A computational study of pulmonary hemodynamics in healthy and hypoxic mice

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Abstract

This study uses a 1D fluid dynamics arterial network model to predict pressure and flow dynamics in healthy and hypoxic mice. Data for this study include blood flow and pressure measurements from the main pulmonary artery of 7 healthy and 5 hypoxic mice. Representative arterial network dimensions for the 21 largest pulmonary arterial vessels are extracted from micro-CT images from healthy and hypoxic lungs. Each vessel is represented by its length and radius, and is assumed to taper longitudinally. Fluid dynamic computations are done assuming that the flow is Newtonian, viscous, laminar, has no swirl, and that the arterial walls are thin. The system of equations is closed by a constitutive equation relating pressure and area, using either a linear model derived from stress-strain deformation in the circumferential direction or a nonlinear model of empirical nature. For each dataset, an inflow waveform is extracted from data, and nominal parameters related the outflow boundary conditions were specified using mean values and timescales computed from the measured flow and pressure waveforms. The model was calibrated for each mouse by estimating parameters using optimization that minimized the least squares error between measured and computed pressure and flow waveforms from the main pulmonary artery. Results show that for healthy animals, the nonlinear wall model is needed to predict flow and pressure characteristics, while for the hypoxic animals both models predict the experimental data well, possibly because vessels are significantly stiffer due to wall remodeling.

1 Introduction

Pulmonary hypertension (PH) is a complex disorder, which is clinically diagnosed when the invasively measured mean blood pressure is greater than 25 mmHg in the main pulmonary artery (MPA). PH is associated with vascular remodeling, including stiffening and thickening of both large and small vessels, as well as microvascular rarefaction [51]. This study examines data from group III pulmonary hypertension, observed clinically in patients with hypoxia and other lung diseases [46], believed to initiate with vascular remodeling at the arteriolar level followed by progressive remodeling of the large arteries [14, 17].
The process of remodeling adversely affects key factors in the cardiopulmonary system, including total pulmonary vascular resistance (PVR), proximal and peripheral arterial compliance (or stiffness), and wave reflection [28]. These factors interact in a complex way to determine the blood pressure and flow relationship at any given location in the pulmonary system. The effects of remodeling can be characterized in terms of parameters, which can be quantified by analyzing the pulmonary hemodynamic data.

To understand the relation between hemodynamics and remodeling, it is essential to analyze the morphometric and hemodynamic data recorded over time during disease progression. In humans, the high fidelity morphometric data can be obtained by non-invasive procedures, like MRI or CT scans [23], but the dynamic pulmonary arterial blood pressure can only be measured invasively using right heart catheterization [41]. Moreover, in humans, the disease takes years to develop making it practically difficult to study its progression. A means to gain understanding without this added complication is to study disease progression based on animal studies, e.g. using the mouse models [34, 45, 48]. The advantage of mouse models is that mice have a relatively short lifespan and it is feasible to generate specific disease groups (e.g. hypoxic mice) within a short time-span (<1 month). Experimental studies in mice are typically done within a specific genetic strain, thus limiting variation among individuals. In most experimental studies (e.g. [45, 33, 48]), hypoxia is used as a model for pulmonary hypertension [50], since it can be induced by placing animals in a hyperbaric chamber. Therefore, investigation of pulmonary hypertension in such mice may provide vital understanding of disease progression in humans with similar pathology [46].

Although the mouse models provide a wealth of data, the analysis is typically limited to approximating the aforementioned parameters using the impedance [24] or wave intensity analysis [32]. The inference of disease progression is then based on statistical analysis of these secondary quantities [25]. However, as noted in our recent study [39], there are discrepancies among methods used to approximate pertinent quantities like the characteristic impedance, a metric of arterial stiffness and pulse wave velocity (PWV). Another limitation is that experimentally it is difficult to obtain waveforms from multiple locations throughout the vasculature, making it difficult to assess how disease impacts the distal vasculature. To mitigate these problems, we propose to use mathematical modeling to analyze morphometric and hemodynamic data from healthy and hypoxic mice to understand how the pulmonary vasculature is remodeled with disease.

Inspired by existing studies, e.g. [3, 18, 27, 30, 36] (most of these in humans), we develop a one dimensional (1D) fluid dynamics network models of the large pulmonary arteries in healthy and hypoxic mice, predicting dynamic flow and pressure propagation. We estimate model parameters predicting specific hemodynamics to understand how the underlying vasculature is altered with disease. Specifically, these models will be set up to reflect conditions observed in C57BL6/J healthy and hypoxic mice [45, 48]. For the 1D domain, we extract an arterial network from micro-CT data and combine it with hemodynamic data to obtain fluid dynamics simulations predicting pressure and flow waves in the
main pulmonary artery (MPA). Only a few previous 1D modeling studies have investigated wave propagation for systemic [6] and pulmonary [18, 39] arteries in mouse networks and, to our knowledge, none of these studies were able to combine imaging data with hemodynamics to predict changes in disease. In this study, we expand upon these prior results by extracting detailed network information and by optimizing hemodynamic predictions, allowing us to understand how underlying parameters change between the two populations. In particular, we develop a model and estimate parameters based on flow and pressure measurements in the MPA of 7 healthy and 5 hypoxic mice.

An important benefit of using the 1D models is that they are capable of accounting for both the local stress-strain relation in the large arteries, which is important for inferring the stiffness response, as well as global network properties, in particular, the pulse wave propagation. Predictions depend on the network structure, and on properties of the vascular wall. This study also focuses on understanding the importance of accounting for nonlinear deformation of the vascular wall. We study this in the time-domain by comparing simulated waveforms to data and via wave intensity analysis, as well as in the frequency domain comparing predictions of impedance spectra. To do so, similar to previous studies [30, 36], we combine equations derived from the Navier–Stokes equations for conservation of momentum and mass with a constitutive equation relating pressure and vessel area. The system will be solved using both a mechanistic linear wall model as well as a nonlinear empirical wall model. Using these models, we compare predictions of flow and pressure in MPA with experimental data.

The advantage of the linear wall model is that it is easy to derive from first principles and it has been shown to be successful [2, 30] within physiological pressure/area values for systemic arteries. Yet, it does not account for the fact that arteries stiffen with increased pressure, a behavior observed in most arteries [9]. Therefore, for a low pressure system like the pulmonary circulation or in patients with hypertension or other pathologies impacting pressure, the linear wall model cannot easily be extended to provide adequate predictions [38]. On the other hand, detailed, structural nonlinear elastic wall models can be derived from first principles, e.g. [14, 15], yet they are difficult to analyze in the context of available data due to the large number of parameters in the model. Moreover, due to high complexity of this model type, coupling with fluid dynamical equations within the 1D framework is mathematically and numerically challenging. Therefore, similar to other fluid mechanics studies [4, 12, 18], we propose to use the simple nonlinear empirical model developed by Langewouters in 1980 [16, 17] in our analysis of flow and pressure in vascular networks relevant to pulmonary hypertension in mice.

The process of modeling requires a priori specification of key parameters, including arterial stiffness, total vascular resistance, and periphery compliance, which are known to vary between individuals. This creates the need for methods to estimate parameters that predict individual waveforms observed experimentally across individual mice. Estimating individual parameters is challenging since data are only available from one location, whereas the model predicts
dynamics in all vessels throughout the network. A few recent studies have engaged in parameter estimation including the study by Hellevik [13], who used polynomial chaos expansion to analyze a stochastic model of pressure waves in the large arteries. To our knowledge, our goal of estimating parameters based on measurements of blood pressure is novel relative to these prior studies. All previous studies estimating pressure dynamics were done either in 0D circuit type models [3, 55] or a single vessel 1D model [21].

In this study, we investigate the extent to which global network parameters can be defined, limiting the number of parameters to be estimated, that allow us to predict observed dynamics in both healthy and hypoxic mice. To do so we first describe how to determine a priori parameter values predicting wall stiffness and outflow conditions by combining available data and existing results in the literature [48, 18]. In the second step, we conduct constrained non-linear optimization to estimate parameters with the aim of predicting the observed dynamics. The resulting estimated parameters are then analyzed to infer differences between healthy and hypoxic hemodynamics, and to investigate the extent to which the nonlinear wall model and compliance in proximal and distal networks enable accurate modeling of the observed dynamics.

2 Methods

2.1 Experimental Methods

This study uses existing hemodynamic and micro-computed tomography (micro-CT) images from healthy and hypoxic mice. Below we highlight the experimental protocols for extracting data analyzed herein. A detailed description of complete protocols can be found in the studies by Tabima et al. [45] and Vanderpool et al. [48], respectively. Both procedures were approved by the University of Wisconsin Institutional Animal Care and Use Committee.

Hemodynamic data. The hemodynamic data include dynamic pressure and flow waveforms obtained from male C57BL6/J mice, 12-13 weeks old with an average body weight of 24 g. The mice were divided into healthy (n = 7) and hypoxic groups (n = 5). The mice in the hypoxic group were exposed to 21 days of chronic hypoxia (10% O2 partial pressure) and both groups were exposed to a 12 hour light-dark cycle. Pressure and flow waveforms were signal-averaged using the ECG as a fiducial point. Twenty consecutive cardiac cycles free of extrasystolic beats were averaged to obtain an ensemble encoding for each mouse in both groups. Hemodynamic data and associated frequency domain signature are shown in Figure 1. Essential cardiovascular parameters are summarized in Table 1. More details on this experimental protocol can be found in the study by Tabima et al. [45].

Imaging data. Stacked planar X-ray micro-CT images of pulmonary arterial trees were obtained from male C57BL6/J mice, average age 10-12 weeks under
Figure 1: (a-d) Simultaneously measured flow and pressure waveforms in the main pulmonary artery (MPA) of healthy control and hypoxic mice. Each waveform was averaged over 20 consecutive cardiac cycles. (e-h) shows associated frequency domain signatures, where $f$ is the frequency, $|Z|$ is impedance modulus and $\theta$ is the associated phase angle (see equation (18)). Note that the healthy animals exhibit a spike in the impedance modulus at the 3rd harmonic.

For this study, two representative networks with 21 vessels were extracted from the images of the healthy and hypoxic mice. The 21 vessel network was chosen since it was the maximal network that could be identified with a one-to-one vessel map in both healthy and hypoxic animals. Network dimensions and connectivities were obtained using the segmentation protocol described by Ellwein et al. [11]. This protocol uses ITK-SNAP [33] to create a 3D geometry using semi-automated “snake evolution” in the regions of interest (the 21 vessels). The image pixel threshold was set at 45 to reduce artifact detection. Paraview (Kitware; Clifton Park, NY) was used to convert file types to vtk polygonal data (.vtp) allowing us to compute centerlines and connectivity using the Vascular Modeling ToolKit (VMTK [5]). The output from VMTK is a $n \times 4$ matrix representing each vessel by a unique set of coordinates $x_i \in \mathbb{R}^3$ ($i = 0, \ldots, n-1$) and the associated radius value, $r_i$, computed from the maximally inscribed sphere within the 3D vessel. For each vessel, the average radius $r_0$ was computed as the mean of all samples $r_i$ along the vessels, while the length, $L$, was calculated as the sum of the shortest distances ($l_i$) between successive points, giving

$$r_0 = \frac{1}{n} \sum_i r_i, \quad L = \sum_i l_i, \quad \text{where} \quad l_i = \sqrt{(\vec{x}_{i+1} - \vec{x}_i)^2}, \quad i = 0, \ldots, n - 1,$$

(1)
Table 1: Average hemodynamic characteristics (mean ± standard error) for the healthy and hypoxic animals.

|                | Healthy (n = 7) | Hypoxia (n = 5) |
|----------------|----------------|-----------------|
| HR (beats/min) | 533±1          | 559±8           |
| CO (ml/min)    | 10.7±0.6       | 9.2±0.3         |
| mPAP (mmHg)    | 13.4±1.2       | 22.2±1.0        |
| sPAP (mmHg)    | 20.2±1.4       | 32.3±1.4        |
| dPAP (mmHg)    | 8.0±1.2        | 14.0±1.0        |
| pPAP (mmHg)    | 12.2±0.5       | 18.8±1.2        |
| $Z_0$ (mmHg.min/ml) | 1.28±0.14   | 2.44±0.17      |

Abbreviations: Heart rate (HR), cardiac output (CO), mean pressure (mPAP), systolic pressure (sPAP), diastolic pressure (dPAP), pulse pressure in the main pulmonary artery (pPAP), total pulmonary vascular resistance ($Z_0$).

$n$ is the total number of samples for the vessel. Using the shared coordinates information, we used the “digraph” function in the Matlab (version 16a) to generate a connectivity map of the 3D structure (see Figure 2(d)). Both healthy and hypoxic networks have the same connectivity illustrated in Figure 2(d), yet the individual vessel radii and length vary as shown in Table 2. The actual unstressed radius (at zero pressure) used to describe the network geometry, is assumed to taper linearly with a factor $\zeta$ along the vessel length, i.e. $r_0(x) = \zeta r_0 + \xi$, where $\zeta$ and $\xi$ are chosen to ensure that $r_0(L/2) = r_0$ (in the center of the vessel).

### 2.2 Fluid Dynamics Model

Dynamics of blood pressure and flow in the pulmonary arteries are governed by the interaction of four major factors: (a) inertial and viscous forces generated by contraction of the heart stimulating motion of the blood, (b) elastic forces generated by interaction of the fluid and the vascular walls, (c) wave reflection within vessels due to tapering, at junctions, and from the outflow boundary representing the microcirculation, and (d) input impedance generated by the micro-circulation. In this study, we use a 1D fluid dynamics model to study pulmonary flow and pressure in healthy and hypoxic mice derived under the assumption that the blood is incompressible and that the flow is Newtonian, axisymmetric and has no swirl. Under these conditions, conservation of mass and momentum [30] can be predicted by

$$\frac{\partial A}{\partial t} + \frac{\partial q}{\partial x} = 0, \quad \frac{\partial q}{\partial t} + \frac{\partial}{\partial x} \left( \frac{q^2}{A} \right) + \frac{A}{\rho} \frac{\partial p}{\partial x} = -\frac{2\pi \nu r}{\delta} q,$$

where $x$ and $t$ are the axial and temporal coordinates, $p(x, t)$ (mmHg) is the blood pressure, $q(x, t)$ (ml/s) is the volumetric flow rate, $A(x, t) = \pi r^2$ (cm²) is the cross-sectional area and $r(x, t)$ (cm) is the vessel radius. The blood density $\rho = 1.057 \pm 0.004$ g/ml [40] and the kinematic viscosity $\nu = 0.0462$ cm²/s,
Figure 2: 1D network extraction: Illustration of segmentation process including: the micro-CT image (a), 3D smoothed network (b), centerline extraction (c), and the directed graph (Matlab) reflecting connectivity of vessels in the network but not their individual radius and length.

Table 2: Dimensions of vessels in the 21-vessel network.

| vessel index | connectivity | radius ($r_0$) (mm) | length ($L$) (mm) | Healthy | Hypoxic |
|--------------|--------------|----------------------|-------------------|---------|---------|
| 1*           | (2,3)        | 0.47                 | 4.10              | 0.51    | 3.58    |
| 2            | (4,5)        | 0.26                 | 4.45              | 0.25    | 4.03    |
| 3            | (6,7)        | 0.37                 | 3.72              | 0.37    | 3.08    |
| 4            | (8,9)        | 0.24                 | 2.41              | 0.25    | 2.92    |
| 5            | –            | 0.13                 | 0.52              | 0.17    | 0.65    |
| 6            | (14,15)      | 0.32                 | 2.02              | 0.28    | 1.60    |
| 7            | –            | 0.17                 | 2.12              | 0.19    | 0.93    |
| 8            | (10,11)      | 0.23                 | 3.11              | 0.26    | 2.06    |
| 9            | –            | 0.17                 | 1.77              | 0.17    | 0.51    |
| 10           | (12,13)      | 0.20                 | 2.62              | 0.22    | 2.37    |
| 11           | –            | 0.16                 | 0.69              | 0.17    | 0.88    |
| 12           | –            | 0.15                 | 1.40              | 0.19    | 1.27    |
| 13           | –            | 0.14                 | 0.62              | 0.15    | 0.51    |
| 14           | (16,17)      | 0.24                 | 0.81              | 0.25    | 1.20    |
| 15           | –            | 0.19                 | 1.84              | 0.19    | 1.55    |
| 16           | (18,19)      | 0.25                 | 0.83              | 0.24    | 0.71    |
| 17           | –            | 0.15                 | 3.02              | 0.18    | 1.68    |
| 18           | (20,21)      | 0.24                 | 4.69              | 0.26    | 3.55    |
| 19           | –            | 0.15                 | 1.77              | 0.18    | 1.86    |
| 20           | –            | 0.22                 | 1.78              | 0.24    | 2.24    |
| 21           | –            | 0.18                 | 0.55              | 0.19    | 1.069   |

* root vessel. Connectivity ($i,j$), $i$ denotes the left daughter and $j$ the right daughter.

Vessels indicated by – are terminal.
measured at shear rate of 94 s\(^{-1}\) \[53\], are assumed constant. The momentum equation is derived under the no-slip condition assuming that the wall is impermeable, that the velocity of the fluid at the wall equals the velocity of the wall. To satisfy this condition, we assume that the velocity over the lumen area is flat, decreasing linearly within the boundary layer with thickness \(\delta = \sqrt{\nu T/2\pi}\) \[19, 49\].

2.3 Wall Model

To close the system of equations, a constitutive equation relating pressure and cross-sectional area is needed. In this study, we compare two models. A linear elastic model derived from balancing the circumferential stress and strain, and an empirical nonlinear wall model (the Langewouters model \[16, 17\]).

Linear wall model. The linear wall model is derived under the assumption that wall is isotropic and elastic, that the vessels are cylindrical, and that the walls are thin (i.e. \(h/r \ll 1\) where \(h\) is the wall thickness). We assume that the loading and deformation are axisymmetric, and that the vessels are tethered in the longitudinal direction. Under these conditions, the external forces can be reduced to stresses in the circumferential direction, i.e. Laplace’s \[28\] and Hooke’s law translates the linear stress-strain relation as

\[
p - p_0 = \frac{Eh}{r_0} \left(1 - \sqrt{\frac{A_0}{A}}\right),
\]

where \(E\) is Young’s modulus in the circumferential direction, \(p_0\) (mmHg) and \(A_0\) (mm\(^2\)) denote the unstressed pressure and associated cross sectional area.

Nonlinear wall model. Langewouters’s empirical wall model \[16, 17\] relates pressure and area via the relation

\[
p - p_0 = p_1 \tan \left(\frac{A}{A_m} - \frac{\pi}{2}\right),
\]

where \(p_0\) is the unstressed pressure, \(A_m = \gamma A_0\), \(\gamma > 1\) represents the maximal lumen area, and \(p_1\) is half-width pressure \[9, 29\], the critical pressure on the pressure-area curve where the vessel compliance is halved and the vessel wall starts to saturate in response to a further increase in pressure.

2.4 Pulse wave velocity

The system of equations is hyperbolic in nature, as a result the pulse wave velocity (PWV) \(c(p)\) can be computed from eigenvalues \[2\] \(\lambda_{1,2} = q/A \pm c(p)\), where

\[
c^2(p) = \frac{A}{\rho} \frac{dp}{dA}.
\]

8
For the linear and nonlinear wall models, respectively

\[
\begin{align*}
\c^2(p)_{\text{linear}} &= \frac{1}{2\rho} \left( \frac{Eh}{r_0} - (p - p_0) \right), \\
\c^2(p)_{\text{nonlinear}} &= \frac{p_1}{\rho} \left( \tan^{-1} \left( \frac{p - p_0}{p_1} \right) + \frac{\pi}{2} \right) \left( 1 + \left( \frac{p - p_0}{p_1} \right)^2 \right) 
\end{align*}
\]

Note that, for the nonlinear wall model (7), the PWV increases with pressure whereas, for the linear wall model (6), PWV decreases with pressure. Moreover, note that at \( p = p_0 \), (6) and (7) reduce to the wave speed \( c_0^2 \) in undeformed state

\[
\begin{align*}
c_{0,\text{linear}}^2 &= \frac{1}{2\rho} \frac{Eh}{r_0}, \quad \text{and} \quad c_{0,\text{nonlinear}}^2 = \frac{\pi p_1}{2\rho} 
\end{align*}
\]

### 2.5 Boundary Conditions

Since the system of equations is hyperbolic, boundary conditions must be specified at the inlet and outlet of each vessel, i.e. the network needs an inflow condition, bifurcation conditions, and outflow conditions.

At the network inlet we specify a flow waveform extracted from hemodynamic data (see Figure 1). At junctions (all bifurcations in the network studied), we impose conservation of pressure and flow of the form

\[
p_p(L, t) = p_{d_i}(0, t) \quad \text{and} \quad q_p(L, t) = \sum_i q_i(0, T), \quad \text{for} \quad i = 1, 2, \tag{9}
\]

where, the subscripts \( p \) and \( d_i \) denote the parent and daughter vessels, respectively.

At the terminal vessels, a Windkessel model (an RCR circuit) is used to relate flow and pressure (see Fig. 2) predicting the outflow impedance \( Z_{wk}(L, \omega) \) given by

\[
Z_{wk}(L, \omega) \equiv \frac{P(L, \omega)}{Q(L, \omega)} = R_1 + \frac{R_2}{1 + i\omega CR_2}, \tag{10}
\]

where \( P(\omega) \) and \( Q(\omega) \) are the pressure and flow in the frequency domain, \( \omega = 2\pi/T \) is the angular frequency and \( T \) is the length of cardiac cycle. \( (R_1, R_2) \) denote the two resistors, and \( (C) \) the capacitor. For each vessel, the total peripheral resistance \( R_T = R_1 + R_2 \), with \( R_1 \) denoting the resistance of the proximal vasculature and \( R_2 \) the resistance if the distal vasculature, whereas \( C \) denotes the total compliance of the vascular region in question.

### 2.6 Parameter Values

Model parameters in this system describe: hemodynamics \( \theta_h = \{T, \nu, \rho, \delta, \zeta\} \), vessel wall stiffness \( \theta_w = \{E\} \) (linear wall model), \( \theta_w = \{p_1, A_m\} \) (nonlinear wall model), and outflow \( \theta_o = \{R_1, R_2, C\} \).
**Hemodynamic parameters** are assumed constant. The length of the cardiac cycle $T = 1/HR$ (ms) is extracted from data (mean HR values for each group is given in Table 1). The kinematic viscosity $\nu = 0.0462\text{cm}^2/\text{s}$, the density $\rho = 1.057$, and the boundary layer thickness $\delta = \sqrt{2\pi\nu/T}$ as discussed earlier. These values represent average values for mice [40, 53]. The vessel tapering factor $\zeta = 0.98$ (2% tapering) was optimized. The nominal value was obtained from analyzing behavior of the principal pathway.

**Vessel Wall stiffness parameter.** For the linear wall model, Young’s modulus $E$ is assumed constant for each vessel. A nominal value for $E$ can be estimated from estimates of the characteristic impedance $Z_c$ and linearization of (2) and (3) about the reference state, $p = p_0$, giving

$$Z_c = \frac{\rho c_0}{A_0} \iff c_0 = \frac{A_0 Z_c}{\rho},$$

where $c_0$ is the wave speed [8], $\rho$ is the blood density, and $A_0$ is the cross sectional area of the unstressed vessel. Substituting $c_0 = c_{0\text{linear}}$ from (8) into (11) gives

$$\sqrt{\frac{1}{2\rho}} \frac{Eh}{r_0} = \frac{A_0 Z_c}{\rho} \Rightarrow \frac{Eh}{r_0} = \frac{2(A_0 Z_c)^2}{\rho}.$$  

A value for $Eh/r_0$ is obtained from estimates of $Z_c$ approximated using the ‘up-slope method’ [10, 20, 39] from the slope of pressure-flow loop during early ejection (see Figure 3(a)).

Given the empirical nature of the nonlinear wall model, nominal parameters were set within physiological range, we let $p_1 = 25$ mmHg and $A_{rm} = 2.5A_0$ mm$^2$.

Substituting $c_0 = c_{0\text{linear}}$ from (8) into (11) gives

$$\sqrt{\frac{1}{2\rho}} \frac{Eh}{r_0} = \frac{A_0 Z_c}{\rho} \Rightarrow \frac{Eh}{r_0} = \frac{2(A_0 Z_c)^2}{\rho}. $$
Also, using the available pressure and flow data, local \( Z_c \) can be approximated for individual mice by implementing the ‘up-slope method’ [10, 20]. This estimates \( Z_c \) as the slope of pressure-flow loop during the early ejection phase (see Figure 3(a)). Substituting \( Z_c \) from the up-slope method into (13), we obtain the local approximation of \( Eh/r_0 \).

**Windkessel outflow condition parameters** must be computed for each vessel. A priori values for these parameters can be obtained from distributing the total peripheral resistance (PVR) \( R_T = \frac{p}{q} \), the ratio of the mean pressure \( p \) to the mean flow \( q \) (the cardiac output, given in Table 1), to each terminal vessel. For vessel \( j \), the total resistance is

\[
R_{T,j} = \frac{p}{q_j},
\]

obtained by assuming that the mean pressure \( p \) remains constant. The flow to vessel \( j \) can be estimated from applying Poiseuille’s law, recursively at each junction, giving

\[
q_{d_i} = \frac{\Omega_{d_i}}{\sum_i \Omega_{d_i}} q_p, \quad \text{where} \quad \Omega_{d_i} = \left( \frac{\pi r_i^4}{8 \mu L} \right)_{d_i}, \quad \text{for} \quad i = 1, 2.
\]

(14)

where \( q_{d_i} \) denote the mean flow to vessel \( i \). Similar to previous studies (REF), the total resistance is distributed as \( R_{1,j} = a R_{T,j} \) and \( R_{2,j} = (1-a) R_{T,j} \), where the priori value of \( a = 0.2 \).

Finally, as suggested by Stergiopulos et al. [43] total network compliance \( C_{T,j} \) is estimated by first estimating the time-constant \( \tau = R_T C_T \) to an equation of the form

\[
p_d(t) = p(t_d) \exp(- (t - t_d)/\tau),
\]

(15)

see figure 3(b). Assuming \( \tau = R_T C_T \) is constant for the entire network, the compliance for each vessel \( C_{T,j} \) is computed as

\[
C_{T,j} = \frac{\tau}{R_{T,j}}.
\]

(16)

### 2.7 Numerical Methods

Similar to previous studies [30, 31], the model was solved numerically using a two-step Lax Wendroff method. To match the model to data, the parameters inferred for the linear wall model were \( \theta = \{ E, a, \tau \} \) and for the nonlinear model were \( \theta = \{ p_1, A_m, a, \tau \} \). We used the function `fmincon` in Matlab under the Sequential Quadratic Programming (SQP) gradient-based method [7] to minimize the least squares error between computed and measured values of flow and pressure at inlet of the main pulmonary artery. Parameters were initialized using the nominal values and the algorithm was iterated until the convergence criterion was satisfied with a tolerance \(< 10^{-11} \).
2.8 Impedance and Wave Intensity Analysis

Similar to previous studies [37], for a further insight into the hemodynamics, we analyzed the wave intensity and impedance predictions. Wave intensity analysis allows us to quantify the type and nature of the reflected waves in the time domain whereas the impedance analysis provides a frequency domain signature, which as shown in Figure 1 differs between the two groups studied.

Impedance analysis (IA). Under the assumptions of periodicity and linearity, the pulsatile pressure and flow waveforms can be approximated by a Fourier series of the form

\[
\tilde{s}(t) = \bar{S} + \sum_{k=1}^{K} \text{Re}[S_k e^{i(\omega_k t + \varphi_k)}]; \quad n = 0, \ldots, N,
\]

where \(\tilde{s}(t)\) is the Fourier series approximation of the original waveform \(s(t)\), \(t_n = n/F_s\) is the time vector for a given sampling rate \(F_s\), \(T = N/F_s\) the period of \(s(t_n)\), \(N = 60 \times F_s/HR\), \(\omega_k = 2k\pi/T\) \((k = 1, \ldots, K)\) are the angular frequencies, \(\bar{S}\) is the mean of \(s(t_n)\), and \(S_k\) and \(\varphi_k\) (rad) are the moduli and phase spectra, associated with each harmonic \(k\), and \(K\) is the smallest resolution of harmonics required for the impedance analysis. Both, \(S_k\) and \(\varphi_k\), are defined in terms of \(a_k\) and \(b_k\), the coefficients of basic trigonometric Fourier series, i.e.

\[
S_k = \sqrt{a_k^2 + b_k^2}, \quad \varphi_k = \tan^{-1}(b_k/a_k),
\]

Setting \(s(t_n)\) as \(p(t_n)\) and \(q(t_n)\) in (17), the impedance spectrum, \(Z(\omega_k)\), can be computed as ratios of harmonics of pressure to flow by

\[
Z(\omega_k) = \frac{P(\omega_k)}{Q(\omega_k)} = \frac{\text{Re}[P_k e^{i(\omega_k t + \alpha_k)}]}{\text{Re}[Q_k e^{i(\omega_k t + \beta_k)}]} = \frac{P_k}{Q_k} \text{Re}[e^{i(\alpha_k - \beta_k)}] \equiv Z_k \text{Re}^{i\theta_k}, \quad (18)
\]

where \(P_k\) and \(Q_k\) are the moduli and \(\alpha_k\) and \(\beta_k\) the phase angles of the pressure and flow harmonics, respectively. \(Z_k\)s are the impedance moduli and \(\theta_k = \alpha_k - \beta_k\) the corresponding phases at a given frequency. Note if \(\theta_k < 0\) then the \(k^{th}\) pressure harmonic lags the \(k^{th}\) flow harmonic, and vice versa. The zeroth harmonic is the mean component known as the vascular resistance \((Z_0)\).

Wave intensity analysis (WIA) allows us to separate simulated waveforms into their incident (+) and reflected components (−). Assuming negligible frictional losses and setting \(q = A u\) where \(u\) is the fluid velocity, the incident and reflected waves can be approximated by

\[
\Gamma_{\pm}(t) = \Gamma_0 + \int_0^T d\Gamma_{\pm} : \Gamma = p \text{ or } u,
\]

where

\[
dp_{\pm} = \frac{1}{2}(dp \pm \rho c(p) du), \quad du_{\pm} = \frac{1}{2} \left( du \pm \frac{dp}{\rho c(p)} \right),
\]

(20)
and $c(p)$ is the PWV computed by [5]. Time-normalized wave intensity is defined as $WI_{\pm} = (dp_{\pm}/dt) (du_{\pm}/dt)$. $WI_+$ along with $dp_+ > 0$ or $dp_+ < 0$ identifies incident waves as compressive or decompressive, and similarly $WI_-$ along with $dp_- > 0$ or $dp_- < 0$ identifies reflected waves as compressive or decompressive, respectively. $WI_-$ indicates the presence of reflected compression or decompression waves corresponding to $dp_- > 0$ or $dp_- < 0$, respectively.

3 Results

This section presents results comparing hemodynamic simulations with experimental data under control (healthy) and hypoxic conditions using the linear and the nonlinear wall models. We first present results from predictions in the main pulmonary artery followed by a comparison of estimated parameter values, and results of wave intensity and impedance analysis. All results are shown for a representative healthy and hypoxic animal. For each group, the representative animal was chosen because its data was closest to the mean of the data analyzed (marked with a thick line on Figure 1).

Figure 4: Simulated pressure and flow in the main pulmonary artery (MPA) using linear (dashed line `-`) and non-linear (dashed dotted lines `-.`) wall models, both for the healthy (cyan) and hypoxic (magenta) hemodynamics. Solid black contours represent actual data, measured at one location only, i.e. the inlet of MPA. (a)-(d): simulated pressure at the inlet of MPA, (e)-(h): simulated flow at the mid point of MPA, (i)-(k): simulated pressure at multiple locations along the MPA.

**Hemodynamic simulations, health vs. hypoxia.** Figure 4 shows optimized simulation results (dashed lines) along with data (black solid lines) for a representative healthy and hypoxic animal. The left four panels show predictions of pressure (a, b) and flow (e, f) for the healthy animal, whereas the right panels (c, d, g, h) show similar results for the hypoxic animal. Pressure
graphs are plotted at the inlet of the main pulmonary artery corresponding to the simultaneously measured flow profiles imposed as inflow condition. It is expected that flow waveforms fit perfectly at the inlet of the main pulmonary artery since the measured waveforms were used as the inflow boundary conditions. Therefore, to observe the effects of model parameters on the flow, the flow graphs are plotted from the centre of the main pulmonary artery. Note that for all predictions the goodness of fit is excellent $R^2 > 0.9$. Predictions with the nonlinear model are slightly better than those obtained using the linear model, in particular the peak of the measured pressure wave is better predicted by the nonlinear wall model. While differences in pressure predicted using linear and nonlinear wall models are small at the inlet of the main pulmonary artery, the two wall models propagate pressure significantly different. In particular, for the healthy animal (compare panels (i) and (j)), whereas little difference can be detected for the hypoxic animal (compare panels (k) and (l)). This suggests that for the hypoxic mouse, the linear or nonlinear wall models are equally good predictors of measured hemodynamic but in the case of healthy mouse there is no clear choice can be made at this point.

Figure 5 provides further insight into the behavior of linear and nonlinear wall models depicting the corresponding pressure–area relationships in the MPA for a representative healthy and hypoxic mouse. As expected, for the healthy animal (panel (a)), the prediction of area as a function of pressure is concave down indicating that the vessels display increased stiffening with a decrease in vessel area. Moreover, note that for both wall models, the nonlinear model makes larger predictions of area at a given pressure than the linear wall model, although both models predict approximately same lumen area at the systolic pressure. For the hypoxic animal (panel (b)), the nonlinear wall model predicts a relatively linear pressure–area relation. The area predicted by nonlinear wall model is larger than the linear wall model throughout the hypoxic pressure regime. However, the gradient of the nonlinear wall model is smaller than that of the linear wall model, indicating a higher stiffness predicted by the nonlinear wall model.
Estimated parameters. Figures 6 summarize variation in optimized parameters, which are averaged over all animals within each group. Panels (a–d) in the top row present analysis of the vessel parameters including tapering factor ($\zeta$), stiffness from the linear wall model ($Eh/r_0$), half width pressure ($p_1$) and constant $\gamma$ that determines the maximal cross-sectional area using the nonlinear wall model. Panels (e–h) in the bottom row present analysis of the optimized Windkessel parameters. Results compare linear vs. nonlinear model and healthy vs. hypoxia.

As expected, the arterial stiffness and total peripheral resistance is higher in hypoxia, whereas the total peripheral compliance is lower (a,e,f). However, the nonlinear wall model predicts relatively small decrease in the total peripheral compliance during hypoxia. Moreover, the halfwidth pressure $p_1$ and the maximal cross-sectional area $A_m$ are also higher during hypoxia (b,c). The later can be explained by the relatively larger total cross-sectional area of the hypoxic network. Panel (d) shows that there is more variation in $\zeta$ across the population and on average the vessels taper more when the linear wall model is used. Finally, the characteristic time-scale $\tau$ is predicted to decrease during hypoxia for the linear wall model whereas an opposite behavior is observed in relation to the nonlinear wall model. Moreover, the graph in panel (g) indicates that the linear wall model predicts proximal resistance to be a small fraction of the total resistance both for the healthy and hypoxic animals. However, the linear wall models predicts an opposite behavior for the healthy and hypoxic groups to that of the nonlinear wall model. For the healthy animals, the linear wall model predicts a proximal resistance to be a smaller fraction of total resistance, which is not the case when the nonlinear wall model was used. Although the resistance ratio $a$ remains about the same during hypoxia for both wall models, the linear wall model predicts and increase in $a$ while the nonlinear wall model predicts a decrease in $a$ during hypoxia. In general, the linear wall model leads to more variation in parameter values across the group.

Impedance analysis The next set of graphs, shown in Figure 7, depicts the impedance moduli, $|Z|$, and phase, $\theta$, spectra for the healthy and hypoxic mice, using measured and simulated pressure and flow at the inlet of MPA. Similar to Figure 4, dashed lines show simulation results and solid black lines show data. The left two columns (a,b,e,f) show results from analysis of a representative healthy animal, while the right graphs (c,d,g,h) show results from a representative hypoxic animals. The impedance spectra were generated both for the linear and nonlinear wall models using equation (18) and plotted for first 13 harmonics excluding the mean component (zeroth harmonic). While time-varying simulations all fit data well ($R^2 > 0.9$), Figure 4 show characteristic differences between the linear and nonlinear wall models for the healthy animal. First, note that the zeroth frequency component is accurately predicted by both models, for both the healthy and hypoxic mice. Comparison of panels (a) and (b) shows that, in the healthy mouse, the nonlinear wall model better captures the low frequency response. In particular, the spike in the impedance moduli
Figure 6: Optimized parameters and their comparison. Box whisker plots represent the optimized values for the healthy and hypoxic groups. On each box, horizontal bar represents the population median whereas the marker represents the population mean, the edges of the box are the 25th and 75th percentiles, the whiskers extend to the most extreme data points the algorithm considers to be not outliers, and the outliers are plotted individually. Black vertical bars in panels (a,e,f,g) represent the mean±SD of the nominal parameters. Top: (a) stiffness ($Eh/r_0$), (b) half width pressure ($p_1$), (c) $\gamma = A_m/A_0$, (d) tapering factor $\zeta$. Bottom: (e) total periphery resistance ($R_T$), (f) total periphery compliance ($C_T$), (g) $a = R_1/R_T$, and (h) characteristic time-scale $\tau$.

at the 3rd harmonic (about 30 Hz) is clearly predicted by the nonlinear wall model. However, at higher frequencies, particularly after the 9th harmonic, the nonlinear wall model constantly deviates from the measured impedance. On the other hand, the linear wall model fails to predict an accurate frequency domain response in the healthy mouse but, compared to the nonlinear wall model, it also deviates less at the higher frequencies. A qualitatively similar observation can also be made for the associated phase oscillation related to the prediction from linear and nonlinear wall models. This should be contrasted with results from the hypoxic animal, where both models predicts the data well. The latter is likely because vessels in the hypoxic group are significantly stiffer than vessels in the healthy group (corroborated by higher value of $R_T$ shown in Figure 6) making the nonlinear effects of wall deformation insignificant.

Wave intensity analysis. Finally, we present results of the wave intensity analysis (WIA) on the simulated waveforms. WIA allows us to investigate the behavior of the local waves, both the incident and reflected waves, in the healthy and hypoxic mice for the linear and nonlinear wall models, respectively. Since the WIA requires measurement of dynamic cross-sectional area and PWV this analysis cannot be done on the experimental data.

Figure 8 shows the separation of the waveforms and the associated wave intensities. Panels (a-d) show the incident and reflected waves for the healthy mouse, for both wall models. It is clear from panel (a) that the amplitude predictions for both the incident and the reflected wave are bigger for the nonlinear wall model than the linear wall model. Further note that while the shape of
the incident pressure and velocity waves are similar for both wall models, the reflected pressure wave predicted by the nonlinear wall model is delayed. For the hypoxic mice (for both wall models), the separation of pressure waves in panel (c) reveals identical components of incident and reflected waves. Panel (d) shows that the linear wall model predicts bigger amplitudes of incident and reflected velocity waves. Panels (e)–(h) show the wave intensity profiles associated with the separated pressure and velocity waves. For the healthy mice, with linear wall model, the wave intensity profile consists of four waves: a forward compression, a forward expansion, and a backward compression waves. On the other hand, the nonlinear wall model reveals additional (unexpected) forward and backward compression waves with a sharp peak near the peak of ejection phase. This feature, is not present in results obtained for the hypoxic mice (panel (h)). Finally, it is worth noting that the both wall models predict a higher peak wave intensity for the hypoxic mice than for the healthy mice, and that the nonlinear wall model predicts displays a smaller peak wave intensity than the linear wall model.

4 Discussion

In this study, we developed and calibrated control and hypoxic models predicting pulse wave propagation in mice pulmonary arteries. We implemented and compared two wall models, a linear mechanistic model and a nonlinear empirical model. Results showed that for healthy mice, the nonlinear model predicted observed dynamics while, while in hypoxia both models could predict the data. The latter is likely a result of remodeling making vessels significantly stiffer in hypoxic mice.

Linear vs. Nonlinear wall model  It is well known that arterial deformation acts nonlinearily imposing increased stiffening with increased pressure [9, 18].
Figure 8: Wave intensity analysis comparing the effects of linear and nonlinear wall models on the patterns of wave reflections in the time domain, both for the healthy (a,b,e,f) and the hypoxic (c,d,g,h) mice. (a) and (c) show the separation of pressure wave into its incident and reflected components whereas (b) and (d) show separated velocity waves. Solid black curves represent the composite pressure and velocity waveforms. The associated wave intensity profiles are given in the bottom row. All these profiles were generated from the simulated waveforms.

Even though most studies confirming this behavior is done in systemic arteries, pulmonary arteries are composed of the same type of tissue and therefore should exhibit similar behavior. The advantage of the linear model developed here is that it can be derived from first principles, yet it exhibits the opposite behavior as illustrated by the green line in Figure 5(a). On the other hand, the nonlinear model is empirical in nature, yet it does include nonlinear stiffening with increased pressure, red line in Figure 5(a). Results showed that the two models act differently for the healthy mice, while results for hypoxic mice can be predicted with either model. Even though both models were able to predict observed dynamics in the main pulmonary artery, the two wall models interact differently with other model components including the vessel tapering factor, the vessel stiffness, and the parameters used to specify the Windkessel boundary conditions, making it challenging to compare the model output.

First, we note (Figure 4(j)) that simulations with the nonlinear wall model leads to pressure augmentation along the main pulmonary artery, which is further exaggerated in the downstream the network. The pressure augmentation is known to be an effect of vessel tapering, however in this case a small tapering with the nonlinear model leads to a significant amount of pressure augmentation. As a result pressure at the terminals are higher increasing the total resistance $R_T$ and decreasing the total compliance $C_T$ imposed at the end of the terminal vessels (Figure 6(e)). As for the linear wall model, although the model assumes overall higher tapering both for healthy and hypoxic mice, the pressure augmentation across the network is only slight. As a result the pressure is small at the terminal leading to low vascular resistance and high compliance.

The other key parameters separating the two models are the wall parameters describing the vessel stiffness. For the linear model, vessel stiffness is encoded in the factor $Eh/r_0$ corresponding to $p_1$ in the nonlinear model. Since both $Eh/r_0$
and $p_1$ has the same dimensions, these are qualitatively comparable parameters under a given condition. For this reason, both parameters assume higher values in the hypoxic animals indicating stiffer vessel. Values for $Eh/r_0$ for the linear model are higher, which is to be expected, as the model needs to compensate from lower downstream “resistance”, which is different from the nonlinear model that has more than one wall parameter $p_1$ and $A_m$ and hence $\zeta$, determining the vessel dynamics. In summary, the linear wall model achieves the system’s energy balance by global interaction of large arterial and vascular bed dynamics whereas the nonlinear wall model concentrates more on local vessel dynamics to achieve the same. In the case of hypoxic animal, overall dynamics is dominated by high arterial stiffness and therefore the behavior of both models closely follow each other.

**Impedance and wave intensity analysis**  As for the linear wall model, although it does not captures the systems’ low frequency response very well, yet it generally predicts a stable high frequency response and an expected wave intensity profile. Since there is only one wall parameter in the linear wall model, the optimization algorithm focuses on the tapering factor $\zeta$ and the distribution of proximal and distal resistance to fit the measured waveform (see Figure 6(d),g). Therefore the the vessel tapering plays a more active role when combined with the linear wall model.

The pressure augmentation observed with the nonlinear wall model can be further explained form its frequency analysis that shows systems’ unstable frequency response at higher frequencies, showing a successive impedance moduli increase (see Figure 7(b)). Moreover, the reflected pressure waveforms and the wave intensity profiles shown in Figure 8 indicate the presence of an unexpected backward compression wave in diastole. This can be explained by analyzing pressure-area graphs and the optimized parameter values. A larger cross–sectional area at diastole and pressure at systole, predicted using the nonlinear wall model in Figure 5 suggests more compliant large arteries. At the same time a reduction in peripheral compliance $C_T$ and an associated increase in total periphery resistance $R_T$. This suggests stiffer and more resistive vascular beds. The small tapering factor (implemented in both models), may explain the impedance mismatch observed at the boundary due to relatively compliant larger arteries and stiffer vascular beds is the prime source of artificial wave reflections, responsible an augmented pressure and frequency response. While simulating the hypoxic hemodynamics, increase in the half-width pressure $p_1$ combined with a relatively unaltered periphery compliance suggest that the nonlinear wall model modulates the large arterial stiffness to predict the high blood pressure. This further supports the argument that the nonlinear wall model accounts for stiffening locally, within the large vessels, whereas for the linear wall model stiffening mainly is facilitated by combination of vessel stiffening and the capacitance in the boundary conditions. The latter is explained by higher total resistance and lower compliance needed to fit measured waveforms for the linear model (see Figure 6). The modulation of larger arterial
stiffness minimizes the impedance mismatch observed in the healthy animals and therefore the systems frequency response more stable.

**Control vs. hypoxia** Comparison of simulations between the two groups (independent of the wall model) showed as expected that hypoxic animals had stiffer vessels than the healthy animals. Results showed that analysis of frequency response is also different. The low frequency response is more dynamic in the healthy animals than for the hypoxic animals, which have significantly stiffer arteries. In particular the third harmonic of impedance is more pronounced in the healthy animals.

Overall, hypoxia can be characterized by a more resistive and less compliant vasculature, which leads to high blood pressure in the pulmonary arteries. Moreover, for the hypoxic animals the differences in prediction using the two wall models are smaller, which is likely due to overall vasculature being significantly stiffer in hypoxia. In general the healthy animals show more variation than the hypoxic animals. This is to be expected, since hemodynamic adaptation related in healthy animal is more dynamic due high compliance. However, it must be considered that the linear and nonlinear wall models distribute the vascular resistance and stiffness (or compliance) through different mechanisms. Therefore the parameter inference and characterization of normal and remodeled vasculature can be different for same condition using each model.

**Model selection** One way to determine a better model choice is via statistical model selection criterion. Here we have two competing models, a fluid dynamic network model coupled with either a nonlinear wall model or a linear wall model with 6-dimensional and 5-dimensional parameter space, respectively. The 6-dimensional model is expected to provide a better fit to the data, as the residual sum of squares (RSS) is smaller when compared to the 5-dimensional model. However, lower RSS is not the selection criterion, since it would always lead to select a model with as many parameters as possible. Instead, a statistical criterion can be used that utilizes trade-off between goodness of fit and model complexity (i.e. number of parameters). To this end, we can use the Akaike Information Criterion (AIC) \[8\] and the Bayesian Information Criterion (BIC) \[42\] for model selection i.e.

\[
\text{AIC} = -2 \log(L) + 2n(\theta), \quad \text{BIC} = -2 \log(L) + n(\theta) \log N, \tag{21}
\]

where \(\log(L)\) is the maximum log-likelihood, \(n(\theta)\) is the number of parameters in the model and \(N\) is the total number of observations. Equations in (21) can be expressed in terms of RSS as

\[
\text{AIC} = \frac{\text{RSS}}{\sigma^2} + N \log \sigma^2 + 2n(\theta) + K, \quad \text{BIC} = \frac{\text{RSS}}{\sigma^2} + N \log \sigma^2 + n(\theta) \log N + K, \tag{22}
\]

\(^1\)Unless the optimization algorithm gets stuck in a local optimum.
where $K = N \log 2\pi$ is a constant. The model with a lower AIC and BIC is preferred. In (22), $N, n(\theta)$ and RSS are known but $\sigma^2$ is unknown, which is the error (noise) variance. We therefore take the inverse approach and calculate what noise variance would make us favor the 6D model over the 5D model. For the hypoxic mouse RSS= 23.16, $n = 1024, n(\theta) = 6$ for the nonlinear wall model (6-dimensional), and in the RSS= 79.66, $n = 1024, n(\theta) = 5$ for the linear wall model (5-dimensional). By substituting these values into (22), we get the following criterion:

- If $\sigma^2 < 28.25$ (signal-to-noise ratio (SNR) > 1.77), the 6D nonlinear wall model is preferred over the 5D linear wall model, according to AIC.
- If $\sigma^2 < 8.15$ (SNR > 6.15), the nonlinear wall 6D model is preferred over the linear wall 5D model, according to BIC.

Similarly, the healthy mouse gives

- If $\sigma^2 < 41.97$ (SNR > 0.35), the 6D nonlinear wall model is favored over the 5D linear wall model, according to AIC.
- If $\sigma^2 < 8.15$ (SNR > 6.15), the nonlinear wall 6D model is favored over the linear wall 5D model, according to BIC.

It should be noted that AIC and BIC are classical model selection criteria based on an asymptotical justification. More recent and more powerful criteria, like WAIC [51] and WBIC [52] (Watanabe, Journal of Machine Learning Research 14 (2013) 867-897), could be computed from MCMC simulations, but that would come with substantially increased computational costs.

Finally, it should be noted that the mice used for imaging were exposed to a slightly different protocol than the ones used in the hemodynamic studies. We anticipate that differences have small impact on computational studies. Both experiments were done in young adults, the severity of hypoxia is assumed similar, one dataset was under higher hypoxic conditions for a shorter time and the other was under lower hypoxic conditions over a longer period time. We expect that the error associated with variation in experimental protocol is not bigger than error associated with using a representative network as described in detail below.

## 5 Conclusion

In this study we have integrated imaging data with in vivo hemodynamic data and used parameter estimation methods to render a mouse specific and disease specific model to predict pressure in the large pulmonary arteries. The analysis in this study illustrates that the presented model and methods can predict the healthy and diseased pulmonary hemodynamics with high accuracy. In particular, the validation of simulated hemodynamics in the time and frequency
domain allows us to compare and infer the underlying factors causing hemodynamic changes due to hypoxia. Moreover, the linear or nonlinear wall models depend on the pressure regime required to be predicted. In a high pressure low compliance environment both models behave in an identical manner. However, in a low pressure and high compliance environment, the nonlinear wall model fit the pressure by modulating the local stiffness whereas the linear wall model modulates the global vascular stiffening as well as vascular geometry.

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