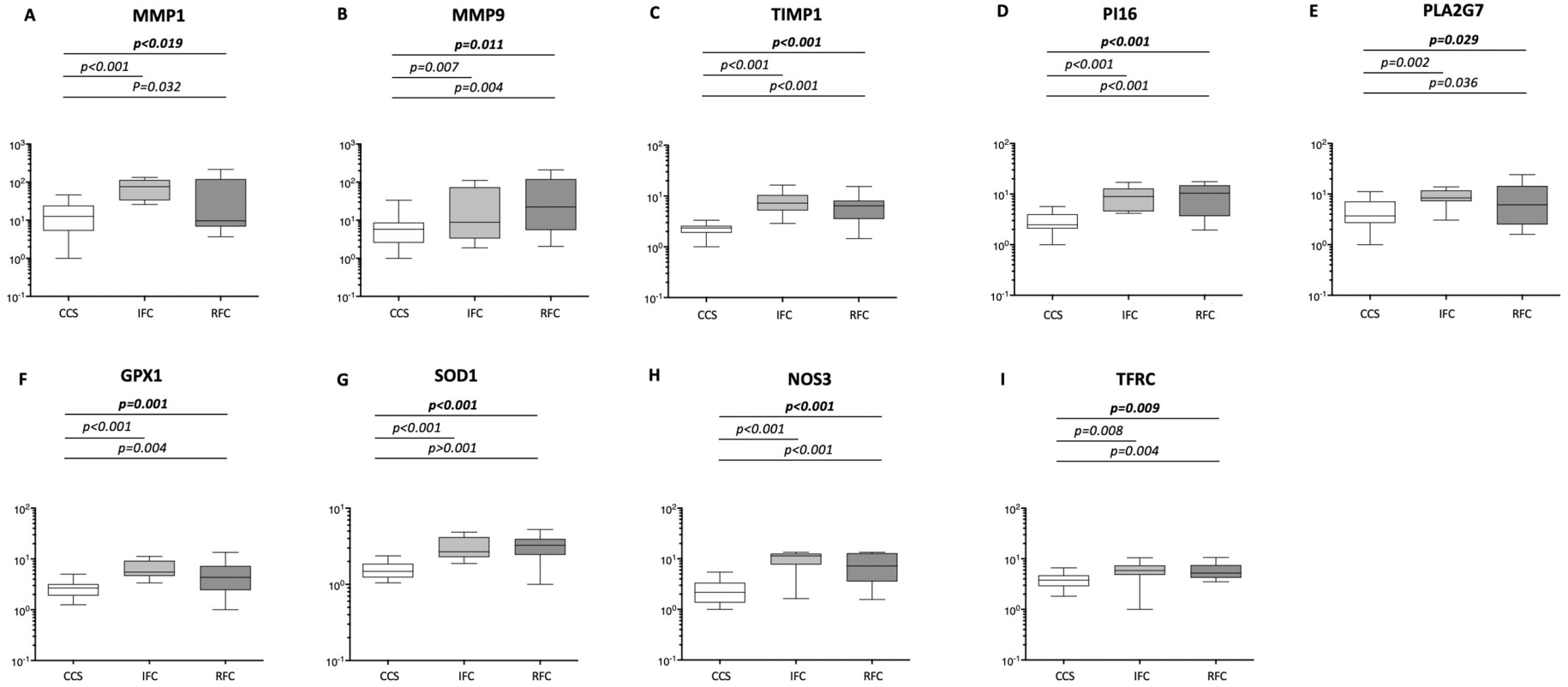


Fig. 2. Box plots showing the gene expression of MMP1 (A), MMP9 (B), TIMP1 (C), PI16 (D), PLA2G7 (E), GPX1 (F), SOD1 (G), NOS3 (H) and TFRC (I) on PBMCs assessed by RT-qPCR in stable (CCS), intact fibrous cap (IFC) and ruptured fibrous cap (RFC) groups. Distribution, median and interquartile range are displayed for each group.

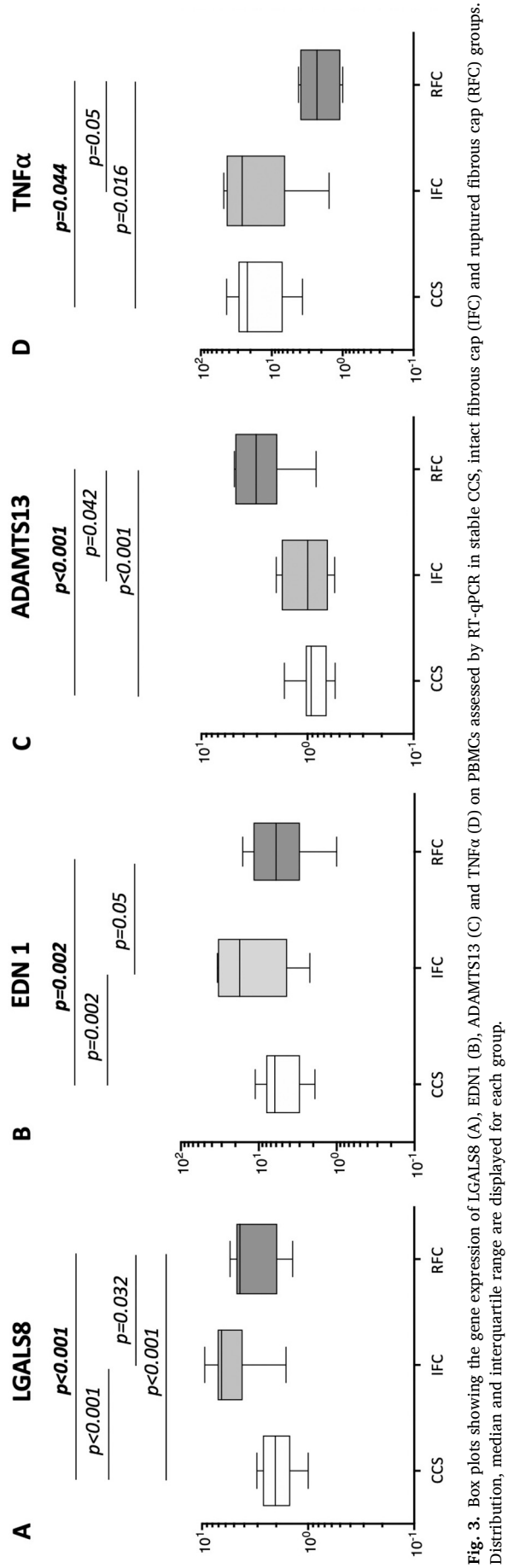


Fig. 3. Box plots showing the gene expression of LGALS8 (A), EDN1 (B), ADAMTS13 (C) and TNFα (D) on PBMCs assessed by RT-qPCR in stable CCS, intact fibrous cap (IFC) and ruptured fibrous cap (RFC) groups. Distribution, median and interquartile range are displayed for each group.

genes) across the three groups of patients.

Of note, four genes (EDN1, TNFα, ADAMTS13, and LGALS8) show a different expression also between IFC and RFC groups.

EDN1 acts as a potent vasoconstrictor of human coronary arteries, induces endothelial dysfunction, and inflammation and its locus are considered among the risk loci for coronary artery disease [40,41]. The effects of WSS on EDN1 are still controversial, although evidence suggests that its expression is dependent on the duration and level of WSS stimulus. Under low WSS conditions, there is an early increase of EDN1, probably through the activation of protein kinase C, whereas prolonged (≥6 h) stimulus with high WSS induces downregulation of EDN1 in primary cultures of human umbilical vein endothelial cells [42,43]. In the present study, the group with the highest WSS (RFC) showed lower EDN than other groups. Despite the small sample size, WSS was inversely correlated to EDN1, confirming the bimodal behaviour of WSS, consistent with previous experiments on human umbilical vein endothelial cells.

Similarly, upregulation of TNFα has been associated with both low and high WSS [44,45]. More recently, a time-dependent response has been described also for this inflammatory cytokine [46]. In our study, TNFα is higher in those groups with lower WSS, in line with previous data indicating an initial upregulation under low WSS conditions [45]. However, the lack of multiple assessments does not allow for establishing temporal trends in the expression of the investigated molecules. It might be hypothesised that TNFα levels would increase under prolonged high WSS conditions.

The role of WSS on ADAMTS13 and LGALS8 is less well-established, although both seem to be activated by high WSS (Table 2). In this study, the overexpression of ADAMTS13 (involved in the regulation of blood clotting), and the expressions of LGALS8, EDN1, and TNFα in the RFC group might be related to the acute event with thrombus formation.

The genes encoding for proteins involved in matrix breakdown (MMP1, MMP9) are more expressed in unstable patients as compared to stable ones, suggesting that the WSS pattern might be directly involved in plaque composition and fate [47,48]. At the same time, unstable patients also have a greater systemic expression of genes involved in anti-oxidant functions (GPX1, NOS3, SOD1) and other counter-regulatory mechanisms, such as the inhibition of platelet activation (PLA2G7) and of matrix degradation (TIMP, PI16).

These data suggest that WSS might be involved in the imbalance of the molecular mechanisms leading to extracellular matrix remodelling, cap thinning, and plaque instability (Fig. 6). In general, the significant differences among the selected genes known to be influenced by WSS support the hypothesis of a close link between coronary WSS and molecular pathways. These findings suggest that the identification of biological markers, associated with increased matrix degradation, might represent an adjunctive tool for the ACS patients' characterization. Finally, the significant association between WSS data and TNFα, MMP9, and EDN1 gene expression in the RFC group further strengthens our hypothesis: despite the small sample size, our findings suggest a prominent role of high WSS in the pathogenesis of plaque rupture, while in CCS and IFC also other molecular as well as biomechanical mechanisms and triggers should be taken into account, confirming recent findings [49].

This study demonstrates a close and complex relationship between WSS and molecular patterns for different types of unstable plaque. However, the correct time frame of events is still to be established in order to determine whether what we are looking at is the cause or the effect of plaque instability. Most likely, a highly complex and dynamic interplay exists among the pathological processes leading to unstable plaques, wall remodelling, and the underlying hemodynamics, which evolves as the pathology progresses. In this sense, the continuous arterial wall remodelling, influenced by flow disturbances, reshapes the local blood flow, contributing to reshaping the lesion, giving rise to a pathological feedback loop. Following the architectural and design motto "*form follows flow*", the hypothesis that the conformation of the

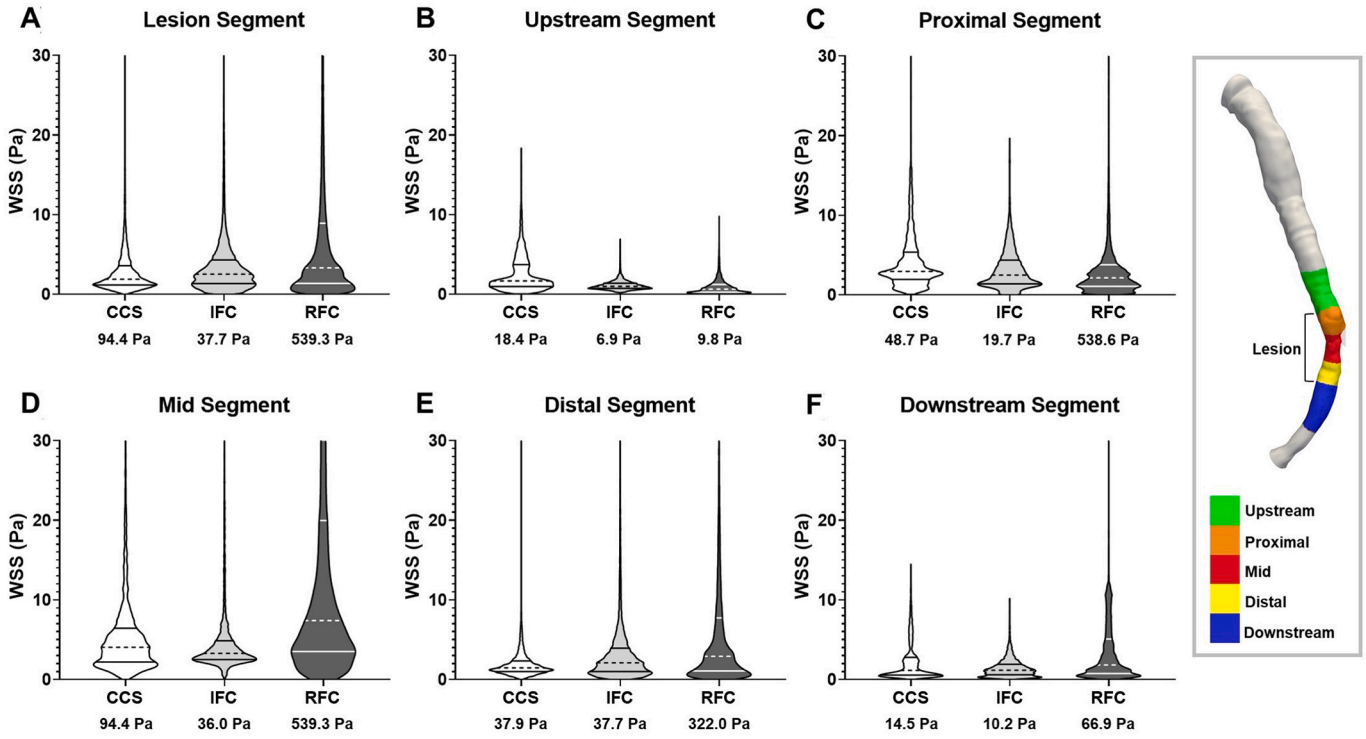


Fig. 4. Violin plots illustrating the distribution of wall shear stress (WSS) along the (A) whole lesion, (B) upstream, (C) proximal, (D) mid, (E) distal, and (F) downstream segment of the lesion for the cases characterized by stable (CCS), intact fibrous cap (IFC) and ruptured fibrous cap (RFC) lesion. The number below each group represent the maximum value of WSS. The panel on the right illustrates the subdivision of the vessel lumen into five segments of interest.

plaque and its vulnerability is the result of mechanical forces acting on the arterial wall and the downstream molecular signalling is the result of counter-regulatory pathways activated as response of an altered WSS. This is based upon the fact that most of the upregulated molecules in ACS belong to anti-oxidant, antithrombotic and anti-inflammatory enzymes.

In conclusion, our findings suggest that the high WSS might have a pathogenetic role in plaque rupture and possibly regulating the expression of several genes. This data might play a fundamental role in diagnostics and therapeutic phases [50]. The multimodality approach also involving biological and fluid dynamic assessment not only is able to improve vulnerable plaque identification and differentiating IFC from RFC but may also guide decisional algorithm on the best treatment to deliver for patients. Further data, with larger sample sizes and focused on the causal relationship between WSS and gene expression, are needed to confirm and develop the hypothesis from this study.

5. Limitations

This study presents some limitations. The unavoidable modelling assumptions and idealisations might have affected the investigated relationships. In particular, steady-state CFD simulations were carried out, neglecting the pulsatile nature of the coronary flow. This choice was based on previous computational studies demonstrating a negligible difference between time-averaged WSS and the steady-state WSS in coronary arteries, with the advantage of reducing the computational cost.

The assumption about the relationship between WSS and gene expression for RFC is based on small sample size (three patients per group for WSS profiling). Moreover, the WSS pattern and peripheral gene expression assessment and their causal relationship could be limited by atherosclerotic disease in other vessels or vascular beds. However, no additional angiographic plaques (other than the studied one) were observed in the investigated vessels. Consequently, to prove this study's hypothesis, further investigations based on animal models are needed.

Moreover, markers with significant changes are all involved in inflammation. Consequently, their behaviour might be influenced by multiple factors and a causal effect between WSS and markers expression cannot be established.

Furthermore, as only a single assessment was performed for both CFD and blood samples, no conclusion could be drawn about dynamic and temporal variations of gene expressions. In addition, although strict exclusion criteria were adopted (Supplementary Material), the three groups showed some differences at baseline (Table 1), which might have influenced gene expression and other conditions possibly associated with ACS. Although the selection of molecules was mainly driven by the existing data showing a connection between WSS and the expression of such genes, this study evaluated only a limited number of molecules, and the influence of WSS on other molecules not investigated in our study cannot be excluded.

6. Conclusions

This study demonstrates that different coronary plaques have different WSS and different molecular patterns and that there might be a close link between them. Further studies are needed to better define the complex interaction between WSS and biology in the setting of ACS. Our data pave the way to a multiparametric approach aimed at identifying and treating ACS patients, in which morphological characteristics obtained by OCT imaging techniques should be integrated with molecular and hemodynamic features and with important implications for therapeutic strategies in the era of personalized medicine.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.10.139.

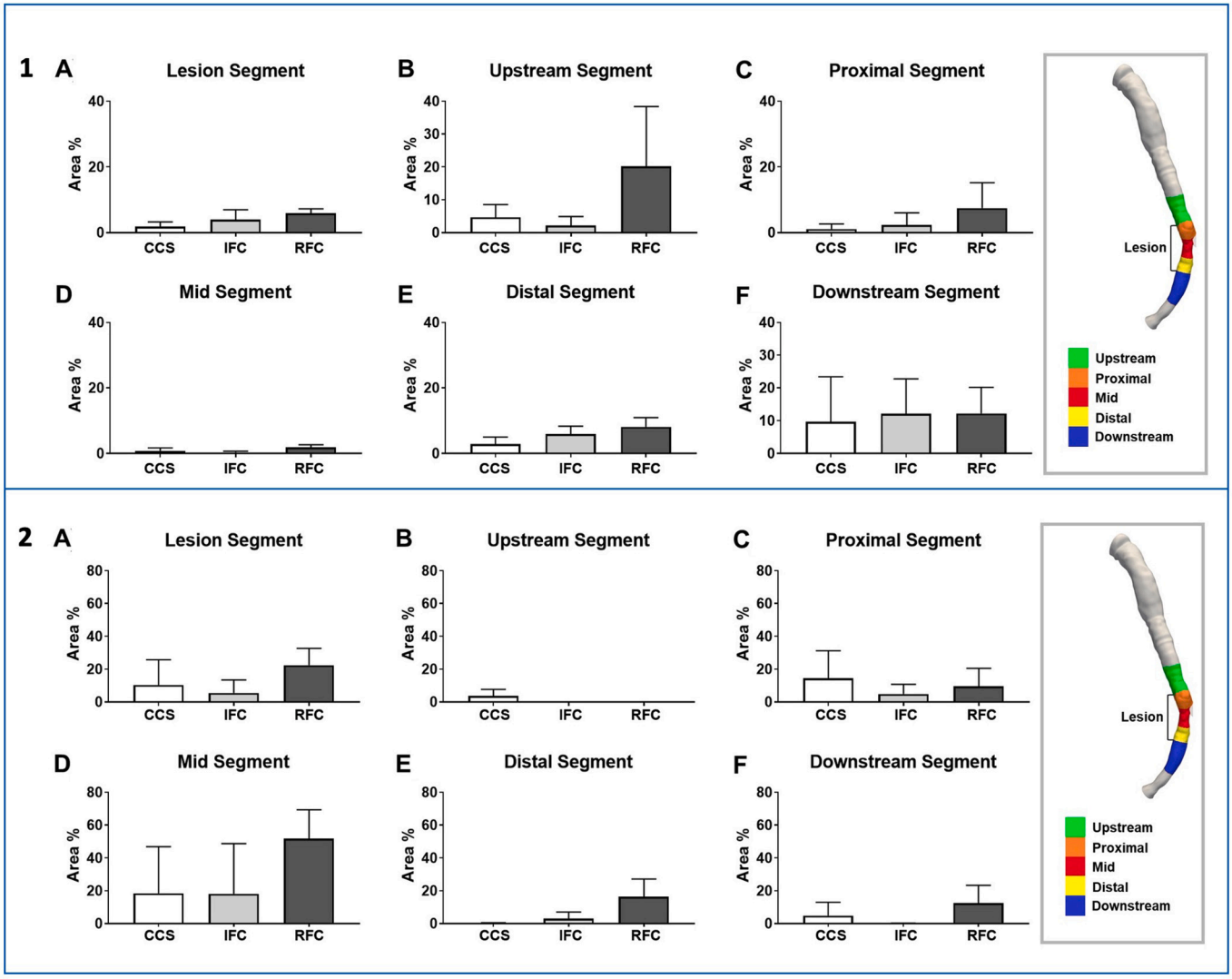


Fig. 5. Panel 1. Bar diagrams of the percentage lumen areas exposed to low wall shear stress (WSS) averaged along the (A) whole lesion, (B) upstream, (C) proximal, (D) mid, (E) distal, and (F) downstream segment of the lesion for the cases presenting stable (CCS), intact fibrous cap (IFC) and ruptured fibrous cap (RFC) lesion. The panel on the right illustrates the subdivision of the vessel lumen into five segments of interest. Panel 2. Bar diagrams of the percentage lumen areas exposed to high wall shear stress (WSS) averaged along the (A) whole lesion, (B) upstream, (C) proximal, (D) mid, (E) distal, and (F) downstream segment of the lesion for the cases presenting stable (CCS), intact fibrous cap (IFC) and ruptured fibrous cap (RFC) lesion. The panel on the right illustrates the subdivision of the vessel lumen into five segments of interest.

Translational perspective

OCT analysis and biological profiling are valuable tools to differentiate eroded from ruptured coronary artery plaques. However, the addition of CFD provides further details to coronary artery plaque identikit and might help to detect prone to rupture plaques. In future perspective, morphological features provided by OCT combined with biological and fluid dynamic characteristics might guide diagnostic and therapeutic strategies and tailor ACS management.

Author contributions

GR and DP contributed to the conception of the work, data collection and interpretation, graphical drawings and to the work draft.

CC contributed to data collection and interpretation, graphical drawings and to the work draft.

RV and LG contributed to data collection, analysis and interpretation.

MLR contributed to data collection, analysis, interpretation and graphical drawings.

MS and AL contributed to data interpretation and work revision.

AD, MB, CA, AB, AB, FD, PC, AZ, LM, MP contributed to data collection and analysis.

CT, MM, DG, FM, FM contributed to data analysis and interpretation.

UM, FB, FC, GL contributed to design of the work and to its revision.

Disclosures

Dr. Russo received fellowship training grant from EAPCI, sponsored by Edwards Lifesciences and speaker's fee from Abiomed.

Dr. Aurigemma has been involved in advisory board activities by Abbott, Abiomed, Medtronic and Biotronic.

Dr. Trani discloses to have been involved in advisory board meetings or having received speaker's fees from Abbott, Abiomed, Medtronic and Biotronic.

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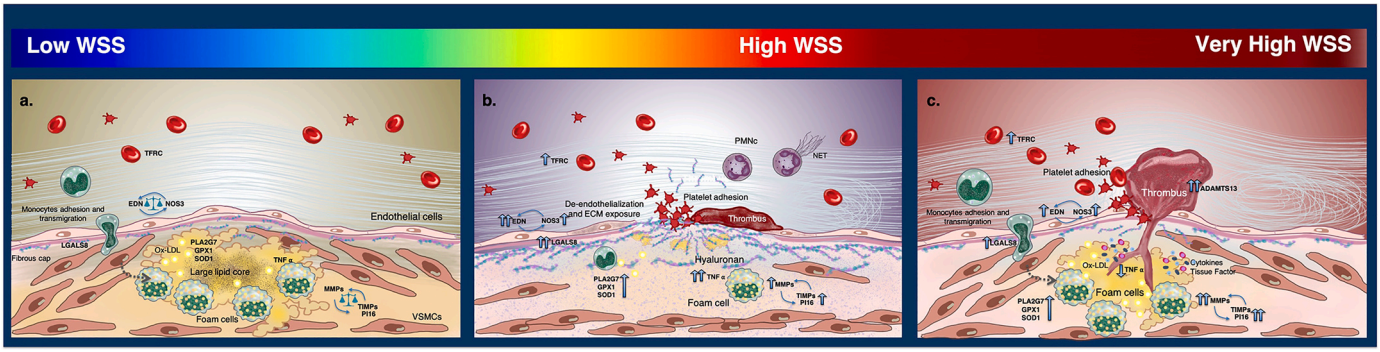


Fig. 6. Panels showing stable coronary plaque (CCS, a), intact fibrous cap unstable plaque (IFC, b) and ruptured fibrous cap unstable plaque (RFC, c). The figure summarizes the driving hypotheses that derive from both the existing literature and the data emerging from this experimental study. WSS influences plaque fate through multiple mechanisms: 1) it acts as a direct mechanical force on the arterial wall, 2) it affects plaque composition and 3) it up−/down-regulates gene expression. Molecular expression might vary in response to both levels, characteristics and duration of WSS. Higher WSS values (panels b and c) are usually associated with increased expression of molecules involved in matrix breakdown (MMPs), cell-matrix interaction and cell adhesion (Galectin-8, LGALS8), vaso-constriction (EDN1) and inflammation (TNFα). Alongside, the increased WSS is also responsible for the activation of counter regulatory mechanisms such as 1) the activation of the lipoprotein-associated phospholipase A2 (LpPLA2, gene PLA2G7) and ADAMTS13 involved in platelet inhibition and regulation of blood clotting; 2) the increased release of nitric oxide, anti-oxidant molecules (SOD1, GPX1) and matrix degradation inhibitors (TIMP, PI16); 3) the inhibition of TNFα function and production for high and very high WSS values. The unbalance between these mechanisms together with mechanical forces acting on the plaque and the activation of specific molecular pathways represent the main triggers leading to plaque instability and thrombus formation.
ADAM metallopeptidase with thrombospondin type 1 motif 13, ADAMTS13; Endotelin-1, EDN1; Glutathione peroxidase 1, GPX1; Matrix metalloproteases, MMPs; Neutrophil Extracellular Trap, NET; Nitric oxide synthase3, NOS3; Peptidase inhibitor 16, PI16; Phospholipase A2 Group VII, PLA2G7; Polymorphonuclear Cells, PMNc; Superoxide dismutase 1, SOD1; Tissue inhibitor of metalloproteinases 1, TIMP1; Tumor necrosis factor α, TNFα; Vascular Smooth Muscle Cells, VSMCs; WSS: Wall Shear Stress.

Medtronic, Edwards Lifesciences, Swissvortex, Perifect, Xeltis, Transseptal solutions, Cardiovalve, Magenta; has Royalty Income/IP Rights Edwards Lifesciences and is co-founder/shareholder of Cardiovalve, Magenta, SwissVortex, Transseptalsolutions, 4 Tech, Perifec and Coregard.

Dr. Burzotta discloses to have been involved in advisory board meetings or having received speaker's fees from Abbott, Abiomed, Medtronic and Biotronic.

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