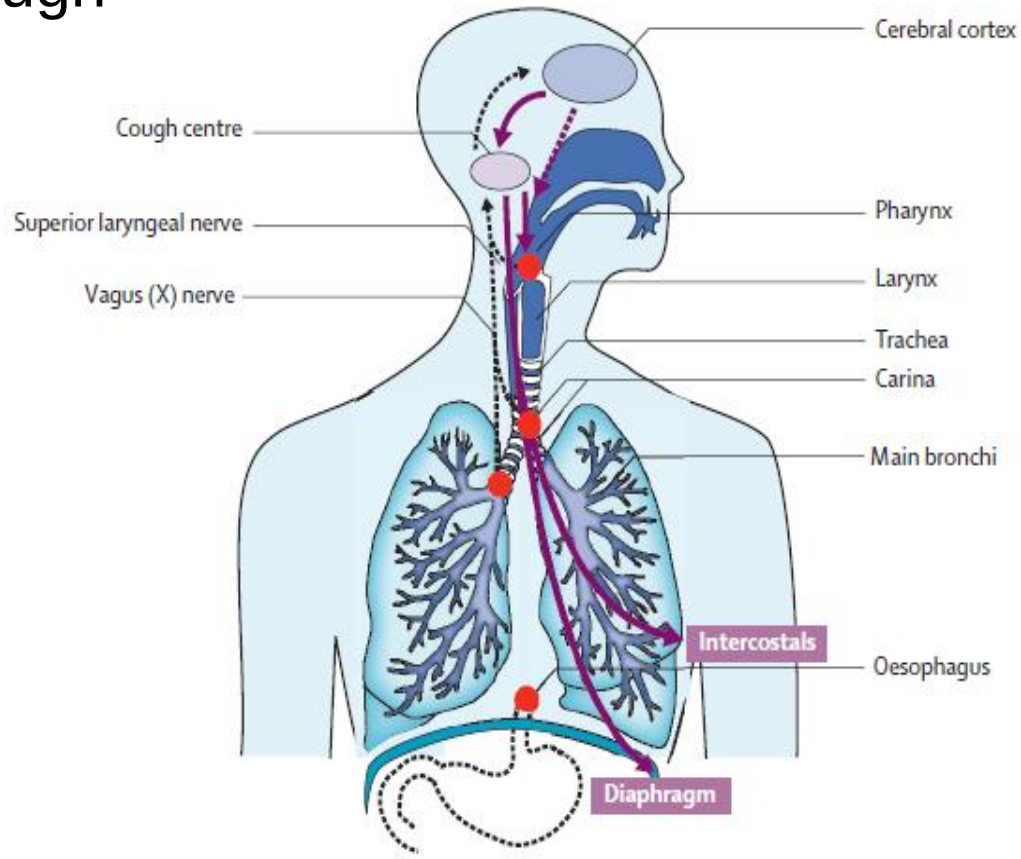
SNUH 분당서울대학교병원
SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

Cough-related Non-pulmonary Disease/Condition

Prof.이예진

Index

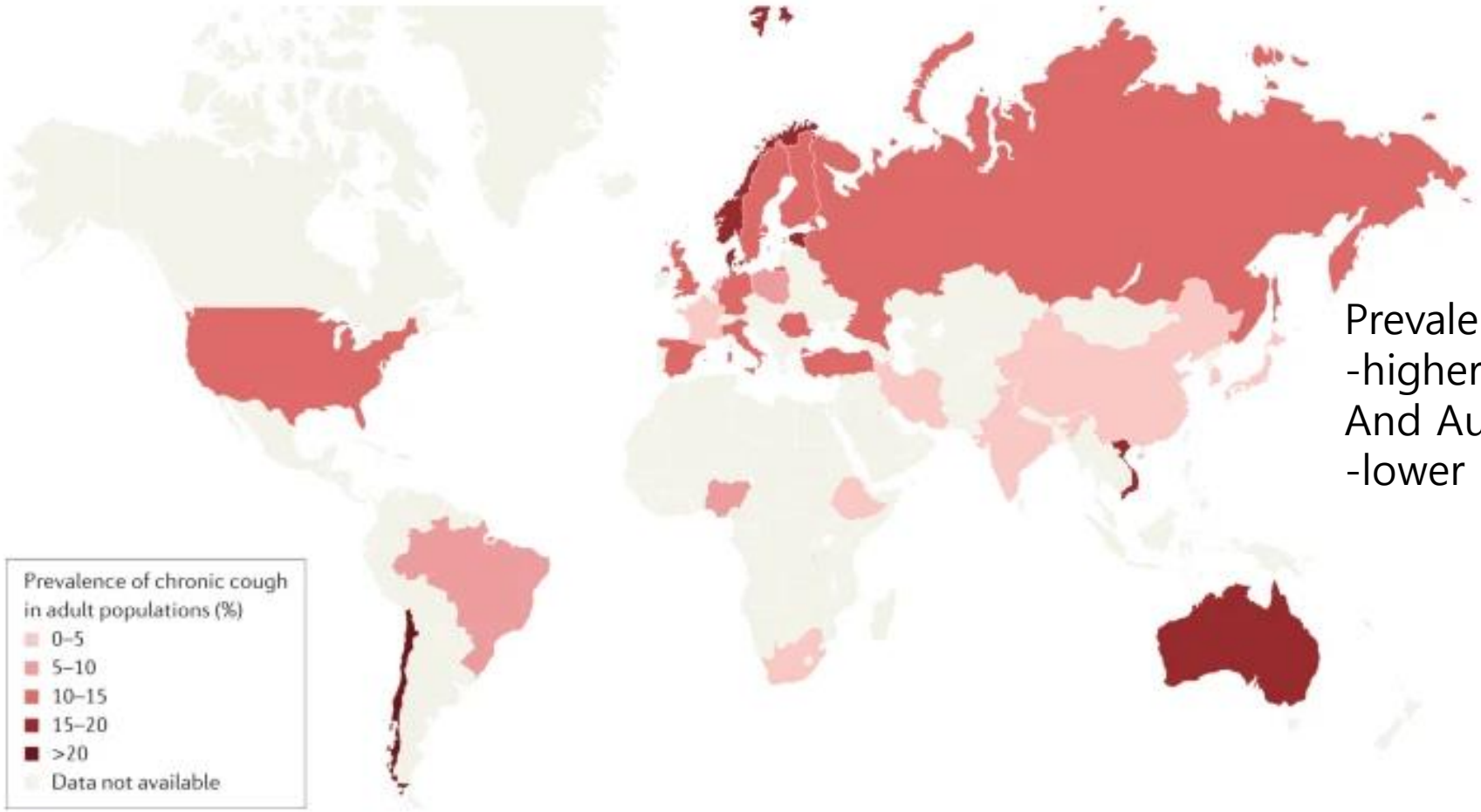
- Etiology of non pulmonary disease related cough
  - Nose: post nasal drip (PND)
  - Heart : heart failure, arrythmia, aortic aneurysm
  - GI tract : reflux esophagitis, recurrent aspiration
  - Ear: irritation of external auditory meatus
  - Vasculitis
  - Somatic cough syndrome
  - Cough hypersensitivity syndrome



Lancet 2008; 371: 1364–74

Prevalence of chronic cough

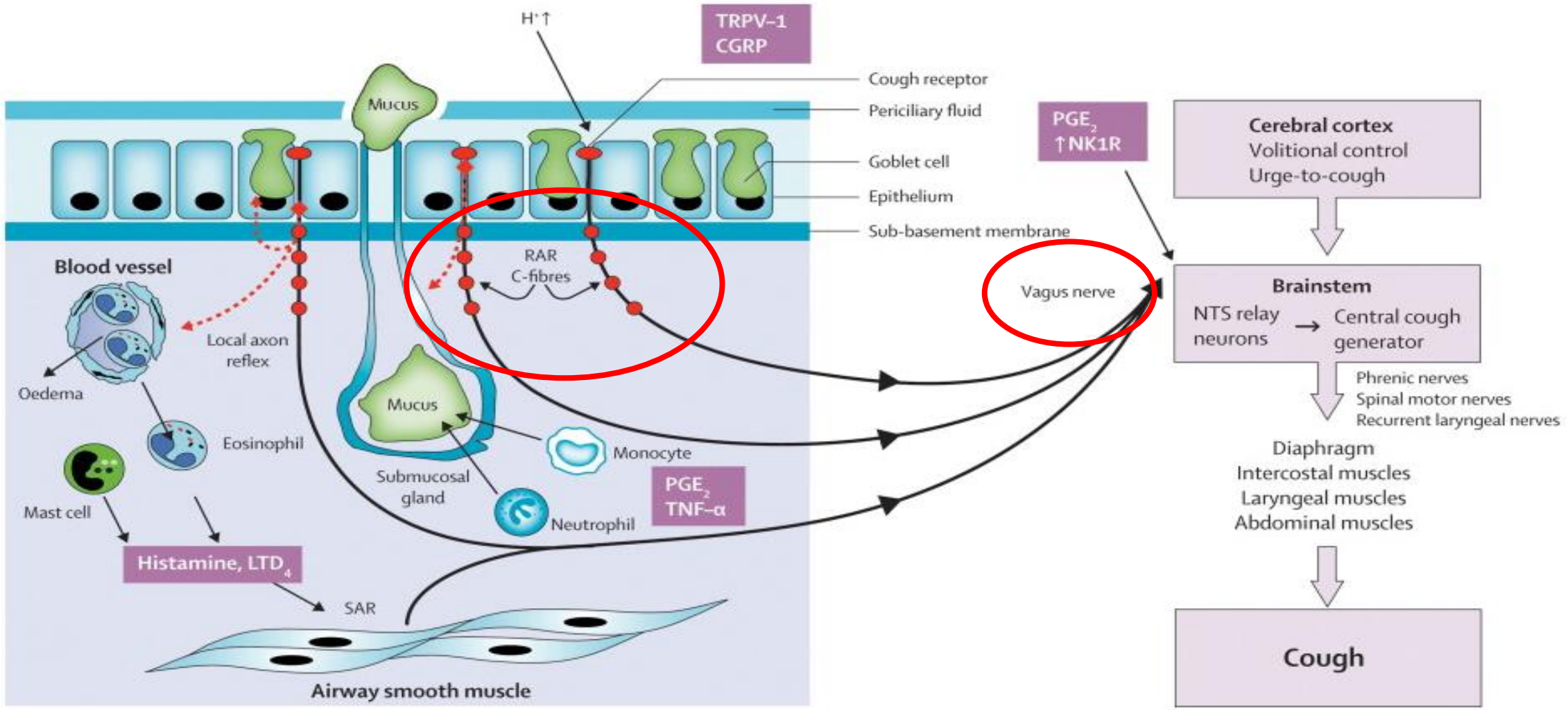
Fig. 1: Global prevalence of chronic cough.



Prevalence of chronic cough
-higher in Europe, America And Australia (10-20%)
-lower in Asia <5%

Nat Rev Dis Primers **8**, 45 (2022).

Pathogenesis of cough



Lancet 2008; 371: 1364–74

Post nasal drip (PND)

- Sensation of nasal secretion or of a drip at the back of the throat
  - Need to clear the throat (throat clearing)
  - Nasal discharge or nasal stuffiness
- Pathogenesis
  - Direct pharyngeal, laryngeal, or sublaryngeal stimulation
  - Inflammatory mediator->enhance cough reflex
- First generation antihistamine + decongestant (pseudoephedrine)
- ENT doctor :cough is not main symptom of PND

	Number (women)	Diagnosis				
		Asthma/CVA/ EB/AC	GORD	PNDS	Idiopathic	Other
USA						
Irwin[54]	102 (59)	24%	21%	41%	1%	CB (5%)
Irwin [55]	49 (27)	43%	10%	47%	0	CB (7%)
Poe[56]	139 (84)	35% (mostly CVA)	5%	26%	12%	CB (7%)
Pratter[57]	45 (28)	31%	11%	87%	0	Overlap of diagnosis with PNDS
Smyrnios[58]	71 (32)	24%	15%	40%	3%	..
Mello[59]	88 (64)	14%	40%	38%	2%	..
French[60]	39 (32)	15%	36%	40%	2%	..
Irwin[61]	24 (13)	21%	33% (rhinitis included)	33% (GORD included)	46%	..
UK						
O'Connell[62]	87 (63)	10%	32%	34%	27%	..
McGarvey[63]	43 (29)	23% (CVA)	19%	21%	19%	..
Brightling[64]	91 (NR)	31% (EB 13%)	8%	24%	7%	..
Birring[65]	236 (NR)	24%	15%	12%	26%	..
Niimi[66]	50 (39)	26%	10%	17%	40%	..
Kastelik[67]	131 (86)	24%	22%	6%	7%	Postviral (8%); bronchiectasis (8%); ILD 8%
Japan						
Fujimura[68]	176 (NR)	66% (36% asthma; 29% atopic cough)	2%	0	12%	Sinobronchial disease in 17%
Shirahata[69]	55 (NR)	42% (CVA)	0	7%	13%	31% improved on non-specific cough therapy
Brazil						
Palombini[70]	78 (51)	59%	41%	58%	0	..
Australia						
Carney[71]	30 (20)	23%	73%	93%	..	ACEI in 23%; overlap of diagnoses or symptoms

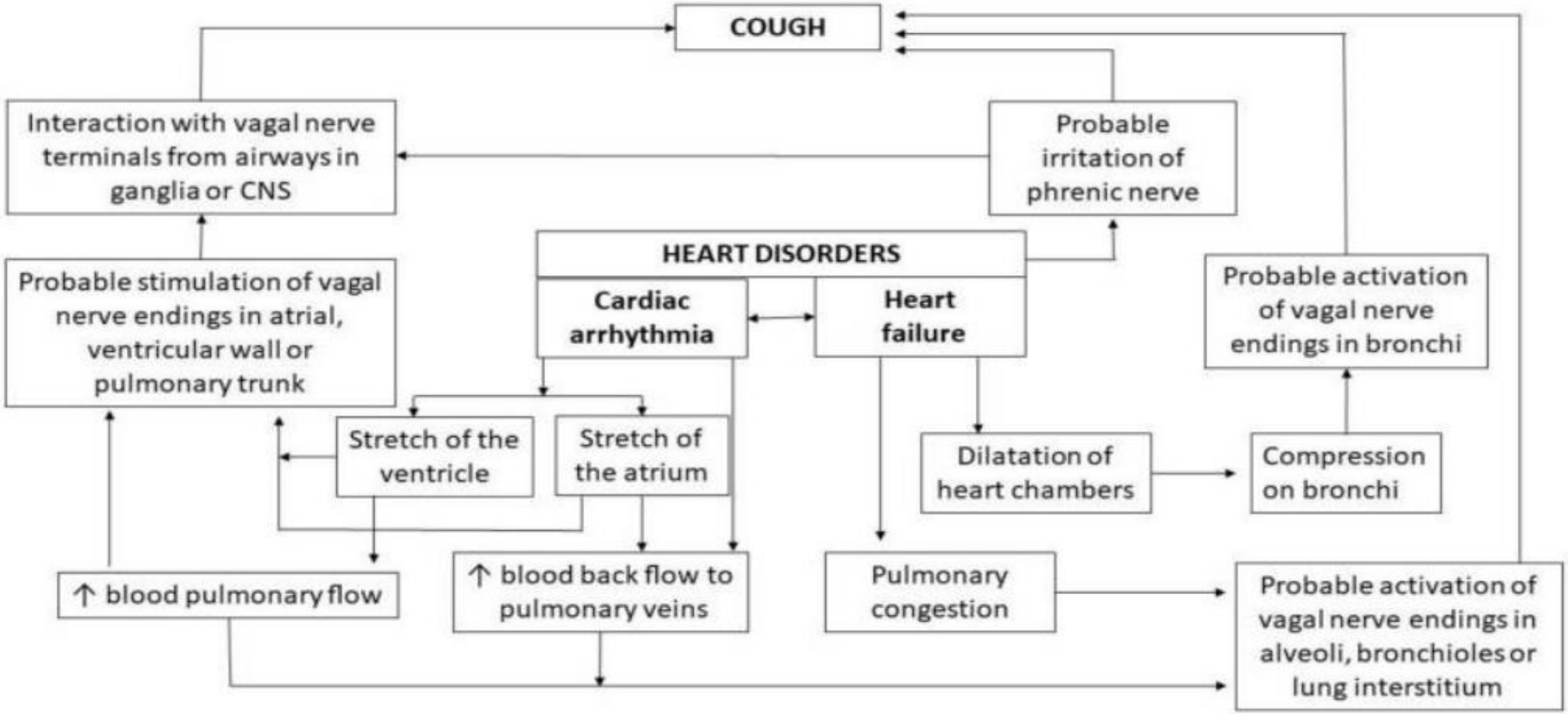
Hospital based clinics with cough study

-PND: 6% - 87%

-Absence of agreed diagnostic criteria

Lancet 2008; 371: 1364–74

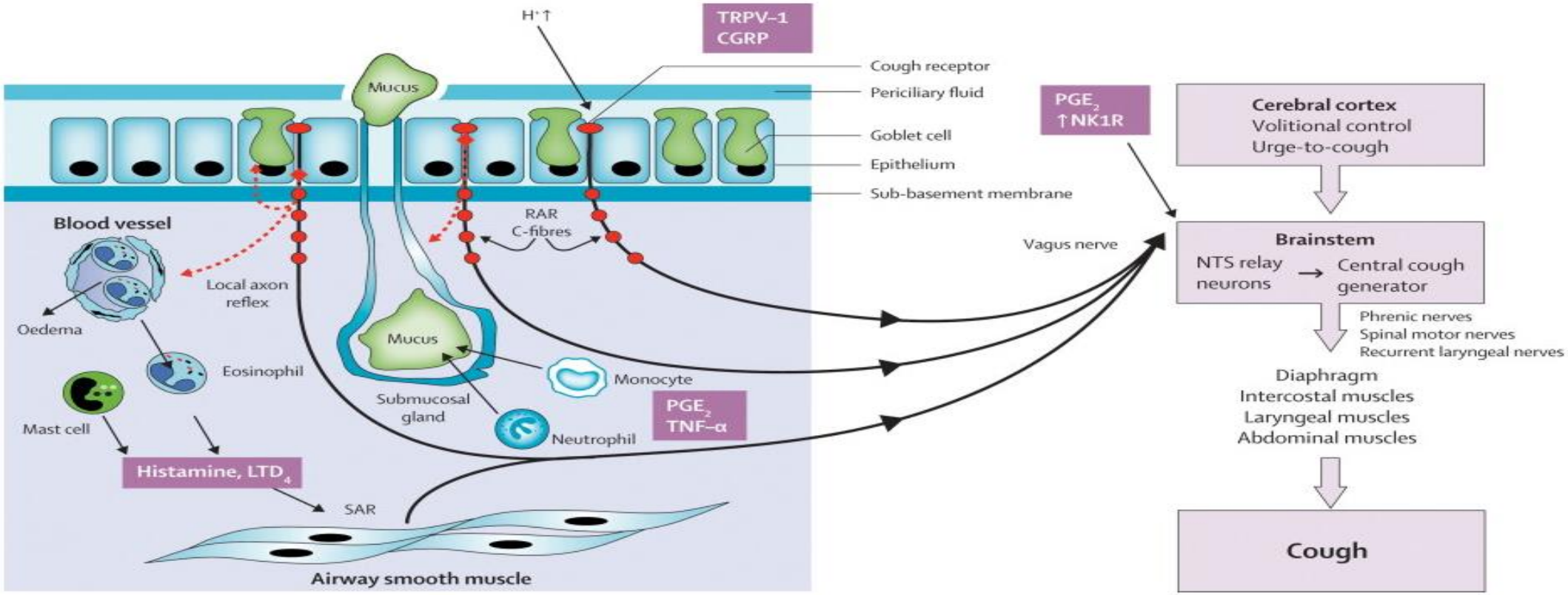
Mechanism of heart dysfunction induced cough



Physiol Res. 2020 Mar; 69(Suppl 1): S105–S121.

Mechanism of heart dysfunction induced cough

- stimulation of vagal nerve terminals in the heart



Heart failure

- Reflex interactions between heart afferent vagus nerves and cough neural pathways
  - Especially C fibers mainly respond to increased volume of the heart
- Hemodynamic changes in lung circulation caused by heart dysfunction
  - Fluid congestion in the pulmonary vasculature -> edematous lung increased A-a gradient and irritates the lung-> cough

Physiol Res. 2020 Mar; 69(Suppl 1): S105–S121.

Prevalence of heart failure related cough

Prevalence of cough and its associated diagnoses among 204,912 patients seen in primary care (PC) in India

Komalkirti Apte, Sapna Madas, Monica Barne, Sushmeeta Chhowala, Jaideep Gogtay, Sundeep Salvi
European Respiratory Journal 2016 48: PA864; **DOI:** 10.1183/13993003.congress-2016.PA864

Results: 7400 PCPs (60.6% GPs, 20.8% GenPs, 18.8% Ps) consented and provided clean data of 204,912 patients. Fever (35.5%) and cough (30%) were the most common symptoms reported. ---28.1%, 25.5% and 41.6% of patients seen by GPs, GenPs and Ps respectively were reported to have cough as a presenting symptom with males showing a higher prevalence [OR 1.2, CI (1.17, 1,23) p<0.0001]. Among reported cases of cough, a conclusive diagnosis was made in only 30.7%, 36.1% and 29.4% by GPs, GenPs and Ps respectively. Diagnoses made in these cases were Upper respiratory Tract Infections (12.2%), Lower Respiratory Tract Infections (8.1%), Asthma (7.4%), COPD (4%), Tuberculosis (2.5%) and Congestive Cardiac Failure (0.5%).

European Respiratory Journal 2016 48: PA864

Prevalence of heart failure related cough

- Electronic health record data of over 50,000 primary care patients
  - Natural language processing: data from the free text
  - Framingham Diagnostic Criteria for Definite Heart Failure
- 4,644 incident HF cases and 45,981 group-matched controls

Framingham Diagnostic Criteria for Definite Heart Failure

MAJOR SYMPTOMS	MINOR SYMPTOMS
1. Paroxysmal Nocturnal Dyspnea (PND) or Orthopnea	1. Bilateral Ankle Edema
2. Neck Vein Distension (JVD)	2. Nocturnal Cough
3. Rales	3. Dyspnea on ordinary exertion
4. Radiographic Cardiomegaly	4. Hepatomegaly
5. Acute Pulmonary Edema	5. Pleural effusion
6. S3 Gallop	6. A decrease in vital capacity by 1/3 of the maximal value recorded*
7. Increased Central Venous Pressure (> 16 cm H2O at RA)*	7. Tachycardia (>120 BPM)
8. Circulation Time of 25 seconds*	
9. Hepatojugular Reflux (HJR)	
10.Weight loss 4.5kg in 5 days in response to treatment	

*Not utilized in this analysis as not documented in routine clinical practice.

J Card Fail. 2014 July ; 20(7): 459–464.

Prevalence of heart failure related cough

Framingham Sign or Symptom	Total HF cases (N = 4,644)		Total Controls (N = 45,981)		p-value (Difference in prevalence between cases and controls)
	Total Cases (% of HF cases who ever had the specific criterion affirmed)	Median and (IQR) number of days between first documented affirmation and diagnosis date in cases	Total Controls (% of controls who ever had the specific criterion affirmed)	Median and (IQR) number of days between first documented affirmation and matched date in controls	
Major Criteria					
Pulmonary Edema	9.0%	145 (632)	2.9%	650 (823)	<0.001
Paroxysmal Nocturnal Dyspnea	41.0%	599 (1064)	28.1%	904 (909)	<0.001
Jugular Venous Distention	15.6%	347 (989)	8.1%	871 (912)	<0.001
Rales	36.4%	408 (956)	18.9%	814 (883)	<0.001
Radiographic Cardiomegaly	28.6%	277 (697)	3.4%	493 (744)	<0.001
S3 Gallop	3.7%	345 (879)	1.9%	834 (927)	<0.001
Hepatojugular Reflux	3.3%	596 (822)	1.3%	824 (851)	<0.001
Weight Loss	3.8%	301 (785)	1.3%	625 (783)	<0.001
Minor Criteria					
Ankle Edema	87.1%	886 (949)	72.3%	1002 (933)	<0.001
DOE	87.4%	780 (1025)	59.9%	985 (920)	<0.001
Hepatomegaly	5.6%	764 (918)	3.8%	869 (926)	<0.001
Night Cough	8.6%	596 (822)	5.5%	747 (866)	<0.001
Pleural Effusion	18.9%	83 (515)	3.0%	574 (758)	<0.001
Tachycardia	9.6%	518 (916)	5.2%	726 (792)	<0.001

J Card Fail. 2014 July ; 20(7): 459–464.

Arrhythmia

- Arrhythmia-induced cough
  - Direct activation of vagal nerve endings (C-fibers) in the left ventricular wall
  - Distention of pulmonary artery and activation of cough receptors as a result of augmented pulmonary blood flow following

Pacing and Clinical Electrophysiology, 2013, 36.5: e156-e158.

Arrhythmia

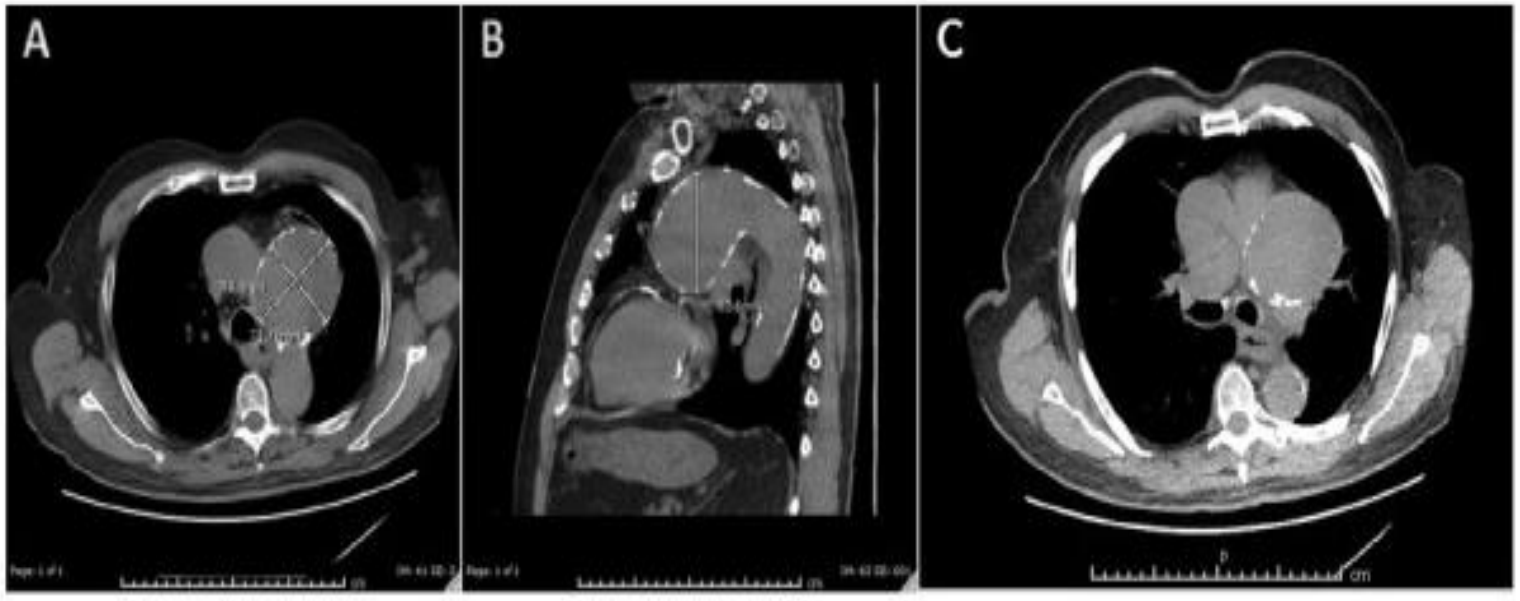
- N=120 frequent symptomatic, idiopathic PVC for ECG
- Questrionnaire

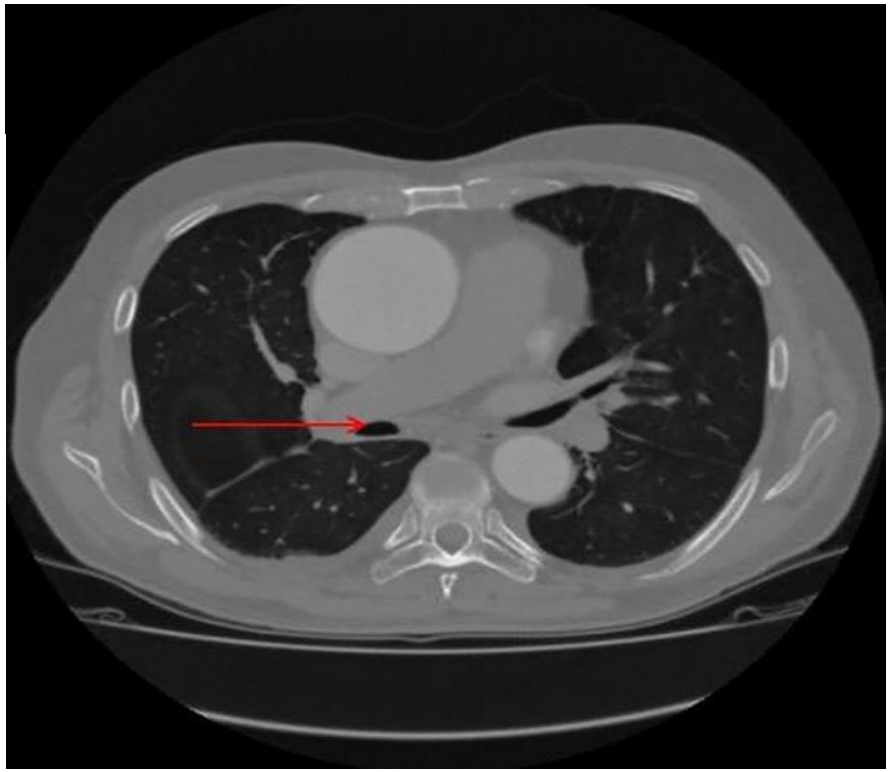
Characteristics	PVC-Associated Cough (n = 6)	Chronic Cough (Other) (n = 4)	No Chronic Cough (n = 110)
Age, yr	49 ± 15	67 ± 5	48 ± 16†
Female gender	6	3	73
PVC count/24 h	12,755 ± 8,150	12,340 ± 8,642	14,053 ± 9,676†
PVC origin			
RVOT	4	0	63
Parahisian/RVIT	1	2	9
LVOT	0	2	10
Aortic cusp	0	0	9
Other	0	0	19
General severity of symptoms associated with PVC, VAS score‡	8.2 ± 0.5	5.0 ± 1.6	5.7 ± 1.6§
Coexisting cough reasons			
Asthma	0	0	NA
NAEB	5	2	NA
GERD	4‖	2	NA
Rhinosinusitis	3	2	NA
COPD	0	1	NA
Long-term treatment of arrhythmia			
Antiarrhythmic drugs	1	2	36
Ablation	4	0	60
No treatment	0	1	6
Spontaneous remission	1	1	8

CHEST 2009;135:1~1541)

Aortic aneurysm

- Case reports
- Presumed to be secondary to bronchial compression from local mass effect





BMJ Case Rep. 2014 Sep 1;2014:

Reflux esophagitis

- Irritated and modulated by stimuli generated outside of pulmonary
  - Extrapulmonary vagal nerve endings founds in the esophagus
- Pathophysiology
  - Microaspiration->airway cough receptor
  - Esophageal cough receptor: direct acid infusion induced cough,pepsin,bile
  - Reflex interaction between esophagus and airway fibers (C-fiber) not manoreceptor
    - Reflux increased cough
    - Cough increased reflux
- Sx: cough with heartburn, chest pain, sour taste, regurgitation

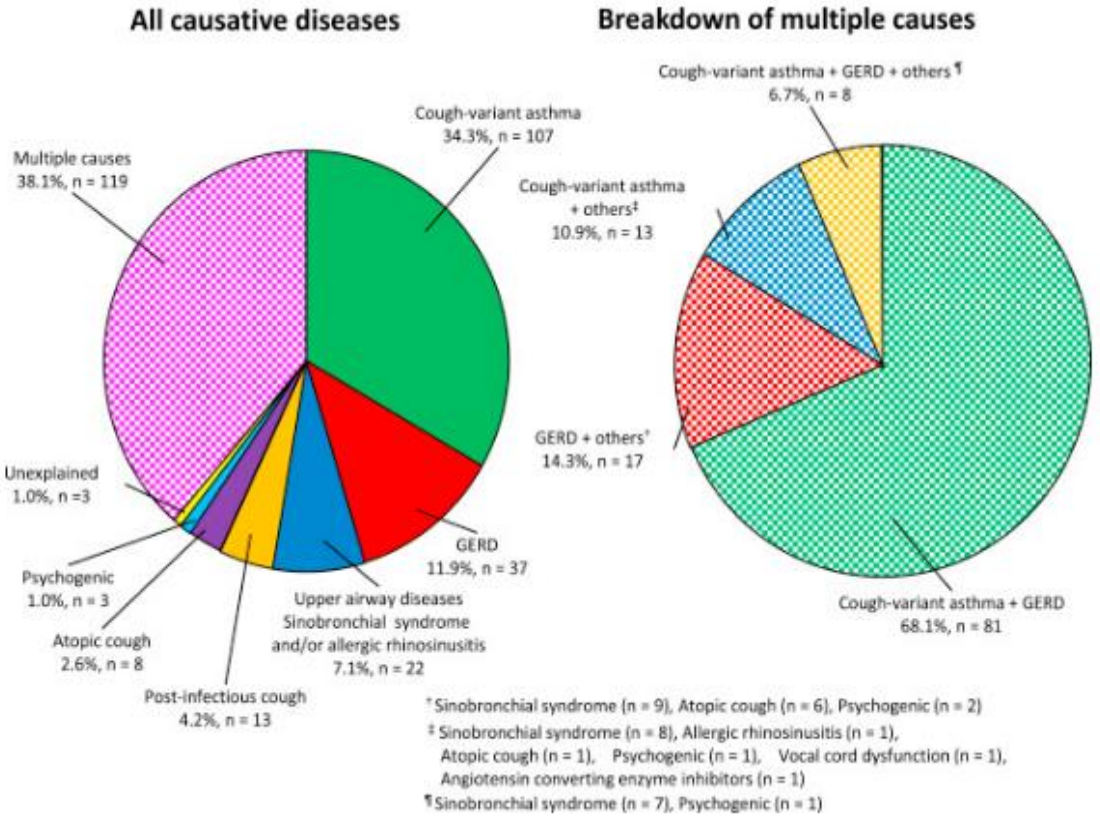
Physiol Res. 2020 Mar; 69(Suppl 1): S105–S121.

Prevalence of esophagitis cough

Table 2 Baseline characteristics of subjects with newly referred CC and RUCC

	Total (n=610)	Newly referred CC (n=434)	RUCC (n=176)	*P* value*
Females, %	66.9%	65.4%	70.5%	0.233
Age, years	59.0 (IQR 43.8–67.0)	58.0 (IQR 41.8–65.0)	62.0 (IQR 49.5–69.0)	0.001
Age at cough onset, years	50.1 (IQR 34.0–61.0)	49.0 (IQR 34.0–60.6)	51.0 (IQR 33.0–62.0)	0.530
Cough duration, years	4.0 (IQR 1.0–10.0)	3.0 (IQR 1.0–10.0)	6.0 (IQR 3.0–10.0)	<0.001
Family history of chronic cough	31.0%	30.0%	33.3%	0.424
BMI, kg/m^2	24.6±4.4	24.7±4.6	24.5±3.8	0.814
Smoking status, %				
Non-smoker	75.7%	75.1%	77.3%	0.573
Ex-smoker	19.7%	19.4%	20.5%	0.757
Current smoker	4.6%	5.5%	2.3%	0.090
Recent ACE inhibitor use, %	0.7%	1.0%	0%	0.327
Comorbidity, %				
Hypertension	26.5%	23.9%	32.8%	0.026
GERD	20.0%	20.8%	17.9%	0.424
Diabetes mellitus	10.4%	10.2%	11.0%	0.767
Asthma	9.1%	7.1%	13.9%	0.009
Thyroid diseases	5.9%	6.2%	5.2%	0.647
Post-tuberculosis lung sequelae	5.2%	5.7%	4.0%	0.417
Arrhythmia	2.4%	2.4%	2.3%	1.000
Heart failure	1.2%	1.2%	1.2%	1.000
Autoimmune diseases	0.7%	0.5%	1.2%	0.584

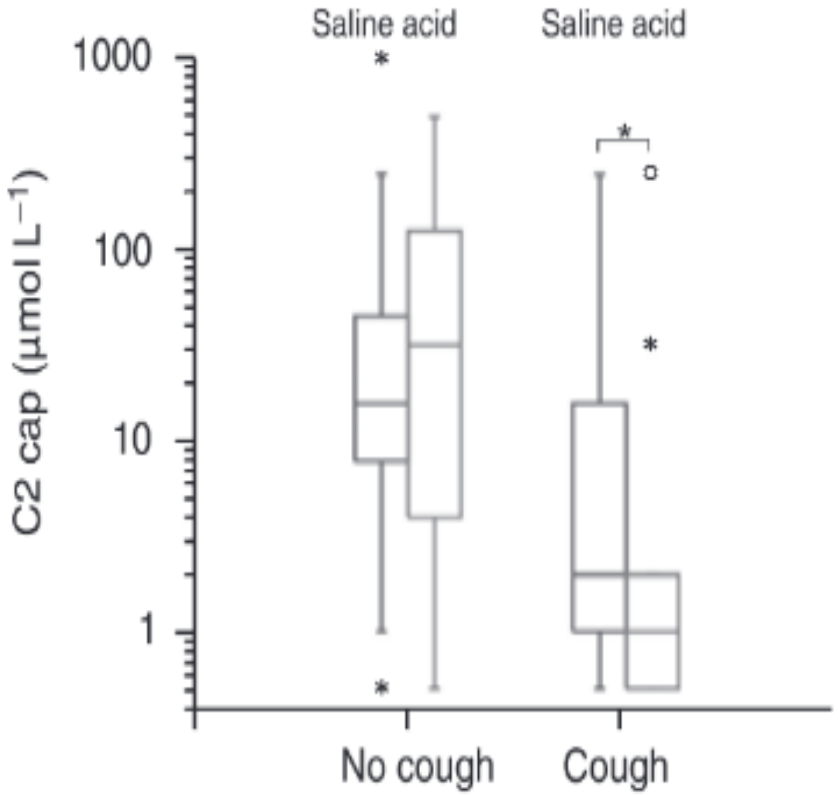
10-59% of chronic cough cased by GERD



Lung (2023), Allergology International 2019, Cochrane Database Syst Rev 2011

Reflux esophagitis

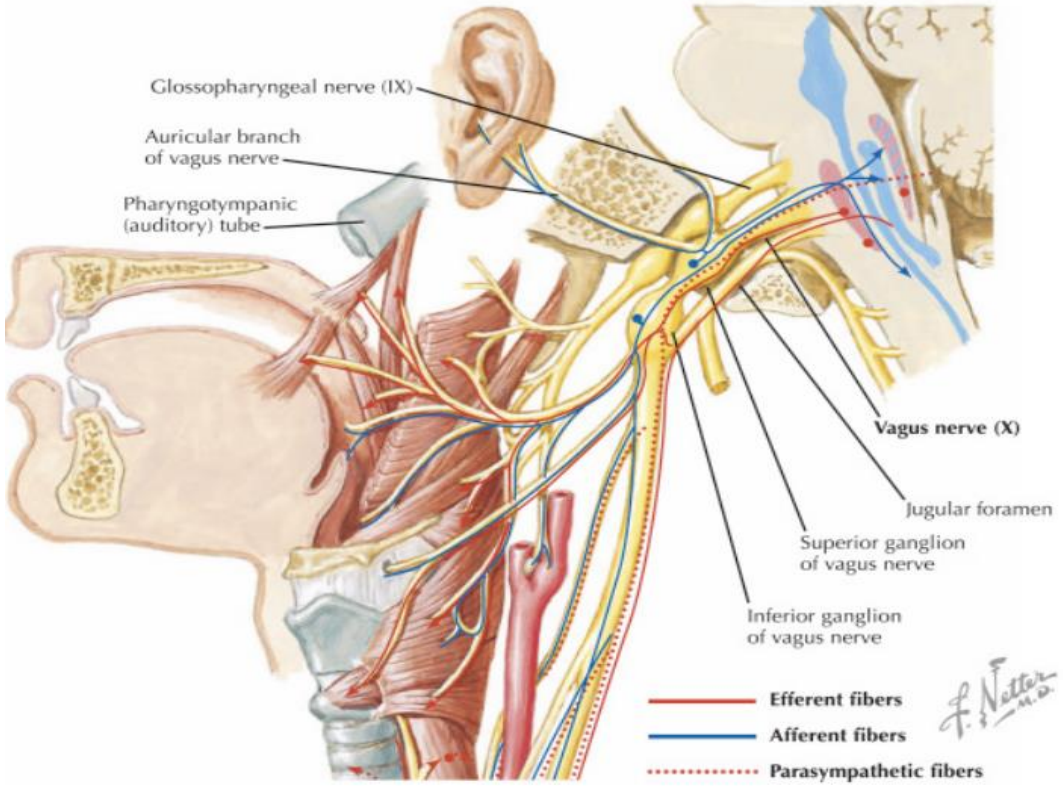
- Increased sensitivity of the cough response to capsaicin
  - Chronic GERD with chronic cough vs Chronic GERD without chronic cough

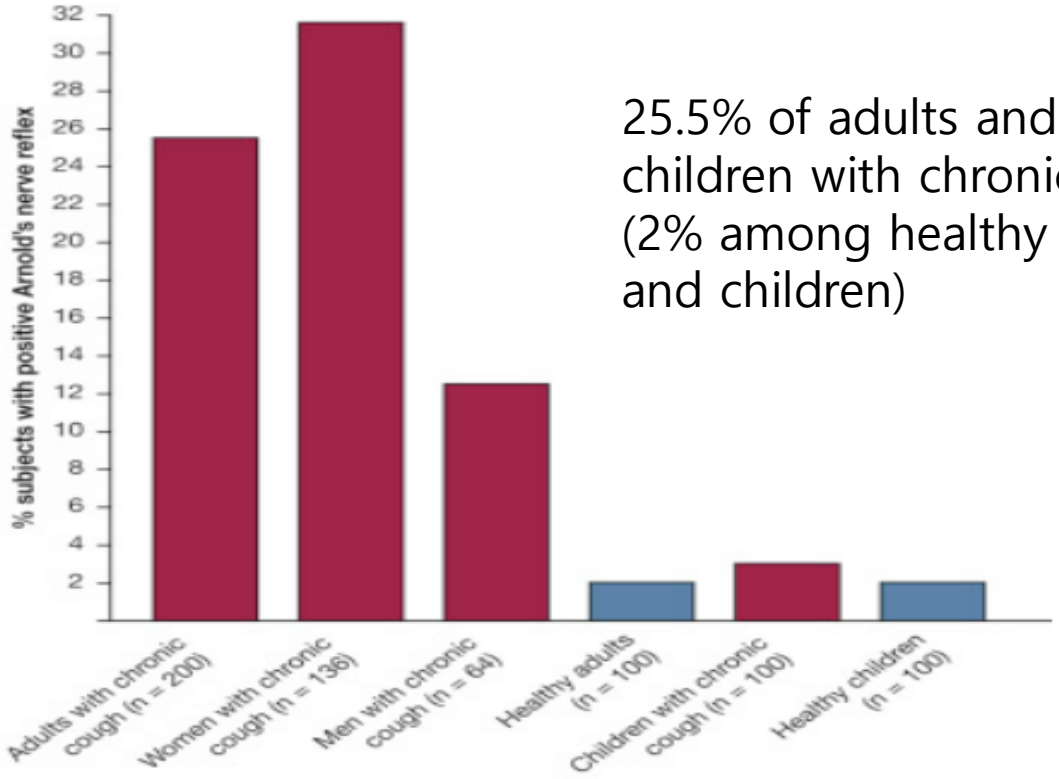


Neurogastroenterol Motil(2008)20,119–124

Ear problems

- Irritation of Arnold's nerve (a branch of the vagal nerve innervating external auditory canal): Irritation of external auditory meatus





25.5% of adults and 3% of children with chronic cough (2% among healthy adults and children)

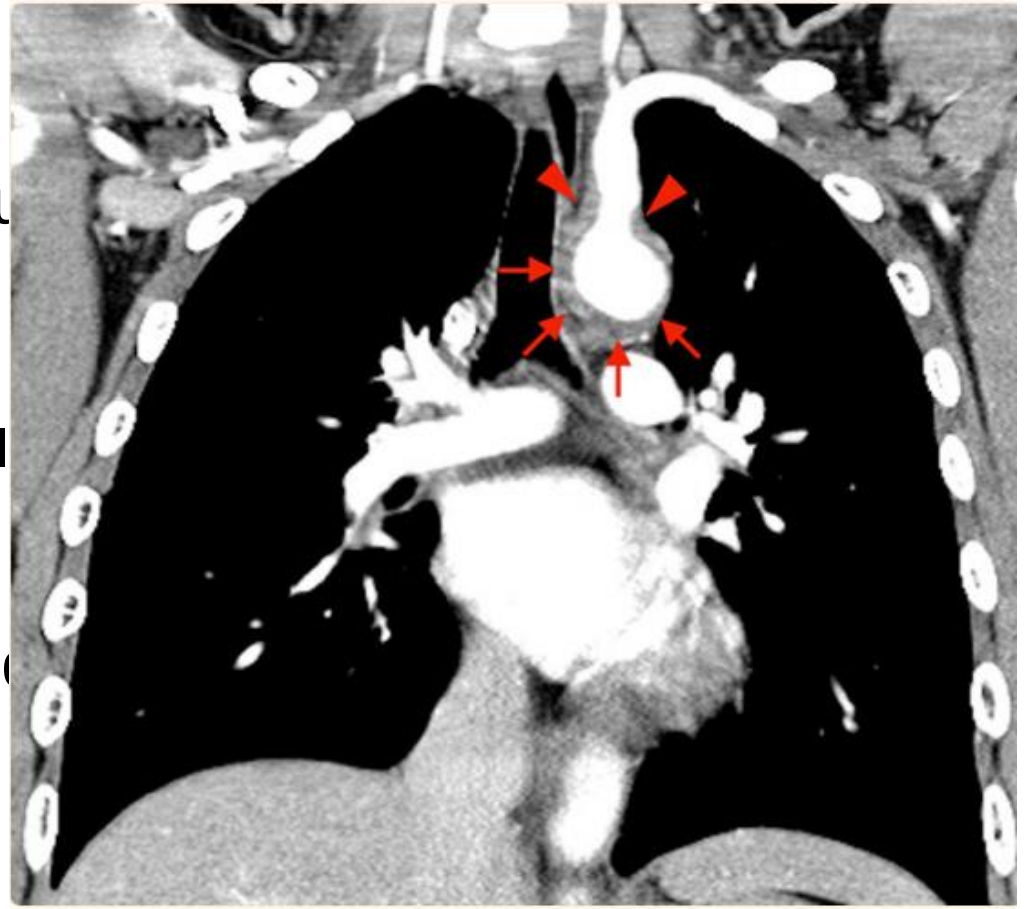
Chest, 2018, 153.3: 675-679.

Irritation of Arnold’s nerve related cough Mx

- Cerumen impaction removal
- Amitriptyline, Gabapentin
  - Associated with cough hypersensitivity syndrome

Vasculitis (not involved lung parenchymal vessel)

- Large vessel vasculitis (Takayasu arteritis)
  - Case report
  - Prevalence: 9% of patients with Takayasu
  - Pathophysiology
    - Vessel inflammation stimulates the cough refl
      nerve
  - Sx: headache, syncope, stroke, arm clau



Internal Medicine, 2018, 153.3: 675-679.

Vasculitis (not involved lung parenchymal vessel)

- Relapsing polychondritis
  - Auto immune disease by recurrent episode of inflammation of cartilaginous and proteoglycan rich tissue
    - Body ,ears, nose, joints, eyes, he
    - 80% of pateitns: auricular chondr
    - Tracheal involvement

Diagnostic criteria for relapsing polychondritis.

McAdam *et al.* (3)	(1) Recurrent chondritis of both auricles (2) Nonerosive inflammatory polyarthritis (3) Chondritis of nasal cartilages (4) Inflammation of ocular structures (5) Chondritis of respiratory tract (7) Cochlear and/or vestibular damage (requirement—three out of six criteria)
Damiani and Levine (5)	(1) Three out of six McAdam *et al.*'s criteria (2) One out of six McAdam *et al.*'s criteria and a positive histologic confirmation (3) Two out of six McAdam *et al.*'s criteria and response to corticosteroid or dapsone (requirement—any of these)
Michet *et al.* (4)	(1) Proven inflammation in two out of three cartilages: auricular, nasal, and laryngotracheal (2) Proven inflammation in one of the above and meeting two other signs from ocular inflammation, hearing loss, vestibular dysfunction, or seronegative inflammatory arthritis (requirement—any of these)

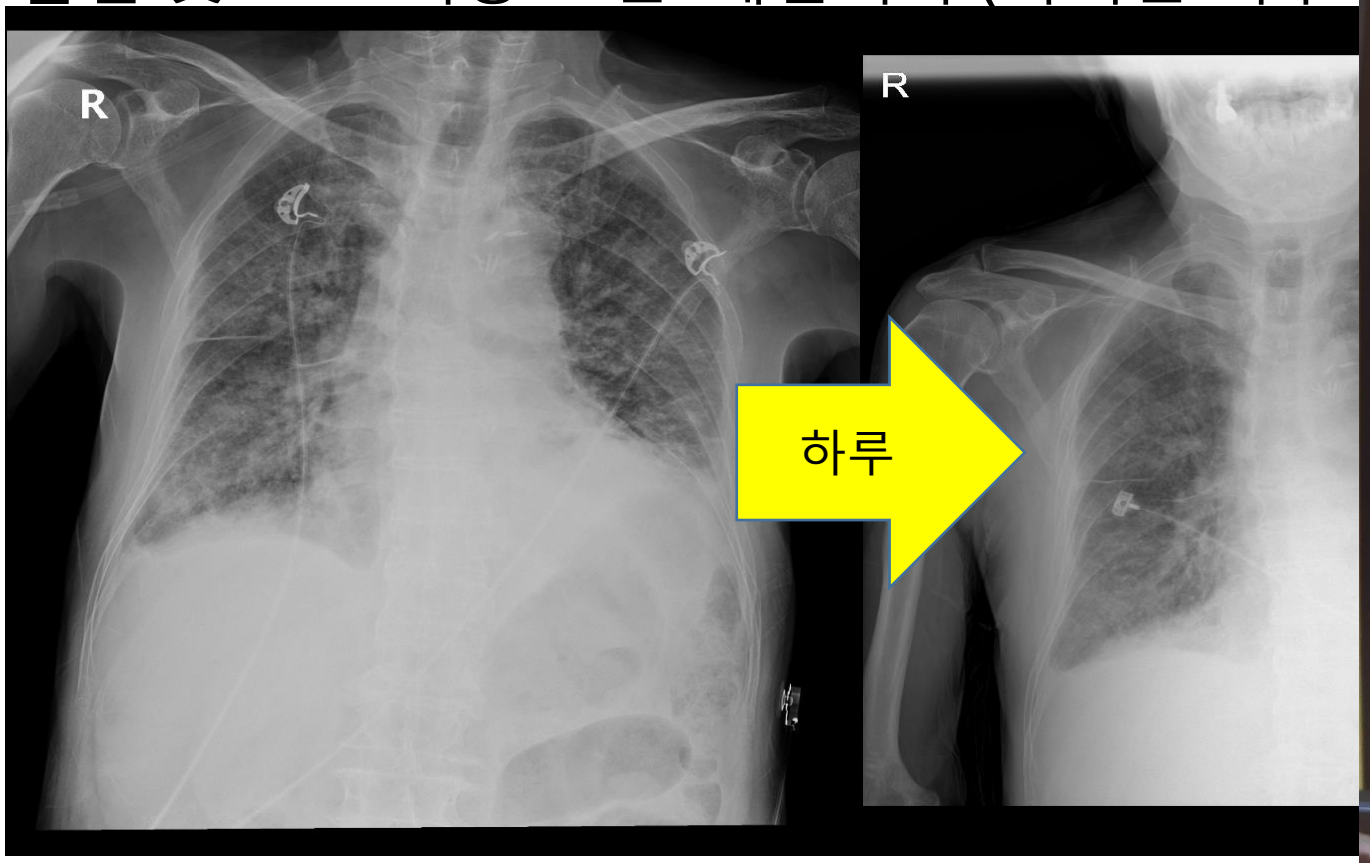
Case, 80/M, recurrent cough with fever

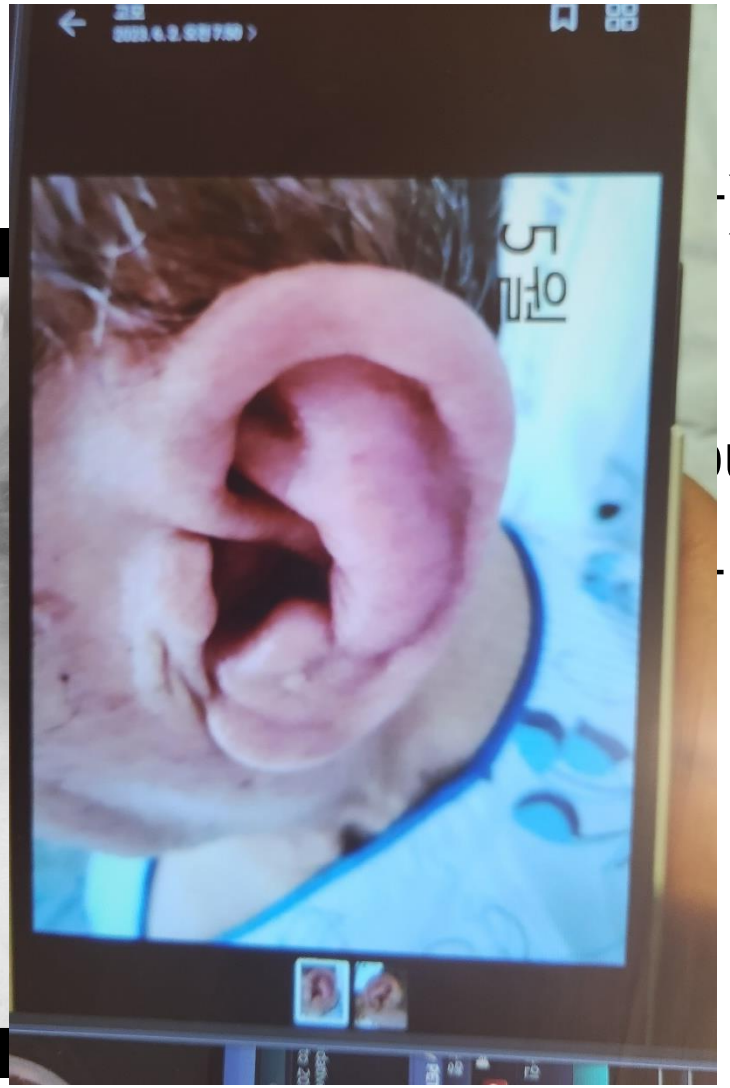
- 2022년 에 타병원
  입원히 견된
  thymo T CT에서 이
  상 lun tion의 병력
  이 있음
  - 진단
  - Ane

히 호전

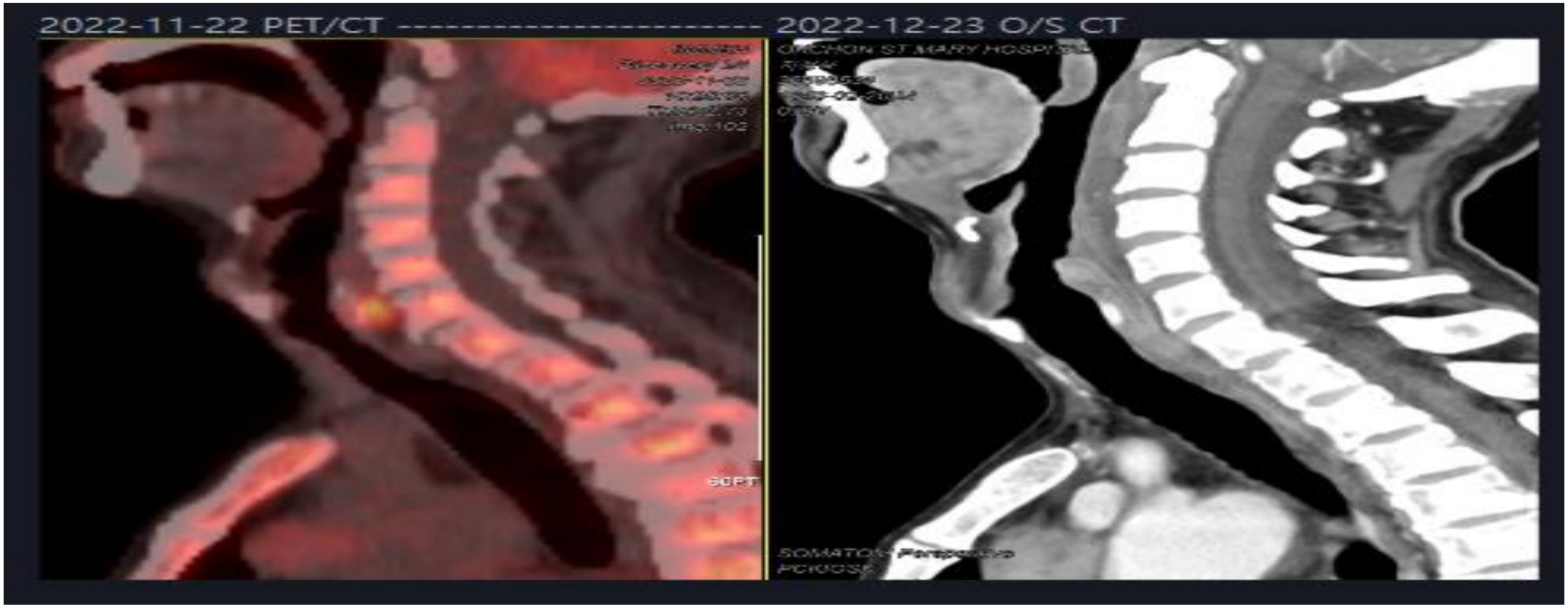
Case, 80/M, recurrent cough with fever

- 2023.6 ER->IMR consult for admission
  - 발열 및 CXR 이상 소견: 폐렴이다 (하지만 너무 -)
  -
  - ure





Case, 80/M, recurrent cough with fever



- 진단: Relapsing polychondritis involvement of trachea, valve involvement induced pulmonary edema

Somatic cough syndrome (psychogenic cough)

- Tic or habit cough in children (rare in adults)
- Anxiety related , usually absent in sleep
- Diagnosis criteria
  - Disruption of daily life
  - Excessive thoughts about the seriousness of the symptoms
  - Persistent anxiety about health or symptoms, or excessive time and energy devoted to symptoms or health concerns
  - Persistence of symptoms (typically more than six months)

Chest **148**, 24–31 (2015).

Cough hypersensitivity syndrome

- 40% of adults with chronic cough
  - Unexplained chronic cough or have persistent cough despite optimal treatment
- 2011, ERS Task Force definition: disorder by troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure
- Sx: Persistent or intermittent tickling, irritating sensation, rawness in the pharynx or laryngeal area (sometimes referred to as a feeling of an itch), a choking sensation in the throat

European Respiratory Journal 2014 , Nat Rev Dis Primers **8**, 45 (2022).

Cough hypersensitivity syndrome

- Neuropathic process
  - Afferent nerves highly susceptible to sensitization by various neuroactive molecules (eg, nerve growth factor (NGF))
  - Laryngeal hypersensitivity and dysfunction
  - Upregulated cough network activity in the midbrain

Lancet Respir Med 2013 Jul;1(5):414-22.

Peripheral and central processes cough sense

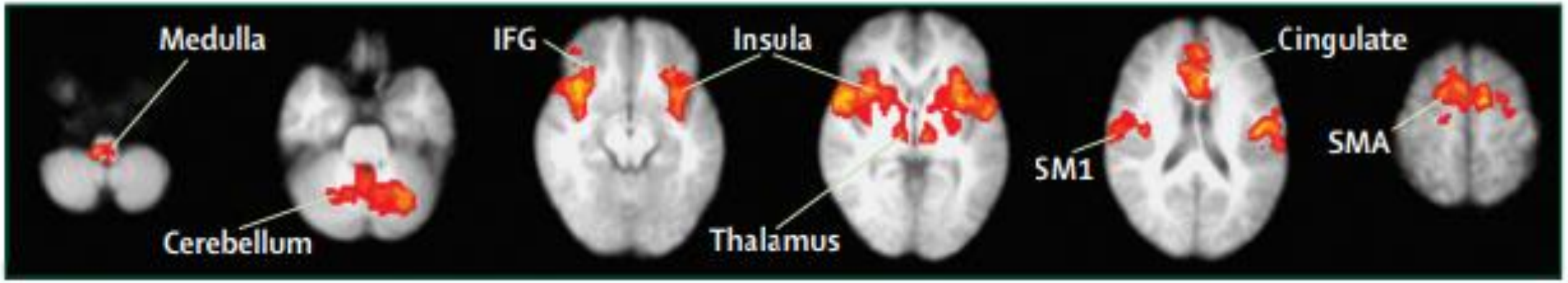
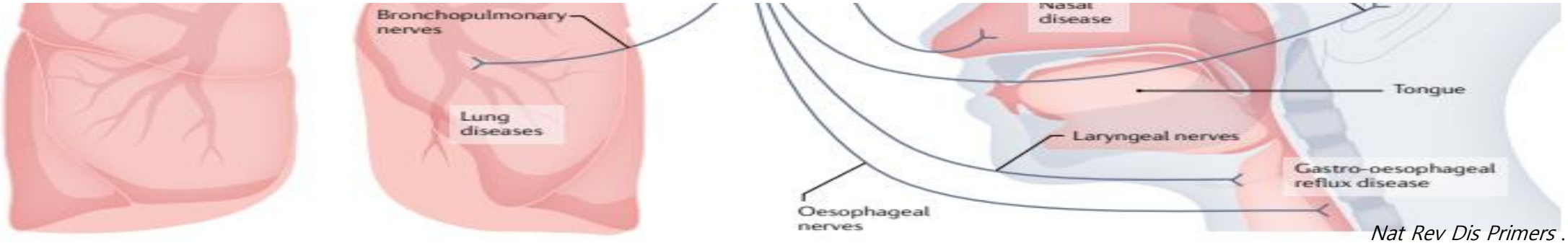


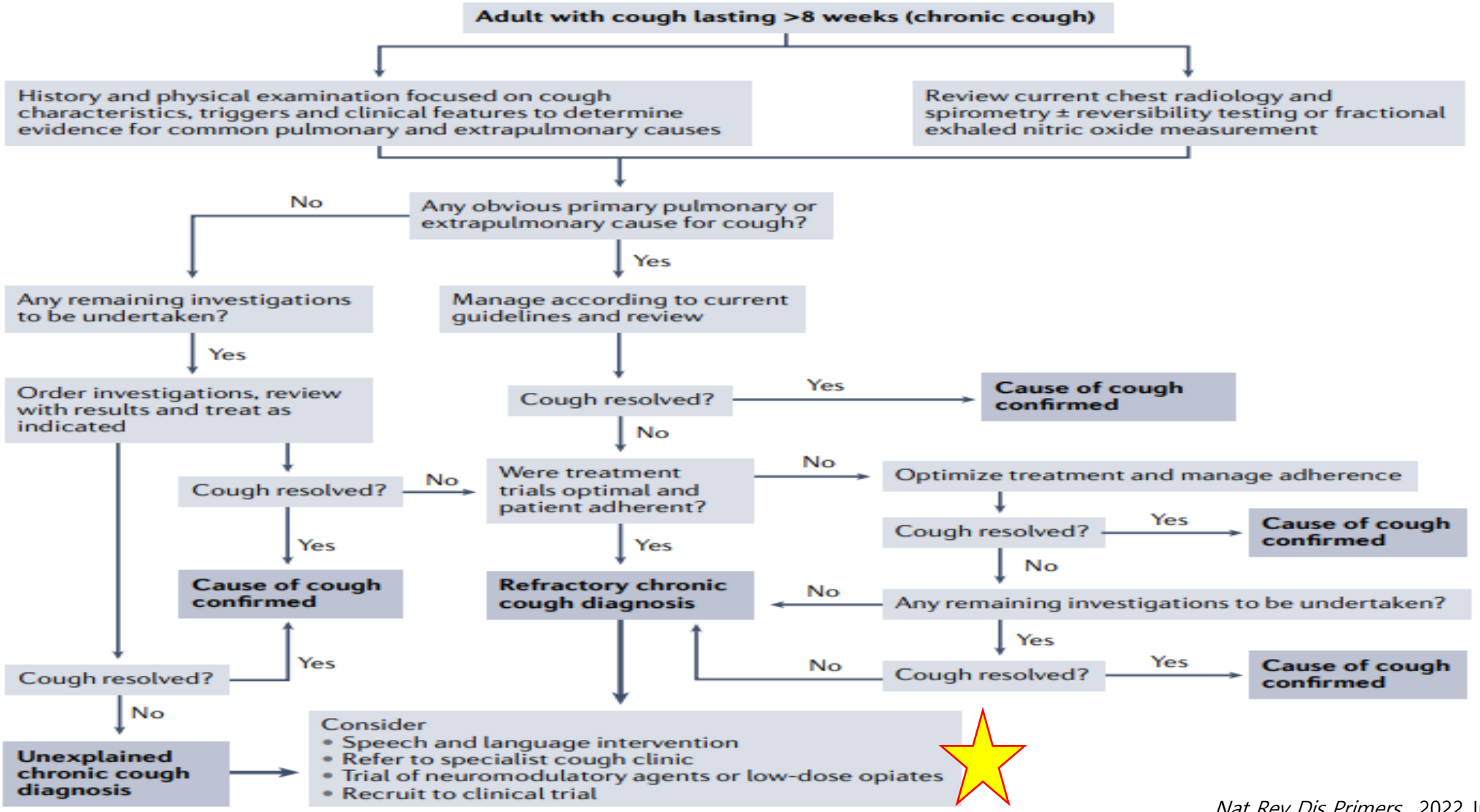
***Figure 3*: Brain circuitry in coughing**

Functional magnetic resonance imaging shows capsaicin-activating responses in the brainstem, cerebellum, inferior frontal gyrus (IFG), insular cortex, thalamus, sensorimotor cortex (SM1), and supplementary motor area (SMA).



Nat Rev Dis Primers . 2022 Jun 30;8(1):45

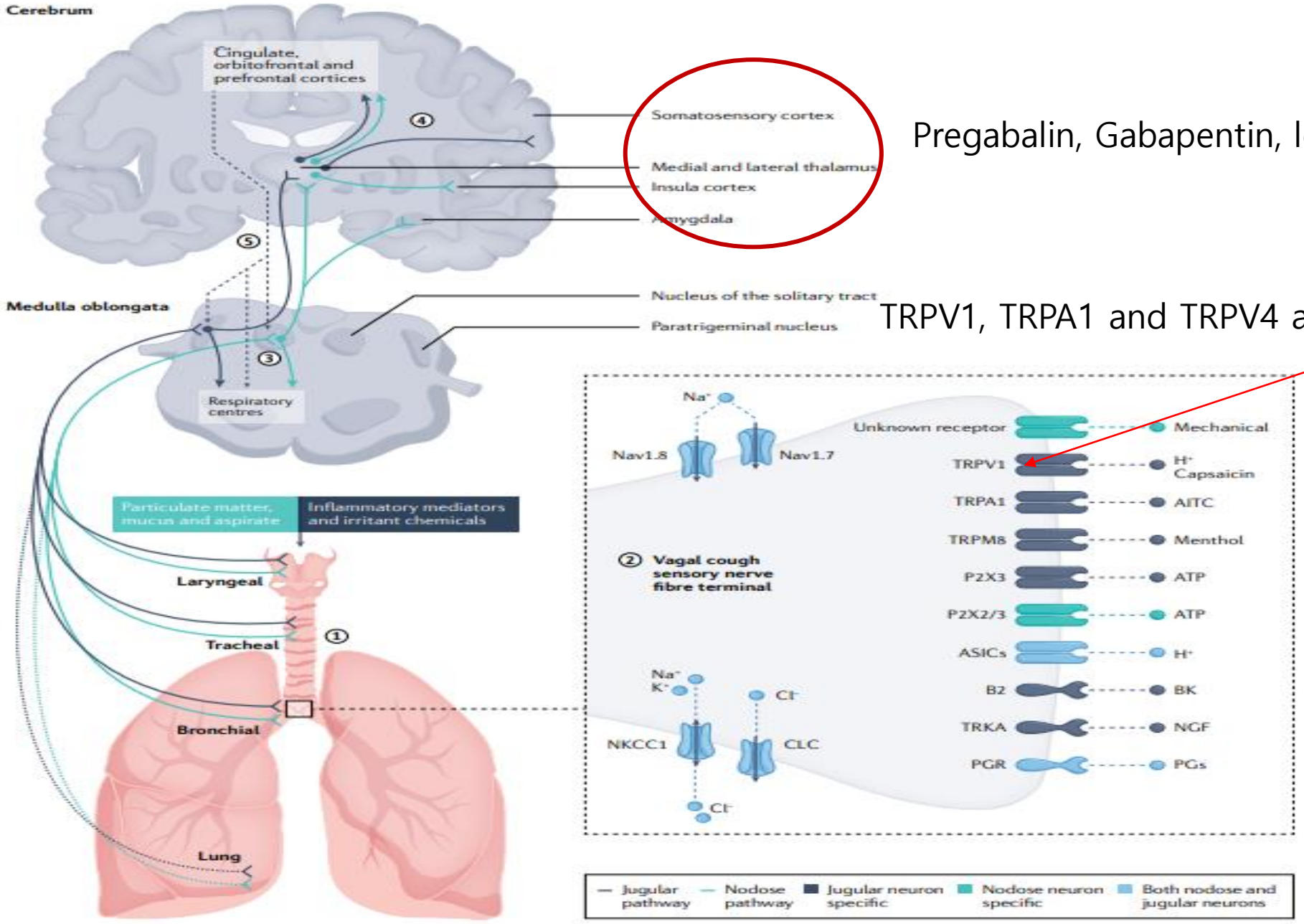
Management of chronic cough



Nat Rev Dis Primers . 2022 Jun 30;8(1):45

Pregabalin, Gabapentin, low dose opioids

TRPV1, TRPA1 and TRPV4 antagonists have failed



Management of chronic cough

SNUH 분당서울대학교병원 SEOUL NATIONAL UNIVERSITY BUNDANG HOSPITAL

Box 4 | **Speech and language therapy management of chronic cough**

The approach to cough-specific speech and language therapy involves four steps.

- Education. Patients are provided education on the biology of coughing, chronic cough and cough hypersensitivity, and the negative effects of repeated coughing and throat clearing are explained.
- Vocal hygiene. Vocal and laryngeal hygiene and hydration are advised with a reduction in caffeine and alcohol intake. Nasal breathing with nasal douching may be recommended with nasal steam inhalation.
- Cough control/suppression training. Following identification of patient cough triggers, patients are taught a range of suppression strategies including forced/dry swallow, sipping water, chewing gum or sucking non-medicated sweets. Breathing pattern re-education is used to promote relaxed abdominal breathing while inhaling through the nose.
- Psycho-educational counselling. Behaviour modification is used to reduce over-awareness of the need to cough and facilitate an individual's internalization of control over their cough and to help manage stress and anxiety.

Nat Rev Dis Primers . 2022 Jun 30;8(1):45

Management of chronic cough-clinical trial

Bellus HEALTH

제목 페이지

임상시험계획서 제목: 원인 미상의 만성 기침을 포함하는 난치성 만성 기침을 하는 성인 참여자에서 BLU-5937 의 공개라벨 연장을 포함한 3 상, 24 주, 무작위, 이중 눈가림, 위약 대조군, 평행군 유효성 및 안전성 시험 (CALM-2)

임상시험계획서 번호: BUS-P3-02(CALM-2)

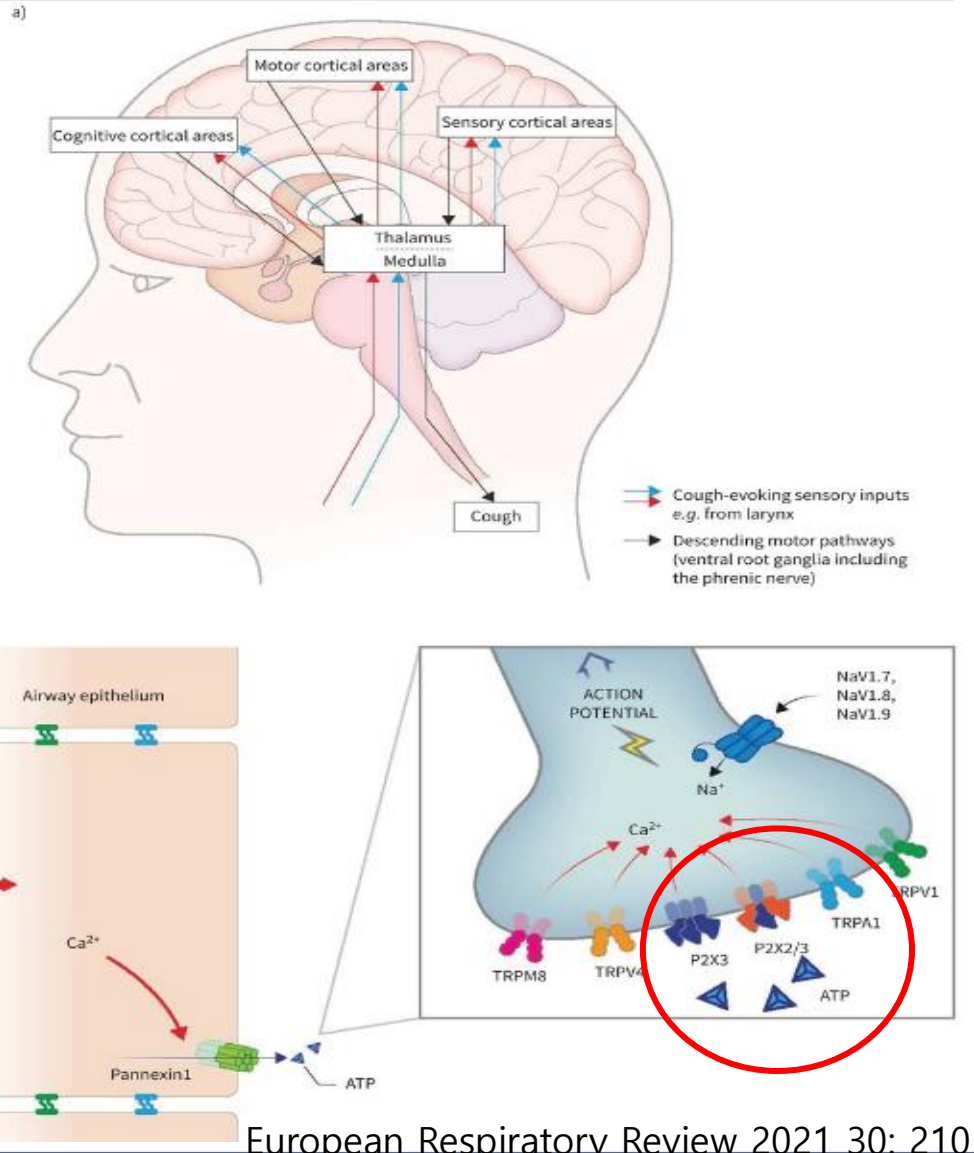
개정 번호: 임상시험계획서 원본

의약품: BLU-5937

약식 제목: 난치성 또는 원인 미상의 만성 기침을 하는 성인 참여자에서 BLU-5937 의 공개라벨 연장을 포함한 3 상, 24 주, 무작위, 유효성 및 안전성 시험

시험 단계: 3 상

의뢰자 이름: Bellus Health, Inc.



European Respiratory Review 2021 30: 210127

Clinical trial

- Camlipixant
  - Potent, noncompetitive P2X3 antagoni
  - Highly selective for P2X3
  - Dose not cross blood brain barrier: onl

약물	휴약기/제한
진해제/요법	
기본적으로 덱스트로메토르판, 벤조나트륨산염 (데살푼 페르레스) 및 아편유사제가 포함된다.	스크리닝 후 1 주일 이내에 허용되지 않으며 본 시험 기간에 걸쳐 금지됨
참고: 인후염용 로젠지 및 구아이페네신(객담제/거담제)은 허용됨	
가바펜틴/프레가발린/바클로펜/삼환계	중단하기 전에 점감해야 하며, 스크리닝 후 2 주 이내에 허용되지 않으며, 본 시험 기간에 걸쳐 금지됨
물리요법/신체/언어 및 언어 치료	참여자가 이 요법 과정을 완료했으며 스크리닝 그리고 본 시험 기간에 걸쳐 안정적인 경우에만 허용됨
천식	
흡입형 코르티코스테로이드, 류코트리엔 억제제, 흡입형 항콜린제, 흡입형 베타 작용제 및 흡입형 기관지 확장제	스크리닝 방문 전 최소 4 주 동안 그리고 본 시험 기간에 걸쳐 안정적 용량
GERD	
GERD 약물(예: 양성자펌프 억제제 또는 항역류 약물). 예외 참조 [a])	스크리닝 방문 전 최소 8 주 동안 그리고 본 시험 기간에 걸쳐 안정적 용량
비염/상기도 기침 증후군	
비강 코르티코스테로이드, 비스테로이드성 비강 스프레이, 류코트리엔 억제제, 경구 항히스타민제 및 비충혈제거제	스크리닝 방문 전 최소 4 주 동안 그리고 본 시험 기간에 걸쳐 안정적 용량
참고: 코르티코스테로이드가 함유된 점안제와 점이제를 사용할 수 있음	
기타 임상 적응증	
만성 전신(예: 프레드니손) 및/또는 관절강내 코르티코스테로이드 사용	스크리닝 후 4 주 이내에 허용되지 않으며 본 시험 기간에 걸쳐 금지됨 [b]
ACE 억제제 요법	스크리닝 후 12 주 이내 그리고 본 시험 기간에 걸쳐 허용되지 않음
임상시험용 의약품(P2X3 길항제 포함)	시험 요법의 최초 투여 후 3 개월 이내에 허용되지 않으며 본 시험 기간에 걸쳐 금지되거나, 시험 완료 후 30 일 이내에 다른 투여를 받을 계획인 경우; COVID-19 백신은 스크리닝 이전 또는 본 시험을 수행하는 동안 언제든지 허용됨
베타 차단제, NSAID 및 아스피린 함유 제품	이러한 제품으로 이전에 기관지 경련 병력이 있는 경우, 본 시험 기간 동안 금지됨
신경조절제(예: 가바펜틴/프레가발린, 바클로펜, 아미트리프틸린 및 기타 임상 적응증을 위해 복용한 기타 삼환계[기침용 제외])	스크리닝 방문 전 최소 8 주 동안 그리고 본 시험 기간에 걸쳐 안정적 용량

Summary

- Cough non pulmonary disease related cough
  - PND/GERD most common
    - PPI, gastric motility drug, first generation of antihistamine + decongestant
  - Heart problem
  - Ear, psychologic problem, vasculitis rare
  - Cough hypersensitivity syndrome (~40% of chronic cough)
    - Education, laryngeal hygiene, psychologic education, clinical trails

- Thank you