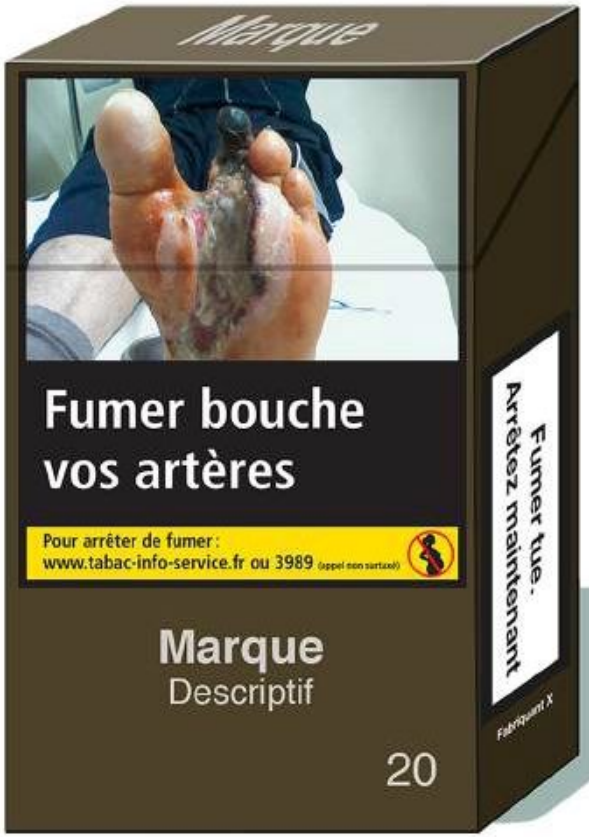
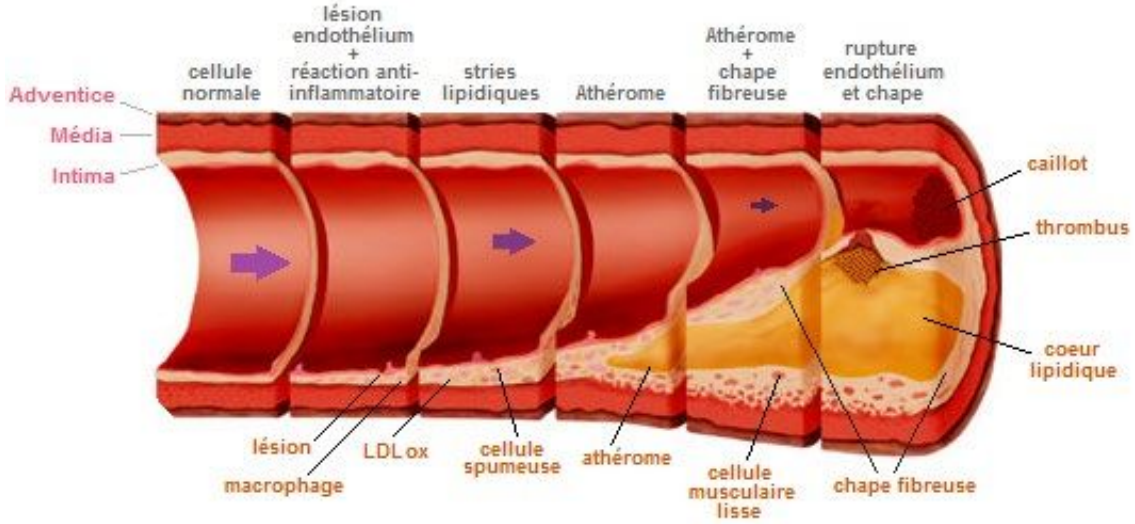
Tabac et athérosclérose : à la recherche du coupable

Pr C. Hanet
CHU UCL Namur
Faculté de Médecine
UNamur





Athérosclérose

Athérosclérose

Pathophysiologie

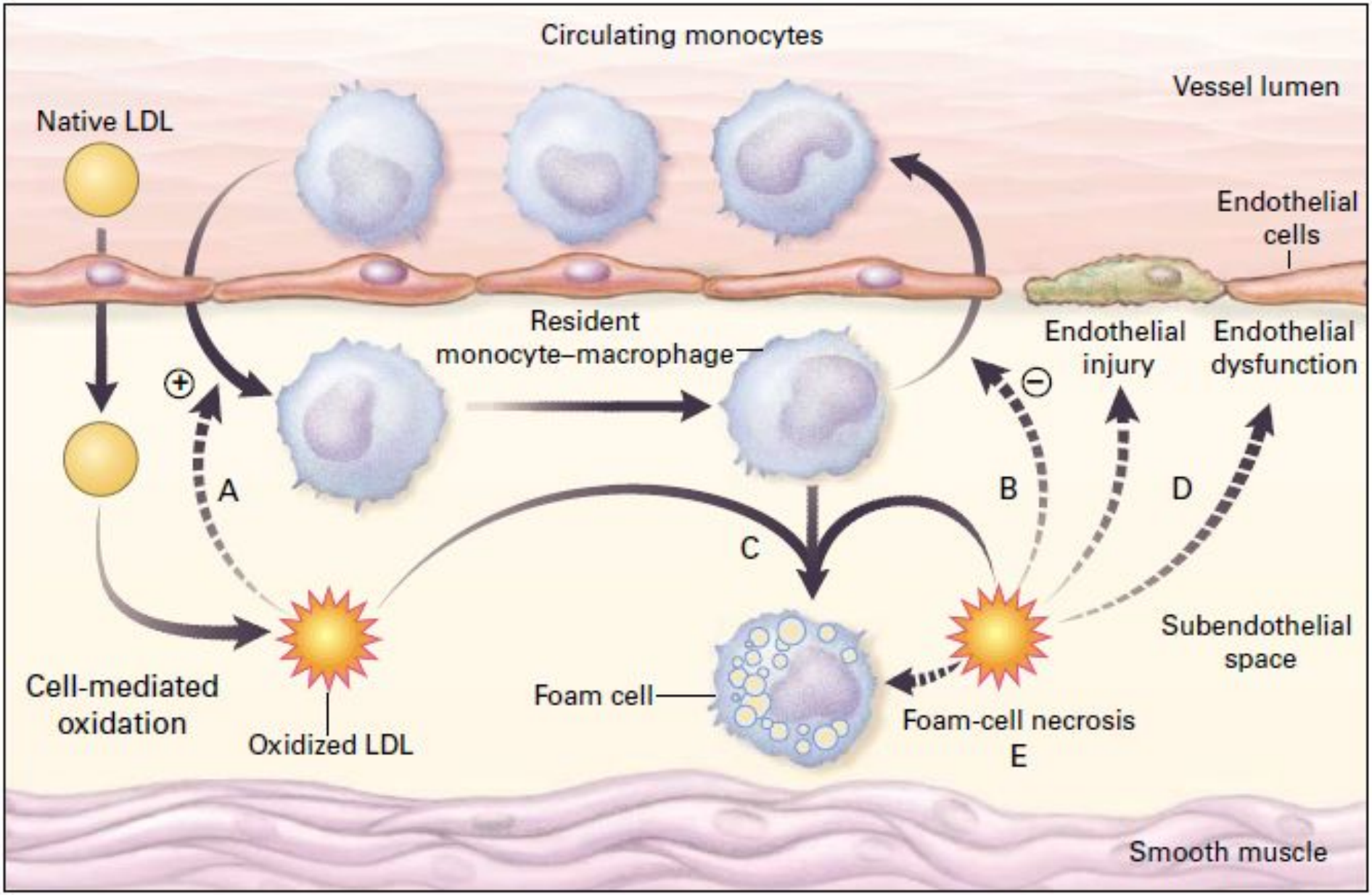
Response to Injury and Atherogenesis

Russell Ross, PhD, John Glomset, MD, PhD, and
Laurence Harker, MD

This hypothesis states that the lesions of atherosclerosis result as a response to some form of injury to arterial endothelial cells that result in their desquamation. The injury may be subtle. There may be many potential sources of injury; these include chronic hyperlipidemia,[9] various chemical factors such as homocystine,[10,11] uremia, metabolites, infections, immunologic injury,[12,13] and mechanical factors.[7,14-17] Mechanical injury may occur at particular anatomic sites as a result of the increased shear of the blood at these agents may lead to cells and between the permitting hemody- ment of the cells from endothelium would

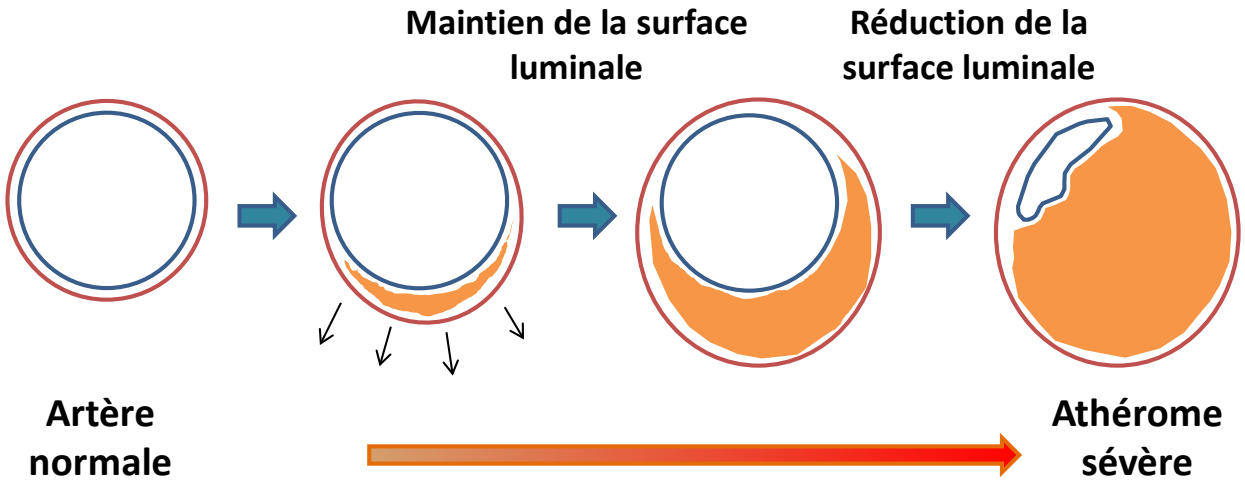
- Stress mécanique (HTA)
- Hypercholestérolémie
- Radicaux libres; stress oxydatif; …
- Infections (chlamydia, virus, ..)

Am J Pathol 86:675-684, 1977

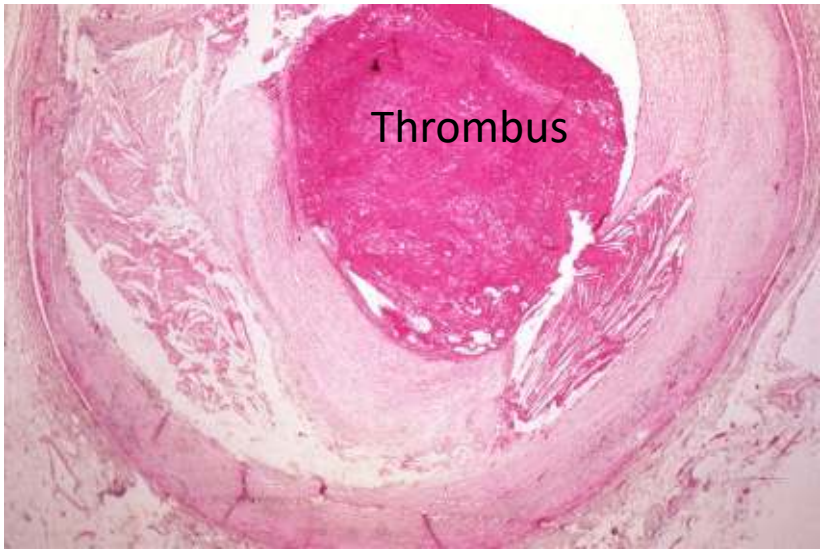

Circulating monocytes
Vessel lumen
Native LDL
Endothelial cells
Resident monocyte–macrophage
Endothelial injury
Endothelial dysfunction
A
B
C
D
Cell-mediated oxidation
Oxidized LDL
Foam cell
Foam-cell necrosis
E
Subendothelial space
Smooth muscle

Athérosclérose - Présentations cliniques

Forme chronique



Accident aigu
« athéro-thrombotique »



Athérosclérose

	Formes cliniques		
	Obstruction progressive	Thrombose aigue	Rupture
Aorte/Iliaques axes fémoro - poplités	Claudication des membres inférieurs	Ischémie aigue	Rupture d'anévrysme
Artères coronaires	Angor ou « Angine de poitrine »	« Syndrome coronaire aigu » Infarctus	exceptionnel
Circulation cérébrale	Démence vasculaire	AVC ischémique	AVC hémorrhagique

AUTOPSIE D'UN MEURTRIER

Lors de sa combustion, la cigarette produit une fumée qui contient environ 4000 substances toxiques (dont au moins 50 cancérigènes). Sur les paquets, seuls goudrons et nicotine sont indiqués. Certains composés proviennent de l'environnement (pesticides, produits radioactifs), d'autres composés sont ajoutés, comme l'ammoniac qui favorise la fixation de la nicotine et la dépendance. Certains plants de tabac sont génétiquement modifiés afin de rendre la nicotine plus «efficace».

SUBSTANCES CANCÉRIGÈNES CONNUES

14, rue Corvisart · 75013 Paris · www.ligue-cancer.net

0810 111 101

CONTRE LE CANCER
LA LIGUE 101 comités
pour la vie

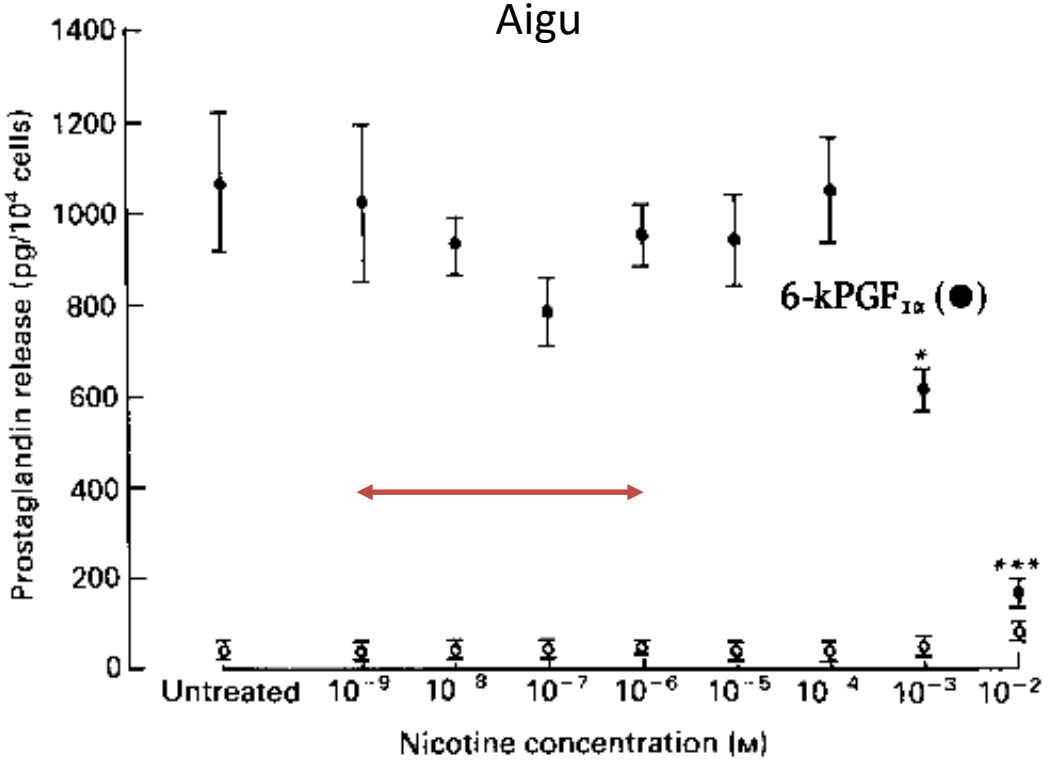
- Tests fonctionnels (fonction endothéliale)
- Données épidémiologiques
- Etudes in vitro

Nicotine

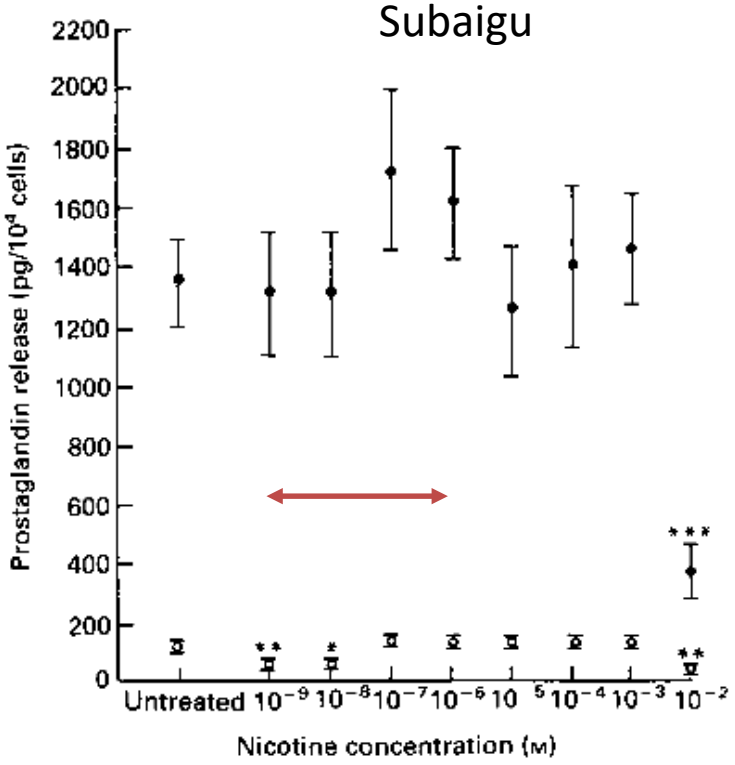
The effect of nicotine on human endothelial cell release of prostaglandins and ultrastructure

Helen A. Bull, R.M. Pittilo*, N. Woolf* and S.J. Machin

Aigu



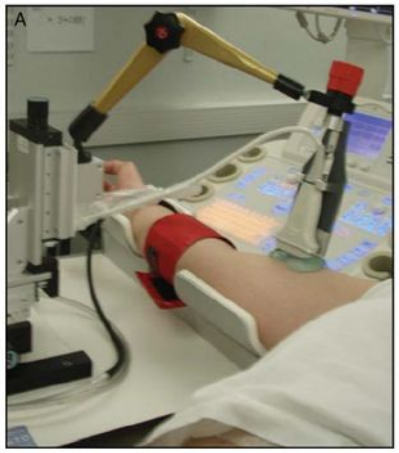
Subaigu

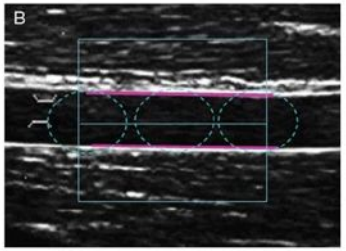


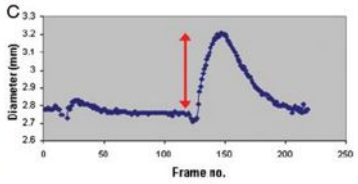
indicated by the negative uptake of oil-red-O and osmium tetroxide. This study shows that concentrations of nicotine comparable to the plasma levels of smokers (10^{-9}–10^{-6}M) do not induce morphological changes or effect the release of endothelial prostaglandins.

Br. J. exp. Path. (1988), 69, 413-421

Contribution of Nicotine to Acute Endothelial Dysfunction in Long-Term Smokers







Neunteufl *et al.*
Nicotine and Endothelial Dysfunction

JACC Vol. 39, No. 2, 2002
January 16, 2002:251–6

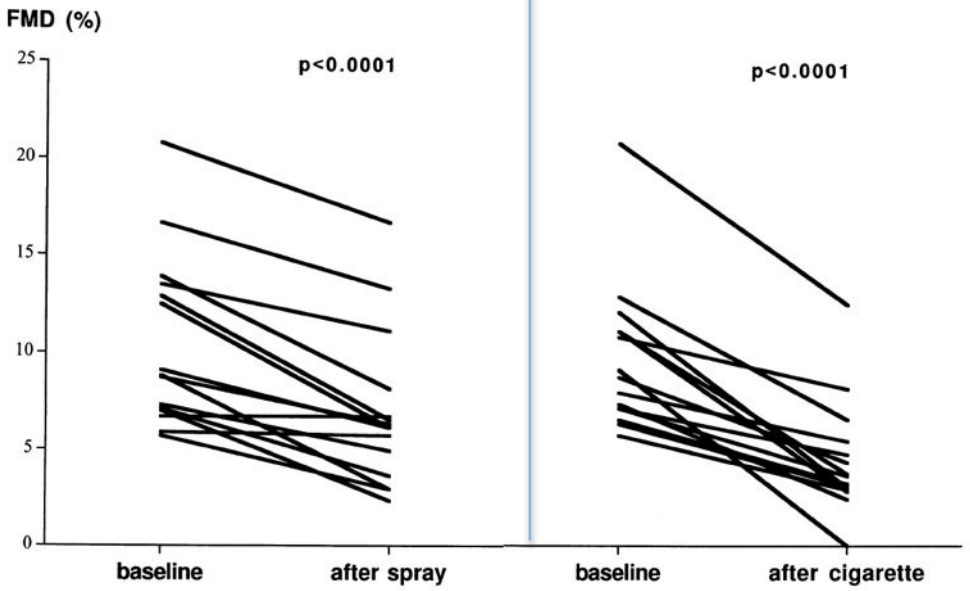
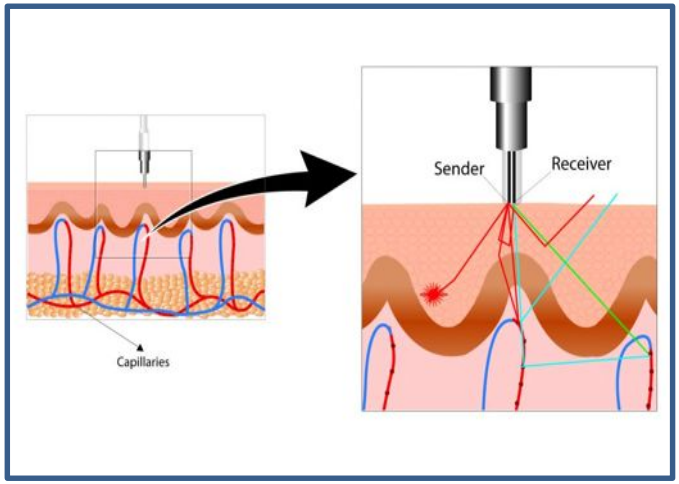


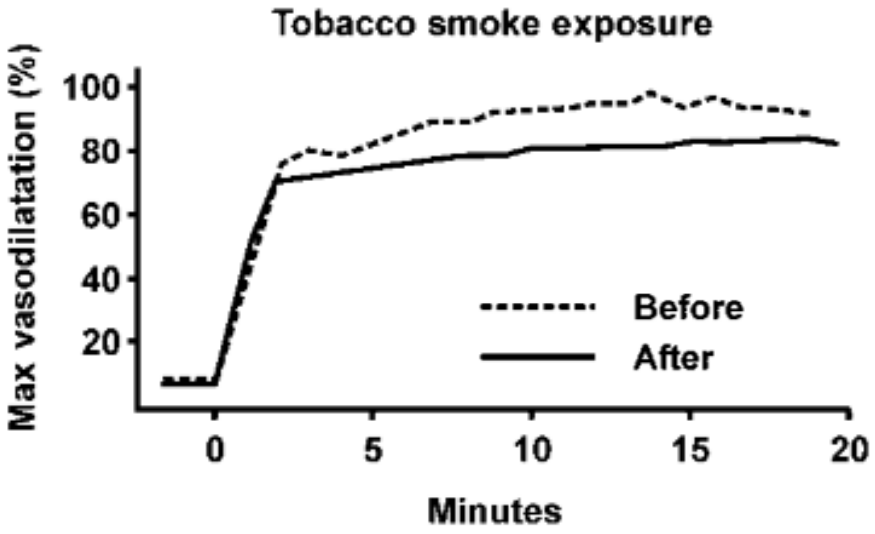
Figure 1. Flow-mediated dilation (FMD) values before and after the administration of nicotine nasal spray (1-mg nicotine) and smoking a cigarette (1-mg nicotine, 12-mg tar), respectively.

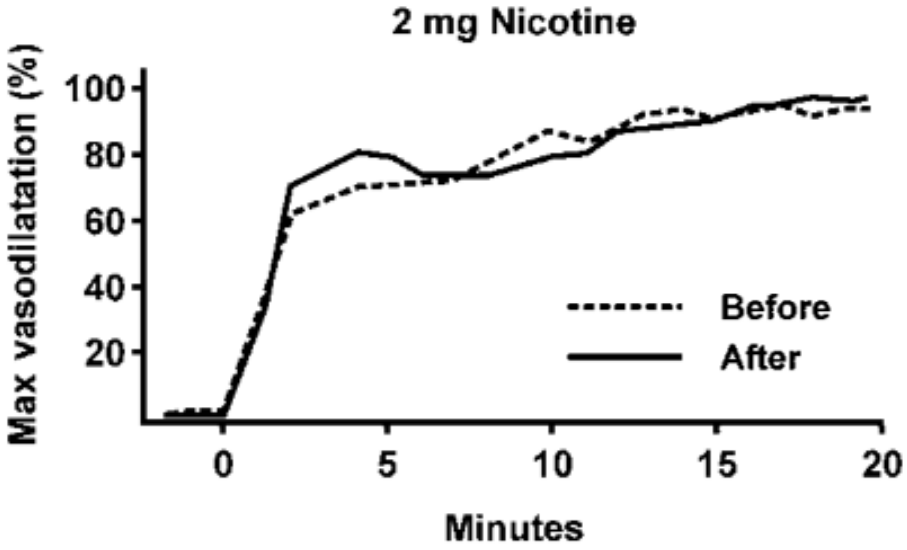
Nicotine

Volontaires sains



Blood flow response to local heating (laser Doppler flowmeter)



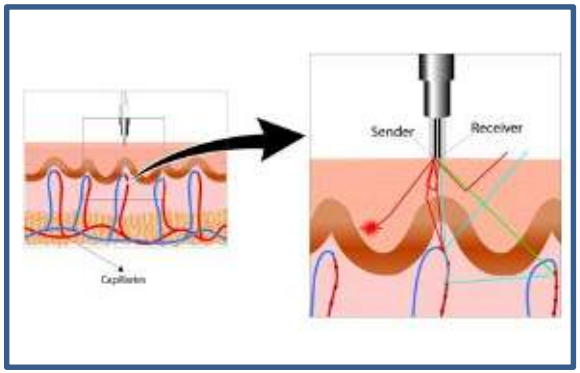


Adamopoulos: Clinical and Experimental Pharmacology and Physiology (2008) **35**, 458–463

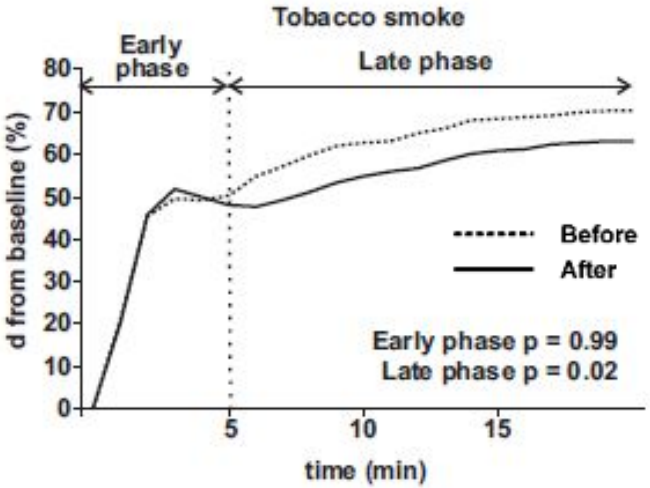
Nicotine

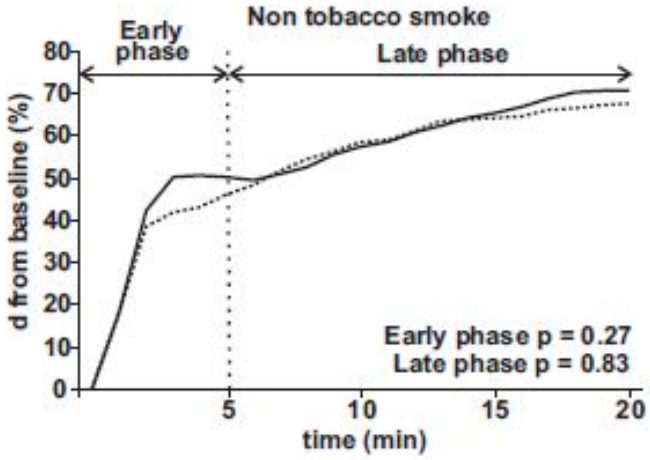
25 volontaires sains exposés pendant 1 heures à :

- Fumée de cigarette
- Fumée sans nicotine



Blood flow response to local heating (laser Doppler flowmeter)





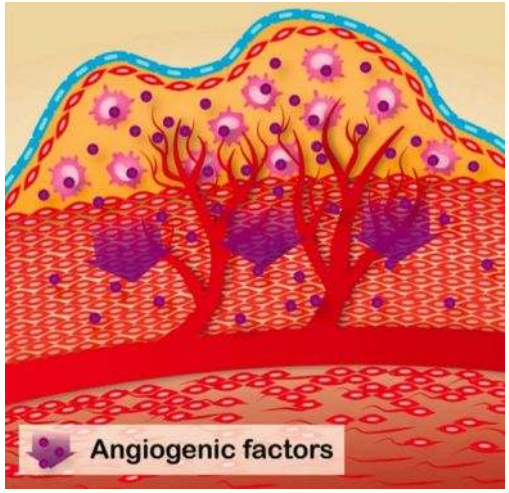
The comparison of the vascular response to passive smoking of a real cigarette and an herbal cigarette reveals a more toxic effect of the tobacco smoke.

At first glance, the main toxic difference between the 2 smokes may reside in the nicotine content of tobacco smoke.

Hypertension. 2008;51:1506-1511

Nicotine

Effet direct sur la progression des lésions

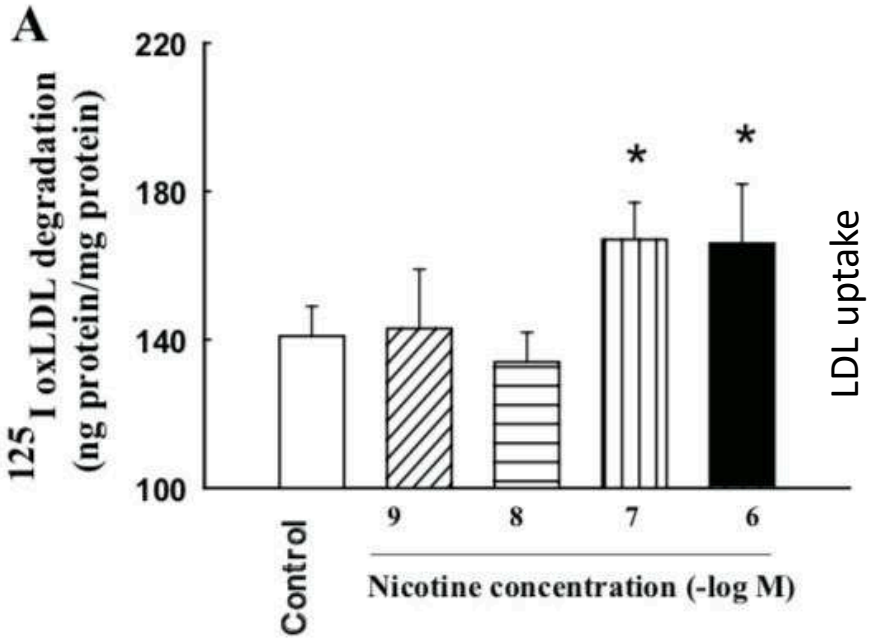


Nicotine and Cotinine Up-Regulate Vascular Endothelial Growth Factor Expression in Endothelial Cells
Brian S. Conklin,*† Weidong Zhao,* Dian-Sheng Zhong,* and Changyi Chen
American Journal of Pathology, Vol. 160, No. 2, February 2002

Stimulation des récepteurs cholinergiques de type nicotinique (α7. nAChR)

- Endothélium
- Cellules musculaires lisses → cytokines, facteurs de croissance cellulaire et angiogenèse

- Macrophages
  - Captation du LDL-cholesterol -> cellules spumeuses
  - Inflammation (métalloprotéinases)

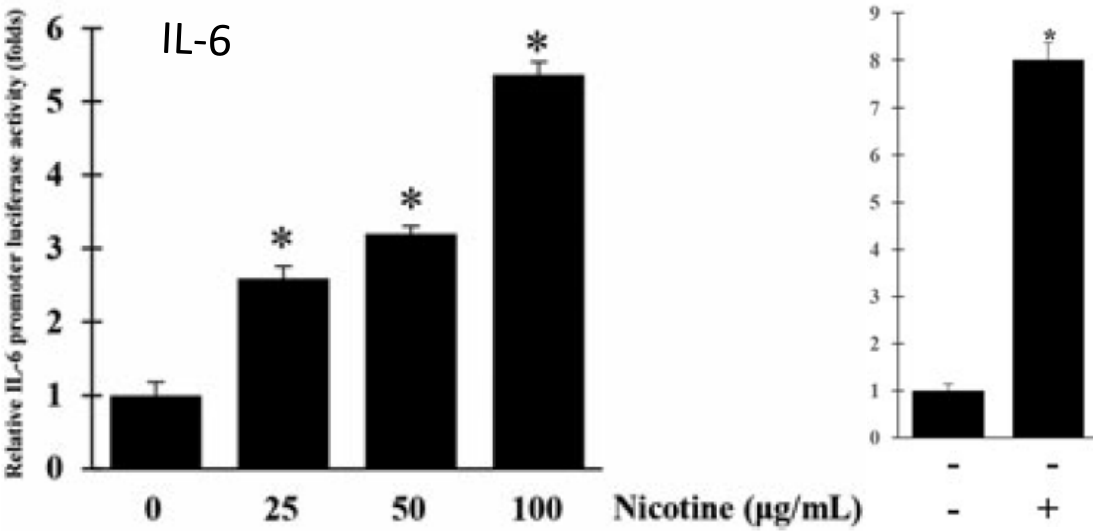


Am J Physiol Heart Circ Physiol 305: H563–H574, 2013

Nicotine

Nicotine stimulates IL-6 expression by activating the AP-1 and STAT-3 pathways in human endothelial EA.hy926 cells

Trong Thuan Ung[1] | Thi Thinh Nguyen[1] | Sen Lian[2] | Shinan Li[1] | Yong Xia[3] | Nam Ho Kim[4] | Young Do Jung[1]



Cellules endothéliales humaines incubées pendant 4h en présence de nicotine

Activation de la migration cellulaire

Our data demonstrate that nicotine induced IL-6 expression, which, in turn, enhanced the invasiveness of endothelial EA.hy926 cells, via activation of the p38 MAPK/AP-1 and ROS/STAT-3 signaling pathways.

J Cell Biochem. 2019;120:5531-5541

Nicotine

Dysfonction endothéliale

- Données cliniques peu concordantes

In vivo

Effet direct sur la progression des lésions

- Captation du LDL-C
- Inflammation
- Angiogenèse

In vitro

Monoxyde de carbone

Eur J Pharmacol. 1992 Sep 1;228(2-3):155-64.

Inhalation of carbon monoxide does not accelerate arteriosclerosis in cockerels.

Penn A[1], Currie J, Snyder C.

Chronic CO inhalation, at levels up to 200 ppm, did not stimulate arteriosclerotic plaque development

When administered concomitantly with cholesterol feeding, CO did not augment plaque development.

ChemComm

FEATURE ARTICLE

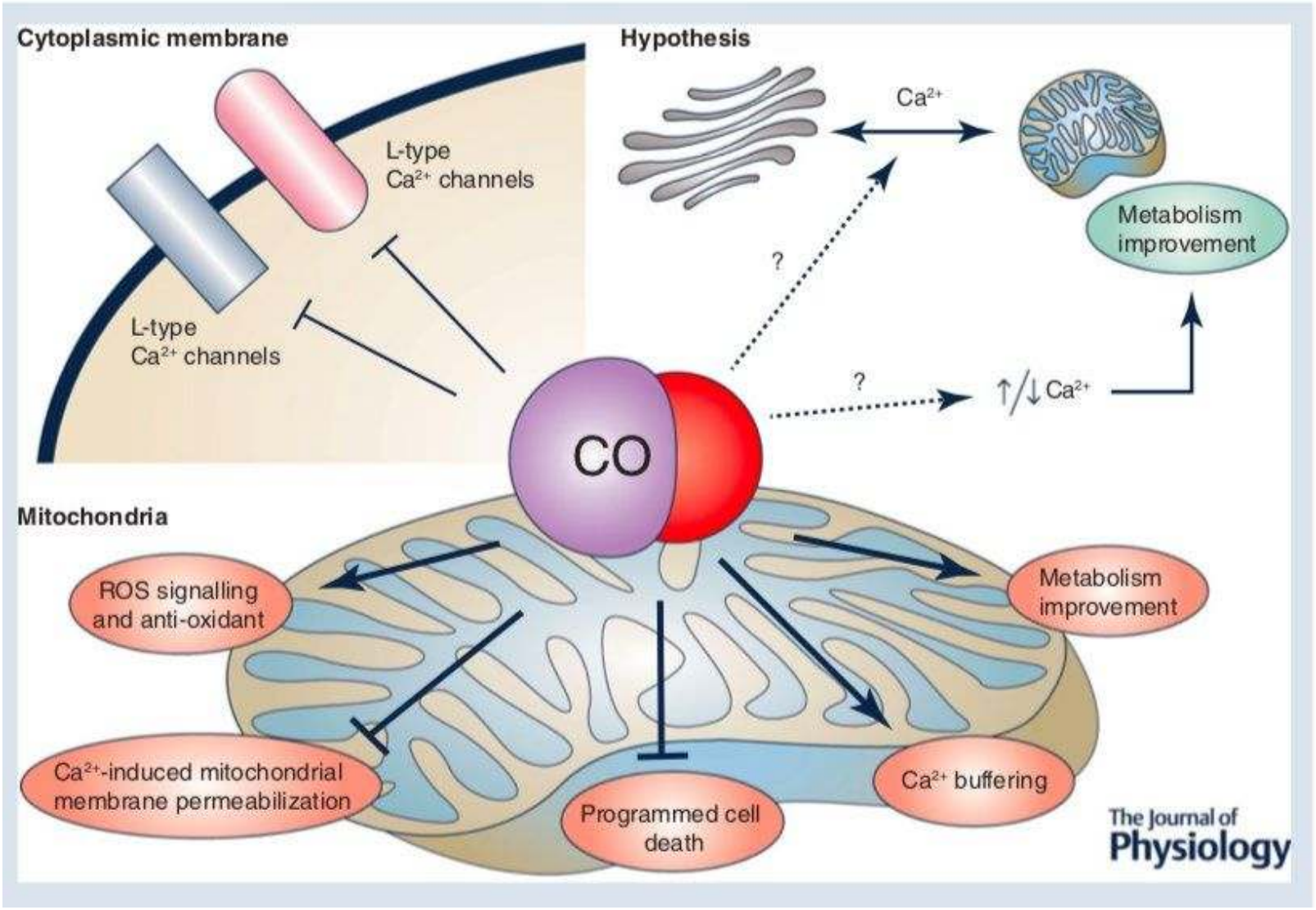
View Article Online
View Journal | View Issue

Carbon monoxide – physiology, detection and controlled release

Cite this: *Chem. Commun.*, 2014, 50, 3644

Stefan H. Heinemann,[ab] Toshinori Hoshi,[c] Matthias Westerhausen[d] and Alexander Schiller*[bd]

Carbon monoxide (CO) is increasingly recognized as a cell-signalling molecule akin to nitric oxide (NO). CO has attracted particular attention as a potential therapeutic agent because of its reported anti-hypertensive, anti-inflammatory and cell-protective effects.


Cytoplasmic membrane
L-type
Ca2+ channels
L-type
Ca2+ channels
Hypothesis
Ca2+
Metabolism
improvement
?
?
↑/↓ Ca2+
CO
Mitochondria
ROS signalling
and anti-oxidant
Metabolism
improvement
Ca2+-induced mitochondrial
membrane permeabilization
Programmed cell
death
Ca2+ buffering
The Journal of
Physiology

Archives of Biochemistry and Biophysics
Volume 677, 30 November 2019, 108185

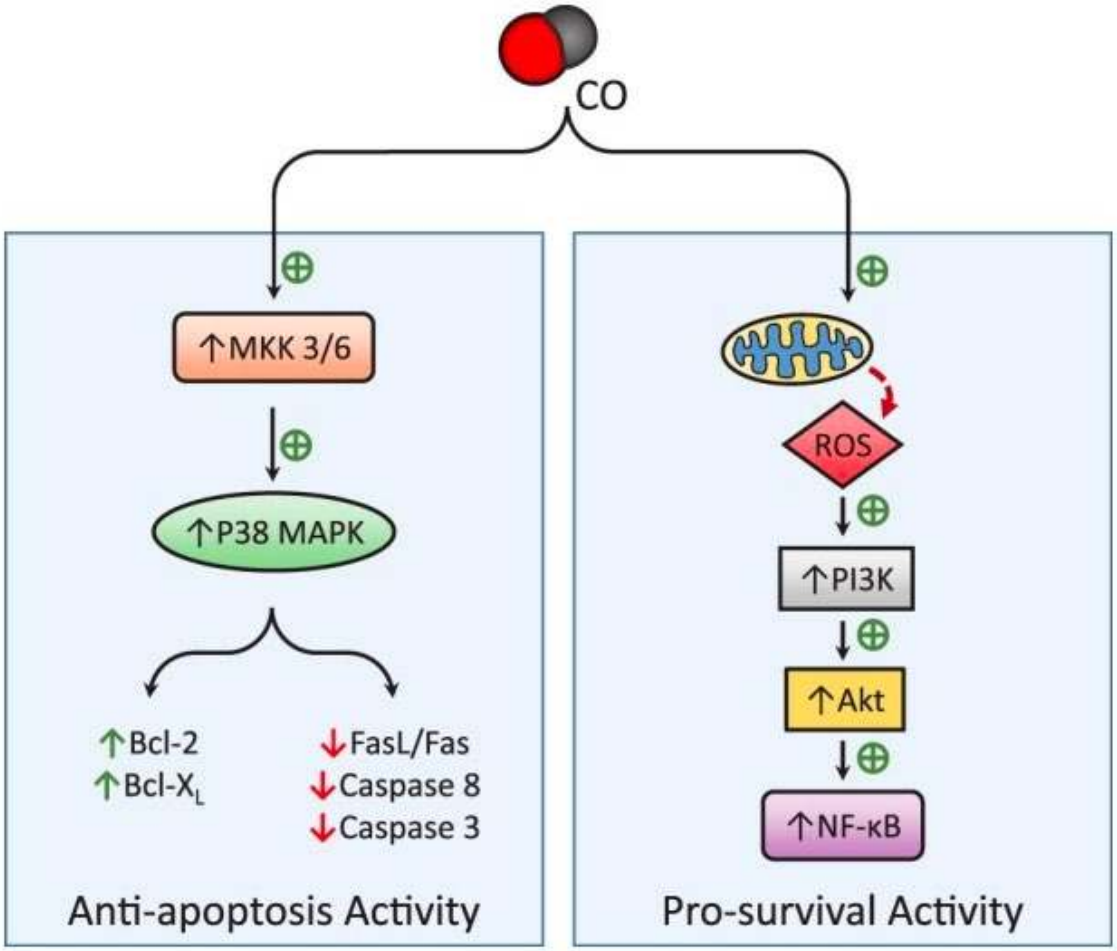
CO ameliorates endothelial senescence induced by 5-fluorouracil through SIRT1 activation

Min Zheng [a, 1], Yubing Chen [b, 1], Jeongmin Park [b], Hyun-Chul Song [b], Yingqing Chen [b, c], Jeong Woo Park [b], Yeonsoo Joe [b], Hun Taeg Chung [b]

Abstract

Endothelial senescence is the main risk factor that contributes to vascular dysfunction and the progression of vascular disease. Carbon monoxide (CO) plays an important role in preventing vascular dysfunction and in maintaining vascular physiology or homeostasis. The application of exogenous CO has been shown to confer protection in several models of cardiovascular injury or disease, including hypertension, atherosclerosis, balloon-catheter injury, and graft rejection.

Inhaled Carbon Monoxide: From Toxin to Therapy



Potentiel thérapeutique évalué dans:

- Ischémie/reperfusion
- Transplantations d'organes
- Sepsis
- HT Pulmonaire

Monoxyde de carbone

Cardiovascular Effects of Carbon Monoxide and Cigarette Smoking

Shoshana Zevin, MD,* Sandra Saunders, MD,† Steven G. Gourlay, MBBS, PHD,†‡
Peyton Jacob III, PHD,† Neal L. Benowitz, MD†

METHODS

In a single-blind, crossover design, 12 healthy smokers inhaled CO at 1,200 ppm to 1,500 ppm to simulate CO intake from cigarette smoking, inhaled air on a similar schedule and smoked 20 cigarettes per day, each for seven days.

Table 1. The Effect of CO, CS and Air Inhalation on HR and Blood Pressure

	CO	CS	Air
HR (beats/min) 24-h mean	66 ± 6	75 ± 7*	67 ± 6
Day	69 ± 6	79 ± 7*	70 ± 6
Night	61 ± 7	67 ± 7*	61 ± 6
SBP (mm Hg) 24-h mean	120 ± 8	124 ± 9	120 ± 9
Day	124 ± 19	129 ± 9	123 ± 11
Night	113 ± 6	115 ± 13	112 ± 9
DBP (mmHg) 24-h mean	66 ± 6	68 ± 6	67 ± 7
Day	69 ± 7	72 ± 7	69 ± 7
Night	62 ± 5	63 ± 6	62 ± 7

Mean ± SD. *$p < 0.05$ compared to carbon monoxide (CO) or air.
CS = cigarette smoking; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

CONCLUSIONS

The results of our study indicate that inhaled CO, delivered to healthy smokers in concentrations similar to those in cigarette smoke, has **little or no effect on heart rate, blood pressure, catecholamine secretion or platelet activation**, at least with exposure for several days, compared to inhalation of air. The effects of smoking on these parameters in healthy smokers are most likely due to other constituents of cigarette smoke.

J Am Coll Cardiol 2001;38:1633–8

Cardiovascular Mortality and Long-Term Exposure to Particulate Air Pollution

Epidemiological Evidence of General Pathophysiological Pathways of Disease

Cancer Prevention Study II (CPS-II) prospective mortality study of ~ 1.2 million adults.

C. Arden Pope III, PhD; Richard T. Burnett, PhD; George D. Thurston, ScD; Michael J. Thun, MD; Eugenia E. Calle, PhD; Daniel Krewski, PhD; John J. Godleski, MD

TABLE 4. Adjusted RRs and 95% CIs for a 10 $\mu g/m^3$ Increase in $PM_{2.5}$ (Average) and for Former and Current Smoker (vs Never Smoker) for Various Cause-of-Death Categories

Cause of Death	$PM_{2.5}$	Former Smoker	Current Smoker
All cardiovascular diseases plus diabetes	1.12 (1.08–1.15)	1.26 (1.23–1.28)	1.94 (1.90–1.99)
Ischemic heart disease	1.18 (1.14–1.23)	1.33 (1.29–1.37)	2.03 (1.96–2.10)
Dysrhythmias, heart failure, cardiac arrest	1.13 (1.05–1.21)	1.18 (1.12–1.24)	1.72 (1.62–1.83)
Hypertensive disease	1.07 (0.90–1.26)	1.21 (1.07–1.37)	2.13 (1.86–2.44)
Other atherosclerosis and aortic aneurysms	1.04 (0.89–1.21)	1.63 (1.45–1.84)	4.21 (3.71–4.78)
Cerebrovascular disease	1.02 (0.95–1.10)	1.12 (1.06–1.18)	1.78 (1.67–1.89)
Diabetes	0.99 (0.86–1.14)	1.05 (0.94–1.16)	1.35 (1.20–1.53)
All other cardiovascular diseases	0.84 (0.71–0.99)	1.22 (1.09–1.38)	1.78 (1.56–2.04)
Diseases of the respiratory system	0.92 (0.86–0.98)	2.16 (2.04–2.28)	3.88 (3.66–4.11)
COPD and allied conditions	0.84 (0.77–0.93)	4.93 (4.48–5.42)	9.85 (8.95–10.84)
Pneumonia and influenza	1.07 (0.95–1.20)	1.23 (1.13–1.34)	1.89 (1.70–2.09)
All other respiratory diseases	0.86 (0.73–1.02)	1.54 (1.36–1.74)	1.83 (1.57–2.12)

Circulation 2004;109:71-77

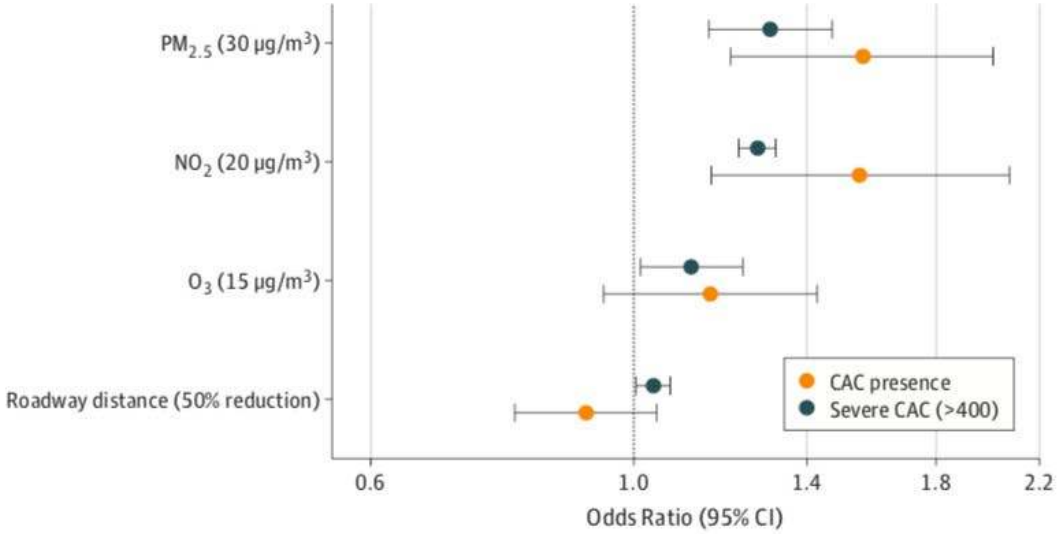
JAMA Network Open

Original Investigation | Environmental Health

Association of Estimated Long-term Exposure to Air Pollution and Traffic Proximity With a Marker for Coronary Atherosclerosis in a Nationwide Study in China

Meng Wang, PhD; Zhi-Hui Hou, MD; Hao Xu, PhD; Yang Liu, PhD; Matthew J. Budoff, MD; Adam A. Szpiro, PhD; Joel D. Kaufman, MD; Sverre Vedal, MD; Bin Lu, MD

Figure 4. Odds Ratio of Detectable and High-Level Coronary Artery Calcium (CAC) Associated With Long-term Exposure Variables



Odds ratios and 95% CIs (error bars) for the presence of CAC and severe CAC (>400 Agatston units) adjusted for age, sex, body mass index, smoking status, smoking years, cigarettes per day, alcohol consumption, education, exercise, urbanization, region, distance to hospital, and Beijing residence (yes or no). NO_2 indicates nitrogen dioxide; O_3, ozone; and $PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 µm.

Pollution athmosphérique et mortalité

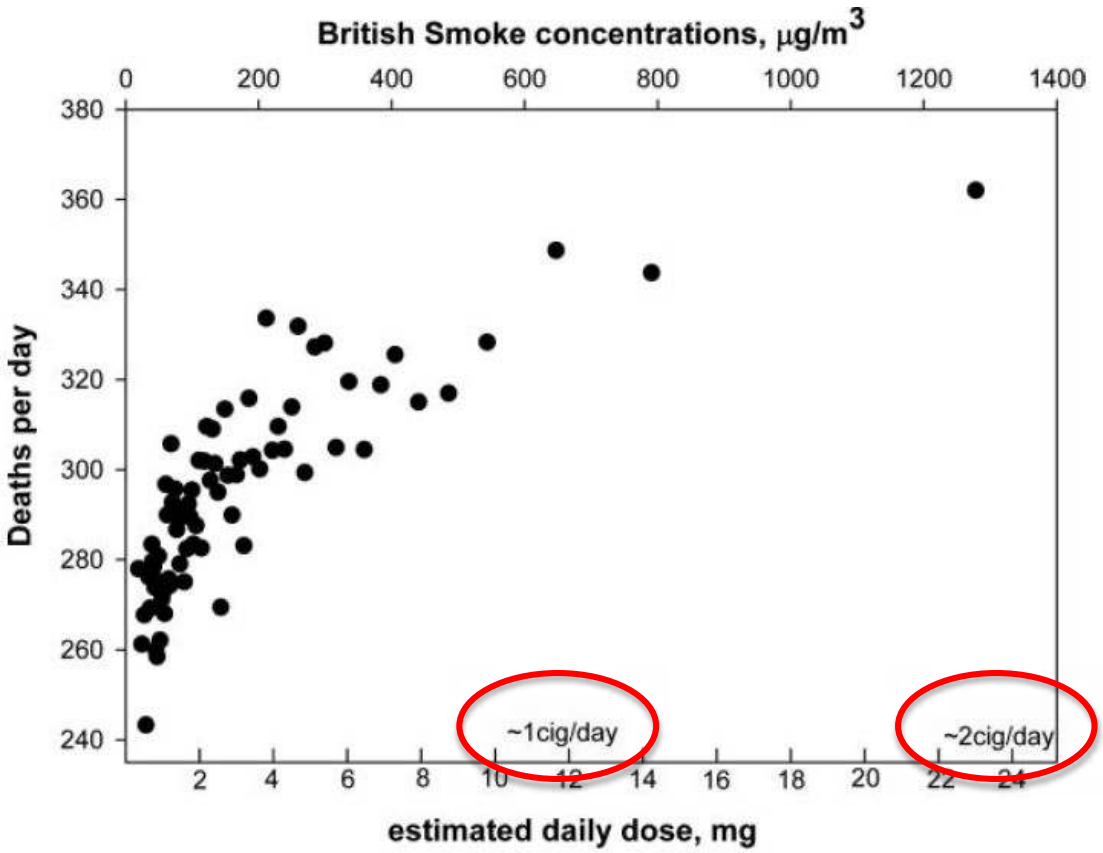


Figure 4. Daily mortality in London for the winters of 1958–1972 plotted over concentrations of particulate air pollution (British smoke, $\mu g/m^3$) and estimated daily dose. Points represent daily means for 20 adjacent values, after sorting by pollution concentrations.

Cardiovascular Mortality and Exposure to Airborne Fine Particulate Matter and Cigarette Smoke

Shape of the Exposure-Response Relationship

C. Arden Pope III, PhD; Richard T. Burnett, PhD; Daniel Krewski, PhD; Michael Jerrett, PhD; Yuanli Shi, MD; Eugenia E. Calle, PhD; Michael J. Thun, MD

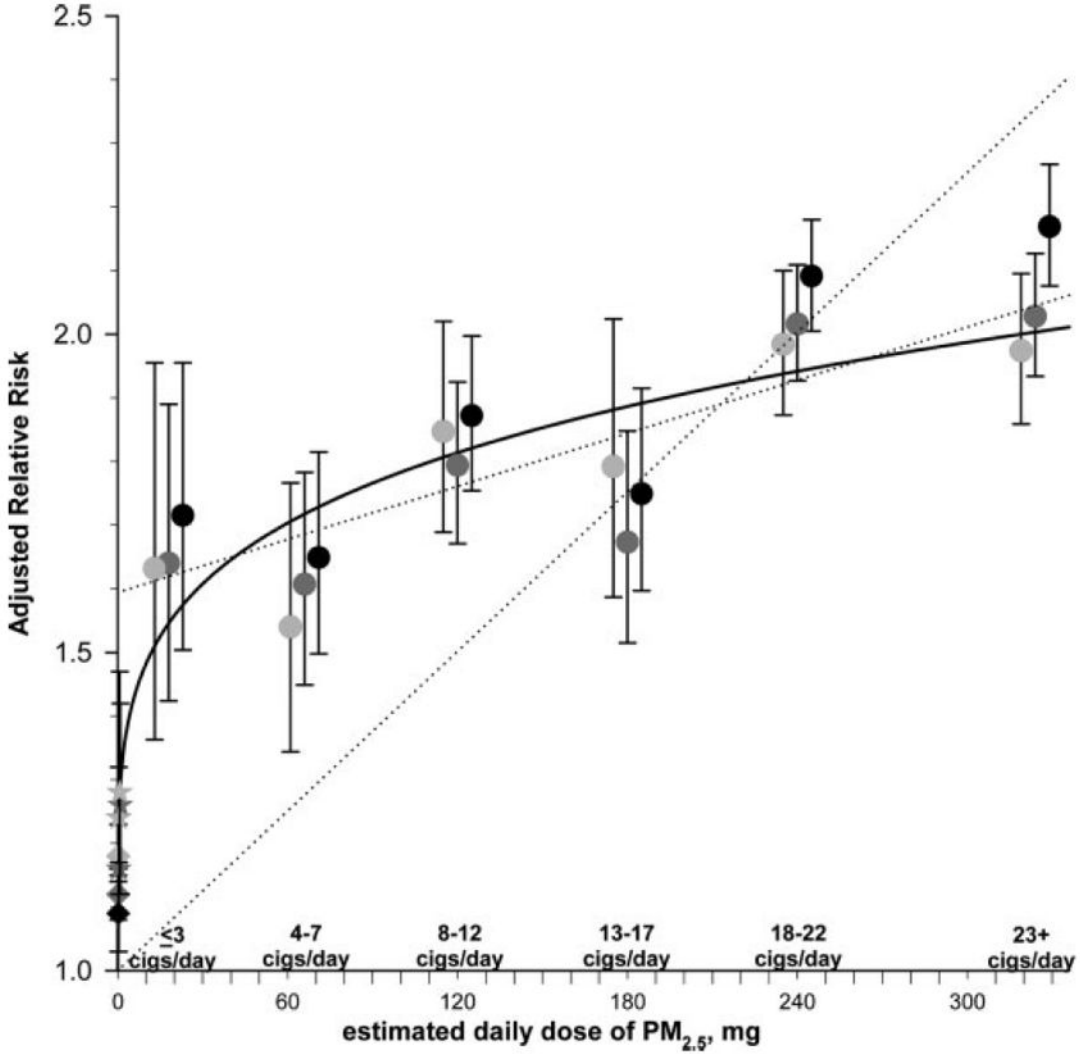
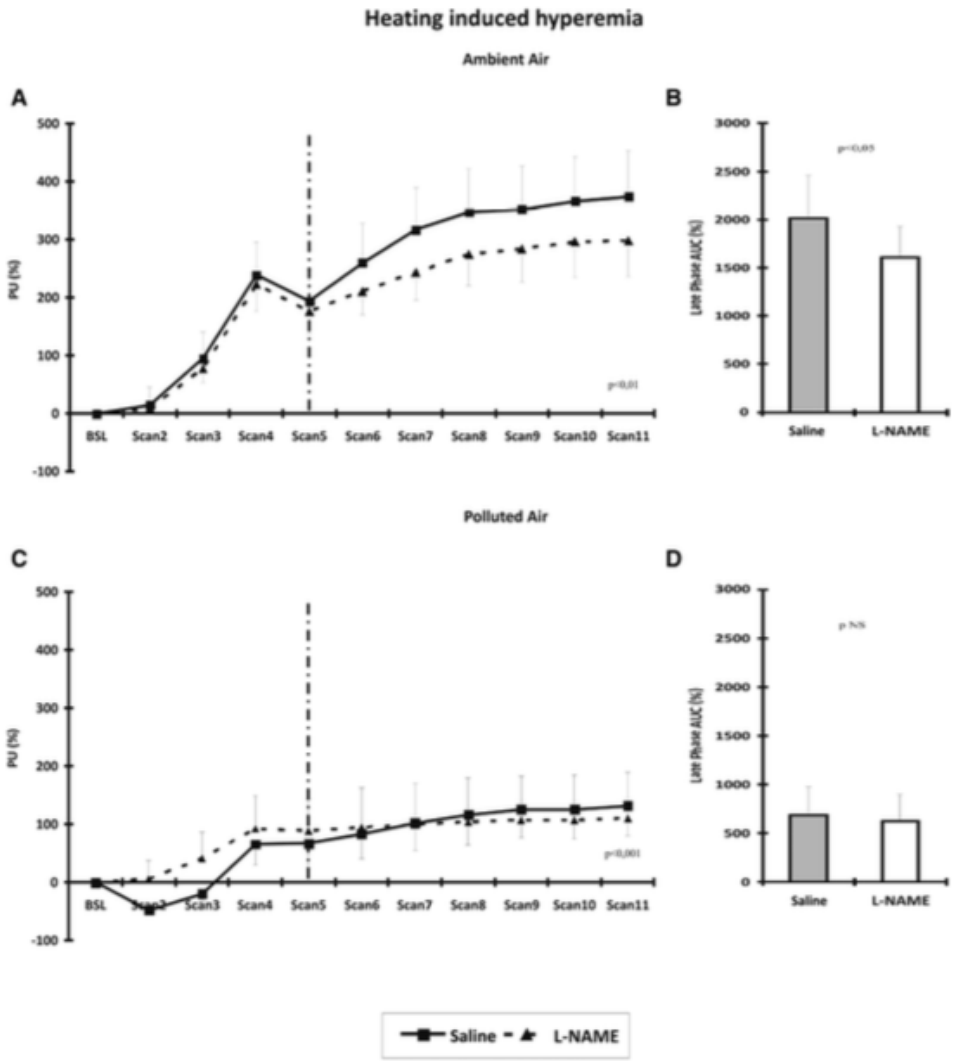


Figure 1. Adjusted relative risks (and 95% CIs) of ischemic heart disease (light gray), cardiovascular disease (dark gray), and cardiopulmonary disease (black) mortality plotted over baseline estimated daily dose of $PM_{2.5}$ from different increments of current cigarette (cigs) smoking (relative to never smokers). Diamonds represent comparable mortality risk estimates for $PM_{2.5}$ from air pollution. Stars represent comparable pooled relative risk estimates associated with SHS exposure from the 2006 Surgeon General's report and from the INTERHEART study. The solid and dotted lines are fitted linear and nonlinear lines illustrating alternative monotonic exposure-response relationships.

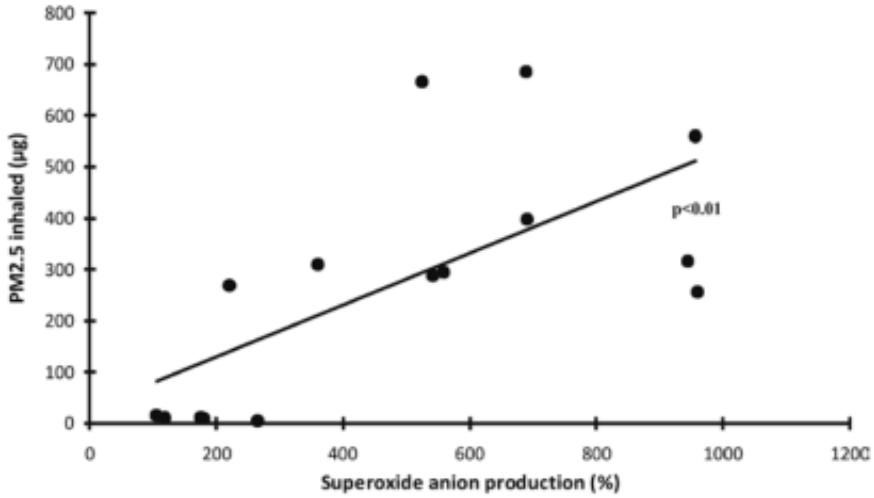
Circulation 2009:120:941-948

Acute Exposure to Diesel Exhaust Impairs Nitric Oxide–Mediated Endothelial Vasomotor Function by Increasing Endothelial Oxidative Stress

Aurélien Wauters, Céline Dreyfuss, Stéphanie Pochet, Patrick Hendrick, Guy Berkenboom, Philippe van de Borne, Jean-François Argacha



Volontaires sains exposés à des fumées de moteur diesel



Superoxide anion production by human umbilical vein endothelial cells (HUVECs) incubated with sera from subjects (n=5)

Stable Compounds of Cigarette Smoke Induce Endothelial Superoxide Anion Production via NADPH Oxidase Activation

Edgar A. Jaimes, Eugene G. DeMaster, Run-Xia Tian, Leopoldo Raij

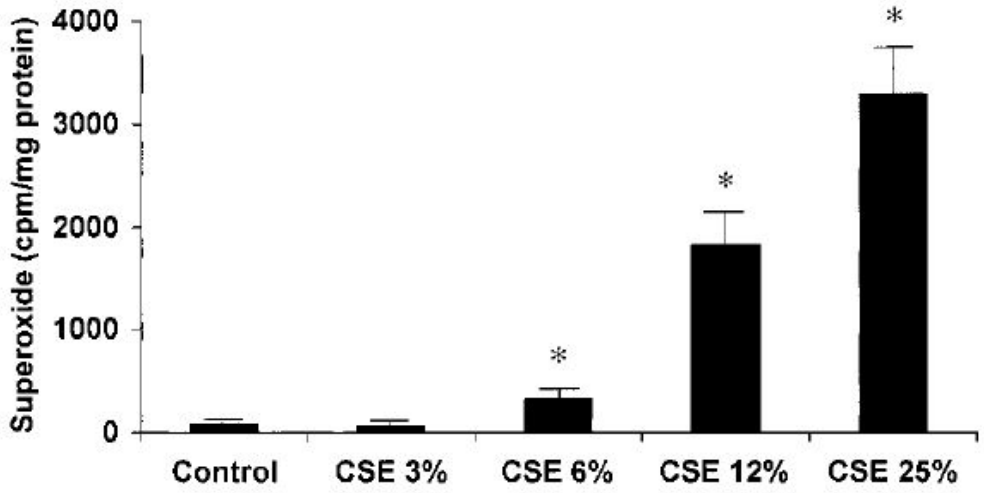
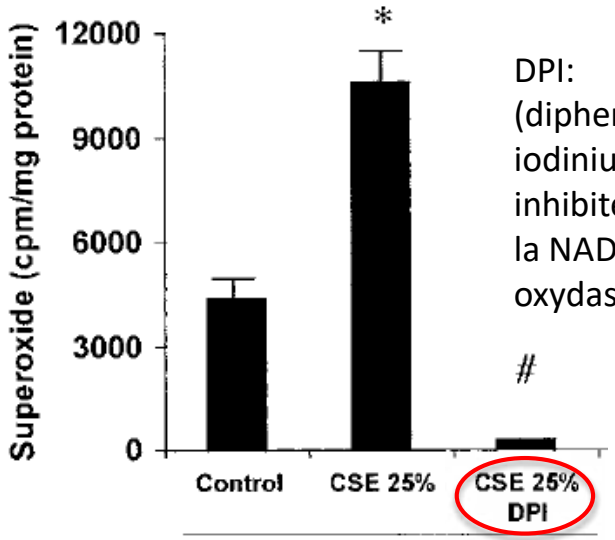


Figure 1. CSE induces O_2^- production in BPAECs in a dose-dependent manner. Values represent mean±SEM of 3 experiments in duplicate. *$P<0.05$ vs control.



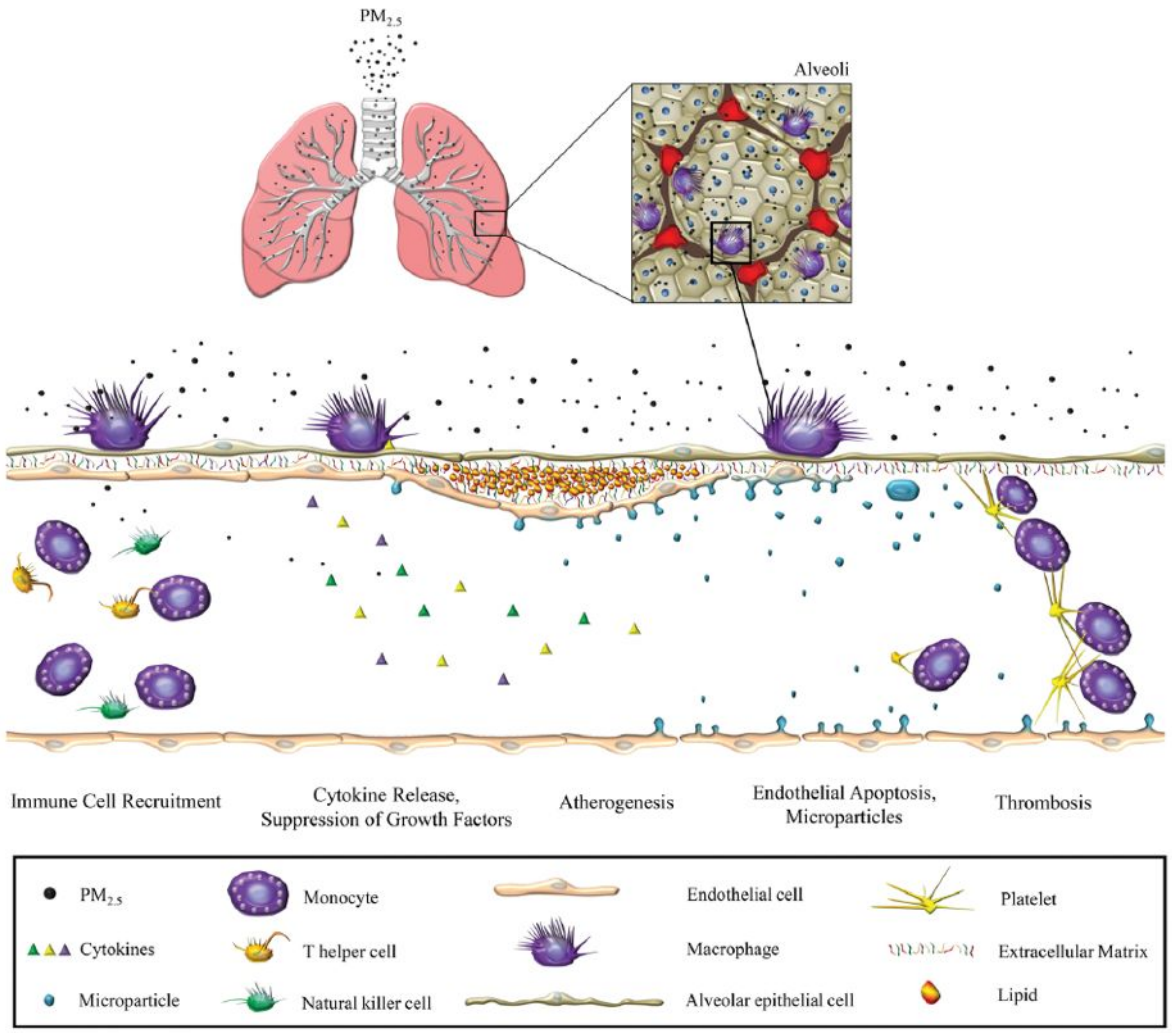
DPI: (diphenyleneiodinium) inhibiteur de la NADPH oxydase

Cultures cellulaires exposées à des extraits de fumée de cigarette

Arterioscler Thromb Vasc Biol. 2004;24:1031-1036

Exposure to Fine Particulate Air Pollution Is Associated With Endothelial Injury and Systemic Inflammation

C. Arden Pope III, Aruni Bhatnagar, James P. McCracken, Wesley Abplanalp, Daniel J. Conklin, Timothy O'Toole



Circ Res. 2016;119:1204-1214

Conclusion

Rôle central du stress oxydatif
(aldéhydes/acroleine, thiol, composants organiques, peroxynitrites, ..)

Rôle présumé de la nicotine dans

- l'initiation des lésions (*controversé*)
- La progression de l'athérome (mécanisme récepteur dépendant)
- La déstabilisation des lésions

Pas d'évidence d'un role délétère du CO

Circulation

ORIGINAL RESEARCH ARTICLE

High Carbon Monoxide Levels from Charcoal Combustion Mask Acute Endothelial Dysfunction Induced by Hookah (Waterpipe) Smoking in Young Adults