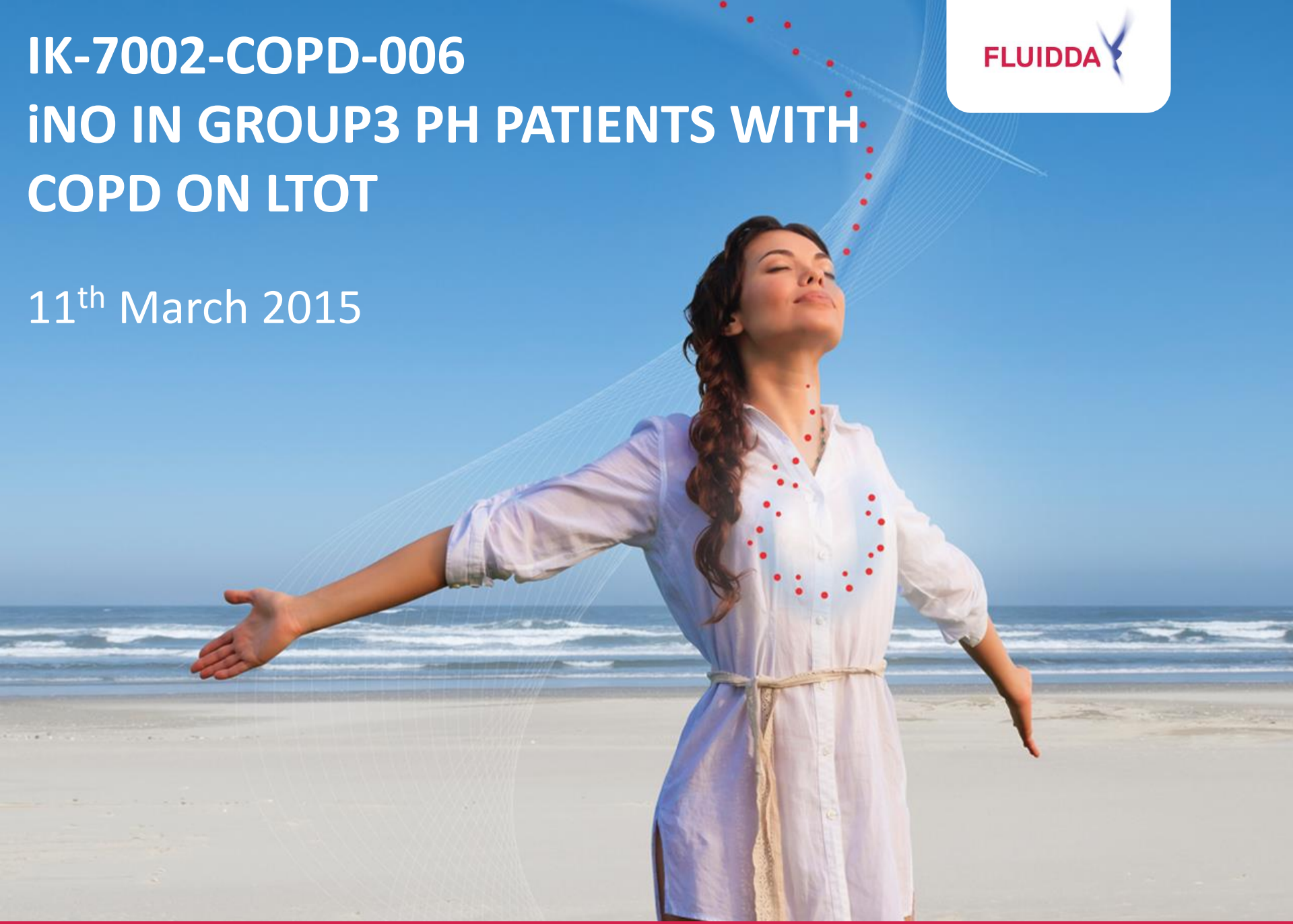
IK-7002-COPD-006
iNO IN GROUP3 PH PATIENTS WITH COPD ON LTOT

11th March 2015



FLUIDDA

STUDY DATA

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STUDY TITLE

An Exploratory, Two-Part, Clinical Study to Assess the Effect of Pulsed, Inhaled Nitric Oxide (iNO) on Functional Pulmonary Imaging Parameters in Subjects with World Health Organization (WHO) Group 3 Pulmonary Hypertension (PH) Associated with Chronic Obstructive Pulmonary Disease (COPD) on Long-Term Oxygen Therapy (LTOT)

STUDY SETUP

- Part 1:

  Acute Treatment, 1 treatment with study drug for at least 20 minutes not to exceed 90 minutes

- Part 2:

  Acute treatment; 2 treatments with study drug – each treatment for at least 20 minutes; each treatment not to exceed 90 minutes

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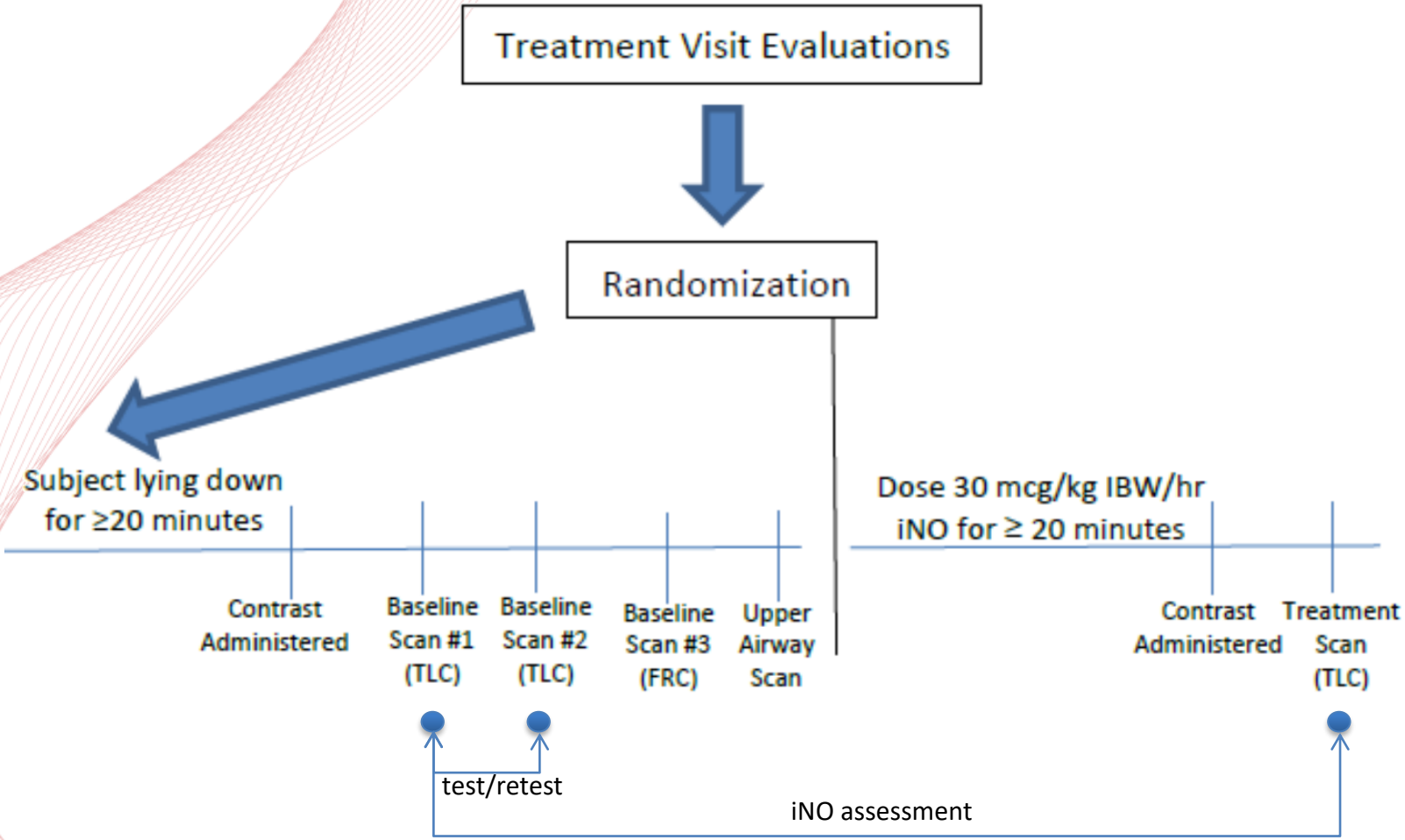
PART 1



Baseline Phase

Room air + LTOT

Treatment Phase

NO + LTOT + Room air

INCLUSION

- 4 patients
  - Patient 1: Female, 67Y, 25.5 pack years, 18 year of LTOT 24h/day
  - Patient 2: Male, 68Y, 90 pack years, LTOT since end 2014 24h/day
  - Patient 3: Female, 76Y, 25.8 pack years, LTOT since mid 2010 16h/day
  - Patient 4: Male, 76Y, 50 pack years, LTOT since 2012 24h/day
  - Patient 5: Male, 68Y, 57.5 pack years, LTOT since 2011 22h/day
  - Patient 6: Female, 79Y, 71.25 pack years, LTOT since 2013 16h/day

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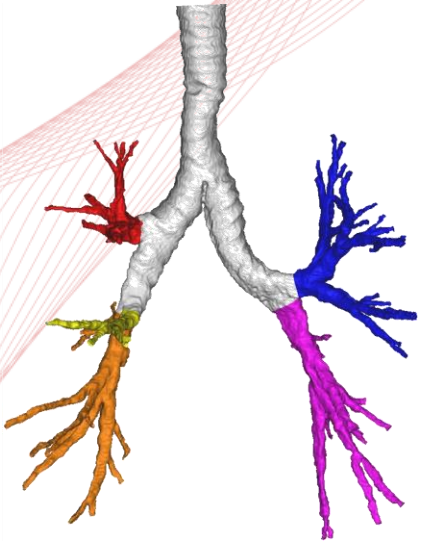
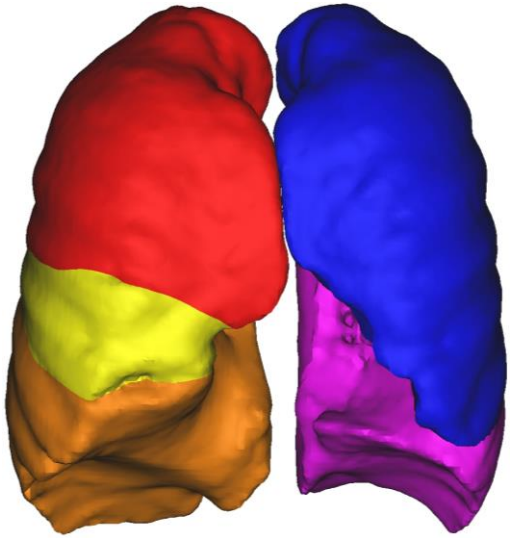
FRI TECHNOLOGY

METHODS

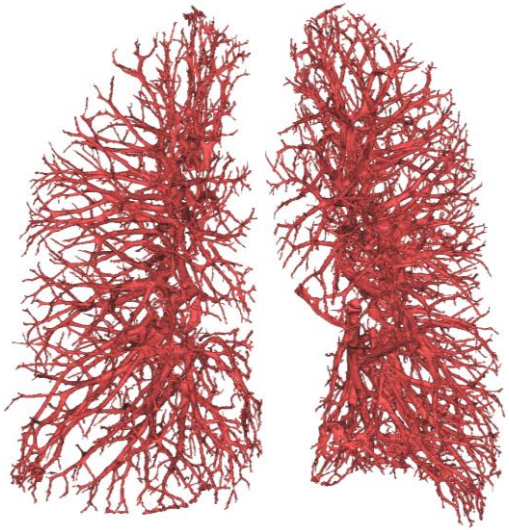
Airway segmentation



Lobe segmentation



Blood vessels segmentation

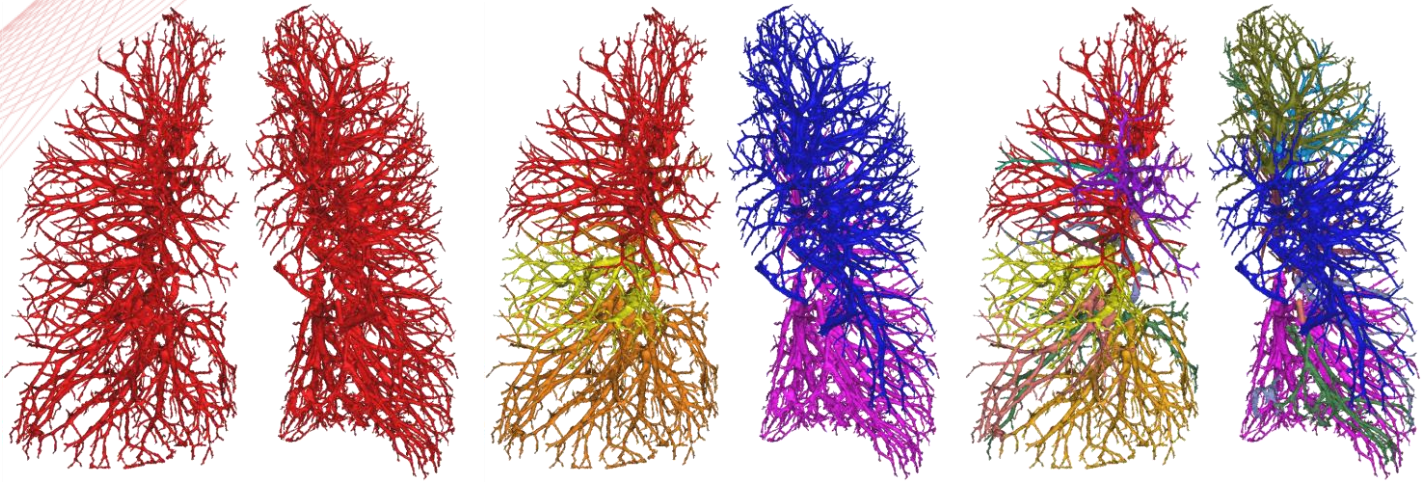


- At baseline: iVaw_baseline, siVaw_baseline, iVaw_retest, siVaw_retest, iVlobeTLC_baseline, iVlobeFRC_baseline, iVlobeTLC_retest, iVbv_baseline, siVbv_baseline, iVbv_retest, siVbv_retest
- After NO: iVaw_post, siVaw_post, iVlobeTLC_post, iVbv_post, siVbv_post

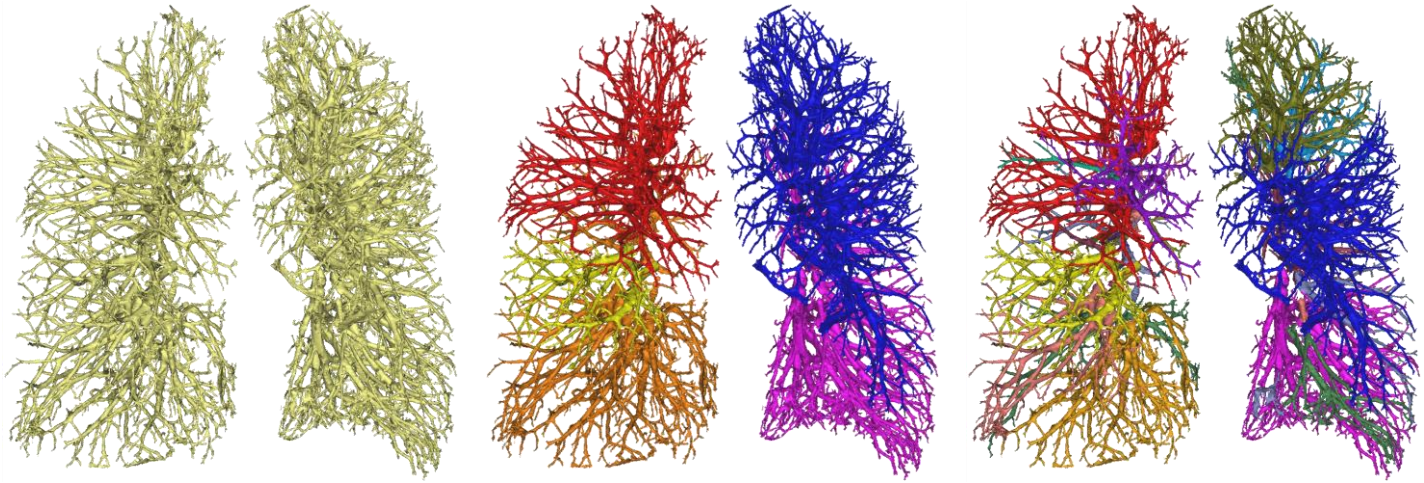
BLOOD VESSELS

The blood vessel volumes can be calculated for the total model, per lobe or per segment for the pre and post models:

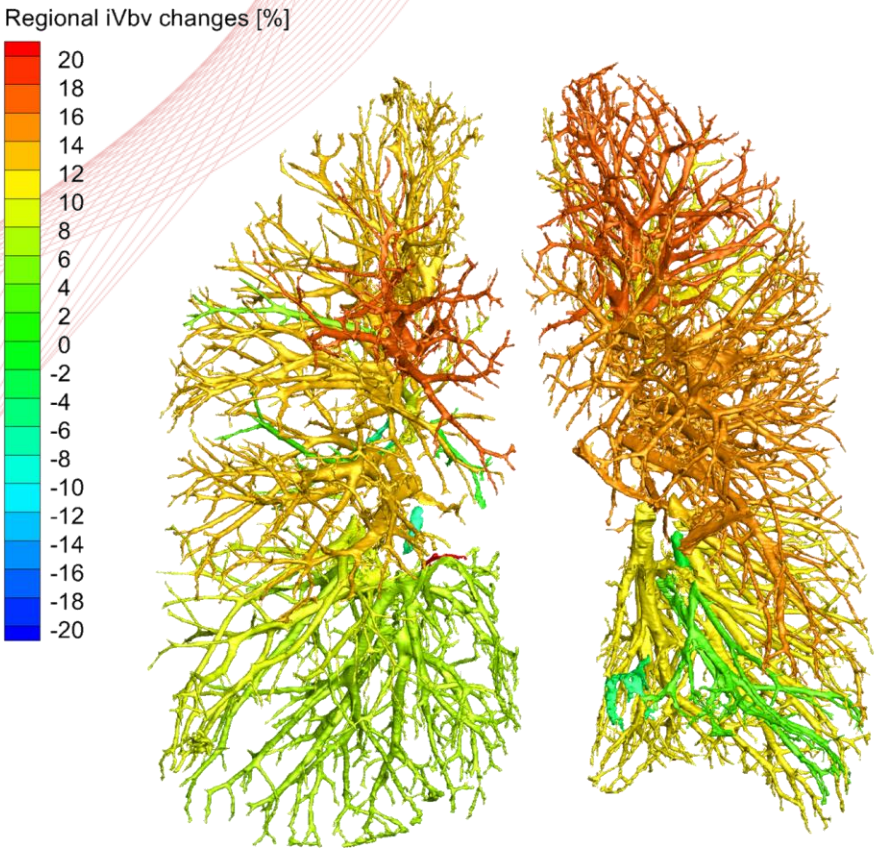
pre



post



BLOOD VESSELS



iVbv changes after 20 min of NO inhalation

	Blood vessel volume		
	pre [mL]	post [mL]	change [%]
RUL	13.867	15.727	13.41
RML	5.694	6.473	13.68
RLL	19.890	21.482	8.00
LUL	26.298	30.219	14.91
LLL	24.885	27.666	11.18

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RESULTS

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VASCULATURE

	Blood vessel volume (mL)		Difference (%)
	Baseline	After NO	
Patient 1	106.48	104.24	-2.1
Patient 2	121.76	139.65	14.7
Patient 3	90.63	101.57	12.1
Patient 4	123.81	129.80	4.8
Patient 5	118.42	125.70	6.2

After iNO

7.14 ± 6.59%

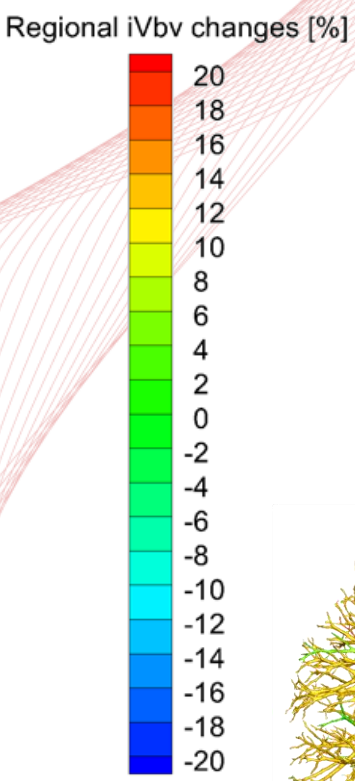
	Blood vessel volume (mL)		Difference (%)
	Baseline	Retest	
Patient 1	100.62	94.00	-6.6
Patient 2	121.88	115.82	-5.0
Patient 3	78.76	80.6	2.3
Patient 4	126.33	127.75	1.1
Patient 5	117.90	118.53	0.5

After test/retest

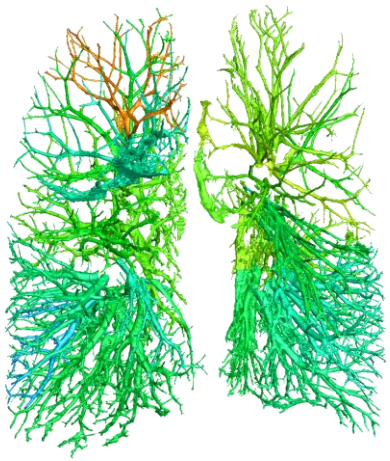
-1.54 ± 3.98%

VASCULATURE

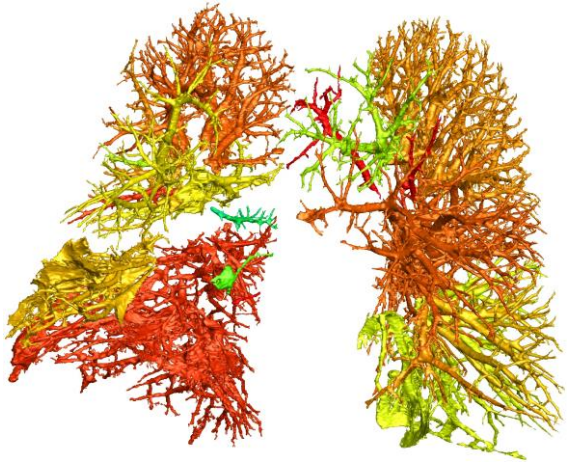
- iVbv changes after 20 min of NO inhalation



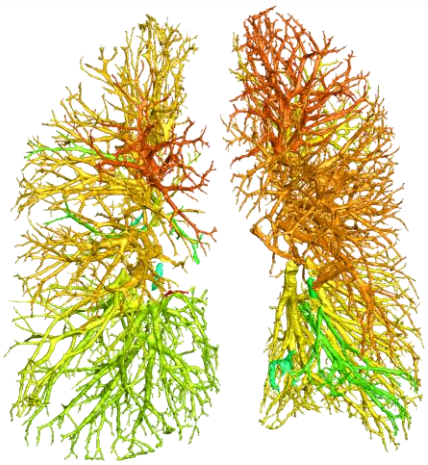
Patient 1



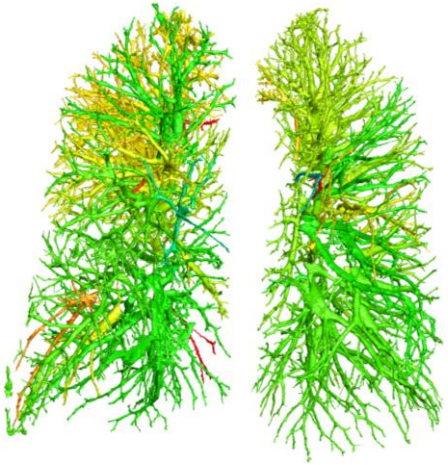
Patient 2



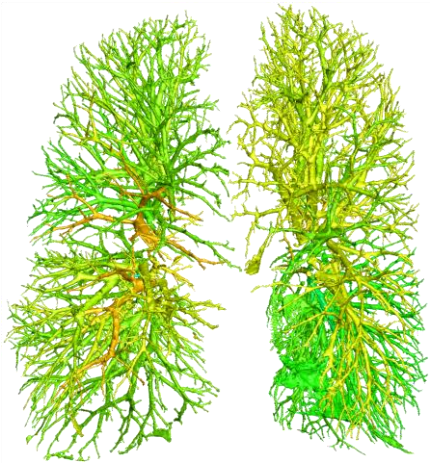
Patient 3



Patient 4



Patient 5



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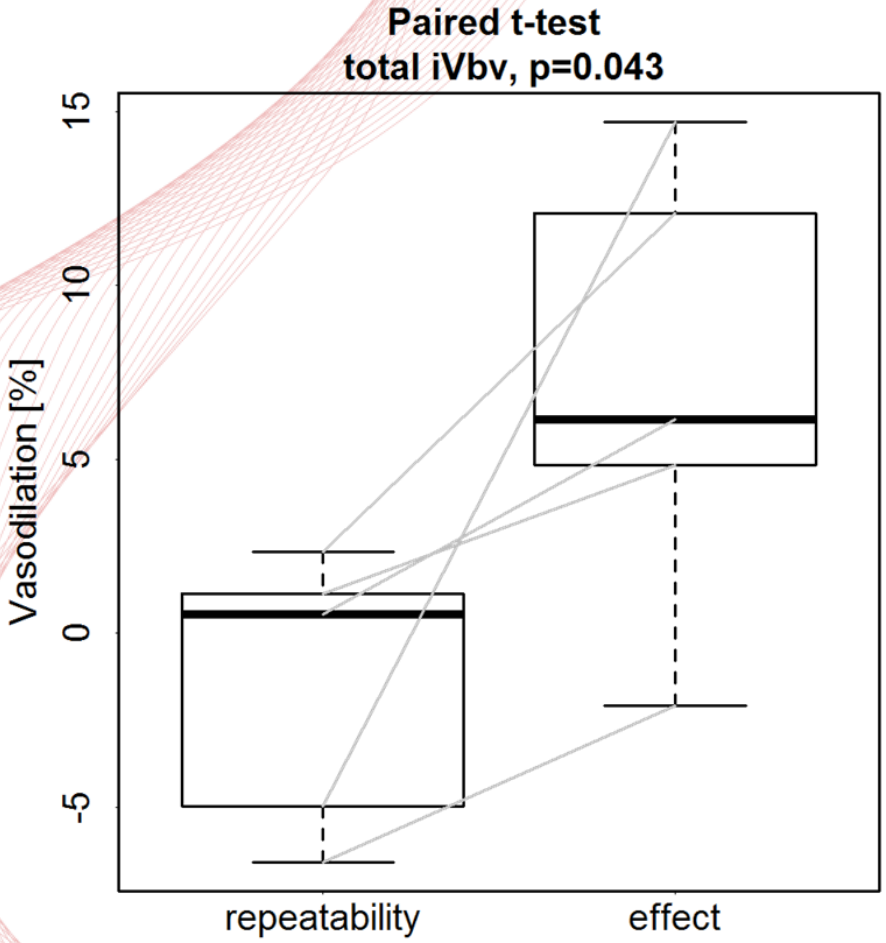
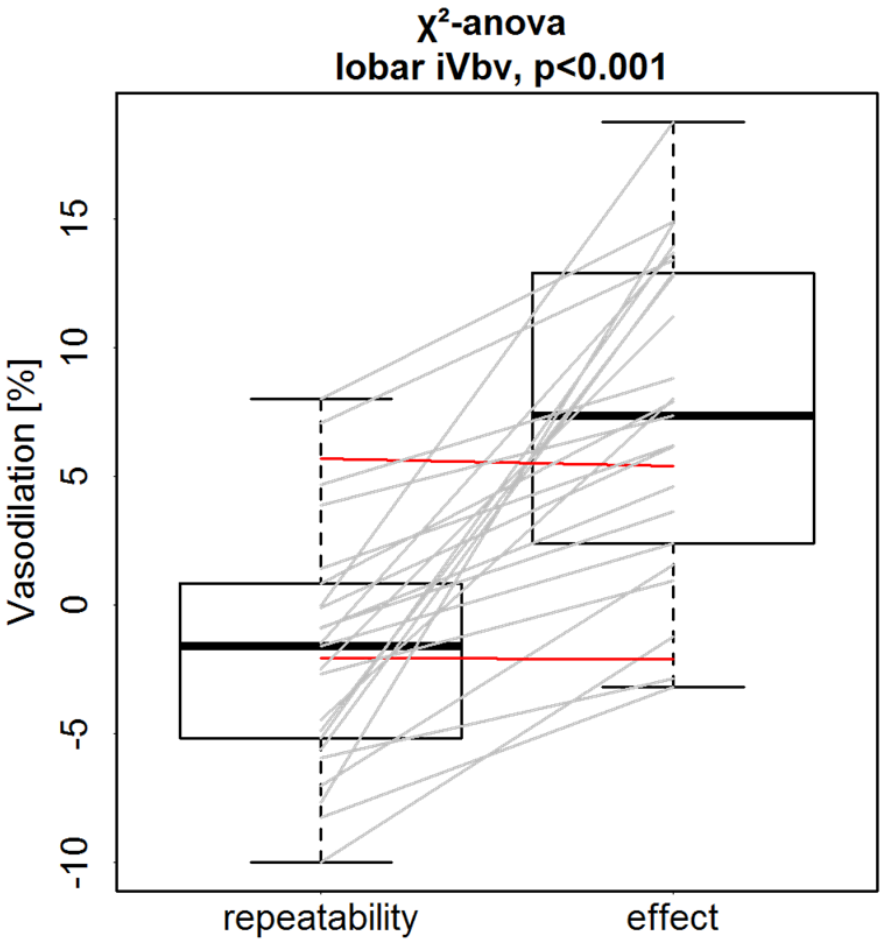
VASCULATURE





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VENTILATION

- At baseline (FRC → TLC)

Lobe	Amount of incoming air (%)				
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
RUL	21.3	23.2	17.0	-13.6	24.8
RML	2.9	2.6	3.4	-5.8	4.5
RLL	28.4	15.4	29.9	78.8	26.0
LUL	19.1	25.0	20.3	-12.7	27.7
LLL	28.2	33.8	29.3	53.8	17.0

FRC scan also taken at TLC

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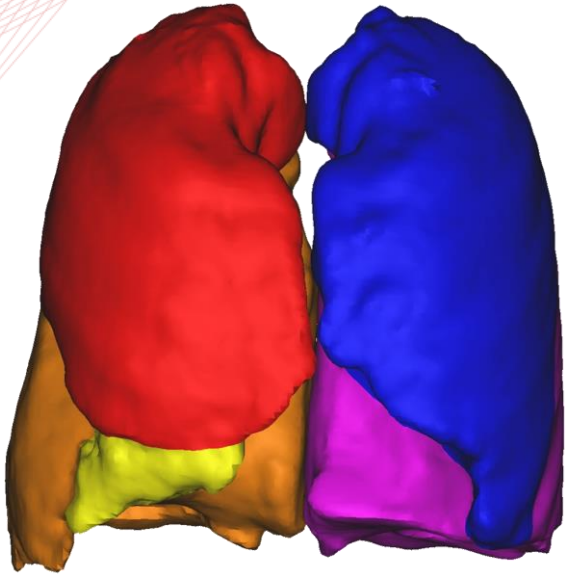
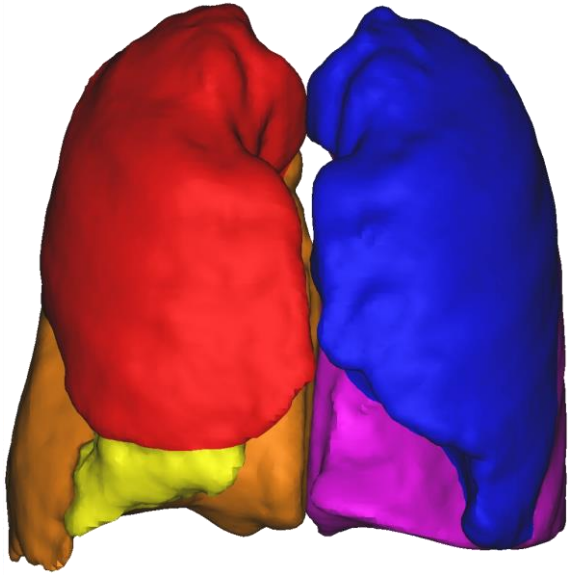
Patient 4 VENTILATION

- Patient did not exhale



Before NO FRC
Lung volume = 7.40L



Before NO TLC
Lung volume = 7.32L

1% difference

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VENTILATION

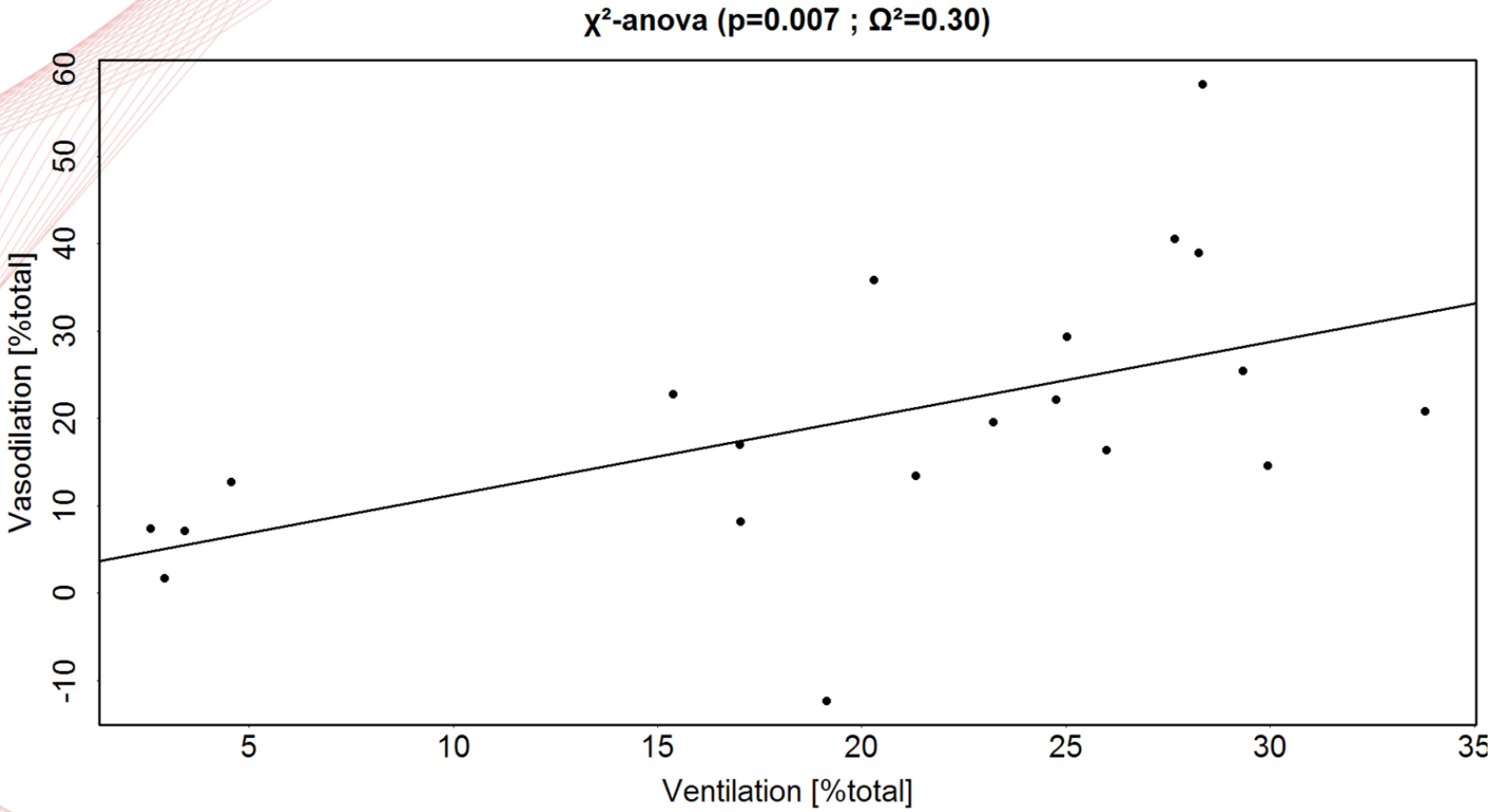
- At baseline (FRC → TLC)

Lobe	Amount of incoming air (%)				
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
RUL	21.3	23.2	17.0	-13.6	24.8
RML	2.9	2.6	3.4	-5.8	4.5
RLL	28.4	15.4	29.9	7[illegible]8	26.0
LUL	19.1	25.0	20.3	-12.7	27.7
LLL	28.2	33.8	29.3	53.8	17.0

Patient excluded from correlation ventilation vs vasodilation

VENTILATION AND VASODILATION

Very good correlation between ventilation and vasodilation **after iNO therapy**: regions with better ventilation experience more vasodilation

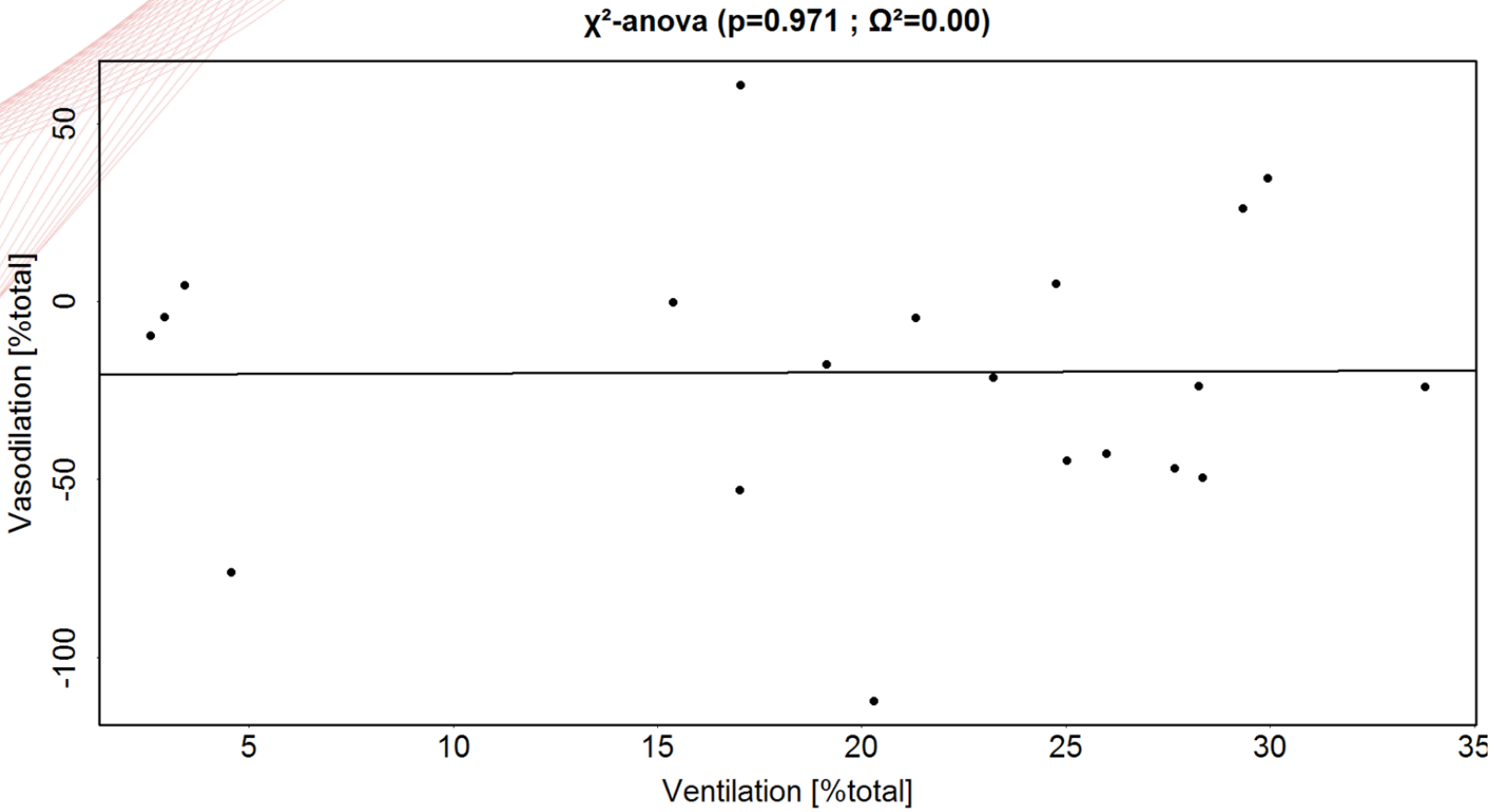


Ω^2 is similar to R^2 but for mixed models

Mixed models correct for the interdependence of lobes (5 lobes in 1 patient)

VENTILATION AND VASODILATION

No correlation between ventilation and vasodilation **after test-retest:** confirmation that the vasodilation is caused by iNO therapy



Ω^2 is similar to R^2 but for mixed models

Mixed models correct for the interdependence of lobes (5 lobes in 1 patient)

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LOBES

	iVlobe TLC (L)			Difference (%)	
	Before NO (baseline)	Before NO (retest)	After NO	Test_retest	Baseline_ After NO
Patient 1	7.82	7.73	7.66	-2.0	-1.0
Patient 2	5.85	6.01	5.87	2.9	0.3
Patient 3	6.13	6.05	6.05	-1.2	-1.3
Patient 4	7.32	7.39	7.22	0.9	-1.4
Patient 5	9.16	9.15	9.02	-0.1	-1.5

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BRONCHIAL TREE

	siVaw (mL/L)		Difference (%)
	Baseline	After NO	
Patient 1	6.66	7.07	6.1
Patient 2	9.82	9.56	-2.6
Patient 3	8.50	8.52	0.2
Patient 4	7.74	7.99	3.3
Patient 5	8.07	8.09	0.2

	siVaw (mL/L)		Difference (%)
	Baseline	Retest	
Patient 1	6.58	6.64	0.9
Patient 2	10.02	10.16	1.3
Patient 3	8.53	8.68	1.8
Patient 4	7.70	7.79	1.2
Patient 5	8.05	7.97	-1.0

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CONCLUSIONS

- FRI is sensitive tool to detect vasodilation from baseline variability
- iNO causes significant vasodilation in COPD patients with PH
- Vasodilation is highly correlated with ventilation
- Level of vasodilation varies between patients (non-responders, weak responders and strong responders)

NEXT STEPS

- Study the effect of upper airway resistance
- Study the effect of NO + O2
- Study the dose response of iNO

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