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## **Deciphering ascending thoracic aortic aneurysm hemodynamics in relation to biomechanical properties**

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1                                   **Deciphering ascending thoracic aortic aneurysm**  
2                                   **hemodynamics in relation to biomechanical properties**

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29

30 **Abstract**

31 The degeneration of the arterial wall at the basis the ascending thoracic aortic aneurysm (ATAA) is  
32 a complex multifactorial process, which may lead to clinical complications and, ultimately, death.

33 Individual genetic, biological or hemodynamic factors are inadequate to explain the heterogeneity  
34 of ATAA development/progression mechanisms, thus stimulating the analysis of their complex  
35 interplay.

36 Here the disruption of the hemodynamic environment in the ATAA is investigated integrating  
37 patient-specific computational hemodynamics, CT-based *in vivo* estimation of local aortic stiffness  
38 and advanced fluid mechanics methods of analysis. The final aims are (1) deciphering the ATAA  
39 spatiotemporal hemodynamic complexity and its link to near-wall topological features, and (2)  
40 identifying the existing links between arterial wall degeneration and hemodynamic insult.

41 Technically, two methodologies are applied to computational hemodynamics data, the wall shear  
42 stress (WSS) topological skeleton analysis, and the Complex Networks theory. The same analysis  
43 was extended to the healthy aorta.

44 As main findings of the study, we report that: (1) different spatiotemporal heterogeneity  
45 characterizes the ATAA and healthy hemodynamics, that markedly reflect on their WSS topological  
46 skeleton features; (2) a clear link (stronger than canonical WSS-based descriptors) emerges  
47 between the variation of contraction/expansion action exerted by WSS on the endothelium along  
48 the cardiac cycle, and ATAA wall stiffness. The findings of the study suggest the use of advanced  
49 methods for a deeper understanding of the hemodynamics disruption in ATAA, and candidate WSS  
50 topological skeleton features as promising indicators of local wall degeneration.

51

52 **Highlights**

- 53 • Different levels of spatiotemporal heterogeneity characterize the aneurysmal and healthy  
54 ascending aorta hemodynamics, reflecting on wall shear stress topological skeleton.
- 55 • Peculiar wall shear stress topological skeleton features are linked to local ascending thoracic  
56 aortic aneurysms stiffness.
- 57 • The topological shear variation index, a measure of wall shear stress luminal  
58 contraction/expansion action variation along the cardiac cycle, is an indicator of local aortic  
59 wall degradation, performing better than canonical wall shear stress-based descriptors of flow  
60 disturbances.
- 61 • Wall shear stress topological skeleton analysis, combined with Complex Networks theory,  
62 contributes to better determine whether arterial wall degeneration, in combination with  
63 hemodynamic insult, leads to aneurysmal progression/rupture.

64

## 65 **Introduction**

66 Ascending thoracic aortic aneurysm (ATAA) is an unphysiological localized ballooning of the aorta  
67 at the ascending segment proximal to the brachiocephalic trunk, which can grow in size and  
68 eventually rupture, leading to serious complications and death. The common clinical treatment of  
69 ATAA consists in surgical repair by replacing the diseased aortic segment with a synthetic graft  
70 [1,2]. Due to significant mortality rates associated to prophylactic surgery (3-5 %) [1], indications  
71 for surgical treatment depend on the estimated maximum aortic diameter, with a suggested  
72 critical threshold value of 5.5 cm (except for patients with Marfan syndrome) [2–4]. However, the  
73 diameter-based criterion for surgical intervention has been widely recognized as inadequate [5,6].  
74 To find complementary or alternative markers of ATAA risk of rupture, a plethora of studies have  
75 focused on, e.g., genetic, biological, structural and biomechanical factors involved in the ATAA wall  
76 dilatation/degeneration [7–13]. However, current evidence is still insufficient to rely on  
77 biomechanical factors alone [10,12], and rather suggests a possible relation between ATAA  
78 hemodynamics and wall mechanical properties, which might better explain the complexity of  
79 ATAA development and progression.

80 In particular, the analysis of aortic hemodynamics, with the assessment of distinguishable  
81 intravascular flow features and wall shear stress (WSS) distribution on the luminal surface as  
82 obtained from *in vivo* [14–17] and patient-specific computational studies [18–22], have been  
83 suggested to derive markers of rupture risk, giving the supposed link between hemodynamic  
84 features and ATAA wall mechanical properties. For instance, previous follow-up studies reported a  
85 significant association between the luminal exposition to relatively low WSS values and ascending  
86 aorta wall weakening and dilatation in ATAA patients [21,23,24].

87 In this context, we propose a framework combining patient-specific computational fluid dynamics  
88 (CFD), advanced fluid mechanics analysis and personalized *in vivo* estimates of the local aortic

89 stiffness. The aims are to interpret the complex role played by local hemodynamics in ATAA and to  
90 decipher the existing links between near-wall features, intravascular flow structures and ATAA  
91 wall stiffness. More specifically, changes in hemodynamics associated with pathologic aortic  
92 dilatation were analyzed by applying two recently proposed methodologies on two subject-  
93 specific (1 healthy - 1 diseased) CFD models. The first approach relies on the analysis of WSS  
94 vector field topological skeleton, essentially consisting of a collection of critical points (i.e.,  
95 locations at the luminal surface of the vessel where the WSS vanishes), and special lines which  
96 separate the luminal surface into areas of different WSS behavior, ultimately identifying where an  
97 expansion/contraction action is exerted by WSS on the endothelium (which is expected to have  
98 biological relevance) [25][26]. The second one exploits Complex Networks (CNs) theory to describe  
99 the spatiotemporal heterogeneity in near-wall and intravascular flow patterns, revealing  
100 information embedded in hemodynamic quantities waveforms (along the cardiac cycle) and useful  
101 to describe nonlinear phenomena involving them [27]. Both approaches were combined here to  
102 relate near-wall hemodynamics and intravascular flow patterns, which are expected to markedly  
103 affect WSS features [28,29]. Finally, ATAA local stiffness was obtained through a recently proposed  
104 inverse method based on gated CT scans [30]. Spatial correlations with WSS features were  
105 extracted from the topological skeleton analysis to ultimately associate ATAA complex  
106 hemodynamic features and wall mechanical properties.  
107

## 108 **Methods**

109 One 36 years old healthy subject with no history of cardiovascular diseases, and one 59 years old  
110 subject with bicuspid aortic valve (BAV), moderate aortic valve insufficiency and a 6.03 cm x 5.95  
111 cm ATAA were enrolled in the study after informed consent. An overview of the methods applied  
112 in this study is provided in Figure 1 and detailed onwards.

### 113 *Medical imaging and geometry reconstruction*

114 The two subjects were imaged by a 3T MR scanner (Siemens Magnetom Prisma) without contrast  
115 agent, using the same 4D flow MRI protocol exhaustively detailed elsewhere [22]. Based on 4D  
116 flow MRI images, the 3D geometries of each subject were reconstructed using CRIMSON  
117 (CardiovasculaR Integrated Modelling and SimulatiON) [31]. The resulting geometries included the  
118 ascending thoracic aorta, the aortic arch, the descending thoracic aorta and the supra-aortic  
119 vessels (brachiocephalic artery - BCA, left common carotid artery - LCCA, and left subclavian artery  
120 - LSA, as shown in Figure 1).

121 Additionally, the diseased subject underwent ECG gated CT imaging in order to identify ATAA wall  
122 local stiffness with a recently proposed inverse method [30] detailed below.

### 123 *In vivo aortic wall stiffness estimation*

124 A recently proposed non-invasive inverse approach was applied here to identify aortic wall  
125 stiffness for the diseased subject. Briefly, ATAA geometries at ten phases along the cardiac cycle,  
126 including diastolic and systolic phases, were (1) reconstructed from gated CT scans using MIMICS  
127 (v.10.01, Materialise NV), and (2) meshed ensuring a set of nodes attached to the same material  
128 points at all the recorded cardiac phases. Based on the Fourier series analysis of temporal changes  
129 in position of each node, the local strain distribution was reconstructed and the wall stiffness at

130 every location was derived by satisfying the local equilibrium equation under the acting tensions.

131 The strategy applied to estimate local wall stiffness *in vivo* is exhaustively detailed elsewhere [30].

132 *Computational hemodynamics*

133 The finite element-based open-source code SimVascular (<http://simvascular.github.io/>) was

134 adopted to solve the governing equations of fluid motion in the two models. In detail, the Navier–

135 Stokes equations, in their discretized form and under unsteady flow conditions, were solved using

136 a stabilized finite element method supporting the use of linear tetrahedral elements (P1–P1) in the

137 SimVascular flow solver for velocity and pressure [32]. Newtonian blood rheology (with prescribed

138 constant density and dynamic viscosity respectively equal to  $1050 \text{ kg m}^{-3}$  and  $0.0035 \text{ Pa s}$ ) and rigid

139 wall with no-slip condition were assumed. To ensure a grid-independent solution, based on a

140 mesh sensitivity analysis, an average tetrahedral element size of  $1.05 \cdot 10^{-3} \text{ m}$  with a near-wall

141 refinement consisting of 12 tetrahedral boundary layers with a decreasing ratio of 0.90 was

142 adopted. The resulting computational grids consisted of 4.13 and 7.97 million elements for healthy

143 and diseased model, respectively.

144 Boundary conditions were prescribed using patient-specific 4D flow MRI measurements. In detail,

145 measured fully 3D phase velocity data were extracted along the cardiac cycle and imposed in

146 terms of Dirichlet inflow boundary conditions (BCs) at the ascending aorta (AAo) inlet section (as

147 detailed in [33]). As regards outflow BCs, 4D flow MRI measured flow rates were prescribed at the

148 supra-aortic vessels [34] in terms of fully developed velocity profiles. A three element Windkessel

149 model was prescribed as BC at the descending aorta (DAo) outlet section, by applying a 3D-0D

150 coupling scheme [22,31]. The three element Windkessel model components (i.e., the impedance -

151  $Z_C$ , the distal resistance -  $R$ , and the capacitor -  $C$ ) were tuned as described in [22], obtaining

152 patient specific values for the healthy ( $Z_C = 1.36 \cdot 10^7 \text{ kg m}^{-4} \text{ s}^{-1}$ ;  $R = 2.28 \cdot 10^8 \text{ kg m}^{-4} \text{ s}^{-1}$ ;  $C = 1.50 \cdot 10^{-8}$



153  $\text{kg}^{-1} \text{m}^4 \text{s}^2$ ) and the pathologic subject ( $Z_c = 5.32 \cdot 10^6 \text{ kg m}^{-4} \text{ s}^{-1}$ ;  $R = 9.02 \cdot 10^7 \text{ kg m}^{-4} \text{ s}^{-1}$ ;  $C = 3.18 \cdot 10^{-8}$   
154  $\text{kg}^{-1} \text{m}^4 \text{s}^2$ ).

155 On the simulated flow fields in the healthy and diseased models, advanced post-processing tools  
156 were applied to better decipher the aortic hemodynamics complexity.

### 157 *Deciphering aortic hemodynamics - WSS topological skeleton analysis*

158 Based upon dynamical systems theory, the topological skeleton of a vector field is made of fixed  
159 points and manifolds, where: (1) a fixed point is a point where the vector field vanishes; (2) vector  
160 field manifolds, connecting fixed points, identify contraction/expansion regions (respectively,  
161 stable/unstable manifolds).

162 Here, a very recently proposed Eulerian method was considered to analyze the topological  
163 skeleton of the WSS vector field across the aortic luminal surface [25]. Based on the Volume  
164 Contraction Theory, it has been demonstrated [25] that specific features of the WSS vector field  
165 topological skeleton, i.e., WSS manifolds, can be easily captured using the divergence of the  
166 normalized WSS vector:

$$167 \quad \text{DIV} = \nabla \cdot \boldsymbol{\tau}_u = \nabla \cdot \left( \frac{\boldsymbol{\tau}}{|\boldsymbol{\tau}|} \right), \quad (1)$$

168 where  $\boldsymbol{\tau}_u$  is the unit vector of WSS vector  $\boldsymbol{\tau}$ . Eq. (1), neglecting the WSS vector magnitude  
169 variation, identifies the WSS spatial contraction/expansion configuration patterns [25]: negative  
170 values of DIV identify contraction regions, approximating attracting manifolds; positive values of  
171 DIV identify expansion regions, approximating repelling manifolds (Figure 2a).

172 According to the scheme proposed elsewhere for the complete WSS topological skeleton  
173 extraction [25], the identification of WSS fixed points location at the luminal surface was  
174 performed by computing a mesh-independent topological index, named Poincaré index. Then, the  
175 identified fixed points were classified using the eigenvalues of the Jacobian matrix, which provide  
176 information about fixed points nature (Figure 2). Technically, the adopted eigenvalue-based

177 criterion allowed to distinguish between fixed point node or focus configurations. The  
 178 combinations of the Poincaré index values and of eigenvalues  $\lambda_i$  ( $i = 1, 2, 3$ ) of the Jacobian matrix  
 179 corresponding to the possible WSS fixed points configurations are summarized in Figure 2b.  
 180 As a first step, here the WSS topological skeleton of the cycle-average WSS vector field  $\bar{\boldsymbol{\tau}}$  at the  
 181 luminal surface of both the healthy and diseased model was analyzed. The unsteady nature of the  
 182 WSS vector field fixed points along the cardiac cycle was investigated using the WSS fixed points  
 183 weighted residence time along the cardiac cycle [25]:

$$184 \quad RT\bar{\nabla}_{x_{fp}}(e) = \frac{\bar{A}}{A_e T} \int_0^T \mathbb{I}_e(\mathbf{x}_{fp}, t) |(\nabla \cdot \boldsymbol{\tau})_e| dt, \quad (2)$$

185 where  $\mathbf{x}_{fp}(t)$  is the WSS fixed point position at time  $t \in [0, T]$ ,  $e$  is the generic triangular element  
 186 of the superficial mesh of area  $A_e$ ,  $\bar{A}$  the average surface area of all triangular elements of the  
 187 superficial mesh,  $\mathbb{I}$  is the indicator function and  $(\nabla \cdot \boldsymbol{\tau})_e$  is the instantaneous WSS divergence.  
 188 Eq. (2) quantifies the fraction of cardiac cycle spent by a fixed point inside a generic mesh surface  
 189 element  $e$  on the aortic luminal surface emphasizing the contribution of fixed points surrounded  
 190 by a marked local contraction/expansion action. In fact, from a physical point of view, the term  
 191  $|(\nabla \cdot \boldsymbol{\tau})_e|$  in eq. (2) allows to measure the strength of the contraction/expansion action of shear on  
 192 the wall.

193 Additionally, here a quantity based on WSS divergence, named Topological Shear Variation Index  
 194 (*TSVI*), is introduced to measure the amount of variation in WSS contraction and expansion action  
 195 exerted at the luminal surface of the vessel. To do that, the root mean square of the normalized  
 196 WSS divergence is computed as follows:

$$197 \quad TSVI = \left\{ \frac{1}{T} \int_0^T [\nabla \cdot (\boldsymbol{\tau}_u) - \overline{\nabla \cdot (\boldsymbol{\tau}_u)}]^2 dt \right\}^{1/2}, \quad (3)$$

198 Roughly speaking, eq. (3) allows to localize regions on the luminal surface of the vessel exposed to  
 199 large variations in the shear contraction/expansion action exerted by the flowing blood along the

200 cardiac cycle.

201

202 *Deciphering aortic hemodynamics - Complex Networks analysis*

203 The spatiotemporal heterogeneity of intravascular and near-wall flow patterns was here  
204 investigated applying a recently introduced approach based on the application of the CNs theory  
205 to computational hemodynamics data [27,35], where the nodes of the network are represented  
206 by the waveforms, along the cardiac cycle, of specific hemodynamic quantities at the nodes of the  
207 aortic computational grid.

208 Here, the CNs-based analysis was applied to the WSS vector magnitude ( $|\tau|$ ) waveforms along the  
209 cardiac cycle, whereas intravascular hemodynamics was described in terms of axial velocity ( $V_{ax}$ )  
210 and kinetic helicity density ( $H_k$ ). In detail,  $V_{ax}$  is the component of blood velocity vector along the  
211 local axial direction, identified as the direction of the tangent to the vessel's centerline [36]. By  
212 definition,  $V_{ax}$  is representative of the main flow direction.  $H_k$  is defined as the internal product  
213 between local velocity and vorticity vectors and its sign is an indicator of the (right- or left-handed)  
214 direction of rotation of helical blood flow patterns. The latter descriptor was involved in the  
215 analysis because of the established physiological significance of helical blood flow in main arteries  
216 [29,37,46,38–45].

217 For both investigated aortic models, three different CNs were built, starting from  $V_{ax}$ ,  $H_k$  and  $|\tau|$   
218 time-histories, respectively. In the here adopted approach [27], two generic nodes  $i$  and  $j$  of the  
219 CN are connected by a topological link  $\{i, j\}$  if the Pearson correlation coefficient  $R_{ij}$  between the  
220 waveforms of each considered hemodynamic quantity at the two nodes is larger than a given  
221 threshold  $\widehat{R}$ . In this sense, each CN can be represented by its *adjacency matrix*  $A_{ij}$  containing the  
222 information about node connectivity as follows:

$$A_{ij} = \begin{cases} 0, & \text{if } \{i, j\} \notin E \text{ or } i = j, \\ 1, & \text{if } \{i, j\} \in E. \end{cases} \quad (4)$$

Here, for each aortic model, and for each of the three CNs based on the hemodynamic quantities  $V_{ax}$ ,  $H_k$  and  $|\tau|$ , respectively, the median values of the single  $R_{ij}$  distributions were set as threshold values  $\hat{R}$  to build up *adjacency matrices*, as proposed elsewhere [27,35].

Three metrics, based on  $A_{ij}$ , were used to characterize the structure of each CN. In detail, here we considered the *degree centrality*  $DC_i$  of node  $i$ , defined as the percentage of nodes of the network connected to node  $i$ , i.e., the so-called *neighbors* of  $i$ :

$$DC_i = 100 \left( \frac{1}{N-1} \sum_{j=1}^N A_{ij} \right) = 100 \left( \frac{1}{N-1} dc_i \right). \quad (5)$$

In eq. (5)  $dc_i$  is the non-normalized degree centrality of node  $i$ . To allow comparisons between the healthy and the diseased model networks, characterized by different number of nodes ( $N$ ),  $dc_i$  was normalized to the total number ( $N-1$ ) of possible neighbors of  $i$ . In summary, for a specific hemodynamic descriptor,  $DC_i$  measures the fraction of time-histories correlated above threshold with the time-history in node  $i$ , quantifying the spatiotemporal homogeneity/heterogeneity of the considered hemodynamic quantity waveform in each node, with respect to the whole network (i.e., the fluid volume for  $V_{ax}$  and  $H_k$ , or the luminal surface for  $|\tau|$ ).

The second CNs metric used in this study was applied to the  $V_{ax}$ - and  $H_k$ -based networks to provide a quantitative measure of the anatomical length of persistence of the correlation of axial velocity and helical flow patterns inside the aorta. To do that, the so-called normalized *average Euclidean distance* ( $AED_i$ ) [27,47] of each node  $i$  of the network from all its neighbors  $n(i)$  was evaluated, defined as:

$$AED_i = \frac{1}{D_{max}} \frac{\sum_{j \in n(i)} l_{ij}}{dc_i}, \quad (6)$$

where  $D_{max}$  is the maximum AAO diameter in the region upstream of the proximal supra-aortic trunk, and  $l_{ij}$  is the Euclidean distance between neighbor nodes  $i$  and  $j$ . In eq. (6),  $AED_i$  was

246 normalized with respect to  $D_{max}$ , in order to account for AAO geometric variability between the  
 247 healthy and the diseased model. To investigate the effect that the presence of the ATAA has on  
 248 the anatomical extent of the spatiotemporal correlations between  $V_{ax}$  and  $H_k$  structures, in both  
 249 models  $AED_i$  was computed only in the aortic region from the inlet section to the first supra-aortic  
 250 vessel bifurcation point.

251 The length of persistence of the correlation of WSS spatiotemporal patterns at the aortic luminal  
 252 surface was evaluated in topological terms in the  $|\tau|$ -based network of the two aortic models. This  
 253 was done computing the *average shortest path length* ( $\overline{SPL}_i$ ) of node  $i$ , defined as:

$$254 \quad \overline{SPL}_i = \frac{1}{N-1} \sum_{j \in V, i \neq j} d_{ij}, \quad (7)$$

255 where  $V$  is the set of nodes of the network, and  $d_{ij} \in Z$  is the shortest topological distance between  
 256 nodes  $i$  and  $j$ , i.e., the minimum number of links connecting node  $i$  with node  $j$  [48] (Figure 1). In  
 257 synthesis,  $\overline{SPL}_i$  is a measure of the topological length of the correlation persistence of the  $|\tau|$   
 258 waveform at each luminal surface node (i.e., the smaller the  $\overline{SPL}_i$ , the larger the topological  
 259 persistence length of the correlation between  $i$  and the rest of the network). In order to be  
 260 consistent with the computation of the anatomical persistence length of correlation (i.e., the  $AED_i$   
 261 metric), also  $\overline{SPL}_i$  was computed only in the aortic region from the inlet section to the first supra-  
 262 aortic trunk bifurcation point.

### 263 *Deciphering aortic hemodynamics – Canonical WSS-based hemodynamic descriptors*

264 In addition to the advanced methods for analyzing aortic hemodynamics introduced above, flow  
 265 disturbances were evaluated here also in terms of canonical WSS-based descriptors (Table 1),  
 266 namely the time-averaged wall shear stress (TAWSS), oscillatory shear index (OSI) [49], and  
 267 relative residence time (RRT) [50]. Moreover, a descriptor of WSS multidirectionality was  
 268 considered (Table 1), i.e., the transversal WSS (transWSS) [51], defined as the average WSS  
 269 component acting orthogonal to the time-averaged WSS vector direction.

270 *Aortic hemodynamics vs. wall stiffness*

271 To investigate the existence of possible relations between ATAA hemodynamics and the  
272 mechanical properties of the aortic wall, an analysis of co-localization between exposure to  
273 “disturbed” hemodynamics vs. wall stiffness was carried out according to schemes proposed  
274 elsewhere [28,29,52]. More specifically, objective thresholds for WSS-based hemodynamic  
275 descriptors and for wall stiffness were identified as the 2<sup>nd</sup> tertile of the respective luminal  
276 distribution (1<sup>st</sup> tertile for TAWSS). The co-localization of luminal surface areas (SAs) characterized  
277 by stiffness and each one of OSI, RRT, transWSS, or *TSVI* values higher (lower for TAWSS) than the  
278 respective thresholds was quantitatively assessed by the similarity index (SI) [52]:

279 
$$SI = \frac{2(SA_{high\ stiffness} \cap SA_j)}{SA_{high\ stiffness} + SA_j}, \quad (8)$$

280 with *j* indicating a generic WSS-based hemodynamic descriptor. SI ranges between 0 (the SAs have  
281 no spatial overlap) and 1 (the SAs are equivalent and perfectly spatially overlapped).

## 282 **Results**

### 283 *ATAA wall stiffness in vivo estimation*

284 The *in vivo* estimated local wall stiffness distribution on the AAo of the diseased subject is  
285 presented in Figure 3. Consistent with previous observations [53,54], local variations in the wall  
286 mechanical properties are evident in the investigated model, where the highest values of the  
287 stiffness are observed at the outer AAo wall. For this reason, in order to investigate the possible  
288 role played by hemodynamic features in the development and progression of aneurysm disease,  
289 the analysis was here focused at the proximal AAo outer wall of both healthy and diseased  
290 models, where the biomechanical wall alteration mainly occurred in the ATAA subject.

### 291 *WSS topological skeleton analysis*

292 As suggested elsewhere [12], here the analysis of the WSS vector field topological skeleton at the  
293 aortic luminal surface was applied in a two-step strategy.

294 As a first step, the aortic cycle-average WSS vector field topological skeleton was identified and  
295 analyzed (Figure 4a) aiming at identifying (on average) differences between the healthy and ATAA  
296 model. It emerged that on both models a line of marked WSS expansion was located at the  
297 proximal AAo outer wall, as identified by positive DIV values. However, the healthy aorta only  
298 presented there an unstable node. Moreover, marked contraction lines characterized the WSS  
299 topological skeleton on the ATAA outer wall, but they were not present on the luminal surface of  
300 the healthy aorta.

301 In the second step, the impact of the WSS vector field dynamics (along the cardiac cycle) on  
302 topological skeleton features was analyzed. The analysis of the luminal surface distribution of fixed  
303 points weighted residence time ( $RT\nabla_{x_{fp}}$ , Figure 4b) highlighted the presence of a wide region at  
304 the AAo outer-wall of the diseased model where instantaneous WSS fixed points appear and  
305 reside for a longer fraction of cardiac cycle. Such region is surrounded by luminal regions with a

306 high local WSS contraction/expansion strength. On the other hand, a completely different  
307 distribution was observed on the outer wall of the healthy model (Figure 4b), mainly characterized  
308 by low  $RT\nabla_{x_{fp}}$  values.

309 The analysis of the *TSVI* luminal distributions (Figure 4c) highlighted that: (1) the highest local  
310 variations in the contraction/expansion action exerted by the WSS on the endothelium along the  
311 cardiac cycle are located at two distinct regions of the AAO outer wall luminal surface, in both  
312 healthy and diseased models; (2) in the diseased model, high *TSVI* and high  $RT\nabla_{x_{fp}}$  regions are  
313 markedly co-localized on the outer wall luminal surface.

#### 314 *CNs analysis*

315 In the attempt to better describe differences between healthy and ATAA models accounting for  
316 possible links between the biomechanical alteration of the wall and hemodynamics, CNs were  
317 applied to the aortic flow and WSS fields.

318 The *DC* distributions of the  $V_{ax}$ ,  $H_k$ - and  $|\tau|$ -based CNs are displayed in Figure 5 for both models.  
319 For visualization purposes, in each CN the *DC* values were classified in “high” and “low” based on  
320 the median value of the *DC* distribution of the healthy subject. Regarding the axial flow in the AAO  
321 of the diseased model (Figure 5a), a predominance of  $V_{ax}$  waveforms with a neighborhood which is  
322 representative of a portion of the whole aortic axial flow smaller than in the healthy model  
323 emerged, as highlighted by the low value *DC* distribution in that region.

324 Regarding  $H_k$ , the *DC* distribution in the AAO (Figure 5b): (1) confirms the presence of counter-  
325 rotating helical flow patterns both in the healthy and in the ATAA model [22,36,38,44], as  
326 suggested elsewhere [27]; (2) highlights that helical flow (characterized considering  $H_k$  waveforms  
327 along the cardiac cycle) presents a spatiotemporal heterogeneity that in the ATAA model is  
328 markedly different from the healthy one, and which could be the consequence of the combination  
329 of the AAO dilatation and of the different shape of the (measured and imposed) inflow velocity



330 profile (reminding that (1) the investigated ATAA subject is affected by BAV, and (2) that the  
331 presence of valvulopathy could markedly affect the AAO hemodynamics [55].  
332 Figure 5 confirms that the differences in the spatiotemporal intravascular complexity  
333 characterizing the ATAA and healthy models reflect WSS magnitude waveforms heterogeneity. In  
334 detail, the distal segment of the AAO of the ATAA model is characterized by an extended region of  
335 the luminal surface of the dilated aorta exposed to  $|\tau|$  waveforms presenting a neighborhood  
336 which is smaller than in the healthy model (low  $DC$  values, Figure 5c). Therefore, in the diseased  
337 subject the pathologic expansion of the aortic wall where stiffness is higher (Figure 3) translates  
338 into WSS magnitude waveforms with a shape markedly different from the rest of the vessel.  
339 The impact of ATAA on the spatiotemporal hemodynamic heterogeneity in the AAO was evaluated  
340 also in terms of anatomical persistence length of the correlation between neighbor waveforms.  
341  $AED$  maps (Figure 6a-b) highlight how the aortic dilation disrupts the persistence of the correlation  
342 of the  $V_{ox}$  and  $H_k$  waveforms, breaking the topological connections among waveforms in the AAO  
343 and shortening the length of correlation, compared to the healthy model. Finally, the  
344 heterogeneity of WSS magnitude spatiotemporal features induced by AAO dilatation, already  
345 emerged from the  $DC$  maps, was confirmed by  $\overline{SPL}$  maps. More specifically, it was observed that  
346 the luminal surface of the distal dilated AAO presents larger areas where the functional length of  
347 correlation of WSS magnitude waveforms is smaller than the healthy AAO (Figure 6c).

#### 348 *Aortic hemodynamics vs. wall stiffness*

349 Here we assess the co-localization of the *in vivo* estimated wall stiffness at AAO outer wall of the  
350 ATAA model with the WSS topological skeleton-based quantities, and with canonical WSS-based  
351 descriptors of disturbed shear. A visual inspection of Figure 7 suggests that an association might  
352 exist between instantaneous WSS fixed points dynamics at the luminal surface and the aortic  
353 stiffness. Interestingly, instantaneous WSS fixed points undergo longer combinations of residence

354 time and marked contraction/expansion strength of the WSS vector field (as expressed by the  
355 quantity  $RT\bar{\nabla}_{x_{fp}}$ ) on those ATAA luminal surface areas where stiffness is high (Figure 7).

356 To explore more in depth the possible connections between peculiar WSS features and the altered  
357 biomechanical properties of the diseased aortic wall, the extent of the co-localization of high  
358 aortic wall stiffness regions with SAs exposed to presumably disturbed shear was quantified. By  
359 visual inspection of Figure 8a, it emerged that high stiffness co-localizes with high *TSVI* better than  
360 with canonical WSS-based descriptors. Of note, it was observed that SAs exposed to low TAWSS  
361 poorly co-localize with high stiffness regions. These observations were quantitatively confirmed by  
362 the SI values (Figure 8b), remarking the stronger capability of the WSS vector field divergence-  
363 based quantity *TSVI* as indicator of altered arterial wall mechanical properties, than the canonical  
364 WSS-based descriptors. Indeed, *TSVI* co-localizes with ATAA wall stiffness 206% more than TAWSS,  
365 15% more than OSI and transWSS, and 45% more than RRT.

366

## 367 **Discussion**

368 Wall dilatation/degeneration of the ascending aorta is a complex multifactorial process promoted  
369 by a unique bio-chemo-mechanical environment, which may ultimately lead to aortic wall  
370 dissection/rupture [7–13]. Despite a large body of literature focused on the role played by  
371 individual biological, chemical, or biomechanical factors in the ATAA development [12], the  
372 heterogeneity characterizing ATAA disease cannot be exhaustively explained by individual features  
373 and the analysis of their complex interplay is still poorly investigated [10,12].

374 In this context, here we aim to highlight the possible links between ATAA hemodynamics, obtained  
375 by CFD simulations and explored with advanced methods, and *in vivo* estimated wall mechanical  
376 properties, inversely derived from gated CT scans [30].

377 The findings of this study confirm, on the basis of an in-depth quantitative exploration, that the  
378 near-wall and intravascular hemodynamic environment characterizing the ATAA model markedly  
379 differs from the healthy aorta.

380 More in detail, the analysis of the WSS topological skeleton highlighted peculiar features on the  
381 ATAA outer wall, which are not or are poorly present on the luminal surface of the healthy  
382 ascending aorta (Figure 4), i.e.: (1) the presence of localized marked WSS contraction regions; (2)  
383 the appearance and persistence of instantaneous WSS fixed points along the cardiac cycle (as  
384 quantified by  $RT\bar{\nabla}_{x_{fp}}$ , which additionally weights the strength of the local contraction/expansion  
385 action exerted by the WSS); (3) a large luminal surface area undergoing marked variation in the  
386 WSS contraction/expansion action on the endothelium over the cardiac cycle (as indicated by  
387 *TSVI*).

388 From the CNS-based analysis, marked differences between ATAA and healthy aorta emerged in the  
389 organization of the intravascular hemodynamic patterns. In detail, here for the first time the  
390 disruption of spatiotemporal homogeneity of intravascular hemodynamic features induced by the

391 AAO dilatation was quantified in terms of the Euclidian length of persistence of the correlation  
392 between flow quantities. As indicated by *AED*, the presence of aortic dilation seems to reduce the  
393 anatomical length of correlation persistence both for the axial velocity and kinetic helicity density  
394 waveforms, compared to the healthy case (Figure 6).

395 This induced-by-aortic-dilation increase in AAO intravascular hemodynamics spatiotemporal  
396 heterogeneity reflects on a reduced functional length of correlation in WSS magnitude waveforms  
397 , localized on the distal outer wall, as indicated by  $\overline{SPL}$  (Figure 6). Such differences between ATAA  
398 and healthy models are further confirmed by the observed WSS magnitude *DC* luminal  
399 distribution, which highlights that in the dilated aorta the topologically isolated region is more  
400 extended than in the healthy one (Figure 5c). The latter result can be explained by the  
401 demonstrated causative role of helical flow in determining WSS patterns at the aortic luminal  
402 surface [28,29].

403 The evidences emerged from the WSS topological skeleton analysis and from the CNs-based  
404 analysis support the hypothesis that a complex interplay exists between hemodynamic features,  
405 aortic wall dilatation and its degradation in terms of wall mechanical properties. This statement is  
406 supported by the main finding of the study, i.e., that in the distal AAO outer wall of the ATAA  
407 model, extended high stiffness regions (indicating a degradation of the mechanical properties of  
408 the wall), co-localize with luminal surface areas of: (1) high instantaneous WSS fixed points  
409 residence time (weighted by WSS divergence value) (Figure 7); (2) large variations in the WSS  
410 contraction/expansion action exerted by the flowing blood along the cardiac cycle, here quantified  
411 by *TSVI* (Figure 8).

412 It is worth noting that the cross-sectional nature of this study does not allow to establish whether  
413 the observed hemodynamic features are responsible for wall dilatation and degradation, or  
414 whether they are consequence of the dilated geometry. However, previous studies suggested that

415 altered aortic flow predisposes the ascending thoracic aorta to wall dilatation/degradation [21,23]  
416 as a consequence of the purported role of endothelial shear in the pathogenesis of ATAA [56]. In  
417 this sense, the findings of this study suggest that future studies addressing the role of  
418 hemodynamics in the ascending thoracic aorta to wall dilatation/degradation should include  
419 descriptors based on the WSS topological skeleton, such as *TSVI* (Figure 8). In fact, such descriptors  
420 show a higher co-localization with regions at the aortic wall characterized by high stiffness than  
421 canonical WSS-based descriptors. The hemodynamic quantities presented here may improve the  
422 prediction of ATAA development and progression and contribute to a deeper understanding of the  
423 underlying hemodynamics-driven processes.

424

#### 425 *Limitations*

426 Several limitations could weaken the findings of this study. The main limitation is that the present  
427 analysis is based on only one ATAA model and one healthy aorta model. For this reason, we  
428 acknowledge that the here reported association between the WSS topological skeleton-based  
429 descriptor *TSVI* and ATAA wall weakening indicator should be confirmed on a larger dataset.  
430 The inverse approach here adopted to estimate local wall stiffness *in vivo* is based on the  
431 assumption that the aortic wall behaves as a membrane with no through-thickness shear [30,57].  
432 The regions near the supra-aortic branches may not satisfy such assumption and were therefore  
433 excluded from the wall stiffness analysis. Moreover, in the perspective of extending the analysis of  
434 aortic stiffness at different stages of ATAA growth, an extensive use of the inverse approach may  
435 be limited by the use of X-ray during the gated CT scans procedure. In this regard, other  
436 techniques, such as ultrasounds [58] or MRI [59], may be adopted as a source of dynamic images  
437 of the aortic wall during the cardiac cycle.

438 Finally, the main limitation regarding the numerical settings of the CFD study is represented by the  
439 rigid wall assumption. However, recent observations have demonstrated that aortic wall motion  
440 has a minor impact on WSS-based descriptors of disturbed shear [60], and on intravascular flow  
441 topology. Concerning the latter, for example, similar helical fluid structures have been observed *in*  
442 *vivo* [38,44,61] and *in vitro* both in rigid and distensible aortic phantoms [62,63]. Therefore, we  
443 believe that the assumption on aortic wall distensibility does not entail the generality of the  
444 present results.

445 **Conclusions**

446 In this study, the integration of computational hemodynamics, *in vivo* stiffness estimation and  
447 advanced fluid mechanics methods allowed to explore more in depth the existence of links  
448 between the altered hemodynamics in the ATAA and the wall biomechanical degradation.  
449 Moreover, combining WSS topological skeleton analysis and CNs-based analysis has highlighted  
450 that WSS topological skeleton features across the luminal surface of the ascending aorta are  
451 markedly affected by the different level of spatiotemporal heterogeneity characterizing the ATAA  
452 and healthy subjects' hemodynamics.

453 In conclusion, despite the exploratory nature of the study, advanced methods of analysis of the  
454 aortic blood flow have shown their very strong potential to decipher the links between local  
455 hemodynamics and the degradation of the mechanical properties of the aortic wall. In this sense,  
456 WSS topological skeleton analysis [25,26] and CNs-based analysis promise to be very effective  
457 tools [25,26].

458

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- 674

675 **Tables**676 *Table 1: Definition of WSS-based hemodynamic descriptors of “disturbed flow”.*

<b>WSS-based hemodynamic descriptors</b>	
Time Average WSS (TAWSS)	$\text{TAWSS} = \frac{1}{T} \int_0^T  \boldsymbol{\tau}  dt$
Oscillatory Shear Index (OSI)	$\text{OSI} = 0.5 \left[ 1 - \left( \frac{\left  \int_0^T \boldsymbol{\tau} dt \right }{\int_0^T  \boldsymbol{\tau}  dt} \right) \right]$
Relative Residence Time (RRT)	$\text{RRT} = \frac{1}{\text{TAWSS} \cdot (1 - 2 \cdot \text{OSI})} = \frac{1}{\frac{1}{T} \left  \int_0^T \boldsymbol{\tau} dt \right }$
Transversal WSS (transWSS)	$\text{transWSS} = \frac{1}{T} \int_0^T \left  \boldsymbol{\tau} \cdot \left( \mathbf{n} \times \frac{\int_0^T \boldsymbol{\tau} dt}{\left  \int_0^T \boldsymbol{\tau} dt \right } \right) \right  dt$

677  $\boldsymbol{\tau}$  is the WSS vector;  $T$  is the period of the cardiac cycle;  $\mathbf{n}$  is the unit vector normal to the arterial  
 678 surface at each element.

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680 **Figures captions**

681 **Figure 1. Schematics of the study.** The diagram shows how imaging data contribute to define vessel  
682 geometry, hemodynamic variables and wall mechanical properties. BCs: boundary conditions; CFD:  
683 computational fluid dynamics; ATAA: ascending thoracic aorta aneurysm; CNs: complex networks.

684 **Figure 2. WSS topological skeleton features.** (a) Configuration of each fixed point-type and  
685 contraction and expansion regions, colored by blue and red respectively. (b) Identification and  
686 classification of fixed points based on Poincaré index and eigenvalues of the Jacobian matrix.

687 **Figure 3. Estimated wall stiffness distribution at the luminal surface of ATAA model.**

688 **Figure 4. Luminal distributions of WSS topological skeleton-based metrics.** Aortic luminal  
689 distributions of (a) cycle-average WSS topological skeleton, (b) WSS fixed points weighted residence  
690 time ( $RT\mathbb{V}_{x_{fp}}$ ), and (c)  $TSVI$ . In panel (a), contraction/expansion regions are colored by blue/red,  
691 respectively, and Line Integral Convolution technique is adopted to visualize WSS vector. The ATAA  
692 and healthy aortic models are displayed in the top and bottom panel, respectively.

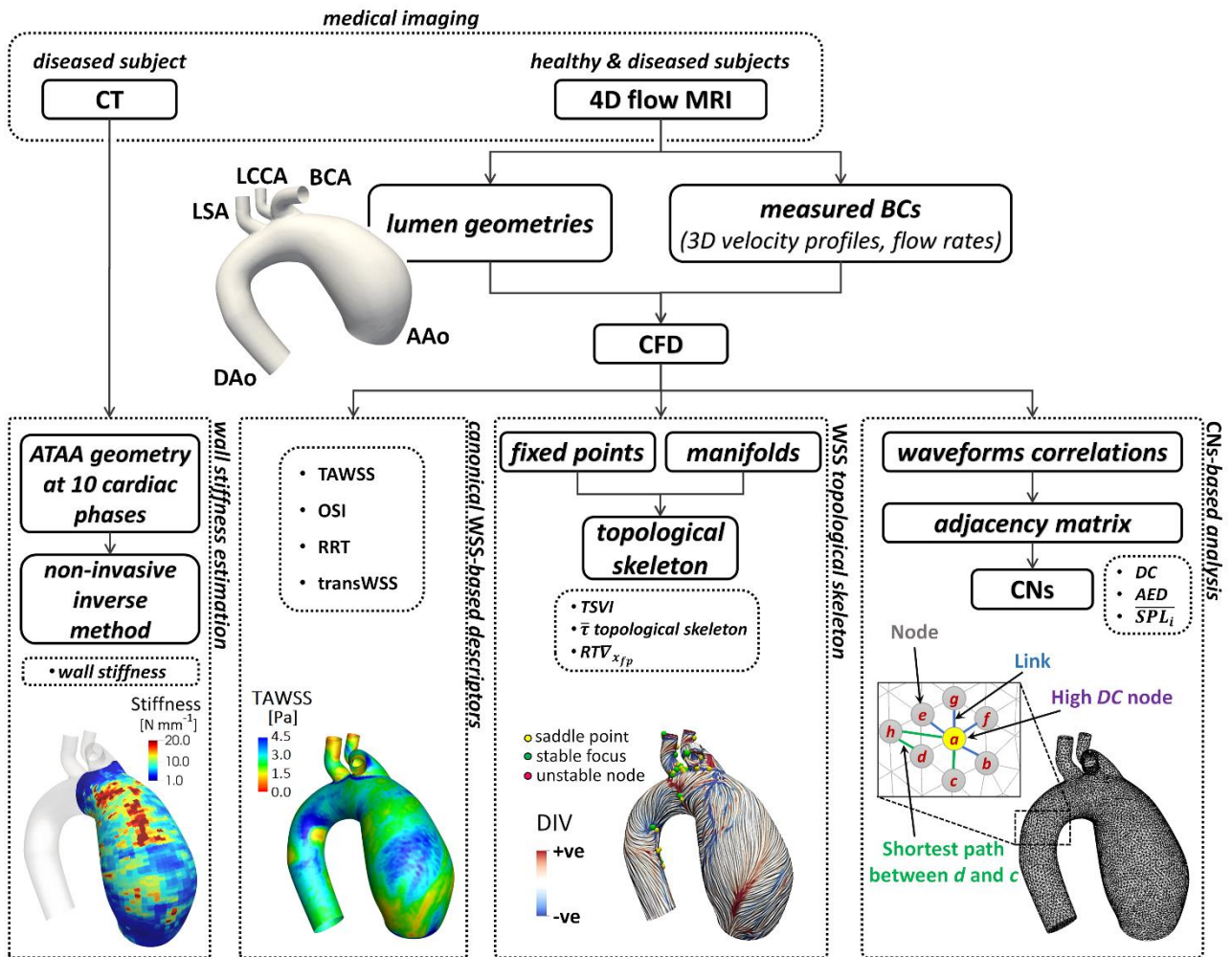
693 **Figure 5. DC distributions of hemodynamic descriptors-based CNs.** The  $DC$  distributions of the (a)  
694  $V_{ax}$ , (b)  $H_k$ , and (c)  $|\tau|$  CNs are displayed for the diseased (top) and healthy (bottom) subjects.

695 **Figure 6. Anatomical and topological length of correlation persistence of hemodynamic**  
696 **spatiotemporal patterns.** The  $AED$  distributions of the (a)  $V_{ax}$ , and (b)  $H_k$  CNs, and (c)  $\overline{SPL}$   
697 distribution of the  $|\tau|$  CNs are displayed for the diseased (top) and healthy (bottom) subjects.  $AED$   
698 and  $\overline{SPL}$  were computed at the ascending aorta segment of each model.

699 **Figure 7. Wall stiffness vs. weighted residence time analysis.** Contour maps of estimated wall  
700 stiffness (left) and WSS fixed points weighted residence time ( $RT\mathbb{V}_{x_{fp}}$  - right) at the luminal surface  
701 of ATAA model. The black contour line represents the 2<sup>nd</sup> tertile of stiffness luminal distribution at  
702 the ATAA outer wall.

703 **Figure 8. Wall stiffness vs. deranged aortic hemodynamics analysis.** (a) co-localization maps of high  
704 stiffness and disturbed shear; (b) similarity indices quantifying the co-localization of luminal SAs  
705 characterized by high stiffness and each descriptor of deranged hemodynamics (i.e., low TAWSS;  
706 high OSI, RRT, transWSS,  $TSVI$ ).

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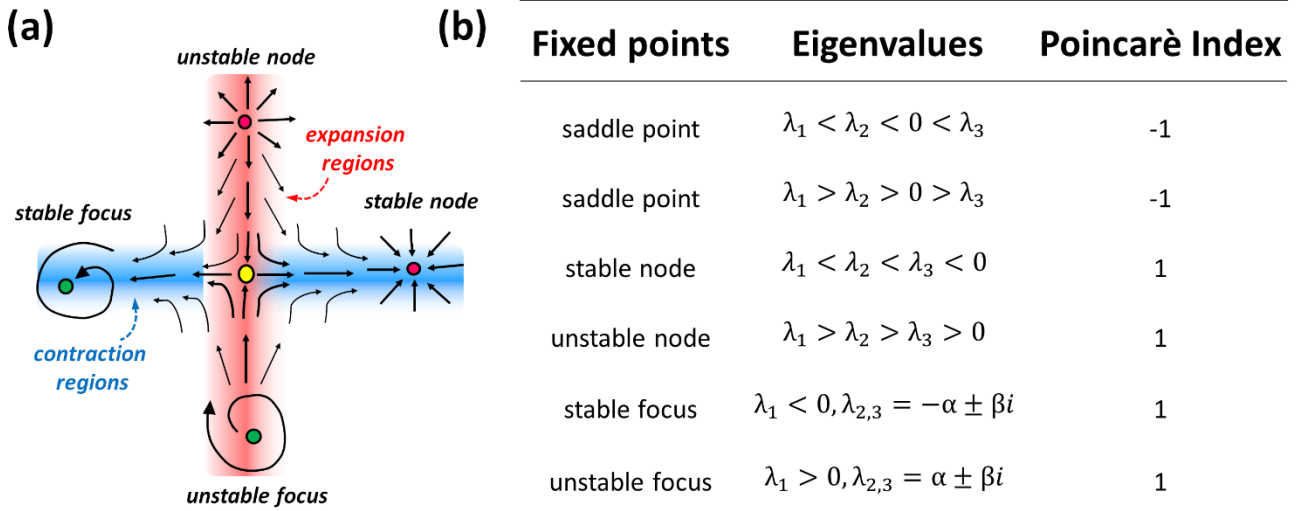


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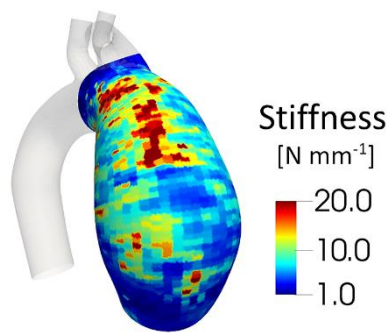
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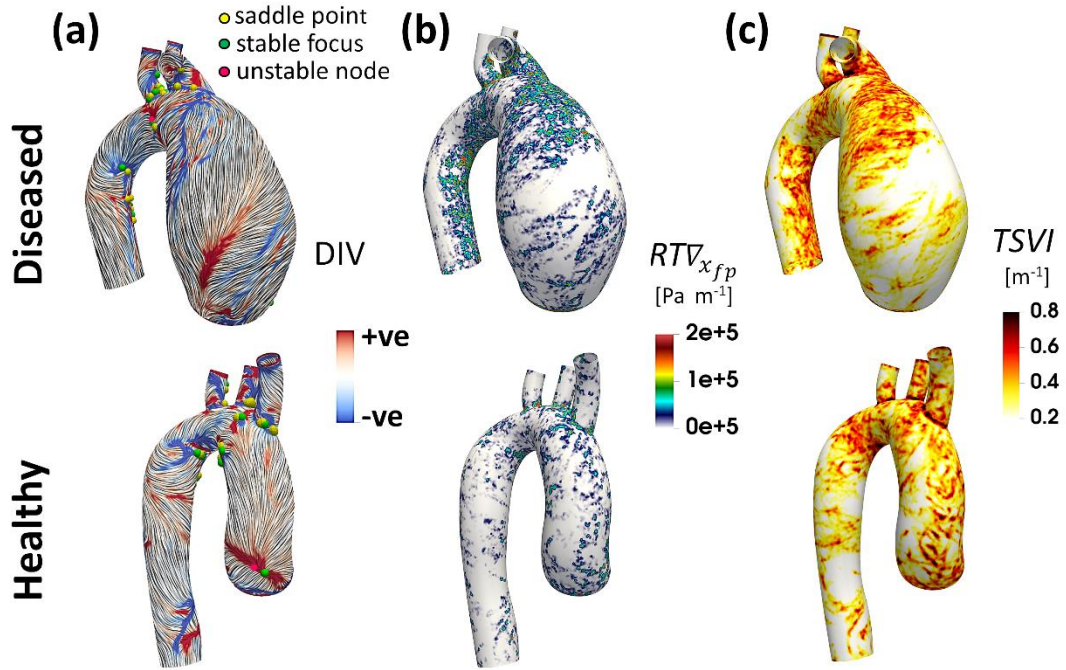
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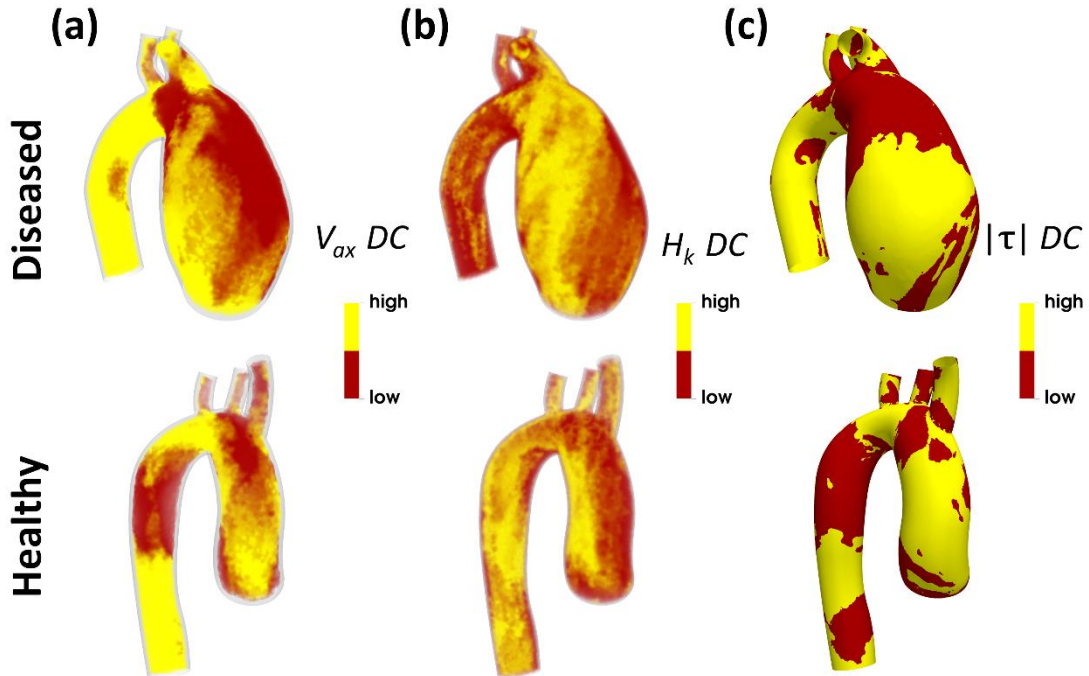
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 731 topological skeleton, (b) WSS fixed points weighted residence time ( $RT\nabla_{x_{fp}}$ ), and (c)  $TSVI$ . In panel (a), contraction/expansion regions  
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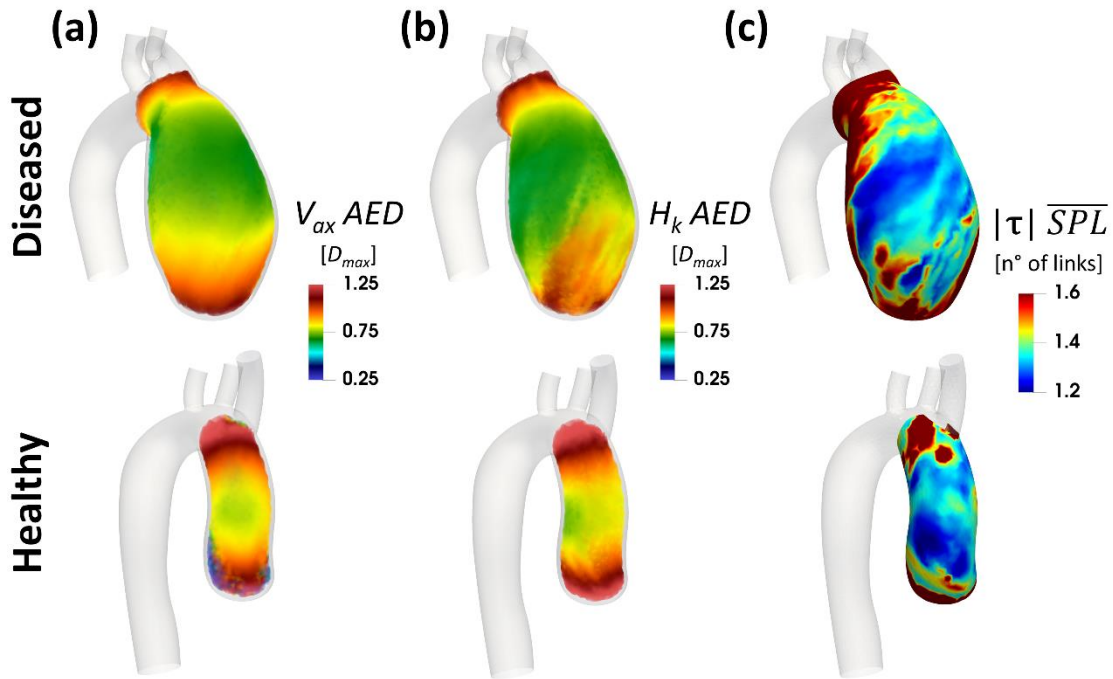
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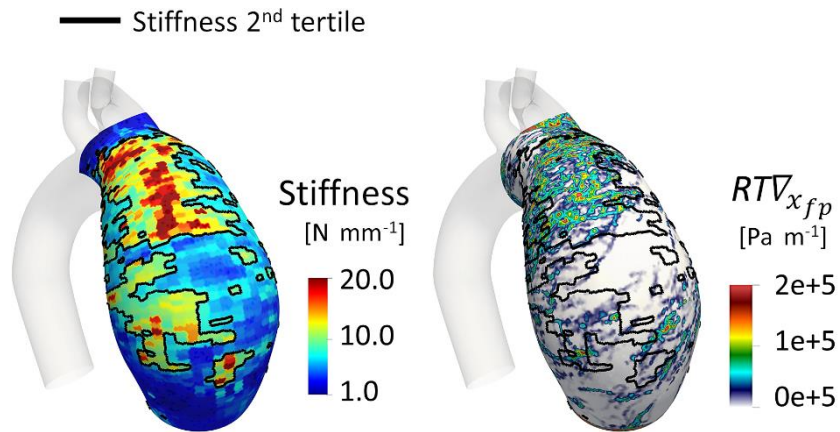
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740  
 741 **Figure 6. Anatomical and topological length of correlation persistence of hemodynamic spatiotemporal patterns.** The *AED*  
 742 distributions of the (a)  $V_{ax}$ , and (b)  $H_k$  CNS, and (c)  $\overline{SPL}$  distribution of the  $|\tau|$  CNS are displayed for the diseased (top) and healthy  
 743 (bottom) subjects. *AED* and  $\overline{SPL}$  were computed at the ascending aorta segment of each model.

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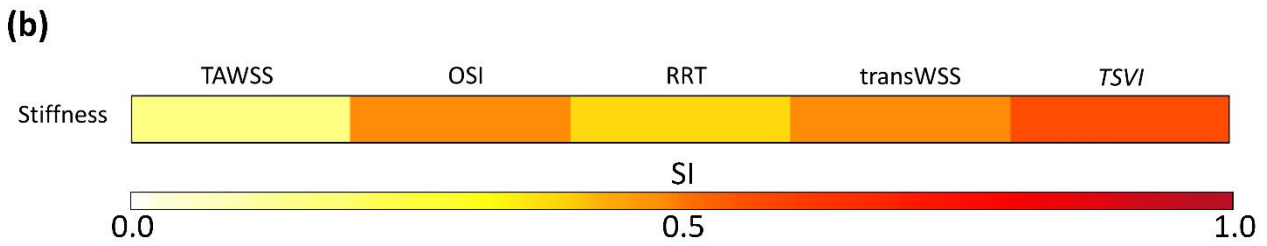
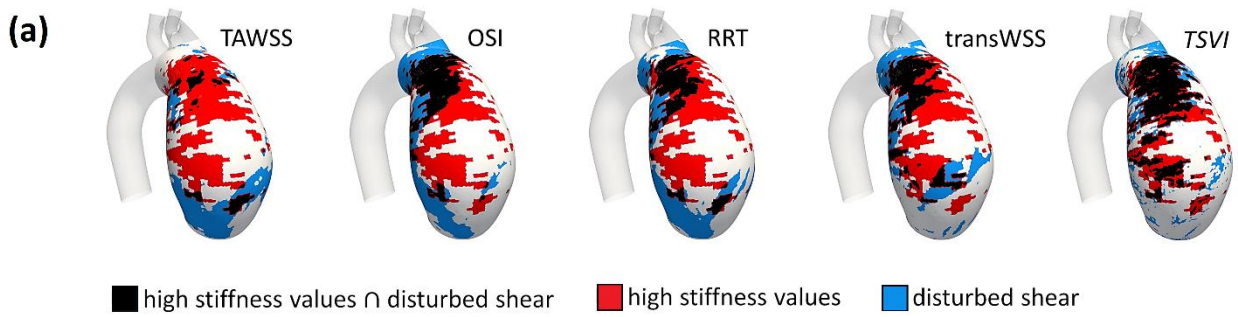
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