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

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Abstract

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

New and noteworthy

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

1. Introduction

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

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

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

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

2. Methods

2.1. Datasets

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

Clinical datasets

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

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

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

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

Datasets of virtual subjects

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

The 0-D dataset was created using a 3-element Windkessel model (Section 2.4). Each virtual subject's cBP wave was simulated using an aortic flow wave generated by the *AorticFlowWave* script (12) based on prescribed values of heart rate (HR) and stroke volume (SV) in combination with prescribed values of R_{T}, C_{T}, Z_0, and P_{out}. CV parameters were selected to create a dataset of cBP waves representative of a sample of healthy adults. To do so: (i) mean (μ) and standard deviation (σ) values of each parameter in healthy adults were identified from the literature (see Appendix A); (ii) five values for each parameter were calculated as μ, $\mu \pm 0.5\sigma$, and $\mu \pm \sigma$; and (iii) a virtual subject was created using each of the 15,625 combinations of CV parameters.

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

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

2.2. Cardiovascular parameter estimation methods

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

2.3. Assessing cardiovascular parameter estimation methods

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

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

$$R_{\text{T}} = \frac{MBP - P_{\text{out}}}{\overline{Q_{\text{in}}}}, \tag{1}$$

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

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

2.4. Central blood pressure estimation algorithms

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

2-element Windkessel (0-D) model

This model, referred to as '2-Wk' hereafter, idealises the arterial system as a reservoir of compliance C_{T}. Blood flows into the reservoir from the heart, $Q_{\text{in}}(t)$, at a pressure $P(t)$,

encounters a resistance to flow, R_{T}, and flows out into the vascular beds at a pressure P_{out} (Figure 1c, top). The governing equation is

$$\frac{dP}{dt} + \frac{P - P_{\mathrm{out}}}{R_{\mathrm{T}} C_{\mathrm{T}}} = \frac{Q_{\mathrm{in}}}{C_{\mathrm{T}}}, \tag{2}$$

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

$$P(t) = P_{\mathrm{out}} + (P_0 - P_{\mathrm{out}}) e^{-\frac{t-t_0}{R_{\mathrm{T}} C_{\mathrm{T}}}} + \frac{e^{-\frac{t}{R_{\mathrm{T}} C_{\mathrm{T}}}}}{C_{\mathrm{T}}} \int_{t_0}^{t} Q_{\mathrm{in}}(t') e^{\frac{t'}{R_{\mathrm{T}} C_{\mathrm{T}}}} dt', \quad t \geq t_0, \tag{3}$$

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

3-element Windkessel (0-D) model

This model, referred to as '3-Wk' hereafter, results from adding an impedance, Z_0, in series to the '2-Wk' model where $R_{\mathrm{T}} = Z_0 + R$ (Figure 1(c), middle). Z_0 is commonly known as the characteristic impedance and was initially introduced to represent the impedance of the aorta (71). The governing equation is

$$\frac{dP}{dt} + \frac{P - P_{\mathrm{out}}}{R C_{\mathrm{T}}} = Z_0 \frac{dQ_{\mathrm{in}}}{dt} + \frac{(Z_0 + R) Q_{\mathrm{in}}}{R C_{\mathrm{T}}}, \tag{4}$$

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

$$\begin{aligned} P(t) = {} & P_{\mathrm{out}} + (P_0 - P_{\mathrm{out}} - Z_0 Q_0) e^{-\frac{t-t_0}{R C_{\mathrm{T}}}} + Z_0 Q_{\mathrm{in}}(t) \\ & + \frac{e^{-\frac{t}{R C_{\mathrm{T}}}}}{C_{\mathrm{T}}} \int_{t_0}^{t} Q_{\mathrm{in}}(t') e^{\frac{t'}{R C_{\mathrm{T}}}} dt', \quad t \geq t_0, \end{aligned} \tag{5}$$

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

1-D aortic model

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

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

Q_{in} was imposed as an inflow boundary condition at the aortic root and '3-Wk' models were coupled to the outlet of each terminal 1-D model segment. The parameters of each outflow model j, $Z^j_{0,\text{Wk}}$, $C^j_{\text{T,Wk}}$ and R^j_{Wk}, were calculated using Q_{in}, Q_{out}, and the outflow distribution (OD) in the supra-aortic arteries, $OD^j_{\text{flow}} = \overline{Q}^j_{\text{out}}/\overline{Q}_{\text{in}}$, under the assumption that DBP, MBP, and P_{out} remain constant within large arteries (2). We used the following equations (5):

$$Z^j_{0,\text{Wk}} = \frac{\rho PWV}{A^j_{\text{out}}}, \tag{6}$$

$$R^j_{\text{Wk}} = \frac{R_{\text{T}}}{OD^j} - Z^j_{0,\text{Wk}}, \tag{7}$$

$$C^j_{\text{T,Wk}} = (C_{\text{T}} - C_{\text{T,art}})\,\frac{R_{\text{T}}}{R^j_{\text{Wk}}}, \tag{8}$$

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

$$C^k_{\text{T,art}} = \frac{\overline{A}^k L^k}{\rho PWV^2}, \tag{9}$$

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

2.5. Assessing central blood pressure estimation algorithms

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

3. Results

3.1. Assessment of CV parameter estimation methods

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

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

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

For both scenarios, $LVET$, P_{out}, R_{T}, C_{T}, and PWV were estimated without any considerable bias of their corresponding reference mean values ($< 6\%$ for 'carotid+' and $< 10\%$ for 'carotid−'). However, Z_0 was overestimated with a much greater bias of its corresponding reference mean value (13% for 'carotid+' and 82% for 'carotid−'). The bias as a function of each CV parameter reference value remained approximately unchanged, with the exceptions of P_{out} (which had a singular reference value) and C_{T} for 'carotid−' (whose absolute bias increased with increasing reference values). The same optimal methods were identified for PWV in both scenarios.

3.2. Assessment of cBP algorithms

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

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

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

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

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

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

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

4. Discussion

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

4.1. Cardiovascular parameter estimation methods

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

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

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

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

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

Changes in arterial compliance (C_{T}) can have important effects on the pulse wave,

left ventricular dynamics, cardiac output, and the ratio of systolic to diastolic flow into capillary beds (51). Our proposed optimised '3-Wk' method for estimating C_{T} led to a MPE $= -0.8 \pm 4.2\%$, outperforming existing methods. Similarly to Stergiopulos *et al.* (62), we found MPE $< 12\%$ for the 'diastolic decay', 'area' and 'two-area' methods, though our MPE for the 'pulse pressure' method was higher (27% vs 17%).

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

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

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

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

4.2. Central blood pressure algorithms

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

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

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

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

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

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

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

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

4.3. Limitations

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

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

4.4. Perspectives

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

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

4.5. Conclusion

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

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

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s).

Data Access Statement

A data supplement related to this manuscript is publicly available at `https://doi.org/10.5281/zenodo.3968540`. These materials are not a part of this manuscript, and have not undergone peer review by the American Physiological Society (APS).

APS and the journal editors take no responsibility for these materials, for the website address, or for any links to or from it. The data collected during the literature review and the results from the 0-D and 1-D simulations, together with the Matlab® code used to generate 0-D datasets, to run 0-D simulations, to create input files for 1-D simulations, and to post-process and analyse this data is available here `https://github.com/jmariscal-harana/cbp_estimation`. Details of the code used to run the 1-D simulations are available at `http://haemod.uk`, and access requests should be addressed to J. Alastruey at jordi.alastruey-arimon@kcl.ac.uk. Details of how to replicate this study can be obtained by contacting J. Mariscal-Harana jorge.mariscal_harana@kcl.ac.uk. Further information about the data and conditions of access can be found by emailing 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†
DBP [mmHg]	53.2 ± 8.9	68.4 ± 10.4[a]	81.8 ± 12.8[a]	64.6 ± 9.0	75.3 ± 7.3
MBP [mmHg]	69.3 ± 9.7	85.6 ± 12.1[b]	102.0 ± 15.8[b]	83.9 ± 11.2	94.2 ± 6.7
$pSBP$ [mmHg]	82.0 ± 15.2	111.4 ± 17.3[c]	129.6 ± 22.6[c]	117.6 ± 21.3	119.3 ± 11.4
$cSBP$ [mmHg]	93.7 ± 11.9	107.2 ± 17.3	126.4 ± 22.2		110.4 ± 12.5
pPP [mmHg]	30.6 ± 13.0	43.2 ± 12.2	48.2 ± 16.0	52.9 ± 16.9	46.5 ± 14.1
cPP [mmHg]	40.5 ± 12.7	38.8 ± 11.0	44.6 ± 15.4		35.1 ± 15.3
SV [mL]	57.4 ± 29.9	100.6 ± 35.3	83.3 ± 32.8	88.4 ± 12.2	60.3 ± 12.3
HR [bpm]	65.1 ± 14.4	62.2 ± 11.2	65.5 ± 10.4	68.8 ± 11.3	75.9 ± 9.3
CO [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. [a]Brachial oscillometric measurement. [b]Radial tonometry measurement. [c]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 ± 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**
Left Ventricular Ejection Time, $LVET$	dP/dt analysis, 1	+	(13)	LV1	‡	0.4 ± 1.0
	dP/dt analysis, 2	+	(32)	LV2	-12.4 ± 0.1	-5.7 ± 4.1
	$0.37\sqrt{T}$	+,−	(7)	LV3	26.1 ± 8.5	6.9 ± 8.1
	Q analysis	+,−	†	LV4	0.1 ± 0.2	0.3 ± 0.6
Outflow Pressure, P_{out}	Diastolic decay fit, 1	+	(24,71)	OP1	0.0 ± 0.0	-5.1 ± 8.0
	Diastolic decay fit, 2	+	(24,60)	OP2	0.0 ± 0.0	-10.5 ± 7.5
	0.5 DBP	+,−	†	OP3	1.6 ± 16.9	9.1 ± 11.0
	0.7 DBP	+,−	(49)	OP4	42.3 ± 23.6	52.7 ± 15.4
Arterial Resistance, R_{T}	$(MBP - P_{\text{out}})/\overline{Q}$	+	(24)	AR1	0.0 ± 0.0	0.0 ± 0.1
	$(DBP + 0.4PP - P_{\text{out}})/\overline{Q}$	+,−	(10,24)	AR2	0.7 ± 5.7	-4.9 ± 2.9
Arterial Compliance, C_{T}	2-point diastolic decay	+	(24)	AC1	-0.1 ± 0.0	-6.5 ± 4.9
	Diastolic decay fit, 1	+	(24)	AC2	0.0 ± 0.0	-6.6 ± 3.3
	Diastolic decay fit, 2	+	(24,60)	AC3	0.0 ± 0.0	-10.2 ± 5.0
	Area method	+	(15,52,71)	AC4	-10.0 ± 4.1	-11.4 ± 4.6
	Two-area method	+	(55,71)	AC5	-10.0 ± 4.1	-7.1 ± 7.1
	DBP method	+,−	†	AC6	-1.5 ± 4.1	-17.3 ± 7.5
	PP method	+,−	(61,71)	AC7	-0.1 ± 0.2	-27.6 ± 11.6
	SV/PP	+,−	(15)	AC8	-13.8 ± 20.3	4.9 ± 18.4
	Optimised 3-Wk	+	†	AC9	0.0 ± 0.3	-0.8 ± 4.2
Pulse Wave Velocity, PWV	Foot-to-foot: Q_{Ao}	+,−	(25)	PV1	-	8.2 ± 6.0
	Foot-to-foot: $P_{\text{c-f}}$	$+^a$	(25)	PV2	-	27.8 ± 10.8
	Least-squares: Q_{Ao}	+,−	(25)	PV3	-	-12.7 ± 8.3
	Least-squares: $P_{\text{c-f}}$	$+^a$	(25)	PV4	-	43.0 ± 36.0
	Sum of squares	+	(17)	PV5	-	33.2 ± 17.2
Characteristic Impedance, Z_0	Frequency methods	+	(1,16,19,30,40,42,50,54)	Z1	2.5 ± 2.1	64.6 ± 44.3
	PQ-loop methods	+	(19,37,63)	Z2	0.2 ± 1.4	13.4 ± 56.6
	0.05 R_{T}	+,−	(41,69)	Z3	-1.5 ± 40.8	133.8 ± 66.7
	$(MBP - DBP)/Q_{\text{max}}$	+,−	†	Z4	-38.7 ± 12.4	82.3 ± 32.6
	$\rho PWV/A$	+,−	(72)	Z5	-	90.4 ± 18.1
	Optimised 3-Wk	+	†	Z6	-0.1 ± 0.7	37.1 ± 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; $\overline{Q}$: mean value of Q over T; SV: stroke volume; 3-Wk: 3-element Windkessel; Q_{Ao}: ascending and descending aorta flow wave pair; $P_{\text{c-f}}$: carotid−femoral blood BP wave pair; Q_{max}: peak aortic flow; ρ: 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. ^{a}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.

		Optimal CV parameter estimation methods (MPE [%])					
Dataset	**Sce**	$LVET$	P_{out}	R_{T}	C_{T}	PWV	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 (μ) and standard deviation (σ) 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).

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

Appendix A. Datasets of virtual subjects

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.

	Variations					
	Negative		Baseline	Positive		
CV parameter [units]	$\mu - \sigma$	$\mu - 0.5\sigma$	μ	$\mu + 0.5\sigma$	$\mu + \sigma$	References
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_{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: μ and σ: mean and standard deviation values, respectively, for each CV parameter from the clinical literature; SV: stroke volume; HR: heart rate; P_{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.

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

Reference Z_0 and C_T values for the 1-D dataset were calculated from aortic root BP (P) and flow (Q_in) waves using an in-house algorithm written in Matlab® and based on the '3-Wk' model (Figure A1). Assuming that P_out is known and that the total resistance $R_\mathrm{T} = Z_0 + R$ is given by Equation (1), a parameter estimation problem can be solved for Z_0 and C_T. The estimated BP at time t_k can be written as

$$P(t_k) = f(Z_0', C_\mathrm{T}', Q_\mathrm{in}(t_k)) + e_k, \tag{A.1}$$

with e_k the residual error between the estimated and reference BP at each time t_k, $k = 1, \ldots, K$, and Z_0' and C_T' the estimated parameters. The problem can be solved through iterative minimisation of the cost function $\mathbf{e}^\top\mathbf{e}$, where $\mathbf{e}$ is the vector containing the residual errors at each time t_k. The iterative procedure starts from an initial estimate ($Z_{0,0}'$, $C_{\mathrm{T},0}'$). The parameters at iteration i+1 are then calculated using the recursive equation

$$(Z_{0,i+1}', C_{\mathrm{T},i+1}') = (Z_{0,i}', C_{\mathrm{T},i}') - \mathbf{H}_i\mathbf{q}_i, \tag{A.2}$$

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

Appendix B. Cardiovascular parameter estimation methods

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

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

*LV1 - dP/dt analysis, 1**

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

LV2 - dP/dt analysis, 2

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

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

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

LV3 - $0.37\sqrt{T}$

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

*LV4 - Q analysis**

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

Appendix B.2. OP - Outflow pressure

OP1 - Diastolic decay fit, 1

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

OP2 - Diastolic decay fit, 2

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

*OP3 - 50% of DBP**

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

OP4 - 70% of DBP

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

Appendix B.3. AR - Arterial resistance

AR1 - Peripheral pressure waveform

R_{T} is calculated using Equation (1) and MBP is calculated as the mean of P.

AR2 - Peripheral DBP and SBP values

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

Appendix B.4. AC - Arterial compliance

AC1 - 2-point diastolic decay

The concept of a diastolic decay fit was first described in (24). Using only the first and last points of the diastolic part of P, C_{T} is calculated as:

$$\frac{T - LVET}{\ln(\frac{P(LVET)-P_{\mathrm{out}}}{DBP-P_{\mathrm{out}}})R_{\mathrm{T}}}. \tag{B.2}$$

AC2 - Diastolic decay fit, 1

Given that $\tau = (R_{\mathrm{T}} - Z_0)C_{\mathrm{T}}$, OP1 can be used to calculate τ, and rearranging:

$$C_{\mathrm{T}} = \frac{\tau}{R_{\mathrm{T}} - Z_0}. \tag{B.3}$$

If τ is negative then P_{out} is set to 0 and τ is recalculated.

AC3 - Diastolic decay fit, 2

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

AC4 - Area method

This method is described in (52). C_{T} is calculated as:

$$\frac{\int_{t_1}^{t_2}(P - P_{\mathrm{out}})dt}{R_{\mathrm{T}}(P(t_1) - P(t_2))}, \tag{B.4}$$

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

AC5 - Two-area method

This method is described in (55). C_{T} is calculated by solving two simultaneous equations of the form:

$$\int_{t_1}^{t_2} Q dt - \frac{1}{R_{\mathrm{T}}}\int_{t_1}^{t_2}(P - P_{\mathrm{out}})dt = C_{\mathrm{T}}(P(t_1) - P(t_2)), \tag{B.5}$$

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

*AC6 - Diastolic blood pressure method**

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

AC7 - Pulse pressure method

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

AC8 - Stroke volume over pulse pressure

This method is described in (15). C_{T} corresponds to SV/PP.

*AC9 - Three-element Windkessel optimisation**

This method is described in Appendix A.2. The initial value of C_{T} is calculated using AC8.

Appendix B.5. PV - Pulse wave velocity

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

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

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

PV1 - Foot-to-foot: aortic flow

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

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

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

PV3 - Least-squares: aortic flow

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

PV4 - Least-squares: carotid–femoral pressures

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

PV5 - Sum of squares

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

$$PWV = \frac{1}{\rho A}\sqrt{\frac{\sum dP^2}{\sum dQ^2}} \tag{B.6}$$

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

Appendix B.6. Z - Aortic characteristic impedance

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

Z1 - Frequency methods

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

Z2 - P-Q loop methods

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

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

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

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

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

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

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

The best performing P-Q loop method, IV, was used to calculate the errors in Table 2. These methods, in their original form, require P and Q measured simultaneously at the ascending aorta. However, for the proposed algorithms, a peripheral P measurement is used instead.

Z3 - 5% of R_{T}

As suggested by Murgo *et al.* Z_0 is estimated as 5% of R_{T} (41).

*Z4 - Approximated aortic characteristics**

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

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

Z5 - Aortic characteristics

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

*Z6 - Three-element Windkessel optimisation**

This method is described in Appendix A.2. The initial values of C_{T} and Z_0 are calculated using the AC8 and Z3 methods, respectively.

Figure B1: Novel method to estimate $LVET$ from the aortic flow wave, Q. $LVET$ 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_{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.