TITLE:

Lack of functional information explains the poor performance of 'clot load scores' at predicting outcome in acute pulmonary embolism

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Abstract

Clot load scores have previously been developed with the goal of improving prognosis in acute pulmonary embolism (PE). These scores provide a simple estimate of pulmonary vascular bed obstruction, however they have not been adopted clinically as they have poor correlation with mortality and right ventricular (RV) dysfunction. This study performed a quantitative analysis of blood flow and gas exchange in 12 patient-specific models of PE, to understand the limitations of current clot load scores and how their prognostic value could be improved. Prediction of hypoxemia in the models when using estimated baseline (non-occluded) minute ventilation and cardiac output correlated closely with clinical metrics for RV dysfunction, whereas the clot load score had only a weak correlation. The model predicts that large central clots have a greater impact on function than smaller distributed clots with the same total clot load, and that the partial occlusion of a vessel only has a significant impact on pulmonary function when the vessel is close to completely occluded. The effect of clot distribution on the redistribution of blood from its normal pattern - and hence the magnitude of the potential effect on gas exchange – is represented in the model but is not included in current clot load scores. Improved scoring systems need to account for the expected normal distribution of blood in the lung, and the impact of clot on redistributing the blood flow.

Keywords: Pulmonary embolism, computational model, perfusion, gas exchange, pulmonary pathology

1 Introduction

Pulmonary embolism (PE) is a major cause of cardiovascular mortality (Douma et al., 2010). Despite this, it remains one of the most challenging medical presentations in the emergency department: it is frequently under-diagnosed and, once diagnosed, accurate prognoses are difficult to make (Abunasser et al., 2012; Collomb et al., 2003; Lee et al., 2005). Although hemodynamic instability as a result of right ventricular (RV) failure is the most important determinant of mortality in PE (Agnelli and Becattini, 2010; Ghaye et al., 2006a; Kasper et al., 1997), a significant 90 day mortality rate (of 8-15%) has been observed in hemodynamically stable - or non-massive - PE, in patients in large multi-center studies (Goldhaber et al., 1999; Kasper et al., 1997; Nijkeuter et al., 2007; van Strijen et al., 2003). Making an accurate prognosis in non-massive PE is essential because patient management and therapeutic strategies rely on the ability to stratify risk effectively (Ghaye et al., 2006a). For this reason several scoring systems have been proposed for risk stratification and to assess the severity of obstruction (Abunasser et al., 2012; Ghaye et al., 2006a; Ghaye et al., 2006b). Many of these scoring systems aim to quantify the level of mechanical obstruction in PE by providing a 'clot load score' based on computed tomography pulmonary angiography (CTPA) (Mastora et al., 2003; Miller et al., 1998; Qanadli et al., 2001; Walsh et al., 1973).

CTPA clot load scores vary in complexity in an attempt to balance the need for simplicity in a clinical environment with prognostic utility. Ghaye et al. (2006a) review the existing scoring systems in detail. The earliest, and simplest, systems were designed for use with pulmonary angiograms, but have on occasion been adapted for use in CT. They allocate points to the pre-segmental pulmonary arteries, with each segment that is occluded receiving the same weighting (a segment in the upper lobe is treated the same as a segment in the middle or lower lobe) (Miller et al., 1998; Walsh et al., 1973). The Qanadli obstruction index (QOI) (Qanadli et al., 2001) further refines the assessment of clot load by accounting for partial occlusion of blood vessels, treating the impact of a partially occluded vessel as half that of a fully occluded one. The percentage QOI is defined by

$$QOI = \sum \frac{nd}{40} \times 100\%,$$

where *n* represents the number of segmental arteries lying distal to the clot (maximum 20), *d* represents its level of occlusion (*d*=0 implies no occlusion, d=1 implies partial occlusion, and *d*=2 implies full occlusion), and the 40 in the denominator represents the maximum possible absolute score (20 segmental arteries that are fully occluded). Isolated emboli in subsegmental arteries are treated as partially occluded segmental arteries and contribute a score of 1 to the QOI. The Mastora score (Mastora et al., 2003) is the most complex scoring system and assigns up to 5 points depending on the percentage of vessel obstruction for each mediastinal, lobar and segmental occlusion. Each point implies an additional 25% occlusion (1 implies <25% occlusion, 2 implies 25-49% occlusion, etc.). The Mastora score can be split into three separate scores: the central score which defines the degree of obstruction to mediastinal and lobar arteries; the peripheral score which defines obstruction to segmental arteries; and a global score which combines the central and peripheral scores. Despite their varying degrees of complexity, the different methods for scoring PE clot load are highly correlated, and there is no significant difference between predicted outcomes using the available scoring systems (Ghaye et al., 2006b).

Although clot load scores can provide some indication of the severity of a PE episode (Collomb et al., 2003), several studies have questioned their efficacy as predictors of mortality or impact on RV function (Araoz et al., 2003; Ghaye et al., 2006a; Ghaye et al., 2006b; Smulders, 2000). Explanations for the failure of these scoring systems to predict RV dysfunction include that mechanical obstruction is not the only factor at play in response to PE; underlying pathologies can influence outcome; small peripheral emboli cannot be detected with conventional imaging; or that clot load scores are too simplistic and do not properly account for the potential functional impact of emboli. A major limitation of clot load scores is illustrated by comparing surgical removal of a whole lung (or unilateral balloon occlusion) with an autologous PE that occludes just 25% of the vascular bed. Obstruction indices would give a higher score for the former case, yet in reality this rarely results in RV failure; in comparison the 25% occlusion by autologous clot can cause significant hypertension (Alpert et al., 1978; McIntyre and Sasahara, 1971b). Vedovati et al. (2012) found that the 30 day rate of all causes of death and/or clinical deterioration, determined in 516 hemodynamically stable PE patients, was dependent on clot location (central, lobar, distal), but not on the level of mechanical obstruction as calculated by the QOI (Qanadli et al., 2001). The question is then, is the concept of a clot load score, as defined by vascular occlusion, too simplistic to be of practical use in assessing the response to PE?

To address this question we employ a combination of computational modeling and analysis of clinical data to assess the functional response to PE. Computational models provide a non-invasive approach to investigating function, and can be used to tease apart the contributions of individual mechanisms to whole organ function in a manner that is not possible by experiment or statistical analysis of clinical data (Tawhai et al., 2011). Using computational models of perfusion (Clark et al., 2011), ventilation (Swan et al., 2012), and oxygen transfer (Burrowes et al., 2011b), we here assess the simplifying assumptions of the scoring systems. We hypothesize that patient-specific hemodynamic models will capture features of the response to a clot load more completely than a simple obstruction score, by including the effects of partial obstruction and central versus peripheral clot loads.

2. Methods

2.1 Patient Data

Volumetric CTPAs were obtained from 12 adult subjects who underwent routine examination for clinically suspected acute PE at Auckland City Hospital. 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. To minimize confounding effects due to other causes of ventilation perfusion ($\dot{V}/\dot{Q}$) mismatch, subjects were excluded if they had known pre-existing lung disease or evidence of lung disease on CT, had recent surgery (up to 10 days), or had a history of ever or current smoking. Subjects who met selection criteria were selected sequentially from patients presenting at Auckland City Hospital, with no restrictions on age, body mass index or gender. Subjects underwent pulmonary function testing following recruitment into the study to confirm normal lung function, and RV function was assessed via transthoracic echocardiography. The data used in this study is summarized in Table 1. All scans were acquired on a Phillips Brilliance 128, multislice CT scanner. CTPA was performed at submaximal inspiration (to prevent the valsalva effect that can occur in full inspiration) using 120ml IV contrast at 4ml/sec delivered by antecubital vein, auto triggered from the left atrium. Acquisition time was 7 seconds. All scans were of good diagnostic quality.

CTPAs were scored retrospectively by a radiologist (D.G.M.). The scans were examined on a workstation and multiplanar reformats were employed so that embolus size could be accurately assessed by the reviewing radiologist. Each visible embolus was identified and a QOI and Mastora percentage was calculated for each subject.

To assess the impact of PE on RV function, transthoracic echocardiography was obtained in each patient and, where possible, measures that could be used to indicate RV failure or pulmonary hypertension were recorded. Systolic pulmonary artery pressure (sPAP) was estimated in 7 of the 12 patients and tricuspid regurgitation velocity (TRV) in 9 of the 12 patients. Patients were classified dependent on whether their echocardiogram indicated RV dysfunction. Each patient's heart rate (HR), respiratory rate (RR), systemic blood pressure and jugular vein pressure were recorded. In addition a CTPA based assessment of the RV was made by calculating the ratio of RV to left ventricle (LV) volume. (RV/LV) was calculated using similar methods to previous studies (Apfaltrer et al., 2011; Henzler et al., 2010; Kang et al., 2011) that have shown RV/LV to be an accurate indicator of RV dysfunction in PE. The ventricles were semi-automatically segmented from the inferior aspect of both ventricles to the valvular plane using the 'Grow Region' tool in OsiriX (Rosset et al., 2004) (version 4.1.2). The pixel attenuation (Hounsfield Unit - HU) for septal myocardium was calculated by using an oval region of interest selector in OsiriX and the mean and standard deviation of the HU values in this region were calculated. Any tissue with HU values in the range of this mean ± one standard deviation was assumed to be myocardium. The valvular plane was manually segmented and the ventricular volume was calculated to be the region surrounded by the myocardium and the valvular plane.

The main pulmonary artery, aorta, superior vena cava and azygos vein diameters were estimated from CTPA for each patient using the OsiriX electronic caliper tool. Measurements were obtained in the plane perpendicular to the long axis of the vessel from adjusted multi-planar reformatted images. The measurement of each vessel was obtained via similar methods to the comparison of Ghaye et al. (2006b) between clot load scores and cardiovascular parameters. That is, the diameter of the main pulmonary artery was obtained proximal to its bifurcation, the ascending aorta was measured in the middle third, the superior vena cava was measured at the level of the azygos arch, and the azygos vein was measured in the portion facing the right tracheal wall.

The Pearson's correlation coefficient was used to assess correlation between variables, and Student's T-tests were used to compare continuous variables between groups and to test the significance of linear correlations between continuous variables.

2.2 Geometric Models

A geometric model of pulmonary arteries, veins, airways and embolus distribution was created for each subject. The lungs, lobes, central airways and blood vessels were segmented from CTPAs using PASS (Pulmonary Analysis Software Suite, University of Iowa (Hu et al., 2001)). This software is able to segment all but the blood vessels that lie between the two lungs, which were manually segmented within the PASS framework. Finite element tree structures were constructed to represent each of the arterial, venous and airway trees to the level of the first sub-segmental branches using CMGUI software (http://www.cmiss.org/cmgui). Each branch was represented in the finite element tree by a vector describing its centerline (or multiple vectors in the case of large curved vessels and airways) and a scalar describing the radius of each branch segment. Vessels beyond this level were generated by a volume-filling branching algorithm, which fills the segmented lung volume and matches as closely as possible the properties of measured human pulmonary trees (in terms of branching angles, number of terminal branches, number of generations/orders and vessel size) (Tawhai et al., 2000). The baseline (unstrained) radius of each vessel was dependent on its Strahler order and defined using previous morphometric studies, as described previously (Clark et al., 2011), and the elastic vessels of the lung were allowed to distend in response to changes in blood pressure.

The three dimensional distribution of emboli within the lung was determined via a semi-automated procedure and validated against radiologist identified emboli (Tawhai et al., 2012). The embolus-detecting algorithm searches first for emboli within major blood vessels by identifying a range of HU values that represent potential emboli, and then removing false positives from this set. The CTPAs were contrast enhanced, hence the non-stationary blood had a higher HU than the thrombi that were identified within the arteries (a thrombus appears as a gray area within a white blood vessel). The detection algorithm, like other algorithms for detecting emboli (Masutani et al., 2002), can identify false positives due to vessel walls and bifurcations, lymph nodes, parenchymal tissue, or veins being incorrectly identified as emboli. False positives due to small regions

incorrectly identified as emboli were first eliminated by smoothing the lung into 4x4x4 mm voxels, and removing potential emboli that filled less than half of this volume. Larger false positives were removed manually. The identified emboli were mapped to the artery in which they reside using the CMGUI software. To do this the element (branch) number corresponding to an occluded artery was linked to an estimate of effective embolus radius. This was calculated by determining embolus volume for an occluded segment. The embolus volume was calculated in a similar manner to the calculation of vessel dimensions by Lee et al. (Lee et al., 2013). That is, the area of regions of interest representing embolus in a single vessel segment was summed and multiplied by the spacing between each image slice to estimate the volume. We then assumed that the embolus spans the whole length of the vessel segment in which it resides, with long vessels being comprised of multiple segments. The calculation of effective embolus radius from its estimated volume may underestimate the true embolus radius (Tawhai et al., 2012).

2.3 Functional Models

Perfusion, ventilation, and oxygen transfer were simulated in each subject. The effect of gravity on pleural pressure was accounted for by assuming a linear gradient in pleural pressure of 0.25 cmH_2O per cm height in the direction of gravity (West, 1995) as in Burrowes and Tawhai (2006), with the main pulmonary artery acting as a reference gravitational height (gravitational pressure head is equal to zero at this location). The pleural pressure acts externally to tissue in which the airways and blood vessels are embedded, with the most gravitationally dependent vessels being subjected to the least negative pleural pressures (Burrowes and Tawhai, 2006). Simulations were conducted in the upright posture with a gravitational acceleration of 9.81 $m.s^{-2}$. Perfusion was simulated using a steady state model of blood flow (Clark et al., 2011). The model assumes Poiseuille flow in elastic extra-capillary blood vessels, and includes a 'ladder-like' model for the intra-acinar circulation at each acinus. The ladder model comprises a symmetric acinar blood vessel structure with capillary sheets connecting each generation of blood vessels (Clark et al., 2010; Fung and Sobin, 1969). This whole circulation model predicts a time-averaged distribution of blood, and mean pulmonary artery pressure (mPAP). Ventilation was simulated via a quasi-steady model (Swan et al., 2012). The model comprises anatomically based conducting airways subtended by compliant acinar tissue units with flow driven by an oscillating driving pressure that acts to expand the lung. The resistance of extra-acinar airways was assumed to be its Poiseulle

resistance modified by turbulent energy loss at airway bifurcations (Pedley et al., 1970). In each compliant acinar unit subtending a terminal bronchiole, air pressures and flows were balanced using an equation of motion (Swan et al., 2012). Oxygen transfer from air to blood was modeled by assuming equilibration of oxygen between air and blood (e.g. Kapitan and Hempleman (1986)) in each acinar unit. That is,

$$\dot{V}_I P_{I_{O_2}} - \dot{V}_E P_{A_{O_2}} = k\dot{Q}_C (C_{c_{O_2}} - C_{\bar{v}_{O_2}}), \quad (1)$$

where $\dot{V}_I$ is the unit's inspired ventilation, $P_{I_{O_2}}$ is inspired oxygen partial pressure, $\dot{V}_E$ is expired ventilation, $\dot{Q}_C$ is the capillary blood flow, $C_{c_{O_2}}$ is the oxygen content in end-capillary blood, $C_{\bar{v}_{O_2}}$ is oxygen content entering the lungs from mixed venous blood, *k* is a constant that accounts for differences between body temperature and pressure and inspired air temperature and pressure as well as allowing consistency between the units of the left and right hand side of eqn. 1. The non-linear Monod-Wyman-Changeaux (Monod et al., 1965) model of the relationship between oxygen content and partial pressure was used. Carbon dioxide transport was also simulated using the same assumption of equilibration between air and blood, with the relationship between carbon dioxide content and partial pressure defined using the Harris model (Harris et al., 1970). The assumption of equilibration breaks down when the red blood cell transit time across the capillary bed is less than the theoretical time for equilibration (0.25 s), however in all simulations conducted here the predicted transit time is greater than 0.25 s so equilibration can be assumed.

Emboli were assumed to act as solid obstructions to blood flow, with radii calculated as described above, and the elastic arterial walls were assumed able to distend around the embolus (Tawhai et al., 2012). If an embolus was of the same size as the blood vessel that contains it, then blood flow through that vessel was assumed negligible. Otherwise, the effective radius of a vessel for perfusion simulation was the radius of the perfused vessel minus the radius of the embolus.

2.4 Simulation studies

Simulations were conducted in the structure-based models that were constructed for each of the 12 subjects 1) under baseline conditions, 2) with systematic occlusions of lobar blood vessels, and 3) with subject-specific occlusions to compare model results with current obstruction indices. Baseline resting cardiac output and tidal

volume were estimated on a subject-by-subject basis based on the height, weight and age of the subject, and assuming a respiratory rate (RR) of 12 breaths per minute and heart rate (HR) of 65 beats per minute. The metabolic rate for each subject at rest in the upright posture was calculated from the formulae of Levine et al. (Levine et al., 2000), and translated to an oxygen uptake rate and ventilation rate (Weir, 1949). Finally, cardiac output was calculated from oxygen uptake rate using the formulae of Stringer et al. (Stringer et al., 1996). Systemic oxygen requirements were assumed to remain the same pre- and post- occlusion, and venous oxygen content was recalculated post-occlusion to satisfy this condition. Ventilation was assumed to remain approximately at baseline conditions post-occlusion, as was assumed in a previous computational model that aimed to capture the impact of $\dot{V}/\dot{Q}$ distributions on respiratory deadspace measurements (Tang et al., 2005). Studies have shown minor changes in ventilation distribution with pulmonary embolism (Altemeier et al., 1998; Tsang et al., 2000; Tsang et al., 2005) and we assume in this study that these changes are negligible.

Each subject considered in this study had elevated HR and RR post-embolus compared to the expected normal values. Ventilation rate and cardiac output were not acquired as part of the routine diagnostic process. The estimated baseline CO and minute ventilation are for resting values, so they may not accurately reflect the CO and minute ventilation post-occlusion. Prior studies show that many patients with PE present with a lower than normal Pa_{CO_2} and respiratory alkalosis, which appears to be the result of increased minute ventilation (Elliot, 1992; Santolicandro et al., 1995; Stein and Levy, 1974). Indeed the respiratory rate of several subjects here implies this might be the case. An elevation in heart rate with a maintained stroke volume would result in increased CO. Some studies have indicated a higher than normal CO in sub-massive PE, in patients with no prior cardio-respiratory disease (McIntyre and Sasahara, 1971b, 1974) . However, most evidence in PE points to reduced or static CO (McIntyre and Sasahara, 1974; Sasahara, 1973). We therefore re-simulated response to PE with two alternate conditions 1) assuming that tidal volume and stroke volume can be maintained such that CO and minute ventilation increase, and 2) assuming that stroke volume is not maintained and CO remains at baseline, but that tidal volume is maintained with increasing RR. These two simulation conditions reflect ‘best-case’ scenarios. The first predicts an idealized situation whereby CO and minute ventilation are proportional to HR and RR respectively, and the second presents a more realistic scenario whereby tidal volume is maintained but right heart strain prevents stroke volume being maintained.

3. Results

Table 1 summarizes the measures obtained from clinical and imaging data in this study. The mean QOI across the 12 subjects considered here was 51% (range 5-78%) and the mean Mastora score was 51% (range 7-77%). There was a statistically significant correlation between the two scores (R^2=0.80, p<0.001). The QOI and Mastora scores are compared as predictors of sPAP and RV/LV in Figure 1. The QOI and Mastora scores have a significant correlation with RV/LV only (p=0.02, and p=0.03, respectively).

3.1 Baseline simulations

In the upright posture (at rest, baseline) without emboli, the model predicted a mean mPAP of 14.7±0.8 mmHg, a mean partial pressure of oxygen in arterial blood (Pa_{O_2}) of 96.1±2.0 mmHg, and a mean partial pressure of carbon dioxide in arterial blood (Pa_{CO_2}) of 37.6±0.4 mmHg over the 12 subjects. All values were within the normal range for each subject: a comprehensive literature review by Kovacs et al. defines normal mPAP as 14.0±3.3mmHg (Kovacs et al., 2009), normal Pa_{O_2} between 80-100 mmHg, and normal Pa_{CO_2} between 35-45 mmHg.

3.2 Systematic occlusion of lobar vessels

Gravitational location and cumulative occlusion: Table 2 shows the effect of occluding each individual lobe (in full) across the 12 subjects on predicted mPAP and Pa_{O_2}. The distribution of left and right lung and lobe volumes from end-inspiratory imaging in the supine posture is given in the third column of Table 2, with the corresponding QOI/Mastora score for occlusion of this volume listed alongside. As we have considered complete occlusion in this case the QOI and Mastora scores are equivalent and roughly proportional to the volume distribution. Flow to each volume in the upright posture is given as the % of CO per % of lung volume. If perfusion were uniform, then this would be unity for all volumes. Flow to the two lungs is distributed in proportion to volume, whereas the gravitational dependence of blood flow causes greater perfusion per volume in the lower than upper lobes (i.e. 29% greater flow to the lower lobes than if the perfusion were uniform). It

is clear that the increase in mPAP or decrease in Pa_{O_2} (both given per % of total lung volume with decreased perfusion) is greater with the whole of the left or right lung occluded than it is for any individual lobe within that lung. mPAP and Pa_{O_2} are more sensitive to occlusion of the lower and middle lobes than the upper. This is illustrated further in Figure 2, which shows the effect of systematically occluding each segmental vessel in the right lung from apex to base in a single representative subject. The model predicts that in the absence of gravity, the influence of segmental vessel occlusion is roughly proportional to the volume of tissue distal to the occlusion There is some non-linearity in this relationship because of uneven segment sizes and a minor influence of the limit of vessel distensibility as more and more vessels are occluded. However, because of the non-uniformity of normal perfusion distribution, when gravity is introduced the effect of occlusion becomes dependent on the gravitational distribution of clot load, with the cumulative upper and middle lobe occlusions having a smaller effect on mPAP when gravity is included, and lower lobe occlusion producing a rapid increase in the effect on mPAP. Occluding vessels from the base to the apex of the lung has the opposite curvature to that shown in Figure 2, with more rapid increases in mPAP than the zero gravity case when the first (basal) vessels are occluded and a lesser effect when the last (apical) vessels are occluded.

Partial occlusion: Clot load scores typically account for partial occlusion with an on/off score, for example the QOI attributes half the score of a fully occluded vessel to each partially occluded vessel. Figure 3 shows the effect of partial occlusion of a single lobar vessel in one subject on the post-occlusion increase in mPAP. The vessel is more than 50% occluded before a significant increase in mPAP occurs, indicating that the impact of partial occlusions on QOI may be over-estimated. The increase in mPAP with partial occlusion approximately follows the relationship $1/r_E^4$ where r_E is effective vessel radius. Regardless of whether the occluded vessel is lobar or segmental, significant increases in mPAP only become obvious when r_E is less than approximately 1.5 mm.

3.3 Patient-specific occlusions

Predicted mPAP was increased above baseline in each subject when patient-specific occlusions were introduced (whilst maintaining baseline CO and minute ventilation). mPAP post-occlusion under these conditions was 19.8±2.7 mmHg. Predicted Pa_{O_2} decreased to 65.2±19.3 mmHg, and predicted Pa_{CO_2} increased

to 60.0±15.1 mmHg. 8 of the 12 subjects were predicted to develop hypoxemia (Pa_{O_2}<80 mmHg) under these conditions, and all but one subject were predicted to be hypercapnic (Pa_{CO_2}>45 mmHg). Each of the subjects that was predicted to be hypoxemic was identified as having RV dysfunction from echocardiogram. In contrast, none of the subjects with predicted Pa_{O_2}>80 mmHg (for baseline CO and minute ventilation) had signs of RV dysfunction. As there is inter-subject variation in predicted baseline mPAP and Pa_{O_2}, the percentage increase from baseline in these measures provides a more meaningful indication of the response to embolization and so these values are used instead of absolute values from this point forward. Table 3 summarizes the predicted responses to subject-specific occlusions.

There was a significant correlation between most of the clinical indicators of RV dysfunction (sPAP, RV/LV and TRV correlated with one another with $p<0.04$ in each case), but no significant correlation between these measures and weight, HR, RR, systemic blood pressures, jugular vein pressure or the ratio of the main pulmonary artery to aorta diameter. Model predictions of pulmonary artery pressure (PAP) and Pa_{O_2} are compared as predictors of sPAP and RV/LV in Figure 4. Model-predicted mPAP and Pa_{O_2} correlate strongly with sPAP and RV/LV ($p<0.01$ in each case). In addition to the correlations shown in Figure 4, predicted mPAP and Pa_{O_2} correlate strongly with TRV ($p<0.001$), whereas QOI and Mastora scores do not ($p=0.14$).

To illustrate why the functional model under baseline CO and minute ventilation correlates more closely with RV dysfunction than the QOI, we consider two subjects with the same QOI (45%) but with differing embolus distribution. Subject 2 (S2) has large central emboli that occlude whole lobes, but few small clots. Subject 8 (S8) has a large embolus that occludes the left upper lobe and several partially occluded segmental vessels in both lungs. Figure 5A shows the predicted redistribution of blood flow in S2 and S8 post-embolus occlusion. The model agrees closely with the QOI in terms of the percentage of capillary bed that is distal to occlusions (41% in each subject). The consequence of this difference is a predicted increase in physiological deadspace and a significantly reduced (hypoxemic) Pa_{O_2} for S2 (a 27% increase in deadspace from baseline and Pa_{O_2} = 66 mmHg) compared with S8 (a 20% increase in deadspace from baseline and Pa_{O_2} = 88 mmHg). Pa_{O_2} for S8 was predicted to be just below normal (Figure 5). S2 also had a higher predicted PAP response than S8. In

general, patients with large central emboli had greater predicted response to occlusion than those with smaller distributed clot loads.

3.3 Increased minute ventilation and cardiac output

Simulations where CO and minute ventilation were increased proportionally to subject-specific HR and RR predicted a further elevation in mPAP in each subject (to mean value of 21.8±3.6 mmHg). Predicted Pa_{O_2} increased in each subject, compared with simulations using resting CO and minute ventilation, to 101±9 mmHg. Predicted Pa_{CO_2} decreased in each subject, to 37.7±12.9 mmHg. Correlations between the model-predicted increase in mPAP and sPAP or RV/LV were strongly correlated (R^2=0.77, p=0.009 and R^2=0.67, p=0.001 for sPAP and RV/LV, respectively). When minute ventilation was increased to match subject-specific RR, and CO was held constant at baseline values, the predicted Pa_{O_2} and Pa_{CO_2} were 96.6±12.7 mmHg and 35.7±10.5 mmHg, respectively. There was no statistically significant difference between predicted Pa_{O_2} and Pa_{CO_2} with and without a simulated increase in CO (p=0.34 and p=0.68, respectively). That there is a relatively minor change in predicted blood gases between these conditions suggests that an increase in minute ventilation has a greater influence on blood gases than changes in CO within the ranges investigated here.

3.4 Predictors of RV dysfunction

Table 4 shows a comparison of quantitative CT measures for subjects classified as with or without RV dysfunction. The measures are separated into non-controversial, controversial (as given by Ghaye et al. (2006a)), and model-predicted (mPAP and Pa_{O_2}). As the model indicates that blood flow redistribution is an important factor in the response to PE, a modified QOI index that weights occlusions of each lobe based on mean baseline flow across the 12 subject models used here was also considered. That is,

$$\text{Flow weighted } QOI = \sum \frac{ndw}{7.74} \times 100\%,$$

where *w* is a weighting factor representing the percentage of flow through each lobe (0.12 for the right upper lobe, 0.12 for the right middle lobe, 0.30 for the right lower lobe, 0.10 for the left upper lobe, 0.11 for the lingula, 0.25 for the left lower lobe). Here 7.74 is the new (flow weighted) maximum absolute score. This

measure is not as simple to apply as the QOI but may be feasible with a spreadsheet or computer based application. The flow weighted obstruction index provided an improvement to the QOI in correlations with sPAP (R^2=0.82, p=0.005) and RV/LV (R^2=0.55, p=0.005) as well as a predictor of RV dysfunction (Table 4). Figure 6 shows these correlations. A flow weighted index that considers only fully occluded vessels, which would be simpler to implement, was also assessed but it did not provide better results than the flow weighted obstruction index.

4. Discussion

PE is difficult to manage clinically as there is considerable variability in severity and patient outcome, even in patients with apparently similar clot loads (McIntyre and Sasahara, 1971a, b). Here we have used anatomically based computational models of 1) systematic occlusion of pulmonary arteries, and 2) subject-specific clot loads from 12 PE patients, to provide new insight into the mechanisms that contribute to response in PE, and to assess clot load scoring. Model-predicted responses to occlusion (with either baseline or patient-specific CO and minute ventilation) correlate well with RV dysfunction estimated from echocardiogram, sPAP, and non-invasively estimated RV dysfunction (RV/LV), all of which have previously been used successfully to determine RV dysfunction in PE patients (Apfaltrer et al., 2011; Henzler et al., 2010; Kang et al., 2011). Model predictions of mPAP and Pa_{O_2} outperform existing clot load scores (represented using QOI) in predicting these measures. The superior performance of the model is because it is able to estimate the functional impact of an occlusion (increase in mPAP and/or decrease in Pa_{O_2}) based on its location in the lung and the partial or complete obstruction of blood vessels. The model therefore explains part of the reason that existing clot load scores can be unsuccessful at predicting outcome in clinical PE (Araoz et al., 2003; Ghaye et al., 2006a; Ghaye et al., 2006b; Smulders, 2000): because they do not describe the nonlinearity in response to partial occlusion or the effect of clot location.

Simple computational models have previously been employed to assess the impact of experimental PE (Mélot et al., 1995; Roselli and Parker, 1987). Mélot et al. (Mélot et al., 1995) used an asymmetric branching geometry, so they could investigate the effect of obstructing individual vessels of a given Strahler order, but did not include the anatomic distribution of vessels within the shape of the lung or the effect of gravity in simulations. With the advent of anatomically-based computational models, such as the one presented here, it

is possible to conduct a simulation experiment to accurately place clots in specified anatomic locations and to 'switch' on and off features of disease. This means that a more complete picture of the impact of a subject's mechanical clot load can be captured and regional blood redistribution and gas exchange assessed. Burrowes et al. conducted this type of experiment in the geometry of a single patient with cumulative occlusion of vessels (Burrowes et al., 2011b), and radiologist indicated clot location superimposed on the same subject geometry (Burrowes et al., 2011a). Here we have included subject-specific lung shape, size, and clot loads to attain a more accurate description of PE on a patient-by-patient basis, along with assessment of individual and cumulative clots in a generic subject with a focus on assessing the assumptions of clot load scoring.

4.1 Clot size and location.

Our study suggests that large central clots have a greater impact on function than distributed clots with the same total clot load (e.g. Figure 4). This is consistent with Vedovati et al. (2012), who found that central emboli were a predictor of death or clinical deterioration, whereas distal emboli were not. Potential explanations for the clinical observation are that large central clots place a sudden load on the RV, which can only poorly adapt; whereas small peripheral clots may not arise at the same time, allowing the RV to adapt. In the latter case circulating vasoactive substances could also have dissipated. Our study suggests an additional and important contribution of mechanical obstruction with respect to the baseline flow that would be expected to be carried by the occluded vessel(s). Figure 7 shows the average arterial blood volume distal to a blood vessel of a given Strahler order in a single subject. This illustrates clearly that in the case of a central clot a significantly larger volume of blood must be redistributed to unoccluded vessels than in the case of peripheral clots. Therefore the difference between large central and multiple smaller distal clots is that in the latter case the redistribution of cardiac output to non-occluded tissue (via recruitment or distension of capillaries) causes only a small reduction in $\dot{V}/\dot{Q}$ in those regions, whereas the large central clot causes significant reduction in $\dot{V}/\dot{Q}$ in recruited regions in addition to elevated $\dot{V}/\dot{Q}$ distal to the clot. This is further illustrated during systematic occlusion of additional pulmonary vessels of interest, where the impact of a central clot (for example a whole lung) is greater on a 'per unit of volume of tissue occluded' basis than occlusion of any one lobar vessel (although the cumulative occlusion of all the lobar vessels in a single lung is of course the equivalent of

occluding the pulmonary artery feeding that lung). RV adaptation and dissipation of vasoactive substances would further diminish the observed clinical response to peripheral compared with central clots.

The model also predicts that the gravitational location of the clot distribution affects functional outcome, with occlusion of gravitationally-dependent tissue having a greater effect on mPAP, and mid-lung occlusions having the greatest effect on Pa_{O_2} (Table 2). mPAP is therefore most sensitive to lower lobe occlusion, because in this case the flow must be diverted in the direction opposing gravity hence requiring higher driving pressure. The effect of occlusion on predicted Pa_{O_2} appears highest when a whole lung or mid-lobe is occluded. The mid-lung usually has $\dot{V}/\dot{Q}$ values closest to 1, with apical lung regions having highest $\dot{V}/\dot{Q}$ and basal regions lowest $\dot{V}/\dot{Q}$. Occlusion to the mid-lung region therefore eliminates gas exchange in units that usually have $\dot{V}/\dot{Q}$ close to 1, and because blood flow increases to all other units, $\dot{V}/\dot{Q}$ elsewhere is reduced. In the basal region this results in worsening of $\dot{V}/\dot{Q}$ matching; in the apical region it can theoretically improve $\dot{V}/\dot{Q}$ matching (shifting $\dot{V}/\dot{Q}$ towards 1) provided that blood flow is not increased so much that it exceeds ventilation. Perfusion of the basal (or gravitationally-dependent) lung is on average greater than perfusion of the apical (gravitationally-nondependent) lung, hence the weighting is towards worsened $\dot{V}/\dot{Q}$ matching.

4.2 Full or partial occlusion

In a study assessing pulmonary embolus location in 76 human lungs, Oser et al. (1996) determined that only 37% of emboli completely occluded vessels. Figures 3 and 5 show that the effect of partial occlusion is small compared with that of complete occlusion, until the effective radius of the vessel is very small. As the resistance of a vessel is approximately proportional to the reciprocal of the fourth power of its radius it makes intuitive sense that the increase in mPAP with partial occlusion approximately follows the relationship $1/r_E^4$. The QOI accounts for a partial occlusion by attributing half the score for a fully occluded vessel. Although it is more complicated than the QOI, the Mastora score also assumes that the impact of partial occlusion is weighted such that the effect of partial occlusion is approximately linear. For example, the effect of a 50% occlusion is 3/5 of that of total occlusion, where from Figure 3 a 50% occlusion may be insignificant and there is in fact a highly

nonlinear effect of partial occlusion on mPAP. The model suggests that the effects of partial occlusion are insignificant until effective vessel radius is small (less than approximately 1.5 mm). In practical terms this means that to successfully account for partial occlusion of a vessel in a clot load score, completely occluded or almost completely occluded vessels have a far greater influence than, for example 50% occlusion of a large vessel. However, incorporating this into a scoring system could add subjectivity to the system, and increase intra-observer variability in scoring.

The results suggest that clot load scores could be improved by including the functional impact of a clot, for example by weighting central and gravitationally dependent clots according to their increased impact on function compared with distal and non-dependent occlusions. We calculated a flow weighted obstruction index for each subject, where the average model-predicted flow per lobe was used as a weighting. This weighted obstruction index performed better than the standard score when compared with indicators of RV dysfunction. However, the question remains whether this kind of weighting can be appropriately implemented into a simple and easy-to-use scoring system that predicts outcome in patients with and without underlying cardiopulmonary pathologies.

4.3 System Responses

Our model predicts the response to occlusion alone, without any systemic response to clot load or localized response to vasoactive mediators. The exact nature of these responses and their time-courses are still to be determined and would require a fully integrated systems model, including the heart, systemic circulation and a description of the communication pathways involved in the localized vasoactive response to a clot. Model predictions of mPAP and Pa_{O_2} correlate well with indicators of RV strain in this study, which indicates that an accurate description of the level of mechanical obstruction due to a clot load plays a key role in the response of a patient to PE. However, the model with baseline CO and minute ventilation predicts hypercapnia rather than the hypocapnia often observed in PE. These baseline simulations indicate the $\dot{V}/\dot{Q}$ mismatch associated with a clot burden alone would result in hypoxemia and hypercapnia. It has been suggested that the hypocapnia associated with PE is due to hyperventilation (Elliot, 1992; Santolicandro et al., 1995; Stein and Levy, 1974), and our results for simulations with patient-specific increase in RR support this. As each subject considered

here had an elevated RR, it is likely that minute ventilation was increased in this population. Indeed when subject specific RRs were simulated (assuming a maintenance of tidal volume), hypocapnia was predicted in 4 out of the 12 subjects, and the predicted extent of hypoxemia lessened in each patient. The effect of PE on CO is less clear (McIntyre and Sasahara, 1974), although it most likely decreases in massive PE when the embolic load is so great that stroke volume cannot be maintained. We simulated an artificially increased CO, assuming maintained stroke volume, which gave small but non-significant increase in Pa_{O_2} and decrease in Pa_{CO_2}. However, an increase in CO did act to increase predicted mPAP above the predicted baseline value, which would put additional strain on the RV. These results are speculative in the absence of invasive hemodynamic data, and likely depend on the level of pre-existing disease in an individual, but nevertheless they highlight the influence that systemic responses to PE can have on observed blood gases (Santolicandro et al., 1995).

Changes in CO and minute ventilation simulated in this study may not completely reflect the clinical response of these variables to PE, as here their values were assumed rather than measured. The assumption that stroke volume can at least be maintained, to maintain CO post-embolisation, may be inaccurate. In fact, CO may well be reduced in acute PE (McIntyre and Sasahara, 1974; Sasahara, 1973). In our model, as CO and oxygen consumption are preserved, this may result in an overestimate of the difference in Pa_{O_2}. In the case of reduced CO and maintained oxygen consumption, is likely that the oxygen content of mixed venous blood returning to the lung would decrease compared with our simulated scenarios, and hence also potentially Pa_{O_2}. This is likely to be most significant in patients with the most severe PE and with right ventricular dysfunction that are highlighted in Table 3. In addition, the hyperventilation observed in PE is most likely attributable to both increased RR and increased tidal volume, whereas our maximum simulated hyperventilatory response had a maintained tidal volume. If minute ventilation were increased further still, with an increase in tidal volume, the predicted Pa_{CO_2} would decrease further from the values given in Table 3. This is consistent with the hypocapnia and respiratory alkalosis that is frequently seen in patients with PE (Torbicki et al., 2008).

4.4 Study limitations

Functional model limitations are described in detail by Burrowes et al. (2011b) and Swan et al. (2012). These limitations include an absence of active response in the pulmonary vasculature (for example vasoconstriction or response to thromboembolitic agents), the impact of which are debated in the literature (Smulders, 2001). The perfusion model assumes a steady-state laminar blood flow. Turbulent flow is unlikely to occur in any but the largest vessels, however these assumptions may affect the absolute values of pulmonary artery pressure predicted by the model. Airflow is also assumed laminar; the impact of this assumption was assessed by Swan et al. (2012), who concluded that its influence on ventilation distribution was minor. Neighboring acinar units are not mechanically coupled, which could affect the accuracy of the model in the presence of severe bronchoconstriction. In addition, although models and imaging studies have previously shown an important influence of lung tissue deformation on the heterogeneity of perfusion and ventilation distributions (Burrowes and Tawhai, 2010; Clark et al., 2011; Hopkins et al., 2007; Swan et al., 2012) this deformation was not explicitly simulated here; rather it was estimated via a gradient in pleural pressure with gravitational height in the lung. In simulations of oxygen transfer, equilibration between airside and bloodside oxygen partial pressures was assumed. This assumption is valid provided that the transit time of red blood cells through the capillaries is > 0.25 s (Wagner and West, 1972), which holds true under the simulation conditions considered here.

It is not possible to identify with complete accuracy every structural parameter required for a truly subject specific model. We have parameterized the most important subject-specific characteristics of each model, and others are determined from average morphometric or physiologic data. For example, as the CTPAs were obtained under abnormal conditions of vascular obstruction, imaging data was not used to define the unstrained blood vessel radii. Instead, the unstrained radius of each blood vessel was taken from morphometric data (as determined by the Strahler order of that vessel in the tree), and the strained radii were simulated. The steady-state distribution of perfusion is not particularly sensitive to small differences in proximal vessel size, however a more accurate definition of proximal vessel radius could become important if we were to consider pulsatile flow. Although the volume of each embolus was calculated on a vessel-by-vessel basis, this volume was converted to an average embolus radius and imposed along the length of a vessel segment (which represents all or part of a vessel). If the physical embolus does not span the whole length of the vessel segment this assumption will under-estimate its radius and over-estimate its length. The smoothing and manual correction

of false positives in embolus identification add significantly to the time taken to identify emboli compared with fully automated methods (Masutani et al., 2002), but as the aim of this study was to locate emboli to map onto a geometric model and not clinical application, increased accuracy was preferred over rapid algorithms.

We have assumed that local changes in ventilation distribution, for example due to hypocapnic bronchoconstriction, are negligible. Several studies have shown no statistically significant changes in ventilation distribution with pulmonary embolism (Altemeier et al., 1998; Tsang et al., 2000; Tsang et al., 2005), whereas some other studies suggest a redistribution of ventilation in PE. Hypocapnic bronchoconstriction has been inferred from: the multiple inert gas elimination technique (MIGET) in animals, due to the observation of increased effective alveolar ventilation over time post-embolization (Ferreira et al., 2006; Levy and Simmons, 1974); from $\dot{V}/\dot{Q}$ scans in some PE patients who were given heparin (Santolicandro et al., 1995); and from positron emission tomography (PET) imaging in sheep (Vidal Melo et al., 2002). However, a quantitative estimate of regional ventilation redistribution in PE in humans is still lacking. If there were a redistribution of ventilation from poorly perfused regions one would expect a reduction in shunt, which would act to improve oxygenation. Therefore, if substantial redistribution of ventilation exists in PE, our model would overestimate the level of hypoxemia but predictions of mPAP would not be affected.

The model only accounts for the age, gender or body mass index (BMI) of the subject via calculations of baseline CO and minute ventilation. Age, gender, and BMI could impact on the gravitational deformation and regional expansion of the lung tissue (via its age-dependent compliance), and on the vascular stiffness. CO and minute ventilation were calculated using normative equations that relate energy expenditure to age, gender and weight. Lack of definition of subject-specific CO and minute ventilation may introduce inaccuracy in the estimation of absolute values of blood pressure and oxygen partial pressures, but would have only a small impact on the predicted changes in these quantities post-occlusion. The study excluded subjects with existing cardiorespiratory disease, as indicated by pulmonary function tests. Comorbidities may significantly reduce the lung's ability to redirect blood flow in PE and so contribute to patient outcome.

As the data used in this study was restricted to that which would be collected during routine diagnosis of PE, or that which could be acquired non-invasively, transthoracic echocardiography was used to inspect the heart

rather than endo-oesophageal ultrasound or pressure monitoring via catheter. The transthoracic echocardiography may include measurement or interpretation errors. We minimized interpretation error by having a single cardiologist acquire and interpret the measurements. More invasive measures of RV function and blood gases would provide additional model validation if this work was extended to a large prospective study. Despite these limitations, the model correlations with clinical data are clear and demonstrate the potential of anatomically-based models to assess clot loads.

The model used here to investigate subject-specific pathology is time consuming to construct and solve so it cannot currently be used in a clinical setting to capture regional variability in perfusion and patient response. However, the model predicts a physiologically-consistent baseline behavior across subjects, and systematic occlusion of vessels in each subject produces similar results. This indicates that the behavior of the model in a small group of subjects could be used to guide assessment of PE on a subject-by-subject basis. The model is able to quantify the relative importance of clots in specific anatomic locations and so may provide a useful tool to quantify the potential effect of clot loads and the impact of, for example, surgical embolectomy on patient outcome.

5. Conclusions

In this study we have assessed the utility of clot load scoring in pulmonary embolism using computational models that fit as closely as possible to the anatomic structure and embolus distributions in 12 patients presenting with acute pulmonary embolism. In these patients the model-predicted pulmonary artery pressures and arterial oxygen partial pressures correlate more closely with clinically determined estimates of RV function than do clot load scores that aim to estimate the percentage of tissue distal to the occlusion. This is because the model is able to incorporate the functional impact of the size of a clot and its location within the lung. The model predicts that a large central clot load is likely to have a greater functional impact than peripherally distributed clots that equate to the same overall clot burden in terms of existing clot load scores. The model also indicates that partial occlusion only has a significant impact on pulmonary vascular resistance once the effective radius of the vessel that it occludes is less than approximately 1.5 mm. The model indicates that accurate scoring of PE using an obstruction index requires including functional information on the preferential distribution of blood flow, i.e. more complex clot load scores must be calculated. While this may be feasible

with the help of desktop computing, it remains to be seen whether adapted clot load scores will become widely used clinically.

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Figure Captions:

Figure 1 A comparison of the Qanadli Obstruction index (QOI) and Mastora scores as predictors of systolic pulmonary artery pressure (sPAP – estimated from echocardiography) and the ratio of right ventricle to left ventricle volume (RV/LV).

Figure 2 The cumulative effect of completely occluding segmental pulmonary arteries systematically from the most apical to the most basal in zero gravity (OG) and 1G in the upright posture on model-predicted mean pulmonary artery pressure (mPAP). Only the right lung is shown, however the results in the left lung are similar. The more gravitationally-dependent the lung tissue that is occluded, the greater the effect on mPAP in 1G conditions.

Figure 3 The effect of partial occlusion of a single lobar vessel in one subject on the post-occlusion increase in mean pulmonary artery pressure (mPAP). The vessel is more than 50% occluded before a significant increase in mPAP occurs. The increase in mPAP with partial occlusion approximately follows the relationship 1/rE4 where rE is effective vessel radius. Results are similar regardless of the choice of vessel occluded.

Figure 4 A comparison of model-predicted pulmonary artery pressure (mPAP) and model-predicted arterial oxygen partial pressure (Pa_{O_2}) as predictors of systolic pulmonary artery pressure (sPAP – estimated from echocardiography) and the ratio of right ventricle to left ventricle volume (RV/LV). The model assumes baseline cardiac output and minute ventilation.

Figure 5 A comparison between (A) the ratio of blood flow rates in embolus (QE) and baseline (QBL) conditions, and (B) end-capillary oxygen distribution in two patients with the same QOI (45%) but differing response to embolization.

Figure 6 The flow weighted Qanadli Obstruction index (QOI) as a predictor of systolic pulmonary artery pressure (sPAP – estimated from echocardiography) and the ratio of right ventricle to left ventricle volume (RV/LV).

Figure 7: Mean arterial blood volume distal to an artery of Strahler order X in a single subject. There is a rapid decrease in distal blood volume, and so the potential volume of the arterial tree occluded over the first four orders of the system.