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An Association between Chronic Obstructive Pulmonary Disease and Abdominal Aortic Aneurysm beyond Smoking
Results from a Case–control Study

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WHAT THIS PAPER ADDS

- The findings of this study suggest that the increased prevalence of chronic obstructive pulmonary disease (COPD) in patients with an abdominal aortic aneurysm (AAA) is independent from smoking. Along with other observed parallels between AAA and COPD, results of this study hint at a predetermined cause of these diseases, warranting further investigation of common genetic, inflammatory and remodelling pathways. Identification of common mechanistic pathways might be highly relevant for future AAA and COPD research and research collaboration initiatives. The burden of undetected COPD is relevant to those involved in the care of AAA patients.

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ABSTRACT

Objectives: It is currently unclear whether the parallels between abdominal aortic aneurysms (AAAs) and chronic obstructive pulmonary disease (COPD) are explained by common risk factors alone, such as cigarette smoking, or by a predetermined cause. Given the persistent controversy with regard to the association between AAA and COPD, we studied this association in depth.
Methods: We conducted a case–control study comparing patients with a small AAA (maximum infrarenal diameter 35–50 mm, $n = 221$) with controls diagnosed with peripheral artery disease (PAD, $n = 87$). The controls were matched to the cases for lifetime cigarette smoking. Pulmonary function was measured by spirometry, and all subjects completed a questionnaire on medical history and smoking habits (current, former and never smokers).
Results: Aneurysm patients were similar to controls with respect to gender ($p = 0.71$), lifetime cigarette smoking (39 vs. 34 pack years, $p = 0.23$) and history of cardiovascular disease (45% vs. 55%, $p = 0.12$). Aneurysm patients had more airway obstruction (forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) (0.69 ± 0.12 vs. 0.78 ± 0.11, $p < 0.001$)), which was most pronounced in never smokers (0.73 ± 0.07 vs. 0.86 ± 0.07, $p < 0.001$). COPD was more prevalent in aneurysm patients (44%; 98/221) than in controls (20%; 17/87) (adjusted odds ratio (OR) 3.0; 95% confidence interval (95%CI) 1.6–5.5, $p < 0.001$). In particular, a major proportion of AAA patients was newly diagnosed with COPD; only 40 of 98 patients (41%) with COPD (mild, moderate or severe/very severe) were known before with obstructive pulmonary defects and received treatment.
Conclusions: This study confirms an association between AAA and COPD and shows that this association is independent from smoking. Findings also demonstrate that COPD is under-diagnosed in AAA patients.

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Several parallels are observed between abdominal aortic aneurysms (AAAs) and chronic obstructive pulmonary disease (COPD), both with regard to risk factors as well as to the underlying pathophysiology. Both diseases have a particularly strong relationship with smoking, and smoking cessation appears to be the principal disease-modifying intervention.[1–3] Moreover, their pathophysiologic bases are best described as a persistent pro-inflammatory response that is associated with proteolysis and excess matrix turnover.[2–5]

A relation between AAA and COPD was first suggested by Cronenwett et al., who reported in 1985 that COPD was more common in patients with a ruptured aneurysm.[6] Several successive reports also indicated an association between AAA and COPD, although the by far largest study in aneurysm patients rejected an independent association (a summary of the reports is found in Table 1).[7–13] Moreover, interpretation of these reports is complicated by considerable heterogeneity in outcome measures, definitions and control populations in these studies. In particular, a relation between AAA and COPD that is beyond that of smoking alone remains unclear.

We performed pulmonary testing in a cohort of patients with a small abdominal aneurysm and compared the results with a control group of patients with clinical peripheral artery disease (PAD). As there is a large overlap in risk factors, in particular the predominance of smoking, and patient characteristics between AAA and PAD populations, it was reasoned that this group constituted the most optimal control group.[3,14] With this study, we aim to test whether the suggested relationship between AAA and COPD extends beyond smoking alone.

Methods and Material

Design

The study enrolled patients with a small infrarenal AAA, who participated in a larger study, the Pharmaceutical Aneurysm Stabilisation Trial (PHAST trial http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1345).

This multicentre trial studied whether 18 months of doxycycline treatment reduced aneurysm progression in 286 randomised Caucasian patients with small AAA (35–50 mm). The trial was conducted between January 2009 and June 2011 in 14 Dutch hospitals (manuscript submitted). Primary approval for the PHAST trial and this sub-study was obtained from the Medical Ethical Review Board of the Leiden University Medical Center.

The presence of AAA and maximum aortic diameter size was assessed by single-observer ultrasound measurement of the anteroposterior diameter (Siemens P50, 1.67–4.0 MHz phased array transducer, Siemens Medical Systems, Mountain View, Ca, USA.). Included were all patients with a confirmed AAA sized 35–50 mm. All measurements were performed at baseline, that is, immediately before randomisation.

The control population consisted of patients with established PAD referred to the outpatient department of vascular surgery at the Leiden University Medical Center and the Deventer Hospital. All patients underwent an abdominal ultrasound to exclude an aortic aneurysm (i.e., infrarenal aortic diameter <25 mm). PAD was defined by a history of manifest intermittent claudication with an ankle–brachial index (ABI) < 0.9, or by a history of lower-extremity

Table 1
Overview of previous reports on the relation between abdominal aortic aneurysm and chronic obstructive pulmonary disease.

Study	Number AAA	Population	Method	Definition	Conclusion	Limitation
Cronenwett 1985[6]	67	AAA patients selected for non-surgical management	Spirometry	Mild to moderate FEV1 ≥ 50% pred., severe FEV1 < 50% pred.	Obstructive pulmonary disease predictive for aneurysm rupture	Relation with aneurysm rupture, no conclusions on non-ruptured aneurysm
Bengtsson 1991[7]	39	AAA screening and general population controls	Spirometry	Unknown	Smokers with affected lung function are at risk for AAA	Unclear definitions of pulmonary function, general population as control
Smith 1993[10]	219	AAA screening population, general population controls	Unknown	Unknown	A relation between AAA and COPD	Unclear definition of pulmonary function, general population as control, no adjustment for smoking
Laarhoven 1993[8]	36	COPD-patients	COPD by hospital record	Mild or severe emphysema, FEV/VC < 55%	High prevalence of AAA in COPD patients	No control population, no statistical analysis
Lindholt 1998[9]	139	AAA screening population, AAA in COPD vs. AAA in non-COPD	COPD by hospital record	As defined by World Health Organization	Association caused by medication and cardiovascular history	COPD underestimation without spirometry testing. No adjustment for smoking
Lederle 2000[13]	1917	AAA screening population	COPD as a questionnaire item	Unknown	No association between AAA and COPD after adjustment for smoking	Questionnaires insufficient to detect COPD
Sakamaki 2002[11]	118	Japanese AA patients, with present AAA or TAA, without AA with CAD, without both	Spirometry with reversibility testing	Airway obstructive disease FEV1/FVC < 0.70	AAA risk factor for COPD	Patients at high surgical risk, exclusion of currently smoking patients and patients treated for COPD
Fowkes 2006[12]	89	AAA surgical waiting-list and general population controls	Spirometry max of three measurements,	Modified GOLD classification	Association, independent of cigarette smoking and cardiovascular history	Significant differences between cases and controls on co-variates smoking and cardiovascular disease

Cronenwett et al.[6] were the first to report on this relation, although they were rather focused on aneurysm rupture. Overtime, these studies show an increase in quality with respect to the used definitions, measures and analyses. However, implication of these studies is complicated by considerable heterogeneity in outcome measures, definitions and control population, in particular with respect to smoking behaviour.

revascularisation. Patients with a known history of lung carcinoma, lung surgery or aneurysmal diseases (i.e., an aneurysm on other locations, e.g., the popliteal artery) were excluded. Because all patients in the AAA group were between the ages of 50 and 89 years, only controls older than 50 years were included.

Prior to measurement of respiratory functions, the controls were matched to the cases for lifetime cigarette smoking (group matching). Matching was performed for four categories of smoked pack years (PYs) (non-smokers (0 PY), 1–20 PY, 21–40 PY and more than 40 PY) based on the frequency distribution of the PHAST cohort.

Measurements

Eligibility was based on the patients' medical records, and all patients were interviewed about smoking habits, presence of a diagnosis of COPD and history of cardiovascular disease. Smoking status was defined by the three categories of current, former and never smokers. Lifetime cigarette consumption was analysed by PYs (number of years smoked * average number of daily smoked cigarettes/20). Referral to or treatment by a physician for COPD was regarded as a previous diagnosis of COPD. Questions on cardiovascular history included myocardial infarction, cerebrovascular accident or transient ischaemic attack, PAD and medication for hypertension or diabetes mellitus. Body mass index (BMI) was calculated as kg m^{-2}.

Pulmonary function was measured by spirometry in all participants with standardised, portable equipment (Microlab 3500, MicroMedical Ltd, CA, USA). Measures of respiratory functions consisted of forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio. Published prediction equations were used to calculate the percentage of predicted FEV1 for each participant (pFEV1%). The maximum of three repeated respiratory tests was used in the analysis. A modification of the Global Initiatives for Chronic Obstructive Lung Disease (GOLD) definitional criteria was used to classify subjects into the mutually exclusive categories of severe/very severe COPD (FEV1/FVC <0.7 and FEV1 <50% predicted), moderate COPD (FEV1/FVC <0.7 and FEV1 50% to <80% predicted) and mild COPD (FEV1/FVC <0.7 and FEV1 ≥80% predicted).[15]

Statistical analysis

Baseline data on respiratory functioning of 221 patients of the PHAST trial were available. Calculation of the sample size was based on the assumption that a 15% difference in mean FEV1 is clinically relevant.[12] To detect a difference with a level of 0.05 and 90% power, 90 control patients were required.

The analysis was carried out by using Statistical Package for Social Sciences (SPSS) version 17 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as means ± standard deviation (SD). The patient characteristics including gender, age, smoking history, BMI and cardiovascular risk factors were systematically recorded and compared descriptively. Continuous variables were analysed with the *t*-test and categorical variables with the chi-square test. We used linear regression analysis to estimate differences in outcome measures between the two groups. Multiple logistic regression analysis was performed to ascertain whether chronic obstructive airway disease was independently associated with the presence of an AAA, compared with gender, age, smoking status, presence of diabetes mellitus and a history of cardiovascular diseases. Differences in change of aneurysm growth parameters were assessed by repeated measurements analysis using linear mixed models with a random intercept and slope per patient. To assess whether growth rates were comparable between patients with and without COPD, or within COPD disease stages, interaction terms between the disease stage and aneurysmal diameter were used. All tests were two-tailed; *p*-values smaller than 0.05 were considered to be statistically significant.

Results

Our study population consisted of 221 patients with an AAA and 87 control patients with PAD without an AAA. The demographic and clinical characteristics of the two groups are outlined in Table 2.

Aneurysm and control groups were similar with respect to gender ($p = 0.71$), lifetime cigarette smoking (39 vs. 34 pack years, $p = 0.23$) and history of cardiovascular disease (45% vs. 55%, $p = 0.12$). The percentage of current smokers was higher in the PAD patient group than in those with AAA (45% vs. 30%, $p = 0.029$). AAA patients were slightly older (71 vs. 69 years, $p = 0.03$) and heavier (BMI 27.4 vs. 26.2 kg m^{-2}, $p = 0.01$) and were less frequently diagnosed with diabetes mellitus (15% vs. 30%, $p = 0.006$).

Significant differences in indices of airway obstruction were found (Table 3). The mean FEV1/FVC ratio was significantly reduced in aneurysm patients compared with controls (0.69 vs. 0.78, $p < 0.001$). This reduced FEV1/FVC ratio in AAA patients was consistently found in all three smoking cohorts, current (0.69 vs. 0.75, $p = 0.013$), former (0.68 vs. 0.79, $p < 0.001$) and never smokers and most pronounced in never smokers (0.73 vs. 0.86, $p < 0.001$). No significant differences were found in FEV1 and pFEV1% measures. In contrast, aneurysm patients had a significantly larger FVC (3.23 vs. 3.46, $p = 0.024$). No relationship was found between annual aneurysm expansion rates in patients with COPD (2.3 mm $year^{-1}$) and those without (2.5 mm $year^{-1}$) ($p = 0.20$) (data not shown).

Classifying the results according to the GOLD criteria revealed that COPD is more prevalent in aneurysm patients (98/221; 44%) than in PAD patients (17/87; 20%). The unadjusted odds ratio of aneurysm patients for COPD is 3.3 (confidence interval 95% (CI95%) 1.8–5.9, $p < 0.001$), and 3.0 (95%CI 1.6–5.5, $p < 0.001$) when adjusted for age, gender, smoking and presence of diabetes mellitus and a history of cardiovascular disease. In particular, a major proportion of aneurysm patients was newly diagnosed with COPD; only 40 of 98 patients (41%) with COPD (mild, moderate or severe/

Table 2
Patient characteristics of cases with abdominal aortic aneurysm and controls.[a]

	PAD $n = 87$	AAA $n = 221$	*p*
Age	69 ± 9	71 ± 7	**0.032**
Male gender	85%	87%	0.71
Body height (cm)	175 ± 8	175 ± 8	0.42
Body weight (kg)	80 ± 13	84 ± 14	**0.014**
BMI	26.2 ± 3.4	27.4 ± 3.7	**0.013**
Smoking			**0.029**
Current	38 (44%)	66 (30%)	
Former	39 (45%)	132 (60%)	
Never	10 (11%)	23 (10%)	
Pack years	34 ± 27	39 ± 31	0.23
DM	25 (29%)	32 (15%)	**0.006**
MI	23 (27%)	62 (28%)	0.89
Stroke	5 (6%)	11 (5%)	0.79
TIA	12 (14%)	20 (9%)	0.21
PAOD	87 (100%)	53 (24%)	**<0.001**
All CVD (other than PAOD)	46 (55%)	98 (45%)	0.12

BMI; body mass index, DM; diabetes mellitus, MI; myocardial infarction, TIA; transient ischaemic attack, PAD; peripheral artery disease, CVD; cardiovascular disease.

[a] Data are presented as means ± SD except for percentages (%) and *p*-values are calculated using logistic regression. Bold *p*-values indicate a significant difference between AAA and PAD groups.

Table 3
Spirometry outcome measures in cases with abdominal aortic aneurysm and controls.[a]

	PAD $n = 87$	AAA $n = 221$	p
FVC (L)	3.23 ± 0.78	3.46 ± 0.83	**0.024**
FEV1 (L)	2.50 ± 0.69	2.39 ± 0.71	0.21
FEV1 % predicted	84.0 ± 17.8	80.4 ± 19.0	0.13
FEV1/FVC ratio	0.78 ± 0.11	0.69 ± 0.12	**<0.001**
Current smokers	0.75 ± 0.11	0.69 ± 0.14	**0.013**
Former smokers	0.79 ± 0.10	0.68 ± 0.12	**<0.001**
Never smokers	0.86 ± 0.07	0.73 ± 0.07	**<0.001**

FVC; forced vital capacity, FEV1; forced expiratory volume in 1 s, L; litre. FVC is slightly increased in aneurysm patients.
Mean FEV1/FVC ratio is significantly reduced in aneurysm patients compared with controls, most pronounced in never smokers.
[a] Data are presented as mean ± SD.

very severe) were known before with obstructive pulmonary defects and received treatment. (Fig. 1)

Discussion

This study demonstrates an increased prevalence of obstructive pulmonary disease in patients with an AAA, a relationship that appears independent from smoking. Our findings clearly support the longstanding notion of an association between AAA and obstructive airway disease. Although a major proportion of COPD in aneurysm patients is most likely smoking-induced, our results suggest a relationship that is beyond that of smoking alone, as clearly illustrated by spirometry results in never smokers. Findings from this study also show that obstructive pulmonary disease often remains unrecognised in aneurysm patients.

In 1985, Cronenwett et al. reported an association between rupture of AAAs and obstructive pulmonary disease.[6] Later reports extended this notion, and described a generally increased prevalence of COPD in AAA patients, and of aneurysmal disease in COPD patients.[7–12] Unfortunately, interpretation of these studies is hampered by methodological shortcomings such as identification of COPD on the basis of medical records or questionnaires, which are known to underestimate the presence of pulmonary disease.[16,17] Moreover, the implication of the studies is complicated by considerable heterogeneity in outcome measures, definitions and control populations. Whether the presumed association is dominated by smoking as the primary risk factor for both diseases remains unclear. In addition, findings from these studies are not supported by the largest study in AAA patients thus far (the Veterans Affairs Aneurysm Detection and Management (VA) study) where the association between COPD and AAA was lost after adjustment for smoking.[13] The reason for this apparent discrepancy is unclear, but may also relate to the use of questionnaires in the VA study to assess the presence of pulmonary disease, which has a positive predictive power of only 58% to recognise COPD.[16,17]

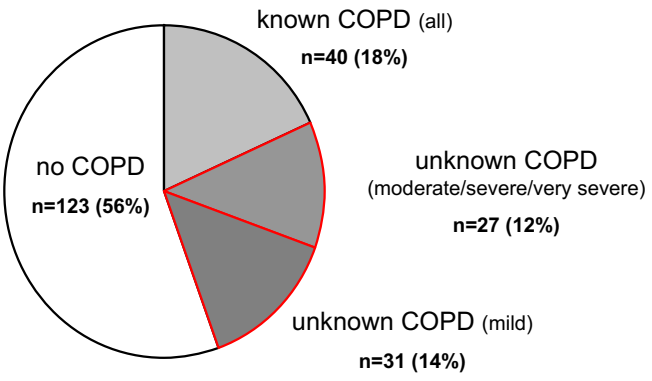

Figure 1. Distribution of chronic obstructive pulmonary disease in AAA patients after spirometry. Of 221 patients with AAA, a total of 98 (44%) patients had COPD, as determined by spirometry and defined by the GOLD classification. 40 patients were previously diagnosed and treated for COPD (all stages of GOLD-classification). An additional 27 patients were newly identified with moderate or severe/very severe COPD and mild COPD was found by spirometry in 31 patients.

Given the contrasting findings and the persistent controversy with regard to the role of cigarette smoking in the association between AAA and COPD, we considered a re-evaluation relevant. The choice for PAD patients as the control population was based on the parallels in risk factors between AAA and PAD, which not only include dominance of smoking as the primary risk factor but also other common non-modifiable risk factors such as age and male gender.[14] As more than 85% of both populations were former or current smokers, with a similar burden of PYs, a considerable proportion of patients with pulmonary impairment was expected in both groups. However, significantly more airway obstruction was present in aneurysm patients, indicating that the high prevalence of COPD is not explained by smoking alone. This observation suggests that the relation between AAA and COPD reflects a common susceptibility, a notion that is supported by converging pathophysiologic pathways including metallopeptidase-9 and neutrophil elastase.[18,19] Such a common predisposition is suggested by the observation that the difference in FEV1/FVC ratio between AAA and PAD patients was most pronounced in never smokers. Identification of common mechanisms or pathways might be highly relevant for future aneurysm and pulmonary research and research collaboration initiatives. In our opinion, further investigation of common genetic, inflammatory and remodelling pathways is warranted.

In line with two previous observations, we found no relationship between the presence of obstructive pulmonary disease and expansion of aneurysm diameter.[9,20] Whether aneurysm growth is related to an actual decline in FEV1 values can, however, not be determined with this study. To that end, a long-term prospective study design would be required including a much larger sample of aneurysm patients, assessing pulmonary changes over time.[2]

This study has limitations. First, we performed a case–control study designed to overcome restraints of previous reports. However, like all observational studies, our results are also subject to bias from confounding factors. We matched both cohorts to reduce imbalance with respect to smoking as the most apparent confounding factor. Yet, small but significant differences with regard to potential confounders remained between the groups. We mathematically adjusted for these potential confounders. Results for this analysis showed that these adjustments only minimally affected the results. Second, we used a 2.5 to 1 ratio for cases and controls. This ratio was based on the power calculations for the study. Although the significant outcomes confirm the adequacy of the power calculation, a larger control group would have resulted in smaller confidence intervals.

Third, we used fixed ratios and cut-off points to determine obstructive pulmonary defects for reasons of simplicity and comparability. While this is a common approach, this may result in over-diagnosis in elderly patients because of the variable nature of obstructive pulmonary diseases and the heterogeneity among patients. Although COPD is operationally defined by results on spirometry, an adequate diagnostic process should include post-bronchodilator spirometry, questionnaires and other clinical, physiological and radiologic measures. It is clear that FEV1 measures and indices alone have epidemiological value but they are not sufficient for clinical decision-making.[2]

Finally, we would consider an additional histopathological analysis of matched aneurysmal and pulmonary tissues from AAA

patients highly relevant. Yet, such a study would rely on tissues obtained during post-mortems. Given the extremely low number of post-mortem nowadays, such a study is extremely hard to conduct and one has to rely on the abundance of literature on inflammatory and proteolytic pathways in both conditions.[3–5,18,19]

Implications

Data from our clinical cohort show that 59% of COPD cases were previously undetected; only 40 of the 98 detected AAA patients had a diagnosis of COPD and received proper treatment. Spirometry more than doubles the number of patients with a diagnosis of COPD, indicating that COPD is under-diagnosed in the AAA patients.[21] This can be partially explained by low physical activity in elderly patients, as symptoms of COPD such as shortness of breath may remain unnoticed. These findings suggest that it is clinically relevant to screen each AAA patient for obstructive pulmonary disease.[22] Early detection of COPD is useful, as appropriate disease modification is available. For COPD, the only approach that has proven useful on modifying the course of the disease is smoking cessation. However, the usefulness of long-acting beta agonists or muscarinic antagonists in alleviation of the symptoms is also well documented, thus enhancing quality of life.[23] Moreover, COPD has been identified as a co-morbidity associated with increased cardiovascular risk and poor outcome for any major vascular procedure.[24,25] Appropriate preoperative care, with a detailed respiratory assessment and careful attention to pulmonary function in the postoperative period, is necessary to favour the post-operative course of aneurysm patients.[26]

Conclusion

The findings of this study show that the increased prevalence of COPD in patients with an AAA is independent from smoking. In addition, COPD often remains unrecognised in aneurysm patients.

Conflict of Interest

None.

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