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Ventilatory and cardiac responses to pulmonary embolism: Consequences for gas exchange and blood pressure.*

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Abstract— **Acute thromboembolic pulmonary embolism (PE) is a life threatening condition that can lead to pulmonary hypertension and right ventricular dysfunction or failure. There is typically an increase in ventilation rate and cardiac output as a response to PE prior to cardiac failure, which is at least in part due to systemic hypoxemia. Here we assess the response of the lungs to changes in these parameters using anatomically-based computational models of pulmonary perfusion, ventilation and gas exchange. We show that increases in ventilation and cardiac output improve overall gas exchange in PE. However, this comes at the cost of an increased pulmonary blood pressure, which may contribute to pulmonary hypertension as a result of PE.**

I. INTRODUCTION

Acute pulmonary embolism (PE) a common, underdiagnosed, and often lethal complication of the pulmonary circulation. In PE, blood clots occlude pulmonary blood vessels, which can lead to a substantial increase in pulmonary artery pressure (PAP); this increase in pressure feeds back to the right ventricle (RV), increasing its volume and afterload and ultimately (if severe and untreated) causing heart failure. It is believed that an increase in pulmonary vascular resistance (PVR) as a result of blood vessel occlusion is primarily responsible for increases in PAP with PE, with additional factors such as vasoconstriction (either due to hypoxia or humoral factors from the clot itself) and systemic hypoxemia contributing to severity [1]. Several clot load scores, which aim to quantify the severity of PE from angiography or computed tomography (CT), have been proposed to give clinical guidance in treating PE (summarized in [1]). Although certain clot load scores are clearly correlated with indicators of PE (e.g. PAP, arterial oxygen), Ghaye et al. [2] found no significant correlation between these scores and survival in severe PE. This is likely because clot load scores account only for blood vessel obstruction, as other contributors to PE severity are not completely understood. Computational modeling of pulmonary function in PE provides a means to separate contributors to response, and to assess their impact on lung function.

Modeling studies have already shown that blood vessel occlusion alone is insufficient to induce hypertension without at least 60%-80% of the pulmonary capillary bed occluded [3], [4]. This compares with occlusion as low as 15% causing hypertension in humans (although with significant variability) [5]. Models have also suggested significant regional hypoxia [3], global hypoxemia [6], and sensitivity to cardiac output (CO) and clot location [3], [4], [6]. Investigating these influences on lung function via computational models will help to guide clinical assessment of PE by determining the major contributors to hypertension and comparing to clinical parameters. Here we investigate whether a cardiac and respiratory response in PE may act to improve systemic oxygen levels, and the consequence of changes in HR on pulmonary blood pressures.

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II. METHODS

We use patient specific models of PE location and size based on computed tomography pulmonary angiograms (CTPAs) in an anatomically based model of the lungs to predict ventilation, perfusion and gas exchange in an acute PE population.

A. Patient Data

Volumetric CTPAs were obtained from 9 adult subjects presenting with clinically suspected acute PE at Auckland City Hospital. The Northern X Regional Ethics Committee and the Auckland District Health Board Research Review Committee approved use of the clinical data. Patients underwent pulmonary function testing, to confirm that their lung function was otherwise normal hence avoiding the complication of prior pulmonary disease complicating outcomes. Echocardiography was used to assess RV failure and/or dysfunction in each patient and clinical parameters (heart rate, respiratory rate, systemic blood pressures) were recorded. A radiologist (D.G.M.) calculated a Qanadli obstruction index (QOI) for each subject [4], [7]. This index aims to quantify the percentage of capillary bed obstruction due to PE where a QOI of 100% represents complete obstruction. The mean QOI across the 9 subjects was 45% (range 5–65%).

B. Geometric Models

For each subject the lungs, lobes, central airways and blood vessels were segmented from CTPAs. All but the blood vessel trunks (the blood vessels that lie between the two lungs) were automatically segmented using PASS (Pulmonary Analysis Software Suite, University of Iowa [8]). The blood vessel trunks were manually segmented. A finite element tree was constructed to represent the centerlines of the arterial, venous and airway stress to the level of the first sub-segmental branches using CMGUI software (www.cmgui.org). A segmental branch is the main vessel

TABLE I

DIFFERENCES IN PREDICTED PULMONARY FUNCTION MEASURES BETWEEN BASELINE, POST-OCCLUSION WITH BASELINE RESPIRATORY AND HEART RATES (PE 1), AND POST-OCCLUSION WITH CLINICALLY REPORTED RESPIRATORY AND HEART RATES (PE 2).

	Baseline	PE 1	PE 2
CO (l/min)	5.3 ± 0.7	5.3 ± 0.7	7.0 ± 2.1
% Tachycardic (HR >100/min)	0%	0%	33%
V (l/min)	5.9 ± 0.6	5.9 ± 0.6	9.7 ± 3.2
% Tachypnic (RR >20/min)	0%	0%	44%
PAP (kPa)	1.97 ± 0.11	2.53 ± 0.37	2.79 ± 0.49
(mmHg)	14.8 ± 0.9	19.1 ± 2.8	21.0 ± 3.7
% Hypertensive (> 25 mmHg)	0%	0%	22%
P_aO_2 (kPa)	12.8 ± 0.2	9.2 ± 2.5	13.4 ± 1.3
(mmHg)	96.0 ± 1.8	69.3 ± 18.9	100.4 ± 9.8
% Hypoxic (< 80 mmHg)	0%	56%	0%

that feeds a lung segment of which there are 20 (10 in each of the left and right lungs). Vessels beyond this level were generated via a volume filling branching algorithm [9], which fills the segmented lung volume and matches as closely as possible the properties of measured pulmonary trees.

Emboli were identified in each patient by a radiologist (D.G.M) and a semi-automated procedure was followed to determine the three dimensional distribution of emboli in the lung. This algorithm has been described in full previously [6]. In brief, the algorithm searches for emboli within major blood vessels by identifying a range of pixel intensity values that represent potential emboli (flowing blood is contrast enhanced and so has a higher pixel intensity than blood clots). False positives due to vessel walls and parenchymal tissue are eliminated by smoothing the lung into $4\times4\times4$ mm voxels and removing potential emboli that fill less than half of this volume. False positives due to reduced contrast intensity in veins compared with arteries are removed manually. CMGUI is used to map emboli to the arteries in which they reside and an effective embolus radius is calculated by determining embolus and vessel volume and assuming that the embolus spans the entire length of the vessel in which it resides.

C. Functional Models

Perfusion, ventilation and gas transfer were simulated using previously described methods [3], [10], [11]. In each model paranchymal tissue deformation was accounted for by assuming a linear gradient of pleural pressure in the direction of gravity. Perfusion was simulated using a steady-state model of blood flow [10], which assumes Poiseuille flow in elastic extra-capillary blood vessels and a symmetric intra-acinar geometry with capillary sheets connecting each generation of blood vessels. Ventilation was simulated using a quasi-steady model [11], assuming a Poiseuille flow in extra-acinar airways driven by an oscillating pressure pulling the exterior of the lung. Oxygen transfer from air to blood was modeled as described by Burrowes et al. [3] by assuming equilibration of oxygen between air and blood. This assumption is valid provided that blood transit times through the capillary bed are longer than 0.25 s, which is the case in the simulations described here. Emboli were assumed to act as solid occlusions around which the pulmonary arteries can distend [6]. The effective radius of a blood vessel for perfusion simulations is then the perfused radius of the vessel minus the radius of the embolus. If an embolus was of the same size as a blood vessel, then blood flow through that vessel was assumed to be negligible. Systemic oxygen requirements were assumed to remain the same pre- and post-embolization and venous oxygen content was recalculated post-embolization to satisfy this condition.

Baseline cardiac outputs and tidal volumes were determined based on height, age and weight, and assuming a respiratory rate (RR) of 12 breaths per minute. The metabolic rate at rest in the upright posture was calculated from the formulae of Levine et al. [12], and translated to an oxygen consumption rate and ventilation rate [13]. Finally cardiac output (CO) was calculated using the formulae of Stringer et al. [14]. A baseline stroke volume (SV) was estimated using the formula CO=SV$\times$HR, where HR is heart rate (assumed to be 65 beats per minute at rest [15]). Simulations were carried out 1) under baseline conditions, 2) with emboli but assuming baseline ventilation (V) and CO (PE1), and 3) with emboli assuming that SV and tidal volume remains unchanged so that CO and minute ventilation (V) are proportional to HR and RR, respectively (PE2). It was also assumed that increased HR and RR act to maintain systemic oxygen consumption; that is, they are a compensation for decreased oxygen tensions rather than a stress response. Under these assumptions CO increased on average by 1.7 l/min and V by 3.8 l/min (Table I, P_aO_2=arterial oxygen partial pressure). A model prediction of capillary obstruction was calculated as the percentages of acini with reduced flow in PE1 conditions compared with baseline conditions.

III. RESULTS AND DISCUSSION

Simulating the effects of PE in the absence of any cardiac or ventilatory response (PE1) results in an increase in PAP in each subject. However, no subject's PAP increased to hypertensive levels (PAP >25 mmHg - Table I). In contrast, five of the nine subjects (56%) have predicted arterial oxygen partial pressure (P_aO_2) of less than 80 mmHg, which implies systemic hypoxemia. Interestingly, although these subjects are not predicted to be hypertensive, each of these subjects has RV dysfunction (as determined clinically using echocardiography). The remaining four subjects (with predicted P_aO_2 >80 mmHg) do not have RV dysfunction. As a predictor for RV dysfunction in this data set, predicted P_aO_2 <80 mmHg performs better than measures of capillary bed occlusion. A QOI >40% correctly predicts the presence or absence of RV dysfunction in 78% of subjects, and model predictions of capillary obstruction >40% correctly predicts RV dysfunction in 89% of subjects.

Increases in RR and HR in PE act together to increase the partial pressure of oxygen returning to systemic arteries

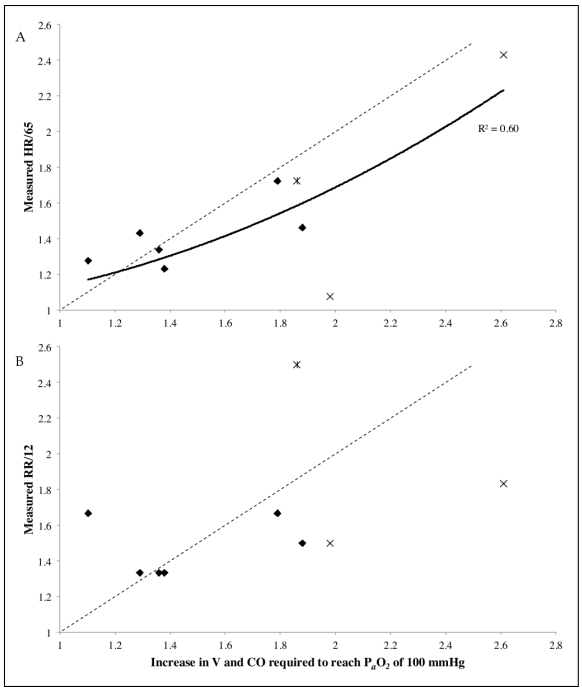

Fig. 1. The increase in ventilation (V) and cardiac output (CO) required for the model to produce a P_aO_2 of 100 mmHg, compared with measured heart rate (HR) and respiratory rate (RR). Subjects with hypoxemia (indicated by P_aO_2 <80 mmHg while breathing room air) are marked with a cross ($\times$) and those with hypocapnia (blood carbon dioxide <30 mmHg while breathing room air) are marked with a star ($*$). Dotted lines show expected results if model predictions exactly matched observed changes in HR and RR.

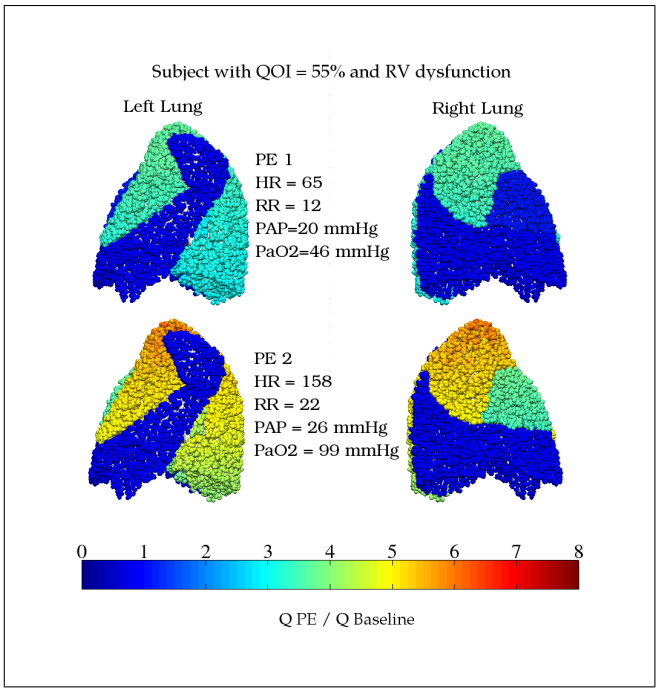

Fig. 2. The redistribution of acinar blood flow post-occlusion (Q PE / Q baseline) for a single subject in the upright posture. Blood flow decreases distal to an occlusion, and increases in other regions. There is a general trend toward redistribution of blood to apical regions as these regions receive the least flow in baseline conditions and so have the most potential for capillary recruitment. With increased cardiac output regions of the lung that are partially occluded (with negligible blood flow) at the baseline cardiac output are able to receive a significant blood flow.

(P_aO_2). This can be seen in Table I (column 3) where patient specific HRs and RRs are used to simulate the effects of PE in an individual. On average P_aO_2 was elevated to a normal value (a normal range is 80-100 mmHg). This suggested that increases in HR and RR may act to return blood gases to as near normal as possible. To test this hypothesis we simulated the effects of increasing both CO and V proportionately and estimating the required increase to elevate P_aO_2 to 100 mmHg in each subject (Fig. 1). There is a positive correlation between the required increase in CO and V in each subject and measured HRs (p=0.03, Fig. 1 A). In general, measured HRs are slightly below the increase in CO that would be required to elevate P_aO_2 to 100 mmHg. Increased stroke volume is thought to occur in PE, along with increased HR, and this may contribute to the increased CO [5]. There is one patient with hypoxemia who is a clear outlier compared with the other subjects, this patient is a current smoker (30 pack years) and so despite having no apparent lung disease they may have underlying cardiac or respiratory abnormalities. A second patient who is hypoxemic is 70 years old and has a very high HR (159 beats per minute). The subject's high HR and age may contribute to an inability to maintain stroke volume and explain the hypoxemia observed clinically. There is no significant correlation between the required increased in CO and V in each subject and measured RR (Fig. 1 B), perhaps because changes in ventilatory rate are related to multiple factors including stress. However, it is clear that hypoxemia is associated with a lower than expected change in RR, and hypocapnia (low arterial carbon dioxide) appears to be associated with a higher than expected change in RR.

Figs. 2 and 3 show how changes in CO and V act to improve gas exchange. Under baseline conditions the distribution of alveolar ventilation to perfusion ratios (V/Q) is bell shaped, and the partial pressure of oxygen leaving alveolar regions is distributed between 80 and 140 mmHg. The introduction of emboli results in a non-uniform distribution of blood flow to the lung (Fig. 2), which results in lower than, and higher than expected V/Q ratios. This means that a multimodal distribution of blood oxygen can form with much blood flowing through poorly oxygenated lung tissue (Fig. 3), this causes the level of oxygen leaving the lung to drop. Increased cardiac output in PE acts to increase pulmonary blood pressures (Table I). This allows vessels to distend and can result in partially occluded regions seeing an increased blood flow compared with what they would encounter if cardiac output remained constant post-occlusion (Fig. 2). This allows for a redistribution of V/Q ratios and an overall increase in arterial oxygen levels (Fig. 3). However, it has the negative consequence of a move in PAP toward hypertensive levels. In two of the nine subjects considered here, assuming that their stroke volume remained constant, this increase in blood pressure was sufficient to reach hypertensive levels (PAP >25 mmHg), and all subjects saw an increase in PAP. In this study of clinical data it appears that subjects

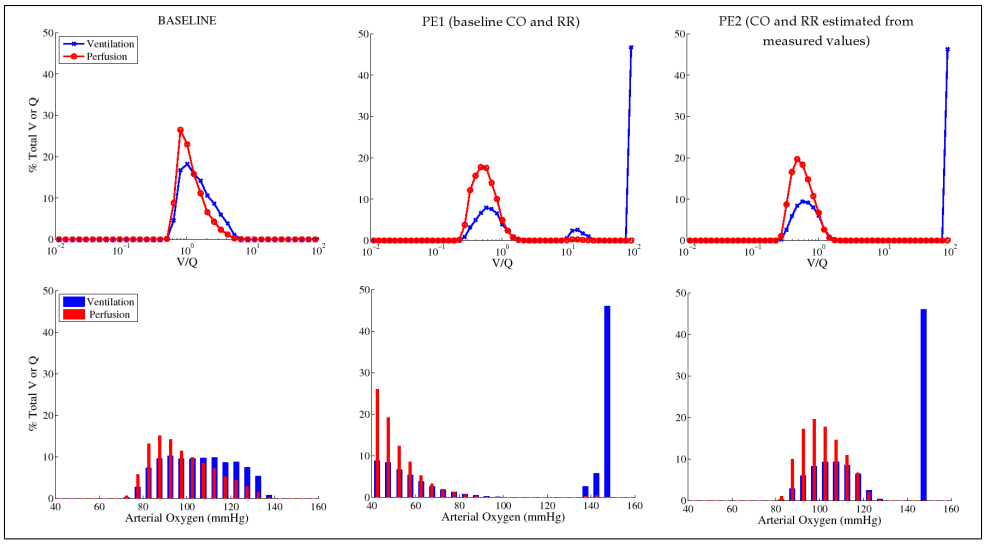

Fig. 3. The redistribution of acinar ventilation perfusion ratios (V/Q), and arterial oxygen partial pressures from baseline conditions, to embolus conditions (PE1), and with emboli and patient specific heart rates (HRs) and respiratory rates (RRs) (PE2). Localized hypoxia (arterial oxygen <80 mmHg) is evident in PE1 conditions and there is a characteristic bimodal distribution of V/Q. However, with increased blood and airflow (PE2) most blood passes thought lung regions that are normoxic, and the distribution of V/Q returns to a unimodal distribution.

with the largest predicted response, for a given level of tissue occlusion, generally have large localized occlusions, rather than more evenly distributed clot loads. As simulated response of arterial oxygen to a clot load was an accurate predictor of RV dysfunction in the subjects considered here, this highlights the importance of clot location as well as size in assessment of PE cases.

IV. CONCLUSIONS

In this study we have used a computational model to predict ventilation, perfusion and oxygen exchange in subjects with clinically indicated PE. RV dysfunction in PE may be explained by a response to systemic hypoxemia, which acts to increase cardiac output and so pulmonary blood pressures, and an insufficient response may contribute to disease severity. The model predicts that an increase in ventilation and cardiac output in PE may improve gas exchange functionality but at the detriment of increasing PAP. Predictive models provide a valuable tool which may allow improvements to be made to clinical management of PE, and the methodology presented here allows subject-specific outcomes to be assessed against model predictions.

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