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Pulmonary Artery Enlargement is Associated with RV Dysfunction and Loss of Blood Volume in Small Pulmonary Vessels in Chronic Obstructive Pulmonary Disease

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Abstract

Background—COPD causes significant morbidity and concomitant pulmonary vascular disease and cardiac dysfunction are associated with poor prognosis. CT-detected relative pulmonary artery enlargement defined as a pulmonary artery to ascending aorta diameter ratio greater than one (PA:A>1) is a marker for pulmonary hypertension and predicts COPD exacerbations. However, little is known about the relationship between the PA:A ratio, pulmonary blood volume, and cardiac function.

Methods and Results—A single-center prospective cohort study of COPD patients was conducted. Clinical characteristics and CT metrics, including the PA:A and pulmonary blood vessel volume were measured. Ventricular functions, volumes, and dimensions were measured by cine cardiac magnetic resonance imaging (cMRI) with 3D analysis. Linear regression examined

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Disclosures

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the relationships between clinical characteristics, CT and cMRI metrics, and 6-minute walk distance (6MWD). Twenty four patients were evaluated and those with PA:A>1 had higher right ventricular (RV) end-diastolic and end-systolic volume indices accompanied by lower RV ejection fraction (EF) (52±7% vs 60±9%, p=0.04). The PA:A correlated inversely with total intraparenchymal pulmonary blood vessel volume and the volume of distal vessels with a cross sectional area of <5 mm^2. Lower forced expiratory volume, PA:A>1, and hyperinflation correlated with reduced RVEF. Both PA diameter and reduced RVEF were independently associated with reduced 6MWD.

Conclusions—The loss of blood volume in distal pulmonary vessels is associated with PA enlargement on CT. CMRI detects early RV dysfunction and remodeling in non-severe COPD patients with a PA:A>1. Both RV dysfunction and PA enlargement are independently associated with reduced walk distance.

Keywords

cardiac MRI; CT; pulmonary hypertension; pulmonary heart disease; smoking; COPD

Chronic Obstructive Pulmonary Disease (COPD) causes significant morbidity and is a complex disease characterized by airflow limitation, inflammation, and vascular changes.[1-4] Functional decline is often associated with concomitant pulmonary hypertension (PH) and right ventricular (RV) dysfunction[2, 5-10]. Cardiac magnetic resonance imaging (cMRI) is the gold standard for the assessment of both the morphological and functional characteristics of the RV particularly in patients with COPD in whom echocardiographic assessment is often not possible[11-14]. Furthermore, cMRI has been used to demonstrate a relationship between progressive airflow obstruction and computed tomography (CT)-detected emphysema and impaired left ventricular (LV) filling, stroke volume (SV), and RV hypertrophy[15-20].

CT-measured relative pulmonary artery enlargement defined by a pulmonary artery (PA) to ascending aorta (A) diameter ratio greater than one (PA:A>1) aids in predicting COPD exacerbations in moderate-to-severe COPD and is a strong predictor of PH in those with severe disease.[1, 2] However, even in severe COPD, relative PA enlargement is only partially explained by overt pulmonary hypertension[2] and other factors may play a role including hyperinflation due to emphysema, reduced cross sectional area of small pulmonary blood vessels, and cardiac dysfunction[2, 3]. In addition, little is known about the relationship between the PA:A ratio and cardiac structure and function in mild-to-moderate COPD. We hypothesized that PA enlargement (PA:A>1) is associated with distal pruning of small pulmonary blood vessels and that these vascular derangements would have direct impact on right ventricular structure and function as detected by cMRI as well as with reduced exercise tolerance.

Methods

The University of Alabama at Birmingham (UAB) is one of the 21 participating clinical centers for the COPDGene trial[21], a multi-center, longitudinal cohort designed to evaluate the underlying genetic factors, clinical information, and radiologic data for patients with COPD. UAB recruited 405 of the 10,500 subjects enrolled in the parent trial. From these

subjects, 129 met inclusion criteria. 44 participants were contacted for enrollment in the current prospective cohort to evaluate the relationship between pulmonary vascular disease, cardiac MRI, and COPD in subjects without known cardiac or pulmonary vascular disease. Subjects with a FEV1/FVC ratio >0.7, known ischemic heart disease, congestive heart failure, structural heart disease (including intra-cardiac shunts), pulmonary hypertension, prior thromboembolic disease, cerebrovascular disease, peripheral arterial disease, known malignancy, or inability to undergo MRI were excluded (Supplemental Figure). Baseline demographic information, pulmonary function testing (PFT)[22, 23], and six-minute walk distance (6MWD) were collected[24]. All subjects underwent CT and cMRI at our institution. The study was approved by the UAB Institutional Review Board at UAB (X110809004) and all subjects gave informed consent. The parent study, COPDGene (ClinicalTrials.gov identifier # NCT00608764) was approved by the IRB at all institutions.

CT measurement of the PA:A ratio, cross sectional area of the pulmonary vessels, percent emphysema, and percent gas trapping

One reviewer blinded to cMRI and baseline data measured the PA and A ratios at the bifurcation of the pulmonary artery using Philips iSite Enterprise Software (Koninklijke Philips N.V.) as previously detailed (**Figure 1A-B**)[1, 2]. Separate blinded investigators measured cross sectional area of the pulmonary vessels using volumetric chest CT scans performed at maximal inflation.[3] Briefly, Airway Inspector (www.AirwayInspector.org) was used to measure emphysema and perform lung lobe segmentation[25, 26]. With in-house software we segmented the pulmonary vasculature from the parenchyma and assessed total blood vessel volume (TBV) in the combined intraparenchymal pulmonary arteries and veins and aggregate blood vessel volume in vessels less than 5 mm^2 in cross-section (BV5) for the whole lung using previously reported derivation equations[27]. Full methods of this technique are included in the data supplement. Vessels that have a cross sectional area of less than 100 mm (approximately 5 mm radius) are used in calculating TBV. These vessels are measured after the first or second branch point of the pulmonary arteries/veins and for most of their length are intraparenchymal. Most of the volume comes from vessels distal to these, and they do not contribute significantly to the measurement of TBV. We calculated the ratio of BV5 to TBV to account for inherent anatomic variability in blood vessel volumes with height as previously described (**Figure 1C-D**)[3]. The loss of blood vessel volume represents both vascular destruction as well as vasoconstriction. Analysis of the lung parenchyma and airways was performed on volumetric CT scans of the chest obtained without the administration of contrast material. Parenchymal analysis was performed with the use of the Slicer software package (www.Slicer.org), and airway analysis was performed with the use of Volumetric Information Display and Analysis (VIDA) Pulmonary Workstation 2 software (www.vidadiagnostics.com). Emphysema was defined by a CT attenuation value of less than −950 Hounsfield units on inspiratory scans obtained at maximal inspiration (total lung capacity, TLC) and gas trapping was defined by a CT attenuation of less than −856 Hounsfield units on expiratory scans obtained at end-tidal expiration (functional residual capacity, FRC). Inspiratory capacity (IC) was defined as the difference between TLC and FRC.

Measurement of cardiac function and dimensions by cMRI

All subjects underwent a 1.5 T scanner (Signa CV/i, GE Healthcare, Milwaukee, WI, USA) using a phased array cardiac coil. Prospective electrocardiographic triggering with retrospective gating was used. Steady state free precession (SSFP) technique that provides maximal contrast between the myocardium and the blood pool was used in all cases. Typical imaging parameters were field of view 36–44 cm, flip angle of 35–45 degrees, matrix size 256 in frequency domain and 128–256 in the phase domain, relaxation time (TR) of 3.7–4.1 ms, and echo time (TE) 1.5–1.7 ms. All studies had horizontal long-axis (HLA) cine views that were obtained in the usual manner. The end-diastolic HLA image provided the reference from which a stack of contiguous short axis slices of 8 mm thickness and 0 mm gap were obtained. LV and RV ejection fraction (EF), end-diastolic (ED) and end-systolic (ES) volume indices (VI), ED and ES mass indices (MI), stroke volume (SV), and remodeling indices (RI) were measured as previously reported[28].

Statistical Analysis

We expressed baseline data as means with standard deviation (SD) for normally distributed values or median with interquartile range for non-normally distributed values and compared continuous variables using two-sided Student *t* tests or Mann-Whitney U tests as appropriate. We used the Shapiro-Wilk test to determine normality for continuous variables. We examined categorical variables by Fisher exact test. Subjects were grouped based on the presence or absence of a PA:A ratio >1 given the clinical importance of PA enlargement and severe COPD exacerbations[1]. Pearson correlation coefficients were calculated to determine the associations between CT metrics, measurements of cardiac function by cMRI, and 6MWD. We used SPSS for Windows Version 20 for all analyses. Statistical tests were two-sided, and significance was assigned to tests with P values < 0.05.

Results

Baseline characteristics

Twenty four patients underwent cMRI and CT scans and their mean age was 60±8 years with 14 (58%) non-Hispanic white and 16 (67%) male participants (**Table 1**). The subjects studied did not differ significantly from those who were not contacted with respect to demographic characteristics and lung function. The average post-bronchodilator forced expiratory volume in 1 second (FEV_1) was 57±27 percent predicted. Patients were separated into cohorts based on the presence or absence of a PA:A ratio >1 on CT scan, with 17 patients having a PA:A≤1 and 7 a PA:A>1 . The PA:A>1 group had higher BMI (33±6 kg/m^2 vs 27±6 kg/m^2, P=0.03) and body surface area (2.15±0.20 m^2 vs 1.93±0.19 m^2, P=0.02) as we previously reported in the parent study[1]. Those with a PA:A>1 had higher resting heart rate (93±12 versus 77±12, p=0.02) without any differences in blood pressure. Subjects in the PA:A>1 group had lower FVC (72±14% vs 89±18%predicted, P=0.04), but otherwise had no statistical differences on pulmonary function testing. Both the PA:A≤1 and PA:A>1 groups had comparable gas trapping and emphysema by CT.

Loss of blood volume in small intraparenchymal vessels

The PA:A>1 group had lower BV5 (130.3±21.9 mL vs 150.7±25.1 mL, *P*=0.07) and TBV (253.7±55.9 mL vs 273.8±54.7 mL, *P*=0.43) compared to those with PA:A≤1, though these differences did not reach statistical significance. Furthermore, as seen in **Figure 2**, the PA:A ratio correlated inversely with BV5 (r=−0.48, p=0.017) and TBV (r=−0.37, p=0.07) and, but not BV5/TBV (r=−0.13, p=0.54). The BV5/TBV was also inversely correlated with RVESVI (r=−0.45, p=0.03) and RVMI (r=−0.39, p=0.05) and trended towards correlation with RVEF (r=0.34, p=0.10) without associations with stroke volume index or CI. The BV5/TLC was correlated with the RVEF (r=0.59, p=0.006) and trended towards significance with LVEF (r=0.39, p=0.09) suggesting both the volume of blood in these small vessels and lung hyperinflation impact ventricular function. The BV5/TBV was not associated with LV volume indices or function. Neither the BV5 nor the TBV was individually associated with cardiac changes on cMRI.

Ventricular dimensions on cMRI

As seen in **Table 2**, LVEDVI (59±11 vs 54±11 mL/m^2, *p*=0.39), LVESVI (22±7 vs 20±7 g/m^2, p=0.42), LVMI (45±11 vs 41±10 g/m^2, p=0.40), LVSVI (37±6 vs 35±8 mL/m^2, *p*=0.50), and LVEF (63±6 vs 64±8%, p=0.71) were not statistically different between subjects with a PA:A>1 or a PA:A≤1. However, a number of significant differences in RV physiology were found. The PA:A>1 group had higher volume indices [RVEDVI (65±17 vs 54±11 mL/m^2, p=0.05) and RVESVI (32±12 vs 21±5 mL/m^2, *P*=0.003)] without differences in RVSVI (33±7 vs 33±7 mL/m^2, *p*=0.95). In addition, in contrast to findings about LV function, subjects with a PA:A>1 had lower RVEF (52±7 vs 60±9%, *P*=0.03). There were no differences in RVRI between groups. There was a trend towards higher RVMI in the PA:A>1 group (15.2±6 vs 12.7±2.4 g/m^2, p=0.17). Standardization for BMI does not change these overall associations (Supplemental Table).

Correlations between cMRI findings and traditional markers of COPD severity

Gas trapping was inversely related to LVEDVI (r=−0.60, *P*=0.008), LVSV (r=−0.66, *P*=0.003), and RVSV (r=−0.64, *P*=0.005) (**Table 3**). Similarly, hyperinflation, defined by IC/TLC ratio, was associated with reduced LVEDVI (r=0.57, *P*=0.02), LVSV (0.47, *P*=0.05), and RVEDVI (r=0.52, *P*=0.03). Percent emphysema was associated with reduced LVSV (r=−0.49, *P*=0.02) and showed a trend toward reduced LVEDVI (r=−0.42, *P*=0.06) without effect on RV parameters. FEV_1, percent emphysema, percent gas trapping, and hyperinflation were not associated with changes in LVEF. However, FEV_1 (r=0.47, *P*=0.02), percent gas trapping (r=−0.48, *P*=0.045), and hyperinflation (r=0.56, *P*=0.02) were associated with RVEF. .

Associations between cardiac function, the PA:A ratio, and exercise capacity

Pearson's correlation analysis was used to identify factors linearly correlated to 6MWD (**Table 4**). The PA:A ratio was inversely related to 6MWD (r=−0.49, *P*=0.02). This was driven primarily by increases in PA diameter (r=−0.58, *P*=0.003), as the A diameter was not associated with 6MWD (r=−0.22, *P*=0.31). RVEF, unlike LVEF, was associated with 6MWD (r=0.47, *P*=0.02).

Discussion

This study combines state-of-the-art CT imaging techniques with cardiac MRI to identify early pulmonary vascular disease and right ventricular dysfunction in COPD patients with only moderate airflow obstruction. We found that in this population without known underlying cardiovascular or pulmonary vascular disease, an elevated PA:A ratio occurs often and directly correlates with increases in RV volume indices and early RV dysfunction. Further, this relative PA enlargement is associated with the loss of blood volume in small pulmonary vessels on CT likely due to a redistribution and centralization of pulmonary blood flow. This early evidence of vascular remodeling and RV dysfunction precedes the development of overt pulmonary hypertension and *cor pulmonale* but both changes are independently predictive of poor exercise capacity. Our results also provide a pathophysiologic basis to explain the inability of patients with PA enlargement to compensate for the metabolic demands that occur during an acute exacerbation, resulting in greater risk of hospitalization.[1]

Our study focuses on well characterized COPD patients and shows correlations between the PA:A>1 on CT with distal small pulmonary vessel pruning and impaired RV function by cMRI, which have been linked with poor outcomes[29, 30] Both BV5 and TBV were lower in the PA:A>1 group, and both were inversely associated with the absolute PA:A ratio. The BV5/TBV ratio was not significantly associated with the PA:A ratio which may be due to the relatively small sample size or from mathematical coupling between the two measures. The BV5/TBV ratio was inversely correlated with RVMI and RVESVI, suggesting that loss of blood volume in vessels with a CSA of $<5mm^2$ has a direct impact on RV mass and volumes. These novel findings are the first to implicate the loss of blood volume in intraparenchymal vasculature with cardiac function.

As we have previously showed, patients with PA:A>1 had higher BMI and BSA, which could explain higher RV and LV filling volumes through a compensatory mechanism in response to increased blood volume from obesity.[1, 31] We excluded those with baseline congestive heart failure thus limiting the likelihood that intrinsic LV or RV dysfunction confounds our results. Furthermore, we found no significant differences in LVEF or LV dimensions between subjects with PA enlargement which is in contrast to changes seen in the RV. Increases in RVEDV have been implicated in patients with COPD and *cor pulmonale*[32] and likely result from increases in pulmonary vascular resistance. Recently, Grau et al described an inverse relationship between percent emphysema and RV size on cMRI[19]. While we did not make the same observations, there were considerable differences between populations and our sample size was insufficient to draw similar conclusions. Our findings represent an important association between subjects with COPD and the RV given the more severe airflow obstruction and extensive smoking history in our cohort. While SVRI values were the not statistically different between the PA:A <1 and PA:A >1 groups, this is in fact an early indication of a failing ventricle, as evidenced by the reduced RVEF, and the increase in RVMI, while not statistically significant, suggests RV hypertrophy is occurring. Our findings support the existing literature suggesting that LV systolic function is usually preserved in patients with COPD while RV dysfunction is more common[7, 33]. The

relatively normal LV function in patients with COPD may be partly explained by flattening of the intraventricular septum allowing compensation for RV hypertrophy.[20]

Subjects with relative PA enlargement had more hyperinflation and reduced cross sectional area of the small pulmonary blood vessels, despite no difference in airflow obstruction or percent emphysema. However, we did find percent emphysema correlated with lower LVEDVI and LVSVI as Barr and colleagues previously reported.[34] The effects of emphysema appear to predominantly affect the LV in contrast to airflow obstruction and hyperinflation, which both impact the LV and RV[19, 35].

These novel findings suggest that the relatively weaker RV may lack the compensatory mechanisms to adequately respond to increased RV filling and places the RV at risk for changes induced by gas trapping and hyperinflation. This is important as hyperinflation is a strong predictor of mortality in this population.[36] The connection between hyperinflation and RV dysfunction could be through changes in pulmonary vasculature and subsequent relative PA enlargement and reduced RVEF as we showed. As Estepar et al posit, hyperinflation and emphysematous destruction of lung tissue cause pathologic changes in pulmonary vasculature including vessel elongation, vasoconstriction, and vascular loss, and this distal pruning of small pulmonary blood vessels correlated with reduced 6MWD.[3]

The most important factors implicated in RV dysfunction were a reduced FEV_1, hyperinflation, and PA enlargement. In turn, both RV dysfunction and PA enlargement are both associated with reduced exercise tolerance. Therapies directed at improving hyperinflation have been shown to have direct impact on 6MWD[37, 38]. In contrast, therapies specifically targeting COPD related-pulmonary hypertension have not been beneficial and in some cases have worsened outcomes[39-41]. This highlights the pathophysiologic impact of PH and RV dysfunction in COPD and the need to discover new therapeutic pathways to target this process.

Our study is limited by its small sample size and single center experience, though we did demonstrate strong correlations between clinical outcomes, CT-metrics, and cMRI-measured ventricular dimensions and function. Our CT measures cannot precisely define the extent of plexiform arteriopathy, smooth muscle proliferation, and vasoconstriction, all pathologic features that contribute to the development of PH. Correlations between these findings and BV5 would require lung biopsy however, the loss of blood volume captured this BV5 metric represents an attractive imaging biomarker for the detection of pulmonary vascular disease. It is also possible that BV5 would be impacted by changes in preload though this would require additional studies in patients with cardiac dysfunction who we specifically excluded from the present analysis. Additional studies with larger sample sizes are needed to more definitively define the complex relationships between emphysema, pulmonary vascular disease and cardiac dysfunction in patients with COPD. This is made more challenging by the cost of cMRI and by the time required for a cMRI session which can be difficult for patients with severe lung disease who may struggle with breath holding. Finally, we did not observe correlations between BV5 and TBV with 6MWD. This may be due in part to the small sample size of the population or that the signal was obscured by the contribution from PA size.

In conclusion, pulmonary vascular disease in the setting of COPD is a complex process. The BV5 and the PA:A ratio are promising imaging biomarkers that can aid in differentiating different disease phenotypes rather than supplanting histopathologic observations. The novel CT metrics and use of cMRI have utility in relating small and large vessel remodeling to cardiac dysfunction and functional outcomes in patients with moderate to severe COPD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Wells JM, Washko GR, Han MK, Abbas N, Nath H, Mamary AJ, Regan E, Bailey WC, Martinez FJ, Westfall E, Beaty TH, Curran-Everett D, Curtis JL, Hokanson JE, Lynch DA, Make BJ, Crapo JD, Silverman EK, Bowler RP, Dransfield MT. Pulmonary arterial enlargement and acute exacerbations of copd. N Engl J Med. 2012; 367:913–921. [PubMed: 22938715]
2. Iyer AS, Wells JM, Vishin S, Bhatt SP, Wille KM, Dransfield MT. Ct scan-measured pulmonary artery to aorta ratio and echocardiography for detecting pulmonary hypertension in severe copd. Chest. 2014; 145:824–832. [PubMed: 24114440]
3. Estepar RS, Kinney GL, Black-Shinn JL, Bowler RP, Kindlmann GL, Ross JC, Kikinis R, Han MK, Come CE, Diaz AA, Cho MH, Hersh CP, Schroeder JD, Reilly JJ, Lynch DA, Crapo JD, Wells JM, Dransfield MT, Hokanson JE, Washko GR. Computed tomographic measures of pulmonary vascular morphology in smokers and their clinical implications. Am J Respir Crit Care Med. 2013; 188:231–239. [PubMed: 23656466]
4. Petty TL. Scope of the copd problem in north america: Early studies of prevalence and nhanes iii data: Basis for early identification and intervention. Chest. 2000; 117:326S–331S. [PubMed: 10843971]
5. Stone AC, Machan JT, Mazer J, Casserly B, Klinger JR. Echocardiographic evidence of pulmonary hypertension is associated with increased 1-year mortality in patients admitted with chronic obstructive pulmonary disease. Lung. 2011; 189:207–212. [PubMed: 21556789]
6. Gologanu D, Stanescu C, Ursica T, Balea MI, Ionita D, Bogdan MA. Prevalence and characteristics of pulmonary hypertension associated with copd - a pilot study in patients referred to a pulmonary rehabilitation program clinic. Maedica (Buchar). 2013; 8:243–248. [PubMed: 24371492]
7. Hilde JM, Skjorten I, Grotta OJ, Hansteen V, Melsom MN, Hisdal J, Humerfelt S, Steine K. Right ventricular dysfunction and remodeling in chronic obstructive pulmonary disease without pulmonary hypertension. J Am Coll Cardiol. 2013; 62:1103–1111. [PubMed: 23831444]
8. Tayyareci Y, Tayyareci G, Tastan CP, Bayazit P, Nisanci Y. Early diagnosis of right ventricular systolic dysfunction by tissue doppler-derived isovolumic myocardial acceleration in patients with chronic obstructive pulmonary disease. Echocardiography. 2009; 26:1026–1035. [PubMed: 19840069]

9. Freixa X, Portillo K, Pare C, Garcia-Aymerich J, Gomez FP, Benet M, Roca J, Farrero E, Ferrer J, Fernandez-Palomeque C, Anto JM, Barbera JA. Echocardiographic abnormalities in patients with copd at their first hospital admission. Eur Respir J. 2013; 41:784–791. [PubMed: 23018914]
10. Gupta NK, Agrawal RK, Srivastav AB, Ved ML. Echocardiographic evaluation of heart in chronic obstructive pulmonary disease patient and its co-relation with the severity of disease. Lung India. 2011; 28:105–109. [PubMed: 21712919]
11. McLure LE, Peacock AJ. Cardiac magnetic resonance imaging for the assessment of the heart and pulmonary circulation in pulmonary hypertension. Eur Respir J. 2009; 33:1454–1466. [PubMed: 19483048]
12. Vonk-Noordegraaf A, Souza R. Cardiac magnetic resonance imaging: What can it add to our knowledge of the right ventricle in pulmonary arterial hypertension? Am J Cardiol. 2012; 110:25S–31S. [PubMed: 22921028]
13. Lorenz CH, Walker ES, Morgan VL, Klein SS, Graham TP Jr. Normal human right and left ventricular mass, systolic function, and gender differences by cine magnetic resonance imaging. J Cardiovasc Magn Reson. 1999; 1:7–21. [PubMed: 11550343]
14. Grapsa J, O'Regan DP, Pavlopoulos H, Durighel G, Dawson D, Nihoyannopoulos P. Right ventricular remodelling in pulmonary arterial hypertension with three-dimensional echocardiography: Comparison with cardiac magnetic resonance imaging. Eur J Echocardiogr. 2010; 11:64–73. [PubMed: 19939819]
15. Sharma B, Neilan TG, Kwong RY, Mandry D, Owens RL, McSharry D, Bakker JP, Malhotra A. Evaluation of right ventricular remodeling using cardiac magnetic resonance imaging in co-existent chronic obstructive pulmonary disease and obstructive sleep apnea. Copd. 2013; 10:4–10. [PubMed: 23272670]
16. Sanz J, Kariisa M, Dellegrottaglie S, Prat-Gonzalez S, Garcia MJ, Fuster V, Rajagopalan S. Evaluation of pulmonary artery stiffness in pulmonary hypertension with cardiac magnetic resonance. JACC Cardiovasc Imaging. 2009; 2:286–295. [PubMed: 19356573]
17. Vonk-Noordegraaf A, Marcus JT, Holverda S, Roseboom B, Postmus PE. Early changes of cardiac structure and function in copd patients with mild hypoxemia. Chest. 2005; 127:1898–1903. [PubMed: 15947300]
18. Gao Y, Du X, Qin W, Li K. Assessment of the right ventricular function in patients with chronic obstructive pulmonary disease using mri. Acta Radiol. 2011; 52:711–715. [PubMed: 21852436]
19. Grau M, Barr RG, Lima JA, Hoffman EA, Bluemke DA, Carr JJ, Chahal H, Enright PL, Jain A, Prince MR, Kawut SM. Percent emphysema and right ventricular structure and function: The multi-ethnic study of atherosclerosis-lung and multi-ethnic study of atherosclerosis-right ventricle studies. Chest. 2013; 144:136–144. [PubMed: 23450302]
20. Vonk Noordegraaf A, Marcus JT, Roseboom B, Postmus PE, Faes TJ, de Vries PM. The effect of right ventricular hypertrophy on left ventricular ejection fraction in pulmonary emphysema. Chest. 1997; 112:640–645. [PubMed: 9315795]
21. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, Curran-Everett D, Silverman EK, Crapo JD. Genetic epidemiology of copd (copdgene) study design. COPD. 2010; 7:32–43. [PubMed: 20214461]
22. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general u.S. Population. Am J Respir Crit Care Med. 1999; 159:179–187. [PubMed: 9872837]
23. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. Standardisation of spirometry. Eur Respir J. 2005; 26:319–338. [PubMed: 16055882]
24. Laboratories ATSCoPSfCPF. Ats statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002; 166:111–117. [PubMed: 12091180]
25. Kindlmann GL, San Jose Estepar R, Smith SM, Westin CF. Sampling and visualizing creases with scale-space particles. IEEE transactions on visualization and computer graphics. 2009; 15:1415–1424. [PubMed: 19834216]
26. Ross JC, San Jose Estepar R, Kindlmann G, Diaz A, Westin CF, Silverman EK, Washko GR. Automatic lung lobe segmentation using particles, thin plate splines, and maximum a posteriori

estimation. Medical image computing and computer-assisted intervention : MICCAI … International Conference on Medical Image Computing and Computer-Assisted Intervention. 2010; 13:163–171.

27. Estepar, RS.; Ross, JC.; Krissian, K.; Schultz, T.; Washko, GR.; Kindlmann, GL. Computational vascular morphometry for the assessment of pulmonary vascular disease based on scale-space particles. Proceedings / IEEE International Symposium on Biomedical Imaging: from nano to macro. IEEE International Symposium on Biomedical Imaging; 2012. p. 1479-1482.
28. Drake D, Gupta R, Lloyd SG, Gupta H. Right ventricular function assessment: Comparison of geometric and visual method to short-axis slice summation method. Echocardiography. 2007; 24:1013–1019. [PubMed: 18001352]
29. Rajaram S, Swift AJ, Capener D, Elliot CA, Condliffe R, Davies C, Hill C, Hurdman J, Kidling R, Akil M, Wild JM, Kiely DG. Comparison of the diagnostic utility of cardiac magnetic resonance imaging, computed tomography, and echocardiography in assessment of suspected pulmonary arterial hypertension in patients with connective tissue disease. J Rheumatol. 2012; 39:1265–1274. [PubMed: 22589263]
30. Akcay M, Yeter E, Durmaz T, Keles T, Akar Bayram N, Uyar M, Davutoglu V, Yuksel I, Kurt M, Bozkurt E. Treatment of acute chronic obstructive pulmonary disease exacerbation improves right ventricle function. Eur J Echocardiogr. 2010; 11:530–536. [PubMed: 20223750]
31. Rider OJ, Petersen SE, Francis JM, Ali MK, Hudsmith LE, Robinson MR, Clarke K, Neubauer S. Ventricular hypertrophy and cavity dilatation in relation to body mass index in women with uncomplicated obesity. Heart. 2011; 97:203–208. [PubMed: 20483890]
32. Gao Y, Du X, Liang L, Cao L, Yang Q, Li K. Evaluation of right ventricular function by 64-row ct in patients with chronic obstructive pulmonary disease and cor pulmonale. European journal of radiology. 2012; 81:345–353. [PubMed: 21112711]
33. Suchon E, Tracz W, Podolec P, Pieculewicz M, Plazak W, Prokop A, Nalepa P. [evaluation of left ventricular function in patients with chronic obstructive pulmonary disease]. Pol Arch Med Wewn. 2007; 117:26–30. [PubMed: 17718049]
34. Barr RG, Bluemke DA, Ahmed FS, Carr JJ, Enright PL, Hoffman EA, Jiang R, Kawut SM, Kronmal RA, Lima JA, Shahar E, Smith LJ, Watson KE. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med. 2010; 362:217–227. [PubMed: 20089972]
35. Jorgensen K, Muller MF, Nel J, Upton RN, Houltz E, Ricksten SE. Reduced intrathoracic blood volume and left and right ventricular dimensions in patients with severe emphysema: An mri study. Chest. 2007; 131:1050–1057. [PubMed: 17426209]
36. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, Celli BR. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005; 171:591–597. [PubMed: 15591470]
37. Cordova F, O'Brien G, Furukawa S, Kuzma AM, Travaline J, Criner GJ. Stability of improvements in exercise performance and quality of life following bilateral lung volume reduction surgery in severe copd. Chest. 1997; 112:907–915. [PubMed: 9377952]
38. Maltais F, Hamilton A, Marciniuk D, Hernandez P, Sciurba FC, Richter K, Kesten S, O'Donnell D. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with copd. Chest. 2005; 128:1168–1178. [PubMed: 16162703]
39. Goudie AR, Lipworth BJ, Hopkinson PJ, Wei L, Struthers AD. Tadalafil in patients with chronic obstructive pulmonary disease: A randomised, double-blind, parallel-group, placebo-controlled trial. The lancet. Respiratory medicine. 2014; 2:293–300. [PubMed: 24717626]
40. Blanco I, Santos S, Gea J, Guell R, Torres F, Gimeno-Santos E, Rodriguez DA, Vilaro J, Gomez B, Roca J, Barbera JA. Sildenafil to improve respiratory rehabilitation outcomes in copd: A controlled trial. Eur Respir J. 2013; 42:982–992. [PubMed: 23429918]
41. Boeck L, Tamm M, Grendelmeier P, Stolz D. Acute effects of aerosolized iloprost in copd related pulmonary hypertension - a randomized controlled crossover trial. PloS one. 2012; 7:e52248. [PubMed: 23300624]

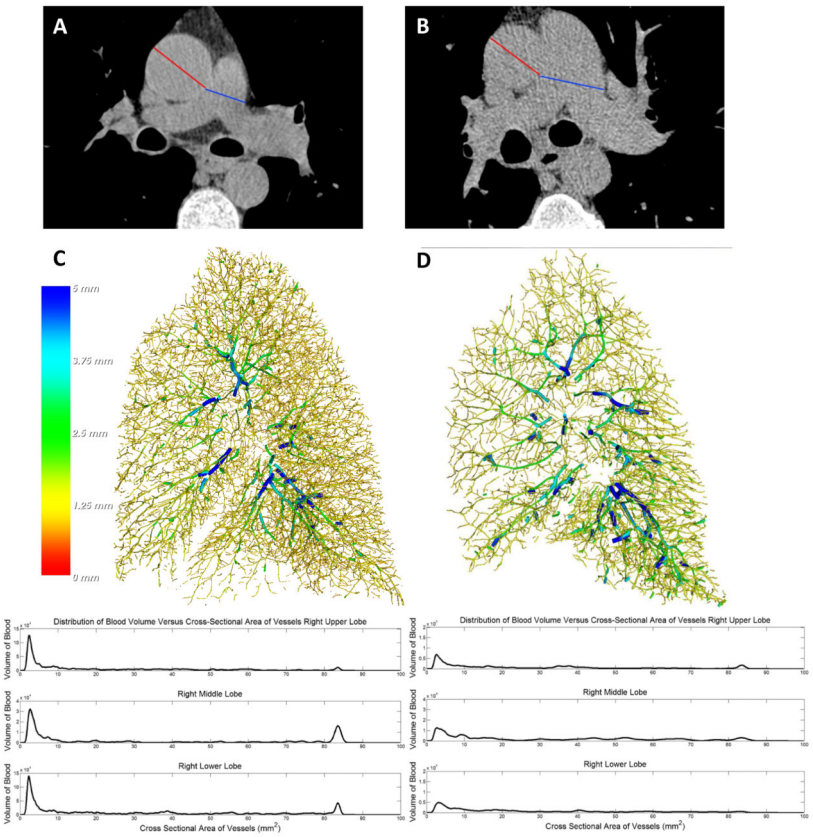

Figure 1.

Pulmonary artery (PA) enlargement is related to loss of blood volume in small intraparenchymal vessels. **Panels A and C** are representative images from a patient with a PA:A ratio <1 and minimal loss of blood volume in small intraparenchymal blood vessels. **Panels B and D** are images taken from a patient with a PA:A ratio >1 and extensive pruning of the small intraparenchymal vasculature. **Panels A and B** are axial images of the PA and ascending aorta (A) taken at the level of the PA bifurcation. **Panels C and D** are image reconstructions of the intra-pulmonary blood volume (BV5/TBV).

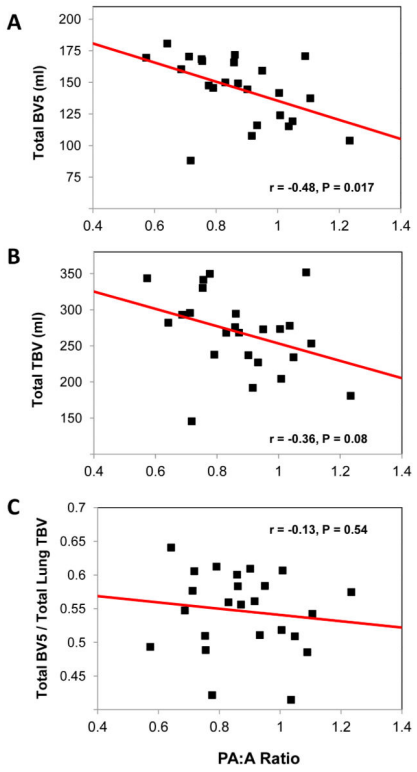

Figure 2.

Correlation between PA:A and BV5, TBV and BV5/TBV. PA:A = pulmonary artery diameter to aortic diameter ratio; TBV = Total intraparenchymal blood vessel volume; BV5 = Pulmonary blood volume in vessels with cross sectional area < 5 mm^2

Table 1

Baseline Characteristics

Variable	Entire Cohort (n=24)	PA:A<1 (n=17)	PA:A>1 (n=7)	*P* Value
Age, years	59±9	61±10	60±6	**0.84**
Caucasian race	14 (58%)	11 (65%)	3 (43%)	0.35
Male gender	16 (67%)	12 (71%)	4 (57%)	0.55
BMI, kg/m^2	29±8	27±8	33±6	**0.03**
BSA, m^2	1.99±0.22	1.93±0.19	2.15±0.20	**0.02**
Systolic BP, mmHg	126 [31]	130 [30]	119 [41]	0.45
Diastolic BP, mmHg	73 [17]	74 [18]	72 [16]	0.57
Heart rate, beats/min	76±14	77±12	93±12	**0.02**
FEV$_1$, % predicted	57±27	62±28	45±22	0.17
FVC, % predicted	80±22	89±18	72±14	**0.04**
FEV$_1$:FVC ratio	0.52±0.16	0.52±0.18	0.47±0.17	0.57
IC:TLC ratio	0.27±0.16	0.32±0.16	0.24±0.08	0.24
% emphysema	8.4 [27.2]	7.2 [31.6]	13.6 [25.5]	0.73
% gas trapping	44±23	46±25	46±24	0.99
Subsegmental wall area (%)	65.2±3.4	65.3±3.7	65.1±4.5	0.94
PA diameter, cm	2.80±0.59	2.52±0.30	3.48±0.55	**<0.001**
A diameter, cm	3.21±0.39	3.19±0.33	3.25±0.54	0.75
TBV, mL	268.0±54.6	273.8±54.7	253.7±55.8	0.43
BV5, mL	144.7±25.6	150.7±25.1	130.3±21.9	0.07
BV5/TBV ratio	0.57±0.06	0.56±0.06	0.52±0.06	0.18

Data are presented as n (%), mean (±SD), or median [interquartile range]. BMI = body mass index; BSA = body surface area; PA = Pulmonary artery; A = Aorta; FEV$_1$ = Forced expiratory volume in 1 second; FVC = Forced vital capacity; IC = Inspiratory capacity; TLC = Total lung capacity; ft = feet; cm = centimeters; PA = Pulmonary artery; A = Aorta; TBV = Total intraparenchymal blood vessel volume; BV5 = Pulmonary blood vessel volume in vessels less than 5 mm^2

Table 2

Comparison of right and left ventricular measurements by cMRI

	PA:A<1 (n=17)	PA:A>1 (n=7)	*P* Value
Left Ventricle			
LVEDVI, ml/m^2	54±11	59±12	0.39
LVESVI, ml/m^2	20±7	22±7	0.42
LVMI, g/m^2	41±10	45±11	0.39
LVSVI, ml/m^2	35±8	37±6	0.50
LVRI, g/ml	0.78±0.21	0.78±0.12	0.96
LVEF, %	64±8	63±6	0.71
Right Ventricle			
RVEDVI, ml/m^2	54±11	65±17	**0.05**
RVESVI, ml/m^2	21±5	32±12	**0.003**
RVMI, g/m^2	12.7±2.4	15.2±6.0	0.17
RVSVI, ml/m^2	33±10	33±7	0.95
RVRI, g/ml	0.24±0.05	0.23±0.04	0.55
RVEF, %	60±9	52±7	**0.03**

Data expressed as mean (±SD). LV = Left ventricle; RV = Right ventricle; ED = End diastolic; ES = End systolic; VI = volume index; SVI = Stroke volume index; VI = Volume index; EF = Ejection fraction; MI = Mass index; RI = Remodeling index

Table 3

Univariate correlations between cMRI measurements and COPD metrics

Variable	FEV_1	Percent Emphysema	Percent Gas Trapping	IC/TLC
LVEDVI, ml/m^2	**0.47 (0.02)**	−0.42 (0.06)	**−0.60 (0.008)**	**0.57 (0.02)**
LVSVI, ml/m^2	**0.45 (0.03)**	**−0.46 (0.04)**	**−0.60 (0.008)**	**0.56 (0.02)**
LVEF, %	−0.03 (0.89)	−0.15 (0.52)	−0.05 (0.83)	0.01 (0.99)
RVEDVI, ml/m^2	0.17 (0.43)	−0.24 (0.30)	−0.39 (0.11)	**0.23 (0.37)**
RVSVI, ml/m^2	**0.44 (0.03)**	−0.37 (0.10)	**0.58 (0.01)**	**0.57 (0.02)**
RVEF, %	**0.47 (0.02)**	−0.36 (0.11)	**−0.48 (0.05)**	**0.56 (0.02)**

Data expressed as Pearson's r *(P* value). LV = Left ventricle; RV = Right ventricle; ED = End diastolic; VI = Volume index; SV = Stroke volume; EF = Ejection fraction; FEV_1 = Forced expiratory volume in 1 second; IC = Inspiratory capacity; TLC = Total lung capacity; PA = pulmonary artery; A=aorta

Table 4

Linear correlations between baseline characteristics and 6MWD

Variable	6MWD, ft
Heart rate, beats per minute	−0.41 (0.12)
A diameter by CT scan, cm	−0.22 (0.31)
PA diameter by CT scan, cm	**−0.58 (0.003)**
PA:A ratio	**−0.49 (0.02)**
LVEF	0.12 (0.59)
RVEF	**0.47 (0.02)**
BV5	−0.02 (0.91)
TBV	0.02 (0.91)
BV5/TBV	0.24 (0.27)
FEV1 (%)	**0.57 (0.004)**
IC/TLC	**0.52 (0.03)**
% **Emphysema**	−0.21 (0.37)

Data expressed as r *(P* value). FEVi = Forced expiratory volume in 1 second; 6MWD = 6 minute walk distance, feet; IC = Inspiratory capacity; TLC = Total lung capacity LV = Left ventricle; RV = Right ventricle; EF = Ejection fraction; PA = Pulmonary artery; A = Aorta; TBV = Total intraparenchymal blood vessel volume; BV5 = Pulmonary blood vessel volume in vessels less than 5 mm^2