Computational models for patient-specific analysis of pulmonary vascular disease

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1 sentence teaser
Advances in structure-based computational models of the pulmonary circulation provide a novel tool for the *in silico* study of patient-specific response to intervention or therapy for pulmonary vascular disease.

Abstract

It is becoming increasingly apparent that personalized therapies are key to successful management of pulmonary vascular disease, but this cannot be achieved without an integrated approach to investigating the condition and an individual's response to therapy. Computational models provide a means to link investigations across the spectrum from cellular mechanisms to potential improvements in pulmonary vascular function over the course of a therapeutic strategy. Here we describe some of the computational tools that will be required for this purpose.

Pulmonary vascular disease most frequently occurs secondary to another condition, for example as a consequence of capillary bed destruction in chronic obstructive pulmonary disease, or through obstruction of the pulmonary arteries by an embolic blood clot or tumour. A common feature of all pulmonary vascular disease is that it increases pulmonary vascular resistance (PVR), and hence the right ventricular (RV) pressure that is required to maintain cardiac output. This can persist as a significant impairment to gas exchange capacity, or progress to right heart failure. Variability in the initiating stimuli and the mechanisms that interact during disease progression means that there is no single therapeutic target. Animal models - particularly those that have been developed to study pulmonary arterial hypertension - replicate only some of the features of human disease [1]. The rodent and large animal models that are typically used experimentally have different vascular branching geometry from human, different proportions of supernumerary to conventional blood vessels [2], and may differ in their vascular reactivity. These species differences have implications for the preferential distribution of blood (and hence transported particulates) in the lung [3,4] and therefore the characteristic way in which blood will redistribute in response to an intervention; translation of animal studies to human pathophysiology is therefore not straightforward. Until recently this translation has been further impeded by a lack of computational models that can explain the interaction of the various biophysical functions that interact to govern blood flow and gas exchange.

Development of detailed computational models for the pulmonary circulation has been limited in number in comparison to parallel studies in the airways. Several groups have proposed structure-based models of individual components of the pulmonary circulation: Burrowes & Tawhai [5] and Kheyfets et al. [6] provide reviews of some model approaches in this area, with the latter emphasising their application in pulmonary hypertension (PH). Here we focus on structure-based models that integrate patient-specific data with mechanistic models of function, and consider how they have advanced our understanding of pulmonary perfusion, and their potential contribution as *in silico* models of pathology.

Synergistic mechanisms in the distribution of pulmonary perfusion

The pulmonary circulatory system is highly dynamic. The pressures that are internal and external to the arteries and veins oscillate with each heart beat and each breath, and the smooth muscle that lines the arterial walls responds to fluctuations in shear stress via endothelial signaling, arterial and alveolar oxygen contents, and other vasoactive mediators. The pulmonary circulatory vessels are suspended within a delicate alveolar tissue that readily deforms under the weight of the blood and extravascular fluid. Determining how these various biophysical factors - which manifest at multiple physical scales - translate to the distribution of blood flow in the lung is challenging. Virtually all lung disease impairs ventilation-perfusion (V/Q) matching, and sufficient V/Q matching is essential for effective gas exchange. Therefore understanding which are the most important factors in determining the normal distribution of perfusion is necessary before we can suggest which are the most sensitive mechanisms that will affect gas exchange as pathology develops.

Early theories to explain the observation of a gravitationally-directed distribution of lung blood flow (from low-resolution external imaging) focused on the balance of blood and air

pressures at the pulmonary capillaries, and how this changes with location in the lung (West's 'zonal' theory [7]). Later animal studies contested this theory, showing large iso-gravitational heterogeneity in blood flow and suggesting that the asymmetric vascular branching geometry plays a major role in determining blood distribution [8,9]. More recent imaging studies in human have suggested that the displacement of the tissue by gravity is a major mechanism, and that blood flow is otherwise minimally altered by a change in posture [10,11]. Resolving the debate [12,13] as to which is the primary determinant of blood flow distribution is not possible using only animal models or human imaging, as it is not possible to independently control each contributing mechanism. In contrast, a computational model can integrate all mechanisms simultaneously to understand their interactions, and then examine the contribution of each mechanism independent from the action of the others. Clark et al. [14] presented a computational model that was uniquely suited to this purpose. The model includes anatomically-consistent vascular branching geometry, gravity acting to deform the lung tissue and providing a hydrostatic pressure gradient, recruitable and distensible capillaries, and elastic arteries and veins (Figure 1). The model behavior was consistent with observations from all of the experimental studies, showing that several hypotheses can be reconciled within a single explanatory model. Each mechanism was shown to make a significant and distinct contribution to the distribution of blood, and some important synergistic interactions were observed. Tissue deformation and the hydrostatic pressure gradient make contributions of similar magnitude to the gravitational gradient of flow; vascular branching asymmetry introduces iso-gravitational heterogeneity; and the zonal effect (i.e. balance of pressures at the capillary level) amplifies the heterogeneity. The Clark et al. [14] study considered human geometry and parameterization, however the model is equally applicable to animal vasculature [3]. These structure-based models are able to communicate with concurrently developed models of tissue mechanics, ventilation and gas exchange (Figure 1) in geometries representing the same subject [15-17]. These geometries are subject-specific insofar as they represent the lung shape and large airway and blood vessel structures to the level that they can be resolved in CT imaging, and in the degree to which they can incorporate subject-specific regional pathology [18]. This computational approach therefore provides a unique tool for understanding how outcomes from experimental studies of pulmonary hemodynamics in animal models will translate to the particular physiology of the human lung.

Computational models to assess patient response to acute disease

Acute pulmonary embolism (APE) can be a 'convenient' model with which to study the interaction of mechanisms that determine perfusion distribution and gas exchange in pulmonary vascular disease, as APE frequently occurs without any pre-existing cardiac or pulmonary condition. APE involves the full or partial occlusion of one or more pulmonary arteries, typically by a blood clot that has fractured from a clot in the systemic circulation. Patient response to APE is variable, and quantitative methods to provide radiological scores for the lung correlate poorly with clinical outcome. Previous clinical and experimental studies have suggested that large central clots have more significant impact on lung function than smaller distributed clots, but the reasons for this were unclear. Using a structure-based model, Burrowes et al. [19] showed that blood preferentially redistributes against gravity, i.e. in proportion to the propensity for recruitment of capillary beds that were unrecruited at baseline. The study suggested that clot size and location could influence the pattern of

redistribution, and this could play a role in gas exchange. The suggestion that redistribution of perfusion was a primary mechanism in the development of hypoxemia was consistent with prior experimental studies [20]. To test this hypothesis, Clark et al. [18] used routinely acquired imaging and functional data from 12 subjects who were diagnosed with APE to construct patient-specific structure-based models. The study included a prediction of baseline lung function (V/Q distribution and arterial blood gases), and function after imposing patient-specific distributions of blood clot and measured heart and ventilation rate. The prediction of the decrease in arterial oxygen partial pressure that would have developed without compensatory adaptation of cardiac output and ventilation rate correlated strongly with clinical measurement of abnormal RV strain. In fact, the prediction of the *potential* for the clot load to establish hypoxemia was able to differentiate between subjects with and without RV dysfunction. The critical factor in the hypoxemic potential was the size and location of emboli: subjects with identical radiological scoring showed a major impact on gas exchange when emboli were large (central) and/or basal; and minimal effect when emboli were smaller and widely distributed. The difference is due to the effect that the redistribution of blood has on the regional V/Q distribution. Small emboli cause small decreases in V/Q in non-occluded regions, whereas large/basal emboli decrease V/Q in non-occluded regions to the extent that regional oxygen partial pressure is decreased. Based on this study, it becomes clear why radiological scoring methods for APE perform so poorly: current 'obstruction indices' estimate the proportion of lung that has a reduced participation in gas exchange, but do not account for the impact of emboli on gas exchange in the non-occluded tissue and how this relates to baseline flow distribution. Computational assessment of APE could be used to develop new scoring methods that include the patient-specific hemodynamic response to vascular occlusion.

Towards computational models of patient-specific chronic disease

Chronic PH is a debilitating and progressive condition that results from a persistent increase in PVR. The initiating stimuli and evolution of PH involves a range of pathologies that variously affect the constriction and/or remodeling of the large and small vessels of the pulmonary circulation [21]. The most recent classification of PH groups together patients with shared pathogenesis and clinical characteristics into five major categories [22]. PH can be secondary to injury, infection, heritable factors, and chronic hypoxia to name but a few [21]. The most common causes of PH identified in Europe and the USA are left heart disease and chronic hypoxic lung disease, whereas in the developing world sickle cell disease and schistosomiasis are prominent [23]. Figure 1 shows some of the factors that interact in the development of PH, including chronic hypoxia and mechanical stress which can both lead to blood vessel remodeling, and short and long term alterations in cardiac and ventilatory dynamics. Because of its diverse etiology, several different therapies have been proposed for the treatment of chronic PH - each with different methods of delivery and potential side effects [21].

There are three major questions that must be considered to successfully treat PH: What is the underlying cause of the disease? Given the cause, how should disease progression be measured? And what combination of therapies will minimize disease progression? Reconciling experimental data to optimize therapeutic strategies is a major challenge. For example, are the pathways that are involved in animal models of PH relevant in human

[24]? And to what extent do cell cultures reflect the complexity of lung tissue *in vivo* [25]? Patient-specific computational models have begun to contribute to our understanding of important mechanisms in PH, and have the potential to improve diagnostic methods, stratify patients into sub-groups, and/or propose targeted therapies.

Volumetric imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI), is often obtained during the diagnosis and management of pulmonary disease. This imaging can be used to construct three-dimensional (3D) patient-specific models of the pulmonary arteries and veins for computational fluid dynamics simulation of local hemodynamics and shear stress distribution [26-28]. Shear stress is a key modulator of arterial wall remodeling in PH, as the endothelial cells that line the arterial wall release vasoactive mediators in response to shear. This is a normal pulmonary response that acts to modulate the PVR during altered hemodynamic states and hence minimize fluctuations in the pressure load against which the RV works. The persistence of abnormally high or low shear or large cyclic changes can stimulate arterial wall remodeling and stiffening, which makes it harder for the pulmonary circulation to respond appropriately to further fluctuations in shear. This initiates a vicious cycle between increasing shear stress and vascular remodeling. 3D computational models in this context have been aimed at understanding the difference in shear stress distribution between normal subjects and those with chronic PH (Figure 2), revealing a complex interdependence between central vessel remodeling, vascular distension, and shear. The ultimate goal of this type of model is to predict regions of the vasculature that are most susceptible to remodeling, and hence are potentially sensitive to targeted therapy. An issue with this approach is that 3D analyses are restricted to relatively small proportions of the vasculature, and imaging-based models necessarily focus on the relatively large vessels that can be resolved from imaging. However, while PH is associated with changes in the mechanical behaviour of the large vessels, it is most commonly thought to be initiated through a reduction in the compliance or diameter - or even complete obliteration - of small vessels (<500 μm). The progression of PH hence occurs throughout the pulmonary arterial tree, with remodeling of small vessels affecting the flow and shear stress that is experienced by the large vessels, and vice versa. Understanding remodeling therefore requires a model representation of the entire pulmonary vascular trees.

Several models have included ‘structured impedance boundary conditions’ to approximate the impedance of the vasculature that sits downstream of the large central vessels (e.g. [26]). This is sufficient for the analysis of local flow and shear stress, but it cannot represent the dynamic adaptive response of the downstream vasculature to changes in hemodynamic conditions. Modeling studies have shown that the geometry of a vascular system can influence the distribution of drug delivery and its interaction with the vascular endothelium, particularly when the size of the drug becomes large (e.g. systems which aim to deliver multiple drug molecules at once) [4]. This means that to translate drug-endothelium interactions observed *in vitro* to the potential sites of action *in vivo*, the geometry of the pulmonary vascular system, and how this influences blood flow, must be described. Computational studies of PH progression therefore need to build upon anatomically-structured models that explicitly include both the large and small arteries and veins (e.g. [14]), with coupling to models of vascular smooth muscle regulation and arterial wall remodeling. At the smaller scale, models have been developed to predict the production

and transport of nitric oxide (reviewed by Tsoukias [29]), and the relationship between calcium dynamics and pulmonary arteriole smooth muscle contraction [30]. Models have also been developed to predict the time course of remodeling in single systemic blood vessels [31,32]. These types of model are potentially very powerful for understanding how best to disrupt a specific pathway to prevent remodeling, and to translate the effect of endothelial targeting therapies that have been studied extensively in cell culture experiments [33] to an *in vivo* response. However an appropriate computational assessment must include the influence of vascular geometry on the dispersion of blood.

Conclusion

There is a significant challenge in translating the results of experimental studies of the pulmonary circulation and pulmonary vascular disease to human whole organ response, partly because of marked differences between animal models and human disease, but also due to intrinsic differences in vascular geometry. Computational models that include species-appropriate vascular geometry and its interaction with tissue mechanics, ventilation distribution, and gas exchange will be key to the translation of animal studies to an understanding of the human response. The development of mechanistic models of drug interactions with the pulmonary endothelium, coupled to whole organ or system models to predict individual patient responses will be an important approach to provide personalized medicine in pulmonary vascular disease.

Conflict of interest

The authors have no conflict of interest to declare.

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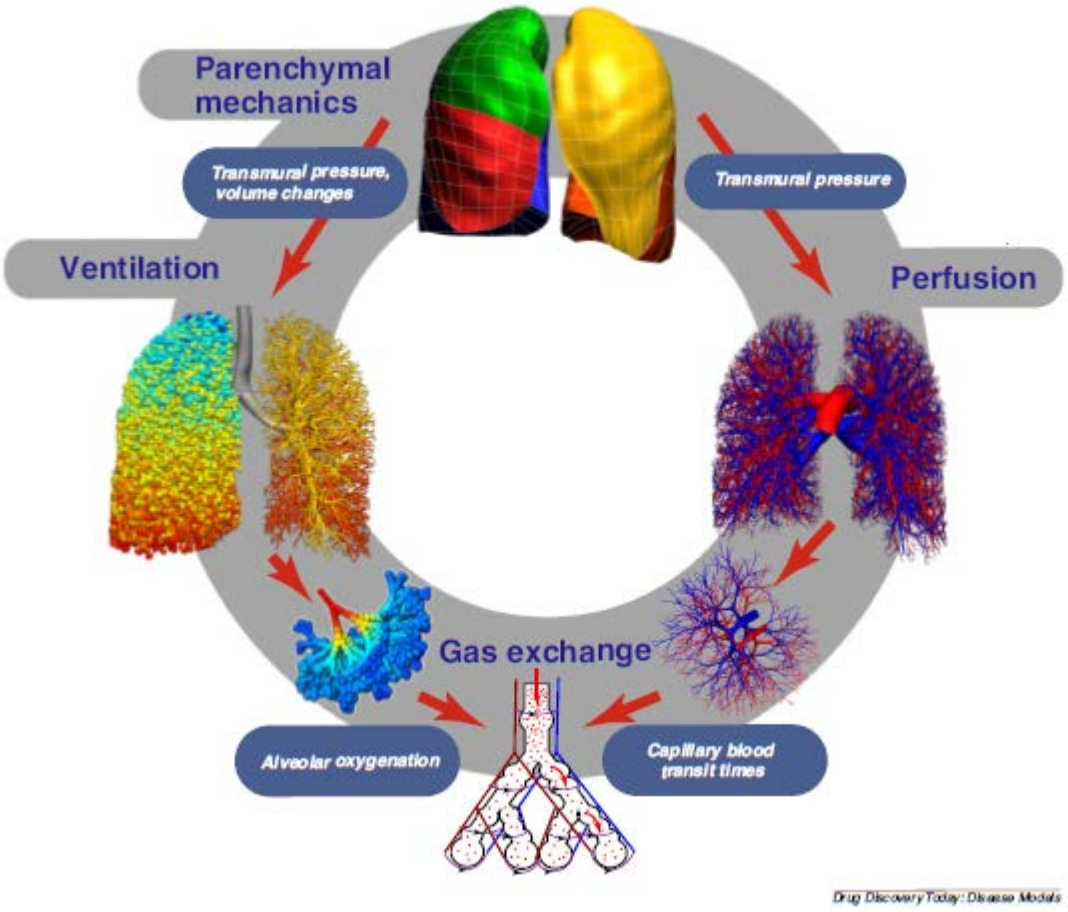

Figure 1: Model components and their interactions in a multiscale model of the human lung. Clockwise from the top the figure shows finite element meshes of the five lobes of a human lung, pulmonary arteries (red) and veins (blue) modeled for this subject using a combination of CT imaging and a volume filling algorithm, the micro-circulation in a single pulmonary acinus modeled as a ladder-like structure, a schematic of the air-blood interface for gas exchange, a multibranching model of the acinar airways, subject-specific conducting airways (right) and ventilation distribution (left).

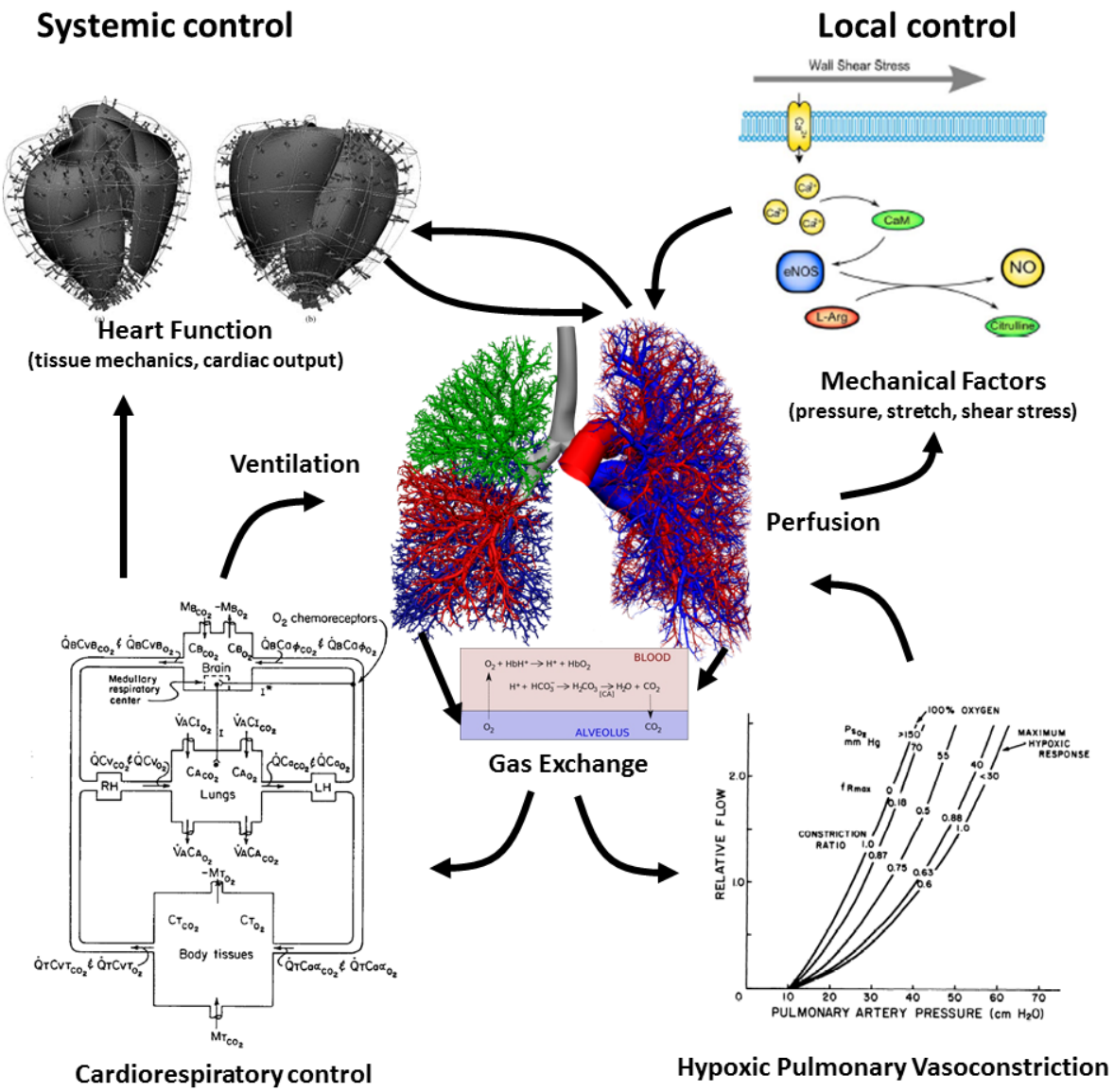

Figure 2: Some of the mechanisms that contribute to pulmonary hypertension and their representation by model systems. Local alterations in oxygenation and/or the mechanical stress felt by pulmonary blood vessels can result in vessel remodeling and long-term changes in pulmonary vascular resistance. The ability of the lung to perform gas exchange and mechanical stress also contribute to systemic alterations via the cardiorespiratory control system and interaction between the pulmonary blood vessels and the heart. Components of this figure have been reproduced from [34-37].

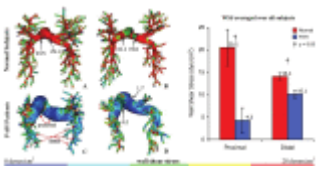

Figure 3: Computational fluid dynamics simulations of time-averaged wall shear stress in subject-specific model geometries of normal subjects and patients with pulmonary arterial hypertension (PAH). These models are able to predict detailed maps of arterial wall shear stress that highlight differences between normal subjects and PAH. In this case the central arteries of patients with PAH are predicted to have a lower than normal average wall shear stress due to significant arterial dilation. This figure was first published in Pulmonary Circulation, volume 2, number 3, [2012] pages 470-476.