INSUFFICIENZA RESPIRATORIA E sNOX2-dp

STUDIO SPERIMENTALE SULLO STRESS OSSIDATIVO NELL'INSUFFICIENZA RESPIRATORIA E SUL RUOLO PROTETTIVO DELLA NIV

E. Bresciani, A. Garramone, E. Fante, M,Corinti, R. Cangemi, P. Pignatelli

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Oxidative Stress in Airway Diseases

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Abstract

Airway oxidative stress is broadly defined as an imbalance between prooxidative and antioxidative processes in the airway. Given its direct exposure to the environment, the lung has several mechanisms to prevent an excessive degree of oxidative stress. Both enzymatic and nonenzymatic systems can buffer a wide range of reactive oxidative species and other compounds with oxidative potential. In diseases like asthma and chronic obstructive lung disease, airway oxidative stress can occur from a number of sources, including greater exposure to environmental prooxidants, airway infiltration of inflammatory cells, metabolic deregulation, and reduced levels of antioxidants. Airway oxidative stress has been associated with worse disease severity, reduced lung function, and epigenetic changes that can diminish response to steroids. Although oxidative stress has been linked to a wide range of adverse biological effects, it has also been associated with adaptive responses and with resolution of inflammation. Therefore, more than being an imbalance with a predictable threshold after which disease or injury ensues, oxidative stress is a dynamic and continuous process. This might explain why supplementing antioxidants has largely failed to improve diseases such as asthma and chronic obstructive pulmonary disease. However, the therapeutic potential of antioxidants could be greatly improved by taking an approach that considers individual and environmental risk factors, instead of treating oxidative airway stress broadly.

Keywords: oxidative stress; asthma; chronic obstructive pulmonary disease

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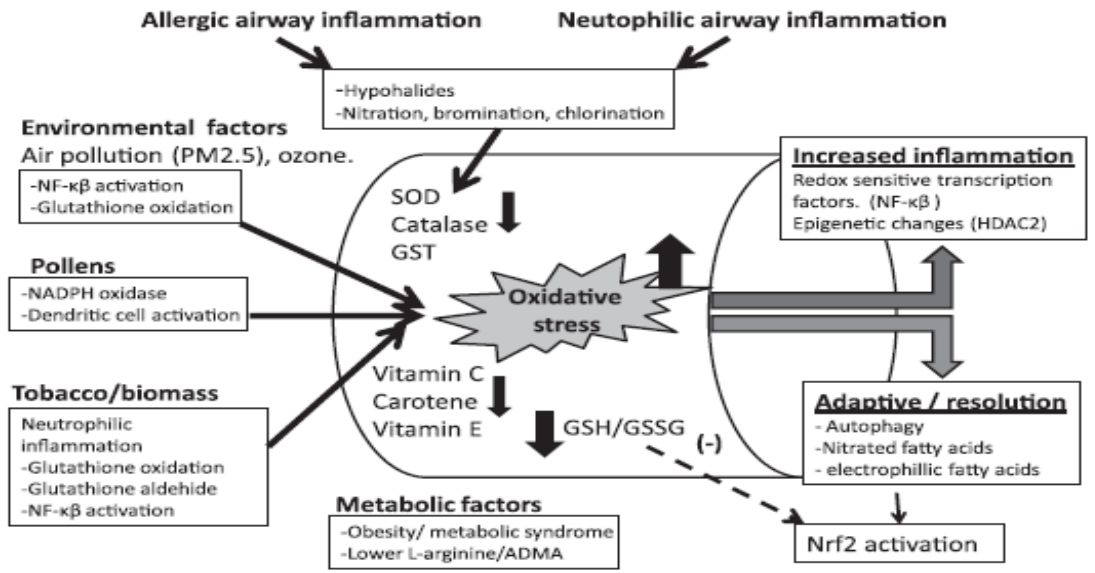

Figure 1. Conceptual overview of airway oxidative stress sources and mechanisms in asthma. The figure captures the conceptual framework related to airway oxidative mechanisms throughout the paper. ADMA = asymmetric dimethylarginine; GSH = reduced glutathione; GSSG = oxidized glutathione; HDAC2 = histone deacetylase–2; NADPH = nicotinamide adenine dinucleotide phosphate; NF-κB = nuclear factor κB; Nrf2 = nuclear factor (erythroid-derived 2)-like 2; PM2.5 = particulate matter < 2.5 μm; SOD = superoxide dismutase.

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Targeting oxidant-dependent mechanisms for the treatment of COPD and its comorbidities☆

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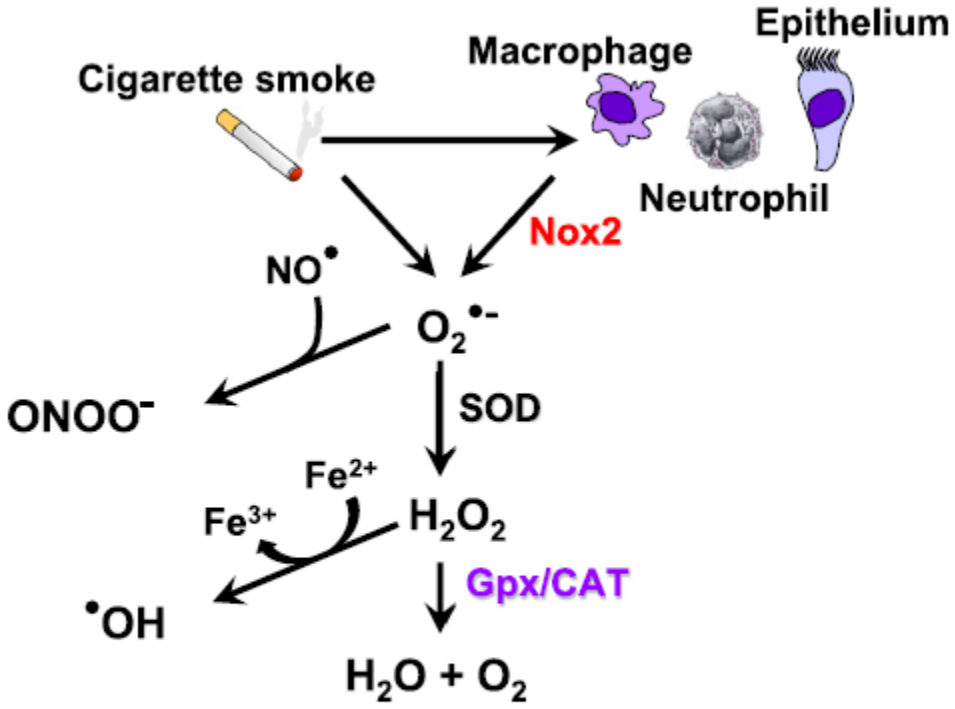

Fig. 2. Cellular generation of reactive oxygen and nitrogen species in COPD. Cigarette smoke acts on inflammatory cells in the lung (e.g., macrophages, neutrophils, epithelium) where activation of NADPH oxidase 2 (Nox2) generates superoxide radicals. ($O_2^{\bullet-}$) which can then either react with nitric oxide (NO•) to form the reactive peroxynitrite molecule ($ONOO^-$) or be rapidly converted to hydrogen peroxide (H_2O_2) via the enzymatic activity of superoxide dismutase (SOD). In the presence of Fe^{2+}, H_2O_2 can be converted into the more damaging hydroxyl radical (•OH) via the Fenton reaction. This reaction causes the oxidation of Fe^{2+} to Fe^{3+}, and in this oxidation state, the presence of iron can directly generate •OH from $O_2^{\bullet-}$. These iron reactions have increased importance in COPD as a higher concentration of iron has been reported in the lungs of smokers, thereby increasing the potential ROS burden (Gloire et al., 2006). The glutathione peroxidase (Gpx) family of enzymes, and catalase (CAT) are responsible for the conversion of H_2O_2 into harmless water and oxygen, which effectively reduces circulating ROS and thus reduces the oxidative burden (Vlahos & Bozinovski, 2013).

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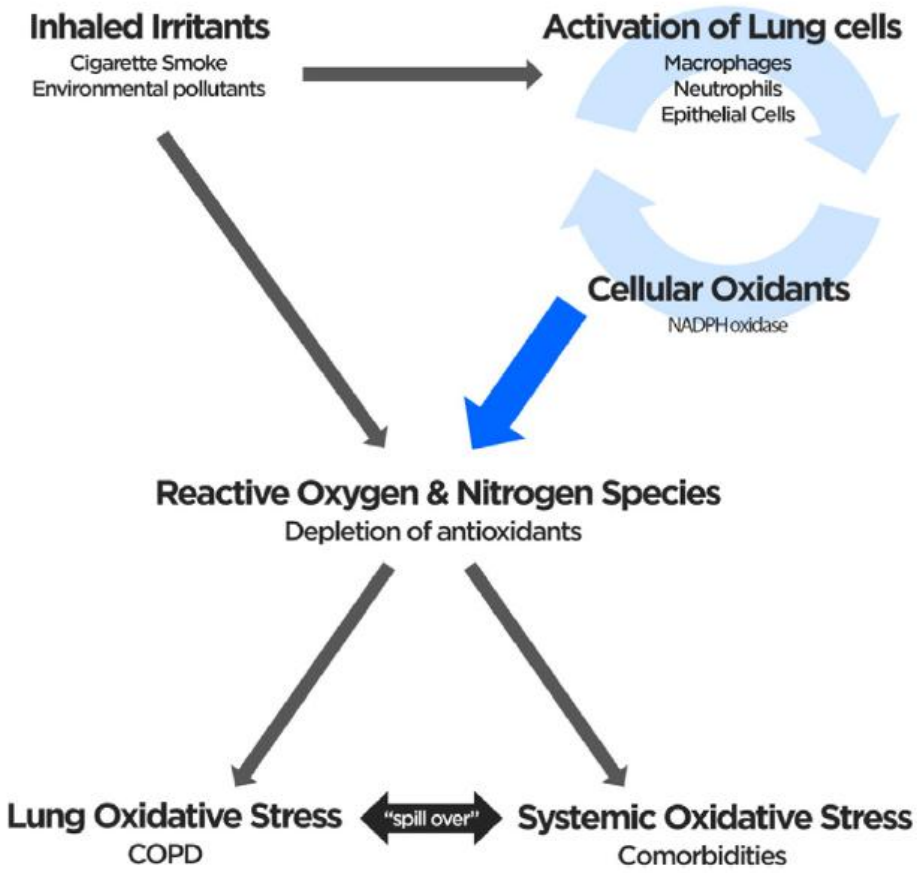

Fig. 1. Overview of oxidative stress in the pathogenesis of COPD. The generation of reactive oxidant species both exogenously and endogenously can lead to the onset and development of COPD and its comorbidities. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are found in cigarette smoke but in COPD the primary sources of ROS and RNS are from inflammatory cells including macrophages, neutrophils and epithelial cells. When activated by inhaled irritants (e.g., cigarette smoke), enzymatic (e.g., NADPH oxidase) generation of oxidants leads to the depletion of scavenging antioxidants (e.g., vitamin E), resulting in oxidative stress.

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Clinical Science (2016) **130**, 1039–1050 doi: 10.1042/CS20160043

Review Article

COPD and stroke: are systemic inflammation and oxidative stress the missing links?

Victoria Austin*, Peter J. Crack†, Steven Bozinovski*‡, Alyson A. Miller*[1] and Ross Vlahos*‡[1]

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"…Evidence indicates that aging and smoking produce vascular impairments, at least in part, by promoting oxidative stress, which is driven primarily by the NADPH oxidases. Perhaps the best characterized mechanism by which oxidative stress can cause vascular dysfunction is via the inactivation of endothelial-derived NO by O2 •−. This reaction reduces the bioavailability of NO and thus nullifies its vasodilator, anti-platelet, anti-proliferative and anti-inflammatory properties. In addition, ROS can directly promote inflammation in the vessel wall by inducing the production of cytokines and pro-inflammatory genes through the activation of NF-κB. Importantly, whereas oxidative stress may set the stage for inflammation, it in turn accentuates ROS production, creating a vicious cycle that worsens vascular dysfunction. Indeed, pro-inflammatory cytokines such as TNF-α and IL-6 alter the functioning of cerebral vessels by increasing ROS production via the NADPH oxidases. Moreover, studies of systemic arteries infer that T-cells and macrophages also contribute. Oxidative stress and inflammation can also alter the structure of cerebral vessels by promoting vascular remodelling, stiffness, atherosclerosis and BBB disruption…"

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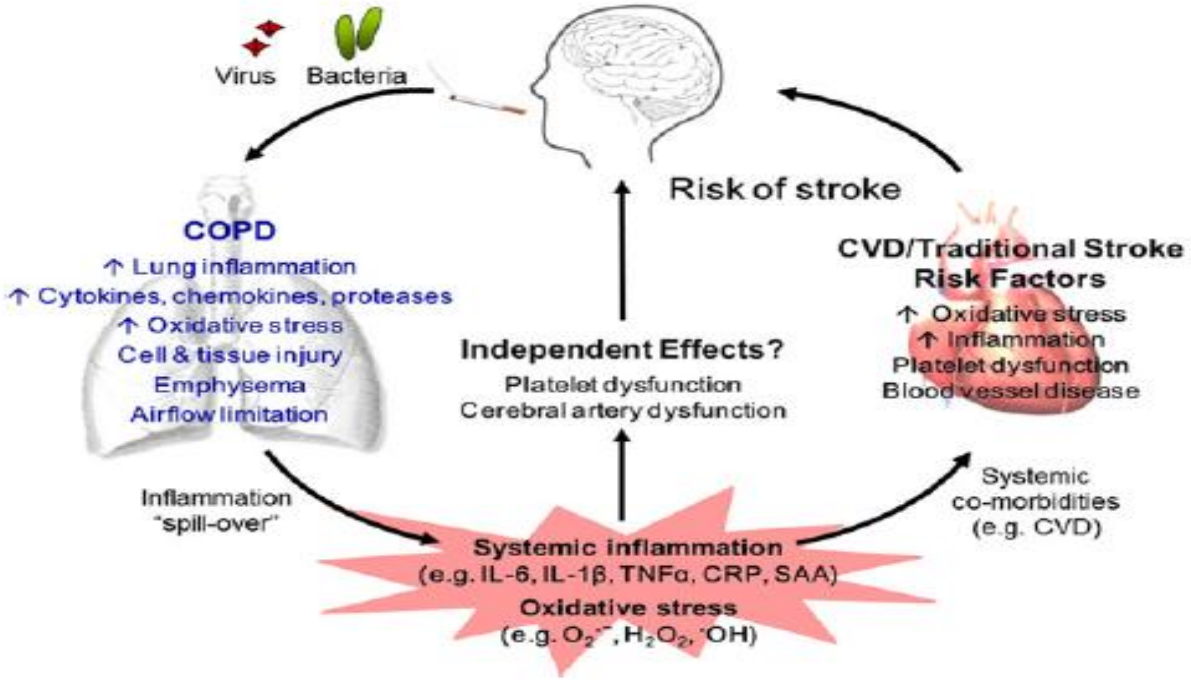

Increased oxidative stress and lung inflammation in response to cigarette smoke causes a spill over of cytokines (e.g. IL-6, TNF-α and SAA) into the systemic circulation

Systemic inflammation in COPD initiates and/or worsens comorbid conditions such as CVD/traditional stroke risk factors and stroke. Viral and bacterial pathogens markedly increase ROS production and systemic inflammation and hence exacerbate COPD and its comorbidities. Targeted co-inhibition of mechanisms underlying both COPD and stroke (e.g. oxidative stress, local and systemic inflammation) may lead to increased survival and improvements in quality of life of patients.

STRESS OSSIDATIVO

Clinical Investigations

Continuous Positive Airway Pressure Therapy Improves Vascular Dysfunction and Decreases Oxidative Stress in Patients With the Metabolic Syndrome and Obstructive Sleep Apnea Syndrome

Jun-ichi Oyama, MD; Hiroaki Yamamoto, MD; Toyoki Maeda, MD; Akira Ito, MD; Koichi Node, MD; Naoki Makino, MD

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"…These data suggest there is a selective and dose-dependent activation of inflammatory pathways by intermittent hypoxia/reoxygenation and support a specific role for this event in the pathophysiology of CV complications in OSAS. In vitro investigations have shown sustained hypoxia activates hypoxia-inducible factor-1–dependent transcription, whereas intermittent hypoxia selectively activates nuclear factor κB (NFκB)-dependent transcription…"

"…We demonstrated that CPAP therapy improves endothelial dysfunction and decreases the levels of oxidative stress and inflammatory cytokines in patients with the MetS and OSAS. As endothelial function provides a prognostic marker of atherosclerotic CV disease, our data suggest that CPAP may be helpful for preventing the progressive development of atherogenic risk factors in patients with the MetS and OSAS…"

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STRESS OSSIDATIVO

Effects of CPAP on oxidative stress and nitrate efficiency in sleep apnoea: a randomised trial

A Alonso-Fernández,[1,2] F García-Río,[3] M A Arias,[4] Á Hernanz,[5] M de la Peña,[1,2] J Piérola,[6,2] A Barceló,[7,2] E López-Collazo,[8,2] A Agustí[1,8,9]

CONCLUSIONI

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Redox Report

Communications in Free Radical Research

ISSN: 1351-0002 (Print) 1743-2928 (Online) Journal homepage: http://www.tandfonline.com/loi/yrer20

Glutathione oxidation correlates with one-lung ventilation time and PO_2/FiO_2 ratio during pulmonary lobectomy

José García-de-la-Asunción, Eva García-del-Olmo, Genaro Galan, Ricardo Guijarro, Francisco Martí, Rafael Badenes, Jaume Perez-Griera, Alejandro Duca, Carlos Delgado, Jose Carbonell & Javier Belda

INSUFFICIENZA RESPIRATORIA E sNOX2-dp

OBIETTIVO PRIMARIO: studiare il livello di stress obiettivo in corso di Insufficienza respiratoria acuta

OBIETTIVO SECONDARIO: verificare se esista una differenza nei livelli di stress ossidativo correlabile ad un diverso trattamento (NIV group vs Oxygen-th. group)

OBIETTIVO TERZIARIO: dimostrare se esista una eventuale correlazione tra i livelli di stress ossidativo ed uno o più parametri emogasanalitici

MATERIALI E METODI

Lo studio è stato condotto presso il Dipartimento di Emergenza-Urgenza del Policlinico Umberto I di Roma dal Marzo al Settembre 2016

CRITERI DI INCLUSIONE:

- età > 18 anni
- DISPNEA
- EGA: paO2 < 60 mmHg e/o P/F ratio < 300 e/o paCO2 > 45 mmHg

CRITERI DI INCLUSIONE PER TERAPIA CON NIV (NPPV/CPAP)

- EGA: acidosi respiratoria (pH 7,10-7,35);
  persistenza di ipossiemia (P/F ratio < 300) dopo tentativo di ossigeno-terapia convenzionale

- DISTRESS RESPIRATORIO: dispnea ingravescente, uso della muscolatura accessoria, FR >25 o < 12 atti/min, alterazione del sensorio (fino al terzo grado della Scala di Kelly)

MATERIALI E METODI

Tempo 0: 3 campioni di sangue (2 plasma, 1 siero)
1 emogasanalisi arteriosa
1 campione di urine

Dopo 180 mimuti: 3 campioni di sangue (2 plasma, 1 siero)
1 emogasanalisi arteriosa
1 campione di urine

I prelievi sono stati conservati a – 80° fino ad analisi presso avvenuta presso un laboratorio dedicato

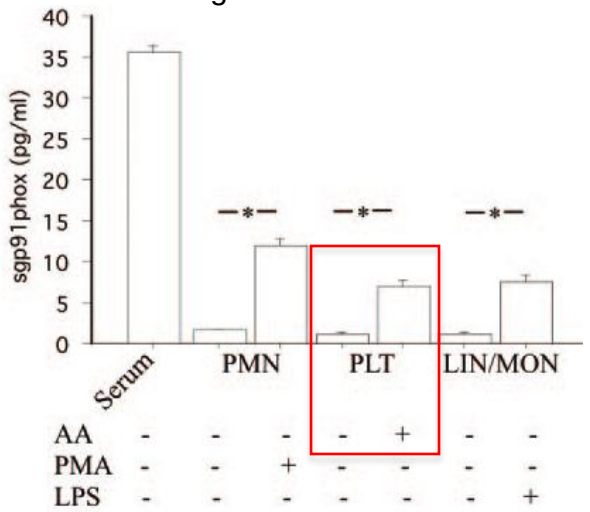
MARKERS DI STRESS OSSIDATIVO:

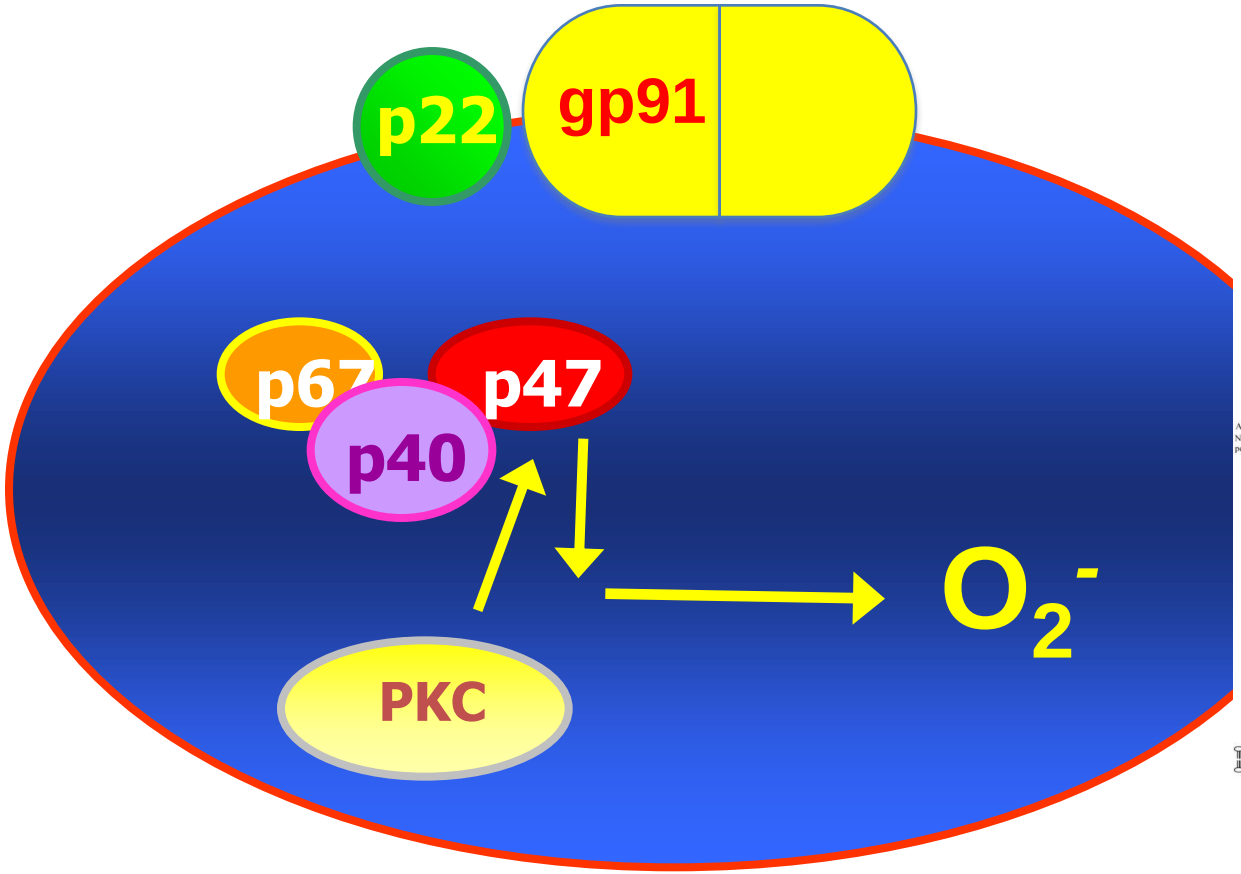
1. **sNOX2-dp:** ELISA method
2. **Isoprostani (8-iso-PGF2α):** EIA method
3. **$H_2O_{2:}$** EIA method

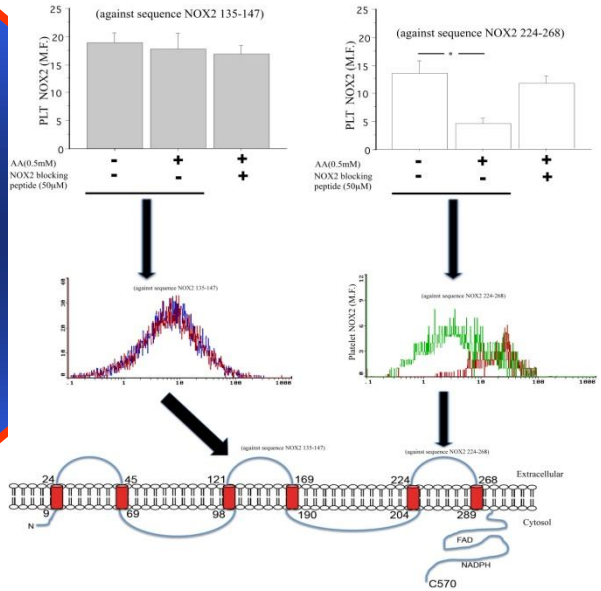
Pignatelli et al . ATVB 2010

NADPH oxidase activation and sNOX2-dp cleavage from cell surface

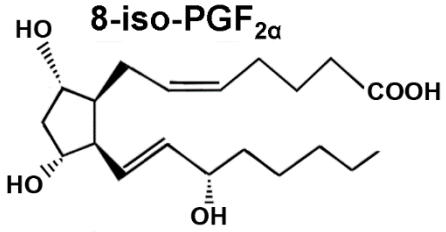
sgp91

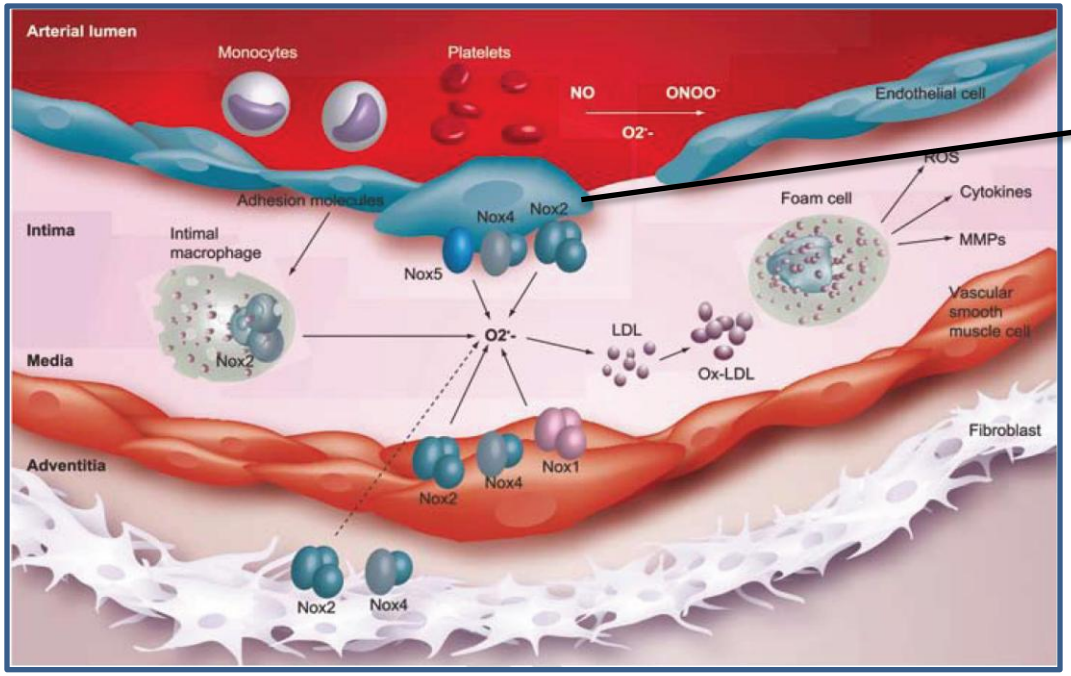




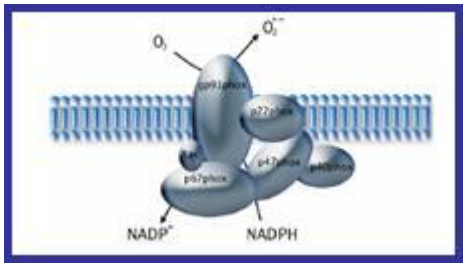


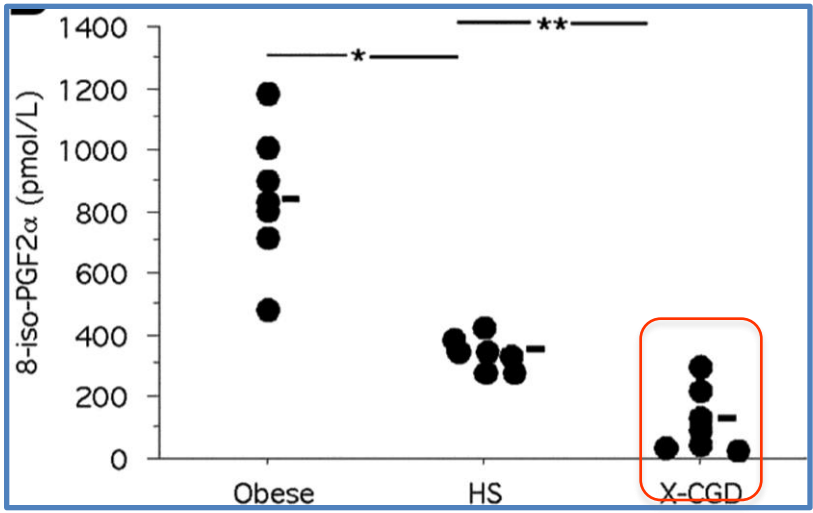
Isoprostanes derive from arachidonic acid interaction with ROS generated by *NOX2*





Violi F. et al Future Cardiology 2009





Violi F et al. Circulation 2009;120:1616-1622

SAPIENZA UNIVERSITÀ DI ROMA

MATERIALI E METODI

Previa firma di consenso informato sono stati arruolati 60 pazienti consecutivi

OXYGEN-THERAPY GROUP: 30 pazienti sono stati trattati con ossigeno-terapia convenzionale (cannule nasali a basso flusso, venturi mask)

NIV GROUP: 30 pazienti sono stati trattati con NIV (20 con NPPV, 10 con CPAP)

BASELINE ASSESSMENT

NOTIZIE ANAMNESTICHE	OVERALL	NIV GROUP (N=30)	OXYGEN-THERAPY GROUP (N=30)	P
Age		77.5±12.3	76.9±13.0	0.860
Male gender (%)	57	40	7	0.018
Asthma (%)	2	3	0	0.305
COPD (%)	52	55	50	0.691
Pulmonary restrictive disease (%)	7	4	12	0.274
Cardiac ischemic disease (%)	17	14	20	0.525
Peripheral artery disease	12	7	17	0.246
Neoplastic disease (%)	15	10	20	0.302
Obesity	15	17	13	0.676
Hypertension (%)	61	65	57	0.486
Dyslipidemia (%)	15	21	10	0.854
Diabetes (%)	30	41	20	0.075
OSAS (%)	5	3	7	0.574
Liver disease (%)	5	3	7	0.574
History of cerebral hemorrhage (%)	3	3	3	0.981
History of Stroke (%)	12	17	7	0.209
Previous pulmonary lobectomy (%)	5	7	3	0.533
History of tvp/pe (%)	5	7	3	0.533
Renal failure (%)	22	21	23	0.807
Atrial fibrillation (%)	41	45	37	0.524
Alcoholism (%)	3	3	3	0.981

BASELINE ASSESSMENT

PHARMACOLOGICAL THERAPY	OVERALL	NIV GROUP (N=30)	OXYGEN-THERAPY GROUP (N=30)	P
Statins (%)	24	27	22	0.691
Aspirin (%)	37	46	29	0.181
ACE-inhibitors (%)	8	8	7	0.936
ARBs (%)	26	31	21	0.434
Calcium channel blockers (%)	15	23	7	0.100
β-blockers (%)	41	42	39	0.821
Anti-diabetic drugs (%)	28	38	18	0.091
Oral anticoagulants (%)	35	35	36	0.933
Proton pump inhibitors (%)	39	27	50	0.082
Corticosteroids (%)	20	8	32	0.026
Nitroderivatives (%)	5	11	0	0.070

CAUSE OF ACUTE RESPIRATORY FAILURE	OVERALL	NIV GROUP (N=30)	OXYGEN-THERAPY GROUP (N=30)	P
COPD acute exacerbation (%)	38	37	40	0.791
ARDS (%)	3	7	0	0.143
Pneumonia (%)	38	40	37	0.791
Acute respiratory insufficiency due to lung cancer (%)	2	0	3	0.321
Cardiogenic pulmonary edema (%)	20	17	23	0.519

Tra le cause di insufficienza respiratoria quelle risultate frequenti sono risultate la BPCO riacutizzata, la polmonite e la dispnea di origine cardiogena con differenze non significative tra i 2 gruppi.

RISULTATI

Baseline EGA	NIV group	OX-therapy	p
paO2	64.2 ± 19.9	51.4 ± 9.5	0.021
paCO2	58.0 ± 18.0	44.9 ± 12.7	0.002
pH	7.29 ± 0.14	7.39 ± 0.09	<0.001
P/F	156 ± 68	209 ± 46	0.042
sNOX2dp (pg/ml)	32.5 [29-35]	21 [17-23]	<0.001
H2O2	28 [23-36]	19.5 [17-22]	<0.001
8-iso-PGF2α	133 [120-154]	111 [89-119]	<0.001

RISULTATI

NIV GROUP	Baseline EGA	EGA after 180’	p
paO2	64.2±19.9	87.0±26.4	0.001
paCO2	58.0±18.0	52.1±13.8	0.015
pH	7.29±0.14	7.34±0.10	0.026
P/F	156±68	196±66	0.001

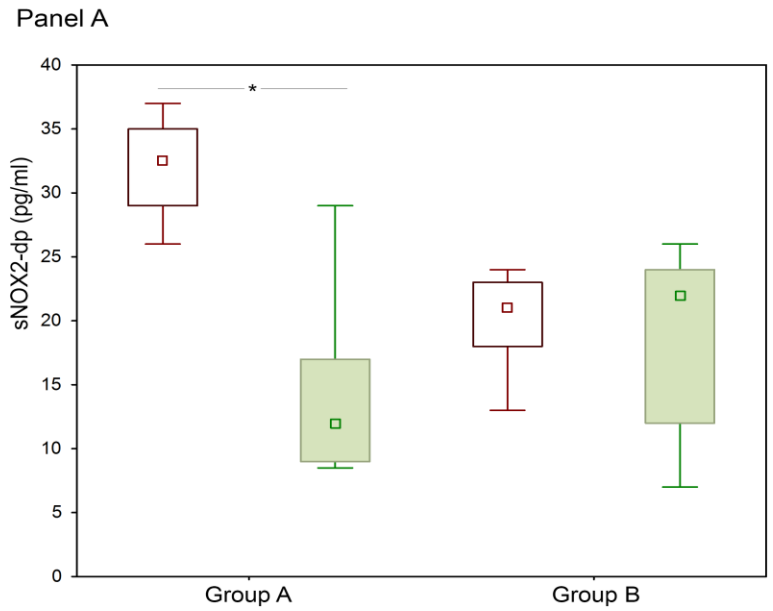
OX-therapy group	Baseline EGA	EGA after 180’	p
paO2	51.4±9.5	81.2±23.9	<0.001
paCO2	44.9±12.7	43.9±11.6	0.365
pH	7.39±0.09	7.42±0.06	0.125
P/F	209±46	215±84	0.729

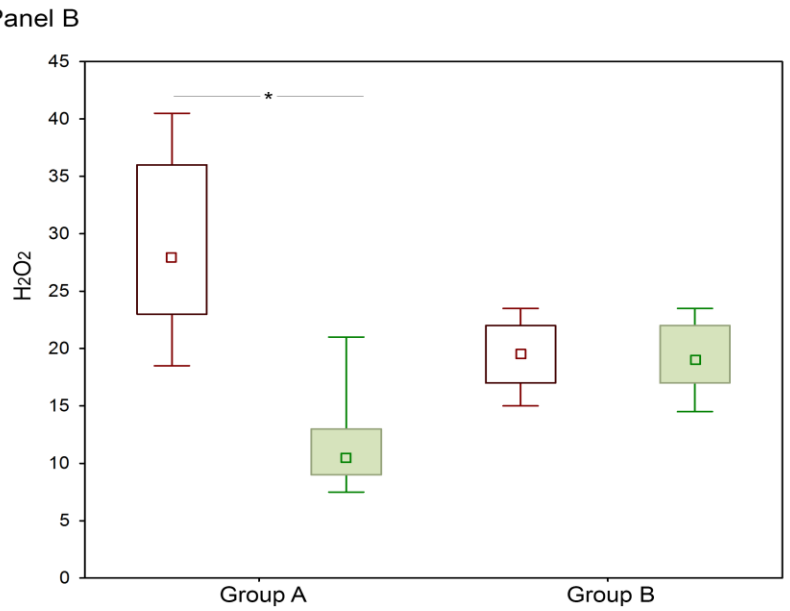
RISULTATI

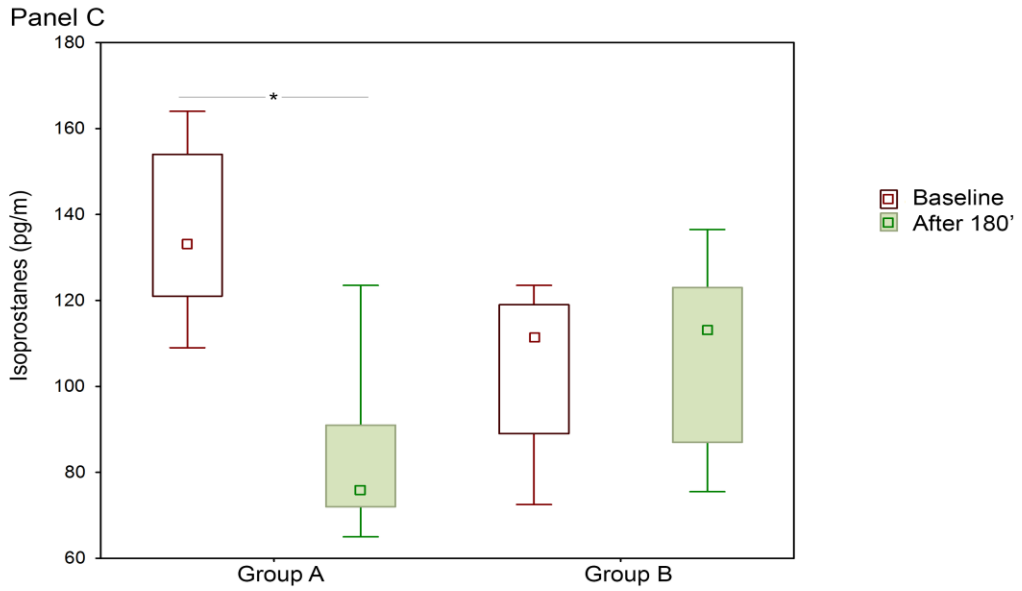
- I livelli sierici di sNOX2-dp ($p<0.001$); H_20_2 ($p<0.001$), and 8- iso-PGF2α ($p<0.001$) risultano ridotti nei pz del gruppo NIV, nonostante un livello basale più elevato, ma non nei pz del gruppo trattato con ossigenoterapia convenzionale (venturi mask, cannule nasali a basso flusso).

- L'analisi dei dati MANOVA ha dimostrato la significatività statistica dei 2 diversi trattamenti (NIV vs Oxygen-therapy) sui markers di stress ossidativo analizzati: **sNOX2-dp ($F=431$; $p<0.001$); H_2O_2 ($F=244$; $p<0.001$); and 8-iso-PGF2α ($F=128$; $p<0.001$).** Al contrario non è riultato nessun effetto statisticamente significativo dell'interazione di tempo, età, sesso e comorbidità sui livelli di stress ossidativo.

RISULTATI


Panel A
sNOX2-dp (pg/ml)
40
35
30
25
20
15
10
5
0
*
Group A
Group B


Panel B
H2O2
45
40
35
30
25
20
15
10
5
0
*
Group A
Group B


Panel C
Isoprostanes (pg/m)
180
160
140
120
100
80
60
*
Group A
Group B
Baseline
After 180'

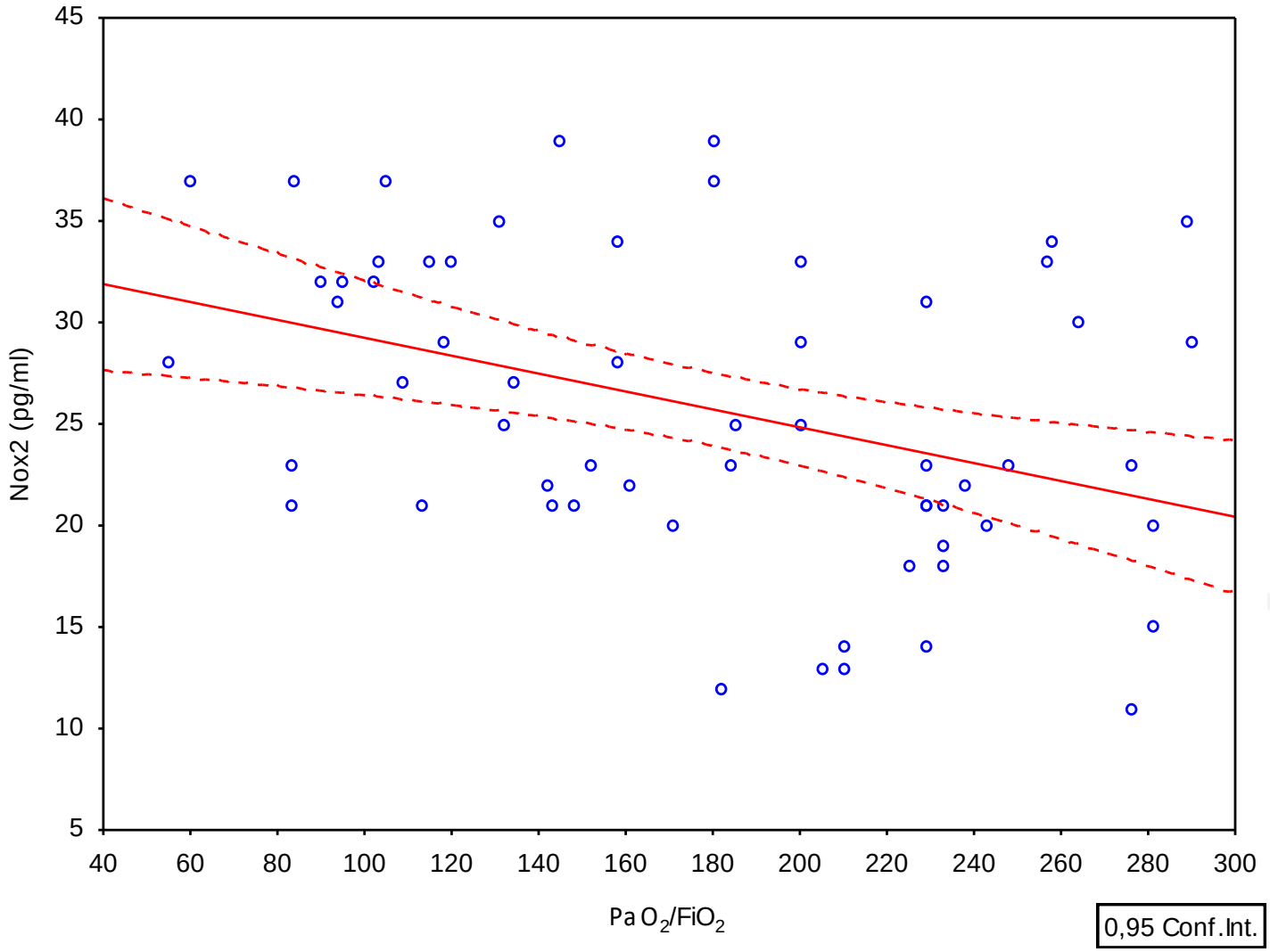
RISULTATI

- Nell'analisi overall dell'intera popolazione i parametri di stress ossidativo correlano in modo significativo con i cambiamenti di **PaO_2/FiO_2 (R=-0.623. p<0.001 per sNOX2-dp; R=-0.428, p<0.001 per H_2O_2; R=-0.548, p<0.001 per 8-iso-PGF2α)**

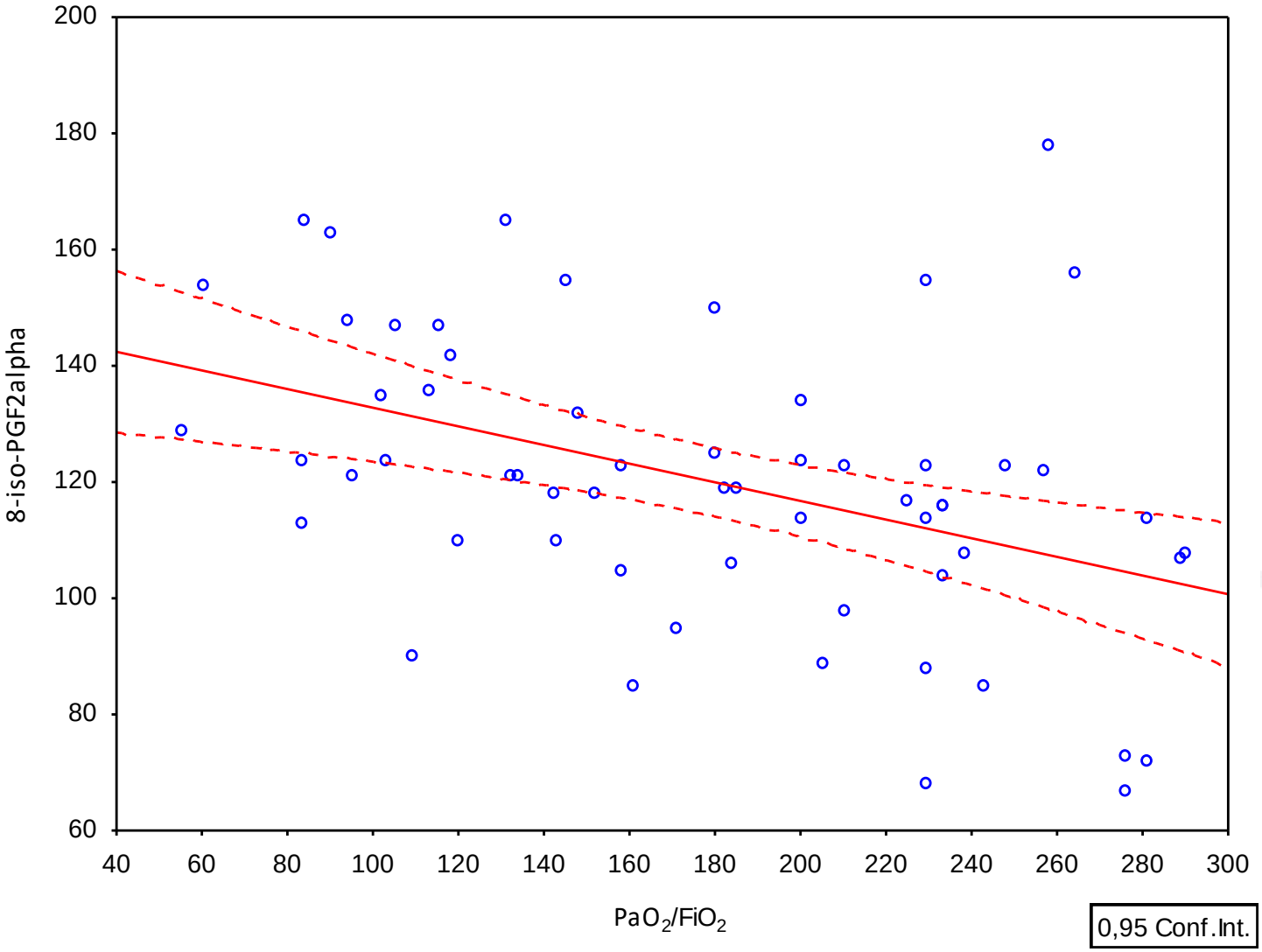
- I markers di stress ossidativo non correlano con i cambiamenti di pO_2, pH or pCO_2.

- I livelli di sNOX2-dp e 8iso-PGF2α correlano solo debolmente con il pH (R=-0.274; p=0.034 e R=-0.253; p=0.061 rispettivemente).
  L' H_2O_2 non ha mostrato alcuna correlazione con il pH.

RISULTATI


45
40
35
30
25
20
15
10
5
Nox2 (pg/ml)
40
60
80
100
120
140
160
180
200
220
240
260
280
300
Pa O2/FiO2
0,95 Conf.Int.

RISULTATI


200
180
160
140
120
100
80
60
8-iso-PGF2alpha
40
60
80
100
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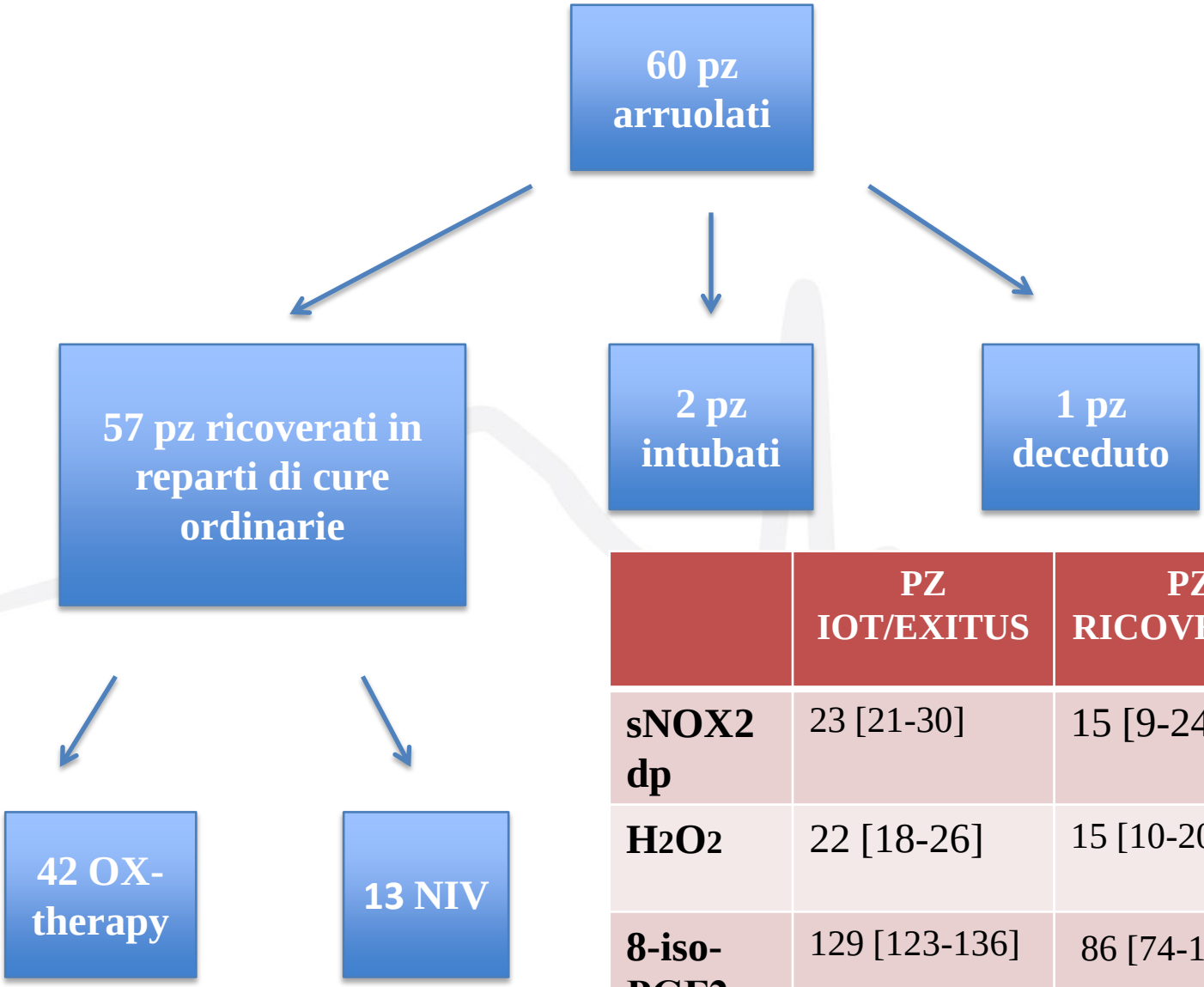
140
160
180
200
220
240
260
280
300
PaO2/FiO2
0,95 Conf.Int.

RISULTATI



	PZ IOT/EXITUS	PZ RICOVERATI	p
sNOX2 dp	23 [21-30]	15 [9-24]	0.153
H_2O_2	22 [18-26]	15 [10-20]	0.061
8-iso-PGF2α	129 [123-136]	86 [74-117]	0,018

CONCLUSIONI

- Il nostro studio ha evidenziato che nell'insufficienza respiratoria acuta i livelli di stress ossidativo risultano tanto più elevati quanto più la situazione emogasanalitica sia compromessa (NIV group vs Ox-therapy group)

- I nostri dati evidenziano una correlazione statisticamente significativa tra i markers di stress ossidativo dosati e la PaO_2/FiO_2 ratio; il miglioramento della ossigenazione sarebbe quindi legato ad una riduzione dei livelli di stress ossidativo.

- La terapia ventilatoria con NIV (NPPV/CPAP) permettendo di ottenere una migliore ossigenazione e miglioramenti emogasanalitici statisticamente significativi svolgerebbe un significativo ruolo protettivo nei confronti dello stress ossidativo.

Grazie.

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