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# Investigating the impact of atrial fibrillation on the vascular onset of glaucoma via multiscale cardiovascular modeling

Stefania Scarsoglio<sup>a,b,\*</sup>, Luca Congiu<sup>a</sup>, Luca Ridolfi<sup>c,b</sup>

<sup>a</sup>*Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Corso Duca degli Abruzzi 24, Turin, (10129), Italy*

<sup>b</sup>*PolitoBioMed Lab, Politecnico di Torino, Corso Duca degli Abruzzi 24, Turin, (10129), Italy*

<sup>c</sup>*Department of Environmental, Land and Infrastructure Engineering, Politecnico di Torino, Corso Duca degli Abruzzi 24, Turin, (10129), Italy*

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## Abstract

Background and objective: Atrial fibrillation (AF) is the most common tachyarrhythmia, exhibiting faster and irregular beating. Although there is growing evidence of the impact of AF on the cerebral hemodynamics, ocular hemodynamic alterations induced by AF are still poorly investigated to date. The objective of this study is to computationally inquire into the role of AF on the ocular hemodynamics as one of the possible vascular triggers of glaucoma, which is the leading cause of blindness due to the damage of the optic nerve.

Methods: A validated 0D-1D multiscale cardiovascular model is exploited to compute the hemodynamic response of AF against sinus rhythm (SR), by simulating 2000 beats for each condition. To mimic AF rhythm, its main features are accounted for: (i) accelerated, variable and uncorrelated beating; (ii) absence of atrial kick; (iii) ventricular systolic dysfunction.

Results: We focused on intraocular pressure (*IOP*), ocular perfusion pressure (*OPP*), and translaminal pressure (*TLP*). Apart from a modest *OPP* decrease, beat-averaged values of *IOP* and *TLP* barely vary in AF with respect to SR. Instead, during AF a significant reduction and dispersion of pulsatile values (i.e., maximum minus minimum values reached in a beat),

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\*Corresponding author: stefania.scarsoglio@polito.it

as well as wave amplitude damping, is observed for *IOP*, *OPP* and *TLP*. The marked variability of pulsatile values, which are hardly measured due to clinical difficulties, can induce transient hypoperfusions and hypo-pulsatility events (for *OPP*) as well as hypertensive episodes (for *TLP*).

Conclusions: Awaiting necessary clinical data which are to date lacking, the present study can enrich - through hemodynamic-driven hints in the AF framework - the vascular theory, which associates reduced ocular perfusion (by means of decreased *OPP* and increased *TLP*) to an augmented risk of glaucoma. In this context, present modeling findings suggest a possible mechanistic link between AF-induced hemodynamic alterations and the increased risk of glaucoma development.

*Keywords:* atrial fibrillation, intraocular pressure, computational hemodynamics, glaucoma, cardiovascular multiscale modeling, ocular perfusion pressure, translaminal pressure

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## 1. Introduction

Atrial fibrillation (AF), characterized by a faster and irregular heart beating, is the most common cardiac arrhythmia and currently affects about 60 million subjects worldwide [1]. Due to the increasing life expectancy in Western countries, its incidence is expected to more than double within the next forty years [2]. Beside disabling symptoms - such as palpitations, chest discomfort and reduced exercise tolerance - there is growing evidence that AF is associated to cognitive decline, independently from clinical strokes [3, 4]. The alteration of cerebral hemodynamics during AF is extremely promising, though one of the least investigated mechanisms possibly relating AF and cognitive decline [4, 5]. Driven by the recent attention regarding the AF impact on the cerebral hemodynamics and considering that cerebral and ocular hemodynamics are intrinsically related through the retrobulbar subarachnoid space which is governed by the intracranial pressure (*ICP*), we here aim at investigating the acute response of ocular hemodynamics to AF events. In particular, we inquire into the role that AF-induced hemodynamics may play in the development of glaucoma.

Glaucoma is the leading cause of blindness due to the damage of the optic nerve, with 80 million people affected worldwide [6]. Although an increased intraocular pressure (*IOP*) is believed to be a major risk factor and the main trigger mechanism for glaucoma [6, 7], the underlying mechanisms are

22 debated. According to the vascular theory, two parameters defined through  
23  $IOP$  - namely the ocular perfusion pressure,  $OPP = Pa_{eye} - IOP$  (where  
24  $Pa_{eye}$  is the arterial pressure at the eye level), and the translaminar pressure,  
25  $TLP = IOP - ICP$  - play a key role. In particular, a decreased  $OPP$  and  
26 an increased  $TLP$  are potential markers associated with the increased risk of  
27 glaucoma development [7–9]. However, existing literature investigating the  
28 link between  $OPP$  and glaucoma is divided, as in subjects with glaucoma  
29 mean  $OPP$  is found to increase [10–12], remain equal [13–15], and reduce  
30 [16–18], with respect to the control population. Thus, definitive findings  
31 either confirming or refuting vascular theory are still missing.

32 *In vivo* measurements investigating the role of AF on the ocular hemo-  
33 dynamics and the development of glaucoma are even more contrasting, also  
34 considering the very few number of studies. A significant association between  
35 AF and glaucoma development was found [19, 20], even if results on  $IOP$   
36 are not definitive, showing a modest increase [21], but also a reduction [22].  
37 In this context of lack of clinical data, the adoption of a cardiovascular mod-  
38 eling framework can be greatly valuable to shed light on the hemodynamic  
39 mechanisms induced by AF able to alter  $IOP$ . Although not focused on  
40 the AF-ocular hemodynamics link, a number of computational approaches  
41 have been in fact successfully proposed to investigate the cardiovascular re-  
42 sponse in presence of cardiac arrhythmias, by focusing on the cerebral [23–28],  
43 cardiac-coronary [29–32], valvular [33, 34], and arterial [35–37] hemodynam-  
44 ics, as well as the thromboembolic risk in the left atrial appendage [38–40].

45 We here propose a 0D-1D multiscale cardiovascular model - previously  
46 exploited and validated in different pathological [29, 30, 35, 41] and altered  
47 gravity [42–46] conditions - to study the AF effects on the ocular hemo-  
48 dynamics and thus contribute to understand the possible vascular link between  
49 AF and glaucoma. The model combines a 1D description of the arterial tree  
50 and coronary circulation, with a 0D representation of the distal circulation,  
51 venous return, cardiopulmonary and cerebro-ocular circulations. The overall  
52 model is equipped with baroreflex and cardiopulmonary regulation mecha-  
53 nisms, as well as cerebral autoregulation, and explicitly accounts for posture  
54 and gravity changes. Through a stochastic modeling, we aim at investigating  
55 the impact of acute AF on the ocular hemodynamics variables with respect  
56 to the sinus rhythm (SR). We considered two representative configurations  
57 of SR and AF rhythms imposed on a generic healthy young patient in supine  
58 posture, by simulating for each condition 2000 beats to guarantee the statis-  
59 tical significance of the outcomes. SR was simulated at the typical resting

60  $HR$  (mean 70 bpm) with Gaussian distributed and time-correlated regular  
61 beats. AF configuration instead accounted for the most important AF fea-  
62 tures: (i) accelerated, variable and uncorrelated beating (mean 90 bpm),  
63 extracted from an exponentially-modified Gaussian distribution; (ii) absence  
64 of atrial kick; (iii) ventricular systolic dysfunction (i. e., reduced left and  
65 right ventricular contraction) [31, 32, 36]. After validating the model by  
66 means of typical central cardiovascular parameters - such as stroke volume,  
67 cardiac output and mean arterial pressure - we focused on significant ocu-  
68 lar circulation parameters,  $IOP$ ,  $OPP$  and  $TLP$ . The comparison between  
69 SR and AF allowed us to quantify the net hemodynamic impact of AF on  
70 the ocular compartment and inquire into its possible mechanistic role in the  
71 development of glaucoma.

## 72 2. Methods

73 The present study was conducted exploiting a 0D-1D multiscale closed-  
74 loop model of the cardiovascular system. The model has been recently and  
75 extensively validated against posture [43, 46, 47] and gravity [42, 44, 45]  
76 changes, as well as in AF conditions [29, 30, 35]. The present modeling ap-  
77 proach allowed to obtain a reliable description of several characteristics of  
78 the cardiovascular system and currently comprises a 1D representation of  
79 the systemic arterial and coronary circulations linked to several 0D lumped  
80 parameter compartments that describe the peripheral, venous, cardiopul-  
81 monary, and cerebral-ocular circulations. In the next sections, we will recall  
82 the most relevant features of the whole model, by focusing on the ocular  
83 compartment. Complete modeling details are offered in the Supplementary  
84 Material. Then, the stochastic approach to simulate SR and AF is presented,  
85 paying attention to the hemodynamic features characterizing AF rhythm.

### 86 2.1. Cardiovascular modeling

87 The 1D model consists of 63 main large arteries, which are described as  
88 straight tapered vessels, with a circular cross-sectional shape. The blood  
89 motion is described by one-dimensional mass and momentum conservation  
90 equations, where the cross-section area  $A(x, t)$  and the flow  $Q(x, t)$  are the  
91 dependent variables, being  $x$  and  $t$  the axial space coordinate and the time,  
92 respectively. At each inlet/outlet, mass and momentum conservation are set  
93 as boundary condition. A constitutive equation, linking  $P(x, t)$  and  $A(x, t)$ ,  
94 is introduced to describe the non-linear mechanical behavior of the large

95 arteries. The blood is modeled as a Newtonian fluid with density  $\rho = 1050$   
96  $\text{kg/m}^3$ .

97 The 1D model is connected to the 0D peripheral circulation compart-  
98 ments, each described by an electric analog circuit. The terminal branches  
99 of the main arteries interface with the arteriolar vessels, which are modelled  
100 using characteristic impedances,  $Z_c$ . Downstream the arteriolar compart-  
101 ments, the terminal of the coronary arteries is connected to a lumped model  
102 of the coronary microcirculation bed, which provides a distinctive identifica-  
103 tion of the vasculature perfusing each myocardial layer - from the subepicar-  
104 dial, through the intermediate midwall, up to the subendocardial circulation  
105 - each described into arterial, intermediate, and venous subcompartments.  
106 The internal carotid and the vertebral arteries are linked to a 0D cerebro-  
107 ocular model, which starts with a lumped representation of the main large  
108 cerebral arteries of the circle of Willis. Then, six branches extend from the  
109 circle of Willis to supply the right and left pial circulation. The pial circu-  
110 lation is followed by the intracerebral arteriolar circulation, which is further  
111 subdivided into anterior, middle, and posterior circulation, interconnected  
112 through collateral vessels. Ultimately, the intracerebral arteriolar circulation  
113 merges into one capillary-venous compartment that, along with the ocular  
114 circulation, connects to the superior vena cava.

115 The remaining terminal branches other than coronary and cerebral arterioles  
116 merge into five macro-regions that describe the microcirculation of legs, lower  
117 abdomen, upper abdomen, arms, and head. Each of the five macro-regions is  
118 divided into three compartments, representing the capillary, venule, and vein  
119 circulations. The leg and arm venous compartments include a model of the  
120 venous valve that prevents the reversal flow. Finally, three compartments  
121 conclude the venous return with the abdominal, inferior, and superior venae  
122 cavae, the latter including a venous collapse mechanism. Additional lumped  
123 parametrizations are adopted for the four cardiac chambers and valves, and  
124 the pulmonary circulation. The cardiac contractility is modeled employing  
125 time-varying elastances, one specific for the atria and one for the ventricles.  
126 The four cardiac valves are represented by four non-ideal diodes, accounting  
127 for various factors affecting the valve leaflets such as tissue friction, pressure  
128 and inertial forces, and the influence of downstream vortexes.

129 The model is equipped with short-term regulation mechanisms, account-  
130 ing for the baroreceptors, the cardiopulmonary reflex, the cerebral autoreg-  
131 ulation and the  $\text{CO}_2$  reactivity regulation. The baroreceptor modeling rules  
132 the chronotropic effect, the inotropic effect of both the ventricles, and the

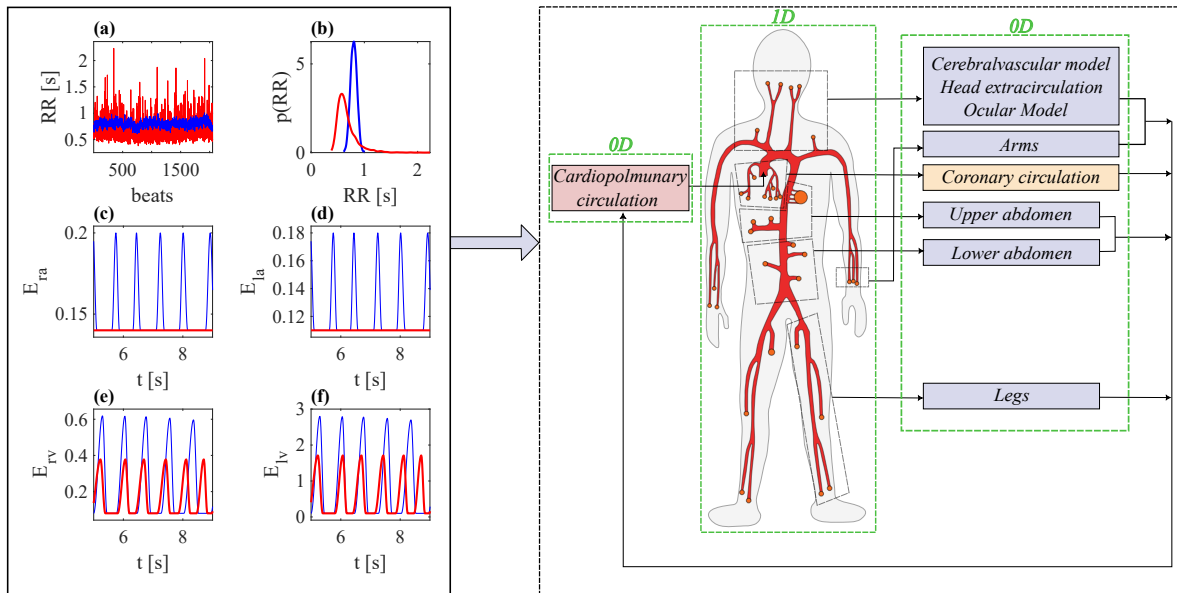


Figure 1: Scheme of the stochastic modeling approach. Left: hemodynamic features of AF (red) versus SR (blue) beating. (a)-(b)  $RR$  time-series and probability density functions (pdfs); (c)-(d) right and left atrial elastances, (e)-(f) right and left ventricular elastances (all the elastances are expressed in mmHg/ml). Right: scheme of the 0D-1D cardiovascular model.

133 regulation of systemic vascular resistances, venous compliances, and venous  
 134 unstressed volumes. The cardiopulmonary reflex plays the same role as the  
 135 baroreceptors, except for the inotropic and chronotropic effects. The cere-  
 136 bral autoregulation and CO<sub>2</sub> reactivity regulation control the resistances and  
 137 compliances of the pial circulation.

138 A schematic picture of the overall model is shown in the right box of Fig.  
 139 1, while details and governing equations are reported in the Supplementary  
 140 Material.

### 141 2.1.1. Ocular Model

142 The 0D ocular model consists of 6 compartments, each describing a fun-  
 143 damental feature of the ocular circulation. The first compartment is the  
 144 retrobulbar arachnoid space (rSAS), anatomically located on the posterior  
 145 eye. While this compartment does not exchange fluids with other compart-  
 146 ments, it affects the total ocular volume by employing *ICP*-driven defor-  
 147 mations described by the compliance  $C_{rg}$ . The aqueous humor compartment  
 148 presents an aqueous humor inflow  $Q_{aq,in}$ , and outflow  $Q_{aq,out}$ , both connected  
 149 to the capillary-venous section of the cerebral model. An additional passive  
 150 compartment accounts for all the eye structures that do not change in vol-  
 151 ume, such as the lens and vitreous humor. Finally, the eye blood circulation  
 152 is modeled by employing three compartments connected in series that ac-  
 153 count for the arterial, capillary, and venous circulation. The circulations  
 154 of the choroid and retina, which collectively encompass all the eye blood  
 155 circulation, are lumped together in the three blood compartments.

156 The equations governing the intraocular pressure (*IOP*) and the globe  
 157 volume ( $V_g$ ) are:

$$\frac{dIOP}{dt} = \frac{1}{C_g} \left( C_{rg} \frac{dICP}{dt} + C_{ag} \frac{dPa_{eye}}{dt} + C_{vg} \frac{dPv_{eye}}{dt} + Q_{aq,in} - Q_{aq,out} \right) \quad (1)$$

$$\frac{dV_g}{dt} = C_{ag} \frac{d(Pa_{eye} - IOP)}{dt} + C_{vg} \frac{d(Pv_{eye} - IOP)}{dt} + Q_{aq,in} - Q_{aq,out} \quad (2)$$

158 The ocular arterial pressure  $Pa_{eye}$  is defined as the average pressure be-  
 159 tween the right and left internal carotids. The ocular venous pressure  $Pv_{eye}$   
 160 is assimilated to the maximum value between the central venous pressure  
 161 (*CVP*) and the episcleral venous pressure (*EVP*):

$$Pa_{eye} = 0.5 (P_{ICA_l} + P_{ICA_r}) - L_{f-b} \rho g \cos \alpha \quad (3)$$

$$EVP = P_{svc} - \rho g \left( \frac{L_H}{2} + \frac{L_{svc}}{2} \right) \sin \alpha - L_{f-b} \rho g \cos \alpha \quad (4)$$

$$Pv_{eye} = \max[CVP, EVP] \quad (5)$$

162 where  $L_{f-b} = 0.03$  m is the perpendicular distance between the globe and  
 163 the mid-coronal plane;  $L_H = 0.15$  m is the vertical anatomical length of the  
 164 head.

165 The aqueous humor inflow is set  $Q_{aq,in} = 0.048 \cdot 10^{-6}$  l/s, while the aqueous  
 166 humor outflow rate  $Q_{aq,out}$  is defined as:

$$Q_{aq,out} = C_{tm} (IOP - EVP) + Q_{uv} \quad (6)$$

167 where  $C_{tm} = 0.0035 \cdot 10^{-6}$  l/(s·mmHg) is the aqueous outflow facility, and  
 168  $Q_{uv}$  is the uveoscleral outflow. The  $C_g$  is the globe compliance, while  $C_{ag}$   
 169 and  $C_{vg}$  are the arterial-globe and venous-globe compliances, respectively,  
 170 defined as:

$$C_g = V_g \left( \frac{C_1}{IOP} + C_2 \right) \quad (7)$$

$$C_{ag} = 0.3V_g \left( \frac{C_1}{IOP} + C_2 - \frac{1}{k_g IOP} \right) \quad (8)$$

$$C_{vg} = 0.7V_g \left( \frac{C_1}{IOP} + C_2 - \frac{1}{k_g IOP} \right) \quad (9)$$

171 where  $C_1 = 4.87 \cdot 10^{-3}$  1/mmHg,  $C_2 = 3.90 \cdot 10^{-5}$  1/mmHg and  $k_g = 312$   
 172 [46].

173 To integrate the ocular model with the global cardiovascular model, ar-  
 174 terial eye input ( $Q_{a_{eye}}$ ) and venous eye output ( $Q_{v_{eye}}$ ) flow are estimated  
 175 as:

$$Q_{a_{eye}} = C_{ag} \left( \frac{d(Pa_{eye} - IOP)}{dt} \right) + Q_{eye} \quad (10)$$

$$Q_{v_{eye}} = Q_{eye} - C_{vg} \left( \frac{d(Pv_{eye} - IOP)}{dt} \right) \quad (11)$$

176 where  $Q_{eye}$  is the eye flow rate and is determined by the equation  $Q_{eye} =$   
 177  $(Pa_{eye} - Pv_{eye})/R_{eye}$ , being  $R_{eye}$  the resistance of the capillary bed (repre-  
 178 sented as a rigid compartment) and set to 4676 mmHg·s/ml. More details on  
 179 governing equations and parameter setting are offered in the Supplementary  
 180 Material.

## 181 2.2. SR and AF features

182 The model was employed to inquire into ocular hemodynamics during  
 183 physiological SR and AF, by simulating the cardiovascular response of a  
 184 generic healthy young patient in supine posture. To avoid the patient-specific  
 185 details (e.g., sex, age, weight, and cardiovascular diseases) inherited by real  
 186  $RR$  beating, we exploited artificially built  $RR$  intervals -  $RR$  [s] is the cardiac  
 187 beating period, with the heart rate,  $HR = 60/RR$ , expressed in [bpm] - in  
 188 both rhythms, as done in previous studies [29, 31, 33–35].

189  $RR_{SR}$  intervals in SR configuration were extracted from a correlated pink  
 190 Gaussian distribution with mean value  $\mu_{SR} = 0.857s$  ( $HR = 70$  bpm) and  
 191 a coefficient of variation  $cv_{SR} = 0.07$  (see [29, 31, 35, 48] and therein ref-  
 192 erences). The  $RR_{SR}$  time-series and the corresponding probability density  
 193 functions (pdfs) are reported in blue in the left box of Fig. 1, panels (a, b).

194 Concerning AF, three typical features were included: (i) faster, irregular,  
 195 and uncorrelated  $RR$  beating; (ii) absence of atrial kick; (iii) left and right  
 196 ventricular systolic dysfunction [31, 32, 35, 36]. The AF beating ( $RR_{AF}$ )  
 197 was obtained by superposing two statistically independent times: the first  
 198 obtained from a correlated pink Gaussian distribution and the second from  
 199 an uncorrelated exponential distribution. The  $RR_{AF}$  (Figure 1a, red curve)  
 200 was extracted from the resulting uncorrelated exponentially-modified Gaus-  
 201 sian distribution (Figure 1b, red curve), with  $\mu_{AF} = 0.67s$  ( $HR = 90$  bpm)  
 202 - as a faster  $HR$  is commonly found in AF -  $cv_{AF} = 0.26$  [48], and  $\gamma = 6$  Hz  
 203 (see [31, 49, 50] and therein references). The absence of atrial kick, which  
 204 characterizes the loss of atrial contraction during AF [51, 52], was simulated  
 205 by imposing a constant left and right atrial elastance (Figure 1, panels c and  
 206 d, red curves) [31, 32, 35, 36]. In this way, the atria contribution of the ven-  
 207 tricles filling (atrial kick) is impaired. Finally, reduced left [53–55] and right  
 208 [56] ventricular systolic function is generally observed during AF and this  
 209 aspect was modeled by decreasing both left and right maximum left ventric-  
 210 ular elastances by 40 % with respect to their baseline values (Figure 1, panels  
 211 e and f, red curves). A moderate ventricular impairment was here chosen,  
 212 given the heterogeneity of clinical [53–56] and modeling [31, 32, 36] literature

213 in this regard and the difficulty in translating ventricular dysfunction into  
214 elastance terms [51].

215 After the modeling system exceeds the numerical transient (first 50 beats),  
216 a total of 2000 beats for each SR and AF condition in supine posture were  
217 simulated to guarantee the results reach a statistical stationarity state. For  
218 the central hemodynamics validation (see Section 3.1), we considered the fol-  
219 lowing parameters: stroke volume  $SV = V_{lved} - V_{lves}$  (where  $V_{lved}$  and  $V_{lves}$   
220 are left ventricular end-diastolic and end-systolic volumes, respectively), ejec-  
221 tion fraction  $EF = SV/V_{lved}$ , cardiac output  $CO = SV \cdot HR$ , mean systemic  
222 (MAP) and pulmonary (MPAP) arterial pressures. For the ocular hemody-  
223 namics (see Section 3.2), we focused on primary ocular variables: the in-  
224 traocular pressure,  $IOP$ , the ocular perfusion pressure,  $OPP = Pa_{eye} - IOP$ ,  
225 and the ocular translaminar pressure,  $TLP = IOP - ICP$ . Such primary  
226 variables involve in their definition some auxiliary variables: arterial and  
227 venous pressures at the level of the eye,  $Pa_{eye}$  and  $Pv_{eye}$  (here in supine po-  
228 sture taken as the internal carotid pressure and the central venous pressure,  
229 respectively), and intracranial pressure,  $ICP$ .

### 230 3. Results

231 To validate our modeling approach, we will first present a comparison on  
232 the central hemodynamics between our model findings and available litera-  
233 ture regarding SR and AF, see Section 3.1. Then, after an overview of the  
234 time-series of ocular variables in SR and AF (Section 3.2.1), we will focus  
235 on a beat-to-beat analysis on the ocular hemodynamic alterations induced  
236 by AF (Section 3.2.2). The few hemodynamic ocular measures in AF will be  
237 discussed in comparison with modeling outcomes in the next sections. We  
238 recall that the present model has been recently and extensively validated  
239 against posture [43, 46, 47] and gravity [42, 44, 45] changes, as well as in AF  
240 conditions [29, 30, 35].

#### 241 3.1. Model validation with literature data: central hemodynamics

242 Table 1 compares the present numerical simulations (left columns) with  
243 clinical data measured in literature (right columns), in terms of common cen-  
244 tral hemodynamic parameters. For validation purposes, we choose to show  
245 only the parameters that are extensively and reliably measured in the litera-  
246 ture. However, it should be recalled that the model can provide many other

|            | Present simulations |       |            |      |      |                           | Clinical literature |       |       |       |            |
|------------|---------------------|-------|------------|------|------|---------------------------|---------------------|-------|-------|-------|------------|
|            | Mean                |       |            | cv   |      |                           | SR                  |       | AF    |       |            |
|            | SR                  | AF    | $\Delta\%$ | SR   | AF   | $\frac{cv_{AF}}{cv_{SR}}$ | Mean                | Std   | Mean  | Std   | $\Delta\%$ |
| HR [bpm]   | 70                  | 90    | 28.57      | 0.07 | 0.26 | 3.78                      | 66.84               | 11.91 | 81.83 | 23.44 | 22.42      |
| SV [ml]    | 76.31               | 50.74 | -33.51     | 0.03 | 0.08 | 3.23                      | 77.48               | 25.57 | 52.13 | 15.98 | -32.72     |
| EF [%]     | 61.61               | 42.06 | -31.74     | 0.02 | 0.07 | 3.56                      | 63.63               | 6.90  | 53.08 | 12.42 | -16.58     |
| CO [l/min] | 5.36                | 4.78  | -10.84     | 0.06 | 0.21 | 3.66                      | 5.35                | 2.28  | 4.29  | 1.46  | -19.83     |
| MAP [mmHg] | 90.74               | 86.73 | -4.42      | 0.03 | 0.05 | 1.92                      | 89.59               | 12.14 | 93.90 | 12.31 | 4.81       |
| MPAP[mmHg] | 15.49               | 15.48 | -0.12      | 0.02 | 0.05 | 2.47                      | 19.06               | 8.51  | 21.51 | 7.25  | 12.87      |

Table 1: Central hemodynamics: present numerical simulations (left) against clinical literature (right). Heart rate ( $HR$ ), stroke volume ( $SV$ ), ejection fraction ( $EF$ ), cardiac output ( $CO$ ), mean arterial pressure ( $MAP$ ), and mean pulmonary arterial pressure ( $MPAP$ ) are listed. The simulations column reports the mean and the coefficient of variation ( $cv$ ) of each signal, along with the percentage differences between the SR and AF mean values and the  $cv$  ratios in AF and SR conditions. Statistically significant differences were found between SR and AF values for all signals by means of the Wilcoxon test ( $p < 0.01$ ). The clinical literature column provides the mean and standard deviation (Std) of the available data in literature, and the percentage differences between the SR and AF mean values.

247 cardiovascular details (such as cardiac-coronary hemodynamics, cerebral cir-  
248 culation, arterial patterns and venous return), here not displayed because  
249 out of the validation scope. The mean and coefficient of variation ( $cv$ ) values  
250 obtained with the model are computed over 2000 beats in SR and AF ( $cv$  is  
251 the ratio between standard deviation and mean values). For literature data  
252 reported in Table 1, the mean value is computed as the average value among  
253 the cited studies and weighted over the sample size of each, while standard  
254 deviation (Std) is computed as referred to the weighted mean value. Table  
255 SM11 in the Supplementary Material reports detailed values and references  
256 for each literature study here exploited for validation. In order to better dis-  
257 play the range of variability of the clinical data, Fig. 2 shows the variations  
258 from SR to AF of the parameters measured in the literature (Mean $\pm$ Std)  
259 and simulated (mean) by the model, as reported in Table 1.

260 Although  $HR$  is an input parameter imposed in our analysis (and not  
261 directly exploitable for validation), a first preliminary comment is due. Lit-  
262 erature results show an overall mean increase in  $HR$  around +22%, when  
263 passing from SR to AF. Thus, the here modelled  $HR$  mean increase from 70  
264 to 90 bpm (about +29%) when passing from SR to AF realistically mimics  
265 the well-known feature of accelerated beating, which is generally found in  
266 AF and documented in literature.

267 Figure 2 makes evident that, for both SR and AF configurations and  
 268 all the parameters analyzed, the mean values predicted by the model (red  
 269 crosses) fall within the measurement range [Mean - Std, Mean + Std] given  
 270 by the clinical literature (black lines). More in details, in clinical literature  
 271 both stroke volume,  $SV$ , and ejection fraction,  $EF$ , exhibit a remarkable  
 272 decrease (-33% and -17%, respectively). In good agreement with measure-  
 273 ments, our model predicts a relevant decrease in AF: -34% and -32% for  
 274  $SV$  and  $EF$ , respectively.  $SV$  (and consequently  $EF$ ) reduction is due to  
 275 three main mechanisms all implemented in our model to simulate AF: (i)  
 276  $HR$  increase, which reduces the necessary time to adequate ventricular emp-  
 277 tying and filling; (ii) absence of atrial kick, responsible of the ventricular  
 278 filling for about 20%; and (iii) reduced ventricular contractility (i.e., ventric-  
 279 ular systolic dysfunction). The fact that  $EF$  decreases more in the model  
 280 (-32%) than in literature (-17%) is due to the interplay between increased  
 281  $HR$  (which decreases  $V_{lved}$ ) and ventricular systolic dysfunction (which in-  
 282 creases  $V_{lved}$  [36]), resulting in a slight change of  $V_{lved}$  in AF, thus inducing  
 283 a marked  $EF$  reduction in AF. Cardiac output,  $CO$ , is measured to reduce  
 284 by about 20% on average during AF, in front of a mean reduction in AF of  
 285 about 11% predicted by the modeling approach. A smaller reduction in  $CO$   
 286 (-11%) compared to the literature (-20%), can be due to a greater increase  
 287 of  $HR$  during AF in our model (+29%) compared to the measurements in  
 288 the literature (+22%). In fact, given a similar  $SV$  reduction (-34% model,  
 289 -33% clinical literature), a higher  $HR$  mitigates the  $CO$  reduction.

290 Mean systemic ( $MAP$ ) and pulmonary ( $MPAP$ ) arterial pressure values  
 291 per beat are perhaps the most controversial hemodynamics variables in AF,  
 292 since the heart rate variability causes problems to oscillometric instruments  
 293 and noninvasive blood pressure measurements [31].  $MAP$  slightly increases  
 294 during measured AF (+5%), while the model predicts a quite negligible re-  
 295 duction (-4%). As for  $MPAP$ , the mean value is observed to mildly increase  
 296 in AF measurements (+13%), while no variation emerges from our numer-  
 297 ical results. The overall picture is that the marginal variations for  $MAP$   
 298 and  $MPAP$  observed by the model are due to the action of baroreceptors  
 299 and cardiopulmonary receptors, which maintain in AF the levels of central  
 300 mean pressures close to the physiological values of the SR. These modest  
 301 variations highlighted by the model fall within the range of variability of the  
 302 data measured in the literature, as shown in Fig. 2.

303 In addition to the mean values of the hemodynamic parameters evaluated  
 304 over 2000 simulated beats and compared with the literature, Table 1 also

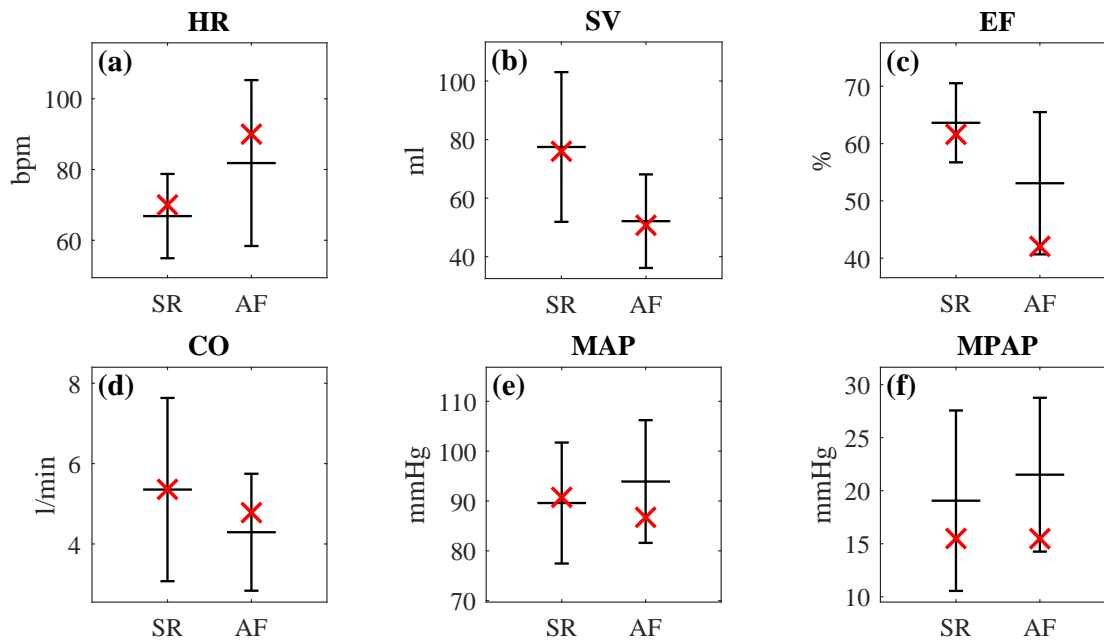


Figure 2: Central hemodynamics in SR and AF: present numerical simulations (red crosses) against the range of variability [Mean - Std, Mean + Std] given by the clinical literature (black lines). (a) Heart rate, HR; (b) stroke volume, SV; (c) ejection fraction, EF; (d) cardiac output, CO; (e) mean systemic arterial pressure, MAP; (f) mean pulmonary arterial pressure, MPAP.

305 reports the cv values obtained from these simulations. All the parameters  
 306 show a more marked variability in AF than SR. It can be observed that the  
 307 higher *RR* variability imposed (cv=0.07 in SR, cv=0.26 in AF) result in cv  
 308 values in AF about 1.9-3.8 times higher than SR. The lowest  $cv_{AF}/cv_{SR}$  ratios  
 309 are found for *MAP* (1.9) and *MPAP* (2.5), again confirming the ability of  
 310 short-term autoregulation mechanisms to counteract AF-induced alterations  
 311 at central (systemic and pulmonary) pressures level.

### 312 3.2. Ocular hemodynamics in SR and AF

#### 313 3.2.1. Overview of the ocular variables

314 To introduce the ocular hemodynamic response to AF, Fig. 3 shows rep-  
 315 resentative time-series of primary (*IOP*, *OPP*, *TLP*) and auxiliary ( $Pa_{eye}$ ,  
 316  $Pv_{eye}$ , *ICP*) variables, as simulated in SR and AF. We will first explain the  
 317 behavior of the primary variables as a function of the auxiliary ones, and  
 318 then we will compare the trends in AF (red curves) with those in SR (blue  
 319 curves).

320 As displayed in Eq. (1), *IOP* in supine posture depends on  $Pa_{eye}$ ,  $Pv_{eye}$ ,  
 321 and *ICP*. Since the retrobulbar subarachnoid space-to-globe compliance,  
 322  $C_{rg}$ , is two orders of magnitude lower than the arterial,  $C_{ag}$ , and venous,  
 323  $C_{vg}$ , blood-to-globe compliances, time derivatives of  $Pa_{eye}$  and  $Pv_{eye}$  terms  
 324 basically rule the *IOP* dynamics. Between these two differential terms, given  
 325 the much higher arterial wave amplitude with respect to the venous one  
 326 (see panels a and b of Fig. 3), *IOP* is mainly governed by  $Pa_{eye}$ . The  
 327 significant dependence of *IOP* on  $Pa_{eye}$  was already observed considering  
 328 posture changes [46]. To this end, a law linking *IOP* variations only to  
 329 changes of blood pressure at the level of the eye has been proposed, which  
 330 is consistent with the understanding that acute *IOP* changes result from  
 331 gravitationally driven blood pressure changes [57]. The strong  $IOP(Pa_{eye})$   
 332 link is here confirmed also in supine condition, as can be observed comparing  
 333 panels (a) and (e) of Fig. 3, and considering that the Pearson correlation  
 334 coefficient between  $Pa_{eye}$  and *IOP* time-series is 0.99 in both SR and AF.

335 As *IOP* time-series is strongly correlated to  $Pa_{eye}$ , *OPP* due to its defi-  
 336 nition ( $Pa_{eye} - IOP$ ) is in turn strictly linked to  $Pa_{eye}$ . Panels (a), (e), and  
 337 (c) clearly show very similar trends for  $Pa_{eye}$ , *IOP*, and *OPP* times-series,  
 338 respectively. We recall that *OPP*, being a pressure difference, is a measure  
 339 of the ocular perfusion and its decrease has been associated to an augmented  
 340 risk for glaucoma according to the vascular theory [7].

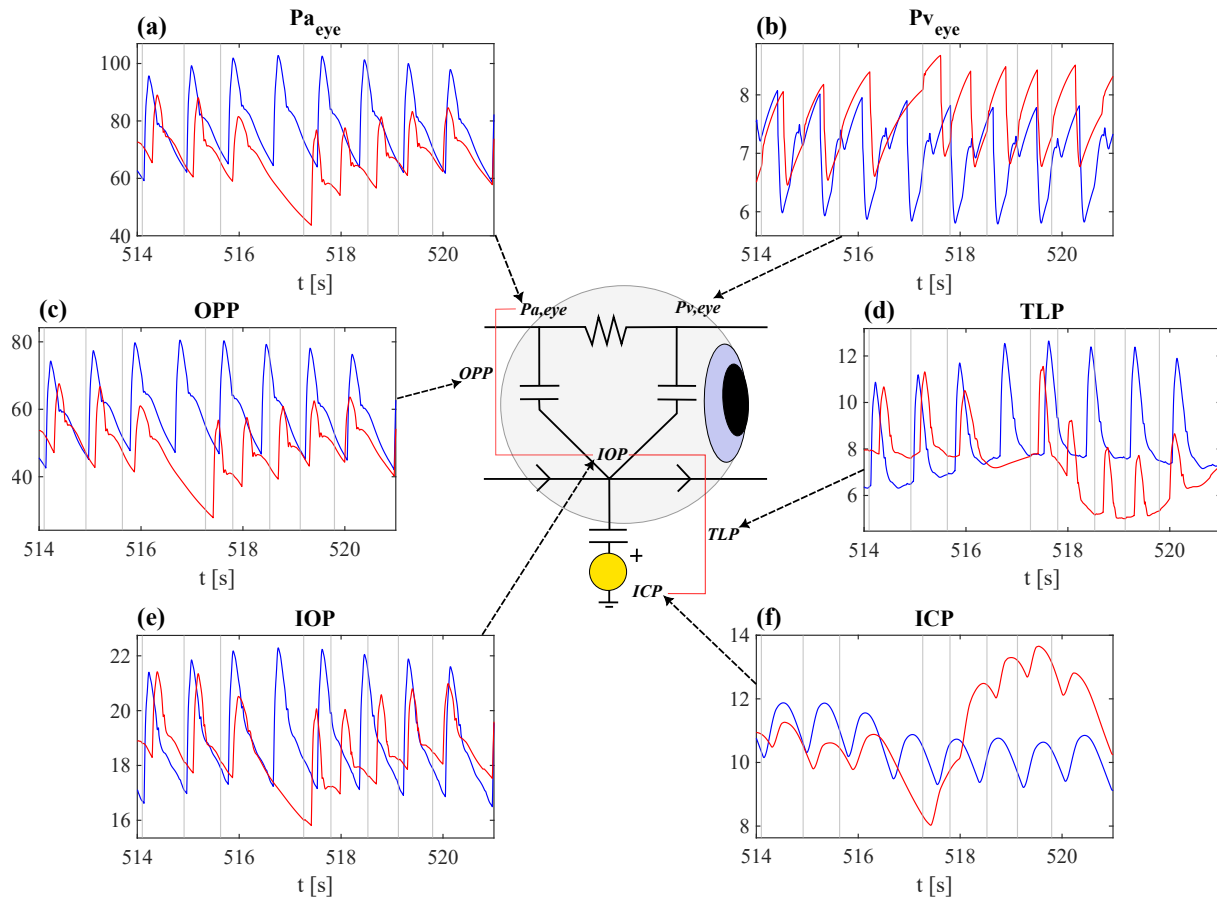


Figure 3: Representative time-series of primary and auxiliary ocular variables in SR (blue curves) and AF (red curves): (a)  $P_{a,eye}$ , (b)  $P_{v,eye}$ , (c)  $OPP$ , (d)  $TLP$ , (e)  $IOP$ , (f)  $ICP$ . All variables are expressed in mmHg.

341 In the end, the ocular translaminar pressure  $TLP$  is driven mainly by  $IOP$   
342 - especially regarding the pulsatile waveform pattern in SR (please, compare  
343 blue curves in panels (e) and (d) of Fig. 3) - as confirmed by the Pearson  
344 correlation coefficient between  $TLP$  and  $IOP$ , that results  $\rho=0.93$  in SR,  
345  $\rho=0.81$  in AF. However,  $ICP$  has a non-negligible effect on  $TLP$  (Pearson  
346 correlation coefficient between  $TLP$  and  $ICP$ ,  $\rho=-0.34$  in SR,  $\rho=-0.49$  in  
347 AF), which is more evident in the increasing/decreasing wave patterns over  
348 several beats occurring in AF (please, compare red curves in panels (d) and  
349 (f) of Fig. 3). Notice that  $TLP$  is a marker for increased glaucoma risk,  
350 being  $TLP$  higher in glaucoma patients [8, 9].

351 Comparing AF with respect to SR, all signals exhibit a higher variability  
352 in AF, by reaching lower diastolic values (and greater wave amplitude) after  
353 long beats and higher systolic values (and smaller wave amplitude) after short  
354 beats. This is especially true for cardiac ( $Pv_{eye}$ ) and proximal ( $Pa_{eye}$ ) signals,  
355 as well as signals ruled by central hemodynamics, that is  $IOP$  and  $OPP$ . For  
356 these four signals (panels (a), (b), (c), (e)), the alteration induced by one  
357 (short or long) beat is almost completely absorbed within the subsequent  
358 1-2 beats. Differently, in the case of  $TLP$ , where the influence of the distal  
359  $ICP$  signal is not negligible, the AF-induced variability is not recovered on a  
360 single beat scale, but gives rise to ascending/descending patterns over several  
361 beats (see panels (d) and (f)). This behavior is entirely attributable to the  
362 distal cerebral hemodynamics, on which  $ICP$  strongly depends. Due to the  
363 complex temporal interplay of distal resistances and compliances acting like  
364 springs in series and parallel, it has been observed that during AF in the  
365 cerebral microcirculation the latency in recovering the equilibrium state is  
366 much higher than at proximal level [24, 26]. As a consequence, when the AF  
367 irregularity propagates towards the distal regions,  $ICP$  and related variables  
368 remain altered for longer, as clearly visible in panels (d) and (f) of Fig. 3.

### 369 3.2.2. Beat-to-beat analysis: mean and pulse values

370 To quantify the AF-induced variability qualitatively described in the pre-  
371 vious section, we here propose a beat-to-beat analysis on the primary and  
372 auxiliary ocular variables in which we investigate the mean and pulsatile  
373 (defined as maximum minus minimum) values calculated over the beat.

374 Table 2 reports mean and cv values of beat-averaged ocular variables,  
375 together with percentage variations of mean values and cv ratios between  
376 AF and SR. Mean values of all primary and auxiliary variables show modest  
377 (within 8%) variations between SR and AF, while cv ratios between AF and

|                     | Mean  |       |            | cv   |      |                           |
|---------------------|-------|-------|------------|------|------|---------------------------|
|                     | SR    | AF    | $\Delta\%$ | SR   | AF   | $\frac{cv_{AF}}{cv_{SR}}$ |
| $P_{a_{eye}}[mmHg]$ | 77.16 | 72.94 | -5.47      | 0.03 | 0.06 | 1.91                      |
| $P_{v_{eye}}[mmHg]$ | 6.99  | 7.38  | 5.52       | 0.01 | 0.03 | 2.23                      |
| ICP[mmHg]           | 10.50 | 10.88 | 3.60       | 0.03 | 0.07 | 2.32                      |
| IOP[mmHg]           | 18.81 | 19.20 | 2.04       | 0.02 | 0.03 | 1.71                      |
| OPP[mmHg]           | 58.34 | 53.74 | -7.89      | 0.03 | 0.07 | 1.97                      |
| TLP[mmHg]           | 8.31  | 8.32  | 0.07       | 0.05 | 0.09 | 2.00                      |

Table 2: Mean and coefficient of variation (cv) values of beat-averaged ocular variables in SR and AF conditions. Percentage variations between the mean values in SR and AF conditions and ratios between cv values in AF and SR are reported. All variables show a statistical significant difference (Wilcoxon test) between SR and AF with p-value < 0.01, with the only exception of *TLP* (p-value=0.025).

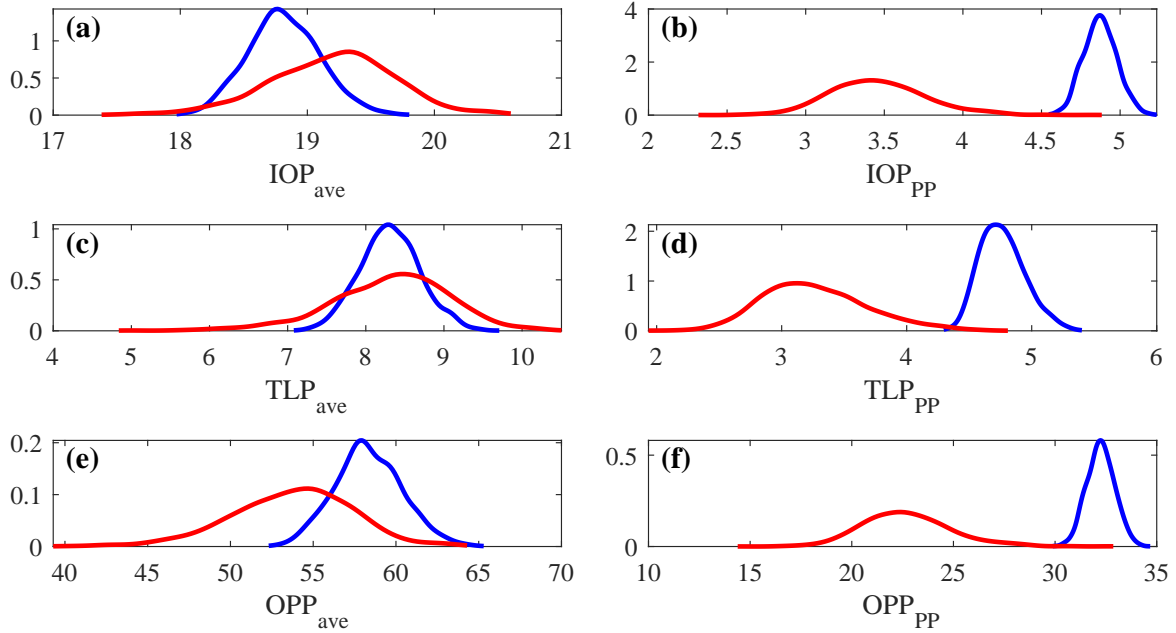


Figure 4: Probability density functions of beat-averaged (left panels) and pulse (right panels) values of primary ocular variables (IOP, TLP, OPP), in SR (blue curves) and AF (red curves). All variables are expressed in mmHg.

|                         | Mean  |       |            | cv   |      |                           |
|-------------------------|-------|-------|------------|------|------|---------------------------|
|                         | SR    | AF    | $\Delta\%$ | SR   | AF   | $\frac{cv_{AF}}{cv_{SR}}$ |
| $Pa_{eye}[\text{mmHg}]$ | 37.12 | 26.16 | -29.53     | 0.02 | 0.10 | 4.50                      |
| $Pv_{eye}[\text{mmHg}]$ | 2.02  | 1.59  | -21.23     | 0.03 | 0.08 | 3.27                      |
| $ICP[\text{mmHg}]$      | 1.51  | 0.84  | -44.29     | 0.12 | 0.32 | 2.72                      |
| $IOP[\text{mmHg}]$      | 4.87  | 3.46  | -29.00     | 0.02 | 0.09 | 4.14                      |
| $OPP[\text{mmHg}]$      | 32.24 | 22.70 | -29.60     | 0.02 | 0.10 | 4.55                      |
| $TLP[\text{mmHg}]$      | 4.77  | 3.27  | -31.48     | 0.04 | 0.13 | 3.40                      |

Table 3: Mean and coefficient of variation (cv) values for the pulsatile pressures of the ocular variables in SR and AF conditions. Percentage variations between the mean values in SR and AF conditions and ratios between cv values in AF and SR are reported. All variables show a statistical significant difference (Wilcoxon test) between SR and AF with p-value < 0.01.

378 SR vary from 1.7 to 2.3. The slight mean variation and the much more  
379 marked variability of beat-averaged values in AF is also observable in the  
380 probability density functions of Fig. 4, where in the left panels distributions  
381 of beat-averaged values of primary ocular variables ( $IOP$ ,  $TLP$ ,  $OPP$ ) are  
382 displayed in SR (blue) and AF (red) conditions. In fact, although SR and  
383 AF distributions are centered around comparable mean values (the highest  
384 variation around 8% is found for  $OPP$ , which reduces as a combination of  
385  $Pa_{eye}$  decrease and  $IOP$  increase), the probability of reaching very high/low  
386 beat-averaged values substantially increases in AF.

387 Table 3 shows mean and cv values of pulsatile pressure for ocular vari-  
388 ables, as well as percentage variations and ratios between AF and SR. Pul-  
389 satile pressure mean values overall decrease in AF for all the variables ob-  
390 served and this is mainly induced by the reduction of  $SV$  (about - 33%) and  
391 central aortic pulse pressure (about -31%). More in details, primary ocular  
392 variables (and also  $Pa_{eye}$ , which is an important determinant of them) ex-  
393 perience mean pulse pressure reduction around 30%, which is close to those  
394 observed by  $SV$  and central aortic pulse pressure.  $Pv_{eye}$  shows smaller mean  
395 pulse pressure variations in AF (about -21%), probably due to the nature  
396 of retrograde pulsatility characterizing venous signals more similarly in SR  
397 and AF.  $ICP$  is instead the variable with the greatest pulsatility reduction  
398 in AF (over -44%) as a consequence of the same mechanism - explained in

399 the previous section - of the greater latency of the cerebral microcircula-  
400 tion in recovering the equilibrium state, which therefore further amplifies the  
401 signal alteration (i.e., pulse pressure reduction) compared to what happens  
402 in the proximal region ( $Pa_{eye}$ ) [24, 26]. We recall that pulsatile pressure  
403 yields important information, and it is difficult to be *in vivo* monitored for  
404 such cerebro-ocular variables. Indeed, current techniques assessing the ocular  
405 blood flow - such as laser Doppler flowmeter and optical coherence tomog-  
406 raphy angiography - present limited temporal resolution which allows only  
407 mean blood flow to be computed. Laser speckle contrast imaging - providing  
408 diastole-to-systole perfusion - is a promising technique, however the manage-  
409 ment of filtering movement artifacts and the choice of exposure time make  
410 it still not entirely suitable for large-scale use. Thus, clinical literature typi-  
411 cally reports only beat-averaged values. The overall mean pulsatile pressure  
412 reduction in AF is itself an index of reduced variability, as the hemodynamic  
413 signals damp their maximum-to-minimum range. This outcome is enriched  
414 by the cv value of pulsatile pressures per beat. The ratio  $cv_{AF}/cv_{SR}$ , spread-  
415 ing between 2.7 and 4.5, evidences a high pulsatile pressure variability in AF.  
416 This means that the probability of having very high or low pulsatile values  
417 markedly increases in AF with respect to SR.

418 Right panels of Fig. 4 display probability density functions of pulsatile  
419 values for primary ocular variables ( $IOP$ ,  $TLP$ ,  $OPP$ ) in SR (blue) and AF  
420 (red) conditions. By graphically highlighting the statistics of Table 3, the  
421 distributions show that in AF the probability of having spread and reduced  
422 pulsatile values significantly increases for the three variables, so that reaching  
423 physiological values of pulsatile pressures in AF is extremely rare (right tails  
424 in AF barely reach SR mean values).

#### 425 4. Discussion

426 Let us focus on the two ocular parameters  $OPP$  and  $TLP$ , by means of  
427 beat-averaged and pulsatile values. Our simulations show that mean values  
428 of beat-averaged  $OPP$  and  $TLP$  slightly differ in AF and SR, while cv values  
429 markedly increase in AF. This implies that mean perfusion and tensile level  
430 are maintained in AF at an adequate level similar to SR. However, the in-  
431 creased variability in AF results in a higher probability of possible transient  
432 hypoperfusions (low  $OPP$ ) and hypertensive events (high  $TLP$ ), which are  
433 potential sources of ocular stress. Although some studies observed that high

434 pulsatile variability could be detrimental at ocular level [58–61], literature is  
435 still debated so that no clear clinical implications can be drawn.

436 Pulsatile values decrease on average by about 30% for both *OPP* and  
437 *TLP* in AF, thus signals amplitude is damped with respect to SR. The main  
438 driver of this mechanism is the reduced central pressure pulsatility, which in  
439 turn is induced by the *SV* reduction (recall that *SV* is proportional to the  
440 central pulsatile pressure [62]). The pulsatility damping at ocular level is  
441 found with the same magnitude as present at central level (the pulsatility of  
442 both *OPP* and *TLP* reduces around -30% similarly to *SV*), and alteration  
443 or dysfunction of short-term regulatory mechanisms (such as dysautonomia)  
444 can further enhance these changes. The reduction of mean pulsatile values  
445 for *OPP* and *TLP*, being itself a marker of reduced variability, should be ac-  
446 counted for together with the strong increase of *cv* values by 3.5 to 4.5 times  
447 in AF. The combination of these two mechanisms (mean value decrease and  
448 *cv* value increase of beat pulsatility) decreases the probability of having phys-  
449 iological pulsatile *OPP* and *TLP* values in AF, as evidenced by the pdfs in  
450 right panels of Fig. 4. Pulsatile pressure - which can be easily deduced by  
451 the modeling approach but hardly measured *in vivo* - is a crucial parameter  
452 to enrich the description of the hemodynamic variability induced by AF. Al-  
453 though there is no clear threshold level of pulsatility reduction beyond which  
454 ocular damage can occur, we recall that myocardial contractility reduction  
455 is considered clinically relevant when EF drops 20% or more [62]. Thus, we  
456 can assume that ocular pulsatility reduction of 20% or more, as happens for  
457 *OPP* and *TLP*, can be as well clinically relevant.

458 To further understand the link between ocular hemodynamics and heart-  
459 beating - which is a fundamental aspect in AF as *RR* beats are accelerated,  
460 uncorrelated and much more disperse - Fig. 5 shows scatterplots of beat-  
461 averaged (left panels) and pulsatile (right panels) values of *TLP* and *OPP*  
462 as function of the previous *RRs* (i.e., the *RR* value of the current beat and  
463 the *TLP* and *OPP* value of the next beat are the coordinates of each point  
464 in the scatterplots). It can be noted that: (i) beat-averaged and pulsatile  
465 values for both *TLP* and *OPP* are quite sparse in SR, as the coefficient of  
466 variation,  $R^2$ , does not exceed 0.3; (ii) for pulsatile values (right panels) the  
467 correlation with the previous *RR* increases in AF, as  $R^2$  is beyond 0.5 for  
468 both *OPP* and *TLP*.

469 By combining the analysis beat-averaged and pulsatile values (Tables  
470 2 and 3, respectively, and Figure 4) together with scatterplots, the overall  
471 picture emerging in AF with respect to SR for *TLP* and *OPP* is the following:

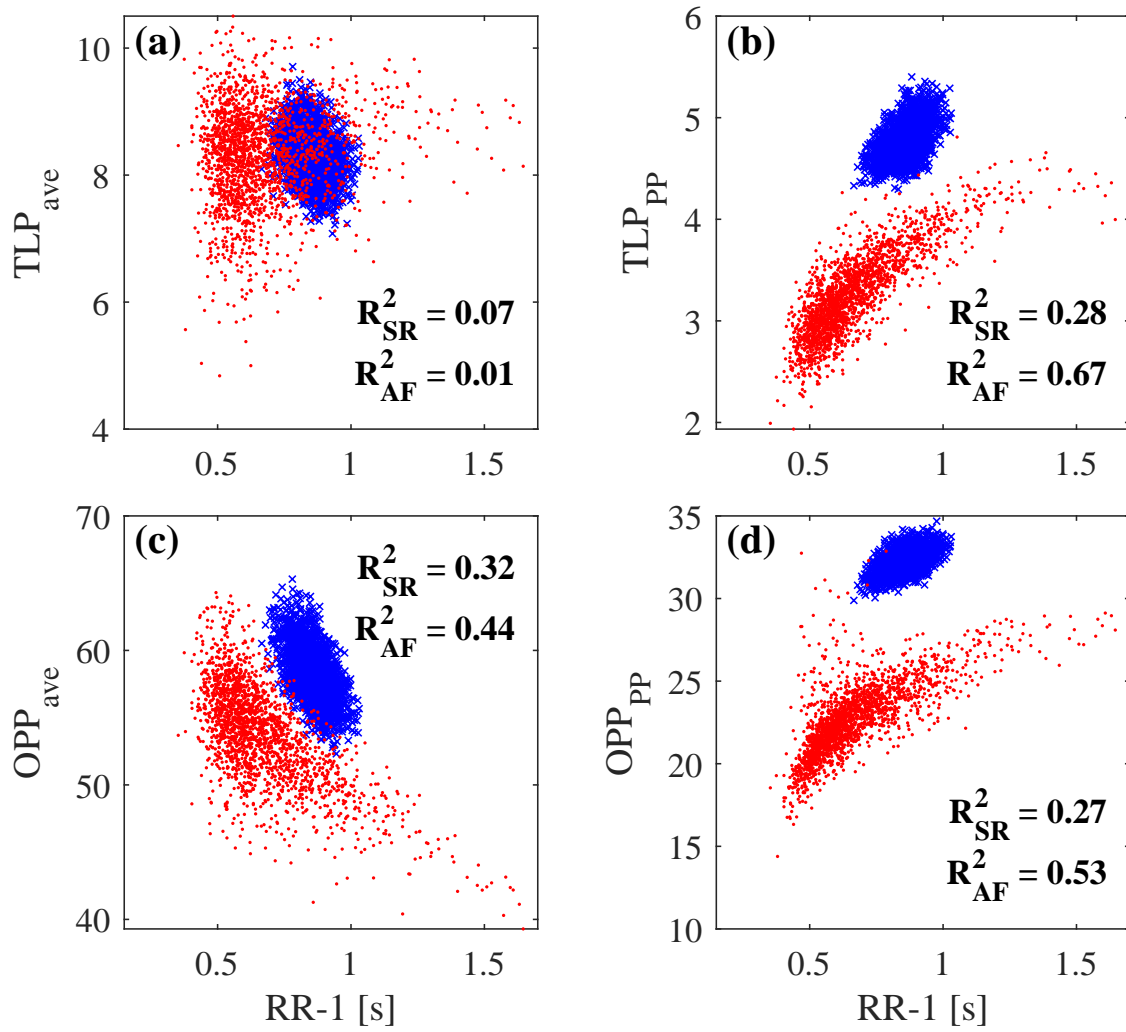


Figure 5: Scatterplots of beat-averaged values and  $RR$  (left panels), pulsatile values and  $RR$  (right panels), with the corresponding coefficients of determination,  $R^2$ , in SR (blue curves) and AF (red curves). Top panels:  $TLP$ . Bottom panels:  $OPP$ .

- 472 • *TLP*. Beat-averaged values show no correlation with *RR* ( $R^2=0.01$ )  
473 and their mean value remains constant, even if the distribution is more  
474 spread enhancing the probability of very high or low values. Instead,  
475 mean pulsatile value decreases significantly. In particular, given the  
476 positive correlation ( $R^2=0.67$ ) between pulsatile values and *RR*, short  
477 beats (which are the majority in the distribution) give rise to an ade-  
478 quate beat-averaged value (see panel 5a), though are not able to tem-  
479 porarily guarantee a physiological perfusion due to the extremely re-  
480 duced pulsatility (see panel 5b). On the other hand, only very long  
481 beats (although AF-induced and out-of-range with respect to SR) pro-  
482 vide a nearly physiological *TLP* response for both beat-averaged and  
483 pulsatile values.
- 484 • *OPP*. Beat-averaged values evidence a negative correlation with *RR*  
485 ( $R^2=0.44$ ) and their mean value slightly decreases. Mean pulsatile  
486 values markedly decrease and (similarly to *TLP*) pulsatile values are  
487 correlated with *RR* ( $R^2=0.53$ ). This framework induces possible tran-  
488 sient ocular hypoperfusions and hypo-pulsatility events triggered by  
489 two mechanisms (see panels (see panel 5c-d)): (i) for long beats, pul-  
490 satile value is almost in the physiological range, but beat-averaged per-  
491 fusion is lower than normal; (ii) for short beats, beat-averaged level is  
492 adequate, but pulsatility is too damped to guarantee a physiological  
493 excursion range.

494 In short, from a hypoperfusion viewpoint, short beats are the most haz-  
495 ardous for *TLP*, while both short and long beats are risky for *OPP*. We  
496 recall that, according to the vascular theory [7], an *OPP* decrease has been  
497 associated to an augmented risk for glaucoma. However, clinical literature  
498 investigating the link between *OPP* and glaucoma is debated, as in subjects  
499 with glaucoma *OPP* is found to increase [10–12], remain equal [13–15], and  
500 reduce [16–18], with respect to the control population. Thus, definitive find-  
501 ings either confirming or refuting the vascular theory are not available to  
502 date.

503 *In vivo* measurements investigating the role of AF on the ocular hemodynam-  
504 ics are very few and for these reaching a clear overall picture is even more  
505 difficult. Some studies concluded that a significant association between AF  
506 and glaucoma development exists [19, 20], even if results on *IOP* are con-  
507 trasting, showing a modest increase [21], but also a reduction [22]. In this

508 clinical picture, the present model reveals a very modest mean *IOP* increase  
509 which, combined to a more consistent  $Pa_{eye}$  reduction, leads to an average  
510 *OPP* decrease by 8%. However, our model unveils that reduced ocular per-  
511 fusion can also be achieved by a waveform damping mechanism related to the  
512 reduction of the signal pulsatility, which to the best of our knowledge is not  
513 reported in literature as hardly measurable. The *OPP* amplitude decrease  
514 captured by the model can yield, especially for short beats, hypo-pulsatility  
515 events due to the non-physiological excursion range. If the overall emerging  
516 picture is interpreted in view of the vascular theory, present modeling find-  
517 ings suggest that AF-induced hemodynamic changes can increase the risk  
518 of glaucoma development. Finally, the marked pulsatility variability (i.e.,  
519 the alternation of hypo/hyper-tensive or hypo/hyer-perfusive events on the  
520 single-beat scale), although not clinically investigated due to experimental  
521 difficulties, could *per se* abnormally stimulate the ocular hemodynamics. If  
522 the link between AF and glaucoma is confirmed, detection of optimal (rate or  
523 rhythm control) strategies in AF management - with their subsequent early  
524 adoption - can in turn reduce AF-related risk of glaucoma or minimize ocular  
525 hemodynamic changes, with an important impact on the burden of health  
526 care costs and quality of life.

527 The present work has some limiting aspects. First, we focused on the  
528 most frequent and typical AF configuration, chosen as representative after  
529 a detailed literature review of the most common AF features. More specific  
530 cases - such as, for example, bimodal *RR* probability distributions or much  
531 higher ventricular rates - were not accounted here. As we are interested in  
532 the net and specific role of AF on the ocular hemodynamics which - without  
533 a computational approach - would be hardly identifiable, we accounted for  
534 a generic healthy subject experiencing an episode of paroxysmal AF and  
535 we evaluated the acute hemodynamic response. Long-term hemodynamic  
536 remodeling effects (e.g., atrial enlargement) and concomitant pathologies -  
537 such as hypertension, diabetes, mitral stenosis/regurgitation - which usually  
538 accompany chronic AF were not considered here and can be included in  
539 future works, together with subject-specific features and higher ventricular  
540 rates.

## 541 5. Conclusions

542 Through a validated cardiovascular multiscale modeling approach, we ob-  
543 served that during AF ocular perfusion and pressure remain on average quite

544 adequate, guaranteeing physiological mean values with respect to SR. How-  
545 ever, transient relevant hypoperfusions (for *OPP*) and hypertensive events  
546 (for *TLP*) can occur, due to the high cv value of beat-averaged variables.  
547 According to the vascular theory, decreased *OPP* and increased *TLP* are  
548 potential markers associated to the increased risk of glaucoma development.  
549 Moreover, ocular hemodynamic signals modify their waveforms in AF, by sig-  
550 nificantly reducing their amplitude. This, in addition to the high variability  
551 of pulsatile pressure, may lead to episodes of *OPP* transient hypo-pulsatility  
552 due to the inadequate signal amplitude. Awaiting necessary clinical data  
553 which are to date lacking, the present study can boost clinical measurement  
554 of specific and more targeted parameters (e.g., ocular pulsatility indexes) and  
555 at the same time enrich - through mechanistic and hemodynamic-driven hints  
556 in the AF framework - the vascular theory relating reduced ocular perfusion  
557 and increased risk of glaucoma. In this context, present findings suggest that  
558 AF may play a role in augmenting the development of glaucoma.

#### 559 **Declaration of competing interest**

560 The authors declare that they have no known competing financial inter-  
561 ests or personal relationships that could have appeared to influence the work  
562 reported in this paper.

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568 (D.D.104 - 02/02/2022). This manuscript reflects only the authors' views  
569 and opinions and the Ministry cannot be considered responsible for them.

#### 570 **References**

- 571 [1] G. A. Roth, G. A. Mensah, C. O. Johnson, G. Addolorato, E. Ammi-  
572 rati, L. M. Baddour *et al.*, Global burden of cardiovascular diseases and  
573 risk factors, 1990-2019: Update from the gbd 2019 study, *J. Am. Coll.*  
574 *Cardiol.* 76(25) (2020) 2982–3021.

- 575 [2] G. Hindricks, T. Potpara, N. Dagres, E. Arbelo, J. J. Bax, C. Blom-  
576 ström-Lundqvist *et al.*, 2020 ESC guidelines for the diagnosis and man-  
577 agement of atrial fibrillation developed in collaboration with the euro-  
578 pean association for cardio-thoracic surgery (EACTS), *Eur. Heart J.*  
579 42(5) (2021) 373–498.
- 580 [3] L. Rivard, L. Friberg, D. Conen, J. S. Healey, T. Berge, G. Boriani *et*  
581 *al.*, Atrial fibrillation and dementia: A report from the AF-SCREEN  
582 international collaboration, *Circulation* 145(5) (2022) 392–409.
- 583 [4] V. Jacobs, M. J. Cutler, J. D. Day, T. J. Bunch, Atrial fibrillation and  
584 dementia, *Trends Cardiovasc. Med.* 25(1) (2014) 44–51.
- 585 [5] A. Kanmanthareddy, A. Vallakati, A. Sridhar, M. Reddy, H. P. Sanjani,  
586 J. Pillarisetti *et al.*, The impact of atrial fibrillation and its treatment  
587 on dementia, *Curr. Cardiol. Rep.* 16 (2014) 519.
- 588 [6] F. Da Silva, M. Lira, Intraocular pressure measurement: A review, *Surv.*  
589 *Ophthalmol.* 67(5) (2022) 1319–1331.
- 590 [7] J. Flammer, S. Orgül, V. Costa, N. Orzalesi, G. K. Kriegelstein, L. M.  
591 Serra *et al.*, The impact of ocular blood flow in glaucoma, *Prog. Retin.*  
592 *Eye Res.* 21(4) (2002) 359–393.
- 593 [8] L. Siaudvytyte, I. Januleviciene, A. Daveckaite, A. Ragauskas, L. Bar-  
594 tusis, J. Kucinoviene *et al.*, Literature review and meta-analysis of  
595 translaminar pressure difference in open-angle glaucoma, *Eye* 29(10)  
596 (2015) 1242–1250.
- 597 [9] L. Siaudvytyte, I. Januleviciene, A. Ragauskas, L. Bartusis, I. Meiliu-  
598 niene, B. Siesky *et al.*, The difference in translaminar pressure gradient  
599 and neuroretinal rim area in glaucoma and healthy subjects, *J. Oph-*  
600 *thalmol.* 2014 (2014) 937360.
- 601 [10] L. Abegão Pinto, K. Willekens, K. Van Keer, A. Shibesh, G. Molen-  
602 bergs, E. Vandewalle *et al.*, Ocular blood flow in glaucoma – the leuven  
603 eye study, *Acta Ophthalmol.* 94(6) (2016) 592—598.
- 604 [11] L. Abegão Pinto, E. Vandewalle, K. Willekens, C. Marques-Neves,  
605 I. Stalmans, Ocular pulse amplitude and doppler waveform analysis in  
606 glaucoma patients, *Acta Ophthalmol.* 92(4) (2014) e280–e285.

- 607 [12] K. Willekens, L. Abegão Pinto, E. Vandewalle, C. Marques-Neves,  
608 I. Stalmans, Higher optic nerve sheath diameters are associated with  
609 lower ocular blood flow velocities in glaucoma patients, *Graef. Arch.*  
610 *Clin. Exp. Ophthalmol.* 252(3) (477–483) 2014.
- 611 [13] M. Hidalgo-Aguirre, S. Costantino, M. Lesk, Pilot study of the pulsatile  
612 neuro-peripapillary retinal deformation in glaucoma and its relationship  
613 with glaucoma risk factors, *Curr. Eye Res.* 42(12) (2017) 1620–1627.
- 614 [14] I. Goharian, S. M. Iverson, R. C. Ruiz, K. Kishor, D. S. Greenfield,  
615 M. Sehi, Reproducibility of retinal oxygen saturation in normal and  
616 treated glaucomatous eyes, *Brit. J. Ophthalmol.* 99(3) (2015) 318–322.
- 617 [15] P. Krzyzanowska-Berkowska, K. Czajor, D. R. Iskander, Associating  
618 the biomarkers of ocular blood flow with lamina cribrosa parameters in  
619 normotensive glaucoma suspects. comparison to glaucoma patients and  
620 healthy controls, *Plos One* 16(3) (2021) e0248851.
- 621 [16] Y. Gao, B. Wan, P. Li, Y. Zhang, X. Tang, Short-term reproducibil-  
622 ity of intraocular pressure and ocular perfusion pressure measurements  
623 in chinese volunteers and glaucoma patients, *BMC Ophthalmol.* 16(1)  
624 (2016) 145.
- 625 [17] A. Samsudin, N. Isaacs, M.-L. S. Tai, N. Ramli, Z. Mimiwati, M. M.  
626 Choo, Ocular perfusion pressure and ophthalmic artery flow in patients  
627 with normal tension glaucoma, *BMC Ophthalmol.* 16(1) (2016) 39.
- 628 [18] M. Modrzejewska, W. Grzesiak, D. Zaborski, A. Modrzejewska, The  
629 role of lipid dysregulation and vascular risk factors in glaucomatous  
630 retrobulbar circulation, *Bosnian J. Basic Med.* 15(2) (2015) 50–56.
- 631 [19] H.-K. Cho, J. Han, J. Choi, J. Chae, R. Kim, Association between atrial  
632 fibrillation and the risk of glaucoma development: a 12-year nationwide  
633 cohort study, *Eye* 37(10) (2023) 2033–2041.
- 634 [20] Y. Suzuki, M. Kiyosawa, Cardiac hypertrophy may be a risk factor for  
635 the development and severity of glaucoma, *Biomedicines* 10(3) (2022)  
636 677.

- 637 [21] A. Zaleska-Żmijewska, M. Janiszewski, Z. M. Wawrzyniak, M. Kuch,  
638 J. Szaflik, J. P. Szaflik, Is atrial fibrillation a risk factor for normal-  
639 tension glaucoma?, *Medicine* 96(43) (2017) e8347.
- 640 [22] R. Peräsalo, C. Raitta, J. Peräsalo, Optic nerve fiber loss in relation to  
641 atrial fibrillation and blood pressure, *Int. Ophthalmol.* 16(4-5) (1992)  
642 259–263.
- 643 [23] T. J. Hunter, J. J. Joseph, U. Anazodo, S. R. Kharche, C. W. McIn-  
644 tyre, D. Goldman, Atrial fibrillation and anterior cerebral artery absence  
645 reduce cerebral perfusion: A de novo hemodynamic model, *Applied Sci-*  
646 *ences* 12(3) (2022) 1750.
- 647 [24] M. Anselmino, S. Scarsoglio, A. Saglietto, F. Gaita, L. Ridolfi, Transient  
648 cerebral hypoperfusion and hypertensive events during atrial fibrillation:  
649 A plausible mechanism for cognitive impairment, *Sci. Rep.* 6(1) (2016)  
650 28635.
- 651 [25] A. Saglietto, S. Scarsoglio, L. Ridolfi, F. Gaita, M. Anselmino, Higher  
652 ventricular rate during atrial fibrillation relates to increased cerebral  
653 hypoperfusions and hypertensive events, *Sci. Rep.* 9(1) (2019) 3779.
- 654 [26] S. Scarsoglio, A. Saglietto, M. Anselmino, F. Gaita, L. Ridolfi, Alter-  
655 ation of cerebrovascular haemodynamic patterns due to atrial fibril-  
656 lation: An in silico investigation, *J. R. Soc. Interface* 14(129) (2017)  
657 20170180.
- 658 [27] S. Scarsoglio, A. Saglietto, F. Tripoli, J. J. M. Zwanenburg, G. J. Bies-  
659 sels, G. M. De Ferrari, *et al.*, Cerebral hemodynamics during atrial fib-  
660 rillation: computational fluid dynamics analysis of lenticulostriate arter-  
661 ies using 7 T high-resolution magnetic resonance imaging, *Phys. Fluids*  
662 34(12) (2022) 121909.
- 663 [28] A. Saglietto, F. Tripoli, J. J. M. Zwanenburg, G. J. Biessels, G. M.  
664 De Ferrari, M. Anselmino, *et al.*, Role of the vessel morphology on the  
665 lenticulostriate arteries hemodynamics during atrial fibrillation: A CFD-  
666 based multivariate regression analysis, *Comput. Meth. Prog. Bio.* 254  
667 (2024) 108303.
- 668 [29] A. Saglietto, M. Fois, L. Ridolfi, G. M. De Ferrari, M. Anselmino,  
669 S. Scarsoglio, A computational analysis of atrial fibrillation effects on

- 670 coronary perfusion across the different myocardial layers, *Sci. Rep.* 12(1)  
671 (2022) 841.
- 672 [30] S. Scarsoglio, C. Gallo, A. Saglietto, L. Ridolfi, M. Anselmino, Impaired  
673 coronary blood flow at higher heart rates during atrial fibrillation: inves-  
674 tigation via multiscale modelling, *Comput. Meth. Prog. Bio.* 175 (2019)  
675 95–102.
- 676 [31] S. Scarsoglio, A. Guala, C. Camporeale, L. Ridolfi, Impact of atrial  
677 fibrillation on the cardiovascular system through a lumped-parameter  
678 approach, *Med. Biol. Eng. Comput.* 52(11) (2014) 905–920.
- 679 [32] M. Corti, A. Zingaro, L. Dede, A. M. Quarteroni, Impact of atrial fibril-  
680 lation on left atrium haemodynamics: A computational fluid dynamics  
681 study, *Comput. Biol. Med.* 150 (2022) 106143.
- 682 [33] S. Scarsoglio, C. Camporeale, A. Guala, L. Ridolfi, Fluid dynamics of  
683 heart valves during atrial fibrillation: a lumped parameter-based ap-  
684 proach, *Comput. Methods Biomech. Biomed. Engin.* 10(19) (2016) 1060–  
685 1068.
- 686 [34] S. Scarsoglio, A. Saglietto, F. Gaita, L. Ridolfi, M. Anselmino, Compu-  
687 tational fluid dynamics modelling of left valvular heart diseases during  
688 atrial fibrillation, *PeerJ* 4 (2016) e2240.
- 689 [35] S. Scarsoglio, C. Gallo, L. Ridolfi, Effects of atrial fibrillation on the  
690 arterial fluid dynamics: A modelling perspective, *Meccanica* 53 (13)  
691 (2018) 3251–3267.
- 692 [36] A. Deyranlou, J. H. Naish, C. A. Miller, A. Revell, A. Keshmiri, Nu-  
693 merical study of atrial fibrillation effects on flow distribution in aortic  
694 circulation, *Ann. Biomed. Eng.* 48(4) (2020) 1291–1308.
- 695 [37] A. Deyranlou, C. A. Miller, A. Revell, A. Keshmiri, Effects of ageing on  
696 aortic circulation during atrial fibrillation; a numerical study on different  
697 aortic morphologies, *Ann. Biomed. Eng.* 49(9) (2021) 2196–2213.
- 698 [38] L. Zhang, M. Gay, Characterizing left atrial appendage functions in sinus  
699 rhythm and atrial fibrillation using computational models, *J. Biomech.*  
700 41(11) (2008) 2515–2523.

- 701 [39] A. Masci, L. Barone, L. Dedè, M. Fedele, C. Tomasi, A. Quarteroni,  
702 *et al.*, The impact of left atrium appendage morphology on stroke risk  
703 assessment in atrial fibrillation: A computational fluid dynamics study,  
704 *Front. Physiol.* 9 (2019) 1938.
- 705 [40] G. Musotto, A. Monteleone, D. Vella, B. Zuccarello, R. Cannova,  
706 A. Cook, *et al.*, Fluid-structure interaction analysis of the thromboem-  
707 bolic risk in the left atrial appendage under atrial fibrillation: Effect of  
708 hemodynamics and morphological features, *Comput. Meth. Prog. Bio.*  
709 246 (2024) 108056.
- 710 [41] C. Gallo, J. Olbers, L. Ridolfi, S. Scarsoglio, N. Witt, Testing a patient-  
711 specific in-silico model to noninvasively estimate central blood pressure,  
712 *Cardiovasc. Eng. Techn.* 12(2) (2021) 144–157.
- 713 [42] C. Gallo, L. Ridolfi, S. Scarsoglio, Cardiovascular deconditioning dur-  
714 ing long-term spaceflight through multiscale modeling, *npj Microgravity*  
715 6(1) (2020) 27.
- 716 [43] M. Fois, S. V. Maule, M. Giudici, M. Valente, L. Ridolfi, S. Scarsoglio,  
717 Cardiovascular response to posture changes: Multiscale modeling and  
718 in vivo validation during head-up tilt, *Front. Physiol.* 13 (2022) 826989.
- 719 [44] M. Fois, L. Ridolfi, S. Scarsoglio, In silico study of the posture-dependent  
720 cardiovascular performance during parabolic flights, *Acta Astronaut.*  
721 200 (2022) 435–447.
- 722 [45] S. Scarsoglio, M. Fois, L. Ridolfi, Increased hemodynamic pulsatility in  
723 the cerebral microcirculation during parabolic flight-induced micrograv-  
724 ity: A computational investigation, *Acta Astronaut.* 211 (2023) 344–352.
- 725 [46] M. Fois, A. Diaz-Artiles, S. Y. Zaman, L. Ridolfi, S. Scarsoglio, Link-  
726 ing cerebral hemodynamics and ocular microgravity-induced alterations  
727 through an in silico-in vivo head-down tilt framework, *npj Microgravity*  
728 10(1) (2024) 22.
- 729 [47] M. Fois, L. Ridolfi, S. Scarsoglio, Arterial wave dynamics preservation  
730 upon orthostatic stress: a modelling perspective, *Roy. Soc. Open Sci.*  
731 10(3) (2023) 221257.

- 732 [48] K. Tateno, L. Glass, Automatic detection of atrial fibrillation using the  
733 coefficient of variation and density histograms of RR and  $\Delta$ RR intervals,  
734 Med. Biol. Eng. Comput. 39(6) (2001) 664–671.
- 735 [49] J. Hayano, F. Yamasaki, S. Sakata, A. Okada, S. Mukai, T. Fujinami,  
736 Spectral characteristics of ventricular response to atrial fibrillation, Am.  
737 J. Physiol. Heart C. 273(6) (1997) H2811–H2816.
- 738 [50] T. Hennig, P. Maass, J. Hayano, S. Heinrichs, Exponential distribution  
739 of long heart beat intervals during atrial fibrillation and their relevance  
740 for white noise behaviour in power spectrum, J. Biol. Phys. 32(5) (5)  
741 (2007) 383–392.
- 742 [51] R. S. Wijesurendra, B. Casadei, Atrial fibrillation: Effects beyond the  
743 atrium?, Cardiovasc. Res. 105 (3) (2015) 238–247.
- 744 [52] E. Anter, M. Jessup, D. J. Callans, Atrial fibrillation and heart fail-  
745 ure: Treatment considerations for a dual epidemic, Circulation 119 (18)  
746 (2009) 2516–2525.
- 747 [53] M. Tanabe, K. Onishi, K. Dohi, T. Kitamura, M. Ito, T. Nobori, *et al.*,  
748 Assessment of left ventricular systolic function in patients with chronic  
749 atrial fibrillation and dilated cardiomyopathy using the ratio of preced-  
750 ing to prepreceding R–R intervals, Int. J. Cardiol. 108(2) (2006) 197–201.
- 751 [54] Y.-M. Cha, A. Wokhlu, S. J. Asirvatham, W.-K. Shen, P. A. Friedman,  
752 T. M. Munger, *et al.*, Success of ablation for atrial fibrillation in isolated  
753 left ventricular diastolic dysfunction: A comparison to systolic dysfunc-  
754 tion and normal ventricular function, Circ. Arrhythmia Elec. 4(5) (2011)  
755 724–732.
- 756 [55] P. Zhu, Y. Zhang, P. Jiang, Z. Wang, J. Wang, X. Yin, *et al.*, Effects of  
757 radiofrequency catheter ablation on left ventricular structure and func-  
758 tion in patients with atrial fibrillation: A meta-analysis, J. Interv. Card.  
759 Electr. 40(2) (2014) 137–145.
- 760 [56] F. Haddad, S. A. Hunt, D. N. Rosenthal, D. J. Murphy, Right ventricular  
761 function in cardiovascular disease, part i: anatomy, physiology, aging,  
762 and functional assessment of the right ventricle, Circulation 117 (2008)  
763 1436–1448.

- 764 [57] E. S. Nelson, J. G. Myers, B. E. Lewandowski, C. Ross Ethier, B. C.  
765 Samuels, Acute effects of posture on intraocular pressure, Plos One 15(2)  
766 (2020) e0226915.
- 767 [58] T. Higashide, S. Udagawa, K. Nakazawa, Y. Yamashita, S. Tsuchiya,  
768 S. Ohkubo, *et al.*, Prediction of glaucoma progression by 24-h contact  
769 lens sensor profile in patients with normal-tension glaucoma, Sci. Rep.  
770 14 (1) (2024) 21564.
- 771 [59] S. Masai, K. Ishida, A. Anraku, T. Takumi, G. Tomita, Pulse Wave-  
772 form Analysis of the Ocular Blood Flow Using Laser Speckle Flowgra-  
773 phy before and after Glaucoma Treatment, J. Ophthal. 2019 (1) (2019)  
774 1980493.
- 775 [60] T. Sugiyama, H. Nakamura, Increased Short-Term Fluctuation in Optic  
776 Nerve Head Blood Flow in a Case of Normal-Tension Glaucoma by the  
777 Use of Laser Speckle Flowgraphy, Vision 1 (1) (2016) 5.
- 778 [61] A. Vinnett, J. Kandukuri, C. Le, K.-A. Cho, A. Sinha, S. Asanad, *et*  
779 *al.*, Dynamic Alterations in Blood Flow in Glaucoma Measured with  
780 Laser Speckle Contrast Imaging, Ophthalmology Glaucoma 5 (3) (2022)  
781 250–261.
- 782 [62] A. C. Guyton, J. E. Hall, Textbook of medical physiology, Elsevier Saun-  
783 ders Philadelphia (2011).