



ASMA

¿Crónico?

¿Inflamatorio?

¿Genético?

¿Incurable?



Taller de Educación Respiratoria

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Prevalencia

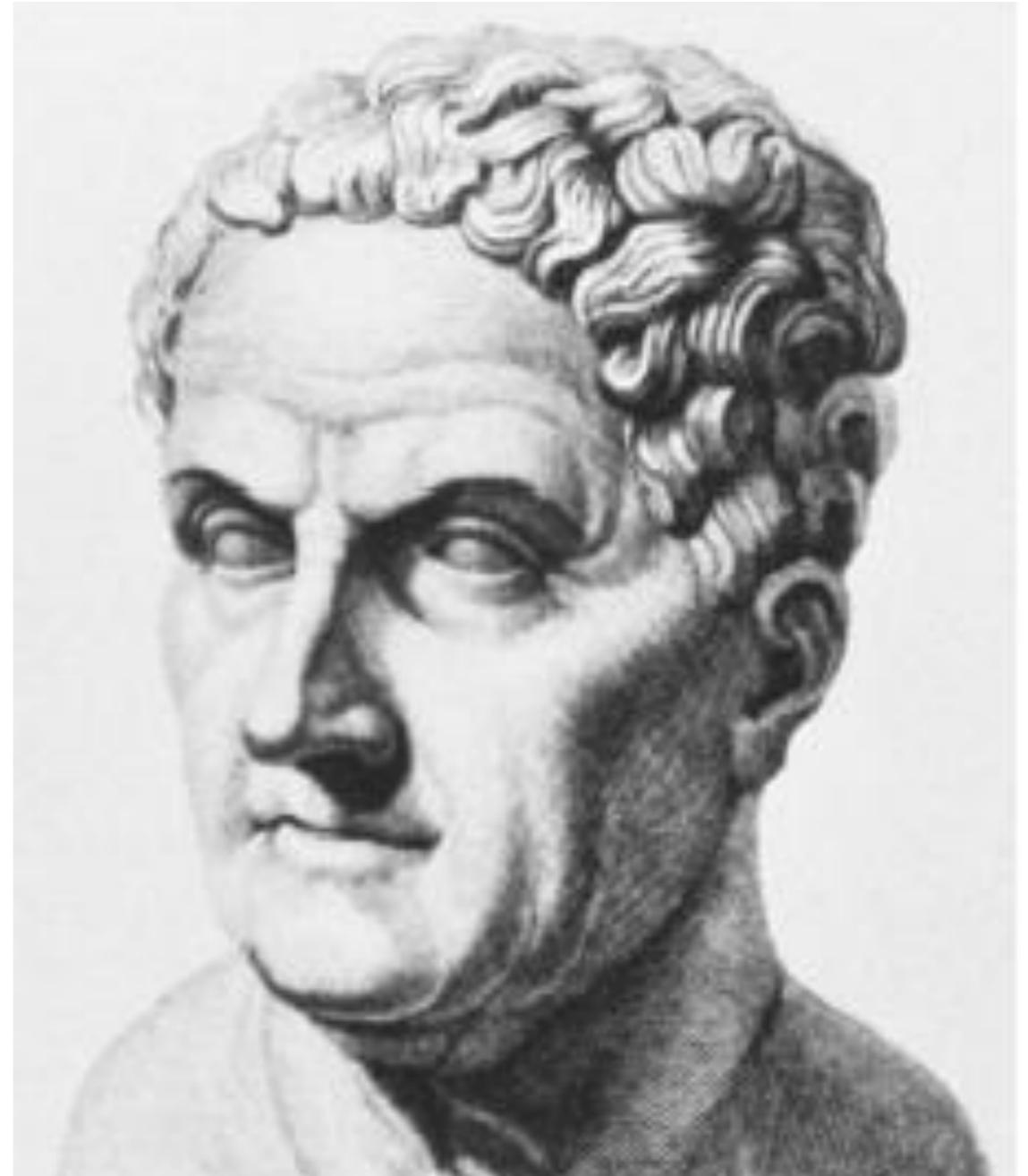
- Más de 300 millones de personas en el mundo padecen asma
- 250,000 mueren cada año (3 cada día en Reino Unido 6 cada día en EEUU)
- En España más de 10% de niños entre 6 y 12 años han sido diagnosticados de asma en algún momento de su vida.

Definiciones

Άσθμα, ασθμαίνω = jadear, falta de aliento

Causa = *Broncoespasmo*

Galeno, 130–200 AD



Definiciones

Trastorno de la vías aéreas
caracterizado por
broncoespasmo

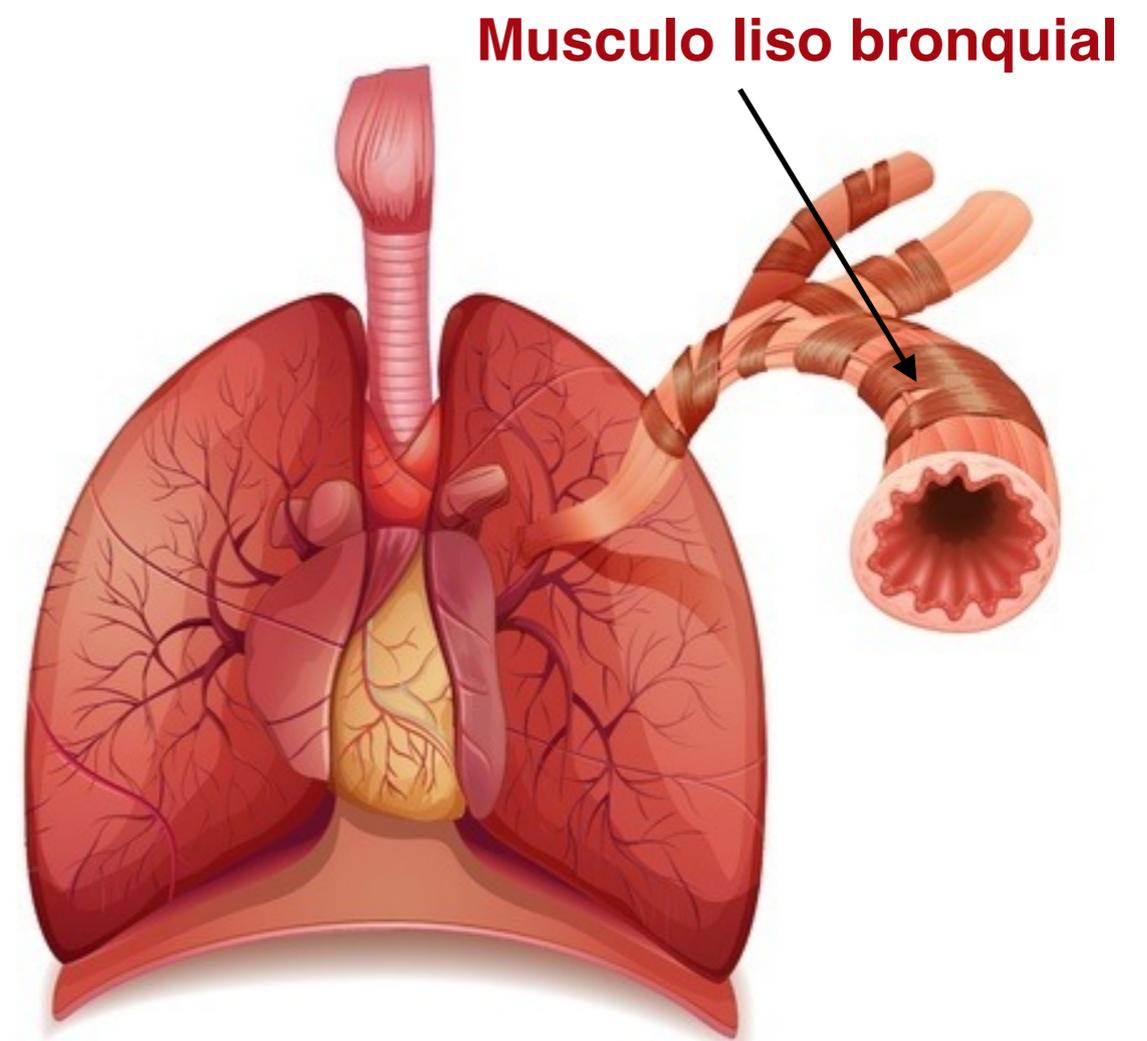
Rene Laennec, 1781–1826



Definiciones

“Enfermedad caracterizada por amplias variaciones, en cortos períodos de tiempo, de la resistencia al flujo de las vías aéreas producida por una *hiperresponsividad del músculo liso bronquial*”

Thorax, 1959; 14:286

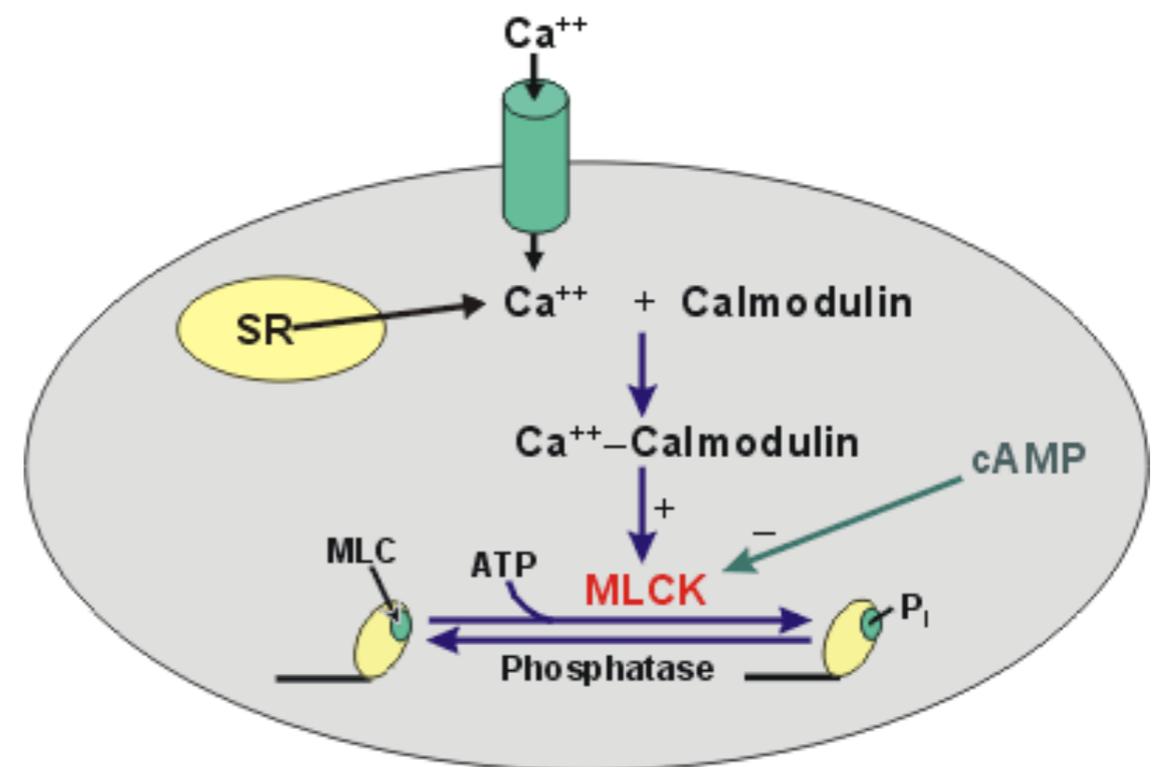


Contracción del músculo liso

Hipocapnia (bajos niveles de CO_2) induce alcalosis que aumenta la concentración de calcio libre intracelular

Sterling GM. Clin Sci 1968; 34:277–285

Lindeman et al. Eur Resp J, 1998; 12:1046–1052



PCO₂ y Broncoespasmo

Animales in vitro e in vivo

Reynolds AM, McEvoy RD. J Appl Physiol **1989**; 67:2454–2460

Ingram RH Jr. J Appl Physiol **1975**; 38:603–607

Kolbe J, Kleeberger SR, Menkes HA, et al. J Appl Physiol **1987**; 63:497–504

Lindeman KS, Croxton TL, Lande B, et al. Eur Respir J **1998**; 12:1046–1052



PCO₂ y Broncoespasmo

Humanos in vivo

D'Angelo E, Calderini IS, Tavola M. *Anesthesiology* **2001**; 94:604–610

Sterling GM. *Clin Sci* **1968**; 34:277–285

Newhouse MT, Becklake MR, Macklem PT, et al. *J Appl Physiol* **1964**; 19:745-749

Nielsen TM, Pedersen OF. *Acta Physiol Scand* **1976**; 98:192-199

O'Cain CF, Hensley MJ, McFadden ER Jr, et al. *J Appl Physiol* **1979**; 47:8 -12

Jamison JP, Glover PJ, Wallace WF. *Thorax* **1987**; 42:809 - 814

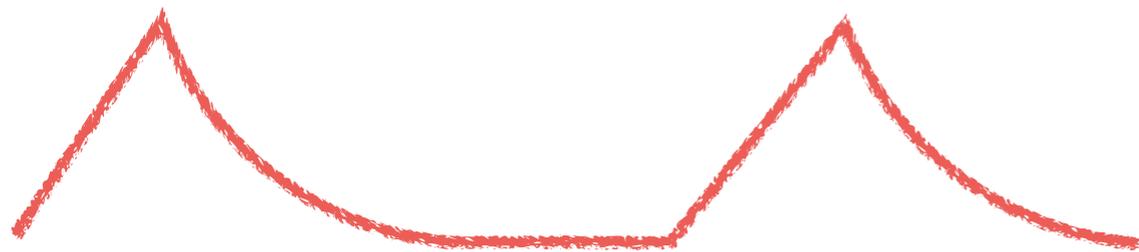
Van den Elshout FJ, van Herwaarden CL, Folgering HT. *Thorax* **1991**; 46: 28 -32

Fisher HK, Holton P, Buxton RS, et al. *Am Rev Respir Dis* **1970**; 101:885- 896

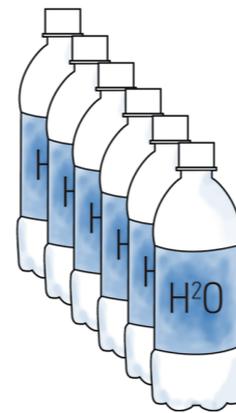
McFadden ER Jr, Stearns DR, Ingram RH Jr, et al. *J Appl Physiol* **1977**; 42:22-27

Bayindir O, Akpınar B, Ozbek U, et al. *Perfusion* **2000**; 15:27-31

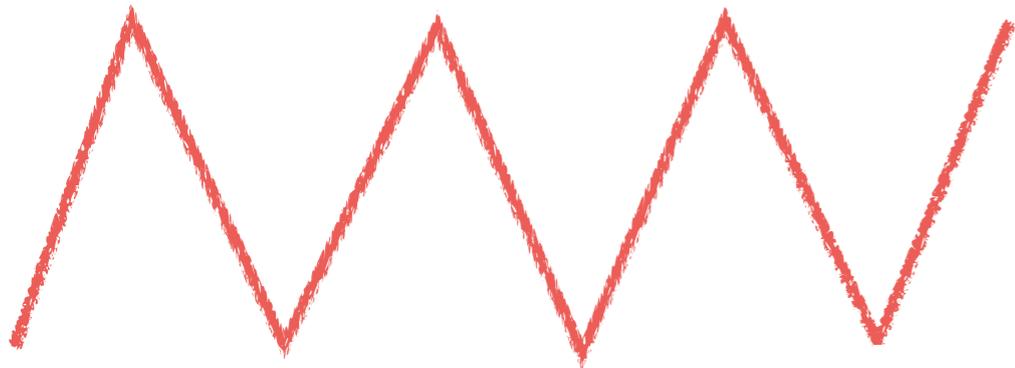
PCO₂ y Respiración



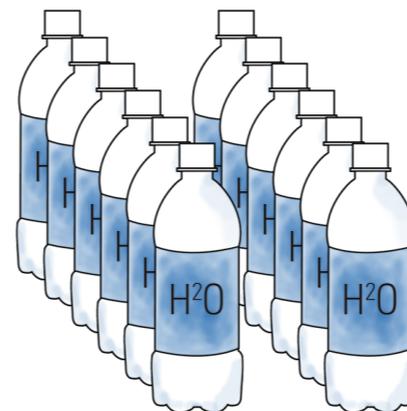
12 x 500 ml = 6 lt/min



PCO₂ = 40 mmHg



15 x 800 ml = 12 lt/min



PCO₂ = 35 mmHg

Systematic review of the effectiveness of breathing retraining in asthma management

Expert Rev. Respir. Med. 5(6), 789–807 (2011)

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In asthma management, complementary and alternative medicine is enjoying a growing popularity worldwide. This review synthesizes the literature on complementary and alternative medicine techniques that utilize breathing retraining as their primary component and compares evidence from controlled trials with before-and-after trials. Medline, PubMed, Cumulative Index to Nursing and Allied Health Literature and the Cochrane Library electronic databases were searched. Reference lists of all publications were manually checked to identify studies not found through electronic searching. The selection criteria were met by 41 articles. Most randomized controlled trials (RCTs) of the Buteyko breathing technique demonstrated a significant decrease in β_2 -agonist use while several found improvement in quality of life or decrease in inhaled corticosteroid use. Although few in number, RCTs of respiratory muscle training found a significant reduction in bronchodilator medication use. Where meta-analyses could be done, they provided evidence of benefit from yoga, Buteyko breathing technique and physiotherapist-led breathing training in improving asthma-related quality of life. However, considerable heterogeneity was noted in some RCTs of yoga. It is reasonable for clinicians to offer qualified support to patients with asthma undertaking these breathing retraining techniques.

KEYWORDS: asthma • Buteyko breathing technique • complementary medicine • respiratory muscle retraining • systematic review

¡Vaya! ¡Cambio de definición!

El asma es un trastorno *inflamatorio crónico* de las vías aéreas, asociado con una obstrucción reversible y una responsividad incrementada a una variedad de estímulos.

Guidelines for the diagnosis and management of asthma. National Heart, Lung, and Blood Institute. National Asthma Education Program Expert Panel Report. J Allergy Clin Immunol 1991;88:425-34.

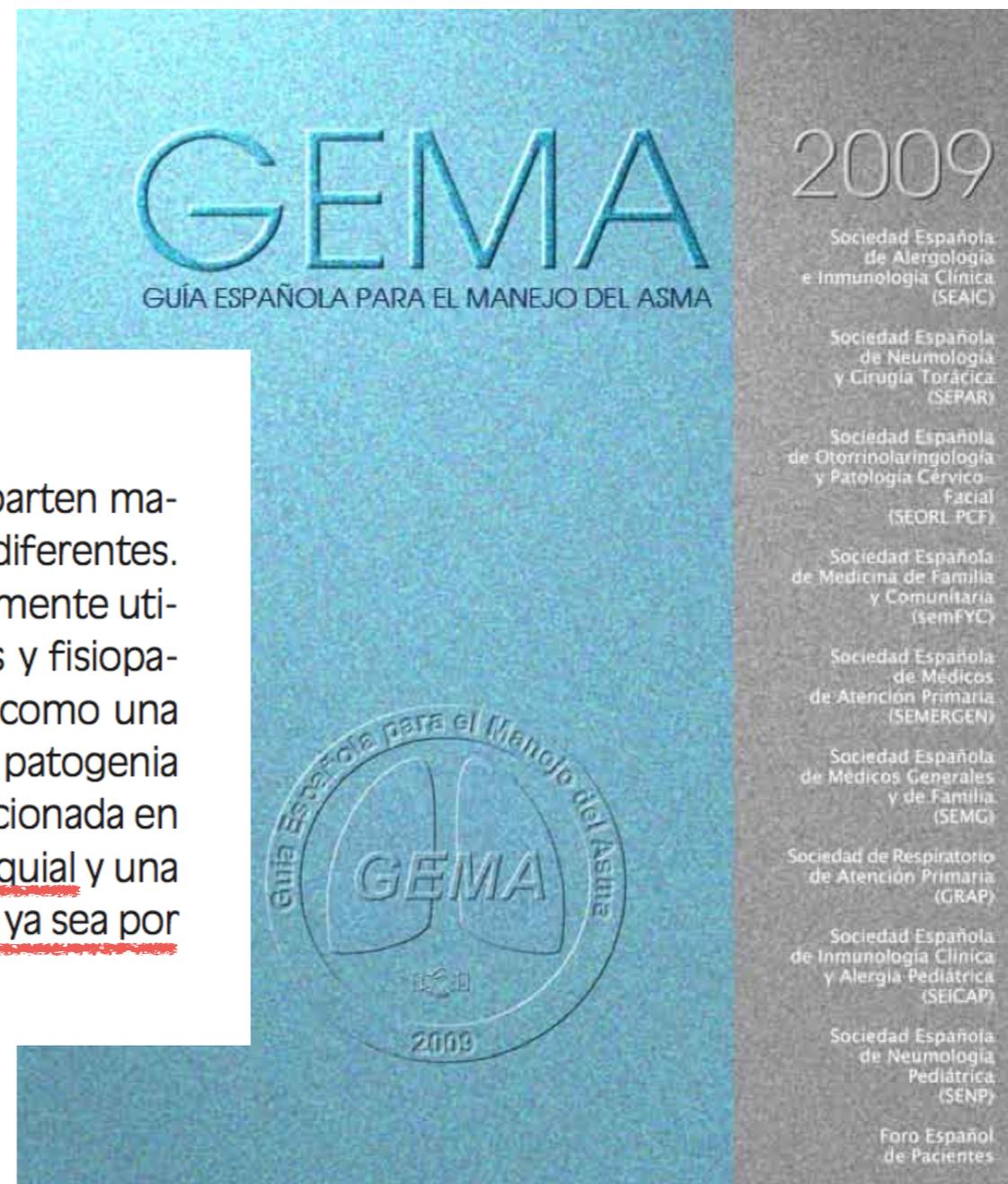
El asma es un trastorno *inflamatorio crónico* de las vías aéreas, en el que muchas células y elementos celulares desempeñan un papel primordial

Global Strategy for Asthma management and prevention. National Institutes of Health. Revised 2002. NIH Publication n.º 02-3659.

¡Vaya! ¡Cambio de definición!

1.1 DEFINICIÓN

El asma es un síndrome que incluye diversos fenotipos que comparten manifestaciones clínicas similares pero de etiologías probablemente diferentes. Ello condiciona la propuesta de una definición precisa; las habitualmente utilizadas son meramente descriptivas de sus características clínicas y fisiopatológicas. Desde un punto de vista pragmático se podría definir como una enfermedad inflamatoria crónica de las vías respiratorias, en cuya patogenia intervienen diversas células y mediadores de la inflamación, condicionada en parte por factores genéticos y que curso con hiperrespuesta bronquial y una obstrucción variable al flujo aéreo, total o parcialmente reversible, ya sea por la acción medicamentosa o espontáneamente.



Airway hyperresponsiveness in asthma: not just a matter of airway inflammation

Vito Brusasco, Emanuele Crimi, Riccardo Pellegrino

Conclusions

Airway inflammation and airway hyperresponsiveness, two major characteristics of bronchial asthma, are loosely related to each other. It seems that the presence of inflammatory cells in the airways is neither sufficient nor necessary for the development of airway hyperresponsiveness. This would imply that an altered response of the target organ is a prerequisite for airway hyperresponsiveness to develop. In this scenario, chronic airway inflammation is likely to play a key role as a stimulus for structural changes (airway wall remodelling, changes in airway to lung interdependence, changes in ASM contractility) affecting the organ response to acute stimuli (fig 1). A practical conclusion is that no inferences about airway hyperresponsiveness can be made from measurements of airway inflammation and vice versa.

Table 1 Studies in human subjects showing (+) and not showing (-) significant correlations between airway inflammation and airway hyperresponsiveness

Authors	Year	Assessment			Marker(s)
		BAL	BB	Sputum	
Kirby <i>et al</i> ⁹¹	1987	+			Eos
Wardlaw <i>et al</i> ⁹²	1988	+			Eos, MBP
Kelly <i>et al</i> ⁹³	1988	-			Eos
Chan Yeung <i>et al</i> ⁹⁴	1988	-			Eos
Pliss <i>et al</i> ⁹⁵	1989	+			Eos
Jeffery <i>et al</i> ⁹⁶	1989		-		Eos
Ferguson <i>et al</i> ⁹⁷	1989	+			Eos
Gibson <i>et al</i> ⁹⁸	1989			-	Eos
Djukanovic <i>et al</i> ⁹⁹	1990		-		EG2
Brusasco <i>et al</i> ⁷²	1990	-			Eos
Foresi <i>et al</i> ¹⁰⁰	1990	-	-		Eos
Adelroth <i>et al</i> ^{101*}	1990	-			Eos, ECP
Bradley <i>et al</i> ⁶⁰	1991		+		EG2
Walker <i>et al</i> ¹⁰²	1991	+			Eos
Bentley <i>et al</i> ¹⁰³	1992		+		EG2
Ollerenshaw <i>et al</i> ¹⁰⁴	1992		-		Eos
Ferguson <i>et al</i> ¹⁰⁵	1992	±			Eos, ECP
Pin <i>et al</i> ¹⁰⁶	1993			+	Eos
Duddridge <i>et al</i> ^{107*}	1993	-			Eos
Iredale <i>et al</i> ¹⁰⁸	1994			-	Eos
Woolley <i>et al</i> ¹⁰⁹	1996	+	+		EG2, Eos
Chetta <i>et al</i> ¹¹⁰	1996		+		Eos
Kidney <i>et al</i> ¹¹¹	1996			-	Eos
Pizzichini <i>et al</i> ¹¹²	1996			+	Eos, MBP
Foresi <i>et al</i> ¹¹³	1997			+	EG2
Crimi <i>et al</i> ¹¹⁴	1998	-	-	-	Eos, ECP

BAL = bronchoalveolar lavage; BB = bronchial biopsy; Eos = number or percentage of eosinophils; ECP = eosinophil cationic protein; MBP = major basic protein; EG2 = cells stained with anti-ECP antibodies.

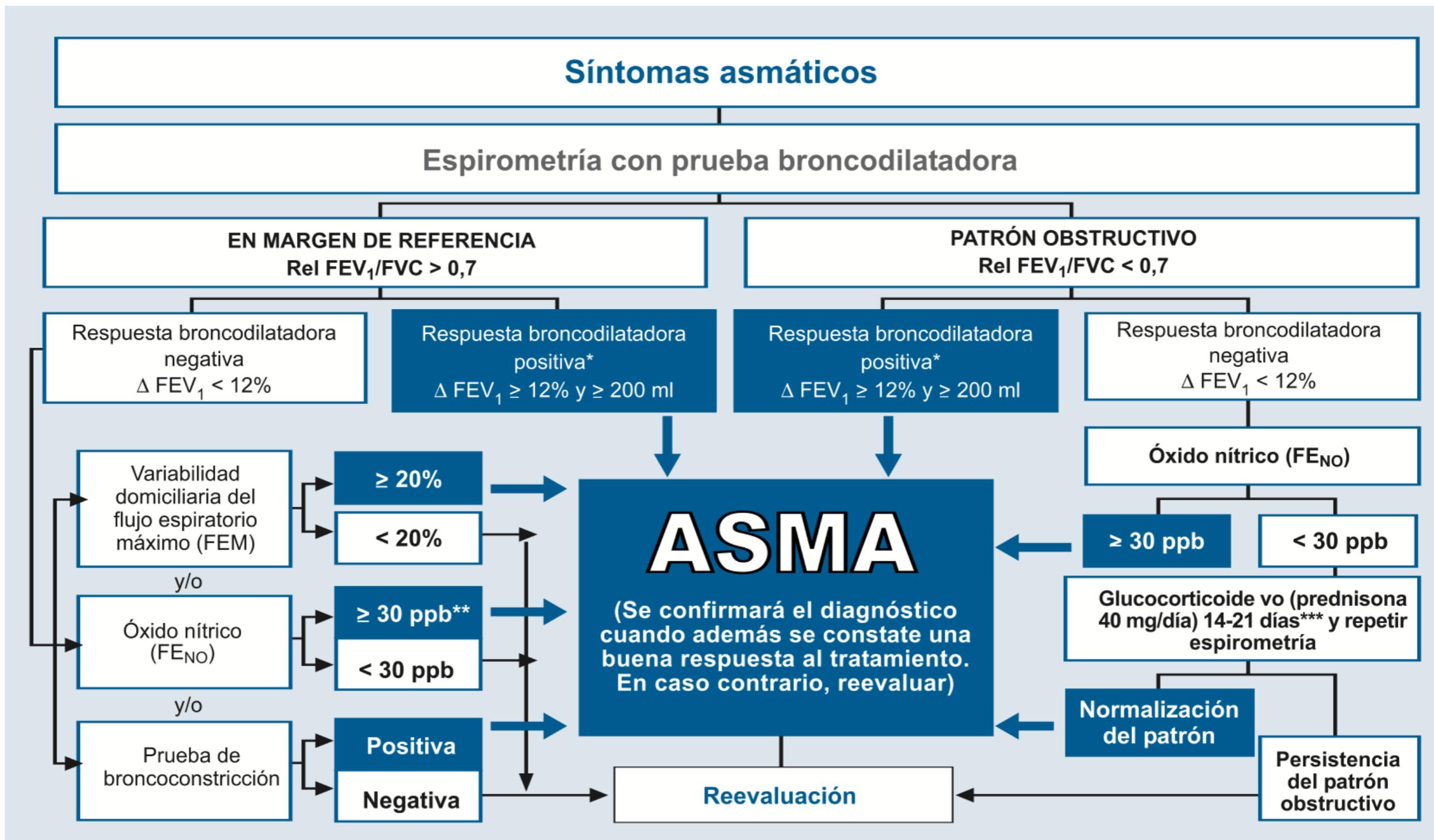
*With anti-inflammatory treatment.

Es evidente que puede haber hiperreactividad sin inflamación y también, inflamación sin hiperreactividad (5, 6). Muchos niños, entre cuyos familiares próximos hay enfermos de asma atópica, tienen sus primeras crisis de disnea en los primeros meses de vida, sin que hayan padecido ninguna infección viral (especialmente virus respiratorio sincitial [VRS]). Esto sugiere la existencia de hiperreactividad bronquial primaria, familiar, al mismo tiempo que la posible predisposición atópica.

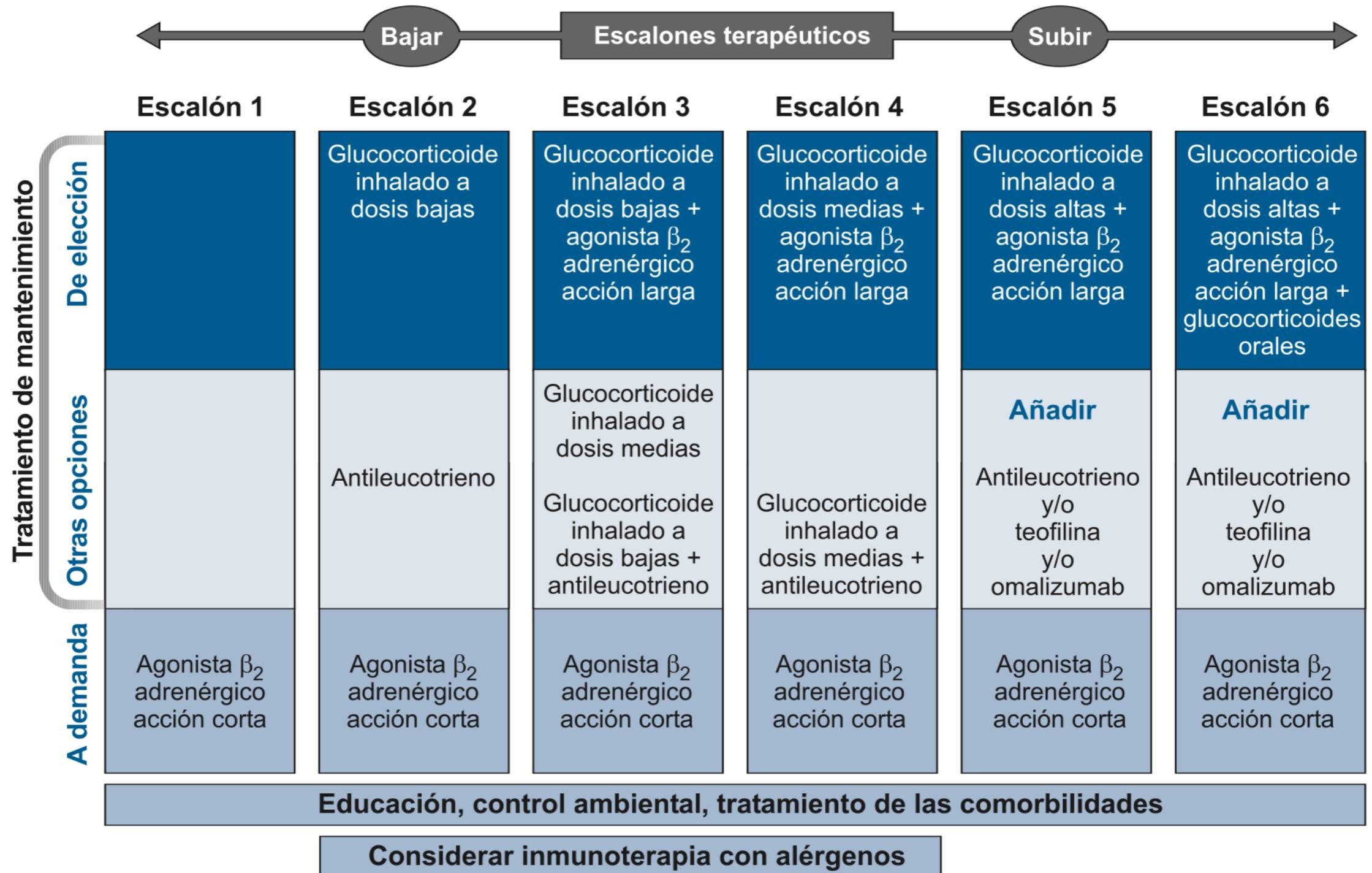
Por consiguiente, sin restar la importancia que indudablemente tiene la reacción inflamatoria en la reducción del flujo aéreo, los trabajos comentados vuelven a situar al músculo liso como primer elemento en la patogenia del asma, con las implicaciones terapéuticas que en un futuro puedan derivarse de este hecho (11, 17, 18).

F. Muñoz-López

El diagnóstico



El tratamiento



Por lo tanto...

- La inflamación no se evalúa. Se infiere cuando los broncodilatadores no son suficientes. **NO SE DEBERIAN ADMINISTRAR CORTICOIDES EN EL PRIMER ESCALÓN**
- El broncodilatador es un medicamento a demanda. **NO SE JUSTIFICA CIENTIFICAMENTE EL USO DE BRONCODILATADORES COMO MEDICAMENTO DE MANTENIMIENTO**
- El broncoespasmo se remite con el aumento de CO_2 . **LA EDUCACIÓN RESPIRATORIA PUEDE SUSTITUIR EL USO DE BRONCODILATADORES A DEMANDA**

Meta-Analysis: Effect of Long-Acting β -Agonists on Severe Asthma Exacerbations and Asthma-Related Deaths

Shelley R. Salpeter, MD; Nicholas S. Buckley; Thomas M. Ormiston, MD; and Edwin E. Salpeter, PhD

Data Synthesis: Pooled results from 19 trials with 33 826 participants found that long-acting β -agonists increased exacerbations requiring hospitalization (OR, 2.6 [95% CI, 1.6 to 4.3]) and life-threatening exacerbations (OR, 1.8 [CI, 1.1 to 2.9]) compared with placebo. Hospitalizations were statistically significantly increased with salmeterol (OR, 1.7 [CI, 1.1 to 2.7]) and formoterol (OR, 3.2 [CI, 1.7 to 6.0]) and in children (OR, 3.9 [CI, 1.7 to 8.8]) and adults (OR, 2.0 [CI, 1.1 to 3.9]). The absolute increase in hospitalization was 0.7% (CI, 0.1% to 1.3%) over 6 months. The risk for asthma-related deaths was increased (OR, 3.5 [CI, 1.3 to 9.3]), with a pooled risk difference of 0.07% (CI, 0.01% to 0.1%).

Conclusions: Long-acting β -agonists have been shown to increase severe and life-threatening asthma exacerbations, as well as asthma-related deaths.

Ann Intern Med. 2006;144:904-912.

For author affiliations, see end of text.

www.annals.org

- **Formoterol (Foradil, Symbicort)**
- **Salmeterol (Seretide, Plusvent, Serevent)**

Asthma mortality rates increased worldwide in the 1960s, when inhaled β -agonists were introduced on the market (92). We have seen another increase in mortality rates in the United States over the past 10 years, since long-acting β -agonists were introduced (92). Similar increases in mortality were seen in New Zealand when the strong inhaled β -agonist fenoterol was introduced; mortality decreased rapidly when use of the drug was severely curtailed and widespread use of inhaled corticosteroids was instituted (92, 93). If long-acting β -agonists were removed from the market in the United States, we might witness a reduction in asthma mortality rates here.

In summary, long-acting β -agonist use increases the risk for hospitalizations due to asthma, life-threatening asthma exacerbations, and asthma-related deaths. Similar risks are found with salmeterol and formoterol and in children and adults. Concomitant inhaled corticosteroids do not adequately protect against the adverse effects. The use of long-acting β -agonists could be associated with a clinically significant number of unnecessary hospitalizations, intensive care unit admissions, and deaths each year. Black box warnings on the labeling for these agents clearly outline the increased risk for asthma-related deaths associated with their use, but these warnings have not changed prescribing practices of physicians (25). This information could be used to reassess whether these agents should be withdrawn from the market.

MEDICATION GUIDE

Foradil® [FOR-a-dil] **Aerolizer®**
(formoterol fumarate inhalation powder)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **SEREVENT DISKUS** safely and effectively. See full prescribing information for **SEREVENT DISKUS**.

SEREVENT DISKUS (salmeterol xinafoate inhalation powder)
FOR ORAL INHALATION USE

Initial U.S. Approval: 1994

WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- Long-acting beta₂-adrenergic agonists (LABA), such as salmeterol, the active ingredient in **SEREVENT DISKUS**, increase the risk of asthma-related death. A US trial showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. (5.1)

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SYMBICORT® 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg)

Inhalation Aerosol

SYMBICORT® 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg)

Inhalation Aerosol

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **SYMBICORT** safely and effectively. See full prescribing information for **SYMBICORT**.

SYMBICORT® 80/4.5 (budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

SYMBICORT® 160/4.5 (budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

FOR ORAL INHALATION

Initial US Approval: 2006

WARNING: ASTHMA-RELATED DEATH (See full prescribing information for complete boxed warning.)

- Long-acting beta₂-adrenergic agonists (LABA), such as formoterol one of the active ingredients in **SYMBICORT**, increase the risk of asthma-related death. A placebo-controlled study with another LABA (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. (5.1)
- When treating patients with asthma, prescribe **SYMBICORT** only for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue **SYMBICORT**) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use **SYMBICORT** for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids. (1.1, 5.1)

Important: Do not swallow FORADIL capsules. FORADIL capsules are used only with the Aerolizer inhaler that comes with FORADIL AEROLIZER. Never place a capsule in the mouthpiece of the AEROLIZER Inhaler.

Read the Medication Guide that comes with **FORADIL AEROLIZER** before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your health care provider about your medical condition or treatment.

What is the most important information I should know about FORADIL AEROLIZER?

FORADIL AEROLIZER can cause serious side effects, including:

1. People with asthma who take long-acting beta₂-adrenergic agonist (LABA) medicines, such as formoterol fumarate inhalation powder (FORADIL AEROLIZER), have an increased risk of death from asthma problems.

- Call your healthcare provider if breathing problems worsen over time while using **FORADIL AEROLIZER**. You may need a different treatment.
- Get emergency medical care if:
 - breathing problems worsen quickly, and
 - you use your rescue inhaler medicine, but it does not relieve your breathing problems.

2791103

Warnings and Precautions

DATA FROM A LARGE PLACEBO-CONTROLLED SAFETY STUDY THAT WAS STOPPED EARLY SUGGEST THAT SALMETEROL, A COMPONENT OF SERETIDE DISKUS, MAY BE ASSOCIATED WITH RARE SERIOUS ASTHMA EPISODES OR ASTHMA-RELATED DEATHS.

The Salmeterol Multi-center Asthma Research Trial (SMART) enrolled long-acting beta₂-agonist-naïve patients with asthma to assess the safety of salmeterol (**SEREVENT Inhalation Aerosol**) 42 mcg twice daily over 28 weeks compared to placebo, when added to usual asthma therapy.

Data from a large US study that compared the safety of **SEREVENT** or placebo added to usual asthma therapy showed no difference between treatments for the primary endpoint which was serious respiratory-related episodes or serious asthma-related episodes (including deaths). However, a higher number of asthma-related deaths or life-threatening experiences (37 vs. 22) and a higher number of asthma-related deaths (13 vs. 3) occurred in the patients treated with salmeterol. Post hoc subgroup analyses revealed no significant increase in respiratory- or asthma-related episodes, including deaths, in Caucasian patients. In African-Americans, the study showed a small, though statistically significantly greater, number of primary events (20 vs. 5), asthma-related deaths or life-threatening experiences (19 vs. 4), and asthma-related deaths (7 vs. 1) in patients taking salmeterol compared those taking placebo. The numbers of patients from other ethnic groups were too small to draw any conclusions in these populations. Even though SMART did not reach predetermined stopping criteria for the total population, the study was stopped due to the findings in African-American patients and difficulties in enrolment. The data from the SMART study are not adequate to determine whether concurrent use of inhaled corticosteroids, such as fluticasone propionate, a component of **Seretide Diskus**, provides protection from this risk. Therefore, it is not known whether the findings seen with **SEREVENT Inhalation Aerosol** would apply to **Seretide**.

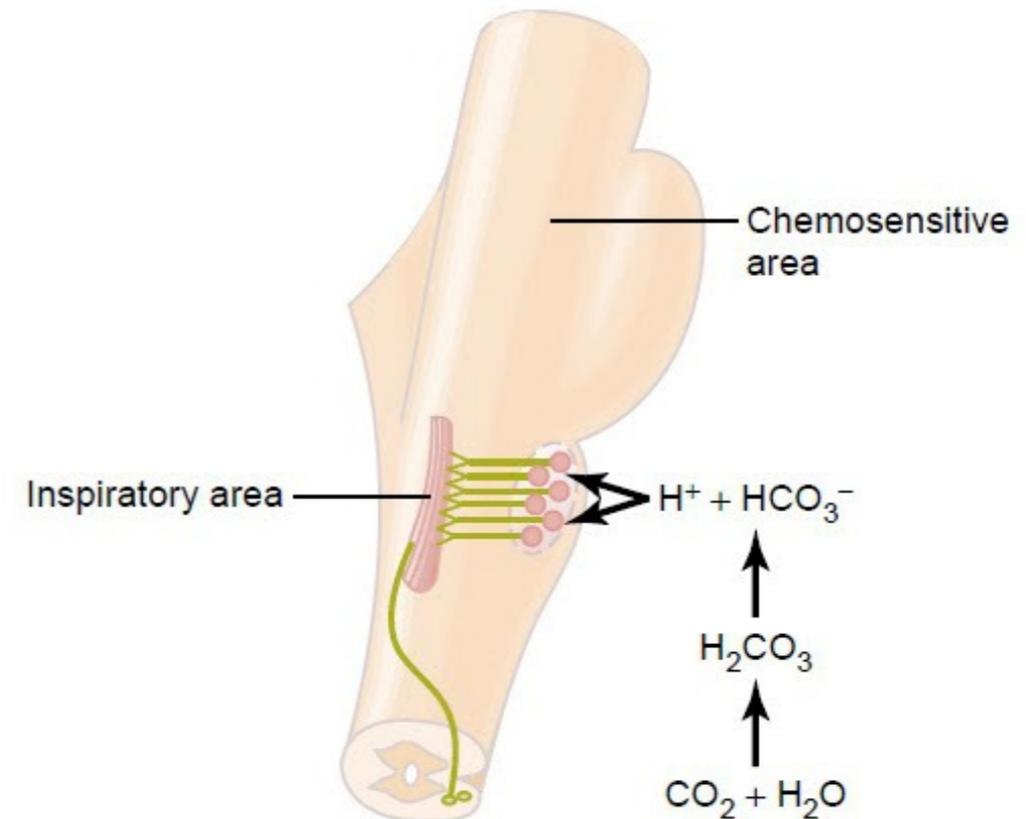
----- RECENT MAJOR CHANGES -----

Por qué respiramos: el mito del CO₂

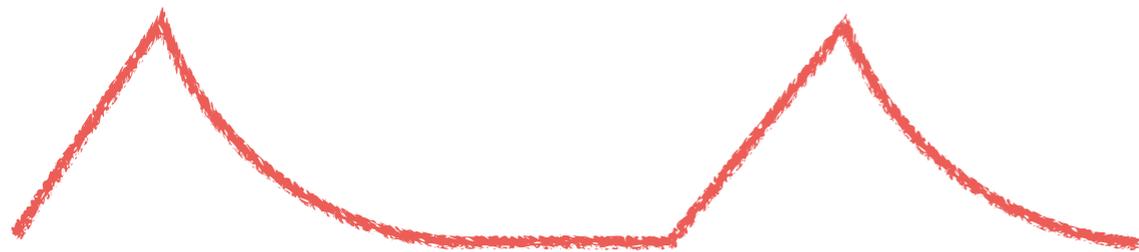
- Equilibrio del pH en la sangre (balance acido-base)
- Regulación del suministro de oxígeno a todas las células del organismo: vasodilatación y efecto Bohr (30% al 40% reducción de flujo sanguíneo cerebral durante sesiones de hiperventilación moderada: **Fried, 1993**).
- Estabiliza la transmisión de señales entre neuronas: “Regulando la respiración el cerebro controla su propia excitabilidad” (**Krnjevic, 1965; Balestrino & Somjen, 1988; Huttunen et. al., 1999**)
- Relajación del músculo liso
- Catalización de numerosas reacciones bioquímicas (**Kazarinov, 1990**)

El control automático de la respiración

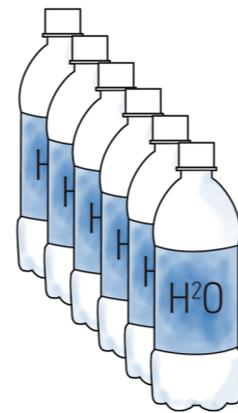
- Centro respiratorio
- Sensores (quimiorreceptores)
- Músculos inspiratorios



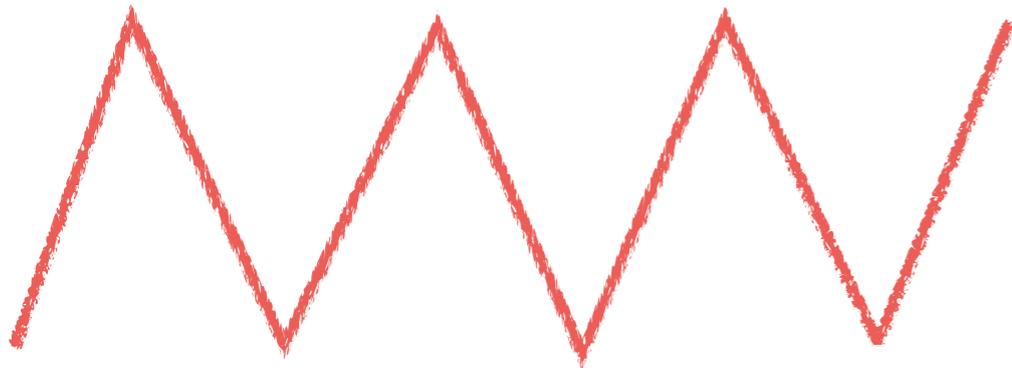
La respiración “normal”



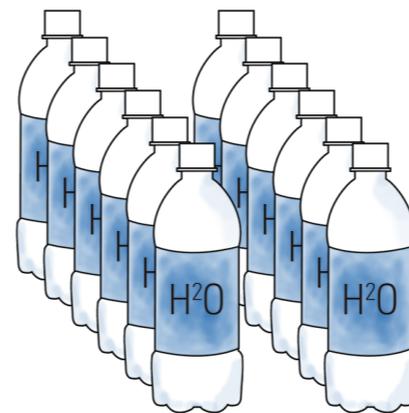
12 x 500 ml = 6 lt/min



$PCO_2 = 40$ mmHg

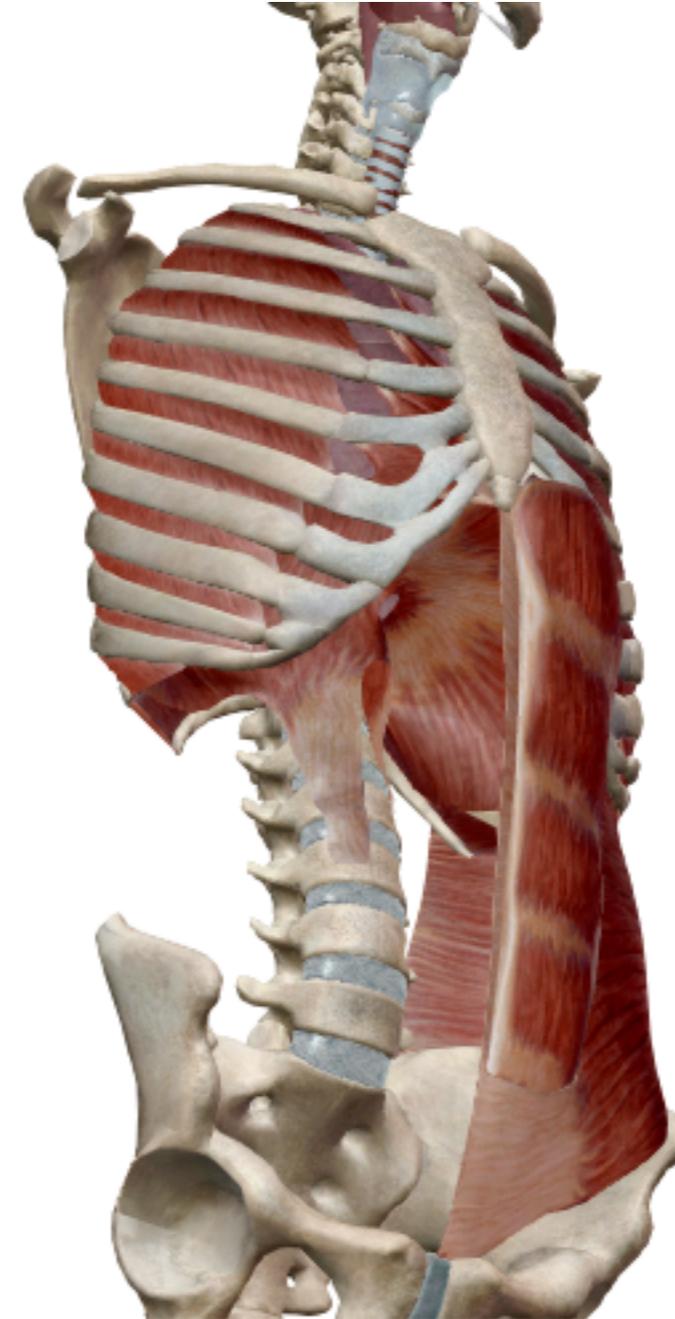
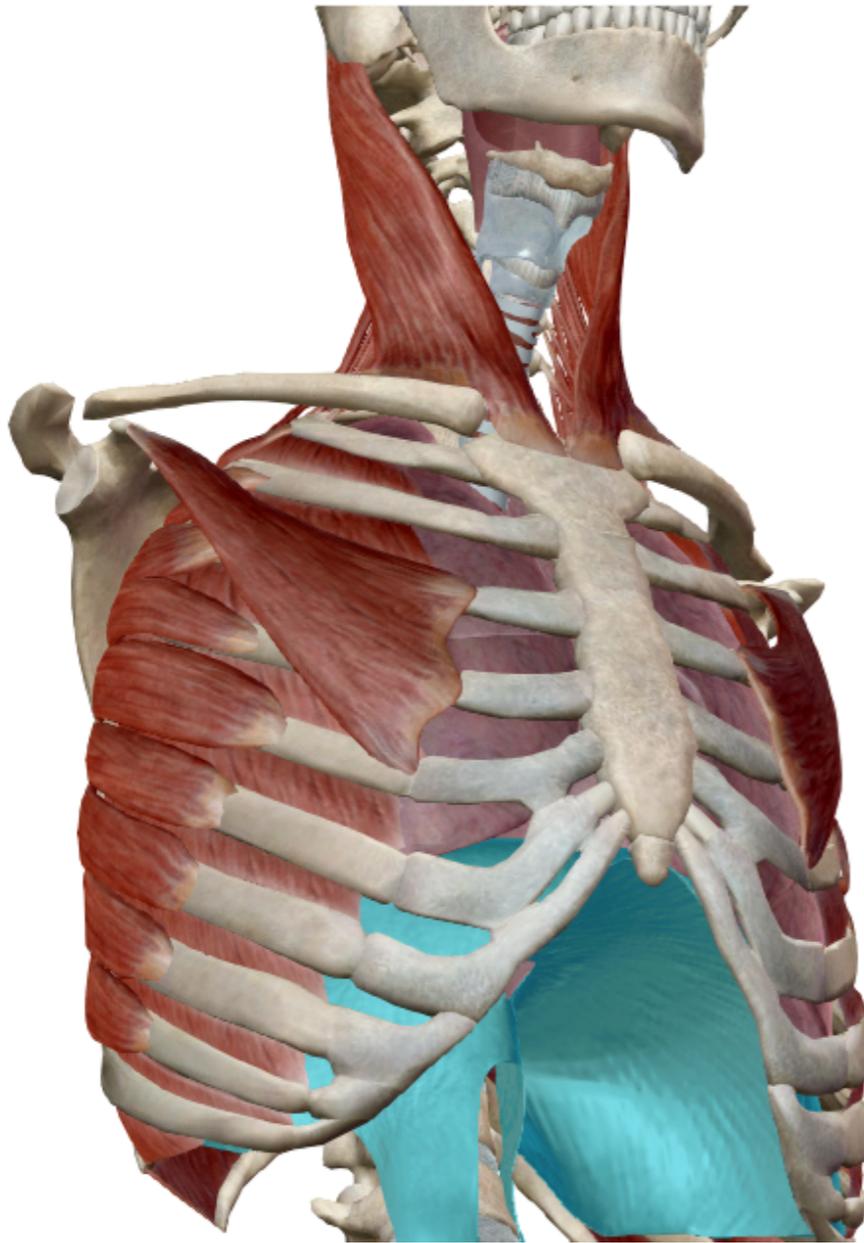


15 x 800 ml = 12 lt/min



$PCO_2 = 35$ mmHg

Músculos respiratorios



El camino hacia la normalización de la respiración

- Conceptos equivocados: respiración profunda, oxígeno vs CO₂
- Postura
- Respirar *siempre* por la nariz
- Relajación de los músculos respiratorios especialmente durante la exhalación
- Ejercicios de hipoventilación
- Estrés, alimentación, temperatura, sueño