Cough

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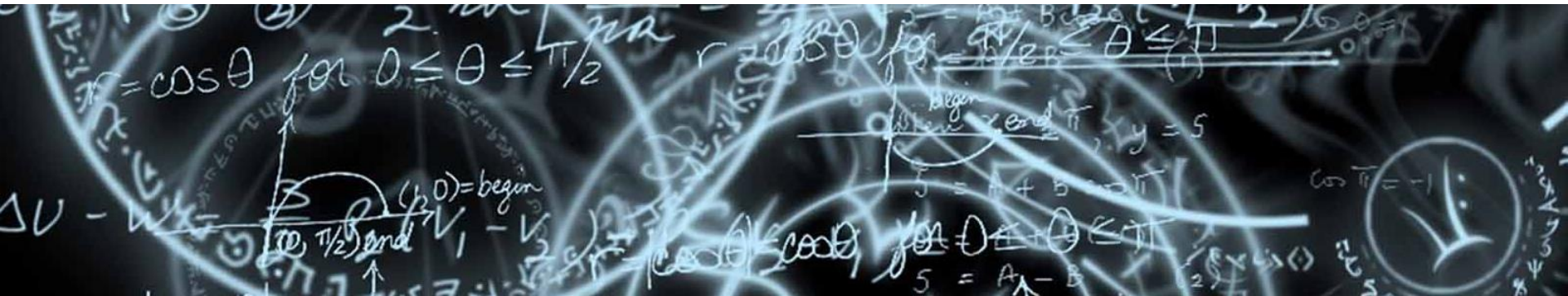


Duration of cough and its common causes

	Duration	Common causes
Acute cough	≤ 3 weeks	**Infection**, aspiration, smoke inhalation, etc.
Subacute cough	3-8 weeks	**Residuum** from respiratory **infection**, such as pertussis or post-viral tussive syndrome
Chronic cough	≥ **8** weeks	**Prerequisite**: nonsmoker, normal x-ray, no ACEI ① Cough variant asthma ② Upper airway cough syndrome (Postnasal drip) ③GE reflux **Idiopathic ⇨ Distressingly common!** ACE inhibitor Smoker's bronchitis Wide variety of cardiopulmonary diseases

Cough, in Harrison's Principles of Internal Medicine, **18th ed.**

Causes of ... tures (%)

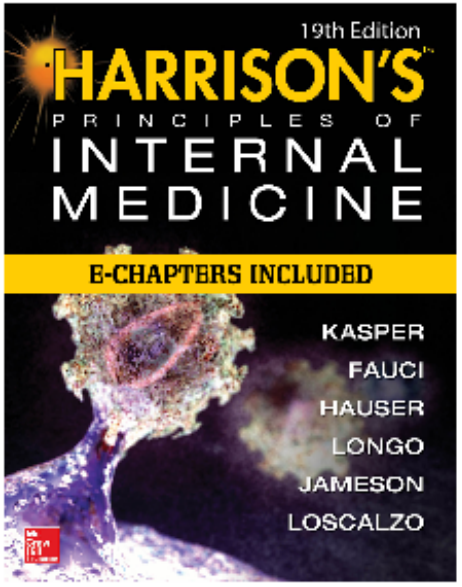
The New England Journal of Medicine

The Diagnosis and Treatment of Cough

Richard S. Irwin, M.D., and J. Mark Madison, M.D.

Multiple studies[1,17,18,27-32] have shown that in approximately 95 percent of cases in immunocompetent patients, chronic cough results from postnasal-drip syndrome from conditions of the nose and sinuses, asthma, gastroesophageal reflux disease, chronic bronchitis due to cigarette smoking or other irritants, bronchiectasis, eosinophilic bronchitis, or the use of an angiotensin-converting–enzyme inhibitor.

Author/Year	P					Misc or Non-Dx
Irwin / 1981						6
Poe / 1982						19
Irwin / 1990						9
Pratter /1993						4
Mello / 1996						8
Palombini / 1999	78	Brazil	94	0	0	6
Puolijoki /						
O'Connell						
McGarvey						
Brightling						
Ayik / 20						
Cho / 199						
Jee / 199						
Jeon / 20						
Lee / 200						



Harrison's Principles of Internal Medicine, 19e

48: Cough and Hemoptysis

Patricia A. Kritek; Christopher H. Fanta

COUGH

Chronic idiopathic cough, also called *cough hypersensitivity syndrome*, is distressingly common. It is often experienced as a tickle or sensitivity in the throat, occurs more often in women, and is typically "dry" or at most productive of scant amounts of mucoid sputum.

Prevalence of chronic cough and possible causes in the general population based on the Korean National Health and Nutrition Examination Survey

Prevalence of chronic cough	**2.5 ± 0.2%** (302/11,626)
Possible causes of cough	
Current smoker	47.7 ± 3.8%
Upper airway cough syndrome	46.8 ± 3.9%
COPD by spirometry	26.4 ± 3.5%
Asthma	14.5 ± 2.8%
CXR abnormality	4.0 ± 1.2%
Chronic laryngitis (≈ GERD)	4.1 ± 1.6%
Multiple causes	50.3 ± 4.5%
No possible causes	14.7 ± 3.1%
Risk factors contributing to chronic cough, multivariate analysis	
Current smoker	OR **3.16** [95% CI, 2.11-4.74], p <0.001
Upper airway cough syndrome	OR **2.50** [95% CI, 1.75-3.56], p <0.001
COPD by spirometry	OR **2.41** [95% CI, 1.59-3.66], p <0.001
Asthma	OR **8.89** [95% CI, 5.32-14.87], p <0.001
CXR abnormality	OR **2.74** [95% CI, 1.30-5.77], p =0.01
Chronic laryngitis (≈ GERD)	OR 1.75 [95% CI, 0.68-4.50], p =0.27

Koo HK, et al. Medicine (Baltimore). 2016;95:e4595

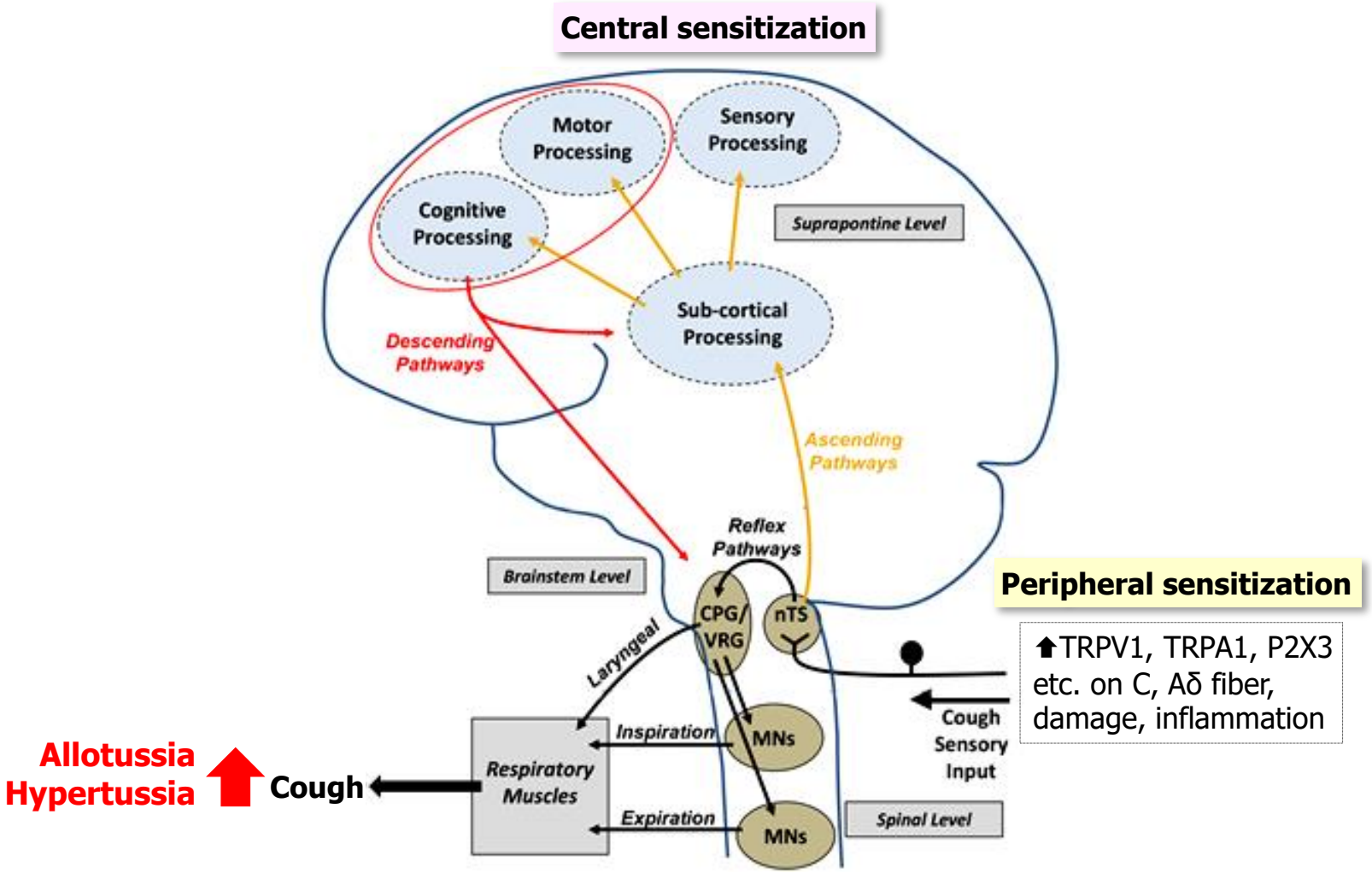
Terminology

Need further study to determine consistent terminology and the optimal method of investigation

	Unexplained CC[1]	Idiopathic CC[2,3]	CC hypersensitivity syndrome[4]	Refractory CC[5]
Enhanced cough reflex	No comment	+	+	+
Diagnostically unexplained	+	+	+	+
	and, or	**and**	**or**	**or**
Response to treatments targeted at any medical condition	Persistent cough after supervised therapeutic trials: 1) BA-ICS 2) UACS-AH 3) GERD-PPI ICS-not indicated in normal MBPT and no eosinophilia (sputum eos, FeNO)	Negative response to treatment including ICS/oral steroid, GERD tx.	Lack or poor, **but not exclusively**	Negative response to treatments for BA, GERD, and UACS
Comment	1) CC with no diagnosable cause 2) Explained but refractory 3) Unexplained and refractory			

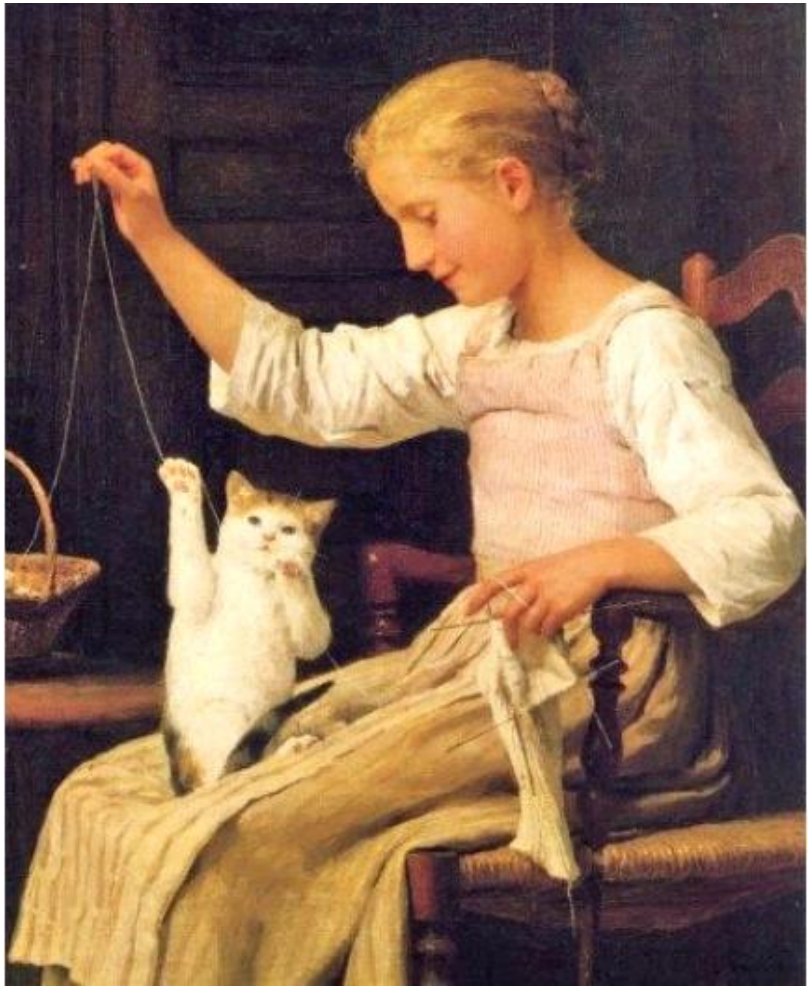
1. Gibson P, et al. Chest. 2016;149:27-44, 2. Birring SS, et al. Thorax 2003;58:1066–70, 3. McGarvey LPA, Cough. 2005;1:9, 4. Chung KF. Pulm Pharmacol Ther. 2011;24:267-71, 5. Ryan NM, et al. Lancet. 2012;380:1583-9.

Cough hypersensitivity



COugh Assessment Test, COAT

- 기침 상태 평가를 위한 1차원 도구
- 최소(5~6) 문항의 자기 기입식 간편설문지
- 기침 상태에 대한 점수화된 지표
- 기침 상태의 객관화, 빠르고 정확한 소통



COAT version **1**

기침이 얼마나 심하십니까? 기침 평가 검사(COAT)를 해주십시오.

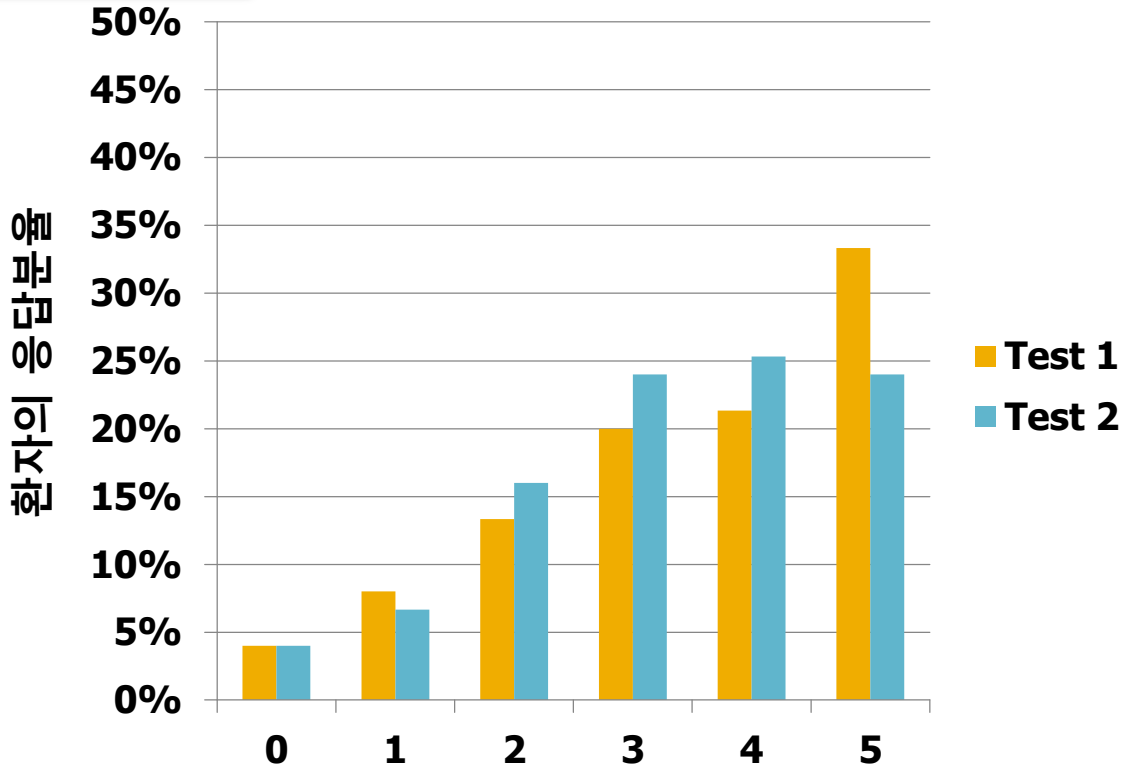
다음 질문들은 기침이 얼마나 심한지 귀하의 육체적, 정신적 건강 상태와, 기침으로 인한 일상생활에 미치는 영향을 평가하기 위한 것입니다. 답안과 검사 점수는 기침 정도 및 상태 변화 평가를 객관화하여 치료효과를 향상시키고자 고안되었습니다. 아래의 각 항목마다 최근 **5일** 간의 귀하의 상태에 해당하는 점수에 체크 표시(V)를 해주십시오.

예: 매우 기쁘다	⓪ ① V ② ③ ④ ⑤	매우 슬프다	점수

기침이 없다	⓪ ① ② ③ ④ ⑤	기침을 하루 종일 한다	
기침이 없어서 일상생활에 지장이 없다	⓪ ① ② ③ ④ ⑤	기침 때문에 일상생활을 할 수 없다	
기침이 없어서 편하게 잘 수 있다	⓪ ① ② ③ ④ ⑤	기침 때문에 잠자기 힘들다	
기침이 없어서 가슴이 아프지 않다	⓪ ① ② ③ ④ ⑤	기침 때문에 가슴이 심하게 아프다	
기침이 없어서 피곤하지 않다	⓪ ① ② ③ ④ ⑤	기침 때문에 많이 피곤하다	
찬 공기, 먼지 많을 때, 자극성 냄새 나는 곳에서도 편안하다	⓪ ① ② ③ ④ ⑤	찬 공기, 먼지 많을 때, 자극성 냄새 나는 곳에서 기침이 심하다	

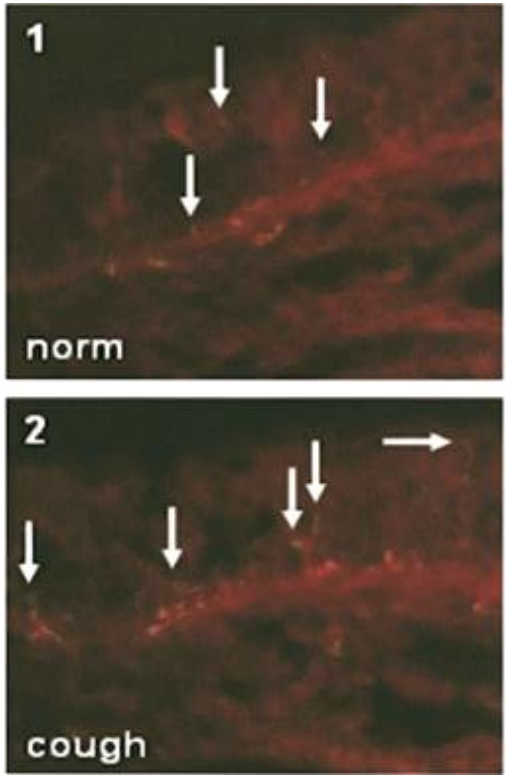
Response to item, COAT.v1_Hypersensitivity

- Chronic cougher
- N=75 (male 44, female 31)
- Age 52.4 ± 17.2 years
- No treatment between test 1 and test 2
- Interval of test 1 & 2: 4.7±4.6d (0~28, med 3d)

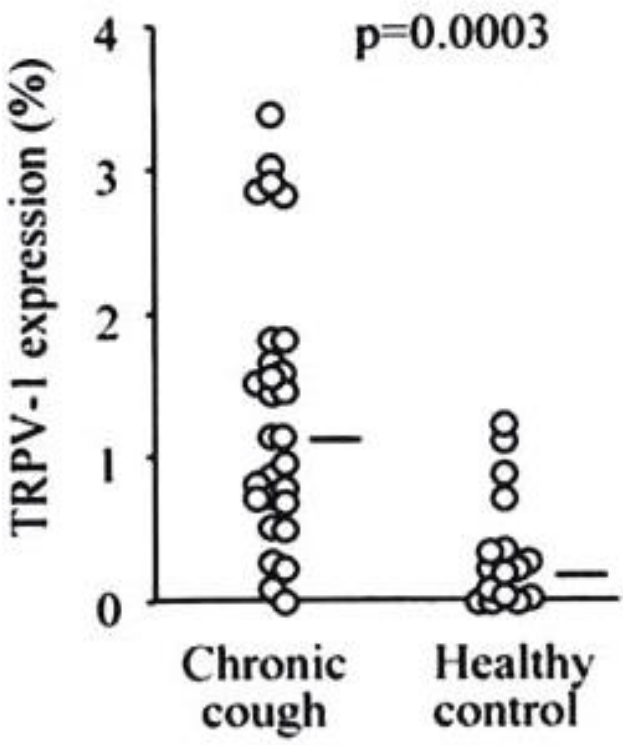


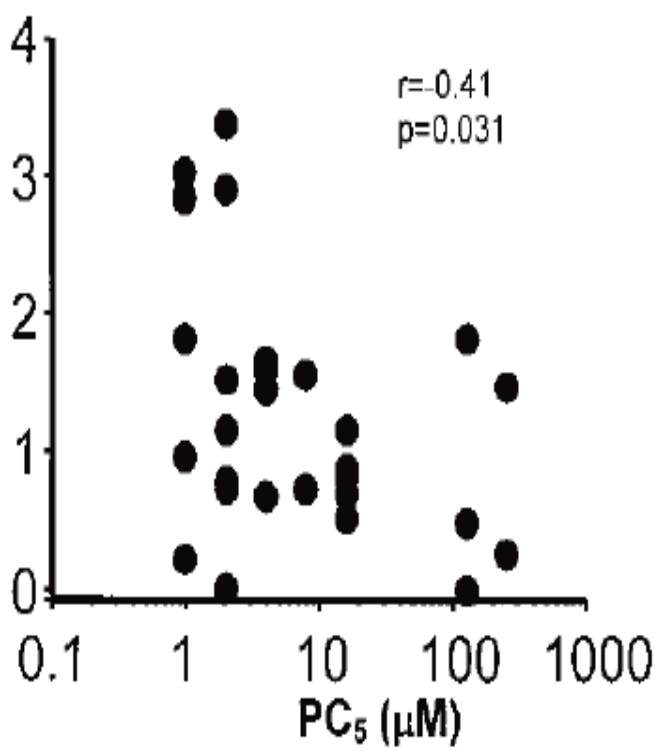
Increased expression of TRPV-1 in airway nerves of chronic cough

- **29 coughers** (mean duration 6.7±1.2 yr; 6 BA, 4 GERD, 4 UACS, 1 BE, 14 UCC) and **16 healthy** subjects
- Bronchial biopsies from segmental and subsegmental carinae, Capsaicin cough challenge



IF staining of airway nerves with an anti–TRPV-1 antibody





Groneberg DA, et al. Am J Respir Crit Care Med. 2004;170:1276-80

Airway inflammation in nonasthmatic subjects with chronic cough

- **19 nonsmoking, non-asthmatic coughers** (mean duration of cough 3.4yr) vs.**10 normal subjects**

	Healthy	Cougher	UACS	GERD	UACS+GERD	No cause
Number	10	19	4	6	5	4
Inflammatory cells in BALF	vs.	↑ (p=0.025)	No difference between the 4 subgroups			
Bronchial biopsy						
Inflammatory cells	vs.	↑ (p=0.005)	No difference between the 4 subgroups			
Epithelial desquamation	vs.	↑ (p=0.004)	No difference between the 4 subgroups			
Submucosal fibrosis	vs.	↑	No difference between the 4 subgroups			
Squamous cell metaplasia	vs.	↑	No difference between the 4 subgroups			
Loss of cilia	vs.	↑	No difference between the 4 subgroups			

- **14**/19 coughers participated in a **RCT** (**ICS (beclomethasone)** vs. **Placebo**, cross-over, for 1 mo each)
- **ICS responder: 6/14 (42.9%)**, Placebo responder: 2/14 (14.3%), No responder: 6/14 (42.9%)
- Pretreatment **bronchial biopsies** of steroid-responsive patients were **similar** to those of nonresponders
- **No correlation** between the **intensity of inflammation** and the short-term **response**
- Mean daily cough scores were not significantly different for the two treatments
  Definition of responder: cough score ≤ 50% baseline during the last 2 week

Boulet LP, et al. Am J Respir Crit Care Med 1994;149:482-9

CHEST

Treatment of Unexplained Chronic Cough

CHEST Guideline and Expert Panel Report

4. In adult patients with unexplained chronic cough and negative tests for bronchial hyperresponsiveness and eosinophilia (sputum eosinophils, exhaled nitric oxide), we suggest that inhaled corticosteroids not be prescribed (Grade 2B).

Inhaled Corticosteroids: ICS were studied in three randomized trials. Different agents were used in each trial and at different comparative doses (mometasone, budesonide, and beclomethasone). ICS were found to improve cough severity in two studies,[28,29] but no other patient-reported outcomes were reported. No adverse effects were reported.

A significant limitation of two of these RCTs[28,29] is that they did not include optimal assessment of asthma (with BHR testing) or eosinophilic bronchitis (with induced sputum testing or exhaled nitric oxide) as part of the cough evaluation when assessing eligibility for study entry. BHR testing was, however, included as part of the follow-up assessment, and BHR was identified in up to 50% of the participants in one study.[28] This finding indicates an intervention fidelity bias in which 50% of included patients may have had asthma rather than UCC.

BHR and induced sputum testing were included in the study by Pizzichini et al.[39] A positive BHR test result was an exclusion criterion. Each of the included participants had a negative result on induced sputum testing for eosinophils. Pizzichini et al[39] found no beneficial effect of inhaled budesonide on cough symptoms in their population of nonasthmatic, noneosinophilic subjects with UCC.

No other patient-reported outcomes
No AE reported
No MBPT, induced sputum, FeNO for eligibility

Treatment with inhaled steroids in patients with symptoms suggestive of asthma but with normal lung function.
Rytilä P, et al. Eur Respir J. 2008;32:989-96

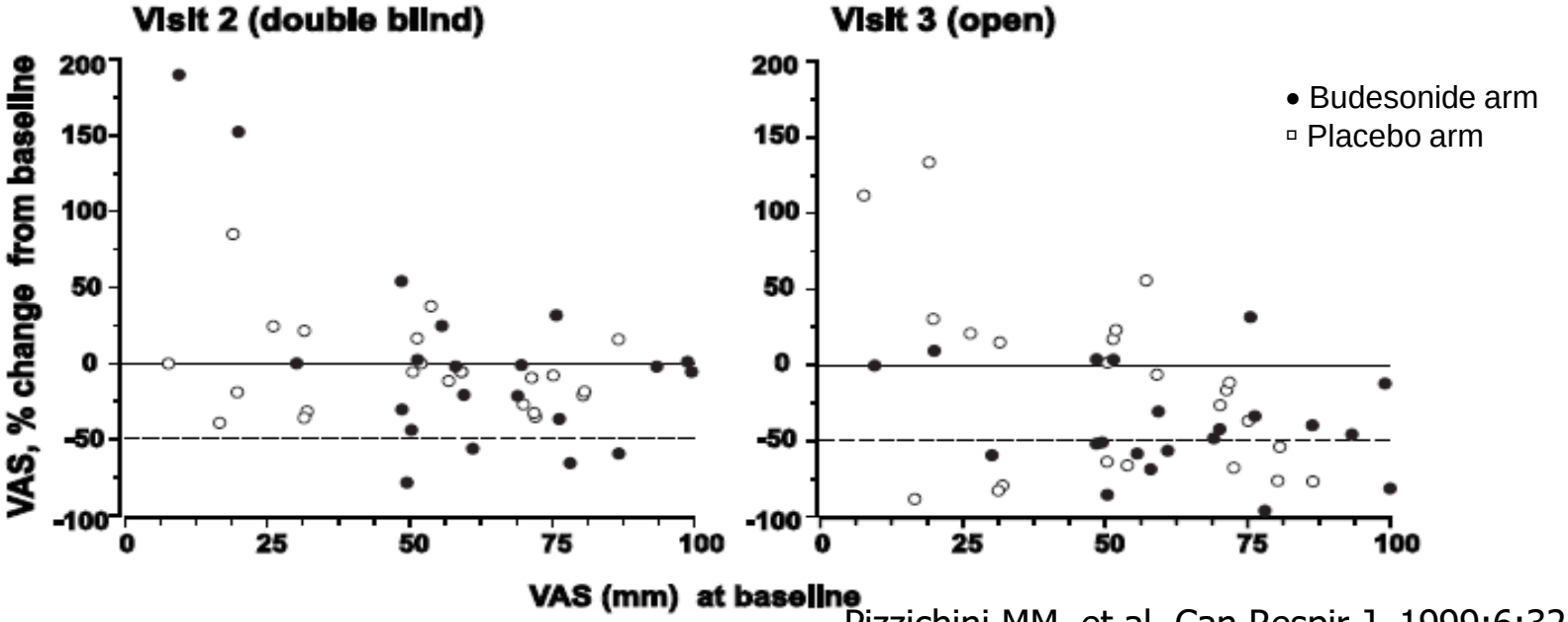
High-dose inhaled beclomethasone treatment in patients with chronic cough (chronic coughers after excluding those with PND, GERD)
Ribeiro M, et al. Ann Allergy Asthma Immunol. 2007;99:61-68.

CHEST Expert Cough Panel. Chest. 2016;149:27-44

Nonasthmatic chronic cough: No effect of treatment with an ICS in patients without sputum eosinophilia

	Placebo (n=23)	Budesonide (n=21)
Primary outcome: cough improvement as measured by cough VAS		
[Clinically important improvement= only if cough VAS reduction **≥ 50%**]		
At Visit 2, Cough VAS ≤ 50% baseline:	**0** (0%)	**4** (19%) (**p=0.028**, χ^2)
% change of VAS from baseline (All patients)	-3.9%	1.3%
% change of VAS from baseline (Baseline VAS >33)	-8.8%	-17.5%

Visit 2: Budesonide 400µg inh bid **2wk** vs. placebo (double blind)
Visit 3: Budesonide 400µg inh bid **2wk** (open label, placebo arm was also treated with budesonide)



Pizzichini MM, et al. Can Respir J. 1999;6:323-30

The primary outcome was improvement in cough discomfort as measured by the VAS, and this was, before analysis, considered clinically important only if cough discomfort was reduced by 50% or greater.

1차 평가변수는 cough VAS의 개선이며, (분석 전에 정하기를) 50% 이상 감소한 경우에만 임상적으로 중요한 것으로 간주하였다.

A reduction of 50% or greater in cough discomfort (from baseline) after two weeks of blind budesonide or placebo occurred in only four patients of the budesonide group.

Cough VAS가 50% 이상 감소한 경우는 2주간의 budesonide 사용 군에서만 4명이 발생하였다.

This is the first randomized, controlled trial to examine the effects of treatment with inhaled steroid on cough discomfort as well as inflammatory indexes. Budesonide 800 µg daily for two or four weeks had no effect.

이것은 기침과 염증지수에 미치는 ICS 치료효과를 평가하기 위한 최초의 무작위 대조임상연구이다. 2주 또는 4주간 사용하는 budesonide 800ug/d는 효과가 없었다.

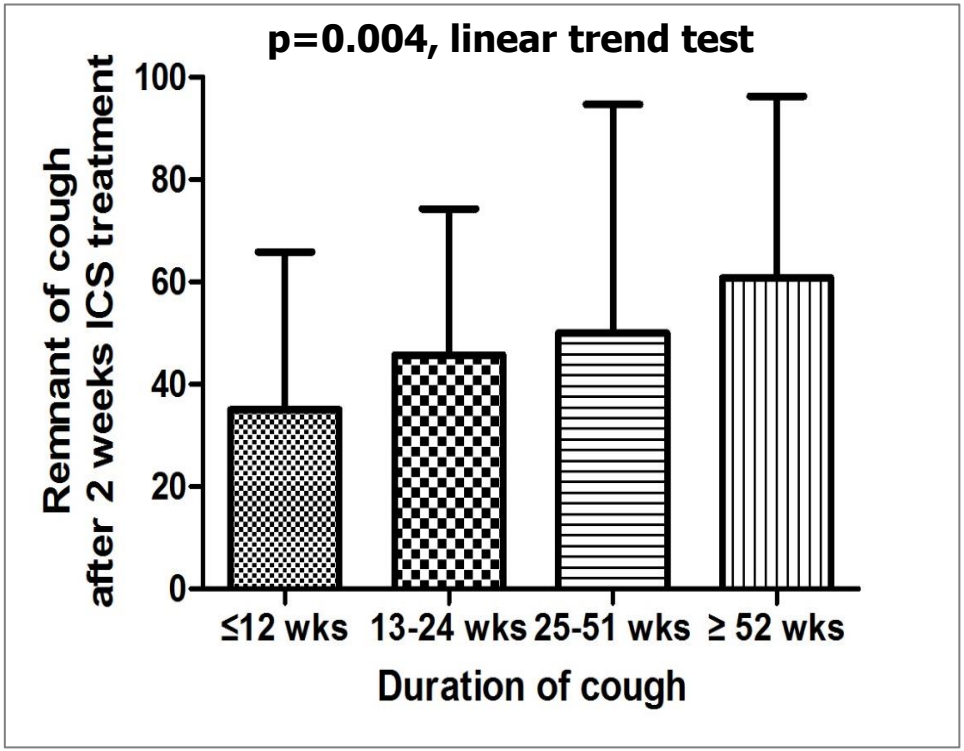
Pizzichini MM, et al. Can Respir J. 1999;6:323-30

Efficacy and response predictors of inhaled corticosteroid treatment on chronic cough

- Prospective observational study, June 2009~December 2015, at Hallym University Sacred Heart Hospital
- UACS (N=68/90) or idiopathic cougher (N=33/42) with cough duration ≥ 8 weeks
- Flixoticasone diskus 250 μg bid or budesonide turbuhaler 400 μg bid for 2 weeks

- **Predictors of short course ICS response**

① Duration of cough < 52 weeks (p=0.018), ② Triggered by cold air (p=0.031), logistic regression analysis



Hong JY, et al. In submission

RCT of ICS vs. Codein/Levotuss for patients with idiopathic chronic cough

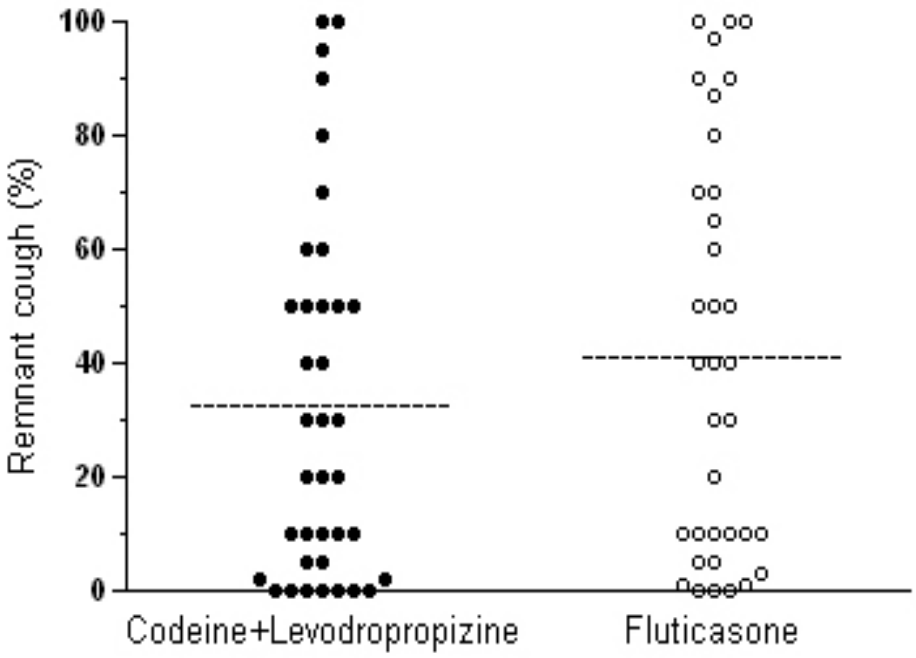
Eligibility criteria

1. Cough > 3 weeks, infection (-)
2. Age over 18 years
3. Never wheezing
4. Never smoker
5. No symptom of reflux
6. Normal CXR, PNS, PFT, MBPT
7. Sputum eosinophil ≤ 1%
8. No ACE inhibitor

Treatment for 2 weeks

1. Codeine 20 mg + Levotuss 60mg tid
2. Fluticasone 250 μg inhalation bid

32.4 ± 32.0% vs. 41.0 ± 35.8%
P = 0.288

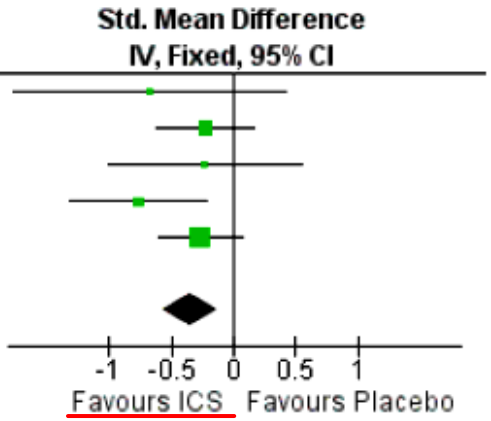


Han B, et al. Tuberc Respir Dis. 2009;67:422-9

Inhaled corticosteroids for subacute and chronic cough in adults

	ICS			Placebo				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Boulet 1994	-1.15	1.56	7	-0.24	0.88	7	3.9%	-0.67 [-1.76, 0.42]
Ponsioen 2005 (1)	-2.3846	1.76484	52	-2	1.66599	50	30.7%	-0.22 [-0.61, 0.17]
Pornsuriyasak 2005	-1.36	1.74	14	-1	1.28	12	7.8%	-0.23 [-1.00, 0.55]
Ribeiro 2007	-1.37	1.21	44	-0.54	0.7	20	15.6%	-0.76 [-1.31, -0.21]
Rytilä 2008 (2)	-0.44	0.669328	70	-0.26	0.66933	70	42.0%	-0.27 [-0.60, 0.07]
Total (95% CI)			**187**			**159**	**100.0%**	**-0.34 [-0.56, -0.13]**

Heterogeneity: Chi² = 3.25, df = 4 (P = 0.52); I² = 0%
Test for overall effect: Z = 3.12 (P = 0.002)



(1) Acute cough patients excluded
(2) Morning cough score

Johnstone KJ, et al. Cochrane Database Syst Rev. 2013;3:CD009305.

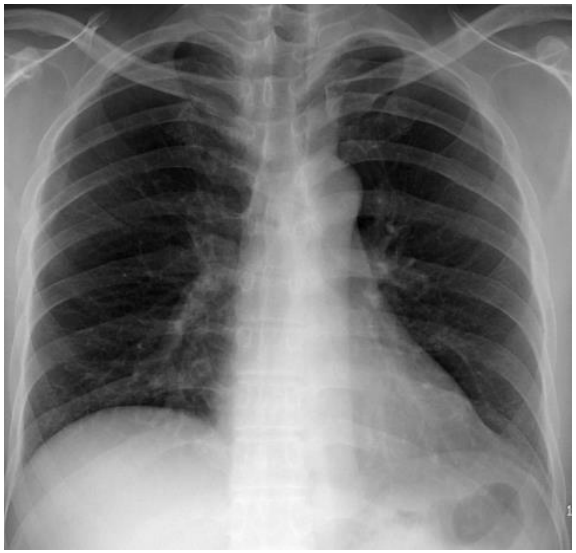
남자 39세

2005년 겨울 기침감기로 병원에 갔다가 축농증이란 진단으로 약 복용 (약 1달).

계속되는 기침 및 호흡곤란으로 **대학병원 진료. 위-식도 역류증 진단 . 이후 약 6개월 약 복용. 기침이 완화되었으나 완치는 안됨. 요즘들어 호흡곤란이 심화됨. 낮에는 괜찮고 밤에 목이 조이는 듯 호흡하기가 힘듦.
기침을 하고 나면 숨쉬기가 수월하다가 10여 초 후 다시 숨쉬기가 힘듦. 한 시간쯤 호흡곤란 후 증세 호전. 기침시 맑은 젤같은 가래가 나옴.

숨 쉴 때 쌕쌕거리는 소리가 난다. 추운 날, 바람이 많은 날 가슴이 답답하고 가랑거리는 숨소리가 들린다.

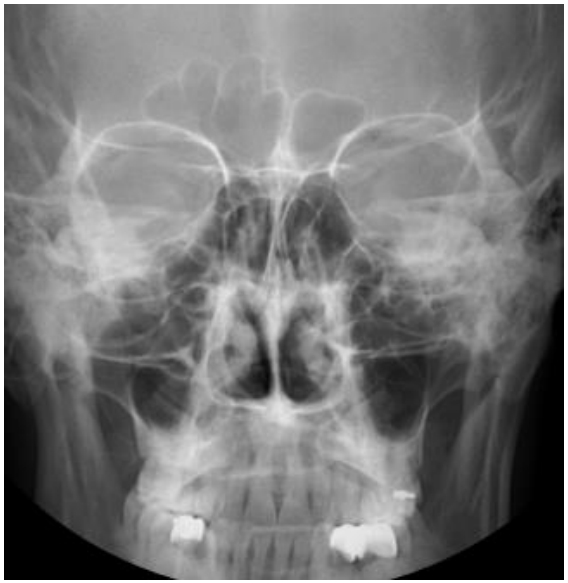
흉부 청진음: 정상

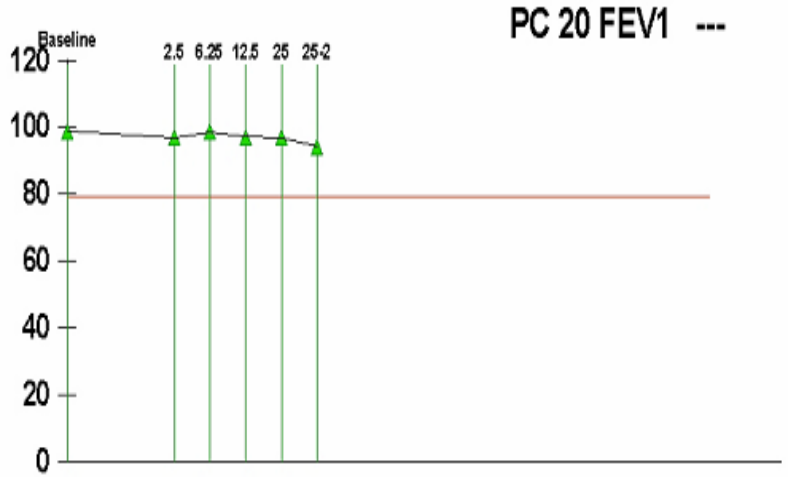


M.Conc(mg/ml)	0.625	1.25	2.5	6.25	12.5	25.0	25(2분)
FVC			4.30	4.42	4.23	4.51	4.49
FEV1			3.72	3.78	3.73	3.72	3.61
FEF25-75%			4.36	4.43	4.63	3.94	3.57
PEF			8.45	8.52	8.89	8.70	8.69

% fall after Saline test

FVC			-9	-6	-10	-4	-5
FEV1			-2	-1	-2	-2	-5
FEF25-75%			15	17	22	4	-6
PEF			-15	-15	-11	-13	-13

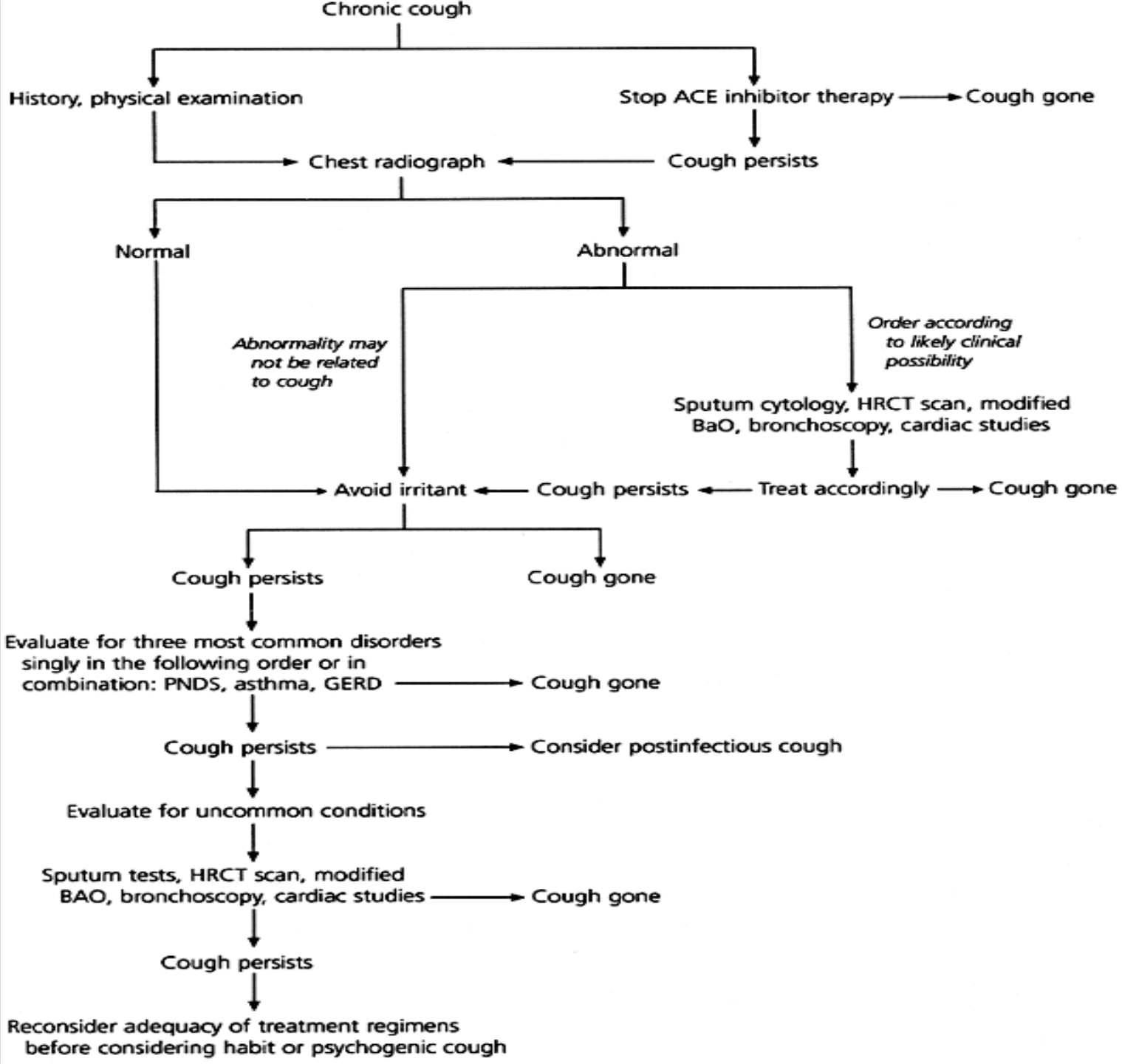




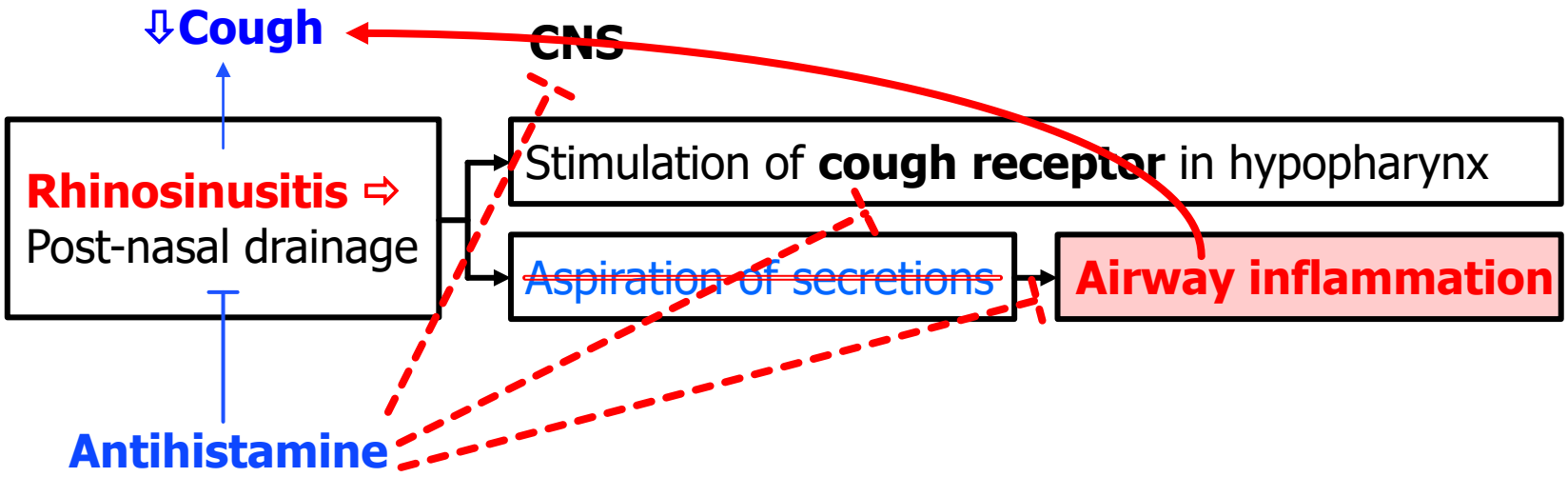
치료경과

Flixotide 250μg inhalation bid, for 2 weeks: cough ↓ (100 → 20% baseline)
Follow-up loss after then

Diagnostic approach for chronic cough



Upper airway cough syndrome
Post-nasal drainage



One airway disease! United airway disease!

- **Many** people who have **chronic PND** do **not** experience **cough**
- **No RCT** about the efficacy of **antihistamine**
- **Inhaled corticosteroid** is also **effective** for chronic cough with **UACS**

Bardin PG et al. J Allergy Clin Immunol 1990;86:82-8
Sadofsky LR, et al. Exp Lung Res. 2008;34:681-93
Cough, in Harrison's Principles of Internal Medicine, 18th ed.

TRPV1-mediated calcium responses are inhibited by the alkylamine antihistamines dexbrompheniramine and chlorpheniramine

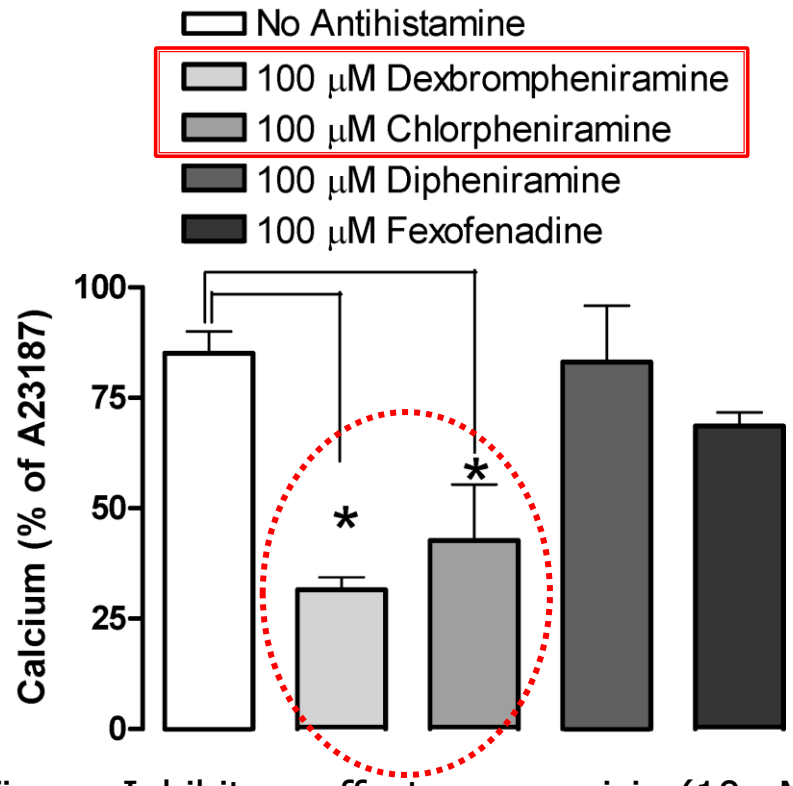
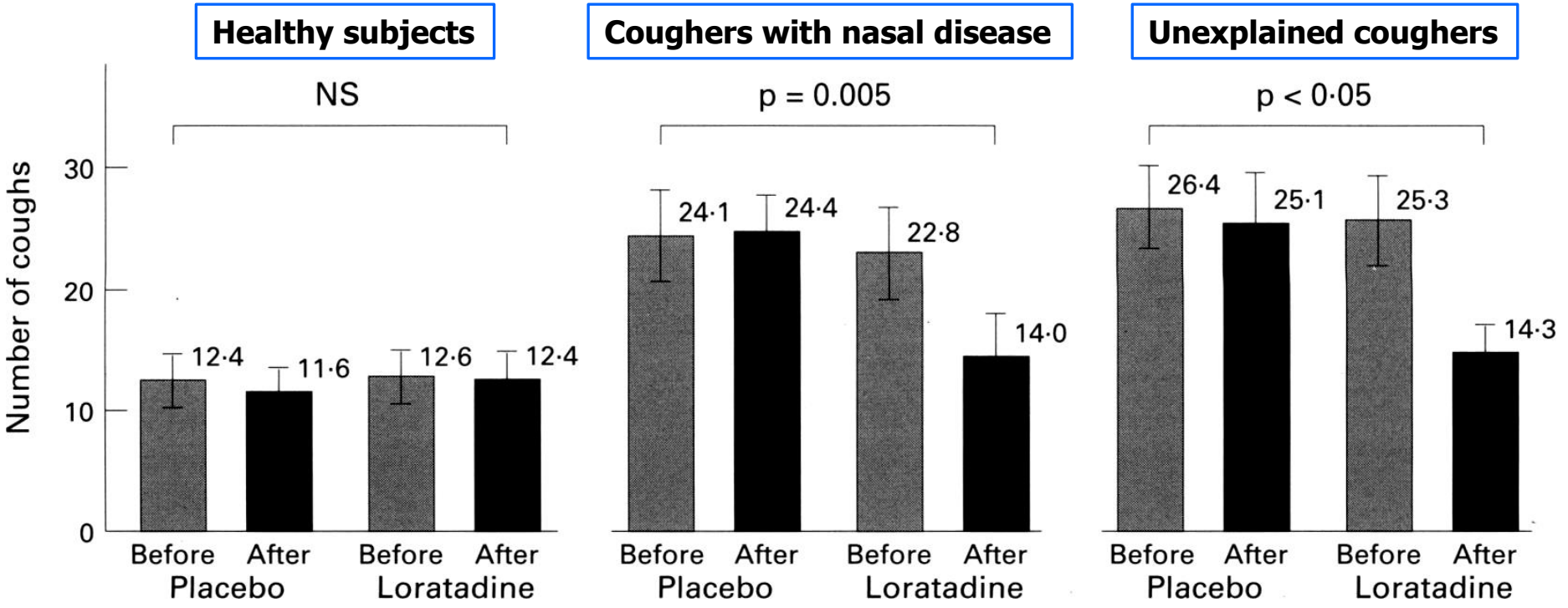


Figure. Inhibitory effect on capsaicin (10 nM) –evoked calcium mobilization in hTRPV1-HEK

Sadofsky LR, et al. Exp Lung Res. 2008;34:681-93

Effect of loratadine, an H_1 antihistamine, on induced cough in non-asthmatic patients with chronic cough

- Cough (≥ 8weeks), non-smoker, non-asthmatics: nasal disease (n=10), unexplained (n=7), healthy (n=11)
- **Loratadine 10mg po** or **placebo** 1hr before **UNDW challenge** for 1 min → **cough count/1min 30sec**
  UNDW (**U**ltrasonically **N**ebulized **D**istilled **W**ater)
- Randomized, double-blind, cross-over design



Tanaka S, et al. Thorax. 1996;51:810-4

RCT of ICS vs. AH for patients with chronic cough with PNSinusitis

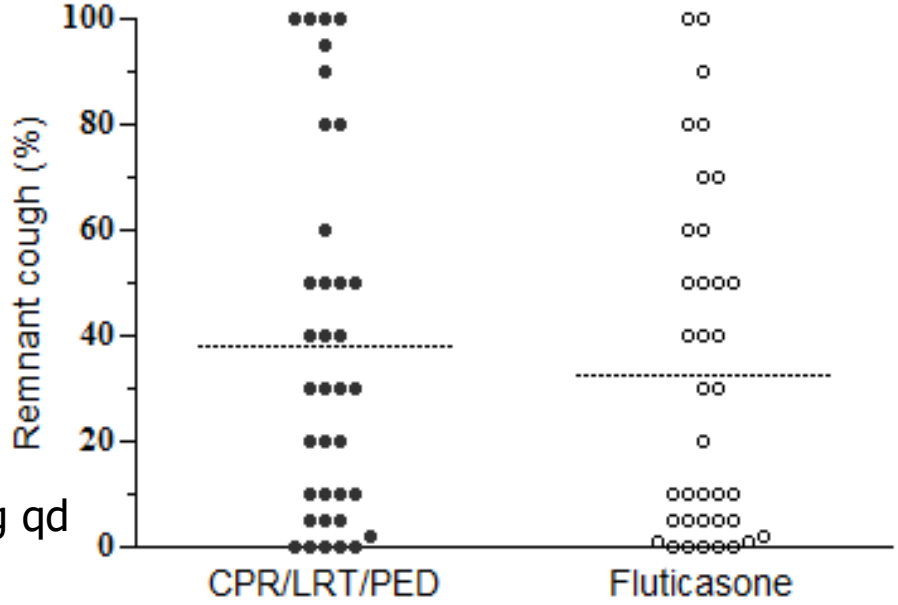
Eligible criteria

1. **Mucosal thickening in PNS radiographs**
2. Cough > 3 weeks, infection (-)
3. Age over 18 years
4. Never wheezing
5. Never smoker
6. No symptom of reflux
7. Normal CXR, PFT, MBPT
8. Sputum eosinophil ≤ 1%
9. No ACE inhibitor

Treatment for 2 weeks

1. CPR 4 mg + PED 60mg tid + LRT 10 mg qd
2. Fluticasone 250 μg inhalation bid

37.8 ± 34.7% vs. 32.1 ± 32.2%
P = 0.469



Jang SH. Unpublished data

Effect of ICS on symptom severity and sputum mediator levels in chronic persistent cough

- **Chronic cough** ≥ 1 year, normal CXR, PFT
- Double-blind, randomized, placebo-controlled, crossover study
- **Fluticasone** inhalation **500µg bid**, **2 weeks**
- Outcome measure: cough VAS

	All causes	PNDS	GERD	CVA	BE	Idiopathic
No.	88	30	18	13	9	10
Age, y	59.0	58.8	67.7	48.5	64.0	57.7
Cough duration, y	16.2	18.6	14.9	13.6	17.8	13.9
Baseline cough VAS	4.1	3.9	3.9	4.7	4.3	4.4
Δ cough VAS	**1.0†**	**0.9†**	**1.2**	**1.4†**	0.7	0.5

Δ cough VAS; change compared with placebo, **†p < 0.05**

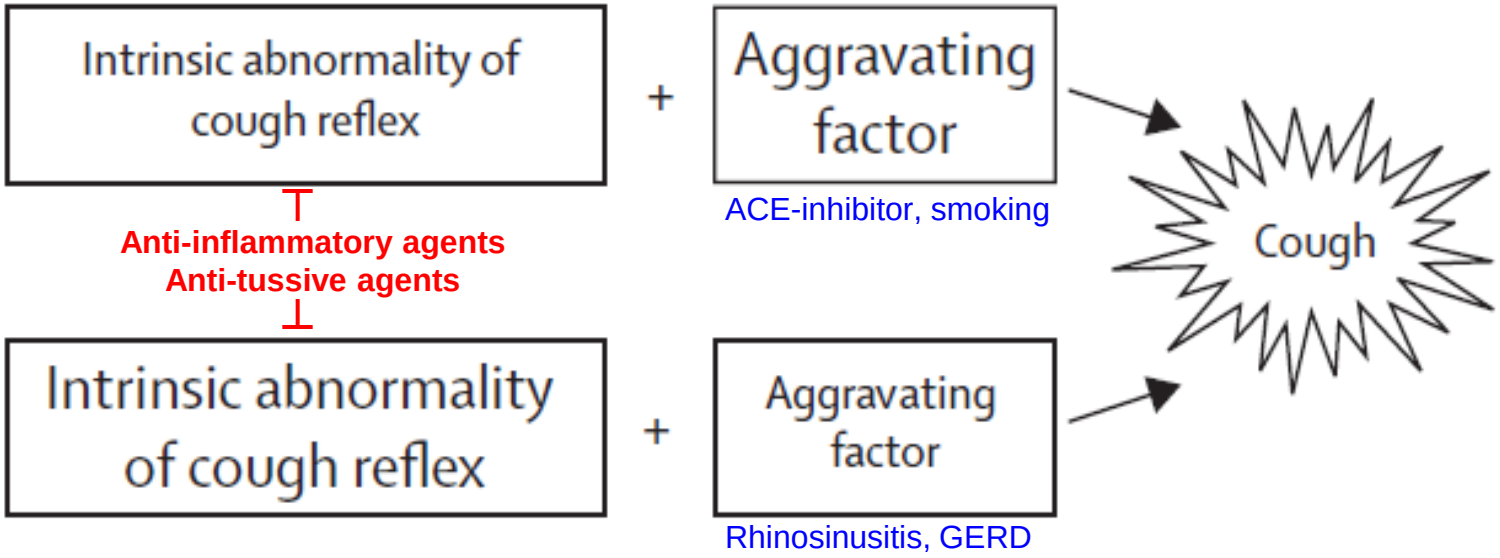
Chaudhuri R, et al. J Allergy Clin Immunol. 2004;113:1063-70

The two major types of chronic cough

	Eosinophilic airway diseases	**Non-eosinophilic** chronic cough
Age	Any	40-60 years
Sex	Equal	Female predominant
Response to corticosteroids	**Responsive**	**Less responsive**
Pathology	Eosinophilic	Non-eosinophilic
Exhaled NO	Raised	Low
Variable airway obstruction	Present in asthma	Absent
Airway hyper-responsiveness	Present in asthma	Absent

Pavord ID, Chung KF. Lancet. 2008;371:1375-84

Model for pathogenesis of non-asthmatic chronic cough



Pavord ID, Chung KF. Lancet. 2008;371:1375-84

Take home messages

❶ **Unexplained chronic cough?**	Common
❷ **Therapeutic diagnosis?**	Impossible, just therapeutic trial!
❸ **ICS effect on UCC?**	Someone may be helped
	No predictable factor
❹ **Anatomic approach** for chronic cough?	??
	Intrinsic abnormality of cough reflex and aggravating factors

경청해 주셔서 감사합니다...^^