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Hypoxic pulmonary vasoconstriction as a contributor to response in acute pulmonary embolism

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Short title:

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Predicting the impact of HPV in pulmonary embolism

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ABSTRACT

Hypoxic pulmonary vasoconstriction (HPV) is an adaptive response unique to the lung whereby blood flow is diverted away from areas of low alveolar oxygen to improve ventilation-perfusion matching and resultant gas exchange. Some previous experimental studies have suggested that the HPV response to hypoxia is blunted in acute pulmonary embolism (APE), while others have concluded that HPV contributes to elevated pulmonary blood pressures in APE. To understand these contradictory observations, we have used a structure-based computational model of integrated lung function in 10 subjects to study the impact of HPV on pulmonary hemodynamics and gas exchange in the presence of regional arterial occlusion. The integrated model includes an experimentally-derived model for HPV. Its function is validated against measurements of pulmonary vascular resistance in normal subjects at four levels of inspired oxygen. Our results show that the apparently disparate observations of previous studies can be explained within a single model: the model predicts that HPV increases mean pulmonary artery pressure in APE (by 8.2±7.0% in these subjects), and concurrently shows a reduction in response to hypoxia in the subjects who have high levels of occlusion and therefore maximal HPV in normoxia.

Key terms: Pulmonary blood flow, vascular occlusion, computational model.

INTRODUCTION

Acute pulmonary embolism (APE) can lead to an increase in right ventricular (RV) afterload and pulmonary artery pressure (PAP) in some patients. This is partly due to mechanical obstruction of the vascular bed and/or vasoconstriction (via neural reflexes, or the release of humoral vasoactive mediators)[34,42] which both act to increase pulmonary vascular resistance (PVR). Some studies have suggested that hypoxic pulmonary vasoconstriction (HPV) also contributes to the elevation of PAP in APE;[1,7,33] however this is contradicted by other studies that observed no increase in PAP,[34] and a diminished HPV response to hypoxia.[12]

HPV provides a regulatory mechanism to maintain efficient local matching between ventilation (V) and perfusion (Q) in the lung. HPV acts to divert blood away from poorly oxygenated regions, through alteration in vasomotor tone in response to local alveolar and blood partial pressures of oxygen.[23,26,36,39] This response is unique to the pulmonary circulation.[23,26,36] Experimental studies have measured the impact of HPV on regional perfusion during normoxic[3,17] and hypoxic conditions (for example[11,19]). From these and similar studies it is known that HPV does not contribute substantially during normoxia;[3] HPV is effective at diverting blood flow from hypoxic to non-hypoxic regions in the presence of *regional* hypoxia (which could be relevant to APE), however during *whole-lung* (global) hypoxia very little blood flow is diverted, and the effect of HPV is predominantly to increase PAP. Previous studies using structure-based models have shown that APE could theoretically cause regional hypoxia that is sufficient to stimulate an HPV response,[7] through the development of areas of low V/Q that are consistent with clinical observations.[20,32] The significance of this response for gas exchange or elevation of PAP is not known.

The purposes of the current study are: 1. to quantify the potential contribution of HPV to the increase in PAP during APE, and 2. to explain the observation of a diminished HPV response to hypoxia in APE. The goal is to use a single computational model to study both elevation of PAP and diminished HPV response, to determine whether these apparently contradictory behaviors can coexist. Computational models have previously been used to quantify the role of HPV in V/Q matching and gas exchange[4,23,26] and to assess the impact of APE on pulmonary hemodynamics.[27] A limitation of these previous 'compartmental' models is that V/Q distributions were *prescribed* rather than *predicted* based on biophysical laws. The current study therefore uses a structure-based model with biophysical equations to predict V, Q, and gas exchange. The appropriateness of the model behavior is confirmed through comparison with measurements acquired during global hypoxia experiments. Only the acute HPV response (occurring within the first 10 minutes of hypoxia) is considered, and not the longer time-scale vasomotor response.

METHODS

Structure-based models

A single structure-based model of vascular anatomy was used in this study. The structural model was derived from volumetric computed tomography (CT) imaging of a normal 25 year old male. The same model has been used in several previous functional studies of the lung.[9,10,35,37] In brief, the structural model includes geometric descriptions of the lung surface, conducting airways (these are the airways not involved in gas exchange), and accompanying arterial and venous blood vessels distributed in a three-dimensional (3D) lung volume. The pulmonary vasculature geometry includes individual arteries and veins from the heart to the level of the pulmonary acinus (the unit of gas exchange). Each terminal artery is joined to a terminal vein by a 'ladder-like' model for the intra-acinar circulation.[9] In the conducting

airway tree each terminal bronchiole is attached to an elastic tissue unit representing the acinar tissue.

Patient-based acute pulmonary embolism models

To simulate APE, patient-based distributions of emboli were superimposed on the structural model. Volumetric CT pulmonary angiograms (CTPAs) with intravenous contrast were acquired from 10 adult subjects undergoing imaging during routine clinically indicated CT examination for acute or chronic PE. The mean patient age was 51.3 years (SD 9.7 years) and all subjects except one were male. All scans were acquired on a Phillips Brilliance 128, multislice CT scanner at submaximal inspiration using IV contrast. The Northern X Regional Ethics Committee (NTX/09/08/074) and the Auckland District Health Board Research Review Committee approved use of the clinical data, and all subjects provided informed consent for participation in our study. In each subject, the emboli were identified by a radiologist (DGM) to one bifurcation below the level of the segmental arteries. The percentage occlusions, estimated manually using the caliper tool in OsiriX (www.osirix.org), were mapped to the corresponding arteries in the structural model. The total extent of obstruction was quantified in the 10 subjects using the Qanadli obstruction index (QOI). This is a CT-based index that estimates the percentage of vascular obstruction based on the proportion of segmental arteries that are occluded.[31]

Functional models

We used previously published models of ventilation (V),[35] blood flow (Q)[10] and oxygen (O_2) transfer,[21] coupled to lung parenchymal tissue deformation,[37] to predict pulmonary function in the structural models. The HPV response to gas partial pressures was modeled using the methods of Marshall and Marshall,[24] which relates mixed venous (P_vO_2) and alveolar oxygen

partial pressures (P_AO_2) to vessel radius. Additional details of each model are provided in the Appendix.

A schematic diagram illustrating the algorithmic steps taken in the solution process is displayed in Figure 1. In summary we execute the following modeling steps:

1. Solution of a model of tissue deformation (Equation A1),[37] which provided values of regional acinar volume and pleural pressure that were incorporated into the ventilation and blood flow models;
2. Solution of a ventilation (V) model[35] - which included airway resistance coupled to the tissue compliance and local elastic recoil pressures - to predict steady-state ventilation distribution to each acinus (see equations A2-A4);
3. Solution of a blood flow (Q) model[10] which predicted regional pressure, flow and radius in the full vascular network (Equations A5-A8);
4. Solution of an oxygen (O_2) transfer model,[21] given V (step 2) and Q (step 3) to each acinus as inputs. This model predicted alveolar P_AO_2 for each acinus (with P_vO_2 set as a boundary condition), and the flow-weighted arterial oxygen partial pressure (P_aO_2) for the whole lung (Equations A9-A11);
5. Calculation of the HPV response (Equations 1-3) as a function of P_AO_2 and P_vO_2 from step 4,[24] which was used to update the peripheral arterial diameters.

Steps 3-5 were repeated until a converged solution was reached (convergence criteria ΔmPAP < 1.33 x 10-5 kPa). Ventilation was assumed unchanged during this procedure, in accordance with studies that have observed only minor changes in ventilation distribution in PE.[2,38] The models are not mathematically coupled: output variables are passed between models and simulations of each model are run independently.

<Insert Figure 1>

The HPV model

To calculate the constriction factor, *K*, in the blood flow model we use equations derived by Marshall and Marshall[24] to describe vascular constriction as a function of graded hypoxia based on experimental measurements of hypoxic flow diversion in dogs.[25] Equations 1-3 relate the stimulus for hypoxia (P_sO_2) - calculated as a function of both alveolar P_AO_2 and P_vO_2 - to the amount of constriction (*K*) of small pulmonary arteries.

$$Ps_{O_2} = P_{AO_2}{}^{0.62} P_{vO_2}{}^{0.38}, \quad (1)$$

$$fR_{\max} = \left(Ps_{O_2}\right)^{-6.32} / \left[\left(1x10^{-11}\right) + \left(Ps_{O_2}\right)^{-6.32}\right], \quad (2)$$

$$K = 1 - 0.87[fR_{\max}] + 0.81[fR_{\max}]^2 - 0.331[fR_{\max}]^3, \quad (3)$$

where fR_{max} is the fraction of maximal HPV response. The HPV response was assumed to act only in arterial vessels less than 500 μm in diameter. Equation 3 gives a range of *K* from 1.0 (unconstricted) to 0.6 (maximum constriction); *K* was multiplied by the predicted unstrained vessel diameter (Equation A8) during the iterative solution. The updated diameter was then calculated. The HPV sensitivity was assumed homogeneous across all acini, and hence varied only as a function of the local acinar P_AO_2 and P_vO_2.

Boundary conditions in normoxia

The lung was assumed to be upright and at functional residual capacity (FRC) for all simulations. Inlet flow at the right ventricle (Q_{RV}) and left atrial pressure (LAP) at the model outlet were set as boundary conditions. A Q_{RV} of 5 L/min and LAP of 0.9 kPa (7 mmHg) were used for baseline normoxic (P_iO_2 = 20.0 kPa, or 150 mmHg) conditions. It was assumed

that mixed venous blood had an oxygen partial pressure of P_vO_2 = 5.3 kPa (40 mmHg). Normoxic simulations gave a physiologically consistent VO_2 of 0.29 L(O_2)/min.

Boundary conditions in global hypoxia

To simulate global hypoxia inspired oxygen was set at values representative of past experimental studies of hypoxia: P_iO_2=13.3 kPa (100 mmHg),[14] P_iO_2=12.4 kPa (93 mmHg)[41] and P_iO_2=9.1 kPa (68 mmHg)[18] (at sea level). Q_{RV} and LAP were set as a function of P_iO_2, by using a quadratic line of best fit (Figure 2, Table 1) to data from the experimental studies considered. For all studies, P_vO_2 was initialized to 5.3 kPa (40 mmHg) at baseline and then was adapted iteratively during the simulation to maintain a fixed body consumption of O_2 (VO_2). A minimum physiological limit of P_vO_2=2.7 kPa (20 mmHg) was assumed; in the most severe hypoxic conditions this meant that VO_2 was not maintained and decreased to 0.26 L/min. Table 1 (see *Results*) summarizes the model boundary conditions (P_iO_2, P_vO_2, Q_{RV} and LAP).

Boundary conditions in APE

The baseline values of Q_{RV} (5 L/min) and LAP (0.9 kPa) were used during simulation of APE. Regional hypoxia was simulated by allowing it to emerge as a consequence of V/Q redistribution during simulation of APE, as described by Burrowes et *al.*[6] To mimic the experimental conditions under which a diminished HPV response in APE has been observed,[12] two levels of inspired oxygen (normoxia, P_iO_2=20.0 kPa, and hypoxia, P_iO_2=9.1 kPa) were used. As in the studies of global hypoxia, P_vO_2 was initialized to 5.3 kPa at baseline and then was adapted iteratively during the simulation to maintain a fixed body consumption of O_2 (VO_2).

< Insert Figure 2 >

RESULTS

The impact of global hypoxia on pulmonary hemodynamics

The blood flow gradient in the direction of gravity (Q gradient, % change in flow/cm lung height) was calculated for each simulation to assess changes in the distribution of perfusion in global hypoxia. The Q gradient is calculated using blood flow to the lung 'tissue' (i.e. acini) only by a linear regression fit to Q and height data. The predicted mean PAP (mPAP), arterial P_aO_2, and the Q gradient as a result of the corresponding boundary conditions for P_iO_2, P_vO_2, $Q_{RV,}$ and LAP are shown in Table 1. mPAP was inversely proportional to P_iO_2, and both P_aO_2 and Q gradient decreased proportionately to P_iO_2 (R^2=0.99 in each case).

< Insert Table 1 >

Figure 3 shows model values for key indicators of lung function for the conditions in Table 1. Figure 3A compares the model's increase in PVR due to HPV from baseline (P_iO_2=20.0 kPa) as a function of P_iO_2 against experimental measurements. These results shows reasonably good agreement between model and data, with the smallest % increase in PVR at the lowest level of P_iO_2 (9.1 kPa). The higher oxygen levels (P_iO_2=13.3 and 12.4 kPa) slightly underestimated the HPV response, but about 3% in both cases. For the lowest oxygen level (P_iO_2=9.1 kPa) the model overestimated the increase in PVR by about 9% - the likely reasons for this are described in the *Discussion*. The alveolar-arterial partial pressure difference (P(A-a), the difference between P_AO_2 and P_aO_2) in Figure 3B, and the change in arterial P_aO_2 in Figure 3C, both show a linear increase with P_iO_2. Note that the P(A-a) values do not include

the contribution of anatomical shunt (approximately 2% of the cardiac output) which would typically reduce P_aO_2 by around 0.67 kPa (5 mmHg).[40]

< Insert Figure 3 >

Model predictions of regional alveolar P_AO_2, V, and Q, as a function of gravitational height - with and without the HPV response - are shown in Figure 4. Results for P_iO_2 = 9.1 kPa (68 mmHg) are shown, to illustrate the most significant HPV response, however other levels of hypoxia showed similar trends. P_AO_2 was lowest in the most gravitationally-dependent region (between about 10-50% lung height, in Figure 4A), corresponding to lower V/Q ratios (V < Q in Figure 4B). This reduction in alveolar P_AO_2 induced the highest HPV response in the gravitationally-dependent lung, subsequently redistributing flow to the non-dependent (cranial) region. This caused a reduction of the gravitationally-dependent perfusion gradient (Figure 4B).

< Insert Figure 4 >

Assessing the impact of HPV in acute pulmonary embolism

The effect of the patient-specific occlusion distributions on blood flow for the 10 subjects with APE has been presented in a previous study.[6] Here we present only the predicted impact of the additional response due to regional hypoxia-induced HPV post embolic occlusion. After occlusion, blood flow that was redistributed to non-occluded tissue produced localized areas of high Q and - because V is assumed unchanged in this study - low V/Q regions. An increased proportion of low V/Q units during APE has been shown clinically.[20] It is within these low V/Q units that HPV occurs. Gas exchange function, assessed as a change in arterial

P_aO_2, improved only marginally with HPV in all subjects (P_aO_2 increased by a mean of 1.5%).

The predicted mPAP and the % increase in mPAP as a result of HPV, when breathing room air (P_iO_2 = 20.0 kPa), are presented for each subject in Figure 5A and B, respectively. mPAP increased by 4 - 28% (mean 8.2%, SD 7.0%) due to regional HPV, corresponding to a mean absolute increase in mPAP of 0.2 kPa (1.6 mmHg). The % increase in mPAP is statistically different from zero (p=0.001). A small but non-significant increase in the impact of HPV on mPAP was observed with increasing clot load. The trend is not statistically significant; this is likely due to inter-subject variability in clot location and size. One subject (with QOI=57.5%) showed a much larger increase in mPAP due to HPV than other subjects (increase = 28%). This subject had occlusion of the entire left lung plus additional emboli in the right lung, and was predicted to have the greatest redistribution of blood flow, with some areas receiving as much as 240% of their baseline (pre-occlusion) flow. This subject also had the lowest P_vO_2 (set to conserve oxygen uptake) which increased the stimulus for HPV. Other subjects had a 'patchier' occlusion distribution and therefore did not have a flow redistribution as large as this subject, and as a consequence other subjects had more modest levels of HPV. When the 'outlier' subject is excluded, the % increase in mPAP is 6.2 ± 2.0 %.

< Insert Figure 5 >

Figure 6 explores the sensitivity of the increase in mPAP via HPV during hypoxia (P_iO_2=9.1 kPa, or 68 mmHg) as a function of the baseline mPAP during normoxia in the 10 subjects. The impact of HPV on mPAP (% increase in mPAP) in Figure 6A diminishes with increasing baseline mPAP during normoxic conditions (which relates to the proportion of vascular

occlusion as shown in Figure 6A). Meaning that when pressures in the model were lower, HPV displayed a larger effect.

Figure 6B plots the mean constriction factor, K, (as defined by Equation 3) against mPAP during normal inspired oxygen conditions. This plot also includes the reduction in K from normoxic to hypoxic conditions. K is inversely proportional to mPAP, indicating that the highest amount of constriction (i.e. lowest K value) was found in the subjects with highest clot load (highest amount of tissue occluded due to emboli). K reduced further in hypoxia, with greatest reduction for the smallest clot loads. The lower limit on K of 0.6 (maximum constriction, see Equation 3) meant that subjects with vessels already at or close to this limit were more limited in the degree to which further HPV could contribute. That is, in the most severe cases, vessels were already constricted at or close to the maximum constriction in normoxia, therefore no further response could be elicited in hypoxia. Simulations using a less hypoxic condition (P_iO_2=12.4 kPa) for comparison were found to be very similar to the results presented in Figure 6 for PiO2=9.1 kPa.

< Insert Figure 6 >

DISCUSSION

The role of HPV in APE is unclear, with some studies suggesting that HPV has a measurable effect on mPAP[1,33] and others suggesting that HPV is not significant in increasing PAP[34], or that there is a diminished HPV response to hypoxia in APE.[12] The current study supports two of these hypotheses that might otherwise seem contradictory: that HPV can make a significant contribution to mPAP in APE, and that the HPV response to hypoxia is concurrently diminished. Our structure-based model explains the pathway for HPV in APE

via development of regions of low V/Q that in turn develop sufficiently low alveolar P_AO_2 to activate the HPV response, while breathing room air. The model shows that there may be a sufficient elevation in mPAP to a level that could be measured experimentally, with the amount of increase depending on clot distribution and severity. The model further explains that subjects with high clot load (severe vascular occlusion) will have a higher proportion of arteries close to maximally constricted by HPV during normal oxygen conditions, when compared with subjects with lower clot load. Therefore their propensity for further vasoconstriction when inspired O_2 is reduced is diminished, corresponding to the diminished responses that are observed experimentally.

Validating the HPV model – comparison with experimental data

The HPV model used here was derived from experimental measurements in dog lungs.[24] Significant species differences in the HPV response have been measured. For example, a study by Peake et *al.*[29] compared HPV in five species (pig, dog, cat, rabbit and ferret) in isolated lung preparations. This study found no substantial HPV response in dog lungs with the largest response observed in the ferret and pig lungs. Numerous other studies have shown significant HPV response in dogs (for example [12,13,25]), nonetheless the Peake et *al.* study highlights the presence of heterogeneity in the HPV response across species and even across subjects within a species. Similar HPV data are not available for humans, therefore before using the HPV model we first confirmed its appropriateness for human by comparing the predicted HPV response with *in vivo* human measurements (Figure 3). These comparisons provide some confidence that the human HPV response, on a global lung scale, is well represented by the relationship used here (Equations 1-3), despite the fact that the model is based on measurements in dogs.

We utilized relevant data from the literature[14,18,41] for comparisons with the model. Three low P_iO_2 conditions were considered, corresponding to conditions from three independent experimental studies. The first (P_iO_2 of 13.3 kPa) was from Dorrington et *al.*,[14] who measured the change in PVR in six healthy volunteers who were taken from a normal end-tidal PO_2 ($P_{ET}O_2$) of 13.3 kPa (P_iO_2 ~20.0 kPa) to a $P_{ET}O_2$ of 6.7 kPa (P_iO_2 ~13.3 kPa). Isocapnic conditions were enforced (by controlling end-tidal alveolar carbon dioxide, P_ACO_2) to exclude any impact of PCO_2 on the vasoconstrictive response. The extended time course of HPV (up to 8 hours) was measured by Dorrington et *al.*, however we considered only the acute (30 minute) response from this experimental study. The second condition (P_iO_2 of 12.4 kPa) was from Westcott et *al.*,[41] who exposed nine healthy volunteers to 13% oxygen for 5-10 minutes. The final condition (P_iO_2 of 9.1 kPa) was from Groves et *al.*,[18] who exposed eight healthy volunteers to a gas mixture containing 9.5% O_2 in N_2 for 10 minutes. Each of these studies provided measurements of cardiac output, mPAP, and mean left atrial pressure (mLAP, inferred from pulmonary capillary wedge pressure), from which we calculated the increase in PVR due to HPV.

The model predictions of the increase in PVR as a function of P_iO_2 compared well with these data (outlined above), with the largest discrepancy between model and data occuring at the lowest level of P_iO_2. There are two likely reasons for this discrepancy. A decrease in regional perfusion due to HPV will reduce P_ACO_2. A reduction in P_ACO_2 is known to decrease the HPV response[5,36]. This effect is currently not included in the model and may be why the model over-predicts the HPV response at this P_iO_2 level (see below for further discussion of this point). In addition this discrepancy may, in part, be due to a diminished HPV response that is known to occur in animals when alveolar P_AO_2<3.3 kPa (25 mmHg).[29,36] However only ~2% of acini in the model reached this criterion (only with P_iO_2=9.1 kPa and not with

any other simulations), and excluding the HPV response entirely reduced the change in PVR by 2.6%. The smallest increase in PVR for both model and experiment also occurred at this low level of P_iO_2. This was due to the increase in cardiac output and the small increase in LAP (from 0.9 to 1.2 kPa) that were induced during this condition. The model predicted a substantial decrease in arterial P_aO_2 with decreasing P_iO_2 (Figure 3C). As P_iO_2 was decreased, the heterogeneity of blood flow also decreased, which led to some improvement in V/Q matching as reflected by the corresponding P(A-a). Further improvement in V/Q resulted from a reduced Q gradient due to the HPV response.

The impact of HPV in APE

In a previous modeling study of APE[7] we found that the redistribution of blood from occluded regions was sufficient to develop high Q regions (therefore low V/Q, assuming V remains unchanged after occlusion). This led to areas of alveolar P_AO_2 that were sufficiently low to experience HPV. The same outcome was observed for all of the 10 patient-specific clot distributions that were used in the current study. HPV increased the mPAP in the model by 4 - 10% for all but one subject, in whom the increase was 28%. The mean increase of 8.2 ± 7.0 % (~0.2 kPa increase in mPAP) – or 6.2 ± 2.0 % when the outlier with largest response is excluded - could be too small an effect in most subjects to be measurable (sub-clinical), however the percentage increase in mPAP tended to increase with clot load, suggesting that this could make an important contribution in subjects with an already high mPAP due to vascular occlusion by emboli. In one of our subjects this difference was sufficient to elevate predicted mPAP from sub-hypertensive to hypertensive levels.

Delcroix et *al.*[12] estimated the HPV response in APE by varying inspired oxygen content (F_iO_2) in dogs with and without autologous blood clots whilst holding cardiac output

constant. They showed that the increase in PVR (using the pressure difference between the pulmonary artery and pulmonary arterial occlusion pressure as a proxy for left atrial pressure) with decreasing F_iO_2 was reduced in the clot conditions compared with the non-occluded cases. They concluded from these measurements that there is a decreased vascular reactivity to hypoxia in APE. Smulders et *al.*[34] further hypothesized that this was due to an abundance of vasoactive mediators in APE, perhaps acting to counter the contracting stimulus of hypoxia. Here we illustrate this same trend, namely a reduction in the HPV response with increasing PE severity, but provide a simpler explanation for its origin.

The only 'active' mechanism in the model is the HPV response, which is dependent on oxygen partial pressures, and limited to a maximal constriction of 0.6 (i.e. an artery can reduce to only 60% of its initial diameter). The HPV response in normoxia increased the mPAP by 4-10% in all but one of the subjects. Vascular constriction occurred in only the small arteries, of which there are on the order of tens of thousands in a parallel circuit arrangement. The parallel arrangement of these small arteries means that their combined resistance is small, and increasing their parallel resistance requires a major decrease in diameter. In the subjects with the largest HPV response in normoxia, arteries that were constricted were close to their maximal allowable constriction (according to the Marshall and Marshall[24] model, Equations 1-3). This means that these arteries were unable to constrict further under hypoxic conditions, as the limit on constriction had already been reached. The HPV response is proportional to the clot load, therefore smaller clot load (or none) equates to a greater propensity to respond to hypoxia via HPV than a higher clot load. The net result is the appearance of a diminished response to HPV in hypoxia, without the need for further vasoactive mechanisms to contribute.

Study limitations

The ventilation and perfusion models that were used to predict gas exchange are quasi-static (non-oscillatory, and not pulsatile), and they do not include any of the peripheral or central control mechanisms that would be required to predict the time-course of response to APE. Including unsteady flow and coupling between the oscillatory cardiac and ventilatory cycles would increase the computational complexity of the model, and it is not clear that it would improve the model accuracy with respect to the aims of the current study. Extending this model to predict the time-course of APE would require including the oscillatory nature of the cardiac and ventilatory cycles and their coupling.

The HPV models that are currently available do not include a time-dependent response as they are empirically derived and are therefore indicative only of the acute (~10 minute) HPV response. The HPV response has been shown to have a slow time response whereby during continued exposure to hypoxia PVR will continue to rise.[14] For this reason the model results were only compared with measurements that were also made during acute hypoxia.

We assumed in our model that HPV is only present in small pre-capillary arteries (<~ 500 μm in diameter). There is some evidence indicating that HPV also occurs within the capillaries and small veins; however, the most significant HPV response occurs in small pulmonary arteries.[36] HPV could also be implemented within the capillary and venous vessels, however the amount of constriction that these vessels undergo is not well known. The only impact of including constriction of these vessels (in addition to constriction of the arteries proximal to them) would be to increase the total impact of HPV on mPAP in the model; regional distribution would be unaffected.

The effects of hypercapnia or hypocapnia on HPV are not currently included. Carbon dioxide (CO_2) is known to affect pulmonary vascular tone in two opposing ways, however these effects have not been quantified well enough to include in the current model. The opposing actions are a direct relaxation of the vascular smooth muscle during alkalosis (hypocapnia), and a constricting effect mediated by a decrease in pH (acidosis, hypercapnia).[5] In theory, an increase in regional P_ACO_2 could cause pulmonary vasoconstriction and thereby contribute to flow diversion; however, the magnitude of this effect is likely to be small, because the maximum possible increase in P_ACO_2 is small when systemic uptake of CO_2 is constant.[36]

The generic model geometry used here was derived using data from a 25 year old healthy male, whereas the mean age of the APE study participants was 51.3 years. The basic geometry of the airway and vascular trees is not expected to change with senescence, so the use of a younger model geometry to represent the older subjects is not likely to be significant for the outcomes of this study. Age-dependent factors that could be important are the lung tissue elastic recoil and loss of terminal airways, both of which would increase ventilation heterogeneity and hence impair V/Q matching and gas exchange. However we note that all of the subjects had normal pulmonary function tests, no prior cardio-respiratory problems, and no evidence of any significant age related decline in lung function. The older lung also experiences loss of gas exchange surface area - which is not represented in the model - but because full equilibration is assumed, the surface area is not relevant within the current model. The older subject can also become less sensitive to hypoxia, and this could potentially affect the cardiorespiratory response in APE. These age-dependent changes are potentially important secondary factors that would be worth considering in future studies.

Summary

We extended an existing, previously passive, model of pulmonary blood flow to include an active HPV response, to explain contradictory experimental observations of the lung's response to APE and hypoxia. The HPV model introduced an active regulatory response of the pulmonary circulation to changes in oxygen partial pressures that resulted from changes in either ventilation or perfusion. Our model is in agreement with studies suggesting that the HPV response is diminished in APE, with a greater reduction in response in subjects with higher levels of arterial occlusion. However, our model suggests that this diminished response to inhaled oxygen can be explained by localized low oxygen regions inducing a close to maximal HPV response, prior to any reduction in inspired oxygen. The model predicts negligible improvement to gas exchange function with HPV in APE.

APPENDIX

Here we provide some additional details for the models used in the current study. Note that each model has previously been published, so further details can be found in the literature.

Lung tissue mechanics

The lung is a non-linearly elastic material which deforms under gravity. A continuum finite element model of lung tissue deformation was proposed by Tawhai et al.[37] in which the lung is assumed to be a compressible, homogenous, isotropic material with the relationship between stress and strain defined by the strain energy density function (W)

$$W = \frac{\xi}{2}\exp(aJ_1^2 + bJ_2), \qquad \text{(A1)}$$

where J_1 and J_2 are the first and second invariants of the Green-Lagrangian finite strain tensor and ξ, a, and b are constant coefficients. This model is solved by assuming that the lung is free to slide within a rigid pleural cavity under gravity loading with the lung parenchyma remaining in contact with the cavity surface. The model predicts regional acinar volumes and pleural pressure, which is used as an input for ventilation and perfusion simulations.

The ventilation model

The distribution of ventilation during normal breathing in the upright posture was simulated using a model of airflow within an anatomically-based structural model of the conducting airways that is coupled to compliant acinar units, as described by Swan et al.[35] The acinar units have volume-dependent compliance, and their initial volume and placement (at FRC) is determined by the gravitational deformation of lung tissue as predicted using the continuum model described above.[37] During breathing the elastic recoil pressure (*Pe*) and compliance

(C) local to each acinar unit is calculated from the same model of tissue mechanics as was solved in the continuum mechanics model using

$$P_e = (\xi e^{\gamma})(3a + b)(\lambda^2 - 1)/(2\lambda), \qquad \text{(A2)}$$

$$C = \frac{\xi e^{\gamma}}{6V_0}\left(\frac{3(3a+b)^2(\lambda^2-1)^2}{\lambda^2} + \frac{(3a+b)(\lambda^2+1)}{\lambda^4}\right), \qquad \text{(A3)}$$

where λ is the isotropic stretch from the undeformed reference volume V_0 and $\gamma = \frac{3}{4}(3a + b)(\lambda^2 - 1)$. The compliant acinar units are coupled to the airway resistance (calculated using a corrected Poiseuille resistance)[30] using an equation of motion at each acinus

$$P_{aw} = V_a/C + R_{aw}Q - P_e, \qquad \text{(A4)}$$

where P_{aw} is the pressure in the terminal conducting airway, V_a is the volume of the acinus, R_{aw} is the resistance of the terminal airway, and Q is the rate of flow in that airway.

The air pressure at the proximal end of the trachea was assumed to be constant and equal to atmospheric pressure throughout the breathing cycle. Pressure values in the model are relative to atmospheric pressure (therefore pressure is equal to zero at the inlet). We neglect the resistance of the upper (oro- or naso-pharyngeal) airway, therefore set the zero pressure boundary condition at the proximal end of the trachea (the 'entrance' to the airway tree model). This assumption is sufficient for the current study in which the distribution of ventilation is the key dependent variable that is predicted by the ventilation model, and this is unaffected by neglecting the normal upper airway resistance. Air was driven into and out of the system via an oscillating muscle pressure boundary condition that acted on each acinar unit. The model presented in Swan et *al.*[35] was implemented in the same subject structural model used in the current study. We therefore use the same model parameters, and hence the

same ventilation distribution was predicted (ventilation gradient = 1.5%/cm, relative dispersion = 20.9% as assessed using 1 cm^3 voxels and acinar ventilation values only).

The blood flow model

In this study, additional functionality is included in the blood flow model that was previously presented by Clark et *al.*,[10] to predict the constriction of vessels as a function of oxygen partial pressures. The components of the model that have been presented previously can be found in references [8-10]. Flow in each pre-capillary artery and vein is defined by

$$\Delta P = (128\mu L)Q/(\pi D^4) + \rho_b g L \cos(\Theta), \quad \text{(A5)}$$

where ΔP is the pressure drop in each vessel segment, μ is the viscosity of blood in the vessel, L is the length of the vessel segment, D is the diameter of the vessel segment, Q is the volumetric blood flow rate in the vessel, ρ_b is the density of blood, g is gravitational acceleration, and Θ is the angle that the vessel makes with the direction of gravity. Conservation of mass is applied at each vessel bifurcation.

The pulmonary capillary beds are treated as lumped parameter 'sheets' using the methods of Fung and Sobin[16]

$$\dot{Q} = (SA)/(\mu f l_c^2).\int H^3 dP_{tm}, \quad \text{(A6)}$$

where A is the alveolar surface area, S is the proportion of this area comprised of capillaries, f is a numerical friction factor, l_c is the average path length from arteriole to venule, H is the thickness of the capillary bed, and P_{tm} is the transmural pressure (transmural pressure is the difference between the internal and external pressure being exerted on a blood vessel). The function H has been well defined by Fung and colleagues[15] over the height of the lung and details of the calculation of the integral term in equation (A6) are given in [9].

Each pulmonary vessel is compliant and Krenz and Dawson[22] showed that the extra-capillary vessels could be modeled using the pressure-diameter relationship

$$D = (D_0)(\alpha P_{tm} + 1), \qquad \text{(A7)}$$

where D is the strained vessel diameter, D_0 is the unstrained (i.e. at zero transmural pressure, Ptm = 0) vessel diameter, and α = 1.49 x 10^{-4} $Pa.s^{-1}$ is vessel compliance.[22] Vessels are assumed to have a circular cross-section, this may introduce some error where vessels are, in reality, elliptical in cross-section (i.e. large veins), however analysis by Yen and Sobin showed that this error will be small (in an extreme case, an ellipse with the major axis twice as large as the minor axes, the mean diameter of the ellipse is only 3.5% larger than that of the circle with an equivalent total circumference).[43] The value for α in Equation A7 is taken from the study of Krenz et al.[22]. In this and earlier studies, α has been found to be essentially independent of vessel diameter, remaining relatively constant over several orders of magnitude from the main pulmonary artery to terminal arterioles. Krenz et al. also compared measurements of pulmonary vascular distensibility from several different studies and found a remarkably similar value (α = 1.49 x 10^{-4} $Pa.s^{-1}$) across all studies. Equation A7 models the nonlinearly elastic vessel wall as distending linearly up to a maximum Ptm of 1.9kPa (14 mmHg); beyond this limit the vessels are inextensible.[44] This does not accurately reflect the nonlinear elastic deformation of the vessel wall, however it is a sufficient approximation for the pressures that are considered in the current study.[22] The vascular networks are tethered to lung tissue, and tissue deformation therefore influences perfusion via shift in the vessel locations and elastic recoil pressures acting to distend the extra-capillary vessels. The continuum mechanics model was used to predict these contributors to flow.

549 The addition of the HPV response in this model impacts on the vessel pressure-diameter
550 relationship (Equation A8) via the resultant constriction factor, *K*, value calculated in
551 Equation 3 such that

552 $$D = (D_0 K)(\alpha P_{tm} + 1). \qquad \text{(A8)}$$

553 With boundary conditions for left atrial pressure (LAP) and flow from the right ventricle
554 (Q_{RV}) predictions can be obtained for the regional distribution of steady-state blood flow and
555 blood pressures (including mean pulmonary arterial pressure, mPAP).

556

557 *The gas transfer model*

558 To estimate the effect of V and Q distributions on gas transfer between air and blood we use
559 a steady-state transfer model based on Kapitan and Hempleman[21] to describe oxygen (O_2)
560 partial pressure balance in each acinus:

561 $$V_I . P_I O_2 - V_A . P_A O_2 = Qk(C_C O_2 - C_v O_2), \qquad \text{(A9)}$$

562 where V_I is the rate of air entering the acinus (L/min), V_A is the rate of air leaving the acinus
563 (L/min), Q is blood flow to the acinus (L/min), k is a constant that accounts for the difference
564 between partial pressure in inspired air and air at body temperature and pressure, $P_j O_2$ is the
565 O_2 partial pressure (kPa, or mmHg), and $C_j O_2$ is the O_2 content in inspired air ($j=I$), alveolar
566 air ($j=A$), end-capillary blood ($j=C$), and the mixed venous blood that enters the lung ($j=v$).
567 The O_2 partial pressure and content (in ml O_2 per 100 ml) in the blood were related by

568 $$C_C O_2 = 15 \times 1.34 \times \rho(P_C O_2) + 0.03 P_C O_2, \qquad \text{(A10)}$$

569 $$\rho(P_C O_2) = \frac{L K_T \sigma P_C O_2 (1 + K_T \sigma P_C O_2)^3 + K_R \sigma P_C O_2 (1 + K_R \sigma P_C O_2)^3}{L(1 + K_T \sigma P_C O_2)^4 + (1 + K_R \sigma P_C O_2)^4}, \qquad \text{(A11)}$$

570 where $\rho(P_C O_2)$ is the oxygen saturation, which is a function of $P_C O_2$.[28] The first term on the
571 right hand side in Equation A13 represents the O_2 bound to hemoglobin, and the second term

572 represents O_2 dissolved in blood plasma. K_T = 10x10^3 L.mol^{-1}, K_R = 3.6x10^6 L.mol^{-1}, L =
573 171.2x10^6, and the O_2 solubility, σ is 1.43x10^{-4} mol.L^{-1}.kPa^{-1}. Refer to [7] for more details.
574
575 The ventilation and blood flow models provide a time averaged V_A and Q, respectively, in
576 each acinus. V_A is corrected for dead space volume, and for the purposes of this study we
577 assume a dead space of 150 ml.[40] To compute this model we must include the additional
578 assumption that alveolar P_AO_2=P_CO_2 at end inspiration (that is, blood remains in the
579 capillaries long enough for O_2 to equilibrate between alveolar air and capillary blood, >0.25
580 s).[40] This enables a solution for P_AO_2 (=P_cO_2) within each acinar unit in the model. To
581 calculate the end expired O_2 partial pressure ($P_{ET}O_2$) an acinar ventilation-weighted sum of
582 P_AO_2 is calculated.
583
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588

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Figure 1: Schematic diagram of the models used and how they interrelate. Details and equations for models are included in the Appendix.

Figure 2: The relationship between inspired oxygen partial pressure (P_iO_2, mmHg) and the % increase in cardiac output from baseline (Q_{RV}, %), using data from [14,18,41]. The relationship was fit using a quadratic curve (dashed line). The fitted function was used to define Q_{RV} (as a model boundary condition) for simulations with different levels of P_iO_2.

Figure 3: The effect of inspired oxygen partial pressures (P_iO_2, mmHg) on (A) increase in pulmonary vascular resistance (PVR) from baseline (normoxic) to hypoxic conditions (NB/ during normoxia, P_iO_2=150 mmHg, simulation and experimental points are overlaid, both equal to zero); (B) P(A-a) gradient; (C) arterial oxygen partial pressure (P_aO_2). Black diamonds show experimental data,[14,18,41] and grey triangles show model results.

Figure 4: The impact of HPV on (A) predicted alveolar oxygen partial pressures (P_AO_2), and (B) acinar blood flow (Q) and ventilation (V). Results are shown for baseline (no HPV, dashed lines) and post-HPV (solid lines) when P_iO_2 is reduced to 68 mmHg. Results for mean acinar values within iso-gravitational slices of 10 mm thickness (including ± one standard deviation) are plotted with respect to gravitationally-dependent lung height along the craniocaudal axis (0% corresponds to the caudal-most point).

Figure 5: The impact of HPV in 10 patient-specific PE distribution models [6] during normoxia (P_iO_2=150 mmHg). (A) Simulation results showing the impact of HPV on mean pulmonary arterial pressure (mPAP) plotted as a function of the embolus obstruction index (QOI, %). Black triangles indicate predictions of mPAP without HPV, and grey diamonds illustrate

mPAP predictions with the HPV mechanism included. Horizontal dashed line at PAP=25 mmHg indicates the threshold for clinically defined PH. (B) % increase in mPAP is plotted for each subject. Dashed line shows a linear fit to the data, although the trend is not statistically significant.

Figure 6: Relationship between mean pulmonary arterial pressure (mPAP) predicted at normoxia (P_iO_2=150 mmHg) and: (A) the % increase in mPAP due to HPV between normoxia and hypoxia (P_iO_2=68 mmHg), (B) the mean constriction factor (K) calculated as described by [24] (see Equation 3) at normoxia (dashed line shows linear fit through this data) and the decrease in this K value at P_iO_2=68 mmHg.