Optimised design of an arterial network model reproduces characteristic central and peripheral hemodynamic waveform features in young adults

Avinash Kondiboyina, Hilary A Harrington, Joseph John Smolich, Michael M H Cheung, and Jonathan Paul Mynard

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Corresponding author(s): Jonathan Mynard (jonathan.mynard@mcri.edu.au)

The following individual(s) involved in review of this submission have agreed to reveal their identity: Niema Pahlevan (Referee #1)

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Dear Dr Mynard,

Re: JP-RP-2022-282942 “Optimised design of an arterial network model reproduces characteristic central and peripheral hemodynamic waveform features in young adults” by Avinash Kondiboyina, Hilary A Harrington, Joseph John Smolich, Michael M H Cheung, and Jonathan Paul Mynard

Thank you for submitting your manuscript to The Journal of Physiology. It has been assessed by a Reviewing Editor and by 2 expert referees and I am pleased to tell you that it is considered to be acceptable for publication following satisfactory revision.

Please advise your co-authors of this decision as soon as possible.

The reports are copied at the end of this email. Please address all of the points and incorporate all requested revisions, or explain in your Response to Referees why a change has not been made.

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If you need to check to make sure that your Methods section conforms to the principles of UK regulations, you may wish to refer to Grundy (2015):
Grundy (2015) J. Physiol. 2015 Jun 15;593(12):2547-9 https://doi.org/10.1113/JP270818

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Yours sincerely,

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- A Statistical Summary Document, summarising the statistics presented in the manuscript, is required upon revision. It must be on the Journal's template, which can be downloaded from the link in the Statistical Summary Document section here: https://jp.msubmit.net/cgi-bin/main.plex?form_type=display_requirements#statistics

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- ‘n’ clearly defined (e.g. x cells from y slices in z animals) in the Methods. Authors should be mindful of pseudoreplication.

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The most appropriate summary statistic (e.g. mean or median and standard deviation) must be used. Standard Error of the Mean (SEM) alone is not permitted.

- Exact p values must be stated. Authors must not use 'greater than' or 'less than'. Exact p values must be stated to three significant figures even when 'no statistical significance' is claimed.

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EDITOR COMMENTS

Reviewing Editor:

Kondiboyina et al. present a new arterial network model characterizing central and peripheral hemodynamic waveform features in young adult humans.

Two expert referees have reviewed this manuscript. Overall, both reviewers were enthusiastic about the novelty and experimental approach to the study, and the quality of the writing. They also had a number of important items for consideration that should be addressed by the authors to improve the transparency and clarity of the information presented.

Please also include the protocol number for the ethics committee approval.

Senior Editor:

Comments for Authors to ensure the paper complies with the Statistics Policy:
Actually mostly the data are okay, but the reviewers have asked for more raw data which is reasonable, and I note one table does not state what the values are mean SD or mean SEM

Comments to the Author:
Table one, are the data mean/SD as per the statistics policy?

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REFEREE COMMENTS

Referee #1:

The authors proposed a new 'YoungAdult' model that considers 1) a new empirical equation for approximating pulse wave velocity, 2) a new arterial junction model, and 3) a new arterial geometry model that eliminated 'within-segment' taper while preserving the impedance taper. The model was compared with clinical data from 7 young adults age 21-25. The results show that this model captures characteristics of central pressure waveforms in young adults. The authors also investigated the effect of vascular bed compliance and reflection coefficient at iliac bifurcation on central and peripheral hemodynamics. The study is novel and well-conducted, and the paper is well-written. However, the below comments should be addressed before acceptance.

Major comments:

1) In the abstract: "The arterial network in healthy young adults is thought to be structured to minimise wave reflection in conduit arteries". Minimization of wave reflection is debatable (i.e. minimization of wave reflection may not be necessarily
favorable for coronary perfusion), please change it to "optimization of wave reflection".

2) Much more details should be provided for implementation of the proposed model on various forms of 1D-arterial formulation (e.g., AU, PU, PQ formulations). This is to ensure the finding of this paper is reproducible (and usable) by other solvers. Some citations were provided, but the manuscript should be self-contained for reproducibility. Also, please provide all algorithms in the main text or as a supplementary.

3) Please add the raw waveform data used in figures 3, 4, 5, 6, and 7.

4) The authors have mentioned that YoungAdult model will be made available upon reasonable request. However, in order to verify the proposed method, they should provide the averaged pressure and velocity waveforms of the 7 volunteers which were used for validation. Of course, more extensive data request (if reasonable) could be referred to the authors later.

Referee #2:

This modeling study proposes a new "YoungAdult" model of the arterial system. Key innovations include 1) carefully matching all arterial junctions to maximize forward transmission of pressure and flow everywhere except the peripheral terminations and 2) creating a formula to estimate local pulse wave velocity (PWV) based on both lumen area and distance from the heart. The authors also examined effects of peripheral compliance and mismatch at the aortic bifurcation on proximal waveform shape.

Major points:

1. The authors have made a foundational assumption that the "beautifully designed... tuning" of the arterial tree requires carefully matched arterial junctions that ensure maximal transmission of forward traveling waves right down to the microcirculation. This premise is based on the simplistic concept that a diastolic reflected wave will markedly reduce load on the heart and profoundly improve diastolic perfusion of the coronary arteries. Yet, the amount of augmentation of the systolic pressure-time integral and reduction of the diastolic pressure-time integral due to an early reflected wave is fairly trivial even when examining just the pressure waveform (i.e., pulse pressure) and is several fold less important when considering that normal diastolic pressure is well removed from zero. So, the benefit to the heart seems fairly trivial. In contrast, the detriment to every other organ in the body is considerable if excessive pulsatile power is transmitted to the microcirculation. Is it reasonable to assume that evolution would favor a trivial reduction in load on the heart in favor of progressive, severe microvascular damage in every other organ? The heart is important, but some would say that the brain, for example, is also somewhat important for survival....

2. Optimally matched junction for forward waveforms does not mean optimally matched junctions for reflected waves. How does the model handle rereflection of backward waves? If there is no amplification during forward transmission, would the reflected wave be trapped by backward mismatch as Davies et al have suggested?

3. It is a bit unclear how many parameters are being optimized in the model fitting. There are >150 arterial segments with properties tabulated. What properties (how many parameters) are actually optimized? As the authors no doubt know, there is a nearly infinite set of potential parameter combinations in a complex model with 100's of parameters that could reproduce any prescribed set of pressure and flow waveforms. What limits this infinite set of possibilities in your model?

4. The assumption that distal wave reflection depends solely on compliance of the peripheral vascular bed is hard to envision. The vascular beds are models are 3-element Windkessels. Clearly a very high C will act as a shunt for Rp (at high frequencies), but what about Rs? Wouldn't there still be a reflection from mismatch between the distal artery and Rs? Or was Rs assumed to be matched to impedance of the upstream feeder artery? If that is the case, it seems the reasoning is circular.

5. What effect does aortic bifurcation RC = 0.00 vs. 0.20 have on the rereflection coefficient in each iliac? With what implications for effects of distal reflection in the legs?
6. It is curious that a change in peripheral compliance in the legs has a major effect on the aortic pressure waveform when bilateral manual compression of the femoral arteries has been shown to have no effect. Please comment.

END OF COMMENTS
Response to Reviewers

We thank the Reviewers for taking the time to assess our manuscript and appreciate the comments. Please find our responses below in blue text. The manuscript has been revised accordingly, with changes indicated with yellow highlights.

EDITOR COMMENTS

Reviewing Editor:

Kondiboyina et al. present a new arterial network model characterizing central and peripheral hemodynamic waveform features in young adult humans.

Two expert referees have reviewed this manuscript. Overall, both reviewers were enthusiastic about the novelty and experimental approach to the study, and the quality of the writing. They also had a number of important items for consideration that should be addressed by the authors to improve the transparency and clarity of the information presented.

Please also include the protocol number for the ethics committee approval.

We have included the protocol number in the revised manuscript.

Senior Editor:

Comments for Authors to ensure the paper complies with the Statistics Policy:
Actually mostly the data are okay, but the reviewers have asked for more raw data which is reasonable, and I note one table does not state what the values are mean SD or mean SEM

Thank you. Please see our response to the reviewer below. The raw waveform data is already presented in the Figures, so we were not sure what further information we could provide. We trust this is sufficient.

Comments to the Author:
Table one, are the data mean/SD as per the statistics policy?

Yes, the data are presented as mean ± SD. We have added a footnote in Table 1 to this effect.

REFEERE COMMENTS

Referee #1:
The authors proposed a new 'YoungAdult' model that considers 1) a new empirical equation for approximating pulse wave velocity, 2) a new arterial junction model, and 3) a new arterial geometry model that eliminated 'within-segment' taper while preserving the impedance taper. The model was compared with clinical data from 7 young adults age 21-25. The results show that this model captures characteristics of central pressure waveforms in young adults. The authors also investigated the effect of vascular bed compliance and reflection coefficient at iliac bifurcation on central and peripheral hemodynamics. The study is novel and well-conducted, and the paper is well-written. However, the below comments should be addressed before acceptance.

Major comments:

1) In the abstract: "The arterial network in healthy young adults is thought to be structured to minimise wave reflection in conduit arteries". Minimization of wave reflection is debatable (i.e. minimization of wave reflection may not be necessarily favorable for coronary perfusion), please change it to "optimization of wave reflection".

Thank you for your comment. We agree that wave reflection in the arterial system as a whole is not minimised. However, our modelling data (along with a range evidence in the literature) strongly suggest that reflection of forward waves is minimised in the main conduit arteries specifically; or in other words, that most wave reflection of forward waves occurs distally in the vicinity of resistance vessels. To clarify this point, we have made the following changes in the manuscript:

"An established arterial network model was optimised by incorporating 1) a more accurate representation of arterial wave speeds, 2) precisely matched junctions, and 3) impedance-preserving tapering, thus minimising wave reflection in conduit arteries in the forward direction."

“Our findings strongly imply that a healthy young arterial system is structured to optimise wave reflection in the main conduit arteries, and that reflection of forward waves primarily occurs in the vicinity of vascular beds."

“The arterial network in healthy young adults is thought to be structured to optimise wave reflection in the arterial system, producing an ascending aortic pressure waveform with three key features: early systolic peak, negative systolic augmentation, and diastolic hump."

“If this is the case, it is likely that the progressive decline in diameter of conduit arteries with distance from the heart occurs primarily in a stepwise manner (decreasing where side branches arise), which allows for the preservation of impedance and minimises reflection of forward waves in the main conduit arteries."

“Model results imply that the arterial network must be exquisitely well-matched to exhibit the observed waveform features that are typical of healthy young adults, with minimal reflection of forward waves in the main conduit arteries (i.e. at junctions or due to within-segment taper), and reflection of forward waves predominantly occurring in the distal vascular beds."

2) Much more details should be provided for implementation of the proposed model on various forms of 1D-arterial formulation (e.g., AU, PU, PQ formulations). This is to ensure the finding of this paper is reproducible (and usable) by other solvers. Some citations were provided, but the manuscript should be self-contained for reproducibility. Also, please provide all algorithms in the main text or as a supplementary.
We have added further details about the model formulation, including the governing equations, in an Appendix. We note that some reference to prior work is necessary, as presenting all modelling details and implementation would make the current paper highly unwieldy. The following has been added in the Methods section:

“In brief, the non-linear 1D form of the Navier-Stokes equations, combined with a non-linear viscoelastic pressure-area relationship (Mynard & Smolich, 2015), were solved using the locally conservative Galerkin finite element method (Mynard & Nithiarasu, 2008), with conservation of mass and continuity of total pressure enforced at junctions. For a detailed description, refer to Appendix B.”

The following has been added in Appendix B:

**Governing Equations**

The equations governing haemodynamics in the YoungAdult model were the 1D Navier-Stokes equations derived from the laws of conservation of mass and momentum (Streeter et al., 1963; Sherwin et al., 2003)

\[
\frac{\partial A}{\partial t} + \frac{\partial Au}{\partial x} = 0 \tag{Equation B1}
\]

\[
\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} + \frac{1}{\rho} \frac{\partial P}{\partial x} = f \tag{Equation B2}
\]

where, \(A\) is area, \(u\) is velocity, \(P\) is pressure, \(\rho\) is blood density (1.06 g/cm³), \(f = -\xi \pi u^2 / A\), where \(\xi\) was calculated using the model described by Bessems et al. (2007). Additionally, a wall law was implemented that governed the relationship between pressure and area

\[
P - P_{\text{ext}} = 2\rho c_0^2 \left[ \left( \frac{A}{A_0} \right)^{\frac{2}{3}} - 1 \right] + \frac{\Gamma}{A\sqrt{A}} \frac{\partial A}{\partial t} + P_0 \tag{Equation B3}
\]

\[
b = \frac{2\rho c_0^2}{P_0 - P_{\text{collapse}}} \tag{Equation B4}
\]

\[
\Gamma = \frac{b_1}{D} + b_0 \tag{Equation B5}
\]

where \(P_{\text{ext}}\) is external pressure (assumed to be 0), \(P_{\text{collapse}}\) is a nominal pressure at which \(A \to 0\) (taken as -10 mmHg (1)), \(P_0\) is a reference pressure (taken to be 80 mmHg), \(c_0\) is the wave speed at \(P_0\), \(A_0\) is the area at \(P_0\), \(\Gamma\) is a coefficient of wall viscosity, \(D\) is vessel diameter, \(b_1 = 100\) g.cm/s, and \(b_0 = 400\) g/s (Mynard & Smolich, 2015).”

“Vascular Bed Model

All terminal 1D arteries were connected to 3-element windkessel compartments, which included 2 resistance elements—characteristic impedance of the terminal 1D artery (\(Z_{\text{art}}\)) and peripheral resistance of the vascular bed (\(R_{\text{bed}}\)—and 1 capacitor element (\(C_{\text{ped}}\)) that represents the compliance of the vascular bed (Figure B2). The venous system is represented as a constant outlet pressure (\(P_{\text{out}}\)) of 5 mmHg. \(Z_{\text{art}}\) was matched to the characteristic impedance of the 1D artery to prevent non-physiological reflection of higher frequency wave components (2, 3). For more detail please refer to Mynard (2011).”
3) Please add the raw waveform data used in figures 3, 4, 5, 6, and 7.

We apologize that we are not certain what the Reviewers means, as in each of these figures the raw waveform data is already presented. We have clarified that this is the case below.

In Figure 3, the waveforms of other models were extracted from published data, while the data from our model is the raw waveform data. We have now stated this in the Results section.

“Figure 3 compares the aortic pressure waveforms from the YoungAdult model with those from previous models, which were extracted from published data.”

For Figures 4, 5 and 6, the raw waveforms of all 7 participants are presented in grey in the top panels. We have now stated this in the Results section and in the corresponding figure legends.

“Participant characteristics are presented in Table 1, and the top panels of Figures 4-6 present the raw waveforms (pressure and velocity) of all 7 participants in grey and the corresponding average waveforms in black.”

“Figure 4: Comparison of the ascending aortic, left common carotid, and left superficial temporal artery waveforms produced by the YoungAdult model (bottom panels) and in vivo data (top panels). The individual waveforms for each participant are shown in grey and the average waveform in black.”

The waveforms presented in Figure 7 are taken directly from the YoungAdult model (i.e. these are raw waveform data).

4) The authors have mentioned that YoungAdult model will be made available upon reasonable request. However, in order to verify the proposed method, they should provide the averaged pressure and velocity waveforms of the 7 volunteers which were used for validation. Of course, more extensive data request (if reasonable) could be referred to the authors later.

We have presented the average pressure and velocity waveforms for all 7 participants in black in the top panels of Figures 4, 5, and 6. We have stated now stated this in the Results section and each of the figure legends (see response to Comment 3).
This modeling study proposes a new "YoungAdult" model of the arterial system. Key innovations include 1) carefully matching all arterial junctions to maximize forward transmission of pressure and flow everywhere except the peripheral terminations and 2) creating a formula to estimate local pulse wave velocity (PWV) based on both lumen area and distance from the heart. The authors also examined effects of peripheral compliance and mismatch at the aortic bifurcation on proximal waveform shape.

Major points:

1. The authors have made a foundational assumption that the "beautifully designed... tuning" of the arterial tree requires carefully matched arterial junctions that ensure maximal transmission of forward traveling waves right down to the microcirculation. This premise is based on the simplistic concept that a diastolic reflected wave will markedly reduce load on the heart and profoundly improve diastolic perfusion of the coronary arteries. Yet, the amount of augmentation of the systolic pressure-time integral and reduction of the diastolic pressure-time integral due to an early reflected wave is fairly trivial even when examining just the pressure waveform (i.e., pulse pressure) and is several fold less important when considering that normal diastolic pressure is well removed from zero. So, the benefit to the heart seems fairly trivial. In contrast, the detriment to every other organ in the body is considerable if excessive pulsatile power is transmitted to the microcirculation. Is it reasonable to assume that evolution would favor a trivial reduction in load on the heart in favor of progressive, severe microvascular damage in every other organ? The heart is important, but some would say that the brain, for example, is also somewhat important for survival....

The reviewer brings up very interesting points that highlight the need for further research in this field. We agree that the benefit of a diastolic return time to coronary perfusion pressure has not been directly proven. The point we are attempting to make in the introduction is that the available evidence strongly supports the contention that junctions of the major conduit arteries are well-matched in the forward direction. For example, Papageorgiou et al. showed that most area ratios of systemic arterial junctions were close to theoretically predicted values for well-matched junctions in the forward direction (4).

The points raised by the Reviewer may arise from the view that wave reflection in conduit arteries needs to be present to shield the microvasculature from excessive pulsatile power. This is an important hypothesis in the field of arterial haemodynamics that requires further investigation, and we believe our study helps add to the discussion. We would point to several lines of evidence that suggest conduit arterial wave reflection may not be the primary mechanism that protects the microvasculature in a young/healthy arterial system. First, as pointed out above, available evidence from geometric measurements suggests that the main conduit arteries are well-matched, whereas one might not expect this to be the case if wave reflection in the conduit arteries were an essential part of an optimised network. Second, a key finding of the present study was that the typical waveform features of a young adult could only be reproduced when the conduit arteries were very well-matched in the model; in the process of designing the model, we found consistently that employing any model configuration that involved even mildly unmatched junctions in the main conduit arteries could not reproduce these waveform features. Third, our recent paper showed that wave reflection in conduit arteries promotes transmission of pulsatile pressure to the microvasculature (5). Conversely, wave reflection limits transmission of pulsatile hydraulic power. This appears to create a conundrum, because if we assume transmission of pulsatile pressure and pulsatile power are both harmful to the microvasculature, then the microvasculature couldn’t win.
with or without wave reflection being present in the conduit arteries. We believe that a key part of the solution to this conundrum may lie in the recognition that there are two factors to consider, 1) the amplitude of the forward wave, and 2) the transmission of the forward wave to the microvasculature. Our prior study (5) suggests that the high arterial compliance in youth (which avoids an excessively large forward wave) is likely to limit both the pulsatile pressure and hydraulic power experienced by the microvasculature, even with well-matched junctions. In other words, the key issue may be the amplitude of the incident wave rather than how it is transmitted (which may be a secondary factor). An attractive aspect of this proposal is that the same arterial network properties that are beneficial to the heart are also beneficial to the microvasculature, and hence there is no ‘competition’ between the heart and the brain, as the Reviewer’s comment implies.

Clearly, these concepts require additional investigation in future work and our comments do not provide a final word or comprehensive answer. However, to address the Reviewer’s comment, we have made the following changes to the Introduction.

“One prominent view is that this occurs, in part, due to the “beautifully designed... tuning” of the arterial tree (O’Rourke & Hashimoto, 2007) with junctions that are well-matched in the forward direction (Papageorgiou et al., 1990) resulting in reflected pressure waves predominantly arriving at the heart during diastole.”

2. Optimally matched junction for forward waveforms does not mean optimally matched junctions for reflected waves. How does the model handle rereflection of backward waves? If there is no amplification during forward transmission, would the reflected wave be trapped by backward mismatch as Davies et al have suggested?

We agree that having well-matched junctions in the forward direction is not accompanied by matching in the backward direction. We optimised the junctions in the forward direction by changing the areas of the daughter vessels by the same ratio (with the wave speed changing in concert with area). In other words, reflection coefficients were not prescribed directly in the model. As such, matching in the forward direction naturally led to substantial negative reflection for backward waves. We have now clarified this throughout the revised manuscript by specifying that it is reflection of forward waves that is minimised by the optimal matching of junctions.

The reviewer is also correct in stating that the reflected waves in the model are trapped and exhibit the ‘horizon effect’ proposed by Davies et al. due to the strong reflection of backward waves at junctions (6). The only additional point we would make is that this wave trapping is not entirely complete (i.e. some reflected low frequency wave energy does make it back to the ventricle) due to the fact that wave transmission in the backward direction is non-zero. Wave trapping involves the existence of a multitude of re-reflected waves, which in turn implies a multitude of small transmitted waves in the backward direction that combine into a smoothed ‘bulk’ reflected wave. This is partly why the reflection coefficient from the viewpoint of the ascending aorta is small at high frequencies but is non-negligible in the low frequency range.

3. It is a bit unclear how many parameters are being optimized in the model fitting. There are >150 arterial segments with properties tabulated. What properties (how many parameters) are actually optimized? As the authors no doubt know, there is a nearly infinite set of potential parameter combinations in a complex model with 100’s of parameters that could reproduce any prescribed set
of pressure and flow waveforms. What limits this infinite set of possibilities in your model?

To achieve well-matched junctions, we applied a single rule that was consistently applied throughout the network. The only parameter that was modified directly was cross-sectional area of the 1D segments. At each junction, the area ratio of daughter vessels was fixed, and the area of both daughter vessels were increased or decreased to achieve matching. Other parameters, such as wave speed were recalculated based on a fixed equation involving area (as described in the manuscript). Similarly, the wall viscoelastic coefficient was also recalculated, as it depends on the diameter via a fixed equation (see Appendix B in the revised manuscript). Therefore, although there are theoretically an infinite number of parameters, our optimisation process was highly constrained. In response to the reviewer’s comments, we have added the following in the Methods section:

“In this manner, the optimisation was highly constrained by only altering the areas; there were some downstream effects on wave speed and wall viscoelastic coefficient, which were determined by the artery area (Equation 2) and diameter (Equation B5; Appendix B), respectively.”

4. The assumption that distal wave reflection depends solely on compliance of the peripheral vascular bed is hard to envision. The vascular beds are models are 3-element Windkessels. Clearly a very high C will act as a shunt for Rp (at high frequencies), but what about Rs? Wouldn’t there still be a reflection from mismatch between the distal artery and Rs? Or was Rs assumed to be matched to impedance of the upstream feeder artery? If that is the case, it seems the reasoning is circular.

Reflection at the 3-element windkessel is frequency-dependent, and we agree it is not solely dependent on compliance, although compliance does have a dominant effect on reflection properties in the model. Rs was indeed matched to the impedance of the upstream feeder artery. This is a standard approach in most modelling studies to avoid non-physiological reflection of high frequencies (2, 3). The main role of Rs is to couple the 0D and 1D sections of the model, and Rs therefore essentially represents the continuation of the connecting 1D vessel. Therefore the ‘vascular bed’ proper should be considered to be represented by Rp and C. We have now stated this in Appendix B.

“All terminal 1D arteries were connected to 3-element windkessel compartments, which included 2 resistance elements—characteristic impedance of the terminal 1D artery (Z_{art}) and peripheral resistance of the vascular bed (R_{bed})—and 1 capacitor element (C_{bed}) that represents the compliance of the vascular bed (Figure B2). The venous system is represented as a constant outlet pressure (P_o) of 5 mmHg. Z_{art} was matched to the characteristic impedance of the 1D artery to prevent non-physiological reflection of higher frequency wave components (2, 3). For more detail, please refer to Mynard (2011).”

5. What effect does aortic bifurcation RC = 0.00 vs. 0.20 have on the rereflection coefficient in each iliac? With what implications for effects of distal reflection in the legs?

Thank you for this interesting question. The reflection coefficients in the backward direction for each iliac artery were -0.5 and -0.6 with an aortic bifurcation reflection coefficient of R = 0 and R = 0.2, respectively. It is difficult to isolate the effect of a local change in reflection properties on the degree of reflection in other parts of the system, and this would require substantial additional work. Hence, we would prefer not to explore this question in detail in the manuscript. However, we have added the following explanation in the Discussion.
To achieve $R = 0.2$, all downstream vessels were reduced in diameter, thus increasing the characteristic impedance of all leg vessels. This would therefore reduce the impedance mismatch between the leg vessels and vascular beds, leading to lesser wave reflection in the legs. Consequently, one may view this change as ‘transferring’ some wave reflection to a more proximal location, leading to a reduced effective length of the arterial network.

6. It is curious that a change in peripheral compliance in the legs has a major effect on the aortic pressure waveform when bilateral manual compression of the femoral arteries has been shown to have no effect. Please comment.

Thank you for raising this important point. It is perhaps debatable whether our model revealed a “major effect” of peripheral compliance on the aortic pressure waveform. Figure 5 in the manuscript (bottom leftmost panel, reproduced below as the left panel) indicates almost no impact on systolic or diastolic pressure, with the main effect being a modulation of the diastolic hump. Similarly, modifying the aortoiliac reflection coefficient from 0 to 0.2 had almost no effect on systolic pressure or augmentation, although it did eliminate the diastolic hump (a change in the shape of the waveform). This data is therefore broadly consistent with the concept that such reflection does not have a major impact on ascending aortic pressure (quantified as pulse pressure for example), although it does suggest that there is some effect on the waveform morphology.

With regards to the effect of bilateral femoral occlusion or distal abdominal aorta on ascending aortic waveforms, the available evidence is inconsistent. Van den Bos et al. (7) reported that “changes in flow and pressure patterns” in dogs with occlusion of the abdominal aortic occlusion were “small”, although pulse pressure increased by up to 36% and calculated arterial compliance decreased by ~25% (implying that a non-negligible effect must have been present). Khir et al. (8) reported that unilateral iliac artery occlusion had no detectable effect on reflected wave intensity in the ascending aorta of dogs, although they did not present wave separation data that would reveal impacts on lower frequency reflected waves. In humans (mean age 62 years), Baki et al reported no significant change in wave reflection index or reflection magnitude at the ascending aorta with unilateral femoral occlusion (9). However, Murgo et al found that bilateral compression of the femoral arteries of young adult humans produced an “immediate” response in the ascending aorta, with Figure 8 of that paper showing a 10 mmHg increase in systolic augmentation pressure (a 100% increase) (10). Similarly, Latham et al reported that in patients with a mean age of 42 “femoral artery occlusion usually changed the character of the secondary systolic wave [of the ascending aortic pressure], which was increased in amplitude and more sharply peaked than at control in some patients” (11). Furthermore, Murakami found that squatting (which is thought to compress the femoral arteries) also caused an increase in the augmentation index of the central pressure waveform of 12 healthy young adults from 6% to 25% (12). Thus, the evidence is conflicting, and we suggest this issue requires further study – for example to assess whether data in dogs is
representative of what occurs in humans, and whether age or other characteristics in humans have an impact.

To address this comment, we have added the following in the Discussion section.

“These findings suggest that the aortoiliac bifurcation (in addition to other arterial junctions in the lower body) may need to be well-matched to obtain a prominent diastolic hump, although this needs to be investigated in future human studies. Interestingly, the effect of occluding the femoral artery (mimicking an increased $R_p$ at the aortoiliac bifurcation) on the ascending aortic pressure waveform has shown mixed results; while some studies have revealed a clear effect (Murgo et al., 1980; Latham et al., 1985), others have not (Khir & Parker, 2005; Baksi et al., 2016). Thus, this warrants further investigation.”

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12. Murakami T. Squatting: The hemodynamic change is induced by enhanced aortic wave reflection. Am J Hypertens. 2002;15(11):986-8.
Dear Dr Mynard,

Re: JP-RP-2022-282942R1 “Optimised design of an arterial network model reproduces characteristic central and peripheral hemodynamic waveform features in young adults” by Avinash Kondiboyina, Hilary A Harrington, Joseph John Smolich, Michael M H Cheung, and Jonathan Paul Mynard

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EDITOR COMMENTS

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Very limited data are included in the statistical summary document (only age, height, and weight information). The purpose of this document is to improve transparency about the statistical approaches used for the key outcomes reported in each published manuscript. Please include all of the relevant details for the statistical tests utilized in this manuscript.

Both reviewers are satisfied with the revised manuscript. Thank you for your thorough responses to their previous comments. Two relatively minor items remain:

1. Reviewer #1 has requested the "raw waveform data" in the form of an Excel or text file, with time and value vectors (i.e. data columns) as a supplementary data file.

2. The statistical summary document has not been completed appropriately. Please include the relevant details for the statistical tests utilized in this manuscript, or provide justification for why this is not applicable for the modelling approaches.
Senior Editor:

The statistical summary document needs some attention. Please see the comments of the Reviewing Editor (above).

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REFEREE COMMENTS

Referee #1:

Thank you for addressing all the comments. Just one minor issue about my third comment: For “raw waveform data”, I meant in the form of excel or text file with time and value vectors (i.e. data columns) as a supplementary.

Referee #2:

The authors have addressed my prior concerns. I think the model will be a useful addition.

END OF COMMENTS

1st Confidential Review
We thank the Reviewers for taking the time to assess our manuscript and appreciate the comments. Please find our responses below in blue text. The manuscript has been revised accordingly, with changes indicated with yellow highlights.

Reviewing Editor:
Both reviewers are satisfied with the revised manuscript. Thank you for your thorough responses to their previous comments. Two relatively minor items remain:

1. Reviewer #1 has requested the "raw waveform data "in the form of an Excel or text file, with time and value vectors (i.e. data columns) as a supplementary data file.

We have included the raw data for the average in vivo pressure and velocity waveforms for each of the arteries in an excel file, corresponding to the thick black lines in the figures. The average waveforms are used to validate the model. We are happy to provide individual waveforms upon reasonable request. However, we would prefer not to provide all of the individual waveforms with the publication, as there is a large number of these, they have significant value for potential future collaborations, and they would not have direct utility for reproducing the findings of our study. We hope this is satisfactory. We have made the following changes in the manuscript:

“Participant characteristics are presented in Table 1, and the top panels of Figures 4-6 present the raw waveforms (pressure and velocity) of all 7 participants in grey and the corresponding average waveforms in black; the raw data for the average waveforms are given in Supplemental File 3”

2. The statistical summary document has not been completed appropriately. Please include the relevant details for the statistical tests utilized in this manuscript, or provide justification for why this is not applicable for the modelling approaches.

This study does not involve any statistical tests or comparisons because it concerns design and evaluation of a deterministic model, along with qualitative comparisons of waveform morphology. The only statistical tool used in this study is calculating the standard deviation of the age, height, and weight of the participants. Hence, we have included only this in the statistical summary document.
Dear Dr Mynard,

Re: JP-RP-2022-282942R2 "Optimised design of an arterial network model reproduces characteristic central and peripheral hemodynamic waveform features in young adults" by Avinash Kondiboyina, Hilary A Harrington, Joseph John Smolich, Michael M H Cheung, and Jonathan Paul Mynard

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REFEREE COMMENTS

Referee #1:

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