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Quantification of the Pulmonary Vascular Response to Inhaled Nitric Oxide Using Non-Contrast CT Imaging

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Advances in Computed Tomographic (CT) image acquisition, reconstruction and post-processing have led to an increasing number of quantitative features that can be used to detect pulmonary vascular disease, stratify severity, define subpopulations with homogeneous characteristics and monitor response to therapeutic intervention[1,2,3]. The goal of this investigation was to develop and examine techniques for the quantification of the pulmonary vascular response to pharmacologic vasodilation using clinically available non-contrast CT imaging. We examined the effect of inhaled nitric oxide (iNO) on the pulmonary arterial and venous vasculature in healthy subjects. Specifically, we examined changes in distal vessel volume in aggregate, and by specific vessel segments. We hypothesized that inhaled nitric oxide would lead to detectable and quantifiable arterial vasodilation on both aggregate and vessel specific analyses.

After obtaining informed consent (IRB# 2011P001880), supine CT scans were obtained in five healthy subjects prior to and while breathing 30ppm iNO and 80% oxygen at relaxed exhalation (Siemens Biograph 64, 160mA, 120 kVp, Convolution Kernel B31f; Total Radiation Exposure ~6.4 mSv). Automated lung segmentation and 3D reconstruction of the vasculature using scale-space particles were performed[1]. The minimum spanning tree was

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used to identify individual vessel segments[2] using a maximum angle of 20 degrees and a maximum gap distance of 2mm. Arterial/venous segmentation was performed using an automated validated Deep Learning approach[4] and validation of the results were performed in three cases by manual tracing of the arteries and veins to the origin. The distribution of vessel volume as a function of cross-sectional area was used to compute the vascular volume in vessels with cross sectional area of less than 5mm^2 (BV5)[1,2] as well as total vessel volume (TBV)

Each image pair was registered by performing an initial alignment of the centers of intensity followed by a three stage sequential scheme: rigid, affine and finally a diffeomorphic Bspline registration[5]. This registration was used to align pre and post iNO arterial and venous vascular trees. The local matching of vessel segments used a combination of subsegment angle and location. Vascular segments present on the iNO but not pre iNO scans were labeled “newly detected”. For matched segments, change in vessel radius was computed and used to color code the vascular reconstructions to create the vascular activity map for each participant.

Examples of CT response and vascular reconstruction is shown in Figure 1(A&B). Overall, there was an increase in both the small vessel volume (BV5: 5.4%±13.5%) and total vessel volume (TBV: 7.2%±7.4%). Arterial and venous trees were labeled in the right lung as shown in Figure 1(C&D). There was an increase in the right lung arterial volumes (aBV5: 12.5%±16.8 Figure 1; aTBV: 12.0%±11.7). The venous volumes showed no average increase in BV5 (vBV5: −0.4%±9.2% Figure 1) and an increase in TBV (vTBV: 3.9%±5.1)

An example of a segment by segment matching is shown in Figure 1(E). In all subjects there were arterial and venous vessels that increased or decreased in diameter. For the distal vasculature (BV5) the ratio of positive to negative change in diameter was uniformly greater than one (ratio: 3.2±1.3 arterial; 1.7±0.3 venous). This ratio was greater for arteries than veins, a difference that reached statistical significance for four subjects (χ^2 test $p \leq 0.001$, ID #4 $p=0.85$ Figure 1). New segments were detected in each subject (754±277 Arterial; 364±90 Venous), and there were more newly detected arterial than venous segments for each subject (ratio: 2.0±0.3).

In this study two complimentary approaches were used to quantify the pulmonary vascular response to iNO. In one approach a volume versus cross-sectional area model was used to quantify the aggregate response of the distal and total vascular volume. This analysis demonstrated that the administration of iNO led to an increase in distal and total vascular volume, an increase that was larger in magnitude and consistency in the arteries. In a segment by segment analysis, a larger number of small vessels increased rather than decreased in diameter, and there was an increase in the number of small vessel segments detected. The extent of this response was once again greater in the arteries. The increase in number of segments likely represents the dilation of vessels that were previously below the threshold of detection.

This study is limited by the number of subjects, lack of control subjects, lack of concurrent hemodynamic measurements and reproducibility of mid-expiratory breath-holds.

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In conclusion, changes in pulmonary vascular caliber and volume in response to inhaled nitric oxide can be detected and spatially quantified using automated methods deployed on clinically available non-contrast CT scans. Future work will examine response in patients with pulmonary vascular disease and relate these markers to other imaging and physiologic markers.. The combination of pulmonary vasodilation as a perturbation and imaging as a window to the physiologic response represents a unique quantitative method to better understand disease phenotypes and potential response to treatment.

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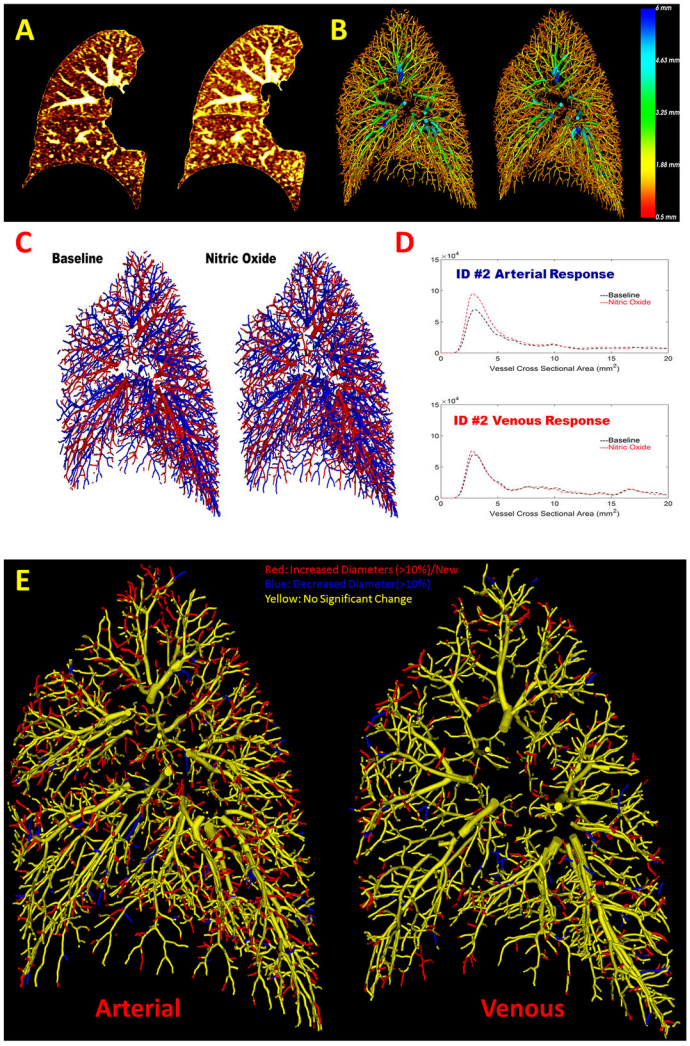

#ID	Pre-Right Arterial BV5	Arterial ΔBV5	Pre-Right Venous BV5	Venous ΔBV5	Arterial +/- Segment Ratio	Venous +/- Segment Ratio	p-value (χ^2) A vs. V
001	34.0ml	+12.6%	22.6ml	-0.5%	3.5	1.5	<0.0001
002	18.0ml	+35.7%	16.5ml	+12.0%	4.3	1.7	<0.0001
003	20.7ml	+8.3%	9.5ml	+4.8%	4.6	2.3	0.001
004	34.7ml	-11.1%	20.2ml	-10.9%	1.5	1.4	0.85
005	41.4ml	+16.8%	28.2ml	-7.3%	2.1	1.6	0.0006

Figure 1:

Two axial cross sections prior to and during the administration of inhaled nitric oxide (iNO) demonstrating increased vascular caliber and parencymal density(A). A 3D vascular reconstruction of the right lung prior to and during iNO with the color of the vessels denoting diameter (red being small vessels) (B). An arterial-venous labeled vascular reconstruction is shown prior to and after iNO administration (C). The accompanying vascular response profile as a function of cross sectional area shows an increase in the arterial volume (D). An arterial and venous vascular activity map in which post iNO vessel segments are matched with the baseline vasculature (E). Red segments represent segments with increase in diameter or newly detected segments whereas blue segments represent those

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with decrease in diameter. The table at the bottom shows measurements of the vasculature for each subject.