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The Impact of Helical Flow on Coronary Atherosclerotic Plaque Development

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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.

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

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

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

Introduction

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

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

Very recently, we showed the existence of distinguishable HF flow features in coronary arteries. These HF features were hypothesized to be atheroprotective, as our data demonstrated a strong association between HF and the luminal surface area exposed to low, proatherogenic WSS [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
76 to the direct measurement of WSS from *in vivo* imaging [17].

Materials and Methods

Animal population and imaging

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

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

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

wall contour, from the distance to the lumen contour. Plaque development over time was quantified in terms of change in WT (ΔWT) between time points T1 and T2. The ΔWT was then adjusted for the number of months between both time points for the individual pigs, resulting in a measure of ΔWT/month. WT measurements were averaged over 3mm/45 degrees sectors of the luminal surface (Figure 2) in order to capture the local effects of HF on plaque development.

Computational hemodynamics

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

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

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

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

Statistical analysis

The existence of possible associations between WSS and HF was investigated considering the 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 artery-specific tertile-division. Statistical significance was assumed for $p<0.05$.

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.

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.

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

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

Link between hemodynamic variables

Regression analysis revealed a significant association between the average values of the WSS-based descriptors and helicity intensity h_2 of each individual coronary artery (Figure 3-F). In detail, TAWSS was strongly and positively associated with both whole volume h_2 (r=0.925, p<0.001) and near-wall h_2 (r=0.629, p<0.01), indicating that the higher the helicity intensity (h_2) is, the higher is the TAWSS value. Moreover, positive, significant associations emerged between the whole volume 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 significant, direct association emerged between near-wall h_2 and $TAWSS_{ax}$ (r=0.629, p<0.05). Only a near-significant association was observed for the near-wall h_2 and $TAWSS_{sc}$ (r=0.468, p=0.081). These results suggest a predominant role for HF intensity in the whole intraluminal volume, rather 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 significant association was observed for the latter with near-wall h_2.

Link between hemodynamic variables and increase in wall thickness

Overall, the 15 pig coronary arteries presented a marked increase in average WT over the follow-up period (WT at T1 = 0.183 ± 0.108 mm, WT at T2 = 0.427 ± 0.313 mm; p<0.001).

Coronary sectors exposed to low TAWSS exhibited a significantly larger ΔWT per month (0.048 ± 0.007 mm/month) compared to regions with either mid (ΔWT/month = 0.035 ± 0.007 mm/month) or high (ΔWT/month = 0.027 ± 0.007 mm/month) TAWSS values (Figure 4 - top panel). The analysis revealed a significant, inverse association between HF and WT progression. In particular (Figure 4 - 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 (ΔWT/month =

202 0.037 ± 0.007 mm/month) or low (ΔWT/month = 0.040 ± 0.007 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 ± 0.002 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.

Discussion

Summary of findings and their implications

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

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

Limitations of the study

Several limitations could weaken the findings of this study. Computational hemodynamic modelling suffers from assumptions and uncertainties, such us rigid walls and absence of the cardiac-induced motion of coronary arteries. However, their impact on the WSS distribution has been demonstrated to be minor, especially when considering time-averaged WSS quantities [29]. 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 allowed for statistically significant relationships to emerge, capturing the links between local 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.

Future perspectives

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 together, these findings suggest that HF intensity may serve as a convenient and pragmatic surrogate marker of low WSS for prediction of WT progression. Although WSS remains the more sensitive hemodynamic indicator for atherosclerotic disease, *in vivo* WSS measurements are less accurate than measurements of intravascular fluid quantities like HF [31]. Furthermore, future advances in phase-contrast magnetic resonance imaging might extend the feasibility of *in vivo* arterial helical flow quantitative analysis, already demonstrated for large arteries [6,11,32-34], to small vessels like the coronary arteries [17,35-39]. This would allow *in vivo*-based prediction of atherosclerotic disease progression based upon helicity-based descriptors and thereby open a clinical translation of the relationships reported in this study.

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 potential biomechanical predictor of atherosclerotic plaque onset and progression.

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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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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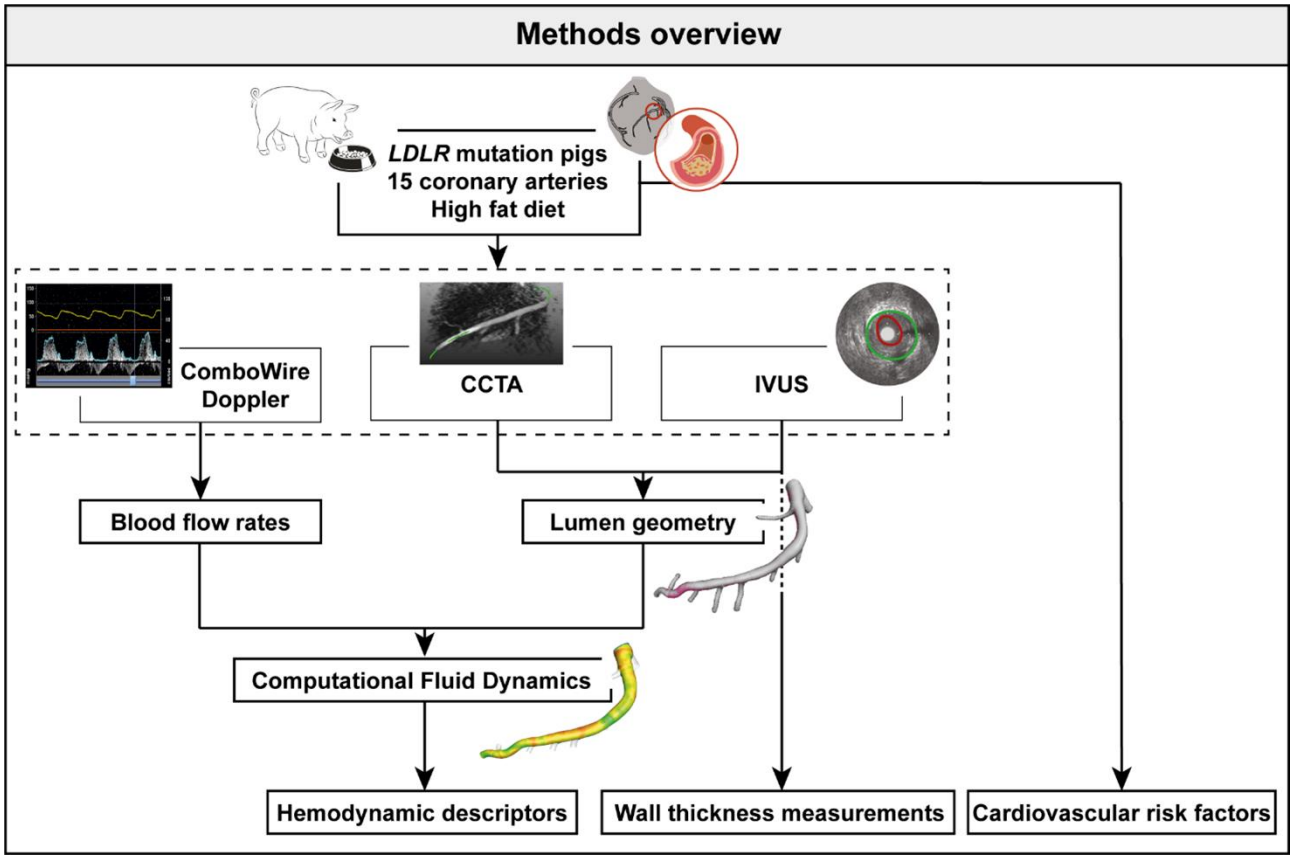
422

423 **Figure**



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

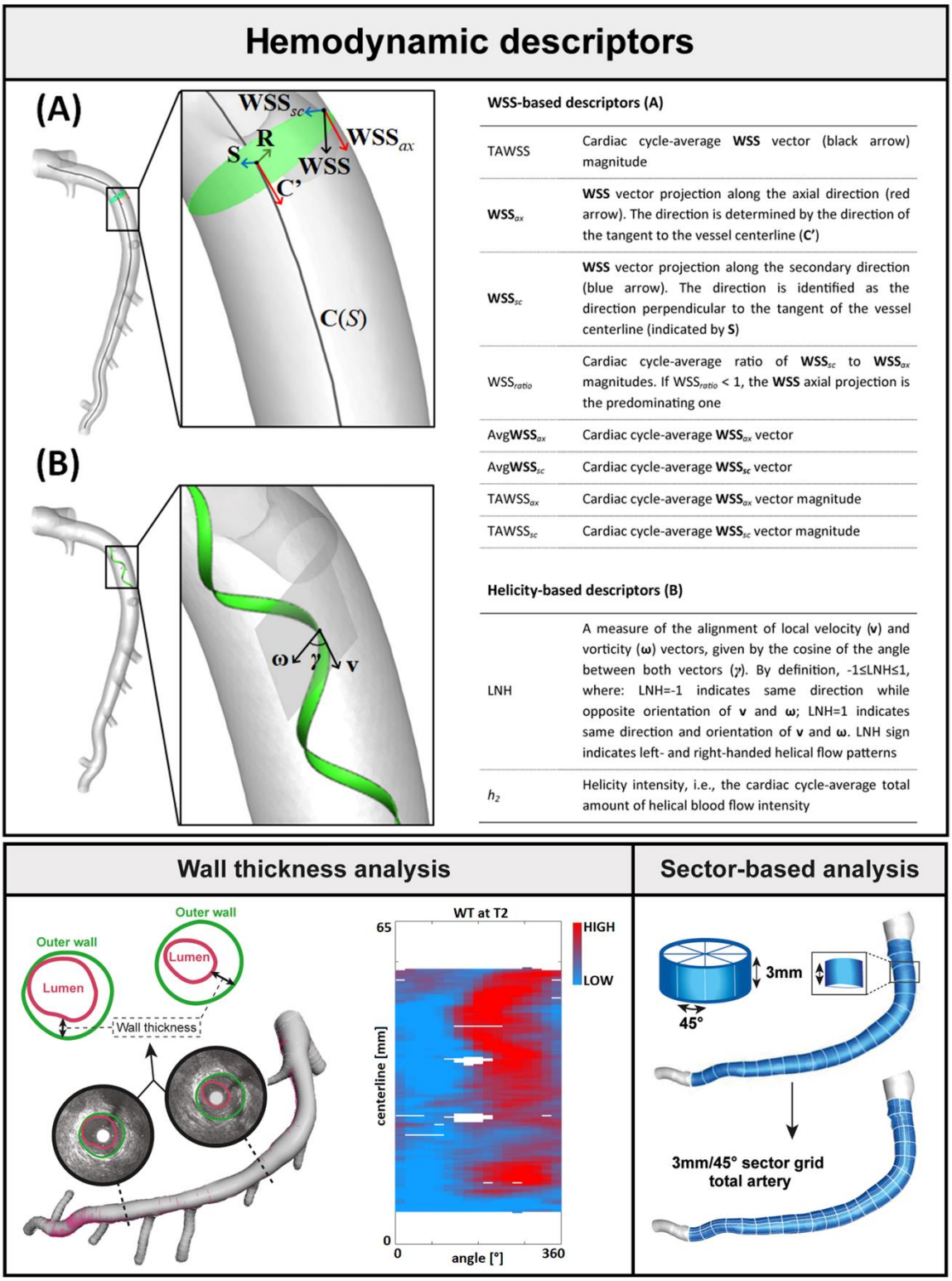

Figure 2. Methodology of hemodynamic descriptors and wall thickness (WT) assessment and analysis. Hemodynamic descriptors panel - Figure (A): example of **WSS** vector acting in a generic point at the luminal surface. Its axial (**WSS**$_{ax}$) and secondary (**WSS**$_{sc}$) components are also displayed. 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. ***γ*** is the angle between local velocity (**v**) and vorticity (**ω**) vectors (LNH = cos(***γ***)). 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.

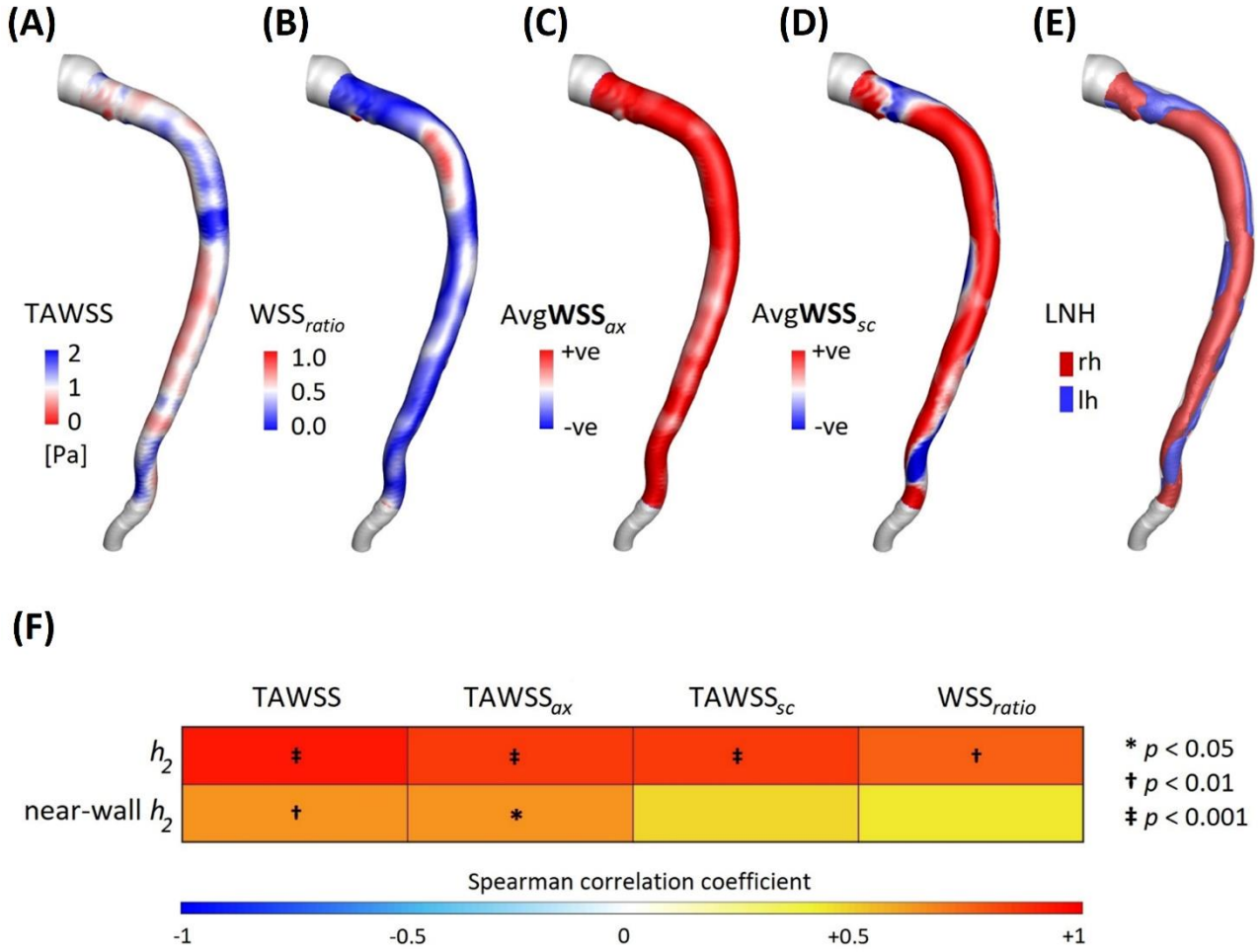

Figure 3. Coronary hemodynamics: general observations and link between hemodynamic variables. (A)-(D) WSS-based descriptors distribution at the luminal surface of a representative LAD coronary artery (a) (see Figure S1 of the Supplementary Materials). For the same explanatory case, visualization of LNH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

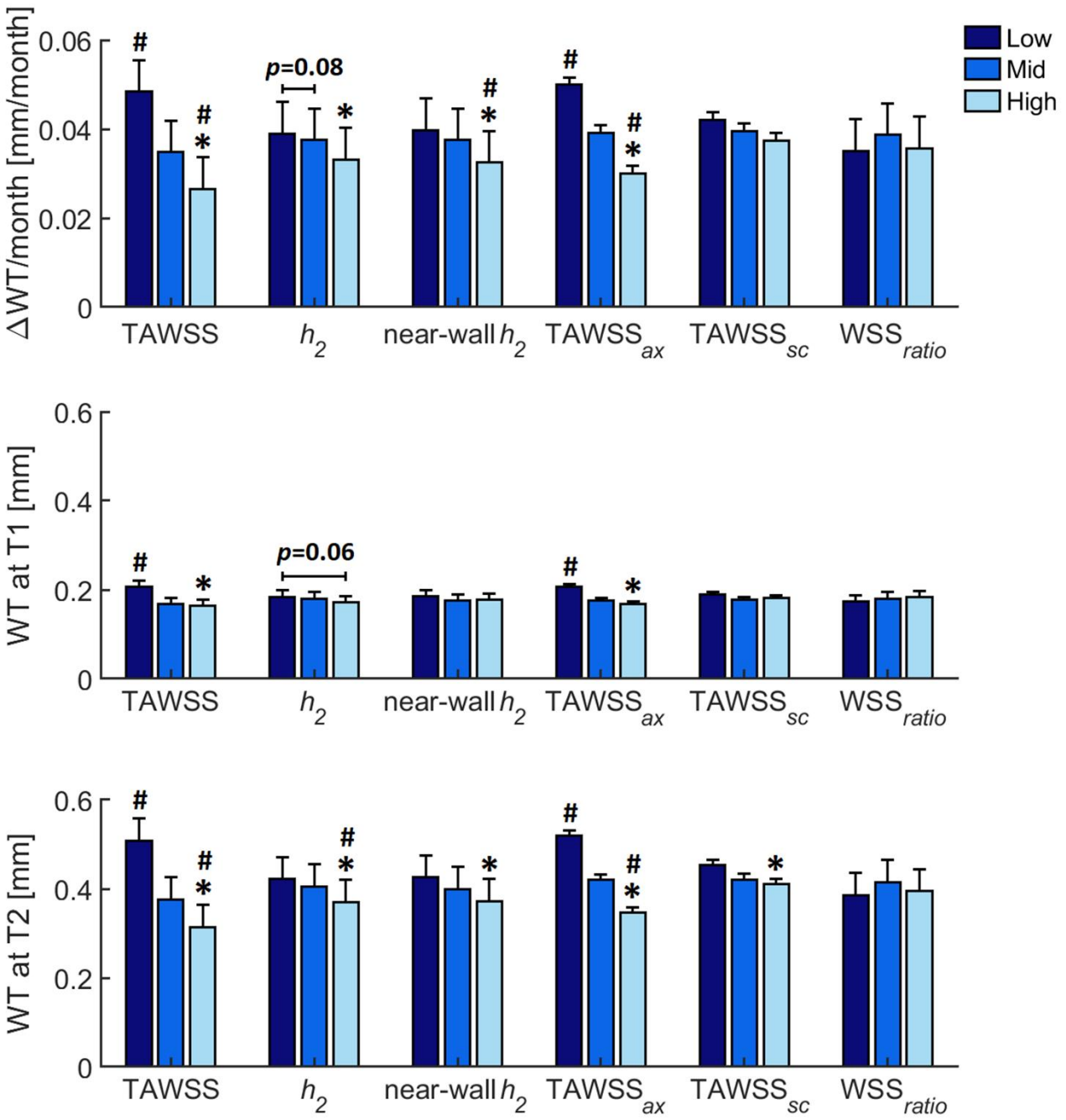

Figure 4. Link between hemodynamic variables and increase in wall thickness. Relationship between baseline (T1) hemodynamic descriptor levels and 1) estimated plaque growth per month (top panel), 2) WT at T1 (middle panel), and 3) WT at T2 (bottom panel). Estimated mean and standard error of the mean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

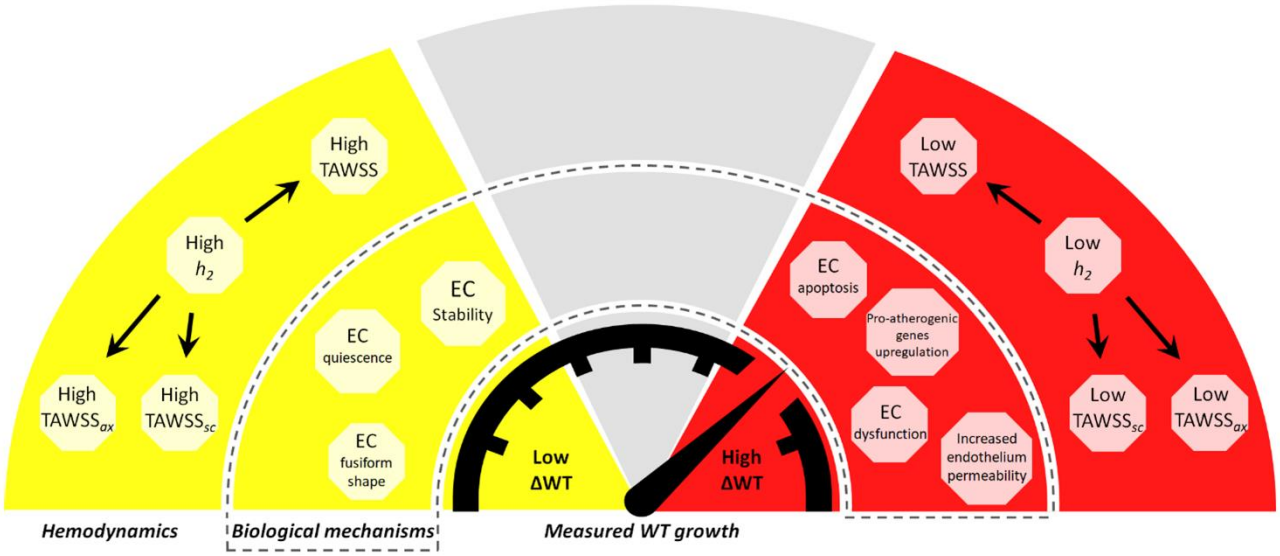

Figure 5. Schematic of the main findings of the study and the relationship with biological mechanisms related to atheroscleros