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# Estimating central blood pressure from aortic flow: development and assessment of algorithms

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## 1 **Abstract**

2 Central blood pressure (cBP) is a highly prognostic cardiovascular (CV) risk factor  
3 whose accurate, invasive assessment is costly and carries risks to patients. We  
4 developed and assessed novel algorithms for estimating cBP from non-invasive aortic  
5 haemodynamic data and a peripheral blood pressure measurement. These algorithms  
6 were created using three blood flow models: the 2- and 3-element Windkessel (0-D)  
7 models and a one-dimensional (1-D) model of the thoracic aorta. We tested new  
8 and existing methods for estimating CV parameters (left ventricular ejection time,  
9 outflow BP, arterial resistance and compliance, pulse wave velocity, and characteristic  
10 impedance) required for the cBP algorithms, using ‘virtual’ (simulated) subjects  
11 (n=19,646) for which reference CV parameters were known exactly. We then tested  
12 the cBP algorithms using ‘virtual’ subjects (n=4064), for which reference cBP were  
13 available free-of-measurement error, and clinical datasets containing invasive (n=10)  
14 and non-invasive (n=171) reference cBP waves across a wide range of CV conditions.  
15 The 1-D algorithm outperformed the 0-D algorithms when the aortic vascular geometry  
16 was available, achieving central systolic blood pressure (*cSBP*) errors  $\leq 2.1 \pm 9.7$  mmHg  
17 and root-mean-square errors (RMSEs)  $\leq 6.4 \pm 2.8$  mmHg against invasive reference  
18 cBP waves (n=10). When the aortic geometry was unavailable, the 3-element 0-D  
19 algorithm achieved *cSBP* errors  $\leq 6.0 \pm 4.7$  mmHg and RMSEs  $\leq 5.9 \pm 2.4$  mmHg  
20 against non-invasive reference cBP waves (n=171), outperforming the 2-element 0-D  
21 algorithm. All CV parameters were estimated with mean percentage errors  $\leq 8.2\%$ ,  
22 except for the aortic characteristic impedance ( $\leq 13.4\%$ ), which affected the 3-element  
23 0-D algorithm’s performance. The freely-available algorithms developed in this work  
24 enable fast and accurate calculation of the cBP wave and CV parameters in datasets  
25 containing non-invasive ultrasound or magnetic resonance imaging data.

## 26 **New and noteworthy**

27 Firstly, our proposed methods for CV parameter estimation and a comprehensive set of  
28 methods from the literature were tested using *in silico* and clinical datasets. Secondly,  
29 optimised algorithms for estimating cBP from aortic flow were developed and tested for  
30 a wide range of cBP morphologies, including catheter cBP data. Thirdly, a dataset of  
31 simulated cBP waves was created using a 3-element Windkessel model. Fourthly, the  
32 Windkessel model dataset and optimised algorithms are freely available.

## 33 1. Introduction

34 Recent clinical studies have shown that central (aortic) blood pressure (cBP) is a better  
35 cardiovascular risk indicator than brachial blood pressure (bBP) (2, 38, 58, 73), since  
36 cBP is more representative of the load exerted on major organs (2, 28). Regardless  
37 of gender or disease, cBPs in subjects with similar brachial systolic blood pressure  
38 (*SBP*) may differ by up to 33 mmHg, resulting in “a significant overlap of central *SBP*  
39 scores between brachial *SBP* risk groups” (56). Furthermore, bBP can be misleading  
40 in healthy young adults due to central-brachial pulse pressure (PP) amplification  
41 of up to 30 mmHg (39). The most direct method to measure cBP is cardiac  
42 catheterisation, which is costly and carries risks to patients (*e.g.* blood clot formation  
43 and embolisation) due to its invasive nature, even when performed in specialised  
44 centres (38). Consequently, there is great value in developing methods for estimating  
45 cBP non-invasively which are less risky and more suitable for frequent use.

46 A potential approach is to use a computational model of the circulation to estimate  
47 cBP from non-invasive measurements of aortic flow and peripheral blood pressure  
48 (BP)(31). Aortic flow can be measured using magnetic resonance imaging (MRI) or  
49 ultrasound (US). Peripheral systolic and diastolic BP can be easily measured using  
50 a brachial cuff, whilst a peripheral BP wave can be measured using, for example,  
51 applanation tonometry. MRI can also measure vascular geometry which can be used  
52 to further refine the model – the importance of aortic geometry was proposed by  
53 Westerhof *et al.* (68). Consequently, computational models could be personalised to  
54 estimate cBP in cardiac MRI and US settings. Moreover, these imaging modalities  
55 are the gold standard when assessing cardiac anatomy (cardiac magnetic resonance and  
56 echocardiography). Combining the information they provide with the knowledge of cBP  
57 could enable the non-invasive derivation of PV-loops and myocardial wall stress, two

58 major indicators of cardiac performance. Although previous studies have used reduced-  
59 order models to estimate cBP non-invasively, they either did not use patient-specific  
60 MRI aortic geometry (26), or did not validate their cBP estimates against invasive cBP  
61 measurements or compare the performance of several algorithms (5, 9, 18, 31, 33).

62 The aim of this study was to develop and assess three novel algorithms of increasing  
63 complexity for estimating the cBP wave from aortic flow, using non-invasive, patient-  
64 specific data from the thoracic aorta (Figure 1). Each algorithm used a different blood  
65 flow model: the 2-element (24) and 3-element (70) zero-dimensional (0-D) Windkessel  
66 models, and a one-dimensional (1-D) model of the thoracic aorta (5). The first step  
67 in each algorithm was to estimate cardiovascular (CV) parameters from non-invasive  
68 haemodynamic data measured in the thoracic aorta and a peripheral BP measurement.  
69 These CV parameters were: left ventricular ejection time (*LJET*), outflow vascular  
70 BP ( $P_{\text{out}}$ ), total arterial resistance ( $R_T$ ) and compliance ( $C_T$ ), aortic pulse wave  
71 velocity (*PWV*), and characteristic impedance ( $Z_0$ ). The second step was to use these  
72 parameters as inputs to one of the three blood flow models to estimate a patient-  
73 specific cBP waveform. In this study we assessed the performance of the CV parameter  
74 estimation methods and cBP algorithms against reference data, including invasive cBP  
75 measurements.

## 76 2. Methods

### 77 2.1. Datasets

78 The CV parameter estimation methods and cBP algorithms were initially developed and  
79 tested using two datasets of virtual subjects. The cBP algorithms were then assessed  
80 using three clinical datasets. The characteristics of each dataset are shown in Table 1.

### 81 *Clinical datasets*

82 The first clinical dataset, called the ‘Aortic Coarctation’ dataset, contains data acquired  
83 from 10 patients with aortic coarctation (59). The St Thomas’ Hospital Research Ethics  
84 Committee approved this prospective study, and informed consent was obtained from  
85 all patients (ethics reference number R&D REC 08/H0804/134). Inclusion criteria  
86 comprised native or residual aortic coarctation. Exclusion criteria were the presence  
87 of stented aortic coarctation or aortic dissection. Data were acquired in a hybrid  
88 magnetic resonance/X-ray suite guidance system. A 1.5-T MRI scanner (Philips Intera,  
89 Philips, Best, The Netherlands) was used to obtain a breath-hold 3-D contrast-enhanced  
90 angiography of the thoracic aorta (used to obtain aortic geometry measurements) and  
91 free-breathing 2-D phase contrast flow velocity through-plane scans at the ascending  
92 and upper-descending aorta (used to obtain flows at both locations). Invasive BP  
93 data were measured using X-ray guided cardiac catheterisation (Philips BV Pulsera).  
94 Measurements were taken simultaneously at the ascending and descending aorta,  
95 immediately after the flow acquisition, using multi-purpose catheters (angiographic  
96 catheter 4F with carbon dioxide-filled balloon).

97 The second and third clinical datasets, called the ‘Normotensive’ and ‘Hypertensive’  
98 datasets, were obtained from (35): (i) 13 normotensive healthy volunteers at baseline  
99 and after the administration of different doses of four inotropic and vasoactive drugs  
100 (dobutamine, norepinephrine, phentolamine, and nitroglycerin); and (ii) 158 subjects  
101 assessed for hypertension (including those found to be normotensive). Both datasets  
102 were approved by the London - Westminster Research Ethics Committee, and written  
103 informed consent was obtained. Aortic flow was obtained by Doppler sonography  
104 and peripheral BP measurements were obtained by carotid applanation tonometry.  
105 Reference cBP measurements were acquired using the SphygmoCor® system (AtCor

106 Medical, Sydney, Australia), which employs a transfer function to calculate cBP from  
107 carotid BP measured non-invasively by applanation tonometry (2,57).

108 The range of cBP waves contained within each clinical dataset is shown in Figure 2.

### 109 *Datasets of virtual subjects*

110 Two datasets of BP and flow waves measured in virtual subjects were created  
111 by simulating arterial haemodynamics using 0-D and 1-D computational models  
112 respectively (Figure 3). A new 0-D dataset, whose reference CV parameter values were  
113 known precisely, was used to initially test existing CV parameter estimation methods  
114 and develop new ones. An existing 1-D dataset was used to further test and refine these  
115 methods and the cBP estimation algorithms, as it is based on a more physiological  
116 model of the arterial circulation (14).

117 The 0-D dataset was created using a 3-element Windkessel model (Section 2.4).  
118 Each virtual subject's cBP wave was simulated using an aortic flow wave generated  
119 by the *AorticFlowWave* script (12) based on prescribed values of heart rate ( $HR$ ) and  
120 stroke volume ( $SV$ ) in combination with prescribed values of  $R_T$ ,  $C_T$ ,  $Z_0$ , and  $P_{out}$ . CV  
121 parameters were selected to create a dataset of cBP waves representative of a sample  
122 of healthy adults. To do so: (i) mean ( $\mu$ ) and standard deviation ( $\sigma$ ) values of each  
123 parameter in healthy adults were identified from the literature (see Appendix A); (ii)  
124 five values for each parameter were calculated as  $\mu$ ,  $\mu \pm 0.5\sigma$ , and  $\mu \pm \sigma$ ; and (iii) a  
125 virtual subject was created using each of the 15,625 combinations of CV parameters.

126 The 1-D dataset was created by using a 1-D blood flow model in the aorta and larger  
127 arteries of the head and limbs. The CV properties of 25-75 year olds were identified  
128 through a comprehensive literature review. Pressure, flow velocity and luminal area  
129 waves were simulated in the aorta and other common measurement sites of 4,374 virtual  
130 subjects and were verified by comparison against clinical data (see (14) for full details).



131 We removed non-physiological data from further analysis, based on limits derived  
132 from the ‘Hypertensive’ and ‘Normotensive’ datasets (see Table 1). Maximum limits  
133 of central systolic BP ( $cSBP$ ) and central pulse pressure ( $cPP$ ) were obtained from  
134 the ‘Hypertensive’ dataset. Minimum limits of central diastolic BP ( $cDBP$ ) and  $cPP$   
135 were obtained from the ‘Normotensive’ dataset. Consequently, we excluded subjects  
136 with  $cSBP > 220$  mmHg,  $cDBP < 44$  mmHg, and  $cPP < 18$  mmHg or  $> 109$  mmHg. 43  
137 subjects were excluded from the 0-D dataset; 310 subjects were excluded from the 1-D  
138 dataset.

### 139 *2.2. Cardiovascular parameter estimation methods*

140 The following CV parameters were required as inputs to at least one of the cBP  
141 estimation algorithms:  $LRET$ ,  $P_{out}$ ,  $R_T$ ,  $C_T$ ,  $Z_0$ , and aortic pulse wave velocity ( $PWV$ ).  
142 A comprehensive literature review of CV parameter estimation methods was performed.  
143 The methods listed in Table 2 and described in Appendix B were implemented and  
144 assessed in this study. To be included, they had to satisfy at least one of the following  
145 inclusion criteria: they were reported as the optimal method (10, 19, 50, 61, 71); their  
146 performance was similar to that of the optimal method (15, 19, 37, 50, 71); they were  
147 the only reported method (1, 4, 7, 13, 16, 17, 24, 25, 30, 32, 40–42, 52, 54, 55, 60, 63, 69, 72);  
148 or their performance had not been sufficiently assessed due to their novelty (13, 25, 32).  
149 Additionally, new, improved methods were developed.

### 150 *2.3. Assessing cardiovascular parameter estimation methods*

151 The performance of the CV parameter estimation methods was assessed using the mean  
152 percentage error (MPE) and  $\sigma$  between estimated and reference CV parameter values  
153 for the two datasets of virtual subjects. Additionally, Bland-Altman plots (8) were  
154 created to show the bias and limits of agreement ( $\pm 1.96$  standard deviation from the

155 bias) between estimated and reference CV parameter values. For the 0-D dataset,  
 156 reference values were obtained from the prescribed values used for each virtual subject  
 157 (Table A1). For the 1-D dataset, reference values for  $LVET$ ,  $P_{out}$  and aortic root  $PWV$   
 158 were obtained from the prescribed values.  $R_T$  was calculated from the aortic root BP  
 159 and flow waves using (24)

$$160 \quad R_T = \frac{MBP - P_{out}}{\overline{Q_{in}}}, \quad (1)$$

161 where  $MBP$  is the mean blood pressure and  $\overline{Q_{in}}$  is the mean blood flow.  $C_T$  and  $Z_0$  were  
 162 extracted from aortic root BP and flow waves using the optimised 3-element Windkessel  
 163 model described in Appendix A.2.

164 Two common clinical scenarios were considered when assessing CV parameter  
 165 estimation methods for each dataset: ‘carotid+’, where the carotid BP wave was  
 166 available; and ‘carotid-’, where only brachial  $DBP$  and  $SBP$  values were available  
 167 (Figure 1a). The 1-D dataset of virtual subjects was used to determine, for each scenario  
 168 and CV parameter, the optimal (*i.e.* smallest MPE and  $\sigma$ ) CV parameter estimation  
 169 methods to be used by the cBP algorithms described in Section 2.4.

#### 170 *2.4. Central blood pressure estimation algorithms*

171 The three algorithms used to estimate cBP each consisted of two stages. Firstly,  
 172 CV parameters were estimated using the optimal CV parameter estimation methods.  
 173 Secondly, a cBP wave was simulated using a computational model of arterial blood flow.  
 174 We considered the following models: the 2-element (24) and 3-element (70) Windkessel  
 175 models, and a 1-D model of the thoracic aorta (5), referred to as ‘1D-Ao’ hereafter.

#### 176 *2-element Windkessel (0-D) model*

177 This model, referred to as ‘2-Wk’ hereafter, idealises the arterial system as a reservoir of  
 178 compliance  $C_T$ . Blood flows into the reservoir from the heart,  $Q_{in}(t)$ , at a pressure  $P(t)$ ,

179 encounters a resistance to flow,  $R_T$ , and flows out into the vascular beds at a pressure  
 180  $P_{\text{out}}$  (Figure 1c, top). The governing equation is

$$181 \quad \frac{dP}{dt} + \frac{P - P_{\text{out}}}{R_T C_T} = \frac{Q_{\text{in}}}{C_T}, \quad (2)$$

182 which can be solved for  $P(t)$  using the integrating factor method,

$$183 \quad P(t) = P_{\text{out}} + (P_0 - P_{\text{out}})e^{-\frac{t-t_0}{R_T C_T}} + \frac{e^{-\frac{t}{R_T C_T}}}{C_T} \int_{t_0}^t Q_{\text{in}}(t')e^{\frac{t'}{R_T C_T}} dt', \quad t \geq t_0, \quad (3)$$

184 where  $t_0$  is the initial time and  $P_0 = P(t_0)$ .

### 185 *3-element Windkessel (0-D) model*

186 This model, referred to as ‘3-Wk’ hereafter, results from adding an impedance,  $Z_0$ , in  
 187 series to the ‘2-Wk’ model where  $R_T = Z_0 + R$  (Figure 1(c), middle).  $Z_0$  is commonly  
 188 known as the characteristic impedance and was initially introduced to represent the  
 189 impedance of the aorta (71). The governing equation is

$$190 \quad \frac{dP}{dt} + \frac{P - P_{\text{out}}}{RC_T} = Z_0 \frac{dQ_{\text{in}}}{dt} + \frac{(Z_0 + R)Q_{\text{in}}}{RC_T}, \quad (4)$$

191 which can be solved analytically for  $P(t)$  using the integrating factor method,

$$192 \quad P(t) = P_{\text{out}} + (P_0 - P_{\text{out}} - Z_0 Q_0)e^{-\frac{t-t_0}{RC_T}} + Z_0 Q_{\text{in}}(t) \\
 193 \quad + \frac{e^{-\frac{t}{RC_T}}}{C_T} \int_{t_0}^t Q_{\text{in}}(t')e^{\frac{t'}{RC_T}} dt', \quad t \geq t_0, \quad (5)$$

194 where  $Q_0 = Q_{\text{in}}(t_0)$ .

### 195 *1-D aortic model*

196 This model uses the 1-D equations of blood flow in the network of compliant vessels  
 197 shown in Figure 1c (bottom) to compute cBP (5). The inputs to the model are: (i)  
 198 the geometry (*i.e.* lengths and cross-sectional areas) of the thoracic aorta, including the  
 199 supra-aortic arteries; (ii) flow waves at the ascending and descending aorta and, when  
 200 available, each supra-aortic artery; and (iii) a peripheral BP measurement.

201 The 1-D and ‘Aortic Coarctation’ datasets contained the vascular geometry and  
 202 *PWV* data required to run the ‘1D-Ao’ algorithm. For the ‘Aortic Coarctation’ dataset,  
 203 the geometry of the thoracic aorta was extracted from MRI data using an in-house  
 204 segmentation software (21, 45). Besides, since peripheral BP measurements were not  
 205 available the BP acquired invasively in the descending aorta was used instead. For  
 206 the 1-D dataset, the geometry was extracted from the corresponding arterial segments.  
 207 For both datasets, volumetric blood flow waves were obtained at the ascending ( $Q_{\text{in}}$ ,  
 208 acquired as close to the aortic root as possible) and descending thoracic ( $Q_{\text{out}}$ ) aorta.  $Q_{\text{in}}$   
 209 and  $Q_{\text{out}}$  were used to calculate the pulse wave velocity, *PWV*, as described in Table 2.

210  $Q_{\text{in}}$  was imposed as an inflow boundary condition at the aortic root and ‘3-Wk’  
 211 models were coupled to the outlet of each terminal 1-D model segment. The parameters  
 212 of each outflow model  $j$ ,  $Z_{0,\text{Wk}}^j$ ,  $C_{\text{T,Wk}}^j$  and  $R_{\text{Wk}}^j$ , were calculated using  $Q_{\text{in}}$ ,  $Q_{\text{out}}$ , and  
 213 the outflow distribution (*OD*) in the supra-aortic arteries,  $OD_{\text{flow}}^j = \bar{Q}_{\text{out}}^j / \bar{Q}_{\text{in}}$ , under  
 214 the assumption that *DBP*, *MBP*, and  $P_{\text{out}}$  remain constant within large arteries (2).

215 We used the following equations (5):

$$216 \quad Z_{0,\text{Wk}}^j = \frac{\rho PWV}{A_{\text{out}}^j}, \quad (6)$$

$$217 \quad R_{\text{Wk}}^j = \frac{R_{\text{T}}}{OD^j} - Z_{0,\text{Wk}}^j, \quad (7)$$

$$218 \quad C_{\text{T,Wk}}^j = (C_{\text{T}} - C_{\text{T,art}}) \frac{R_{\text{T}}}{R_{\text{Wk}}^j}, \quad (8)$$

219 where  $C_{\text{T,art}}$  is the total compliance of the 1-D model arterial segments calculated as  
 220 the sum of each segment compliance,

$$221 \quad C_{\text{T,art}}^k = \frac{\bar{A}^k L^k}{\rho PWV^2}, \quad (9)$$

222 with  $\bar{A}^k$  the average area and  $L^k$  the length of the arterial segment  $k$ . When  $\bar{Q}_{\text{out}}^j$  were  
 223 unavailable at each outflow  $j$ , the difference between the mean values of  $Q_{\text{in}}$  and  $Q_{\text{out}}$   
 224 was distributed among the supra-aortic arteries proportionally to their outlet areas,  
 225  $A_{\text{out}}^j$ , as  $OD_{\text{area}}^j = (\bar{Q}_{\text{in}} - \bar{Q}_{\text{out}}) A_{\text{out}}^j / \sum A_{\text{out}}^j$ .

## 226 2.5. Assessing central blood pressure estimation algorithms

227 The performance of each cBP estimation algorithm was assessed by comparing estimated  
 228 cBP values to corresponding reference values in all clinical datasets and in the 1-D  
 229 dataset. Performance was quantified using the  $\mu$  and the  $\sigma$  of the errors for central  
 230 diastolic (*cDBP*) and systolic (*cSBP*) blood pressure. Additionally, the root mean  
 231 square error (RMSE) between estimated and reference cBP waves was computed.  
 232 Similarly to Section 2.3, Bland-Altman plots were used to show the bias and limits of  
 233 agreement between estimated and reference BP values. Finally, the correlation between  
 234 estimated and reference cBP values was assessed using the coefficient of determination  
 235 ( $R^2$ ).

## 236 3. Results

### 237 3.1. Assessment of CV parameter estimation methods

238 The last two columns of Table 2 show mean percentage error (MPE) and standard  
 239 deviation ( $\sigma$ ) for all CV parameter estimation methods assessed in the two datasets of  
 240 virtual subjects. MPE for the 1-D dataset was reduced by at least 40% if the carotid  
 241 BP wave ('carotid+') was used instead of brachial *DBP* and *SBP* values ('carotid-').

242 Table 3 displays the methods that led to the smallest MPE for each clinical scenario  
 243 and dataset. By using these optimal methods, all six CV parameters were calculated in  
 244 less than 1 second for each virtual subject, and in less than 1 hour for the entire 0-D or  
 245 1-D dataset using a Dell Precision M4800 laptop (Round Rock, Texas, United States).

246 All parameters from the 0-D dataset were estimated with  $MPE < 2\%$  in both  
 247 clinical scenarios (Table 3, top). Figure 4 shows Bland-Altman plots for all CV  
 248 parameters estimated using the optimal methods obtained from the 1-D dataset (Table 3,  
 249 bottom). These methods were then used in the cBP estimation algorithms (Section 3.2).

250 For both scenarios,  $LRET$ ,  $P_{\text{out}}$ ,  $R_T$ ,  $C_T$ , and  $PWV$  were estimated without any  
 251 considerable bias of their corresponding reference mean values ( $< 6\%$  for ‘carotid+’  
 252 and  $< 10\%$  for ‘carotid-’). However,  $Z_0$  was overestimated with a much greater bias  
 253 of its corresponding reference mean value ( $13\%$  for ‘carotid+’ and  $82\%$  for ‘carotid-’).  
 254 The bias as a function of each CV parameter reference value remained approximately  
 255 unchanged, with the exceptions of  $P_{\text{out}}$  (which had a singular reference value) and  $C_T$  for  
 256 ‘carotid-’ (whose absolute bias increased with increasing reference values). The same  
 257 optimal methods were identified for  $PWV$  in both scenarios.

### 258 3.2. Assessment of cBP algorithms

259 The cBP algorithms employed the optimal CV parameter estimation methods obtained  
 260 from the 1-D dataset (Table 3, bottom). Table 4 shows the estimation errors for all  
 261 three cBP algorithms, with each algorithm evaluated in four datasets for both clinical  
 262 scenarios. In the 1-D dataset, RMSEs for ‘carotid+’ ( $\mu \pm \sigma: < 3.4 \pm 1.7$  mmHg) were  
 263 lower than those for ‘carotid-’ ( $< 5.1 \pm 2.5$  mmHg). In the clinical datasets, RMSEs  
 264 were similar for both scenarios and larger than those obtained in the 1-D dataset. The  
 265 ‘1D-Ao’ algorithm led to the smallest RMSEs in the 1-D ( $2.0 \pm 1.0$  mmHg) and ‘Aortic  
 266 Coarctation’ ( $6.4 \pm 2.8$  mmHg) datasets. The ‘3-Wk’ algorithm led to the smallest  
 267 RMSEs in the ‘Normotensive’ ( $5.9 \pm 2.4$  mmHg) and ‘Hypertensive’ ( $5.7 \pm 2.4$  mmHg)  
 268 datasets (these did not contain the aortic geometry data needed to run the ‘1D-Ao’  
 269 algorithm).

270 Overall, estimation errors for  $cDBP$  and  $cSBP$  were smaller in the 1-D dataset  
 271 compared to the clinical datasets, for all cBP algorithms and clinical scenarios.  
 272 Furthermore,  $cDBP$  errors were smaller than  $cSBP$  errors for all algorithms, datasets,  
 273 and scenarios. However, within each dataset and scenario,  $cDBP$  and  $cSBP$  errors  
 274 changed considerably depending on the cBP algorithm used. For both clinical scenarios

275 in the Aortic Coarctation and 1-D datasets, the ‘1D-Ao’ algorithm led to *cSBP* errors  
276 that were smaller or similar compared to the 0-D models ( $< 2.2 \pm 5.3$  mmHg vs  $< 4.5$   
277  $\pm 5.9$  mmHg for the 1-D dataset;  $< 2.1 \pm 9.7$  mmHg vs  $< 17.3 \pm 7.9$  mmHg for the  
278 ‘Aortic Coarctation’ dataset). The 0-D algorithms performed similarly in both datasets  
279 and led to smaller *cDBP* errors than the ‘1D-Ao’ algorithm in the ‘Aortic Coarctation’  
280 dataset.  $R^2$  correlation values between reference and estimated cBP calculated using  
281 the best performing (*i.e.* 1-D aortic) algorithm and scenario in the 1-D dataset were:  
282 0.834 for *cDBP* and 0.976 for *cSBP* (all  $p < 0.001$ ). In the ‘Aortic Coarctation’ dataset  
283 they were: 0.776 for *cDBP* and 0.903 for *cSBP* (all  $p < 0.001$ ).

284 The ‘Normotensive’ and ‘Hypertensive’ datasets contained non-invasive reference  
285 cBP waves calculated by the SphygmoCor® device using a transfer function. For  
286 ‘carotid–’, both 0-D models estimated *cDBP* and *cSBP* values with errors  $< 6.0 \pm 4.7$   
287 mmHg, though the ‘3-Wk’ algorithm led to smaller RMSEs in both datasets and  
288 scenarios. All errors for the ‘3-Wk’ algorithm were larger for ‘carotid+’.  $R^2$  correlation  
289 values for these clinical datasets using the best performing 0-D algorithm (*i.e.* ‘3-Wk’)  
290 and scenarios were: 0.949 for *cDBP* and 0.997 for *cSBP* (all  $p < 0.001$ ).

291 An extended version of Table 4, which also contains errors for *cMBP* and *cPP*, is  
292 provided as Supplement Table at <https://doi.org/10.5281/zenodo.3968540>. Bland-  
293 Altman plots of *cDBP*, *cSBP*, *cMBP*, and *cPP* are also available (see Supplement  
294 Figures S1 to S8). Supplement Figures S3 and S4 show increases in the absolute  
295 bias for *cSBP* with increasing reference BP values in the 1-D, ‘Normotensive’, and  
296 ‘Hypertensive’ datasets for ‘carotid–’. Remaining estimates were less affected by varying  
297 reference BP values.

298 Supplement Figures S9 to S16 show individual cBP wave estimations by each cBP  
299 algorithm for a set of randomly chosen subjects in the 1-D dataset and for all subjects

300 in the ‘Aortic Coarctation’, ‘Normotensive’ and ‘Hypertensive’ datasets, in both clinical  
301 scenarios. Using a Dell Precision M4800 laptop, the 0-D algorithms took less than 1  
302 second per patient to compute the cBP wave, whereas the ‘1D-Ao’ algorithm took less  
303 than 1 minute (both times include the time required to calculate all patient-specific CV  
304 parameters).

## 305 4. Discussion

306 We have developed fast algorithms to estimate several clinically relevant haemodynamic  
307 parameters of the systemic circulation and reconstruct the cBP wave from non-invasive  
308 data. Our algorithms are based on physical phenomena occurring in the thoracic aorta  
309 and are patient-specific for all physical parameters except for blood density and viscosity.  
310 We have tested them in several *in silico* and clinical datasets with a wide range of  
311 cBP wave morphologies. The ‘1D-Ao’ algorithm outperformed the 0-D algorithms at  
312 estimating cBP wave morphology when the aortic vascular geometry was available.  
313 Both 0-D models estimated cBP values with similar errors when only the aortic flow  
314 and peripheral BP waves were available, though the ‘3-Wk’ algorithm produced the  
315 smallest RMSEs. The aortic characteristic impedance was the most challenging CV  
316 parameter that needed to be estimated, limiting the ability of the ‘3-Wk’ algorithm to  
317 achieve smaller cBP errors. The novel Windkessel model dataset and optimised cBP  
318 algorithms are a valuable resource for developing and testing new, improved algorithms  
319 to estimate CV parameters and cBP waves.

### 320 4.1. Cardiovascular parameter estimation methods

321 Obtaining reliable *in vivo* reference values for the CV parameters required to estimate  
322 cBP is challenging. We therefore assessed the accuracy of several CV parameter



323 estimation methods using datasets of virtual subjects for which theoretical reference  
 324 values were either known exactly (all parameters for the 0-D dataset;  $LRET$ ,  $P_{out}$   
 325 and  $PWV$  for the 1-D dataset) or could be estimated from the aortic BP and flow  
 326 waves without measurement error ( $R_T$ ,  $C_T$  and  $Z_0$  for the 1-D dataset). Unlike the  
 327 0-D models, the 1-D model accounts for wave propagation phenomena and can capture  
 328 high-frequency features of the pressure wave such as the first systolic shoulder, thus  
 329 providing information which can be derived through pulse wave analysis. The 1-D  
 330 dataset, therefore, provided the optimal combination of methods for the cBP algorithms  
 331 and identified accurate methods for estimating CV parameters that, by themselves, can  
 332 be used to assess cardiovascular function from non-invasive data available in the clinic.

333 Left ventricular ejection time ( $LRET$ ) is a valuable metric of left ventricular  
 334 performance both in health and disease (27). According to our results, it can be  
 335 estimated accurately from the aortic flow wave using the novel  $LV4$  method (MPE  
 336  $\pm \sigma$ :  $0.3 \pm 0.6\%$ ).

337 The physiological meaning and range of values of the asymptotic BP ( $P_{out}$ ) are  
 338 still not fully understood (49). According to some studies,  $P_{out}$  is related to capillary  
 339 and venous BP (65), though others argue this pressure is larger than the venous BP  
 340 due to waterfall effects (3, 11, 66). We have found that estimation methods based on  
 341 an exponential fit to the diastolic part of the BP wave outperformed those using a  
 342 percentage of  $DBP$  ( $-5.1 \pm 8.0\%$  vs  $9.1 \pm 11.0\%$ ).

343 Arterial resistance ( $R_T$ ) is also an important parameter for assessing small blood  
 344 vessel function (44,46). According to our results, calculation of  $R_T$  from peripheral  $DBP$   
 345 and  $SBP$  values underestimated reference  $R_T$  values by 5% on average. More accurate  
 346 estimates could be obtained when using the whole peripheral BP wave ( $0.0 \pm 0.1\%$ ).

347 Changes in arterial compliance ( $C_T$ ) can have important effects on the pulse wave,

348 left ventricular dynamics, cardiac output, and the ratio of systolic to diastolic flow into  
 349 capillary beds (51). Our proposed optimised ‘3-Wk’ method for estimating  $C_T$  led to  
 350 a  $MPE = -0.8 \pm 4.2\%$ , outperforming existing methods. Similarly to Stergiopoulos *et*  
 351 *al.* (62), we found  $MPE < 12\%$  for the ‘diastolic decay’, ‘area’ and ‘two-area’ methods,  
 352 though our  $MPE$  for the ‘pulse pressure’ method was higher (27% vs 17%).

353 Pulse wave velocity ( $PWV$ ) provides a direct measure of aortic stiffness and is  
 354 an independent predictor of cardiovascular risk (6, 53). We found that methods for  
 355 estimating  $PWV$  which used the ascending and descending aorta flows outperformed  
 356 those using the carotid and femoral BP waves, in agreement with the study by Obeid  
 357 *et al.* (43) which also involved *in silico* data and theoretical reference  $PWV$  values.

358 Aortic characteristic impedance ( $Z_0$ ) is directly related to aortic stiffness (42,64). In  
 359 the 1-D dataset, the PQ-loop methods led to smaller  $MPE$  (13.4%) than other methods  
 360 ( $> 37.1\%$ ), including those with  $MPE < 3\%$  when run on the 0-D dataset. Most  
 361 methods involving BP and flow waves require these to be measured simultaneously at  
 362 the same location, but in this study BP was taken from the periphery and combined with  
 363 the aortic flow wave, resulting in large  $MPE$  for the 1-D dataset ( $> 13.4\%$ ). PQ-loop  
 364 methods only require a linear proportionality between aortic BP and flow in early systole  
 365 which, according to our results, is maintained between peripheral BP and aortic flow.  
 366 In fact, BP and flow morphology in early systole is mainly dictated by the propagation  
 367 of a pulse wave travelling from the heart to the periphery, with the backward-travelling  
 368 wave having little influence (34). This observation led to the derivation of the novel  
 369 method Z4 which provided the smallest  $MPE$  for ‘carotid-’ ( $82.3 \pm 32.6\%$ ).

370 Lastly we note that all CV parameters were estimated individually from the clinical  
 371 data. However, due to the interdependence between some CV parameters (*e.g.*  $R_T$   
 372 and  $P_{out}$ ), performance may be improved via simultaneous or iterative estimation, as

373 suggested in (49), though this was beyond the scope of our study.

#### 374 4.2. Central blood pressure algorithms

375 We have developed algorithms which estimate the cBP wave from non-invasive, patient-  
376 specific measurements by using 0-D and 1-D blood flow modelling. 0-D models were  
377 chosen for their simplicity and low number of CV parameters that have to be estimated.  
378 The ‘1D-Ao’ model was chosen because it captures pulse wave propagation phenomena,  
379 though at the expense of a much larger number of parameter estimations. Only the  
380 thoracic aorta was simulated using 1-D model segments since cardiac MRI usually  
381 provides vessel anatomy and blood flow in the upper part of the aorta only. Furthermore,  
382 previous work has shown that it is possible to reduce the topological complexity of the  
383 arterial network and, hence, the number of parameters to be estimated, while sufficiently  
384 capturing relevant BP values such as  $cSBP$  and  $cPP$  (20, 23).

385 We tested the cBP algorithms in several clinical datasets to cover a wide range  
386 of cBP wave morphologies, including those seen in hypertensive subjects and in  
387 normotensive subjects under the effect of four inotropic and vasoactive drugs which  
388 significantly affect BP wave morphology (22). When the aortic vascular geometry was  
389 available, the ‘1D-Ao’ algorithm outperformed the 0-D algorithms at estimating cBP  
390 wave morphology as well as  $cSBP$  values, leading to RMSEs  $< 2.0 \pm 1.0$  mmHg in  
391 the 1-D dataset and  $< 6.4 \pm 2.8$  mmHg in the ‘Aortic Coarctation’ dataset. When the  
392 aortic vascular geometry was unavailable, the 3-element 0-D algorithm achieved RMSEs  
393  $< 2.0 \pm 1.7$  mmHg for *in silico* data and  $< 5.9 \pm 2.4$  mmHg for clinical data from the  
394 ‘Normotensive’ and ‘Hypertensive’ datasets.

395 Relative errors for cBP estimates were smaller in the 1-D dataset than in the clinical  
396 datasets since all haemodynamic data in the former were free of measurement error and  
397 inconsistencies that are inherent to clinical datasets (*e.g.* heart rate differences between

398 pressure and flow waves) (5). Therefore, results obtained from the 1-D dataset provided  
399 a theoretical lower bound of cBP errors to be expected when analysing clinical datasets.

400 Recent (2017) clinical guidelines for the validation of non-invasive cBP devices  
401 propose a mean absolute difference  $\leq 5$  mmHg with  $\sigma \leq 8$  mmHg compared with the  
402 reference *cSBP* (57). The potential of the algorithms used in this study to achieve mean  
403 absolute differences which are almost within recommended values in clinical cohorts  
404 with either invasive reference cBP values ('Aortic Coarctation' dataset) or cBP values  
405 calculated by the widely used SphygmoCor® device ('Normotensive' and 'Hypertensive'  
406 datasets) has been shown. On the one hand, the '1D-Ao' algorithm achieved mean  
407 absolute differences  $< 2.1 \pm 9.7$  mmHg for *cSBP* values in the 'Aortic Coarctation'  
408 dataset for both scenarios. On the other hand, the 0-D models achieved mean absolute  
409 differences  $< 8.6 \pm 5.0$  mmHg in the 'Normotensive' dataset and  $< 8.0 \pm 10.6$  mmHg  
410 in the 'Hypertensive' dataset. Furthermore, the lower-bound RMSEs obtained when  
411 testing all algorithms in the measurement error-free 1-D dataset were even smaller  
412 ( $< 3.4 \pm 1.7$  mmHg for 'carotid+' and  $< 5.0 \pm 2.5$  mmHg for 'carotid-'), suggesting  
413 that our algorithms' performance could be within recommended values if measurement  
414 error and data inconsistencies could be reduced further during data acquisition.

415 Central BP estimates for some subjects in the 'Normotensive' and 'Hypertensive'  
416 datasets showed large errors ( $> 50$  mmHg). These subjects had 'noisy' ultrasound  
417 velocity time integral (VTI) waves (used to calculate aortic flow waves) characterised  
418 by either an extended diastolic phase (resulting in *LVEF*  $> 50\%$  of the cardiac cycle  
419 duration) or a large second peak after the systolic peak. Both artefacts could explain  
420 the smaller cBP estimation errors for the 0-D models in the more challenging 'carotid-'  
421 scenario compared to 'carotid+'.

422 A review of methods to estimate *cSBP* from arterial pulse waves (47) found a

423 mean error (95% confidence interval) of -1.1 (-2.8 – 0.7) mmHg when calibrated using  
424 invasive BP values, and a mean error of -5.8 (-7.8 – -3.8) mmHg when calibrated  
425 using non-invasive BP values. In our study, the ‘1D-Ao’ algorithm was found to  
426 have mean errors of: 0.0 (-6.0 – 6.0) when calibrated using an invasive BP waveform  
427 (‘carotid+’ scenario in the ‘Aortic Coarctation’ dataset); -2.1 (-7.8 – 3.6) when using  
428 invasive BP values (‘carotid-’ scenario in the ‘Aortic Coarctation’ dataset); and the  
429 ‘2-Wk’ algorithm was found to have mean errors when calibrated non-invasively of:  
430 -3.3 (-3.9 – -2.7) (‘carotid-’ scenario in the ‘Normotensive’ dataset) and -5.5 (-6.1 – -  
431 4.9) (‘carotid-’ scenario in the ‘Hypertensive’ dataset). Thus, the mean *cSBP* error  
432 provided by the models presented in this study was comparable to those observed  
433 in previous studies of *cSBP* estimation methods. Unlike transfer function methods,  
434 our proposed cBP algorithms do not need to be trained on existing clinical datasets  
435 and make no assumptions regarding generalisability, since they simulate patient-specific  
436 haemodynamic phenomena occurring in the aorta where cBP is calculated. This may  
437 be advantageous when applying these algorithms to the wider population, including  
438 patients suffering from a range of CV diseases or under pharmacological treatment.  
439 However, a direct comparison against such techniques was not possible due to the lack  
440 of required data and corresponding devices.

#### 441 4.3. *Limitations*

442 The peripheral pressure wave ( $P$ ) required by the cBP algorithms was measured  
443 invasively in the descending aorta in the ‘Aortic Coarctation’ dataset. Since this  
444 may give the algorithms an advantage compared to non-invasive methods using  
445 cuff or tonometry measurements, the 1-D dataset – which contained  $P$  at the  
446 required peripheral locations – was also used for the final cBP algorithm assessment.  
447 In the ‘Normotensive’ and ‘Hypertensive’ datasets, since invasive reference cBP

448 measurements were not available, non-invasive measurements were obtained using the  
449 SphygmoCor® device. Although these measurements are not exactly equivalent to  
450 invasive cBP, they allowed us to compare the performance of the cBP algorithms to  
451 a widely used non-invasive device. We note that the ‘Aortic Coarctation’ dataset  
452 contained data from 10 subjects – in the future further studies should verify the  
453 conclusions presented here using additional data with invasive reference measurements.

#### 454 *4.4. Perspectives*

455 Patients with cardiovascular disease would benefit from an accurate non-invasive  
456 assessment of their cBP. Our approach removes the risk of complications due to cardiac  
457 catheterisation and allows for a more regular assessment of a patient’s cBP, due to its  
458 non-invasive nature. Moreover, it is relatively quick: it only takes a few seconds (when  
459 using the 0-D algorithms) or a few minutes (‘1D-Ao’ algorithm) to compute cBP on  
460 a Dell Precision M4800 laptop. The 1-D algorithm is particularly relevant in clinical  
461 cardiology, where cardiac MRI is increasingly used. Indeed, the detailed geometric and  
462 flow data obtained using MRI can lead to important improvements in non-invasive cBP  
463 estimation, which could lead to a better adaption in clinical practice. Additionally, the  
464 0-D algorithms can be used in combination with US scans to obtain patient-specific cBP  
465 estimates.

466 The novel Windkessel model dataset and optimised cBP algorithms are freely  
467 available (DOI of repository will be made available prior to publication) to develop  
468 and test new, improved algorithms for estimating CV parameters and cBP waves.

#### 469 *4.5. Conclusion*

470 We have presented freely-available, fast, patient-specific algorithms to estimate clinically  
471 relevant CV parameters and reconstruct the cBP wave from the aortic flow wave, using

472 non-invasive data and patient-specific models of aortic blood flow. We have tested our  
473 algorithms against a wide range of cBP morphologies from several clinical datasets, one  
474 of which included catheter cBP waves. Finally, we have shown the potential of our  
475 algorithms to estimate cBP values within guideline recommended values. Our approach  
476 could improve CV function assessment in clinical cohorts for which aortic ultrasound or  
477 magnetic resonance imaging data is available.

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499 [https://github.com/jmariscal-harana/cbp\\_estimation](https://github.com/jmariscal-harana/cbp_estimation). Details of the code used  
500 to run the 1-D simulations are available at <http://haemod.uk>, and access requests  
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502 of how to replicate this study can be obtained by contacting J. Mariscal-Harana  
503 [jorge.mariscal\\_harana@kcl.ac.uk](mailto:jorge.mariscal_harana@kcl.ac.uk). Further information about the data and conditions  
504 of access can be found by emailing [research.data@kcl.ac.uk](mailto:research.data@kcl.ac.uk).

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Table 1: Datasets’ characteristics.

|                    | Dataset     |                           |                           |              |              |
|--------------------|-------------|---------------------------|---------------------------|--------------|--------------|
|                    | Ao Co       | Normotensive              | Hypertensive              | 0-D dataset  | 1-D dataset  |
| Subjects (males)   | 10 (9)      | 13 (10)                   | 158 (80)                  | 15582 (N/A)  | 4064 (N/A)   |
| Age [years]        | 20.8 ± 9.1  | 48.4 ± 9.4                | 46.2 ± 16.7               | N/A          | 50 ± 17.1†   |
| <i>DBP</i> [mmHg]  | 53.2 ± 8.9  | 68.4 ± 10.4 <sup>a</sup>  | 81.8 ± 12.8 <sup>a</sup>  | 64.6 ± 9.0   | 75.3 ± 7.3   |
| <i>MBP</i> [mmHg]  | 69.3 ± 9.7  | 85.6 ± 12.1 <sup>b</sup>  | 102.0 ± 15.8 <sup>b</sup> | 83.9 ± 11.2  | 94.2 ± 6.7   |
| <i>pSBP</i> [mmHg] | 82.0 ± 15.2 | 111.4 ± 17.3 <sup>c</sup> | 129.6 ± 22.6 <sup>c</sup> | 117.6 ± 21.3 | 119.3 ± 11.4 |
| <i>cSBP</i> [mmHg] | 93.7 ± 11.9 | 107.2 ± 17.3              | 126.4 ± 22.2              |              | 110.4 ± 12.5 |
| <i>pPP</i> [mmHg]  | 30.6 ± 13.0 | 43.2 ± 12.2               | 48.2 ± 16.0               | 52.9 ± 16.9  | 46.5 ± 14.1  |
| <i>cPP</i> [mmHg]  | 40.5 ± 12.7 | 38.8 ± 11.0               | 44.6 ± 15.4               |              | 35.1 ± 15.3  |
| <i>SV</i> [mL]     | 57.4 ± 29.9 | 100.6 ± 35.3              | 83.3 ± 32.8               | 88.4 ± 12.2  | 60.3 ± 12.3  |
| <i>HR</i> [bpm]    | 65.1 ± 14.4 | 62.2 ± 11.2               | 65.5 ± 10.4               | 68.8 ± 11.3  | 75.9 ± 9.3   |
| <i>CO</i> [L/min]  | 3.6 ± 1.7   | 6.2 ± 2.5                 | 5.3 ± 1.9                 | 6.1 ± 1.3    | 4.6 ± 1.1    |

Abbreviations: **Ao Co**: ‘Aortic Coarctation’ dataset. *DBP* and *MBP*: diastolic and mean BP (central values, which are similar to peripheral ones, are used here); *pSBP* and *cSBP*: peripheral and central *SBP*, respectively; *pPP* and *cPP*: peripheral and central *PP*, respectively; *SV*: stroke volume; *HR*: heart rate; *CO*: cardiac output. †Age ranges from 25 to 75 years, with 10 year intervals. <sup>a</sup>Brachial oscillometric measurement. <sup>b</sup>Radial tonometry measurement. <sup>c</sup>Carotid tonometry measurement.



Table 2: CV parameter estimation methods assessed in this study. Performance was assessed in two clinical scenarios (‘carotid+’: carotid BP wave available; ‘carotid-’: only brachial *DBP* and *SBP* available) using the 0-D and 1-D datasets (Figure 1a). Errors are presented as the mean  $\pm$  standard deviation of the percentage error between estimated and reference CV parameter values.

| Parameter  | Description                       | Sce            | Ref                             | Abb | Percentage error [%] |                  |
|--|-----------------------------------|----------------|---------------------------------|-----|----------------------|------------------|
|  |                                   |                |                                 |     | 0-D dataset          | 1-D dataset      |
| <b>Left Ventricular Ejection Time, <math>LVET</math></b> | $dP/dt$ analysis, 1               | +              | (13)                            | LV1 | ‡                    | $0.4 \pm 1.0$    |
|  | $dP/dt$ analysis, 2               | +              | (32)                            | LV2 | $-12.4 \pm 0.1$      | $-5.7 \pm 4.1$   |
|  | $0.37\sqrt{T}$                    | +,−            | (7)                             | LV3 | $26.1 \pm 8.5$       | $6.9 \pm 8.1$    |
|  | $Q$ analysis                      | +,−            | †                               | LV4 | $0.1 \pm 0.2$        | $0.3 \pm 0.6$    |
| <b>Outflow Pressure, <math>P_{out}</math></b>            | Diastolic decay fit, 1            | +              | (24, 71)                        | OP1 | $0.0 \pm 0.0$        | $-5.1 \pm 8.0$   |
|  | Diastolic decay fit, 2            | +              | (24, 60)                        | OP2 | $0.0 \pm 0.0$        | $-10.5 \pm 7.5$  |
|  | $0.5 DBP$                         | +,−            | †                               | OP3 | $1.6 \pm 16.9$       | $9.1 \pm 11.0$   |
|  | $0.7 DBP$                         | +,−            | (49)                            | OP4 | $42.3 \pm 23.6$      | $52.7 \pm 15.4$  |
| <b>Arterial Resistance, <math>R_T</math></b>             | $(MBP - P_{out})/\bar{Q}$         | +              | (24)                            | AR1 | $0.0 \pm 0.0$        | $0.0 \pm 0.1$    |
|  | $(DBP + 0.4PP - P_{out})/\bar{Q}$ | +,−            | (10, 24)                        | AR2 | $0.7 \pm 5.7$        | $-4.9 \pm 2.9$   |
| <b>Arterial Compliance, <math>C_T</math></b>             | 2-point diastolic decay           | +              | (24)                            | AC1 | $-0.1 \pm 0.0$       | $-6.5 \pm 4.9$   |
|  | Diastolic decay fit, 1            | +              | (24)                            | AC2 | $0.0 \pm 0.0$        | $-6.6 \pm 3.3$   |
|  | Diastolic decay fit, 2            | +              | (24, 60)                        | AC3 | $0.0 \pm 0.0$        | $-10.2 \pm 5.0$  |
|  | Area method                       | +              | (15, 52, 71)                    | AC4 | $-10.0 \pm 4.1$      | $-11.4 \pm 4.6$  |
|  | Two-area method                   | +              | (55, 71)                        | AC5 | $-10.0 \pm 4.1$      | $-7.1 \pm 7.1$   |
|  | $DBP$ method                      | +,−            | †                               | AC6 | $-1.5 \pm 4.1$       | $-17.3 \pm 7.5$  |
|  | $PP$ method                       | +,−            | (61, 71)                        | AC7 | $-0.1 \pm 0.2$       | $-27.6 \pm 11.6$ |
|  | $SV/PP$                           | +,−            | (15)                            | AC8 | $-13.8 \pm 20.3$     | $4.9 \pm 18.4$   |
|  | Optimised 3-Wk                    | +              | †                               | AC9 | $0.0 \pm 0.3$        | $-0.8 \pm 4.2$   |
| <b>Pulse Wave Velocity, <math>PWV</math></b>             | Foot-to-foot: $Q_{Ao}$            | +,−            | (25)                            | PV1 | -                    | $8.2 \pm 6.0$    |
|  | Foot-to-foot: $P_{c-f}$           | + <sup>a</sup> | (25)                            | PV2 | -                    | $27.8 \pm 10.8$  |
|  | Least-squares: $Q_{Ao}$           | +,−            | (25)                            | PV3 | -                    | $-12.7 \pm 8.3$  |
|  | Least-squares: $P_{c-f}$          | + <sup>a</sup> | (25)                            | PV4 | -                    | $43.0 \pm 36.0$  |
|  | Sum of squares                    | +              | (17)                            | PV5 | -                    | $33.2 \pm 17.2$  |
| <b>Characteristic Impedance, <math>Z_0</math></b>        | Frequency methods                 | +              | (1, 16, 19, 30, 40, 42, 50, 54) | Z1  | $2.5 \pm 2.1$        | $64.6 \pm 44.3$  |
|  | PQ-loop methods                   | +              | (19, 37, 63)                    | Z2  | $0.2 \pm 1.4$        | $13.4 \pm 56.6$  |
|  | $0.05 R_T$                        | +,−            | (41, 69)                        | Z3  | $-1.5 \pm 40.8$      | $133.8 \pm 66.7$ |
|  | $(MBP - DBP)/Q_{max}$             | +,−            | †                               | Z4  | $-38.7 \pm 12.4$     | $82.3 \pm 32.6$  |
|  | $\rho PWV/A$                      | +,−            | (72)                            | Z5  | -                    | $90.4 \pm 18.1$  |
|  | Optimised 3-Wk                    | +              | †                               | Z6  | $-0.1 \pm 0.7$       | $37.1 \pm 20.0$  |

Abbreviations: **Sce**: clinical scenarios (+: ‘carotid+’, −: ‘carotid-’); **Ref**: references; **Abb**: coded abbreviations used to refer to each method;  $P$ : peripheral BP waveform;  $T$ : duration of cardiac cycle;  $Q$ : aortic root flow waveform;  $DBP$ ,  $MBP$ ,  $PP$ : diastolic, mean, and pulse BP values from  $P$ , respectively;  $\bar{Q}$ : mean value of  $Q$  over  $T$ ;  $SV$ : stroke volume; 3-Wk: 3-element Windkessel;  $Q_{Ao}$ : ascending and descending aorta flow wave pair;  $P_{c-f}$ : carotid–femoral blood BP wave pair;  $Q_{max}$ : peak aortic flow;  $\rho$ : blood density;  $A$ : aortic root cross-sectional area. †Newly proposed methods (described in Appendix B). ‡BP waves from the 0-D dataset do not present a second systolic peak as required by LV1. <sup>a</sup>BP waves at the carotid and femoral arteries required.

Table 3: Optimal CV parameter estimation methods for both datasets and clinical scenarios. The abbreviations for each method (*e.g.* LV4) correspond to those described in Table 2.

| Dataset     | Sce | Optimal CV parameter estimation methods (MPE [%]) |             |            |             |            |           |
|-------------|-----|---|-------------|------------|-------------|------------|-----------|
|             |     | <i>LVET</i>                                       | $P_{out}$   | $R_T$      | $C_T$       | <i>PWV</i> | $Z_0$     |
| 0-D dataset | +   | LV4 (0.3)   | OP1/2 (0.0) | AR1 (0.0)  | AC2/3 (0.0) | N/A        | Z6 (-0.1) |
|             | -   |   | OP3 (-2.0)  | AR2 (0.9)  | AC7 (-0.1)  |            | Z3 (-1.5) |
| 1-D dataset | +   | LV4 (0.3)   | OP1 (-5.1)  | AR1 (0.0)  | AC9 (-0.8)  | PV1 (8.2)  | Z2 (13.4) |
|             | -   |   | OP3 (9.1)   | AR2 (-4.9) | AC8 (4.9)   |            | Z4 (82.3) |

Abbreviations: **Sce**: clinical scenarios (+: ‘carotid+’, -: ‘carotid-’); **MPE**: mean percentage error for the entire dataset; *LVET*: left-ventricular ejection time;  $P_{out}$ : outflow BP;  $R_T$ : arterial resistance;  $C_T$ : arterial compliance; *PWV*: pulse wave velocity;  $Z_0$ : characteristic impedance.

Table 4: Performance of cBP estimation algorithms. Results are presented as mean ( $\mu$ ) and standard deviation ( $\sigma$ ) errors between estimated and reference values of *cDBP* and *cSBP*. The RMSE between estimated and reference cBP waves is shown in the last column. Each cBP algorithm was assessed in four datasets and two clinical scenarios: ‘carotid+’ (peripheral BP wave available) and ‘carotid-’ (only peripheral *SBP* and *DBP* available).

| Dataset            | Scenario | Algorithm | Estimation error ( $\mu \pm \sigma$ ) [mmHg] |                 |                |
|--------------------|----------|-----------|--|-----------------|----------------|
|                    |          |           | <i>cDBP</i>                                  | <i>cSBP</i>     | RMSE           |
| 1-D dataset        | carotid+ | 2-Wk      | 1.2 $\pm$ 0.7                                | 1.0 $\pm$ 0.8   | 3.4 $\pm$ 1.1  |
|                    |          | 3-Wk      | 0.1 $\pm$ 1.0                                | 1.8 $\pm$ 1.9   | 2.0 $\pm$ 1.7  |
|                    |          | 1D-Ao     | 0.1 $\pm$ 1.1                                | 2.2 $\pm$ 1.8   | 2.0 $\pm$ 1.0  |
|                    | carotid- | 2-Wk      | 0.8 $\pm$ 1.5                                | -4.5 $\pm$ 5.9  | 5.0 $\pm$ 2.5  |
|                    |          | 3-Wk      | -2.6 $\pm$ 0.8                               | -0.2 $\pm$ 4.7  | 5.1 $\pm$ 2.0  |
|                    |          | 1D-Ao     | -1.5 $\pm$ 1.2                               | -1.7 $\pm$ 5.3  | 4.2 $\pm$ 2.1  |
| Aortic Coarctation | carotid+ | 2-Wk      | 0.8 $\pm$ 3.1                                | -15.7 $\pm$ 7.2 | 10.1 $\pm$ 3.9 |
|                    |          | 3-Wk      | 0.2 $\pm$ 2.8                                | -15.4 $\pm$ 7.4 | 8.0 $\pm$ 3.2  |
|                    |          | 1D-Ao     | -3.4 $\pm$ 4.8                               | -0.0 $\pm$ 9.7  | 6.4 $\pm$ 2.8  |
|                    | carotid- | 2-Wk      | -1.5 $\pm$ 2.4                               | -17.3 $\pm$ 7.9 | 10.9 $\pm$ 4.3 |
|                    |          | 3-Wk      | -1.8 $\pm$ 2.5                               | -17.2 $\pm$ 7.9 | 8.4 $\pm$ 3.6  |
|                    |          | 1D-Ao     | -6.1 $\pm$ 2.8                               | -2.1 $\pm$ 9.2  | 7.8 $\pm$ 3.3  |
| Normotensive       | carotid+ | 2-Wk      | 4.7 $\pm$ 1.9                                | -8.6 $\pm$ 5.0  | 10.3 $\pm$ 3.0 |
|                    |          | 3-Wk      | -4.4 $\pm$ 3.5                               | 13.4 $\pm$ 13.4 | 8.6 $\pm$ 5.5  |
|                    |          | 2-Wk      | -0.1 $\pm$ 0.5                               | -3.3 $\pm$ 3.5  | 11.0 $\pm$ 3.5 |
|                    | carotid- | 3-Wk      | 0.2 $\pm$ 0.5                                | -3.7 $\pm$ 4.0  | 5.9 $\pm$ 2.4  |
|                    |          | 2-Wk      | 5.0 $\pm$ 3.2                                | -8.3 $\pm$ 6.3  | 10.6 $\pm$ 4.1 |
|                    |          | 3-Wk      | -2.9 $\pm$ 3.6                               | 8.0 $\pm$ 10.6  | 7.1 $\pm$ 4.2  |
| Hypertensive       | carotid- | 2-Wk      | -0.3 $\pm$ 0.8                               | -5.5 $\pm$ 4.0  | 11.1 $\pm$ 4.2 |
|                    |          | 3-Wk      | 0.0 $\pm$ 0.6                                | -6.0 $\pm$ 4.7  | 5.7 $\pm$ 2.4  |

Figure 1: Study methodology. (1) cBP estimation algorithms consisted of three steps. (a) Clinical data acquisition and pre-processing: blood flow measured at the ascending and descending (1-D algorithm only) aorta; peripheral BP measurement; and aortic anatomy (1-D algorithm only). (b) Cardiovascular (CV) parameters estimated from clinical data. (c) These parameters, along with the non-invasive clinical data, were used as inputs to one of three cBP models. (2) Algorithm performance was assessed by comparing cBP estimates provided by each model to reference values.

Figure 2: Clinical cBP wave morphologies: (left) ‘Aortic Coarctation’ dataset (obtained invasively); (middle) ‘Normotensive’ (non-invasive) dataset; and (right) ‘Hypertensive’ (non-invasive) dataset. Black lines illustrate a random patient’s cBP waveform. Shaded regions represent the range of cBP waves within each dataset.

Figure 3: Generating datasets of virtual subjects. (a), top: a range of values for each CV parameter was obtained from the clinical literature for healthy individuals (see Table A1). (a), bottom: the thick line illustrates the flow wave corresponding to the baseline values of SV and HR, and the shaded region represents the range of flow waves corresponding to all SV and HR variations. (b) Two reduced-order models were used to generate cBP waves. (c) cBP waves generated by each model: black lines illustrate the cBP wave corresponding to the baseline set of parameter variations, and shaded regions represent the range of cBP waves within each dataset.

Figure 4: Bland-Altman plots for the optimal CV parameter estimation methods. They were obtained from all 1-D dataset waves using clinical+ (top) and clinical− (bottom).

728 **Appendix A. Datasets of virtual subjects**729 *Appendix A.1. 0-D dataset: CV parameter variations*

Table A1: CV parameter variations used for the 3-element Windkessel (0-D) dataset. These values are based on observations in healthy humans from the clinical literature.

| CV parameter [units]    | Variations     |                   |          |                   |                | References |
|-------------------------|----------------|-------------------|----------|-------------------|----------------|------------|
|                         | Negative       |                   | Baseline | Positive          |                |            |
|                         | $\mu - \sigma$ | $\mu - 0.5\sigma$ | $\mu$    | $\mu + 0.5\sigma$ | $\mu + \sigma$ |            |
| $SV$ [mL]               | 71.2           | 79.8              | 88.4     | 97.0              | 105.7          | (67)       |
| $HR$ [bpm]              | 52.9           | 60.8              | 68.8     | 76.7              | 84.7           | (67)       |
| $P_{\text{out}}$ [mmHg] | 31.7           | 32.5              | 33.2     | 34.0              | 34.7           | (48)       |
| $R_T$ [mmHg·s/mL]       | 0.468          | 0.484             | 0.500    | 0.516             | 0.532          | (60)       |
| $C_T$ [mL/mmHg]         | 2.20           | 2.23              | 2.27     | 2.30              | 2.34           | (36)       |
| $Z_0$ [mmHg·s/mL]       | 0.0256         | 0.0358            | 0.0485   | 0.0644            | 0.0847         | (6, 29)    |

Abbreviations:  $\mu$  and  $\sigma$ : mean and standard deviation values, respectively, for each CV parameter from the clinical literature;  $SV$ : stroke volume;  $HR$ : heart rate;  $P_{\text{out}}$ : outflow vascular pressure;  $R_T$ : total arterial resistance;  $C_T$ : total arterial compliance; and  $Z_0$ : aortic characteristic impedance.

Figure A1: Extracting reference  $Z_0$  and  $C_T$  values at the aortic root. (a) Reference cBP wave for a 1-D model virtual subject, and corresponding initial and optimal estimates. (b) Contour plot (in mmHg) of the mean difference between the estimated and reference cBP waves, with  $Z_0$  in the x-axis and  $C_T$  in the y-axis. Each iteration is shown in white squares; iterations 0 and 5 correspond to the initial and optimal cBP estimates, respectively. (c) The values of  $Z_0$ ,  $C_T$ , and the cBP mean difference are shown for the initial estimate and for every iteration until numerical convergence is reached.

730 *Appendix A.2. 1-D dataset: calculating reference  $Z_0$  and  $C_T$  values at the aortic root*

731 Reference  $Z_0$  and  $C_T$  values for the 1-D dataset were calculated from aortic root BP ( $P$ )  
 732 and flow ( $Q_{in}$ ) waves using an in-house algorithm written in Matlab® and based on the  
 733 ‘3-Wk’ model (Figure A1). Assuming that  $P_{out}$  is known and that the total resistance  
 734  $R_T = Z_0 + R$  is given by Equation (1), a parameter estimation problem can be solved  
 735 for  $Z_0$  and  $C_T$ . The estimated BP at time  $t_k$  can be written as

$$736 \quad P(t_k) = f(Z'_0, C'_T, Q_{in}(t_k)) + e_k, \quad (\text{A.1})$$

737 with  $e_k$  the residual error between the estimated and reference BP at each time  $t_k$ ,  
 738  $k = 1, \dots, K$ , and  $Z'_0$  and  $C'_T$  the estimated parameters. The problem can be solved  
 739 through iterative minimisation of the cost function  $\mathbf{e}^\top \mathbf{e}$ , where  $\mathbf{e}$  is the vector containing  
 740 the residual errors at each time  $t_k$ . The iterative procedure starts from an initial estimate  
 741  $(Z'_{0,0}, C'_{T,0})$ . The parameters at iteration  $i+1$  are then calculated using the recursive  
 742 equation

$$743 \quad (Z'_{0,i+1}, C'_{T,i+1}) = (Z'_{0,i}, C'_{T,i}) - \mathbf{H}_i \mathbf{q}_i, \quad (\text{A.2})$$

744 where  $\mathbf{H}_i$  and  $\mathbf{q}_i$  are the Hessian and the gradient, respectively, of the cost function  
 745 evaluated at iteration  $i$ . This equation can be obtained by approaching the cost function  
 746 by a second-order Taylor expansion and minimising the approached function. The  
 747 ‘mean cBP difference’ shown in Figure A1(b,c) was calculated for each iteration as  
 748  $\frac{1}{K} \sqrt{\sum_{k=1}^K e_k^2}$ , with  $e_k$  the residual error at time  $t_k$ . The iterative procedure was stopped  
 749 when either (i) the change in both  $Z_0$  and  $C_T$  estimates between iterations was smaller  
 750 than  $10^{-6}$ , or (ii) after 15 iterations.

## 751 **Appendix B. Cardiovascular parameter estimation methods**

752 All CV parameter estimation methods used in this study are described next. Novel  
 753 methods are marked with an asterisk in the title.

754 *Appendix B.1. LV - Left ventricular ejection time, LVET*

755 *LV1 - dP/dt analysis, 1\**

756 The method is described in (13). *LVET* corresponds to the point of peak pressure after  
757 the pressure systolic peak.

758 *LV2 - dP/dt analysis, 2*

759 This method is described in (32). *LVET* coincides with the minimum of

$$760 \quad \frac{dP}{dt} \left( 0.5 - \left| 0.5 - \frac{HR \cdot t}{60} \right| \right)^2, \quad (\text{B.1})$$

761 where  $P$  is a peripheral BP wave and  $HR$  represents the heart rate in bpm.

762 *LV3 -  $0.37\sqrt{T}$*

763 *LVET* is calculated using the empirical relationship described in (7):  $0.37\sqrt{T}$ , where  $T$   
764 is the duration of the cardiac cycle in seconds.

765 *LV4 - Q analysis\**

766  $Q$  is analysed from the global minimum after peak flow to 50% of  $T$  (Figure B1). If  
767 all  $Q$  values are smaller than 1% of maximum  $Q$ , *LVET* corresponds to the time of  
768 the global minimum. Otherwise, starting from the time of the global minimum, all sign  
769 changes (from negative to positive), all maxima, and all zero values are found. *LVET*  
770 corresponds to either the first sign change, the first local maximum, or the first zero  
771 value (whichever one occurs first). If all else fails, method *LV3* is used.

772 *Appendix B.2. OP - Outflow pressure*

773 *OP1 - Diastolic decay fit, 1*

774 The concept of a diastolic decay fit was first described in (24).  $P$  is analysed between  
 775  $LVET$  and the end of diastole ( $P_d$ ). The multidimensional unconstrained nonlinear  
 776 minimisation (Nelder-Mead) Matlab® function *fminsearch.m* is used to find the best  
 777 fit between  $P_d$  and an exponential decay curve of the form:  $P_{exp} = P_{out} + (P_{exp}(t_0) -$   
 778  $P_{out})e^{-(t-t_0)/\tau}$ , where  $t_0 = LVET$ . To avoid non-physiological values of  $P_{out}$ , the  
 779 following filters are applied: if  $\tau < 0$  or  $P_{out} < 0$ ,  $P_{out}$  is set to 0; and if  $P_{out} \geq DBP$ ,  
 780  $P_{out}$  is set to  $0.5DBP$ .

781 *OP2 - Diastolic decay fit, 2*

782 Similarly to OP1, but using  $t_0 = \frac{2}{3}LVET + \frac{1}{3}T$  instead, as described in (60).

783 *OP3 - 50% of DBP\**

784  $P_{out}$  is estimated as 50% of  $DBP$ .

785 *OP4 - 70% of DBP*

786 As suggested by Parragh *et al.*  $P_{out}$  is estimated as 70% of  $DBP$  (49).

787 *Appendix B.3. AR - Arterial resistance*

788 *AR1 - Peripheral pressure waveform*

789  $R_T$  is calculated using Equation (1) and  $MBP$  is calculated as the mean of  $P$ .

790 *AR2 - Peripheral DBP and SBP values*

791 Similarly to AR1, but using  $MBP = 0.4SBP + 0.6DBP$  instead, as described in (10).



792 *Appendix B.4. AC - Arterial compliance*

793 *AC1 - 2-point diastolic decay*

794 The concept of a diastolic decay fit was first described in (24). Using only the first and  
795 last points of the diastolic part of  $P$ ,  $C_T$  is calculated as:

$$796 \quad \frac{T - LVET}{\ln\left(\frac{P(LVET) - P_{\text{out}}}{DBP - P_{\text{out}}}\right) R_T} \cdot \quad (\text{B.2})$$

797 *AC2 - Diastolic decay fit, 1*

798 Given that  $\tau = (R_T - Z_0)C_T$ , OP1 can be used to calculate  $\tau$ , and rearranging:

$$799 \quad C_T = \frac{\tau}{R_T - Z_0}. \quad (\text{B.3})$$

800 If  $\tau$  is negative then  $P_{\text{out}}$  is set to 0 and  $\tau$  is recalculated.

801 *AC3 - Diastolic decay fit, 2*

802 Similarly to AC2, but using  $t_0 = \frac{2}{3}LVET + \frac{1}{3}T$  instead, as described in (60).

803 *AC4 - Area method*

804 This method is described in (52).  $C_T$  is calculated as:

$$805 \quad \frac{\int_{t_1}^{t_2} (P - P_{\text{out}}) dt}{R_T(P(t_1) - P(t_2))}, \quad (\text{B.4})$$

806 where  $t_1$  and  $t_2$  are equal to  $\frac{2}{3}LVET + \frac{1}{3}T$  and 90% of  $T$ , respectively.

807 *AC5 - Two-area method*

808 This method is described in (55).  $C_T$  is calculated by solving two simultaneous equations  
809 of the form:

$$810 \quad \int_{t_1}^{t_2} Q dt - \frac{1}{R_T} \int_{t_1}^{t_2} (P - P_{\text{out}}) dt = C_T(P(t_1) - P(t_2)), \quad (\text{B.5})$$

811 from the start of the cycle to  $LVET$ , and from  $LVET$  to  $T$ .

812 *AC6 - Diastolic blood pressure method\**

813  $C_T$  is calculated by minimising the relative error,  $DBP_{err} = (DBP_{est} - DBP_{ref})/DBP_{ref}$ ,  
 814 between the estimated ( $DBP_{est}$ ) and reference ( $DBP_{ref}$ ) values of  $DBP$ , as seen  
 815 in Figure B2. For each iteration,  $j$ ,  $DBP_{est}$  is calculated as the minimum of the  
 816 estimated BP,  $P_{est}$ , using the three-element Windkessel model (Equation (5)). The  
 817 initial conditions are  $C_{T,0} = SV/PP$  and  $P_0 = DBP_{ref}$ . While  $DBP_{err} > 1\%$ ,  
 818  $C_{T,j} = C_{T,j-1}/DBP_{err}^2$ .  $C_T$  corresponds to the final value of  $C_{T,j}$ .

819 *AC7 - Pulse pressure method*

820 This method is described in (61). Similarly to AC6, but minimising the relative  $PP$   
 821 error,  $PP_{err}$ , instead.

822 *AC8 - Stroke volume over pulse pressure*

823 This method is described in (15).  $C_T$  corresponds to  $SV/PP$ .

824 *AC9 - Three-element Windkessel optimisation\**

825 This method is described in Appendix A.2. The initial value of  $C_T$  is calculated using  
 826 AC8.

827 *Appendix B.5. PV - Pulse wave velocity*

828 The foot-to-foot ( $PV1$  and  $PV2$ ) and least-squares ( $PV3$  and  $PV4$ ) methods used here  
 829 are described in (25). Both methods require the measurement of two pulse waves at both  
 830 ends of a given arterial path of length  $L$ . The foot-to-foot method focuses on detecting  
 831 the ‘feet’ (*i.e.* minimum value) of both pulse waves to calculate the transit time ( $TT$ )  
 832 between them. For each pulse wave, the ‘foot’ is detected as the intersection between a

833 horizontal projection of the minimum value and a projection of the maximum slope of  
 834 the systolic upstroke.

835 The least-squares method calculates the sum of the squared differences between  
 836 the systolic upstroke of both waves multiple times, by fixing one wave and shifting the  
 837 other one by one datapoint at a time. The temporal shift which minimises the squared  
 838 differences is used to estimate  $TT$ . For both methods,  $PWV$  is then calculated as  
 839  $PWV = L/TT$ .

840 *PV1 - Foot-to-foot: aortic flow*

841 The inputs are two non-invasive flow waves at the ascending and descending aorta.

842 *PV2 - Foot-to-foot: carotid–femoral pressures*

843 The inputs are two non-invasive BP waves at the carotid and femoral arteries.

844 *PV3 - Least-squares: aortic flow*

845 The inputs are two non-invasive flow waves at the ascending and descending aorta.

846 *PV4 - Least-squares: carotid–femoral pressures*

847 The inputs are two non-invasive BP waves at the carotid and femoral arteries.

848 *PV5 - Sum of squares*

849 This method has been adapted from the original one described in (17).  $PWV$  is  
 850 calculated from the peripheral BP,  $P$ , and aortic flow,  $Q$  waves using

$$851 \quad PWV = \frac{1}{\rho A} \sqrt{\frac{\sum dP^2}{\sum dQ^2}} \quad (\text{B.6})$$

852 where  $\rho$  is the blood density,  $A$  is the cross-sectional area at the aortic root,  $dP$  and  
853  $dQ$  are differences in  $P$  and  $Q$ , respectively, between two adjacent time points, and the  
854 sums extend over a cardiac cycle.  $P$  and  $Q$  do not need to be aligned in time.

#### 855 *Appendix B.6. Z - Aortic characteristic impedance*

856 Method *Z2* is sensitive to temporal misalignments between  $P$  and  $Q$ , so the following  
857 restrictions were applied to account for waves which were not recorded simultaneously  
858 and/or at the same site: (i)  $P$  is shifted so that its value at the start of the cycle  
859 coincides with  $DBP$ , and (ii)  $Q$  is shifted so that its value at the start of the cycle is  
860 as close as possible to the intersection between the  $x$ -axis and the tangent of  $Q$  at the  
861 time of maximum  $dQ/dt$  in early systole.

#### 862 *Z1 - Frequency methods*

863 Frequency domain methods to estimate characteristic impedance ( $Z_0$ ) are based on the  
864 Fourier analysis of  $P$  and  $Q$  extracted simultaneously at the ascending aorta.  $Z_0$  is  
865 usually estimated as the average impedance modulus over a range of frequencies where  
866 fluctuations – due to wave reflections – above and below the characteristic impedance  
867 value are expected to cancel each other out. The following harmonic ranges, extracted  
868 from the literature, have been assessed in this study: 2-12th (42), 6-10th (54), 1-8th (16),  
869 1-9th (19), 2-10th (40), 3-10th (30), 4-10th (63), 6-8th (1), and 4-8th (50) harmonics.  
870 These methods, in their original form, require  $P$  and  $Q$  measured simultaneously at the  
871 ascending aorta. However, for the proposed algorithms, a peripheral  $P$  measurement is  
872 used instead.

873 *Z2 - P-Q loop methods*

874 P-Q loop methods analyse the relationship between aortic  $P$  and  $Q$  during early systole,  
 875 assuming that during this interval the effects of wave reflections are minimal (19, 37),  
 876 and hence

$$877 \quad Z_0 \simeq \frac{P(t) - DBP}{Q(t) - Q(0)}, \quad (\text{B.7})$$

878 where  $Q(0)$  is the value of  $Q$  at the start of the cycle (normally zero). In this study,  
 879 four P-Q loop methods were assessed where  $Z_0$  was estimated as:

880 I the mean value of Equation (B.7) between the start of the cycle and the time of  
 881 maximum  $Q$ ;

882 II the slope of the linear least squares fit to the ratio between  $P$  and  $Q$  between the  
 883 start of the cycle and the time of maximum flow;

884 III the value of Equation (B.7) at the time of maximum  $dQ/dt$  in early systole; and

885 IV the mean value of Equation (B.7) between the start of the cycle and the time of  
 886 maximum  $dQ/dt$  in early systole.

887 The best performing P-Q loop method, IV, was used to calculate the errors in Table 2.

888 These methods, in their original form, require  $P$  and  $Q$  measured simultaneously at the  
 889 ascending aorta. However, for the proposed algorithms, a peripheral  $P$  measurement is  
 890 used instead.

891 *Z3 - 5% of  $R_T$* 

892 As suggested by Murgo *et al.*  $Z_0$  is estimated as 5% of  $R_T$  (41).

893 *Z4 - Approximated aortic characteristics\**

894 During early systole, wave reflections reaching the aortic root are assumed to be absent,  
 895 and characteristic impedance can be estimated as  $Z_0 = \Delta P / \Delta Q$ , where  $\Delta P$  and  $\Delta Q$

896 are the changes in BP and flow rate, respectively (30). Peak flow,  $Q_{\text{peak}}$ , and the first  
 897 systolic shoulder/peak,  $P1$ , occur at a similar time, so  $\Delta Q = Q_{\text{peak}}$  and  $\Delta P = P1$ , and  
 898 therefore  $Z_0 \simeq P1/Q_{\text{peak}}$ , as seen in Figure B3. Assuming that  $DBP$  and  $MBP$  remain  
 899 constant within the large arteries,  $P1$  is approximated as  $MBP - DBP$  extracted from  
 900 a peripheral  $P$  measurement. Hence,  $Z_0 \simeq (MBP - DBP)/Q_{\text{peak}}$ .

#### 901 *Z5 - Aortic characteristics*

902 This method is described in (72). Assuming that the aortic radius is much larger than  
 903 the aortic wall thickness,  $Z_0$  corresponds to  $\rho PWV/A$ , where  $\rho$  is the blood density,  
 904  $PWV$  is the aortic pulse wave velocity, and  $A$  is the aortic-root cross-sectional area.

#### 905 *Z6 - Three-element Windkessel optimisation\**

906 This method is described in Appendix A.2. The initial values of  $C_T$  and  $Z_0$  are calculated  
 907 using the AC8 and Z3 methods, respectively.

Figure B1: Novel method to estimate  $LRET$  from the aortic flow wave,  $Q$ .  $LRET$  corresponds to the time of the first sign change (green circle), which occurs earlier than the local maximum (red triangle).

Figure B2: Novel iterative method to estimate  $C_T$  from the aortic flow and peripheral pressure (pBP) waves.  $C_T$  estimates are calculated by minimising the relative error between the estimated and reference values of  $DBP$ . The latter is obtained from the pBP wave (black dashed line). The BP waves corresponding to the initial and optimal estimates of  $C_T$  are shown in red and blue lines, respectively.

Figure B3: Novel method to estimate aortic characteristic impedance from the aortic flow and peripheral BP waves. Pressure (top) and flow (bottom) waves at central (left) and peripheral (right) arterial locations for a subject from the 1-D dataset. The time of  $Q_{\text{peak}}$  and  $P1$  is indicated by the vertical, red, dashed line. The value of  $P1$  is approximated as  $MBP - DBP$  calculated from the peripheral BP wave.