Oxidative stress in health and disease

Current role of antioxidants in lung diseases

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Where to start……

Questions arising in our minds ???

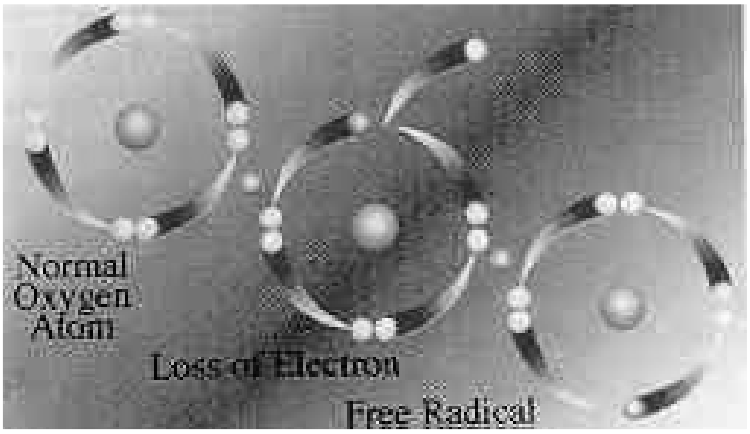
What are free radicals ?
What are reactive oxygen species ?
How do they cause injury ?
What are the consequences ?
What are the defense mechanisms ?
etc etc etc….

Basics of oxidative stress

What are free radicals

- Any species capable of independent existence that has one or more unpaired electrons
- Free radicals are highly unstable and reactive
- Stability can only achieved when they these electrons get paired
  - Superoxide ion $O_2^{\cdot}$
  - Hydroxyl radical $OH^{\cdot}$

Basics of oxidative stress



Basics of oxidative stress

- Oxygen radicals vs reactive oxygen species.
- A radical may donate or accept electron becoming either a reducing or oxidizing radical
- Reactions of free radicals proceed as chain reactions

Basics of oxidative stress

- Reactive oxygen species (ROS) - oxygen radicals and certain non radical oxidizing agents.
- Major oxygen radicals are ;
  - Superoxide
  - Hydroxyl
  - Peroxyl
  - Hydroperoxyl
  - Nitric oxide
  - Nitrogen dioxide

Basics of oxidative stress

- And reactive oxygen species are
  - Hydrogen peroxide
  - Hypochlorous acid
  - Ozone
- How do the free radicals react ?

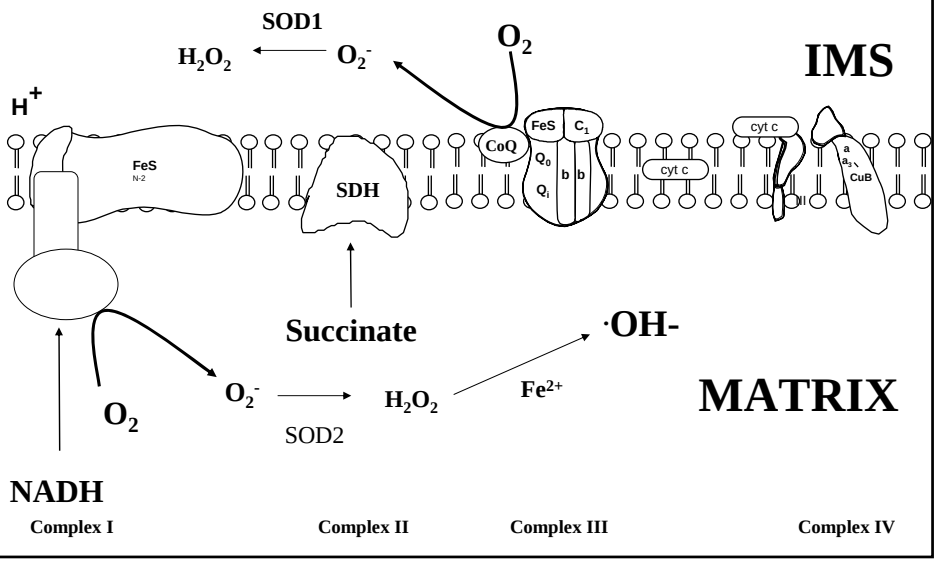
  Radical + Radical (pairing of electrons)

  $A^{\bullet} + A^{\bullet} \rightarrow A - A$

  Radical + Non-radical (transfer of electrons)

  $A^{\bullet} + B \rightarrow A + B^{\bullet} \rightarrow$ chain reaction…….

Reactive Oxygen species and the Respiratory Chain



Basics of oxidative stress

- Oxidative stress; implicated in various diseases.
- Why lungs??
  - exposed to higher concentrations of O_2
  - Larger surface area (approx. 100 m^2)
- Oxidants play imp. role in various pulmonary disorders

BPD
Asthma
COPD
Fibrosing alveolitis
ARDS
Bronchogenic carcinoma

Basics of oxidative stress

- ROS are produced in vivo in
  - Mitochondria to produce ATP by oxidative phosphorylation
  - Macrophages and neutrophils to kill bacteria
  - Reactions involved in cell signaling
- Most important are the reaction catalyzed by
  - NADPH (Nicotinamide dinucleotide phosphate)
  - XOR (Xanthine oxidoreductase)
  - MPO (Myeloperoxidase)

Basics of oxidative stress

- Major exogenous sources of ROS are
  - Air pollution
  - Tobacco smoke
  - Toxic wastes
  - Sunlight
  - Radiation

Basics of oxidative stress

- Superoxide
  - Most reactive oxygen metabolite
  - Generated in mitichondrial NADH dehydrogenase and the ubiquinone Q cytochrome B complex
  - Microsomal and nuclear membrane cytochromes
  - Cytoplasmic enzymes like Xanthine oxidase
  - Activated inflammatory cells
  - Endothelial cells
  - Spontaneously dismutates or scavenged by antioxidant mechs.

Basics of oxidative stress

- Hydrogen peroxide
  - More stable than superoxide - mitochondria, cytoplasm and endoplasmic reticulum through enzymatic and non enzymatic dismutation
  - Other enzymes like peroxisomal oxidases such as D-amino oxidase, urate oxidase and fatty acyl CoA oxidase.
  - Activated inflammatory cells
  - Also readily scavenged locally
- Hydroxyl radical
  - Formed in Fenton and Haber Weiss reaction
  - Detected at sites where superoxide and H_2O_2 are generated

Basics of oxidative stress

- Nitric oxide
  - EDRF formed from terminal guanidine nitrogen atom of L-arginine by NADPH dependent oxidation
  - Two principal forms iNOS and cNOS
  - Can be produced in neutrophils, macrophages and neuronal tissue.
  - iNOS are expressed in neutrophils, mast cells, smooth muscle cells, bronchial epithelial cells and fibroblasts and cNOS in endothelial cells, platelets, bronchial epithelial cells and neutrophils.
  - It can react with superoxide radicals to generate peroxynitrite
  - Has got both pro oxidant and anti oxidant properties.

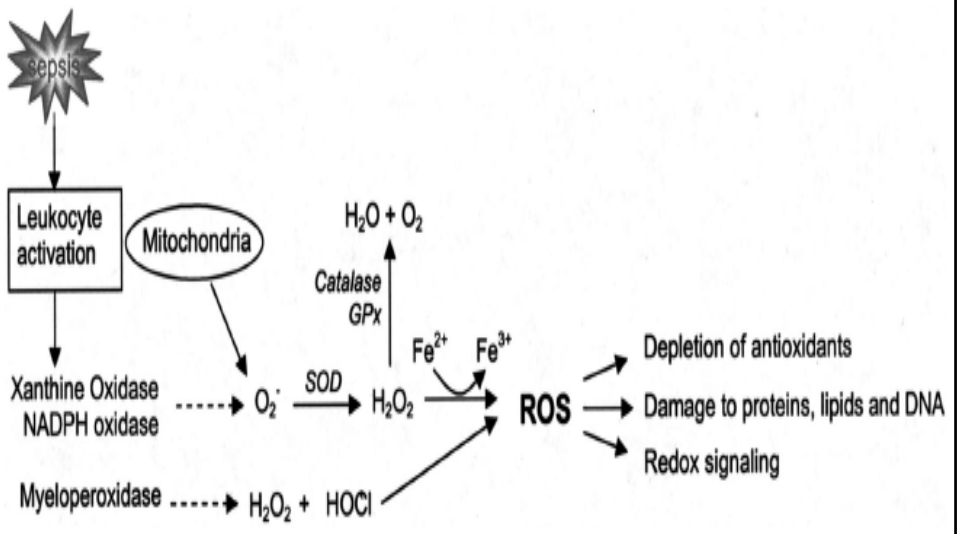
Basics of oxidative stress

- Other ROS
  - Hydroxyperoxyl radicals - superoxide -accepting one proton.
  - More reactive and causes more harm
  - Singlet oxygen can be formed from hydrogen peroxide and the hypochlorite ion

Effects of oxidative stress

- ROS - interact with numerous cellular components including DNA, lipids and proteins
- DNA base damage, single strand breaks ,protein cross links, DNA without base (apurinic and apyrimidinic sites)
- PUFAs are very susceptible to oxidant injury and can trigger lipid peroxidation
- Lipid radicals ;combine with dissolved oxygen and form peroxyl radical →attack membrane proteins / PUFA and propagate lipid peroxidation.

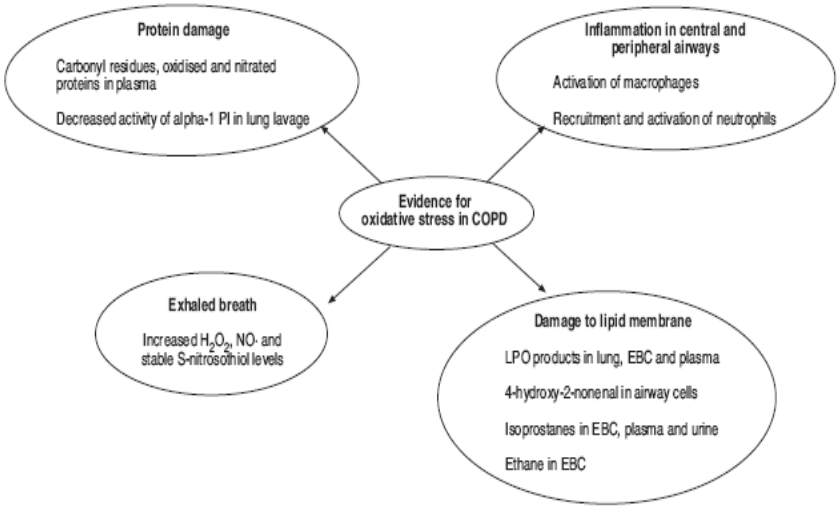
Effects of oxidative stress



Effects of oxidative stress

- Markers of oxidative stress
  - Elevated breath hydrogen peroxide and 8-isoprostane levels
  - Decrease plasma antioxidant capacity
  - Elevated plasma lipid peroxide levels
  - Plasma protein sulphahydryl oxidation
  - Increased exhaled CO levels
  - Release of ROS from peripheral blood neutrophils and AMs
  - Increased urinary isoprostane $F_{2\alpha}$-III levels

Effects of oxidative stress



Effects of oxidative stress

- Airway wall
  - Contraction of airway smooth muscle
  - Impairment of β - adrenoceptor function
  - Stimulation of airway secretion
- Pulmonary vascular smooth muscle
  - relaxation or contraction
  - Activation of mast cells
- Alveolar epithelial cell layer
  - Increased permeability by detachment
  - Decreased adherence
  - Increased cell lysis

Effects of oxidative stress

- Lung matrix
  - Decreased elastin synthesis and fragmentation
  - Decreased collagen synthesis and fragmentation
  - Depolymerisation of proteoglycans
  - Inactivation of α1-proteinase inhibitor
  - Inactivation of secretory leukoprotease inhibitor
- Pulmonary microcirculation
  - Increased permeability
  - PMN sequestration
  - Increased PMN adhesion to endothelium of arterioles and venules
  - Switch-on of TNF-α, IL-8 and other inflammatory protein genes

What are antioxidants??

- Antioxidants are substances whose presence in relatively low concentrations significantly inhibits the oxidation of the substrate/target
- Major natural antioxidants are:
  - Superoxide dismutase (SOD)
  - Catalase
  - Glutathione peroxidase

Antioxidant defense mechanisms

- Lungs have efficient antioxidant defense mechanisms
  - Thin and highly complex layer of lining fluid (RTLF)
  - Vitamin C, Urate, Vitamin E and extracellular SOD, catalase and glutathione peroxidase.
  - Mucopolypeptide glycoproteins, cerruloplasmin, Fe binding proteins and small molecules like bilirubin.

Antioxidant defense mechanisms

- Major enzymes include
  - SOD
  - Glutathione peroxidase
  - Catalase
- SOD has got central role in protecting tissues against oxidative stress
- Three different types are known
  - CuZnSOD (Cytosol)
  - MnSOD (Mitochondria)
  - ECSOD (Extracellular matrix)

Antioxidant defense mechanisms

- ECSOD - least abundant in tissues ;major antioxidant in the extracellular spaces
- Catalase decomposes H_2O_2 to water and oxygen - peroxisomes.
- Glutathione redox cycle - central mechanism in scavenging alkyl hydroxyperoxides, but it also metabolizes H_2O_2.
- The two main enzymes involved are glutathione peroxidase and glutathione reductase
- Severe stress - catalase

Antioxidant defense mechanisms

- Lung cells differ profoundly in in their resistance to oxidative stress
- Little known about the antioxidant enzyme distribution
- Antioxidant enzymes - expressed in human airways Bronchial epithelial cells - low MnSOD and catalase activities.
- Human alveolar macrophages - efficient antioxidant capacities and express the mRNA for MnSOD
- Epithelial lining fluid have fair antioxidant activity

Antioxidant defense mechanisms

- Regulation of antioxidant mechanisms - complex.
- Related to cytokine release and not only hyperoxia
- Major cytokines taking part are TNF-α, IL-1, IL-6 and endotoxins
- Exogenous toxins induce protein transcription like asbestos, other fibrogenic materials and radiation etc.
- The balance of oxidant and antioxidant activity is more important than individual enzyme activity

This the essence of oxidative stress

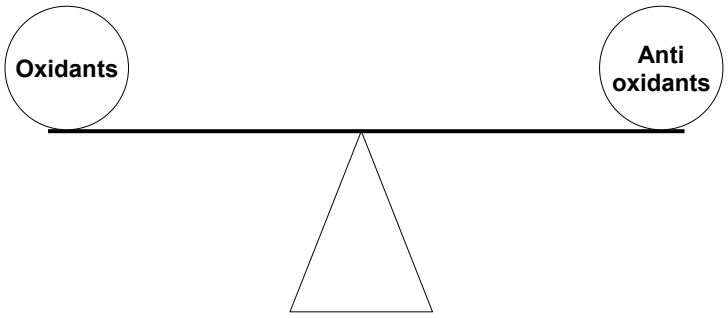
What is oxidative stress??

- A <u>disturbance in the pro-oxidant – anti-oxidant balance</u> in favor of the pro-oxidant leading to potential damage

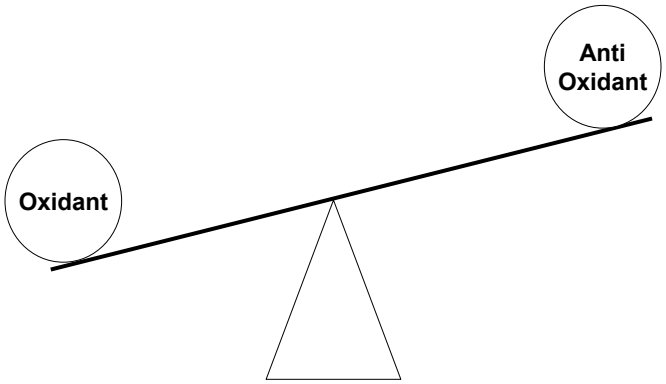
<u>OR</u>

- A process whereby the metabolic balance of a cell is disrupted secondary to accumulation of free-radicals

Oxidative stress



Oxidative stress



Life is full of stress !!!

Oxidative challenge throughout life

Birth and premature infant

- Exposure to sudden high concentration of o_2 at birth
- Premature infants are predisposed to oxidant damage and have high risk of developing BPD

  Vyas et al 2001, Boda et al 1998
- Antioxidant supplementation may help but evidence is lacking

  Rosenfield et al 1996, Davis et al 2000

Life is full of stress !!!

Childhood

- Lung growth continues throughout early childhood into adulthood
- Chronic pulmonary diseases - maximum lung size, length of plateau and rate of decline of lung function.
- Vitamin C and A supplementation → affect normal development and prevention of lung function decline

  Soutar et al 1997, Romieu and Trenga 2001
- Decreased incidence of asthma and eczema with maternal intake of Vitamin E

  Martindale et al 2005

Life is full of stress !!!

- Various reports of poor lung function with diet deficient in fruits and vegetables and vitamin A,C and E

Gilliand et al 2003

- Others - inconsistent with vitamin C supplementation and no association between vitamin C concentration and FEV_1

Cook et al 1997

Life is full of stress !!!

Adulthood

- In adults - increasing evidence that diet rich in fruits and vegetables has protective action on lung function

Britton et al 1995

- Individuals with higher vitamin A intakes tend to have better lung function

Tockman et al 1986, Morbia et al 1989

- Vitamin C is positively associated with FEV_1(NHANES)

Life is full of stress !!!

- Vitamin C and β carotene but not vitamin E are positively associated with FEV_1

  MORGEN STUDY

- Higher intake Vitamin C but not A, E and Mg are associated with slower rate of decline of FEV_1

  Mc Keever et al 2002

Life is full of stress !!!

- Relationship between concentration of antioxidant and lung function -not clear
- Vitamins required to provide protection to healthy adult is finite but FEV_1 - unaffected by vitamin supplementation in vitamin replete individuals

  Mudway et al 2000

- Decrease in decline in lung function with vitamin supplementation

  Romieu et al 1998 and Greivank et al 1999

Life is full of stress !!!

Old age

- Increasing age is accompanied with a progressive decline in lung function
- Quality of diet may affect the loss of lung function

  Kelly et al 2003
- Vitamin E in elderly subjects has been correlated to lung function

  Dow et al 1996

Oxidative stress in respiratory disease

Asthma

- Convincing evidence that acute asthma on adults is accompanied by oxidative and nitrosative stress

  Henricks and Nijkamp 2001
- Inflammatory cells from peripheral blood and BALF of asthmatic subjects generate more superoxide ions and exhaled air also shows increased concentrations of markers oxidative and nitrosative stress.

  Cluzel et al 1987, crappo and Day 1999, Montuschi et al 1999, Corradi etal 2001, Kaminsky et al 1999
- Low levels of antioxidants have also been demonstrated in subjects with asthma.

Oxidative stress in respiratory disease

- Bronchial epithelial cells - patients with asthma not receiving corticosteroids - found to possess less CuSOD
- Loss of SOD activity was also seen within minutes of instillation of antigen in the lung of individuals with atopic asthma.

  De Raeve et al 1997, Comhair et al 1997
- Changing eating habits - correlated with increasing incidence of asthma in westernized societies

  Mc Keever and Britton 2004, Seaton et al 1994, Chen et al 2004

Oxidative stress in respiratory disease

- Reduced risk of asthma - vitamin A,C,E, flavones and flavinoids ,Mg, Ca, Na, Cu, Zn, and fatty acids

  Schwartz and Weitz 1990, Greene 1995, bodner et al 1995, Smit et al1999, Fogarty and Britton 2000, Grievink et al2000, Hijazi et al 2000, Romieu and Trenga 2001, Smit 2001
- However longitudinal studies have shown that only vitamin E has got protective effect.

  Troisi et al 1995
- In a recent review - diet playing a major role in asthma severity is far from being proved

  Mc Keever and Britton 2004

Oxidative stress in respiratory disease

- Evidence in support of the concept that antioxidants might influence asthmatic pathobiology
  - T-helper 1 and 2 cytokines are differently regulated under conditions of oxidative stress (*Malmberg et al 2001*)
  - Apoptotic pathways are modulated by antioxidants(*Droge 2002*)
  - Decreased phagocytic and non phagocytic NADPH oxidase activities (*Halliwel 2000*)
  - Production of NO (*Mak et al 2002*)
- No effect - vitamin C, E and Mg on asthma control.

Fogarty et al 2003, Pearson et al 2004

Oxidative stress in respiratory disease

- N-acetyl cysteine is a cellular precursor of glutathione and becomes deacetylated in gut to cysteine.It has potential to counteract oxidative stress.
- Ambroxyl a mucolytic also scavenges $OH^{\bullet}$ and HOCl
- Apocyanin a NADPH oxidase inhibitor prevents generation of ROS by inflammatory cells
- SOD also can combat oxidative stress.

No clinical trials on above agents in Asthma

Oxidative stress in respiratory disease

Chronic obstructive airway disease

- Cigarette smoke contain 10^{12} free radicals - potent source of oxidants
- Deficiency of antioxidants - correlated with low FEV_1 and FVC in patients with COPD

  Taylor et al 1986
- Plasma antioxidant capacity - decreased in patients with COPD.

  Rahman et al 1996, 2002
- Depletion of vitamin C, E ,β carotene and Se in COPD

  Pelletier et al 1970, chow et al 1986, Bridges et al 1990, Mezzeti et al 1995, Brown et al 1997

Oxidative stress in respiratory disease

- Elevated levels of GSH - BALF of subjects with COPD

  Cantin et al 1987, Linden et al 1989
- Marginal increase in Vitamin C and decreased vitamin E

  Bui et al 1992, Pacht et al 1991
- Erythrocytes from cigarette smokers - increased levels of SOD and catalase - protect endothelial cells from H_2O_2

  Toth et al 1986

Oxidative stress in respiratory disease

- Diet - an important risk factor for COPD
- Most cross-sectional studies show a beneficial effect of β-carotene and vitamin C

  Britton et al 1995, Chuwers et al 1997, Grievink et al 1998 and Hu et al 1998

- Many other studies - no beneficial effects with intake vitamin C, E or β carotene

  Miedema et al 1993, Grievink et al 1998, 2000, Tabak et al 1998

Oxidative stress in respiratory disease

- NHANES II did observe beneficial effect of dietary and vitamin C on chronic bronchitis symptoms
- ATBC trial - beneficial association with presence of COPD at baseline but not after 6 years
- Results confusing and inconsistent

Lag time - lung function differs from that for respiratory symptoms
Lung functions are more sensitive measure than symptoms

Oxidative stress in respiratory disease

- Some evidence that vitamins can decrease oxidative stress
- Oral use of NAC ↓ the number of exacerbations

  Boman et al 1983, Rasmussen and Glengow 1988, British thoracic society research committee 1985, Bridgmen et al 1991,1994
- Nacystelyn - lysine salt of NAC - an aerosol without side effects

  Gillisen et al 1997
- Molecularly manipulated glutathione and recombinant SOD

Oxidative stress in respiratory disease

- NAC has been extensively studied in COPD for its efficacy as an antioxidant
- It has got antioxidant activity, mucolytic properties and anti-inflammatory activity
- Carrier of free thiol (SH) group

  $2(R\text{-}SH) + H_2O_2 \rightarrow R\text{-}S\text{-}S\text{-}R + 2\ H_2O$
- Reduces the production of superoxide anion
- Powerful scavenger of HOCl (causes proteolytic damage), $OH^{\cdot}$

Oxidative stress in respiratory disease

- NAC: a precursor of Glutathione
- NAC penetrates the cell & is deacylated to form cysteine
- This cysteine is then used for the synthesis of GSH

Results demonstrate the ability of NAC to reduce sputum consistency rapidly & completely in both mucoid & purulent secretions

Am Rev Respir Dis 1967;96(5): 962-70

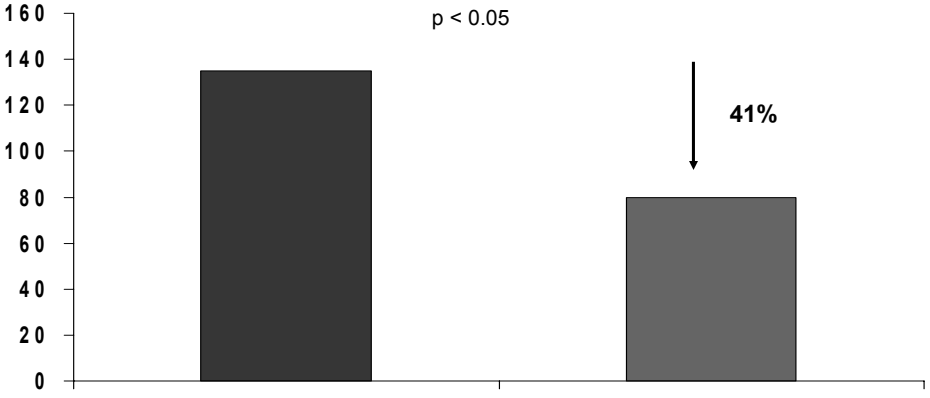
Oxidative stress in respiratory disease

Other effects of NAC

- Increase in phagocytic activity of alveolar macrophages
- Decrease in the amounts of superoxide radicals
- Reduction in activity of ECP, lactoferrin, anti- chymotrypsin
- Elastase activity reduced
- Inhibition of the activation of NF-κB
- Inhibits the expression of VCAM-1
- Inhibition of 'acrolein', toxic substance in cigarette smoke
- NAC prevents the cigarette smoke induced small airways alterations in rats

NAC in COPD

Reduction in exacerbations



N = 169
T = 6 mnths
Baseline FEV1: ~ 60 % pred

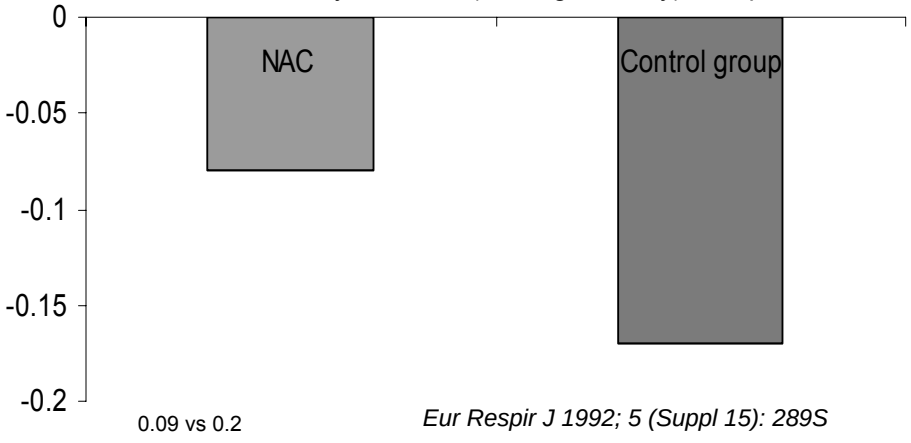
Respiration 1999;66:495-500

Standard therapy: β_2 agonists,anticholinergics, theophylline, ICS/OCS

NAC in COPD

Lower decline in lung function

Results after 2 years NAC (300 mg x 2 daily), 140 pts



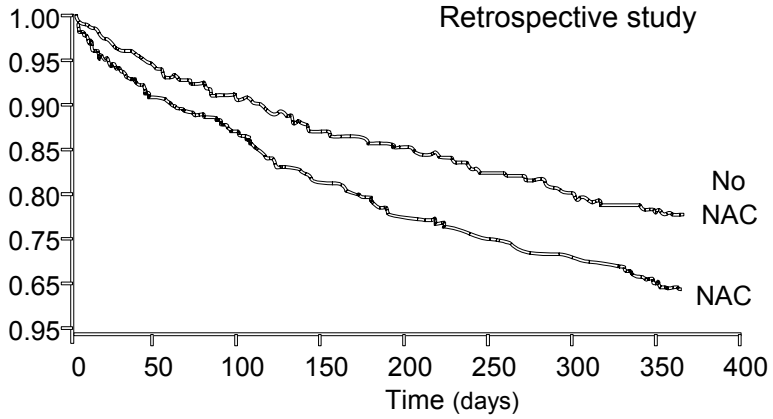
0.09 vs 0.2

* P =0.03

Eur Respir J 1992; 5 (Suppl 15): 289S

NAC in COPD

Lower risk of re- hospitalisation

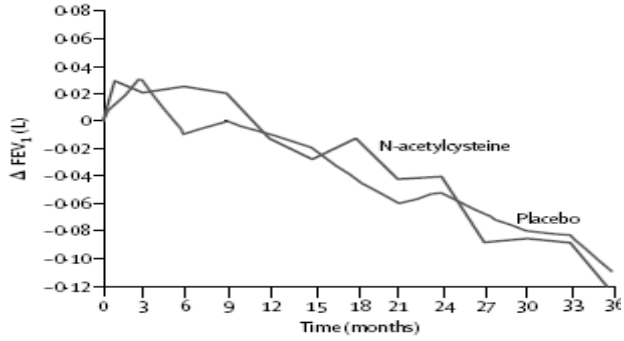


~ 30 % risk reduction

Eur Respir J 2003;21(5): 795-798

BRONCUS study

- **50 centers, 523 COPD patients, RCT**
- **600 mg/d NAC or placebo**



Lancet 2005; 365: 1552-1560

BRONCUS study

- Number of exacerbations/year- did not differ between groups
- No change in HRQOL scores
- Subgroup analysis- exacerbation rate ↓ in patients not treated with ICS
- Subgroup analysis- ↓ in hyperinflation

Lancet 2005; 365: 1552-1560

Oxidative stress in respiratory disease

Idiopathic pulmonary fibrosis

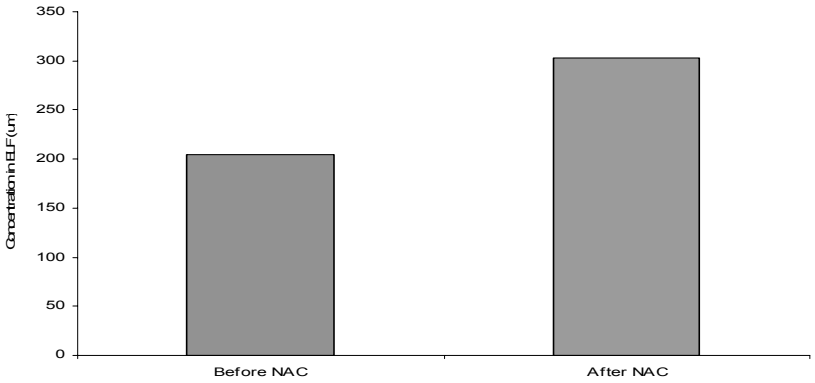
- ELF GSH shows a 4 - fold decrease in levels in patients with IPF

Am Rev Respir Dis 1989; 139: 370-372

- Alveolar macrophages in patient with IPF produce significantly more superoxide than controls
- Recently - patient with IPF have higher serum levels of CuZnSOD - correlate with disease activity
- Antioxidant may have a role in combating oxidative injury in patients with IPF

Oxidative stress in respiratory disease

Increase in ELF GSH



600 mg x 3; 12 wks; + std therapy,

18 pts; P < 0.005

Am J Respir Crit Care Med 1997; 156: 1897-1901

Oxidative stress in respiratory disease

- IFIGENIA trial (Idiopathic pulmonary Fibrosis International Group Exploring NAC I Annual)
- 600 mg tid NAC + standard therapy

  (azathioprine 2 mg/kg/day + prednisolone 0.5 mg/kg/day)
- 155 patients, 12 months

N Engl J Med 2005 353;21

Oxidative stress in respiratory disease

	Baseline	NAC	Placebo	
	Mean ± SD	Adjusted means (SE)	Adjusted means (SE)	p
				0.019
				0.011

9% improvement in VC

24% improvement in DL_{CO}

First study to show positive results for a pharmacologic therapy in IPF

VC: Vital Capacity

DL_{CO}: diffusion capacity of the lung for carbon monoxide

N Engl J Med 2005 353;21

Oxidative stress in respiratory disease

- Dyspnea : 22%
- CRP : 8.6%
- V_{O_2} : 7.5%
- W_{max} : 4.0%

A trend for better evolution by adding NAC to standard treatment

CRP: Clinical, radiological, physiological scores

VO_2: the oxygen uptake

Wmax: Maximum work rate

N Engl J Med 2005 353;21

Oxidative stress in respiratory disease

- Aerosolized NAC- 30 patients with IPF
- No benefit in physiological variables

Respirology 2005; 10: 449–455

Other compounds not studied ; No data

Oxidative stress in respiratory disease

Cystic fibrosis

- Patients with cystic fibrosis - evidence linking an intake of dietary antioxidants with higher FEV_1 and FVC
- Malabsorption of fat soluble vitamins contribute.

Bye et al 1985, Hommick et al 1993

- Recurrent respiratory infections activate repeated oxidative stress and low levels of vitamin C - documented
- Supplementation of β carotene reduces markers of oxidative stress

Brown et al 1997 , Winklhoofer-Roob et al 1997

Oxidative stress in respiratory disease

- Vitamin C - effect functioning of CFTR gene ; nasal instillation have been documented to increase Cl^- transport *in vivo*.
- Vitamin C may act as effective nutraceutical and pharmaceutical to decrease respiratory infection in these patients

No clinical data

Oxidative stress in respiratory disease

Acute respiratory distress syndrome

- Cochrane et al - showed that α_1 proteinase inhibitor is inactivated in in RTLF of patients with ARDS
- Enhanced oxidant generation and inadequate antioxidants - progression of ARDS.

  Pacht et al 1991, Repine et al 1992, Metnitz et al 1992, Lang et al 2002
- Decreased plasma concentration vitamin C, ubiquinol-10 vitamin E, β carotene and Se have been documented in ARDS

  Cross et al 1990, Metnitz et al 1999

Oxidative stress in respiratory disease

- ARDS - marked reduction in GSH levels have been shown by Pacht et al
- Antioxidant therapy may be beneficial in ARDS
- Several studies have attempted use of NAC as a therapeutic agent in ARDS

Suter et al 1994, Wash and Lee 1999

- Glutathione deficiency was corrected ; progression, morbidity and mortality unchanged

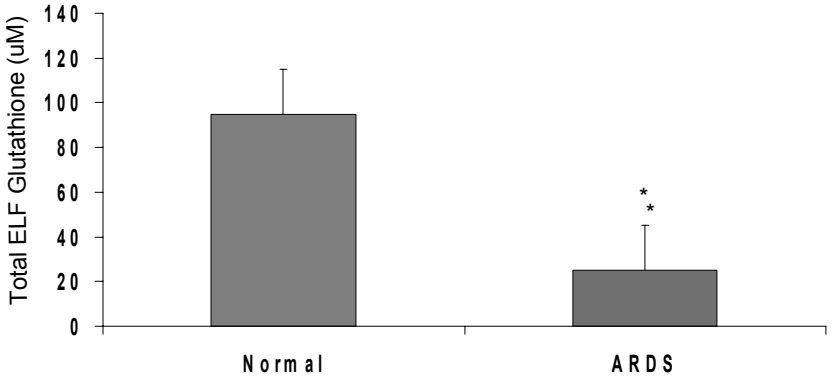
Bernard et al 1997

- Prophylactic supplementation with vitamin C and E - decreased morbidity in critically patients

Nathens et al 2002

ELF GSH concentrations in ARDS

Concentration of GSH in alveolar fluid of patients with ARDS is **fourfold to five fold lower** than that in normals



Total GSH concentration in ELF of patients with ARDS compared to normal subjects. There was a significant deficiency of GSH in patients with ARDS compared to normal subjects (p=0.002)

Chest 1991;100:1397-1403

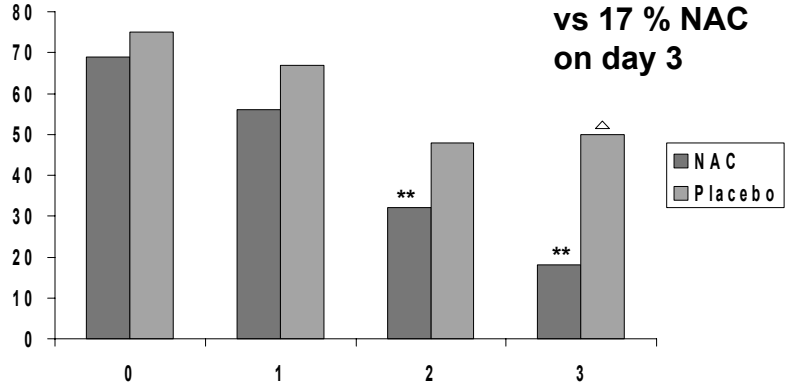
NAC in ARDS

- NAC 40 mg/kg/day (IV) for 3 days in patients with mild to moderate (LIS :1.38 ± 0.95) ARDS in addition to standard therapy
- 61 patients

Chest 1994;105:190-194

Reduced need for ventilatory support

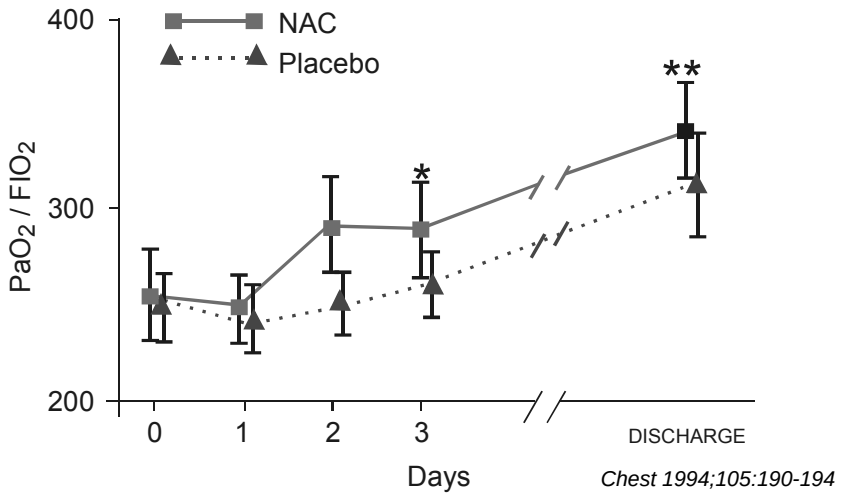
69 % placebo vs 17 % NAC on day 3



Percentage of patients requiring mechanical ventilatory support in the N-acetyleysteine (NAC) and placebo group. Evolution form days 0 (admission) through day 3 (end of NAC treatment). The triangle identifies a significant difference between the two groups at day 3 (p = 0.01). The asterisks identify a significant difference in the treated group on day 2 and 3 vs admission (day 0; p = 0.01).

Chest 1994;105:190-194

Significant improvements in oxygenation index



Chest 1994;105:190-194

NAC in ARDS

- Difference between FiO_2 between the 2 groups was significant on day 3
- **Lung injury score decreased** from 1.39 $\pm$ 0.95 to 0.67 $\pm$ 0.7 ($p<0.01$), between ICU admission & day 10
- 1 month **mortality rate was 22% for NAC** group and 35 % for the placebo group (NS)
- Fewer patients in the NAC group required mechanical ventilation

NAC in ARDS

- Although early results of anti-oxidant therapy were promising…
- N-acetylcysteine (five trials - 239 patients- RR 0.89, 95% CI 0.65 - 1.21)
- A large phase III trial of procysteine was stopped early - mortality in the treatment arm
- No role in routine management of ARDS

Brower RG, et al. Chest 2001; 120:1347-1367

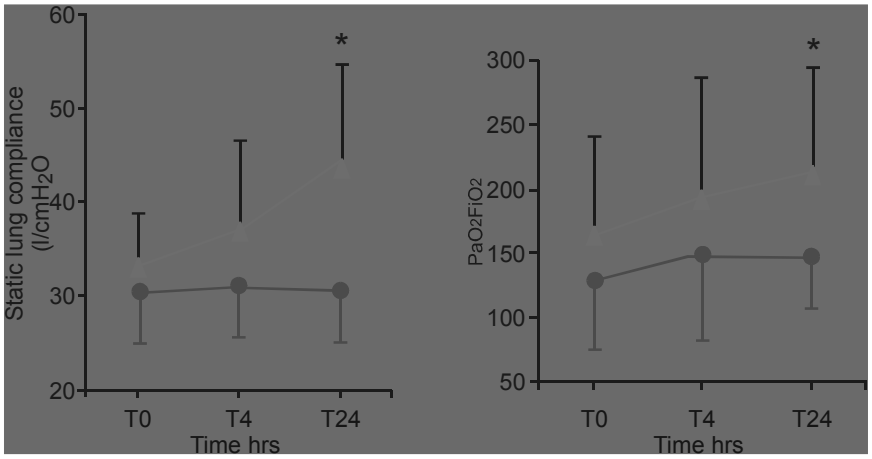
Adhikari N et al, Cochrane Database Syst Rev 2004; 4: CD004477

Oxidative stress in respiratory disease

Septic Shock

- NAC + std Rx vs. Placebo + std Rx
- NAC administered in 5% dextrose:
  - 150 mg/kg in 250 ml over 15 mins, followed by a continuous infusion of 50 mg/kg in 500 ml over 5 hrs
- Standard therapy: fluid administration with crystalloids & colloids, dobutamine, dopamine and/or norepinephrine, broad spectrum antibiotics

Improvement in systemic & pulmonary hemodynamics



△ NAC,○ placebo

Chest 1998;113:1616-24

Improvement in systemic & pulmonary hemodynamics

- Hospital mortality was similar in both groups.
- NAC treated survivors had shorter duration of MV & Shorter ICU stay
- Less complicated weaning period

Chest 1998;113:1616-24

NAC in severe sepsis

NAC treatment aggravated sepsis-induced organ failure, in particular cardiovascular failure (35 patients)

Role of NAC in severe sepsis- NOT CLEAR

SALVAGE

Chest 2005; 127:1413–1419

Oxidative stress in respiratory disease

Lung Cancer

- High content of oxidants in smoke - causation of lung cancer and its progression
  Pryor et al 1997, Hecht et al 1999, Chandel and Schumacker 2000
- Reduced risk of lung cancer with diet rich in vegetables and fruits
  Steinmetz and potter et al 1991
- β carotene inversely related to risk of lung cancer
  Nomura et al 1985, Menkes et al 1986,, Wald et al 1988, comstock et al1997

Oxidative stress in respiratory disease

- ATBC and CARET - increased risk of developing lung cancer
- Vitamins have not been linked with risk of lung cancer in most of studies
- Other studies show a variable results
- Supplementation with antioxidant and vitamins can not be recommended for prevention of lung cancer.

Oxidative stress in respiratory disease

NAC in contrast induced nephropathy

- Prevention
- 600 mg 12 hrs before procedure immediately before and 12 hrs. after procedure
- 8 meta-analyses have shown benefit with use NAC prevention of CIN

Oxidative stress in respiratory disease

Other lung diseases and complications

- Free radicals also participate in the pathogenesis of sarcoidosis and asbestosis

  Kastella et al 1989, kamp et al 1991 ,Kinnula et al 1999

- Paraquat induced lung injury - oxidative stress

- Chemotherapeutic agents like anthracyclines, bleomycin, antimetabolites and antibiotics also lead to lung injury by ROS mediated mechanisms

  Tamagawa et al2000, Halliwell and Guteridge 1996

Oxidative stress in respiratory disease

- Oxidative stress has also been linked to OSAHS
- The severity of OSA is independently associated with oxidative stress.

  (Chest 2005; 127:1674–1679)

- Oxidative stress levels - higher in exudative pleural effusions compared to transudative effusions, probably due to reactive oxygen species produced in the former.

  (Chest 2005; 128:3291–3297)

- No data to support or refute use of antioxidants in these situations

Carry home messages!!

- Oxidative stress implicated in a host of pulmonary diseases
- Increasing role of application of antioxidants in various pulmonary diseases
- Can be promising therapy in ARDS, IPF and other inflammatory conditions
- More large controlled trials needed to form an opinion