CT Quantification of Morphological Changes in Pulmonary Vasculature in Pulmonary Arterial Hypertension
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I. INTRODUCTION
Pulmonary arterial hypertension (PAH) occurs in idiopathic form and is associated with diseases, such as congenital heart malformation, scleroderma, HIV, and cirrhosis. Severe PAH is rare but has a dismal prognosis. Even contemporary therapy provides only a 75% 3-year survival. In PAH, small and medium arteries are progressively occluded by vascular and inflammatory cells. Although better and more convenient therapies are needed, such therapeutic advances will require a more thorough understanding of vascular remodeling, right ventricular (RV) compensation, and RV failure. The extraction of quantitative morphological features of pulmonary vasculature is important for the diagnosis of progression of PAH and is critical for the assessment of the efficacy of emerging drugs and interventions intended to improve outcomes in animal models and patients. The purpose of this work is to develop automated extraction of pulmonary vascular tree features from 3D-CT images and identify and quantify key biomarkers of disease progression in a rat model.

II. METHODS
We used a seeded region growing method [1,2] to segment the pulmonary vasculature and a fast marching algorithm [3] to extract the morphology of the pulmonary arterial vasculature. A sequence of operations and parameters were empirically derived or created to accomplish the objectives.

- Place a seed point manually in a tree vessel.
- If difference in grayscale intensity between the region mean intensity and neighboring voxels is positive, then add it to region growing.
- View with the least positive difference is labeled as the next seed point and difference is assigned to the variable (β).
- Update the region mean with the average voxel intensity in region growing.
- Exceed max threshold or number of included voxels?
- Segment lung vessels.
- Label seed point at zero distance and mark it as trial.
- Calculate the distance at k neighborhood voxels using the eikonal equation. Label seed point as alive and neighbors as trial.
- Select trial voxel with minimum distance and mark it as a new seed point.
- Check if all segmented voxels are alive.
- Check if all distances were travelled. Check for new branch.
- Calculate metrics of morphology, such as radius, length, branch angle, tortuosity, vascular volume, and spatial fractal dimension (SFD) value varies from -2 for healthy to -1.7 for severe PAH; marker to measure PAH progression.
- Assign branch number to child branch. Check whether the parent branch satisfies branch criteria and save parent to child relationship. Classify each voxel into corresponding branch and determine centerline.
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Figures 1-4 illustrate the methodological sequence of operations and the generated morphological results on a representative 3D volume of the healthy rat hemi-lung before and after segmentation. The images are rendered using the 3D registration software and the 3D rendering software of the computer-aided design software. The registration algorithm was implemented on a virtual phantom, and the results were validated using a virtual phantom from a patient with severe PAH.

III. RESULTS
Figure 1. Images A, B, and C show the 3D rendering of rat pulmonary vasculature. Image D shows extracted morphology in a 2D phantom. Image A shows a representative 3D volume of the healthy rat hemi-lung before segmentation. Image B shows a representative 3D volume of the hemi-lung after segmentation. Image C shows the 3D volume of the diseased hemi-lung. Image D shows the output of our algorithm applied to a 2D phantom, where each branch is given a unique color.

Figure 2. Rendering in 3D of the intermediate steps at every 200k voxels in the morphological extraction of an anthropomorphic phantom dataset [4]. The algorithm is stopped intermittently to mimic the progression of pulmonary vessel occlusion and the loss of vascular volume that is expected going from severe PAH to a normal lung.

Figure 3. Each point represents the mean number of branches in bin size across 4 normal (red curve) and 3 PAH rats (blue curve). In figure A, the smaller and medium-sized vessels ranging from 50-100 um are pruned in large number in PAH rats, as compared to 150-250 um vessels. Figure B shows that a larger number of vessels ranging from 100-1500 um length are affected in PAH.

Figure 4. Histogram of the ratio of branch length over branch radius. Each bar in the graph represents the mean of the ratio of each branch in the bin size of 100 um radius, and the x-axis represents bins of different radii. The ratio of branch length over branch radius is higher for the PAH rat because of the pruning of smaller branches, which causes a decrease in the mean length of the branch. In PAH rats, the ratio of the branches decreases, and the bar shifts to left, thus, there are no branches in the 400-500 um bin.

Table 1. Comparison of different metrics of vessel morphology to distinguish changes in vascular tree size when using different percentage maximal voxel counts in the reconstruction of the vessels from the CT anthropomorphic phantom dataset.

IV. CONCLUSIONS/FUTURE WORK
- Developed and implemented a semi-automated algorithm for extraction of lung vessel morphology and quantification of morphological changes in a PAH rat model using metrics of morphology. The algorithm was developed and tested initially on virtual phantoms and subsequently on X-ray CT scans of an anthropomorphic lung phantom.
- The aim of this work is to minimize human intervention and effort and to better quantify pulmonary vascular morphological changes.
- Future work will include application to patients and animal models at varying stage of disease progression and comparison of disease progression and treatment response in males and females.

V. REFERENCES

VI. ACKNOWLEDGEMENTS
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