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Arterial and venous pulmonary vascular morphology and their relationship to findings in cardiac MRI in smokers

Farbod. N. Rahaghi, M.D. Ph.D.^{1,*}, J. Michael Wells, M.D.^{2,3,4}, Carolyn E. Come, M.D.¹, I. de La Bruere¹, Surya Bhatt, M.D.^{2,3}, James C. Ross, Ph.D.⁵, Gonzalo Vegas-Sánchez-Ferrero, Ph.D.⁵, Alejandro A. Diaz, M.D.¹, Jasleen Minhas, M.D.¹, Mark T. Dransfield, M.D.^{2,3,4}, Raul San José Estépar, Ph.D.⁵, George R. Washko, M.D.¹, and the COPDGene Investigators

¹Brigham and Women's Hospital, Pulmonary and Critical Care Division of Department of Medicine 75 Francis Street, PBB – CA 3 Boston, MA 02115

²Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL 35294

³UAB Lung Health Center, University of Alabama at Birmingham, Birmingham, AL 35294

⁴Birmingham VA Medical Center, AL 35233

⁵Department of Radiology Harvard School of Medicine Surgical Planning Laboratory, 1249 Boylston Street, 2nd Floor, Room 216, Boston, MA 02215

Abstract

Objective—Prior work has described the relationship between pulmonary vascular pruning on CT scan and metrics of right heart dysfunction in smokers. In this analysis we sought to look at pruning on a lobar level as well as examine the effect of the arterial and venous circulation on this association.

Methods—Automated vessel segmentation applied to non-contrast CT scans from the COPDGene study in 24 subjects with cardiac MRIs was used to create a blood volume distribution profile. These vessels were then manually tracked to their origin and characterized as artery or vein.

Results—Assessment of pruning on a lobar level revealed associations between pruning and right ventricular function previously not observed on a global level. The right ventricular mass index (RVMI), the right ventricular end systolic volume index (RVESVI) and pulmonary arterial to aorta ratio (PA/A) were associated with both arterial and venous pruning, whereas right ventricular ejection fraction was associated with only arterial pruning.

Conclusions—Lobar assessment as well as segmentation of the parenchymal vasculature into arterial and venous component provide additional information about the relationship between loss of vasculature on CT scans and right ventricular dysfunction.

*To whom correspondence should be addressed: Brigham and Women's Hospital, Pulmonary and Critical Care Division of Department of Medicine, 75 Francis Street, PBB – CA 3, Boston, MA 02115, frahaghi@partners.org.

Keywords

Pulmonary vascular; emphysema; chronic obstructive pulmonary disease; cardiac magnetic resonance imaging; arterial; venous; computed tomography; 3D reconstruction

Introduction

It is estimated that 30–70% of patients with chronic obstructive pulmonary disease (COPD) have clinically significant pulmonary vascular disease (PVD)(4, 5, 9, 18). While these estimates are broad, it is increasingly clear that PVD is a clinically relevant feature of COPD in smokers. Its presence is associated with increased healthcare resource utilization, is an independent predictor of mortality, and has been implicated as being part of the causal pathway of disease development (12, 23) (3, 10, 11, 24)

The gold standard for detection of pulmonary vascular disease remains invasive right heart catheterization(18). These techniques, however, are impractical for clinical studies involving large cohorts of subjects. Because of this, non-invasive techniques such as computed tomographic (CT) and magnetic resonance (MR) imaging are increasingly being leveraged to provide metrics of pulmonary vascular morphology(19)

Previously we have reported that distal pruning of the intraparenchymal macrovasculature was an independent predictor of clinical measures of disease severity in smokers (15, 16). Those with a reduced ratio of small blood vessel volume to total intraparenchymal blood vessel volume had reduced lung function, shorter distance walked in 6 minutes, poorer health status, and increased dyspnea(7).

Recently we demonstrated that MRI based measures of cardiac function were related to quantitative assessments of the diameter of the main pulmonary artery and aorta(22) . We further began to explore the relationship of cardiac function with intraparenchymal vascular morphology using a metrics of small vessel density (volume of blood vessels less than 5mm² in cross sectional area divided by total lung volume:) and small vessel volume fraction (of blood vessels less than 5mm² in cross sectional area divided by total intraparenchymal blood vessel volume). These measures were variably associated with right and left ventricular volume and function(22) but these analyses did not selectively examine the effects of the changes in the parenchymal arterial and venous tree. Such additional data could provide further insight into symmetric or asymmetric involvement of arterial and venous vascular beds in lung disease resulting from chronic tobacco smoke exposure.

To explore potential differences in the arterial and venous macrovascular pulmonary circulation we performed an objective assessment of arterial and venous vascular morphology in 24 COPD Gene subjects, each with volumetric CT scans and corresponding cardiac MRI data. With these data we could examine the distributions of blood vessel volume as well as correlations with right ventricular function.

Materials and Methods

The COPDGene Study is a multi-center study focused on understanding the epidemiologic and genetic associations of COPD in smokers(20). Participants underwent detailed clinical characterization including inspiratory and expiratory CT scans of the chest and spirometric measures of lung function before and after the administration of short acting bronchodilating medications(1, 2). Subjects with active lung diseases other than COPD and asthma were excluded from participation.

As described previously, 24 subjects free of a documented history of pulmonary vascular or cardiac disease underwent cardiac MRI at a single center(22). Images were obtained using a 1.5 T scanner (Signa CV/i, GE Healthcare, Milwaukee, WI) with a phased array cardiac coil and prospective electrocardiographic triggering with retrospective gating. Steady-state-free precession 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 to 44 cm, flip angle of 35 to 45 degrees, matrix size 256 in frequency domain and 128 to 256 in the phase domain, relaxation time of 3.7 to 4.1 ms, and echo time 1.5 to 1.7 msec. All studies had horizontal long-axis cine views that were obtained in the usual manner. The end-diastolic (ED) horizontal long-axis image provided the reference from which a stack of contiguous short-axis slices of 8-mm thickness and 0-mm gap was obtained. LV and RV ejection fraction (EF), ED and end-systolic (ES) volume indices (VI), ED and ES mass indices (MI), stroke volume (SV) were measured(6).

Standardized volumetric CT scans of the chest were acquired at full inspiration following the COPDGene Study imaging protocol with 120 kVp, 200 mAs, and 0.5 rotation time. The PA:A ratio was measured at the bifurcation of the PA using Philips iSite Enterprise Software (Koninklijke Philips N.V.). The lungs and lobes were segmented and a 3 dimensional reconstruction of the intraparenchymal vasculature was generated as described previously(7, 8, 13, 21).

Following visual inspection of these 3D reconstructions, blood vessel volume was reported as a function of vascular cross sectional area. The specific measures of interest included the blood vessel volume for vessels less than 5mm^2 in cross section (BV5), and the total blood vessel volume (TBV). Prior investigation suggested that distal measures of blood vessel volume (i.e. BV5) tends to assess vascular pruning while larger cutoffs in CSA (i.e. $\text{BV} > 5\text{mm}^2$) tends to assess more proximal vascular morphology(15–17). The BV measures were then divided by TBV of that lobe as a means of normalizing the metrics across the cohort, a value which we will refer to as the **small vessel fraction**.

The minimum spanning tree model was used to separate each vessel segment from the vascular tree(14). Hilar vasculature was labeled as being artery or vein by tracing their origin to the main pulmonary artery and central pulmonary veins. From these anatomically labeled vascular trunks the distal vasculature was labeled as artery or vein (A/V segmented) based upon the origin of their feeding vessels. All labeling was performed by a single operator and vessel morphology was calculated for the right upper (RUL) and right lower lobe (RLL) of all subjects. A small vessel fraction was calculated for both the arterial and venous

component of the circulation. A/V ratio for both the small and large vessel fractions consisted of dividing the arterial volume in that fraction by the venous volume in each individual lobe.

All statistical analyses were performed using SAS 9.3 (SAS institute, Cary, North Carolina). Continuous variables are presented as means and standard deviations for the purposes of demographic information. For the purpose of evaluating correlations, a non-parametric approach, the spearman correlation was used. P values of less than 0.05 were considered significant. The study was approved by the University of Alabama at Birmingham Institutional Review Board at University of Alabama at Birmingham (X110809004) and all subjects gave informed consent. The parent study, COPDGene (ClinicalTrials.gov identifier # NCT00608764) was approved by the institutional review board at all institutions

Results

Demographic and functional data of the 24 subjects are provided in Table 1. The mean age was 59 ± 9 years, the mean FEV1 was $57 \pm 27\%$ with 2/3 of the cohort being male. The pulmonary vasculature was successfully reconstructed and segmented by lobe and arterial/venous vascular bed in all subjects. Examples of this 3D reconstruction are provided in Figure 1 with the corresponding arterial/venous segmentation in Figure 2.

RVMI and RVESVI were both also negatively correlated with the small vessel fraction in both lobes, with the same relationship present in both arterial and venous component of the pulmonary circulation in both lobes (Table 2). The PA/A was similarly negatively correlated with the small vessel fraction, however the degree to which this was dependent on the arterial versus the venous circulation was lobe dependent. In the RUL, PA/A was negatively correlated with the Arterial small vessel fraction ($R = -0.46$, $p = 0.02$), whereas the venous association did not reach statistical significance ($R = -0.26$, $p = 0.22$). Conversely, for the RLL, the association with the arterial small vessel fraction missed statistical significance ($R = -0.39$, $p = 0.06$) whereas the correlation with the venous small vessel fraction was present ($R = -0.53$, $p = 0.008$). The RV ejection fraction correlated directly with the small vessel fraction in both lobes, but the correlation was confined to the arterial small vessel fraction (RUL $R = 0.58$, $p = 0.003$; RLL $R = 0.54$, $p = 0.007$).

The small vessel fraction can be affected by both loss of distal vasculature and increase in the size of proximal vasculature. To examine the source of the asymmetry in the arterial and venous components of the association of vessel volume with RVEF, we examined the A/V ratios for both small vessels and large vessels. There was a decrease in the RVEF associated with increase A/V ratio in the large vessels (RUL $R = -0.40$, $p = 0.05$; RLL $R = -0.47$, $p = 0.02$), whereas there was an increase in RVEF associated with increase in the A/V ratios in the smaller vessels in the RUL only ($R = 0.66$, $p = 0.006$).

Discussion

Previously, we had reported the associations between small vessel volume fraction and markers of right ventricular dysfunction in the right lung showing that the smaller the fraction of the volume in small vessels ($<5\text{mm}^2$ in cross sectional area), the more evidence

of RV dysfunction. In this investigation, we examined these findings in two distinct lobes, the right upper lobe and the right lower lobe and found that these relationships were present in both locations, and in some cases the association reached statistical significance where it had not with the (right lung/whole lung) data. This was the case with PA/A as well as RVEF where the association between the small vessel fraction (termed BV5/TBV in prior references) and these metrics did not reach statistical significance. This suggests that lobar examination of these measures may provide additional information and that combining these findings across lobes may be reducing the robustness of vascular volume ratios, which may have lobe specific ranges.

We then proceeded to manually segment the vascular trees into arterial and venous branches. Two of the measures, the RVMl and RVEDVI were related to the small vessel fraction in both the arterial and venous component of the circulation. For the PA/A, the statistical significance of the arterial or venous relationships were dependent on the lobe. In contrast, the relationship between small vessel fraction and RVEF appears driven by the arterial small vessel fraction. In the case of RVEF, there was an inverse relationship with increasing arterial large vessel fraction, suggesting that right ventricular function decreases with increases arterial as compared to venous engorgement.

The process of loss of distal vasculature in smokers is thought to be a complex interplay of arterial remodeling, loss of parenchyma, hypoxemic vasoconstriction and compression due to hyperinflation, with each of these having variable impact likely due to the specific subject's genetic and environmental variables. The small vessel fraction provides an index normalized for each subject that represents this "pruning". These results suggest that pruning of both the arterial and venous phases seem to have an association with pulmonary vascular disease, although the results may not symmetric for every marker and the underlying physiological pathway may be different.

The ratio of the PA to A is a commonly employed radiologic indicator for the presence of pulmonary vascular disease (23). The PA trunk is a high capacitance vessel and as pulmonary arterial vascular resistance increases, the central vessels tend to dilate. In the prior right lung analysis, the relationship between small vessel fraction and PA/A was not detected, but the lobe specific measurements presented here suggest that a similar phenomenon may be observed within the parenchymal pulmonary vasculature and that increases in PA/A may be linked to loss of distal blood vessel volume. Pruning of the distal intraparenchymal vasculature was associated with dilation and hypertrophy of the RV (as indicated by increases in the RVESVI and RVMl) with reductions in ejection fraction, suggesting that loss of macrovascular blood vessel volume is of hemodynamic consequence and that this process can be objectively assessed by CT scan. While conjecture about causality must be tempered in small cross-sectional studies, it is possible that these hemodynamic effects are potentially mediated by the increase in pulmonary vascular resistance resulting from loss of cross sectional area of flow through the mechanisms mentioned above.

Both arterial and venous pruning negatively affect RVMl and RVESVI, suggesting that the effects that pruning of both arterial and venous systems may serve as biomarkers of vascular

disease. In contrast, RVEF was related only the arterial pruning. To examine this relationship closer, we calculated the A/V ratios for the small and larger vessels. The A/V ratio provides a subject normalized marker for relative dilation of the arteries as compared to the veins. These results showed that RVEF decreases with increasing arterial to venous volume in the large vessel. This suggests that proximal dilation of the arteries in the parenchyma (as normalized by the volume in the veins) provides another potential hemodynamically relevant marker of pulmonary vascular disease. Furthermore, it may be that the relationship between RVEF and arterial small vessel fraction is mediated in part by increase in the total blood volume in the arterial phase due to proximal dilation. The relationship between RVEF and small vessel A/V was equivocal.

These lobe specific arterial and venous measures of blood vessel morphology cannot absolutely confirm or refute the presence of differential remodeling of the arterial vs venous vascular trees in smokers. While the general trend in correlations with the cardiac MR data suggest that the changes in arterial morphology may be of greater hemodynamic relevance, further work in a larger cohort of smokers is required.

There are several limitations to this investigation including the size and nature of the study. This was a cross sectional examination of data from 24 smokers from the COPDGene Study who underwent cardiac MRI at a single center. As is the nature of all observational studies, there is inherent bias in the study cohort where only those well enough to participate contribute data to the investigation. Further, the small size of the cohort precludes more definitive statements about the associations observed. Many of the relationships that were explored approached but did not reach statistical significance. The regionality of these associations or lack of associations should not be overstated given the small sample size. Future examination in a larger cohort may convincingly demonstrate that these associations are uniform in the RUL and RLL. A further constraint to the CT based assessment of pulmonary vascular morphology is its limits of resolution. The signal processing methods employed in this investigation cannot assess the more distal macro vasculature or microvascular remodeling. Finally, the intra-parenchymal vascular tree is a complex branching structure and our current methods of quantitative analysis do not provide data by generation. It is entirely possible that a 5th generation vessel of the RLL is comparable to a 4th generation vessel of the RUL. This limitation is only partially addressed through the quantitative assessment of common bins of vascular cross sectional area (i.e. $<5\text{mm}^2$). Creation of generation specific vascular measures is the subject of future investigation.

In this paper we examined the small vessel fraction as a function of arterial, venous and lobar circulation in the lung, as well as the Arterial to Venous ratios of the blood volumes for large vessels. These measures capture two phenomenon that have been previously described: the loss distal vasculature (presumably due to compression or loss of parenchyma) and proximal dilation of vessels (previous work was confined to the main pulmonary artery). These results suggest that lobar examination of the segmented intraparenchymal vasculature can provide additional imaging based biomarkers of pulmonary vascular disease in smokers and should continue to be explored as a feature of interest in clinical, epidemiologic, and genetic investigation.

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Figure 1.

Two examples of 3D intraparenchymal vascular reconstruction in the right upper Lobe. Color indicates vessel diameter. On the Left is a subject with relatively full vascular tree, on the right is a subject showing both distal pruning (loss of the smaller vessels) as well as proximal dilation vessels as compared to the first subject. Below each image is a quantitative representation of the distribution of blood plotted against cross sectional area of the vessels. Note the higher peak in the subject with less pruning and quantitative shift of volume to the larger vessels. The fall between 0–2 mm^2 is due to the resolution limitations of CT scan.

Figure 2.

The arterial and venous segmentation of the two cases shown in figure 1. Blue (deoxygenated) denotes arterial and red (oxygenated) denotes venous blood vessel volumes.

Table 1

Demographic, pulmonary function tests as well as both cardiac MRI and CT based reported markers of pulmonary vascular disease in 24 smokers enrolled in this study.

Variable	Cohort (N = 24)
Demographics	
Age (Years)	59±9
White Race	14 (58%)
Male Sex	16 (67%)
BMI	29±8
6 Minute Walk Distance (ft)	1069±209
Lung Function	
FEV ₁ % predicted	57±27
FEV ₁ :FVC Ratio	0.52±0.16
TLCpp (Race Adjusted, L)	102±14
cMRI Heart Markers	
LVEF (%)	64±8
RVEF (%)	58±10
RVESVI	24±9
RVMI	13±4
CT Based Markers	
PA/A ratio	0.88±0.16

Data represent as n (%) and mean (±SD). BMI, body mass index; BSA, estimated body surface area; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity. TLCpp, Total Lung Capacity, percent predicted; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end systolic volume index; RVMI, right ventricular mass index; PA/A ratio, the ratio of the PA diameter to aortic diameter.

Table 2

Correlations between metrics of evidence of right ventricular dysfunction, PA/A ratio and intraparenchymal both combined and av segmented small vessel volume fractions.

	Un-AV-Segmented Small Vessel Fraction		Arterial Small Vessel Fraction		Venous Small Vessel Fraction	
	RUL	RLL	RUL	RLL	RUL	RLL
RVMI	-0.51 (0.01)	-0.48 (0.02)	-0.41 (0.04)	-0.45 (0.03)	-0.55 (0.006)	-0.46 (0.02)
RVESVI	-0.73 (<0.001)	-0.48 (0.02)	-0.59 (0.002)	-0.70 (0.0002)	-0.65 (0.0006)	-0.45 (0.03)
PA/A	-0.42 (0.04)	-0.48 (0.02)	-0.46 (0.02)	-0.39 (0.06)	-0.26 (0.22)	-0.53 (0.008)
RVEF	0.50(0.01)	0.46 (0.02)	0.58 (0.003)	0.54 (0.007)	0.31 (0.15)	0.14 (0.50)

RVMI: Right Ventricular Mass Index. RVESVI: Right ventricular end diastolic volume index. PA/A: the ratio of the diameter of the pulmonary artery to the aorta. RVEF: The right ventricular ejection fraction.

Table 3

Correlates between A/V fraction in the small and large vessels with RV ejection fraction

	Small Vessel A/V		Large Vessel A/V	
	RUL	RLL	RUL	RLL
RVEF	0.66 (0.006)	0.03 (0.90)	-0.40 (0.05)	-0.47 (0.02)

RVEF = Right Ventricular Ejection Fraction; PTAD = Peak tricuspid annular displacement. Small Vessel A/V is computed by taking the arterial vessel volume in vessels with cross sectional area of less than 5mm^2 and dividing by the venous volume in the same size vessels. Large Vessel A/V is obtained by dividing the arterial vessel volume in vessels with cross-sectional area of greater than 5mm^2 and dividing by the venous volume in the same size vessels. Reported values are Pearson correlation coefficients and associated p-values.