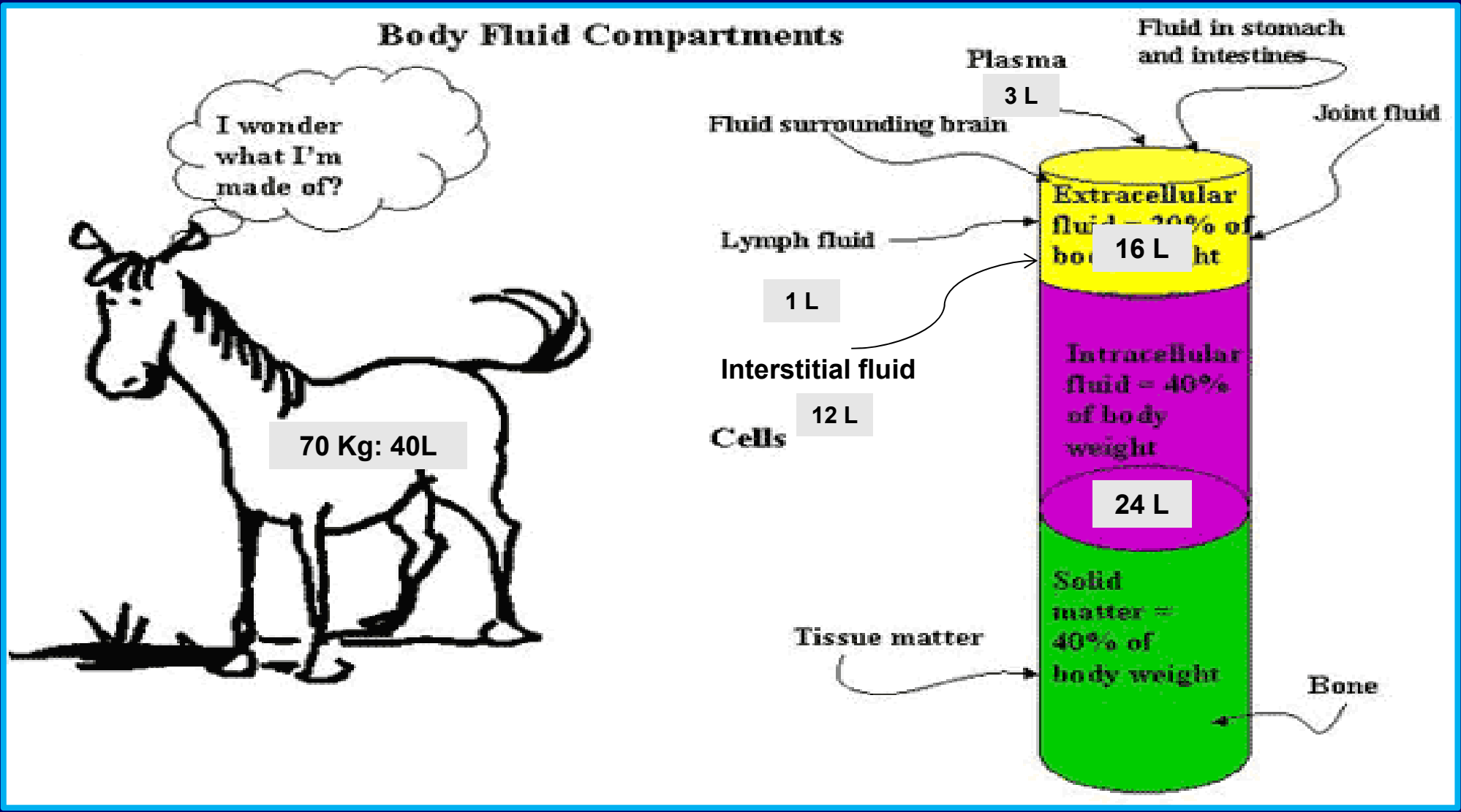
2012 순환기 춘계통합학술대회

Edema in Heart Failure
: Pathophysiology & Management

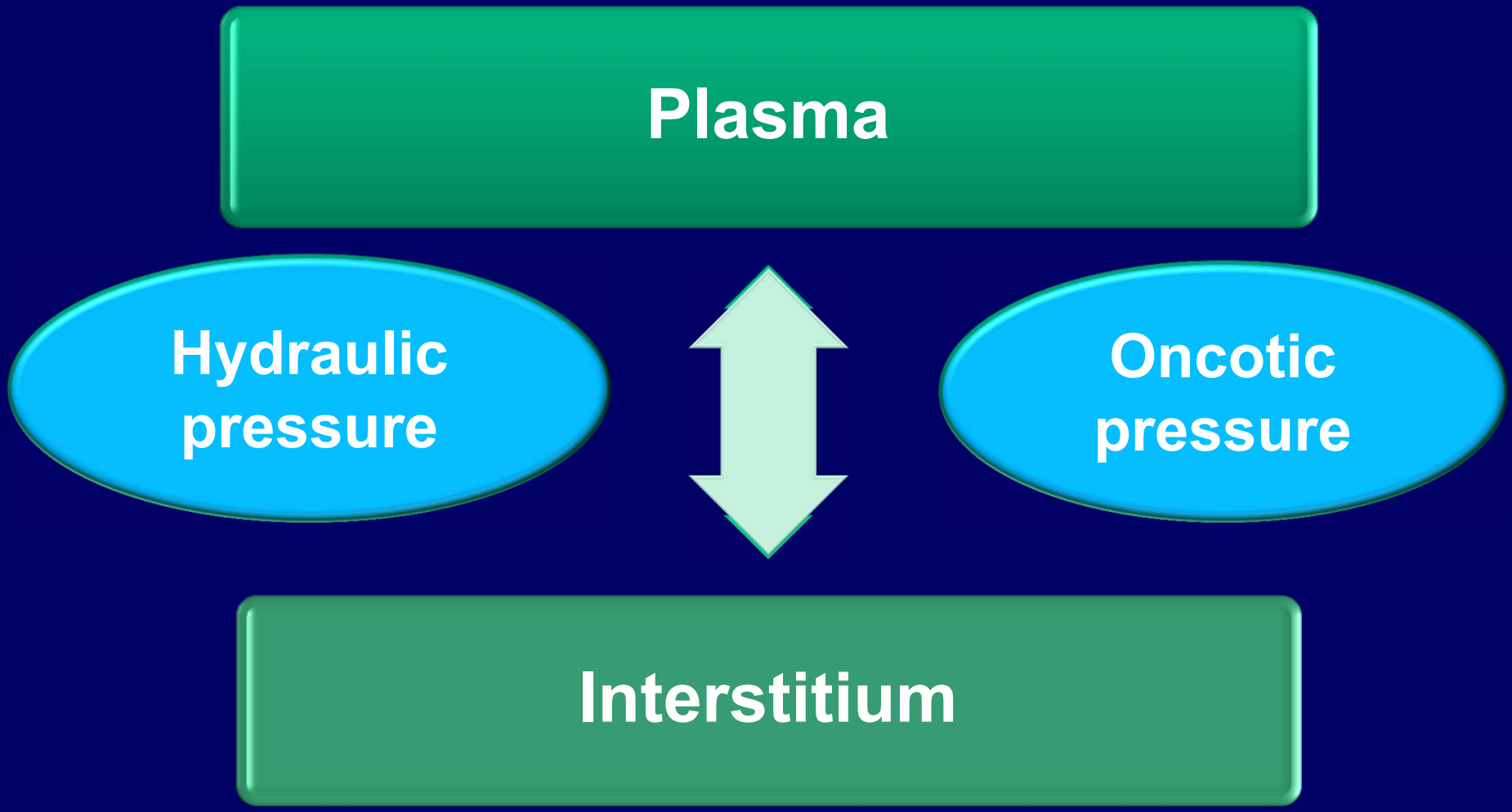
김 계 훈

전남의대 순환기내과

Body Fluid Compartments



Water Exchange or Balance: Starling's Law



Water Exchange or Balance: Starling's Law

$$\textit{Net filtration} = \textit{LpS} \times (\Delta\ \textit{hydraulic pressure} - \Delta\ \textit{oncotic pressure})$$

$$= \textit{LpS} \times [(\textit{Pcap} - \textit{Pif}) - \textit{s}(\textit{ncap} - \textit{nif})]$$

Lp = unit permeability of the capillary wall

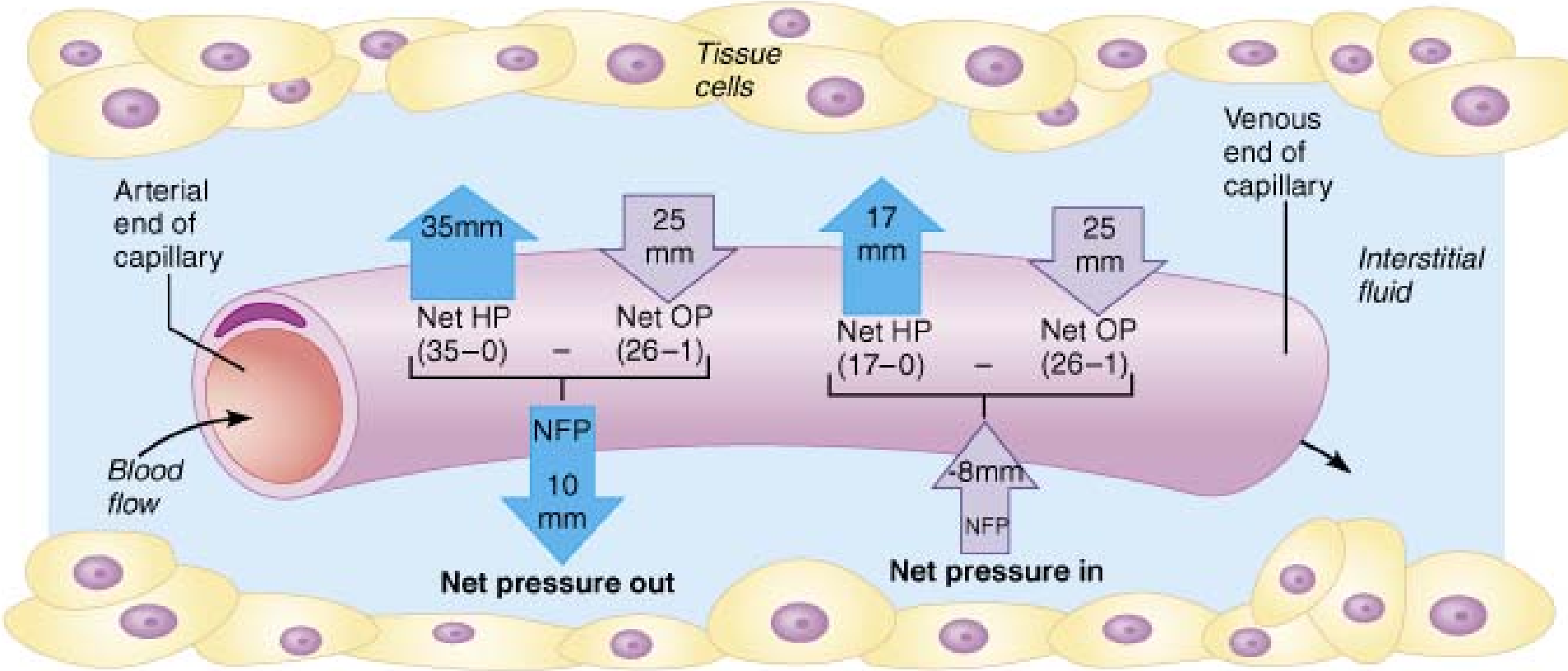
S = surface area for fluid movement

Pcap & Pif = capillary & interstitial fluid hydraulic pressure

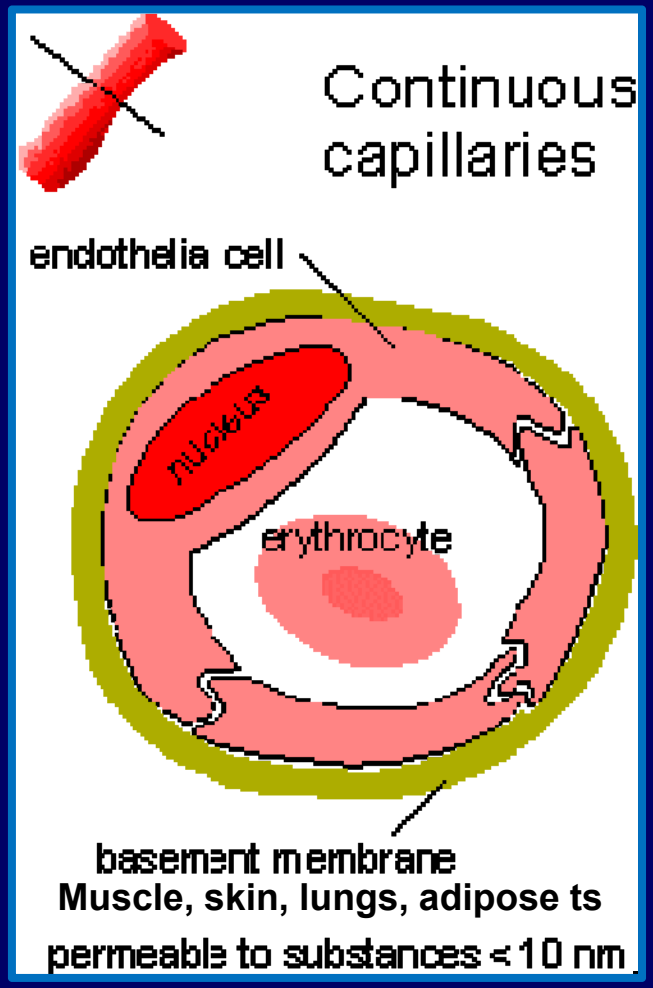
ncap & nif = capillary & interstitial fluid oncotic pressures

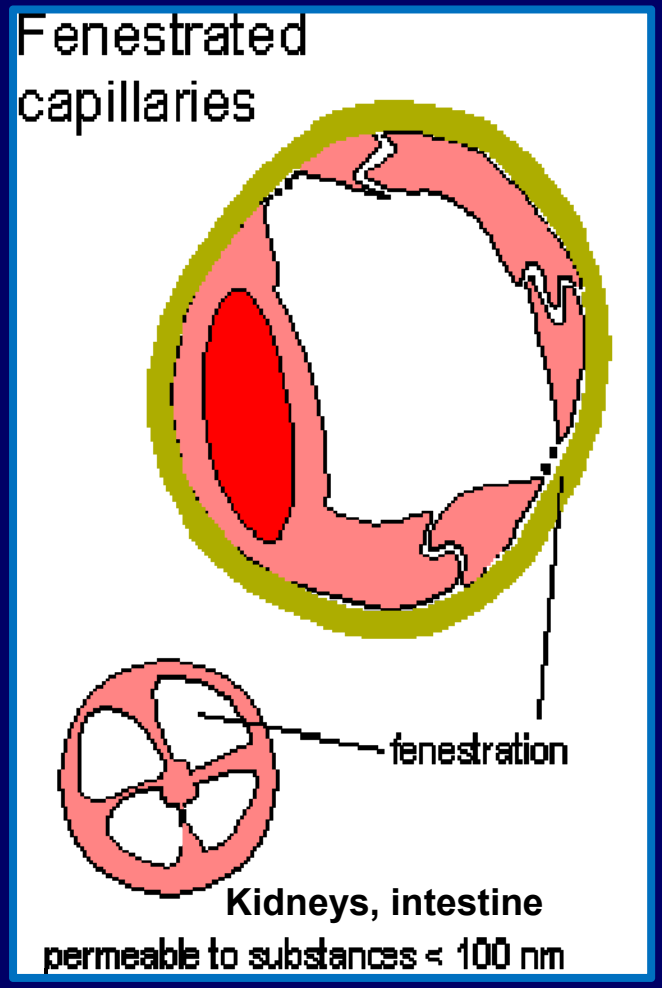
S = reflection coefficient of proteins across the capillary wall (0~1)

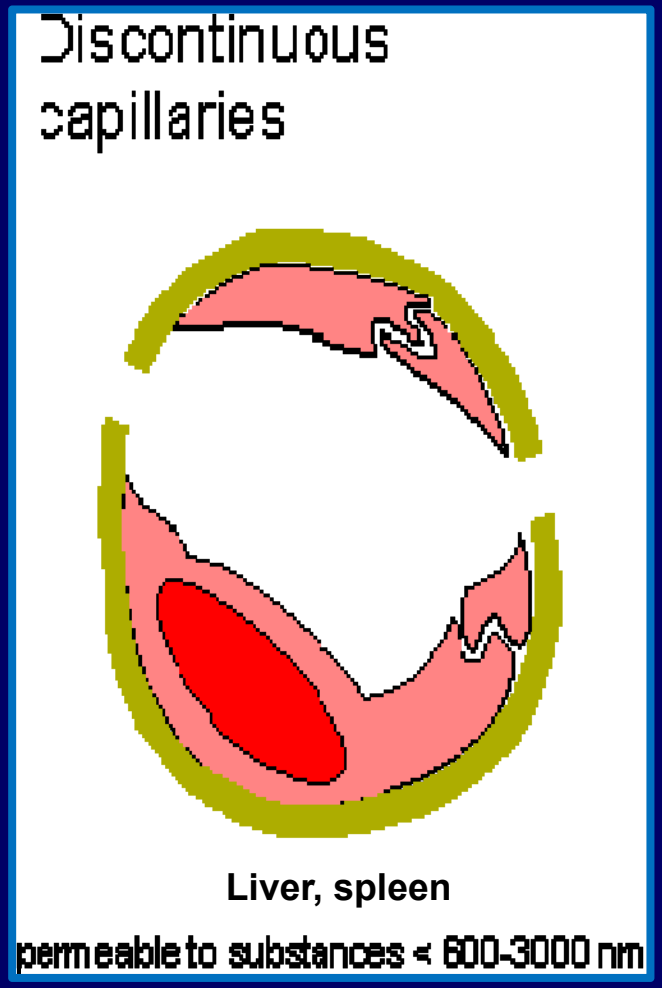
Water Exchange or Balance: Starling's Law



Water Exchange or Balance: Capillary Permeability







Definition: What is Edema?

- A palpable swelling from fluid accumulation in body tissues (interstitial space or cavities of the body) produced by the expansion of the interstitial fluid volume
- Does not include fluid within the bladder or in the gastrointestinal tract (gut)
- May be generalized or localized

Edema Terminology

- Peripheral edema
- Edema in 3rd spaces

  : Pleural effusion, pericardial effusion, ascites
- Pulmonary edema

  : Accumulation of fluid in the interstitial air spaces (alveoli)
- Anasarca

  : Severe, widespread accumulation of fluid in the all of the tissues and cavities of the body at the same time

Types of Edema

- Pitting edema

  : Swelling of a body p

  after pressure is app

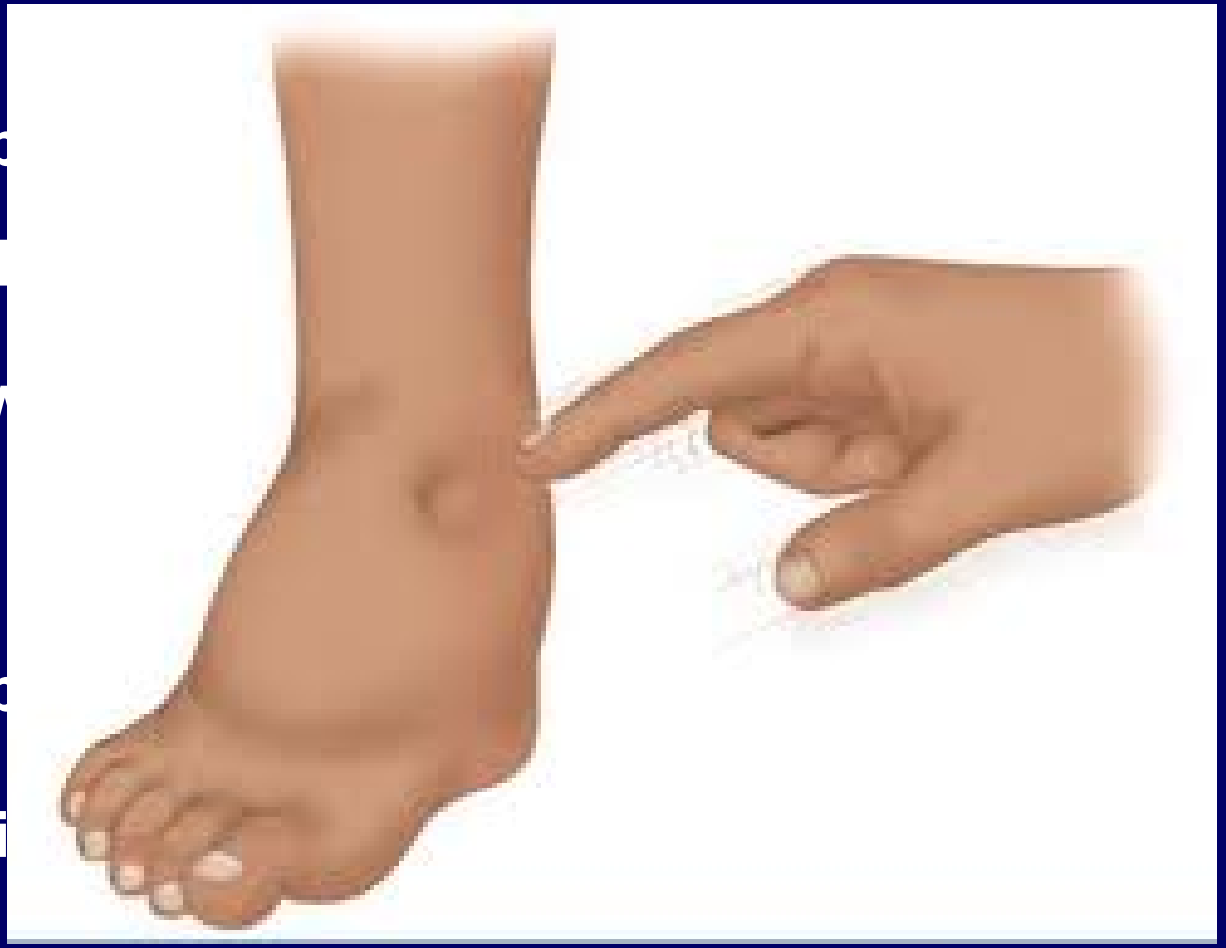
  : Indentation will slow

- Non-pitting edema

  : Swelling of a body p

  : Lymphedema, pre-ti

  : Diuretics are generally not effective



Etiologic Mechanisms of Edema Formation

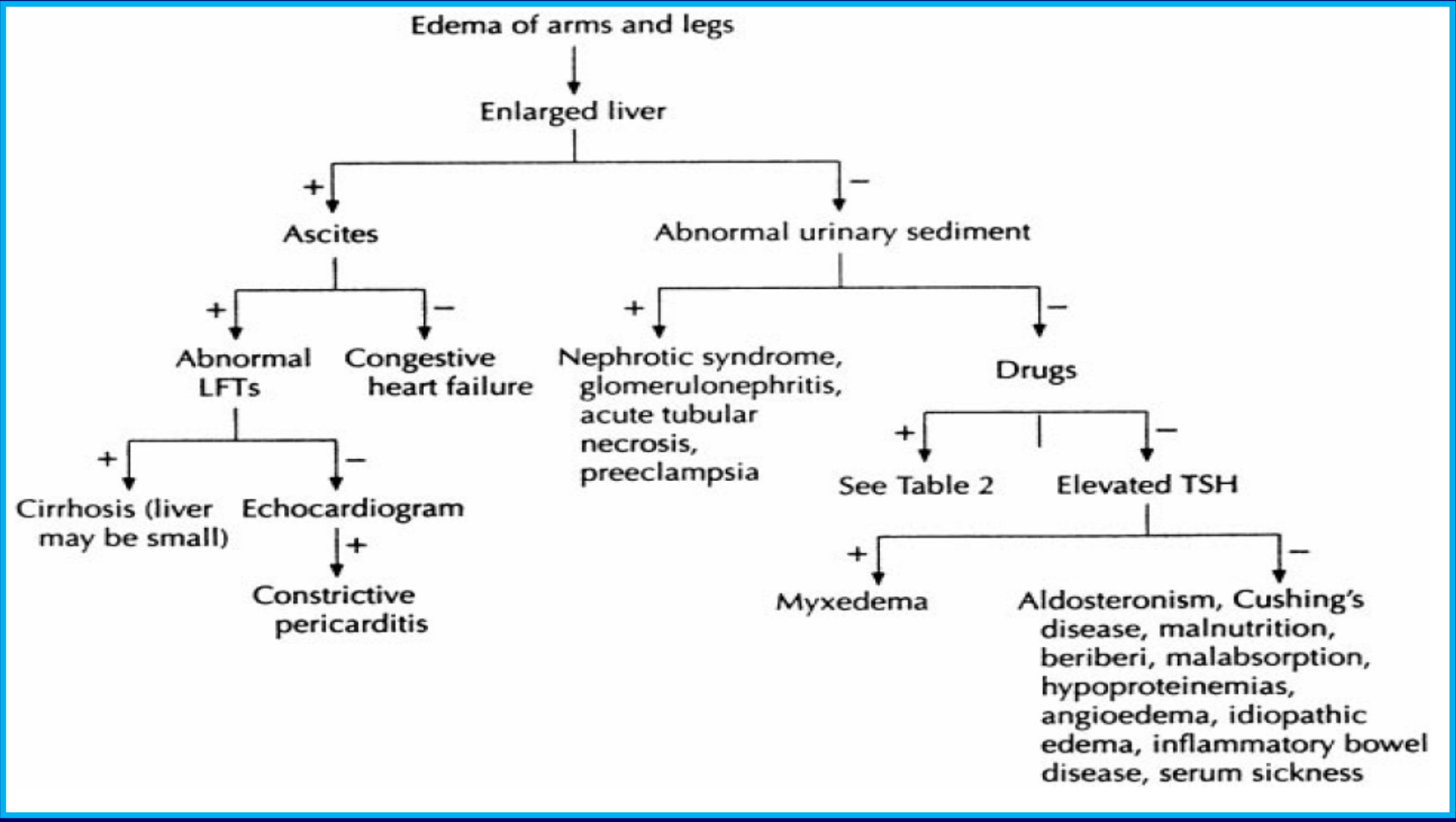
- Heart failure
- Cirrhosis
- Nephrotic syndrome
- Capillary leak syndrome

Generalized edema

- Venous obstruction
- Lymphatic obstruction

Localized edema

Evaluation of the Patients with Edema



Pathophysiology of Edema: Two Basic Steps

Alteration in capillary haemodynamics

: Movement of fluid from intravascular space into interstitium

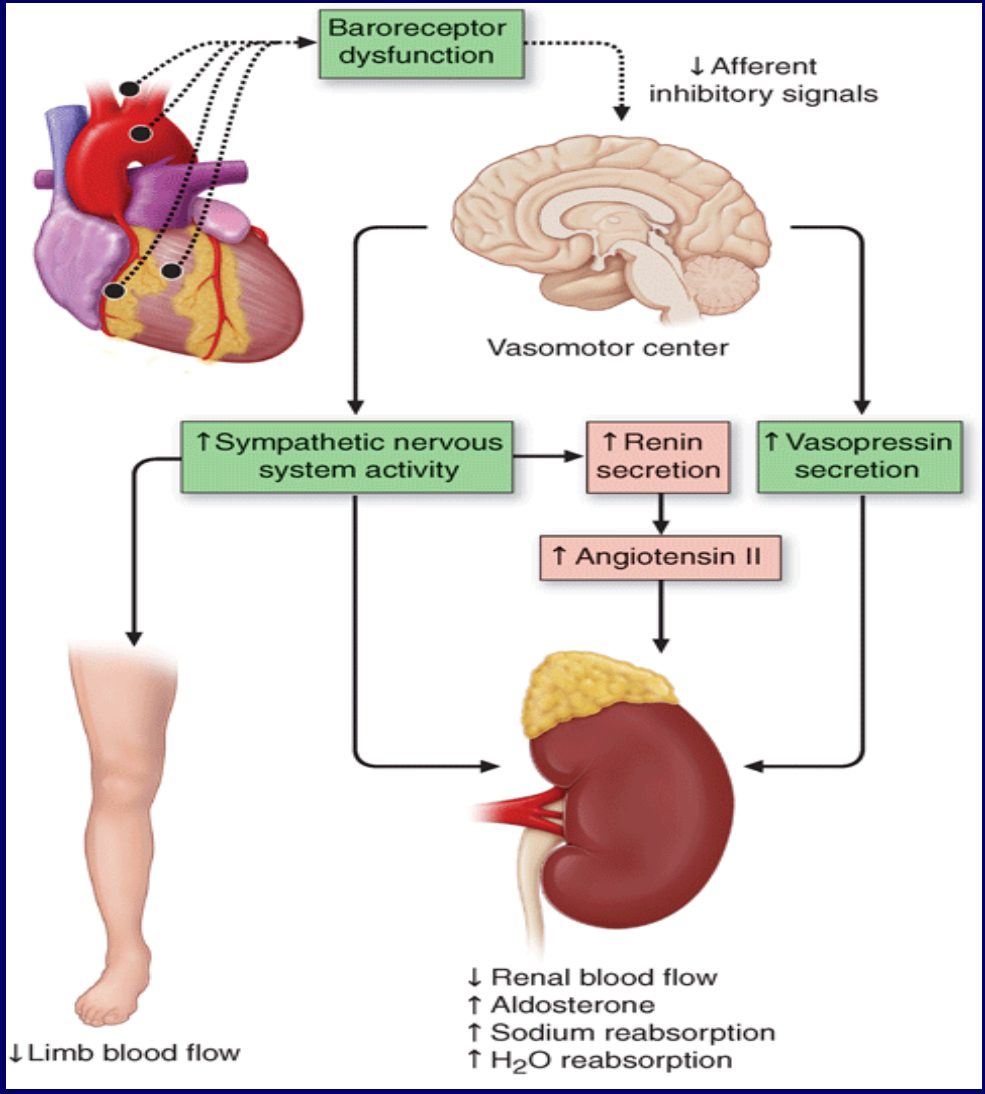
Retention of dietary or intravenously administered sodium and water by the kidneys

Neurohormonal Activation in CHF and Edema

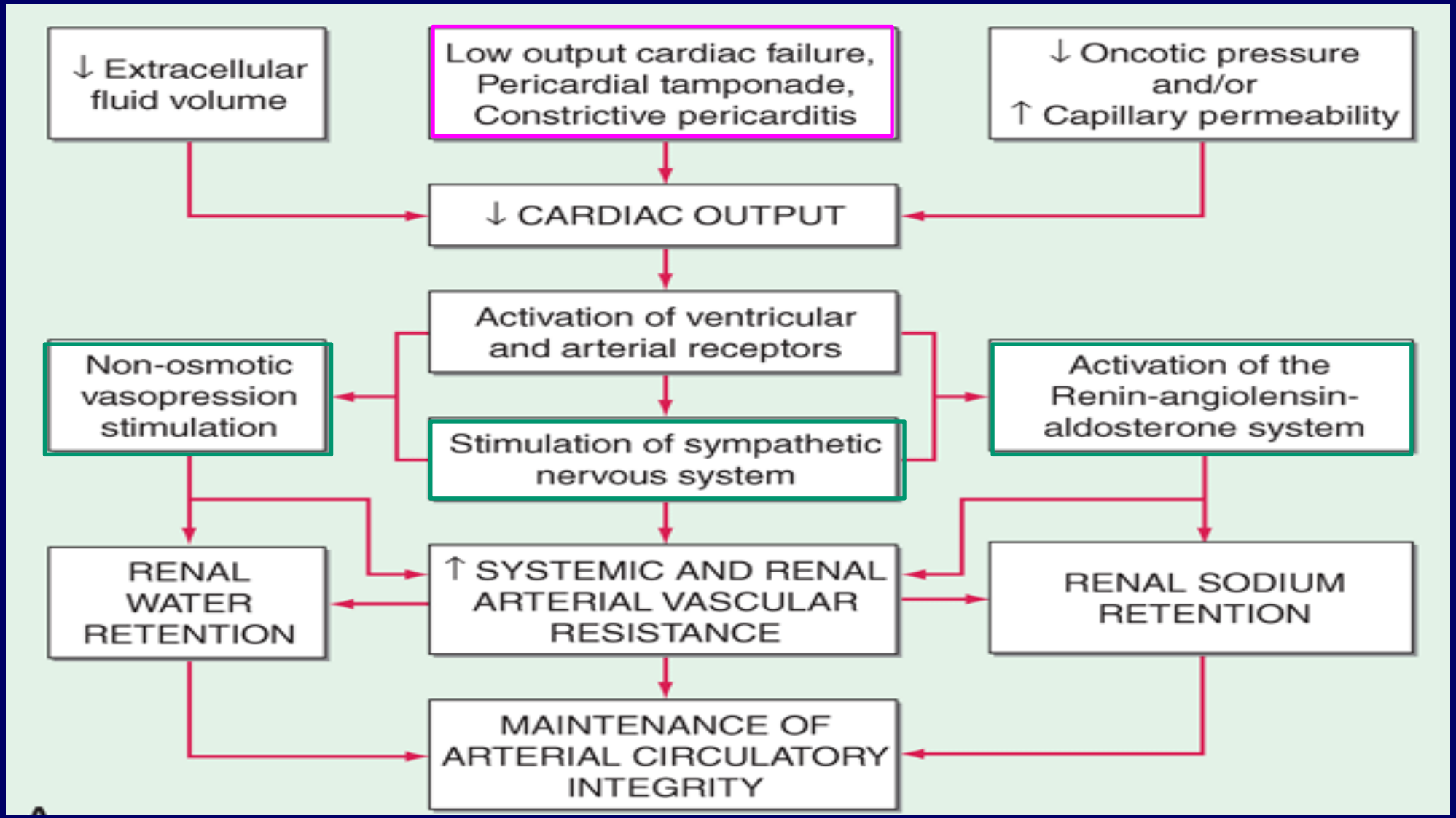
Decreased CO in HF

↓

Unloading of high pressure baroreceptors

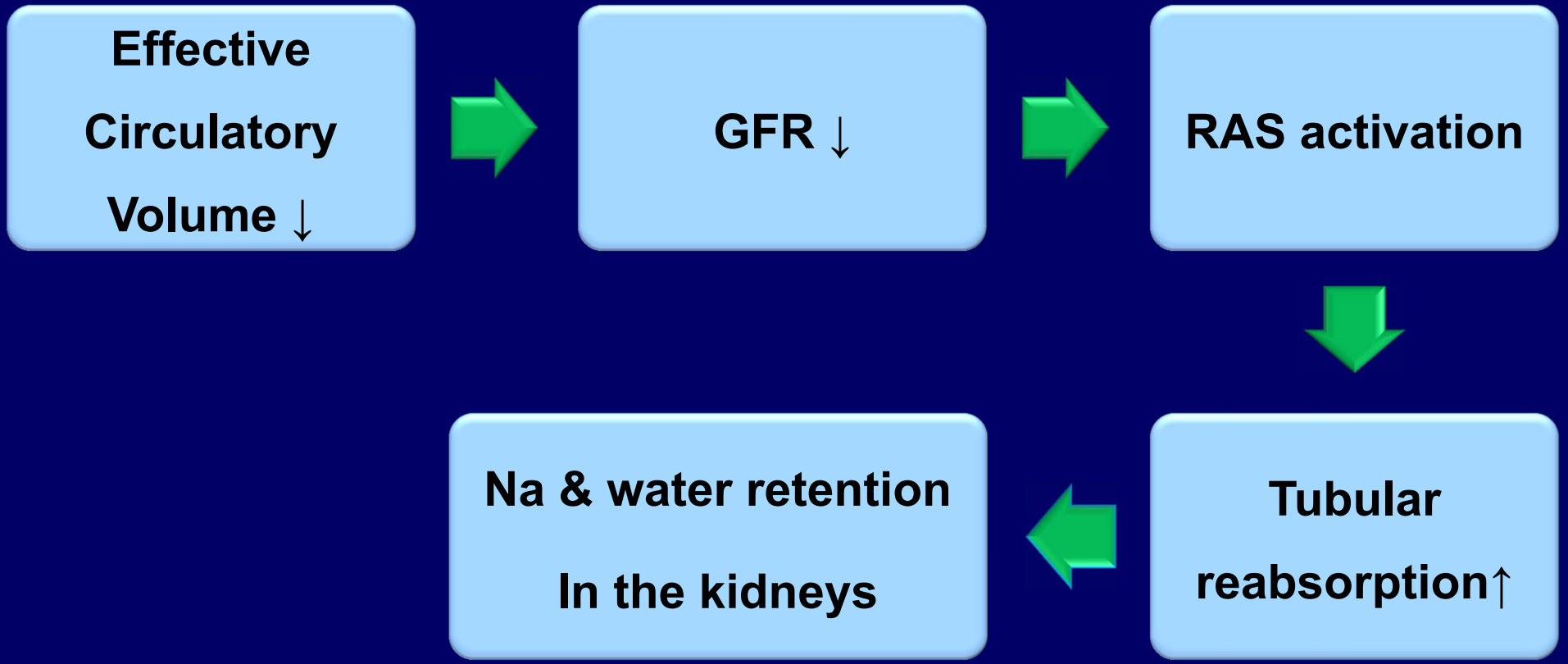


Pathophysiologic Mechanism of Edema in CHF

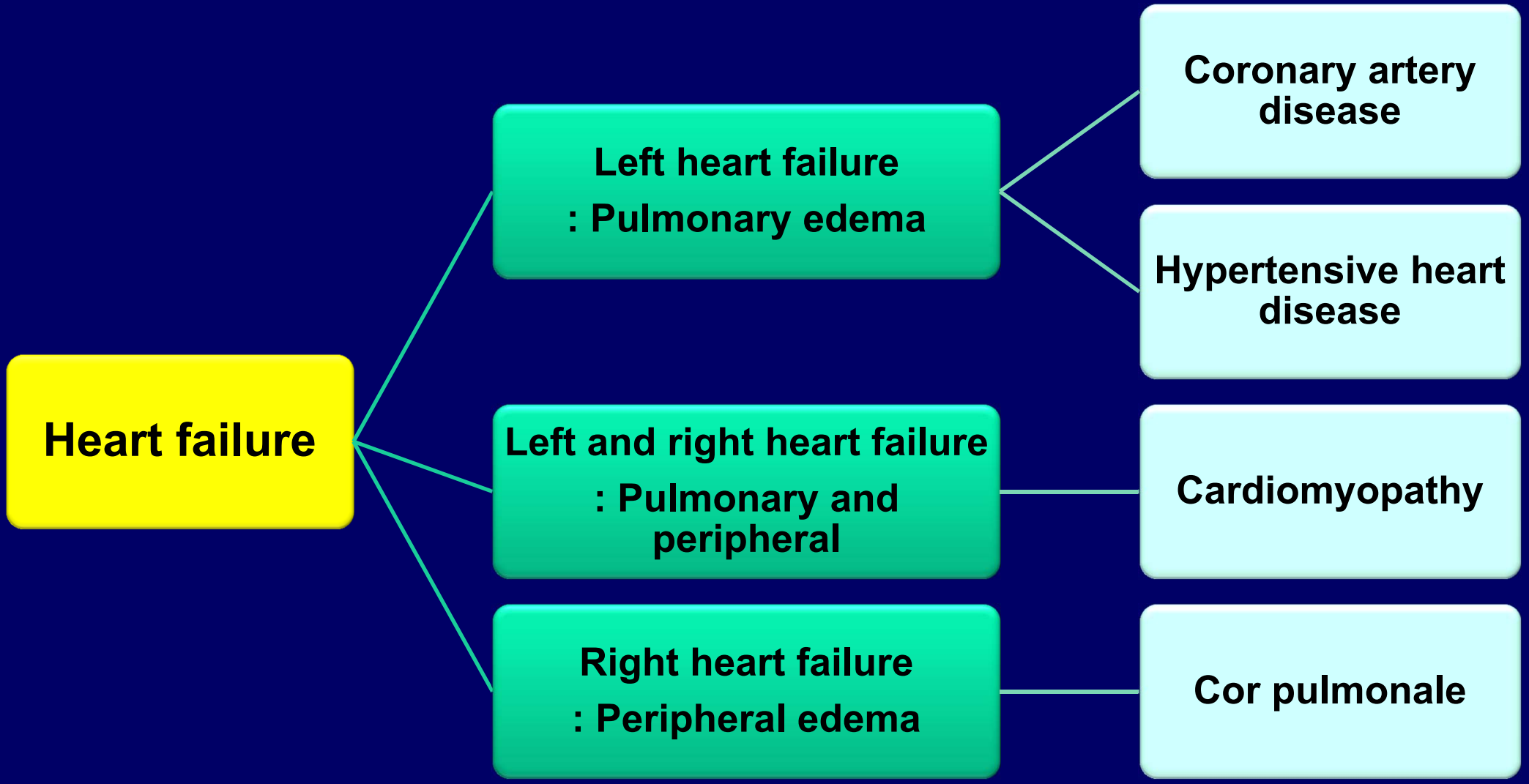


Renal Sodium Retention in CHF

- Cadiac output is reduced, kidney attempts to restore the effective circulating volume by Na and water retaining



Site and Nature of Edema in Cardiac Diseases



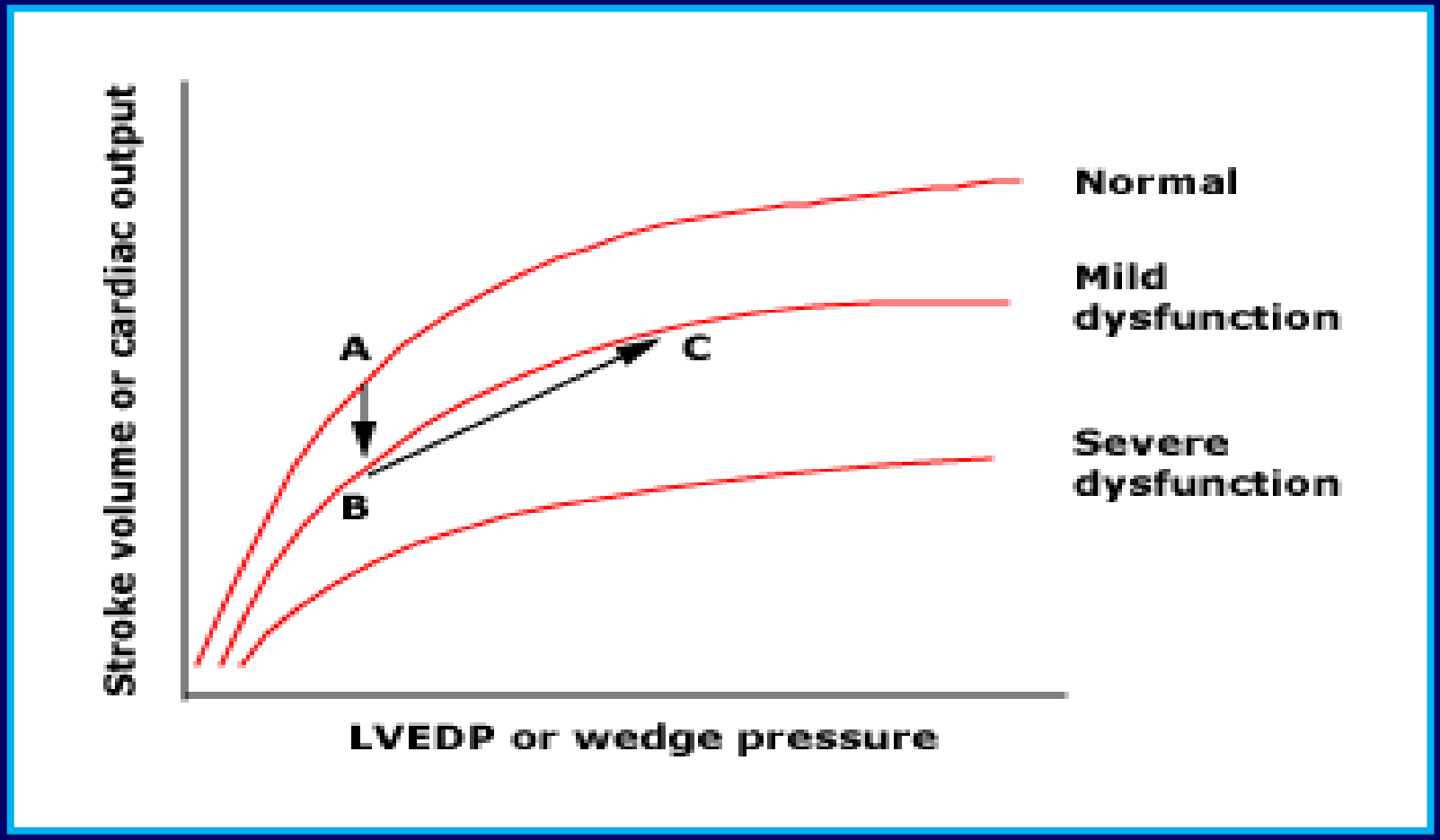
Edema in Chronic Heart failure

- **Forward hypothesis**

  : Plasma expansion

↓Cardiac output → Activation of sympathetic and RAAS system → ↑LVEDP : sufficient level to produce pulmonary edema

Frank Starling Curves in Heart Failure



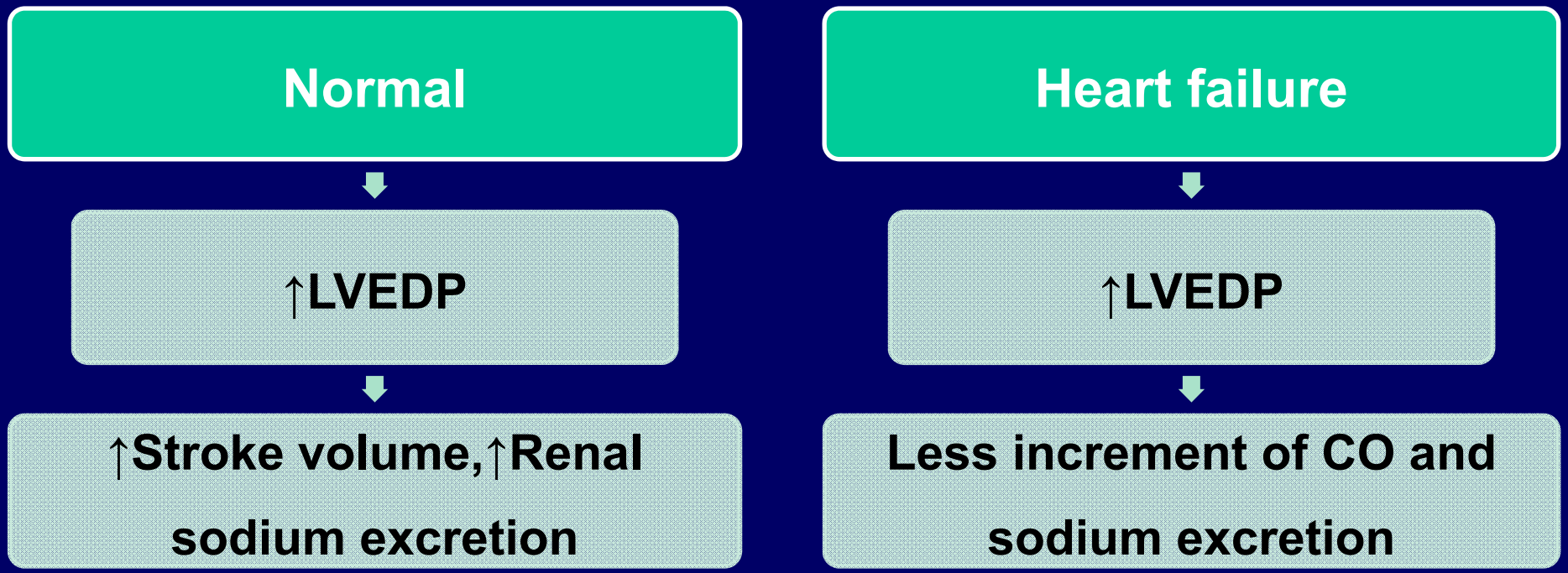
- Increments in plasma volume and LVEDP will augment cardiac output in cardiac dysfunction

Edema in Chronic Heart Failure

- **Mild to moderate heart failure**

  : Well preserved cardiac output with mild renal impairment of sodium excretory ability

  : No edema with dietary sodium restriction !



Edema in Chronic Heart failure

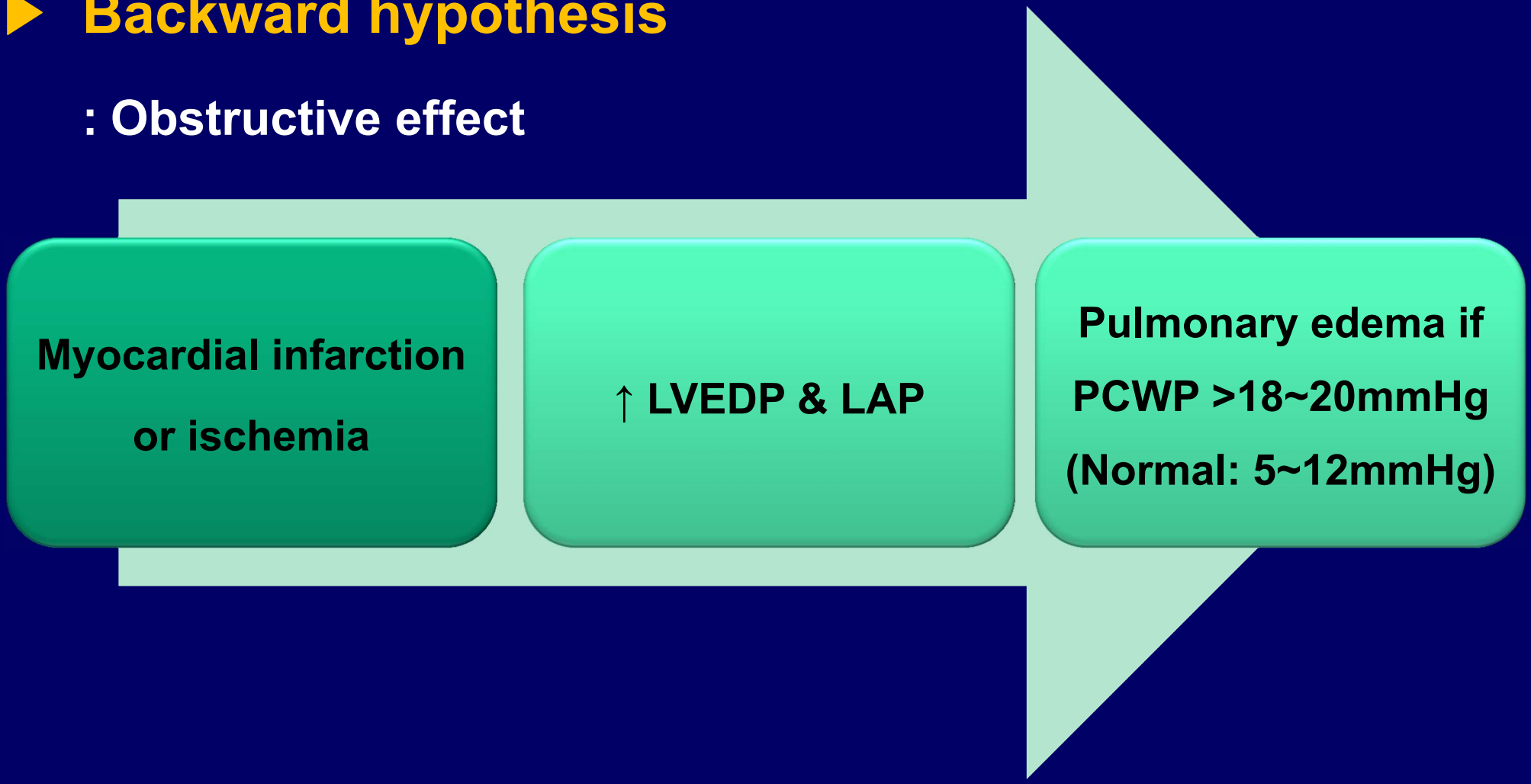
- **Severe heart failure**

  : Increasing in LVEDP cannot normalize the stroke volume

Edema in Acute Heart failure

- **Backward hypothesis**

  : Obstructive effect

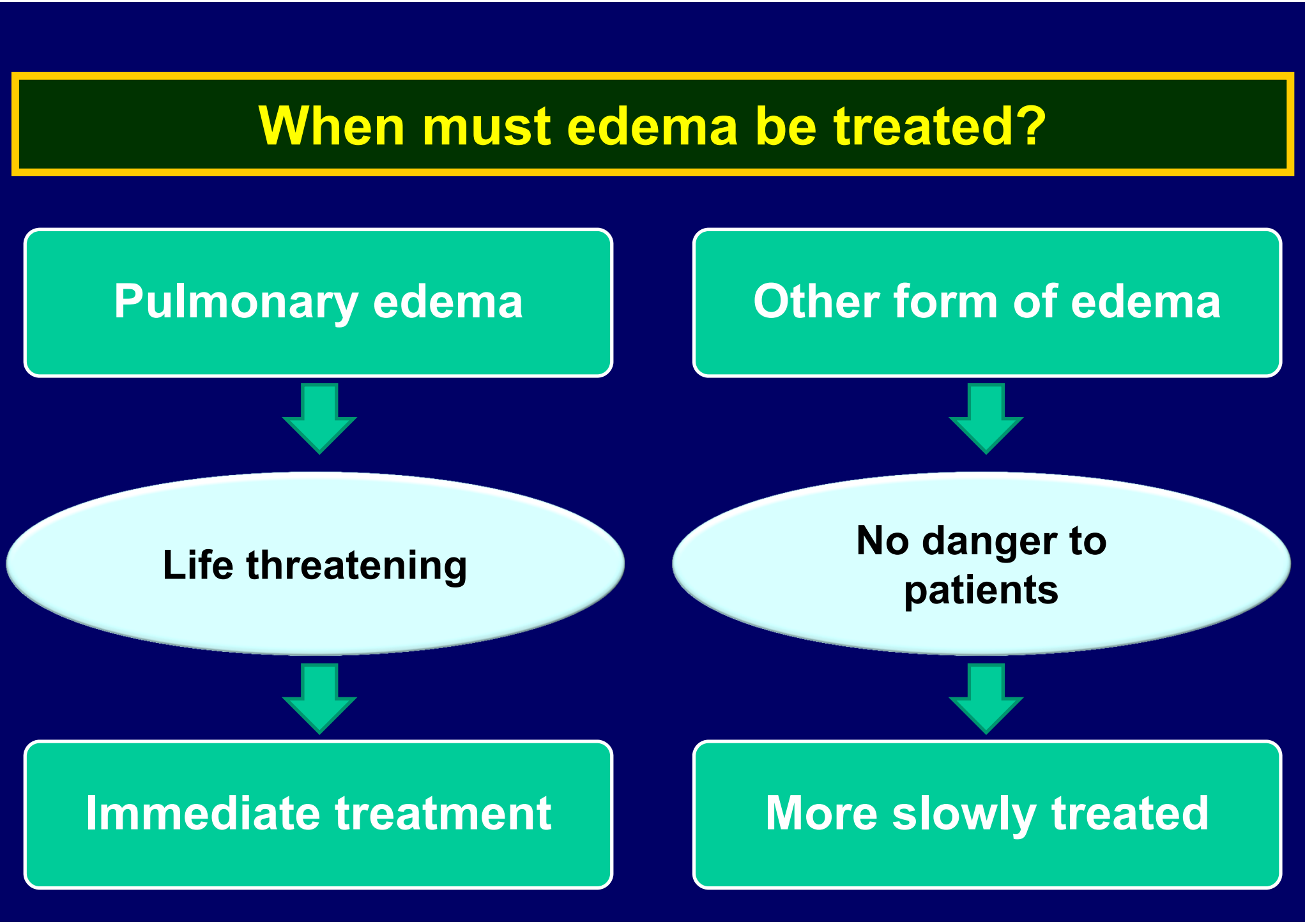


Treatment of edema

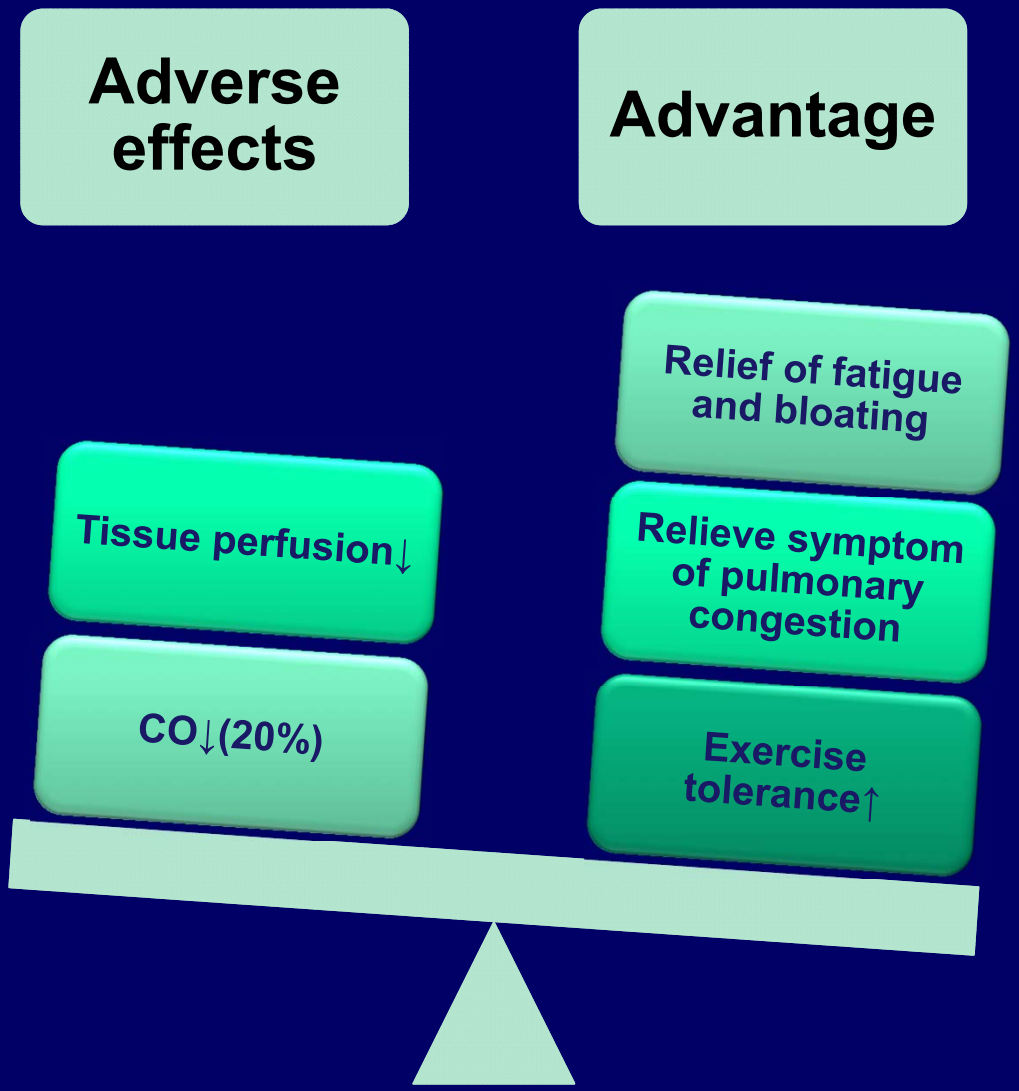
- **General principles of therapy**
  - : Reversal of heart disease if possible
  - : Dietary sodium restriction (to minimize fluid retention)
  - : Diuretic therapy

- **Important consideration before diuretic therapy**
  - : When must edema be treated ?
  - : What are the consequences of the removal of edema fluid?
  - : How rapidly should edema fluid be removed?

When must edema be treated?



Consequences of the Removal of Edema Fluid?



- Despite reduction in the effective circulating volume, most patients benefit from the appropriate use of diuretics

Estimate Adequacy of Tissue Perfusion

- **Monitor the blood urea nitrogen and serum creatinine**

  : Unexplained elevation in the BUN and Cr indicate further fluid removal should be avoided and that other therapeutic measures should be attempted such as vasodilators, inotropic therapy

- **Other symptoms of decline in tissue perfusion**

  : Weakness, fatigue, postural dizziness, and lethargy and confusion due to decreased cerebral blood flow

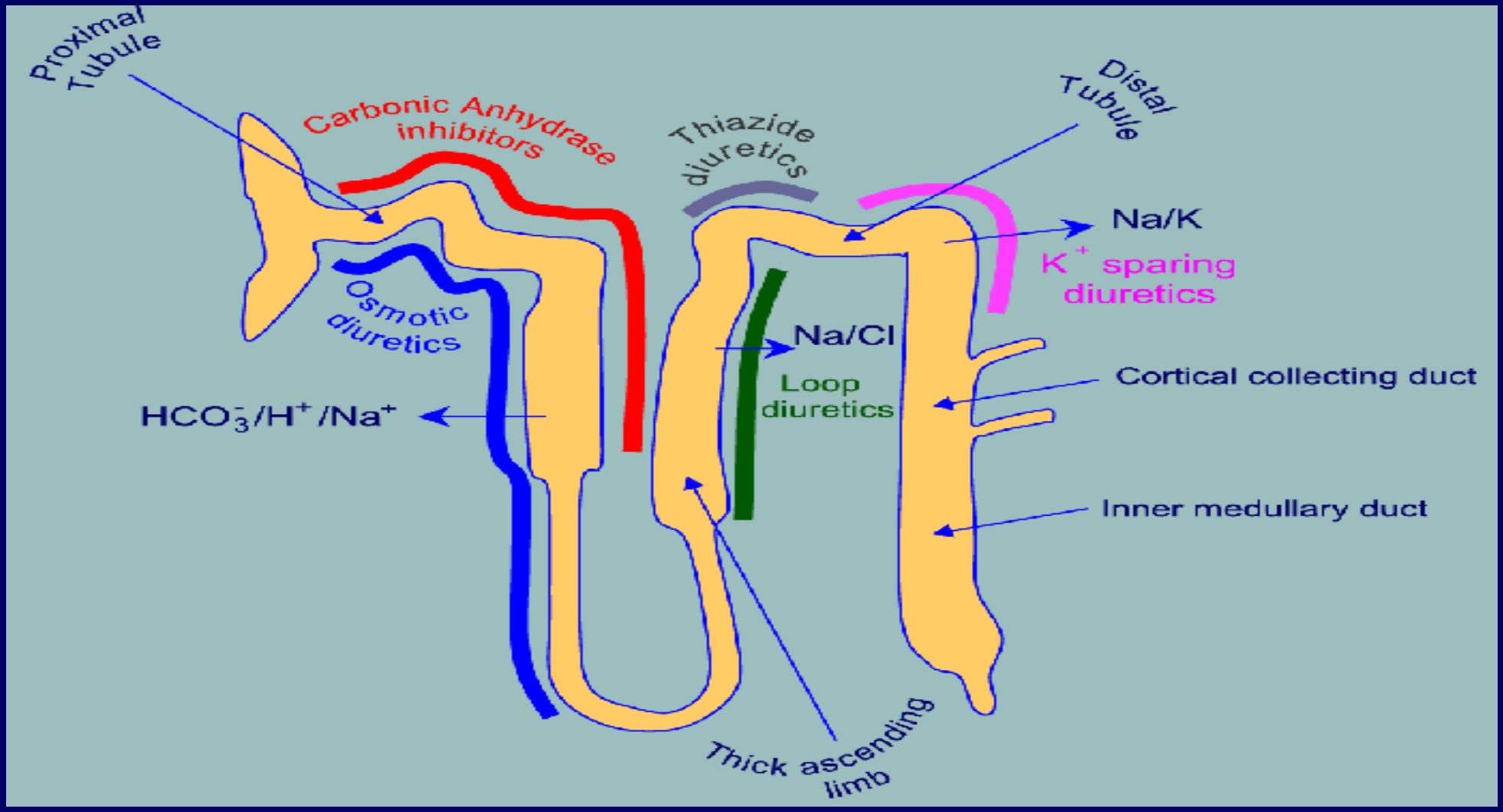
How Rapidly Should Edema Fluid Be Removed?

How diuretics effect?

Intravascular volume↓ → Capillary hydraulic pressure↓ → Mobilization of edema fluid into vascular space

LC & acites	HF, Nephrotic syndrome
→ Fluid can only mobilize via peritoneal capillaries	→ Fluid can mobilize by most capillary bed
→ 300~500 ml/day	→ 2~3 L/day

Management: Diuretics



Management: Diuretics

- Generally start diuretic therapy with furosemide

  : Can be switched to torsemide or bumetanide

- Patients with acute decompated heart failure

  : Administer without delay

  : IV therapy is preferred

  : Diuresis within 30min and peak diuresis at 1~2 hours in loop acting diuretics

Dosing of Loop Diuretic

- **IV bolus furosemide**

  : 20 to 40 mg or 2.5 X chronic oral dose (initially)

  → Doubled at 2hr interval (little or no response)

  : Maximal dose 40 to 80mg in normal, 160 to 200mg in renal failure

- **IV continuous furosemide**

  : 5mg/hr with relative intact renal function (GFR > 75ml/min)

  : Rate up to 20 mg/hr (GFR < 30 ml/min)

Dosing of Loop Diuretic: Chronic Therapy

Patients who do not received prior loop diuretic therapy

- Usual starting dose
- Furosemide: 20~40mg once or twice a day (maximum 40~80mg)
- Torsemide : 5~10mg (maximum 100mg)
- Bumetanide : 0.5~1mg (maximum : 10mg)

Patients who received prior loop diuretic therapy

- Oral dose is usually twice the intravenous dose

Management: Diuretics

- Electrolyte imbalance should be monitored

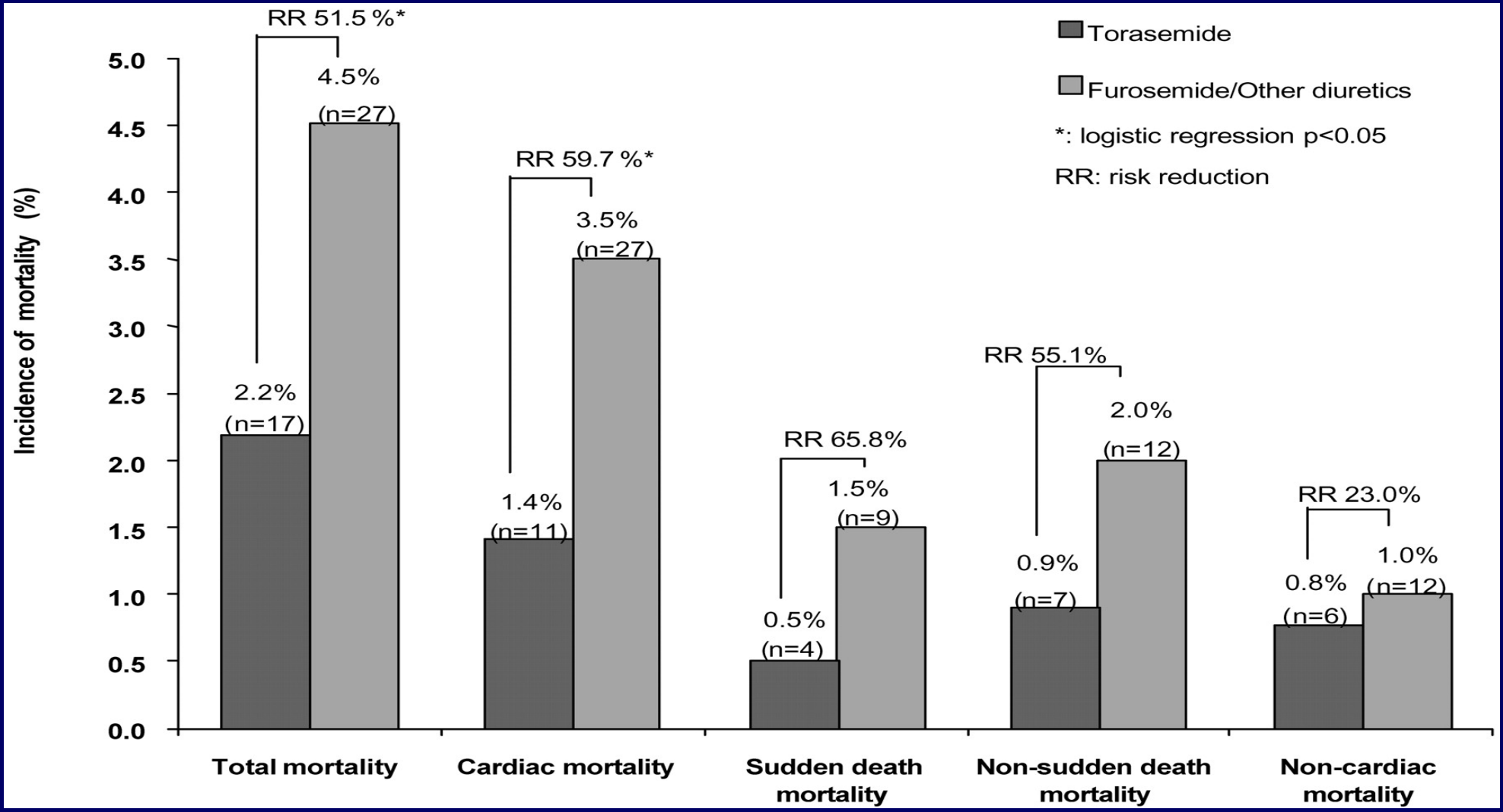
  : Paticularly Hypokalemia, Hypomagnesemia

- If hypotension or worsening renal function develops before adequate diuresis

  : Diuresis may be slowed but diuresis should be maintained until fluid retension is eliminated

ACC/AHA guildline (2009 updated)

Management: Diuretics



Eur J Heart Fail. 2002 Aug;4(4):507-13.

Diuretics: Treatment Failure

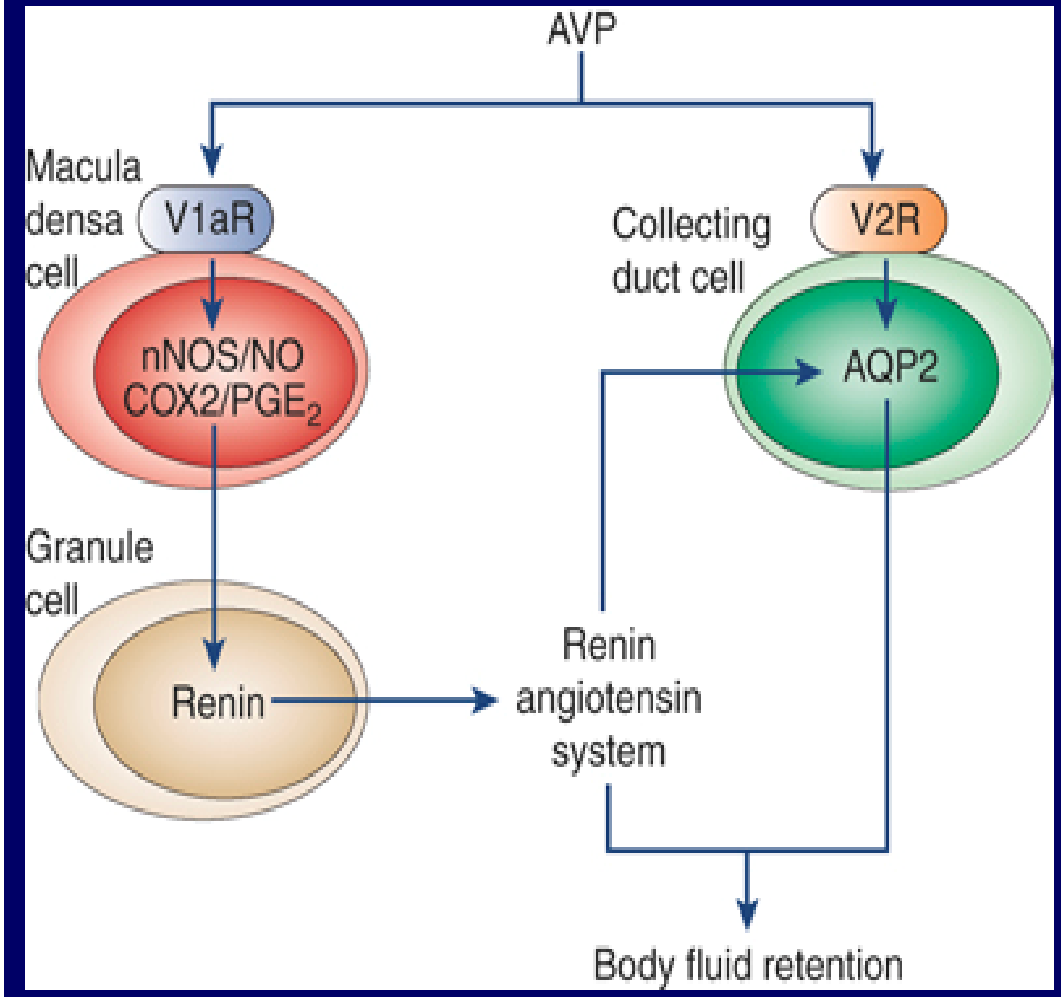
- Noncompliance
- Non-adherence to drug regimen
- Non-adherence to sodium restriction
- True diuretic resistance
- Altered intestinal absorption of loop diuretics
- Decreased renal perfusion caused by low volume, arterial ds, or drug use

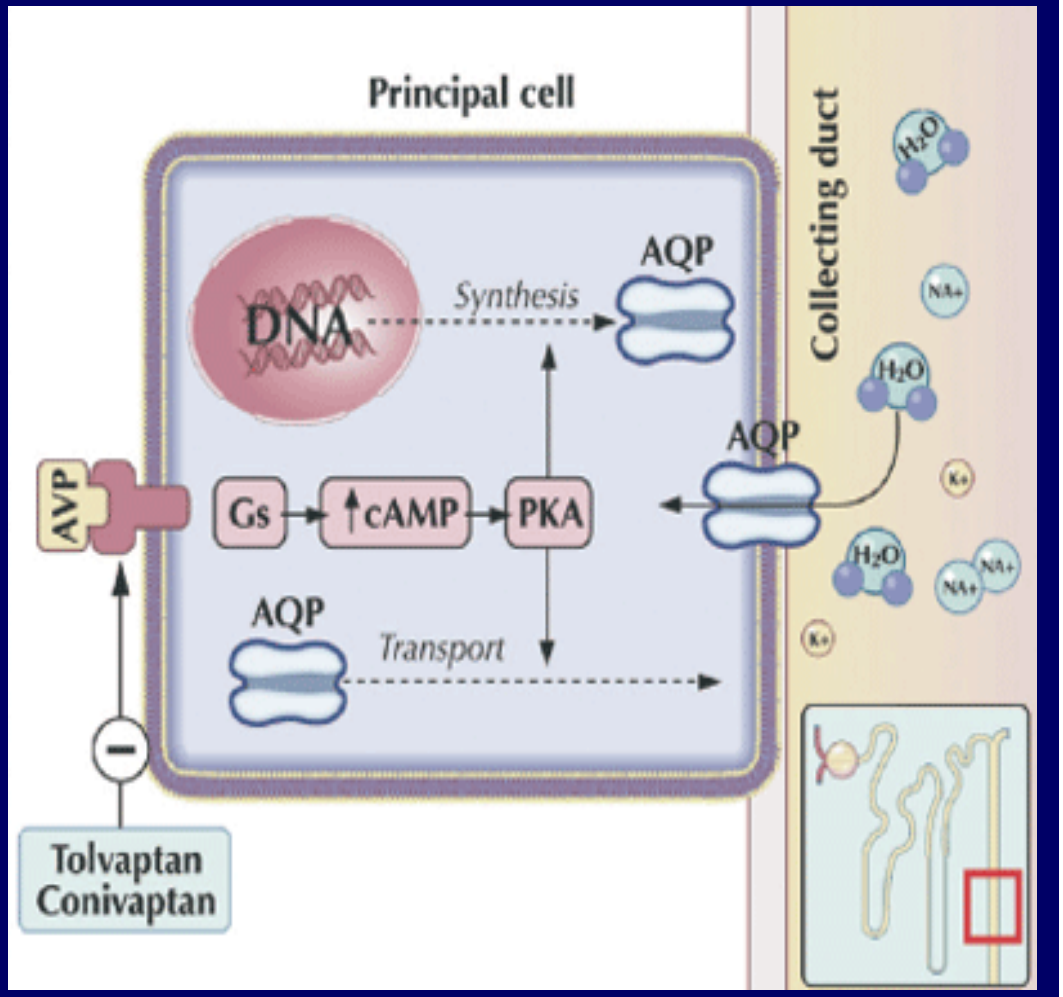
  (e.g., ACE inhibitors, NSAIDs)
- Pharmacokinetic causes related to diuretic half-life
- Reduced tubular secretion caused by low volume, kidney ds, or drug use

Diuretics: Aldosterone Antagonist

- Recommendation
  - : NYHA class II HF and LVEF <30%
  - : NYHA class III to IV HF and LVEF <35%
  - : Post-myocardial infarction with an LVEF <40% with either symptomatic heart failure or DM
- Aldosterone antagonist (spiractone or eplerenone)
  - : Hyperaldosteronism (contribute to cardiovascular disease, diuretics resistance)

Vasopressin V2 receptor Antagonist





Vasopressin V2 receptor Antagonist

JAMA. 2004 Apr 28;291(16):1963-71.

Results Median (interquartile range) body weight at 24 hours after randomization decreased by −1.80 (−3.85 to −0.50), −2.10 (−3.10 to −0.85), −2.05 (−2.80 to −0.60), and −0.60 (−1.60 to 0.00) kg in the groups receiving tolvaptan 30, 60, and 90 mg/d, and placebo, respectively ($P \leq .008$ for all tolvaptan groups vs placebo). The decrease in body weight with tolvaptan was not associated with changes in heart rate or blood pressure, nor did it result in hypokalemia or worsening renal function. There were no differences in worsening heart failure at 60 days between the tolvaptan and placebo groups ($P = .88$ for trend). In post hoc analysis, 60-day mortality was lower in tolvaptan-treated patients with renal dysfunction or severe systemic congestion.

Conclusion Tolvaptan administered in addition to standard therapy may hold promise for management of systemic congestion in patients hospitalized for heart failure.

hospitalized for heart failure.

Vasopressin V2 receptor Antagonist

JAMA. 2007 Mar 28;297(12):1332-43. Epub 2007 Mar 25.

Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials.

Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators.

Division of Cardiology, Northwestern University, Feinberg School of Medicine, Chicago, Ill 60611, USA. m-gheorghiade@northwestern.edu

Abstract

CONTEXT: Heart failure causes more than 1 million US hospitalizations yearly, mostly related to congestion. Tolvaptan, an oral, nonpeptide, selective vasopressin V2-receptor antagonist, shows promise in this condition.

OBJECTIVE: To evaluate short-term effects of tolvaptan when added to standard therapy in patients hospitalized with heart failure.

DESIGN, SETTING, AND PATIENTS: Two identical prospective, randomized, double-blind, placebo-controlled trials at 359 sites in North America, South America, and Europe were conducted during the inpatient period of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) between October 7, 2003, and February 3, 2006. A total of 2048 (trial A) and 2085 (trial B) patients hospitalized with heart failure and congestion were studied.

INTERVENTION: Patients were randomized to receive either tolvaptan (30 mg/d) or matching placebo, within 48 hours of admission.

MAIN OUTCOME MEASURES: Primary end point was a composite of changes in global clinical status based on a visual analog scale and body weight at day 7 or discharge if earlier. Secondary end points included dyspnea (day 1), global clinical status (day 7 or discharge), body weight (days 1 and 7 or discharge), and peripheral edema (day 7 or discharge).

RESULTS: Rank sum analysis of the composite primary end point showed greater improvement with tolvaptan vs placebo (trial A, mean [SD], 1.06 [0.43] vs 0.99 [0.44]; and trial B, 1.07 [0.42] vs 0.97 [0.43]; both trials P<.001). Mean (SD) body weight reduction was greater with tolvaptan on day 1 (trial A, 1.71 [1.80] vs 0.99 [1.83] kg; P<.001; and trial B, 1.82 [2.01] vs 0.95 [1.85] kg; P<.001) and day 7 or discharge (trial A, 3.35 [3.27] vs 2.73 [3.34] kg; P<.001; and trial B, 3.77 [3.59] vs 2.79 [3.46] kg; P<.001), whereas improvements in global clinical status were not different between groups. More patients receiving tolvaptan (684 [76.7%] and 678 [72.1%] for trial A and trial B, respectively) vs patients receiving placebo (646 [70.6%] and 597 [65.3%], respectively) reported improvement in dyspnea at day 1 (both trials P<.001). Edema at day 7 or discharge improved significantly with tolvaptan in trial B (P = .02) but did not reach significance in trial A (P = .07). Serious adverse event frequencies were similar between groups, without excess renal failure or hypotension.

CONCLUSION: In patients hospitalized with heart failure, oral tolvaptan in addition to standard therapy including diuretics improved many, though not all, heart failure signs and symptoms, without serious adverse events.

V2 receptor Antagonist: Patient with Improvement

Condition, by Day*	No. (%) of Patients		*P* Value†
	Tolvaptan	Placebo	
Dyspnea			
1	933 (51.6)	853 (47.1)	.006
2	1244 (68.2)	1160 (63.7)	.001
3	1374 (75.2)	1330 (73.0)	.02
4	1456 (79.7)	1431 (78.5)	.04
Orthopnea			
1	668 (63.1)	631 (59.2)	.01
2	840 (78.6)	793 (74.1)	.006
3	893 (83.4)	863 (80.4)	.03
4	913 (85.3)	915 (85.0)	.06
Fatigue			
1	673 (40.7)	644 (38.8)	.19
2	923 (55.3)	886 (53.1)	.07
3	1074 (64.3)	1007 (60.2)	.02
4	1147 (68.6)	1107 (66.1)	.03
JVD			
1	698 (48.6)	631 (43.8)	.03
2	923 (63.7)	855 (59.1)	.01
3	1030 (71.0)	953 (65.6)	.002
4	1077 (74.3)	1014 (69.8)	.06
Rales			
1	744 (45.8)	711 (43.7)	.03
2	1067 (65.3)	1041 (63.6)	.07
3	1201 (73.4)	1166 (71.1)	.006
4	1274 (77.9)	1259 (76.7)	.02
Edema			
1	913 (57.6)	832 (52.6)	<.001
2	1229 (76.9)	1169 (73.5)	.002
3	1340 (83.8)	1296 (81.4)	<.001
4	1381 (86.4)	1371 (86.0)	.004

Vasopressin V2 receptor Antagonist

JAMA. 2007 Mar 28;297(12):1319-31. Epub 2007 Mar 25.

Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial.

Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators.

Division of Cardiology, Tufts-New England Medical Center, Boston, Mass, USA. mkonstam@tufts-nemc.org

Abstract

CONTEXT: Vasopressin mediates fluid retention in heart failure. Tolvaptan, a vasopressin V2 receptor blocker, shows promise for management of heart failure.

OBJECTIVE: To investigate the effects of tolvaptan initiated in patients hospitalized with heart failure.

DESIGN, SETTING, AND PARTICIPANTS: The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST), an event-driven, randomized, double-blind, placebo-controlled study. The outcome trial comprised 4133 patients within 2 short-term clinical status studies, who were hospitalized with heart failure, randomized at 359 North American, South American, and European sites between October 7, 2003, and February 3, 2006, and followed up during long-term treatment.

INTERVENTION: Within 48 hours of admission, patients were randomly assigned to receive oral tolvaptan, 30 mg once per day (n = 2072), or placebo (n = 2061) for a minimum of 60 days, in addition to standard therapy.

MAIN OUTCOME MEASURES: Dual primary end points were all-cause mortality (superiority and noninferiority) and cardiovascular death or hospitalization for heart failure (superiority only). Secondary end points included changes in dyspnea, body weight, and edema.

RESULTS: During a median follow-up of 9.9 months, 537 patients (25.9%) in the tolvaptan group and 543 (26.3%) in the placebo group died (hazard ratio, 0.98; 95% confidence interval [CI], 0.87-1.11; P = .68). The upper confidence limit for the mortality difference was within the prespecified noninferiority margin of 1.25 (P<.001). The composite of cardiovascular death or hospitalization for heart failure occurred in 871 tolvaptan group patients (42.0%) and 829 placebo group patients (40.2%; hazard ratio, 1.04; 95% CI, 0.95-1.14; P = .55). Secondary end points of cardiovascular mortality, cardiovascular death or hospitalization, and worsening heart failure were also not different. Tolvaptan significantly improved secondary end points of day 1 patient-assessed dyspnea, day 1 body weight, and day 7 edema. In patients with hyponatremia, serum sodium levels significantly increased. The Kansas City Cardiomyopathy Questionnaire overall summary score was not improved at outpatient week 1, but body weight and serum sodium effects persisted long after discharge. Tolvaptan caused increased thirst and dry mouth, but frequencies of major adverse events were similar in the 2 groups.

CONCLUSION: Tolvaptan initiated for acute treatment of patients hospitalized with heart failure had no effect on long-term mortality or heart failure-related morbidity.

Vasopressin V2 receptor Antagonist

J Card Fail. 2011 Dec;17(12):973-81. Epub 2011 Sep 9.

A multicenter, randomized, double-blind, placebo-controlled study of tolvaptan monotherapy compared to furosemide and the combination of tolvaptan and furosemide in patients with heart failure and systolic dysfunction.

Udelson JE, Bilsker M, Hauptman PJ, Sequeira R, Thomas I, O'Brien T, Zimmer C, Orlandi C, Konstam MA.

Division of Cardiology and the CardioVascular Center, Tufts Medical Center, Boston, MA 02111, USA. JUdelson@tuftsmedicalcenter.org

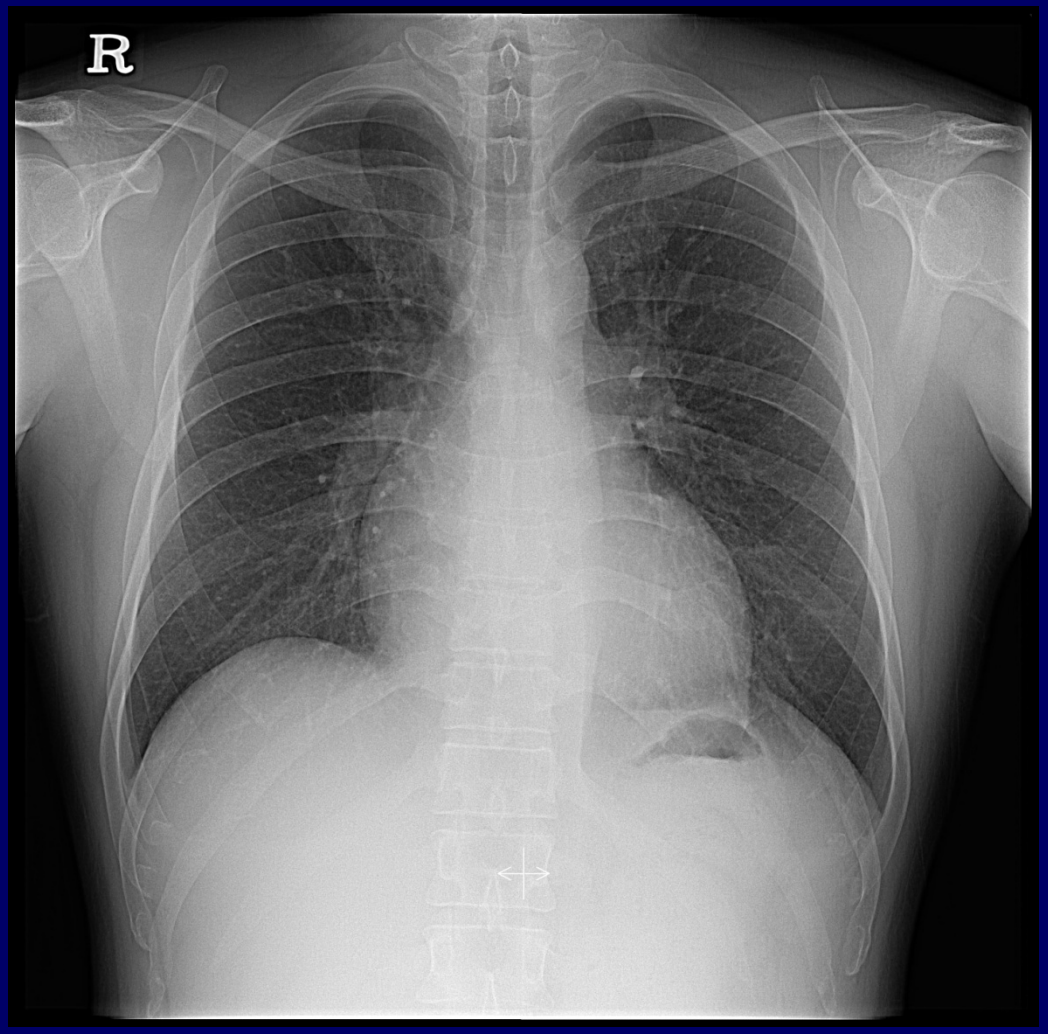
Abstract

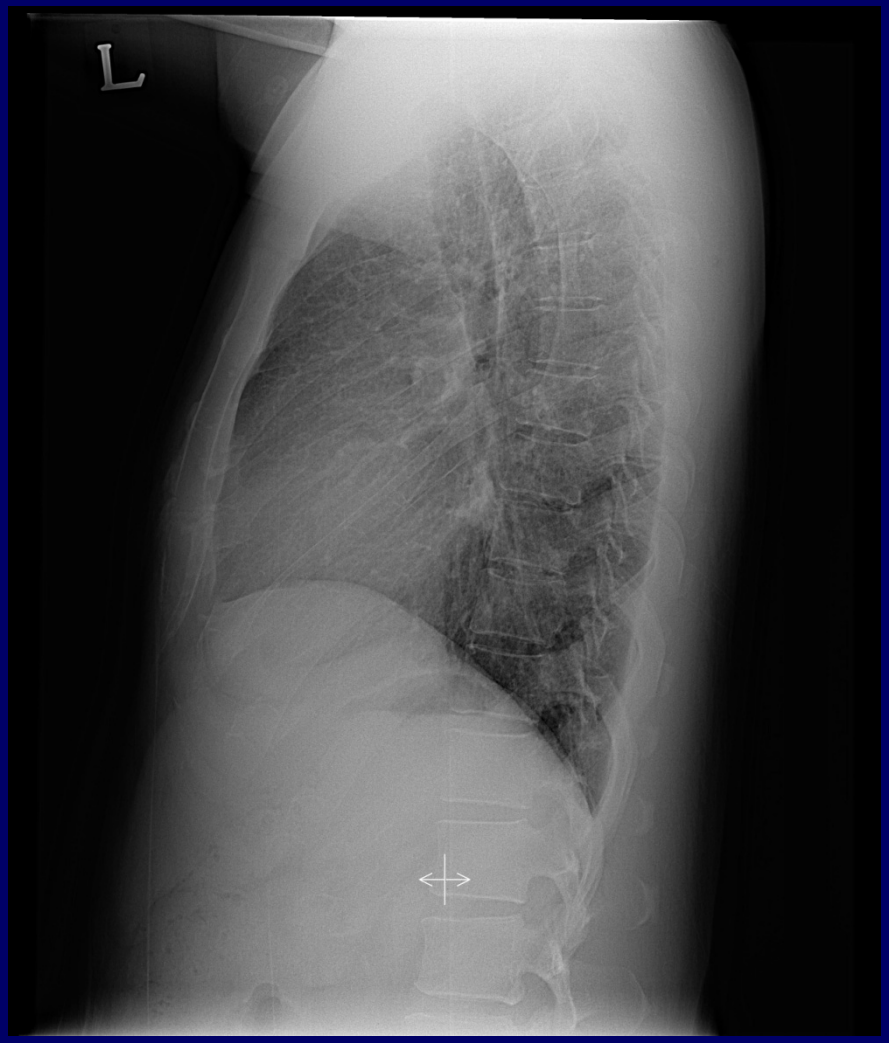
BACKGROUND: Increased vasopressin levels may be present in patient with chronic heart failure (HF) and contribute to pathophysiology through effects on the vasopressin V2 receptor. The presence of background diuretic therapy may confound evaluations of vasopressin receptor antagonists (VRA).

METHODS AND RESULTS: Eligible patients had HF (New York Heart Association Class II-III), systolic dysfunction (left ventricular ejection fraction ≤0.40) and signs of congestion (eg, edema, rales). At screening, patients were removed from baseline diuretic therapy and placed on a low-sodium diet (2 g/day). After a 2-day run-in period, 83 patients were randomized to placebo (n = 21), monotherapy with the vasopressin V2 receptor antagonist tolvaptan (TLV) 30 mg (n = 20), monotherapy with furosemide 80 mg (FURO, n = 22) or both TLV 30 mg and FURO 80 mg (n = 20) once daily for 7 days. Patients were on standard background therapy and not fluid-restricted throughout the study. A decrease in body weight of -1.37 ± 1.61, -0.54 ± 1.59, and -1.13 ± 1.49 kg was observed versus baseline for TLV, FURO, and TLV+FURO, respectively, at day 8. At the same point, the placebo group showed a body weight increase of +0.72 ± 2.42 kg versus baseline (P = .0006 for TLV versus placebo). Increases in urine volume from baseline were greater with TLV alone (2646 ± 1503 mL/24 hours) than with FURO (894 ± 853 mL/24 hours, P < .001), or PLC (423 ± 786 mL/24 hours, P < .001), and similar to TLV+FURO (2585 ± 2119 mL/24 hours). An increase in serum sodium within the normal range was also observed in TLV-treated patients (P < .02 versus placebo; P < .01 versus FURO). No changes in serum potassium, other laboratory values, or blood pressure were observed. TLV therapy was well tolerated.

CONCLUSIONS: In patients with HF and signs of volume overload, TLV monotherapy without concomitant loop diuretic therapy reduced body weight when compared to placebo without adverse changes in serum electrolytes, during a sodium restricted diet while on background medications including angiotensin-converting enzyme inhibitors and β-blockers.

Kim O O (34/M): DOE (NYHA 3)





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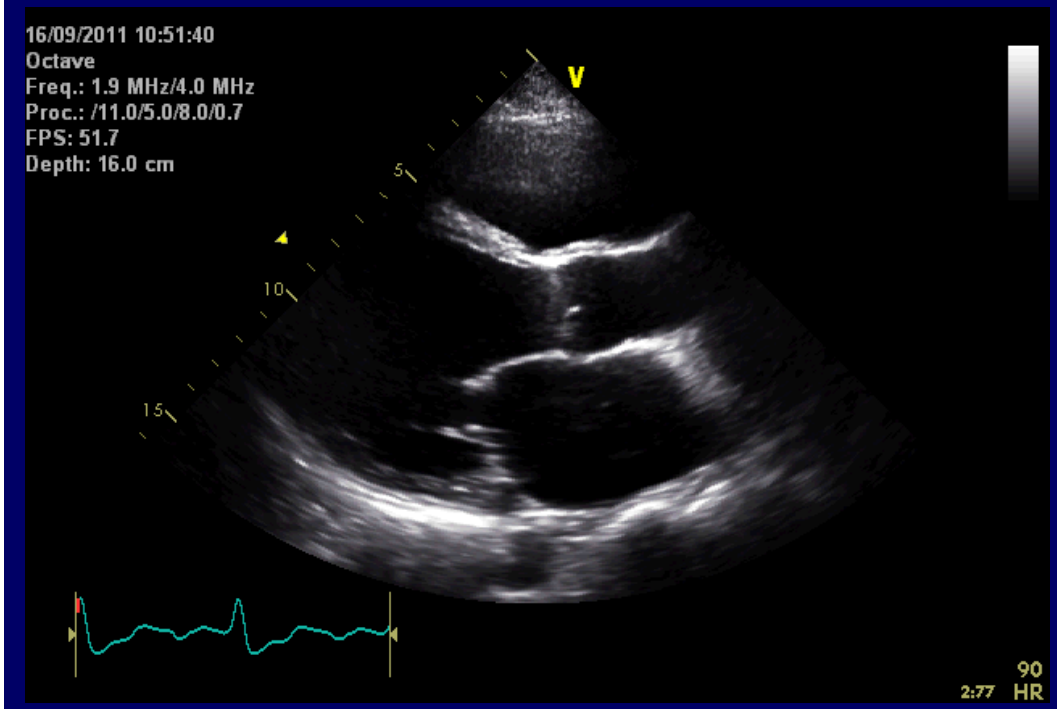
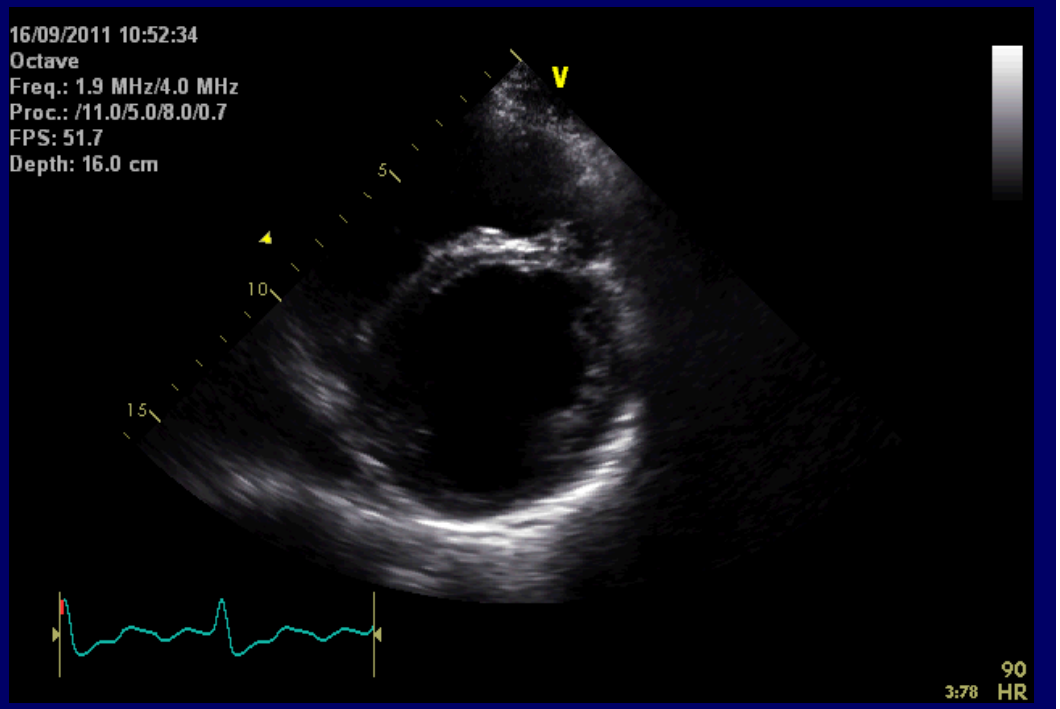
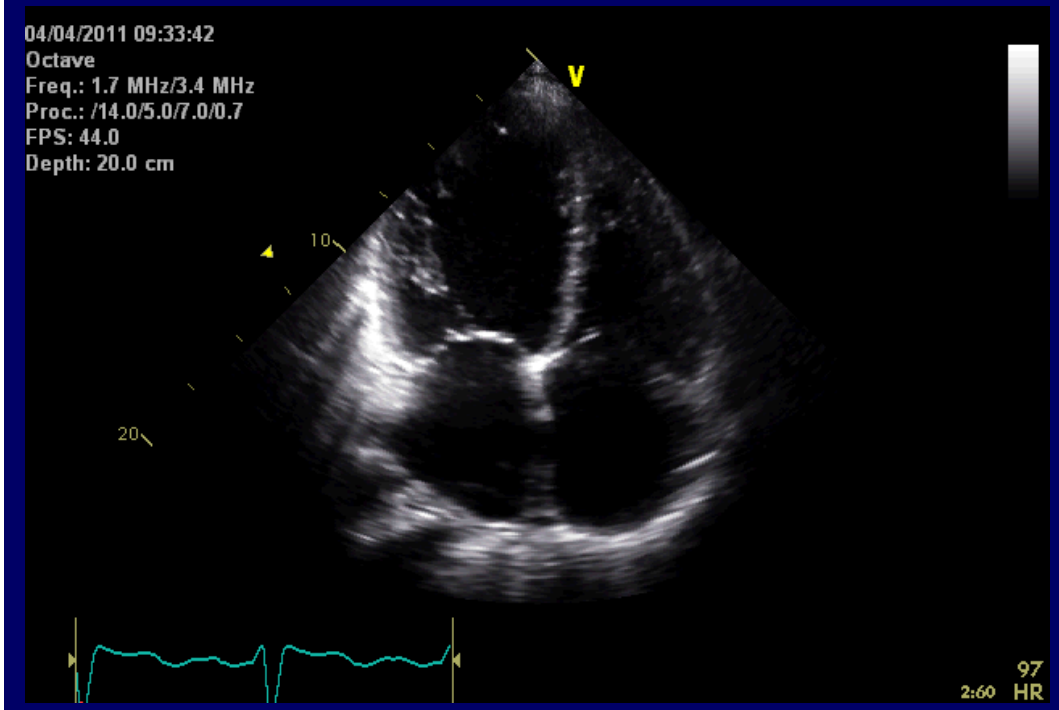
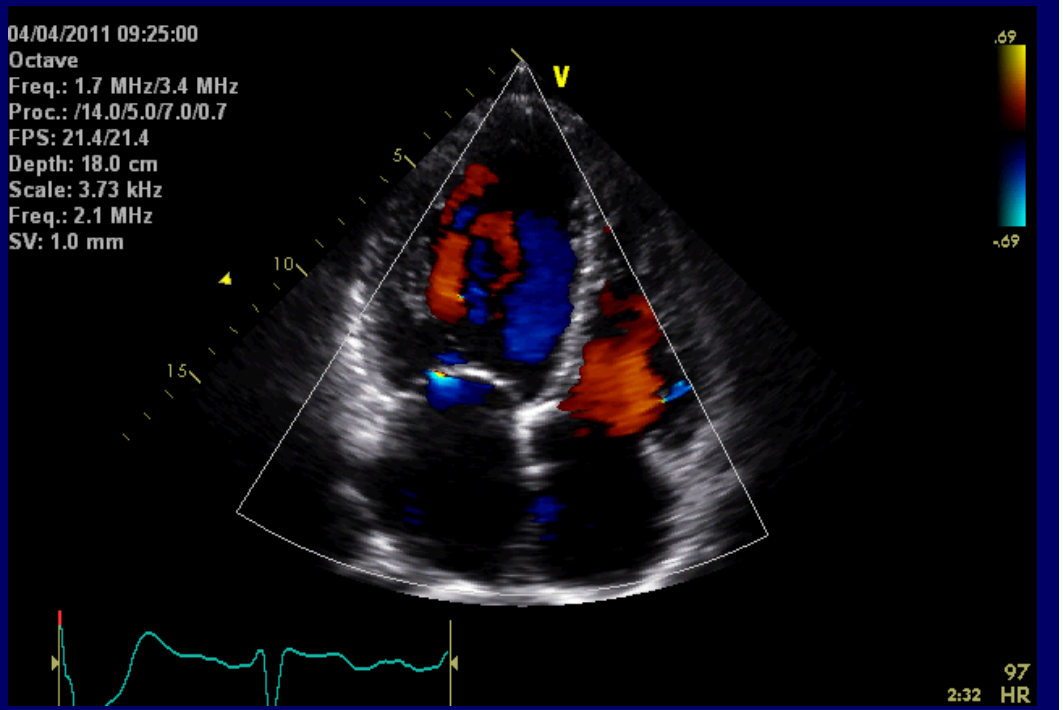


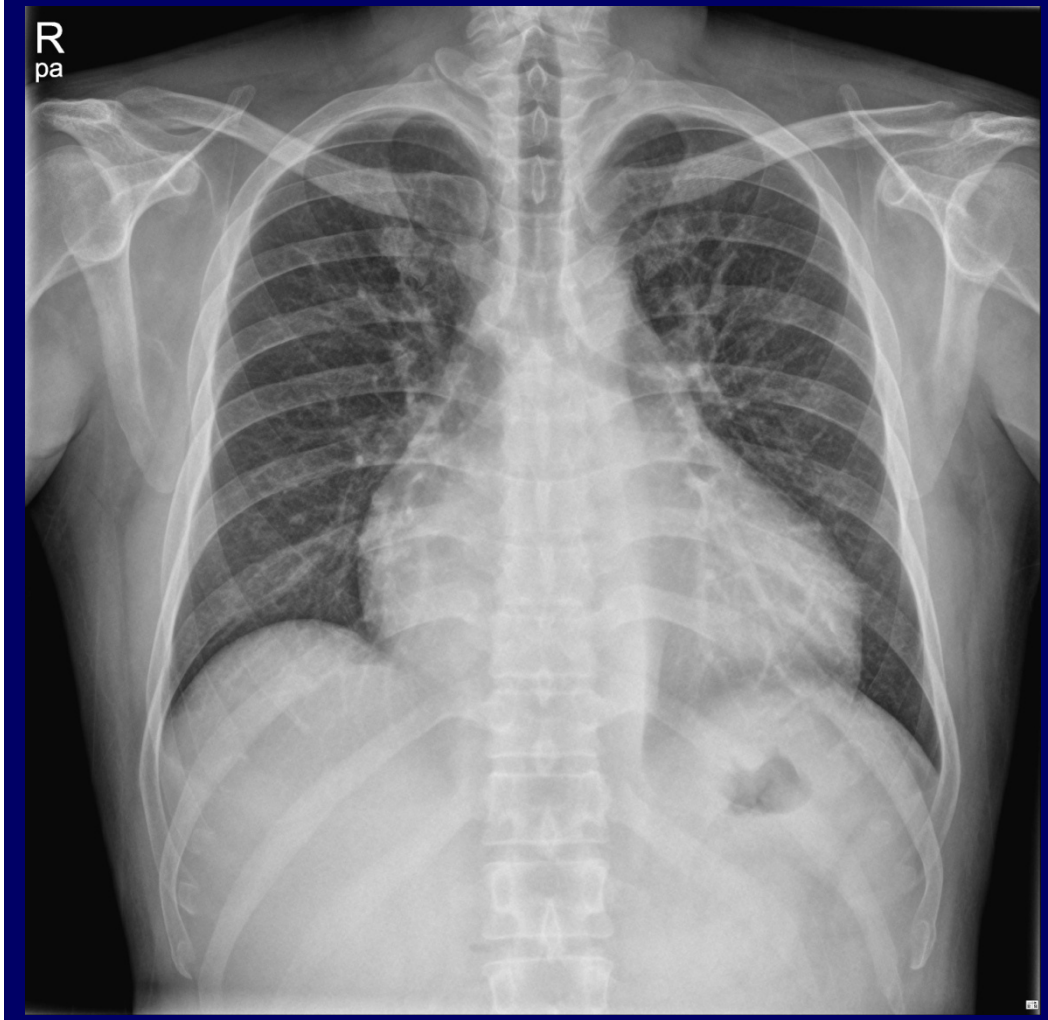


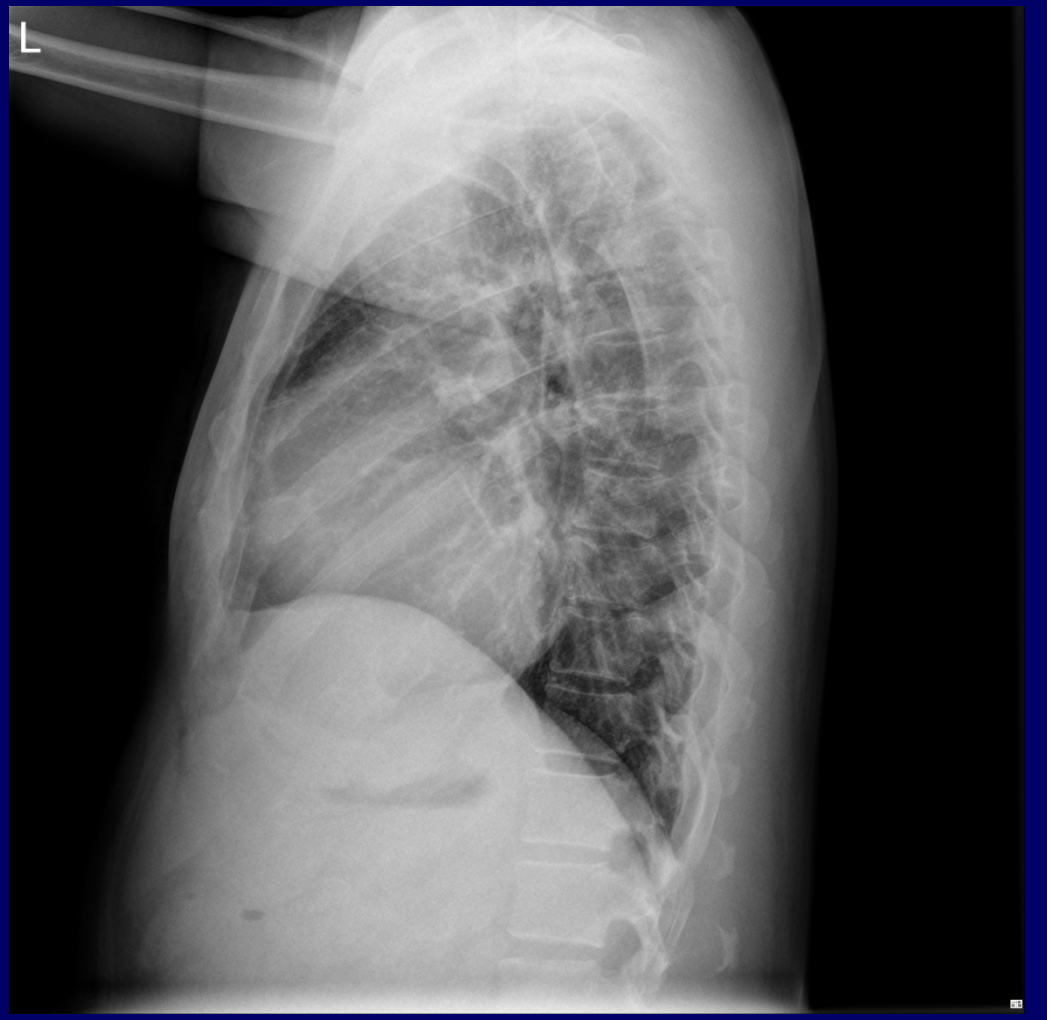
Kim O O (34/M): DOE (NYHA 3)



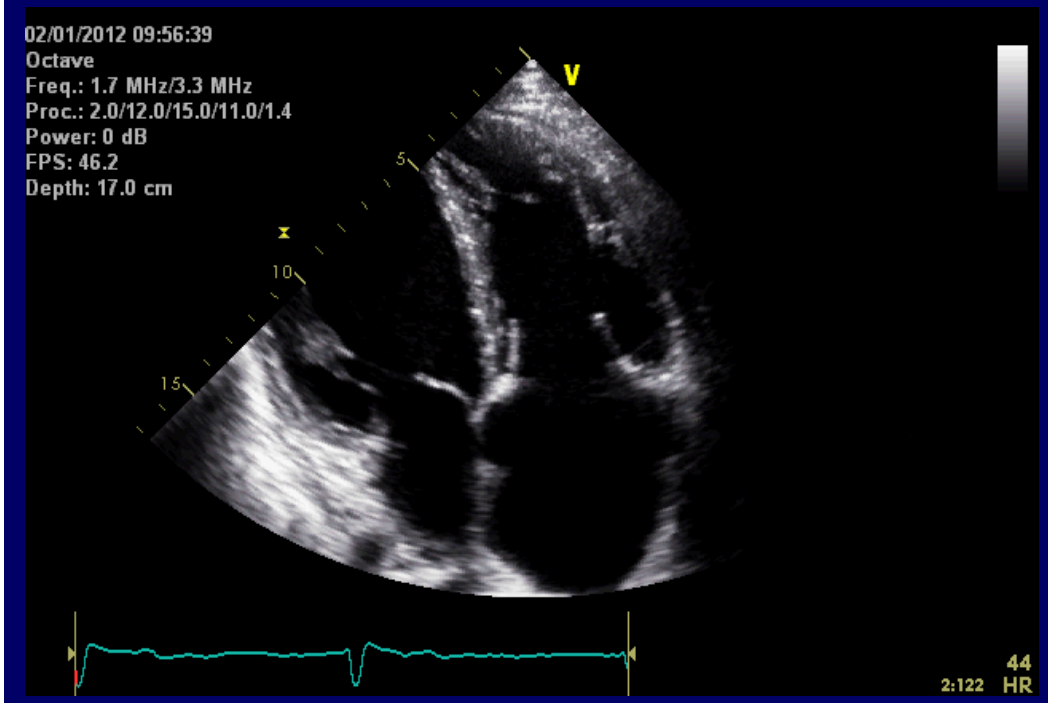


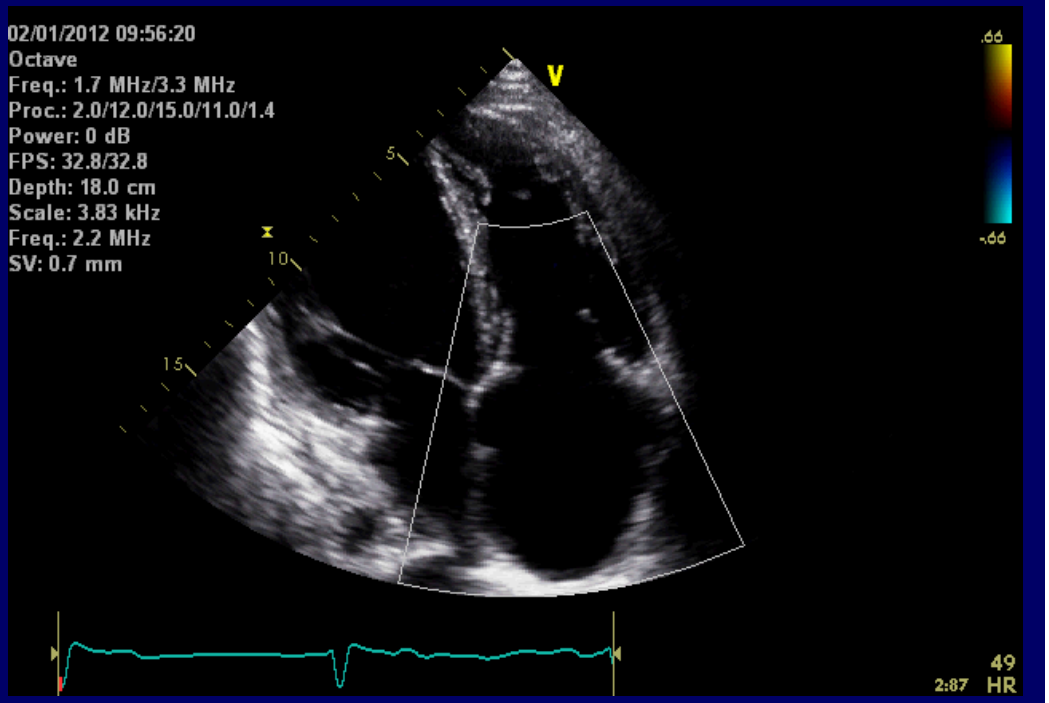
Kim O O (35/M): Edema and Fatigue





Kim O O (35/M): Edema and Fatigue





Take Home Messages

- Important pathophysiologic concepts in edema formation
  - : Effective circulatory volume
  - : Neurohormonal activation
- Other potential causes of edema should be considered
  - : Non-cardiac or cardiac
- Keep in mind the potential benefits and risks of diuretic therapy
- Newer promising drugs: vaptans