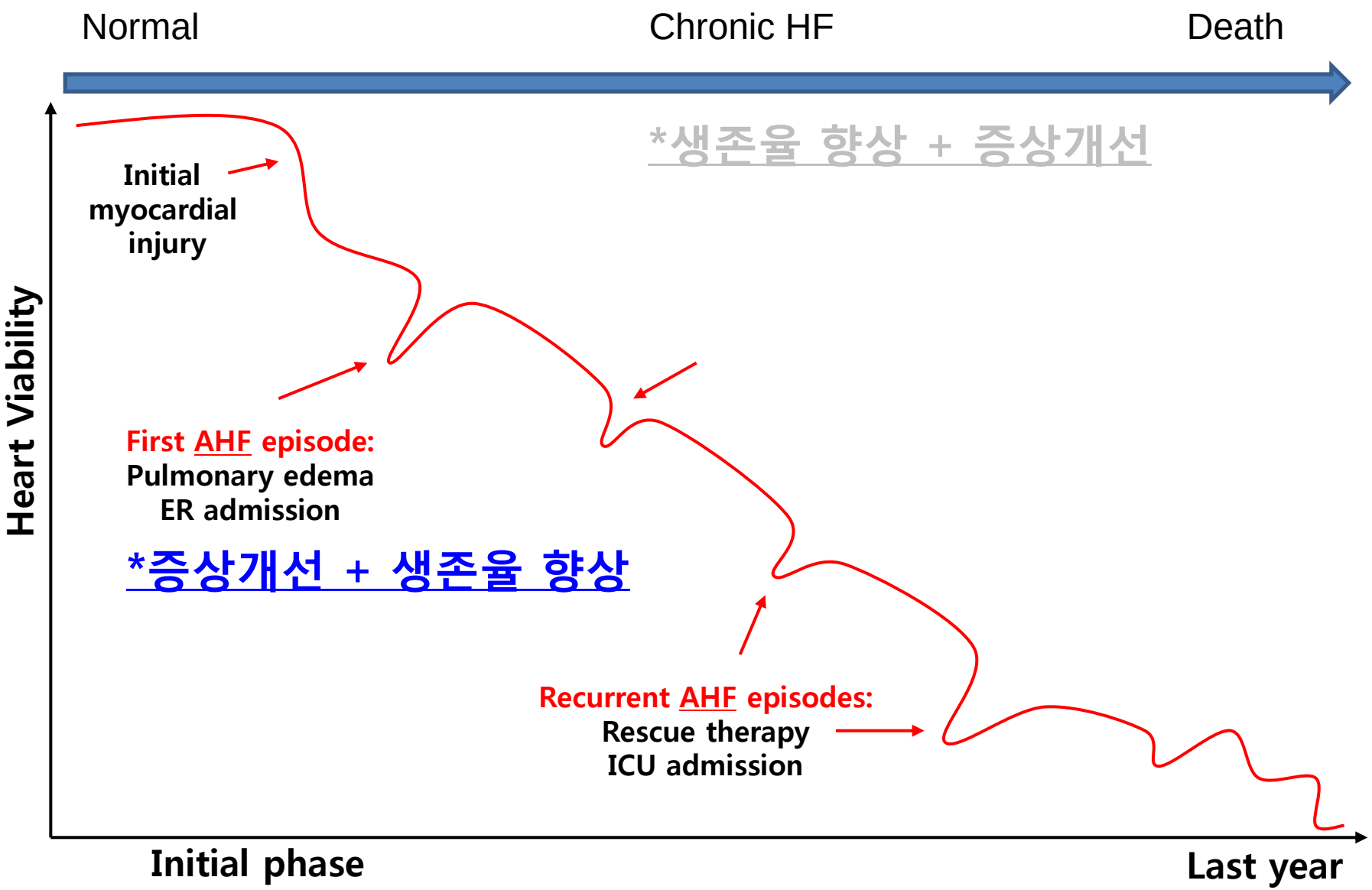
급성심부전의 표준치료

서울대학교병원
심혈관센터, 순환기내과

조 현 재

Natural history of heart failure



Gheorghiade M. Am J Cardiol. 2005;96(suppl 6A):1-4G.

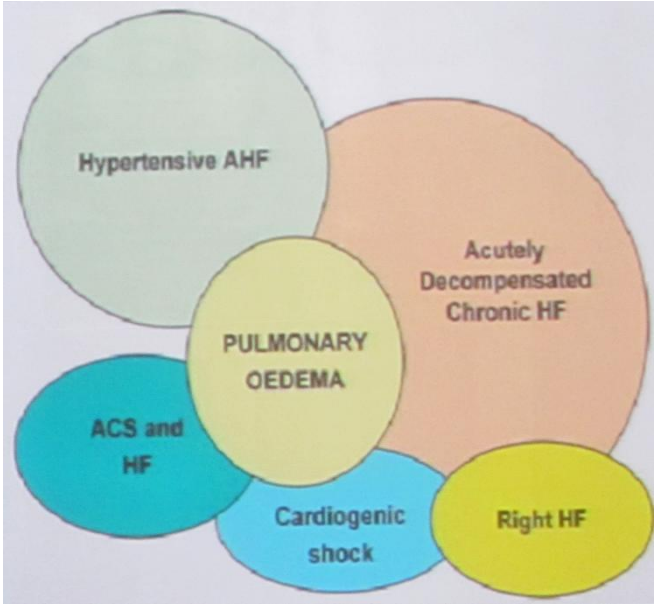
Classification of acute heart failure

[1] Classification by 2008 ESC guidelines

- New onset of *de novo* HF
- Worsening chronic HF

[2] Classification by the EuroHeart Failure Survey II (EHFS II)

- Worsening or decompensated HF
- Clinical pulmonary edema
- Hypertensive HF
- Cardiogenic shock
- Isolated right–sided HF
- ACS and HF

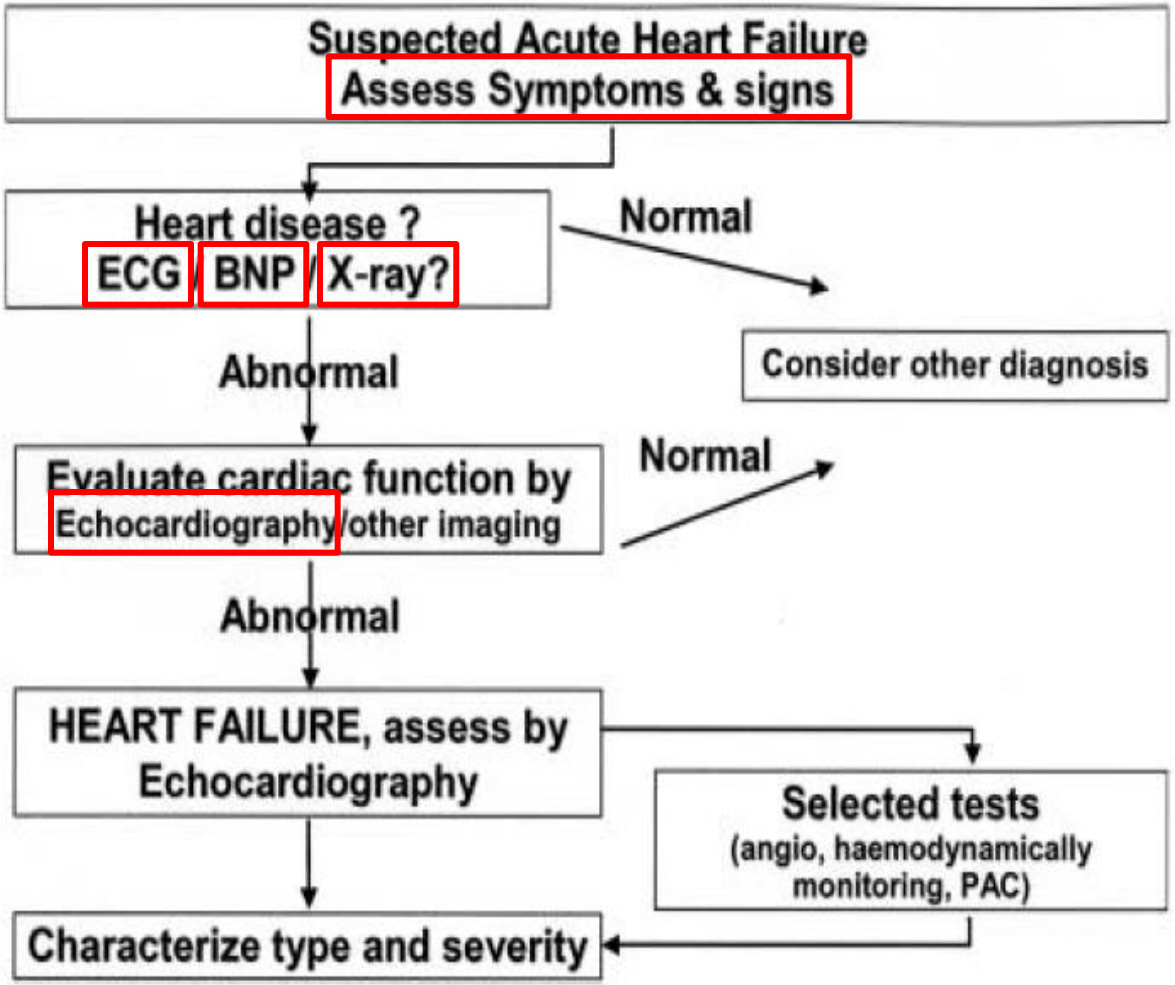


Diagnosis of acute heart failure

- Based on signs & symptoms
  - Decreased tissue perfusion
    ; fatigue, weakness, decreased urine output
  - Systemic or pulmonary congestion
    ; dyspnea, orthopnea, jugular venous distension
    hepatomegaly, hepatojugular reflux, rale

- Objective evidence of heart disease
  - Chest X-ray
  - Electrocardiography (ECG)
  - Echocardiography
  - BNPs
  - Etc.

Diagnosis of acute heart failure



Precipitating, aggravating factors

- ✓ Acute coronary syndromes/ischemia
- ✓ Severe hypertension
- ✓ Atrial or ventricular tachyarrhythmia
- ✓ Bradyarrhythmia
- ✓ Infection
- ✓ Pulmonary emboli
- ✓ Renal failure
- ✓ Medications (e.g. NSAIDs)
- ✓ Non-adherence (including high salt diet)

BNPs in acute heart failure

- Pro-BNP from myocytes → BNP + NT-proBNP in plasma
- Mirror elevation of ventricular filling pressures in HF patients
- Differential diagnosis of patients presenting in the ER with dyspnea
  - NT-proBNP level <300 pg/ml 98% negative predictive value for a diagnosis of HF.
  - BNP <100 pg/ml 90% sensitivity and 76% specificity
- Changes in PCWP do correlate directly with changes in BNP concentration during hospitalization (treatment monitoring)
- Prognosis

BNPs in acute heart failure

- Pitfalls
  - BNP levels may be low in obesity, very early presentation with AHF, and acute mitral regurgitation
  - Elevated without HF

    : Renal dysfunction, elderly, women, lung disease

→ BNP testing result should be interpreted within a comprehensive clinical evaluation.

Natriuretic peptide: diagnosis, management & prognosis

***Acute heart failure is a clinical diagnosis, but BNP (pro-BNP) may be useful when there is diagnostic uncertainty**

Current medical management of acute heart failure

Forrest classification

Tissue perfusion
Pulmonary congestion

Evidence for congestion (elevated filling pressure)

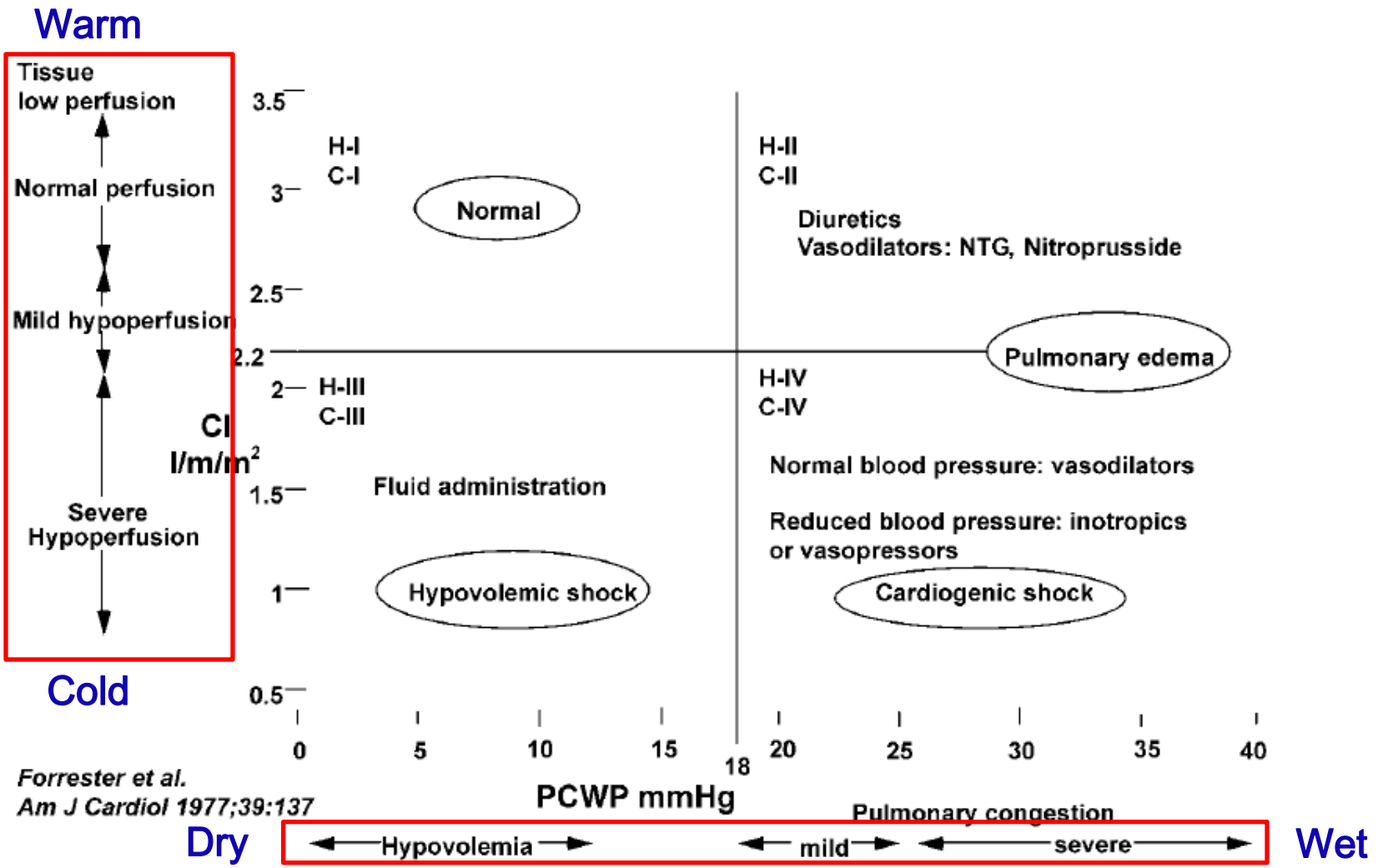
- Orthopnea
- High jugular venous pressure
- Increasing S3
- Loud P2
- Edema
- Ascites
- Rales (uncommon)
- Abdominojugular reflux
- Valsalva square wave

Evidence for low perfusion

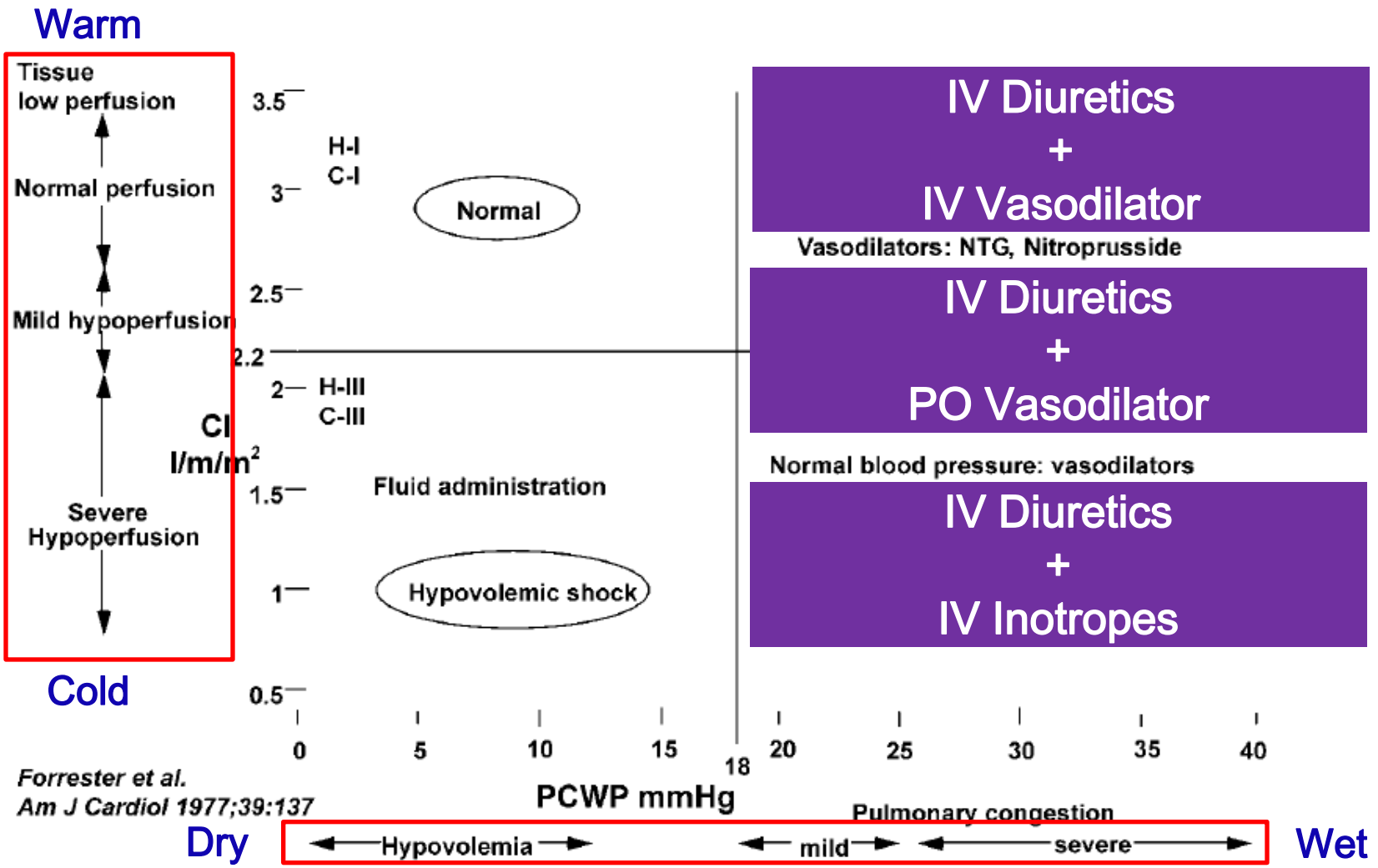
- Narrow pulse pressure
- Pulsus alternans
- Cool forearms and legs
- May be sleepy, obtunded
- ACE inhibitor-related symptomatic hypotension
- Declining serum sodium level
- Worsening renal function

Low perfusion at rest?	Congestion at rest? No	Congestion at rest? Yes
No	Warm and dry	Warm and wet
Yes	Cold and dry	Cold and wet

Forrest classification



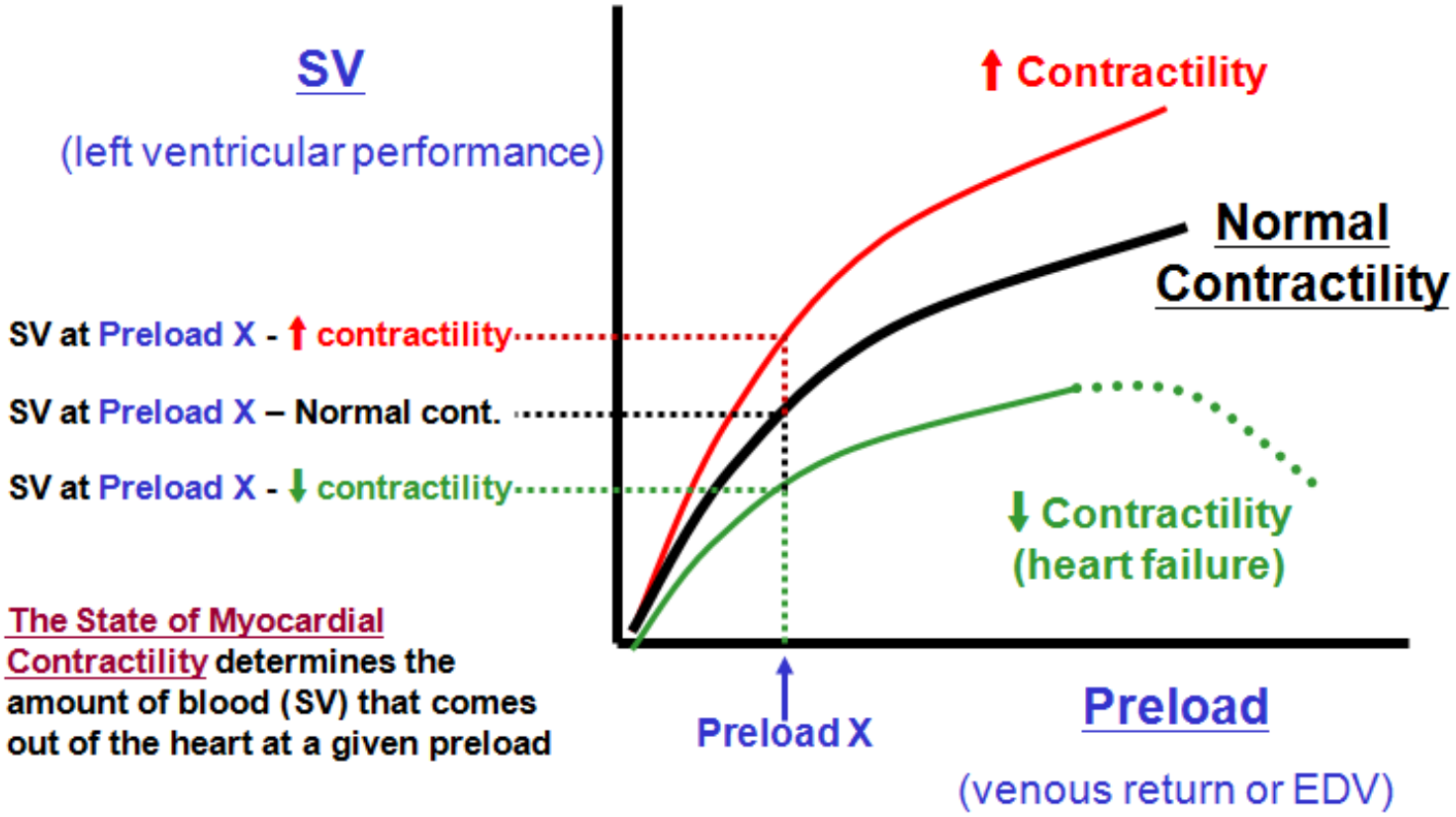
Forrest classification



응급실에서는 왜 Dobutamine/NG/Lasix 를 routine 으로 사용할까요?

Starlings Law of the Heart and Contractility

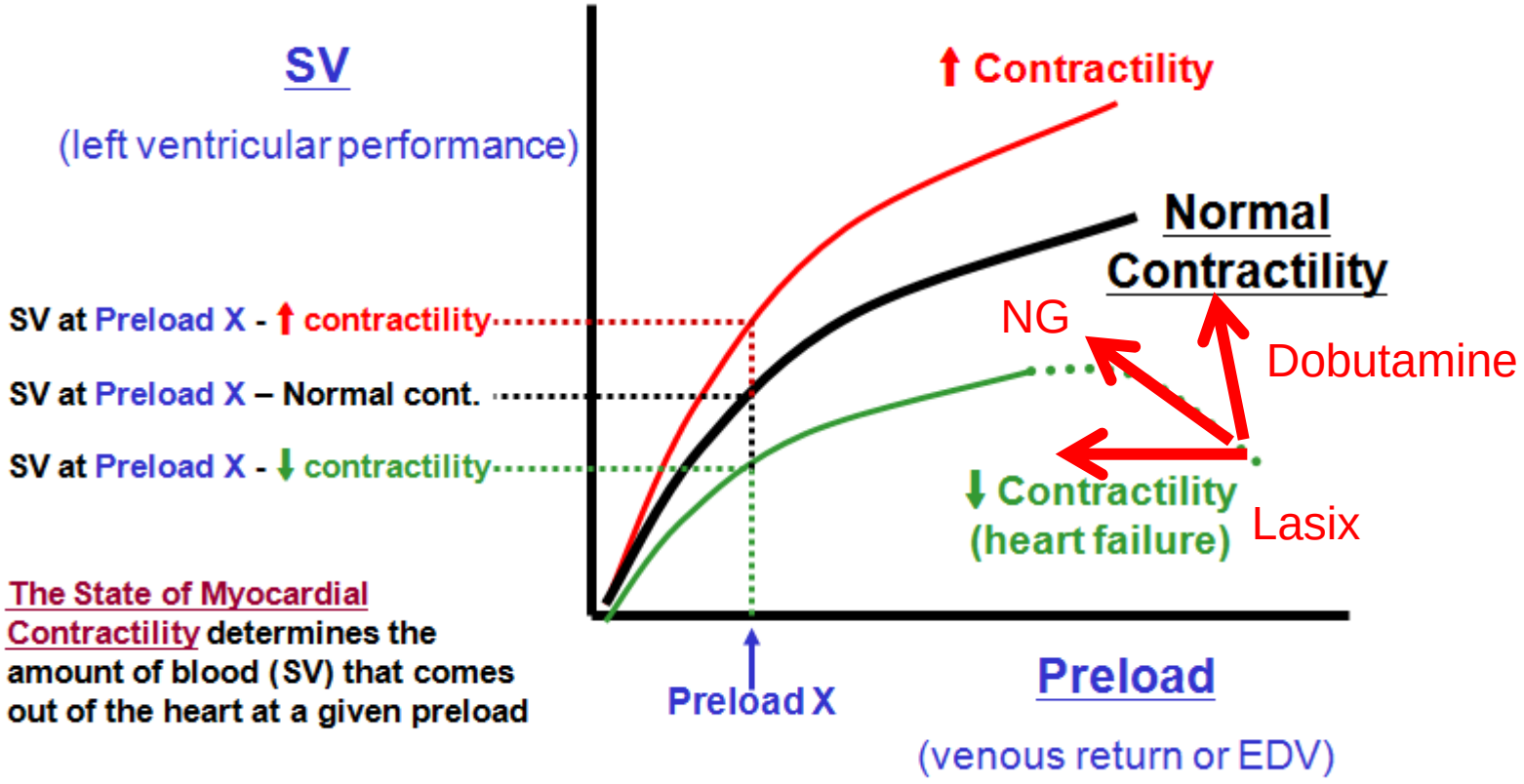
Starling's Law:
The greater the EDV (blood going in the heart), the more blood comes out of the heart



The State of Myocardial Contractility determines the amount of blood (SV) that comes out of the heart at a given preload

Management of acute decompensated HF

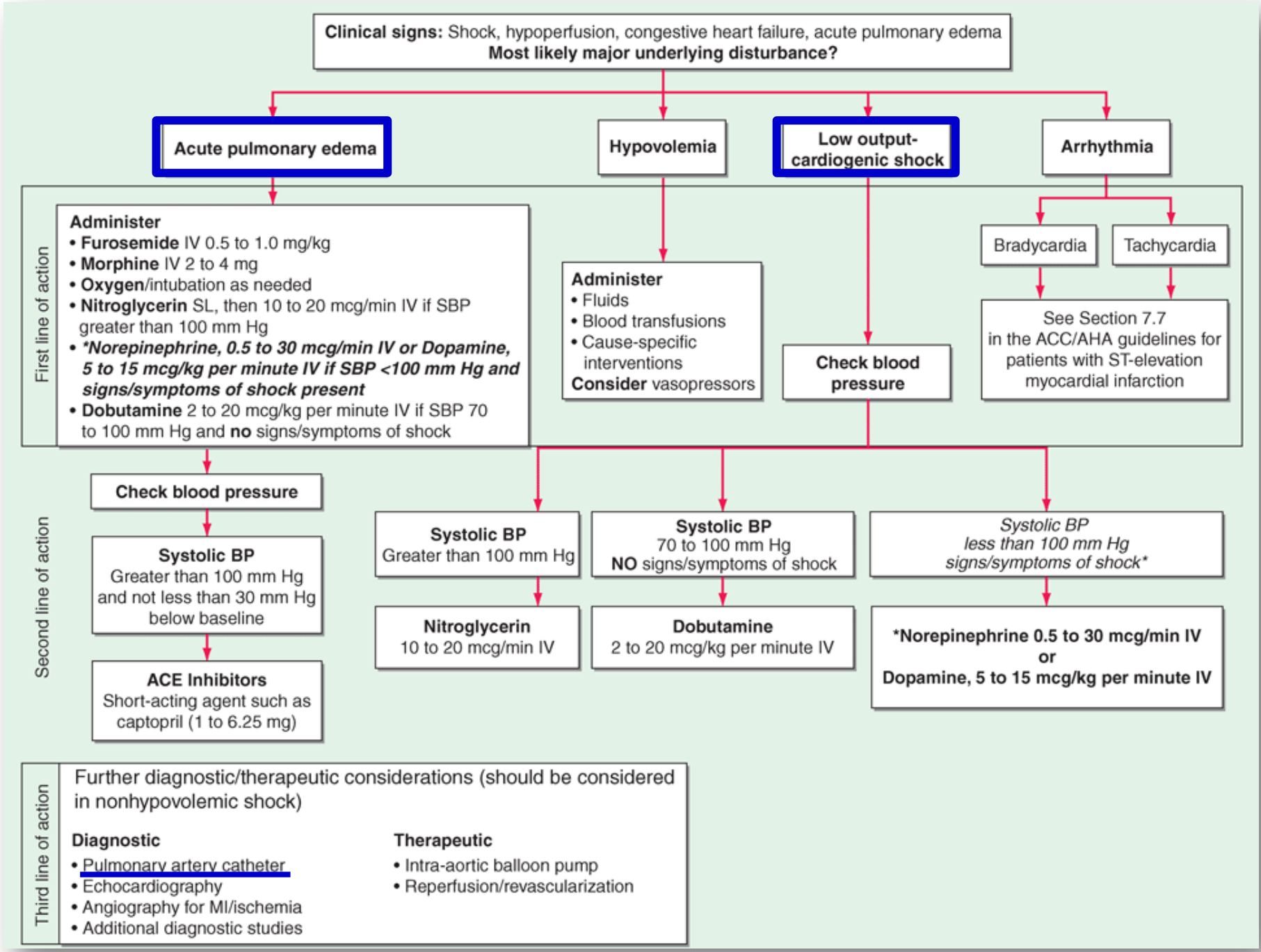
NG 와 Dobutamine 중 어떤 것을 먼저 고려해야 할까요?



Frank-Starling law

General therapeutic approach

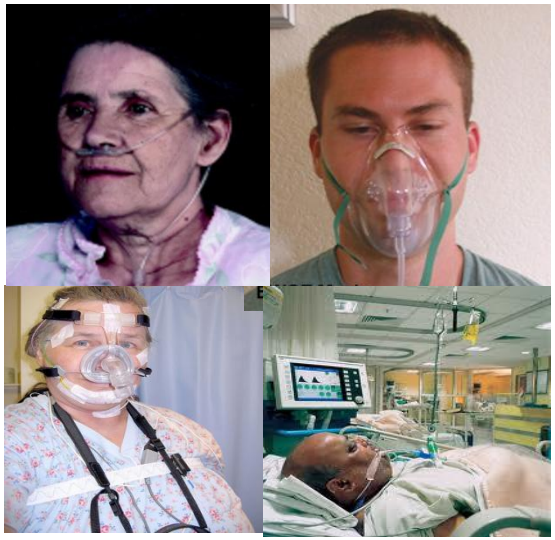
Hemodynamic Characteristic	Suggested therapeutic approach				
C.I. PCWP SBP mmHg	Decreased Low -	Decreased Normal >85	Decreased High <85	Decreased High >85	Decreased High
Outline of therapy	Fluid loading	Vasodilator Fluid loading may become necessary	Inotropic agents IV diuretics	Vasodilator IV diuretics Inotrope	IV diuretics Inotropes vasoconstrictive if SBP is low,


Clinical signs: Shock, hypoperfusion, congestive heart failure, acute pulmonary edema
Most likely major underlying disturbance?
Acute pulmonary edema
Hypovolemia
Low output-cardiogenic shock
Arrhythmia
First line of action
Administer
• Furosemide IV 0.5 to 1.0 mg/kg
• Morphine IV 2 to 4 mg
• Oxygen/intubation as needed
• Nitroglycerin SL, then 10 to 20 mcg/min IV if SBP greater than 100 mm Hg
• *Norepinephrine, 0.5 to 30 mcg/min IV or Dopamine, 5 to 15 mcg/kg per minute IV if SBP <100 mm Hg and signs/symptoms of shock present
• Dobutamine 2 to 20 mcg/kg per minute IV if SBP 70 to 100 mm Hg and no signs/symptoms of shock
Administer
• Fluids
• Blood transfusions
• Cause-specific interventions
Consider vasopressors
Check blood pressure
Bradycardia
Tachycardia
See Section 7.7 in the ACC/AHA guidelines for patients with ST-elevation myocardial infarction
Second line of action
Check blood pressure
Systolic BP
Greater than 100 mm Hg and not less than 30 mm Hg below baseline
ACE Inhibitors
Short-acting agent such as captopril (1 to 6.25 mg)
Systolic BP
Greater than 100 mm Hg
Nitroglycerin
10 to 20 mcg/min IV
Systolic BP
70 to 100 mm Hg
NO signs/symptoms of shock
Dobutamine
2 to 20 mcg/kg per minute IV
Systolic BP
less than 100 mm Hg
signs/symptoms of shock*
*Norepinephrine 0.5 to 30 mcg/min IV
or
Dopamine, 5 to 15 mcg/kg per minute IV
Third line of action
Further diagnostic/therapeutic considerations (should be considered in nonhypovolemic shock)
Diagnostic
• Pulmonary artery catheter
• Echocardiography
• Angiography for MI/ischemia
• Additional diagnostic studies
Therapeutic
• Intra-aortic balloon pump
• Reperfusion/revascularization

Therapeutic approach - Oxygen

- Oxygen should be administered as early as possible by a nasal cannula or facemask
- Noninvasive ventilation with PEEP should be considered for more severe forms of hypoxia (SaO2 <90%)

- Non-invasive ventilation
  - Reduce respiratory distress
  - Improve LV function
    by reducing afterload.



Therapeutic approach - Diuretics

- Fluid overload is treated with loop diuretics, usually intravenously

Severity of fluid retention	Diuretic	Dose (mg)	Comments
Moderate	Furosemide, or	20–40	Oral or intravenous according to clinical symptoms
	Bumetanide, or	0.5–1.0	Titrate dose according to clinical response
	Torasemide	10–20	Monitor Na^+, K^+, creatinine, and blood pressure
Severe	Furosemide, or	40–100	Intravenously
	Furosemide infusion	5–40 mg/h	Better than very high bolus doses
	Bumetanide, or	1–4	Orally or intravenously
	Torasemide	20–100	Orally
Refractory to loop diuretics	Add HCTZ, or	25–50 twice daily	Combination with loop diuretic better than very high dose of loop diuretics alone
	Metolazone, or	2.5–10 once daily	Metolazone more potent if creatinine clearance <30 mL/min
	Spironolactone	25–50 once daily	Spironolactone best choice if patient not in renal failure and normal or low serum K^+
In case of alkalosis	Acetazolamide	0.5	Intravenously
Refractory to loop diuretic and thiazides	Add dopamine for renal vasodilataion, or dobutamine as an inotropic agent		Consider ultrafiltration or haemodialysis if co-existing renal failure

Therapeutic approach - Diuretics

- Target doses of diuretics
  - Optimal volume status with relief of signs and symptoms of congestion (edema, elevated JVP, dyspnea)
- Without symptomatic hypotension and/or worsening renal function, abnormal serum electrolytes (arrhythmia, muscle cramp), gout
- Routine use of a Foley catheter: not recommended
- Monitoring: serum Na, K, Mg levels at least daily

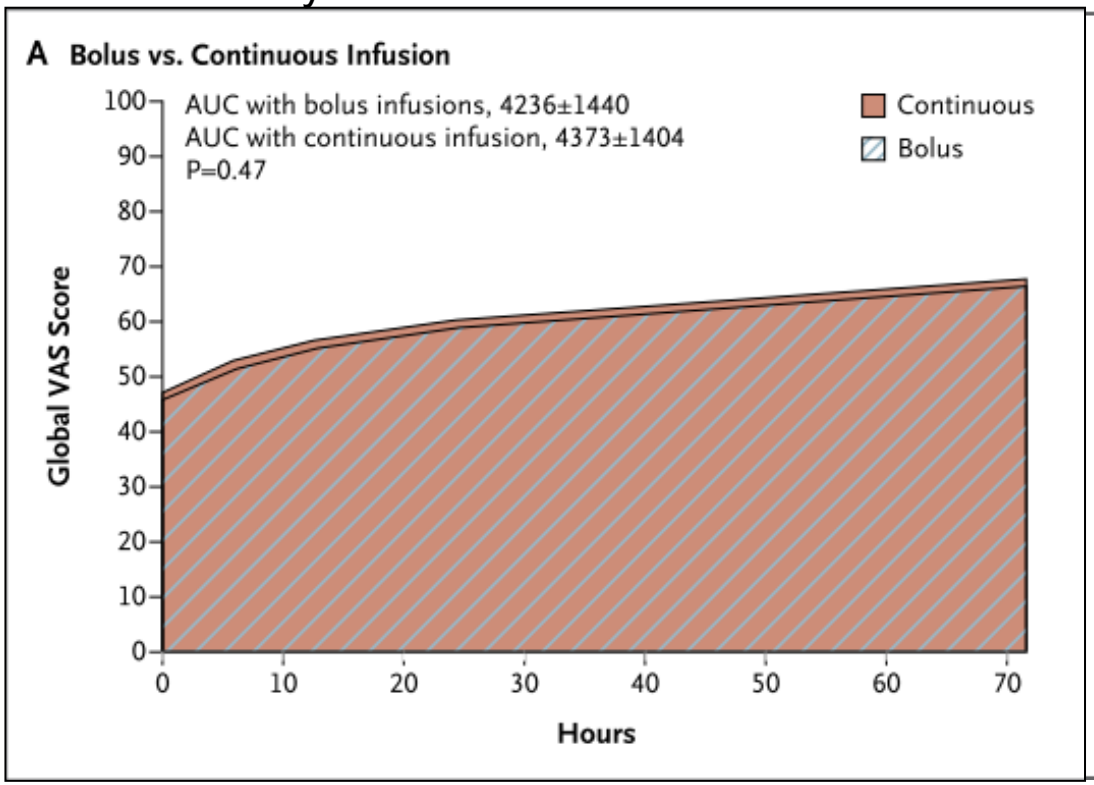
Agent	Initial Daily Dose (mg)	Maximum Total Daily Dose (mg)	Elimination	Duration of Action (hr)
Furosemide*	20–40 mg qd or bid	600 mg	65%R 35%M	4–6
Bumetanide*	0.5–1.0 mg qd or bid	10 mg	62%R 38%M	6–8
Torsemide*	10–20mg qd	200 mg	20%R 80%M	12–16
Ethacrynic acid*,+	25–50 mg qd or bid	200 mg	67%R 33%M	6

Equivalent doses: furosemide 40 mg = bumetanide 1 mg = torsemide 20 mg = ethacrynic acid 50 mg.
R = renal; M = metabolic; B = excreted into bile; U = unknown.

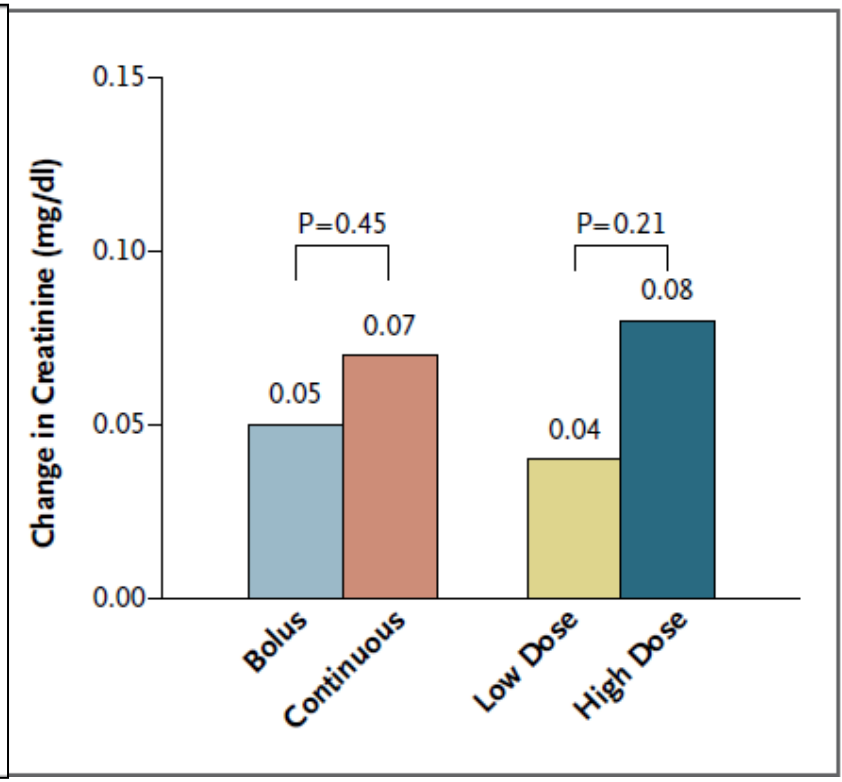
Diuretics dose and types of infusion - DOSE trial

- Bolus vs. Continuous

Patients' Global Assessment of Symptoms during the 72-Hour Study-Treatment Period.



Serum creatinine change



- High vs. Low

Felker, G.M. et al. N Eng J Med 2011;364:797-805

Poor response to diuretics

- Re-evaluating presence or absence of congestion
- **Sodium and fluid restriction**
- Addition of a second type of diuretic
  - Metolazone, spironolactone, chlorothiazide
- Inotropes
- **Adjustment of RAS blockers**
- **Ultrafiltration, may be considered**
  - Ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy (Class IIa, Level of Evidence: B)

Vasodilators - Nitrates

- Veno-dilatory effect in low does
  - Decrease pulmonary venous and LV filling pressure
  - Improve pulmonary congestion
  - Reduce dyspnea
  - Decrease myocardial oxygen consumption
- Arterial vasodilation in the systemic and coronary circulation
- PDE 5 inhibitor (sildenafil, tadalafil, and vardenafil) use should be ruled out before use
- Tolerance within 24hrs
- 20% no hemodynamic response

Vasodilators – Nesiritide

- Recombinant form of human BNP
- Balanced vasodilation
- Increase in cardiac output independent of changes in cardiac contractility and heart rate and less consistently natriuresis and diuresis
- Negative clinical outcome (증상개선, 생존율 향상) is published in 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Nesiritide in Patients with Acute Decompensated Heart Failure

Inotropes

- To relieve symptoms and improve end-organ function in patients with advanced HF
  - LV dilatation
  - Reduced LVEF
  - Low output syndrome
- Particularly for
  - Patients with **marginal systolic blood pressure (< 90 mmHg)**
  - Symptomatic hypotension despite adequate filling pressure
  - Unresponsive to/or intolerant of intravenous vasodilators
- Patients with fluid overload
  - poor response to intravenous diuretics
  - **worsening renal function**

Inotropes

- Major adrenergic receptors

Receptor	Location	Effect
β1	Myocardium	Increase atrial and ventricular contractility
	SA node	Increase heart rate
	AV node	Increase AV conduction
β2	Arterioles	Vasodilatation
	Lungs	Bronchodilation
α	Arterioles	Vasoconstriction

Inotropes

- Adrenergic receptor activity and other properties of sympathomimetic amines

	α (pph. vasoconstriction)	B1 (cardiac contractility)	β2 (pph. vasodilation)	Chronotropic effect
Norepinephrine	++++	+++	0	+
Epinephrine	+++	++++	+	++
Dopamine	++	+++	+	+
Dobutamine	0	+++	++	+
Isoproterenol	0	++++	+++	++++
Phenylephrine	++++	0	0	0

Inotropes - Dobutamine

- Beta 1,2 receptor agonist (3:1) – positive inotropic and chronotropic effect and **secondary vasodilatory effects**
- Tachyphylaxis, increased risk of arrhythmia
- 2-20mcg/kg/min
- For beta blocker users, usually higher dose is required (15-20mcg/kg/min)
- Combination with milrinon: hemodynamically additive effects

Inotropes - Dopamine

- At low doses ≤ 2mcg/kg/min
  - vascular D1 receptors in the coronary, renal and mesenteric beds with vasodilation and **natriuresis**
- At intermediate doses: 2-5mcg/kg/min
  - myocardial beta1 receptors with positive inotropic effects.
  - Increase SBP and heart rate
  - No change in diastolic pressure and peripheral vascular resistance.
- ≥5mcg/kg/min : triggers vasoconstriction.

- Low-dose dopamine (1-2mcg/kg/min) has been used together with dobutamine because dobutamine may decrease renal perfusion.

Inotropes - Milrinone

- Increased myocardial contractility and decreased systemic and pulmonary vascular tone
- Less chronotropic effects (Milirone < dobutamine)
- Less interaction with beta blocker
- IV bolus – associated with hypotension (10%)
- Initially 0.1 mcg/kg/min and titrate to 0.2 to 0.3 mcg/kg/min, up to 0.75 mcg/kg/min
- Effects on HF symptom and sign - uncertain
- Not indicated for routine use as an adjunct to standard therapy in patients with an exacerbation of HF.
- Increase mortality in patients with CAD→ extreme caution in patients with CAD and should be used only in patients with a low cardiac output state not responding to other noninotropic therapy

Digoxin – reconsidered in AHF management

- Ideal properties for the treatment of AHFS in patients with reduced ejection fraction with or without atrial fibillation
- No trials have investigated its role in this setting
- Digoxin rapidly improves hemodynamics without increasing heart rate or decreasing blood pressure
- Should be considered in patients with a low blood pressure due to a low cardiac output.
- Rapid IV administration may cause vasoconstriction.
- Ischemia, **hypokalemia**, and hypomagnesemia may increased the likelihood for development of digitalis intoxication.
- Digoxin should not be used in patients with moderate to severe renal impairment , ongoing ischemia, or advanced atrioventricular block

Heart transplantation in AHF

- Hemodynamic compromise due to HF

  - Refractory cardiogenic shock

  - Documented dependence on IV inotropic support

  - Peak VO2 < 10 ml/kg/min

    * peak VO_2 >14mL•kg^{-1}•min^{-1} : 1 year survival 94%

- Severe ischemic symptoms not amenable to CABG or PCI

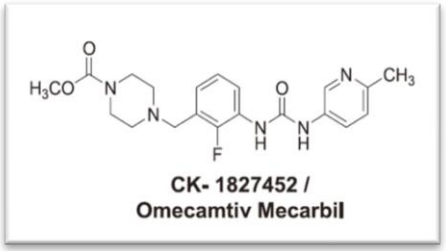
- Recurrent and refractory symptomatic ventricular arrhythmias

- Low LVEF alone is insufficient for TPL indication

New medical management of acute heart failure (잃어버린 10년 ?)

- Arginine Vasopressin antagonists - failed
- Soluble guanylate cyclase activator - failed (?), satety (?)
- Adenosine antagonists - failed
- Endothelin antagonists - failed
- Calcium sensitizer and ATP dependent Kch opener – failed

- Cardiac myosin activators
  - Increased cardiac muscle contractility
  - No increase in overall myocardial oxygen consumption
  - No influence on calcium
  - Clinical trial is impending



Discharge criteria

- Exacerbating factors addressed
- Near optimal volume status observed
- **Oral medication stable for 24 hrs**
- **No IV vasodilator or inotropes for 24 hrs**
- Near optimal pharmacologic therapy achieved, including ACE inhibitor and beta blocker
- Ambulation before discharge

- Post-discharge management plan
  : Patient and family education, Life style modification
  : Smoking cessation counseling
  : 1 or 2 weeks later follow-up at outpatient clinic

Dilemma in AHF management

- Therapies aiming to improve signs, symptoms and hemodynamics, such as diuretics, vasodilators, and **inotropes**, may theoretically precipitate or aggravate myocardial and kidney injury.

- Proven therapies for chronic HF, such as **beta blockers, ACE inthibitors, and ARBs** may worsen hemodynamics and kidney function.

Summary

- Management of acute heart failure remains an unmet need
- Remind Treatment Goals
  - Rapid control of symptoms, oxygenation/perfusion, volume
  - **Etiology and precipitating factors**
  - Adjunctive acute therapy
    : vasodilator vs. inotropes vs. diuretics
  - Optimize chronic therapy
  - Education
- Novel therapies are emerging in development
- Individualized and evidence-based approach

Management of acute decompensated HF

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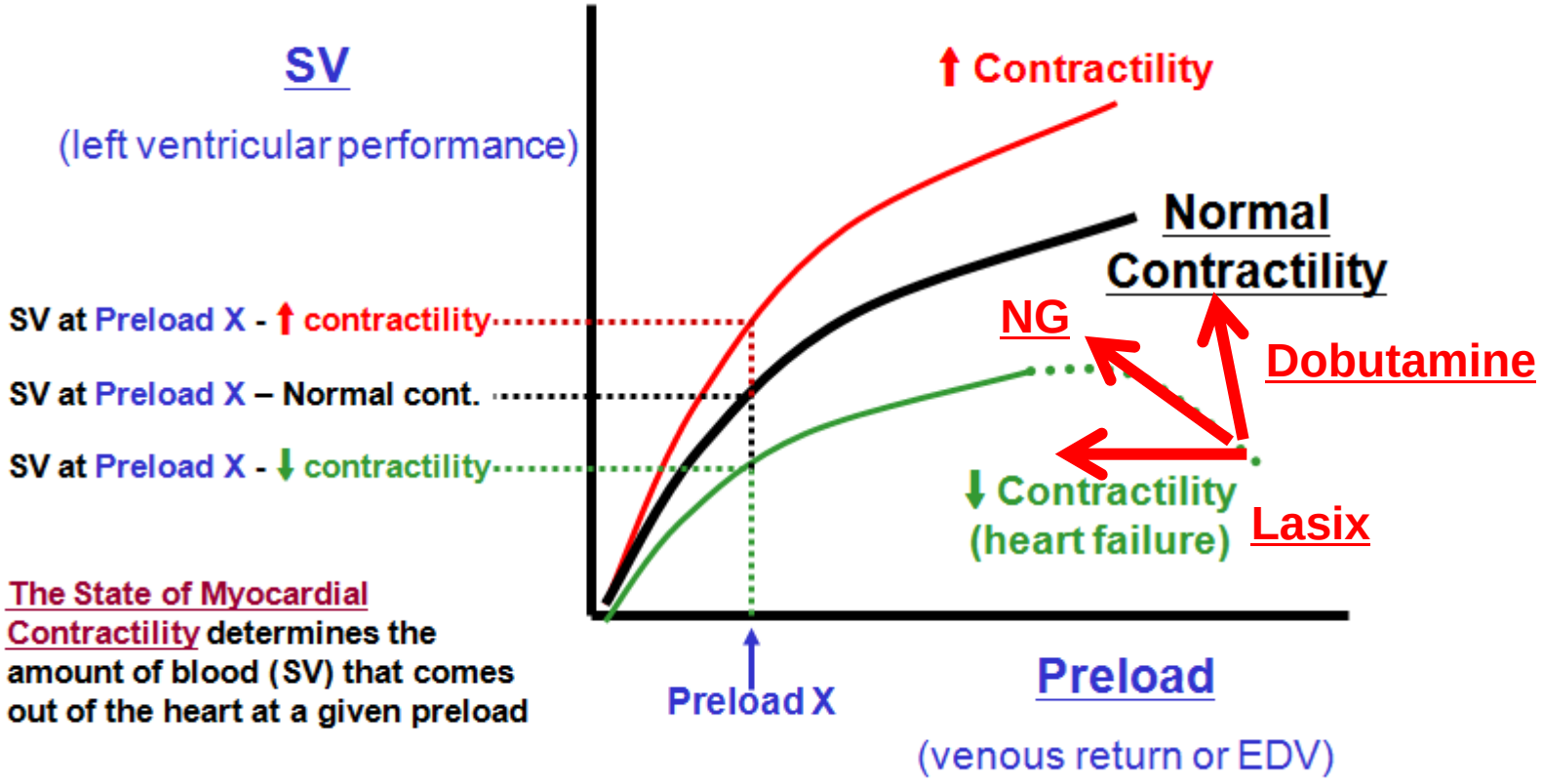

서울대학교병원
SEOUL NATIONAL UNIVERSITY HOSPITAL

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