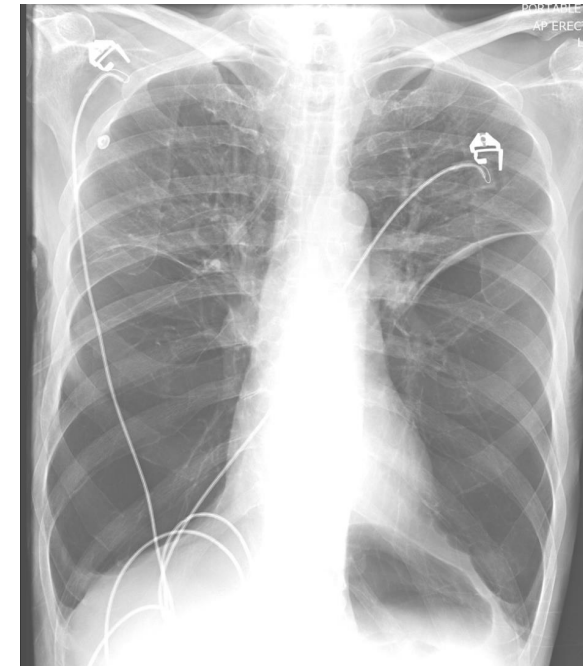
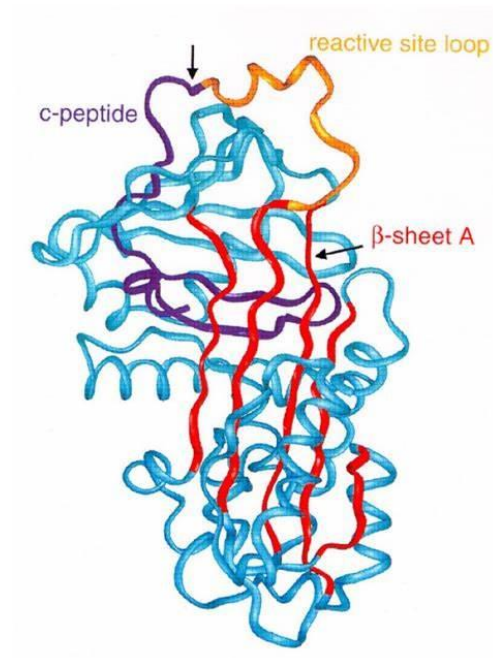


Diagnosis and Clinical Management: Lung Disease

David Parr



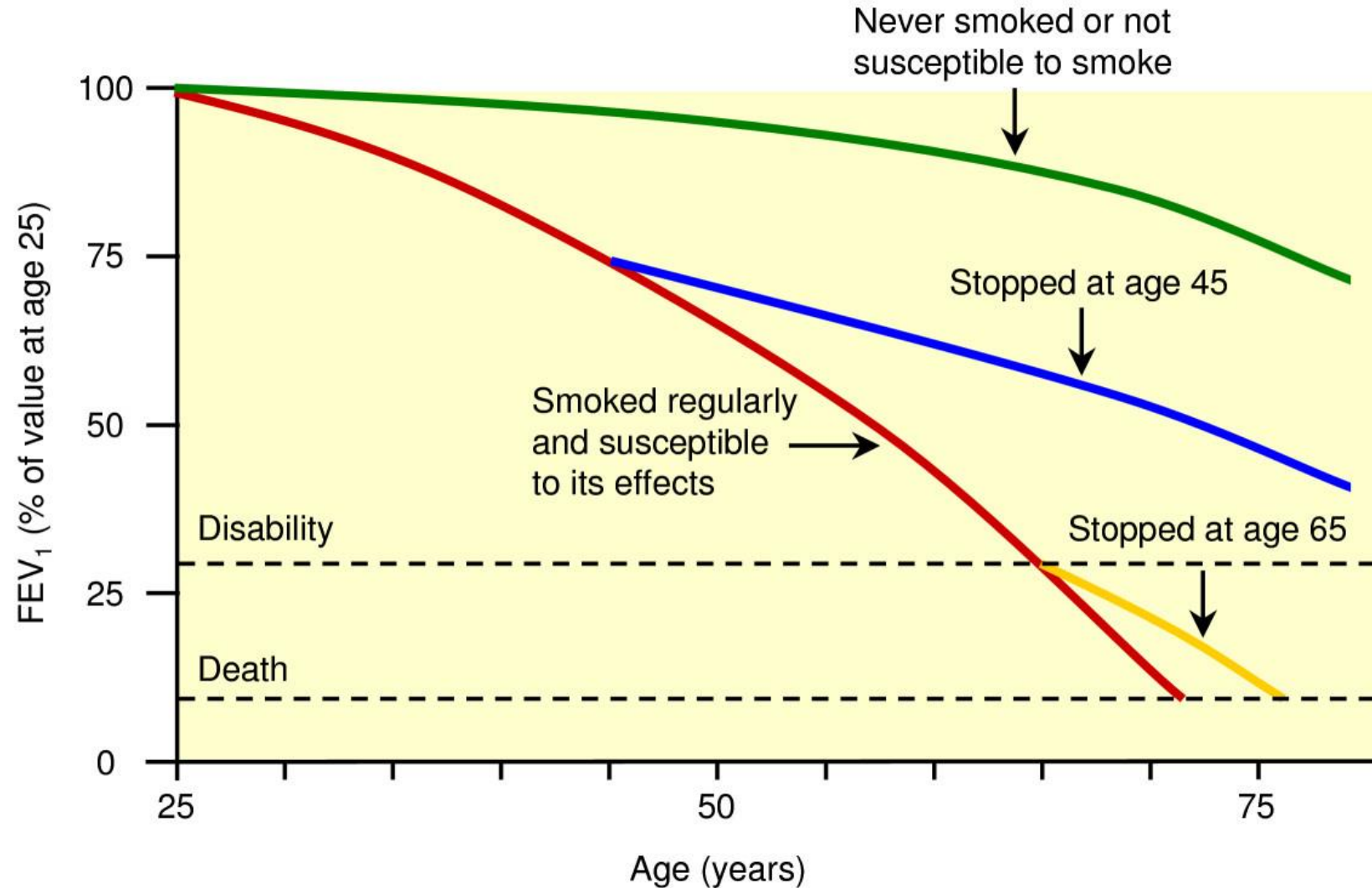
What are the commonest clinical presentations I see in my AATD clinic?

- 'Asthma' that doesn't respond as expected
- Breathlessness on exertion
- Wheezing
- Cough and sputum
- Recurrent 'chest infections'
- Chest pains
- Ankle swelling
- AATD diagnosis from screening or a 'chance' finding

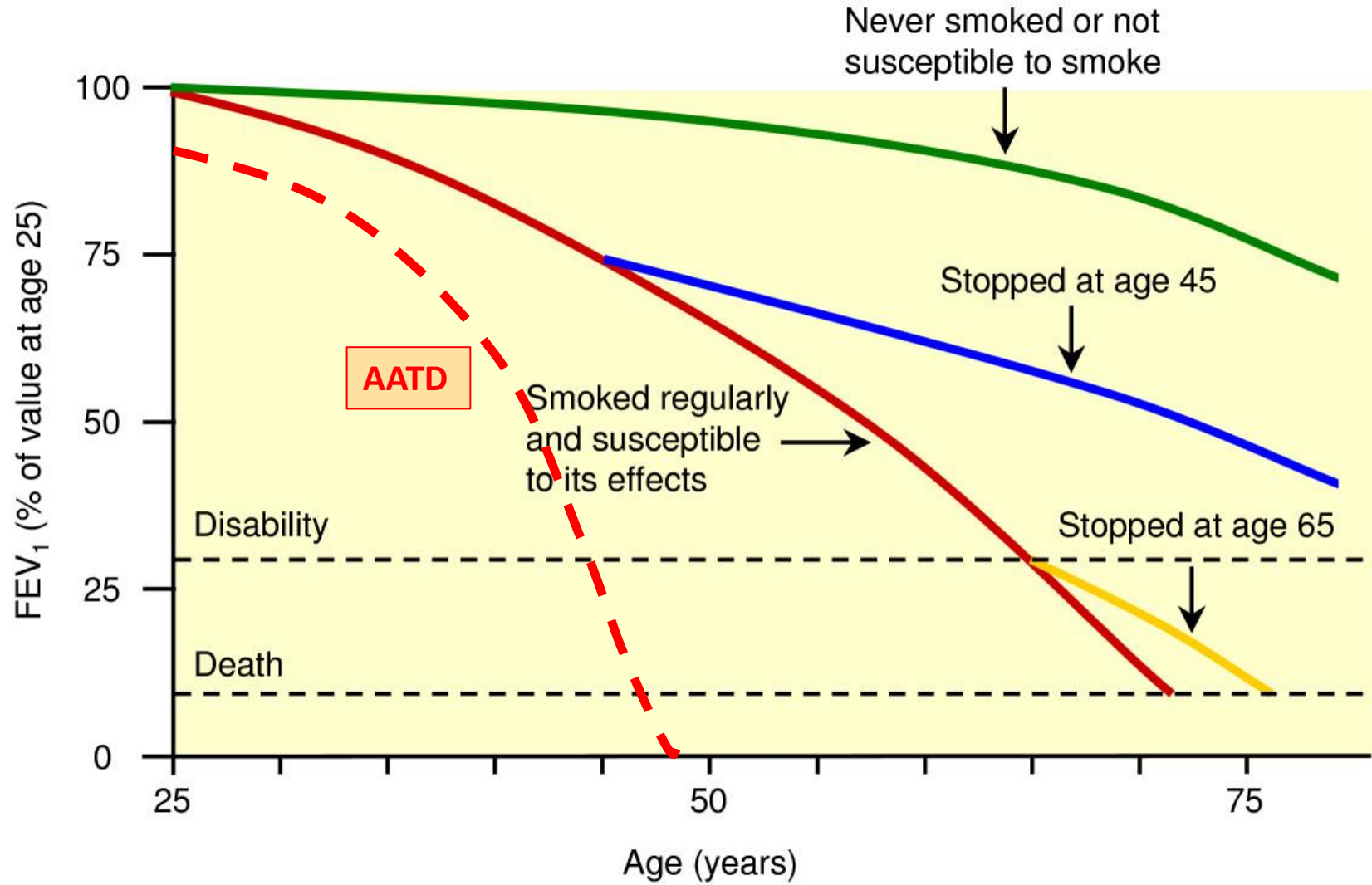
What are the commonest questions I get asked by patients in clinic?

- What's wrong with me?
- How bad is it?
- What's going to happen in the future?
- What are you going to do about it?
- What can I do about it?

The 'conventional' view of COPD (and AATD) circa 1976



The 'conventional' view of COPD (and AATD) circa 1976



What the AATD experts say.....

- Lung disease in AATD generally presents at a younger age than “usual” COPD and may be misdiagnosed as asthma
- Patients with AATD are more likely to have basal emphysema than patients with usual COPD
- ***The clinical impact of AATD is highly variable. Heterogeneity in lung disease is only partly explained by exposure to known risk factors, such as cigarette smoke***
- ***The complexity of interpreting the genetic variants, their importance and the role of patient and family screening as well as disease management requires expertise only gained by seeing patients on a regular basis***

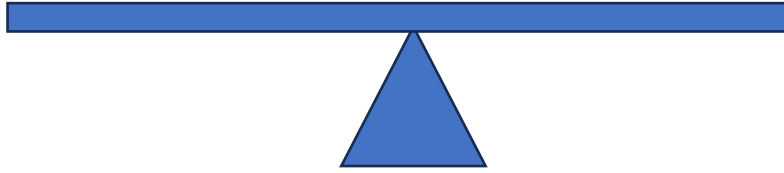
ERS Statement: diagnosis and treatment of pulmonary disease in α_1 -antitrypsin deficiency, 2017

The role of AATD: mechanisms of lung disease

1

Alpha-1 AT

Inflammation

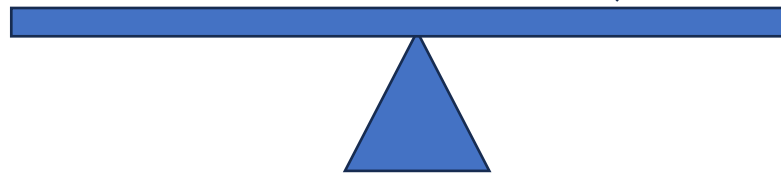


Healthy person who is well

2

Alpha-1 AT

Inflammation

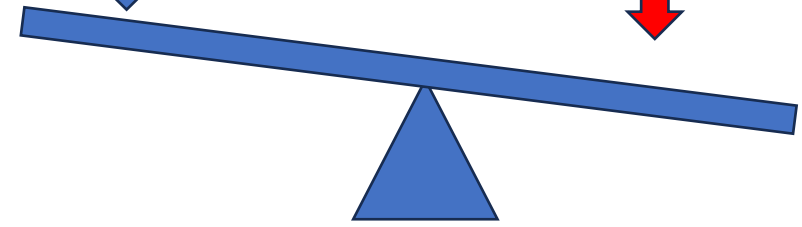


Healthy person with acute illness

3

Alpha-1 AT

Inflammation

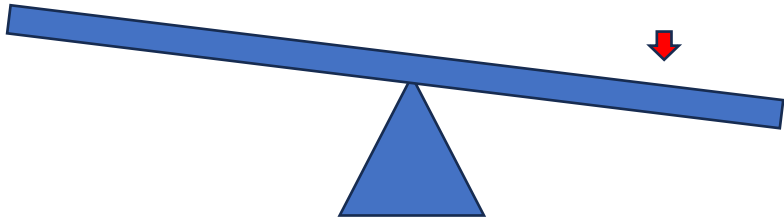


In usual COPD

4

Alpha-1 AT

Inflammation

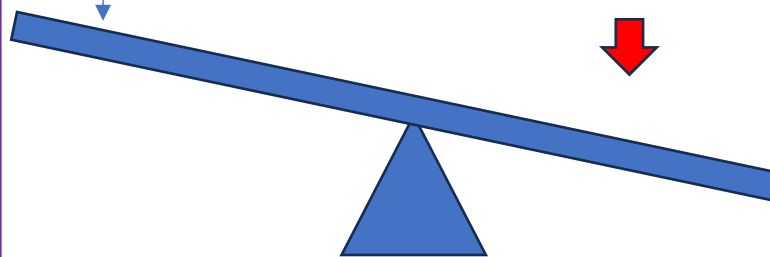


In AATD and 'well'

5

Alpha-1 AT

Inflammation

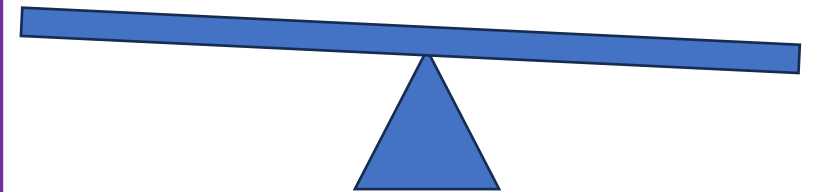


In AATD with exacerbating factors

6

Alpha-1 AT

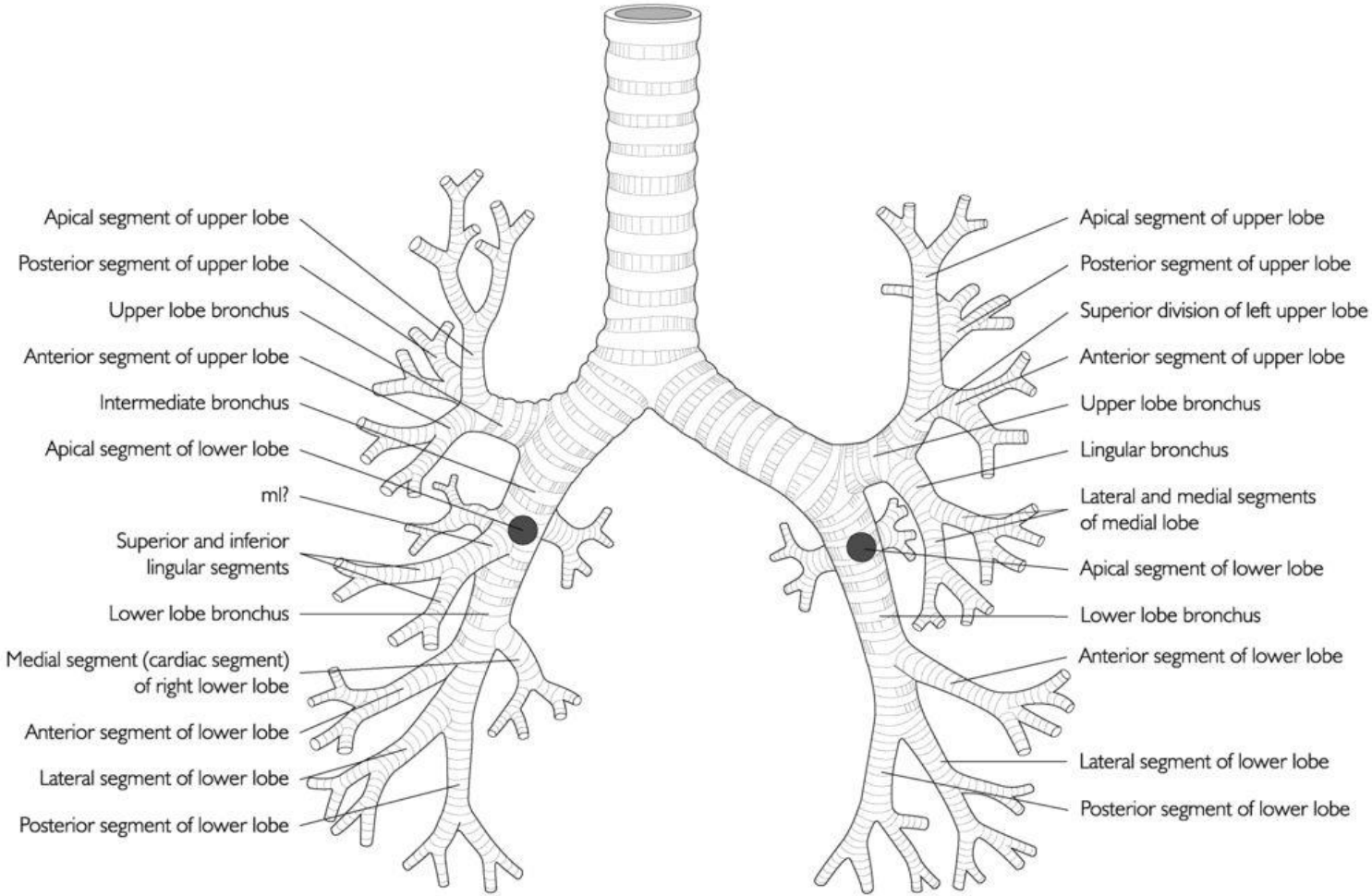
Inflammation



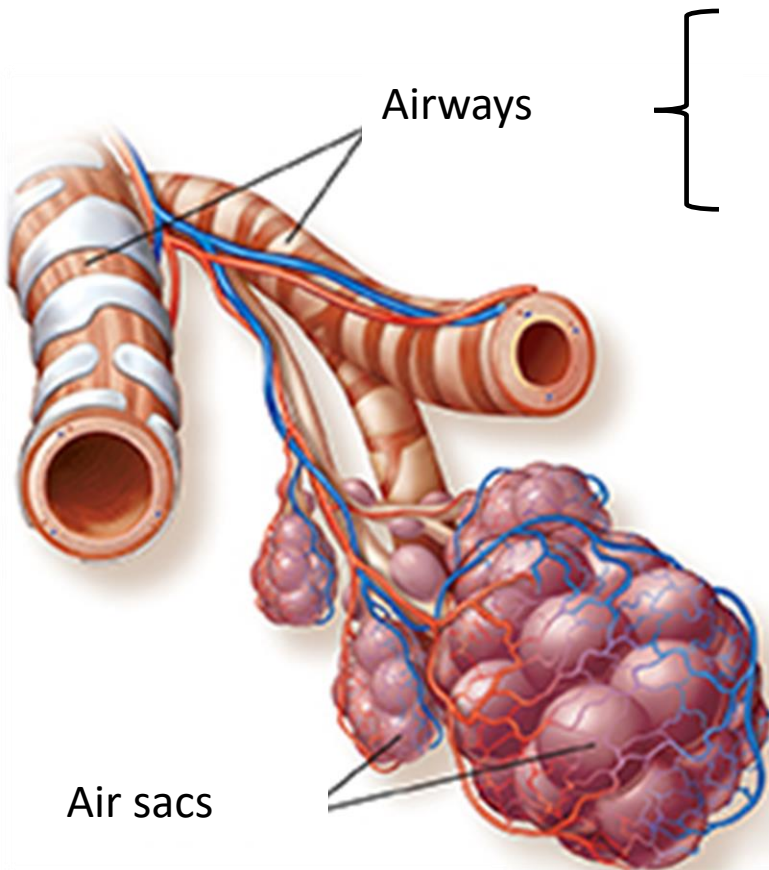
In AATD with augmentation therapy (?)

Slide 7

Lung Structure and Function: 'Lung Function Tests'



Lung Structure and Function: 'Lung Function Tests'



Trachea
Bronchi
Bronchioles

Pulmonary arterioles
Alveolar membrane
Alveolar capillaries
Pulmonary venules

Spirometry:

- FEV₁
- FVC
- FEV₁/FVC
- FEF25-75%

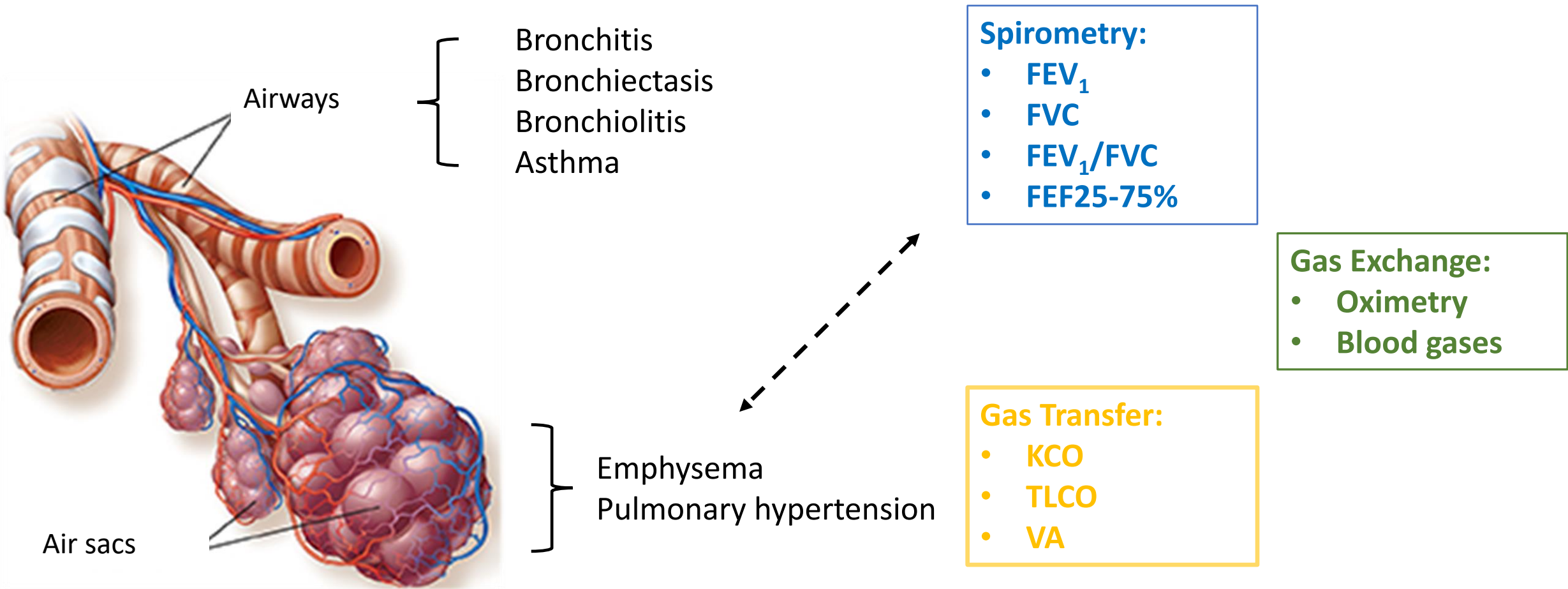
Gas Exchange:

- Oximetry
- Blood gases

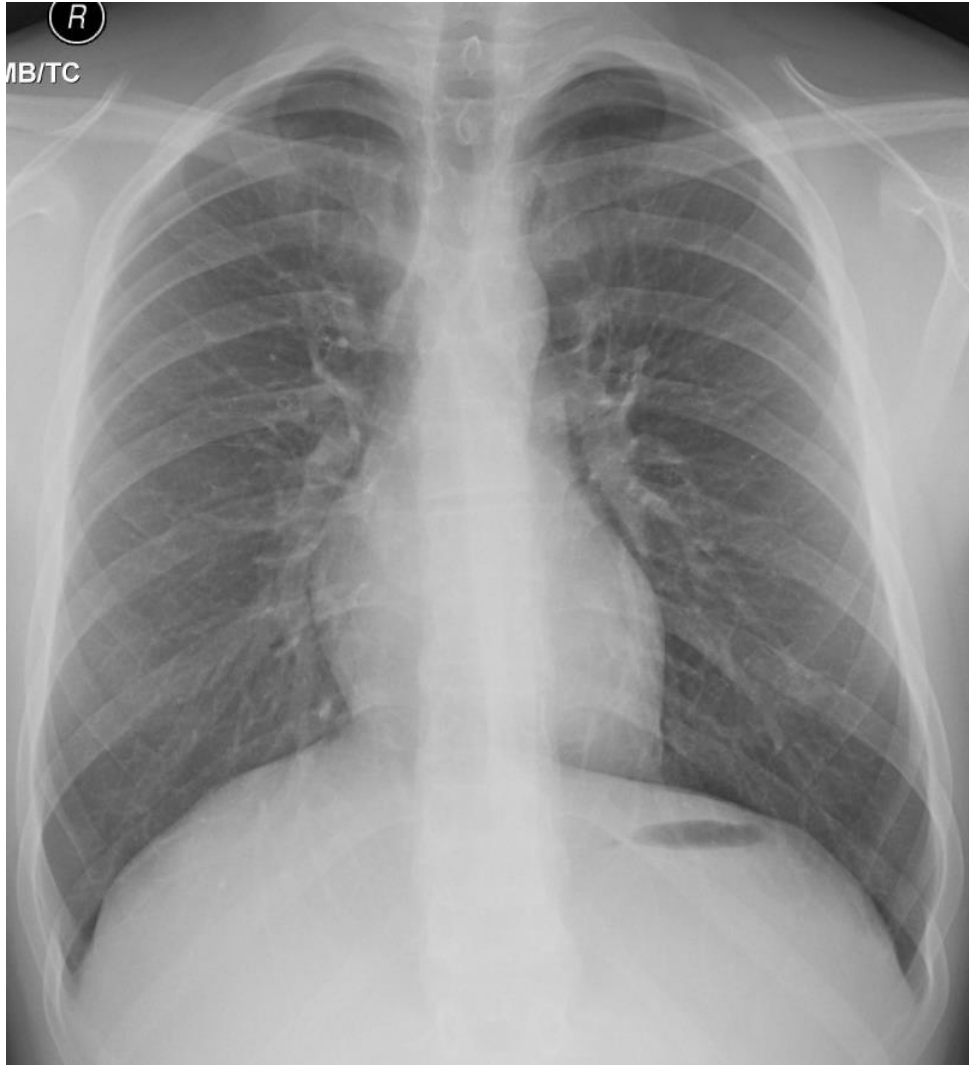
Gas Transfer:

- KCO
- TLCO
- VA

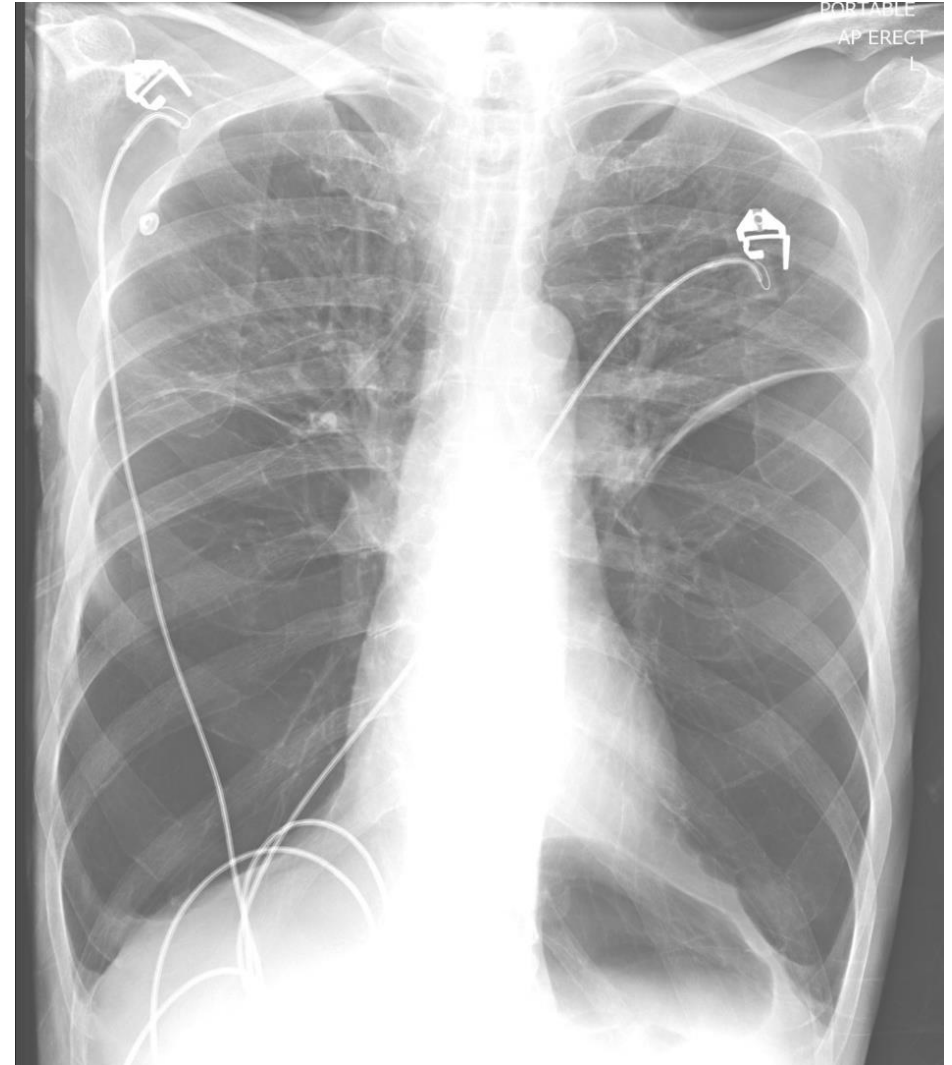
Lung Structure and Function: AATD Lung Disease



AATD Lung Disease: emphysema



Normal CXR

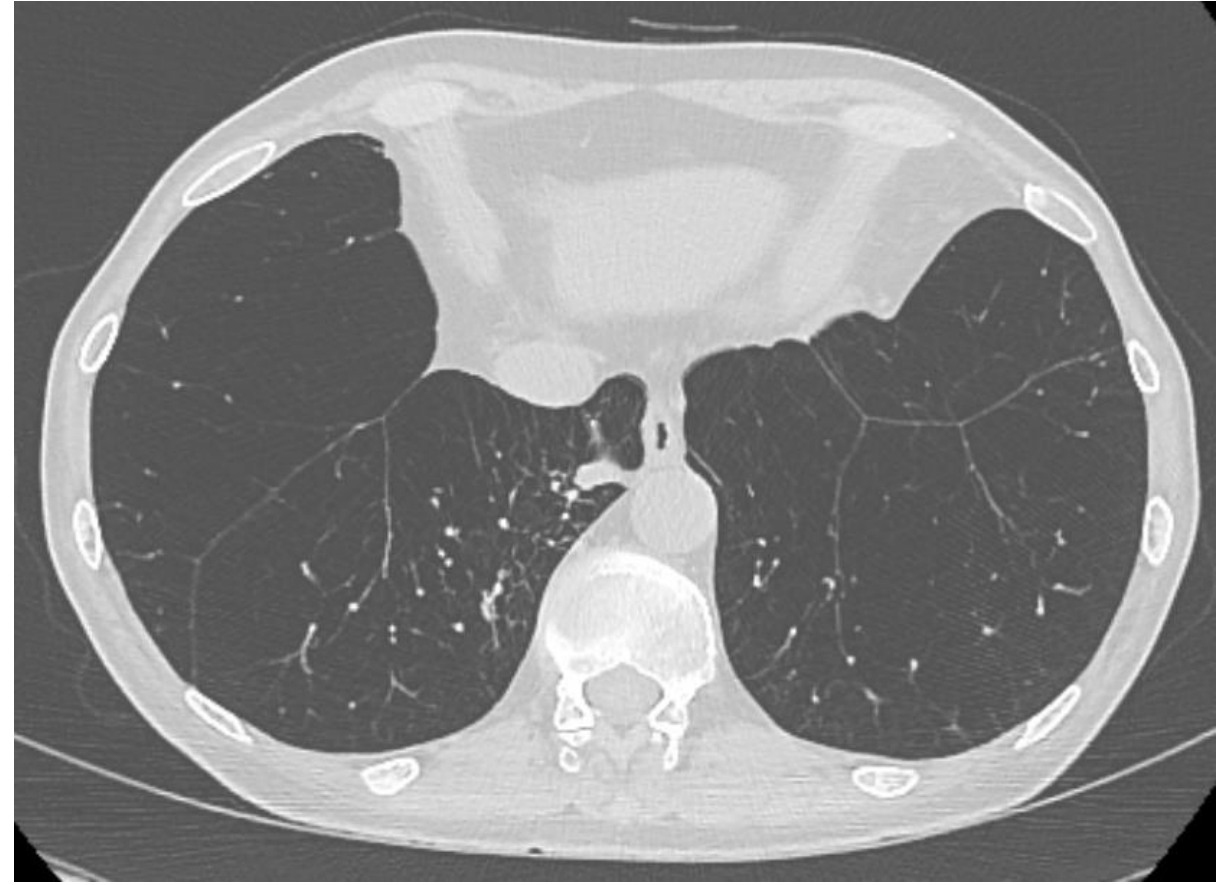


CXR of severe panlobular emphysema

AATD Lung Disease: emphysema



Normal CT

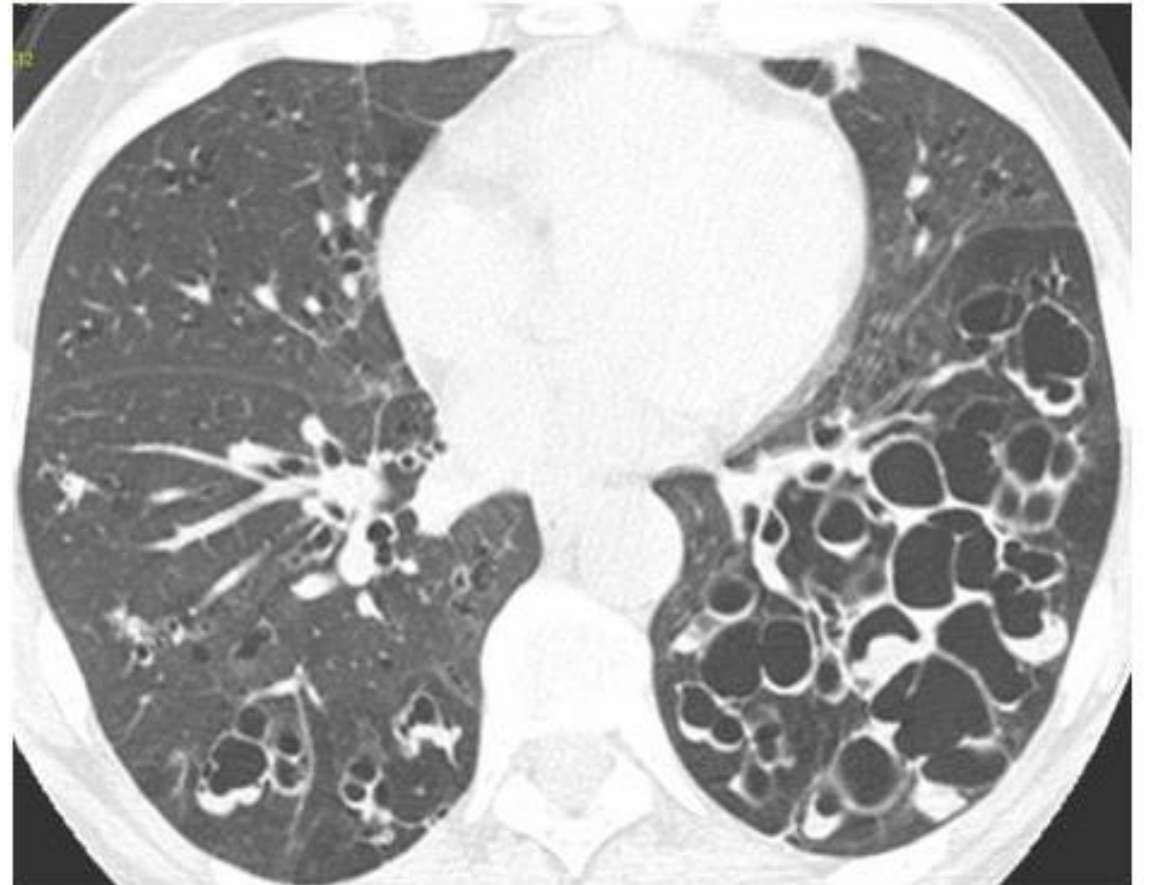


CT of severe panlobular emphysema

AATD Lung Disease: bronchiectasis



Normal CT



CT of severe bronchiectasis

Emphysema: the effects on lung function tests

	<u>Pred</u>	<u>Actual</u>	<u>%Pred</u>	<u>LLN</u>	<u>ULN</u>
SPIROMETRY					
FEV1 (L)	2.88	0.61	21	2.04	3.72
FVC (L)	3.75	1.64	43	2.74	4.76
FEV1/FVC (%)	74.63	37.10	49	62.80	86.46
SVC (L)	3.75	2.02	53	2.74	4.76
FEV1/SVC (%)	76.80	30.12	39		
FEF Max (L/sec)	7.71	2.35	30	5.71	9.71
FEF 25% (L/sec)	5.91	0.47	7	3.32	8.50
FEF 50% (L/sec)	3.38	0.27	7	1.17	5.59
FEF 75% (L/sec)	0.93	0.20	21	-0.24	2.10
FIF Max (L/sec)		3.05			
LUNG VOLUMES					
SVC (L)	3.75	2.02	53	2.74	4.76
IC (L)	3.10	1.12	36		
TGV (L)	3.56	7.22	202	2.57	4.55
RV (Pleth) (L)	2.56	6.32	246	1.88	3.24
TLC (Pleth) (L)	6.66	8.34	125	5.51	7.81
RV/TLC (Pleth) (%)	41	76	184	33	49
DIFFUSION					
TLCUnc (mM/min/kPa)	8.47	2.44	28	6.14	10.80
TLCUnc (mM/min/kPa)	8.47			6.14	10.80
KCO (mM/min/kPa/L)	1.29	0.80	61	0.84	1.74
VA (L)	6.66	3.06	46	5.51	7.81
BLOOD GASES					
SpO2		94%			

Emphysema: the effects on lung function tests

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The complexity of assessing lung disease in AATD

Problem 1: predicting future decline is extremely difficult

- Referred to local chest physician with breathlessness – aged 59
- Never smoker (except for passive smoke exposure)
- Diagnosed PiZZ aged 60
- Discharged from clinic with perceived ‘stability’

The complexity of assessing lung disease in AATD

Problem 1: predicting future decline is extremely difficult

- Referred to local chest physician with breathlessness – aged 59
- Never smoker (except for passive smoke exposure)
- Diagnosed PiZZ aged 60
- Discharged from clinic with perceived ‘stability’
- ***Seen several years later in specialist AATD clinic***
- Worsening respiratory failure with increasing oxygen dependence
- Transplant assessment - declined due to age and heart disease
- Severe loss of weight and muscle strength
- Worsening immobility
- Died aged 74 (14 years after being first diagnosed)

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VA (L)	6.66	3.06	46
BLOOD GASES			
SpO2		94%	

The complexity of assessing lung disease in AATD

Problem 2: worsening FEV₁ is not always due to emphysema progression

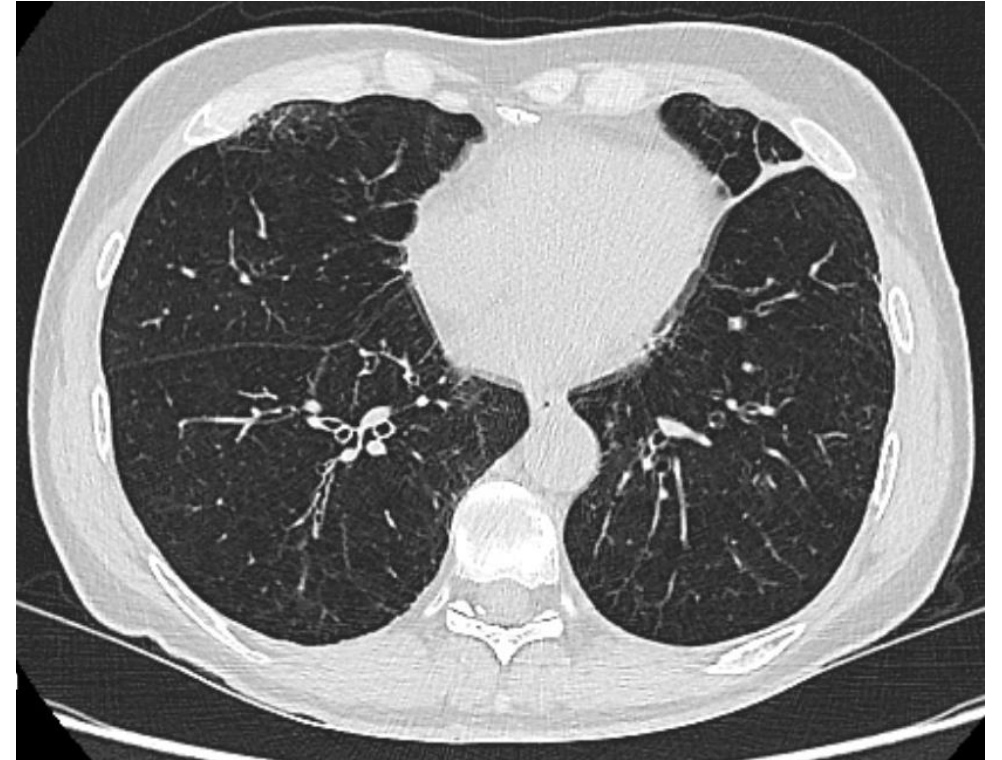
- Smoker between 18-38 years old (10 - 20 pack years)
- Breathlessness and productive cough from aged 20
- Diagnosed with asthma aged 45 but inhalers unhelpful
- Referred to Teaching Hospital Respiratory Department and diagnosed PiZZ aged 50
- **Referred to specialist AATD Clinic aged 53**

	<u>Pred</u>	<u>Actual</u>	<u>%Pred</u>
SPIROMETRY			
FEV1 (L)	2.34	1.73	73
FVC (L)	2.90	2.67	92
FEV1/FVC (%)	81.19	64.71	79
FEF Max (L/sec)	5.97	5.67	94
FEF 25-75% (L/sec)	2.33	0.92	39
FEV1/SVC (%)	80.69	58.46	72
LUNG VOLUMES			
SVC (L)	2.90	2.95	101
IC (L)	2.05	1.82	88
TGV (L)	2.59	4.31	166
RV (Pleth) (L)	1.72	3.18	184
TLC (Pleth) (L)	4.64	6.13	132
RV/TLC (Pleth) (%)	37	52	140
DIFFUSION			
TLCOunc (mM/min/kPa)	7.56	4.91	64
TLCOcor (mM/min/kPa)	7.56		
KCO (mM/min/kPa/L)	1.69	0.98	57
VA (L)	4.64	5.02	108
BLOOD GASES			
SpO2		95%	

The complexity of assessing lung disease in AATD

Problem 2: worsening FEV₁ is not always due to emphysema progression

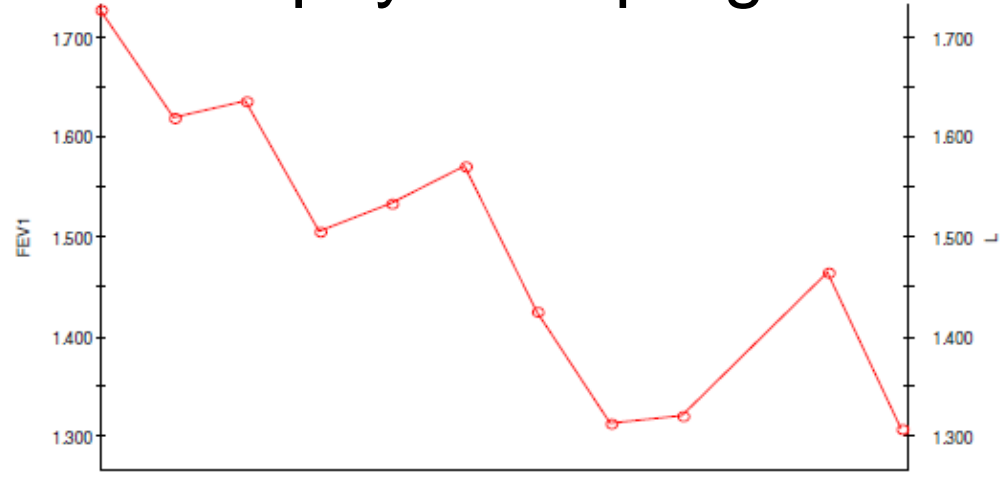
- Smoker between 18-38 years old (10 - 20 pack years)
- Breathlessness and productive cough from aged 20
- Diagnosed with asthma aged 45 but inhalers unhelpful
- Referred to Teaching Hospital Respiratory Department and diagnosed PiZZ aged 50
- ***Referred to specialist AATD Clinic aged 53***



The complexity of assessing lung disease in AATD

Problem 2: worsening FEV₁ is not always due to emphysema progression

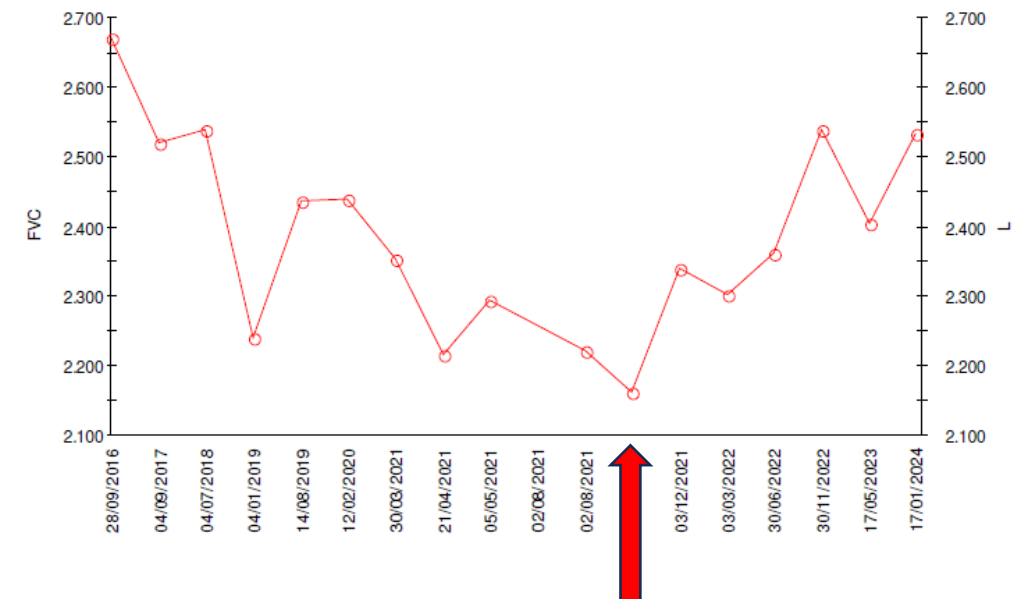
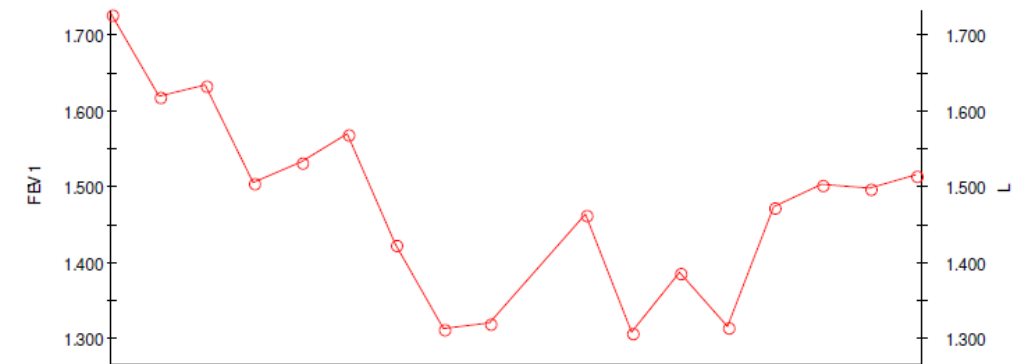
- Emphysema with asthmatic features (increased FeNO)
- Allergic bronchopulmonary aspergillosis (ABPA) suspected and excluded
- Gradually worsening breathlessness but with marked deterioration and wheeze within hours of home move
- Blood count showed high white cell count (increased eosinophils) suggesting an allergic process
- Commenced on increased inhaled steroids with little benefit and continued deterioration in FEV₁



The complexity of assessing lung disease in AATD

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- Diagnosed (in addition to emphysema) with bronchiolitis
- Treated with an 'anti-inflammatory', low dose of erythromycin



The complexity of assessing lung disease in AATD

Problem 3: worsening TLCO is not always due to emphysema progression

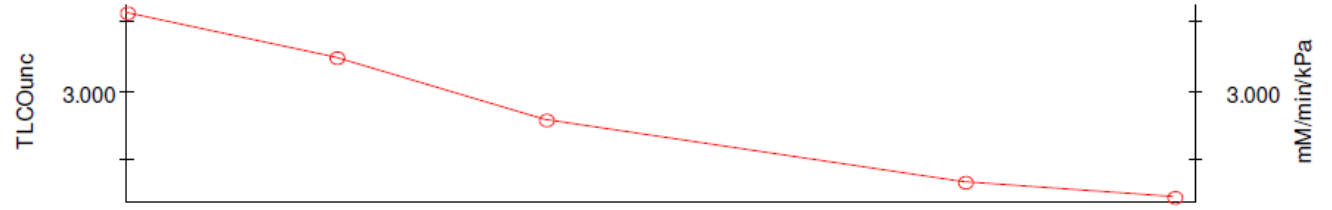
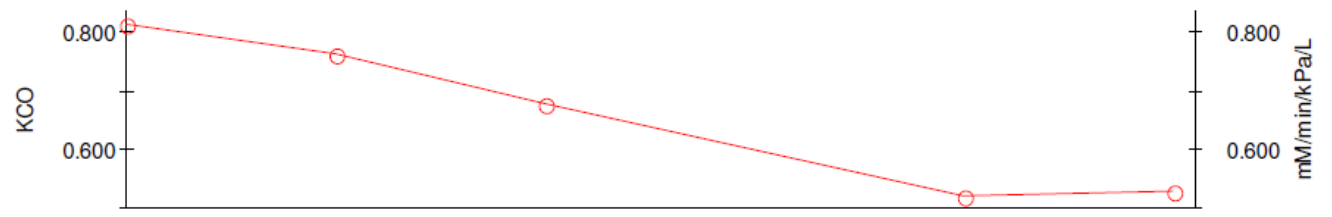
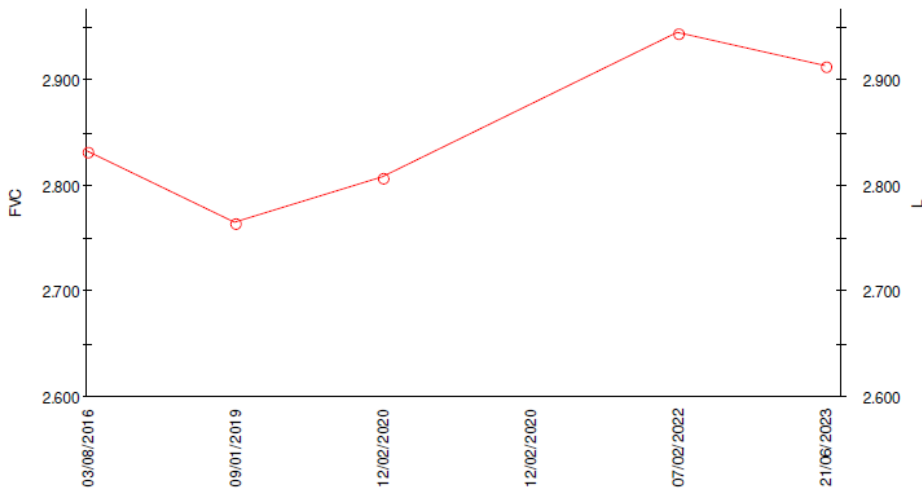
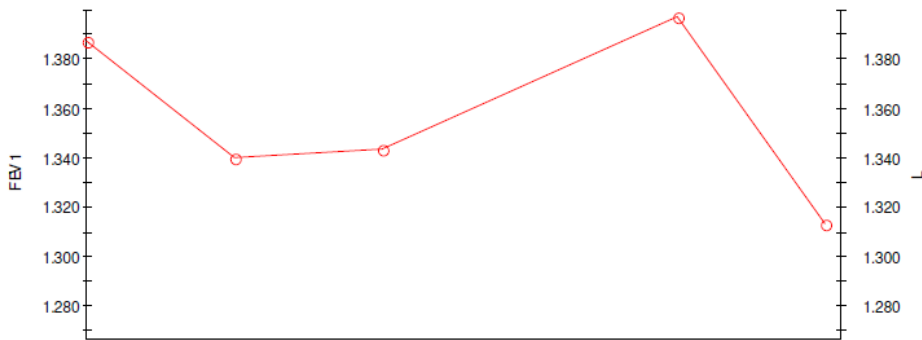
- Smoker of 10/day for about 10 years
- Breathlessness and cough, diagnosed with asthma in 30s
- Referred to local chest physician with worsening breathlessness
- Diagnosed PiZZ at 50
- Previous cancer treated with surgery and radiotherapy

- ***Referred to specialist AATD clinic aged 60***
- Basal (panlobular) and apical (centrilobular) emphysema on CT
- Fibrosis and fatty liver on fibroscan – weight loss advised (BMI 40)

- Polycythaemia (increased red blood cells) developed gradually over 3 years
- ECG abnormalities (suggestive of strain on the heart from problems in the lungs)

The complexity of assessing lung disease in AATD

Problem 3: worsening TLCO is not always due to emphysema progression



The complexity of assessing lung disease in AATD

Problem 3: worsening TLCO is not always due to emphysema progression

- Suspected pulmonary hypertension (in addition to emphysema, but of a different cause)
- Request for GP to refer to local Cardiologist for cardiac catheter BUT was admitted as emergency with acute pulmonary embolism requiring anticoagulation
- Pulmonary hypertension confirmed on cardiac catheter

- Further investigations undertaken which identified multiple underlying causes
 - Pulmonary embolism (chronic thromboembolic pulmonary hypertension - CTEPH)
 - Sleep apnoea – treatment commenced with CPAP and oxygen overnight
 - Liver cirrhosis with portal hypertension leading to porto-pulmonary hypertension
 - Connective tissue disorder requiring immunosuppression

- Long term oxygen therapy (LTOT) and ambulatory oxygen therapy (AOT)

Therapy for AATD Lung Disease

Generally Accepted

- Smoking cessation
- Pulmonary rehabilitation
- Inhaled bronchodilators and steroids
- Treatment of exacerbations
- IV AAT augmentation therapy
- Lung transplantation

Potentially beneficial

- Lung volume reduction therapies
- Novel anti-inflammatories
- Gene therapies

Ideal Management of AATD-associated lung disease

- Early recognition and diagnosis of AATD
- Referral to expert AATD centre (+ shared care with local hospital)
- Accurate diagnosis, including genetics and clinical 'phenotype'
- Early therapeutic intervention, as clinically appropriate
- Regular detailed monitoring of lung condition AND other potential health problems
- Voluntary participation in national and international AATD registries
- Voluntary participation in research
- Active participation in patient support groups and political lobbying