Dynamic blood flow and wall shear stress in pulmonary hypertensive disease

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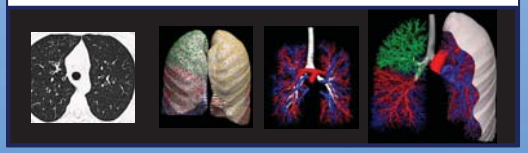
Rationale

Pulmonary hypertension (PH) is a debilitating condition with a range of contributing factors, making it difficult to assess and manage. Common to most types of PH is a remodelling of the medial and intimal layers of the vessel wall, which can progress to complete occlusion of the pulmonary arteries, fibrosis and lesions. Progression of remodelling is difficult to assess from clinical data (imaging and haemodynamic data) as it typically has an effect on small pulmonary arteries. Predicting the level of remodelling present in a patient from clinically obtainable data would allow stratification of patients to optimise treatment in PH. In this study we present a pulsatile model of blood flow in the pulmonary arteries of individuals which incorporates the key remodelling steps involved in PH and demonstrate how it can be used to assess disease progression.

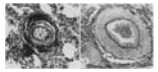
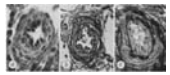
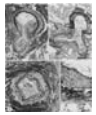
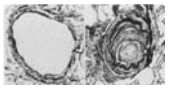
Geometric Model

An anatomically based geometric model representing the lungs of an individual [1] was created by:

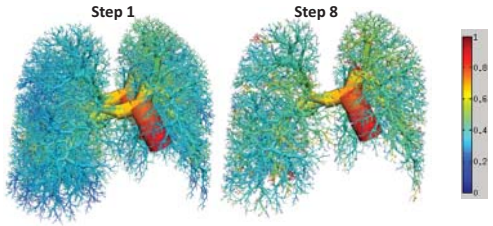
- Segmenting the lungs, lobes, and central airways, arteries and veins from CTPA images.
- Volume-filling airways, arteries and veins to the acinar (gas exchange unit) level.



Arterial Remodelling [4]

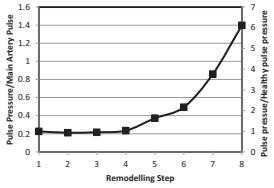
Histology	Description	Model Implementation
	**Grade 1 Remodelling.** Proliferation of endothelial cells in the intima layer of small muscular arteries results in an increase in wall thickness and decrease in lumen diameter.	**Step 1:** No significant remodelling – normal vessels (vessel compliance = α). **Step 2:** Decrease in compliance of vessels 100-1000 um in diameter to 0.83 α (hypertropy).
	**Grade 2 Remodelling.** More proliferation of endothelial cells in the intima layer and smooth muscle cell hypertrophy. Loss of some small vessels.	**Step 3:** Compliance 100-1000um vessels 0.67α. Vessel lumen in 30-300um vessels decreased to 92.5% baseline values. 6.25% of vessels <300 um pruned. **Step 4:** Compliance 100-1000um vessels 0.5α. Vessel lumen in 30-300um vessels decreased to 85% baseline values. 12.5% of vessels <300 um pruned.
	**Grade 3 Remodelling.** Proliferation of endothelial cells in larger arteries, smooth muscle cell hypertrophy and complete occlusion of some vessels.	**Step 5:** Compliance 100-1000um vessels 0.33α. Vessel lumen in 30-500um vessels decreased to 77.5% baseline values. 18.75% of vessels <500 um pruned. **Step 6:** Compliance 100-1000um vessels 0.17α (hypertrophy) and 30-500um vessel compliance reduced by 1/6 (fibrosis). Vessel lumen in 30-500um vessels decreased to 70% baseline values. 25% of vessels <500 um pruned.
	**Grade 4 Remodelling.** Arteries lose structure, plexiform lesions appear with some vessels becoming large thin walled sacs. Other arteries are thick-walled and stiff.	**Step 7:** Compliance 30-500um vessels reduced by to 0.83 of the value at step 6 (fibrosis). Vessel lumen in 30-500um vessels decreased to 55% baseline values. 31.25% of vessels <500 um pruned. **Step 8:** Compliance 30-500um vessels reduced by to 0.67 of the value at step 6 (fibrosis). 37.5% of vessels <500 um pruned.

Pulse Propagation

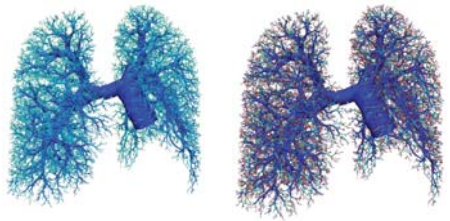


Pulse pressure is visualised here (normalised to main pulmonary artery pulse pressure. Step 1 (no remodelling) and Step 8 (severe grade 4 remodelling) are shown. An increased fraction of inlet pulse pressure is propagated to the periphery in severe cases of remodelling creating high oscillatory pressure changes in regions of the lung.

The pulse pressure at the terminal arteries increases with remodelling and becomes a higher fraction of the inlet pulse pressure. By step 8 of remodelling the mean terminal artery pulse pressure is predicted to be 7 times the normal healthy value.

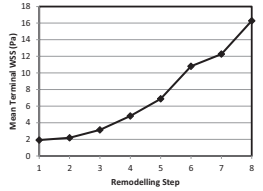


Shear Stress and Further Remodelling

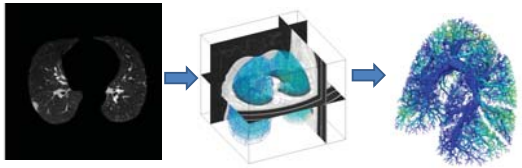


Changes in wall shear stress are known to drive arterial remodelling. Wall shear stress increases in the terminal arteries with increasing remodelling, potentially contributing to a 'vicious cycle' in chronic disease.

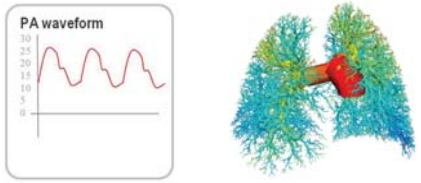
With no disease wall shear stress is highest in the terminal blood vessels (the smallest vessels). As remodelling progresses high shear regions propagate proximally up the tree. This occurs prior to progression of remodelling to larger vessels and confirms a link between wall shear stress and remodelling.



Use of Clinical Data



Computed Tomography: Computed tomography (CT) pulmonary angiograms often show regions of hypo- and hyper-attenuation in pulmonary hypertension. These regions are mapped to anatomically based models of the pulmonary circulation in an individual to identify regions of reduced flow due to vessel occlusion (either via thromboembolic material, fibrosis, or severe remodelling).



Pulmonary Haemodynamics: Cardiac catheterisation is a common part of the clinical work-up in pulmonary hypertension. In chronic disease peripheral remodelling means that CT estimated occlusion is not sufficient to elevate model predicted pulmonary artery pressures to clinically measured values. By comparing predictions of pressure magnitudes at each step of arterial remodelling we can estimate disease progression in an individual.

Admittance of the pulmonary arteries

Terminal elements :

1. Characteristic admittance (Y) is calculated for each terminal element

$$Y = \left(\frac{A}{\rho c}\right) \times \sqrt{\epsilon_r}\ , (1)$$

where A is the cross sectional area of the vessel, ρ is blood density, c is the wavespeed in that vessel, and ϵ_r is a viscous factor, dependent on Reynold's number [2].

2. Boundary conditions are set terminal elements. By assuming that venous admittance is negligible, acinar admittance is calculated using a previously published description of the acinar 'resistance' vessels [3].
3. A reflection coefficient (R) is set at each terminal element, this is assumed to be $R = 0$.

Stepping backward through the tree from terminals:

1. The characteristic admittance of each element is calculated using equation (1).
2. The effective admittance (Y_e) of an element is calculated from the admittance of its two daughters (Y_1 and Y_2), its characteristic admittance, vessel length l, and frequency of the input waveform ω:

$$Y_e = Y\left(\frac{Y_1+Y_2+iY\tan\frac{\omega l}{c}}{Y+i(Y_1+Y_2)\tan\frac{\omega l}{c}}\right),$$

3. The reflection coefficient of an element is defined as:

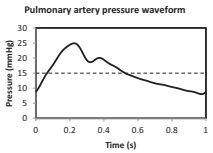
$$R = \frac{Y_e-(Y_1+Y_2)}{Y_e+Y_1+Y_2}.$$

Pressure and flow though the tree

Pulmonary artery pressure is defined as a Fourier decomposition of the pressure waveform in that artery and pressure (p) and flow (q) are then defined as:

$$p(x,t) = p_o e^{i\omega\left(t-\frac{x}{c}\right)} + Rp_0 e^{i\,\omega\left(t+\frac{x}{c}-\frac{2l}{c}\right)},$$

$$q(x,t) = \left(\frac{A}{\rho c}\right)p_o e^{i\omega\left(t-\frac{x}{c}\right)} - \left(\frac{A}{\rho c}\right)Rp_0 e^{i\,\omega\left(t+\frac{x}{c}-\frac{2l}{c}\right)}.$$



The pressure amplitude p_0 is calculated as a function of upstream and downstream reflection coefficients:

$$p_{0,down} = p_{0,up}\frac{(1+R_{up})e^{-\frac{i\omega l_{up}}{c_{up}}}}{1+R_{down}e^{-\frac{2i\omega l_{down}}{c_{down}}}}.$$

Conclusions

We have developed a computational model of the propagation of pulmonary arterial pressure pulses in anatomically based models of the lungs of an individual. This model includes a staged progression of blood vessel remodelling typical in pulmonary hypertension.

The model predicts significant increases in arterial pulse pressure and mean wall shear stress in the peripheral arteries with remodelling. As arterial remodelling is associated with both shear stress magnitude and oscillatory changes in shear this suggests that vessel remodelling in early stages of pulmonary hypertension contribute to a transmission of shear stress proximally in the arterial tree and so to a 'vicious cycle' of remodelling.

Our model predictions can be related to an individual patient's state via clinical measurements made routinely in patients with pulmonary hypertension, hence providing the potential to assess the level of vessel remodelling in an individual when planning therapies.

References & Acknowledgements

[1] Clark et al. J Appl Physiol, 2011, 110:943-945.
[2] Duan & Zamir, Annals Biomed Eng, 1995, 23(6)794-803.
[3] Clark et al. J Appl Physiol, 2010, 108(5):1116-1126.
[4] Heath & Edwards, Circulation, 1958, 18(4):533-547.

Funding: New Zealand Health Research Council 09/143, Aotearoa Foundation Fellowship (Clark)