Inotrope used in the termination of CPB

고려대학교 안암병원
김희중

Separation from CPB

- CPB -> Native circulation
- Protamine infusion
- Cannulas removal

Mechanism of Postop. LCO

- Cardioplegia induced myocardial dysfunction
- Precipitation of cardiac ischemia during aortic cross-clamping
- Reperfusion injury
- Activation of inflammatory and coagulation cascades
- The presence of nonrepaired preexisting cardiac disease.

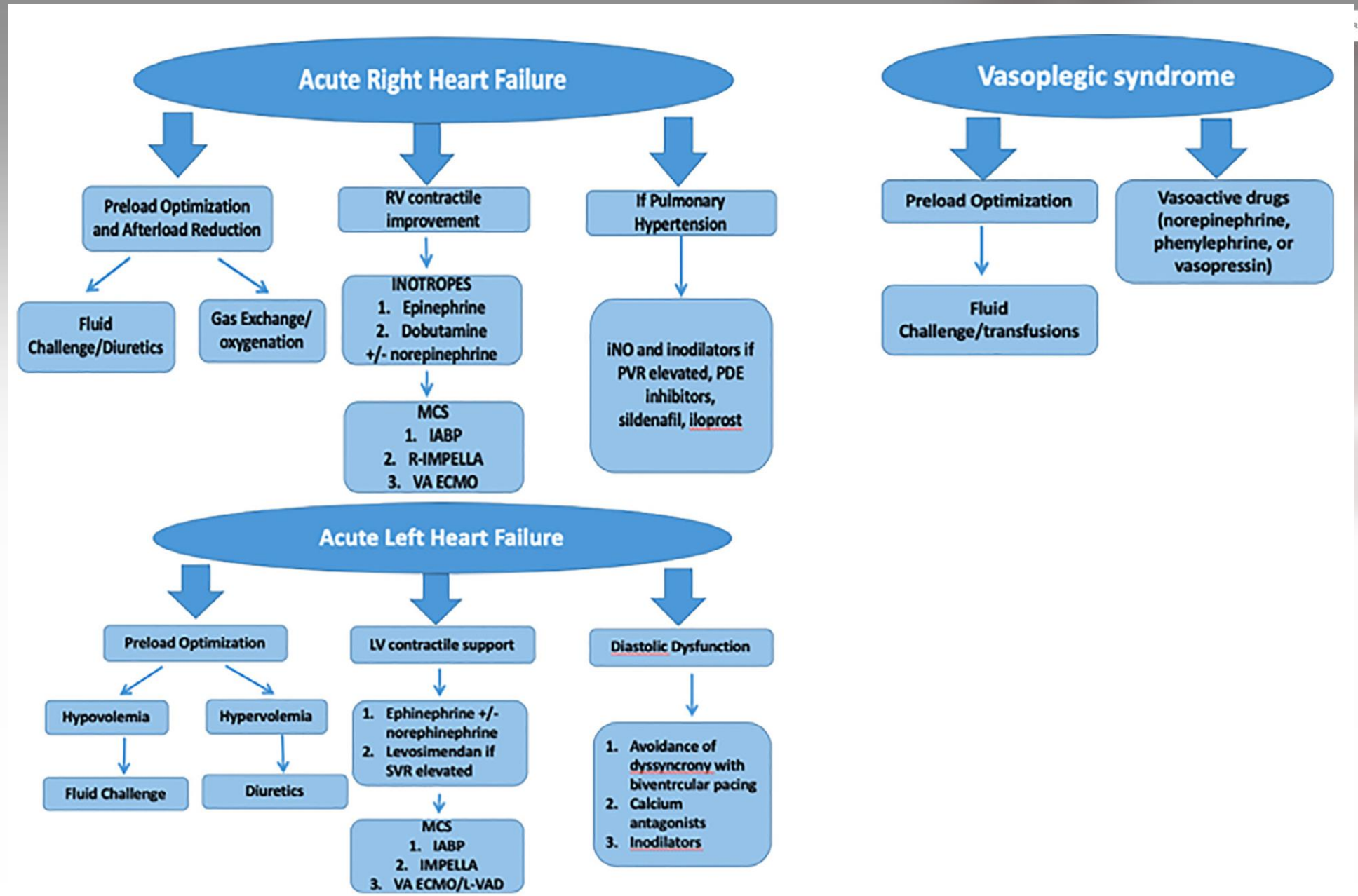


Fig. 1. Assessment and management of difficult cardiopulmonary bypass separation.

Difficult separation from CPB

- Difficulty separation

- At least, 2 kinds of inotropes or vasopressor

- Very difficulty or complex separation

- Pump weaning fail or mechanical circulatory support

VIS value
10 : easy
10-30 : difficult
30 : complex

How to Calculate Vasoactive and Inotropic Scores

Vasoactive and Inotropic Score (VIS)=	dopamine dose (μg/kg/min) +
	dobutamine dose (μg/kg/min) +
	enoximone dose (μg/kg/min)
	100 × epinephrine dose (μg/kg/min) +
	100 × norepinephrine dose (μg/kg/min)
	10 × milrinone dose (μg/kg/min) +
	10.000 × vasopressin dose (U/kg/min)

Modified from Zangrillo A, Alvaro G, Pisano A, et al. A randomized controlled trial of levosimendan to reduce mortality in high-risk cardiac surgery patients (CHEETAH): Rationale and design. Am Heart J 2016;177:66-73.[6]

Hazards of complex separation

- 19 tertiary hospitals, Blood Conservation Using Antifibrinolytics in a Randomized Controlled Trial (BART) cohort
- 2331 patients undergoing cardiac surgery
- Easy, vs difficult, vs complex separation from CPB

Difficult and complex separation from cardiopulmonary bypass in high-risk cardiac surgical patients: a multicenter study
J Cardiothorac Vasc Anesth. 2012 Aug;26(4):608-16.

Hazards of difficult separation

35% 15%

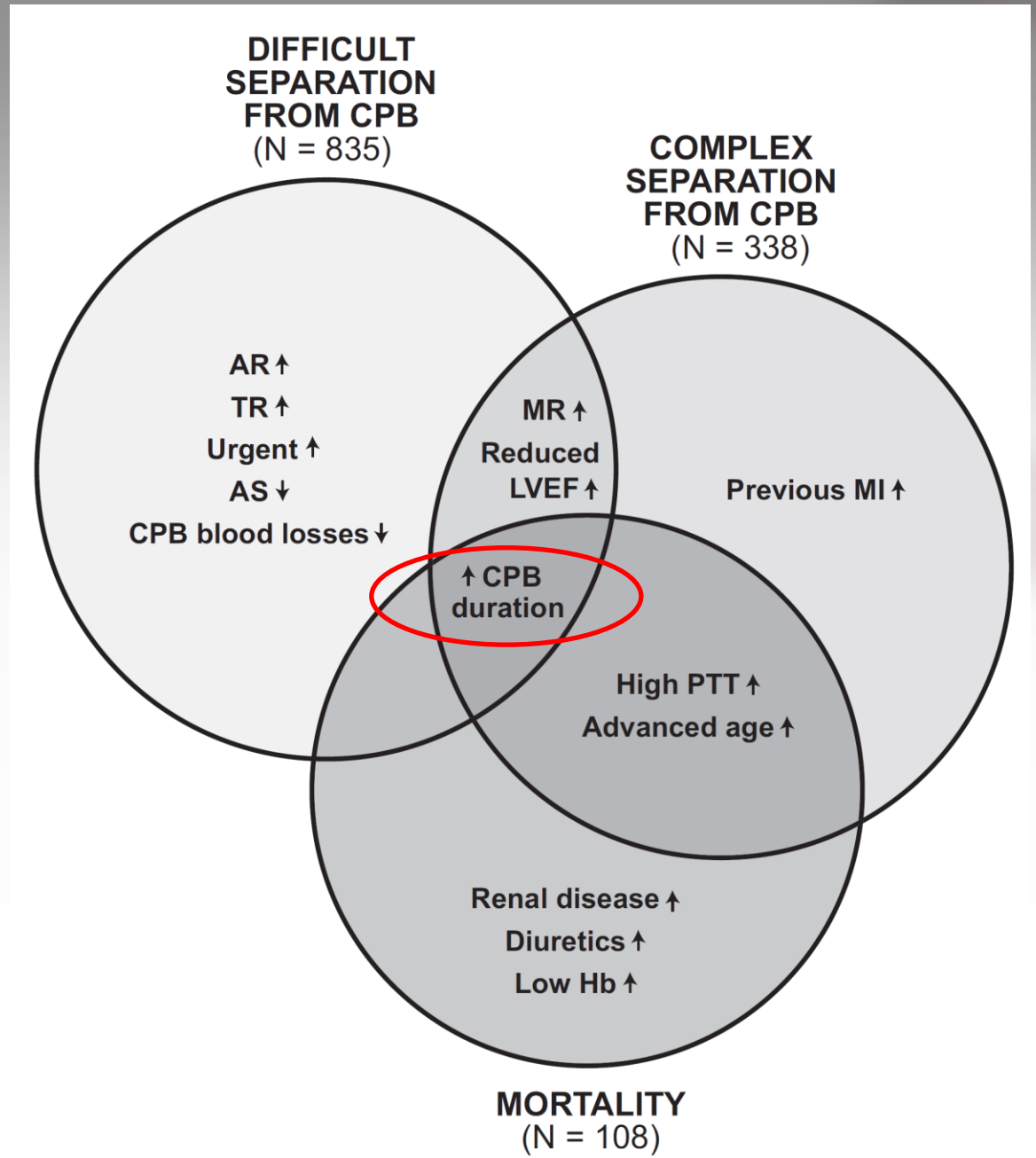
Table 5. Postoperative Outcome

Variable	Population (n = 2,331)	Easy (n = 1,158)	Difficult (n = 835)	Complex (n = 338)	Mortality (n = 108)
Mortality	108 (4.6)	24 (2.1)	39 (4.7)	45 (13.3)	
Stroke <30 days	72 (3.1)	29 (2.5)	25 (3)	18 (5.3)	15 (13.9)
Myocardial infarction <30 days	83 (3.8)	21 (1.8)	34 (4.1)	28 (8.3)	16 (14.8)
Cardiogenic shock	332 (14.2)	85 (7.3)	143 (17.1)	104 (30.8)	45 (41.7)
Respiratory failure	294 (12.7)	87 (7.5)	113 (13.5)	94 (27.8)	54 (50.0)
New-onset renal failure	299 (12.9)	102 (8.8)	126 (15.1)	71 (21.0)	47 (43.5.)
Massive bleeding	261 (11.2)	94 (8.1)	102 (12.2)	65 (19.2)	45 (41.7)
Intensive care unit length of stay (days)	3.2 ± 6.9	2.3 ± 4.4	3.5 ± 6.9	5.7 ± 11.9	4.5 ± 6.1
Hospital length of stay (days)	11.9 ± 12.6	10.2 ± 8.7	12.6 ± 12.2	15.9 ± 21.3	7.9 ± 7.6

Table 7. Predictors of Mortality

Variables	B ± SE	OR	95% CI	*p*
Age	0.0443 ± 0.0131	1.557	1.213-2.028	0.0007
Renal disease	0.6526 ± 0.3184	1.921	1.029-3.585	0.0404
Use of diuretics	0.5644 ± 0.2355	1.758	1.108-2.790	0.0165
Hemoglobin	−0.0147 ± 0.00692	0.985	0.972-0.999	0.0342
Partial thromboplastin time	0.0091 ± 0.00316	1.096	1.024-1.164	0.0039
Easy *v* difficult separation from CPB	0.5155 ± 0.2875	1.674	0.953-2.942	0.0730
Easy *v* complex separation from CPB	1.1285 ± 0.3033	3.091	1.706-5.601	0.0002
CPB duration	0.0097 ± 0.0013	1.788	1.529-2.103	<0.0001

KOREA UNIVERSITY MEDICAL CENTER


DIFFICULT SEPARATION FROM CPB
(N = 835)
COMPLEX SEPARATION FROM CPB
(N = 338)
AR ↑
TR ↑
Urgent ↑
AS ↓
CPB blood losses ↓
MR ↑
Reduced LVEF ↑
Previous MI ↑
↑ CPB duration
High PTT ↑
Advanced age ↑
Renal disease ↑
Diuretics ↑
Low Hb ↑
MORTALITY
(N = 108)

INOTROPES AND VASOPRESSOR

Categories of inotropes

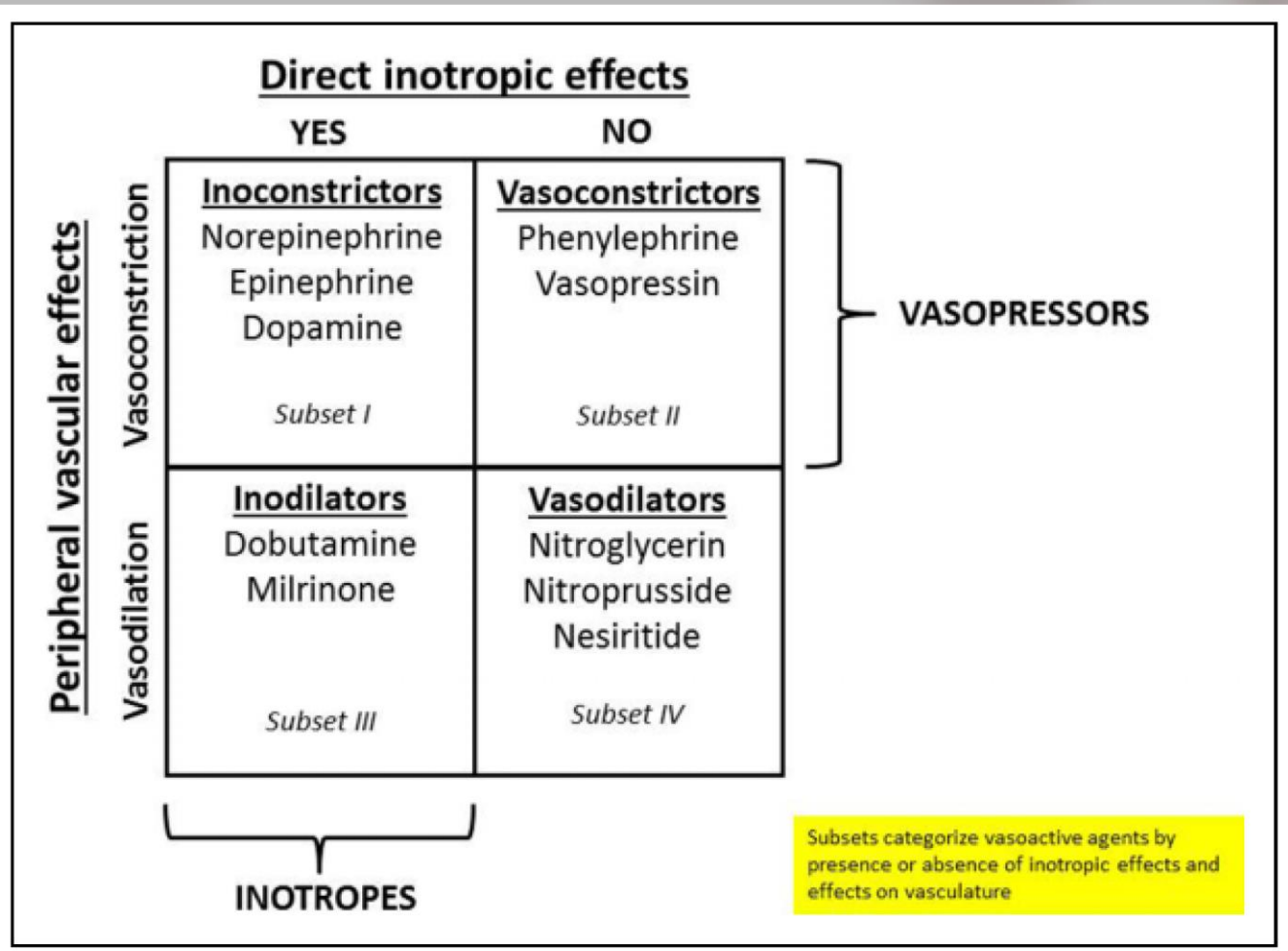


Figure 1. Proposed classification of vasoactive agents.

Summary of locations and responses of common adrenergic receptors

Receptor	Location	Response to stimulation
β1	Heart	Positive inotropic effect
β2	Vascular and bronchial smooth muscle	Vasodilation, bronchodilation
α1	Heart, vascular smooth muscle	Positive inotropy, vasoconstriction
α2	Vascular smooth muscle	Vasoconstriction
D1	Renovascular smooth muscle	Renal vasodilation
V1	Vascular smooth muscle	Vasoconstriction
V2	Renal collecting ducts	Antidiuresis

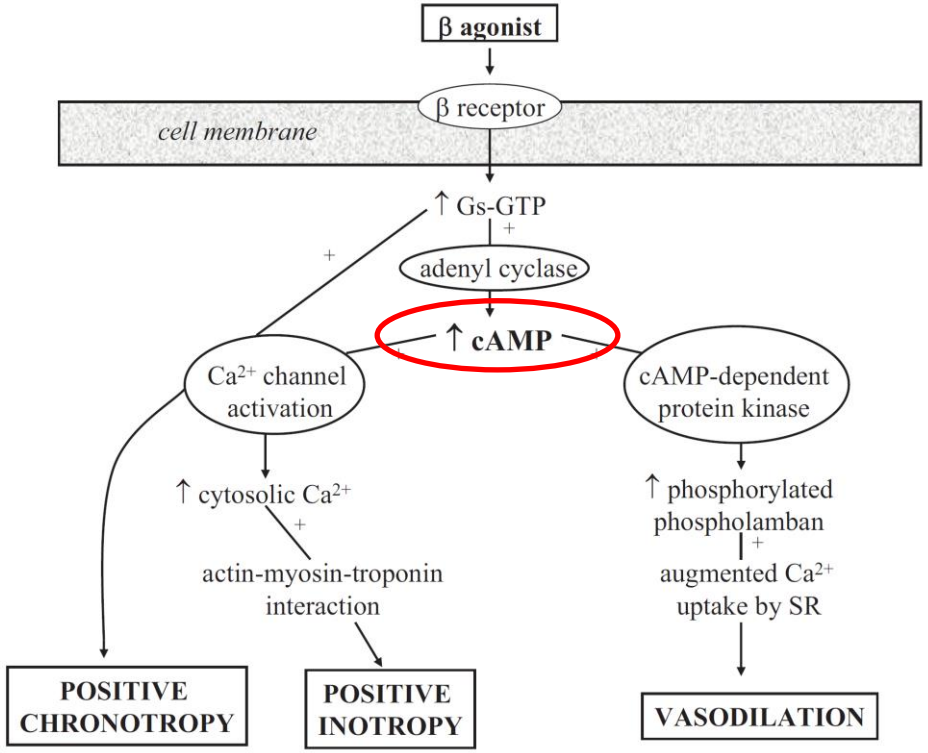


Figure 1. Simplified schematic of postulated intracellular actions of β-adrenergic agonists. β-Receptor stimulation, through a stimulatory Gs-GTP unit, activates the adenyl cyclase system, which results in increased concentrations of cAMP. In cardiac myocytes, β_1-receptor activation through increased cAMP concentration activates Ca^{2+} channels, which leads to Ca^{2+}-mediated enhanced chronotropic responses and positive inotropy by increasing the contractility of the actin-myosin-troponin system. In vascular smooth muscle, β_2-stimulation and increased cAMP results in stimulation of a cAMP-dependent protein kinase, phosphorylation of phospholamban, and augmented Ca^{2+} uptake by the sarcoplasmic reticulum (SR), which leads to vasodilation. Adapted from Gillies et al[3] with permission of the publisher.

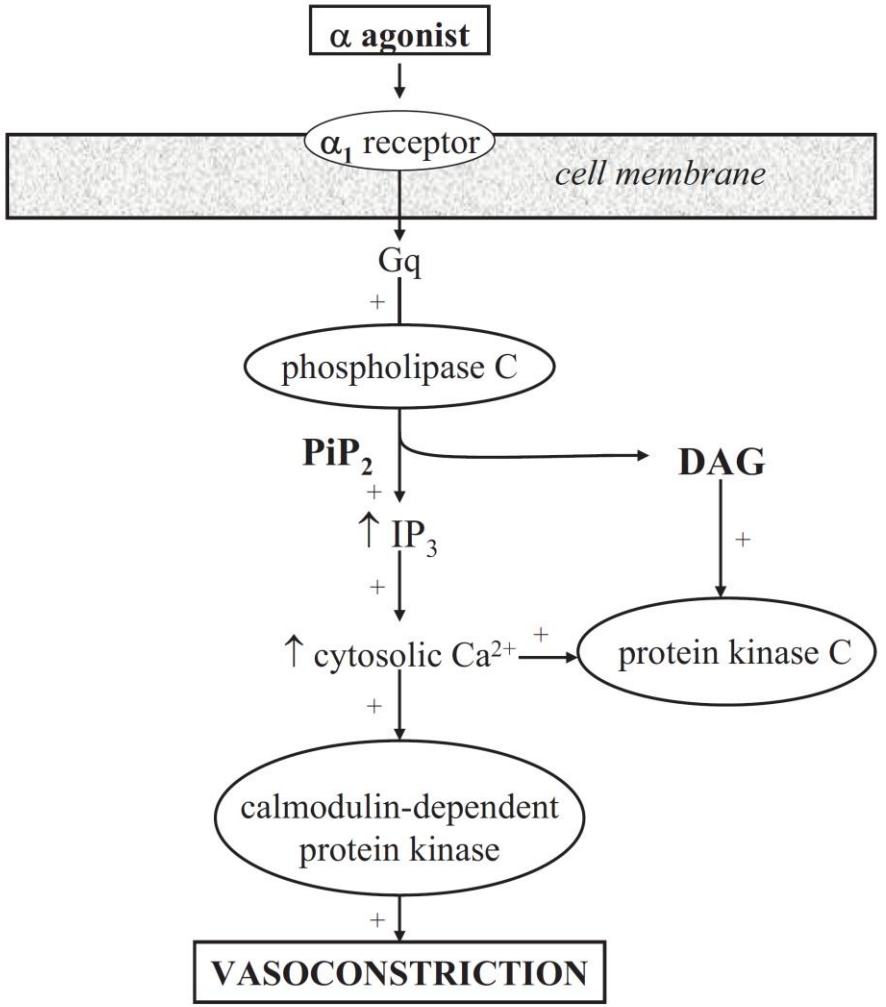


Figure 2. Schematic representation of postulated mechanisms of intracellular action of α_1-adrenergic agonists. α_1-Receptor stimulation activates a different regulatory G protein (Gq), which acts through the phospholipase C system and the production of 1,2-diacylglycerol (DAG) and, via phosphatidyl-inositol-4,5-biphosphate (PiP_2), of inositol 1,4,5-triphosphate (IP_3). IP_3 activates the release of Ca^{2+} from the sarcoplasmic reticulum (SR), which by itself and through Ca^{2+}-calmodulin–dependent protein kinases influences cellular processes, leading in vascular smooth muscle to vasoconstriction. Adapted from Gillies et al[3] with permission of the publisher.

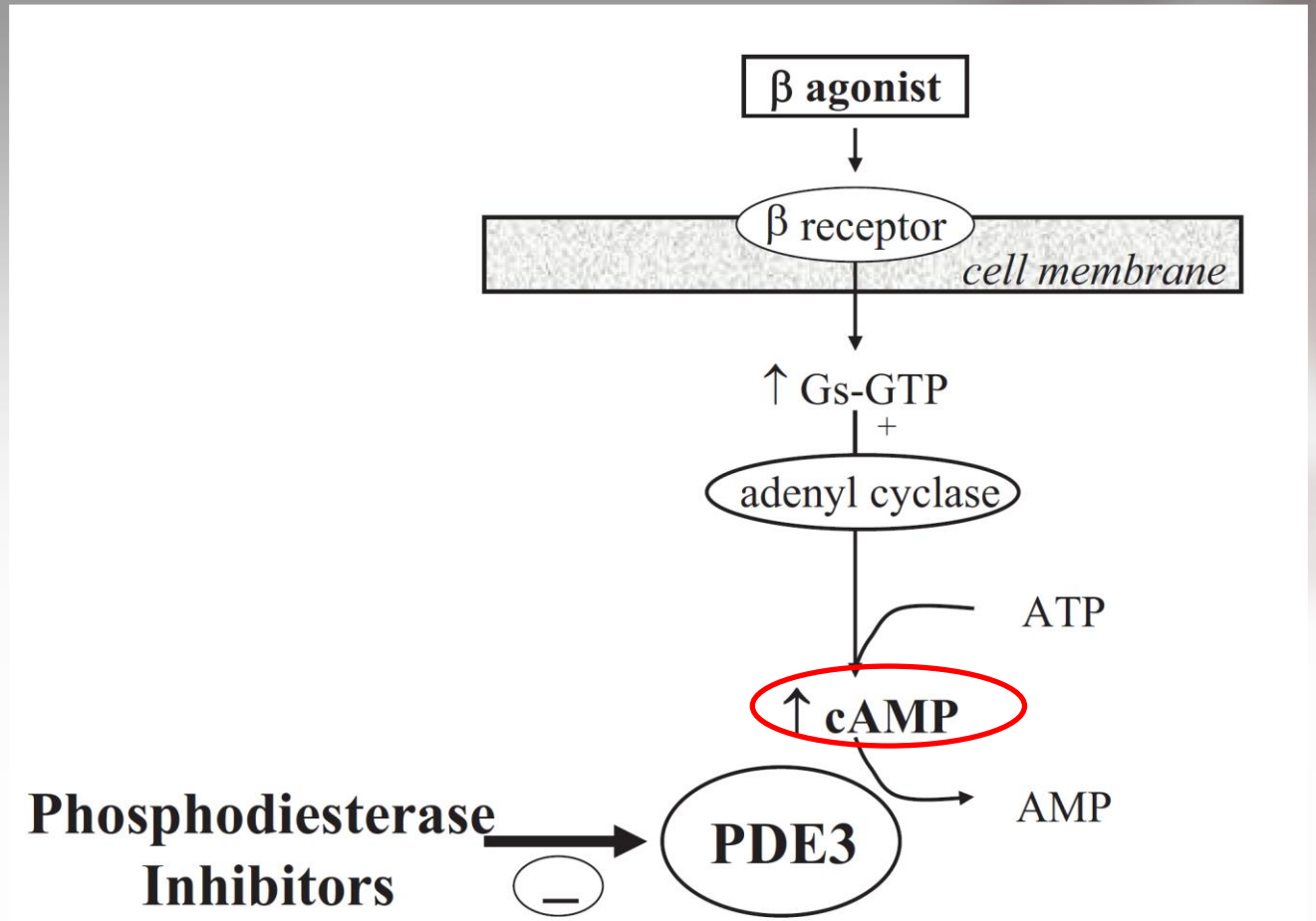


Figure 4. Basic mechanism of action of PDIs. PDIs lead to increased intracellular concentration of cAMP, which increases contractility in the myocardium and leads to vasodilation in vascular smooth muscle.

Dobutamine

- α1, β1, β2
- Dose dependent
- Inotropy and chronotropy
- Vasodilatation: SVR, PVR ↓

-> CO ↑

- High dose : low vasoconstriction
- First line drug for cardiogenic shock

Dopamine

- α1, β1, dopaminergic
- Dose dependent
- Low dose – renal vasodilatation “renal dose”
- Intermediate - inotropy
- High dose - vasoconstriction
- Less effective than norepinephrine

Norepinephrine

- α, β1, β2
- Powerful vasoconstrictor
- Moderate inotropic properties
- CO ↑↓
- First line drug for various shock
- Effective for cardiogenic shock presenting hypotension

Epinephrine

- α, β
- Low dose : β dominant
- High dose: α1
- Inotropic ↑ ↑, Vasoconstriction ↑ ↑
- Myocardial ischemia ↑ in cardiogenic shock
- Peripheral ischemia

Phenylephrine

- Only α agonist
- Increase peripheral vascular resistance
- Bolus injection
- Negative effect on CO

Milrinone

- Phosphodiesterase-3 inhibitor -> cAMP ↑
- Vasodilatation effect : > dobutamine
- Pulmonary capillary wedge pressure & SVR ↓
- Second line drug for cardiogenic shock
- If pul. HTN, milrinone is preferred.

Vasopressin

- Antidiuretic hormone
- V1a receptor : vascular smooth muscle
- Strong vasoconstriction
- Effective for vasoplegic syndrome

Calcium-sensitizing agent

- Levosimendan
- Inodilator
- Binds to cardiac troponin C -> increase inotropy
- Relax smooth muscle -> decrease in PVR
- Good hemodynamic effect but no proved survival benefit
- Not available

Table 1. Clinical Pharmacology and Use of Vasopressors and Inotropes.

	Mechanism	Usual Dose Range	Inotropy	Clinical Use
Vasoconstrictors				
Phenylephrine	α_1	0.1-1 μg/kg/min	0	Tachyarrhythmias, dynamic LVOT obstruction
Vasopressin	V_{1a}	0.03-0.06 U/min	0	Tachyarrhythmias, vasoplegia
Angiotensin-II	AT_1	10-40 ng/kg/min	0	Refractory shock
Inoconstrictors				
Norepinephrine	$\alpha_1 > \beta_1$	0.01-0.3 μg/kg/min	+	First-line for all forms of shock
Epinephrine	$\beta_{1/2} > \alpha_1$	0.01-0.3 μg/kg/min	+++	Second-line vasopressor or inotrope
Dopamine	$\beta_1 > \alpha_1$	2-10 μg/kg/min	+++	Second-line inotrope or bradycardia (low dose)
Inodilators				
Dobutamine	$\beta_{1/2} > \alpha_1/\beta_2$	2-10 μg/kg/min	+++	First-line inotrope for shock
Isoproterenol	$\beta_{1/2}$	0.01-0.1 μg/kg/min	+++	Bradycardia
Milrinone	PDE_3I	0.1-0.5 μg/kg/min	++	First-line inotrope for heart failure
Levosimendan	PDE_3I[a]	0.05-2 μg/kg/min	++	Not FDA-approved for clinical use in USA

Abbreviations: FDA, Food and Drug Administration; LVOT, left ventricular outflow tract; PDE-3I, phosphodiesterase-3 inhibitor.
[a] Also sensitizes myofilaments to calcium.

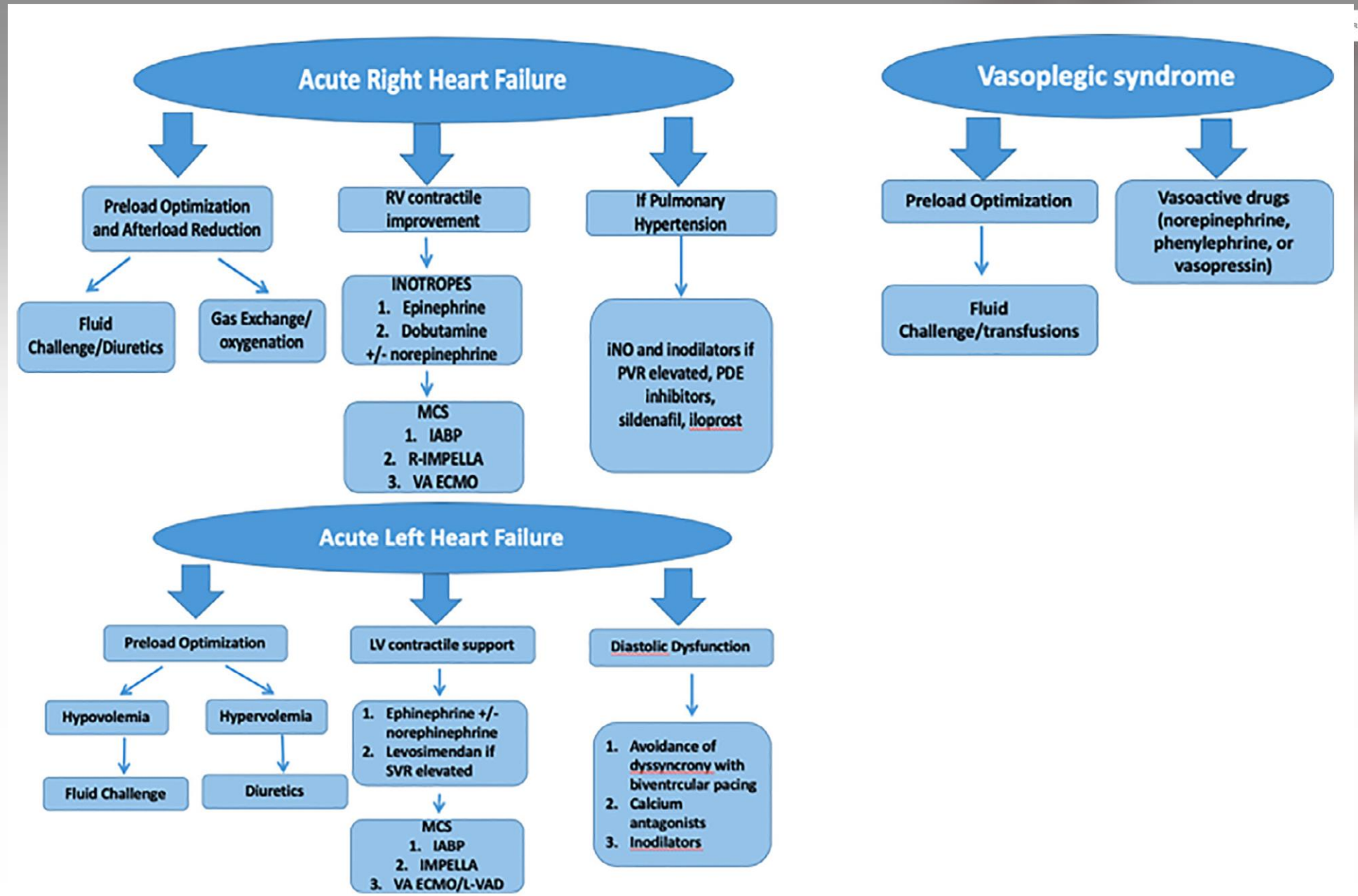


Fig. 1. Assessment and management of difficult cardiopulmonary bypass separation.

LV dysfunction

- Suboptimal myocardial protection or prolonged aortic clamping time
- LV dysfunction -> CO ↓ (< 2.0 L/min/m2, low systolic blood pressure < 90 mmHg, and signs of tissue hypoperfusion)
- First line drug – dobutamine
- SVR low -> norepinephrine
- SVR high -> nitroprusside or milrinone

RV dysfunction

- Coronary ischemia, myocardial stunning, arrhythmia, air embolism, thromboembolism
- Frequently associated with Pul. HTN
- CVP ↑, RV distention(D-shape LV) during weaning
- Tx: optimizing preload, reduce the afterload, improve the contractility

Tx for RV dysfunction

- Reduce RV volume – drain to reservoir, use of diuretics
- Firstline drug – dobutamine
- Biventicular failure - epinephrine
- If linked to pul. resistance↑, inodilators(dobutamine or milrinone) or NO or iloprost inhalation

Vasoplegic syndrome

- Incidence: 9% in cardiac surgery
- Mortality: 5-15%

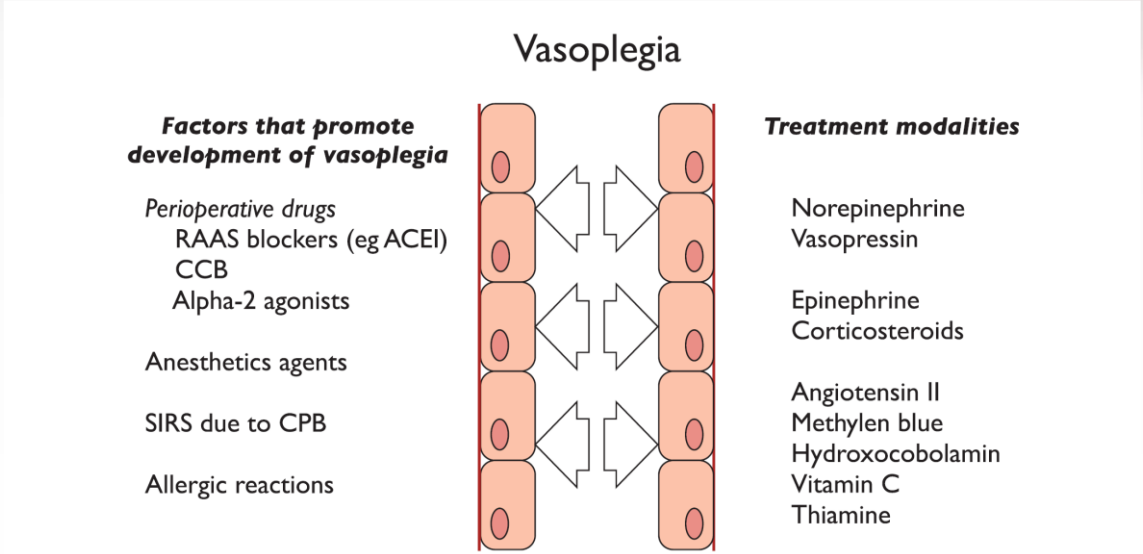


Fig. 2. Causes and treatment modalities for perioperative vasoplegia.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blockers; CPB, cardiopulmonary bypass; RASS, renin-angiotensin-aldosterone system; SIRS, systemic inflammatory response syndrome.

Vasoplegia criteria

- Hypotension (mean arterial pressure <50 mmHg or systolic blood pressure <85 mmHg)
- Low systemic vascular resistance (<600-800 dynes s cm5, or systemic vascular resistancesindices <1800 dyne s cm5 m2),
- normal or high systemic flows (cardiac index >2.5 L min m2),
- normal or reduced central filling pressures (CVP < 10 mmHg and pulmonary wedge pressure <10 mmHg),
- by an increased need for vasopressors (0.2-0.5 mg/kg/min of norepinephrine with normal intravascular volume)

Vasoplegic syndrome: An update on perioperative considerations. J Clin Anesth 2017;40:63–71.

Vasopressin vs. Norepinephrine for Vasoplegic shock

- 330 randomized, vasoplegic shock after cardiac surgery
- 149 vasopressin, 151 norepinephrine

Table 2. Primary and Secondary Outcomes in the Two Groups

Variable	Norepinephrine (n = 151)	Vasopressin (n = 149)	Unadjusted Odds Ratio or Hazard Ratio or Between-group Difference (95% CI)	*P* Value	Adjusted* Odds Ratio or Hazard Ratio or Between-group Difference (95%CI)	*P* Value
Primary outcome, n (%)	74 (49.0)	48 (32.2)	0.55 (0.38 to 0.80)	0.0014	0.52 (0.36 to 0.75)	0.0005
30-d mortality	24 (15.9)	23 (15.4)	0.99 (0.56 to 1.76)	0.98	1.11 (0.62 to 1.96)	0.73
MV > 48 h	13 (8.6)	8 (5.4)	0.62 (0.26 to 1.49)	0.28	0.62 (0.26 to 1.51)	0.30
Sternal wound infection	15 (9.9)	7 (4.7)	0.46 (0.19 to 1.13)	0.09	0.48 (0.19 to 1.18)	0.11
Reoperation	10 (6.6)	10 (6.7)	0.8 (0.52 to 1.23)	0.31	0.79 (0.51 to 1.22)	0.28
Stroke	4 (2.6)	4 (2·7)	1.03 (0.26 to 4.11)	0.97	1.08 (0.27 to 4.39)	0.91
Acute renal failure	54 (35.8)	15 (10.3)	0.26 (0.15 to 0.46)	< 0.0001	0.26 (0.15 to 0.46)	< 0.0001
Secondary outcomes, n (%)						
Infection	23 (15.2)	16 (10.7)	0.67 (0.34 to 1.33)	0.25	0.71 (0.35 to 1.42)	0.33
Septic shock	13 (8.6)	9 (6.0)	0.68 (0.28 to 1.65)	0.40	0.73 (0.3 to 1.81)	0.50
Atrial fibrillation	124 (82.1)	95 (63.8)	0.38 (0.22 to 0.65)	0.0004	0.37 (0.22 to 0.64)	0.0004
Ventricular arrhythmias	32 (21.2)	27 (18.1)	0.82 (0.46 to 1.46)	0.50	0.8 (0.45 to 1.43)	0.45
Length of ICU stay (d), median (IQR)	6 (4 to 9)	5 (4 to 7)	−2.42 (−4.11 to −0.73)	0.0050	−2.28 (−3.94 to −0.62)	0.0071
Length of hospital stay (d), median (IQR)	13 (10 to 20)	10 (8 to 12)	−3.76 (−6.1 to −1.42)	0.0016	−3.66 (−6.01 to −1.32)	0.0022

*Adjustment was performed for predictive variables of the combined endpoint: chronic renal failure, initial hematoc
nephrine. Hazard ratio was used for primary outcomes. Odds ratio or between-group difference was used for secon
ICU = intensive care unit; IQR = interquartile range; MV = mechanical ventilation.

Anesthesiology
. 2017 Jan;126(1):85-93

KOREA UNIVERSITY GLOBAL PRIDE

EVIDENCE

KOREA UNIVERSITY MEDICAL CENTER

Dobutamine vs milrinone

- Randomized 60 vs 60 after cardiac surgery

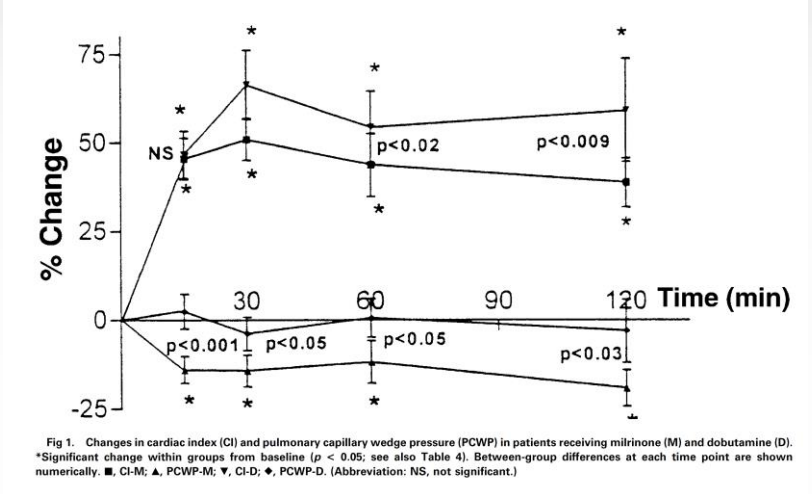
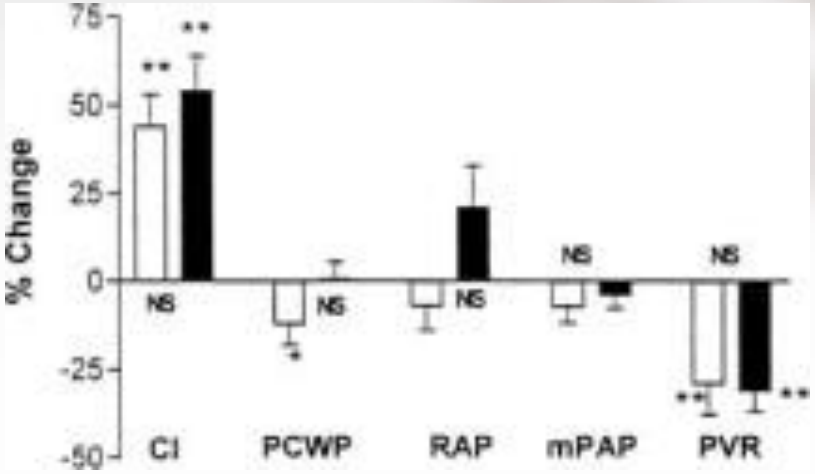
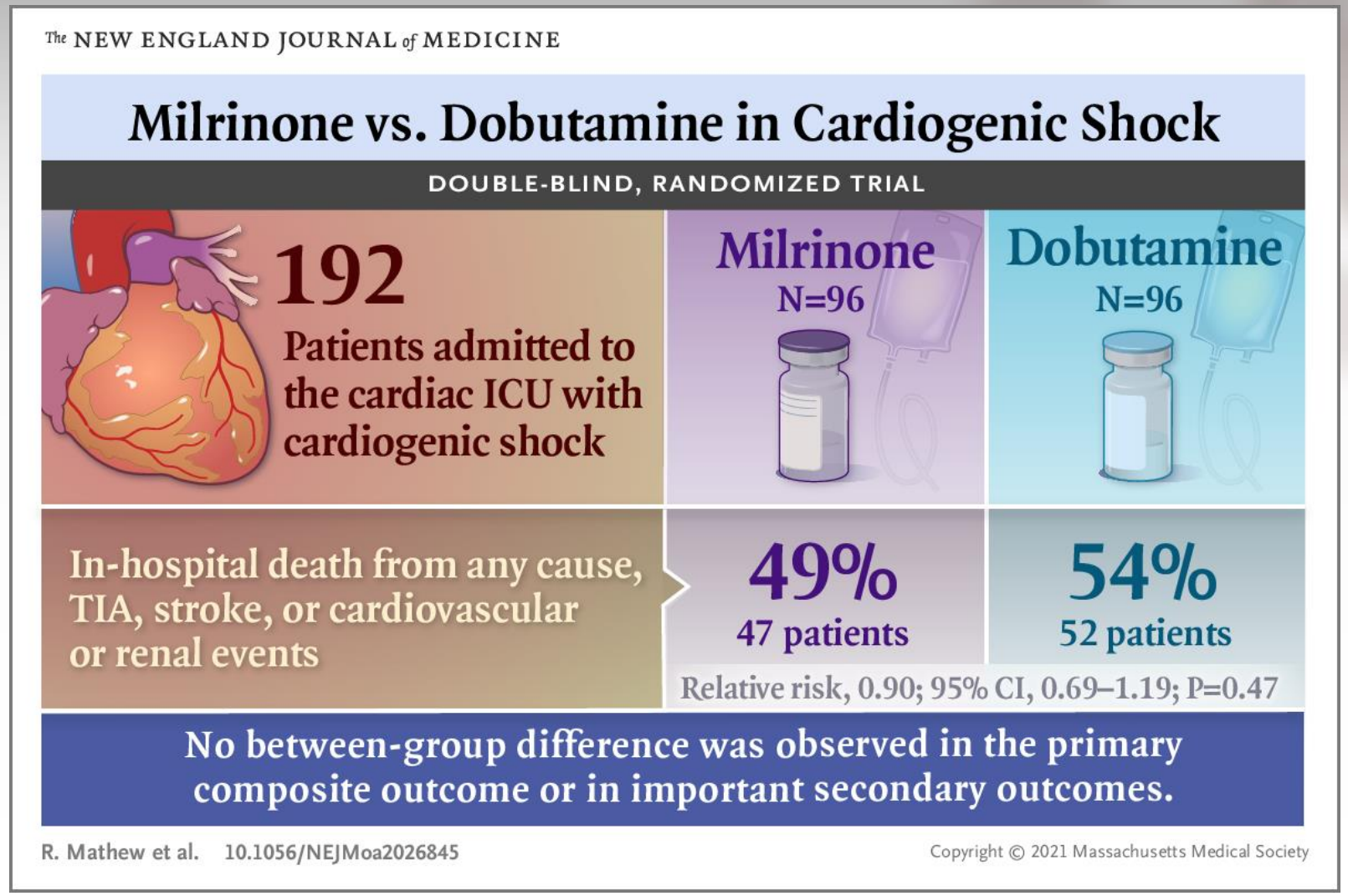


Fig 1. Changes in cardiac index (CI) and pulmonary capillary wedge pressure (PCWP) in patients receiving milrinone (M) and dobutamine (D). *Significant change within groups from baseline ($p < 0.05$; see also Table 4). Between-group differences at each time point are shown numerically. ■, CI-M; ▲, PCWP-M; ▼, CI-D; ◆, PCWP-D. (Abbreviation: NS, not significant.)



J Cardiothorac Vasc Anesth. 2001 Jun;15(3):306-15

Dobutamine Compared with Milrinone (DOREMI) trial



Dobutamine vs milrinone

- 1452 patients undergoing cardiac surgery
- Dobutamine versus milrinone

Table 2 Difference in standardized mortality rates according to intraoperative inotrope treatment

Statistical model	Number of patients	Standardized risk difference (%)(95% CI)	*p* value
Main analyses			
Crude 30-day mortality, milrinone vs dobutamine	1452	4.2 (1.6; 6.8)	< 0.01
Adjusted 30-day mortality, milrinone vs dobutamine	1452	4.1 (1.2; 6.9)	< 0.01
Crude 1-year mortality, milrinone vs dobutamine	1452	6.1 (2.2; 10.1)	< 0.01
Adjusted 1-year mortality, milrinone vs dobutamine	1452	4.8 (0.4; 9.2)	0.03
Sensitivity analyses on subpopulations			
Adjustment for anesthetist's preference of milrinone			
Crude 30-day mortality, milrinone vs dobutamine	817	7.4 (4.4; 10.3)	< 0.01
Adjusted 30-day mortality, milrinone vs dobutamine	817	6.2 (2.7; 9.6)	< 0.01
Adjustment for hemodynamic status prior to cardiopulmonary bypass			
Crude 30-day mortality, milrinone vs dobutamine	533	2.1 (−2.2; 6.4)	0.34
Adjusted 30-day mortality, milrinone vs dobutamine	533	1.4 (−3.6; 6.4)	0.59

Intraoperative milrinone versus dobutamine in cardiac surgery patients: a retrospective cohort study on mortality
Crit Care. 2018 Feb 26;22(1):51

EACTS guideline for separation from CPB (2019)

Recommendations	Class[a]	Level[b]	Ref[c]
Positive inotropic and/or vasopressor agents are recommended as a first-line treatment to reduce mortality rates in patients with haemodynamic instability.	I	A	[342]
The use of phosphodiesterase inhibitors should be considered to increase weaning success.	IIa	B	[344, 345]
The prophylactic infusion of levosimendan to reduce adverse events and mortality is not recommended.	III	A	[347, 348]
Levosimendan as a therapeutic strategy in selected difficult-to-wean patients having CPB may be considered.	IIb	C	
In patients requiring haemodynamic support after cardiac surgery, adding levosimendan to other positive inotropes or vasopressors is not recommended.	III	B	[349]

KOREA UNIVERSITY MEDICAL CENTER

2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery
European Journal of Cardio-Thoracic Surgery, Volume 57, Issue 2, February 2020, Pages 210–251

Prophylactic PDEi

- 234 patient undergoing cardiac surgery
- Amrinone versus placebo

	Amrinone ($n = 115$)	Placebo ($n = 114$)	p
Failure to wean	8 [7]	24 [21]	0.002
Failure to wean controlling for LVEF			
Normal function; >55%	4/56 [7]	11/54 [20]	0.04
Mild dysfunction; 46–55%	2/25 [8]	4/22 [18]	0.29
Moderate dysfunction; 36–45%	2/30 [7]	7/32 [22]	0.08
Severe dysfunction; <35%	0/3 [0]	2/6 [33]	0.25
Criteria for failure to wean			
Mean arterial pressure <65 mmHg	8	20	
Cardiac index <2 $l.min^{-1}.m^{-2}$	7	18	
PAD >25 mmHg or prebypass	8	20	
Gross ventricular hypokinesis	3	15	
Gross ECG changes*	1	2	
Failure to wean per surgeon			
A	2/42 [5]	10/42 [23]	
B	3/36 [8]	7/41 [17]	0.88
C	3/37 [8]	7/31 [23]	

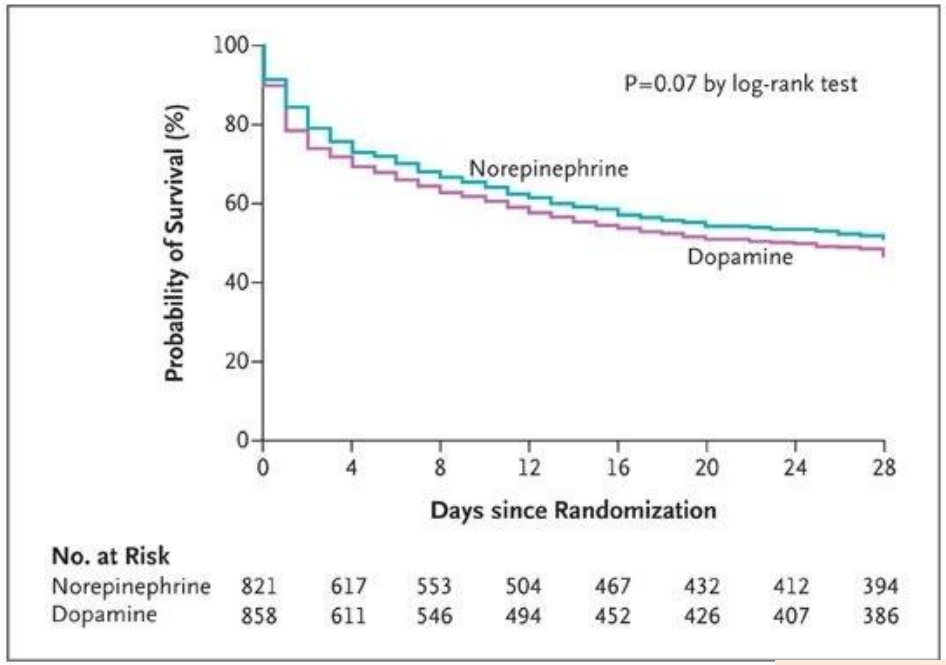
*Two of these patients had intractable ventricular tachycardia, the third had global ST segment elevation on ECG. LVEF, left ventricular ejection fraction; PAD, pulmonary artery diastolic pressure.

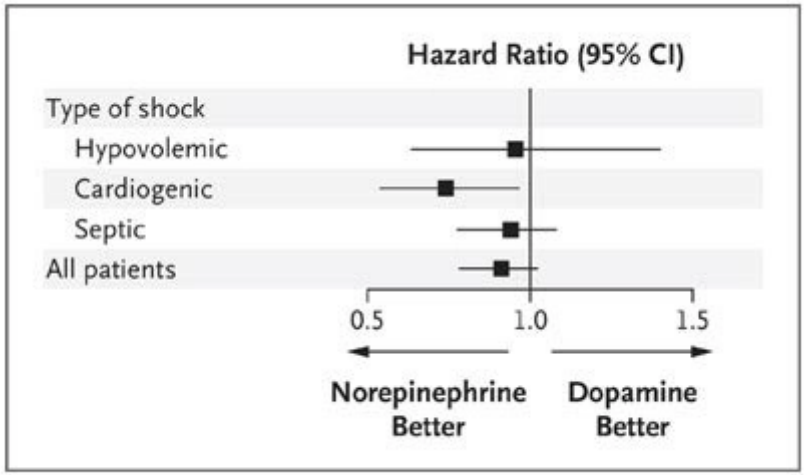
Prophylactic amrinone for weaning from cardiopulmonary bypass

Anaesthesia.
2000 Jul;55(7):627-33

Dopa vs. Norepi.

- Randomized 1679 patients
- Subgroup = cardiogenic shock, higher rate of arrhythmia





Comparison of dopamine and norepinephrine in the treatment of shock
N Engl J Med . 2010 Mar 4;362(9):779-89

Inhaled NO

- Meta-analysis of RCT

Table 1
Characteristics of Included Studies

Study	Comparator	Population	Surgery	Nitric Oxide Dose	Nitric Oxide Initiation Setting
Cai et al[19]	Milrinone	Pediatric	CHD Fontan-type	< 20 ppm	Intensive care unit
Checchia et al[20]	Placebo	Pediatric	CHD (Fallot repair)	20 ppm	Operating room
Chung et al[21]	Iloprost	Adult	CABG	20 ppm	Operating room
Fattouch et al[22]	1-PGE1 2-Nitroprusside	Adult	MVR ± TVr	20 ppm	Intensive care unit
Fattouch et al[23]	1-PGI2 Epoprostenol 2-intravenous vasodilators	Adult	MVR or MVr	Unclear	Operating room
Fernandes et al[24]	Oxygen	Adult	MVR or MVr	10 ppm	Operating room
Gianetti et al[12]	Standard care	Adult	AVR + CABG	20 ppm	Operating room
James et al[25]	Standard care	Pediatric	CHD repair	20 ppm	Operating room
Kirbas et al[26]	Iloprost	Pediatric	CHD repair	20 ppm	Operating room
Knothe et al[27]	Standard care	Adult	Cardiac surgery	30 ppm	Operating room
Miller et al[28]	Placebo	Pediatric	CHD repair	10 ppm	Intensive care unit
Prendergast et al[29]	Standard care	Adult	CABG	10-40 ppm	Intensive care unit
Rajek et al[30]	PGE1	Adult	Heart transplantation	4-24 ppm	Operating room
Solina et al[31]	Milrinone	Adult	Cardiac surgery	20/40 ppm	Operating room
Solina et al[32]	Milrinone	Adult	Cardiac surgery	10/20/30/40 ppm	Operating room
Wagner et al[33]	Nitroglycerine	Adult	Valve replacement	40 ppm	Operating room
Winterhalter et al[34]	Iloprost	Adult	Cardiac surgery	20 ppm	Operating room
Zhang et al[35]	Standard care	Adult	Valve replacement	20 ppm	Operating room

J Cardiothorac Vasc Anesth. 2018 Dec;32(6):2512-2519

Inhaled NO

- No difference in Mean PAP and survival
- Decrease in ICU stay, mechanical ventilation

- There is no strong evidence of survival benefit of inhaled NO compared to standard care or other vasodilator drug.

Early MCS support

- Consider MCS (IABP, ECMO, or VAD) to reduce cardiac stress derived from fail of CPB separation
- High VIS score, severe RV dysfunction, remnant cardiac disease

Summary

- Dobutamine is first line drug for cardiogenic shock after cardiac surgery.
- Presenting pulmonary hypertension : dobutamine+nitroprusside, milrinone, inhaled NO or iloprost
- If vasopressor required: norepinephrine > dopa
- Vasoplegic syndrome : adding vasopressin reduce quantity of norepinephrine

Conclusion

- Careful assessments for hemodynamic and causes of LCO are important to choose and escalate inotropes or vasopressors.
- High dose inotropes (VIS > 30) is associated with higher risk of complex CPB separation.
- Early mechanical circulatory support in complex CPB separation patients is better option to reduce perioperative complications. (Bridge to recovery)

KOREA UNIVERSITY GLOBAL PRIDE

경청해주셔서 감사합니다.

KOREA UNIVERSITY MEDICAL CENTER