ASTHMA-COPD OVERLAP SYNDROME (ACOS) IN SMOKERS and NON-SMOKERS

DUTCH vs BRITISH HYPOTHESIS

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POTENTIAL CONFLICTS OF INTEREST

- Advisor to Boehringer Ingelheim, Astra Zeneca
- Received funding for participating in clinical trials for Boehringer Ingelheim/Pfizer, Forest, GSK, Pearl Therapeutics/Astra Zeneca and Novartis
- Speaker for Boehringer Ingelheim, Astra Zeneca, GSK, Forest

Dutch Hypothesis

- During the First Bronchitis Symposium held in Groningen, the Netherlands in 1961, the intuitive Orie and colleagues hypothesized that the various forms of airway obstruction, such as asthma, chronic bronchitis, and emphysema, should be considered, as different clinical and phenotypic expressions of one common disease origin. They named this entity “chronic nonspecific lung disease (CNSLD)”. They proposed that multiple exogenous and endogenous factors including atopy and hyperresponsiveness influenced pathogenesis. Subsequently, at the Third International Bronchitis Symposium in the Netherlands in 1969, Fletcher and Pride suggested the term “Dutch hypothesis” for the original proposal of Orie and colleagues.

British Hypothesis

- Alternatively, in 1991 Vermeire and Pride emphasized that despite common clinical and phenotypic features in COPD and asthma, the origins were distinctly different. In 2006, Kraft and Barnes debated the clinical and pathophysiologic similarities (Dutch Hypothesis) versus differences (British Hypothesis) between asthma and COPD.

Dutch vs British Hypothesis

- Orie NGM et al. *Bronchitis* Assen the Netherlands Royal Van Gorcum 1961; 43-59
- Fletcher CM and Pride NB 1969 Ciba Symposium. Thorax 1984; 39: 81-85
- Vermeire PA Pride NB ERJ 1991; 4: 490-496
- Kraft M AJRCCM 2006; 174: 238-240
- Barnes PJ AJRCCM 2006; 174: 240-243

Postma DS et al. JACI 2015; 136: 521-529

Postma DS Rabe KF. N Engl J Med 2015; 373: 1241-1249

Barnes PJ Chest 2016; 149: 7-8

Asthma-COPD Overlap Syndrome (ACOS) in Smokers

- Former or current chronic cigarette smokers with persistent expiratory airflow limitation, partial reversibility
- Hyperresponsive airways
- History of preceding asthma before smoking and COPD
- Increased blood/sputum eosinophilia and serum IgE, Type 2 inflammation
- More frequent exacerbations and hospitalizations than COPD without ACOS
- Treatment emphasis on asthma paradigm: ICS, SABA, SAMA, LABA, LAMA, oral CS, omalizumab(IgE)

ACOS IN SMOKERS

Postma and colleagues recently provided an in-depth analysis of the multiple endogenous and exogenous factors that influence the phenotypic homogeneity and heterogeneity in asthma versus COPD and the Asthma-COPD Overlap Syndrome (ACOS).

Postma DS et al. JACI 2015; 136: 521-529

Postma DS, Rabe KF. NEJM 2015; 373: 1241-1249

Augusti A et al ERJ 2016;47: 410-419

Sterk P. ERJ 2016; 47: 359-361

ACOS IN SMOKERS

Gibson PG, McDonald VM. ACOS 2015;Thorax 70; 683-691

Barrecheguren M, et al. ACOS COPM 2015; 21(1): 74-79

Cosio BG, et al. ACOS. Chest 2016; 149: 45-52

Nielsen M, et al. ACOS Int J COPD 2015; 10:1443-1454

Bujarski S, et al. ACOS Curr Allergy Asthma Rep. 2015;15:509

Bateman ED, et al. ACOS Lancet Respir Med. 2015; 3: 719-728

Soler X, Ramsdell JW. ACOS JACI Pract. 2015; 3(4): 489-495

de Marco R et al. ERJ 2015; 46: 671-679

Miravitlles M et al.Int J Chron Obsruct Pulm Dis 2015;10: 321-330

Aalbers R, van den Berge M. J Asthma Allergy 2016; 9: 27-35

Lange P et al. TheLancet Resp Med 2016 (online)

Barnes PJ. Chest 2016; 149: 7-8

Genomic Signatures of Type 2 Inflammation in Asthma vs COPD vs ACOS

Similar airway gene expression alterations can co-occur in asthma and copd and acos

Christenson SA et al. AJRCCM 2015; 191: 758-766

- Ghebre MA et al. JACI 2015; 135: 63-72

Genetic components different in asthma vs copd

Hardin M et al. Eur Respir J 2014; 44: 341-350

- Smolonska J et al. Eur Respir J 2014; 44: 860-872

ACOS JACI 2015; 136: SEPTEMBER

Postma DS et al Revisiting the Dutch Hypothesis 521-529

Reddel HK Treatment of ACOS-guidelines 546-552

Barnes PJ Therapeutic approaches to ACOS 531-545

Gelb AF and Nadel JA ACOS Commentary 553-555

"ACOS" in Non-Smoking Chronic Asthmatics

- Type 2 inflammation, eosinophils, IgE
- Despite treatment have persistent expiratory airflow limitation, with partial reversibility, and who
- Develop a COPD phenotype with loss of lung elastic recoil, and
- Normal or mildly abnormal high resolution-thin section (1mm) CT lung with normal voxel quantification (<10% -950HU) and
- Maintain normal diffusing capacity
- Unsuspected mild diffuse centrilobular emphysema in all 4 autopsied asthmatics and 1 asthmatic post lung transplant presumably due to proinflammatory pathway and proteolytic cascade

"ACOS" IN NON-SMOKERS

Gelb AF, Christenson SA, Nadel JA. Review of ACOS Curr Opin Pulm Med 2016; 9:100-105

Gelb AF Nadel JA ACOS Commentary JACI 2015; 136: 553-555

Gelb AF et al. ACOS in Non-Smokers Chest 2015; 148: 313-320

Rabe KF. Editorial in Chest 2015; 148: 297-298

Gelb AF et al. JACI 2014; 133: 263-265, Erratum 1232

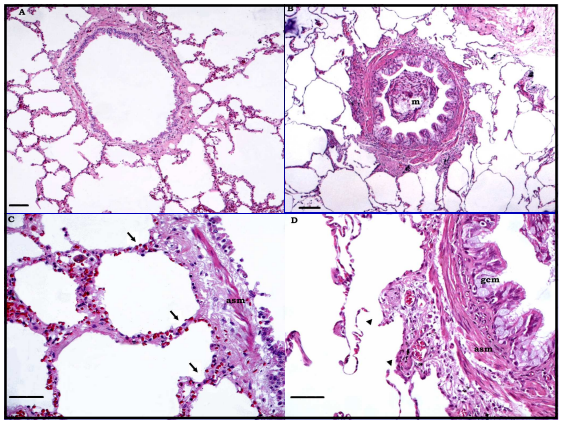
Arthur F. Gelb MD, Noe Zamel MD
Unsuspected Pseudo-Physiologic Emphysema in Chronic Persistent Asthma
Am J Respir Crit Care Med
162: 1778-1782, 2000

Demonstrated loss of lung elastic recoil and its significant contribution to expiratory airflow limitation. Both high resolution-thin section lung CT (1 mm) and diffusing capacity were normal

PATHOLOGY BACKGROUND

Mauad T Silva LFF Santos MA Grinberg L
Bernardi FD Martins MA Saldiva PH Dolhnikoff M
Abnormal Alveolar Attachments with Decreased Elastic Fiber Content in Distal Lung in Fatal Asthma
AJRCCM 2004; 170: 857-62

Localized *peribronchiolar* parenchymal emphysema in fatal asthmatics but no overt emphysema. Decreased elastic fiber content in small airway adventitial layer, and in peribronchial alveoli but not in distal alveoli.
(No imaging and lung function studies included)



UNSUSPECTED MILD EMPHYSEMA IN NON-SMOKING PATIENTS WITH CHRONIC ASTHMA WITH PERSISTENT AIRWAY OBSTRUCTION

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- JAY A NADEL MD Cardiovascular Research Institute and Dept Medicine, Physiology and Radiology, University of California, San Francisco Medical Center, San Francisco, CA

- JACI 2014; 133: 263-265 Erratum JACI 2014; 133: 1232

ACKNOWLEDGEMENT

- PATHOLOGY: Ranna Patel BS, HT, ASCP LRMC Dept Pathology
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- Randy Newsom RCP CPFT Lakewood
- GRAPHICS: Jennifer Klotchman PhD
- Bob Ward BS, MS (EE) Dept Computer Science CSULB
- LUNG CT VOXEL QUANTIFICATION: Ouided Rouabhi and Susan Wood PhD
  Vida Diagnostics Inc, Cupertino, CA and Coralville, Iowa

and

PHYSIOLOGY COLLABORATION: Professor Noe Zamel MD Pulm Div Mt. Sinai Hosp University of Toronto, Toronto, Ontario, Canada

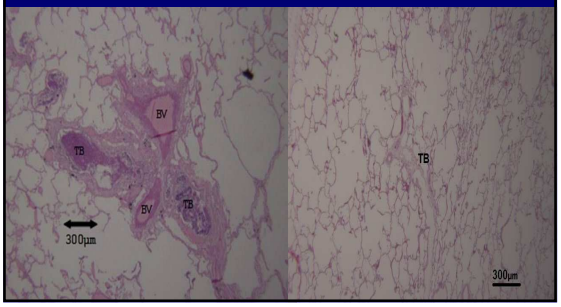
RESULTS

- Asthma Control Test 16-19
- Total blood eosinophils 206(131-260) cells/μL (median, 1-3 IQ) (normal <300)
- Serum IgE 280(31-500) kμ/L (normal <100)
- Thurlbeck lung CT emphysema score ≤10 in 9 asthmatics (2 died) and 15 and 20 in 2 asthmatics who died consistent with mild emphysema
- Voxel quantification ≤-950 HU: nl or trivial emphysema/hyperinflation

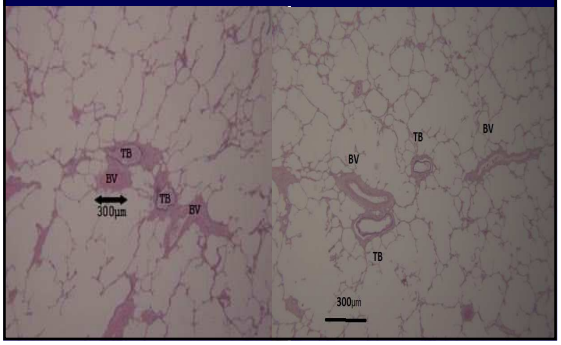
RESULTS

- FEV_1 2.5±0.4L (mean±SD) (69±14)% pred (post 270µg albuterol sulfate MDI with spacer)
- FVC 4.0±1.0L (88±13) %pred
- FEV_1/FVC 63±9%
- SGaw 0.06(0.05-0.09)(median 1-3 IQ) lps/cmH_2O/L 24(23-37)% pred
- RV 3.4(2.8-3.5)L 143(141-176)%pred
- FRC 4.3(3.5-4.4)L 123(109-142)%pred
- TLC 7.3(6.8-7.5)L 110(108-119)%pred
- D_LCO/V_A 5.5(4.6-6.0) ml/min/mmHg/L 130(112-141)%pred

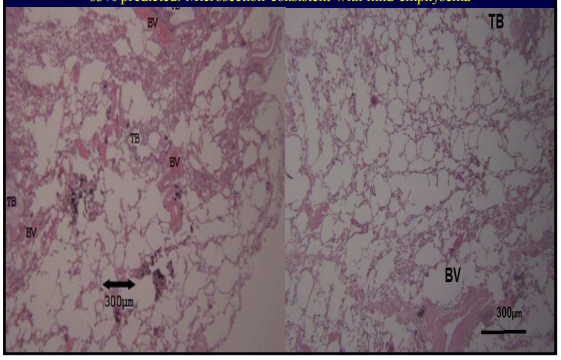
SENTINEL CASE: RUL(left) Case #9 72 yr F with lung CT and autopsy lung macrosection Thurlbeck Emphysema Score 20 (mild) and FEV_1 (L) 42%pred. Microsection: mild emphysema
Control Case: RUL(right) 82 yr old F asthmatic with ***normal*** PFT, lung CT, macrosection and voxel quantification. Microsection: mild to moderate alveolar duct ectasia consistent with aging lung and no emphysema
(Verbeken EK et al Chest 1992; 101: 793-9 and 800-9)



LUL (left) and RLL (right) in Case #10, 82yr old F
Lung CT and autopsy lung macrosection Thurlbeck Emphysema Score 10 (very mild) with normal voxel quantification and FEV_1 (L) 52% predicted.
Microsection with borderline-to-mild emphysema and hyperinflation

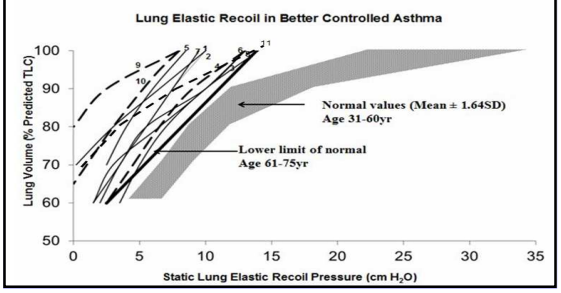


LUL (left) and RLL (right) in Case #4 42yr old M
Lung CT and lung macrosection Thurlbeck Emphysema Score 15 (mild) and FEV_1 (L) 63% predicted. Microsection consistent with mild emphysema



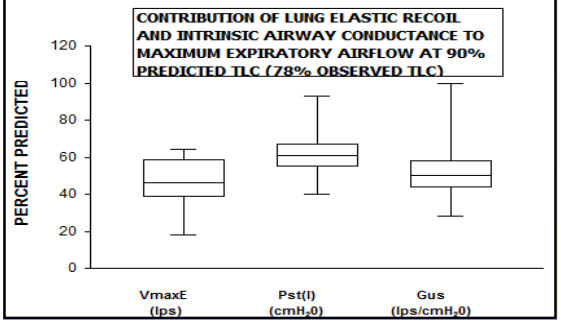
Loss of Lung Elastic Recoil in All 11 Asthmatics Including 4 Who Died (Dashed Line)

(Normal data from Gelb AF and Zamel N Chest 1975; 68: 538-41)

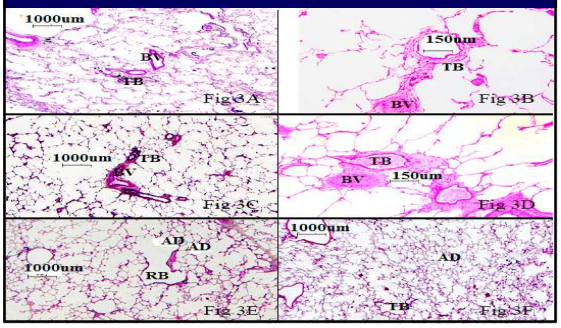


LOSS OF LUNG ELASTIC RECOIL CONTRIBUTES SIGNIFICANTLY TO EXPIRATORY AIRFLOW LIMITATION

Vmax= Pst (l) X Gus (Mead J. JAP 1967; 22: 95-108)



Gelb AF, Yamamoto A, Verbeken EK, Nadel JA
Unraveling the pathophysiology of the ACOS
CHEST 2015, 148: 313-320
Figs 3AB and 3CD:asthma+emphysema,3E: asthma, no emphysema, 3F: nl control



CONCLUSION

- We believe there is pathologic evidence for diffuse lung tissue breakdown of terminal bronchiolar-alveolar attachments within the lung matrix (Mauad T et al AJRCCM 2004;170:857-62) ***and mild diffuse centrilobular emphysema.*** This may be responsible for the heretofore unexplained loss of lung elastic recoil in non-smoking asthmatics with chronic expiratory airflow limitation. A proinflammatory pathway and proteolytic cascade may be operant. Additional on-going and future patho-imaging-physiologic correlative studies will be needed for confirmation.

QUESTIONS

- 1. Do you accept there is a probable pathophysiologic, generic, and clinical overlap between asthma and copd (ACOS) even in non-smokers?
- A. yes B. no C. maybe
- 2. If you accept ACOS, original credit goes to?
- A. Orie and Dutch Hypothesis B. British Hypothesis
- C. French Hypothesis
- 3. Treatment in symptomatic patients with ACOS with abnormal expiratory spirometry could include?
- A. ICS, SABA, LABA
- B. ICS, SABA, LABA, SAMA, LAMA,
- C. ICS, SABA, LABA, SAMA, LAMA, tapering oral CS, omalizumab