# The mitigation of increased pulmonary vascular resistance in experimental acute pulmonary embolism

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## Rationale

Acute pulmonary embolism (APE) can cause acute pulmonary hypertension in some subjects, but only if the pulmonary vascular resistance (PVR) is sufficiently increased to require a higher pulmonary artery pressure (PAP) than at baseline [1, 2].

PVR can be increased by embolic occlusion of arteries, or by release of vasoconstrictive substances from blood clot emboli. Hypoxic pulmonary vasoconstriction (HPV) could also play a role.

Alternatively, **PVR increase can be mitigated** by recruitment of capillaries, and potentially by **recruitment of arterio-venous shunts** (AVS) or **supernumerary vessels** (SVs) [3, 4] .

## Methods

***Animal studies:***

Four pigs were included in this study. * Volumetric CT imaging acquired with animals supine. Animals ventilated with 100% $O_2$, hence HPV assumed insignificant. PAP, pulmonary capillary wedge pressure ($P_{cw}$), cardiac output (CO), and blood gases measured at baseline and following each intervention. APE simulated by occluding a lower lobe sub-segmental artery ('occlusion 1'), the majority of the lower lobe ('occlusion 2'), and a major pulmonary artery ('occlusion 3') in left lung for Subject 1 and 4; in right lung for Subject 2 and 3. The occluded tissue is illustrated for Subject 1 in Figure 1.

***Biophysical model:***

An **anatomically-structured pulmonary vascular model** created for each animal, including animal-specific arterial and venous geometries, ladder-like microvascular model [5] including recruitable capillary sheets, hydrostatic pressure gradient. Baseline and post-embolus perfusion distributions were simulated, with measured CO and left atrial pressure (i.e. $P_{cw}$) as boundary conditions to the model (Table 1).

***Blood flow distribution*** *and* ***PAP****:* simulated in response to animal-specific boundary conditions, and location of emboli.

## Aims & Objectives

- To validate a structure-based biophysical model for perfusion of the porcine lung.
- To determine whether vascular distension and recruitment – as described within the biophysical model – is sufficient to mitigate PVR increase in APE.
- To estimate the contribution of alternate perfusion pathways ( AVS and/or SVs**) to mitigating PVR.**

## Work Flow Schematics

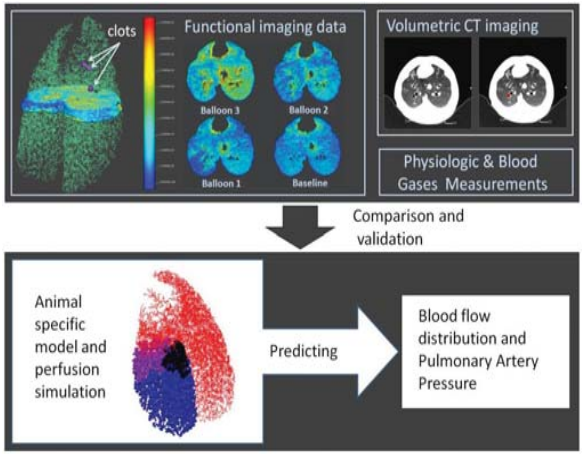


*Figure 1. Schematic of validating an anatomically-structured porcine pulmonary vascular model by using functional imaging data, volumetric CT imaging, physiological measurements, and image intensity, to predicting blood flow distribution and pulmonary artery pressure.*

## Validation of Baseline Model

| | | subject 1 | subject 2 | subject 3 | subject 4 |
|---|---|---|---|---|---|
| Experimental data | LAP (mmHg) | 4.00 | 5.00 | 5.00 | 5.30 |
| | CO (L/min) | 2.61 | 4.96 | 5.02 | 3.80 |
| | MPAP (mmHg) | 18.00 | 19.00 | 18.00 | 21.00 |
| | PVR (mmHg·min/L) | 5.36 | 2.82 | 2.59 | 4.13 |
| Model predictions | PAP (mmHg) | 18.00 | 19.01 | 18.03 | 21.01 |
| | PVR (mmHg·min/L) | 5.36 | 2.82 | 2.60 | 4.13 |

*Table 1. Comparison between physiological measurements and simulation results for all 4 subjects (with PAP and LAP in mmHg, CO in l/min and PVR in mmHg*min/l) pre-occlusion.*

## Mitigation of Increased PVR

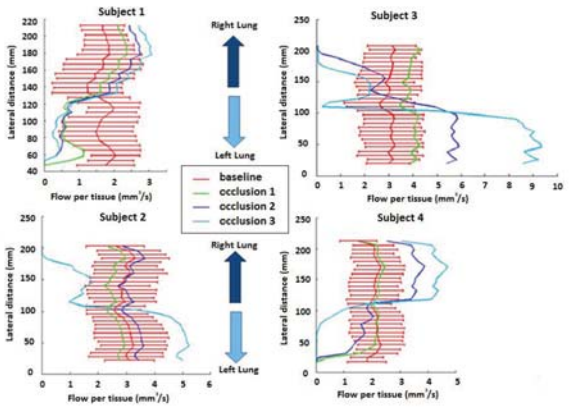


*Figure 2. Blood flow distribution in the medial-lateral axis for four animals at baseline and four three levels of arterial occlusion. Flow is averaged within 10 mm sections. Results shown in this axis to illustrate change in perfusion between the two lungs of the individual animals.*

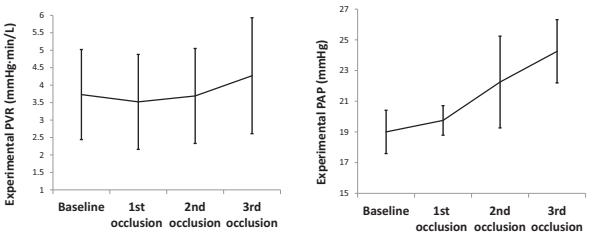


*Figure 3. Mean experimental PVR (Left) and PAP (Right) for baseline and post-occlusion conditions. PVR was unchanged post-occlusion, whereas PAP increased to accommodate increased CO. Arterial occlusion without capillary recruitment would increase the PVR.*

## Evidence for Alternate Pathways

| | % occlusion ± SD | % PAP difference between model and data (range) | % PVR difference between model and data (range) |
|---|---|---|---|
| **Baseline** | 0.00 ± 0.00 | 0.39 (0.03 - 1.32) | 0.50 (0.04 - 1.70) |
| **1st occlusion** | 9.00 ± 11.12 | 4.93 (-0.77 - 8.59) | 7.15 (-1.21 - 11.66) |
| **2nd occlusion** | 28.15 ± 3.05 | 6.36 (1.60 - 8.80) | 9.69 (1.96 - 14.53) |
| **3rd occlusion** | 41.15 ± 7.66 | 11.86 (-1.16 - 39.33) | 15.48 ( -1.80 - 52.12) |

*Table 2. Percentage of occlusion ± standard deviation, and percentage of difference between model and experimental PAP and PVR (range of difference). Animal-specific PAP was predicted by the model at baseline with error < 1.33%, indicating a good baseline model predictions; and PAP was over-predicted for post-occlusion simulation. Model predicted PVR at baseline with error < 1.71 %.*

## Summary & Discussion

Animal-specific PAP was predicted by the model at baseline (Table 2), indicating a **good model representation of each animal's baseline PVR**.

The model predicted **recruitment of previously un-perfused capillaries and increased flow heterogeneity following occlusion** (Figure 3), consistent with prior experimental and modelling studies [5].

The experimental animals were able to **maintain PVR post-occlusion** (Figure 2), even with almost whole lung occlusion. This is driven by increased CO post-occlusion, which reduces PVR by recruiting previously unperfused pathways.

**PVR and hence PAP were consistently over-predicted** for the post-occlusion simulations, with over-prediction increasing to ~12% and ~15% for PAP and PVR, respectively. Alternate mechanisms – not included in the model – are likely acting to reduce PVR.

Model does not include **AVS** or **SV recruitment**; their recruitment is the most likely explanation for **additional mitigation of PVR during vascular occlusion**.

**References**

[1] Tapson, 2004 *Cardiol Clin* 22: 253-265;
[2] Elliot, 1992 *Chest J* 101: 163S-71S;
[3] Bates et al, 2012 *J Appl Physiol* 112: 1915-20;
[4] Shaw et al, 1999 *J Appl Physiol* 87: 2348-56;
[5] Clark et al, 2011 *J Appl Physiol* 110:943-55

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* Animal studies referred in to in this work were approved by the University of Iowa Institutional Review Board and Animal Ethics Committee. *The experiment* was conducted at the University of Iowa I-CLIC (Iowa Comprehensive Lung Imaging Center).