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Patient-Specific Computational Modeling of Blood Flow in the Pulmonary Arterial Circulation

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Abstract

Computational fluid dynamics (CFD) modeling of the pulmonary vasculature has the potential to reveal continuum metrics associated with the hemodynamic stress acting on the vascular endothelium. It is widely accepted that the endothelium responds to flow-induced stress by releasing vasoactive substances that can dilate and constrict blood vessels locally. The objectives of this study are to examine the extent of patient specificity required to obtain a significant association of CFD output metrics and clinical measures in models of the pulmonary arterial circulation, and to evaluate the potential correlation of wall shear stress (**WSS**) with established metrics indicative of right ventricular (RV) afterload in pulmonary hypertension (PH). Right heart catheterization (RHC) hemodynamic data and contrast-enhanced computed tomography (CT) imaging were retrospectively acquired for 10 PH patients and processed to simulate blood flow in the pulmonary arteries. While conducting CFD modeling of the reconstructed patient-specific vasculatures, we experimented with three different outflow boundary conditions to investigate the potential for using computationally derived spatially averaged wall shear Stress (**SAWSS**) as a metric of RV afterload. **SAWSS** was correlated with both pulmonary vascular resistance (**PVR**) ($R^2 = 0.77$, $P < 0.05$) and arterial compliance (**C**) ($R^2 = 0.63$, $P < 0.05$), but the extent of the correlation was affected by the degree of patient specificity incorporated in the fluid flow boundary conditions. We found that decreasing the distal **PVR** alters the flow distribution and changes the local velocity profile in the distal vessels, thereby increasing the local **WSS**. Nevertheless, implementing generic outflow boundary conditions still resulted in statistically significant **SAWSS** correlations with respect to both metrics of RV afterload, suggesting that the CFD model could be executed without the need for complex outflow boundary conditions that require invasively obtained patient-specific data. A preliminary study investigating the relationship between outlet diameter and flow distribution in the pulmonary tree offers a potential computationally inexpensive alternative to pressure based outflow boundary conditions.

Keywords

pulmonary hypertension; computational fluid dynamics; pulmonary vascular resistance; hemodynamics; boundary conditions; vessel diameter

INTRODUCTION

Pulmonary hypertension (PH) is a degenerative disease that eventually leads to right heart failure [1, 2]. In this work, we present a preliminary investigation of the role of wall shear stress (**WSS**), estimated by time averaged computational fluid dynamics (CFD), in PH disease progression. Previous studies have shown that **WSS** decreases in PH patients relative to healthy controls [3, 4], making it a potential comprehensive prognostic characteristic encompassing fluid flow kinematics, vessel wall structural mechanics, bulk hemodynamics, and an underlying biological response.

Biomechanics of PH

There are three primary domains in the PH pathological cardio-pulmonary system: RV, proximal pulmonary vasculature, and the distal pulmonary vasculature. The proximal arteries act as a hydraulic damper to the distal vasculature [5]. Endothelial cells lining the distal vessels respond to local flow conditions by adjusting their cross-sectional area [6], thereby influencing the local pressure, wave reflection dynamics [7], and arterial tension in the (upstream) proximal vasculature. Therefore, these two domains are undoubtedly coupled (each domain responds to and impacts the other) and must share common characteristics in the maintenance of total system behavior, likely having a synergetic effect on PH disease progression. Furthermore, given that proximal-distal pulmonary coupling influences wave reflection phenomena and distensibility, the interaction between these domains will strongly influence flow pattern formation in the proximal vasculature.

While PH originates in the pulmonary vasculature, the resulting lethality lies in the inevitable RV dysfunction that occurs as a result of increased afterload [8]. The steady and pulsatile components of afterload are believed to be dictated by distal constriction and proximal stiffness, respectively [2, 9]. Therefore, pulmonary vascular resistance (**PVR**) and compliance (**C**) are the dominating patient disease progression characteristics available from Right Heart Catheterization (RHC), which are indicative of both the resistive and reactive components of impedance [10], respectively. Therefore, these metrics must be strongly coupled to the local flow dynamics and continuum metrics (e.g., **WSS**) common to both domains.

Abnormal WSS Contributes to Disease Progression

Intrinsic pressure regulation mechanisms signal smooth muscle cells (SMC) to adjust conduit area and regulate blood flow to match the local perfusion needs of tissue [11]. Endothelial cells (EC) are responsible for maintaining homeostasis by sensing non-physiological flow and signaling SMC to adjust accordingly. Impaired endothelial response can lead to vascular disease [12] and initiate a destructive cycle that will ultimately lead to stiffening of the proximal pulmonary vessels and RV dysfunction [13]. Currently, it is not yet known what triggers the change that results in the pulmonary vasculature's inability to regulate pressure and vascular resistance. For intrinsic pressure regulation, EC release vaso-constrictors/dilators and control their orientation based on the pulsatility and mean direction of **WSS** [6, 12, 14]. Intramural stress and **WSS** can also alter gene expression and signal collagen synthesis to increase vessel thickness and decrease compliance [6, 15].

Inter-dependence between *PVR* and Compliance, and its impact on *WSS*

Pulmonary vascular compliance can be approximated as the ratio of the stroke volume to the pulse pressure (PP), which is known to be linearly proportional to the true compliance, but is a slight overestimation of the compliance calculated from the parameter optimization of a Windkessel model [16]. The stiffness of the proximal vasculature and resistance of the distal vasculature both contribute to RV afterload, and are linearly related [2]. Thus, the two metrics are not independent, as an increase in distal resistance will increase the proximal pressure, causing the vessel walls to be taut [15]. Moreover, prolonged exposure to elevated pressures will result in collagen synthesis, thereby altering the inherent mechanical properties of the proximal vessels [17] and undoubtedly weaken its ability to act as a hydraulic damper to the distal vasculature [18].

Computing *WSS* in the Pulmonary Vasculature and its Implication for PH

Pulmonary arterial flow patterns can be visualized from imaging modalities [19, 20] or predicted with computational models. 4D magnetic resonance imaging (MRI) is noisy and offers low temporal and spatial resolution, which is a shortcoming for estimating fluid shear. Computational models have been used previously to simulate the pulmonary flow dynamics [13]. They offer unparalleled advantages over reconstructing patient-specific flow patterns with 4D MRI, in terms of spatial and temporal resolution, and can be used to simulate pathological hemodynamic challenges.

Tang et al. [21] implemented CFD analysis to show that increased cardiac output (*CO*), resulting from exercise, results in an increase in *WSS*. Further computational work, comparing pulmonary hemodynamics in the PH patient population with a healthy dataset, revealed a decreased in *WSS* PH [4], which we recently correlated with an increase in impedance using a similar computational framework [22]. However, the considerations critical to computational modeling of the pulmonary vasculature or the mechanisms driving this *WSS* decrease remain unaddressed. Similarly, Hunter et al. [14] used computational modeling to show that mitigation of hypertension in pediatric patients can reduce *WSS*. They simulated the hemodynamics in the proximal pulmonary arteries of two patient-specific geometries. In one case, a decrease in *CO* and vascular stiffness as the result of a septal defect closure led to reduced *WSS*. In the second case, a decrease in distal resistance and vascular stiffness did not have a significant impact on *WSS*. Su et al. [23] used an ideal fluid-structure interaction (FSI) model to investigate the influence of stiffness on local hemodynamics. They found that chronic increases in pressure, likely due to increased distal resistance, resulted in decreased *WSS* in the proximal vasculature.

As all systematic changes associated with PH disease progression are strongly coupled to the *WSS* acting on the proximal and distal endothelium, we hypothesize that spatially averaged wall shear stress (*SAWSS*), estimated using a patient-specific CFD model, will decrease in patients with PH concomitant with the reactive and resistive components of RV afterload. If true, it is conceivable that changes in *WSS* precede morphological remodeling, thereby leading to significant breakthroughs in strategies for risk stratification, and frequently monitoring disease progression and treatment efficacy. Furthermore, *WSS* could dictate

pathological vs. adaptive vascular remodeling, alluding to disease reversibility and driving treatment decision making [24].

The Role of Computational Analysis in Clinical Evaluation

Clinicians must be equipped with tools for evaluating treatment efficacy that are reproducible, affordable, and minimally invasive for the patient. The current protocol for patients admitted with PH symptoms is to perform RHC [25] to measure CO , pressure in the main pulmonary artery (MPA), pulmonary capillary wedge pressure ($PCWP$) and, from these, compute PVR [26].

These metrics can give an indication of RV workload at the onset of PH, where regulation of RV function is typically homeometric [27]. RHC is invasive and occasionally requires the patient to be sedated. Therefore, essential RHC data is only available to the physician as a pre-treatment baseline and it may be unfeasible to obtain repeatedly for assessing disease progression and treatment efficacy. A fast and reliable CFD model would have a vast clinical application, but the feasibility and reliability of modern day CFD analysis in pulmonary hemodynamics remains largely unexplored.

Study Objectives

In this study, we present an efficient computational estimate of WSS in adult patients with PH and interrogate the association between computed $SAWSS$ with PVR (resistive impedance) and C (reactive impedance). We utilize the flexibility of computational modeling to identify patient phenotypes (e.g. morphology, hemodynamics) that dictate the relationship between computed $SAWSS$ and afterload. Furthermore, modeling is used to explain the flow distribution in a 6-generation pulmonary tree structure, which could be used in future modeling studies to dictate the outflow boundary condition and estimate local WSS in distal vessels. The overall goal of the present work is to utilize CFD for assessing WSS in pulmonary arterial geometries of human subjects with PH. As evidence shows WSS to decrease in PH patients when compared with healthy controls [4], the objectives of this work are two-fold: (i) to examine the extent of patient specificity required to obtain a significant association of CFD output metrics and clinical measures, and (ii) to evaluate the potential correlation of with established metrics indicative of RV afterload in PH. Particularly, we correlate WSS with the most clinically universal metric of RV workload: PVR . In addition, as RV workload and distal flow dynamics are also influenced by proximal compliance [5, 23] we show that $SAWSS$ can also be used to assess pulmonary vasculature characteristics that are typically associated with the reactive component of vascular impedance [10].

METHODS

Ten patients admitted to Allegheny General Hospital (Pittsburgh, PA) suspected of having PH underwent routine RHC. Table 1 shows measurements acquired during RHC, using a Swan-Ganz Standard Thermo-dilution Catheter, which were used to calculate PVR (Eq. (1)) and compliance (C) (Eq. (2)) [2]. Upon diagnosis of PH, disease severity and RV function were qualitatively assessed according to the World Health Organization Pulmonary Arterial Hypertension Function Classification.

$$PVR = \frac{mPAP - PCWP}{CO} \quad (1)$$

$$C = \frac{CO}{HR * PP} \quad (2)$$

In addition to RHC hemodynamics data, each subject underwent a contrast-enhanced CT scan. The images were used to create a virtual reconstruction of the pulmonary vasculature and pre-processing for CFD analysis, as illustrated in Fig. 1. CT images with a voxel size $0.68 \times 0.68 \times 1.25$ mm for all CT datasets were imported into Mimics 14.4 (Materialise, Leveum, Belgium) in DICOM format and a contrast window-level ratio was determined based on contrast clarity between blood vessels and airways. An iterative process of thresholding, region growing, and multiple slice editing was utilized to segment the vasculature of each image dataset up to the 6th generation of vessels, limited only by image resolution, considering the MPA as generation 0. Arteries were manually isolated from veins according to vessel orientation with respect to neighboring airways and continuity to the MPA. A 3D surface of the patient-specific vasculature was reconstructed from the segmented map and subjected to 0-3 iterations of smoothing. Finally, a centerline was computed for the vasculature and the surface exported to 3-Matic (Materialise, Leveum, Belgium), where the domain inlet and outlets were truncated perpendicular to the centerline, and each inlet and outlets extended approximately 10 times their hydraulic diameter (D_h).

Numerical Modeling

The pulmonary computational domain was discretized using ICEM-CFD (Ansys Inc., Canonsburg, PA). A tetrahedral mesh, progressively growing in element size from the endoluminal surface to the volume core, was generated for each patient-specific vasculature. A WSS-based grid independence study was conducted according to the protocol outlined in [13, 28]. Each patient-specific geometry varied in size and morphology, therefore requiring different mesh densities to generate the CFD models. Nevertheless, the consistent mesh parameter for each model was an allowable edge length of 0.84 mm for all meshes used in this study (see Fig. 2).

An implicit finite volume method (ANSYS Fluent, Canonsburg, PA), with a SIMPLE discretization scheme, was used to solve the governing equations (Eqs. 3-4):

$$\iint_S \vec{v} \cdot \vec{n} \, dS = 0 \quad (3)$$

$$\iint_S p \vec{v} \cdot \vec{n} \, dS = \iint_S \vec{T} \cdot \vec{n} \, dS \quad (4)$$

$$\bar{\vec{T}} = -P\bar{p}\bar{\vec{I}} + \mu \left[\left(\nabla \vec{v} + \nabla \vec{v}^T \right) \right] \quad (5)$$

where is $\vec{v}$ the velocity vector, $\vec{S}$ is the element surface area, $\vec{n}$ is the unit vector orthogonal to $\vec{S}$, ρ is the density (1.05 g/cm³), and $\bar{\vec{T}}$ is the stress tensor. In Eq. (5), p is the pressure, μ is the dynamic viscosity (0.035 Poise), $\bar{\vec{I}}$ is the unit tensor, and ∇ is the gradient operator. Blood is assumed to behave as a Newtonian fluid since patient-specific rheology was not available and typical vessels in the computational domain are larger than 0.5 mm in diameter to justify this assumption. Furthermore, applying the same rheological characteristics across the entire population might have an impact on the resultant **WSS** magnitude, but will likely have little impact on the correlations. Based on the range of **CO** and MPA diameters used in this study, the Reynolds number in the proximal pulmonary vasculature is less than 900 for all patient-specific models, justifying the use of a laminar flow assumption.

Constant flow rate simulations were carried out for each patient-specific model until the velocity and mass conservation non-dimensional residuals fell below 10^{-7} . The constant flow rate assumption has been shown reliable for computing mean and peak velocities and pressures representative of discrete time points in the cardiac cycle [29]. An additional validation was performed in which we compared **SAWSS** and time averaged **SAWSS** computed using a steady and a pulsatile flow simulation, respectively, with matching **CO** and geometry, respectively. The results showed a 3.6% difference, providing evidence that a constant flow rate assumption yields a small error compared to a pulsatile flow simulation. Furthermore, as no patient-specific transient velocity data was available for the PH subjects studied retrospectively in the present work, the constant flow inlet boundary condition allowed us to maintain patient specificity without having to assume a generic flow waveform for the inlet boundary condition. A Poiseuille velocity profile was imposed at each non-circular inlet by implementing a protocol based on Schwartz-Christoffel mapping, which we explain in detail in our previous work [30]. A no-slip boundary condition was assigned to the fluid-solid interface. Three different simulations were carried out for the reconstructed vasculature of each dataset: (1) a constant inlet flow rate (90 cm³/s) and zero-traction outflow boundary conditions; (2) a patient-specific inlet flow rate obtained from RHC **CO** measurements with zero-traction outflow boundary conditions; and (3) a patient-specific inlet flow rate with structured tree outflow boundary conditions.

Resistance-based Structured Tree Outflow Boundary Condition

Amongst the cohort of reconstructed patient-specific arterial vasculatures, the total number of truncated outlets in each computational model ranges from 90 to 274. To account for the unique distal resistance of a given truncation, the outflow boundary condition at each outlet must be specific to that outlet and to that subject. A resistance structured tree outflow boundary condition [31] allows for an analytical expression for the total resistance of the truncated vasculature, which is proportional to the outlet radius. In theory, the truncated tree distal to an outlet with a smaller radius would reach the capillaries sooner than a larger outlet, resulting in a larger total resistance. The present outflow boundary condition derives a relationship between outlet radius and distal arterial resistance, with patient specificity

derived from RHC data incorporated into the tree morphology. A complex pulmonary vascular tree consists of separate segments of blood vessels, starting with the main pulmonary artery, that are gradually decreasing in cross-sectional area with each generation. Each vessel contains a single inlet and outlet, but the outlet is typically perfusing two daughter vessels, unless that vessel is known as a “terminal” vessel. Each segment has a resistance, dictated by its length and radius (Eq. (6)), which contributes to the resistance of the tree.

Knowing the **PVR** and MPA diameter for a given patient, we attempt to create a hypothetical tree of the entire pulmonary vasculature. The geometry of the tree is characterized by two coefficients: α and β , which govern the decrease in cross-sectional area between a parent vessel and its daughter vessels (see Fig. 3a). The α and β coefficients are numerical values ranging from 0 to 1, where the area of a given vessel is a function of: α , β , the generation of the vessel with respect to the MPA (n), and the parent vessel's cross-sectional area. The following protocol was coded to create a patient-specific tree: (1) The area of the RPA ($n = 2$): $A_{RPA} = \alpha^n \cdot A_{MPA}$; (2) The area of the LPA ($n = 2$): $A_{LPA} = \beta^{n-1} \cdot A_{MPA}$. After creating the MPA and RPA, (3) any daughter right vessel area is given by $A_{right_daughter} = \alpha^{n+1}\beta^n \cdot A_{parent}$; and (4) any daughter left vessel area is given by $A_{right_daughter} = \alpha^n\beta^{n+1} \cdot A_{parent}$, where n is the generation of the parent vessel at any bifurcation. Steps 3 and 4 were repeated until reaching a preset minimum radius, which was considered the terminal vessels. Figure 3a shows an exemplary tree, extending to the 5th generation. The objective of this protocol is to find α and β for each patient, such that the resistance of the resulting tree is equal to the **PVR** measured from RHC. Once α and β have been identified, a tree can be generated at any CFD model outlet given the outlet's cross-sectional area, thereby allowing to estimate a resistance that is unique for each outlet in a patient-specific geometry.

The Structured Tree as the Outflow Boundary Condition

Assuming a fully developed, laminar flow in all distal vessels, the resistance of each vessel was computed using Eq. (6), where the length-to-radius (l/r) ratio was found from human lung morphometric data [32] and μ is the blood dynamic viscosity at normal hematocrit (3.5 cP). Ohm's law is used to determine the total resistance by equating an electrical analog to the reconstructed tree:

$$R = \frac{8\mu}{\pi r^3} \left(\frac{l}{r} \right) \quad (6)$$

Once a unique tree structure was determined for each dataset, based on the subject's arterial anatomy and **PVR**, the patient-specific α and β values were used to calculate **PVR_i**, the pulmonary vascular resistance of the tree distal to each (i) truncated outlet (see Fig. 3b). Therefore, a unique structured tree was developed for each subject – with a unique hyperbolic function (see Fig. 4) relating outlet cross-sectional area and the resistance distal to a given outlet.

Calculating the unique resistance at each outlet (PVR_i) from the structured tree, the pressure to volumetric flow rate relationship applied to each outlet is given by Eq. (7):

$$P_i = PVR_i Q_i + PCWP \quad (7)$$

The PVR at a given outlet, PVR_i , is an approximation of the resistance distal to each truncation, as a function of the outlet cross-sectional area. In each numerical iteration, P_i is a uniform pressure applied to each outlet facet and Q_i is determined by numerically integrating the velocity vectors over the outlet area. $PCWP$ is a constant approximation of left atrial pressure, unique to each subject, obtained from RHC measurements. Upon carrying out the CFD simulations, the PVR function is iteratively adjusted by a multiplication constant (< 1) to achieve the RHC-measured pressure in the MPA [33].

Post-Processing

A single quantitative metric, assumed to be independent of the 3D reconstruction, was chosen to represent the WSS acting on the pulmonary vasculature. In Eq. (8), the WSS magnitude is integrated over the entire discrete vascular luminal area (A), and normalized by the total area to minimize the influence of arbitrary distal truncation. As the number of generations of the pulmonary tree varied among computational models, and considering that the surface area of the distal generations is substantially larger than the proximal ones, this normalization led to a metric independent of CT image resolution:

$$SAWSS = \frac{1}{A} \int_A WSS dA \quad (8)$$

Due to the limited in-plane resolution, isolated computational cells in the distal vasculature yielded non-physiological, high focal WSS . During post-processing, facets with WSS greater than 50 dyn/cm² were considered anomalies product of the image resolution and were not included in the $SAWSS$ calculation. The 50 dyn/cm² threshold was chosen as previous work [21] suggests that this is an approximate physiological maximum in healthy subjects. Furthermore, incremental increases of this threshold, i.e. beyond 50 dyn/cm², revealed insignificant changes in $SAWSS$.

Statistical Analysis

The statistical significance of all correlations is indicated with a two-tailed probability. A correlation within a 95% confidence interval ($P < 0.05$) was considered to be statistically significant.

RESULTS

Traditional Clinical Qualitative/Quantitative Assessment of the Patient Cohort

A trained cardiologist's assessment of RV morphology on echocardiograms revealed substantial RV remodeling and function changes in patients with high PVR . For example, the subject with the highest PVR (1,316 dyn·s/cm⁵) presented a severely dilated RV with severe RV dysfunction. The subject with the second highest PVR (777 dyn·s/cm⁵) showed a mild to moderately dilated RV with severe systolic dysfunction. Finally, a third subject with

elevated **PVR** (408 dyn-s/cm⁵), but relatively low compared to the first two, revealed normal RV size and systolic function. Some subjects with lower **PVR**, but elevated relative to healthy **PVR**, still revealed moderate hypertrophy and systolic dysfunction. Therefore, within our dataset, **PVR** offered an inconsistent prognostic indication of the RV's functional characteristics.

Since is **mPAP** a key clinical metric used to diagnose PH, assess reactivity, and monitor disease progression, we investigated its association with both components of impedance in our population sample. **mPAP** revealed a moderate positive correlation with the resistive component of afterload (**PVR**: $R^2 = 0.53$, $P < 0.05$ – see Fig. 5a) and a reasonably good negative correlation with the reactive component of afterload (**C**: $R^2 = 0.80$, $P < 0.05$ – see Fig. 5b). Therefore, **mPAP** increases concurrently with an increase in resistance and stiffness.

Patient Specificity in the Calculation of Wall Shear Stress

Figure 6 shows exemplary **WSS** maps obtained for four PH patient-specific models, which typically reveal high **WSS** concentrations in the small, distal vessels. Figure 7a shows a power regression correlation between **SAWSS** and **C** ($R^2 = 0.63$, $P < 0.05$), and **SAWSS** and **PVR** ($R^2 = 0.77$, $P < 0.05$), for simulations implementing patient-specific inlet velocity and the structured tree outflow boundary conditions. Figure 7b shows the same correlations (**SAWSS** vs. **C**: $R^2 = 0.60$, $P < 0.05$ and **SAWSS** vs. **PVR**: $R^2 = 0.72$, $P < 0.05$) for similar simulations but with a zero-traction outflow boundary condition. Figure 7(c) reveals poor correlations **SAWSS** of with **C** and **PVR** (**SAWSS** vs. **C**: $R^2 = 0.34$, $P > 0.05$ **SAWSS** and vs. **PVR**, $R^2 = 0.30$; $P > 0.05$) when the only patient-specific characteristic of the model was the arterial geometry. Thus, each simulation illustrated in Fig. 7c was carried out with an inlet flow rate of 90 cm³/s and zero-traction outflow boundary conditions. Interestingly, the correlation factors between RHC-measured **CO** and **PVR**, and **CO**, were 0.45 ($P < 0.05$) and 0.08 ($P > 0.05$), respectively (not shown in Fig. 7). Therefore, a CFD analysis that considers the combined effect of **CO** and the patient-specific vascular geometry as a means to calculate **SAWSS** yields a stronger correlation with the two primary indicators of RV afterload than **CO** alone. The correlations in Fig. 7 suggest that decreases in **PVR** correspond to increases in **SAWSS**. Secondly, increases in **C** estimated from RHC data reveal a corresponding increase in **SAWSS**.

Does elevated **PVR** contribute to a decrease in **WSS**?

We performed an additional study involving a single vascular geometry with the same inlet flow condition as the other patient-specific models, but subject to two different outflow resistance boundary conditions. The overall resistance was varied by a coefficient (1 or 0.5) multiplying the equation shown in Fig. 4 that relates outlet area with resistance. Figure 8 shows that a higher distal **PVR** causes a flattened velocity profile (lower profiles in Figs. 8c-e) in both the proximal and distal vessels, thus leading to an overall decrease in **SAWSS**.

Is the Structured Tree Outflow Boundary Condition Necessary?

Given the relatively little difference between simulations implementing the structured tree and zero-traction outflow boundary conditions, we performed a second, brief, study to

determine the impact of these boundary conditions on flow distribution in the pulmonary vasculature. We based it on a single healthy volunteer (i.e., not included in the PH study) who had no available RHC data and the reconstructed vasculature resulted in 274 outlets. Figure 9 shows the relationship between outflow and hydraulic diameter for 3 outflow boundary conditions: (1) zero traction; (2) constant resistance at all outlets; and (3) structured tree outflow. While the outflow boundary condition has little impact on the flow distribution in the proximal vessels, the CFD model reveals a substantial impact on flow distribution in the higher generation (i.e., distal) vessels. Unlike zero traction and constant resistance, the structured tree condition leads to a different correlation of outlet hydraulic diameter and outlet volumetric flow rate (Q).

DISCUSSION

The data presented in this study is sufficient to reject the null hypothesis and confirm that **SAWSS**, estimated by CFD simulations with a constant flow rate, changes in PH manifestation concurrent with changes in afterload. Furthermore, as opposed to imaging modalities with limited spatial resolution (e.g. 4D MRI), CFD analysis can offer the resolution necessary for a reliable estimate of **SAWSS**, which is improved as boundary conditions are more representative of the patient-specific hemodynamic environment.

SAWSS Correlation with *PVR* and *C*

In this study, flow and pressure data was retrospectively acquired for 10 patients diagnosed with PH. Furthermore, a chest contrast-enhanced CT scan was done for each patient within days of the RHC procedure and the pulmonary vasculature reconstructed from the CT images to conduct CFD analysis.

Because mPAP is currently a key clinical prognostic value in diagnosing PH and assessing disease progression and reactivity, we compared how it relates to both metrics of afterload. RHC data revealed moderate correlations between mPAP and two primary factors that are indicative of RV afterload: compliance (*C*) and pulmonary vascular resistance (*PVR*), which are measures of the reactive and resistive components of pulmonary vascular impedance, respectively. The correlation of mPAP with *C* is not surprising, as the calculation of compliance is a function of systolic PAP, which correlates well ($R^2 = 0.91$) with mPAP. However, unlike vascular stiffness [34], mPAP is a poor predictor of mortality [35] and the mPAP correlation with *PVR* is relatively weak, which might suggest that mPAP is not a particularly reliable estimate of RV afterload and that it is likely also a product of the *CO*. Most importantly, the endothelium is subjected to a hemodynamic environment that is poorly explained by mPAP. Therefore, it offers little insight into risk stratification, RV-PA decoupling (the ability of the RV to accommodate an increase in afterload with an increase in contractility), or RV function.

To arrive at a metric more representative of the hemodynamic environment, we investigated the relationship between **SAWSS** and RV afterload by comparing how it correlated with *PVR* and *C*. Tang et al. [4] showed that computationally measured **WSS** is decreased in adult PH, when compared against a healthy control population, which we recently correlated with impedance [22]. Truong et al. [3] used phase-contrast MRI to confirm the same finding

in pediatric patients. Finally, Barker et al. [36] re-evaluated adult PH patients using 4D MRI further confirming the same outcome. As PH is generally associated with increased *PVR* and decreased *C*, our results are consistent with these previous findings, but also directly correlate *WSS* to measures of RV afterload.

Computed *SAWSS* correlated well with clinical *PVR* and *C*, suggesting that *SAWSS* plays an important role in possibly dictating, or is dictated by, RV afterload and has the potential to be an invaluable clinical metric. The correlations for both metrics (*PVR* and *C*) with *SAWSS* are non-linear. This is somewhat intuitive considering that both resistance and compliance must be asymptotic and bound within some physiological limit. Noteworthy is that the distal resistance used in the structured tree outflow boundary condition dictates the flow split rather than total pulmonary resistance, as it was iteratively tuned to yield the RHC measured inlet pressure (mPAP). The strong correlation of *SAWSS* with *PVR* and *C* suggests that: (1) as endothelial cells lining the pulmonary vasculature have been shown to respond to shear by proliferation and the release of vasoactive agents, a change in *SAWSS* could be partially responsible for the cycle that perpetuates the progression of the disease [13]; and (2) *SAWSS* derived from CFD analysis could be used as a non-invasive alternative to *PVR* and *C* for assessing disease progression.

Given the relationship between *WSS* and vascular remodeling (e.g., proliferation and collagen synthesis) [6], the correlation found between *SAWSS* and *C* offers further evidence that circumferential stress [15] is only partially responsible for triggering this mechanism. Furthermore, morphological changes to tortuosity [37] and diameter only further act to alter local flow dynamics, thus possibly strongly perpetuating the disease cycle.

While *CO* is certainly a significant contributor to the relationship between *SAWSS* and disease progression (increasing afterload), it is important to consider the coupling relationship between proximal flow patterns and distal resistance. Given the aforementioned cellular response to flow, proximal flow patterns undoubtedly contribute to the vascular dysfunction that leads to increasing *WSS*. However, computational modeling shows that an increase in *PVR* causes a flattened velocity profile in the proximal and distal vasculature (as seen in Fig. 8), causing a further decrease in *WSS*. Furthermore, some patients in the current cohort were in the latent phases of the disease, undergoing adaptive RV remodeling and preserved *CO*. Therefore, particularly in latent PH, it is likely that an increase in afterload causes the initial decrease in *WSS*, which is later exacerbated in manifest PH by a decrease in *CO*.

Relationship between Vessel Diameter and Flow

The CFD model of the healthy control subject was used to assess the relationship between D_h and Q in the pulmonary vasculature. Previous attempts to investigate this relationship only considered the influence of diameter of the vessel of interest. Considering an idealized vascular tree with a fully developed laminar flow assumption, the minimization principle [10] leads to a volumetric flow rate that is proportional to the local vessel diameter. The diameter-flow relationship found by Horsfield and Woldenberg [38] used diameter measurements made from a cast of an inflated lung, but did not consider the influence of the

proximal arterial geometry or distal resistance in dictating the flow distribution. Both techniques yielded a relationship of the power-law form with a power of 2.3 [38] or 3.0 [10]. Two of our models, using a zero-traction or constant resistance outflow boundary condition, revealed a power-law relationship within the range reported in the aforementioned studies. When implementing a structured tree to dictate the flow distribution, the flow-diameter relationship drastically changed to almost linear and the flow was more evenly distributed among the various generations of pulmonary arteries. This might be explained by the fact that the zero-traction and constant resistance simulations only made use of the patient-specific geometry to dictate the flow distribution, while the structured tree simulation calculated the flow distribution based on geometry and the inversely proportional Q vs. PVR relationship. This finding suggests that our current understanding of the diameter-flow relationship in vascular trees might be more complex than originally thought. Additional work is required before implementing this knowledge as a computational outflow boundary condition. Specifically, because it appears that distal resistance is not the only contributing factor, we infer that proximal vessel geometry and respiratory motion must also significantly influence the flow distribution.

CFD as a Clinical Tool

We compared the $SAWSS$ vs. PVR and $SAWSS$ vs. C correlations for simulations with various combinations of inflow/outflow boundary conditions. Our results suggest that the correct patient-specific inflow condition significantly contributes to the inversely proportional relationship between $SAWSS$ and PVR , and that the influence of proximal geometry alone is secondary.

Remarkably, the CFD simulations that incorporated both patient-specific CO and geometry resulted in $SAWSS$ with a significantly stronger correlation to both metrics of RV afterload compared to geometry alone. Thus, suggesting a synergetic effect of CO and geometry on the ensuing $SAWSS$ appears to be intuitive considering that WSS in a vessel is a function of the local velocity, cross-sectional area, and conduit curvature. Moreover, as patient-specific CO can be measured using non-invasive techniques (e.g., Doppler ultrasound or velocity-encoded magnetic resonance imaging), $SAWSS$ obtained without the use of complex structured tree outflow BCs that require RHC input data shows promise as a future estimate of RV afterload. However, based on a the flow modeling study performed with a single vascular geometry, flow distribution in the distal vessels could be highly dependent on the outflow BC, while possibly having minimal effect on the area-integrated WSS . Therefore, the estimation of patient-specific outflow BCs should be considered in future CFD studies of the pulmonary arteries.

Study Limitations and Future Work

The primary limitation of the present work is the lack of experimental validation of the CFD results. Therefore, within this limitation, the practical outcome of this work is that a CFD-estimated flow metric, dictated by the patient-specific geometry and boundary conditions, appears to correlate with metrics of RV afterload with high statistical significance. A true validation of the current model would be comparison with an in-vivo flow imaging modality (e.g. 4D MRI [19, 20]), which was not available for the current dataset as MRI is not a part

of the standard of care follow-up protocol for PH. The fact that the computationally derived flow metrics correlate with RHC data is a promising finding. Furthermore, the correlations improve as we add patient specificity to the boundary conditions. While this is not indicative of an in-vivo validated CFD model, it demonstrates that computationally obtained flow characteristics offer prognostic value for PH.

Another limitation of the present work, and of any study involving CFD in the pulmonary vasculature, is that the arbitrarily chosen point to truncate the vessels could have an impact on the overall CFD results. We have discussed this limitation, originating from the limited clinical image resolution, in our previous work [13]. Furthermore, our computational model did not include compliant vessels. This assumption has been shown to impact the resulting **WSS** [39], and would have strong implication on the computed hemodynamics, particularly for a pulsatile flow simulation.

The CFD models used in this work were based on constant flow rate conditions. As temporal patient-specific inlet flow waveforms were unavailable, we avoided using a generic inlet flow profile while limiting the simulation parameters to clinically available patient data. However, as the input parameters are representative of time averaged flow conditions, the calculated **SAWSS** is also time averaged and oscillatory flow indices are unavailable.

Correlations of oscillatory shear stress derived indices with clinical **PVR** and **C** could further enhance the importance of CFD as a non-invasive tool for assessing RV afterload in PH patients. Moreover, we did not include the effects of blood-vessel interaction or respiratory motion in the computational models, which should provide more accurate predictions of **SAWSS**. Lastly, the present predictions of **SAWSS** originate from the use of 10 patient-specific PH models; the statistical significance of the results described herein can be assessed by extending the work to a larger population size. However, the two-tailed p-values were below 0.05 for **SAWSS** correlations with **PVR** and **C**, making these statistically significant with $n = 10$ subjects.

The aforementioned limitations are important to consider in future work, but are reasonable considering the relatively little attention dedicated to hemodynamics modeling in the pulmonary vasculature. Moreover, in spite of these limitations, we present compelling correlations of **SAWSS** and metrics of RV afterload, suggesting great potential for future studies.

These should investigate if **WSS** is the cause or effect of the degenerative cycle that ultimately leads to advanced PH. If **WSS** is the effect, it becomes important to identify its prognostic sensitivity to the disease. In this study, we showed that using a structured tree outflow boundary condition combined with a patient-specific derived inflow boundary condition leads to a strong correlation between **SAWSS** and metrics of RV afterload. If both an individual outflow boundary condition and the computational domain can be derived from serial imaging, **SAWSS** has the potential for being an alternative to RHC data and a metric of disease progression and treatment efficacy.

CONCLUSION

Spatially averaged wall shear stress (**SAWSS**) computed from patient-specific CFD models is inversely correlated with distal pulmonary vascular resistance and compliance in subjects with pulmonary hypertension. In addition, **SAWSS** is statistically correlated with afterload when considering only patient specific geometry and **C**. Implementing a structured tree outflow boundary condition in the CFD model further improves this correlation because elevated distal resistance acts to flatten the velocity profile in all generations of the vascular tree. Therefore, this could be the mechanism for the initial decrease in **WSS**, seen in latent PH, which would engage a “snowball” effect consisting of increasing **PVR** + decreasing **CO** = decreasing . Finally, we offer preliminary evidence that previous flow-diameter relationships derived from experimentation or through mathematical formulations should not be directly applied for estimating flow in the pulmonary vasculature. Identifying the ideal relationship between flow distribution and outlet area could be used to significantly decrease the computational cost of these simulations and estimate **WSS** in the distal vessels.

NOMENCLATURE		
<i>TERM</i>	<i>DESCRIPTION</i>	<i>UNIT</i>
<i>CFD</i>	Computational Fluid Dynamics	
<i>FSI</i>	Fluid-Structure Interaction	
<i>PH</i>	Pulmonary Hypertension	
<i>RV</i>	Right Ventricle	
<i>R²</i>	Coefficient of Determination	
<i>RHC</i>	Right Heart Catheterization	
<i>MPA</i>	Main Pulmonary Artery	
<i>mPAP</i>	Mean Pulmonary Arterial Pressure	mmHg
<i>sPAP</i>	Systolic Pulmonary Arterial Pressure	mmHg
<i>dPAP</i>	Diastolic Pulmonary Arterial Pressure	mmHg
<i>PP</i>	Pulse Pressure = sPAP – dPAP	mmHg
<i>PVR</i>	Pulmonary Vascular Resistance	dyn·s/cm ⁵
<i>WSS</i>	Wall Shear Stress	dyn/cm ²
<i>SAWSS</i>	Spatially Averaged Wall Shear Stress	dyn/cm ²
<i>CO</i>	Cardiac Output	cm ³ /s
<i>BSA</i>	Body Surface Area	m ²
<i>CI</i>	Cardiac Index	cm ³ /s/m ²
<i>HR</i>	Heart Rate	beats/min
<i>PCWP</i>	Pulmonary Capillary Wedge Pressure	mmHg
<i>C</i>	Compliance	cm ³ /mmHg
<i>A</i>	Vascular Luminal Area	cm ²
<i>D_h</i>	Hydraulic Diameter	cm

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REFERENCES

1. Nauser TD, Stites SW. Diagnosis and treatment of pulmonary hypertension. *Am Fam Physician*. 2001; 63(9):1789–1798. [PubMed: 11352291]
2. Wang Z, Chesler NC. Pulmonary vascular wall stiffness: An important contributor to the increased right ventricular afterload with pulmonary hypertension. *Pulm Circ*. 2011; 1(2):212–223. [PubMed: 22034607]
3. Truong U, Fonseca B, Dunning J, Burgett S, Lanning C, Ivy DD, Shandas R, Hunter K, Barker AJ. Wall shear stress measured by phase contrast cardiovascular magnetic resonance in children and adolescents with pulmonary arterial hypertension. *J Cardiovasc Magn Reson*. 2013; 15:81. [PubMed: 24034144]
4. Tang BT, Pickard SS, Chan FP, Tsao PS, Taylor CA, Feinstein JA. Wall shear stress is decreased in the pulmonary arteries of patients with pulmonary arterial hypertension: An image-based, computational fluid dynamics study. *Pulm Circ*. 2012; 2(4):470–476. [PubMed: 23372931]
5. Scott-Drechsel D, Su Z, Hunter K, Li M, Shandas R, Tan W. A new flow co-culture system for studying mechanobiology effects of pulse flow waves. *Cytotechnology*. 2012; 64(6):649–666. [PubMed: 22526489]
6. Ando J, Yamamoto K. Effects of shear stress and stretch on endothelial function. *Antioxid Redox Signal*. 2011; 15(5):1389–1403. [PubMed: 20854012]
7. O'Rourke MF. Vascular impedance in studies of arterial and cardiac function. *Physiological reviews*. 1982; 62(2):570–623. [PubMed: 6461866]
8. Bellofiore A, Chesler NC. Methods for measuring right ventricular function and hemodynamic coupling with the pulmonary vasculature. *Ann Biomed Eng*. 2013; 41(7):1384–1398. [PubMed: 23423705]
9. Wang Z, Chesler NC. Role of collagen content and cross-linking in large pulmonary arterial stiffening after chronic hypoxia. *Biomech Model Mechanobiol*. 2012; 11(1-2):279–289. [PubMed: 21538012]
10. Zamir, M. *The Physics of Pulsatile Flow*. Springer-Verlag; New York, US.: 2000.
11. Hall, JE. *Textbook of Medical Physiology*. Saunders, Elsevier; Philadelphia, PA.: 2011.
12. Ando J, Yamamoto K. Vascular mechanobiology: endothelial cell responses to fluid shear stress. *Circ J*. 2009; 73(11):1983–1992. [PubMed: 19801852]
13. Kheyfets VO, O'Dell W, Smith T, Reilly JJ, Finol EA. Considerations for numerical modeling of the pulmonary circulation—a review with a focus on pulmonary hypertension. *J Biomech Eng*. 2013; 135(6):61011–61015. [PubMed: 23699723]
14. Hunter KS, Lanning CJ, Chen SY, Zhang Y, Garg R, Ivy DD, Shandas R. Simulations of congenital septal defect closure and reactivity testing in patient-specific models of the pediatric pulmonary vasculature: A 3D numerical study with fluid-structure interaction. *J Biomech Eng*. 2006; 128(4):564–572. [PubMed: 16813447]
15. Humphrey JD. Mechanisms of arterial remodeling in hypertension: coupled roles of wall shear and intramural stress. *Hypertension*. 2008; 52(2):195–200. [PubMed: 18541735]
16. Muthurangu V, Atkinson D, Sermesant M, Miquel ME, Hegde S, Johnson R, Andriantsimivona R, Taylor AM, Baker E, Tulloh R, Hill D, Razavi RS. Measurement of total pulmonary arterial compliance using invasive pressure monitoring and MR flow quantification during MR-guided cardiac catheterization. *Am J Physiol Heart Circ Physiol*. 2005; 289(3):6.

17. Schreier D, Hacker T, Song G, Chesler N. The role of collagen synthesis in ventricular and vascular adaptation to hypoxic pulmonary hypertension. *Journal of biomechanical engineering*. 2013; 135(2):021018. [PubMed: 23445063]
18. Scott D, Tan Y, Shandas R, Stenmark KR, Tan W. High pulsatility flow stimulates smooth muscle cell hypertrophy and contractile protein expression. *Am J Physiol Lung Cell Mol Physiol*. 2013; 304(1):L70–81. [PubMed: 23087017]
19. Reiter G, Reiter U, Kovacs G, Kainz B, Schmidt K, Maier R, Olschewski H, Rienmueller R. Magnetic resonance-derived 3-dimensional blood flow patterns in the main pulmonary artery as a marker of pulmonary hypertension and a measure of elevated mean pulmonary arterial pressure. *Circulation. Cardiovascular Imaging*. 2008; 1(1):23–30. [PubMed: 19808511]
20. Fenster BE, Schroeder JD, Hertzberg JR, Chung JH. 4-Dimensional cardiac magnetic resonance in a patient with bicuspid pulmonic valve: characterization of post-stenotic flow. *Journal of the American College of Cardiology*. 2012; 59(25):e49. [PubMed: 22698496]
21. Tang BT, Fonte TA, Chan FP, Tsao PS, Feinstein JA, Taylor CA. Three-dimensional hemodynamics in the human pulmonary arteries under resting and exercise conditions. *Ann Biomed Eng*. 2011; 39(1):347–358. [PubMed: 20640512]
22. Kheyfets V, Thirugnanasambandam M, Rios L, Evans D, Triston S, Schroeder T, Mueller J, Murali S, Lasorda D, Spotti J, Finol E. The role of wall shear stress in the assessment of right ventricle hydraulic workload. *Pulm Circ*. 2015; 5(1):90–100. [PubMed: 25992274]
23. Su Z, Hunter KS, Shandas R. Impact of pulmonary vascular stiffness and vasodilator treatment in pediatric pulmonary hypertension: 21 patient-specific fluid-structure interaction studies. *Comput Methods Programs Biomed*. 2012; 108(2):617–628. [PubMed: 21975085]
24. Dolan JM, Kolega J, Meng H. High wall shear stress and spatial gradients in vascular pathology: a review. *Ann Biomed Eng*. 2013; 41(7):1411–1427. [PubMed: 23229281]
25. Stringham R, Shah NR. Pulmonary arterial hypertension: an update on diagnosis and treatment. *Am Fam Physician*. 2010; 82(4):370–377. [PubMed: 20704168]
26. Dorrington KL, Talbot NP. Human pulmonary vascular responses to hypoxia and hypercapnia. *Pflugers Arch*. 2004; 449(1):1–15. [PubMed: 15322849]
27. de Vroomen M, Cardozo RH, Steendijk P, van Bel F, Baan J. Improved contractile performance of right ventricle in response to increased RV afterload in newborn lamb. *Am J Physiol Heart Circ Physiol*. 2000; 278(1):H100–105. [PubMed: 10644589]
28. Prakash S, Ethier CR. Requirements for mesh resolution in 3D computational hemodynamics. *J Biomech Eng*. 2001; 123(2):134–144. [PubMed: 11340874]
29. Steinman DA, Hoi Y, Fahy P, Morris L, Walsh MT, Aristokleous N, Anayiotos AS, Papaharilaou Y, Arzani A, Shadden SC, Berg P, Janiga G, Bols J, Segers P, Bressloff NW, Cibis M, Gijzen FH, Cito S, Pallares J, Browne LD, Costelloe JA, Lynch AG, Degroote J, Vierendeels J, Fu W, Qiao A, Hodis S, Kallmes DF, Kalsi H, Long Q, Kheyfets VO, Finol EA, Kono K, Malek AM, Lauric A, Menon PG, Pekkan K, Esmaily Moghadam M, Marsden AL, Oshima M, Katagiri K, Peiffer V, Mohamied Y, Sherwin SJ, Schaller J, Goubergrits L, Usera G, Mendina M, Valen-Sendstad K, Habets DF, Xiang J, Meng H, Yu Y, Karniadakis GE, Shaffer N, Loth F. Variability of Computational Fluid Dynamics Solutions for Pressure and Flow in a Giant Aneurysm: The ASME 2012 Summer Bioengineering Conference CFD Challenge. *J Biomech Eng*. 2013; 135(2):021016. [PubMed: 23445061]
30. Chandra SC, Raut SS, Jana A, Biederman RW, Doyle M, Muluk SC, Finol EA. Fluid structure interaction modeling of abdominal aortic aneurysms: the impact of patient specific inflow conditions and fluid/solid coupling. *J Biomech Eng*. 2013; 135(8):81001–81014. [PubMed: 23719760]
31. Olufsen MS. Structured tree outflow condition for blood flow in larger systemic arteries. *Am J Physiol*. 1999; 276(1):H257–H268. [PubMed: 9887040]
32. Huang W, Yen RT, McLaurine M, Bledsoe G. Morphometry of the human pulmonary vasculature. *J Appl Physiol*. 1996; 81(5):2123–2133. [PubMed: 8941537]
33. Spilker RL, Feinstein JA, Parker DW, Reddy VM, Taylor CA. Morphometry-based impedance boundary conditions for patient-specific modeling of blood flow in pulmonary arteries. *Ann Biomed Eng*. 2007; 35(4):546–559. [PubMed: 17294117]

34. Gan CT, Lankhaar JW, Westerhof N, Marcus JT, Becker A, Twisk JW, Boonstra A, Postmus PE, Vonk-Noordegraaf A. Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. *Chest*. 2007; 132(6):1906–1912. [PubMed: 17989161]
35. van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, Boonstra A, Marques KM, Westerhof N, Vonk-Noordegraaf A. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *Journal of the American College of Cardiology*. 2011; 58(24):2511–2519. [PubMed: 22133851]
36. Barker AJ, Roldan-Alzate A, Entezari P, Shah SJ, Chesler NC, Wieben O, Markl M, Francois CJ. Four-dimensional flow assessment of pulmonary artery flow and wall shear stress in adult pulmonary arterial hypertension: Results from two institutions. *Magnetic Resonance in Medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. 2014
37. Kulik TJ, Clark RL, Hasan BS, Keane JF, Springmuller D, Mullen MP. Pulmonary arterial hypertension: what the large pulmonary arteries tell us. *Pediatric Cardiology*. 2011; 32(6):759–765. [PubMed: 21455751]
38. Horsfield K, Woldenberg MJ. Diameters and cross-sectional areas of branches in the human pulmonary arterial tree. *The Anatomical Record*. 1989; 223(3):245–251. [PubMed: 2923275]
39. Scotti CM, Jimenez J, Muluk SC, Finol EA. Wall stress and flow dynamics in abdominal aortic aneurysms: finite element analysis vs. fluid-structure interaction. *Computer Methods in Biomechanics and Biomedical Engineering*. 2008; 11(3):301–322. [PubMed: 18568827]

HIGHLIGHTS

- We applied computational fluid dynamics modeling to 11 pulmonary vascular trees
- Patient-specific cardiac output is necessary to obtain accurate wall shear stress
- Spatially averaged wall shear stress is highly correlated with pulmonary vascular resistance
- Spatially averaged wall shear stress is highly correlated with arterial compliance
- Structured-tree outflow boundary conditions improve these correlations

Figure 1.

Protocol for conducting patient-specific CFD analysis. CFD analysis is performed on the patient-specific vasculature reconstructed from CT scans yielding velocity (V_x , V_y , V_z , in the x, y, z directions, respectively) and pressure throughout the computational domain. In the Pre-Processing step, each outlet is extended by ten diameters and a volumetric non-uniform grid is generated during the meshing step.

Figure 2.
WSS grid independence study results for an exemplary reconstructed pulmonary vasculature.

(a)

(b)

Figure 3.

Structured tree outflow boundary condition: (a) a patient-specific model's unique α and β are determined to reconstruct the entire pulmonary vasculature equivalent to the RHC-measured PVR ; (b) schematic of structured tree outflow boundary condition applied to three outlets of the computational domain. Reproduced with permission from [31].

Figure 4. Schematic showing how the structured tree outflow boundary condition computes a patient-specific function that relates outlet radius to the outflow resistance at that radius (example shown using $\alpha = \beta = 0.67$).

(a)

(b)

Figure 5.

Linear regression correlations of mPAP with *PVR* (a) and Compliance (b). *PVR* calculated from Eq. (1) revealed a linear correlation with mPAP of $R^2 = 0.53$. Compliance calculated from Eq. (2) revealed a linear correlation with mPAP of $R^2 = 0.80$. The two-tailed probability of all given correlations are below 0.05 ($P < 0.05$).

Figure 6. Exemplary CFD results, illustrating a WSS map for a patient-specific geometry simulated with a structured tree outflow boundary condition and patient-specific *CO*. Note: WSS is bounded at 50 dyn/cm².

Figure 7.

Correlation of SAWSS with PVR and Compliance: (a) correlation when using patient-specific inlet CO and structured tree calculated from RHC-measured PVR; (b) correlation

when using patient-specific inlet CO and zero-traction outflow BC; (c) correlation when using an inlet CO = 90 cm³/s and zero-traction outflow boundary condition. Note: Patient-specific HR was measured during CT scan.

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Figure 8.

Computational evidence of a flattened velocity profile in the proximal and distal vessels of the pulmonary vasculature with elevated PVR. The simulations were carried out using a structured tree outflow boundary condition on the geometry shown in (a). Local WSS is largely dependent on the gradient of the velocity profile (u/z) shown in (b). (c-e) show that the velocity profile is flattened for a larger PVR (lower curves) in the proximal and distal vessels.

Figure 9.

Outlet volumetric flow rate (Q) vs. hydraulic diameter (D_h) for simulations conducted with (a) a healthy patient-specific vasculature (anterior and posterior views) for a Poiseuille inlet velocity profile corresponding to a constant flow rate of $95 \text{ cm}^3/\text{s}$ and three outflow boundary conditions: (b) zero traction; (c) a constant $40 \text{ dyn}\cdot\text{s}/\text{cm}^2$ resistance at all outlets; and (d) a structured tree. The Q vs. D_h relationship from the structured tree model is shown fitted to both power and linear regression curves. This patient-specific model consisted of 274 outflow boundary surfaces.

PH subject population data reviewed for the current study. WHO refers to the World Health Organization functional classification of PH progression.

Table 1

Subject	Age	Gender	WHO	sPAP	dPAP	mPAP	PCWP	BSA	CI = CO/BSA	HR
1	50	M	II	28	17	21	13	1.8	2.2	80
2	65	F	III	73	19	39	10	1.9	3.7	73
3	63	F	III	76	21	46	20	1.9	2.6	80
4	62	M	III	51	17	29	11	2.2	2.5	64
5	50	M	II	52	16	30	6	2.1	3.6	74
6	59	M	III	59	23	38	17	2.1	3.3	72
7	59	F	III	48	20	30	11	1.6	4.9	77
8	67	M	IV	90	30	52	2	2.1	1.5	72
9	50	M	III	43	25	33	21	2.3	2.3	82
10	56	M	II	57	22	35	3	2.2	1.8	64