The association between carotid-femoral pulse-wave velocity and lung function in the Swedish CArdioPulmonary bioImage study (SCAPIS) cohort

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1. Introduction

Low levels of lung function have a long and well-known history of being strongly associated with cardiovascular disease (CVD) and CVD mortality [1–4]. The presence of this association in life-long never-smokers [5] and its persistence even after controlling for potential confounders suggests that it needs to be further understood [6].

Both lung function and arterial stiffness (arteriosclerosis) are strongly related to age. Arterial ageing is characterised by degradation of elastic fibres, reduced compliance and increased stiffness of the large elastic arteries. This process, which is mainly of non-atherosclerotic origin, can be non-invasively assessed by measurement of aortic pulse wave velocity (aPWV). Pulse-wave velocity (PWV) has been found to be an independent predictor of cardiovascular risk [7] and a strong predictor of both CVD and all-cause mortality [8] in both healthy and at-risk populations [9]. Although a well-established association between chronic obstructive pulmonary disease (COPD) and arterial stiffness exists, the association between pulmonary function in the general population and arterial stiffness has not been explored in as much detail.

The Whitehall II cohort study assessed the longitudinal relationship between low levels of lung function and arterial stiffness as measured by
carotid-femoral PWV (c-f PWV) and found low levels of pulmonary function to have a predictive role in the future increase in c-f PWV and suggested lung function could be a novel marker for vascular ageing [10]. The Caerphilly Prospective Study found lung function in mid-life to be a stronger predictor of arterial stiffness compared to later life in men [9]. A cross-sectional association between arterial stiffness and reduced spirometry measures has also been found in general population studies where either c-f PWV or brachial-ankle PWV (ba-PWV) were found to be significantly and negatively associated with forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) [11–13]. Another general population study found conflicting results, where no independent association was found between aPWV and impaired spirometry [14], however reduced lung capacities have been found to have significant inverse relationships with ba-PWV, the FEV₁/FVC ratio has not been associated with arterial stiffness in subjects with no airflow limitation on spirometry [16].

Diffusing capacity for carbon monoxide (DLCO) can give important information on the nature of respiratory pathology that may be present, and can potentially provide an indication of early disease not yet measurable by spirometry. We are not aware of any studies from the general population assessing the association between DLCO with arterial stiffness. The aim of the present cross-sectional study is to assess the association between lung function (as measured by spirometry and DLCO) and c-f PWV using middle-aged subjects enrolled in a large population based study, the Swedish CArdioPulmonary bioImage Study (SCAPIS).

2. Methods

2.1. Study population

SCAPIS is a national multi-centre population based study initiated as a joint national effort to prevent CVD and COPD by improving the risk prediction of cardiopulmonary conditions. It has been formed through collaboration between six Swedish universities (Gothenburg, Linköping, Malmö/Lund, Stockholm, Umeå, and Uppsala) [17]. Nationwide, 30,154 men and women aged 50–64 years participated. Overall, participation in the SCAPIS cohort nationwide was 49.5%. Enrolment took place by random selection from the Swedish population register. Study participants took part in a comprehensive questionnaire, biochemistry, extensive physical examinations, lung function tests and imaging as previously described [17]. Some measurements were specific to certain sites. C-f PWV was measured only in Malmö and Linköping. From the population of Malmö, 6251 individuals took part in the study, and the participation rate in Malmö was 53%. From the population of Linköping, 5057 individuals took part and the participation rate was 58%. The study was approved by the Regional Ethical Review Board in Umeå (2010-228-31 M), Lund (2016/1031) and Linköping (2018/478–31). Study participants gave their written and informed consent.

2.2. Baseline examinations

Height was measured to the nearest centimetre (cm), without footwear. Weight (kg) was measured in light indoor clothing on a digital scale, without footwear. Venous blood samples for immediate laboratory analysis of C-reactive protein (CRP), cholesterol and haemoglobin were taken after an overnight fast (at least 8 h). Smoking status (current, ex-smoker or never smoker) was ascertained from questionnaire responses. Prevalent diabetes was defined as either self-reported physician-diagnosed diabetes or a new diagnosis of diabetes at baseline. Brachial systolic blood pressure readings were taken before the PWV measurement using an automatic device from the left arm after 5 min of rest in the supine position.

2.3. Lung function measurement

Dynamic spirometry (Jaeger MasterScreen PFT, Carefusion, Hoechberg, Germany) was performed 15 min after bronchodilation using 400 µg of Salbutamol with subjects in the sitting position and wearing a nose clip. FEV₁ and FVC were obtained according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) standards [18, 19]. Reference values by Hedenström et al. [20, 21] were used for the calculation of FEV₁%predicted and FVC%predicted. DLCO was measured using a single-breath carbon monoxide diffusion test (Jaeger Master-Screen PFT) according to ATS/ERS standards, and was performed in a sitting position and wearing a nose clip. DLCO and alveolar volume (VA) were calculated using the single-breath carbon monoxide diffusing capacity test with helium as the tracer gas. DLCO and the carbon monoxide transfer coefficient (DLCO/VA) were used for further analysis. European reference values were used for the calculation of DLCO%predicted and DLCO/VA%predicted [22].

2.4. PWV measurement

C-f PWV was used to determine arterial (aortic) stiffness, and was measured using the device Sphygmocor Xcel (Atcor Medical, Australia) [23]. Prior to the examination, participants were instructed to refrain from caffeine and a heavy meal for 3 h, nicotine for 4 h and alcohol for 12 h. Blood pressure cuffs were attached to the upper left arm and to the right thigh (10–20 cm below the groin). The distances from the femoral pulse to the upper edge of the thigh cuff (femoral-cuff distance), and from the carotid pulse to the upper edge of the thigh cuff (carotid-cuff distance) were taken. The distances were then multiplied by 0.8 [24]. The final distance was calculated by subtracting the femoral-cuff distance from the carotid-cuff distance.

PWV measurement was done using an applanation tonometer to register the signal from artery carotis simultaneously as the blood pressure cuff on the thigh obtain the signal from artery femoralis. C-f PWV was measured twice at each assessment, however if the difference between the two measurements was >0.5 m/s, a third measurement was
performed. The participants with two values for PWV were included in the study and the average of the measurements was used in the analysis. Systolic and diastolic blood pressure were measured twice after 5 min of supine rest before the PWV measurement and mean arterial pressure (MAP) was calculated (systolic blood pressure + (diastolic blood pressure × 2))/3. No PWV measurements were taken after bronchodilation. Mean heart rate was calculated as the mean from the heart rate obtained from the two PWV measurements.

2.5. Analysis of data

All analyses were carried out on SPSS version 24 and 26 (IBM Corp, Armonk, New York, USA). Of a total cohort of 11,308, subjects without two valid measurements of c-f PWV were excluded (n = 1991). Subjects with missing information on key variables were excluded (n = 277). For the total study cohort assessing spirometry and c-f PWV, a further 99 subjects were excluded with missing spirometry (total cohort = 8941 subjects). For the study cohort assessing DLCO and c-f PWV, a further 424 subjects were excluded with either missing or outlying values of DLCO or DLCO/VA (n = 15 subjects with DLCO/VA > 4 mmol (min kPa) L) (total cohort = 8616 subjects).

Quartiles of lung function were created for each study cohort (Q1 highest lung function category) and general linear models were used to estimate mean c-f PWV by quartiles of lung function. The p-value was calculated for the difference in mean c-f PWV for Q1 vs Q4. Additionally, linear regression was used to estimate the change in c-f PWV per 1-standard deviation (SD) increase in the lung function parameter (unstandardized beta coefficients). Two models were used for adjustments for confounding variables known from the literature. The basic model included covariates needed for correct interpretation of spirometry or DLCO and PWV (age, sex, height, MAP and mean heart rate). The advanced model was further adjusted for factors potentially associated with spirometry or DLCO and cardiovascular outcomes (smoking, inflammation, cholesterol levels, diabetes and BMI). The DLCO model was further adjusted for haemoglobin levels to correct DLCO for anaemia. All models were adjusted for site as measurements were taken at two different geographical locations within Sweden. Diffusion capacity models were additionally adjusted for haemoglobin. A p-value <0.05 was regarded as statistically significant.

Additional general linear models were analysed in all life-long never smokers for quartiles of spirometry and diffusion capacity measures (n = 4335 and 4197, respectively). Further sensitivity analyses were performed for DLCO and c-f PWV in all those without COPD and without any airflow limitation on spirometry (defined by FEV1/FVC <0.70).

3. Results

Baseline characteristics for participants are shown in Table 1. From the cohort of 8941 subjects, 5675 were from Malmö and 3266 from Linköping. The prevalence of current smokers was relatively low in the cohort (approximately 15%) and almost half of the cohort were life-long never-smokers.

### Table 1

**Baseline characteristics of the study population (n = 8941) from SCAPIS.**

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>Mean (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.5 (±4.3)</td>
</tr>
<tr>
<td>Gender (women, %)</td>
<td>51.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.0 (±9.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.7 (±15.4)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>7.6</td>
</tr>
<tr>
<td>- Current</td>
<td>14.7</td>
</tr>
<tr>
<td>- Former</td>
<td>36.8</td>
</tr>
<tr>
<td>- Never</td>
<td>48.5</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td></td>
</tr>
<tr>
<td>- CRP (mg/L)*</td>
<td></td>
</tr>
<tr>
<td>- Hb (g/L)</td>
<td>142.6 (±11.8)</td>
</tr>
<tr>
<td>- Cholesterol (mmol/L)</td>
<td>5.47 (±1.05)</td>
</tr>
<tr>
<td>- Mean c-f PWV (m/s)</td>
<td>8.53 (±1.3)</td>
</tr>
<tr>
<td>- Mean arterial pressure (mmHg)</td>
<td>94 (±11)</td>
</tr>
<tr>
<td>- Mean heart rate (bpm)</td>
<td></td>
</tr>
<tr>
<td>- Systolic BP (mmHg)</td>
<td>128 (±15)</td>
</tr>
<tr>
<td>Prevalent diagnosed COPD (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td>Airflow limitation on spirometry (%) (FEV1/FVC&lt;0.70)</td>
<td>9.2</td>
</tr>
</tbody>
</table>

### Lung function measures

- FEV1 (L) 3.22 (±0.76)
- FEV1 (predicted) 96.7 (±3.5)
- FVC (L) 4.14 (±0.98)
- FVC (predicted) 94.7 (±12.1)
- FEV1/FVC 0.782 (±0.06)
- DLCO (L CO·min·kPa) 9.24 (±4.15)
- DLCO/VA (predicted) 97.2 (±15.1)

Mean ± standard deviation unless otherwise stated. *median values (25th-75th percentile).


<0.01) even after adjustments for potential confounders (model 2).

After adjustment for confounders (model 1), DLCO had a significant inverse relationship with c-f PWV. This association was seen even after adjustment for confounders in model 2, including haemoglobin (Q1 vs Q4 of DLCO: PWV (m/s) 8.46 vs 8.60, p-value 0.002), and change in PWV per 1-SD increase in DLCO (−0.06 (m/s), p-value <0.001)). After further adjustment for FEV1 (L), results remained significant (Q1 vs Q4 of DLCO: PWV (m/s) 8.48 vs 8.59, p-value 0.022), and change in PWV per 1-SD increase in DLCO (−0.05 (m/s), p-value <0.012) (based on 8567 subjects). Similar associations were seen between DLCO/VA and c-f PWV. In a sub-analysis of never smokers, n = 4197), the results remained significant even after further adjustment for haemoglobin for DLCO (Q1 vs Q4 of DLCO: PWV (m/s) 8.43 vs 8.59, p-value 0.017; but not for DLCO/VA Q1 vs Q4: c-f PWV (m/s) 8.45 vs 8.53, p-value 0.101). We performed a sensitivity analysis after excluding subjects with diagnosed COPD, airflow limitation on spirometry or missing information on either of these. In the remaining subjects (n = 7580), significant associations remained between DLCO and c-f PWV after full adjustments (model 2) Q1 vs Q4 c-f PWV (m/s) 8.44 vs 8.55, p-value 0.022. Change in PWV per 1-SD increase in DLCO -0.052 (m/s), p-value <0.01). We also performed a sensitivity analysis for subjects with DLCO after excluding those with restrictive spirometry defined by the criteria FEV1/FVC<0.70 AND.
FVC ≤ 0.80% predicted. After excluding 785 subjects fulfilling this criteria, we found the association between D\textsubscript{LCO} and c-f PWV remained significant after full adjustments (model 2) (Q1 vs Q4 c-f PWV (m/s) 8.44 vs 8.58, p-value <0.001). Change in PWV per 1-SD increase in D\textsubscript{LCO} was -0.070 m/s, p-value <0.001.

There was a significant interaction between gender and the lung function measures FEV\textsubscript{1}, FVC and D\textsubscript{LCO}. We therefore carried out additional analyses of linear regression models for these measures after adjusting for potential confounders (change in PWV (m/s) per 1-SD increase in D\textsubscript{LCO} -0.070 m/s, p-value <0.001).

### 4. Discussion

One of the most significant findings of this study was that D\textsubscript{LCO} was significantly and inversely associated with c-f PWV. Similar findings have been reported in patients with COPD [25-27] however, this is a novel finding in subjects from a general population study, replicated in never smokers and in those without COPD or airflow limitation. It should be acknowledged that although statistically significant, the effect size of this relationship was small in this study and the significant association between both FEV\textsubscript{1} and D\textsubscript{LCO} with c-f PWV in the general cohort was reflected in men only.

Increased arterial stiffness has been independently linked to the presence of COPD [28-32] and COPD severity [33]. Other than the direct effects of smoking, suggested mechanisms linking COPD to arterial stiffness have included hypoxia [33], systemic inflammation [34]; specifically the emphysematous COPD phenotype, where higher levels of matrix metalloproteinase (MMP)-9 are associated with both emphysema and arterial connective tissue damage [28,35]. A possible explanation for a cross-sectional association between reduced pulmonary function and arterial stiffness has included ageing - a common physiological process that affects both. Age-related changes in the lungs include decreases in lung elastic recoil, in chest wall compliance and in respiratory muscle strength [36], resulting in an age-related decline in FEV\textsubscript{1} of up to 30 mL/year [37]. Age-related changes in the arteries include increasing thickness of the arterial walls as well as progressive stiffening and dilatation of the arteries, measurable by PWV [38]. However, the associations we found were present even after taking age into account, and in this cohort mean values of spirometry and D\textsubscript{LCO} parameters and of c-f PWV were within healthy normal ranges. Early vascular ageing that may correspond to a similar ageing effect in the lungs could be another possible explanation, where premature biological ageing may affect both large arteries and lung tissue. This process could have begun many years prior. However, as both mean spirometry values and PWV remain within normal ranges for this age group, the notion of early or premature ageing again may not be the main explanation for our findings.

The role of spirometry as a predictor of arterial stiffness has been proposed by a few previous studies [9,10]. The mechanisms by which this may occur include acute or chronic inflammation in the respiratory tract (resulting in lower levels of lung function) leading to low grade systemic inflammation [10]. The systemic inflammation may then in turn cause vascular remodelling leading to increased arterial stiffness [39]. The role of inflammation has also been proposed in cross-sectional studies [11]. CRP has been found to play an active role in the promotion of vascular inflammation and reducing endothelial function [40] which leads to arterial stiffness. We found associations to remain even after adjustment for CRP, however, there have been other inflammatory markers suggested in the relationship between systemic inflammation.
and vascular injury and arterial stiffness such as interleukin-6 (IL-6) and MMPs [40], therefore the role of inflammation cannot be fully excluded. Other proposed mechanisms include the possibility that both reduced spirometry measures and arterial stiffness may have some shared genetic or inherited component [9]. There also could be common early life factors that may predispose to both lower levels of spirometry and the development of arterial stiffness. This may include Barker’s hypothesis of the foetal origins of adult disease. Lower birth weight has been found to be associated with worse adult lung function [41] and the origin of hypertension [42] in middle age, and therefore it is possible that low birth weight is an explanation for lower levels of spirometry and DLCO found in combination with higher c-f PWV later in life.

The association between DLCO measures and arterial stiffness has been investigated in COPD patients [26] where arterial stiffness as measured by the augmentation index in COPD patients has been related to the severity of emphysema as measured by DLCO [26]. Additionally, greater arterial stiffness as measured by aortic PWV was found in COPD patients with mild disease and was related to the emphysema burden and low DLCO, regardless of FEV1 impairment. It was concluded that even in mild COPD patients, if emphysema and gas exchange impairment is present, they could be at risk of greater arterial stiffness and hence cardiovascular outcomes [27]. However, these studies have been carried out in COPD patients (+/− controls), and have generally included small study populations. In our study we found DLCO to be strongly associated with c-f PWV even after adjustment for FEV1, after excluding those with COPD/airflow limitation, and in never-smokers. Therefore our findings are indicative of gas exchange impairment being associated with higher levels of arterial stiffness not fully explained by smoking and emphysema.

The mechanisms by which DLCO measures are associated with arterial stiffness have been hypothesised in patients with emphysema, where the inflammatory processes involved in the origins of emphysema may also have actions in arteries leading to the loss of elasticity and impairment in endothelial function [27]. Those exhibiting a degree of emphysema may also be less physically active, which in turn may increase the risk of systemic vascular dysfunction [27]. Our current findings indicate that decrements in DLCO even within a healthy range, are associated with increased c-f PWV, suggesting these processes may be occurring independently of emphysematous inflammatory processes. As restrictive spirometry has also been associated with arterial stiffness [43], the association between DLCO and PWV in our study could also reflect thickening of the alveolar-capillary membrane due to conditions such as interstitial lung disease. However, when excluding subjects with pulmonary restriction in our study (using the FEV1/FVC ratio and FVC% predicted), we found the association between DLCO and c-f PWV remained significant. This would suggest that pulmonary restriction may not fully explain the findings for this study, however future studies should confirm this by using total lung capacity (TLC) in the criteria for defining restriction. Findings from computerised tomography (CT) scanning in future SCAPIS studies could be used both to assess if the burden of emphysema is associated with c-f PWV at a stage when patients are relatively symptom-free and to assess total lung volume on CT (as a proxy for TLC) to confirm associations between c-f PWV and restrictive lung impairment.

4.1. Study limitations

It is unclear how generalizable these results would be to a wider age-range. However, the findings may have more significance for the 50–64yr age group as both lung function decline and arterial stiffness are associated with an increasing age. There is also a degree of selection bias or “healthy volunteer bias” to be considered with observational
studies of this nature. We know from the pilot study that low socioeconomic status was associated with lower participation rate [44]. However, the prevalence of certain important risk factors such as smoking in this cohort was comparable to that of the smoking prevalence in Sweden in 2018 (both between 14 and 15%) [45]. There may also be a degree of residual confounding in the relationship between both spirometry and c-f PWV and D_{LCO} and c-f PWV. We did not control for underlying respiratory health as this would result in adjustment of the main exposure. Additionally, the role of occupational airborne exposure, both long and short term was not analysed as part of this study. As occupational airborne exposure may affect lung function and is associated with COPD [46], this may potentially explain some of the observed association in our study. The cross-sectional design limits the interpretation of the results, where we cannot comment on cause and effect between spirometry or D_{LCO} and PWV but only that an association exists between the two. However, previous longitudinal studies have found impaired spirometry to be a predictor of arterial stiffness. Reverse causation has been investigated in the past by a study that found weak evidence to support this [10].

The large sample size of the SCAPIS cohort adds power to the small but significant findings in this cohort. Arterial stiffness was determined by a direct measure considered the gold standard [47]. Post-bronchodilatation spirometry and D_{LCO} measurements also ensured that any defects found were likely to reflect chronic, non-reversible airflow limitation. This is also the first population-based study to assess the relationship between D_{LCO} measures and c-f PWV in the general population, which has implications for the early detection of those subjects with lower levels of D_{LCO} at risk of subclinical atherosclerosis.

5. Conclusions

A reduction in spirometry and D_{LCO} is associated with elevated arterial stiffness as measured by c-f PWV in middle-aged men. A reduction in D_{LCO} is associated with higher c-f PWV, even in never smokers and in those without COPD or airflow limitation on spirometry.

Patient consent

Study participants gave their written and informed consent.

Data statement

Data can be made available to researchers upon request, subject to a review of secrecy and approved ethical application. More information can be found at http://scapis.org/.

Ethical approval

The study was approved by the Regional Ethical Review Board in Umeå (2010-228-31M), Lund (2016/1031) and Linköping (2018/478–31).

CRediT authorship contribution statement

Sumeela Zaigham: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft. Carl-Johan Ostgren: Methodology, Investigation, Data curation, Writing – review & editing, Funding acquisition. Margaretha Persson: Investigation, Data curation, Writing – review & editing. Iram Faqir Muhammad: Data curation, Writing – review & editing. Peter M. Nilsson: Writing – review & editing. Per Wollmer: Investigation, Data curation, Writing – review & editing. Jan Engvall: Investigation, Writing – review & editing. Gunnar Engstrom: Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PW reports grants from the Swedish Heart and Lung Foundation during the conduct of the study and personal fees from Chiesi Pharmaceuticals and from GlaxoSmithKline, outside the submitted work. PW also has a patent “Method and device for pulmonary function measurement” issued.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2021.106504.

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