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Gregory M. Scalia, Isabel G. Scalia, Rebecca Kierle, Rebekka Beaumont, David B. Cross, John Feenstra, Darryl J. Burstow, Benjamin T. Fitzgerald, David G. Platts

PII: S0167-5273(16)30445-4
DOI: doi: 10.1016/j.ijcard.2016.03.035
Reference: IJCA 22164

To appear in: International Journal of Cardiology

Received date: 20 October 2015
Revised date: 28 February 2016
Accepted date: 13 March 2016

Please cite this article as: Scalia Gregory M., Scalia Isabel G., Kierle Rebecca, Beaumont Rebekka, Cross David B., Feenstra John, Burstow Darryl J., Fitzgerald Benjamin T., Platts David G., ePLAR – The echocardiographic pulmonary to left atrial ratio – A novel non-invasive parameter to differentiate pre-capillary and post-capillary pulmonary hypertension, International Journal of Cardiology (2016), doi: 10.1016/j.ijcard.2016.03.035

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ePLAR – The echocardiographic Pulmonary to Left Atrial Ratio – A novel non-invasive parameter to differentiate pre-capillary and post-capillary pulmonary hypertension.

Gregory M Scalia¹ ² ³ ⁴
Isabel G Scalia⁴
Rebecca Kierle ²
Rebekka Beaumont ³
David B Cross ² ³
John Feenstra ³
Darryl J Burstow ¹ ⁴
Benjamin T Fitzgerald¹ ² ³
David G Platts ¹

¹. The Prince Charles Hospital. Brisbane Australia 4032
². Heart Care Partners. Brisbane Australia. 4066
³. The Wesley Hospital. Brisbane Australia 4066
⁴. University of Queensland. Brisbane Australia 4068

Corresponding Author:
Assoc Prof Gregory M Scalia
30 Chasely St
Auchenflower QLD AUSTRALIA 4066
gmscalia@gmail.com

All authors have no conflict of interest.
Abstract

**Background:** Right heart catheterisation is the gold-standard for differentiating *pre-capillary* pulmonary hypertension (high mean pulmonary artery pressure, normal pulmonary wedge pressure) from *post-capillary* physiology (elevated pulmonary wedge pressure). The new non-invasive parameter, ePLAR (echocardiographic Pulmonary to Left Atrial Ratio) is calculated from the maximum tricuspid regurgitation continuous wave Doppler velocity (m/s) divided by the transmitral E wave: septal mitral annular DTI E' wave ratio (TRV<sub>max</sub>/E:E').

**Methods:** Pulmonary hypertension patients (mean pulmonary artery pressure >25mmHg, n=133, 66 male, average 65.0±16.8 years) were classified by right heart catheterisation as *pre-capillary* or *post-capillary* [subdivided into isolated post-capillary (diastolic pulmonary gradient <7mmHg) or combined pre- and post-capillary cases]. The ePLAR values of these groups were compared to each other and to a population sample of 16356 population reference echocardiograms.

**Results:** ePLAR values for the normal reference population of 16356 echocardiograms (age 56±16.6yrs) were 0.30±0.09m/s. *Pre-capillary* pulmonary hypertension patients (n=35, 26 male, PAP<sub>sys</sub> 63.9±16.6mmHg, PAP<sub>dias</sub> 24.1±7.3mmHg, PAP<sub>mean</sub> 37.9±9.4mmHg, PCWP 10.6±2.7mmHg) had significantly higher ePLAR values than *post-capillary* cases (n=98, 40 male, PAP<sub>sys</sub> 59.9±17.6mmHg, PAP<sub>dias</sub> 25.0±7.4mmHg, PAP<sub>mean</sub> 38.1±9.8mmHg, PCWP 23.5±6.4mmHg) – ePLAR (0.44±0.22m/s vs 0.20±0.11m/s, p<0.001). ePLAR values were significantly lower in isolated post-capillary pulmonary hypertension than in combined pre- and post-capillary cases (0.18±0.08m/s vs 0.28±0.18m/s, p<0.001).

**Conclusions:** ePLAR is a simple echocardiographic parameter which can accurately differentiate the smaller subset of patients with *pre-capillary* pulmonary hypertension from the more common *post-capillary* etiology. The use of this easily obtained non-invasive
parameter has the potential to enhance non-invasive triage of patients for specific pulmonary vasodilator therapy.
Background

The management of pulmonary arterial hypertension (PHT) has been revolutionised over the last decade with the advent of specific pulmonary vasodilator therapies (1, 2). These new drugs have delivered both symptomatic and prognostic benefit to patients with previously bleak outlooks. Echocardiography, with assessment of right ventricular function and estimation of right ventricular systolic pressure is the principle first-line clinical investigation and screening tool in these patients. However, even current guidelines(3), support invasive measurements of pressures and cardiac output obtained via right heart catheterisation (RHC) as the gold-standard for assessment of pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP) as a surrogate for left atrial pressure (LAP), calculated trans-pulmonary gradient (TPG = PAP\text{mean} - PCWP), calculated diastolic pressure gradient (DPG = PAP\text{diast} - PCWP) and pulmonary vascular resistance (PVR = TPG/Cardiac Output)(4).

For the purposes of triage and therapy selection, patients with pulmonary hypertension (invasive PAP\text{mean}>25mmHg(5)) are divided into two major physiologies (6). Pre-capillary PHT patients are defined hemodynamically as having a PAP\text{mean}>25mmHg, with normal LAP (\leq15mmHg). Typically these patients have intrinsic pulmonary vascular obstruction. Arteriolar disease may be idiopathic (pulmonary arterial hypertension(6)), or related to connective tissue disorders (7, 8)). Parenchymal lung diseases (6) such as idiopathic pulmonary fibrosis(9) and severe chronic obstructive pulmonary disease(10), may cause secondary destruction of pulmonary capillary beds. Chronic thromboembolic pulmonary hypertension (CTEPH) will exhibit pre-capillary physiology with obstruction of small and medium-sized arteries. These patients, by definition, have normal left heart filling pressure (PCWP <15mmHg). Some of these patients may be candidates for specific therapies such as targeted pulmonary vasodilator therapy, anticoagulation or pulmonary thromboembolectomy (PTE) surgery.
Numerically however, the commonest cause of PHT is left heart disease [6]. These post-capillary PHT patients are defined as having $PAP_{\text{mean}} > 25\text{mmHg}$ with an elevated LAP (>15mmHg). This left atrial hypertension is usually secondary to left ventricular systolic and/or diastolic dysfunction from one or more of a variety of etiologies (such as hypertension, coronary artery disease, hypertrophic cardiomyopathy or valvular heart disease [11, 12]). Resultant pulmonary venous congestion translates to elevated pulmonary artery pressures. These post-capillary cases are then divided into two groups. Isolated post-capillary PHT, with no secondary reactive pulmonary arteriolar disease, has a low DPG (<7mmHg) and PVR (<3WU). However with chronicity or intercurrent lung disease, many patients with elevated left atrial pressure develop secondary perivascular pulmonary arteriolar sclerosis resulting in increased DPG (>7mmHg) and/or PVR (<3WU) [13]. This phenomenon has variously been labelled “reactive” PHT, “out of proportion” PHT, or more recently “combined post-capillary and pre-capillary PHT” [3, 14]. These patients have typically hitherto not been candidates of specific pulmonary vasodilator therapy. More recently, some patients in this “out-of-proportion” combined pre- and post-capillary group have been treated with sildenafil, with some benefit [15].

**ePLAR – conceptualising a new parameter**

There are echocardiographic surrogates for both elements of trans-pulmonary gradient – pulmonary artery pressure and left atrial pressure. Echocardiographic right ventricular systolic pressure (RVSP) is routinely calculated from the continuous wave Doppler tricuspid regurgitant velocity envelope via the modified Bernoulli equation, with an addition of a nominal estimate of right atrial pressure (RAP) [16, 17] based on standardised criteria (RVSP = $4 \times TRV_{\text{max}}^2 + \text{RAP}$) [18, 19]. Numerically, the dominant element of this parameter is an accurate measure of $TRV_{\text{max}}$. A well validated and accepted surrogate of LAP can be
obtained from the quotient of the peak transmitral pulsed-wave Doppler E-wave velocity divided by the mitral annular (septal or lateral) tissue Doppler tissue imaging E-prime (E:E’)(20). While there are a variety of confounders to this assessment (21-23), the E:E’ parameter has broadly been adopted by the echocardiography community as an indicator of normal versus elevated LAP(20, 24).

The new parameter ePLAR,

\[ ePLAR_{(\text{m/s})} = \frac{\text{TRV}_{\text{max}} \text{(m/s)}}{\text{mitral E:E’}} \]

is proposed as an echocardiographic surrogate for TPG and its interaction with LAP (figure 1). This parameter utilises the TRV_{max} (measured in metres/second), as a simplified indicator of pulmonary artery pressure and mitral E:E’ (which is dimensionless) as a surrogate for LAP. The ePLAR is thus an “analogue” of the PAP/LAP gradient (TPG) and its units “metres/second” are conceptually appropriate as Doppler flow velocities are directly related to pressure gradients by the Bernoulli equation.

In pre-capillary PHT, the PAP (and TRV_{max}) will increase without significant elevations of LAP (and therefore E:E’). The ePLAR quotient will thus be expected to be higher than normal. In post capillary PHT, both the PAP (and TRV_{max}) and the LAP (and E:E’) will increase. Numerically, the magnitude of the E:E’ changes are an order of magnitude greater than any increase in TRV_{max}. This will drive the ePLAR quotient lower than normal cases in post-capillary cases.

We hypothesised that ePLAR will differentiate pre-capillary pulmonary hypertension (elevated PAP_{mean} with normal PCWP) from post-capillary pulmonary hypertension (elevated PAP_{mean} and PCWP with or without elevated DPG) when compared to the gold standard of right heart catheterisation. We predicted that ePLAR will be higher in the pre-capillary PHT...
group, and lower in post-capillary PHT. Further, within the post-capillary group, isolated post-capillary cases are hypothesised to have the lower ePLAR values than those with combined pre- and post-capillary PHT.

Methods

Patient Selection
Consecutive patients studied with right heart catheterisation, found to have PHT (PAP_{mean} >25mmHg), who had complete echocardiographic data available, were studied. These patients were referred for investigation of dyspnoea. All had tricuspid regurgitation profiles measurable. Patients with previous mitral or tricuspid surgery or pericardial constriction were excluded. Patients with atrial fibrillation and/or pacing were included, with 3-5 beats of Doppler data averaged as required. All patients with elevated PCWP were deemed to have heart failure with either preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF).

Invasive Testing

Patients were fasted for four hours prior to the procedure. Access was obtained from the right femoral vein and Swan-Ganz fluid filled catheters were employed to measure all pressures. Pulmonary capillary wedge pressure was obtained by the averaging of three measurements during relaxed apnoea. Cardiac output was measured using the thermodilution technique, averaged over three injections of cold saline. Pulmonary vascular resistance was calculated from derived transpulmonary gradient (PAP_{mean} – PCWP) divided by cardiac output. Patients were then classified with contemporary guideline criteria(3) into two major hemodynamic groups: pre-capillary (PCWP<15mmHg) and post-capillary (PCWP≥15mmHg). Post capillary cases were then secondarily divided into isolated post-capillary PHT (DPG <7mmHg) and combined pre- and post-capillary PHT (DPG
≥7mmHg). The latter group conceptually will have increased PVR in addition to their elevation of PCWP.

**Echocardiographic Methods.**

Contemporaneous comprehensive transthoracic echocardiograms were performed with continuous wave Doppler assessment of tricuspid regurgitation peak velocity (TR $V_{\text{max}}$) and left heart trans-mitral pulsed-wave Doppler E-wave. Doppler tissue imaging peak e’ velocities were obtained from the septal mitral annulus. Data from 3-5 beats was averaged in atrial fibrillation cases. Calculated ePLAR values from for all groups were summarised and compared.

As ePLAR is a hitherto uncharacterised parameter, reference population values for ePLAR, $TRV_{\text{max}}$, and E/e’ were obtained from a retrospective review of 16356 routine echocardiograms. Major pathology was excluded from this reference data set using these criteria: left ventricular ejection fraction $\geq$50%, $TRV_{\text{max}}$ <2/9m/s, left atrial area <22cm$^2$, mitral E:E’ <12, mean mitral gradient <5mmHg, peak trans-aortic velocity <2m/s, ventricular septal thickness < 12mm and moderate or less left heart valve regurgitation. The population was analysed with simple linear regression across decades.

**Statistical Methodology:**

Continuous variables were expressed as mean ± 1 standard deviation. Comparison between the continuous variables was performed using an unpaired t-test. Categorical variables were expressed as absolute values. The individual components of the ePLAR ($TRV_{\text{max}}$, E-wave, E’ wave and E:E’)) were compared against their invasive counterparts by simple linear regression. Receiver operator characteristic testing was used to assess the discriminatory power of ePLAR (for *pre-* versus *post-capillary*) and all of its components. Sensitivity and specificity data generated optimal discriminatory cut-offs for ePLAR. A $p$ value of <0.05 was
considered as statistically significant. Statistical analysis was performed using Analyse-it® software (Leeds, United Kingdom).

Results

Patient Profile.

A group of 133 patients (66 male, average 65.0±16.5 years) with pulmonary hypertension (PAP mean ≥ 25mmHg) on right heart catheterisation, with comprehensive transthoracic echocardiograms was studied. Of the Pre-capillary PHT cases (n=35, 26 male, 67±15 years), provisional diagnoses were idiopathic pulmonary arterial hypertension (43%), CTEPH (8%), Scleroderma / CREST / mixed connective tissue disease / lupus (20%) and pulmonary fibrosis/chronic obstructive airways disease (23%), bronchiectasis (3%) and bronchiolitis obliterans (3%). Post-capillary cases (n=98, 40 male, age 64±17 years) had preserved ejection fraction (HFpEF) in 62% and reduced left ventricular function in 32%. The principle clinical diagnosis in 6% of these cases was idiopathic pulmonary arterial hypertension. The finding of elevated PCWP in such pulmonary patients raises issues about the strict applicability of these invasive criteria.

Invasive Hemodynamics

Pre-capillary PHT cases had PAP sys 63.9±16.6mmHg, PAP diast 24.1±7.3mmHg, PAP mean 37.9±9.4mmHg, PCWP 10.6±2.7mmHg, TPG 26.7±8.0mmHg and DPG 12.8±6.6mmHg – See Table 1. Using thermodilution technique, cardiac output was 4.7±1.4 l/min and calculated PVR was 6.5±3.6 WU. Post-capillary cases had PAP sys 59.9±17.6mmHg, PAP diast 25.0±7.4mmHg, PAP mean 38.1±9.8mmHg, PCWP 23.5±6.4mmHg, TPG 15.0±9.3mmHg and DPG 1.5±6.6mmHg. Using thermodilution technique, cardiac output was 4.7±1.7 l/min and calculated PVR was 3.7±2.9WU.
Isolated post-capillary PHT cases (n=81, 34 male), had $PAP_{\text{sys}}$ 56.5±16.0mmHg, $PAP_{\text{diast}}$ 23.5±6.6mmHg, $PAP_{\text{mean}}$ 36.1±8.6mmHg, PCWP 24.3±6.6mmHg, TPG 12.3±6.7mmHg and DPG -0.8±4.2mmHg. Using thermodilution technique, cardiac output was 4.6±1.8 l/min and calculated PVR was 3.1±2.7WU. Combined pre- and post-capillary PHT cases (n=17, 6 male), had $PAP_{\text{sys}}$ 76±16.6mmHg, $PAP_{\text{diast}}$ 32.1±6.6mmHg, $PAP_{\text{mean}}$ 47.7±9.7mmHg, PCWP 19.9±4.3mmHg, TPG 28.2±8.4mmHg and DPG 12.2±5.3mmHg. Using thermodilution technique, cardiac output was 5.2±1.6 l/min and calculated PVR was 6.0±3.0WU.

Echocardiographic data - ePLAR

The ePLAR was significantly higher in the pre-capillary PHT group than the total post-capillary group (0.44±0.22m/s vs 0.2±0.11m/s, p<0.001) (figure 2A). There was composed of a significantly higher TR $V_{\text{max}}$ (4.0±0.5m/s vs 3.3±0.7m/s, p<0.001) and a significantly lower transmitral E:E' (11.7±7.2 vs 21.6±14.6 p<0.001). Isolated post-capillary PHT patients had significantly lower ePLAR values than combined pre- and post-capillary PHT cases (0.18±0.08m/s vs 0.28±0.18m/s, p<0.001). There was composed of a significantly lower TR $V_{\text{max}}$ (3.2+/-0.7 m/s vs 3.8+/-0.8±0.6m/s, p<0.001) with no significant difference in transmitral E:E' (21.2+/-12.6 vs 18.5+/-22.6 p=ns). By way of reference, the normal reference population of 16356 echocardiograms (age 56±16.6yrs) yielded a mean ePLAR of 0.30±0.09m/s. This was a slight but significant reduction in the ePLAR across the age range studied (figure 2B).

Receiver operator characteristic analysis showed that ePLAR had a high discriminating power (AUC = 0.87, p<0.05) for distinguishing between pre-capillary and total post-capillary PHT groups. The components of the ePLAR (TR$V_{\text{max}}$, transmitral pulsed wave Doppler E-wave, mitral annular E-prime and E:E') were also analysed against the RHC gold standard.
(figure 3A). Each component showed weaker discriminatory power for pre- versus total post-capillary PHT than the composite ePLAR parameter (TRVmax AUC = 0.76, E-wave AUC = 0.75, E' AUC = 0.60, E:E' AUC = 0.796). Sensitivity analysis suggests a proposed optimal cut-off value for ePLAR of approximately 0.28m/s, with sensitivity and specificity of approximately 83% (see figure 3B). Receiver operator characteristic analysis showed that ePLAR had a high discriminating power (AUC = 0.76) for differentiating pre-capillary PHT from combined pre- and post-capillary PHT (see figure 3C). Finally, receiver operator characteristic analysis showed that ePLAR had a modest discriminating power (AUC = 0.69) for differentiating isolated post-capillary from pre- and post-capillary PHT (see Figure 3D).

Each of the elements of the ePLAR quotient was compared by linear regression with the relevant invasive parameter. There was modest correlation of TRVmax with PAPsys, E:E' with PCWP and ePLAR with both TPG and DPG – see Figure 4).

Discussion
Differentiation of pre-capillary from post-capillary pulmonary hypertension has important clinical implications. Current specific vasodilator therapy is expensive, not without side-effects, and appropriate for a very well characterised minority of patients with PHT(1, 2). As can be seen in our patient groups, only approximately one quarter of all patients undergoing RHC for investigation of elevated RVSP by echocardiography will have pre-capillary hypertensive physiology. Until now, this triage process has mandated invasive cardiac catheterisation(25). A reliable and robust non-invasive differentiator of these physiologies could potentially reduce the number of costly, invasive, and potentially futile RHC procedures(26). With the advent of specific pulmonary arterial hypertension units, an effective non-invasive screening tool offers the potential timely and appropriate referral of patients suitable for pulmonary vasodilator therapy and reduce the number of unnecessary referrals of patients with post-capillary physiology (27, 28). In practical terms, elevated
ePLAR values found in patients with elevated RVSP undergoing routine echocardiography should prompt the clinician to consider pre-capillary PHT conditions.

The fundamental tenet of the ePLAR is physiologically plausible. Pre-capillary PHT patients have elevated trans-pulmonary gradients levels, related to intrinsic pulmonary vascular obstructive disease (perivascular fibrosis in pulmonary arterial hypertension(5) or scleroderma(7, 29)) and/or intrinsic parenchymal lung conditions (such as idiopathic pulmonary fibrosis(9, 30) or emphysema(10, 31)) which destroy vascular beds. Right ventricular afterload is elevated and trans-pulmonary pressure transmission to the left atrium is impaired. It follows that LAP will be low-normal in these patients, in the absence of left heart disease. The more severe the pulmonary vascular obstructive disease, the wider the gap between PAP and LAP (i.e. increased TPG). It was hypothesised that this same trend would paralleled in the non-invasive parameter, ePLAR. The data from this foundation study supports this prediction.

The corollary should be true in post-capillary PHT. Whilst TRV_{max} will rise above normal (e.g. from approx. 2.3m/s to 3.3m/s), the E:E’ in patients with clinically significant left atrial hypertension (LAP>15mmHg) will rise numerically much more (e.g. from E:E’ = 8.3 to E:E’ = 21.6). The quotient ePLAR will progressively fall as the LAP (and therefore E:E’) rises. More severe the left atrial hypertension yields lower the ePLAR values.

In this foundation group, there was a very clear dichotomy of the ePLAR in the pre-capillary PHT cases (which were significantly higher than normals) and the post-capillary PHT cases (which were significantly lower than normals). Receiver operator analysis showed a powerful differentiating ability of the ePLAR against the invasive RHC gold standard.
Importantly, the ePLAR had a greater discriminating power than any of its components. This also is biologically plausible. The ePLAR has the advantage of deriving Doppler parameters from both sides of the heart. Conceivably, the same confounders of the Doppler determinations of PAP and LAP, may “cancel out” by this numeric division in each patient. This internal consistency and the numerical divergence of the factors of the equation, probably both contribute to the differentiating power of the ePLAR.

In this data set, as in most published series, Doppler predications of PAP (such as RVSP via $\text{TRV}_{\text{max}}^{(29)}$, $\text{PAP}_{\text{mean}}$ via pulmonary acceleration time(32)) and of LAP (via E:E’ and other complex diastolic algorithms(24)) show at best, approximations of invasive right and left heart pressures(33, 34). There are various explanations for the apparent disconnect between Doppler and invasive measures in this part of the circulation (35). In the pre-capillary PHT group, the echocardiographic RVSP (76.1 +/- 16.6 mmHg) significantly over-estimated the invasive PAP$_{\text{sys}}$ (63.9 +/- 16.6 mmHg, $p<0.001$) and in the post-capillary group the echocardiographic RVSP (55.4 +/- 21.3 mmHg) significantly under-estimated the invasive PAP$_{\text{sys}}$ (59.9 +/- 17.6 mmHg, $p=0.003$). These errors may relate to the estimation of RAP (16) and issues related to the accurate echocardiographic measurement of the $\text{TRV}_{\text{max}}$.

Differentiating those patients with isolated post-capillary PHT from the combined pre- and post-capillary PHT groups is of some clinical significance. In some countries, use of the pulmonary vasodilator sildenafil, has been employed in this group of patients with reactive pulmonary vascular obstruction in the setting of left heart disease with some benefit (15). This more subtle determination was evident in this study. The ePLAR parameter did increase in post-capillary patients as the DPG rose “out-of-proportion” in the combined pre- and post-capillary group, becoming statistically similar to age-related normal values. As all patients in this study had PHT, the finding of a “normal” ePLAR implies rising TPG in patients with elevated E/e’.
The reference 16356 “normal” population data reviewed for this study shows a trend towards slightly lower mean ePLAR values with increasing age. This needs to be taken into account when considering the ePLAR in a given patient. Specifically, in the older patient, the threshold to consider that pre-capillary physiology is present may be slightly lower. Clinically, it desirable to have a slightly higher sensitivity so as to minimise the false negative rate (patients who may be “ruled out” as potential candidates for specific pulmonary vasodilator therapy by this non-invasive screening test.

ePLAR is a an echocardiographic parameter that could be applied to routine echocardiograms on virtually every patient with a tricuspid regurgitant envelope, utilising the easily obtained parameters of TRV_{max} and transmitral E:E'. The finding of modest elevations of RVSP is common in clinical practice, triggering a consideration of clinical significance and possible etiologies. Clinical and ancillary echocardiographic parameters (septal flattening, dilated right atrium etc) raise the suspicion of significant pulmonary hypertension(3). The majority of these patients will not proceed to RHC, or referral to a dedicated PHT unit. The practical question for these patients is, “Is this elevation of TRV_{max}/RVSP “in proportion” to the level of transmitral E:E’ (likely post-capillary physiology) or “out of proportion” (likely pre-capillary physiology)? Assessing ePLAR, could help guide clinicians down the appropriate investigation pathway.

No single parameter will define such a heterogeneous patient group (36), though several non-invasive parameters are established as predictors of outcome and prognosis (37). Right ventricular function is an obvious target. The tricuspid annular plane systolic excursion (TAPSE) as a quantification of right ventricular function, predicts long term prognosis (16, 38, 39). The relationship between TAPSE and PAP_{sys} is shifted in post-capillary cases (40).
Yeo et al (41) analysed a Doppler right ventricular time-based index (isovolumic contraction time plus isovolumic relaxation time divided by ejection time) in patients with primary (pre-capillary) pulmonary hypertension which was shown to be a predictor of outcome. Most recently, right ventricular mechanical performance as quantified by dP/dt has been shown to predict outcome (42).

The actual flow characteristics of the pulmonary circulation are assessed invasively via the trans-pulmonary gradient and pulmonary vascular resistance on RHC. Non-invasive pulmonary vascular resistance (PVR) has been derived from TRV_{\text{max}} as a surrogate for PAP_{\text{sys}} and RVOT VTI as a correlate of cardiac output, without (43, 44) and with (45) heart rate being incorporated into the formula. Pulmonary vascular resistance derived from Doppler tissue imaging of the tricuspid annulus also predicted prognosis(46).

However, in this era of specific pulmonary vasodilator drugs, determination of etiology/physiology arguably is more important clinically than prognostic quantification. Visual inspection of the shape of the right ventricular outflow tract pulsed wave Doppler envelop has been proposed as a marker of the aetiology of PHT (47). This has been incorporated into a scoring system by Opotowsky et al (48, 49) which predicts well the differentiation between pre-and post-capillary PHT. The combination of parameters used in this algorithm (E:E'>10, left atrial AP dimension>4.2, left atrial AP dimension<3.2cm, RVOT PW Doppler mid-systolic notch or AccT < 80ms) basically address the same physiologic imperatives as the ePLAR (PAP and LAP).

D’alto et al have a competing algorithm (50) with multiple components including right versus left heart chamber size, right ventricular apical anatomy, left ventricular eccentricity index,
pericardial effusion, notching of the RVOT Doppler profile, IVC diameter/collapsibility, mitral E/E’ ratio and moderate to severe mitral or aortic valve disease. It should be noted that ePLAR had stronger discriminating power by ROC analysis (AUC = 0.87) than the D’Alto scoring system (AUC = 0.756) and similar to Opotowsky et al (48) (AUC = 0.881) with simplicity of a single composite parameter easily and routinely derived from everyday standard echocardiographic measures.

**Future Directions**

This research outlines for the first time a novel, non-invasive parameter (ePLAR) obtained from routinely and readily available transthoracic parameters, which helps discriminate between pre-capillary and post-capillary hypertension. Future research should focus on prospective analysis with near simultaneous acquisition of echocardiographic and RHC data to help validate this novel parameter. Providing that ePLAR is found to be a robust parameter in the assessment of pulmonary hypertension, its clinical utility may extend beyond just the non-invasive dichotomisation of pre-capillary versus post-capillary pulmonary hypertension, to numerous other cardio-respiratory related conditions such as acute pulmonary embolism, sleep apnoea and structural cardiac intervention cases.

**Limitations**

The main limitation of this study is the non-simultaneous collection of the echocardiographic and invasive RHC data. This allows for the confounder of changed in loading conditions. In pre-capillary patients, variation in filling status will be expected to have very little effect on hemodynamics with fixed elevations of TPG being the main physiologic determinant. The ePLAR in this group would not be expected to be significantly affected by changes in filling
status. In post-capillary (left heart driven) cases, changes in filling may be reflected as changes in E:E’. Specifically, diuretic therapy will lower the E/e’ (and probably the TRV_{max}) with associated increases in the ePLAR. The E/e’ parameter has its own limitations. It is less reliable in special diseases, e. g. in healthy persons or hypertrophic cardiomyopathy etc. In the specific situation of pericardial constriction, the E/e’ value is low, but the filling pressure is very high. Further, a sub-group of patients with pulmonary hypertension do not have a measurable spectral Doppler tricuspid regurgitant jet. As such, the ePLAR cannot be calculated in these individuals.

Conclusions

Pulmonary hypertension is a common condition with a heterogeneous range of aetiologies. Tailored treatment modalities for specific pre-capillary physiologies now offer hope to a subgroup of these patients. Transthoracic echocardiography is typically the initial investigation of choice in patients with suspected pulmonary hypertension, but is often a poor discriminator in the key dichotomisation of pre-capillary versus post-capillary causes. This research applied a novel, non-invasive, easily obtained echocardiographic parameter, ePLAR, to a broad range of pulmonary hypertensive patients to discriminate between pre-capillary and post-capillary hypertension. ePLAR demonstrates a gradient from lowest values in isolated post-capillary PHT cases, through intermediate in combined pre- and post-capillary PHT cases, to highest values in the post-capillary PHT cases. This ePLAR parameter may offer value as a broadly applicable non-invasive screening tool for consideration of specific pulmonary vasodilator therapies.
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Figure 1. ePLAR explanation and example data. A. The ePLAR comprises three simple measurements: peak tricuspid regurgitation continuous wave velocity (m/s) divided by the transmitral peak pulsed wave Doppler E wave (cm/s) : peak Doppler tissue imaging mitral septal annular e’ wave (cm/s). B. The four nominal patient subsets clinically encountered are demonstrated with predicted bell curves displayed (C). Normal cases (red) will have normal PAP\textsubscript{mean} (<25mmHg), normal TRV\textsubscript{max} (e.g. 2.4m/s), normal LAP (<15mmHg) and normal E/e’ (e.g. 8) and predicted ePLAR of approximately 0.30m/s. Patients with left heart failure (LHF) but with normal pulmonary arterial pressures (PAP\textsubscript{mean} < 25mmHg) will have normal TRV\textsubscript{max} (e.g. 2.4m/s) with a high E/e’ (e.g. 20) yielding an ePLAR of approximately 0.12m/s (orange). Patients with post-capillary PHT secondary to LHF will have a high TRV\textsubscript{max} (e.g. 4.0m/s) and a high E/e’ (e.g. 20) yielding an ePLAR of approximately 0.20m/s (blue). Patients with pre-capillary PHT will have a high TRV\textsubscript{max} (e.g. 4.0m/s) with a normal E/e’ (e.g. 8) yielding the highest of ePLAR values - approximately 0.50m/s in this example (green). C. ePLAR will be higher than normal in patients with pre-capillary physiology (rising trans-pulmonary gradient, TPG) and lower than normal in patients with post-capillary physiology (rising LAP).

Figure 2. A ePLAR values Pre-capillary PHT (n=35), Post-capillary (all) PHT (n=98), Isolated post-capillary PHT (n=81) and Combined pre- and post-capillary PHT (n=17) by RHC displayed as median, quartiles and range graphically and numerically as mean +/- SD. Significance p-values at 95% confidence level by student t-test. B. ePLAR values by decade of age in for reference population (n=16356) displayed as mean +/- SD by decade.

Figure 3A. Receiver operator characteristic analysis of ePLAR and its individual component parameters in differentiating pre-capillary from post-capillary (all) pulmonary hypertension. ePLAR had the strongest discriminating power, with an area under the curve (AUC) of 0.87.
ePLAR had stronger predictive power than any of its components in isolation (E-wave AUC = 0.75, e’ AUC = 0.60, E/e’ AUC 0.795, TRVmax AUC 0.754). B. Sensitivity analysis of ePLAR, testing cut-off values of 0.2m/s, 0.24m/s, 0.28m/s and 0.30m/s, with associated sensitivities and specificities. C. Receiver operator characteristic analysis showed that ePLAR had a high discriminating power (AUC = 0.76) for differentiating pre-capillary PHT from combined pre- and post-capillary PHT. D. Receiver operator characteristic analysis showed that ePLAR had a modest discriminating power (AUC = 0.69) for differentiating isolated post-capillary from pre- and post-capillary PHT.

Figure 4. A. Linear correlation of invasive PAPsys with echocardiographic TRVmax shows modest linear relationship ($r^2 = 0.44$, p<0.001). B. Linear correlation of invasive PCWP with echocardiographic E/e’ shows weak linear relationship ($r^2 = 0.12$, p = 0.013). C. Linear correlation of echocardiographic ePLAR with invasive TPG with shows a weak linear relationship ($r^2 = 0.27$, p<0.001). Linear correlation of echocardiographic ePLAR with invasive DPG, a modest linear relationship ($r^2 = 0.29$, p<0.001).

Table 1 Invasive (RHC) and non-invasive echocardiographic data for 133 patients undergoing RHC for PHT. The echocardiographic data for 16356 population studies is provided as a reference. (* p<0.05 pre-capillary vs post-capillary (all) PHT, # p<0.05 isolated pre-capillary vs combined pre- and post-capillary PHT, & p<0.05 pre-capillary vs combine pre- and post-capillary PHT).
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ePLAR</td>
<td>echocardiographic Pulmonary to Left Atrial Ratio</td>
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<tr>
<td>PHT</td>
<td>Pulmonary hypertension</td>
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<td>RHC</td>
<td>Right heart catheterisation</td>
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<td>PAP</td>
<td>Pulmonary artery pressure</td>
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<tr>
<td>LAP</td>
<td>Left atrial pressure</td>
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<tr>
<td>TRV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Transmitral maximum continuous wave Doppler velocity</td>
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<td>RVSP</td>
<td>Right ventricular systolic pressure</td>
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<td>TPG</td>
<td>Trans-pulmonary gradient</td>
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<tr>
<td>DPG</td>
<td>Diastolic pressure gradient</td>
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<tr>
<td>PVR</td>
<td>Pulmonary vascular resistance</td>
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<tr>
<td>PCWP</td>
<td>Pulmonary capillary wedge pressure</td>
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<tr>
<td>E/e’</td>
<td>Transmitral pulsed wave Doppler early diastolic wave divided by septal mitral annular Doppler Tissue Imaging peak early diastolic wave</td>
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Figure 1
Figure 2
Figure 3
Figure 4
Table 1

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<th>Pre-Capillary Pulmonary Hypertension</th>
<th>Post-Capillary Pulmonary Hypertension (All)</th>
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<th>Combined pre-and post-capillary Pulmonary Hypertension</th>
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<tr>
<td>(n=133)</td>
<td>n=35</td>
<td>n=98</td>
<td>n=81</td>
<td>n=17</td>
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<td>76±16.6 # &amp;</td>
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<tr>
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<td>0.28±0.18 # &amp;</td>
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