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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.

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, 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

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

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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, 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 120 ml IV contrast at 4 ml/s delivered by antecubital vein, auto triggered from the left atrium. Acquisition time was 7 s. 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 $\pm$ 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.