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The impact of helical flow on coronary atherosclerotic plaque development

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1	The Impact of Helical Flow on Coronary Atherosclerotic Plaque Development
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28 Abstract

Background and aims - Atherosclerosis has been associated with near wall hemodynamics and wall shear stress (WSS). However, the role of coronary intravascular hemodynamics, in particular of the helical flow (HF) patterns that physiologically develop in those arteries, is rarely considered. The purpose of this study was to assess how HF affects coronary plaque initiation and progression, definitively demonstrating its atheroprotective nature.

Methods - The three main coronary arteries of five adult mini-pigs on a high fat diet were imaged by computed coronary tomography angiography (CCTA) and intravascular ultrasound (IVUS) at 3 (T1, baseline) and 9.4±1.9 (T2) months follow-up. The baseline geometries of imaged coronary arteries (n=15) were reconstructed, and pig-specific computational fluid dynamic simulations were performed. Local wall thickness (WT) was measured on IVUS images at T1 and T2, and its temporal changes were assessed. Descriptors of HF and WSS nature were computed for each model, and statistically compared to WT data.

41 **Results** - HF intensity was strongly positively associated with WSS magnitude (p<0.001). Overall, 42 coronary segments exposed to high baseline levels of HF intensity exhibited a significantly lower 43 WT growth (p<0.05), compared to regions with either mid or low HF intensity.

44 **Conclusions** - This study confirms the physiological significance of HF in coronary arteries, 45 revealing its protective role against atherosclerotic WT growth and its potential in predicting 46 regions undergoing WT development. These findings support future *in vivo* measurement of 47 coronary HF as surrogate atherosclerotic risk marker, overcoming current limitations of *in vivo* 48 WSS assessment.

49 **Keywords:** Atherosclerosis; Computational fluid dynamics; Wall shear stress; plaque progression.

50 Introduction

51 Coronary atherosclerosis is a complex and multifactorial disease, influenced by local biological, 52 biomechanical, and systemic factors [1,2]. The underlying mechanisms of the transformation from 53 a healthy to a diseased coronary artery are still incompletely understood. As a consequence, a 54 robust arsenal of predictive tools for this mostly asymptomatic disease has not been identified yet. 55 Among the biomechanical factors that promote atherosclerotic plaque onset and progression in 56 coronary arteries, local hemodynamics plays a major role [2,3]. In particular, low wall shear stress 57 (WSS) is widely recognized as an independent, albeit moderate, predictor of plaque development 58 [4,5].

59 Besides the widely investigated WSS, physiological helical flow (HF) has also been 60 hypothesized to have a relevant impact on vascular disease. HF, consisting of a helical-shaped 61 arrangement of the streaming blood (as given by the combination of translational and rotational 62 blood flow motions), is known to markedly characterize arterial hemodynamics [6-9]. The 63 physiological significance of arterial HF, in particular its atheroprotective nature, has emerged in 64 the last decade in the human aorta [6,10-12] and in the human carotid bifurcation [13-15]. All 65 those studies highlighted the role played by HF in mitigating near-wall flow disturbances, thereby 66 suppressing the area exposed to low WSS, which protects from atherosclerosis development [2].

67 Very recently, we showed the existence of distinguishable HF flow features in coronary
68 arteries. These HF features were hypothesized to be atheroprotective, as our data demonstrated a
69 strong association between HF and the luminal surface area exposed to low, proatherogenic WSS
70 [16].

Following these recent findings, the final goal of this study was to demonstrate the protective role
of HF for atherosclerotic plaque development over time. Findings from this work would contribute
(1) to further clarify the physiological significance of HF in coronary arteries, and (2) to the debate

- 74 on a possible future use of HF-based hemodynamic descriptors as in vivo surrogate markers of
- 75 WSS for diagnostic/prognostic purposes overcoming current limitations and inaccuracies related
- to the direct measurement of WSS from *in vivo* imaging [17].

77 Materials and Methods

78 Animal population and imaging

79 Five adult familial hypercholesterolemia Bretoncelles Meishan mini-pigs with a mutation in the 80 low-density lipoprotein receptor (LDLR) (age of 34±3 months, castrated male) were put on a high 81 fat diet to trigger atherosclerosis development. As described in detail elsewhere [16,18], the 82 animals underwent computed coronary tomography angiography (CCTA) and intravascular 83 ultrasound (IVUS) imaging of the three main coronary arteries (left anterior descending - LAD, left 84 circumflex - LCX, and right coronary artery - RCA). The imaging protocol was performed at 3 85 months after the start of the diet (T1, considered as the baseline in this study), and after 9.4±1.9 86 months (T2). At T1, Doppler-based blood flow velocity measurements were recorded in each 87 artery at the inflow section and immediately upstream and downstream of each side branch, using 88 the ComboWire (Volcano Corp., Rancho Cardova, CA, USA). An overview of the methods is 89 provided in Figure 1. In addition, some classical risk factors were measured in the 5 investigated 90 animals including weight, leukocytes, Total cholesterol, LDL-C, HDL-C and LDL-C/HDL-C ratio.

91 The study was performed according to the National Institute of Health guide for the Care and Use
92 of Laboratory animals [19]. Ethical approval was obtained from the local animal ethics committee
93 of the Erasmus MC (EMC nr. 109-14-10).

94 *Plaque growth measurements*

To quantify the local wall thickness (WT), the lumen and vessel wall contour of each of the 15 investigated coronary arteries (5 LAD, 5 LCX and 5 RCA, Figure S1 of the Supplementary Materials) were semi-automatically detected on IVUS images at T1 and at T2 using QCU-CMS software (version 4.69, Leiden University Medical Centre, LKEB, Division of Image Processing), as depicted in Figure 2. WT was assessed by subtracting the distance between the lumen center and the outer 100 wall contour, from the distance to the lumen contour. Plaque development over time was 101 quantified in terms of change in WT (Δ WT) between time points T1 and T2. The Δ WT was then 102 adjusted for the number of months between both time points for the individual pigs, resulting in a 103 measure of Δ WT/month. WT measurements were averaged over 3mm/45 degrees sectors of the 104 luminal surface (Figure 2) in order to capture the local effects of HF on plaque development.

105 *Computational hemodynamics*

106 The 3D geometry of coronary arteries at T1 was reconstructed by stacking segmented IVUS lumen 107 contours on the CCTA 3D centerline using Mevislab (Bremen, Germany), as described in detail 108 elsewhere [16]. Unsteady-state CFD simulations were performed on the reconstructed geometries 109 to quantify near-wall and intravascular hemodynamic features. The finite volume method was 110 used to numerically solve the governing equations of fluid motion. Blood was assumed as an 111 incompressible, homogeneous, non-Newtonian fluid. No-slip condition was assumed at the 112 arterial wall. Personalized boundary conditions were derived from individual in vivo velocity 113 ComboWire Doppler measurements at several locations along the vessel. The most proximal 114 measurement was used to estimate the flow rate value, prescribed as inlet boundary condition in 115 terms of time-dependent flat velocity profile. At each side branch, the measured flow ratio was 116 estimated as the difference between upstream and downstream velocity-based flow rate 117 measurements and applied as outflow condition. If flow velocity measurements were inaccurate 118 or not available, a diameter-based scaling law [20] was applied to estimate the flow ratio [16].

119 *Hemodynamic descriptors*

The hemodynamic descriptors considered for the analysis are listed in Figure 2 (see Table S2 of the Supplementary Materials for their mathematical formulation). In short, helical flow in the 15 coronary artery models at T1 was assessed in terms of average helicity intensity (h_2), which gives a measure of the strength of the pitch and torsion of coronary blood flow and is given by the cardiac

124 cycle- and volume-averaged value of the unsigned internal product of local velocity and vorticity 125 vectors [13]. In this work, to characterize each coronary model with a representative helicity 126 intensity value, h_2 was analyzed in the near-wall volume (i.e., defined by the outer 10% of the local 127 radius) and in the whole volume (i.e., defined by the entire local radius) of the main vessel. 128 Moreover, helicity intensity data were calculated over 3mm/45 degrees sectors, considering both 129 near-wall and entire local radius volumes. The consideration of the near-wall volume was 130 motivated by the recently observed link between HF and WSS patterns perpendicular to the 131 centerline of coronary arteries, quantified by the so-called secondary WSS [16]. In addition, the 132 local normalized helicity (LNH) [21] was adopted to visualize right- and left-handed helical fluid 133 patterns inside coronary arteries (respectively, positive and negative LNH values, [11].

134 To complement the HF characterization, the luminal distribution of time-averaged wall shear 135 stress (TAWSS) and of three descriptors of WSS multidirectionality were evaluated at baseline 136 (Figure 2, Table S2). In short, WSS multidirectionality was described considering two projections of 137 WSS vector [22]: (1) along the centerline of the artery, defining the "axial direction" (WSS_{ax}); (2) 138 perpendicular to the centerline, defining the secondary direction (WSS_{sc}). The WSS_{ax} and WSS_{sc} 139 local vectors were averaged over the cardiac cycle (AvgWSS_{ax} and AvgWSS_{sc}, respectively). 140 Moreover, their cycle-average magnitude was evaluated (TAWSS_{ax} and TAWSS_{sc}, respectively). To 141 detect regions at the luminal surface where the local secondary WSS component predominates 142 over the axial one, the ratio of the secondary to axial WSS magnitudes (WSS_{ratio}) was computed 143 [22]. The WSS-based descriptors were also averaged over the same 3mm/45 degrees sectors at 144 the luminal surface as WT data.

145 Statistical analysis

146 The existence of possible associations between WSS and HF was investigated considering the 147 average values of the WSS-based descriptors and the helicity-based descriptor h_2 over each individual coronary artery. Regression analysis was used to identify relations between each pair of
 hemodynamic descriptors and reported as Spearman correlation coefficients.

The analysis of the relation between plaque growth and hemodynamic descriptors was conducted using the sector-based data applying a mixed model with hemodynamic descriptors as fixed factors, the individual vessel as random factor to correct for clustering of the analyzed sectors per vessel and the average cholesterol levels as covariate (IBM SPSS Statistics, version 24.0). The values of the hemodynamic descriptors were classified as low, mid or high, based on arteryspecific tertile-division. Statistical significance was assumed for p<0.05.

156 **Results**

Classical cardiovascular risk factors, weight, leukocytes, cholesterol, LDL-C, HDL-C and LDL-C/HDL-C
ratio did not significantly change over time for the investigated 5 pigs and are presented in Table
S1 of the Supplementary Materials.

160 Coronary hemodynamics: general observations

For each investigated coronary artery model, the distribution of the WSS-based descriptors was assessed, as shown for a representative case in Figure 3 (panels A-D). A similar approach was used for studying the HF features: the LNH red and blue colors indicate right-handed and left-handed HF patterns, respectively. Thereby, the presence of two distinguishable counter-rotating HF patterns was observed in this case (Figure 3-E) and reflects the arrangement in counter-rotating helical structures in all coronary arteries.

167 Figure 3-A shows the luminal distribution of TAWSS highlighting, as expected, the presence of 168 case-specific focal low TAWSS regions located at the distal portion of the main branch. 169 Furthermore, the figure shows in the other panels (B-D) that WSS was predominantly aligned with 170 the forward flow direction (i.e., positive Avg**WSS**_{ax} values), which was representative for all cases. 171 Moreover, it emerged that the organization of coronary blood flow in two counter-rotating helical 172 structures, which is evident from LNH visualization, influences the near-wall hemodynamics of 173 coronary vessels. Considering the coronary artery depicted in Figure 3-D, positive/negative values 174 of AvgWSS_{sc}, indicating left-handed and right-handed directions respectively, resemble the 175 rotating direction of helical flow structures given by the LNH (Figure 3-E). In addition, the analysis 176 of the luminal distributions of the WSS_{ratio} revealed that WSS in the axial direction (WSS_{ax}) was 177 dominant over the **WSS** perpendicular to the vessel centerline (**WSS**_{sc}). In fact, the WSS_{ratio} was <1

over most of the lumen of all the investigated coronary arteries (around 94% of the investigatedluminal surface sectors, see also Figure 3-B).

180 Link between hemodynamic variables

181 Regression analysis revealed a significant association between the average values of the WSS-182 based descriptors and helicity intensity h_2 of each individual coronary artery (Figure 3-F). In detail, 183 TAWSS was strongly and positively associated with both whole volume h_2 (r=0.925, p<0.001) and 184 near-wall h_2 (r=0.629, p<0.01), indicating that the higher the helicity intensity (h_2) is, the higher is 185 the TAWSS value. Moreover, positive, significant associations emerged between the whole volume 186 h_2 , and both TAWSS_{ax} (r=0.843, p<0.001) and TAWSS_{sc} (r=0.843, p<0.001). A weaker, but still 187 significant, direct association emerged between near-wall h_2 and TAWSS_{ax} (r=0.629, p<0.05). Only 188 a near-significant association was observed for the near-wall h_2 and TAWSS_{sc} (r=0.468, p=0.081). 189 These results suggest a predominant role for HF intensity in the whole intraluminal volume, rather 190 than only near-wall, in determining secondary WSS magnitude. Last, a direct, significant association between the whole volume h_2 and WSS_{ratio} (r=0.757, p<0.01) emerged, but no 191 192 significant association was observed for the latter with near-wall h_2 .

193 Link between hemodynamic variables and increase in wall thickness

194 Overall, the 15 pig coronary arteries presented a marked increase in average WT over the follow-

195 up period (WT at T1 = 0.183 ± 0.108 mm, WT at T2 = 0.427 ± 0.313 mm; *p*<0.001).

196 Coronary sectors exposed to low TAWSS exhibited a significantly larger Δ WT per month (0.048 ± 197 0.007 mm/month) compared to regions with either mid (Δ WT/month = 0.035 ± 0.007 mm/month) 198 or high (Δ WT/month = 0.027 ± 0.007 mm/month) TAWSS values (Figure 4 - top panel). The analysis 199 revealed a significant, inverse association between HF and WT progression. In particular (Figure 4 -200 top panel), in luminal sectors where near-wall h_2 was high, significantly low WT growth rate (0.032 ± 0.007 mm/month) was observed, compared to luminal sectors with either mid (Δ WT/month = 202 $0.037 \pm 0.007 \text{ mm/month}$) or low ($\Delta WT/month = 0.040 \pm 0.007 \text{ mm/month}$) near-wall h_2 . A similar 203 relation emerged for h_2 . Among the investigated descriptors of WSS directionality, only high 204 TAWSS_{ax} was significantly associated with lower WT progression ($0.030 \pm 0.002 \text{ mm/month}$ for the 205 highest TAWSS_{ax} tertile).

206 In addition, the results of the time-specific statistical analysis are reported in Figure 4 (T1 - mid 207 panel; T2 - bottom panel). In detail, the association between h_2 and WT at T1 was only near 208 significant (p=0.06), while no significant association emerged between near-wall h_2 and measured 209 WT at T1 (Figure 4 - mid panel). As for WSS distribution, luminal sectors exposed to high TAWSS at 210 T1 significantly displayed the lowest T1 WT values. Similar results (but with smaller standard 211 errors), were observed for TAWSS_{ax}. However, neither TAWSS_{sc} nor WSS_{ratio} were significantly 212 associated with WT at T1. The analysis of the relations between hemodynamic descriptors at T1 213 and WT at T2 revealed similar results to those found for the overall WT growth per month 214 between T1 and T2 (Figure 4 - lower panel). In contrast to the ΔWT/month analysis, in the analysis 215 of WT at T2, luminal sectors exposed to higher TAWSS_{sc} values at T1 exhibited significantly lower 216 WT values at T2.

217 **Discussion**

218 Summary of findings and their implications

In the present study, we investigated the association between local hemodynamics and 219 220 atherosclerosis progression in a representative dataset of 15 pig coronary arteries. The study 221 highlighted the existence of a clear association between HF intensity (h_2) at baseline and plaque 222 development over time in coronary arteries. In detail, sectors at the luminal surface with the 223 lowest WT growth rate values were preceded by higher baseline values of helicity intensity, 224 suggesting a beneficial role of the HF patterns in coronary arteries. The atheroprotective role of HF 225 was confirmed when extending the analysis to WSS, a factor known to be involved in 226 atherosclerotic disease [23]. These findings confirm and strengthen our previously reported 227 associations between helicity intensity and WSS-based hemodynamic descriptors in coronary 228 arteries [16].

229 A schematic of the main findings is reported in Figure 5 to summarize the hemodynamics-related 230 mechanisms that might be involved in atherosclerotic disease progression: (1) helical blood flow 231 patterns characterized by high helicity intensity (h_2) stabilize coronary hemodynamics, thus reduce 232 flow disturbances resulting in more atheroprotective WSS levels at the luminal surface (e.g., Figure 233 3-F); (2) atheroprotective WSS values maintain endothelial cells (EC) quiescence and junctions 234 stability [3,23,24], contributing to prevent plaque initiation. The already highlighted role of low 235 WSS as predictor of plaque development in coronary vessels [3,5,24] also clearly emerged in this 236 study (Figure 4 - top panel). In detail, low baseline values of TAWSS, which are associated to a low 237 HF intensity (Figure 3-F), might trigger biological mechanisms, i.e., EC polygonal shaping, pro-238 atherogenic genes upregulation, nitric oxide reduction inducing EC dysfunction [3,23,24], 239 promoting the atherogenic plaque onset and faster disease development.

In this study the commonly used multidirectional WSS metric oscillatory shear index (OSI) was not analyzed since previous studies demonstrated that coronary arteries develop very low OSI values [16,18]. Moreover, the already observed scarce multidirectionality of WSS in coronary vessels [16] was confirmed here by assessing its axial and secondary components. The WSS_{ratio} assumed values lower than 1 over most of the lumen of all the investigated coronary arteries, indicating that the WSS is markedly aligned with the main flow direction (see explanatory case in Figure 3-B).

The association of hemodynamic quantities with WT at T1 was significant only for TAWSS and TAWSS_{ax}. Eventhough plaque growth was just initiated; the plaque location showed to comply with the local TAWSS. Luminal regions exposed to higher TAWSS_{sc} values were significantly associated to lower WT at T2, reflecting that high (atheroprotective) values of TAWSS generally result in higher values of TAWSS_{sc}.

Furthermore, the findings of this study serve to quantitatively explain for the first time the irregular helical-shaped distribution of fatty and fibrous plaques in coronary artery reported by previous ex vivo studies [25-28], and hinted at by the WT patterns shown for the representative case in Figure 2, where the high WT region seems to follow a helical distribution.

255 Limitations of the study

256 Several limitations could weaken the findings of this study. Computational hemodynamic 257 modelling suffers from assumptions and uncertainties, such us rigid walls and absence of the 258 cardiac-induced motion of coronary arteries. However, their impact on the WSS distribution has 259 been demonstrated to be minor, especially when considering time-averaged WSS quantities [29]. 260 Moreover, the findings of the study are based upon a relatively modest number of coronary artery models (N=15). Nevertheless, the consideration of multiple sectors within each coronary artery 261 262 allowed for statistically significant relationships to emerge, capturing the links between local 263 hemodynamics, WT, and WT progression, when using a linear mixed-effects model correcting for

intra-vessel and cholesterol WT dependence. The here adopted division of the hemodynamic variables in tertiles could be considered arbitrary. However, the lack of established threshold values justifies this objective and conservative choice. Lastly, this study was carried out on a pig model. However, the established similarity between pig and human coronary anatomy and hemodynamics [30] supports the translation of the findings of this study to human coronary arteries.

270 *Future perspectives*

271 In addition to the causative role of helical flow in determining WSS, a beneficial relation between HF intensity at baseline and WT and its progression in the follow-up emerged here. Taken 272 273 together, these findings suggest that HF intensity may serve as a convenient and pragmatic 274 surrogate marker of low WSS for prediction of WT progression. Although WSS remains the more 275 sensitive hemodynamic indicator for atherosclerotic disease, in vivo WSS measurements are less 276 accurate than measurements of intravascular fluid quantities like HF [31]. Furthermore, future 277 advances in phase-contrast magnetic resonance imaging might extend the feasibility of in vivo 278 arterial helical flow quantitative analysis, already demonstrated for large arteries [6,11,32-34], to 279 small vessels like the coronary arteries [17,35-39]. This would allow in vivo-based prediction of 280 atherosclerotic disease progression based upon helicity-based descriptors and thereby open a 281 clinical translation of the relationships reported in this study.

282 Conclusions

This study in coronary arteries confirms a clear association between helical flow, anti-atherogenic wall shear stress patterns and protection from plaque progression over time in an atherosclerotic pig model. In detail, the study confirmed the role of helical blood flow features (in terms of HF intensity) in conditioning WSS luminal distribution, which in turn interacts with the pathophysiology of atherosclerotic plaque formation. Due to its role in determining WSS, HF intensity could act as a practical surrogate marker of low WSS and, thus, as a potentialbiomechanical predictor of atherosclerotic plaque onset and progression.

290 **Conflict of Interest**

The authors state no conflict of interest for the study object of the manuscript. The research was not supported financially by private companies. None of the authors has a financial agreement with peoples or organizations that could inappropriately influence their work.

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297 Author contributions

G.D.N., A.H., C.C, D.G., U.M. and J.J.W.: conception and design of the study; A.H.: acquisition and analysis of in vivo data; G.D.N. and A.M.K.: computational simulation and analysis of simulation data; G.D.N, D.G., C.C., U.M., and J.J.W.: drafting of the manuscript. All authors revised the manuscript critically for important intellectual content and provided final approval for publication.

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423 Figure



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Figure 1. Schematic diagram of the study design, showing how imaging data contribute to define
 vessel geometry and hemodynamic variables. *LDRL*: low-density lipoprotein receptor; CCTA:
 coronary computed tomography angiography; IVUS: intravascular ultrasound.



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Figure 2. Methodology of hemodynamic descriptors and wall thickness (WT) assessment and analysis. Hemodynamic descriptors panel - Figure (A): example of **WSS** vector acting in a generic point at the luminal surface. Its axial (**WSS**_{ax}) and secondary (**WSS**_{sc}) components are also displayed. C(S): vessel centerline; **C'**: vector tangent to the centerline; **R**: vector perpendicular to **C'** directed from the centerline to the generic point at the arterial surface; **S**: vector orthogonal to vectors **R** and **C'**. Table (A): WSS-based descriptors involved in the analysis. A short caption for each descriptor is provided. Figure (B): example of the helical-shaped trajectory described by an element of blood moving within the coronary artery. **y** is the angle between local velocity (**v**) and vorticity (**w**) vectors (LNH = $\cos(y)$). Table (B): helicity-based descriptors involved in the analysis. A short caption for each descriptor is provided. **Wall thickness analysis panel** - Example of lumen (pink contour) and vessel outer wall (green contour) segmentation on two IVUS frames of an explanatory case. The obtained 2D distribution of WT at T2 is also shown. The angle indicates the circumferential direction around the arterial lumen. The top of the graph is the proximal region and the bottom of the graph the distal region of the artery. **Sector-based analysis panel** - Example of IVUS-imaged segment (blue colored) region in 3mm/45 degrees luminal sectors for an explanatory case.



441 442 Figure 3. Coronary hemodynamics: general observations and link between hemodynamic 443 variables. (A)-(D) WSS-based descriptors distribution at the luminal surface of a representative 444 LAD coronary artery (a) (see Figure S1 of the Supplementary Materials). For the same explanatory 445 case, visualization of LNH cycle-average isosurfaces is also provided in panel (E). For TAWSS 446 (WSS_{ratio}), the low (red) and high (blue) values are indicated. For cycle-average axial (AvgWSS_{ax}) 447 WSS vector projections, colors identify the forward (red) and backward (blue) flow direction, 448 respectively. As for LNH, also for the cycle-average secondary (AvgWSS_{sc}) WSS vector projections 449 blue and red colors identify the left and right-handed direction, respectively. +ve: positive; -ve: 450 negative; rh: right-handed; lh: left-handed. (F) Spearman correlation coefficients between WSS-451 based and helicity-based descriptors. The average value of the hemodynamic descriptors for each 452 individual case was considered. For statistically significant relations, p values are also reported.



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454 Figure 4. Link between hemodynamic variables and increase in wall thickness. Relationship 455 between baseline (T1) hemodynamic descriptor levels and 1) estimated plaque growth per month 456 (top panel), 2) WT at T1 (middle panel), and 3) WT at T2 (bottom panel). Estimated mean and 457 standard error of the mean (SEM) values are reported. The hemodynamic descriptors were divided 458 in low (dark blue bars), mid (blue bars) and high (light blue bars) tertiles per artery. The average 459 value of the hemodynamic descriptors and WT measurements in the 3mm/45 degrees sectors was 460 considered. *p<0.05 compared to low tertile, #p<0.05 compared to the mid tertile of all 461 parameters.



Hemodynamics Biological mechanisms Measured WT growth
 Figure 5. Schematic of the main findings of the study and the relationship with biological
 mechanisms related to atheroscleros