Peripheral Vascular Ageing in Pulmonary Arterial Hypertension as Assessed by Common Carotid Artery Intima Thickness and Intima/Media Thickness Ratio: An Investigation Using Non-Invasive High-Resolution Ultrasound

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Background Pulmonary arterial hypertension (PAH; World Heath Organization [WHO] Group 1) is associated with increased pulmonary arterial pressure and resistance, with pulmonary vascular remodelling. The vascular anatomy of the systemic arteries has been less well studied.

Method Nineteen (19) patients with PAH, confirmed by right heart catheterisation (RHC), 14 patients with left ventricular heart failure with reduced ejection fraction (LVrEF), and 30 healthy subjects were enrolled. Common carotid artery (CCA) intima thickness, intima/media (I/M) thickness ratio, and intima-media thickness (IMT) were assessed using non-invasive ultrasound (22 MHz centre frequency).

Results The CCA intima thickness was correlated with several RHC variables (all p < 0.05). The intima was 56% thicker (+0.05 mm; 95% CI 0.03, 0.06; p < 0.0001) and the I/M thickness ratio was 128% greater (+0.21; 95% CI 0.13, 0.28; p < 0.0001) in patients with PAH than healthy subjects. These values were also significantly higher than in patients with LVrEF. In ROC curve analysis, the c-values for CCA intima thickness (0.92) and I/M ratio (0.87), but not for IMT, correctly indicated which individuals belonged to the PAH or healthy control groups. The CCA IMT showed no corresponding significant group differences or associations and was of no use according to receiver operating curve analysis.

Conclusions Patients with PAH displayed signs of peripheral vascular remodelling, challenging the common opinion that vascular changes in PAH are restricted to the lung vasculature. Correlations with cardiopulmonary variables from RHC support peripheral vascular coupling and the association with vascular ageing. Results from this pilot study warrant further confirmation.

Keywords Pulmonary arterial hypertension • Vascular ageing • High-resolution ultrasound • Intima thickness and intima/media thickness ratio • Common carotid artery
Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterised by increased pressure in the pulmonary vasculature, which leads to right ventricular heart failure in the later stages [1-3] and is associated with thicker intima and thicker media layers in the pulmonary vasculature [4]. The common belief is that vascular changes in PAH are restricted to the pulmonary vasculature; whether PAH patients also have more generalised changes, with vascular remodelling in the peripheral vasculature, has not been well studied.

The common carotid artery intima-media thickness (CCA-IMT) was the 'gold' standard for assessing the risk of cardiovascular disease (CVD) for many years, as recommended by the American Heart Association [5]. However, current American College of Cardiology/American Heart Association guidelines recommend against measuring the CCA-IMT in routine clinical practice for risk assessment of the first atherosclerotic CVD event [6]. With advancing age and development of atherosclerosis, the intima layer becomes thicker and the media layer becomes thinner [7,8]; this process is not captured by conventional IMT measurement (8–10 MHz) but can be seen with an ultrasound probe at higher frequencies [9]. Thickening of the arterial intima layer is an early morphological sign of developing subclinical atherosclerosis [10]. However, the intima/media (I/M) thickness ratio may be a more sensitive method of grading atherosclerosis in peripheral arterial disease, as suggested earlier [11,12]. It is believed that no previous study has examined the individual artery wall layer dimensions in the peripheral arteries of patients with PAH. The current study hypothesised that patients with PAH might have peripheral vascular ageing compared with healthy controls. In addition, it compared the results with those of patients with left ventricular heart failure with reduced ejection fraction (LVrEF) and tested correlations between cardiopulmonary variables in patients with PAH and their common carotid artery (CCA) wall layer dimensions.

Materials and Methods

The Pulmonary Arterial Hypertension Patient Group

This study was a group-comparative study that included 19 patients with PAH (World Health Organization [WHO] Group 1), according to the current WHO classification of PAH [2]. These patients fulfilled the following criteria: mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg, mean pulmonary arterial wedge pressure (mPAWP) $\leq$ 15 mmHg, and pulmonary vascular resistance (PVR) $>3$ WU, based on right heart catheterisation (RHC) performed at Uppsala University Hospital, Uppsala, Sweden. Their median age was 53 years (range, 27–84; interquartile range [IQR], 41–69). All PAH patients were receiving PAH-specific medication: sildenafil (15 patients), bosentan (six patients), ambrisentan (one patient), and iloprost (four patients). Some of the PAH patients were receiving combination therapy comprising sildenafil combined with bosentan (five patients), sildenafil with ambrisentan (one patient), or sildenafil with bosentan and iloprost (two patients). Additional patient characteristics are given in Table 1.

Haemodynamic Measurements

Right heart catheterisation was carried out for all PAH patients after an overnight fast at Uppsala University Hospital during 2005–2010; it was indicated either as a clinically warranted haemodynamic follow-up for known PAH or for diagnostic purposes of new PAH/pulmonary hypertension. Patients were resting in the supine position during RHC and no medication was given prior to the intervention. A fiberoptic thermodilution pulmonary artery catheter, Becton Dickinson Criticath SP5 107 HTD catheter (Becton Dickinson and Company, Franklin Lakes, NJ, USA) was inserted through the right internal jugular vein into the pulmonary artery; correct position was verified by fluoroscopy. Blood pressure was registered with a Cathcor system (Siemens, Erlangen, Germany) and blood flow was calculated using the thermodilution technique or Fick’s principle. Patients with tricuspid valve regurgitation $>\text{grade 1}$ were evaluated using Fick’s principle because of greater variation with the thermodilution technique. The patients were hospitalised one day before the RHC intervention. The procedure has also been described in previous publications [13-15]. Pulmonary vascular resistance was estimated by dividing the trans-pulmonary pressure gradient (mPAP – mPAWP) by the cardiac output.

The Left Ventricular Heart Failure With Reduced Ejection Fraction Patient Group

Fourteen (14) patients with a diagnosis of LVrEF were included as an additional patient group for comparison; their median age was 67 years (range, 48–82; IQR, 60–79). Additional characteristics are given in Table 1.

Additional Assessments in the Pulmonary Arterial Hypertension and Left Ventricular Heart Failure With Reduced Ejection Fraction Groups

Blood samples were obtained from peripheral veins and collected in EDTA tubes (BD Diagnostics, Burlington, NC, USA), as previously described [14]. The 6-minute walking distance (6MWD) test was carried out in the PAH group, in accordance with the American Thoracic Society’s guidelines [16]. Body mass index (BMI) was calculated as weight (kg)/height (m)$^2$. Blood pressure was oscillometrically measured (Henry Eriksson AB, Sweden) using an appropriate dimension of cuff, applied to the upper right arm, at the same visit as the ultrasound examination.
Healthy Subjects

The CCA wall dimensions were obtained from 30 healthy subjects with a median age of 62 years (range, 27–82; IQR, 49–69). Recruitment of healthy male subjects was performed consecutively by convenient sampling. Healthy females of similar age were recruited from a previous study [17]. All healthy subjects were non-smokers and without known prior history of documented heart or arterial disease and without any medication likely to affect the arterial wall.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PAH (n=19)</th>
<th>LVrEF (n=14)</th>
<th>Controls (n=30)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53 (41, 69)</td>
<td>67 (60, 79)</td>
<td>62 (49, 69)</td>
</tr>
<tr>
<td>Men/women</td>
<td>6/13</td>
<td>6/8</td>
<td>11/19</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168 (161, 179)</td>
<td>165 (158, 182)</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72 (60, 81)</td>
<td>86 (69, 96)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.7 (21.9, 28.3)</td>
<td>30.5 (24.5, 34.1)</td>
<td></td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>89 (75, 102)</td>
<td>108 (80, 116)</td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>120 (110, 130)</td>
<td>122 (112, 141)</td>
<td></td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>75 (65, 84)</td>
<td>71 (64, 81)</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>3 (16%)</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Months since PAH dx</td>
<td>36 (10, 49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific PAH medication</td>
<td>19/19</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (16%)</td>
<td>2 (14%)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (5%)</td>
<td>1 (7%)</td>
<td></td>
</tr>
<tr>
<td>Right heart catheterisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA, mmHg</td>
<td>6 (3, 13)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>RA O₂, % saturation</td>
<td>68 (62, 71)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>RV SBP, mmHg</td>
<td>71 (54, 92)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>RV EDP, mmHg</td>
<td>9 (7, 16)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>RV O₂, % saturation</td>
<td>69 (61, 72)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>PA SBP, mmHg</td>
<td>71 (54, 91)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>PA DBP, mmHg</td>
<td>37 (23, 39)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>MPAP, mmHg</td>
<td>46 (36, 60)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>PA O₂, % saturation</td>
<td>69 (59, 73)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>9.0 (8.5, 12)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>8.7</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.24 (2.3, 5.6)</td>
<td>na</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>288 (116, 1753)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Plasma lipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.6 (3.6, 5.9)</td>
<td>5.3 (4.3, 5.9)</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.3 (1.9, 3.3)</td>
<td>3.1 (2.3, 4.1)</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.3 (1.0, 1.6)</td>
<td>1.2 (0.8, 1.5)</td>
<td></td>
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<tr>
<td>LDL/HDL ratio</td>
<td>2.2 (1.6, 2.5)</td>
<td>2.5 (2.2, 3.5)</td>
<td></td>
</tr>
<tr>
<td>Apo A1, g/L</td>
<td>1.4 (1.3, 1.7)</td>
<td>1.6 (1.4, 2.0)</td>
<td></td>
</tr>
<tr>
<td>Apo B, g/L</td>
<td>0.8 (0.7, 1.0)</td>
<td>0.9 (0.7, 1.1)</td>
<td></td>
</tr>
<tr>
<td>Apo B/A1</td>
<td>0.5 (0.5, 0.7)</td>
<td>0.7 (0.6, 0.8)</td>
<td></td>
</tr>
</tbody>
</table>

All values are expressed as median (IQR) or number (%).

*All control subjects were healthy non-smokers without known prior history of documented heart and/or arterial disease and without any medication likely to affect the arterial wall.

#p<0.05.

Abbreviations: PAH, pulmonary arterial hypertension (WHO Group 1); LVrEF, left ventricular heart failure with reduced ejection fraction; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; dx, diagnosis; na, not applicable; 6MWT, 6-minute walking test; RA, right atrium; RV, right ventricle; EDP, end-diastolic pressure; PA, pulmonary artery; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; NT-proBNP, N-terminal prohormone BNP; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
High-Resolution Ultrasound of the Artery Wall

The right CCA was assessed using a high-resolution broadband probe with 22 MHz centre frequency to yield point estimates of the near artery wall layers (Collagenoson, Minhorst Company, Meudt, Germany), as previously described [9,17,18] (Figure 1). All scans were sampled by the same technician and blindly analysed by the same investigator (T.N.). In the laboratory, the intra-reader coefficient of variation calculated from double estimates, based on the mean of five or more measurements in 20 subjects, was about 4.3% for intima thickness. To further reduce the variability, final values for each participant were based on a mean of ≥10 measurements. The inter-reader variability was about 5.4% [19]. A thick intima layer and a high I/M thickness ratio are signs of subclinical atherosclerosis.

Ethical Considerations

The study was approved by the local Ethics Committee of the Medical Faculty of Uppsala. Informed written consent was obtained from each included participant in the study. Healthy female controls had previously given their consent [17].

Statistical Analysis

Data are presented as medians and IQRs (25%, 75%). Because several of the artery wall parameters were not normally distributed, non-parametric statistical tests were preferably applied. Between-group comparisons were assessed using the Mann-Whitney U test and comparisons of medians with 95% confidence intervals (CI) were assessed using the Hodges-Lehmann estimator, with visually fairly symmetrical distribution around the medians in both groups, especially for the I/M thickness ratio. Non-parametric partial regression was used to adjust for covariates such as age and gender. Correlations between variables were assessed using the Spearman rank correlation test. Non-parametric receiver operating characteristic (ROC) curve analysis was undertaken to illustrate and compare the ability of CCA intima thickness, I/M thickness ratio, and IMT to correctly indicate the group to which the individual belonged: PAH or healthy subjects. JMP software version 15.0 (SAS Institute Inc., Cary, NC) and SPSS software version 27 (for non-parametric partial regression) were used. All tests were two-sided, and p<0.05 was considered statistically significant.

Results

The median age of the PAH group (53 years) was numerically lower than that of the other two groups, but they did not significantly differ. The proportion of men in the PAH, LVrEF, and healthy control groups was 32%, 43%, and 37%, respectively. Ten (10), seven, and two patients with PAH were assigned to New York Heart Association functional classes 2, 3, and 4, respectively. Descriptive characteristics in the two patient groups (PAH and LVrEF) did not significantly differ, except for lower median ApoB/A1 values in the PAH group (Table 1).

Correlation of Right Heart Catheterisation Haemodynamic Variables With Common Carotid Artery Wall Layer Dimensions

The CCA wall layer dimensions in patients with PAH were significantly correlated with several RHC variables. The CCA intima thickness was correlated with right ventricular systolic pressure ($r_s=0.54; p=0.017$), pulmonary artery...
systolic pressure ($r_s=0.51;\ p=0.028$) (Figure 2), and mPAP ($r_s=0.51;\ p=0.027$). The CCA I/M thickness ratio was correlated with pulmonary capillary wedge pressure ($r_s=0.49;\ p=0.048$). The CCA IMT showed no significant correlation with RHC variables. No correlation was found with NT-proBNP levels.

**Common Carotid Artery Wall Layer Dimensions by Study Group**

The patients with PAH had 56% thicker intima layer ($+0.05\ \text{mm};\ 95\%\ CI\ 0.03,\ 0.06;\ p<0.0001$), 26% thinner media ($–0.11\ \text{mm};\ 95\%\ CI\ –0.24,\ –0.03;\ p<0.01$), and 128% greater I/M ($+0.21;\ 95\%\ CI\ 0.13,\ 0.28;\ p<0.0001$) than the healthy subjects (Table 2, Figures 2 and 3). The median group differences for intima thickness and I/M thickness ratio remained significant after adjustment for age and gender, both separately and together (all $p<0.001$). In addition, patients with PAH displayed more signs of peripheral vascular ageing than patients in the LVrEF group: with 27% thicker intima layer ($+0.03\ \text{mm};\ p<0.001$) and 28% greater I/M thickness ratio ($+0.09;\ p<0.03$) in patients with PAH. The values in the LVrEF group fell between those in the PAH and control groups (Figure 3 A–B). There were no significant group differences in CCA IMT.

**Correlation of Common Carotid Artery Wall Layer Dimensions With Age and Time Since Pulmonary Arterial Hypertension Diagnosis**

In healthy subjects, increased age correlated logically with the expected signs of vascular ageing: increased CCA intima thickness ($r_s=0.51;\ p=0.004$) (Figure 4), greater I/M thickness ratio (0.73; $p<0.0001$), and reduced media thickness ($–0.66;\ p<0.0001$). Similar age-related changes in the artery wall layer dimensions were found in patients with LVrEF. In contrast, patients with PAH showed signs of substantial vascular ageing at a young age and, if anything, there was a tendency for reduction (improvement) in intima thickness at increased ages rather than the expected worsening with age that had occurred in the control subjects (Figure 4). The test for interaction between study group (PAH/controls) and age was significant for the CCA intima thickness ($p<0.001$) and I/M thickness ratio ($p<0.05$). The impression of improved intima thickness with ageing in patients with PAH remained even after adjustment for time since PAH diagnosis; the expected adverse effect of age per se (see controls) seemed to be reversed for intima thickness in patients with PAH ($–0.35;\ p<0.004$).

**Type of Pulmonary Arterial Hypertension Medication and Common Carotid Artery Wall Layer Dimensions**

There were too few numbers for meaningful comparisons of the artery wall layer dimensions for sildenafil only users versus endothelin receptor antagonists (ERA) only users and their comparisons with combined therapies. However, patients on ERA (bosentan or ambrisentan) solely or in combinations (seven) versus all other therapies (12) showed a significantly thicker media layer ($0.11\ \text{mm};\ p=0.031$) and a numerically smaller I/M thickness ratio ($–0.12;\ p=0.091$), which if anything might indicate a healthier artery wall. However, patients with ERA therapies were numerically younger, had a longer duration since PAH diagnosis ($p=0.01$), and numerically higher MPAP values ($p=0.08$); factors that might have affected the results.

**Receiver Operating Characteristic Curve Analysis**

In the receiver operating curve (ROC) analysis, the CCA intima thickness and I/M thickness ratio were associated with excellent c-values (0.92 and 0.87), correctly indicating which individuals belonged to the PAH or healthy control groups. The CCA IMT measurement was not useful for correctly discriminating between the groups (Figure 5).
Discussion

The results of this study challenge the common opinion that the vascular effects of PAH are largely restricted to the lung vasculature and do not affect the peripheral vasculature [3]. The current study found that signs of vascular remodelling were more extensive in the CCA of patients with PAH than in healthy controls or patients with LVrEF. In the PAH group, several RHC cardiopulmonary results significantly correlated with the CCA wall layer dimensions, indicating

### Table 2 Common carotid artery all-layer dimensions in patients with pulmonary artery hypertension, healthy control subjects and patients with left ventricular heart failure with reduced ejection fraction.

<table>
<thead>
<tr>
<th>CCA Layer Dimensions</th>
<th>PAH (n=19)</th>
<th>Healthy Controls (n=30)</th>
<th>% Difference</th>
<th>Difference (95% CI)*</th>
<th>LVrEF (n=14)</th>
<th>% Difference (PAH vs. LVrEF)</th>
<th>Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intima, mm</td>
<td>0.14 (0.12, 0.15)c,c</td>
<td>0.09 (0.07, 0.11)</td>
<td>+56%</td>
<td>0.05 (0.03, 0.06)</td>
<td>0.11 (0.10, 0.12)</td>
<td>+27%</td>
<td>0.03 (0.01, 0.04)</td>
</tr>
<tr>
<td>Media, mm</td>
<td>0.32 (0.29, 0.42)b,ns</td>
<td>0.43 (0.35, 0.67)</td>
<td>–26%</td>
<td>–0.11 (–0.24, –0.03)</td>
<td>0.36 (0.30, 0.41)</td>
<td>–11%</td>
<td>–0.01 (–0.07, 0.07)</td>
</tr>
<tr>
<td>I/M ratio</td>
<td>0.41 (0.33, 0.52)c,a</td>
<td>0.18 (0.12, 0.30)</td>
<td>+128%</td>
<td>0.21 (0.13, 0.28)</td>
<td>0.32 (0.27, 0.38)</td>
<td>+28%</td>
<td>0.09 (0.01, 0.17)</td>
</tr>
</tbody>
</table>

Data are presented as medians (first and third quartiles) or percentage difference. Statistical significance levels are presented as PAH vs Controls, PAH vs LVrEF.

*p<0.05  
bp<0.01  
cp<0.001

*Mean difference (95% CI): according to Hodges-Lehmann.

Abbreviations: CCA, common carotid artery; PAH, pulmonary arterial hypertension (WHO Group 1); LVrEF, left ventricular heart failure with reduced ejection fraction; I/M ratio, intima/media thickness ratio.

**Figure 4** Age versus common carotid artery intima thickness (mm), by study group. Healthy controls (solid line); LVrEF, patients with left ventricular heart failure with reduced ejection fraction (dotted line); and PAH, patients with pulmonary arterial hypertension, WHO Group I (dashed line). Abbreviations: LVrEF, left ventricular heart failure with reduced ejection fraction; PAH, pulmonary arterial hypertension; WHO, World Health Organization.
cardiovascular coupling and an association with disease severity. The correlation between CCA intima thickness and mPAP was statistically significant, and was stronger than that reported by Stacher et al., based on the histomorphometry of pulmonary arteries [4]. In ROC curve analysis, both the CCA intima thickness and I/M thickness ratio had excellent c-values, correctly indicating the group to which the individual belonged: PAH or healthy controls. There was no significant correlation with NT-proBNP results, most likely because several PAH therapies improve NT-proBNP values.

In their investigation of the remodelling of pulmonary arteries, Stacher et al. found significantly thicker intima layers in PAH patients than in controls (potential organ donors) [4], in accordance with the current results. However, in contrast to the current results, they also found a slightly thicker media layer in PAH patients, with significant correlations with mPAP and PVR. According to current knowledge, PAH patients have a thick media layer in the pulmonary arteries due to proliferation of smooth muscle cells causing narrowing of the artery, which leads to development of high pressure and resistance in the pulmonary vasculature. This is supported by significant correlations of the media thickness in the pulmonary arteries with mPAP and PVR, as reported by Stacher et al. However, the current study examined a peripheral artery (CCA) in PAH patients with low or normal peripheral blood pressure. The difference in blood pressure in the pulmonary and peripheral circulation might thus contribute to the contrasting findings regarding the arterial media thickness in the two studies. In fact, patients with PAH in the current population had a thinner media layer in CCA than healthy controls, contributing to the multiplicative effect/difference (128%) in the I/M thickness ratio between PAH and the healthy control group. The findings of a reduced CCA media thickness, increased intima thickness, and increased I/M thickness ratio are in accordance with signs of peripheral arterial ageing and development of atherosclerosis [7–9,12,17]. However, it is likely that the pulmonary arteries in patients with PAH had similar changes in the two populations.

Chronological age correlated logically and significantly with CCA intima thickness in healthy subjects, with similar results in the LVrEF group, in accordance with the effects of ageing in previous reports based on histomorphometry [7] and intravascular ultrasound [8]. In contrast, patients with PAH showed substantially affected arteries at a young age–similar to the values seen in the oldest control subjects. Unexpectedly, increased time since PAH diagnosis correlated with ‘healthier’ arteries, and in analysis adjusted for time since diagnosis, increasing age correlated with ‘healthier’ arteries in patients with PAH. Thus, it appears that the normal adverse vascular effects of ageing, as seen in the healthy control subjects, were negated in patients with PAH. Given that the time since PAH diagnosis correlated reasonably well with the duration of PAH therapy, it could be surmised that PAH therapy may have mitigated the expected effects of ageing per se or conversely that the results may have been affected by the early deaths of those with more severe PAH and more severely affected arteries. The time since PAH diagnosis seemed, if anything, slightly longer in younger patients, which supports the theory of early death affecting the results. Thus, older patients with PAH might
have had the disease for a shorter time and/or have had less severe disease, which might both have contributed to the current findings.

Thickening of the arterial intima layer is an early morphological sign of atherosclerosis [10]. It has been suggested for many years that the carotid artery intima thickness and I/M thickness ratio be used for estimating atherosclerosis progression instead of the classical IMT measurement. This approach has yielded logical and significant study group differences and associations that have not been obtained with IMT measurements [9,17–26]. In Swedish 70-year-olds, the CCA intima was significantly thicker in those with prevalent CVD, myocardial infarction, stroke, hypertension, or hyperlipidaemia, and increased intima thickness was significantly associated with higher BMI, larger waist circumference, and increased years of hypertension, years of hyperlipidaemia, and number of cigarettes smoked/week [9]. In fact, according to recent guidelines, IMT measurement is no longer recommended for assessing the risk of first atherosclerotic CVD events [6]. In addition, recent reports have confirmed that intima thickness is a more accurate marker of atherosclerosis than IMT [27] and that intima thickness in different arteries can more accurately identify patients with ischaemic stroke than IMT [28]. Many years ago, a report based on histology found that the I/M thickness ratio was the best dimension for estimating the degree of atherosclerosis [12]. The current institution prefers to assess both the intima thickness and the I/M thickness ratio because together they better reflect and capture the differential changes occurring during the atherosclerotic process: the initial increase in intima thickness followed by the subsequent reduction in media thickness, resulting in an amplified increase in the I/M thickness ratio, better reflects the effects of ageing and the duration of the condition under study [17].

**Limitations and Strengths**

Right heart catheterisation, the gold standard method, was used to diagnose PAH. Despite the limited sample size, analysis revealed significant group differences in artery wall layer dimensions, as well as consistent and logical associations with haemodynamic variables from RHC. In addition, the results of the PAH patients were compared with those of two other groups: healthy controls and patients with LVrEF. One limitation of the study was that ultrasound of the CCA was not performed at the time of diagnosis or before the start of PAH medication. The principles used for assessing CCA vascular ageing/subclinical atherosclerosis (arterial intima thickness and I/M thickness ratio) are supported by studies based on histomorphometry [7] and intravascular ultrasound [8] and have repeatedly given superior results to those associated with the use of conventional IMT assessments [9,17–26].

**Conclusions**

These results challenge the common belief that vascular effects in patients with PAH are restricted to the pulmonary vasculature. Patients with PAH displayed more extensive signs of peripheral vascular remodelling than healthy controls or patients with LVrEF. The CCA intima thickness was significantly

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**Abbreviations:** CCA, common carotid artery; PAH, pulmonary arterial hypertension; Athscl, atherosclerosis; Subc, subcutaneous; Adv, adventitia; Med, media; Int, intima layer.
correlated with several cardiopulmonary variables from RHC, indicating cardiovascular coupling and an association with vascular ageing. The ROC analysis resulted in excellent c-values indicating whether the subjects had PAH or were healthy controls. A graphical abstract (Figure 6, Central Illustration) summarises our main suggestion that PAH is associated with peripheral subclinical atherosclerosis in the CCA. The prevalence and risk of peripheral vascular ageing should be considered in patients with PAH and future prospective studies should monitor the effects of different PAH therapies on peripheral vascular remodelling.

Disclosures

G. Wikström (GW) has received lecture fees from Actelion Pharmaceuticals Sweden AB, Bayer Health Care and GlaxoSmithKline AB. GW has been an investigator in PAH trials for GlaxoSmithKline, Actelion Pharmaceuticals Sweden AB, Pfizer AB, Bayer Health Care and United Therapeutics and in heart transplantation trials for Novartis Sverige AB. GW has been on advisory boards for Actelion Pharmaceuticals Sweden AB, Bayer Health Care, Eli Lilly Sweden AB, GlaxoSmithKline AB, and Sanofi AB. D. Henrohn (DH) is an employee of Pfizer AB, in Sweden. TN and GE report no competing interests.

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