Φλεβική Συμφόρηση
στην Χρόνια Πνευμονική Νόσο

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Patient **with COPD** presents with *peripheral edema /*

respiratory rales and *pulmonary congestion* on CXR

Dilemma :

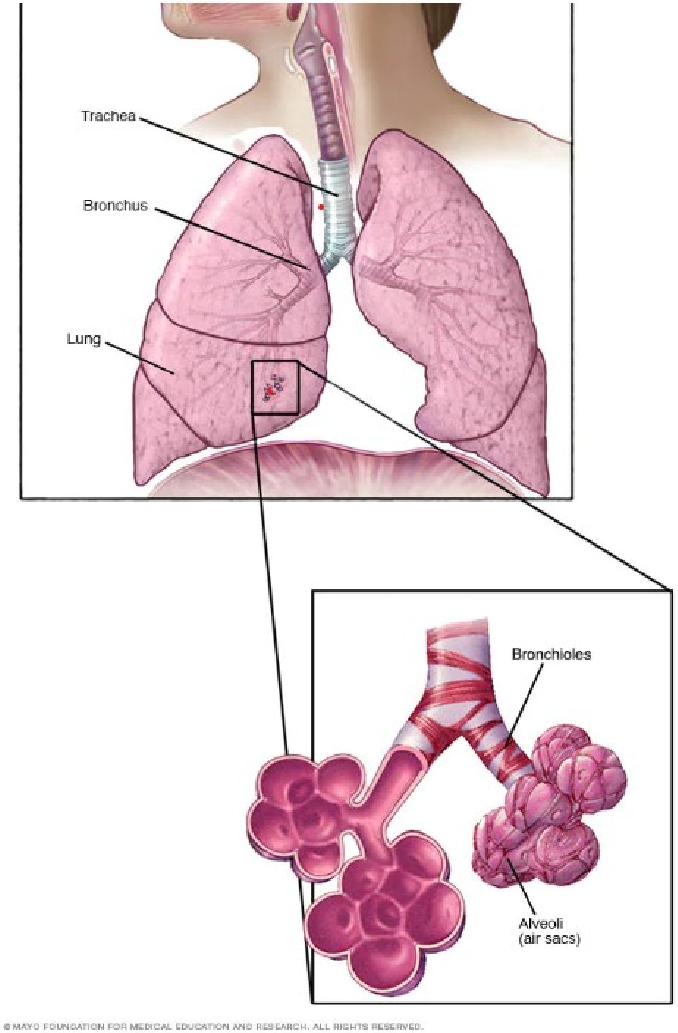
Is this an exacerbation / acute decompensation of Chronic Heart Failure or water retention due to Chronic Lung Disease

?

In this Supplement of the *European Respiratory Journal* special attention is given to the systemic effects of chronic obstructive pulmonary disease (COPD). One of the manifestations of this illness is the development of (sometimes massive) oedema or, for that matter, disturbed volume control. The present paper aims to review some of the mechanisms that are involved in this complication. In that regard, the paper will first focus on the normal regulation of fluid homeostasis.

Eur Respir J 2003; 22: Suppl. 46, 33s–40s
DOI: 10.1183/09031936.03.00000603a

Pre-occupied with lung / bronchi / alveoli (L)



Forget Pulmonary vasculature (R)

Alveoli in the lungs.
Dorling Kindersley / Getty Images

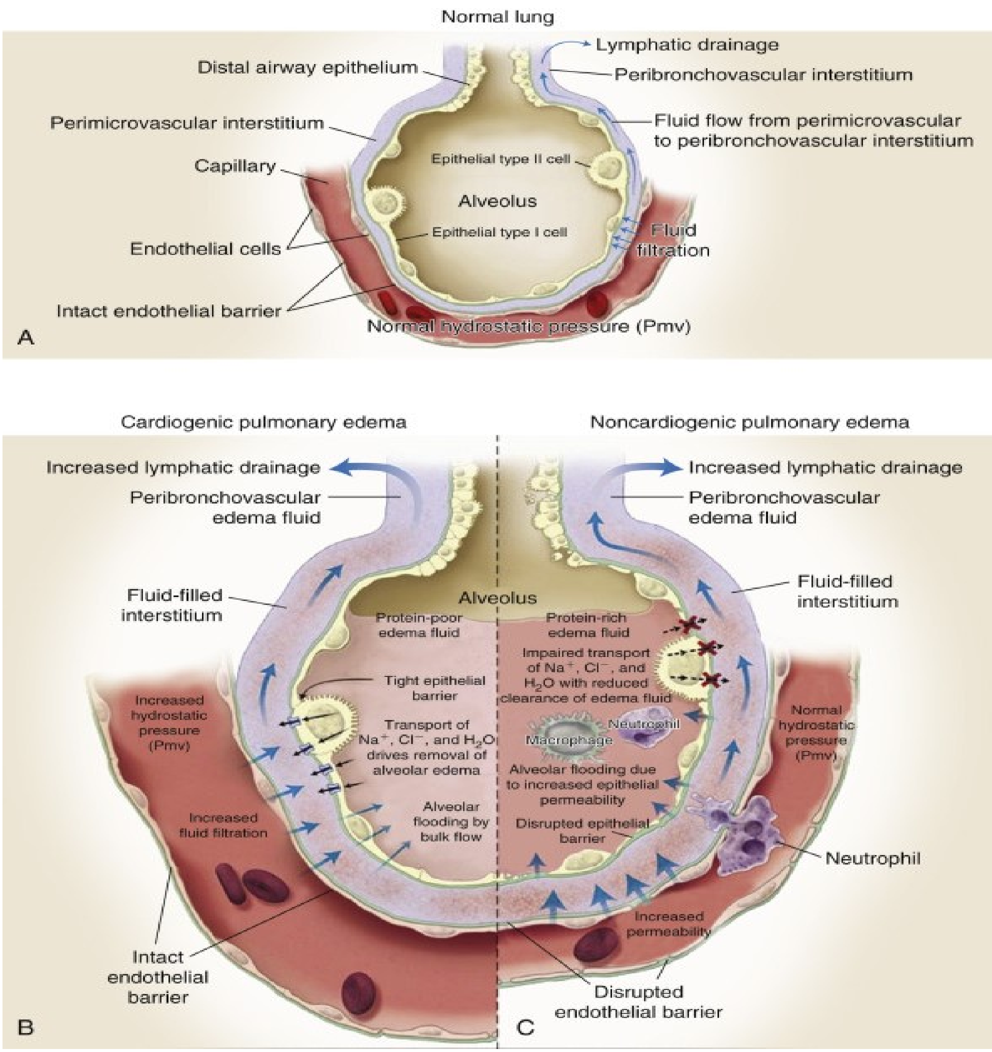
Why the Pulmonary vasculature leaks ?

Cardiogenic

-Increased hydrostatic pressure

- Transudative characteristics

- Oncotic drive



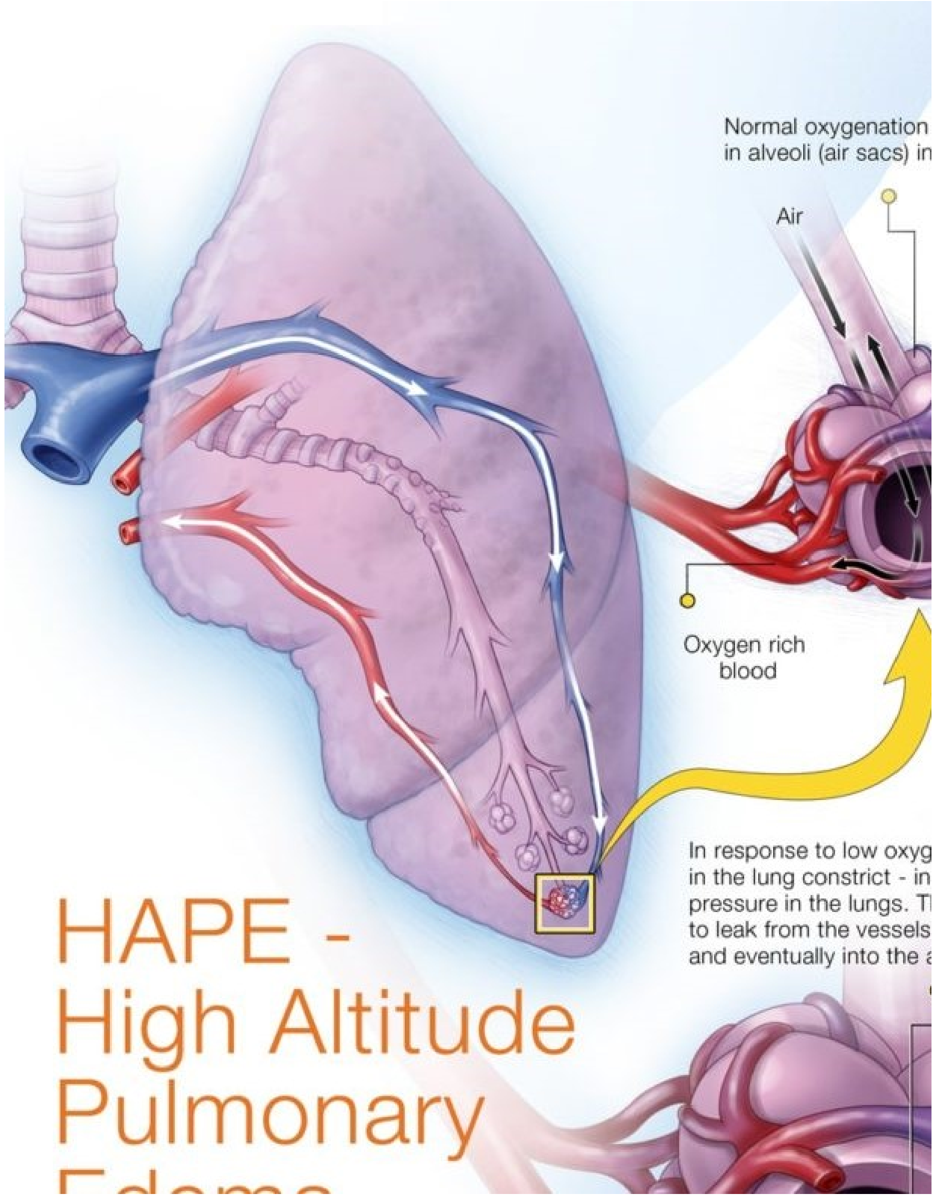
Non-Cardiogenic

-increased permeability

-Exudative characteristics

-Osmotic drive

Are there mixed phenotypes ?



High altitude Pulmonary edema

A mixed phenotype pulmonary leakage

A culprit disease to study…

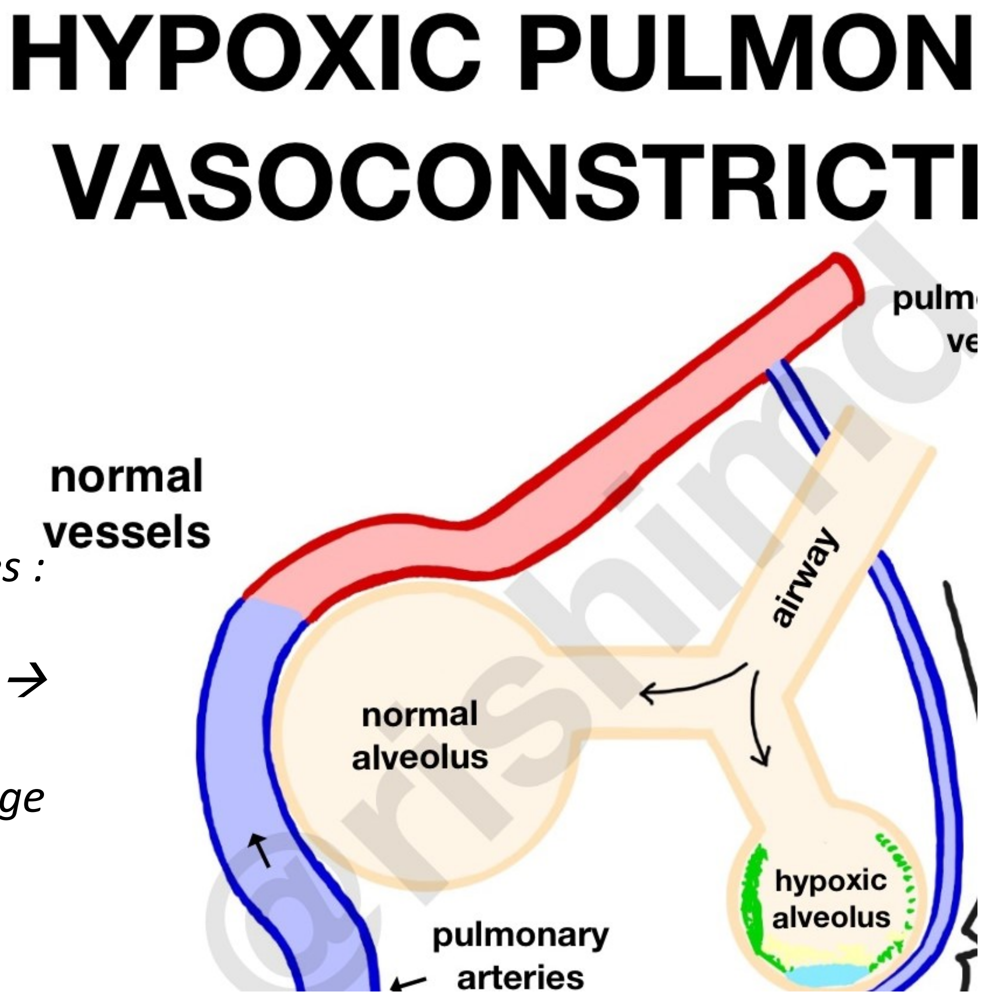
- ❑ Trans-arteriolar leakage due to increased pulmonary pressures
- ❑ Heterogeneous regional hypoxic vasoconstriction
- ❑ Trans-venular leakage due to hypoxia venoconstriction
- ❑ Impaired alveolar fluid clearance
- ❑ Increased permeability of alveolar capillary barrier

Heterogeneous regional in COPD

Higher flows – increased pressures :

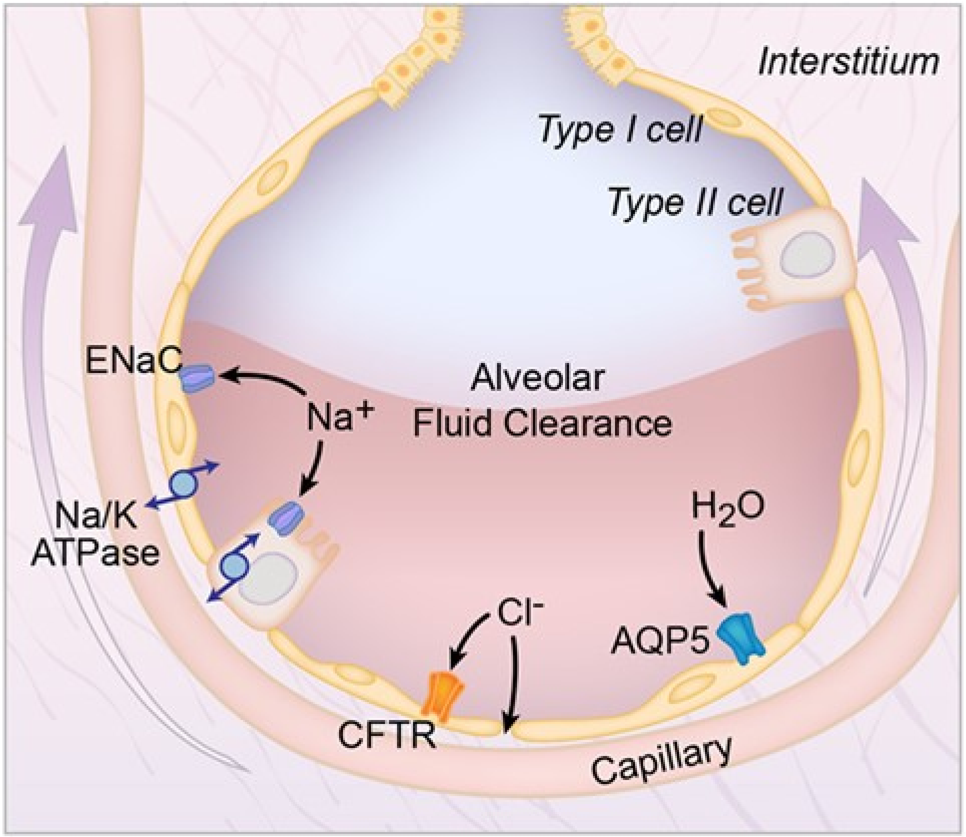
Increased hydrostatic pressures →

Leakage



Alveolar fluid clearance in COPD

Hypoxia decreases the trans-epithelial Na^+ transport reducing activity of ENaC, N/K ATPase and other ion transporters through β2-signaling



Extracellular Volume Increase in COPD

Pathogenesis of Congestive State in Chronic Obstructive Pulmonary Disease

TABLE 2. Water Volumes and Renal Function in Patients With Edema From COPD, Normal Subjects, and Patients With Edema From Myocardial Disease

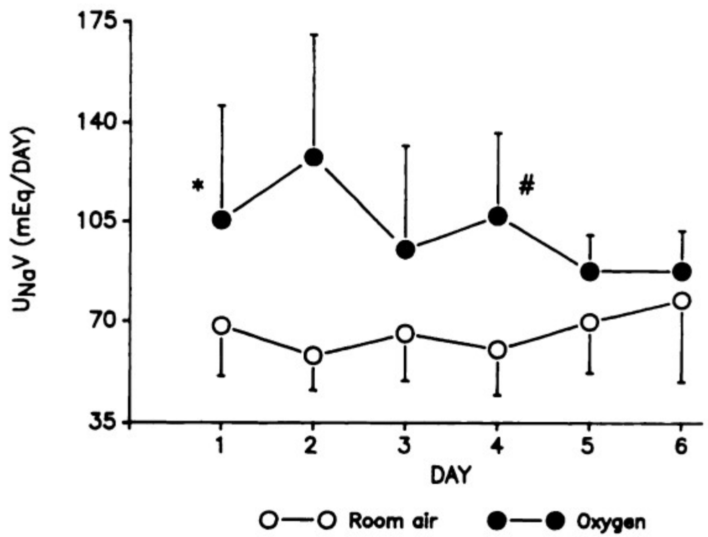
Patients	PV (ml/kg)	PCV (%)	BV (ml/kg)	ECV (ml/kg)	GFR (ml/min · 1.73 m²)	ERPF (ml/min · 1.73 m²)	Serum Na (mmol/l)	TBNaE (mmol/kg)	TBW (ml/kg)
COPD									
1	65.7	47	101.0	311	85	281	130	58	630
2	61.6	52	111.8	468	57	93	138	72	741
3	87.5	58	175.3	279	73	144	130	71	636
4	38.9	53	71.7	282	69	201	126	52	585
5	27.1	62	58.3	223	21	46	128	52	547
6	73.2	47	123.3	401	36	76	134	70	708
7	51.2	60	106.4	254	117	363	132	66	621
8	103.3	58	207.1	496	58	142	140	...	773
9	53.8	50	94.2	243	90	241	139	54	601
Mean	62.5	54.1	116.6	329	67.4	176.2	133	61.8	649.2
SEM	1.4	1.8	15.8	31.7	9.0	32.8	1.3	3.0	23.7
n	9	9	9	9	9	9	9	8	9
Normal subjects									
Mean	43.2	45.6	71.6	227.0	99.0	479.0	139	44.7	536.0
SEM	3.0	1.3	5.7	13.0	3.0	19.0	1	1.9	20.0
n	11.0	7	11	11	9	11	11	10	9
p (vs. COPD)	0.024	0.0032	0.0032	0.007	0.005	0.0001	0.002	0.0002	0.0026
Congestive heart failure									
Mean	57.9	39.3	87.7	301.0	65.00	140.0	133	61.3	623.0
SEM	2.9	1.6	4.0	24.0	8.00	25.0	2.0	3.3	24.0
n	6	6	7	6	6	6	7	8	7
p (vs. COPD)	0.65	0.0001	0.17	0.57	0.87	0.46	0.44	0.90	0.47

(*Circulation* 1992;86:12–21)

Renal Sodium Retention in COPD

The Effect of Oxygen on Sodium Excretion in Hypoxemic Patients with Chronic Obstructive Lung Disease*

Hypoxia results in sodium retention in patients with COPD



(Chest 1990; 97:840-44)

Renal Hemodynamics / GFR in COPD

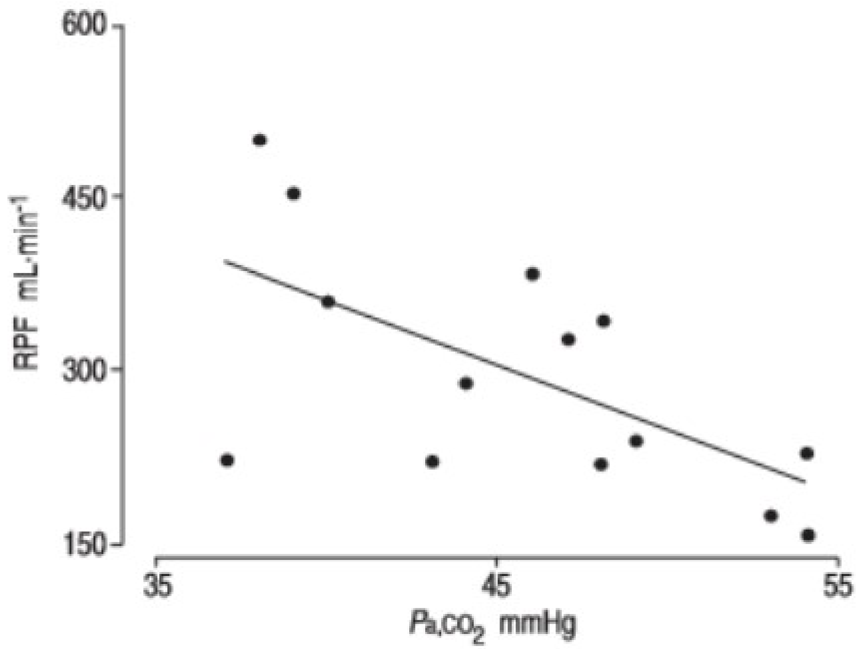
Fluid homeostasis in chronic obstructive lung disease

Hypoxia + Hypercapnia reduces Renal Blood flow

GFR remain constant

Filtration Fraction is increased

→ Increased Sodium Re-absorption



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Tubular Function in COPD

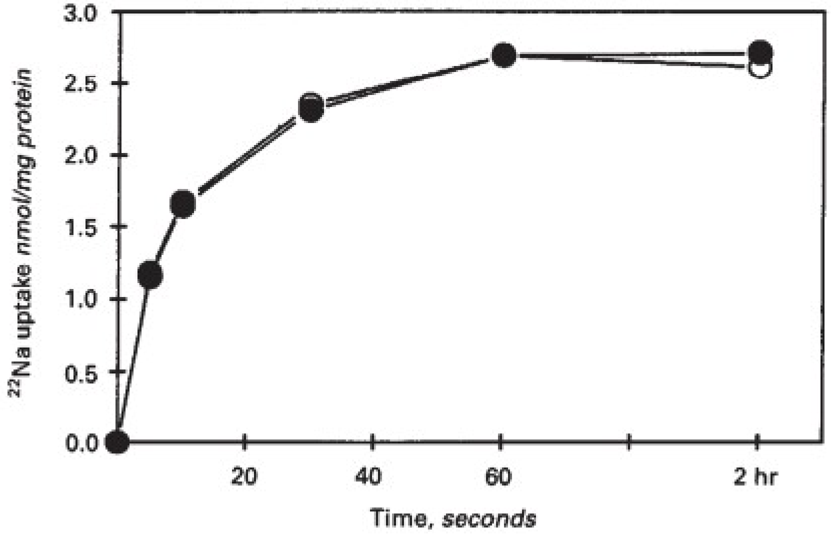
Regulation of Na/H exchange in renal microvillus vesicles in chronic hypercapnia

Hypercapnia leads to respiratory acidosis

Activation of Carbonic Anhydrase
& Activation of Na^+/H^+ transporter in proximal tubules

Excretion of H+ / Re-absorption of $HCO3^-$

→Increased Sodium Re-absorption



Kidney International, Vol. 34 (1988), pp. 60–66

Neurohormonal factors in COPD

Adrenergic system

Renin-Angiotensin-Aldosterone

Endothelin

Prostoglandins

Vasopressin

ANP

Dopamine

Vasoconstriction
Sodium Retention

Vasodilation
Sodium Excretion

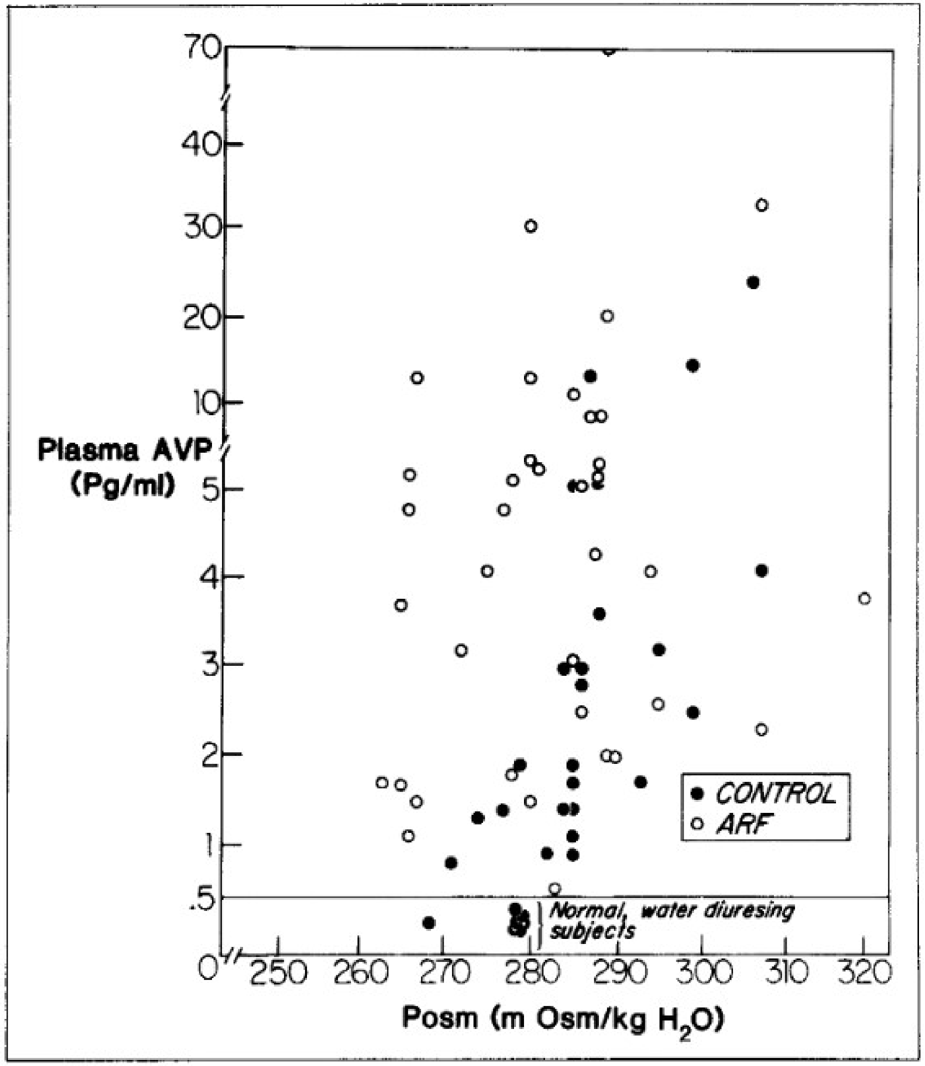
Hypoxia + Hypercapnia

Neurohormonal factors in COPD

Hypoxia → increased AVP

Inappropriately high compared to hyponatremia or hypoosmolality levels

Other non-osmotic stimuli lead to AVP secretion



April 1982 The American Journal of Medicine Volume 72 583

Theories for Venous Congestion in COPD

Renal Theory

Sodium retention mainly through hypercapnia → respiratory acidosis → Na/H+ transport

Renal Vasoconstriction → Sodium Retention

Cardiac Theory

Hypoxia → Pulmonary Vasoconstriction / Pulmonary Hypertension / Right Heart Failure → Venous Congestion

Vascular Theory

Hypercapnia → Peripheral Vasodilation → ↓ Systemic Vascular Resistance → Baroreceptors → Hormonal Activation

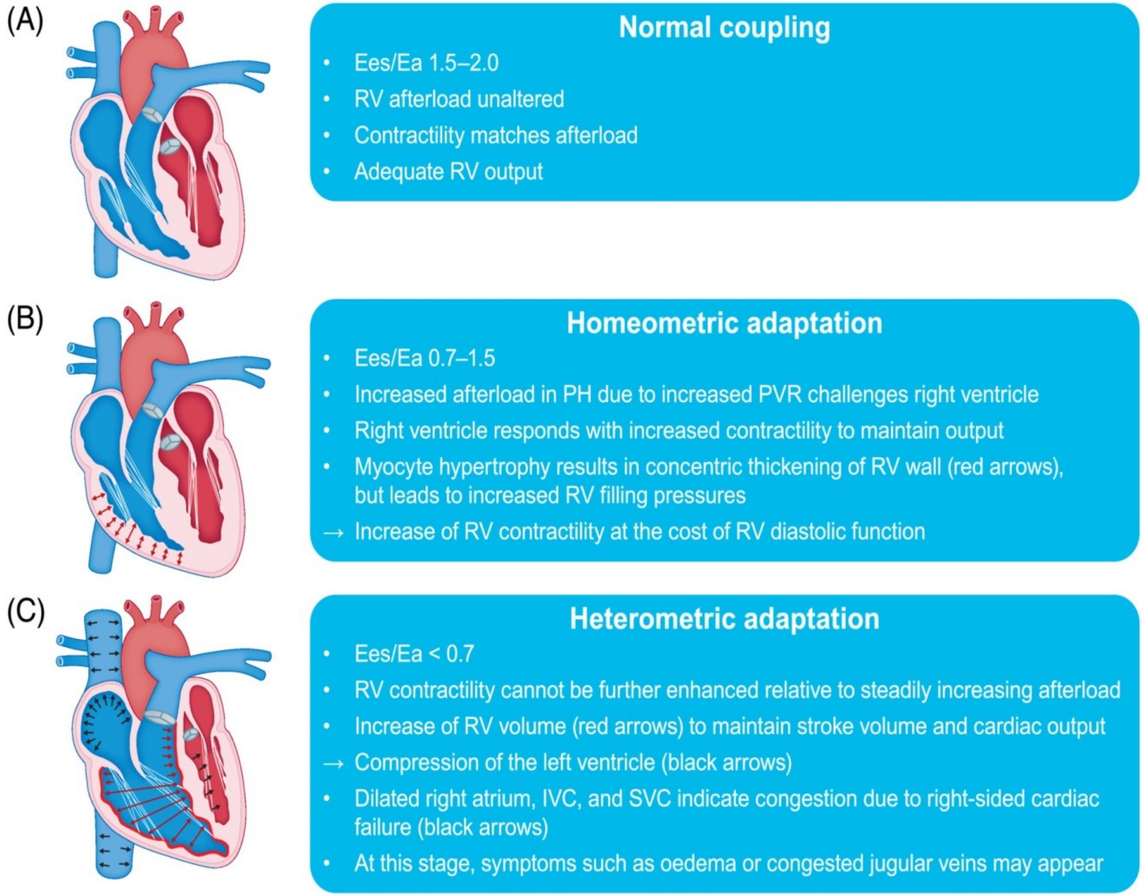
Pulmonary Theory

Hypoxia → Pulmonary Vasoconctriction → Heterogeneous regional hypoxic vasoconstriction + Impaired alveolar fluid clearance + Leakage

Cardiac Theory

Cor Pulmonale is rare in patients with COPD

RV / PA uncoupling is a more sensitive and early measure for Right Heart Failure



Lessons up to now

In patients with COPD there is a possibility for

Water and Sodium retention in pulmonary circulation

Water and Sodium retention in systematic venous circulation

OR

In patients with COPD there is a possibility for

Non-cardiogenic Venous Congestion

Non-Cardiogenic Pulmonary edema

How I (cardiologist) think

In a patient with a COPD medical history or a clinical profile for COPD

\+ Respiratory acidosis (hypoxia + hypercapnia)

\- Reduced LV Ejection fraction

\- Increased LA pressures with normal LV Ejection Fraction

\- Structural Heart Disease (CM or valvular disease)

\+ Right Heart Failure or Increased Pulmonary Hypertension

\+ RV – RA uncoupling (TAPSE / PASP < 0.31 mm/mmHg)

→ **Venous Congestion** or **Pulmonary Congestion** is of
PULMONARY ORIGIN

How you (Pulmonologist) should think

Table 1 Common findings at pulmonary function test in patients with HF, according to clinical status, comorbidities, and treatment

	Acutely decompensated or severe HF	At discharge after acute HF decompensation	Stable HF	Nonselective beta-blockers	HF + smoking history	HF + COPD	COPD without HF
References	[29, 92–94]	[13••, 92, 95]	[13••, 28, 82, 95, 96]	[81, 82, 97, 98]	[28]	[5, 13••, 98, 99]	[100]
FEV_1 (% predicted)	↓↓ (48–73%)	↓ (72–85%)	↓ = (90%)	=↓	↓↓ (65%)	↓↓↓ (54–64%)	Various degrees of ↓ according to disease severity
FVC (% predicted)	↓ (57–86%)	↓ = (83–92%)	↓ = (90%)	=	↓ (73%)	↓ (75–78%)	=↓
FEV_1/FVC (%)	↓ = (60 to >80%)	↓ = (64 to >80%)	=(80%)	=↓ (>70%)	↓ (69%)	↓↓ (63%)	↓↓ (<70%)
$FEF_{25–75}$ (% predicted)	↓↓↓ (32–65%)		↓ = (70–90%)		↓↓↓ (49%)		
DLCO (% predicted)	↓↓ (49 to >90%)		↓ = (80–90%)	↓ (80%)	↓↓ (72%)	↓↓ (56%)	↓=
RV (% predicted)		=(100%)	=				↑
ITGV (% predicted)		=(105%)	=				↑
TLC (% predicted)		=↓ (95%)	=↓				↑

Interval of percentage of predicted values taken from cited studies are reported between brackets

HF heart failure, *COPD* chronic obstructive pulmonary disease, *ITGV* intrathoracic gas volume, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, $FEF_{25–75}$ forced expiratory flows at 25–75% of the pulmonary volume, *DLCO* diffusing lung capacity for carbon monoxide, *RV* residual volume, *TLC* total lung capacity

How you (Pulmonologist) should think

Table 2 Time-related changes of pulmonary function tests in patients with HF only, COPD only, and HF + COPD

	Soon after decompensation		Months after recompensation	
	FEV_1/FVC	FEV_1	FEV_1/FVC	FEV_1
HF only	< or >0.7	↓	>0.7	=
HF + COPD	<0.7	↓↓↓	<0.7	↓↓
COPD only	<0.7	↓↓	<0.7	↓↓(↓)

As shown, the FEV_1/FVC ratio soon after decompensation might not accurately discern between patients affected by HF only and those affected by a combination of HF and COPD, while repeated testing in stable clinical condition can. Similarly, at discharge after HF decompensation, FEV_1 may overestimate the severity of an eventual concomitant obstructive ventilatory disease, which would be resized in clinically stable conditions. "COPD only" patients will always have a FEV_1/FVC of <0.7 at repeated testing in clinically stable conditions, but they should display stable or even worsened FEV_1 values, up to −100 mL per year

Does it matter ?

Diuretics use :

- Reduction in intravascular volume → Viscious cycle of peripheral vasodilation → hormonal activation

- Hyponatremia → increase secretion of renin and AVP

- Hypochloremic metabolic alkalosis due to volume contraction → reduce respiratory drive → hypoxemia → more water and sodium retention

Diuretic Resistance / resilient edema / difficult to treat
Hypoxia and Hypercapnia

What to do in COPD edematous patients ?

Table 1. - Therapeutic interventions for "Cor-pulmonale" in COPD

Therapeutic intervention	Note
• Oxygen Supplementation	• It is the mainstay of treatment. The lowest dose (FiO_2 24%), to keep oxygen saturation > 90% should be used, in order to limit respiratory acidosis
• Bronchodilatators	• The highest possible broncho-dilatation should be promoted
• Water restriction	• Usually results in stabilization and slight increase in plasma Na^+
• Corticosteroids	• The use of these drugs should be limited because induces Na^+ retention
• NIV	• May reduce arterial CO_2. More studies are needed
• Diuretics	• To be avoided. The use of diuretics may results in metabolic alkalosis and hypoventilation
• Digitalis	• Not to be used. May expose to arrhythmias
• ACE-inibitors	• The use of these drugs is still debated

+ acetazolamide / SGLT-2 inhibitors ?