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Subject-specific simulation for non-invasive assessment of aortic coarctation: towards a translational approach

Massimiliano Mercuri^{a,b}, Kerstin Wustmann^c, Hendrik von Tengg-Kobligk^d, Cemil Göksu^d,
D Rodney Hose^{d,f}, Andrew Narracott^{d,e}

^a*Mathematical Modelling in Medicine Group, Department of Infection, Immunity and Cardiovascular Science, University of Sheffield, Sheffield, United Kingdom.*

^b*Therenva, Rennes, France.*

^c*Center for Congenital Heart Disease, Cardiac Magnetic Resonance Imaging, Department of Cardiology, University Hospital Bern, Bern, Switzerland.*

^d*Department of Diagnostic, Interventional and Pediatric Radiology, University of Bern, Bern University Hospital, Bern, Switzerland*

^e*INSIGNEO Institute for in Silico Medicine, The University of Sheffield, Sheffield, U.K.*

^f*Department of Circulation and Medical Imaging, NTNU, Trondheim, Norway*

Abstract

We present a multi-scale CFD-based study conducted in a cohort of 11 patients with aortic coarctation (CoA). The study explores the potential for implementation of a workflow using non-invasive routinely collected medical imaging data and clinical measurements to provide a more detailed insight into local aortic haemodynamics in order to support clinical decision making. Our approach is multi-scale, using a reduced-order model (1D/0D) and an optimization process for the personalization of patient-specific boundary conditions and aortic vessel wall parameters from non-invasive measurements, to inform a more complex model (3D/0D) representing 3D aortic patient-specific anatomy. The reliability of the modelling approach is investigated by comparing 3D/0D model pressure drop estimation with measured peak gradients recorded during diagnostic cardiac catheterization and 2D PC-MRI flow rate measurements in the descending aorta. The current study demonstrated that the proposed approach requires low levels of user interaction, making it suitable for the clinical setting. The agreement between computed blood pressure drop and catheter measurements is 10 ± 8 mmHg at the coarctation site. The comparison between CFD derived and catheter measured pressure gradients indicated that the model has to be improved, suggesting the use of time varying pressure waveforms to further optimize the tuning process and modelling assumptions.

Keywords: haemodynamics, subject-specific modelling, magnetic resonance imaging, aortic coarctation, multi-scale models, computational fluid-dynamics

1 words count: 4868.

2 **1. Introduction**

3 Coarctation of the Aorta (CoA) is a Congenital Heart Disease (CHD) accounting for 5-8 %
4 of all congenital cardiac defects [1, 2], it is the fifth most common CHD [3].

5 CoA is characterized by a localized stenosis of the descending aorta, in most cases located after
6 the origin of the left subclavian artery (patent ductus arteriosus region). The obstruction alters
7 blood pressure distribution and perfusion, causing upper body and cerebral hypertension, left
8 ventricular hypertrophy with diastolic and later systolic dysfunction, coronary artery disease,
9 cerebral haemorrhage, stroke and aortic ruptures [4, 5]. Patients with untreated coarctation have
10 an average survival age of 35 years, with 75 % chance of dying by 46 years of age [6, 7].

11 Treatments include surgical repairs, stent implantation and balloon angioplasty [8]. Current
12 guidelines recommend intervention if the peak-to-peak coarctation gradient (the difference in
13 peak pressure at the proximal aorta and beyond the coarctation site) exceeds 20 mmHg at rest
14 [6]. In clinical practice, invasive cardiac catheterization is considered the gold standard for the as-
15 sessment of trans-coarctation gradient. Despite its accuracy, the technique is an invasive method
16 with rare but potential complications. Trans-coarctation gradient can be estimated non-invasively
17 from arm/leg blood pressure measurements or from imaging methods, such as Doppler ultra-
18 sound (DUS) or phase contrast magnetic resonance imaging (PC-MRI). From imaging data, the
19 pressure drop over the stenosis is derived from a simplified Bernoulli's equation with measured
20 peak velocity provided as input [9, 10]. Both techniques have been shown to provide good overall
21 correlation with invasive cardiac catheterization peak-to-peak measurements, but in many cases
22 overestimate this value since they do not take into account for unsteady and viscous losses, ve-
23 locity profile contribution on pressure decay and pressure recovery effects downstream of the
24 coarctation [11, 12].

25 With the advance of Computational fluid dynamics (CFD) it has been possible to improve the
26 non-invasive estimation of the peak-to-peak pressure gradients with patient-specific model, de-
27 rived from imaging data. Several computational studies have been published in the last decade
28 focused on subject-specific CoA cases. They differ in the approaches used to model haemody-
29 namics, the representation of aortic distensibility and the strategies used to derive boundary con-

30 ditions (BCs) from the available clinical data. The computational problem has been approached
31 using both three-dimensional (3D) models [13–22] and one-dimensional (1D) models [23, 24],
32 with a range of different assumptions: rigid [13, 16, 18–21] or deformable walls [14, 15, 17, 22–
33 24], simple BCs such as literature derived flow-split conditions [18, 19], flow-split conditions
34 together with time-varying clinically measured pressure waveforms [13, 22] or more complex
35 BCs such as coupled (0D) Windkessel models to represent the circulation beyond the local aortic
36 region [14–17, 20, 21, 23, 24]. The flow-split assumption provides a fast and easy way to model
37 the outlet flow distribution but lacks realism since flow rate is assumed to have a constant ratio
38 over the cardiac cycle; patient-specific pressure or flow rate waveforms can be applied at each
39 outlet but they are not often routinely collected. Although more complex, Windkessel models
40 improve the accuracy of outlet models whilst requiring relatively little clinical data, nonetheless
41 the tuning process of Windkessel parameters can be a time-consuming task, especially if per-
42 formed iteratively using 3D models.

43 In this article, we describe a computational workflow that, from non-invasive data typically avail-
44 able for all CoA patients, offers a detailed insight into the local aortic fluid-dynamics. The final
45 aim of this work is to provide computational clinical decision support that can be integrated
46 within an existing commercial software framework (Endosize) developed by Therenva (Rennes,
47 France).

48 First, we describe the clinically available patient-specific data collection and processing. Next,
49 we describe the 1D/0D and 3D/0D model set-up followed by the tuning process used to obtain
50 parameters for the 0D components. When compared with the literature, the approach used in
51 this work represents aortic haemodynamics using multiple geometrical modelling approaches to
52 automatically tune Windkessel boundary conditions from available clinical data. Data process-
53 ing of model outputs is described followed by results, including comparison between predicted
54 and measured pressure gradient across the coarctation and descending aortic flow rate. The dis-
55 cussion focusses on potential future application of the workflow within the clinical setting and
56 comparison with previously reported approaches.

57 **2. Materials and Methods**

58 **2.1. *In vivo data: acquisition and model generation***

59 This section details the analysis of clinical data obtained from 11 patients undergoing as-
60 sessment of severity of aortic coarctation. The cohort was heterogeneous and included patients
61 who had already undergone coarctation repair (see Table 1). The clinical data collected includes
62 contrast-enhanced magnetic resonance angiography (CE-MRA) images of aortic geometry, two-
63 dimensional phase contrast magnetic resonance imaging (2D PC-MRI) measurement of aortic
64 flow rate in the ascending and descending aorta (proximal and distal to the coarctation site), cuff
65 pressure measurements from the right arm and at the foot. All data were collected at Bern Uni-
66 versity Hospital, following a protocol approved by the local ethics committee and the volunteers
67 provided written informed consent (Swiss Adult Congenital Heart disease Registry, SACHER,
68 ClinicalTrials.gov Identifier NCT 02258724).

69 **2.1.1. *Aortic geometry***

70 A contrast-enhanced magnetic resonance angiography (CE-MRA) was performed as a first
71 assessment for clinical suspicion of aortic coarctation or as a follow-up exam after previous sur-
72 gical intervention for all 11 patients.

73 The subjects were scanned in the supine position with a 1.5T MAGNETOM Aera scanner (Siemens
74 Healthcare, Erlangen, Germany) using a T1 weighted, k-space, spoiled gradient recalled echo se-
75 quence (echo time: 1.1 ms , repetition time: 3.17 ms , flip angle: 30° , field of view: 370-420
76 mm, slice thickness: 1-1.2 mm, acquisition matrix: 384 x 250 reconstructed to 512 x 512) and
77 an intravenous Gadolinium-based contrast medium injection with optimal contrast timing to en-
78 hance the thoracic aorta (contrast flow at 3.5 ml/s) through the test-bolus technique (see Figure
79 1 (a)).

80 The 3D geometry was then reconstructed using a semi-automatic segmentation software (Philips
81 Intellispace, Philips, Koninklijke, Netherlands) to provide geometry in the form of an STL file
82 (see Figure 1 (b)). The STL file was post-processed manually using the open source software
83 Autodesk MeshMixer (Autodesk, Inc). The final STL was truncated to obtain four outlets (cut-
84 ting the surface perpendicular to the extracted centerline) using the vmtk toolkit [25] as shown
85 in Figure 1 (c). The typical geometry processing time is less than 15 minutes.

86 *2.1.2. Aortic flow rate*

87 Volume flow rate waveforms were obtained at two planes perpendicular to the aorta: at the
88 ascending aorta at the level of the right pulmonary artery and at the descending aorta at the
89 diaphragmatic level, using retrospectively ECG-triggered 2D PC-MRI data (echo time: 2.47 ms
90 , repetition time: 37.12 ms , flip angle: 20° , field of view: 320-370 mm, slice thickness: 6
91 mm, acquisition matrix: 192 x 119, velocity encoding 150-200 $cm \cdot s^{-1}$, temporal resolution 30
92 phases/cardiac cycle).

93 *2.1.3. Patient-specific coarctation pressure drop*

94 Resting blood pressure cuff measurements were taken at the right arm and at the leg as re-
95 ported in Table 2 using an appropriately sized sphygmometer cuff. Right cubital blood pres-
96 sure was measured using an automatic oscillometric method (Dinamap Procare 300, GE Health-
97 care) after resting for more than 5 minutes. Systolic blood pressure in one of the legs (dorsalis
98 pedis artery or posterior tibial artery) was measured by an appropriately sized cuff placed around
99 the lower calf and using a Doppler probe (Huntleigh dopplex D900, Huntleigh Healthcare Ltd,
100 Cardiff, UK).

101 Mostly, blood pressure measurements were performed either simultaneously at the arm and the
102 leg, or within 3 minutes of each other. Blood pressure difference was calculated between the
103 proximal (arm) and distal (leg) systolic blood pressure. All non-invasive blood pressure data
104 were obtained during routine clinical follow-up visit in a centre for congenital heart disease.

105 Diagnostic catheterization to assess invasive aortic pressure gradients was performed in order
106 to evaluate the need for intervention. Invasive blood pressure curves in the ascending and de-
107 scending aorta were obtained either simultaneously with the insertion of two catheters (5 French,
108 Cordis, Cardinal Health, US) using a radial and femoral arterial access or by pullback technique
109 using one catheter. All measurements were collected over 5 cardiac cycles and the peak-to-peak
110 pressure gradient was calculated by the integrated pressure monitoring system (Siemens Health-
111 care, Erlangen, Germany). The computational models were not informed by catheter-based pres-
112 sure measurements and the peak-to-peak measurement was used only for validation to compare
113 with the simulation results.

114 2.2. Modelling approach

115 Two distinct models were informed by the available clinical dataset. The first model was a
 116 1D/0D numerical model and the second a 3D/0D numerical model. In this section the formu-
 117 lation of these two models is provided, together with a description of the required physical and
 118 geometrical input parameters and the simulated quantities that are relevant for this study.

119 2.2.1. One-dimensional formulation

120 In the 1D/0D modelling framework, the aortic geometry was divided into a series of intercon-
 121 nected segments. For each segment a system of one dimensional nonlinear hyperbolic equations
 122 was defined, derived from the continuity and Navier-Stokes equations for incompressible flow
 123 within a deformable elastic vessel [26], as follows

$$\begin{cases} \frac{\partial A}{\partial t} + \frac{\partial Au}{\partial x} = 0, \\ \frac{\partial u}{\partial t} + u \frac{\partial}{\partial x}(u) + \frac{1}{\rho} \frac{\partial P}{\partial z} = \frac{f}{\rho A}, \\ P = P_{ext} + \beta \left[\sqrt{\frac{A}{A_0}} - 1 \right], \quad \beta = \sqrt{\frac{\pi}{A_0}} \frac{Eh_0}{1-\nu^2}, \end{cases} \quad (1)$$

124 where t is the time, x is the axial coordinate along the vessel, $A(x, t)$ is the cross-sectional area
 125 of the vessel lumen, A_0 is the reference cross-sectional area (when $P = P_{ext}$), h_0 is the reference
 126 wall thickness, $u(x, t)$ and $P(x, t)$ are the axial blood velocity and blood pressure averaged over
 127 the cross-section, ρ is the density of blood assumed constant, while $f(x, t)$ is the frictional force
 128 per unit length.

129 The frictional losses were computed by assuming a flat velocity profile (the corresponding Wom-
 130 erlsey numbers derived at the inlet of the aorta varies from 11 to 30) with a polynomial order of
 131 9 ($\zeta = 9$) with

$$f = -2 \cdot (\zeta + 2) \cdot \mu \cdot \pi \cdot u(x, t) \quad (2)$$

132 where μ is the viscosity of blood. This assumption provides best fitting when compared to
 133 experimental results in a human arterial tree [27]. Following this assumption the momentum
 134 correction factor (or Coriolis coefficient) was set constant in time and space and equal to 1 [28].

135 The system of equations in (1) was solved using a finite-volume numerical scheme formulation
136 provided by Melis et al. [26]. For all the simulations, the density and viscosity of blood were
137 assumed constant ($\mu = 4.5 \text{ mPa} \cdot \text{s}$ [24] and $\rho = 1060 \text{ kg} \cdot \text{m}^{-3}$).

138 The stability of the scheme was guaranteed by the computation of the time step for each iteration
139 in all vessels depending on their maximum local wave speed c_{max} and the element length Δx as

$$\Delta t = C_{cfl} \cdot \frac{\Delta x}{c_{max}} \quad (3)$$

140 where the Courant number was set to $C_{cfl} = 0.9$ and Δt was set to the smallest computed
141 value over all elements.

142 2.2.2. Three dimensional formulation

143 The Navier-Stokes (NS) and continuity equations were solved in 3D over time using a tran-
144 sient analysis with the finite volume CFD-based solver ANSYS-FLUENT 17.2 (ANSYS Inc.,
145 PA, USA). Local aortic distensibility was included using a compressible fluid strategy as de-
146 scribed by Brown et al. [29]. Blood density changes were related to pressure changes via an
147 ideal gas with the fluid wave speed, c , as input. The inflow boundary condition was provided
148 by imposing the time-varying mass flowrate waveform at the inlet (assuming a flat velocity pro-
149 file and an initial density of $1060 \text{ kg} \cdot \text{m}^{-3}$). The viscosity of blood was set equal to $\mu = 4.5$
150 $\text{mPa} \cdot \text{s}$ using a Newtonian model. The simulation was run with a laminar flow model, the cases
151 were peak Reynolds numbers at the coarctation site exceeded the limit imposed by the classical
152 turbulence analysis (3500) were recomputed using an SST turbulence model. The solution was
153 performed using a double precision solver with a second order discretization coupled scheme for
154 pressure-velocity coupling and a time step of 10^{-4} s to ensure convergence over the entire cardiac
155 cycle. Simulations were run for three to five cardiac cycles until the mass flow rate and pressure
156 fields yielded consistent solutions over successive cycles (change in peak pressure and mass flow
157 rate less than 1 %).

158 2.3. Three-dimensional and one dimensional meshes

159 For the three-dimensional model, the mesh was generated with FLUENT automatic mesh
160 library starting from the STL file using polyhedral elements with 5 prism layers at the wall. The
161 number of elements varied from 105205 to 564822 element volumes and edge lengths varied
162 from $3.00 \cdot 10^{-13} \text{ m}^3$ to $1.71 \cdot 10^{-9} \text{ m}^3$ and from $6.93 \cdot 10^{-5} \text{ m}$ to $2.94 \cdot 10^{-4} \text{ m}$, respectively.

163 For the 1D model formulation the vessel centerlines were extracted from the STL files using vmtk
 164 libraries and tools [25]. Four centerlines were extracted: through the aorta itself and the three
 165 supra-aortic vessels: the brachio-cephalic artery (BCA), the left common carotid artery (LCA)
 166 and the left-subclavian artery (LSUB). Along these vessel centerlines the perpendicular vessel
 167 cross-section was computed every 5 mm (see Figure 1 (e)), defining the vessel segments for the
 168 1D formulation. For each vessel segment the finite volume mesh was defined with an element
 169 length of 1 mm. The 1D/0D model was initialized with the cross-sectional area extracted from the
 170 CE-MRA geometry as the luminal area A_d at diastolic pressure P_d , and the initial area A_0 found
 171 using the pressure-area relationship (or tube-law) in 1. The wall thickness (h_0) was defined as
 172 function of lumen radius (R_0) [30], as follows

$$\frac{h_0}{R_0} = ae^{bR_0} + ce^{dR_0}, \quad (4)$$

173 Where a, b, c and d are constants. Young's modulus was defined based on the measured pulse
 174 wave velocity (c) derived as described in section 2.4, through the equations

$$c = \sqrt{\frac{\beta}{2\rho\sqrt{A_0}}A_d^{\frac{1}{4}}}, \quad (5)$$

175 and

$$\beta = \sqrt{\frac{\pi}{A_0}} \frac{Eh_0}{1 - \nu^2} \quad (6)$$

176 2.4. Mechanical properties

177 In both the 3D and 1D models, the mechanical properties for the arterial wall were derived
 178 from the estimation of the pulse wave velocity, c . The value of c was assumed to be uniform over
 179 the aortic geometry and was derived from the 2D PC-MRI data using the transit-time method (or
 180 foot-to-foot method) [31] as follows

$$c = \frac{\Delta x}{\Delta t} \quad (7)$$

181 where Δx is the distance along the vessel centerline between the proximal plane of the 2D PC-
 182 MRI measurement in the ascending aorta at the level of the right pulmonary artery, and the distal
 183 plane of the 2D PC-MRI measurement in the descending aorta at the level of the diaphragm;

184 while Δt is the time taken for changes in the flow waveform to travel from the proximal to the
185 distal location.

186 This value is determined from the calculation of the foot of the flow rate curves at the ascending
187 and descending aorta. For each flow waveform, the foot is derived from the intersection between
188 the gradient during initial flow increase, defined by a line connecting points at 20% and 80%
189 of the maximum flow rate, and the minimum flow rate (also referred as baseline). This method
190 of assessing aortic compliance accounts for variability in aortic stiffness between measurement
191 points, which would not be captured by a local measure of distensibility based on local changes
192 in aortic area and pressure.

193 The values of pulse wave velocity obtained are reported in Table 3. For patients 1,4,6 and 7 the
194 resulting pulse wave velocity generated instability in the solution of the 1D model, as a result
195 the pulse wave velocity was increased to ensure convergence of the model over the entire cardiac
196 cycle (see Table 3).

197 2.5. Boundary conditions: overall approach

198 The same inflow and outflow boundary conditions were imposed for the 1D and 3D solutions
199 (see Figure 2 (b) and Figure 2(c)). At the inlet, the aortic flow waveform $Q_{asc}(t)$ measured by
200 2D PC-MRI was applied using a Fourier Series reconstruction to increase the time resolution.
201 At each of the four outlets, a three-element Windkessel model, representing the downstream vas-
202 culature, was coupled as reported elsewhere [29, 32]. These 0D models consist of a proximal
203 resistance Z , in series with a parallel combination of a distal resistance, R and a compliance, C .
204 These parameters were found using an iterative scheme proposed by Xiao et al. [33] (see Figure
205 2 (a)).

206 The scheme starts from estimating the total peripheral compliance, C_T , and the total peripheral
207 resistance, R_T , representing the equivalent resistance and compliance of the whole 1D/0D sys-
208 tem. Following the process described in 2.5.1 and 2.5.2 below, the values for the Windkessel
209 parameters were derived for all the outlets (ie, BCA, LCA, LSUB and DescAo) of the 1D/0D
210 domain.

211 To tune the 1D/0D model coupled system was solved with iterative adjustment C_T and R_T to
212 match the pressure at the aortic inlet to the measured systolic and diastolic cuff pressures, P_s and
213 P_d respectively, assuming that the pressure measured at the right arm is equal to the pressure at
214 the ascending aortic root (see Figure 2 (a)).

215 *2.5.1. Calculating the peripheral resistances of the outflow 0D models*

216 The total resistance, R_T , at the outlet of the 1D/0D network was defined as

$$R_T = \frac{P_m}{\bar{Q}_{in}}, \quad P_m = P_d + \frac{1}{3}(P_s - P_d) \quad (8)$$

217 where P_m is the mean aortic pressure, P_s and P_d are the systolic and diastolic cuff pressures,
218 respectively, while \bar{Q}_{in} is the mean aortic flow rate measured at the ascending aorta from 2D
219 PC-MRI data. The total resistance is then distributed over the outlets of the model as follows

$$R_{tot}^j = Z^j + R^j = R_T \frac{\bar{Q}_{in}}{\bar{Q}_{out}^j} \quad (9)$$

220 where $j = 1, 2, 3, 4$ refers to the four outlet interfaces of the 1D/0D multiscale model (BCA,
221 LCA, LSUB and DescAo), while \bar{Q}_{out}^j is the mean aortic flow rate at the outlet j . The values for
222 \bar{Q}_{out}^j were assumed to be proportional to the square of the radius [34] of each the supra-aortic
223 vessels as follows

$$\bar{Q}_{out}^j = \bar{Q}_i \cdot \frac{r_i^2}{\sum_{i=1}^{j=3} r_i^2} \quad (10)$$

224 where r_i is the radius of the supra-aortic branch $i = 1, 2, 3$ (ie, BCA, LCA and LSUB) and \bar{Q}_i
225 is the total mean flow rate for the supra-aortic branches, obtained from the difference between the
226 mean aortic flow of the inlet and the mean aortic flow of the descending aorta, derived from the
227 time average of the 2D PC-MRI flow waveform measurements. The proximal resistances, Z^j , at
228 the four outlets (ie, BCA, LCA, LSUB and DescAo) were assumed to match the characteristic
229 impedance of the terminal vessel j , in order to minimize artificial wave reflections, as described
230 elsewhere [35]. For a new iteration $n + 1$, R_T is updated via a first-order Taylor expansion of (8)
231 around the measured diastolic pressure P_d as follows

$$R_T^{n+1} = R_T^n + \frac{\Delta P_m^n}{\bar{Q}_{in}}, \quad \Delta P_m^n = P_d - P_d^n \quad (11)$$

232 *2.5.2. Calculating the peripheral compliances of the outflow 0D models*

233 The total compliance, C_T , was calculated as in [36]

$$C_T = \frac{Q_{max} - Q_{min}}{P_s - P_d} \Delta t \quad (12)$$

234 where Q_{max} and Q_{min} are the maximum and minimum ascending aortic flow rate values, Δt is
 235 the time delay between Q_{max} and Q_{min} , and P_s and P_d are the systolic and diastolic cuff pressures,
 236 respectively.

237 Following the work of Alastruey et al. [36] the total compliance, C_T , is equivalent to the sum of
 238 the compliance 0D Windkessel elements, C_p , and the compliance that given by the sum of all the
 239 1D model segments, C_c , as

$$C_T = C_c + C_p, \quad (13)$$

240 From Equation (13) the total peripheral compliance of the outflow models can be derived
 241 and distributed to the outflow branches in proportion to the flow distribution as reported by
 242 Stergiopoulos et al. [28]. For a new iteration $n + 1$, C_T is updated via a first-order Taylor expansion
 243 of (12) around the measured diastolic pressure P_{pulse} as follows

$$C_T^{n+1} = C_T^n + \frac{Q_{max} - Q_{min}}{(P_{pulse}^n)^2} \Delta t \Delta P_{pulse}^n, \quad \Delta P_{pulse}^n = P_{pulse} - P_{pulse}^n \quad (14)$$

244 The Windkessel parameters for the outlets compliances and resistances found via the 1D/0D
 245 models are then applied to the 3D/0D counterparts. The results obtained from the 3D/0D model
 246 were compared to the measured data in terms of 2D PC-MRI measured descending aortic wave-
 247 forms and catheter derived peak-to-peak pressure gradient.

248 2.6. Severity of the coarctation

249 For all patients the severity of the coarctation was quantified from the geometrical 3D ex-
 250 tracted shape, using the measure reported by Goubergrits and colleagues [19], the degree of
 251 stenosis (DS)

$$DS = \left(1 - \frac{A_{st}}{A_d}\right) \quad (15)$$

252 Where A_{st} is the cross-sectional area at the stenosis (the minimum reported value along the
 253 vessel's centerline) and A_d is the cross-sectional area measured 150 mm downstream from the
 254 ascending aorta.

255 2.7. Pressure gradients

256 Coarctation pressure gradients were reported using the 3D/0D model strategy to capture the
257 nature of the complex haemodynamics in the region of the coarctation. A single value was used
258 for clinical assessment, reported as the difference in peak pressure between the waveform mea-
259 sured in the ascending aorta and that measured in the descending aorta. As the simulation pro-
260 vides the pressure waveform simultaneously at all locations, the following values were reported
261 for comparison with the clinical value:

- 262 • Difference in peak pressure between ascending (inlet) and descending (outlet) aorta ($Max_{AscAo} -$
263 Max_{DescAo});
- 264 • Maximum instantaneous pressure gradient across the full computational domain over the
265 full cardiac cycle ($Max_{gradient}$);
- 266 • Pressure gradient across the full computational domain at peak systole ($Sys_{gradient}$);
- 267 • Pressure gradient over the coarctation region at peak systole ($CoA_{gradient}$).

268 3. Results

269 3.1. Arterial geometries and flow rates

270 The arterial geometry was successfully segmented for the 11 patients from CE-MRA. The
271 geometries extracted are reported in Figure 3 together with the signal acquired from the 2D PC-
272 MRI at the two different planes. For patient 11 the temporal resolution of the acquired signal
273 was equal to 20 phases per cardiac cycle with an equivalent signal time around 40 ms. For the
274 remaining patients the 2D PC-MRI temporal resolution was equal to 30 phases/cardiac cycle
275 with an equivalent signal time between 30 and 40 ms.

276 The length of each supra-aortic branch varied due to loss of signal towards the borders of the
277 volume, which may result in reduced accuracy of the segmentation in these regions [23].

278 The severity of the coarctation is reported in Table 4. For patient 3 the DS value was not reported
279 as this case represents a hypoplastic descending aorta. The mean value of DS was $48 \pm 23\%$ in
280 line with previous published works such as Goubergrits et al. [19] $54.8 \pm 19.21\%$, Itu et al. [24]
281 $48.2 \pm 7\%$, Ralovich et al. [23] $41 \pm 9.5\%$.

282 *3.2. Effectiveness of the tuning process*

283 The effectiveness of the 1D/0D tuning process is detailed for the 11 patients in Table 5.
284 The errors between the 1D/0D and 3D/0D solutions and the systolic and diastolic cuff pressure
285 measurements at the aortic inlet are reported as a percentage.

286 When solving using the 1D model, the tuning process resulted in errors less than 10% for all
287 patients except for patient 5,9 and 10. The highest relative errors were observed in tuning the
288 systolic pressure, while for patient 9 significant error was observed in both systolic and diastolic
289 values. When the solution was re-computed using the 3D approach, the error increased in most
290 cases but remained below beyond the 10% for 6 of the 11 cases. For an example of comparison
291 between the 1D and 3D model tuning see Figure 4.

292 *3.3. Descending aortic flow rate*

293 Figure 5 compares the mass flow rate measured with 2D PC-MRI with that computed by the
294 3D/0D CFD model at the descending aorta (measured at the diaphragmatic level). The errors are
295 normalized by the peak flow over the cardiac cycle to avoid division by small values, as reported
296 elsewhere [33]. The overall average errors were below 1%. Peak flow was over-estimated by
297 more than 10% for cases 3,4,5,6 and 9.

298 *3.4. Pressure gradients*

299 Pressure gradient measures are reported in Table 6 from the 3D/0D model along with the
300 pressure catheter measurement. From these results it is observed that the CFD derived metric in
301 best agreement with the measured pressure is the CoA gradient catheter data, MB, of -9 mmHg
302 and standard deviation from the mean difference (LOA, upper limit = 10 mmHg, lower limit =
303 -28 mmHg). The absolute error is 10 ± 8 mmHg. However, direct comparison of the peak-to-
304 peak difference in pressure between the ascending and descending aorta is in poor agreement
305 between the CFD derived metric and the catheter reported values.

306 **4. Discussion**

307 This study takes advantage of recent developments in modelling methods to build an engi-
308 neering workflow for subject-specific modelling of the haemodynamics in a cohort of 11 patients
309 who were assessed both before and after aortic coarctation repair. Key factors for successful

310 clinical translation of such technologies include the ability to inform the workflow using non-
311 invasive routinely collected clinical data and the feasibility for robust, repeatable application in
312 a clinical environment.

313 By exercising the workflow on retrospective data acquired using standard clinical protocols, this
314 study demonstrates the feasibility of using only CE-MRA images, flow rate waveforms acquired
315 via 2D PC-MRI and systolic and diastolic cuff pressure values from the right arm, to construct
316 two levels of model with a relatively low level of user interaction. Compared to previous work,
317 the compressible fluid strategy adopted for the 3D/0D multiscale model allows aortic distensi-
318 bility to be included without the use of a full FSI model, saving computational cost, simulation
319 time and reducing the level of user interaction required to set-up the model.

320 This is an advance in the current state of 3D model simulation of CoA patients compared with
321 the approach of Goubergrits et al. [18, 19] where, despite the good agreement with catheter data,
322 aortic distensibility and transient effects were neglected.

323 This study includes patient-specific aortic distensibility informed by 2D PC-MRI data assuming
324 the elastic properties of the aorta were uniform over the 1D/3D region. This is supported by
325 evidence that the use of non-uniform properties may lead to overestimation of the aortic stiff-
326 ness [37] and it is well suited to deployment of this approach with existing clinical workflows,
327 where 2D PC-MRI flow rate waveforms are typically available at two locations (aortic root and
328 diaphragmatic aorta).

329 Compared to previous published reports of 3D/0D approaches this study provides a more patient-
330 specific assessment than La Disa et al. [14] and Coogan et al. [15] who both used mechanical
331 properties derived from literature-based data.

332 Ralovich et al. [23] and Itu et al. [24] used the same approach proposed here (foot-to-foot
333 method) to inform the deformability of a 1D/0D model from 2D PC-MRI. Their model repre-
334 sented the coarctation site with a time constant nonlinear resistance that incorporated the effect of
335 energy dissipation due to turbulence but did not capture the influence of 3D anatomical features
336 such as curvature, bending, bifurcation and tapering. The importance of such effects, especially
337 at systolic phases, are illustrated in Figure 4 (b) where recirculation and helical flow clearly
338 occurs [33]. Furthermore, it is possible that including a nonlinear resistance may result in arte-
339 factual pressure/flow wave reflections due to compliance mismatch.

340 Despite the limitation of 1D approaches to fully capture geometric effects, a 1D/0D multi-scale

341 model provides a useful tool for tuning outflow boundary conditions and mechanical properties
342 for the 3D model. The automatic tuning process adopted in this study offers the advantages
343 of requiring only systolic and diastolic cuff pressures, diaphragmatic mean flow rate, and pulse
344 wave velocity from 2D PC-MRI as input data. This avoids manual operator tuning that has been
345 adopted in previous studies [14–17]. Alternative approaches have been proposed such as the use
346 of a detailed velocity profile map extracted from 4D flow MRI [18, 19] or UDS [21], or a detailed
347 catheter-derived pressure waveform applied at the domain boundaries [13, 22], but these require
348 data are often not routinely collected in the clinical environment.

349 The 1D model showed some instabilities at lower values of measured wave speed, which limits
350 the robustness of the tuning process. However, it should be noted that the aortic mechanical
351 properties are derived from the wave speed calculation informed by both 2D PC-MRI and ge-
352 ometrical features, both associated with measurement uncertainties. The 1D/0D tuning process
353 was successful in most cases and the 3D/0D models, with the tuned Windkessel parameters,
354 captured the systolic and diastolic cuff pressure measurements reasonably well. Tuning through
355 iterative solution of the coupled 3D/0D system is possible but introduces very highly computa-
356 tional costs. All 1D simulations were solved on an Intel Xeon E5-1620, 8 cores, 16 GB RAM and
357 took maximum 30 minutes per cardiac cycle. 3D simulations were run using a workstation with
358 3 processor Intel E5-620 and 12 GB of RAM and took a minimum of 12 hours to a maximum of
359 22 hours.

360 The computational method underestimates measured catheter gradients compared with previous
361 published studies [13, 19, 23, 24]. These increased errors may partially arise from the clinical
362 data acquisition process, as data were processed retrospectively and not specifically for this com-
363 putational study.

364 The pressure gradient across the coarctation at peak flow provides an assessment of the poten-
365 tial for reduction of the flow limiting effect of the coarctation following treatment, an advantage
366 of the computational approach is the ability to examine this effect in isolation. Due to delayed
367 augmentation in pressure in the descending thoracic aorta predicted by the CFD approach in sev-
368 eral cases agreement between peak-to-peak measures of pressure gradient is poor. This suggests
369 that, in addition to measurement errors previously discussed, assumptions made in the general
370 nature of the tuning approach (i.e. distribution of resistance and compliance based on generic
371 relationships based on vessel radius) may lead to poor representation of patient-specific pressure

372 transmission between the local 3D domain and the Windkessel outlet conditions. A more de-
373 tailed understanding of these effects would be provided by analysis of the time varying form of
374 the pressure catheter measurements used to provide the clinical peak-to-peak pressure gradient,
375 which was not available during this study.

376 Several limitations are associated with routine imaging and pressure measurement as aortic imag-
377 ing by MR, non-invasive blood pressure measurements and invasive measurements by catheter-
378 ization are typically not performed simultaneously. Furthermore, catheter measurements were
379 performed at rest but without sedation and the location of 2D PC-MRI measurements may be
380 different from that at which the catheter data were obtained. All these limitations may contribute
381 to variability between the model and measured results.

382 In this study, the effects of collateral flow (due to vertebral, internal mammary, intercostal or
383 collateral arteries that join the descending thoracic aorta distal to the coarctation site) have been
384 neglected because it has not been possible to segment these vessels for all patients, due to the
385 small size of these vessels and limited spatial resolution of MR angiography. Some studies
386 have included such vessels in their models [14, 15] but only starting from the native supra-aortic
387 branch point to the conjunction at the coarctation site without the need for supplementary BCs.

388 At supra-aortic branches (BCA, LCA, LSUB arteries) no 2D PC-MRI flow rate (as in the case
389 of LaDisa et al. [14]) nor catheter/tonometry derived blood pressure measurements (as described
390 in the work of Alastruey et al. [37]) were available therefore the mean flow rate was imposed
391 based on radii of the vessels, consistent with the report by Zamir et al. [34]. This may introduce
392 some limitations in this study, but the automatic process described here can be simply adapted
393 for future applications if such measurements are routinely acquired.

394 It should be noted that the same uniform aortic compliance was used for both patients after
395 coarctation repair and unrepaired cases. The possible interaction between the rigid patch (in
396 one patient) and the end-to-end anastomosis and the native aortic wall is expected to increase
397 the number of reflected waves towards the proximal aorta, thus increasing the pressure gradient.
398 In literature, this mechanism has been investigated for CoA patients treated with an aortic stent
399 placement, by increasing the mechanical stiffness of the stented region up to 15 times the normal
400 aortic compliance [15, 23].

401 This study was conducted using retrospectively collected data obtained from patients at rest,
402 which is likely to increase the uncertainty associated with comparison between CFD and mea-

403 sured data, in previous research studies under stress conditions the pressure gradient has been
404 shown to reach values above 40 mmHg [22]. However, the rest condition represents the clinical
405 protocol for assessment of coarctation patients under current guidelines [6].

406 **5. Conclusion**

407 This study has demonstrated the feasibility of constructing a workflow using non-invasive
408 routinely collected clinical data to predict the pressure gradient in coarctation patients using
409 patient specific CFD simulation, with relatively low levels of user interaction required. Further
410 work is required to enhance the tuning process to improve agreement with measured catheter
411 data.

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414 innovation programme under the Marie Skłodowska-Curie grant agreement no. 642612,
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416

417 **Declaration statements**

417

418 **Conflicts of interest:** None.

418

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421 VPH-CaSE (www.vph-case.eu).

421

422 **Ethical Approval:** All data were collected at Bern University Hospital, following a protocol
423 approved by the local ethics committee and the volunteers provided written informed consent
424 (Swiss Adult Congenital Heart disease Registry, SACHER, ClinicalTrials.gov Identifier NCT
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425

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Table 1: Patient cohort classification: native, surgically repaired or hypoplastic descending aorta. Information about sex and age are reported for each case (average age: 32.89 ± 14.66 years old, 55 % of males)

	Sex	Age	Type
Patient 1	male	28	native
Patient 2	female	59	native
Patient 3	female	20	hypoplastic descending aorta
Patient 4	male	21	surgically repaired (end-to-end anastomosis)
Patient 5	male	58	surgically repaired (patch repair)
Patient 6	female	34	surgically repaired (end-to-end anastomosis)
Patient 7	male	36	native
Patient 8	female	41	surgically repaired (end-to-end anastomosis)
Patient 9	female	25	native
Patient 10	male	22	native
Patient 11	male	18	surgically repaired (end-to-end anastomosis)

Table 2: Cuff pressure measurements for the 11 reported patients, systolic blood pressure, SBP, and diastolic blood pressure, DBP (NA = not available).

	SBP	DBP	SBP
	right arm	right arm	leg
Patient 1	152	85	130
Patient 2	125	75	95
Patient 3	131	60	100
Patient 4	134	66	120
Patient 5	147	95	120
Patient 6	150	83	115
Patient 7	138	69	110
Patient 8	167	75	NA
Patient 9	130	100	95
Patient 10	125	60	95
Patient 11	144	48	130

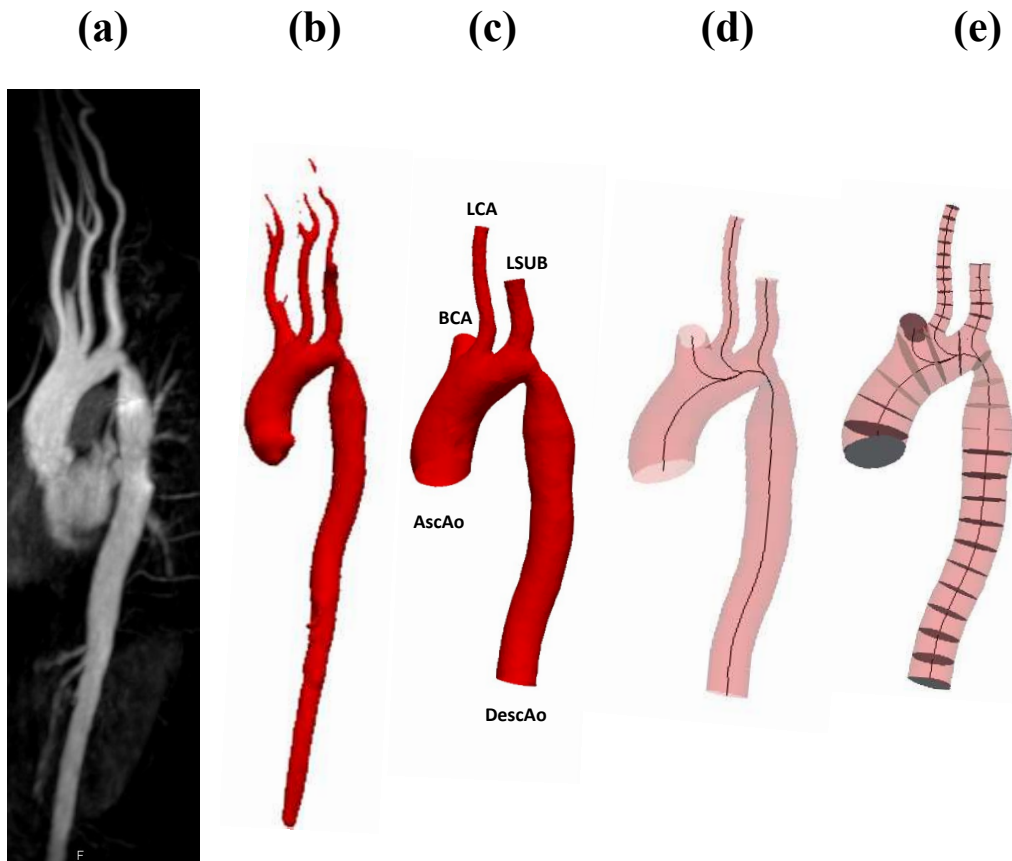


Figure 1: Patient-specific one dimensional and three-dimensional model construction. (a) Maximum intensity projection of the thoracic aorta from the contrast-enhanced magnetic resonance images (CE-MR). (b) 3D reconstructed geometry. (c) Post-processed 3D geometry (including surface smoothing) with truncation to obtain four outlets representing the ascending aorta, the descending aorta (truncated at the plane where MRI measurements were taken), the brachiocephalic artery (BCA), the left common carotid artery (LCA) and the left subclavian artery (LSUB). (d) Centreline and (e) cross-sectional area extraction used to define the segments of the 1D geometry.

Table 3: Foot-to-foot method parameters and resulting pulse wave velocity (c) derived for the 11 patients and the value used in the simulations.

	Δx (m)	Δt (s)	c derived ($m \cdot s^{-1}$)	c simulation ($m \cdot s^{-1}$)
Patient 1	0.359	0.0845	4.68	7
Patient 2	0.290	0.0263	11	11
Patient 3	0.231	0.0475	4.87	4.87
Patient 4	0.250	0.0538	4.64	6
Patient 5	0.296	0.0254	11.65	11.65
Patient 6	0.250	0.0501	4.99	6.5
Patient 7	0.280	0.0689	4.06	5.0
Patient 8	0.19	0.0218	8.70	8.70
Patient 9	0.3	0.0351	8.55	8.55
Patient 10	0.238	0.0218	10.9	10.9
Patient 11	0.250	0.0445	5.61	5.61

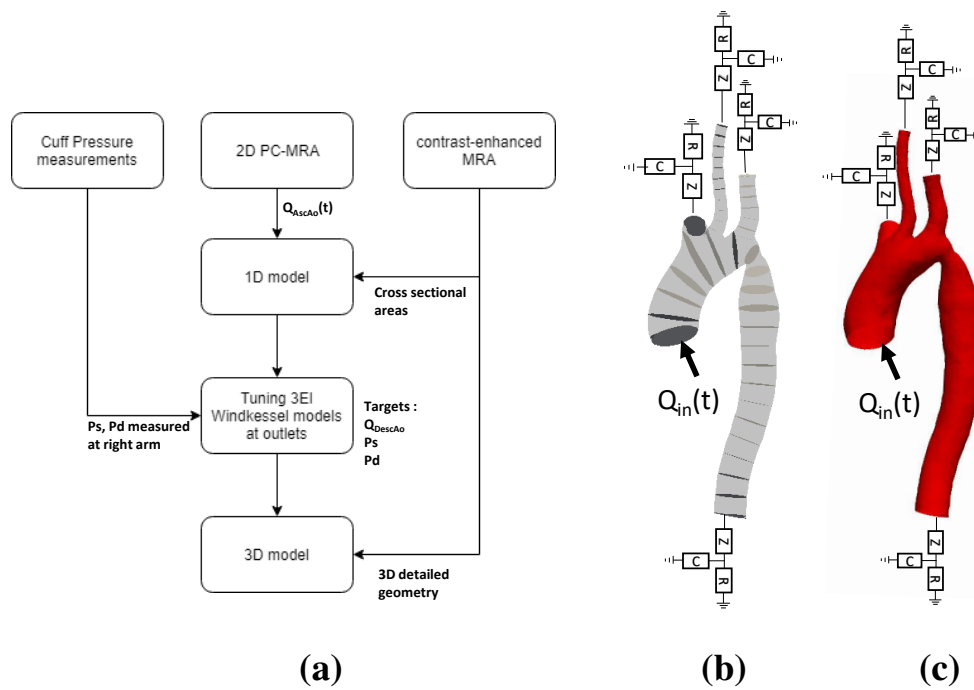


Figure 2: Schematic representing the multi-scale model domain and tuning process used to find the boundary conditions (BCs). (a) Flow chart representing the procedure used to find the WK parameters of the outflow BCs. (b) Schematic of the one-dimensional modelling approach: time-varying flow rate derived from 2D PC-MRI ($Q_{in}(t)$) is directly applied at the inlet of the model and three-element Windkessel models are coupled at the outlets. The tuning process using the 1D model computes outflow Windkessel parameters for BCs based on mechanical properties derived from patient-specific available data. These parameters are then directly applied to the three-dimensional model imposing the same time-varying flow rate ($Q_{in}(t)$) at the inlet and the same mechanical properties used for the one-dimensional model.

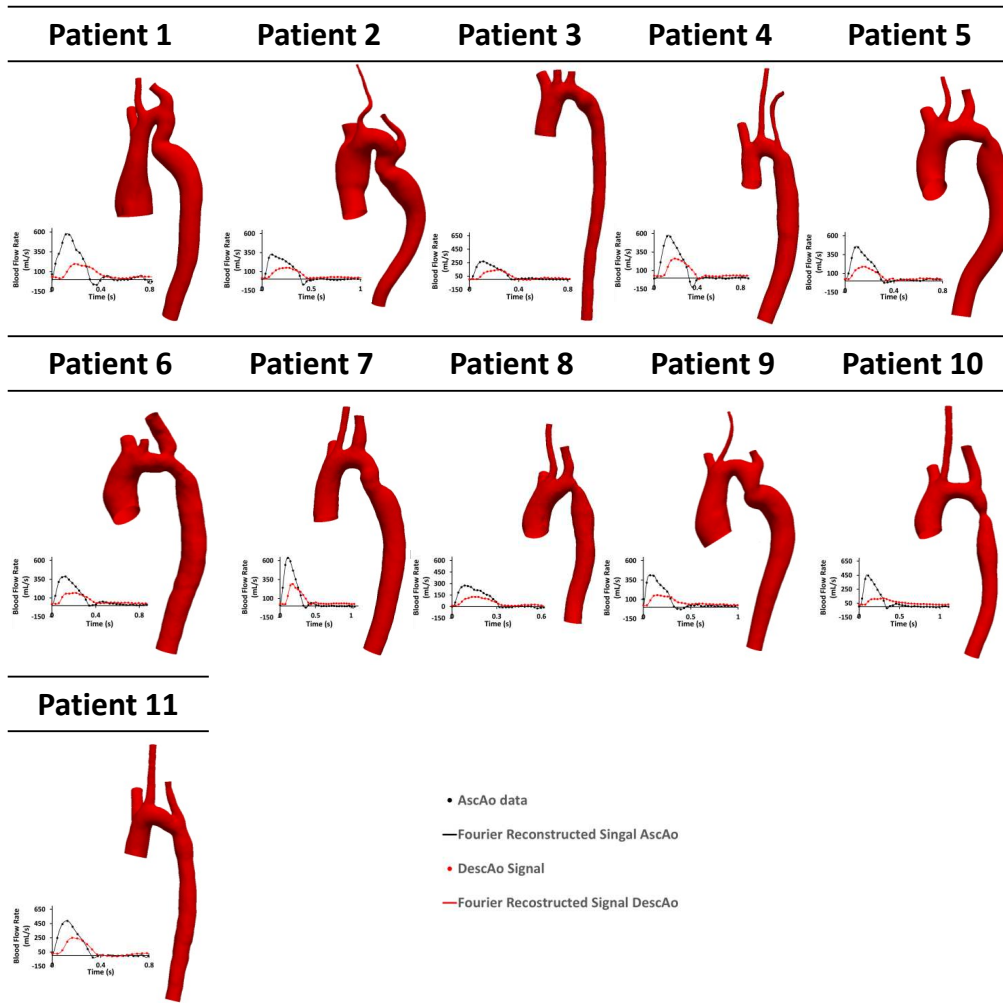


Figure 3: Segmented aortic anatomies extracted from MRA after the post processing and truncation step with aortic flow rates extracted from 2D PC-MRI data at the aortic root plane and diaphragmatic aortic plane, the original data had a temporal resolution of 20-30 phases per cardiac cycle, for the modelling approach the signal's temporal resolution was increased through a Fourier Series transformation.

Table 4: Degree of Stenosis reported for each of 11 patients in the cohort study. For patient 3 geometrical values were not reported as this case represents a hypoplastic descending aorta.

	Inlet diameter (mm)	Reference diameter (mm)	Stenosis diameter (mm)	DS (%)
Patient 1	45	21	18	10
Patient 2	29	29	23	36
Patient 4	21	23	15	59
Patient 5	29	27	14	79
Patient 6	26	23	13	68
Patient 7	23	20	16	22
Patient 8	27	18	10	69
Patient 9	32	26	16	45
Patient 10	24	14	8	72
Patient 11	24	17	15	23

Table 5: Effectiveness of the 1D/0D tuning strategy when compared with systolic and diastolic cuff pressure measurements and correspondence between the 1D/0D model and 3D/0D model in predicting ascending aortic pressures for the 11 cases. SBP refers to the systolic blood pressure, DBP refers to the diastolic blood pressure. Errors are reported in percentage (%).

	Measured		1D/0D Tuned		No. iterations	Errors (%)		3D/0D Simulation		Errors (%)	
	SBP	DBP	SBP	DBP		SBP	DBP	SBP	DBP	SBP	DBP
	Patient 1	152	85	151		84	7	-1	-1	150	84
Patient 2	125	75	128	75	60	+2	0	130	77	+4	+3
Patient 3	131	60	131	60	3	0	0	128	60	-2	0
Patient 4	134	66	139	63	34	+4	-5	158	65	+18	+2
Patient 5	147	95	161	95	25	+10	0	166	100	+13	+5
Patient 6	150	83	150	83	4	0	0	162	78	+8	-6
Patient 7	138	69	138	69	8	0	0	142	70	+3	+1
Patient 8	167	75	167	75	5	0	0	169	79	+1	+5
Patient 9	130	100	156	81	35	+20	-19	177	86	+36	+14
Patient 10	125	60	164	61	34	+31	+2	195	69	+56	-15
Patient 11	144	48	145	48	9	-1	0	160	39	+11	-19

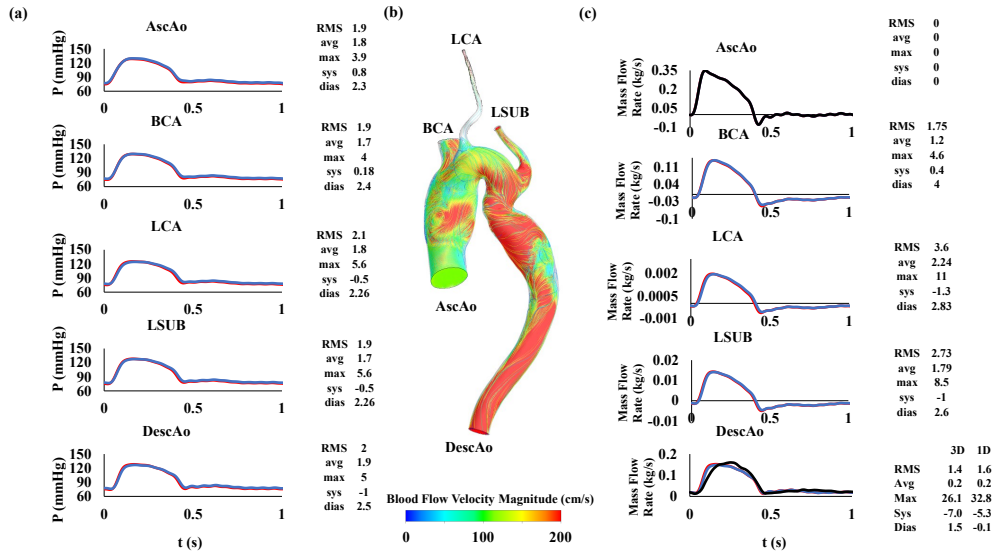


Figure 4: (a) Blood flow (Mass Flow Rate) and (c) Pressure (P) waveforms computed using the 1D (red lines) and 3D (blue lines) models at several locations: ascending aorta (AscAo), Brachiocephalic artery (BCA), left common carotid artery (LCA), left subclavian artery (LSUB) and descending aorta (DescAo) with comparison with available in-vivo data (black lines) for Patient 2. (b) velocity streamlines representing the velocity magnitude at systole.

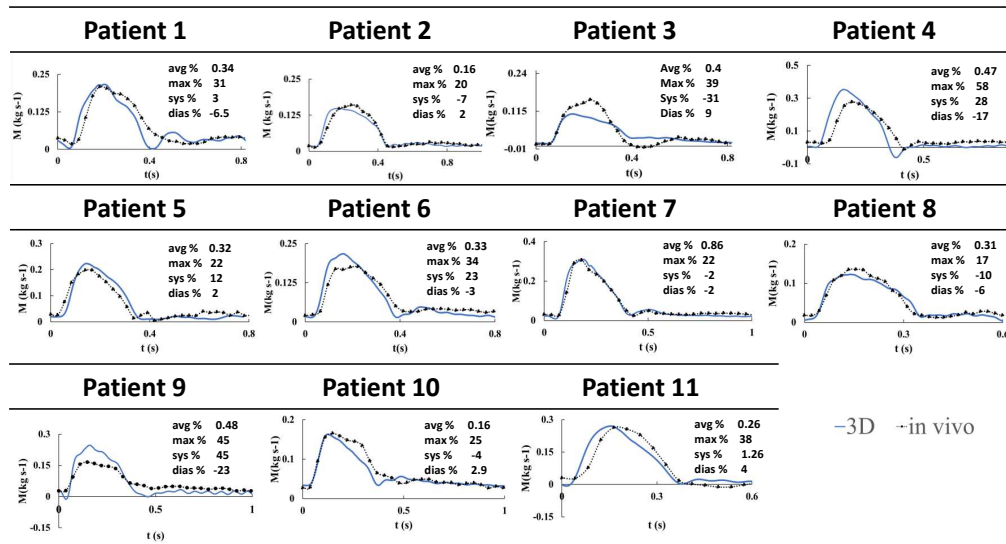


Figure 5: Comparison between computed and measured mass flow rate at the descending thoracic aorta (diaphragmatic level). CFD results extracted from 3D/0D models are presented with blue lines, while 2D PC-MRI data are shown by the black lines.

Table 6: Pressure gradients computed in the 3D/0D model, measured using the cuff arm-leg method and obtained from catheterization (NA= not available) reported in mmHg. Peak Reynolds number are reported at the coarctation site. Laminar (L) and turbulence SST model (T) are reported for the cases where the peak Reynolds number exceeds the limit imposed by the classical turbulence analysis (3500).

	peak Re	$Max_{AscAo} - Max_{DescAo}$		$Max_{gradient}$		$Sys_{gradient}$		$CoA_{gradient}$		Cuff arm-leg	Cath
Native											
		L	T	L	T	L	T	L	T		
Patient 1	3405	1	-	35	-	18	-	9	-	22	32
Patient 2	1861	3	-	18	-	9	-	7	-	30	20
Patient 3	2948	15	-	39	-	20	-	20	-	31	31
Patient 7	5554	1	1	43	43	20	20	14	17	28	14
Patient 9	4341	15	16	47	48	24	24	22	18	35	34
Patient 10	5969	59	59	67	66	59	61	41	42	30	38
Surgically Repaired											
		L	T	L	T	L	T	L	T		
Patient 4	6824	14	14	37	37	22	23	18	18	14	19
Patient 5	4617	9	9	33	33	24	23	23	22	27	23
Patient 6	4848	1	1	29	29	18	15	20	23	26	21
Patient 8	3482	4	-	23	-	20	-	21	-	NA	42
Patient 11	5031	2	1	38	36	23	16	8	12	14	30

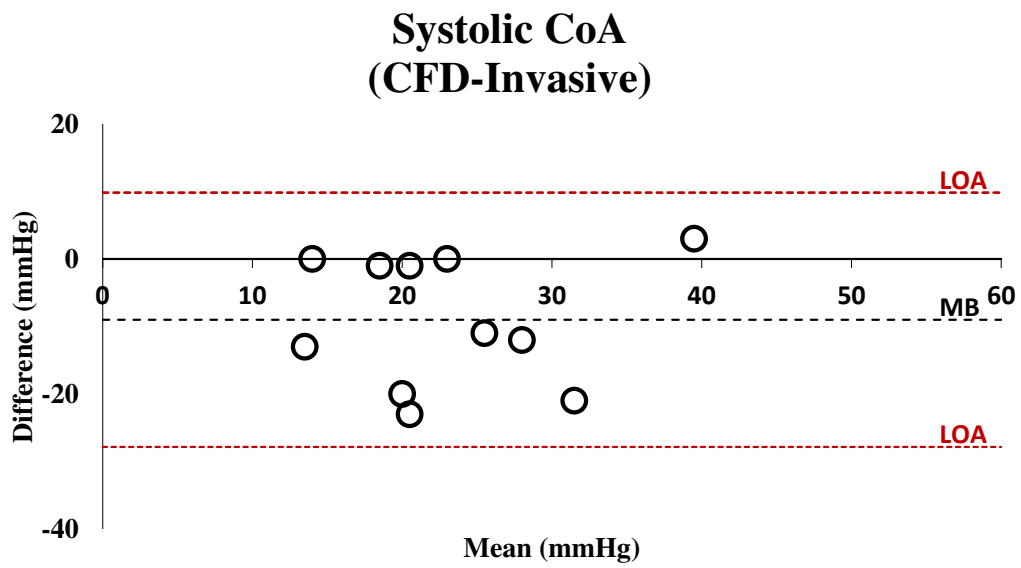


Figure 6: Bland-Altman plot: comparison of the invasive catheter measurement and computed CFD pressure gradient (mmHg) across the aortic coarctation for each case. Dashed red lines represent two standard deviations from the mean difference (LOA, 95 % limits of agreement) while the black dashed line represents the mean difference between the CFD and invasive data (MB).