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High-Resolution Chest Computed Tomography Findings Do Not Predict The Presence of Pulmonary Hypertension in Advanced Idiopathic Pulmonary Fibrosis

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Abstract

Background—Reliable, noninvasive approaches to the diagnosis of pulmonary hypertension in idiopathic pulmonary fibrosis are needed. We tested the hypothesis that chest computed tomography-determined extent of pulmonary fibrosis and/or main pulmonary artery diameter can be used to identify the presence of pulmonary hypertension in patients with advanced idiopathic pulmonary fibrosis.

Methods—Cross-sectional study of 65 patients with advanced idiopathic pulmonary fibrosis with available right-heart catheterization and high-resolution chest computed tomography. An expert radiologist scored ground-glass opacity, lung fibrosis, and honeycombing in the computed tomography images on a scale of 0–4. These scores were also summed into a total profusion score. The main pulmonary artery was measured at its widest dimension on the supine full chest sequence. At this same level, the widest aorta diameter was measured.

Results—Chest computed tomography-determined fibrosis score, ground-glass opacity score, honeycombing score, total profusion score, diameter of the main pulmonary artery, and the ratio of the pulmonary artery to aorta diameter did not differ between those with and without pulmonary hypertension. There was no significant correlation between mean pulmonary artery pressure and any of the chest computed tomography-determined measures.

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Conclusions—High-resolution chest computed tomography-determined extent of pulmonary fibrosis and/or main pulmonary artery diameter cannot be used to screen for pulmonary hypertension in advanced idiopathic pulmonary fibrosis patients.

Keywords

pressure, pulmonary artery; hypertension, pulmonary; pulmonary fibrosis; high-resolution chest computed tomography; diagnosis

Introduction

Idiopathic pulmonary fibrosis is a specific form of chronic fibrosing interstitial pneumonia associated with the histological appearance of usual interstitial pneumonia (UIP)¹. Pulmonary hypertension (PH) commonly complicates advanced IPF and is associated with worse prognosis²⁻⁶.

Right heart catheterization (RHC) is the “gold standard” test to diagnose PH in IPF. However, RHC is invasive, costly and associated with complications. Although echocardiography is the most commonly used test to screen for PH in patients with ILD, it is not a reliable screening test^{5,7}. Reliable, noninvasive approaches to the diagnosis of PH in IPF would improve patient safety and reduce cost.

Previous studies in patients with pulmonary vascular disease and diverse lung conditions suggested that chest computed tomography (CT)-determined pulmonary artery diameters can be used to predict PH⁸⁻¹². However, this has not been tested in a homogeneous sample of patients with well-characterized IPF. Mechanistically, the severity of lung fibrosis should correlate with the prevalence and degree of PH. However, the relationships between CT assessments of lung fibrosis and pulmonary artery pressure have not been studied in patients with IPF. Therefore, in this study, we examined whether the CT-determined extent and severity of pulmonary fibrosis and diameter of the main pulmonary artery could be used to diagnose PH in advanced IPF patients.

Methods and Materials

Study sample

We retrospectively reviewed the medical records of all patients with IPF who were seen at our institution between July 1999 and June 2006. During their initial visit, all patients prospectively provided written informed consent (approved by the UCLA IRB) to use their clinical and demographic information for research purposes. All patients met accepted diagnostic criteria for IPF and the majority (74%) had histopathologic evidence of usual interstitial pneumonia¹. Three hundred and twenty two patients with well-documented IPF were seen at the center during this period and were candidates for inclusion in this study. To be included in the study, participants had to have had a high-resolution chest computed tomography (HRCT) within one month of the RHC. RHC were performed as part of the lung transplant evaluation (74%) or for participation in a clinical trial (ClinicalTrials.gov identifier: NCT00352482). Sixty-five patients met this entry criterion. Twenty-seven of them had PH.

Measurements

RHC data included measurements of pulmonary arterial pressures with the patient at rest. We defined PH as resting MPAP of > 25 mm Hg¹³.

After at least five minutes of rest, pulse oximetry (SpO₂) was measured on room air. Standard methodology was used for obtaining pulmonary function tests (PFT) and six-minute walk distance (6MWD) ¹⁴⁻¹⁷.

High-resolution Chest Computed Tomography (HRCT) Scoring System

All HRCTs were performed in the prone position acquiring 1.0- or 1.5-mm-thick sections at 1-cm throughout the entire thorax and then in the supine position. Full volume CT scans reconstructed every 3mm were acquired at suspended inspiration. HRCTs were reconstructed with a sharp kernel (Siemens, B50) and field of view (FOV) of widest outer rib to outer rib dimension. All studies were scored by one expert thoracic radiologist (JG) blinded to the patient's clinical and hemodynamic information, using a Likert scale (0 = absent, 1 = 1-25%, 2 = 26-50%, 3 = 51-75% and 4 = 76-100%) for extent of parenchymal abnormality in three categories: ground-glass opacity, lung fibrosis, and honeycombing. These scores were also summed into a total CT profusion score. This scoring system is based on that reported by Kazerooni *et al* ¹⁸. The following radiographic definitions were employed: ground-glass opacity: hazy parenchymal opacity in the absence of reticular opacity or architectural distortion; lung fibrosis: reticular opacification, traction bronchiectasis and bronchiolectasis; honeycombing: clustered air-filled cysts with dense walls. Each lung lobe was scored separately (upper: lung apex to aortic arch, middle: aortic arch to inferior pulmonary veins, and lower: inferior pulmonary veins to diaphragm) and the mean score over all five lobes was computed for each category of parenchymal abnormality: fibrosis (CT-fib), ground glass opacity (CT-alv), honeycombing (CT-hc) and total profusion (CT-tot = CT-fib + CT-alv + CT-hc). Lobe scores were also weighted by typical relative size (right upper lobe: 0.0935; right middle lobe: 0.0935; right lower lobe: 0.363; left upper lobe: 0.155; and left lower lobe: 0.297) and summed to create weighted scores for fibrosis (wCT-fib), ground-glass (wCT-alv), honeycombing (wCT-hc) and total profusion (wCT-tot). We also created a maximum fibrosis score (mCT-fib) based on the most affected lobe.

The main pulmonary artery diameter (MPAD) was measured at its widest dimension on the supine full chest sequence. At this same level, the widest aorta diameter (AD) was measured and the MPAD/AD ratio was calculated. MPAD was also normalized by body surface area (BSA, m²) which was calculated according to the following equation: $BSA = 0.00718 \times W^{0.425} \times H^{0.725}$, where W is body weight (kg), and H is body height (cm) ¹⁹.

Statistical Analysis

We compared mean values of all putative predictors of PH in patients with and without PH, using the Student *t* test. We also examined the Pearson correlation coefficient between MPAP and each of the putative predictors of PH. We then regressed MPAP on CT-fib, wCT-alv, wCT-hc and MPAD/AD in a multivariable linear regression model. The CT-derived scores chosen for the model were the ones with the highest correlation with MPAP in each category (fibrosis, ground glass opacity, honeycombing, and PA size).

All tests were two-tailed, and p values of < 0.05 were required for statistical significance. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, N.C., USA).

Power Calculations

Our study was designed to have 80% power to detect 0.75σ or larger differences in putative predictors between the PH and no PH groups (where σ is the common standard deviation in the 2 groups) and to detect correlations of 0.34 or larger between MPAP and putative predictors.

Results

The study sample (n=65) had more advanced pulmonary disease (with lower FVC, DL_{CO}, and room air SpO₂) than the rest of the cohort (n=257), but was representative of the cohort with respect to age, gender, and race (Table 1). Mean MPAP in the study sample was similar to the mean MPAP in the 56 patients with RHC data who were excluded from the study because their RHC was more than one month distant from their HRCT.

Comparisons of Patients With and Without Pulmonary Hypertension

Patients with and without PH did not differ with respect to age, gender, race and BSA (Table 2). As expected, those with PH had significantly lower DL_{CO}, FVC/DL_{CO}, 6MWD and resting room air SpO₂ and significantly higher MPAP than those without PH, but they did not perform significantly worse on FVC or DL_{CO}/VA and had similar CT-derived scores for extent and severity of parenchymal disease and CT-derived MPAD, MPAD/AD and MPAD/BSA. Similarly, CT scores weighted by relative lobar size and the maximum CT-derived fibrosis score over all lobes did not differ between those with or without PH.

Correlation Between Mean Pulmonary Artery Pressure and Putative PH Predictors

As shown in table 3, there were strong and statistically significant correlations in the expected directions between MPAP and both 6MWD and resting room air SpO₂. We observed a modest and significant correlation between MPAP and DL_{CO}, DL_{CO}/VA% and FVC%/DL_{CO}%. However, there was no correlation between MPAP and FVC, CT-fib, CT-alv, CT-hc, CT-tot, MPAD, AD, MPAD/AD or the MPAD/BSA ratio (Figures 1 and 2). Similarly, there was no correlation between MPAP and CT scores weighted by relative lobar size or the CT-derived maximum fibrosis score. Furthermore, we found no correlation between other RHC-derived measurements (right atrial pressure, pulmonary vascular resistance, cardiac output, cardiac index) and any of the chest computed tomography-determined measures (data not shown).

Multivariable Linear Regression of MPAP on CT-derived Predictors

We regressed the MPAP on the CT scores (one from each category) with the highest correlation with MPAP (namely, CT-fib, wCT-alv, wCT-hc and MPAD/AD) in a multivariable linear regression model. The model adjusted R-square was 0.008 (p=0.35).

Discussion

Pulmonary hypertension is common in patients with advanced IPF and its presence has a significant adverse impact on survival^{2,3}. Noninvasive approaches to the diagnosis of PH in IPF are needed. In this study, we found that the CT-determined extent and severity of pulmonary fibrosis and main pulmonary artery diameter do not help in identifying PH in advanced IPF patients.

Intuitively, the severity of lung fibrosis should correlate with the prevalence and degree of PH. It seems logical that as the patient's IPF progresses and their lungs become more fibrotic, the cross-sectional area of the pulmonary vascular bed is reduced, the pulmonary vascular resistance rises, and pulmonary hypertension ensues; however, in this study, MPAP did not correlate with CT-based measurements of lung fibrosis and these variables did not differ between those with and without PH. Previously, we and others have shown that MPAP does not correlate with the degree of restrictive physiology (FVC, TLC) in IPF^{2-5,20}. PH is also disproportionate to the degree of restrictive ventilatory impairment (FVC) in patients with sarcoidosis and pulmonary Langerhan's cell histiocytosis^{21,22}. This study provides the first radiographic confirmation of the notion that the loss of pulmonary vascular conductance in IPF is not proportional to the extent of fibrosis. Vascular remodeling in IPF has been the subject

of intense investigation over the last few years²³⁻²⁷. There is evidence of regional heterogeneity with some areas demonstrating increased vascularity and other areas demonstrating decreased vascularity²³⁻²⁷. While fibroblastic foci are notable for the absence of blood vessels, they are surrounded by a rich network of vessels²⁸. That is probably why there is little correlation between extent of fibrosis and MPAP. Although a higher extent of lung fibrosis on CT has been associated with worse outcome in IPF patients²⁹⁻³¹, our findings suggest that it is unlikely that a higher CT-fibrosis portends poor prognosis in connection with PH in IPF patients. By contrast, hypoxemia is an independent predictor of mortality in IPF³²⁻³⁴ and it is also strongly linked to PH. This study and previous studies by us and others have consistently observed a strong association between high MPAP and low SpO₂, suggesting that vasoconstriction in response to hypoxia is an important factor in the development of PH in IPF²⁻⁵. Although initially reversible, the pathologic changes induced by hypoxia-induced vasoconstriction ultimately result in irreversible vascular remodeling^{35,36}.

Previous studies of the association between pulmonary artery size and pulmonary artery pressure have been inconsistent, with some investigators finding correlations in the expected direction^{9,11,37-39}, and others reporting no correlation⁴⁰⁻⁴². Our results support the previous studies that have found no correlation between pulmonary arterial diameter and pulmonary artery pressure⁴⁰⁻⁴². It should be emphasized that our study population consisted of a homogeneous group of well-characterized IPF patients, whereas other investigators have focused on a wide spectrum of cardiopulmonary diseases^{9,12,40,42}, with a large proportion of patients with pulmonary vascular disease (PVD) such as idiopathic pulmonary arterial hypertension or chronic thromboembolism^{10,11,39,41,42}. Although we cannot explain these disparate findings with certainty, it is quite possible that pulmonary artery size and pressure are correlated only in PVD and not in IPF. It is also possible that PH in our patients was not severe enough to cause increase in MPAD. In previous studies that have found associations between pulmonary artery size and PH, the PH cases were predominantly composed of patients with PVD with greater pulmonary artery pressures than our IPF patients with PH^{8,11}. Haimovici *et al* observed that when the severe PH cases were omitted by excluding patients with IPAH and patients with Eisenmenger's syndrome, the correlation between CT-measured pulmonary artery size and MPAP dropped⁹. In a separate study, inclusion of PVD patients increased the MPAP of the PH group from 35.1 to 45.3 mm Hg. In that study, MPAD increased from 33 to 35 mm when PVD patients were included in the PH group⁴², and the sensitivity and specificity of MPAD in predicting PH was lower in the subgroup of patients with parenchymal lung disease when compared to patients with PVD⁴². Our study is consistent with these findings and together they suggest that PH due to IPF may not increase MPAD. It is also conceivable that the restrictive lung physiology in IPF may result in a traction effect on the mediastinal vascular structures, distending the pulmonary artery independent of the underlying pulmonary artery pressure; this effect may dampen the influence of the pulmonary artery pressure on the MPAD in patients with IPF. Ng *et al* showed in multivariable analysis that TLC, a marker of traction on mediastinal structures, independently contributed to MPAD¹². Consistent with this hypothesis, the pulmonary artery diameter in our control group (IPF patients without PH) was greater (31.3 ± 4 mm) than the values reported by others in their controls without cardiopulmonary disease (e.g., 24.2 ± 2 mm¹¹; 27.2 ± 3 mm⁸).

Certain limitations of our study need to be acknowledged. This was a retrospective review of patients evaluated at a single center. Most of our patients underwent evaluation for lung transplantation, reflecting the presence of patients with more advanced IPF; hence, our results may not apply to the general population of IPF patients. However, we and others have shown that PH is more prevalent in patients with severe IPF (defined by reduced DLco and/or SpO₂)²⁻⁶; hence, this population is the one in whom identification of PH is more critical. Similar to other studies on this topic^{37,39-41}, CT scores were read by a single radiologist; however, since interobserver accuracy in measuring MPAD and extent of pulmonary fibrosis has been

shown to be good^{8,12,18}, we do not believe that lack of additional readings by more than one expert radiologist biased our findings. Ours is a cross-sectional study of the association between CT-derived measures and PH in IPF patients. Hence, we cannot conclude that PH secondary to IPF is causally unrelated to changes in CT. That would require a longitudinal study. However, we can say that CT-derived measures of parenchymal disease and MPAD cannot be used to screen for PH in advanced IPF patients. Finally, our sample size may have limited our ability to find a real underlying association between CT-derived measures and PH. Since our study was powered to find correlations of 0.34 or larger, we can infer only that if there are undetected correlations between MPAP and one or more of the CT-derived measures, they are likely to be smaller than 0.34. Since this and previous studies^{4,5} have found correlations between MPAP and simple measurements (such as 6MWD, SpO₂, and PaO₂) of the order of 0.5 and 0.7, we can conclude that HRCT-derived measures cannot distinguish between PH and no PH as well as simple clinical measurements such as oxygenation and the distance walked in six minutes.

In summary, HRCT-determined severity and extent of pulmonary fibrosis and pulmonary artery size cannot be used to screen for PH in advanced IPF patients.

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Abbreviations

AD	CT-measured diameter of the ascending aorta
BSA	body surface area
CT-alv	CT-determined ground-glass score
CT-fib	CT-determined fibrosis score
CT-hc	CT-determined honeycomb score
CT-tot	CT-determined total profusion score
DLco	diffusing capacity for carbon monoxide
FOV	field of view
FVC	forced vital capacity
ILD	interstitial lung disease
IPF	

	idiopathic pulmonary fibrosis
IRB	institutional review board
mCT-fib	maximum CT-derived fibrosis score over all lobes
MPAD	CT-measured main pulmonary artery diameter
MPAP	mean pulmonary artery pressure
PaO₂	arterial blood oxygen tension
PFT	pulmonary function tests
PH	pulmonary hypertension
RHC	right-heart catheterization
SpO₂	resting room air pulse oximetry
wCT-alv	weighted CT-determined ground-glass score
wCT-fib	weighted CT-determined fibrosis score
wCT-hc	weighted CT-determined honeycomb score
wCT-tot	weighted CT-determined total profusion score
VA	alveolar volume
6MWD	six-minute walk distance

Figure 1. Relationship between CT-determined fibrosis score (CT-fib) and measured mean pulmonary artery pressure (MPAP)

MPAP = mean pulmonary artery pressure, CT-fib = CT-determined fibrosis score

Figure 2. Relationship between CT-determined main pulmonary artery diameter (MPAD) and measured mean pulmonary artery pressure (MPAP)

MPAP = mean pulmonary artery pressure, MPAD = CT-determined main pulmonary artery diameter

Table 1

Descriptive statistics for major characteristics

Characteristic	Mean (SD) or %	Mean (SD) or % [*]	P-value
	Study sample (n=65)	Excluded (n=257)	
Age (years)	66.7 (8.2)	66.9 (9.6)	0.886
Males (%)	60.0	63.4	0.610
Race (%)			0.663
Caucasian	78.5	76.1	
Hispanic	16.9	15.7	
Other ^{**}	4.6	8.2	
FVC (L)	2.0 (0.7)	2.4 (0.9)	0.0008
FVC % predicted	54.3 (16.7)	64.5 (18.8)	0.0002
DLco (mL/mm Hg/min)	7.5 (3.5)	9.7 (4.3)	<0.0001
DLco % predicted	31.1 (13.4)	42.1 (18.7)	<0.0001
Room air SpO ₂ (%)	90.8 (4.7)	92.8 (4.9)	0.007
MPAP (mm Hg)	26.1 (8.9)	27.5 (10.8) [§]	0.44

^{*} Age and gender available in all 322 patients; race available in 320 of 322; forced vital capacity (FVC, absolute and % predicted) available in 304 of 322; diffusing capacity (DLco, absolute and % predicted) available in 293 of 322; Resting room air pulse oximetry (SpO₂ %) available in 266 of 322; mean pulmonary artery pressure (MPAP) available in 121 of 322; SD = standard deviation.

[§] These 56 patients had RHC data but were excluded because their RHC were not performed within one month of the HRCT.

^{**} Includes Asian and African-American.

Table 2
Patient Characteristics Based on the Presence or Absence of PH by RHC

Characteristic	Mean (SD) or %	Mean (SD) or %	P-value
	MPAP ≤ 25 (n=38)	MPAP > 25 (n=27)	
Age (years)	65.8 (7.3)	67.9 (9.1)	0.31
Males (%)	60	40	1.00
Race (%)			1.00
Caucasian	79	78	
Hispanic**	16	18	
Other	5	4	
BSA	1.9 (0.2)	1.9 (0.3)	0.60
CT-fib	2.3 (0.6)	2.4 (0.7)	0.80
mCT-fib	2.9 (0.7)	2.9 (0.8)	0.81
wCT-fib	2.4 (0.6)	2.4 (0.7)	0.94
CT-alv	1.7 (0.9)	1.9 (1.0)	0.60
wCT-alv	1.7 (1.0)	1.9 (1.0)	0.50
CT-hc	1.3 (0.4)	1.3 (0.4)	0.80
wCT-hc	1.4 (0.5)	1.4 (0.5)	0.70
CT-tot	5.2 (1.6)	5.5 (1.6)	0.31
wCT-tot	5.5 (1.7)	5.8 (1.5)	0.37
AD (mm)	32.0 (2.6)	32.1 (2.4)	0.71
MPAD (mm)	31.3 (3.7)	33.1 (2.4)	0.19
MPAD/AD	0.98 (0.1)	1.03 (0.1)	0.10
MPAD/BSA	16.8 (2.6)	17.5 (2.7)	0.40
FVC (L)	1.9 (0.6)	2.0 (0.8)	0.81
FVC % predicted	52.3 (14.4)	57.1 (19.7)	0.61
DLco (mL/mm Hg/min)	8.0 (3.4)	6.5 (3.6)	0.06
DLco % predicted	33.5 (13.9)	27.0 (11.7)	0.04
FVC%/DLco%	1.8 (0.8)	2.5 (1.6)	0.04
DLco/VA % predicted	59.4	48.8	0.10
SpO ₂ (%)	93.3 (2.9)	87.4 (4.6)	<.0001
6MWD (m)	229 (163)	61 (30)	0.04
MPAP (mm Hg)	20.5 (3.1)	33.9 (8.6)	<.0001

AD = CT-measured ascending aorta diameter, BSA = body surface area, CT-fib = CT-determined fibrosis score, CT-alv = CT-determined ground-glass score, CT-hc = CT-determined honeycomb score, CT-tot = total profusion score (CT-fib + CT-alv + CT-hc), FVC = forced vital capacity, DLco = diffusing capacity, MPAD = CT-measured main pulmonary artery diameter, mCT-fib = maximum CT-derived fibrosis score over all lobes, MPAP = mean pulmonary artery pressure, SpO₂ = resting room air pulse oximetry, wCT-fib = weighted CT-determined fibrosis score, wCT-alv = weighted CT-determined ground-glass score, wCT-hc = weighted CT-determined honeycomb score, wCT-tot = weighted total profusion score, VA = alveolar volume, 6MWD = six-minute walk distance while breathing room air.

** Includes Asian and African-American. SD = standard deviation.

Table 3

Pearson correlation coefficients between the mean pulmonary artery pressure (MPAP) and putative predictors of pulmonary hypertension (PH)

Variable	n	r	P-value**
CT-fib	65	0.042	0.74
wCT-fib	65	0.022	0.86
mCT-fib	54	0.004	0.97
CT-alv	65	0.153	0.22
wCT-alv	65	0.171	0.17
CT-hc	65	0.009	0.94
wCT-hc	65	0.025	0.84
CT-tot	65	0.009	0.38
wCT-tot	65	0.119	0.34
MPAD (mm)	65	0.148	0.24
MPAD/AD	65	0.203	0.10
MPAD/BSA	63	0.136	0.29
FVC (L)	64	0.150	0.23
FVC % predicted	64	0.235	0.10
DLco (mL/mm Hg/min)	59	-0.295	0.02
DLco % predicted	59	-0.307	0.02
DLco/VA % predicted	52	-0.408	0.003
FVC%/DLco%	59	0.435	0.0006
SpO ₂ (%)	59	-0.527	<0.0001
6MWD (m)	17	-0.569	0.002

AD = CT-measured ascending aorta diameter, BSA = body surface area, CT-fib = CT-determined fibrosis score, CT-alv = CT-determined ground-glass score, CT-hc = CT-determined honeycomb score, CT-tot = total profusion score (CT-fib + CT-alv + CT-hc), FVC = forced vital capacity, DLco = diffusing capacity, mCT-fib = maximum CT-derived fibrosis score over all lobes, MPAD = CT-measured main pulmonary artery diameter, MPAP = mean pulmonary artery pressure, SpO₂ = resting room air pulse oximetry, wCT-fib = weighted CT-determined fibrosis score, wCT-alv = weighted CT-determined ground-glass score, wCT-hc = weighted CT-determined honeycomb score, wCT-tot = weighted CT-determined total profusion score, VA = alveolar volume, 6MWD = six-minute walk distance while breathing room air.

**
p value for test of zero correlation