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Computational Simulation of the Pulmonary Arteries and its Role in the Study of Pediatric Pulmonary Hypertension

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Abstract

The hemodynamic state of the pulmonary arteries is challenging to routinely measure in children due to the vascular circuit's position in the lungs. The resulting relative scarcity of quantitative clinical diagnostic and prognostic information impairs management of diseases such as pulmonary hypertension, or high blood pressure of the pulmonary circuit, and invites new techniques of measurement. Here we examine recent applications of macro-scale computational mechanics methods for fluids and solids – traditionally used by engineers in the design and virtual testing of complex metal and composite structures – applied to study the pulmonary vasculature, both in healthy and diseased states. In four subject areas, we briefly outline advances in computational methodology and provide examples of clinical relevance.

Introduction

The pulmonary circulation serves the vital function of delivering blood for oxygenation. Due to its location – it is contained almost entirely within the lungs – its characterization is frequently more invasive than that of the systemic circulation, particularly with regards to pressure. This invasive nature alone is problematic, but children face additional difficulties in a catheterization lab such as exposure to ionizing radiation, and younger children must frequently be under general anesthesia. However, a definitive diagnosis of a disease such as pulmonary hypertension (PH), which is chronic elevation of pulmonary pressures, can currently only be made through invasive measurement of main pulmonary artery pressure (mPAP)[1]. Noninvasive methods to measure PH severity include echocardiographic imaging (echo) and magnetic resonance imaging (MRI); however echo can only provide screening level diagnostics, while MRI is frequently too expensive for general use at many institutions. Diagnosis and management of pediatric PH suffers from these limitations.

An inability to routinely measure physical phenomena, due either to cost or difficulty, has been a driving force for the development of computational mechanics methods. These methods, which saw their modern birth during the 1960s in the simulation of aerospace

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structures, are now sufficiently advanced to tackle the constitutive, geometric, and rheological complexities inherent in living systems. Computational mechanics applied to the pulmonary circuit offers the possibility of simulating existing vascular scenarios in order to obtain more detailed information (such as shear or flow efficiency) or to predict future vascular scenarios that may come into existence due to surgical intervention or other treatment. Many reviews of vascular mechanics already exist, covering experimental and computational fluid dynamics (CFD) [2,3]; flows in flexible tubes [4] or stenosed vessels [5]; computational challenge problems [6]; surgical optimization and risk evaluation [7]; patient-specific mesh creation [8]; and even one already covering certain aspects of pulmonary simulation [9]. Here we review recent advances in computational fluid and solid macro-scale mechanics which have relevance towards the pulmonary circulation and PH. These advances hold promise to significantly improve the simulation and prediction of pulmonary vascular behavior, which in turn may lead to improved – and less invasive – diagnosis and treatment of pediatric PH.

Advances in Pulmonary Vascular Computational Modeling

We researched this article by performing electronic literature searches on both PubMed (publicly available at <http://www.ncbi.nlm.nih.gov/pubmed/>) and the Thomson/Reuters ISI Web of Science (available through subscription at many academic institutions, <http://www.isiknowledge.com>). Key word searches included: pulmonary or pulmonary hypertension, combined with: computational; finite element; computational fluid; numerical; simulation; solid or fluid mechanics. The bibliographies of established articles were also examined for other relevant papers and reviews. We limit this work to approximately the past ten years and, unless the advance may be generally applied, to pulmonary-specific works. Four subject areas emerged from these searches: distal vasculature morphology and associated function; boundary conditions or more specifically, coupling of different model types; constitutive behavior, i.e. how the vessel wall deforms under loading; and blood-wall interaction. These topics are briefly reviewed below, each followed by a discussion of clinical and basic science observations that motivate further advances in computational fluid and solid mechanics.

Distal Morphology

Pulmonary vascular resistance (PVR), equal to the pressure drop across the pulmonary circuit divided by the blood flow through it, has long been the definitive PH diagnostic [1,10]. Elevations in PVR are associated with distal vasoconstriction, remodeling, proliferation, or other effects [11]. These distal pathologies, which all affect distal vascular diameter or overall flow area of the distal pulmonary circulation, are primarily responsible for increases in mPAP (and afterload) in PH. Thus, afterload is strongly dependent on the geometry and structure – the morphology – of the distal circulation.

Many examinations of structure/function in the distal vasculature utilized symmetric or self-similar fractal trees, which are problematic in that they are not true representations of pulmonary branching and lack compete orientation information. Such details were needed by Burrowes et al [12] for their studies of function. Extending their previous bronchi model, they developed a branching model of the distal circulation that started with patient-specific proximal vascular morphology based on multidetector row computed tomography imaging, and completed the distal tree structure based on “growing” bifurcating tress with supernumerary vessels towards points in a grid cloud representative of the lung acinar structure. This procedure produced average morphology results that were in good agreement with several sets of direct lung measurements, although detailed, generation by generation comparisons were not provided. When a simple flow model was applied, the model structure

displayed much greater flow heterogeneity compared to a typical symmetric branching structure. The group used this model to explore the impacts of gravity [13], orientation (with gravity) [14], and species (humans and sheep) on flow distribution at acinar locations within the lung. The first two of these were found to minimally affect mean flow at distal locations, suggesting that the branching structure most strongly influences flow distribution; similarly, differences between flow distributions in man and sheep were primarily due to differences in branching asymmetry, i.e. differences in structure. Additionally, Clark, Burrowes and Tawhai [15] proposed a lung perfusion model based on the observation that vascular tree generations as high as the 8th (with the 1st corresponding to the smallest non-capillary vessels, i.e. terminal arterioles) can have 1st generation daughter branches. Thus by their model, capillary sheets may connect arterioles and venules at much higher structural generations than previously considered. When subjected to constant flow, this “ladder-like” structure of parallel capillary sheets displayed reduced PVR, a smaller pressure drop across the capillary sheet, and a higher rate of flow (for a given pressure difference) compared to the traditional (symmetric) model in which capillary sheets only connect terminal (1st generation) vessels.

Clinical Significance

Distal pulmonary vascular morphology cannot be imaged due to its small size, but has been quantified in several human lungs with several slightly different generational numbering techniques (for a brief comparison, see [16]), enabling the construction of distal tree models based purely on these direct measurements. However, the total number of human lungs thus investigated is quite small. Models of distal structure may provide a more patient-specific ability to study distal perfusion heterogeneity, capillary recruitment, and gas exchange. As computational power improves, coupling large vessel models (as detailed below) with such distal models may enable, for example, the study of vasodilator drug transport into the pulmonary tree and vascular reactivity.

Fluid Boundary Conditions / Model Coupling

The pulmonary vasculature is comprised of millions of vessels; due to requirements on time or computing resources, pulmonary simulations can obviously consider only part of the tree. While vessel walls provide natural model boundaries for blood flow, truncating vessel at some arbitrary longitudinal position requires proper handling of flows and pressures at the point of truncation, so that realistic results may still be obtained within the region of interest, or primary model. Early modeling attempts would enforce constant pressure or simple time-varying flow conditions at these primary model boundaries. Obviously, such simple *boundary conditions* (BCs) are not good physical representations of the complex systems (heart, vessels) that lie outside the primary model.

In the past ten years BCs have evolved considerably: they now couple the primary model to separate, simpler models that actually incorporate reduced physics of the neglected portions of the circulation – so they aspire to properly account for the afterload provided by the distal vessels, or how each ejected stroke volume travels down the vasculature (i.e. pulse or flow propagation), or how the heart responds to changes in afterload. The models themselves are fairly well known in clinical circles: Windkessel [17] or “transmission-line” [18] models (TLMs) are used to provide the afterload of the distal vasculature in the form of mechanical impedance, while the time-varying elastance model of ventricular contraction [19,20] is used to simulate heart function. In practice, the primary model is frequently a *distributed* model, in the sense that it considers spatial variations in material properties, geometry, flow, and/or material deformation, while simplified models can be distributed or *lumped*, meaning they represent only global behavior.

Distal Vasculature

Windkessels, or lumped models of the distal pulmonary circulation, had been used as pulmonary vascular model BCs in the 1980s and 1990s, and provide a simple 2-4 parameter representation of afterload [17]. However, consistent with clinical complaints regarding their use [21], they do not properly model pulse wave propagation in the vasculature, and thus produce non-physical wave reflections within the region of interest when used as a BC; additionally, although they have few parameters and are thus easily “fit” to a particular afterload, the parameters have no relationship to any physiological aspects of the vasculature. In contrast, a TLM model is an assembly of physiologically realistic arterial segments, each with defined geometry and elasticity.

Overcoming the Windkessel limitations on wave propagation at the boundary was the motivation for Olufsen [22] and Olufsen et al [23], who coupled one-dimensional (1D) equations describing the distributed flow and wall displacements in the larger systemic arteries to multiple TLMs that provided simplified models of the loads due to small artery and capillary networks, such as appear in organs. The TLM geometries were defined by structured, bifurcating trees, their flows and pressures were governed by the wave equation, and their solid mechanics described by an experimental compliance curve. Comparing this new BC first to Windkessel-based and resistance-only BCs, each applied at the end of a simple tube model, they showed that the TLM BC resulted in greater phase differences between pressure and flow throughout the tube, displayed reduced wave reflection at the exit boundary of the 1D model, and included high-frequency oscillations seen in vascular input impedance data taken from real human subjects. Further, when multiple TLMs were used to bound a more geometrically realistic 1D model of the systemic circulation, the resulting coupled model predicted flows in good agreement with clinical flow time histories measured with MRI in nine selected systemic arteries.

Model coupling has continued to evolve since this first application: almost immediately after Olufsen's work, Quarteroni et al [24] described a two-dimensional (2D) mathematical framework in which distributed flow models could be coupled to lumped parameter models. This introduced the idea of interface conditions between two fluid models, rather than considering a simpler model as a mere boundary condition to a primary model. Formaggia et al [25] then modeled blood flow in a cylindrical geometry, in two distributed models of different dimensionality (three-dimensional (3D) and 1D), and included the effects of wall deformation. Although their results were examined in a constant diameter straight tube, the implications were clear: the same advantages noted by Olufsen when coupling a 1D distributed model to a TLM were also seen when coupling more spatially intricate (3D) models to a 1D model. Thus, coupling at multiple dimensional scales of vascular modeling were defined; what remained was to describe the general mathematical formulation for coupling. This description was provided shortly thereafter (via the method of weighted residuals, the standard approach for developing finite element methods) by Vignon and Taylor [26], and Vignon-Clementel et al [27] for coupling any simple outlet model to 1D or 3D distributed models, respectively. They demonstrated in both 1D and 3D systemic models that use of constant pressure exit conditions detrimentally affected the prediction of both pressure and flow, and thus wall shear stress. Vignon-Clementel et al [28] have also recently updated their formulation for the treatment of coupled 3D fluid-structure systems.

Two pulmonary specific examples of proximal-to-distal model coupling exist. Spilker et al [29] coupled a 1D finite-element fluid model, with geometry derived from 3D images of the proximal pulmonary arteries, to multiple TLM models of the distal vasculature that were based on in-vitro measured morphology data [16]. A TLM, as used in their work and elsewhere, parameterizes the afterload of an arterial structure with specific diameters, lengths, and compliances; as such, it may be “tuned” to provide different input impedance

(e.g. afterload) conditions by changing those parameters. Through iteratively tuning their distal TLM model resistances, their coupled model well replicated flow splits and mPAP measured with MRI and invasive catheters, respectively, in a pig model of pulmonary stenosis. They further demonstrated the predictive capability of this method through modeling the repair of an apparent left pulmonary artery stenosis in a 16-year old boy with repaired tetralogy of Fallot; the model suggested that stenosis repair would not beneficially improve hemodynamics. These simulations were completed in very short order (< 20min), making their use in surgical planning a more realistic possibility.

In a second pulmonary-specific example, Clipp and Steele [30] also coupled a 1D finite element fluid model, with geometry based on casts of lamb pulmonary vessels, to TLM models in order to explore the effects of respiration on pulmonary hemodynamics. To account for breathing, a global respiration factor f_c or spatially-specific respiration factors f_p were introduced to vary the TLM impedance across all boundary exits or for exits in specific portions of the modeled lung, respectively. Additionally, other TLM parameters, such as the ratio of the artery segment length to its radius (LRR), and the parent to daughter ratio (k), were allowed to vary to achieve the optimal fit of the simulated main pulmonary artery pressure time history to one experimentally measured in a lamb model. Use of an optimization algorithm yielded both parameter estimates and excellent agreement between the modeled and measured pressure time histories, although only modest agreement existed between measured and modeled MPA input impedance at higher frequencies.

Heart Function

In order to study the impacts of varying afterload on ventricular function, Segers et al [31] coupled a 4-element Windkessel lumped model of the vasculature to a time-varying elastance lumped model of the heart. The coupled system, which also incorporated valve resistance, consisted of only three ordinary differential equations, with five and four parameters characterizing the heart and vasculature, respectively. Elastance parameters were either directly taken or simply derived from pressure-volume conductance catheter measurements in the LV of a pig or RV of a dog, while Windkessel parameters were obtained through iterative means [32] from aortic or pulmonary artery pressure time histories. Predicted aortic and LV pressure time histories over a single cardiac cycle were in excellent agreement with their equivalent in-vivo time histories, while predicted pulmonary and RV pressure time histories displayed good agreement. They have since used this model to simulate the degree to which increased vascular resistance and reduced vascular compliance cause the LV to decouple from the aorta [33], although both works are somewhat limited in their representation of afterload due to the use of Windkessel models. Although no other RV-pulmonary coupling models exist, the computational framework for coupling a time-varying elastance model to distributed models, namely a 1D finite-element model of the systemic network (Formaggia et al [34]) and to a patient-specific, 3D model of the Aorta (Kim et al [35]), have been developed, and demonstrate the great utility of coupling this heart model with more advanced computational methods.

Clinical Significance

Computational simulations of surgical interventions, such as the total cardiopulmonary connection (TCPC) or the Fontan procedure (also reviewed in this volume), have demonstrated how to increase connection efficiency and even have defined new surgical standards [7]. In this application of computational mechanics, different model geometries may be tested for energy (pressure) losses; clearly the most energy conserving flow system is vital for children with single-ventricle anomalies. However, as was demonstrated [26,27], constant pressure or flow boundary conditions do not provide as good of predictive simulation as do more advanced, coupled models. The vast majority of single-ventricle

simulations to date have used simple BCs [36], suggesting there remains much advocacy and modeling work to be done to improve clinical applicability.

Inclusion of more realistic heart function would provide additional indicators of surgical success including estimates of myocardial efficiency and ventricular-vascular coupling, both from predicted ventricular pressure-volume behavior [37]. Including such measures along with vascular efficiencies in any evaluation process would properly consider heart function in the prediction of heart failure, and shift focus towards the diagnosis of the whole, coupled cardiovascular system.

In the context of surgical optimization or simply providing more hemodynamic detail, accuracy in velocity (and in turn, flow) is necessary for prediction of wall shear stress (WSS). “Abnormal” or “elevated” WSS has been cited numerous times in the last ten years as integral to the PH disease process [38,39], based on many in-vitro studies which associate it with pathological cellular signaling [40,41,42,43,44], but it has only seldom been actually measured [45,46] due to the difficulty in measuring the complete velocity field required for its calculation. Computational models of the pulmonary vasculature can provide WSS values, which could be valuable in both diagnosis/prognosis and in basic science studies of disease progression. One very recent example of this computational approach to determine shear – and other novel hemodynamic diagnostics – is found in Tang et al [47]. They simulated blood flow at both normal (resting) and exercise states in six patient-specific, MRI-derived models of the proximal and distal branches of the pulmonary tree, thereby obtaining WSS, oscillatory shear index (OSI), and energy efficiencies. Exercise was found to substantially increase shear in both proximal and distal locations, while OSI decreased in proximal vessels and increased in distal vessels; efficiency also was found on average to decrease in exercise. While these results were not directly validated and could change somewhat with inclusion of proximal deformation and distal compliance effects, their novelty and level of detail – clearly unattainable in any current clinical imaging modality – strongly demonstrate the significant contribution simulations promise to make in treatment and/or surgical planning decisions.

Constitutive Behavior

Pulmonary vascular tissue displays deformation-, direction-, and time-dependent passive material properties; these complicating factors are known respectively as material and geometric nonlinearity, anisotropy, and viscoelasticity. The tissue is hyperelastic, meaning it can undergo large deformations reversibly (without damage), and is typically treated as incompressible (e.g. incapable of changing in volume). Changes in artery wall geometry that occur during in-vitro processing indicate that the wall carries an internal load even when not under transmural pressure; histology clearly indicates the wall is structurally heterogeneous; and smooth muscle cells (SMCs) may affect both wall geometry and stiffness. Some of these many complexities have been considered in the development of *strain energy function* (SEF) based constitutive models of the tissue. SEFs were originally developed for hyperelastic rubber materials, and may be purely phenomenological or have a structural basis (i.e. they explain constitutive function based on the arrangement of extracellular matrix proteins and/or the molecular and cellular composition of the artery wall). More recently, structural SEFs for arterial tissue incorporate anisotropy, and their parameters are found by fitting their predicted force-stretch behavior to geometric and mechanical data obtained from experiments. Two general forms of these SEFs have also recently emerged: *composite-material* forms, which incorporate macroscale material observations or protein structure, and *microstructural* forms, which model the protein/cellular structure at the molecular and cellular level.

The first composite-material SEF was introduced by Holzapfel et al [48]. They treated the adventitial and medial layers of the artery as fiber-reinforced composites, each containing an isotropic linearly-elastic material (primarily associated with elastin) and two families of collagen fibers, which are helically and symmetrically wound about the artery longitudinal axis. Due to this fiber configuration, arterial anisotropy is made purely a function of the fiber family helical pitch. These features yielded slightly improved agreement between model predicted results and experimental data obtained from a rabbit carotid artery, but the real achievement was inclusion of gross structural details in the model formulation itself: the model considers arterial tissue as an isotropic ground matrix with direction-dependent collagen fiber reinforcement. This basic model was later refined by Zulliger et al [49] who additionally parameterized elastin and collagen area fractions of each layer and assumed that unloaded collagen is a wavy, coiled structure that must straighten prior to carrying load. As the material is stretched, the probability of collagen uncoiling and carrying load increases, until finally the collagen is said to be engaged or completely supporting tensile load. A fiber-reinforced composite structure was also utilized by Kao et al [50], who modeled the collagen fiber bundles as sinusoid-shaped elastic beams with a finite bending modulus. In this approach, the engagement of the collagen fibers is dictated by the unbending and extension of the modeled beam, which has lower complexity than the approach of Zulliger et al. As of yet, only the first of these [48] has been applied towards modeling any type of vascular tissue.

The alternate, microstructural formulation was introduced by Arruda and Boyce [51] and later modified by Bischoff et al [52,53]. Together they proposed an eight-chain unit element, resembling a cube with chains running from each corner towards their meeting at the cube's center, as the basic underlying molecular arterial microstructure. Orthotropic behavior is obtained by varying the lengths of the chains in the three orthogonal material directions, while a network of these elements combines to provide continuum material behavior. Zhang et al [54] applied this model to the specific study of pulmonary tissues from a chronically hypoxic rat model of PH. Fitted model parameter results indicated that PH was associated with increased chain density – suggesting increased molecular cross-linking – and a reduction in the extensibility of the chains, associated with strain-stiffening. Zhang et al [55] then applied the microstructural model [51,52,53] – with parameters obtained from rat experimental data – to study the effects of anisotropy in 3D patient-specific geometries. The model, first applied in a simple tube configuration, was validated through comparisons of predicted pressure-diameter loops in both normotensive and PH constitutive conditions to clinically measured loops in the RPAs of normal and PH children. Agreement was only fair, but overall trends, such as passive strain-stiffening, were well-represented. In the 3D patient specific model, Zhang et al demonstrated that switching from isotropic to orthotropic behavior had significantly greater impact on the deformation state compared to increasing wall thickness by 60%.

Clinical Significance

Multiple clinical studies have shown that local or global increases in vascular stiffness occur in PH [56,57,58,59,60,61], and energy measures indicate it can contribute significantly to right heart afterload, especially in the setting of PH [57,62]. Despite this knowledge existing since the 1960s, it is only recently been considered as a research diagnostic [63], likely due to difficulties in its clinical measurement. However, new imaging methodologies have made measurement of pulmonary vascular input impedance [57,61], proximal pulmonary stiffness [64], and proximal stiffness proxies [60] more routine. To the best of our knowledge, in-vitro data on human proximal pulmonary mechanical properties has not been published, although evidence exists that such stiffening occurs in adult [60] and pediatric PH [46,65].

Proximal wall stiffening has been associated with vascular remodeling in multiple chronically hypoxic animal models of PH [66,67,68]. These studies suggest that changes in extracellular matrix elastin and collagen are the primary modes of mechanical stiffening. Interestingly, the (adult) rat model displays much greater remodeling in collagen due to exposure to chronic hypoxia, while a neonatal calf model primarily remodels in elastin; this could be due to the observation that the larger animal's proximal vessels have a more complex cellular composition [69], but age may also play a role. Regardless, such differences will influence how stiffness afterload increases in PH, given the significant difference in elastin and collagen mechanical behavior. For instance, collagen engagement is shifted to lower strains in the adult chronically hypoxic rat [70,71] which would yield very stiff vessels, whereas elastin remodeling appears to be a beneficial adaptation which maintains Windkessel function in the hypertensive calf [66]. Modeling such complex mechanical behavior, potentially coupled with blood flow, may provide diagnostic insight based on which extracellular matrix (ECM) is carrying load, as well as greater understanding into how stiffness impacts afterload as PH progresses.

Aside from providing insight into remodeling and vascular physiology, these studies in animals also supply mechanical data to validate material models. Model data and tests of model assumptions may also be obtained from imaging studies [72], which have begun to dissect the structure of mechanically relevant ECM components. For example, average collagen fiber angles or tortuosity may be discerned (with some effort) from 2-photon excitation microscopy. However, it has not been shown that these measured angles or the ratio of unstretched to stretched collagen fiber lengths agree with the fitted constitutive model parameters of fiber angles or collagen engagement strains, respectively. Such agreement would validate these constitutive models, and in turn validated models can be used in more advanced simulations to explore the effects of stiffening on hemodynamics and afterload, as outlined in the next section.

Fluid-Structure Interaction

The impacts of vessel deformation on blood flow can be considered in simulations that combine both solid and fluid models and consider their interactions; such models are said to incorporate *fluid-structure interaction* (FSI). Application of FSI has often relied on the method of *partitioned analysis* [73], in which preexisting models (and their corresponding computer programs) for handling fluid or solid mechanics alone are loosely coupled to obtain a modeled interaction. This approach, while inexpensive from a development standpoint (the component pieces already exist), can be problematic in that solutions can be difficult to obtain, and too expensive in time and modeling effort to be frequently applied, especially in the practice of clinical medicine.

The alternate *monolithic* method combines both fluid and solid mechanics in a single solution procedure. Two new monolithic approaches have been recently introduced with the same goal of reducing solution time, an important consideration given the clinical need for rapid turnaround for timely diagnosis. One approach accomplishes this by simplifying the physics of the solid problem, while the other seeks to efficiently use massively parallel machines (e.g. containing 64-1024 processors, or more). The former is not accurate for large arterial deformations, in that the fluid geometry is not updated. Updating this geometry adds additional computational complexity and solution time, but may be necessary for modeling larger proximal vessels, especially in acute loading scenarios or under higher pressures associated with PH.

On the massively parallel side, Heys et al [74] demonstrated optimal scaling in their FSI algorithm, which was used to model a blood flow and a linear-constitutive artery capable of

large deformation. Unfortunately, each time step in the solution process is very computationally expensive, suggesting the method is best for steady state simulations; however as computational power continues to improve, this method may have great utility in the simulation of flow through the proximal pulmonary arteries. Barker and Cai [75] combined a number of existing solution methods to develop a new massively parallel FSI approach, with their 2D results also focused on parallel performance and scalability. They too found nearly optimal scaling, with greatly reduced time requirements for each time step; however their FSI method has not yet been applied to 3D domains.

In contrast, by implementing a simplified model of the arterial wall, Figueroa et al [76] sharply focused on clinical utility. They implemented a linearly constitutive structure and assumed that arterial wall deformations were small enough to be negligible on fluid flow geometry – both reasonable assumptions in their chosen modeled vessels, the human carotid artery and abdominal aorta – thereby yielding a method that properly accounted for pulse-wave propagation with minimal increase in computation time over simply modeling the fluid alone. Their approach is likely the most practical one for many modeling scenarios, but is limited to regions where wall displacement remains small – thus, simulations of the large proximal arteries may not be feasible.

Clinical Significance

The deformation of the proximal pulmonary vessels is believed to be important to proper vascular function [77,78] in that the vessels dilate in systole and contract in diastole, thereby buffering (smoothing) the highly pulsatile flow exiting the heart. Indeed, reduced pulsatility of the main pulmonary artery, defined as the difference between systolic and diastolic artery cross sectional areas divided by the diastolic area, is highly prognostic in adult PH [60], with stiffer arteries being associated with poorer PH outcomes. Global stiffening, as assessed by invasive hemodynamics, is also a good prognostic in adult PH [58,59]. In a pediatric population, this association has been demonstrated with pulmonary vascular input impedance [79], and preliminary data also exists that suggests proximal stiffness is prognostic [65].

From a technical standpoint, inclusion of FSI allows the model to be as functionally realistic as possible by maintaining the inherently coupled dynamics between arterial motion and blood flow. In this, FSI allows prediction of wall motion and its impact on flow. Recent clinical studies have shown that changes in pulmonary stiffness can alter overall ventricular workload [57]; in FSI simulations one can discern changes in blood flow dynamics as well with PA stiffening, indicating that stiffness affects not only overall workload but local flow features as well. Indeed, clinical studies have found that decreased pulsatility of the great arteries – i.e. the deformation state – changes local wall shear stress [54], which as noted earlier have been associated with adverse changes in cellular signaling.

Summary

Computational simulations offer far more spatial detail than do any current imaging modality or invasive measurement, and thus have potential to enhance prognosis and diagnosis as well as serve as useful tools for hypothesis generation. Over the last ten years, the modeling of the macro-level solid and fluid mechanics of the pulmonary circulation has markedly improved. New models of distal morphology, advances in coupling fluid models of different complexity and constitutive models of soft tissue, and new techniques to model fluid-structure coupling have been introduced. Many challenges still remain, however, including the development of better solid boundary conditions (i.e. vessel support), inclusion of remodeling processes (for example, see [80]), material transport, and potentially even molecular/cellular processes that are essential to disease progression [6]. We note that a

mere 30 years progressed from the birth of modern computational methods until they had advanced enough to play a significant role in the design and simulation of aerospace structures. If the aerospace industry is a relevant example, perhaps we will see routine use of computational tools in the diagnosis and prognosis of pediatric pulmonary hypertension in the lifetimes of children born today.

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