
# *La EPOC como Factor de Riesgo Cardiovascular Emergente*

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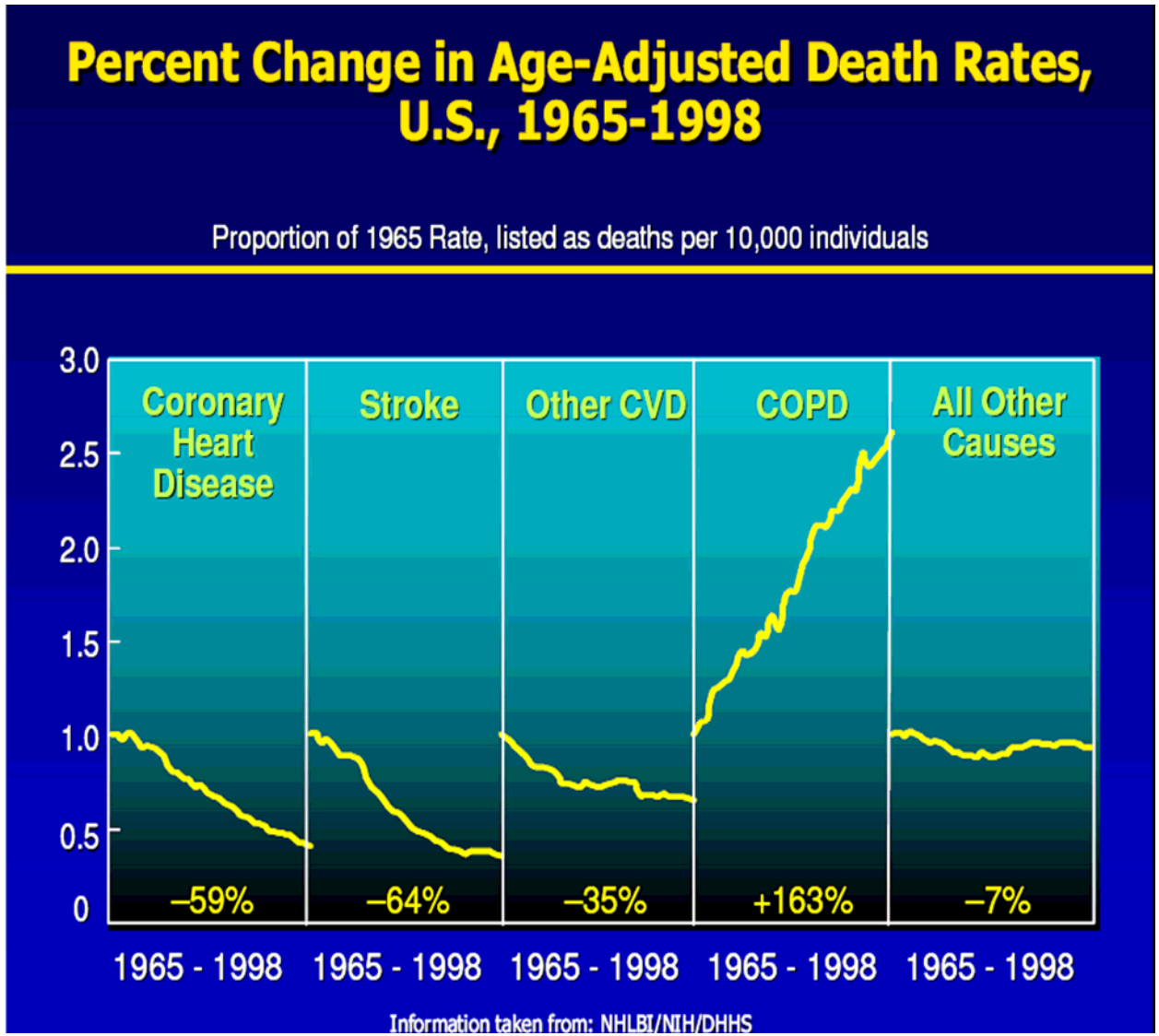
# Introducción

- EPOC: problema de salud pública.
- Una de las principales causas de morbilidad
  - mayor coste económico genera.
  - elevado número de hospitalizaciones
- 5ª causa de muerte.
- Impacto médico y social
  - incremento en el número de publicaciones

**Chest. 2005; 128: 2068-75**
**Chest. 2005 ;128: 2005-11**
**Chest. 2005;128: 2640-6**


Percent Change in Age-Adjusted Death Rates, U.S., 1965-1998
Proportion of 1965 Rate, listed as deaths per 10,000 individuals
3.0
2.5
2.0
1.5
1.0
0.5
0
Coronary Heart Disease
Stroke
Other CVD
COPD
All Other Causes
–59%
–64%
–35%
+163%
–7%
1965 - 1998
1965 - 1998
1965 - 1998
1965 - 1998
1965 - 1998
Information taken from: NHLBI/NIH/DHHS

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# Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

**N= 6111,**

**Mortalidad: 875 muertes**

| Variable | Placebo Group (N=1524) | Salmeterol Group (N=1521) | Fluticasone Group (N=1534) | Combination Therapy Group (N=1533) |
|---|---|---|---|---|
| **Mortality analysis** | | | | |
| No. of deaths from any cause | 231 | 205 | 246 | 193 |
| Probability of death at 3 yr — % | 15.2 | 13.5 | 16.0 | 12.6 |
| Primary cause of death up to 3 yr — no. (%) | | | | |
| Cardiovascular **(24%)** | 71 (5) | 45 (3) | 61 (4) | 60 (4) |
| Pulmonary **(35%)** | 74 (5) | 80 (5) | 91 (6) | 61 (4) |
| Cancer **(21%)** | 45 (3) | 44 (3) | 51 (3) | 44 (3) |
| Other | 23 (2) | 22 (1) | 30 (2) | 11 (1) |
| Unknown | 18 (1) | 14 (1) | 13 (1) | 17 (1) |

# Factor de riesgo

"Característica (congénita, hereditaria o derivada de una exposición o del hábito de vida) que se asocia con la aparición de una enfermedad"

Principios básicos investigación clínica 2001

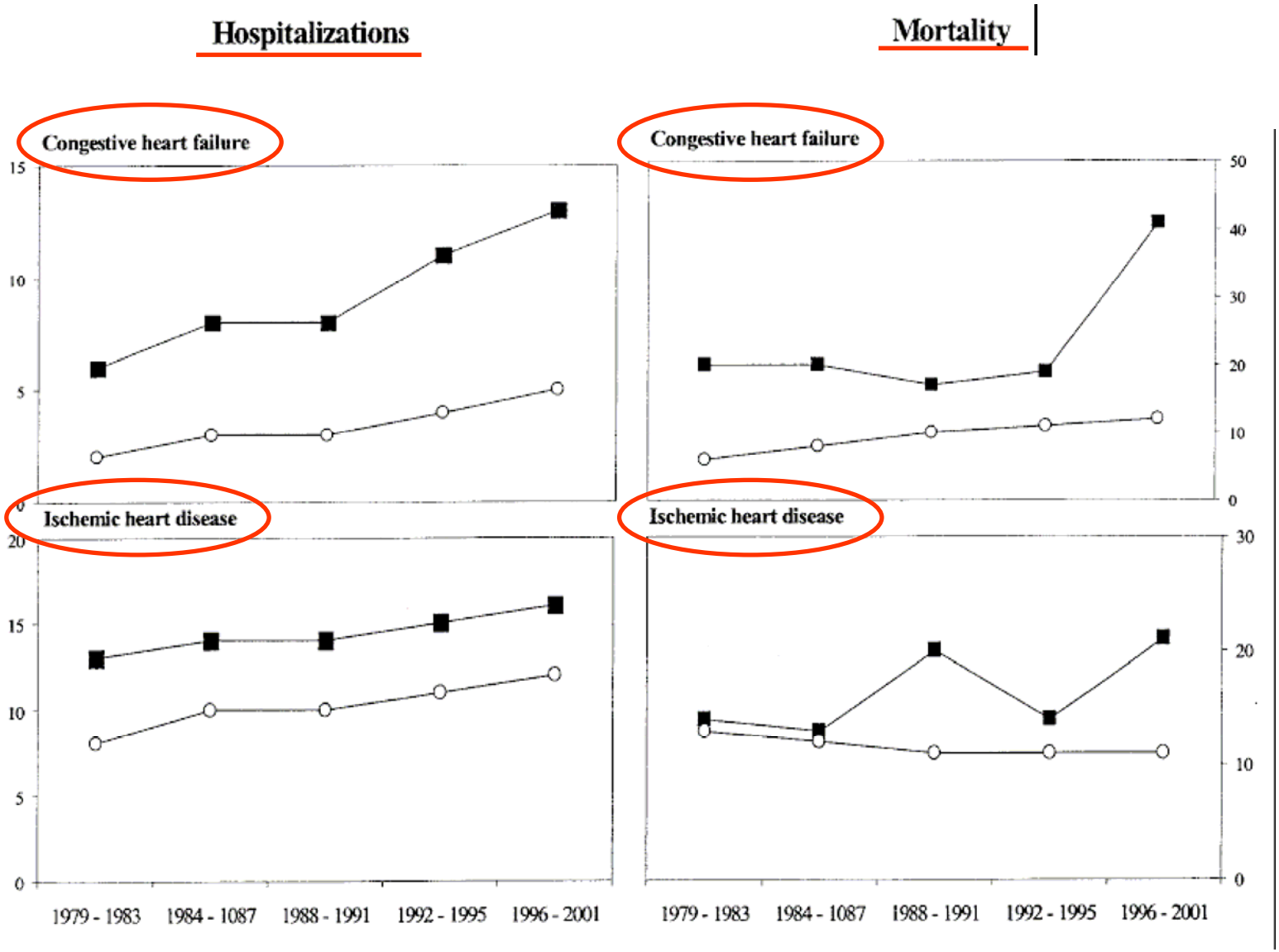
# Comorbidity and Mortality in COPD-Related Hospitalizations in the United States, 1979 to 2001*

*Fernando Holguin, MD; Erik Folch, MD; Stephen C. Redd, MD; and David M. Mannino, MD, FCCP*

**Table 1—*Age Distribution of Hospital Discharges and In-hospital Mortality by a Primary or Secondary Discharge Diagnosis of COPD, NHDS 1979 to 2001***

| Age, yr | All Hospitalizations, No.* | Hospital Discharges With Diagnosis of COPD, %† | In-hospital Mortality Among Discharges With Diagnosis of COPD, %‡ | In-hospital Mortality Among Discharges Without Diagnosis of COPD, %‡ |
|---|---|---|---|---|
| 25–64 | 325,400,000 | 4.1 | 2.6 | 1.2 |
| 65–74 | 101,500,000 | 15.0 | 5.3 | 4.1 |
| 75–84 | 91,400,000 | 15.1 | 7.4 | 6.0 |
| > 84 | 42,640,000 | 11.3 | 9.9 | 9.0 |
| Total | 560,900,000 | 8.5 | 5.9 | 3.0 |

***CHEST 2005; 128:2005–2011***




***CHEST 2005; 128:2005–2011***

# Chronic Obstructive Pulmonary Disease as a Risk Factor for Cardiovascular Morbidity and Mortality

Don D. Sin and S. F. Paul Man

TABLE 1. BASELINE CHARACTERISTICS OF INCLUDED STUDIES REPORTED SINCE 1990 AND THE ASSOCIATION BETWEEN $FEV_1$ AND CARDIOVASCULAR MORTALITY

| Author | Study Population | Sample Size | Age (*yr*) | Male (%) | Mean $FEV_1$ (*L or % of predicted*) | Current Smokers (%) | $FEV_1$ Categorization (*% predicted or L*) | Follow-up (*yr*) | RR of Cardiovascular Mortality (*95% CI*) | Adjusted Factors |
|---|---|---|---|---|---|---|---|---|---|---|
| Hole (12) | Renfrew & Paisley, UK | 15,411 | 45–64 (range) | 46 | 2.83* | 36 | Quintiles | 15 | 1.56 (1.26, 1.92)* | Age, smoking status & history, blood pressure, serum cholesterol, BMI, social class |
| | | | | | 1.99† | | (≤ 73-75% vs. ≥ 108–113%) | | 1.88 (1.44, 2.47)† | |
| Schunemann (16) | Buffalo/Erie County, U.S. | 1,195 | 47 | 46 | 2.8 | 58 | Quintiles | 29 | 2.11 (1.20,3.71)* | Age, education, smoking status, blood pressure, BMI |
| | | | | | | | (< 80% vs ≥ 109–114%) | | 1.96 (0.99,3.88)† | |
| Hospers (17) | Vlagtwedde-Vlaardingen, Netherlands | 5,382 | 36 | 54 | 98% | 55 | <80% vs. ≥ 100% | ~25 | 1.82 (1.42,2.34) | Sex, age, smoking status, BMI |
| Knuiman (18) | Busselton, Australia | 4,277 | 49 | 49 | 95%*/100%† | 45*/24† | 10% decrease in $FEV_1$ percent predicted | 20 to 26 | 1.10 (1.03, 1.18)* | Age, smoking status & history, symptoms, coronary heart disease, cardiovascular risk factors |
| | | | | | | | | | 1.07 (1.00, 1.24)† | |

* Male values.
† Female values.

Proc Am Thorac Soc Vol 2. pp 8–11, 2005

# Cardiovascular Morbidity and Mortality in COPD*

*Laetitia Huiart, MD; Pierre Ernst, MD; and Samy Suissa, PhD*

**Table 3—*SRRs for CVD Hospitalizations Adjusted for Age, Gender, and Calendar Year***

| Cause of Hospitalization (ICD-9 Codes) | Events Observed, No.* | SRR† | 95% CI |
|---|---|---|---|
| CVD (390–459) | 4,374 | 1.89 | 1.83–1.94 |
| Ischemic heart disease (410–414) | 1,063 | 1.47 | 1.38–1.56 |
| Acute myocardial infarction (410) | 306 | 1.30 | 1.15–1.44 |
| Heart failure (428) | 1,403 | 3.07 | 2.91–3.23 |
| Cerebrovascular disease (430–438) | 519 | 1.27 | 1.16–1.38 |

**Table 5—*SMRs for CVD Adjusted for Age, Gender, and Calendar Year***

| Cause of Death (ICD-9 Codes) | Events Observed, No. | SMR* | 95% CI |
|---|---|---|---|
| CVD (390–459) | 960 | 1.95 | 1.83–2.07 |
| Ischemic heart disease (410–414) | 460 | 1.91 | 1.74–2.09 |
| Acute myocardial infarction (410) | 201 | 1.63 | 1.41–1.86 |
| Heart failure (428) | 121 | 2.83 | 2.32–3.33 |
| Cerebrovascular disease (430–438) | 165 | 1.60 | 1.36–1.85 |

**(> 55 years old receiving a first treatment for COPD:1990-1997)**

***CHEST 2005; 128:2640–2646***

# Pathogenesis and Pathophysiology

- **Pathogenesis**
  - Tobacco smoking is the main risk factor for COPD, although other inhaled noxious particles and gases may contribute.
  - In addition to inflammation, an imbalance of proteinases and antiproteinases in the lungs, and oxidative stress are also important in the pathogenesis of COPD.

- **Pathophysiology**
  - The different pathogenic mechanisms produce the pathological changes which, in turn, give rise to the physiological abnormalities in COPD:
    - mucous hypersecretion and ciliary dysfunction,
    - airflow limitation and hyperinflation,
    - gas exchange abnormalities,
    - pulmonary hypertension,
    - **systemic effects.**

**Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2006**

"La EPOC es una enfermedad caracterizada por una limitacion al flujo aereo que no es reversible en su totalidad, que es progresiva y se asocia a una respuesta anómala inflamatoria de los pulmones a gases o particulas nocivas".

*Global Obstructive Lung Disease Initiative (GOLD)*

Aumento de (PCR), fibrinógeno, interleucinas (IL), (especialmente IL-6), (TNF-$\alpha$) y leucocitos

La enfermedad cardiovascular arterioesclerótica es la principal causa de muerte en el mundo occidental

Why Are Patients With Chronic Obstructive Pulmonary Disease at Increased Risk of Cardiovascular Diseases?

The Potential Role of Systemic Inflammation in Chronic Obstructive Pulmonary Disease

Don D. Sin, MD, MPH; S.F. Paul Man, MD

## Vínculo entre la EPOC y la enfermedad cardiovascular

- inflamación sistémica en pacientes con reducción leve o moderada del flujo respiratorio (FEV1 50-80%)
- la importancia del incremento en las concentraciones séricas tanto de la PCR como del fibrinógeno.
- incremento x2-3 de morbimotalidad cardiovascular
- corticoides orales o inhalados reducen los niveles de PCR
- posibilidad de nuevas estrategias de tratamiento

***Circulation*** **2003;107;1514-1519**

# C-reactive protein levels and clinically important predictive outcomes in stable COPD patients

J.P. de Torres*, E. Cordoba-Lanus*, C. López-Aguilar*, M. Muros de Fuentes#, A. Montejo de Garcini*, A. Aguirre-Jaime*, B.R. Celli¶ and C. Casanova*

Eur Respir J 2006; 27: 902–907

**TABLE 3** Results of multivariate linear regression analysis#

| Predictive parameter | Regression coefficient | | | | p-value |
|---|---|---|---|---|---|
| | Value | SEM | 95% CI | Standardised | |
| $P_{a,O_2}$ | -0.011 | 0.004 | -0.18– -0.004 | -0.271 | 0.003 |
| 6MWD | -0.001 | 0.001 | -0.002– -0.001 | -0.206 | 0.048 |
| $FEV_1$ % | 0.006 | 0.008 | -0.010–0.023 | 0.298 | 0.457 |
| FVC % | -0.008 | 0.005 | -0.18–0.003 | -0.395 | 0.142 |
| GOLD | -0.015 | 0.125 | -0.263–0.233 | -0.031 | 0.905 |
| IC/TLC | 0.051 | 0.703 | -1.340–1.442 | 0.010 | 0.942 |
| BODE | -0.022 | 0.037 | -0.096–0.051 | -0.103 | 0.549 |
| BMI | 0.006 | 0.008 | -0.010–0.023 | 0.075 | 0.465 |

# Respuesta inflamatoria pulmonar

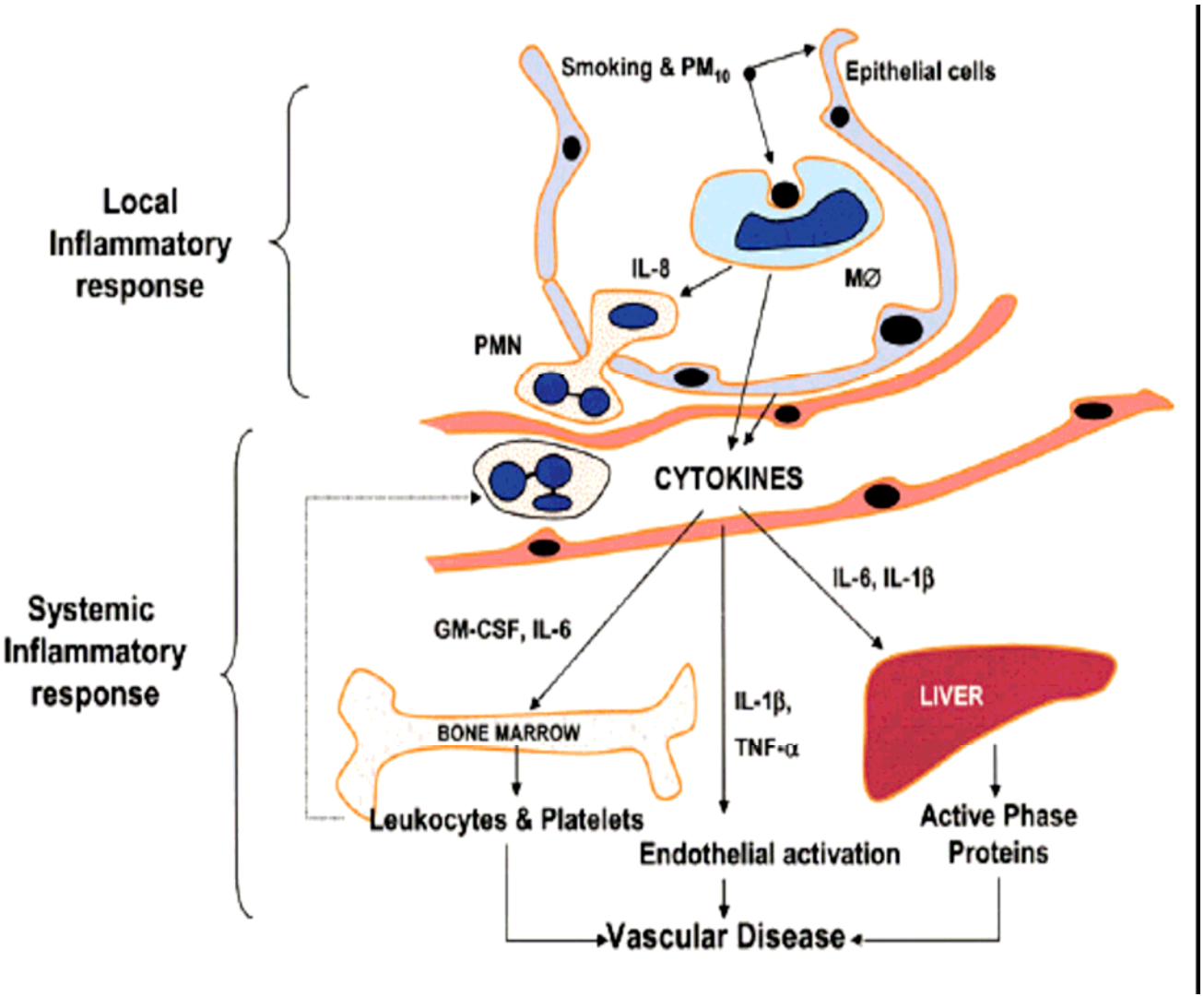
- ↑ neutrófilos, macrófagos y linfocitos T (T8)
- ↑ citoquinas proinflamatorias: IL-6, IL-8, TNF- $\alpha$
- estrés oxidativo por inhalación de agentes oxidantes

# Respuesta inflamatoria sistémica

- incluso en pacientes estables
- citoquinas proinflamatorias: IL-6, IL-8, PCR, TNF- $\alpha$
- inflamación pulmonar: fuente de inflamación sistémica

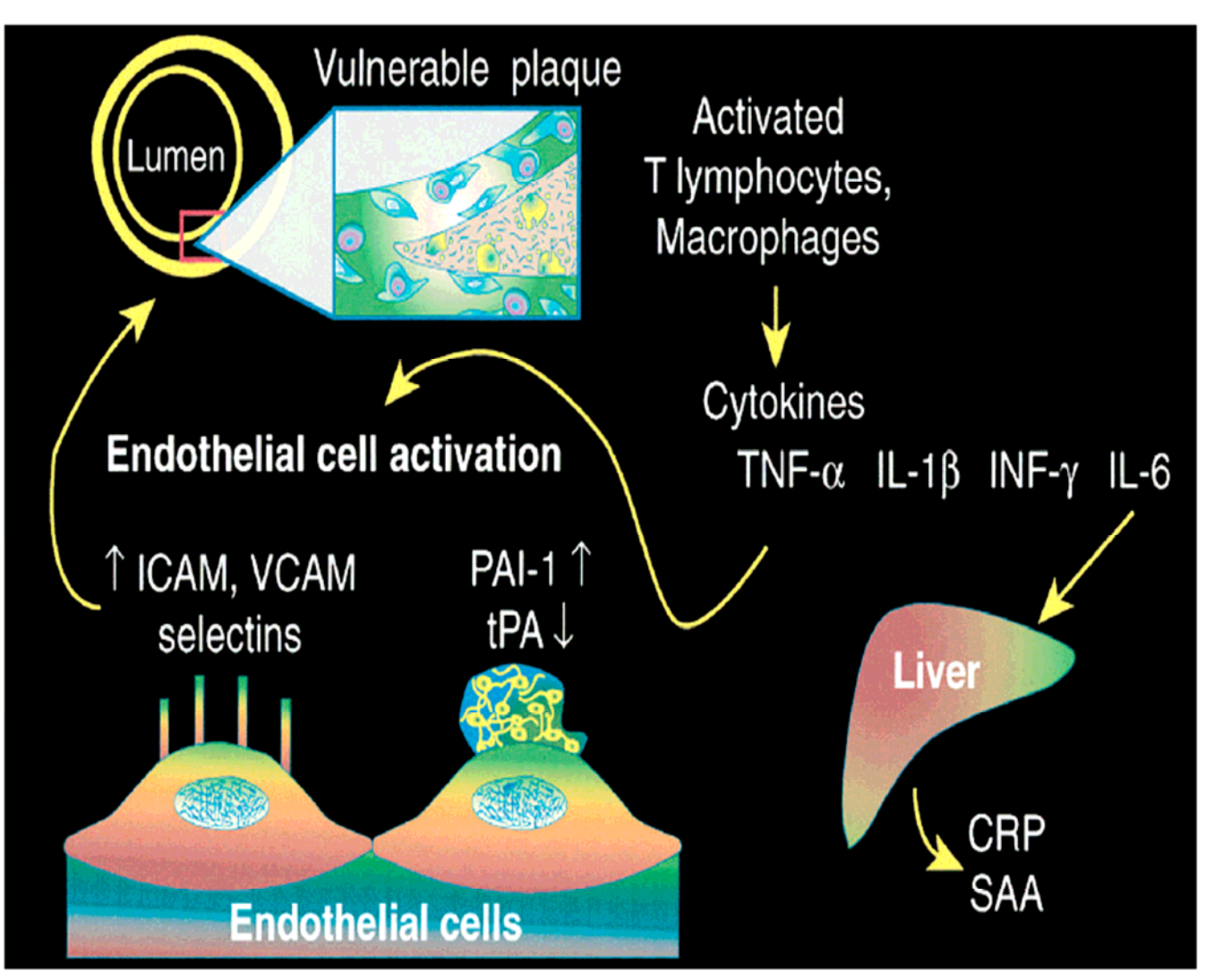
**Thorax 1996; 51:819-824**
**Am J Respir Cri Care Med 2001; 164:1414-18**
**Eur Resp J 2003; 21:347-60**

# Repuesta inflamatoria en la EPOC




Proc Am Thorac Soc 2005; 2: 61–67

# Inflamación y arterioesclerosis




Am J Cardiol 2003;91:9B–13B

# Recomendaciones clínicas

- **Identificar y tratar FRCV clásicos**
  - obesidad,
  - hipertensión arterial
  - hipercolesterolemia, etc.
- **Consideraciones especiales**
  - obesidad: claro factor de riesgo vascular,
  - EPOC: mayor mortalidad con el descenso de peso ¿mediada por las citocinas inflamatorias (TNF-$\alpha$)?.

# En resumen……

- Fuerte evidencia de asociación entre EPOC y enfermedad cardiovascular.
- Nexo de unión: actividad mantenida del sistema inflamatorio.
- Posibilidad de determinar biomarcadores: pronóstico
- El conocimiento de la fisiopatología abre nuevas perspectivas terapéuticas.

Vall d'Hebron Hospital

Grupo de EPOC
Enfermedad Pulmonar Obstructiva Crónica

Breathless not Helpless!

World COPD Day 2007

November 14, 2007

# gracias por su atención

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE™