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ORIGINAL RESEARCH

Statin Therapy is Associated with Decreased Pulmonary Vascular Pressures in Severe COPD

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Background: **Pulmonary hypertension (PH) in COPD carries a poor prognosis. Statin therapy has been associated with numerous beneficial clinical effects in COPD, including a possible improvement in PH. We examined the association between statin use and pulmonary hemodynamics in a well-characterized cohort of patients undergoing evaluation for lung transplantation.** ***Methods:*** **We conducted a cross-sectional analysis of 112 subjects evaluated for lung transplant with a diagnosis of COPD. Clinical characteristics, pulmonary function, cardiac catheterization findings and medical comorbidities were compared between statins users and non-users.** ***Results:*** **Thirty-four (30%) subjects were receiving statin therapy. Statin users were older and had an increased prevalence of systemic hypertension and coronary artery disease (CAD). Mean pulmonary arterial pressure (mPAP) in the statin group was lower [26 $\pm$ 7 vs 29 $\pm$ 7 mmHg, p = 0.02], as was pulmonary artery wedge pressure (PAWP) [12 $\pm$ 5 vs. 15 $\pm$ 6 mmHg, p = 0.02]. Pulmonary vascular resistance did not differ between the groups. In multiple regression analysis, statin use was associated with a 4.2 mmHg (95% CI: 2 to 6.4, p = <0.001) lower PAWP and a 2.6 mmHg (95% CI: 0.3 to 4.9, p = 0.03) reduction in mPAP independent of PAWP.** ***Conclusions:*** **In patients with severe COPD, statin use is associated with significantly lower PAWP and mPAP. These finding should be evaluated prospectively.**

Keywords: Statin, Pulmonary pressures, Chronic obstructive pulmonary disease

INTRODUCTION

The presence of pulmonary hypertension (PH) in COPD is well recognized as an independent prognostic indicator (1,2). In addition to increased mortality, PH in COPD is associated with increased hospitalization rates (3) and decreased exercise capacity (4). Mechanisms for the development of pulmonary hypertension in COPD include both lung parenchymal and vascular pathologies (5). Conventionally, PH in COPD has been thought to be primarily related to hypoxic vasoconstriction. However, other and perhaps more important mechanisms may include structural remodeling and endothelial dysfunction of the pulmonary vasculature (6,7), elevated left heart filling pressures associated with cardiovascular disease, and mechanical factors related to increased alveolar and intrathoracic pressures (8,9).

Experience with therapies proven beneficial in pulmonary arterial hypertension (PAH) have been disappointing in patients with COPD, with studies revealing either lack of clinical benefit or even harmful effects (10–13). Observational studies suggest that statin therapy may be associated with benefits which are not explained through traditional lipid-lowering mechanisms (14). These pleiotropic effects are usually attributed to a reduction in isoprenoid synthesis and consequent reduction in Rho and other small G-protein signaling pathways. Statins have been shown to inhibit progression of emphysema and pulmonary hypertension associated with tobacco exposure and chronic hypoxia in murine models (15–17). Beneficial effects described in COPD have included a slower decline in pulmonary function (18), reduced frequency of exacerbations and intubations (19), and improved exercise capacity coupled with reduced pulmonary pressures estimated by echocardiography (20). In this study, we examined the relationship between statin use and cardiopulmonary hemodynamics through a cross-sectional analysis of COPD patients undergoing lung transplant evaluation.

METHODS

The methods of this study were reviewed and approved by our institution's investigational review board. Two hundred and eighty-nine consecutive COPD patients evaluated at our center for lung transplantation from 1995 to 2009 were screened for inclusion in the analysis. Subjects were excluded for the following reasons: 7 had no diagnosis of COPD, and

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23 had an additional lung disease such as interstitial lung disease or sarcoidosis. Of the remaining 259 subjects, hemodynamics were available in 112. The following data were recorded: demographics, anthropometrics, pulmonary function, medical comorbidities, medications, fasting lipid profile values, and results of right and left heart catheterization performed as part of the transplant evaluation. Lipid profiles were determined using the Friedewald calculation. Diagnoses such as diabetes mellitus, congestive heart failure, hypertension, and hyperlipidemia were defined by mention in the medical record or by medication use. Coronary artery disease (CAD) by angiography, was defined as either ≥50% stenosis of the left main coronary vessel, ≥70% stenosis in another vessel, or revascularization intervention.

Statistical analysis

Continuous data are expressed as mean (SD), and categorical data are presented as counts and percentages. Univariate analyses included Student's *t*-test, Chi^2-test, and Fisher's exact tests as appropriate. Pearson correlation coefficient was used to assess the relationship between continuous variables. Two separate multiple linear regression models were built to assess predictors of mPAP and PAWP. Covariates were included in the regression model if they varied by statin use at the 0.1 significance level in univariate analyses or were thought to be of clinical importance. Reverse stepwise regression modeling was performed with a p-value inclusion threshold of 0.2 to generate the final multiple regression models. Underlying modeling assumptions were checked graphically. Analysis was performed using Stata Statistical Software, Release 10.0 (Stata Corporation; College Station, TX).

RESULTS

Clinical characteristics of the study subjects are described in Table 1. Subjects were primarily Caucasian with severe COPD reflected by a mean FEV_1% predicted of 21 ± 8. Ninety percent used supplemental oxygen. Ninety-two percent of subjects were found to have mean pulmonary arterial pressure (mPAP) ≥20 mmHg, and 66% of these also had pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg. Fifty seven percent were found to have mPAP ≥25 mmHg, and 53% of these also had PAWP ≤ 15 mmHg. Six percent of our subjects were found to have mPAP ≥ 40 mmHg, and all but one of these had PAWP >15 mmHg. Coronary angiographic data were available in 96 subjects. Nineteen percent of subjects had significant CAD at catheterization. The presence of CAD was not associated with differences in mPAP or PAWP.

Thirty percent of subjects were receiving statin therapy. Of those with CAD, 67% were using a statin. The specific agents were primarily atorvastatin (53%) and simvastatin (35%). Systemic hypertension, hyperlipidemia, and angiographically proven CAD were present in a significantly higher proportion of statin users and this group was older. Despite these comorbidities, mPAP in the statin group was lower (26 ± 7 vs. 29 ± 7 mmHg; p = 0.02). This difference in mPAP was accompanied by a similarly lower value of PAWP in those patients receiving statin therapy (12 ± 5 vs. 15 ± 6 mmHg, p = 0.02) and not by differences in cardiac output or pulmonary vascular resistance (Table 1). Statin users also had a slightly higher FVC% predicted, a somewhat lower oxygen requirement, and were more likely to be taking a calcium channel blocker. After adjustment for age, race, gender, BMI, hypertension, use of calcium channel blockers, diuretic use, pulmonary function (FEV_1 and DLCO), $PaCO_2$, oxygen requirement, and presence of CAD, statin use was associated with a 5.2 mmHg lower mPAP (95% CI, 1.9 to 8.5) and a 4.3 mmHg lower PAWP (95% CI, 2.0 to 6.6) (Table 4).

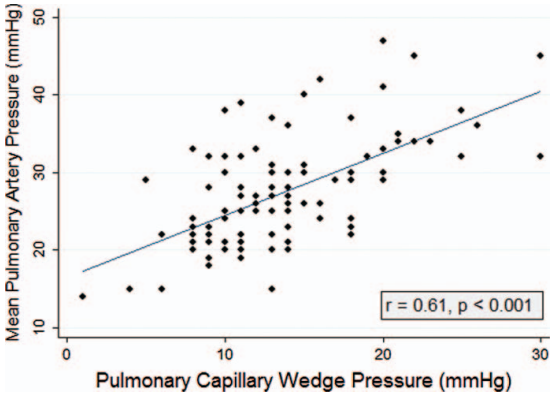

Figure 1. Scatterplot with Pearson's Correlation Between Pulmonary Arterial Wedge Pressure and Mean Pulmonary Arterial Pressures.

There was a strong linear correlation between mPAP and PAWP (Figure 1). PAWP, age, BMI, and non-use of statin were the only significant determinants of mPAP in the univariate analysis (Table 3). No significant association was observed between mPAP and any pulmonary function variable. A marginal trend was observed with oxygen requirement. Statin use, lower BMI, and Caucasian race were associated with lower PAWP in the univariate analysis (Table 2). Variables evaluated in the stepwise model for mPAP included statin use, PAWP, BMI, age, race, calcium channel blocker use, and oxygen use in liters per minute. Reverse stepwise regression modeling demonstrated persistence of statin effect after controlling for PAWP (Table 3). BMI, age, and PAWP were also significant independent determinants of mPAP. Variables evaluated in the stepwise model for PAWP included statin use, age race, BMI, CAD, HTN, calcium channel blocker use, diuretic use, and oxygen use in liters per minute. Only non-statin use and BMI were significant independent determinants of PAWP.

DISCUSSION

Our study is the first to show an association between statin use and reduced pulmonary arterial and wedge pressures obtained invasively in subjects with COPD. Furthermore, we demonstrated these reductions to be independent of relevant clinical factors, and that the reduction in mPAP persisted after controlling for PAWP.

PH is defined as a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, but PH complicating pulmonary disease is defined by many experts in the field as a mPAP ≥

Table 1. Clinical characteristics of study subjects

	Entire Cohort	Statin [-] (N = 78)	Statin [+] (N = 34)	p-value†
Age (years)	58 (8)	55 (9)	58 (6)	*
Male	41%	37%	50%	NS
Caucasian	86%	81%	97%	*
BMI	24 (5)	24 (5)	25 (5)	NS
Tobacco exposure (pack-years)	53 (29)	52 (31)	56 (22)	NS
Comorbidity				
Diabetes mellitus	11%	12%	9%	NS
CHF history	7%	8%	6%	NS
DVT/PE history	5%	5%	6%	NS
Hypertension	44%	35%	65%	**
Hyperlipidemia	29%	5%	85%	***
CAD††	19%	9%	41%	***
Medications				
Theophylline	41%	42%	38%	NS
ACE/ARB	14%	12%	21%	NS
Calcium channel blocker use	27%	19%	44%	**
Diuretic use	24%	24%	24%	NS
Lipid Profile				
Total chol (mg/dL)	217 (51)	216 (49)	218 (57)	NS
TG (mg/dL)	131 (105)	130 (105)	133 (106)	NS
LDLc (mg/dL)	113 (39)	114 (36)	113 (46)	NS
HDLc (mg/dL)	76 (29)	76 (29)	77 (31)	NS
Pulmonary Function				
Supplemental O_2 use	90%	88%	91%	NS
O_2 use (liters per minute)	2.6 (1.3)	2.7 (1.4)	2.2 (1.1)	*
$PaCO_2$ (mmHg)	49 (12)	50 (13)	46 (7)	NS
FVC%	47 (14)	45% (14)	50 (15)	*
FEV_1%	21 (8)	21% (8)	22% (7)	NS
FEV_1/FVC	36 (9)	37% (9)	34% (9)	NS
TLC%	114 (22)	113% (24)	117% (16)	NS
VC%	59 (18)	58% (17)	62% (21)	NS
RV%	212 (59)	212% (67)	211% (33)	NS
RV/TLC	66 (9)	66% (10)	66 (7)	NS
6MWD (meters) (n = 60)	249 (111)	243 (120)	259 (94)	NS
Pulmonary Hemodynamics				
CI (l/min/m^2 BSA)	2.9 (0.7)	2.9 (0.7)	2.8 (0.6)	NS
RAP (mmHg)	9.8 (5)	10.3 (5)	8.6 (5)	NS
mPAP (mmHg)	28 (7)	29 (7)	26 (7)	*
PAWP (mmHg)	14 (5)	15(5)	12 (6)	*
PVRI (Wood units/m^2 BSA)	5 (2.3)	5.0 (2.2)	5.0 (2.6)	NS

Values presented are means with SD in parentheses.
†p value refers to the difference between statin groups.
††Defined as ≥ 50% stenosis in left main coronary, ≥ 70% elsewhere, or intervention performed. CI = Cardiac index, RAP = Right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, PVRI = pulmonary vascular resistance index.
* $p \leq 0.05$.
** $p \leq 0.01$.
*** $P \leq 0.005$.

20 mmHg (21). Pulmonary pressures in our cohort were similar to those previously reported in comparable patient populations. We found a 92% prevalence of mPAP ≥ 20 mmHg, which is quite similar to that reported by Scharf et al., who found a prevalence of 91% at this threshold in patients evaluated for lung volume reduction surgery (22). We also found mPAP ≥ 25 mmHg in 57% of subjects, which is similar to the prevalence of 50% at this higher threshold described in a cohort of 215 patients evaluated for lung volume reduction surgery or lung transplantation (23). Subjects with PAWP > 15 mmHg (32 out of 247) were excluded from that study. Six percent of our subjects were found to have mPAP ≥ 40 mmHg, which is much higher than the 2.7% prevalence described in a large cohort of patients with COPD (24). This difference may be explained by the greater severity of illness in our subjects whose mean percent predicted FEV_1 was 21% versus 33% observed in that study.

Numerous studies have consistently found a strong relationship between mPAP and PAWP in COPD (22,23,25). Among 120 patients in the National Emphysema Treatment Trial (NETT), PAWP exceeded 12 mmHg in over 60% and 15 mmHg in 38% (22), which is comparable to the 60% and 29% at these respective thresholds in our cohort. Multiple regression analysis found that PAWP, along with FEV_1 and

Table 2. Regression models of correlates to pulmonary artery wedge pressure

	PAWP		
	β	95% CI	p- value
Univariate Analysis			
• BMI	0.43	0.24 to 0.63	< 0.001***
• Non-Caucasian Race	3.2	0.4 to 5.9	0.024*
• Statin	−2.3	−4.4 to −0.1	0.037*
• Age	0.09	−0.03 to 0.22	0.149
• Female Gender	−0.9	−3.0 to 1.1	0.359
• CAD†	−0.2	−2.8 to 2.5	0.899
• FEV1% predicted	−0.09	−0.23 to 0.04	0.174
• Hypertension	1.2	−0.8 to 3.2	0.226
• Diuretic use	0.8	−1.6 to 3.2	0.500
• Ca^{++} channel blocker use	−0.5	−2.7 to 1.8	0.686
• O_2 use (liters per minute)	−.2	−0.4 to 1.1	0.409
Reverse Stepwise Regression Model††			
• Statin	−4.2	−6.4 to −2.0	< 0.001***
• BMI	0.39	0.20 to 0.58	< 0.001***
• Age	0.13	−0.01 to 0.28	0.067
• Non-Caucasian Race	2.0	−0.8 to 4.7	0.158
• Hypertension	1.4	−0.6 to 3.4	0.160
• O_2 use (liters per minute)	−0.5	−0.13 to 0.2	0.169

†Defined as in Table 1.
††Variables evaluated included statin use, age, race, BMI, CAD, HTN, calcium channel blocker use, diuretic use, and oxygen use in liters per minute.
*p ≤ 0.05.
**p ≤ 0.01.
***P ≤ 0.005.

Table 3. Regression models of correlates to mean pulmonary artery pressure

	mPAP		
	β	95% CI	p-value
Univariate Analysis			
• PAWP	0.8	0.6 to 1.0	< 0.001***
• Age	0.29	0.13 to 0.45	< 0.001***
• BMI	0.45	0.18 to 0.71	0.001***
• Non-Caucasian Race	4.6	0.9 to 8.2	0.015*
• Statin	−2.9	−5.8 to −0.1	0.040*
• Female Gender	−1.8	−4.5 to 0.8	0.179
• CAD†	0.4	−3.3 to 4	0.841
• FEV1% predicted	−0.04	−0.22 to 0.14	0.663
• Hypertension	1.6	−1.0 to 4.3	0.224
• Diuretic use	2.0	−1.1 to 5.0	0.202
• Ca^{++} channel blocker use	−0.9	−3.9 to 2.1	0.549
• O_2 use (liters per minute)	1.0	−0.05 to 2.0	0.063
Reverse Stepwise Regression Model††			
• PAWP	0.59	0.37 to 0.82	< 0.001***
• Age	0.27	0.14 to 0.41	< 0.001***
• Statin	−2.6	−4.9 to −0.3	0.028*
• BMI	0.28	0.05 to 0.51	0.019*

†Defined as in Table 1.
††Variables evaluated included statin use, PAWP, BMI, age, race, calcium channel blocker use, and oxygen use in liters per minute.
*p ≤ 0.05.
**p ≤ 0.01.
***P ≤ 0.005.

DLCO predicted mPAP (22). Similarly, PAWP was strongly and independently related to mPAP, along with PaO_2 and the alveolar-arterial oxygen gradient, in a large group of COPD subjects referred for lung volume reduction surgery or lung transplantation (23). We could not detect a relationship between pulmonary function variables and mPAP, a finding noted in other series (25). We found only a weak association between oxygen requirement and mPAP. However, this may have been due to clustering of these values and underrepresentation of subjects without hypoxemia, as 90% of patients in the current study used supplemental oxygen. Arterial blood gas measurements while breathing room air were not available for most subjects.

Table 4. Regression models of correlates to mean pulmonary artery pressure and pulmonary artery wedge pressure

	mPAP			PAWP		
	β	95% CI	p-value	β	95% CI	p-value
Fully Adjusted Model						
• Statin	−5.2	−8.5 to −1.9	***	−4.3	−6.6 to −2	***
• BMI	0.56	0.25 to 0.86	***	0.44	0.22 to 0.66	***
• Age	0.34	0.10 to 0.57	**	−0.003	−0.17 to 0.16	NS
• Gender	−1.4	−4.3 to 1.5	NS	−0.2	−2.3 to 1.9	NS
• Race	0.8	−3.6 to 5.2	NS	−0.4	−3.5 to 2.7	NS
• CAD†	1.5	−2.6 to 5.5	NS	0.3	−2.6 to 3.2	NS
• FEV1% predicted	−0.09	−0.26 to 0.09	NS	−0.13	−0.25 to −0.01	*
• DLCO% predicted	−0.02	−0.10 to 0.06	NS	0.04	−0.02 to 0.09	NS
• Hypertension	−1.5	−5.5 to 2.4	NS	1.8	−0.9 to 4.6	NS
• Diuretic use	1.0	−2.4 to 4.3	NS	−1.4	−3.8 to 1.1	NS
• Ca^{++} channel blocker use	1.4	−2.9 to 5.8	NS	−0.8	−3.9 to 2.3	NS

†Defined as ≥50% stenosis in left main coronary, ≥70% elsewhere, or intervention performed.
*p ≤ 0.05.
**p ≤ 0.01.
***P ≤ 0.005.

The basis for the high prevalence of elevated PAWP in our series, as well as others (22,23) is likely multifactorial. It is well recognized that cardiovascular disease (CVD) is highly prevalent in COPD and accounts for a substantial proportion of morbidity and mortality (26). We found a weak relationship between PAWP and systemic HTN, but not CAD. Subclinical systemic vascular disease in the form of atherosclerosis (27) with consequent endothelial dysfunction and arterial stuffiness (28) may lead to LV diastolic dysfunction. The strong influence of BMI on PAWP noted here is consistent with the recognized increased risk of nonsystolic heart failure with obesity (29). Mean pulmonary arterial pressures and PAWP typically rise with exercise in advanced COPD. This rise has been shown to occur with hyperventilation alone (30), indicating a contribution from air trapping and consequent hyperinflation. We found no association between pulmonary function measures of hyperinflation and resting mPAP or PAWP. In the series of Scharf et al., mPAP was not related to lung volumes or emphysema scores by computed tomography (22).

Statins have numerous beneficial effects in CVD that could account for the lower PAWP observed in this study. Their use is associated with small reductions in blood pressure (31–33) as well as reduced left ventricular hypertrophy and fibrosis both in experimental animal models and in humans (34–36). Statins increase arterial distensibility (32, 37) and induce regression of aortic atherosclerosis (38), likely through beneficial effects on endothelial function (39–43). At a cellular level, normal myocardial relaxation requires calcium scavenging through a process dependent upon sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) activity, the impairment of which has been associated with diastolic dysfunction (44). Endothelin may also promote diastolic dysfunction by a mechanism involving induction of intracellular alkalosis which in turn affects myofilament Ca^{2+} sensitivity. Statins could improve diastolic function through their beneficial effects on SERCA (45) as well as reduced endothelin activity in the heart (46).

Despite the high prevalence of elevated PAWP in PH associated with COPD, the primary pathophysiologic mechanism is felt to be structural remodeling of the small pulmonary arteries, which occurs early in the disease (47). Recent data from the NETT trial found a strong correlation between mPAP and the cross-sectional area of the small pulmonary vessels by computed tomography (48). Statins possess numerous properties that would be expected to retard pulmonary vascular remodeling, including inhibition of vascular smooth muscle cell (VSMC) proliferation and migration, induction of VSMC apoptosis, and have been shown to be effective in several animal models of PH (15,16,49,50). Despite no effect on PVR, our observation of reduced mPAP independently of PAWP in statin users suggests that these drugs may reduce pulmonary vascular remodeling in COPD.

The association between age and mPAP, but not PAWP, was unexpected. Advanced age is well known to correlate with left ventricular diastolic dysfunction (51,52), and so a correlation with PAWP would have been predicted. Longitudinal studies have shown a mPAP rise of 0.4 to 0.6 mmHg per year in patients with COPD (53,54), which is in line with our β coefficient estimate. Thus, increased age with consequent longer disease duration, may be associated with more pulmonary vascular remodeling. Cross sectional studies, however, are significantly affected by survival bias and rarely demonstrate this correlation. A large series presented by Bishop et al., including 595 subjects with COPD, found no correlation between mPAP and age (55).

The primary limitation of this study is the retrospective nature of the data collection. Statin use was nonrandom, and although regression models were able to control for many clinical differences, it is still possible that unknown confounders exist. Significantly more patients receiving statin therapy were taking calcium channel blockers. It is unlikely, however, that this could have affected mPAP or PAWP in our population as long-term studies have shown no significant change in these values with their use in COPD (12) and there was no association between calcium channel blocker use and mPAP or PAWP in our population. The clinical implications of these findings are not clear, particularly since no effects were observed on resting cardiac index or PVR. A recent placebo-controlled trial demonstrated a 52% increase in treadmill exercise time and significant improvement in Borg dyspnea score associated with a reduction in systolic PAP assessed by Doppler echocardiography after 6 months of pravastatin therapy (20).

CONCLUSIONS

In patients with severe COPD, statin use is associated with significantly lower mPAP and PAWP despite older age and a higher prevalence of medical comorbidities such as HTN and coronary disease. Improvements in pulmonary hemodynamics may represent an addition to the growing list of potential benefits of statin use in COPD (56). Prospective clinical trials are required to assess the long-term clinical impact of statin therapy in this population.

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