Statins Attenuate Pulmonary Hypertension, a common complication of COPD Probably Through IL17 Pathway in Smoking Rats

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The latest WHO mortality data reports that one in eight of total global deaths as a result of air pollution exposure in 2012. Air pollution is now the world's largest single environmental health risk.

--WHO news in March 25,2014

Outdoor air pollution sources are cars, industries, power plants and forests fire; indoor sources are cigarettes smoke, second hand smoke and wood burning stove)

Outdoor air pollution-caused deaths:

- **40% – ischaemic heart disease;**
- **40% – stroke;**
- 11% – chronic obstructive pulmonary disease (COPD);
- 6% - lung cancer;
- 3% – acute lower respiratory infections in children.

Indoor air pollution caused deaths:

- 26% - ischaemic heart disease;
- 22% - COPD;
- 12% - acute lower respiratory infections in children
- 6% - lung cancer.

--WHO news in March 25,2014

Is COPD Really a Cardiovascular Disease? (Chest 2009 136(2):329-330)

--Dr. Don Sin brought out this question because in an autopsy study, among 43 consecutive hospitalized and died COPD patients for an acute exacerbation, there were 37% die from cardia failure and 21% from thromboembolic events, 28% from pneumonia. Only 14% die from respiratory failure secondary to COPD.

COPD, the fourth leading cause of morbidity and mortality, accounts for more than $18 billion in direct medical cost in USA, $1.4 billion in UK;

Because of lacking of effective therapy, a significant number of patients develop pulmonary hypertension(PH) over the course of COPD. PH will lead to heart failure affecting quality of patients daily life and mortality;

However, the pathogenesis of PH in COPD remains to be explored.

--Wright JL, Levy RD and Churg A. Thorax 2005 60:605-609 (review)

Statins, a group of inhibitors of 3-hytroxy-3-methylglutaryl coenzyme A (HMC-CoA) reductase, used to apply for lowering cholesterol levels.

Recently, Statins have been reported to signicantly reduce the mortality and morbidity of cardiovascular diseases with COPD. But detail mechanism is unknown.

In order to improve the prognosis of COPD, reduce the medical cost, we establish a smoking rat model, discuss the pathogenesis of PH in COPD, study therapeutic potential of statins in COPD resulted from smoking.

Methods:

Animal Handling:

66 six weeks rats are randomly designed into three groups (22/each): control group, smoking group and statins group.

Rats in smoking group expose in smoke one hour in a self-made box where burning 20 cigarettes, twice a day for 4 weeks.

Rats in Statins group are intergastrically administrated statins (Simvastatin, 5mg/kg) right before exposing into smoke box (same as smoking group).

(Diamond filter cigarette: Tar, 11mg; Nicotine, 1.0mg; Carbon Monoxide, 11mg)

After anesthetization,

12 rats of each grup are performed intratracheal administration to assess lung function: Inspiratory resistance(Ri), expiratory resistance (Re); the valley value of lung dynamic compliance (Cdy); the forced expiratory volume in 0.3 second (FEV0.3); forced vital capacity (FVC)

10 rats of each group are performed right heart catheterization, inserting a catheter into pulmonary artery for measurement of pulmonary artery pressure.

Then euthanatization,

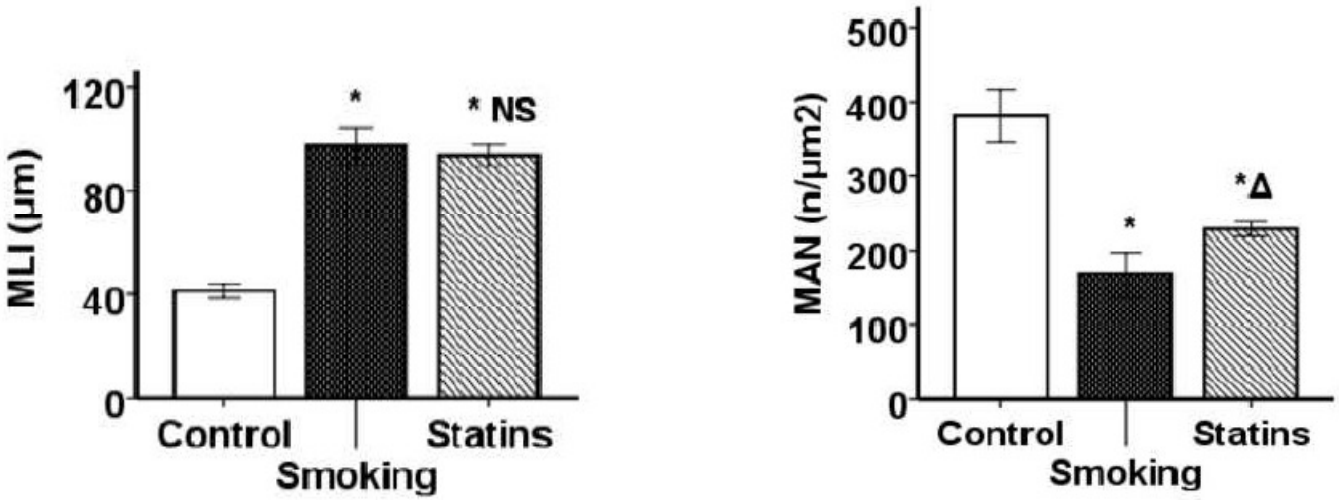
Two lobes of right lung are immediately frozen for isolating RNA later; Real-time RT-PCR are performed to assess the mRNA levels of IL17, IL21 and RORγt

Remaining two lobes of right lung are fixed for histology (H&E staining) and pathology study (IHC of IL17, IL21 and RORγt)

Left lung remains for collecting Bronchoalveolar Lavage Fluid (BALF) for cell counting

Results

Figure1, Structural changes of lung tissue in smoking rats



Mean Linear Intercept(MLI): mean inner diameter of alveoli
Mean Alveolar Number(MAN): the alveolar density

Smoking result in emphysema, statins milded emphysema with limitation

Figure2, Cell counting of BALF:

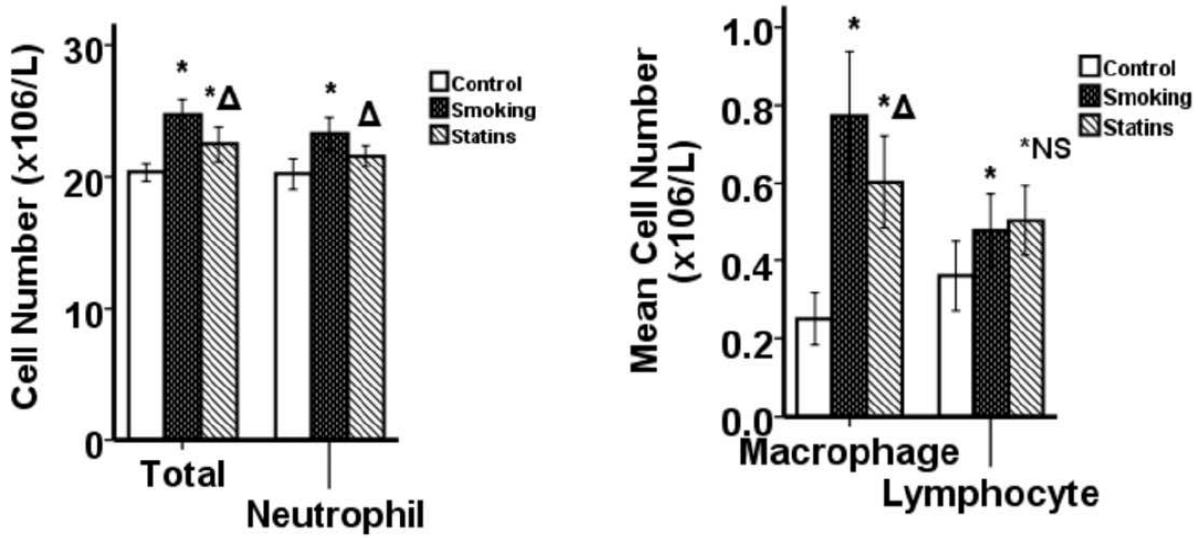
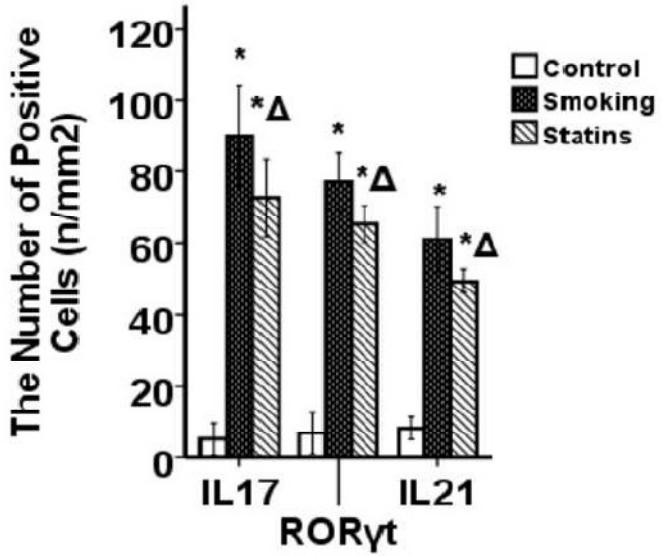


Figure3, IHC staining of IL17, IL21 and RORgt in lung tissue and bronches.



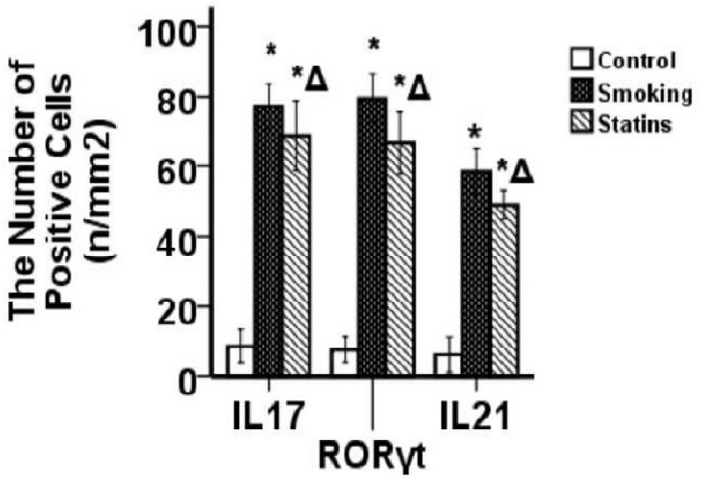


Figure 4. Real time RT-PCR of IL17, IL21 and RORγt of lung tissue.

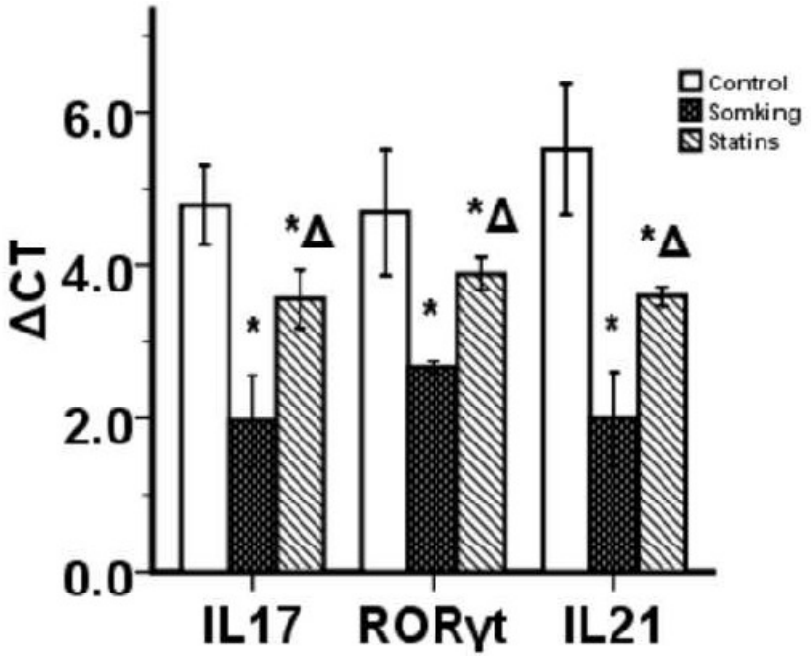
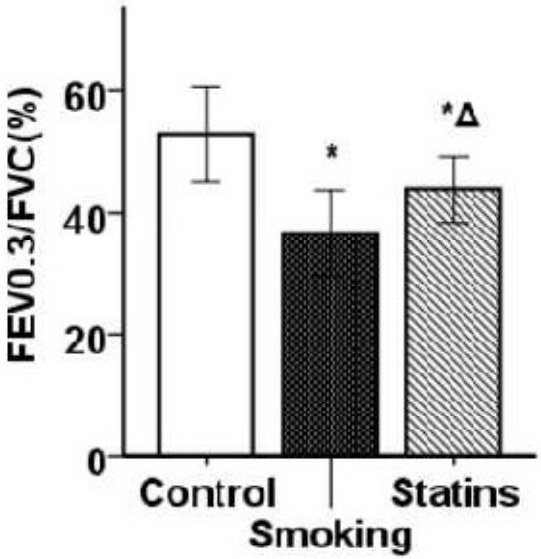
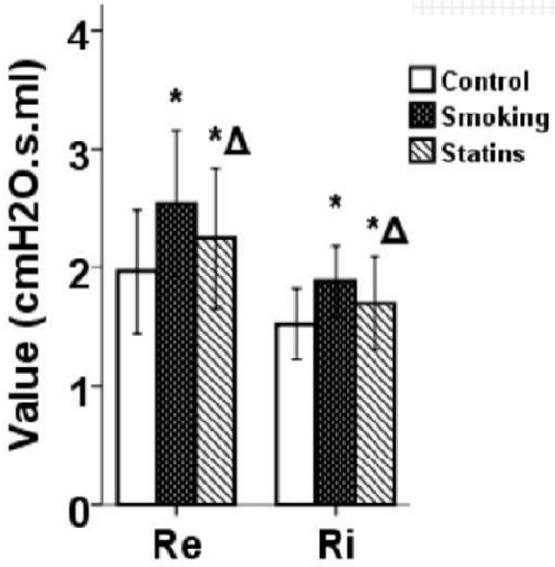


Figure5, Respirotary Function:





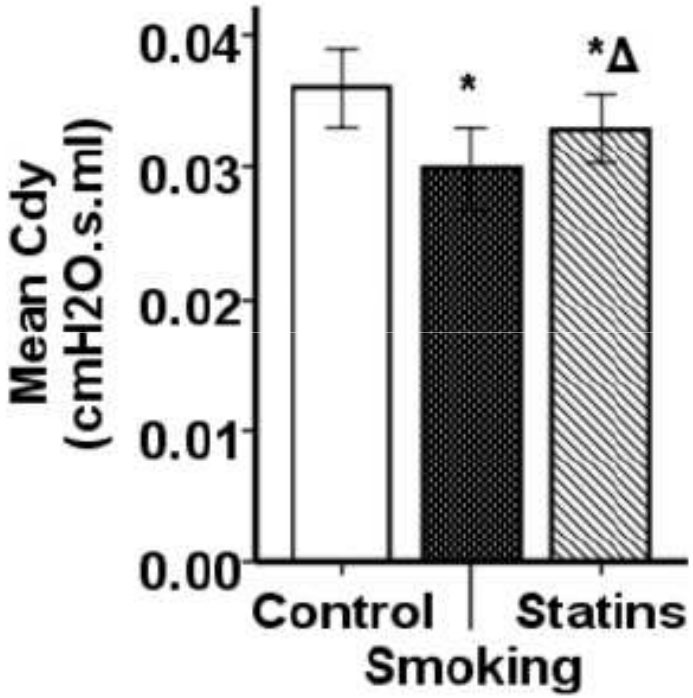
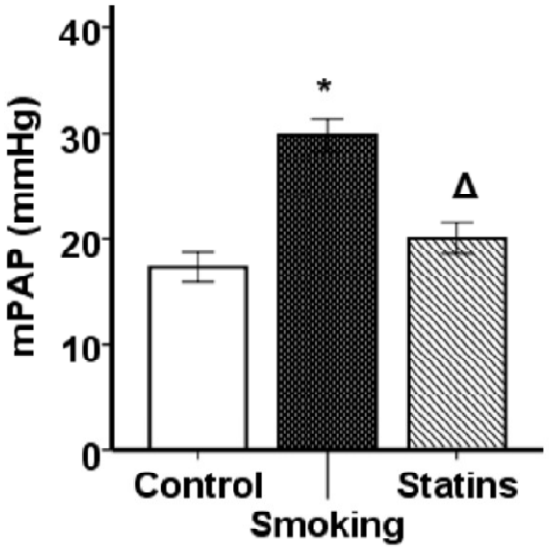

Mean Cdy
(cmH2O.s.ml)
0.04
0.03
0.02
0.01
0.00
*
*Δ
Control
Statins
Smoking

Figure6, Pulmontary Artery Pressure:



Conclusion:

1, COPD with PH rat model is well established, statins therapy only limitedly reversed the inflammation induced structral changes of lung

2, Expression of IL17, IL21 and RORγt increases at both transcript and translational levels, statins reduce their expression in smoking rats

3, Statins slightly improve the damaged respiratory function

4, Statins profoundly attenuate the palmonary hypertension

Thank You!