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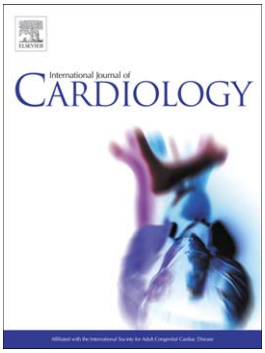

Incremental value of ePLAR – echocardiographic Pulmonary to Left Atrial Ratio – in the diagnosis of chronic thromboembolic pulmonary hypertension

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Letter to the Editor

Incremental value of ePLAR – echocardiographic Pulmonary to Left Atrial Ratio – in the diagnosis of chronic thromboembolic pulmonary hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a distinct pulmonary vascular disease characterised by the presence of numerous organised occlusive thrombi or emboli in the elastic pulmonary vascular tree after at least 3 months of effective anticoagulation [1-4]. CTEPH is distinguishable from pulmonary arterial hypertension (PAH) by the nonhomogeneous distribution of thrombus within various segments of the pulmonary vasculature (main, lobar, segmental, subsegmental) and its association with venous thromboembolism (VTE) [3, 5]. CTEPH is progressive and carries a poor prognosis when established pulmonary pressures are severely elevated, unless amenable to pulmonary thromboendarterectomy (PTE) [5, 6]. If left untreated, patients with CTEPH develop irreversible disease progression associated with a significant risk of death from right heart failure [3, 7]. It is often diagnosed late. However, early diagnosis allows institution of long-term anticoagulant therapy and referral to an appropriate pulmonary hypertension centre to initiate timely therapeutic interventions [3]. This includes assessment for operability in severe cases of CTEPH by an experienced PTE surgeon [4].

Given that CTEPH presents clinically with non-specific symptoms of exertional dyspnoea, fatigue, chest pain, and exercise induced syncope, which are ubiquitous with other common cardiopulmonary conditions, diagnosis is often delayed [8]. More frequently, common conditions are implicated as causal, such as left heart disease, which often culminates in *post-capillary* pulmonary hypertension (PHT). Patients with CTEPH have *pre-capillary* PHT. Hemodynamically, obstructed trans-pulmonary flow will yield elevated mean

pulmonary artery pressures (PAP_{mean} >25 mmHg) in the setting of normal/low left atrial filling pressures (LAP <15 mmHg).

There is therefore significant scope for the implementation of a more readily available, less invasive, cost effective test to predict the presence of *pre-capillary* PHT, of which CTEPH is a life-threating cause. The echocardiographic Pulmonary to Left Atrial Ratio (ePLAR), has been validated as a non-invasive surrogate of trans-pulmonary gradient, and is an effective differentiator of *pre-capillary* from *post-capillary* PHT [9, 10]. The ePLAR (m/s) is calculated from the maximum tricuspid regurgitation continuous-wave Doppler velocity (m/s) divided by the trans-mitral E-wave : septal mitral annular Doppler Tissue Imaging e'-wave ratio **(ePLAR (m/s) = TRV_{max} (m/s) / E/e')** [9, 10]. Higher ePLAR values reflect increasing trans-pulmonary gradient (TPG) consistent with *pre-capillary* PHT physiology. Lower ePLAR values indicate elevated left heart pressures as the driver for *post-capillary* PHT (see figure 1A). An ePLAR cut-off value of 0.28 m/s has >80% sensitivity and specificity for distinguishing *pre-capillary* from *post-capillary* PHT [9].

Any patient with *pre-capillary* PHT should be evaluated for CTEPH [4]. Ventilation perfusion (V/Q) scintigraphy is the preferred screening test for chronic pulmonary thromboembolic disease, despite advances in computed tomography pulmonary angiography (CTPA) and magnetic resonance angiography (MRA) of the lungs [2, 6]. We report 2 cases of CTEPH where the diagnosis of *pre-capillary* PHT initially was initially considered clinically

unlikely. The cases demonstrate the incremental value of ePLAR in provoking diagnostic workup of *pre-capillary* causes for PHT, including CTEPH.

Case 1

A 71-year-old female experiencing progressive exertional dyspnoea demonstrated no significant abnormality on standard cardiorespiratory testing including spirometry, gas transfer, chest X-ray and high resolution CT. Echocardiography showed normal left ventricular size and systolic function (EF 60%) with no significant valvular disease and normal left heart filling (mitral E/e' 10). Mild PHT was evident (TRV_{max} 3.1m/s, RVSP 43mmHg – see figure 1A). The ePLAR was elevated at 0.31m/s, consistent with *pre-capillary* PHT physiology. Despite a normal D-dimer, a V/Q scintigram revealed multiple bilateral mismatched defects. Anticoagulation was instigated and at six months, the patient was clinically improved, though all echocardiographic parameters were unchanged. CTEPH was diagnosed and long-term anticoagulation mandated.

Case 2

A 43-year-old male presented with decompensated restrictive cardiomyopathy. The initial clinical presentation with anasarca, breathlessness and anorexia was rapid in onset, possibly coincident with the onset of atrial fibrillation. Urgent echocardiography showed severe global systolic left ventricular dysfunction (EF 20%) with severe concentric wall thickening. Doppler displayed markedly elevated filling pressures, and mild PHT (TRV_{max} 3.1m/s, RVSP = 55mmHg). The ePLAR was elevated at

0.44m/s consistent with *pre-capillary* PHT (see figure 1A). Initial therapy with diuretics and ACE inhibitors, improved his clinical status, with 15kg of fluid weight loss. The rapid resolution of congestive symptoms and signs with diuretics rendered obstructive pulmonary vascular symptoms unlikely at that time. Formal anticoagulation with rivaroxiban 20mg/d for atrial fibrillation was instituted. At 6 month follow up, with stable clinical status, echocardiography showed similar left ventricular thickening, systolic dysfunction and left heart filling parameters (E/e' 8.3). Mild PHT persisted (TRV_{max} = 3.0m/s, RVSP = 40-44mmHg) and ePLAR remained elevated at 0.36m/s, consistent with *pre-capillary* PHT physiology.

Clinical deterioration at 7 months, with progressive breathlessness in the absence of recurrent fluid retention, prompted repeat echocardiography. The patient remained fully anticoagulated. Left heart systolic and diastolic function was unchanged with the ejection fraction moderately reduced at 36% and filling pressures not elevated with mitral E/e' 9. There was worsening of pulmonary hemodynamics (TRV_{max} 3.5m/s, RVSP 61mmHg). The ePLAR remained elevated at 0.39m/s consistent with *pre-capillary* PHT physiology. Dilated main pulmonary arteries with no filling defects or obstruction were evident on CT pulmonary angiography. However, V/Q scintigraphy showed bilateral mismatched defects – despite compliance with novel anticoagulant therapy (see figure 1B). Heparin and warfarin therapy was commenced.

A small minority of patients with exertional dyspnoea will have *pre-capillary* PHT as their fundamental hemodynamic disturbance. Aetiologies within this

group include PAH, connective tissue disease, parenchymal lung disease and a very small subset will have CTEPH [9]. Patients with *pre-capillary* PHT will undergo a standardised testing sequence including V/Q scintigraphy, which if suggestive of CTEPH, will lead to lifelong anticoagulation with significant prognostic advantage and possibly PTE surgery [3, 7]. However, because of the subtlety of presenting symptoms and frequently, the absence of any discernible acute pulmonary embolic event, the diagnosis of CTEPH is easily overlooked. Echocardiography is commonly used in the clinical workup of exertional breathlessness. These cases demonstrate the incremental value of ePLAR in prompting clinical consideration of causes of *pre-capillary* pulmonary hypertension, such as CTEPH.

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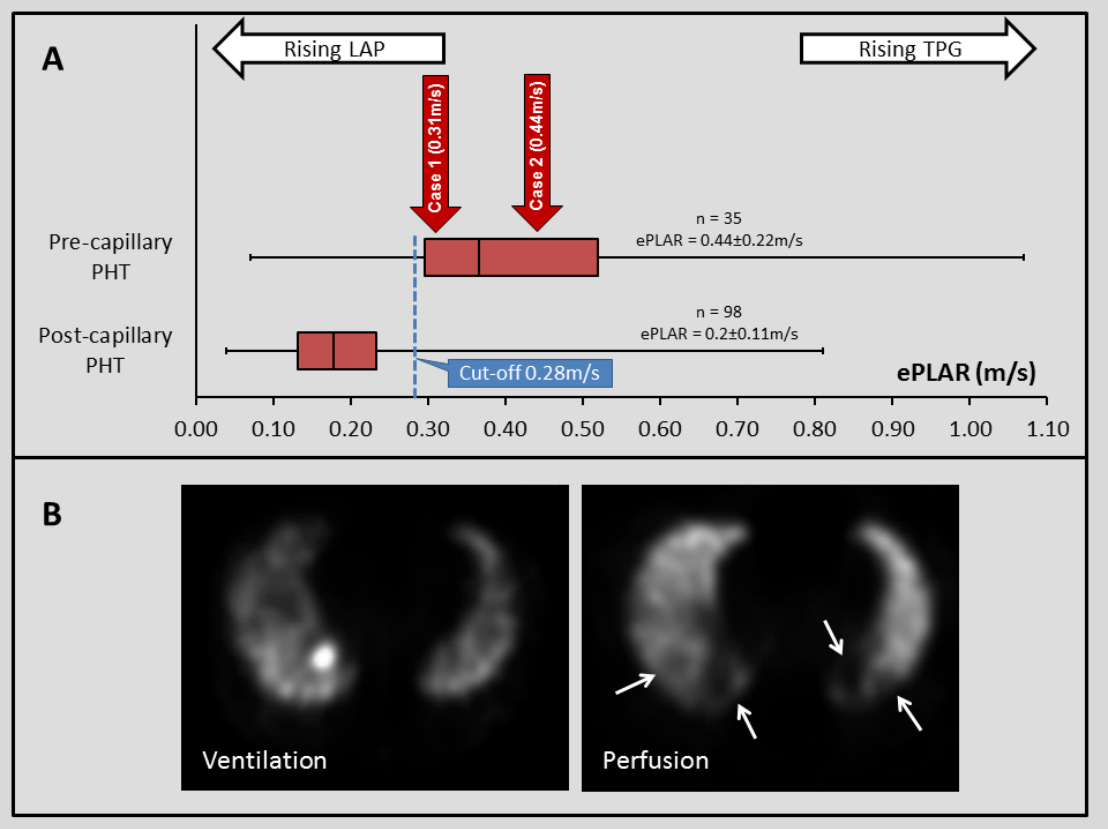

Figure 1. A. Box and whisker display of distribution of ePLAR values for patients with *pre-capillary* PHT (0.44±0.22 m/s) and *post-capillary* PHT (0.20±0.11 m/s)

– boxes represent middle quartiles and whiskers represent range, LAP = left atrial pressure, TPG = trans-pulmonary gradient. In that data, an optimal ePLAR cut-off value of 0.28 m/s yielded >80% sensitivity and specificity for differentiating *pre-capillary* from *post-capillary* PHT (modified and reproduced with permission [9]). Case 1 and case 2 demonstrate ePLAR values of 0.31 m/s and 0.44 m/s respectively, both of which fall within the *pre-capillary* PHT range. ePLAR (m/s) = peak tricuspid regurgitation continuous-wave Doppler velocity (m/s) divided by the trans-mitral peak pulsed-wave Doppler E-wave (cm/s) : peak Doppler Tissue Imaging mitral septal annular e'-wave (cm/s). B. Ventilation/perfusion scintigraphy of case 2 demonstrating bilateral mismatch perfusion defects (arrows) after >3 months of anticoagulation consistent with multiple chronic pulmonary emboli – CTEPH.