Pharmacologie cardio-vasculaire

Résidents anesthésie

2 décembre 2021

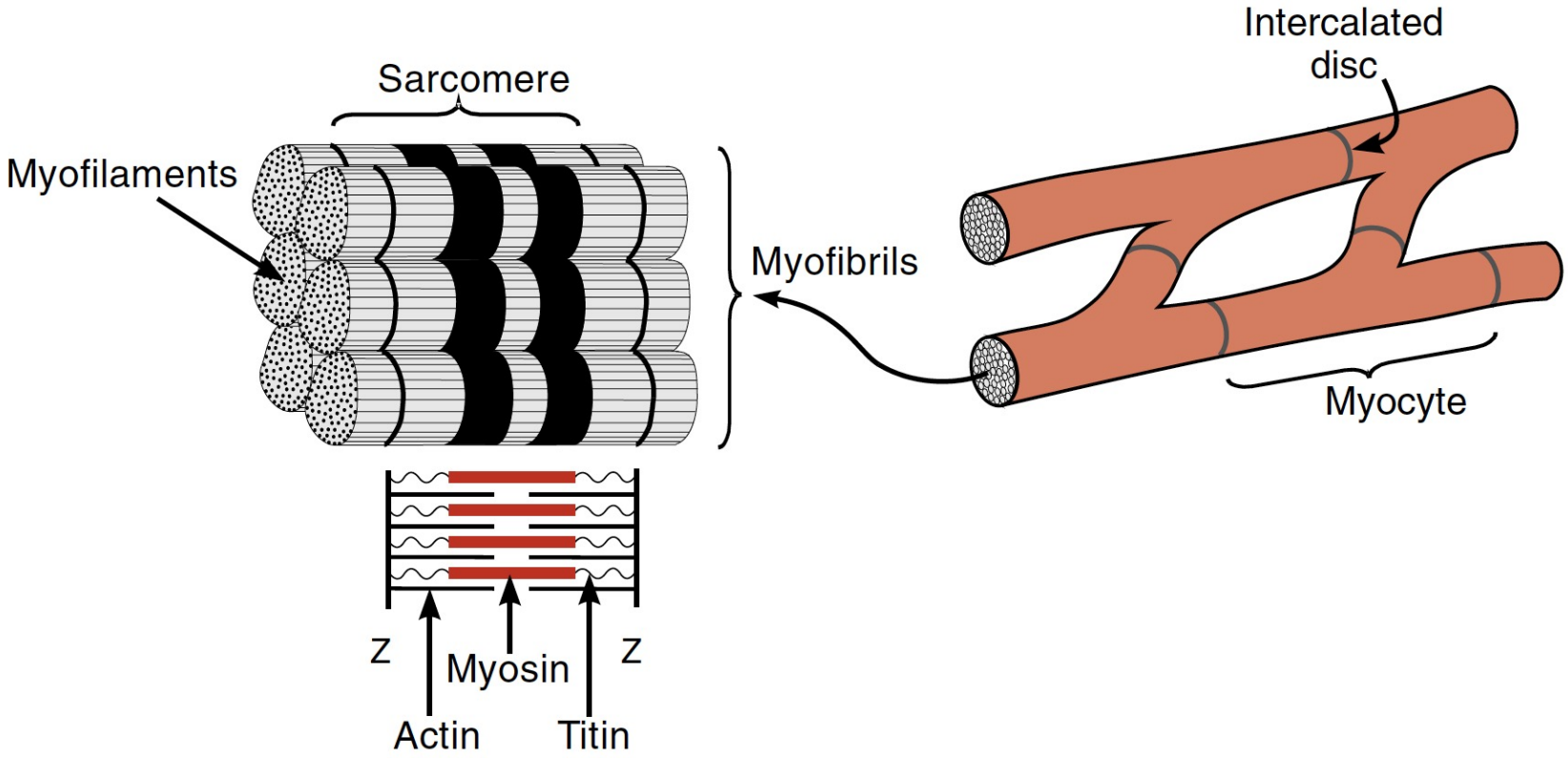
Conflits d’intérêt

- Aucun financier
- Préférence lévo-dobu plutôt que vaso-milri
- Rare utilisateur de l’épinéphrine

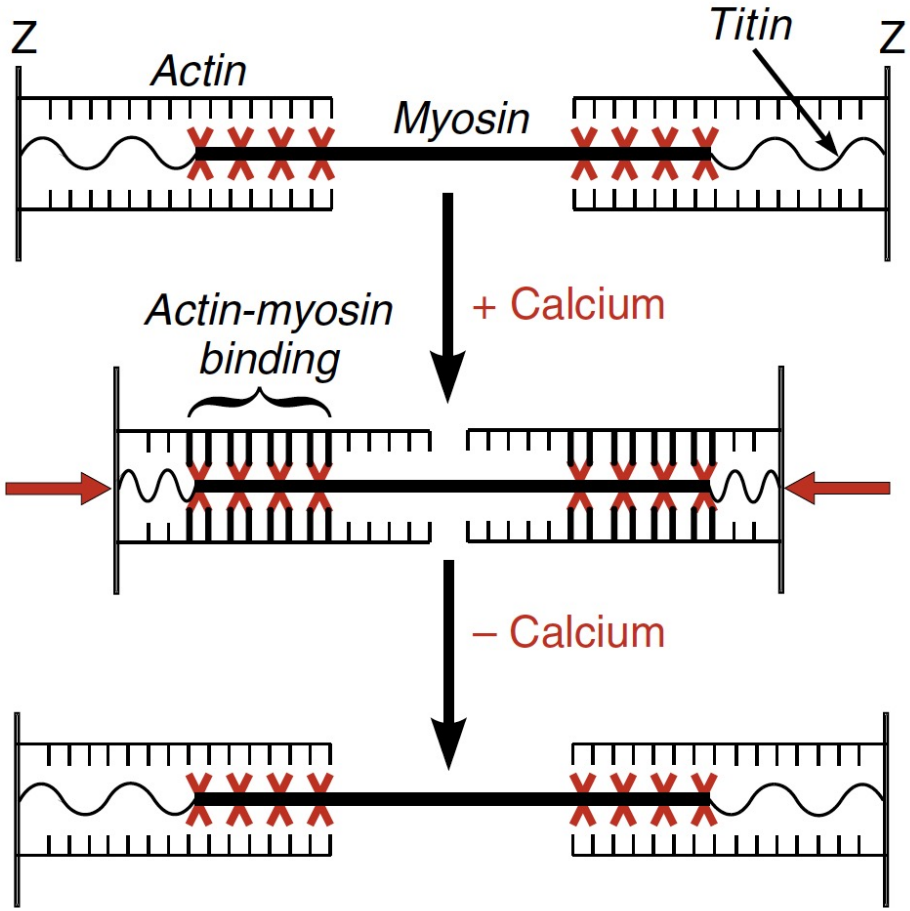
Plan

- Physiologie
  - Contraction myocardique
  - Vasoréactivité
- Agents vasoactifs: inotropes et vasopresseurs
  - Milrinone vs dobutamine
  - Vasopressine ou pas
- Vasodilatateurs

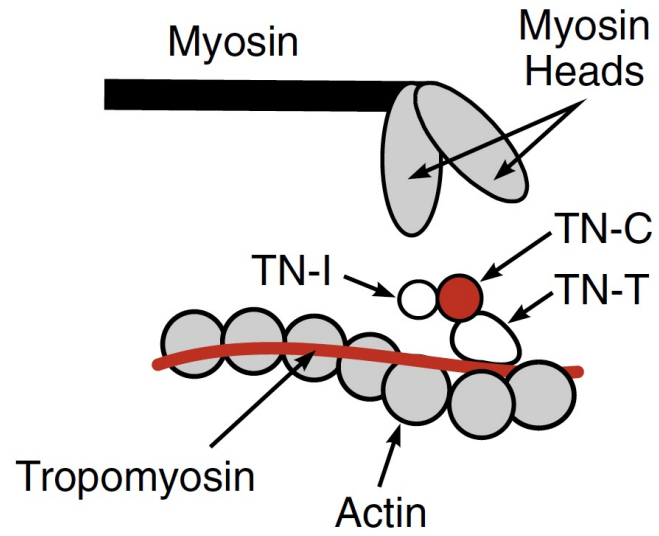
Contraction myocardique



Contraction myocardique



Contraction myocardique



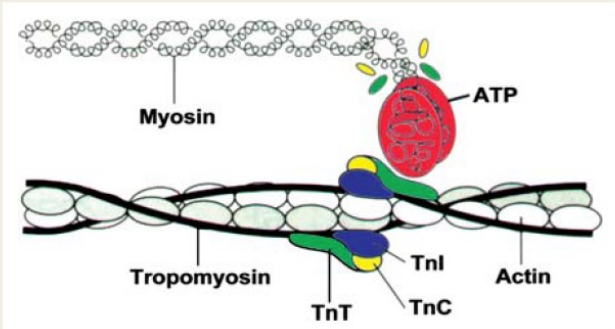
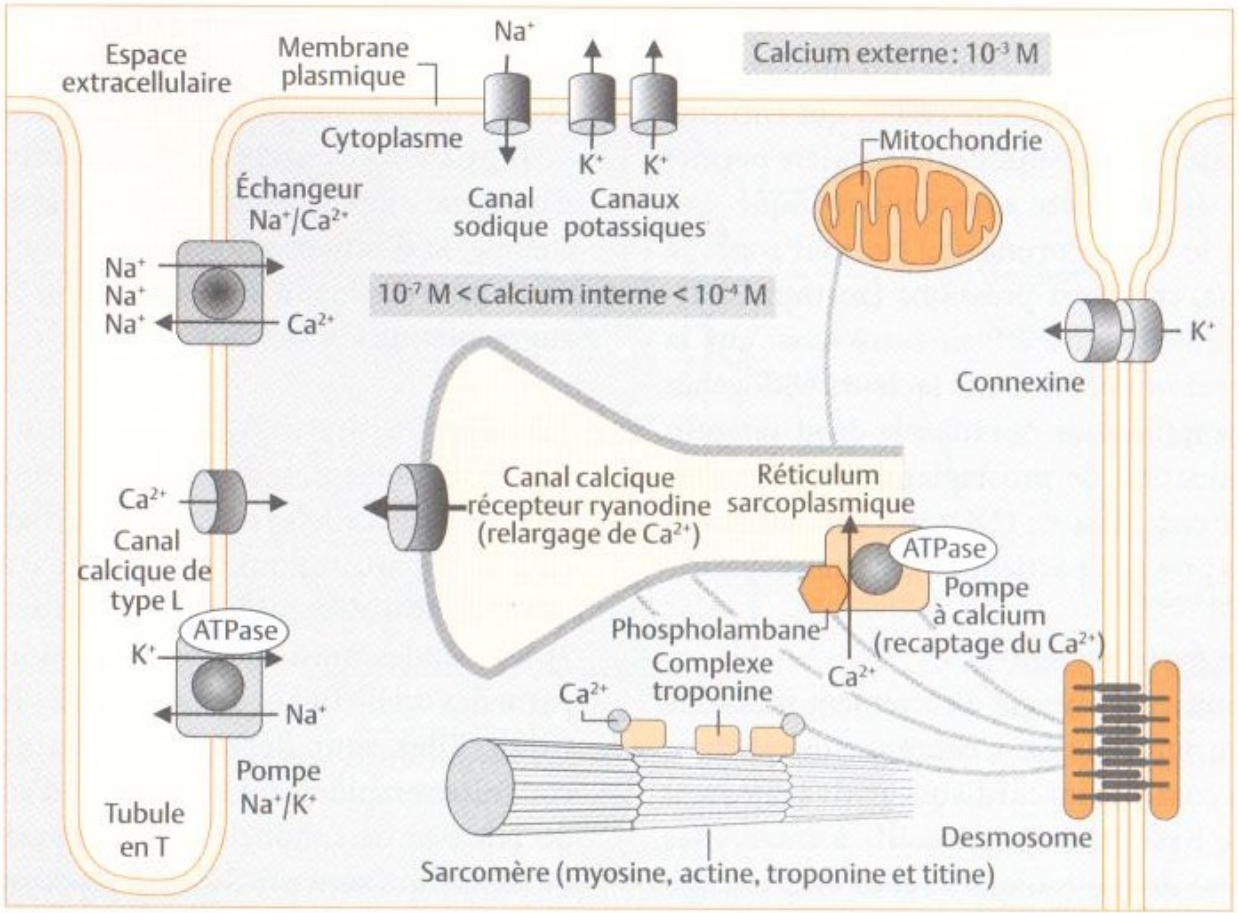
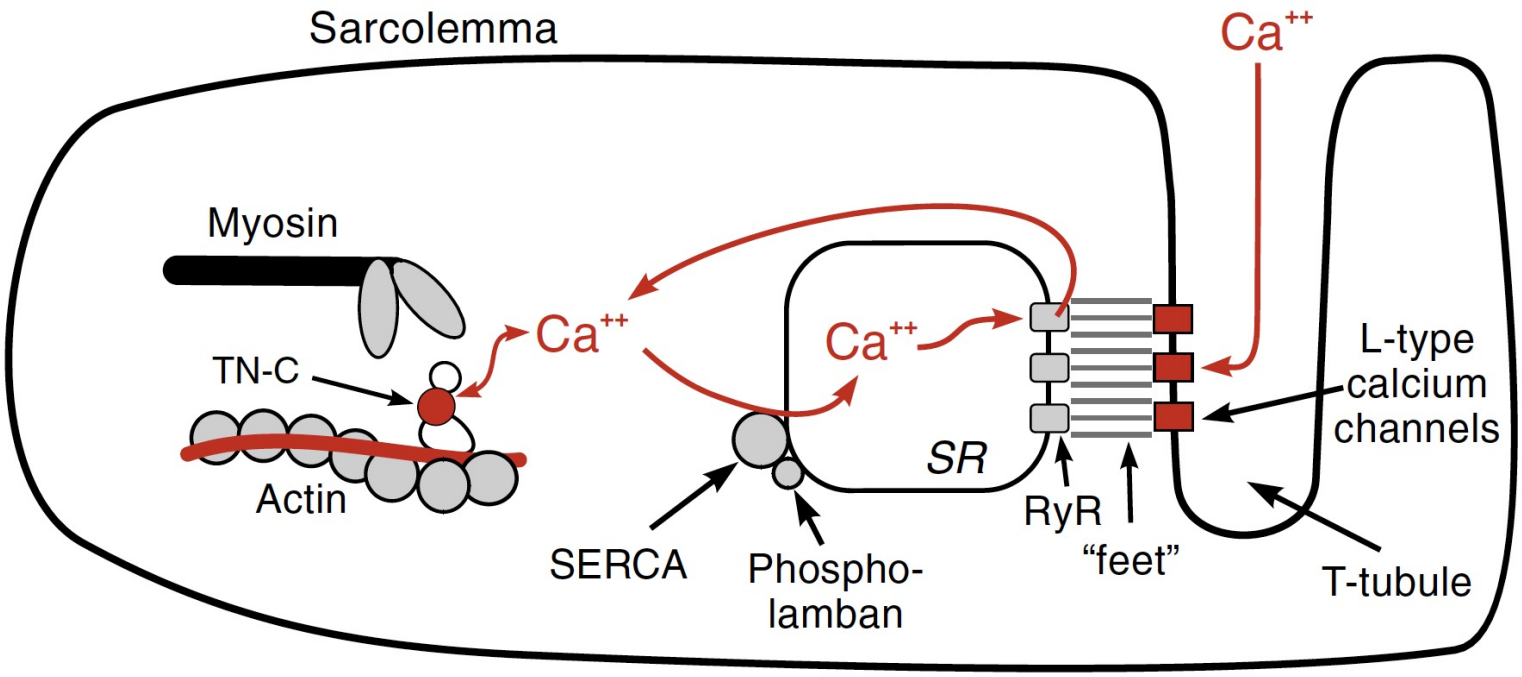


Figure 1 Acto-myosin interaction. The myosin head carrying the ATPase site combines with actin to produce force. Calcium binding to troponin C (TnC) results in a conformational change of tropomyosin, troponin I (TnI), and troponin T (TnT), allowing the myosin head to attach to actin, facilitating the acto-myosin cross-bridge to cycle (see also *Figures 2* and *6*).



Beaulieu et al. Précis de pharmacologie

Contraction myocardique



Inotropie

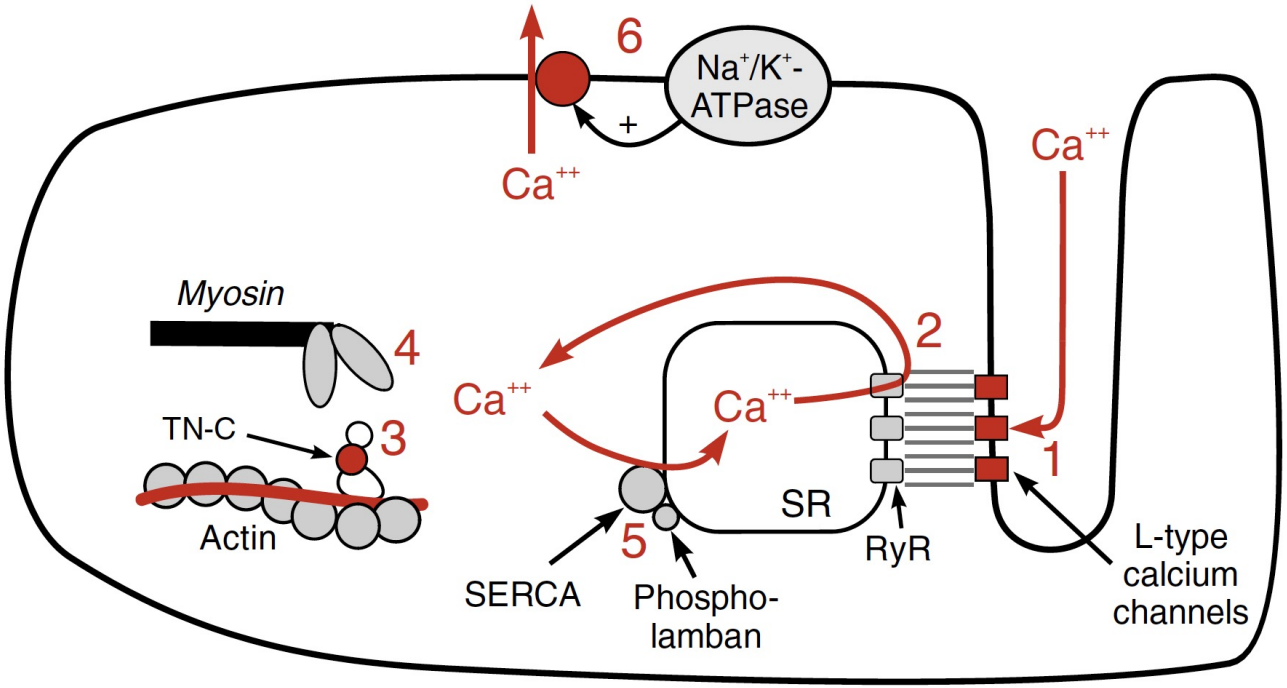


FIGURE 3-5 Intracellular mechanisms regulating inotropy. Inotropy can be increased by increasing Ca^{++} influx through L-type Ca^{++} channels (site 1); increasing release of Ca^{++} by the sarcoplasmic reticulum (*SR*) (site 2); increasing troponin-C (*TN-C*) affinity for Ca^{++} (site 3); increasing myosin-ATPase activity through phosphorylation of myosin heads (site 4); increasing sarco-endoplasmic reticulum calcium ATPase (*SERCA*) activity by phosphorylation of phospholamban (site 5); or inhibiting Ca^{++} efflux across the sarcolemma (site 6), which can occur secondarily to inhibition of the Na^{+}/K^{+}-ATPase.

Contractilité

Régulation endogène de l'inotropie

- Précharge
- Fréquence
- Inotropes (Beta-agonistes)
- Postcharge

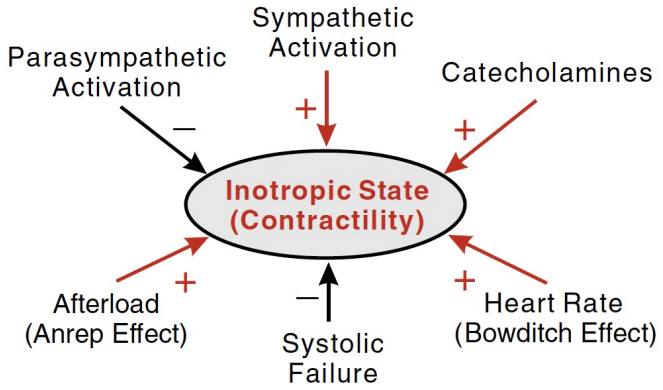


FIGURE 4-25 Factors regulating inotropy. (+), increased inotropy; (−), decreased inotropy.

Inotropie

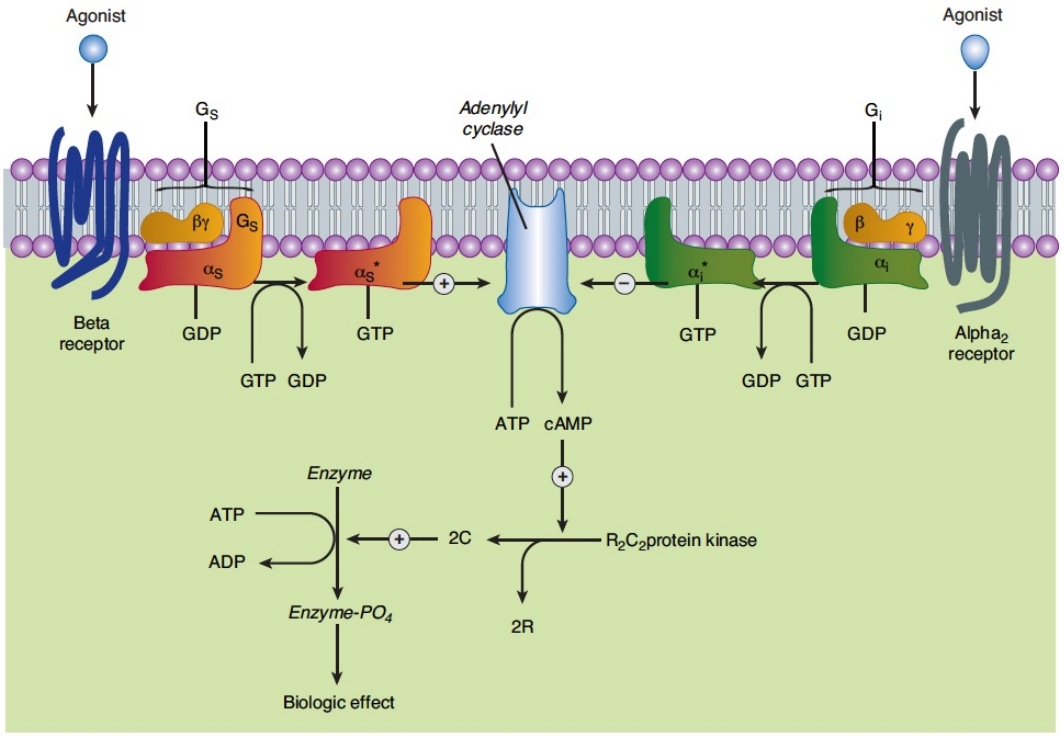


FIGURE 9–2 Activation and inhibition of adenylyl cyclase by agonists that bind to catecholamine receptors. Binding to β adrenoceptors stimulates adenylyl cyclase by activating the stimulatory G protein, G_s, which leads to the dissociation of its α subunit charged with GTP. This activated α_s subunit directly activates adenylyl cyclase, resulting in an increased rate of synthesis of cAMP. Alpha$_2$-adrenoceptor ligands inhibit adenylyl cyclase by causing dissociation of the inhibitory G protein, G_i, into its subunits; ie, an activated α_i subunit charged with GTP and a $\beta\gamma$ unit. The mechanism by which these subunits inhibit adenylyl cyclase is uncertain. cAMP binds to the regulatory subunit (*R*) of cAMP-dependent protein kinase, leading to the liberation of active catalytic subunits *(C)* that phosphorylate specific protein substrates and modify their activity. These catalytic units also phosphorylate the cAMP response element binding protein (CREB), which modifies gene expression. See text for other actions of β and α_2 adrenoceptors.

Inotropie

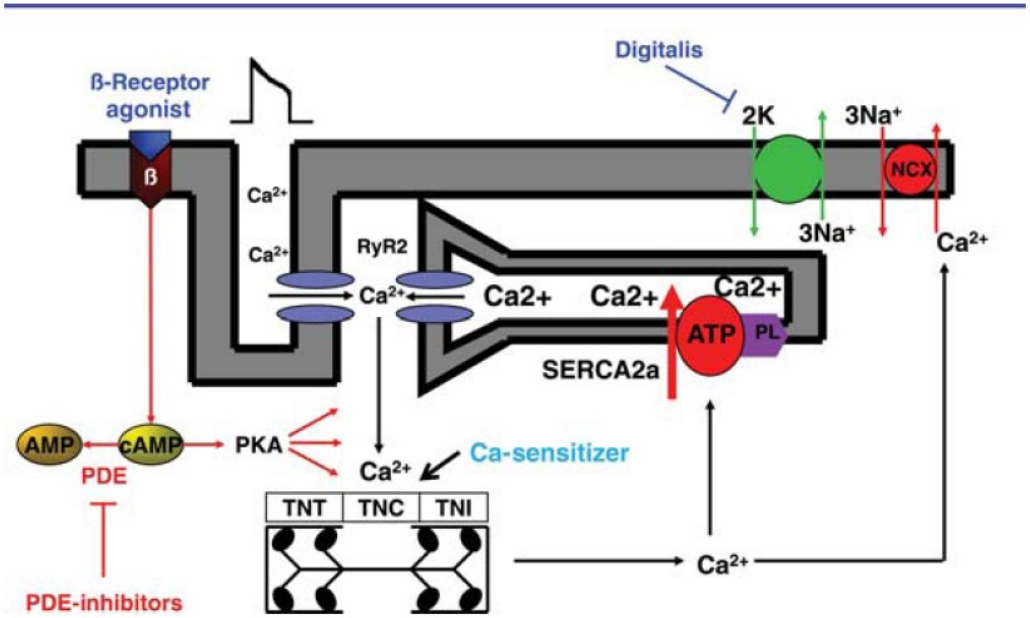
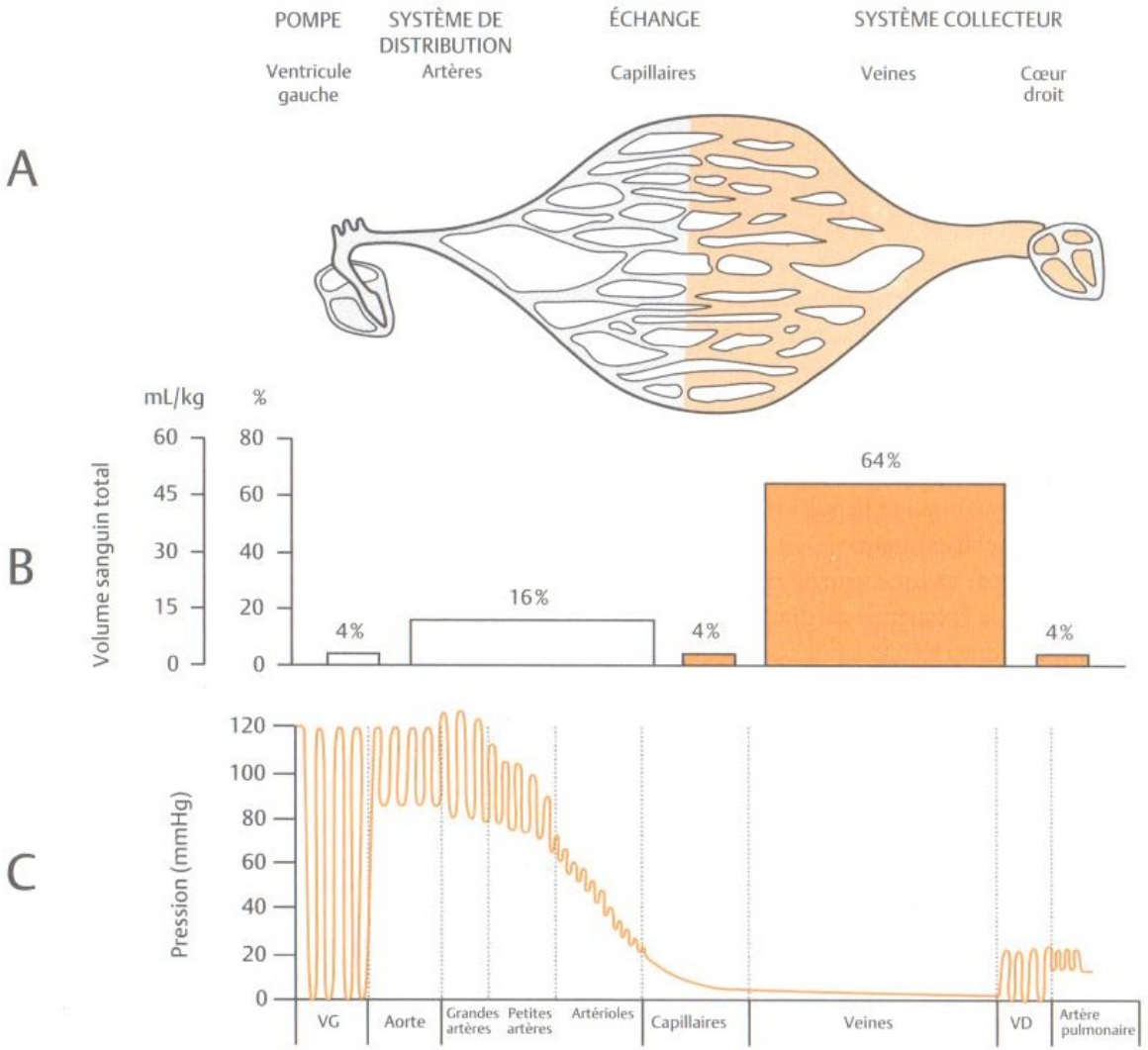


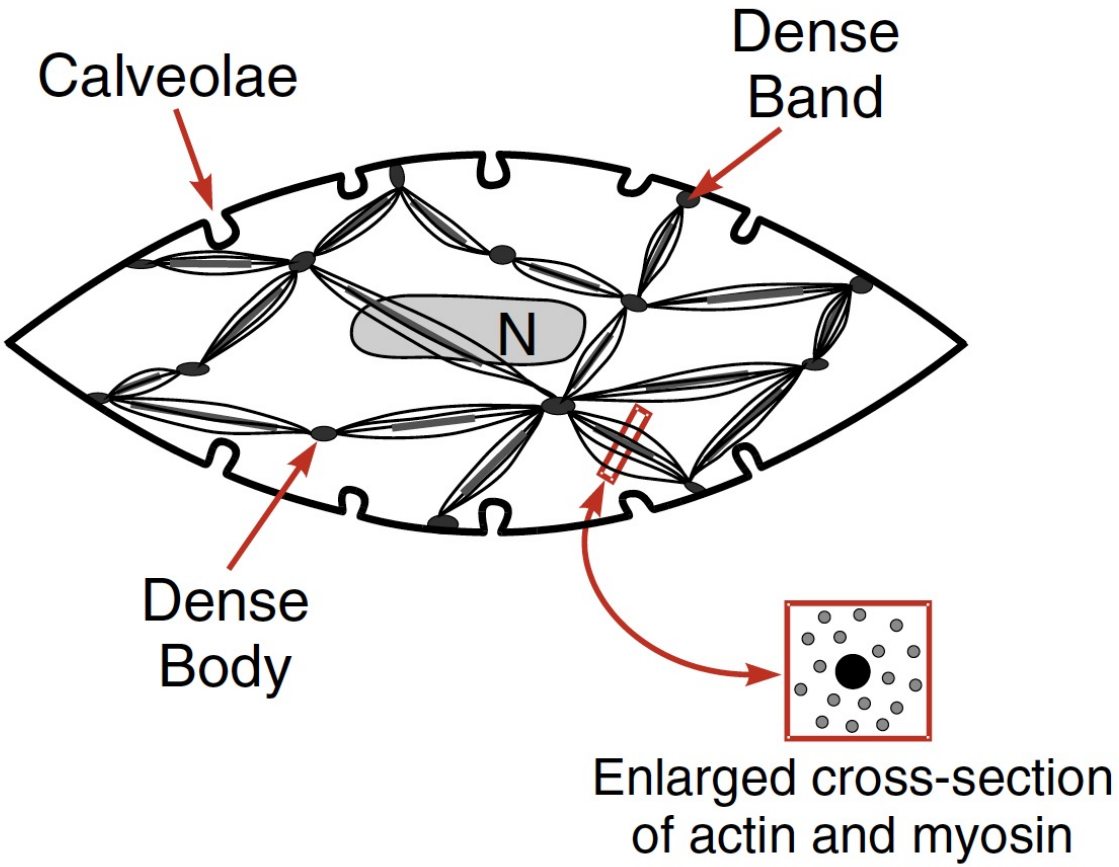
Figure 4 Inotropic mechanisms and current inotropic interventions. Activation of the β-adrenoceptor stimulates adenylyl cyclase to produce cAMP, which activates protein kinase A (PKA) to phosphorylate intracellular calcium-cycling proteins. Phosphodiesterases (PDEs) degrade cAMP. Phosphodiesterases are inhibited by Phosphodiesterase inhibitors. Digitalis inhibits transport of three sodium ions for two potassium ions through Na/K-ATPase. Calcium sensitizers increase the affinity of troponin C for calcium.

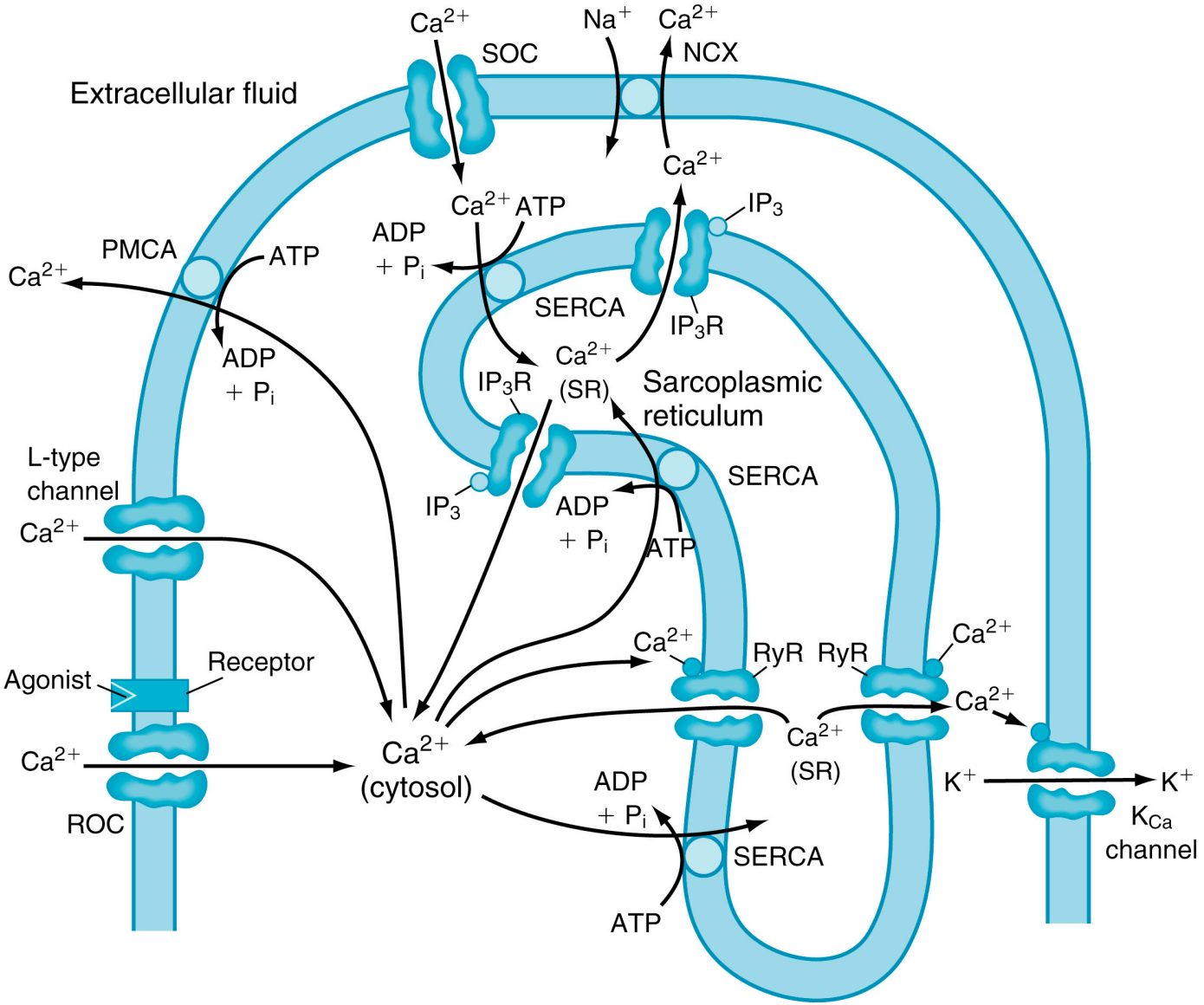
Vasoréactivité



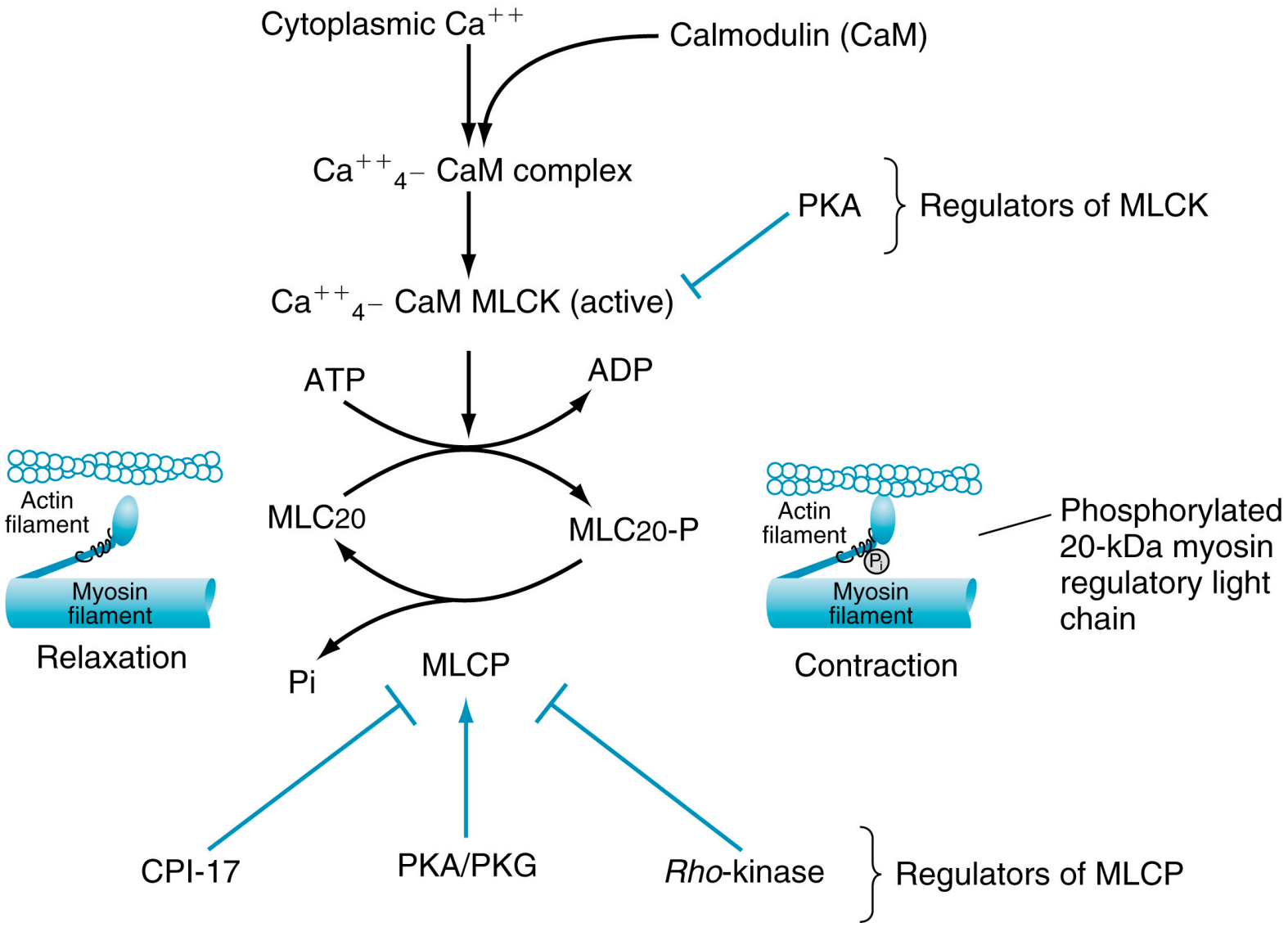
Beaulieu et al. Précis de pharmacologie

Vasoréactivité



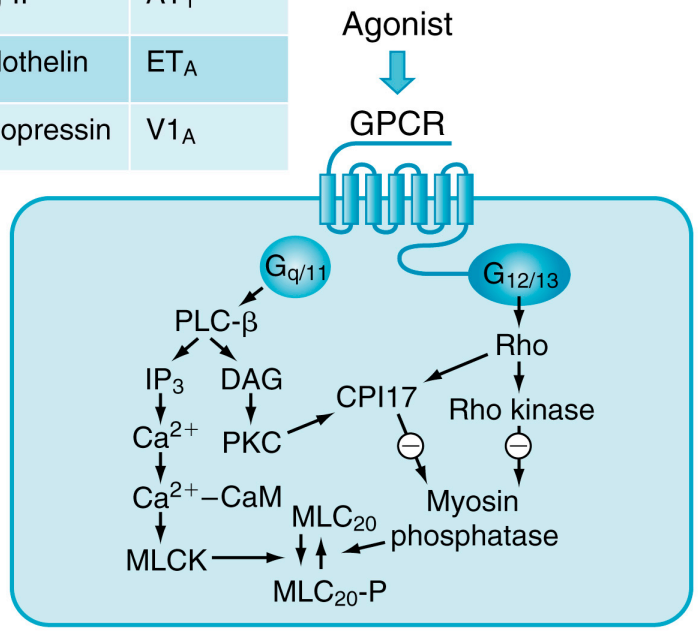


Papano, Achilles, Cardiovascular Physiology 11th Edition

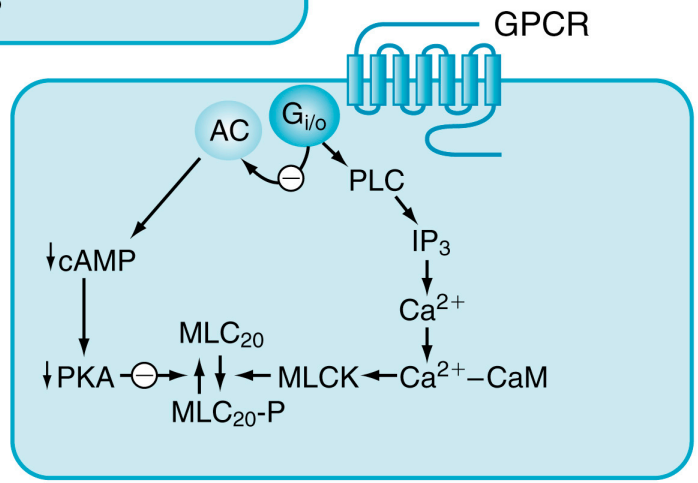


Papano, Achilles, Cardiovascular Physiology 11th Edition

Agonist	Receptor (GPCR)
NE	α_1-AR
Ang-II	AT_1
Endothelin	ET_A
Vasopressin	$V1_A$



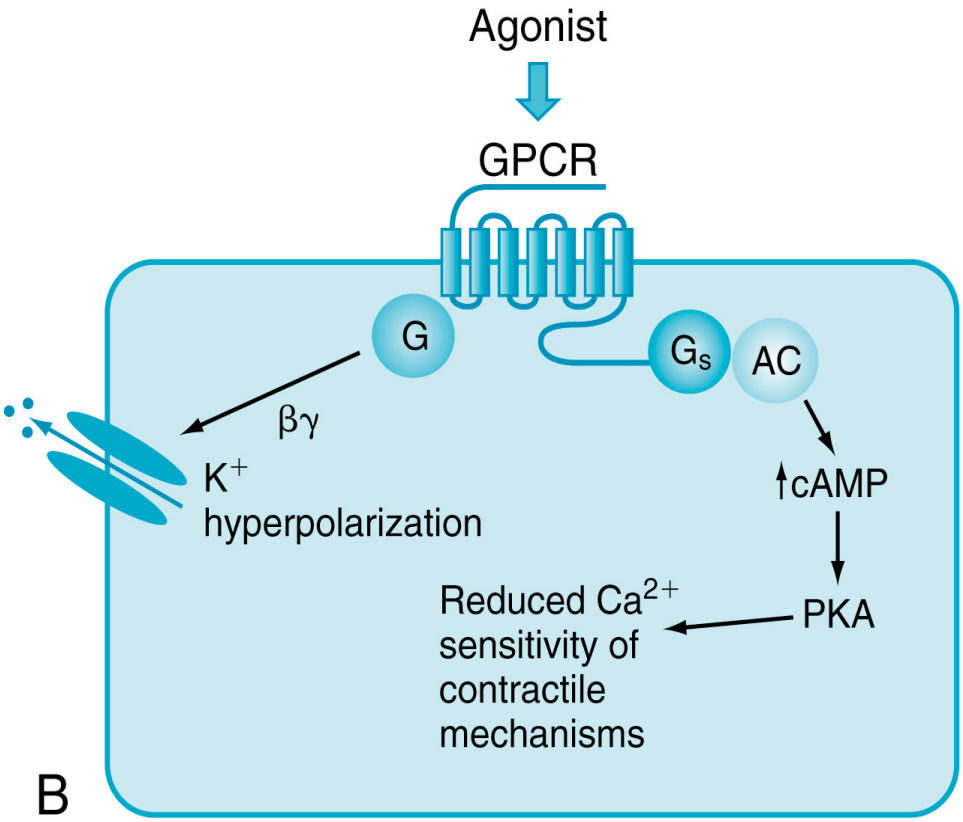
Agonist	Receptor (GPCR)
Neuropeptide Y	Y_1



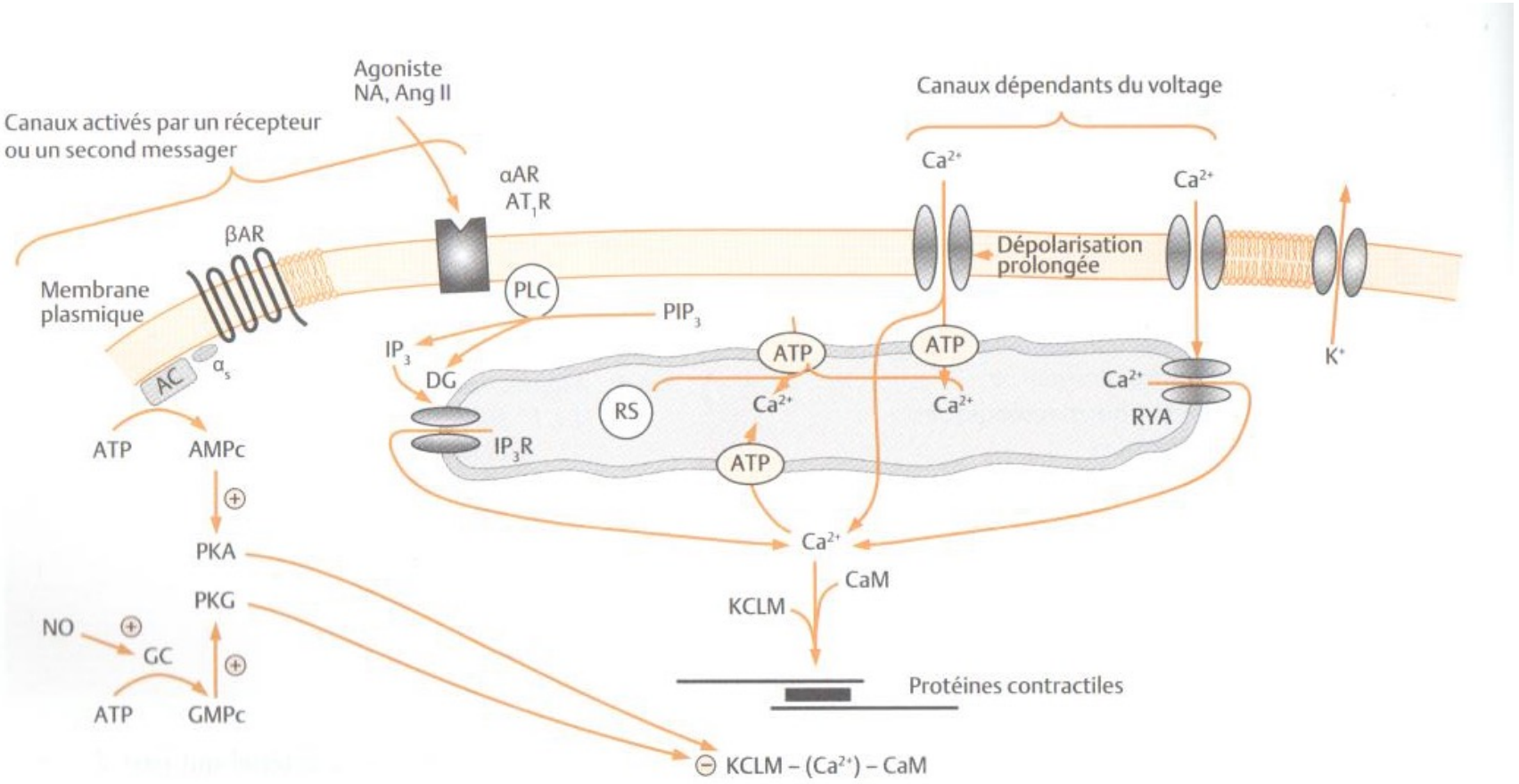
Vascular smooth muscle cells

A

Agonist	Receptor (GPCR)
Epinephrine	Beta-2 (β_2)



Papano, Achilles, Cardiovascular Physiology 11th Edition



Beaulieu et al. Précis de pharmacologie

Vasoréactivité

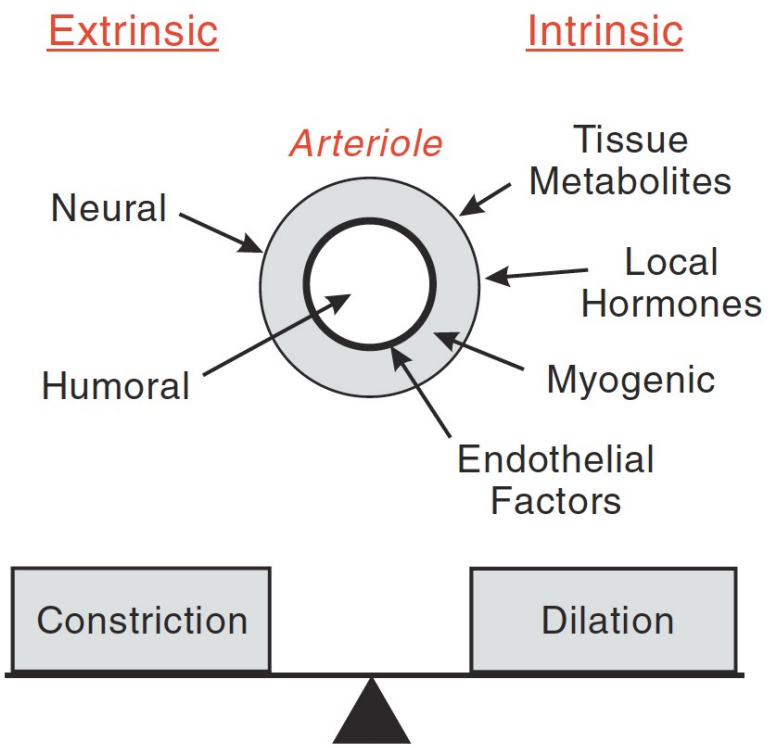
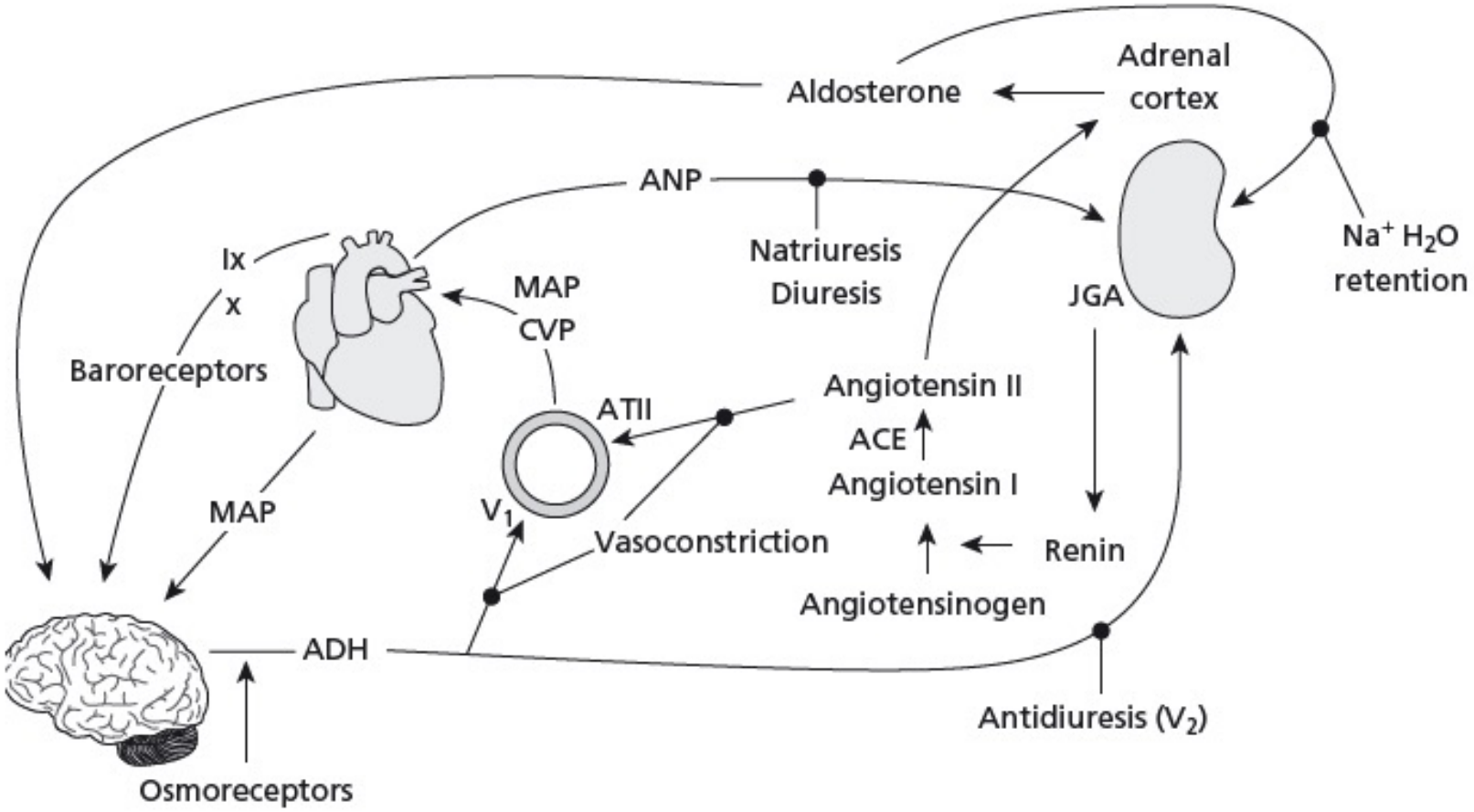
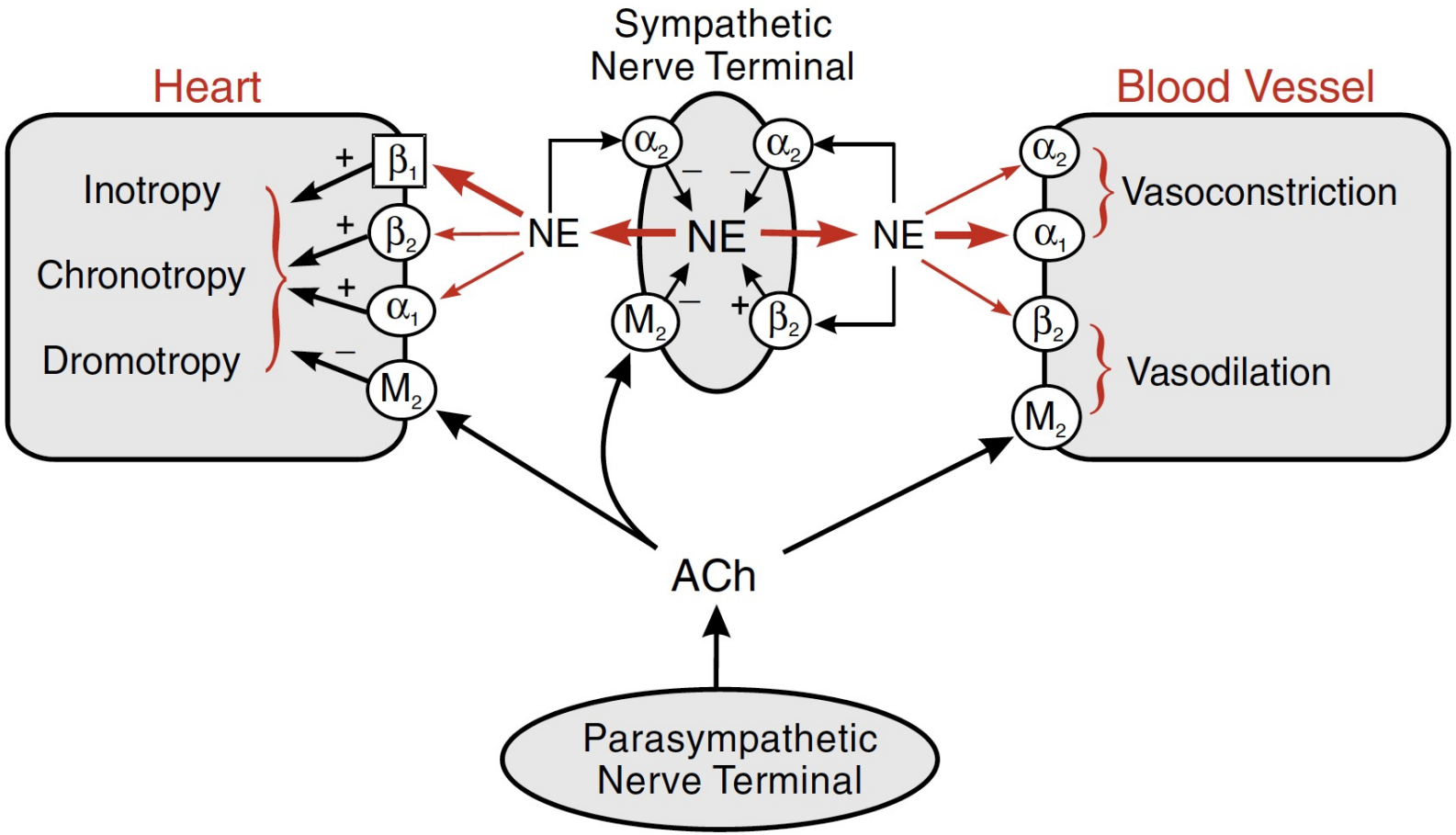


FIGURE 5-9 Vascular tone. The state of vessel tone is determined by the balance between constrictor and dilator influences.

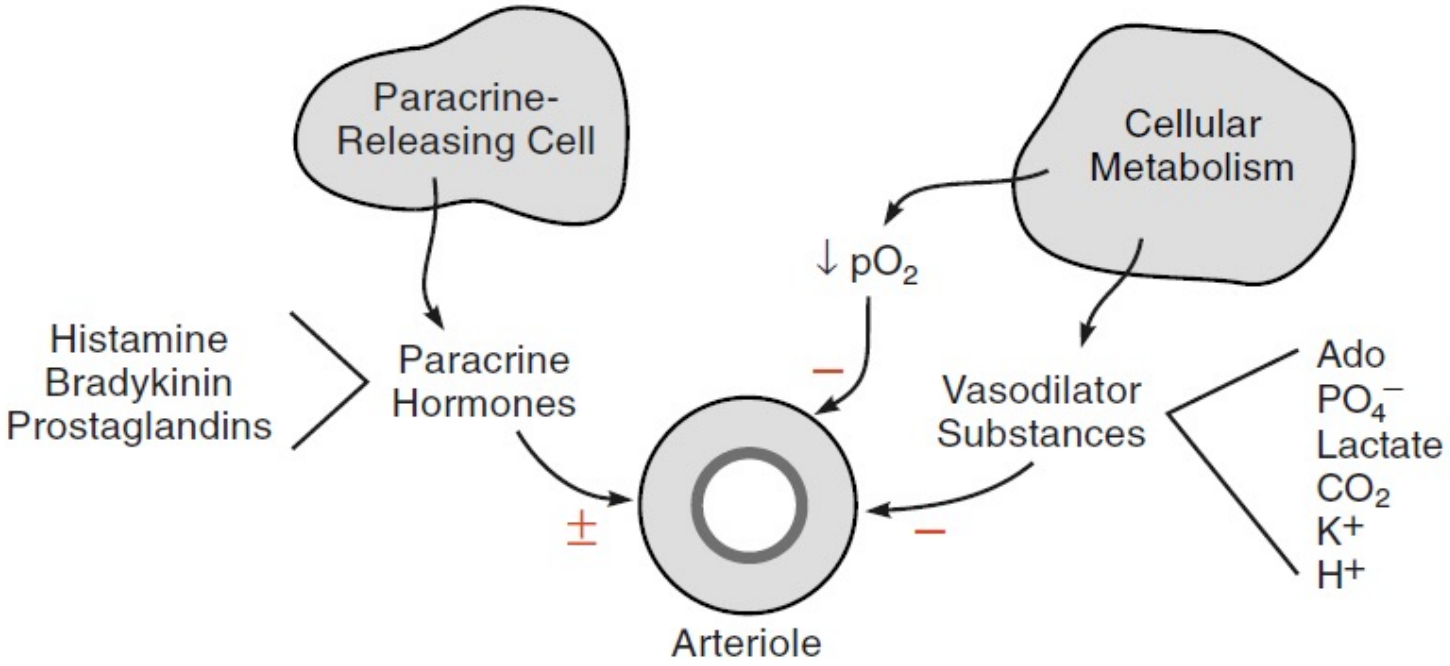
Vasoréactivité

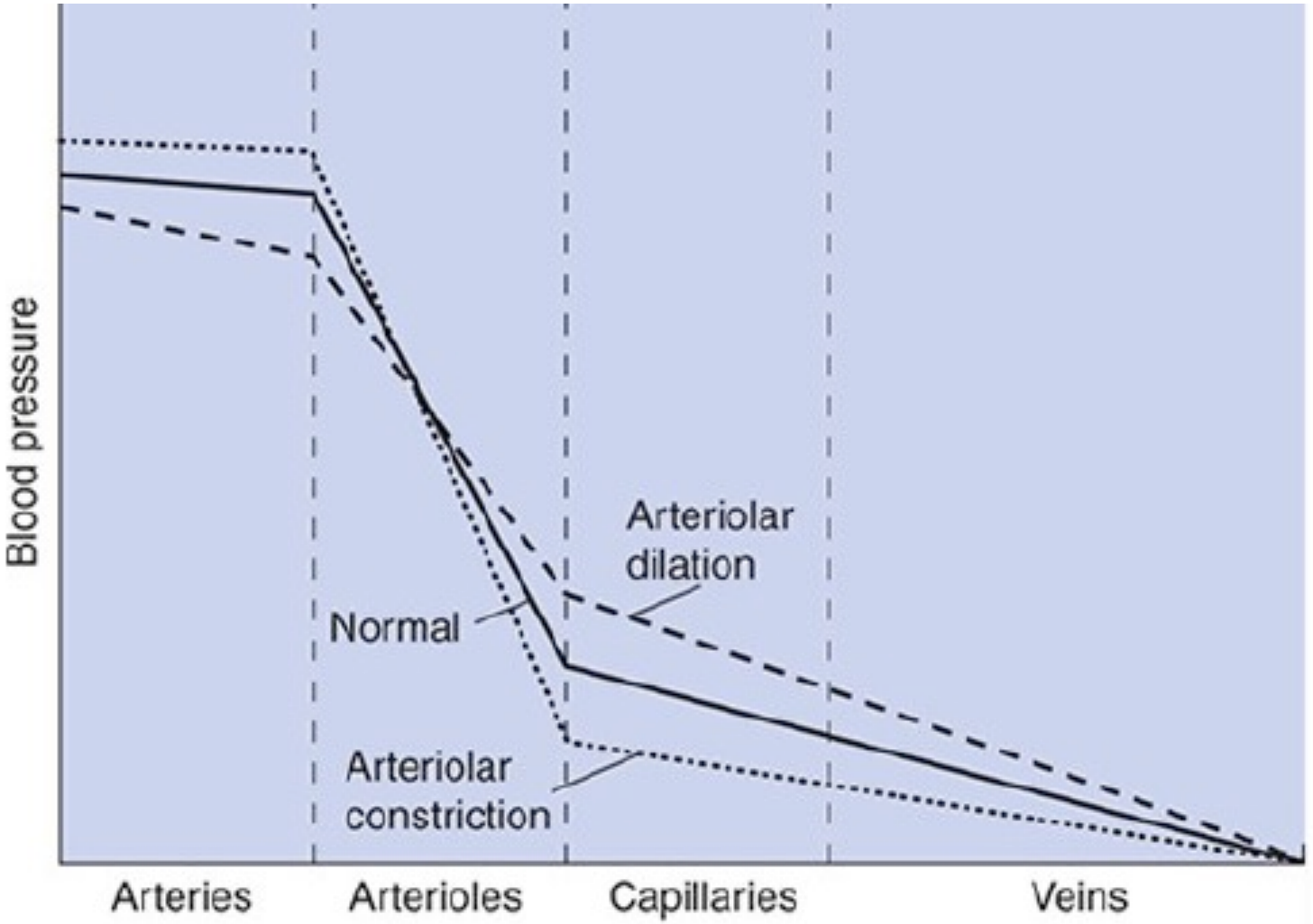


Vasoréactivité – Système nerveux autonome



Vasoréactivité





Source: David E. Mohrman, Lois Jane Heller: *Cardiovascular Physiology*, 9e
Copyright © McGraw-Hill Education. All rights reserved.

Mohrman, Heller, Cardiovascular Physiology 9th edition

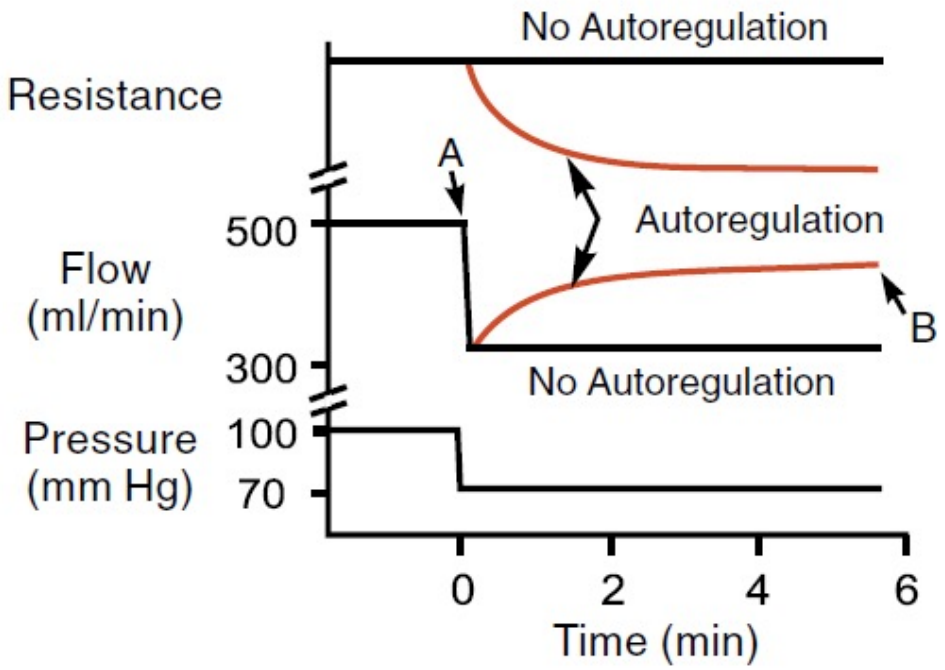
Vasoréactivité

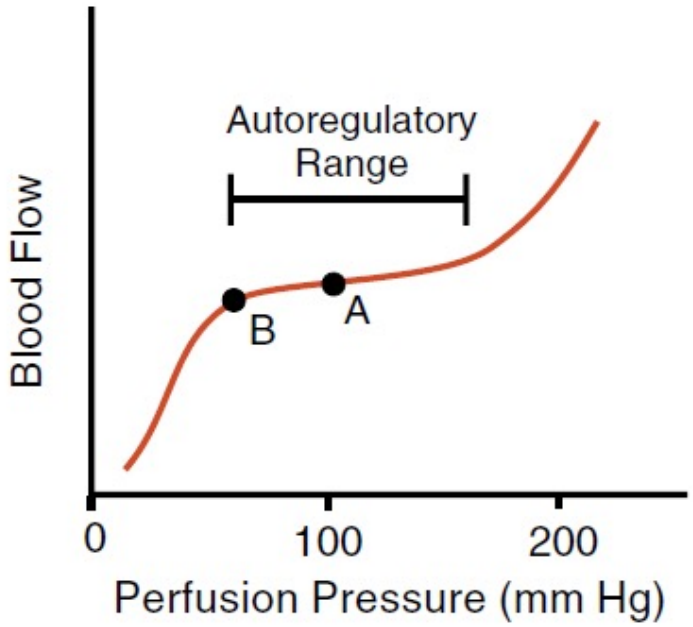
TABLE 7-2 COMPARISON OF VASCULAR CONTROL MECHANISMS IN DIFFERENT VASCULAR BEDS

CIRCULATORY BED	SYMPATHETIC CONTROL	METABOLIC CONTROL	AUTOREGULATION
Coronary	+[1]	+++	+++
Cerebral	+	+++	+++
Skeletal muscle	++	+++	++
Cutaneous	+++	+	+
Intestinal	+++	++	++
Renal	++	+	+++
Pulmonary	+	+[2]	+

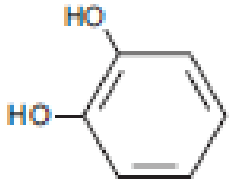
+++, strong; ++, moderate, +, weak. [1] Sympathetic vasoconstriction in the coronaries is overridden by metabolic vasodilation during sympathetic activation of the heart. [2] Hypoxia causes vasoconstriction, the opposite of all other organs.

Vasoréactivité

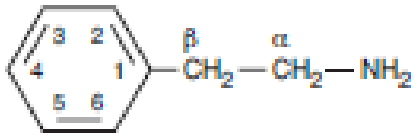




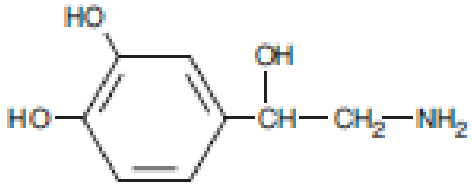
Cathécholamines



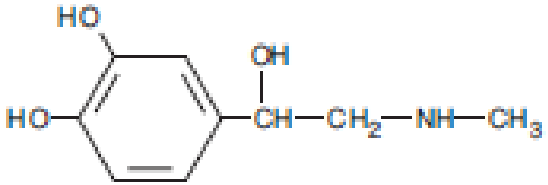
Catechol



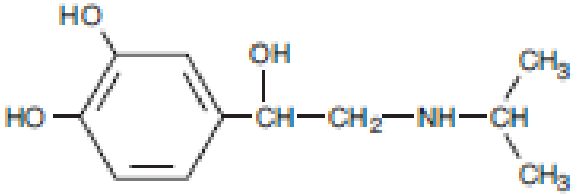
Phenylethylamine



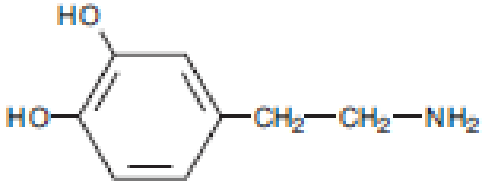
Norepinephrine



Epinephrine

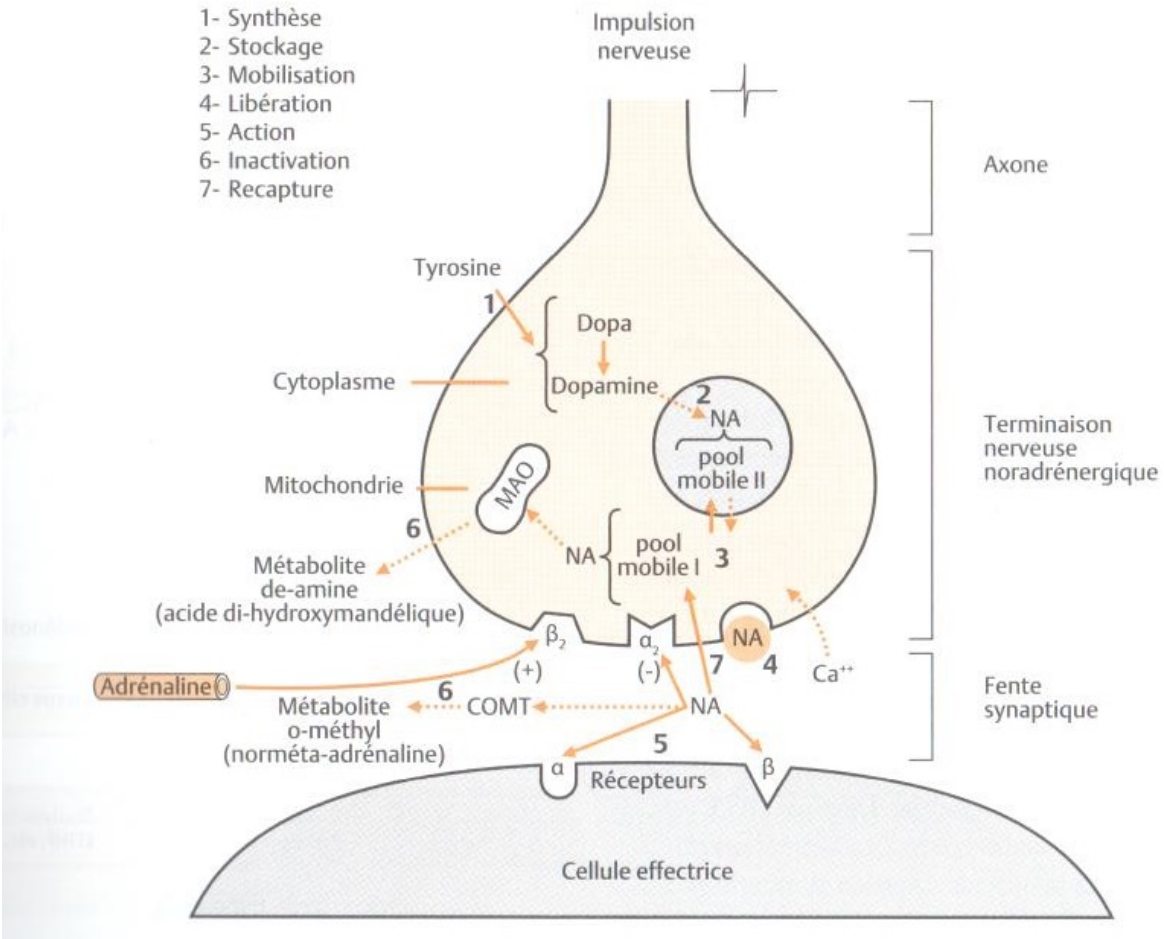


Isoproterenol



Dopamine

Cathécholamines

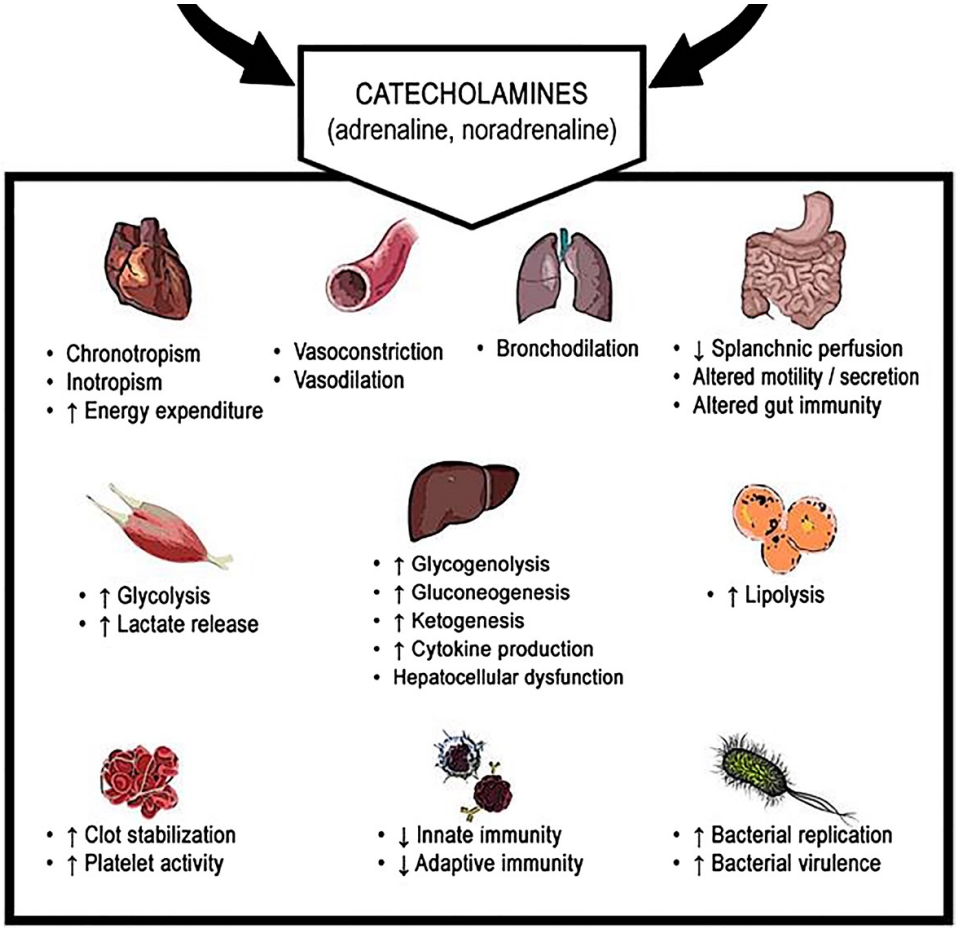


Beaulieu et al. Précis de pharmacologie

TABLEAU 11.1 Système sympathique

Organe effecteur	Tissu ou cellule	Action / fonction	Sous-types de récepteurs
Artérioles	peau et muqueuses, glandes salivaires	contraction	α_1, α_2
	coronaires, rénales	contraction	α_1, α_2
	muscle squelettique, cérébrales, pulmonaires, viscères abdominaux	contraction	α_1
Veines		contraction	α_1
Bronches	glandes	inhibition	α_1
Tractus gastro-intestinal	muscle lisse, sphincters	contraction	α_1
	muscle lisse, paroi	diminue motilité et tonus	α_1, α_2
	sécrétion	inhibition	α_2
Foie		fonctions métaboliques : néoglucogenèse et glycogénolyse	α_1
Pancréas	îlots de Langherans	diminue sécrétion d'insuline et de glucagon	α_2
Rate	capsule	contraction	α_1
Vessie	trigone et sphincter	contraction	α_1
Uretères	muscle lisse	inhibe motilité et tonus	α_1
Pénis	vésicule séminale	éjaculation	α_1
Peau	muscle pilomoteur	contraction	α_1
Glandes sudoripares	apocrines, paumes des mains et autres régions (stress)	augmente la sécrétion (sudation adrénergique)	α_1
Glandes salivaires		sécrétion épaisse et visqueuse	α_1
Glandes lacrymales		sécrétion	α
Œil	muscle radial de l'iris	contraction (mydriase)	α_1
Artérioles	muscle squelettique, pulmonaires, viscères abdominaux	dilatation	β_2
	coronaires, rénales	dilatation	β_2
Veines		dilatation	β_2
Poumons-bronchioles	muscle lisse	relaxation	β_2
Bronches	glandes	stimulation	β_2
Cœur	oreillettes, ventricules (myocytes)	augmente la contractilité	β_1
	nœud auriculoventriculaire, système His-Purkinje	augmente la vélocité de la conduction	β_1
	nœud sinoauriculaire	augmente la fréquence cardiaque	β_1
Tractus gastro-intestinal	muscle lisse paroi	diminue motilité et tonus	β_2
Foie		fonctions métaboliques : néoglucogenèse et glycogénolyse	β_2
Pancréas	îlots de Langherans	augmente sécrétion d'insuline et de glucagon	β_2
Rate	capsule	relaxation	β_2
Glandes salivaires		sécrétion amylase	β_2
Rein	cellules juxtaglomérulaires	augmente sécrétion de rénine	β_1
Vésicule biliaire	muscle lisse	relaxation	β_2
Vessie	muscle détrusor	relaxation	β_2
Appareil génito-urinaire	muscle lisse, utérus gravide et non gravide	relaxation	β_2
Tissus adipeux		lipolyse	β_1, β_3
Œil	muscle ciliaire	relaxation pour la vision lointaine	β_2

- Artérioles:
  - Alpha1 : vasoconstriction
  - Beta2 > Beta 1 : vasodilatation
- Coeur
  - Beta 1 : inotropie, chronotropie, dromotropie, lusitropie
  - Beta 2 : chronotropie > inotropie



g. 3 Pleiotropic effects of neurally released (via the sympathetic nervous system) and circulating (produced by the adrenal medulla) catecholamines

Andreis et Al. ICM 2016

Agents vasoactifs

- Récepteurs
- Effets hémodynamiques: PAM, D.C., F.C., SVR, lits vasculaires
- ½ vie
- Effets secondaires
- Indications

Inotrope vs vasopresseur

- PA = Débit cardiaque / Résistances

- On regarde surtout la pression…

Intensive Care Med (2012) 38:422–428
DOI 10.1007/s00134-011-2457-0

ORIGINAL

Charalampos Pierrakos
Dimitrios Velissaris
Sabino Scolletta
Sarah Heenen
Daniel De Backer
Jean-Louis Vincent

Can changes in arterial pressure be used to detect changes in cardiac index during fluid challenge in patients with septic shock?

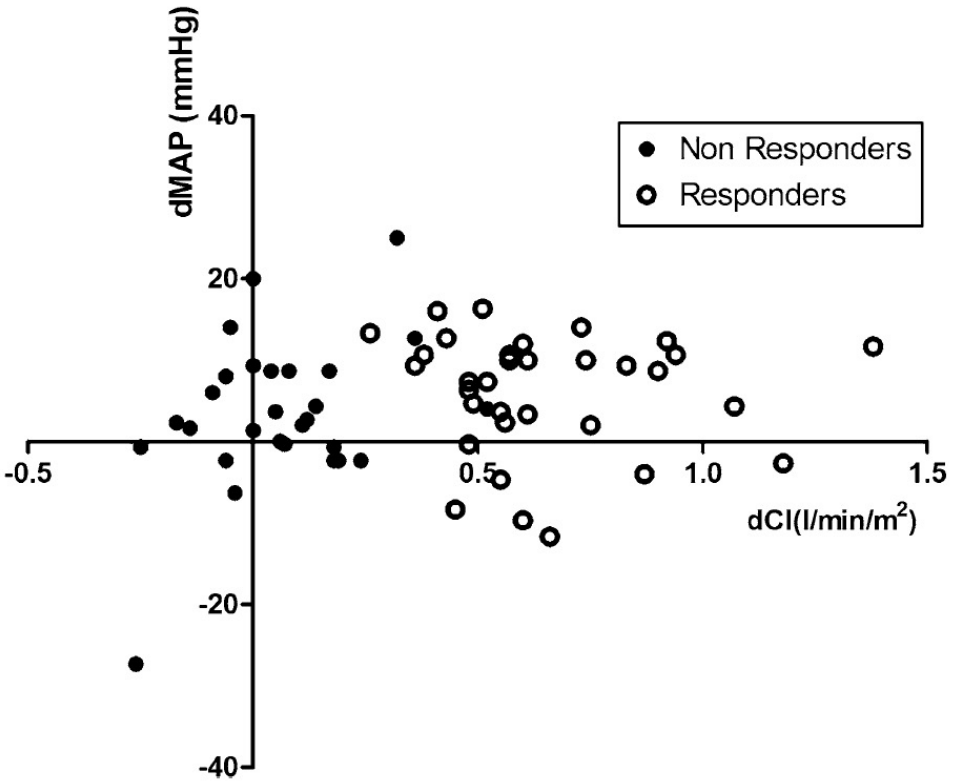
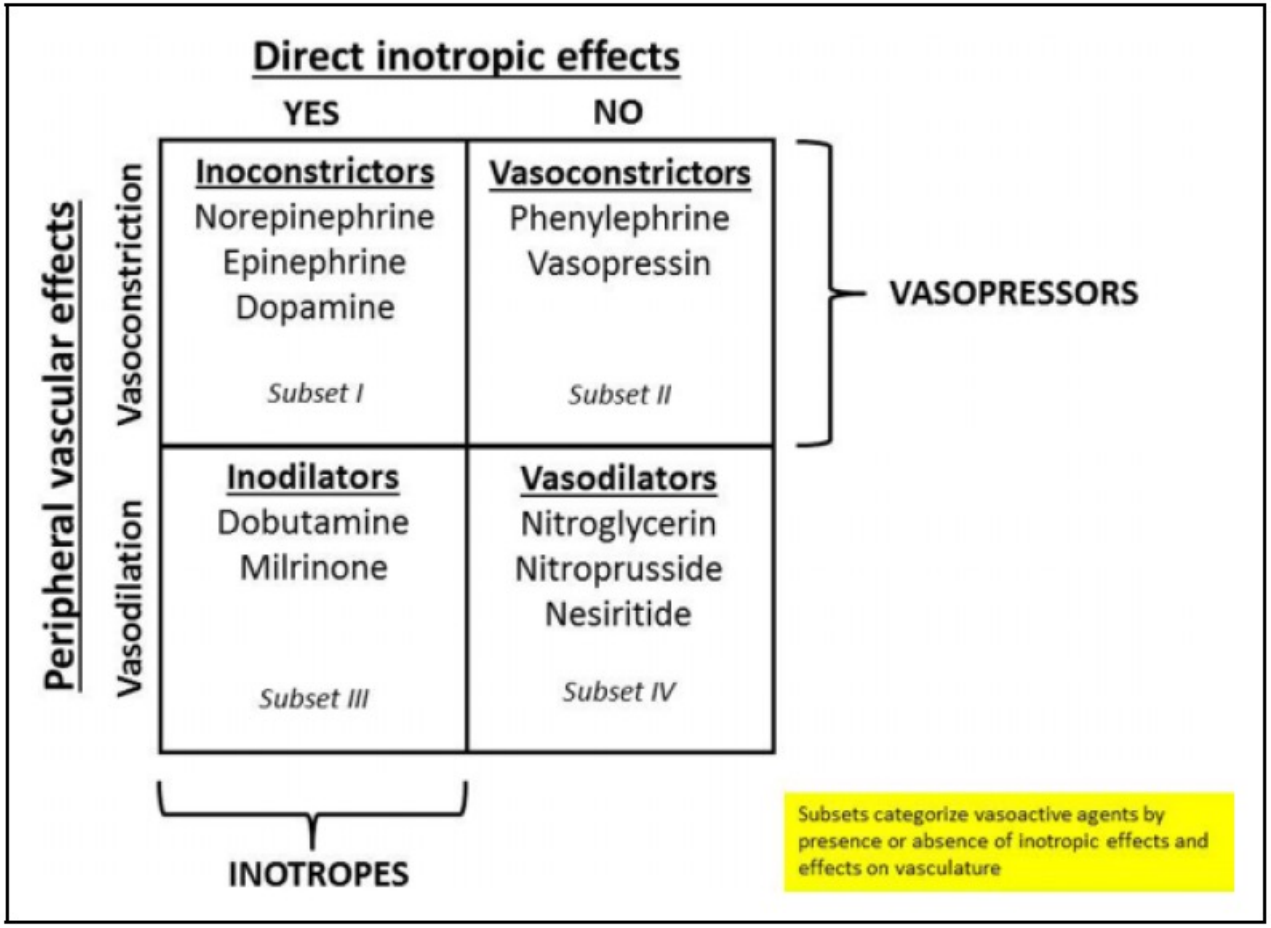
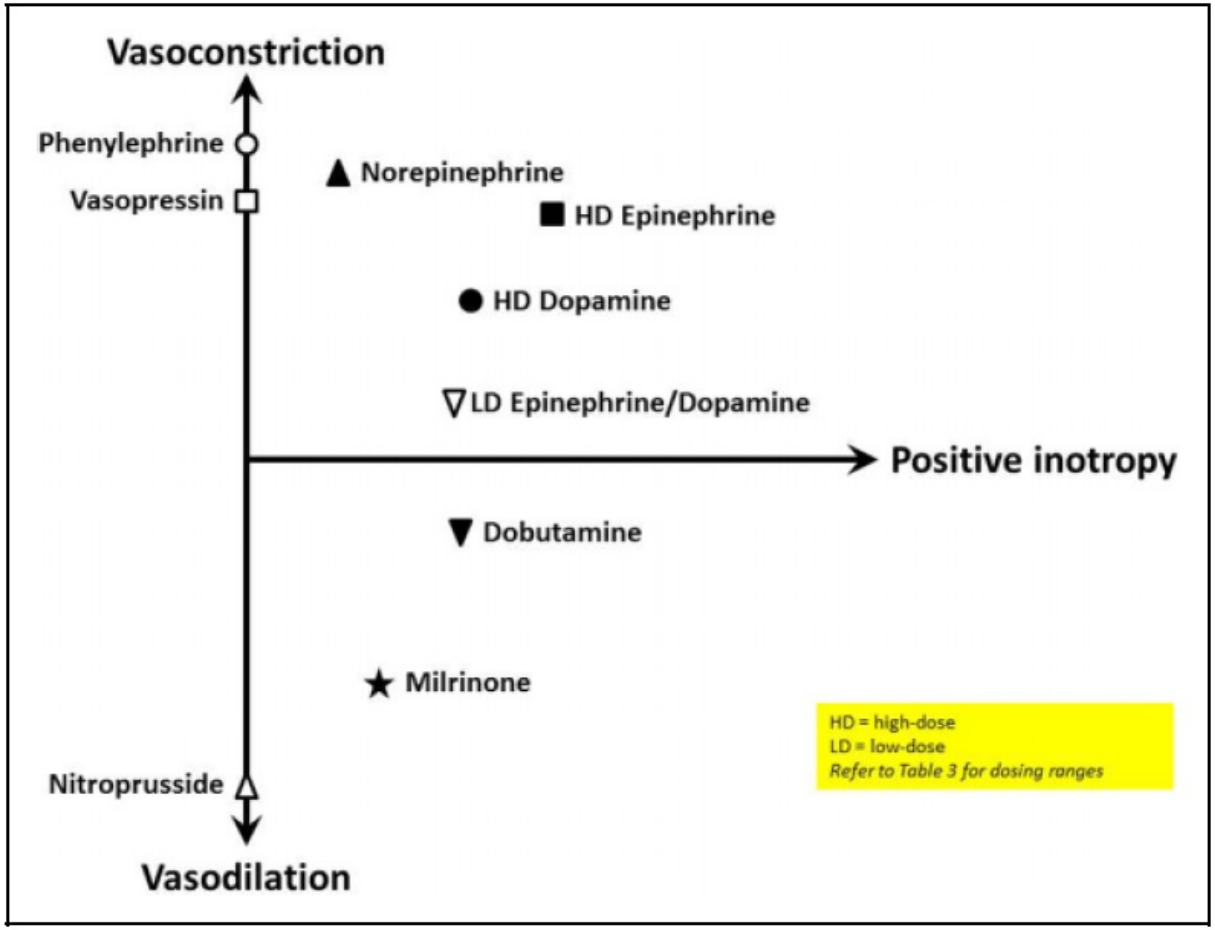


Fig. 2 Correlation between absolute changes in cardiac index (*dCI*) and absolute changes in mean arterial pressure (*dMAP*) ($r^2 = 0.08$, $p = 0.06$)



Jentzer et al. J Cardiovasc Pharm Ther 2014


Vasoconstriction
Phenylephrine
Vasopressin
Norepinephrine
HD Epinephrine
HD Dopamine
LD Epinephrine/Dopamine
Positive inotropy
Dobutamine
Milrinone
Nitroprusside
Vasodilation
HD = high-dose
LD = low-dose
Refer to Table 3 for dosing ranges

Noradrenaline

- Neurotransmetteur terminaisons nerveuses sympathiques
- Récepteurs:
  - Agoniste alpha > beta1
  - Effet linéaire selon logarithme des concentrations
    - Effet max à 1000 fois la dose seuil
- Hémodynamique:
  - PAM: augmentée
  - D.C.: maintenu ou augmenté
  - FC: peu changée (baroreflex mais chronotropie)

Veinoconstriction et débit cardiaque

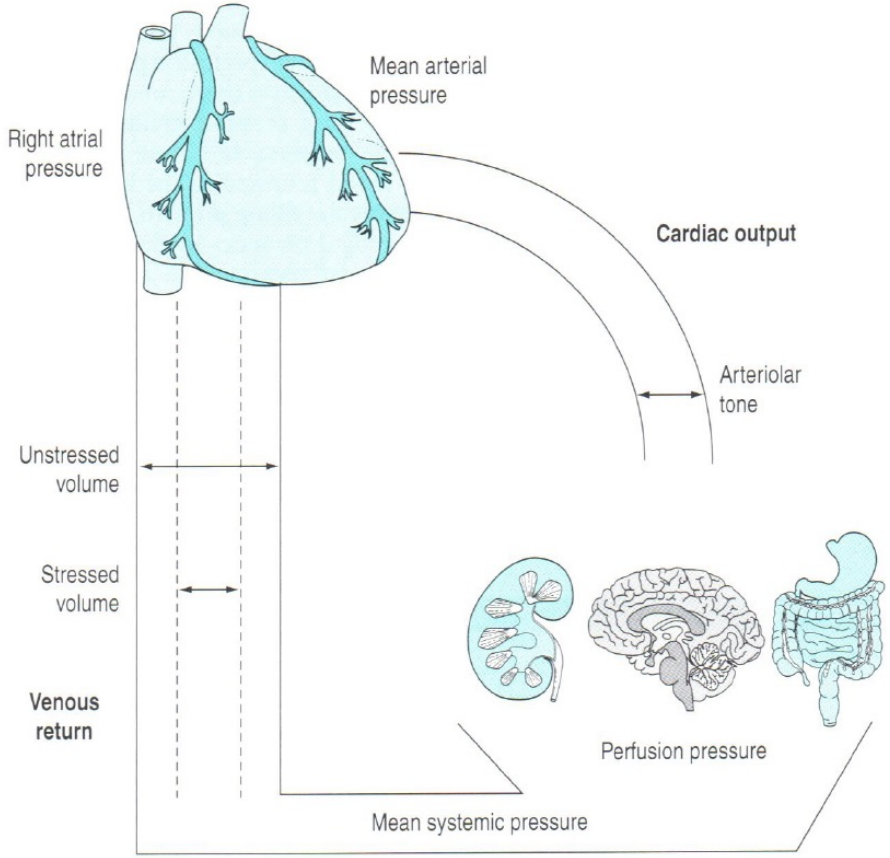
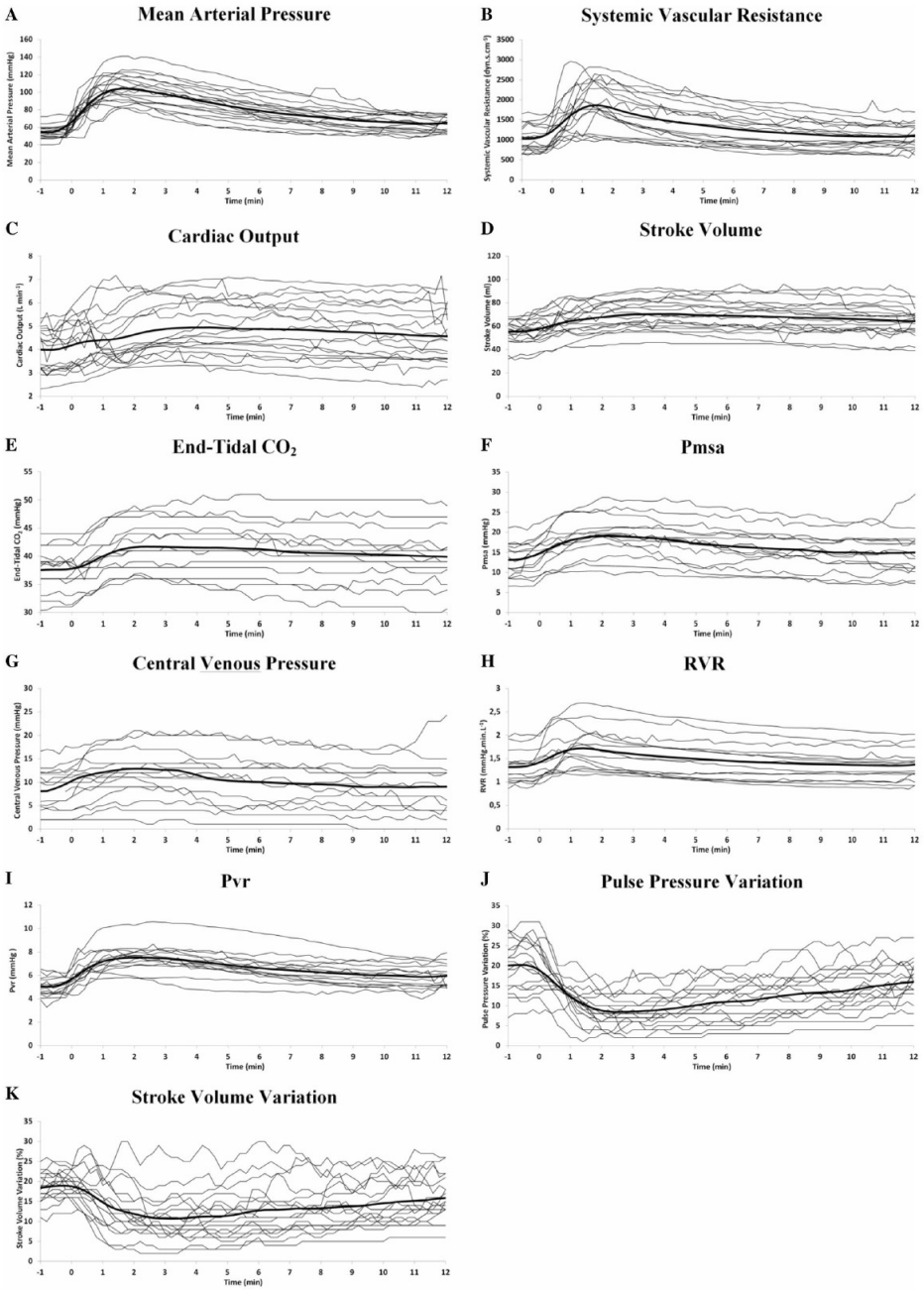


Figure 82.1 Schematic relationship of the determinants of cardiac output and venous return.


A
Mean Arterial Pressure
Mean Arterial Pressure (mmHg)
Time (min)
B
Systemic Vascular Resistance
Systemic Vascular Resistance (dyn.s.cm⁻⁵)
Time (min)
C
Cardiac Output
Cardiac Output (L.min⁻¹)
Time (min)
D
Stroke Volume
Stroke Volume (ml)
Time (min)
E
End-Tidal CO2
End-Tidal CO2 (mmHg)
Time (min)
F
Pmsa
Pmsa (mmHg)
Time (min)
G
Central Venous Pressure
Central Venous Pressure (mmHg)
Time (min)
H
RVR
RVR (mmHg.min.L⁻¹)
Time (min)
I
Pvr
Pvr (mmHg)
Time (min)
J
Pulse Pressure Variation
Pulse Pressure Variation (%)
Time (min)
K
Stroke Volume Variation
Stroke Volume Variation (%)
Time (min)

Noradrénaline

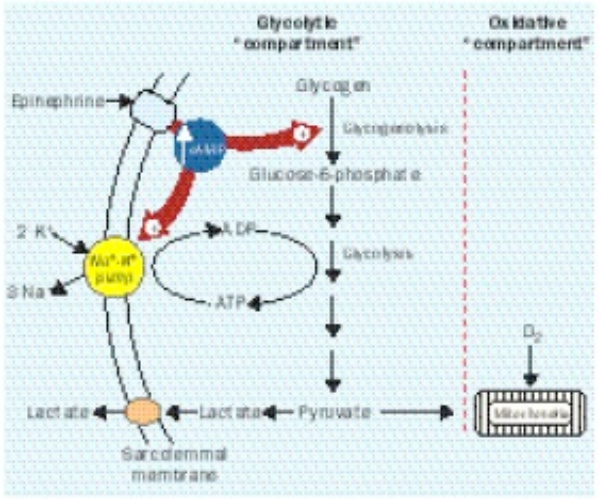
- Hémodynamique:
  - SVR: augmenté
  - Lit vasculaire: augmentation des résistances pulmonaires à haute dose?
- ½ vie: minutes
- Indications:
  - Choc septique
  - Pour augmenter TAM dans toute hypotension

Adrenaline

- Hormone sécrétée par medulla de la surrénale
- Récepteurs:
  - Agoniste alpha, beta1, beta2
  - Surtout beta ad 0,1 mcg/kg/min (environ 100 X dobu)
  - Alpha plus prédominant si > 0,1-0,5 mcg/kg/min
- Hémodynamique
  - PAM: augmentée
  - D.C.: augmenté
  - F.C.: augmentée
  - SVR: augmentée
  - Lits vasculaires: VC splanchnique à haute dose?
- ½ vie: minutes
- 1 à 10 mcg/min

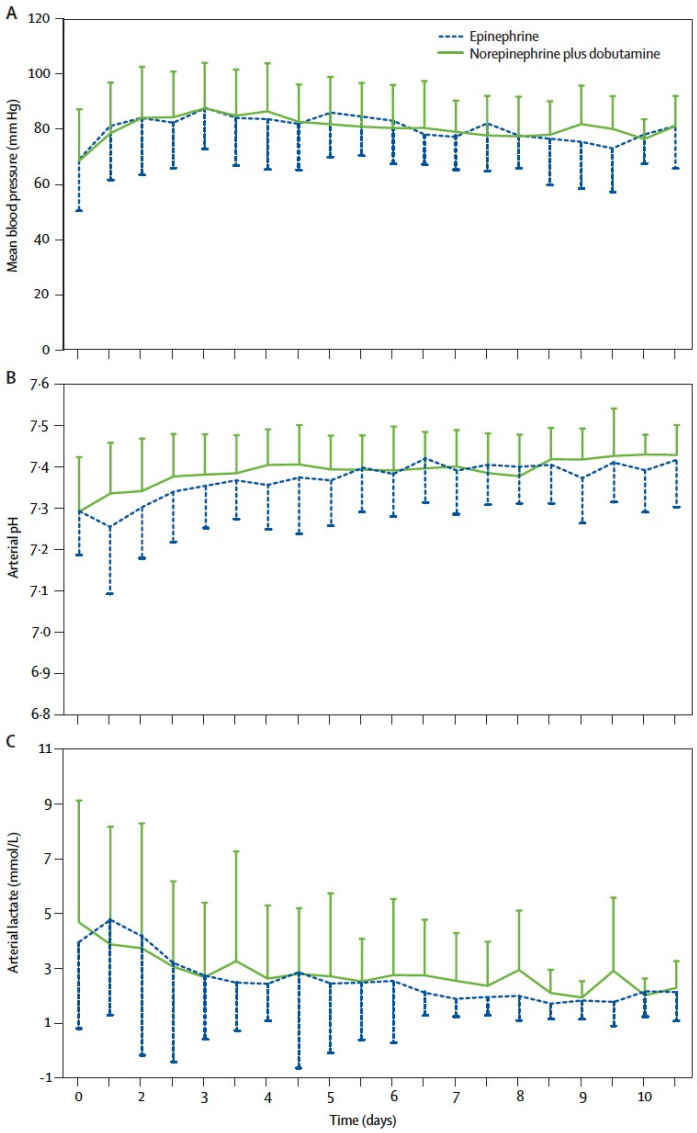
Adrénaline

- Effets secondaire:
  - Hyperlactatémie
    - Beta-2: glycolyse a/n musculaire > demande (capacité oxydative)
      - Via Na-K ATPase
    - Hyperglycémie par glycogénolyse, gluconéogénèse, aug glucagon
    - Diminution clairance hépatique
    - Auto-limité 24h
    - Effet protecteur? Présent en choc même sans épi exogène?
  - Arrythmogène
  - Ischémie myocardique
  - Catabolisme et effets immuns
- Indications:
  - ACR
  - Anaphylaxie
  - Chronotropie
  - Inotrope chez un patient vasoplégique?

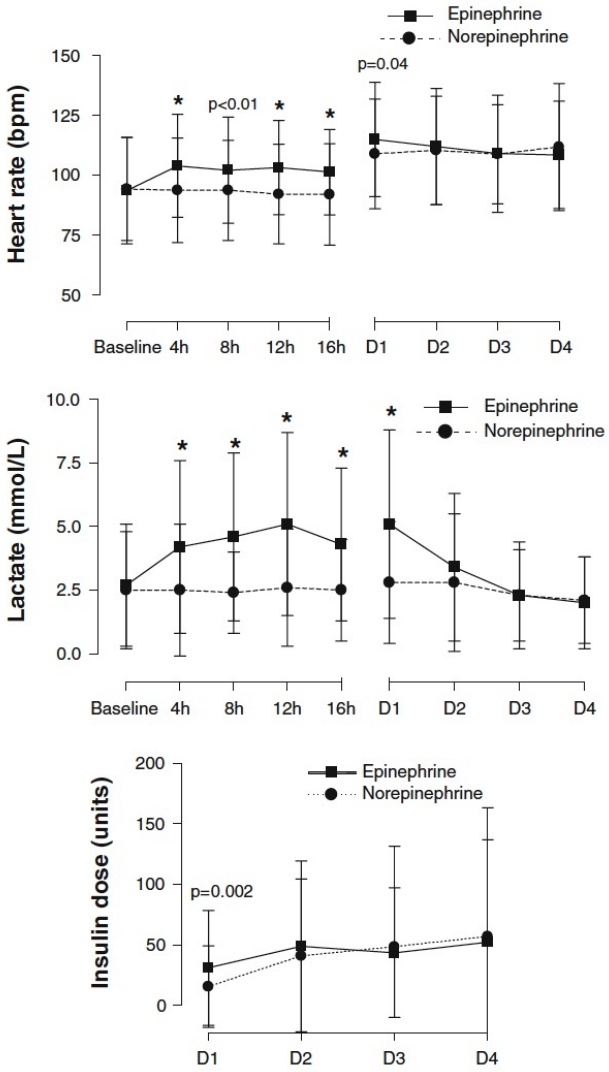


Stimulation by epinephrine of compartmentalised glycolysis coupled to Na^+, K^+-ATPase activity

Lancet 1999; **354:** 505–08



Lancet 2007; 370: 676–84



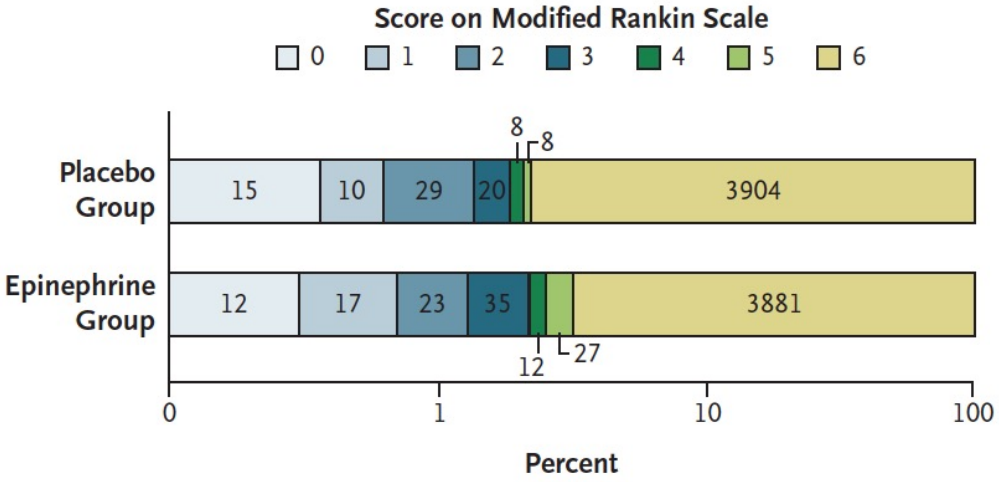
Intensive Care Med (2008) 34:2226–2234
DOI 10.1007/s00134-008-1219-0

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 23, 2018 VOL. 379 NO. 8

A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest

G.D. Perkins, C. Ji, C.D. Deakin, T. Quinn, J.P. Nolan, C. Scomparin, S. Regan, J. Long, A. Slowther, H. Pocock, J.J.M. Black, F. Moore, R.T. Fothergill, N. Rees, L. O'Shea, M. Docherty, I. Gunson, K. Han, K. Charlton, J. Finn, S. Petrou, N. Stallard, S. Gates, and R. Lall, for the PARAMEDIC2 Collaborators*



Intensive Care Med (2018) 44:847–856
https://doi.org/10.1007/s00134-018-5222-9

SYSTEMATIC REVIEW

Epinephrine and short-term survival in cardiogenic shock: an individual data meta-analysis of 2583 patients

Valentine Léopold[1], Etienne Gayat[1], Romain Pirracchio[2], Jindrich Spinar[3], Jiri Parenica[3], Tuukka Tarvasmäki[4,5], Johan Lassus[4], Veli-Pekka Harjola[4], Sébastien Champion[6], Faiez Zannad[7], Serafina Valente[8], Philip Urban[9], Horng-Ruey Chua[10,11,12,13,14], Rinaldo Bellomo[10,11,12,13], Batric Popovic[15], Dagmar M. Ouweneel[16], José P. S. Henriques[16], Gregor Simonis[17,18], Bruno Lévy[19], Antoine Kimmoun[19], Philippe Gaudard[20], Mir Babar Basir[21], Andrej Markota[22], Christoph Adler[23], Hannes Reuter[23], Alexandre Mebazaa[1,24*] and Tahar Chouihed[1,7,25,26]

© 2018 Springer-Verlag GmbH Germany, part of Springer Nature and ESICM

Abstract

Objective: Catecholamines have been the mainstay of pharmacological treatment of cardiogenic shock (CS). Recently, use of epinephrine has been associated with detrimental outcomes. In the present study we aimed to evaluate the association between epinephrine use and short-term mortality in all-cause CS patients.

Design: We performed a meta-analysis of individual data with prespecified inclusion criteria: (1) patients in non-surgical CS treated with inotropes and/or vasopressors and (2) at least 15% of patients treated with epinephrine administrated alone or in association with other inotropes/vasopressors. The primary outcome was short-term mortality.

Measurements and results: Fourteen published cohorts and two unpublished data sets were included. We studied 2583 patients. Across all cohorts of patients, the incidence of epinephrine use was 37% (17–76%) and short-term mortality rate was 49% (21–69%). A positive correlation was found between percentages of epinephrine use and short-term mortality in the CS cohort. The risk of death was higher in epinephrine-treated CS patients (OR [CI] = 3.3 [2.8–3.9]) compared to patients treated with other drug regimens. Adjusted mortality risk remained striking in epinephrine-treated patients ($n = 1227$) (adjusted OR = 4.7 [3.4–6.4]). After propensity score matching, two sets of 338 matched patients were identified and epinephrine use remained associated with a strong detrimental impact on short-term mortality (OR = 4.2 [3.0–6.0]).

Conclusions: In this very large cohort, epinephrine use for hemodynamic management of CS patients is associated with a threefold increase of risk of death.

Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: Which is best?*

Daniel De Backer, MD, PhD; Jacques Creteur, MD, PhD; Eliézer Silva, MD, PhD;
Jean-Louis Vincent, MD, PhD, FCCM

Objective: To assess the effects of different doses of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in patients with septic shock.

Design: Prospective, randomized, open-label study.

Setting: A 31-bed, medicosurgical intensive care unit of a university hospital.

Patients: Convenience sample of 20 patients with septic shock, separated into two groups according to whether (moderate shock group, n = 10) or not (severe shock, n = 10) dopamine alone was able maintain mean arterial pressure >65 mm Hg.

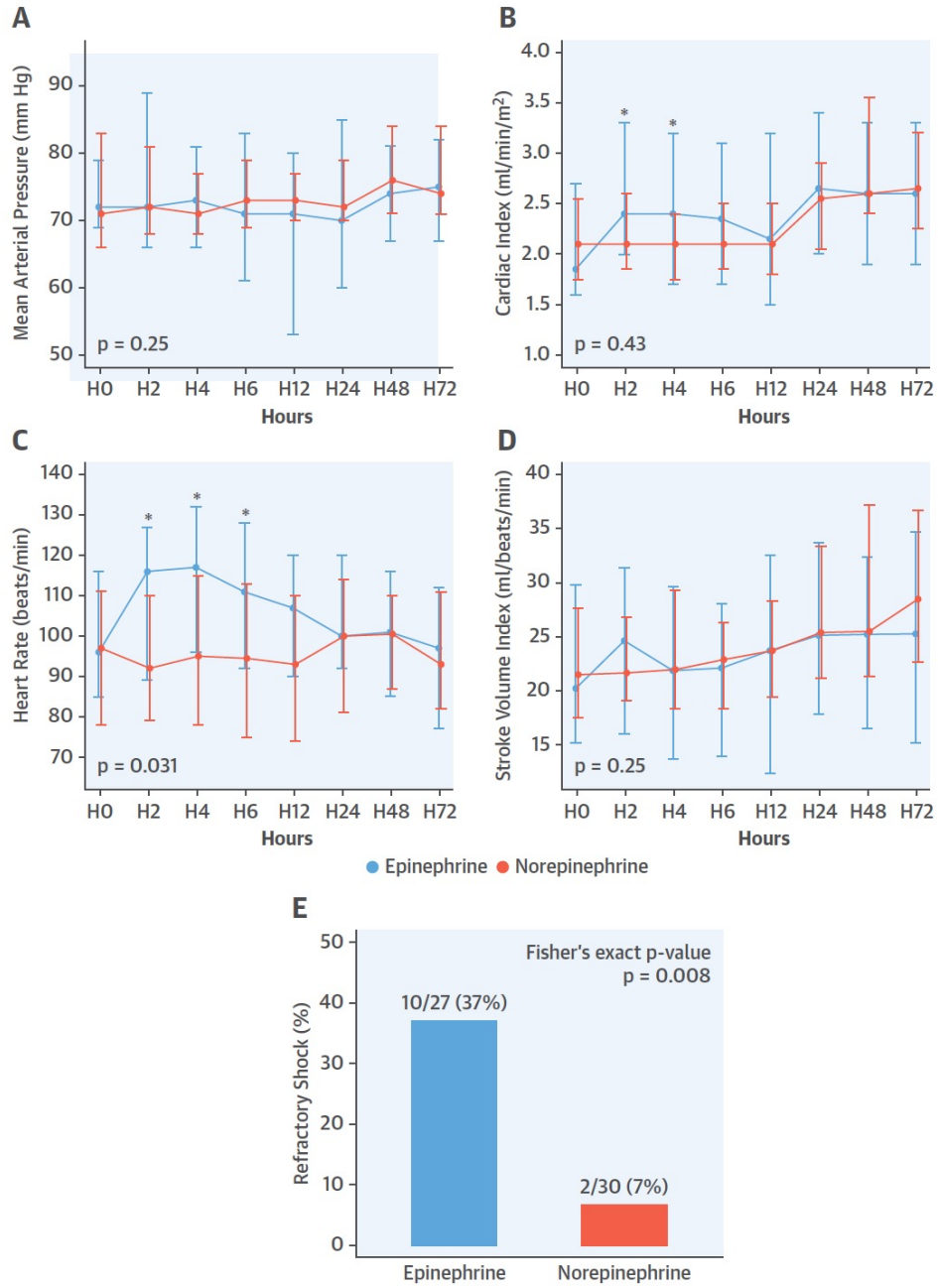
Interventions: Dopamine was progressively withdrawn and replaced successively by norepinephrine and then epinephrine (the order of the two agents was randomly determined) to maintain mean arterial pressure constant (moderate shock) or to increase mean arterial pressure above 65 mm Hg (severe shock).

Measurements and Main Results: Systemic circulation (pulmonary artery catheter) and splanchnic circulation (indocyanine green dilution and hepatic vein catheter) and gastric mucosal P_{CO_2} (gas tonometry) were measured during dopamine (moderate shock only), norepinephrine, and epinephrine administration (both groups). Data were analyzed with nonparametric tests and are presented as median [percentiles 25–75]. In moderate shock, cardiac index was similar to dopamine and norepinephrine (3.1 [2.7–3.8] vs. 2.9 [2.7–4.1] L/min·m^2, p = nonsignificant) but greater with epinephrine (4.1 [3.5–4.4] $p < .01$ vs. dopamine and norepinephrine). Splanchnic blood flow was similar with the three agents (732 [413–1483] vs. 746 [470–1401] vs. 653 [476–1832] mL/min·m^2, p = nonsignificant). The gradient between mixed-venous and hepatic venous oxygen saturations was lower with dopamine than with norepinephrine and epinephrine, but the P_{CO_2} gap was similar with the three agents. In severe shock, cardiac index was higher, but splanchnic blood flow was lower, with epinephrine than with norepinephrine (4.6 [3.7–5.3] vs. 3.4 [3.0–4.1] L/min·m^2, $p < .01$ and 860 [684–1334] vs. 977 [806–1802] mL/min·m^2, $p < .05$, respectively). Epinephrine increased the mixed-venous and hepatic venous oxygen saturation gradient but did not alter P_{CO_2} gap.

Conclusions: Dopamine and norepinephrine have similar hemodynamic effects, but epinephrine can impair splanchnic circulation in severe septic shock. (Crit Care Med 2003; 31:1659–1667)

KEY WORDS: cardiac output; splanchnic blood flow; tonometry; hepatic vein oxygen saturation; adrenergic agents; lactate

CENTRAL ILLUSTRATION Epinephrine Versus Norepinephrine in Cardiogenic Shock After Acute Myocardial Infarction



Levy, B. et al. J Am Coll Cardiol. 2018;72(2):173–82.

Dopamine

- Précurseur synthèse noadrénaline, neurotransmetteur
- Récepteurs:
  - D1 effet VD rein, splanchnique, cerveau, coronaires + natriurèse
  - Active récepteurs adrénergiques selon la dose
- 0 à 3-5 mcg/kg/min: VD, augmente D.C.
- 5 à 10-15 mcg/kg/min: beta surtout
- Plus de 10-15: de plus en plus alpha
- Indications? Brady et très faible risque arrythmique…
- Effet neuro-humoral (prolactine, TSH, GH)

Dopa vs Norepi

- 1679 patients en choc (62% septique)
- Plus d'arrythmies avec dopa (24 vs 12%)

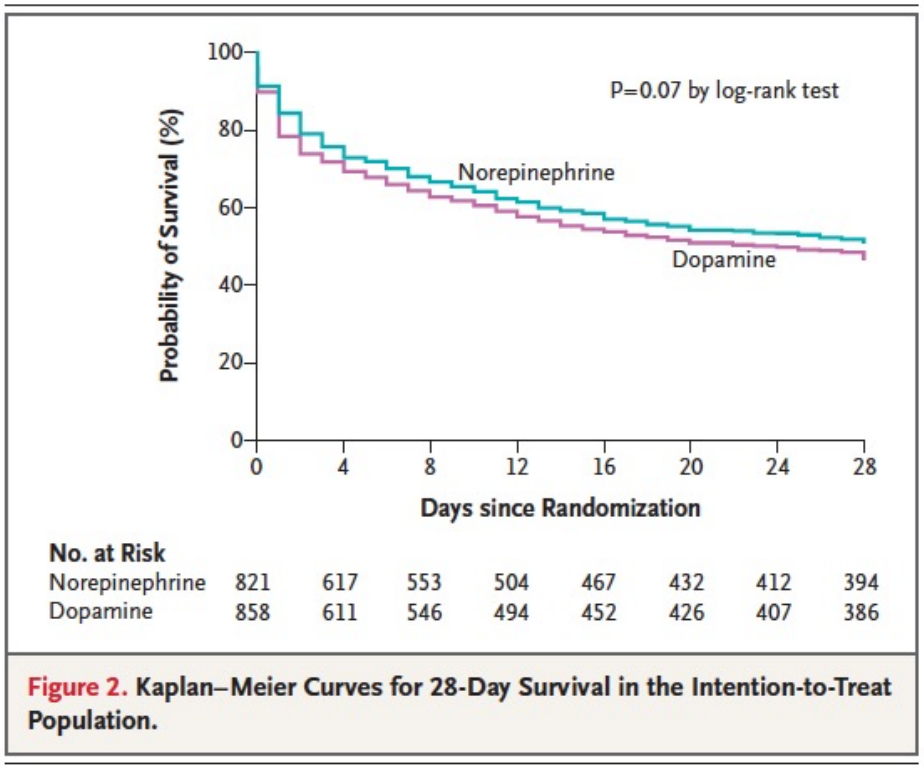
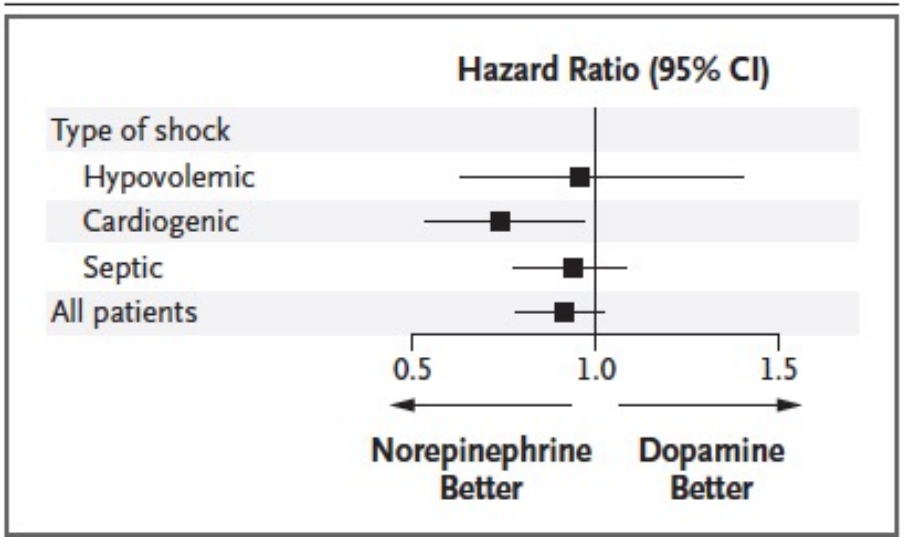


Figure 2. Kaplan–Meier Curves for 28-Day Survival in the Intention-to-Treat Population.



De Backer NEJM 2010

Isoproterenol

- Récepteurs: Beta 1 et 2 +++
- Hémodynamie:
  - PAM: diminuée (sauf si effet D.C. > SVR)
  - FC: augmentée
  - D.C.: augmenté
  - SVR: diminuée
- Hyperlactatémie comme adrénaline
- ½ vie: minutes
- 1-10 mcg/min, titrer pour FC désirée
- Indications:
  - Bloc/brady, greffe cardiaque, torsades

Dobutamine

- Récepteurs:
  - 2 isomères: effet B1:B2 (3:1)
    - D: Beta 1 et Beta 2
    - L: Beta 1 et alpha 1
  - Léger effet alpha1 plus proéminent à haute dose
- Hémodynamique
  - PAM: lég diminuée ou idem
  - FC: augmentée
  - D.C.: augmenté
  - SVR: lég diminuée

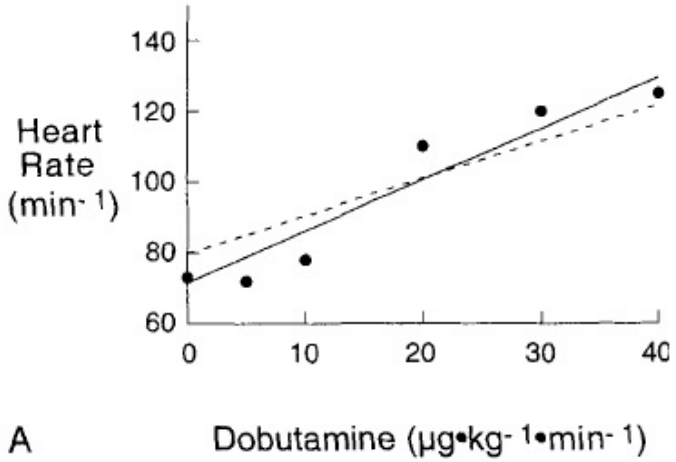
Dobutamine

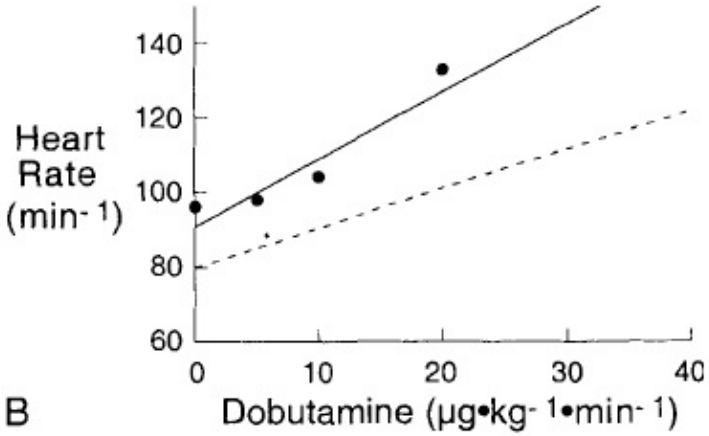
- À doses > 5 mcg/kg/min, peu d'effet inotropique supplémentaire et plus d'effet chrono et arrythmiques
- Tachyphylaxie 48-72h
- Down-regulation chez défaillant cardiaque, beta-bloqueurs…
- Effet sur microcirculation?
- ½ vie: minutes
- 2.5-10 mcg/min
- Arrythmogène
- Indications: choc cardiogénique

Anesthesiology
1999; 91:1318–28
© 1999 American Society of Anesthesiologists, Inc.
Lippincott Williams & Wilkins, Inc.

Effects of Dobutamine on Hemodynamics and Left Ventricular Performance after Cardiopulmonary Bypass in Cardiac Surgical Patients

Joseph L. Romson, M.D., Ph.D., Jacqueline M. Leung, M.D., M.P.H.,† Wayne H. Bellows, M.D.,‡ Merrill Bronstein, M.D.,§ Fraser Keith, M.D.,‖ William Moores, M.D.,# Keith Flachsbart, M.D.,# Richard Richter, M.D.,# Darwin Pastor,** Dennis M. Fisher, M.D.††*





Milrinone

- Bipyridine, inhibiteur PDE 3 sélectif
- Hémodynamie
  - PAM: diminuée
  - FC: lég augmentation (moins que dobu)
  - D.C.: augmenté
  - SVR: diminuée (plus que dobu)
  - Lits vasculaires: VD pulmonaire non sélective
- ½ vie: 30-60 min
  - Bolus 20-50 mcg/kg, perfusion 0,2-0,75 mcg/kg/min
- Élimination rénale: diminuer dose ad 0,2 mcg/kg/h re: risque intox

Milrinone

- Arrythmogène (similaire à dobu)
- Indication:
  - Dysfonction VD? (attention si vasoplégie importante, hypoxémie ou insuf. rénale)
  - Choc cardiogénique prolongé
  - Choc cardiogénique sous beta-bloqueurs
  - Choc cardiogénique avec résistances périphériques élevées

Effects of *Milrinone* on Pulmonary Gas Exchange in Catecholamine-Dependent Heart Failure

Maria Koreny, MD, Alexander Geppert, MD, Michael Wutte, MD,
Georg Delle Karth, MD, Gottfried Heinz, MD, and Peter Siostrzonek, MD

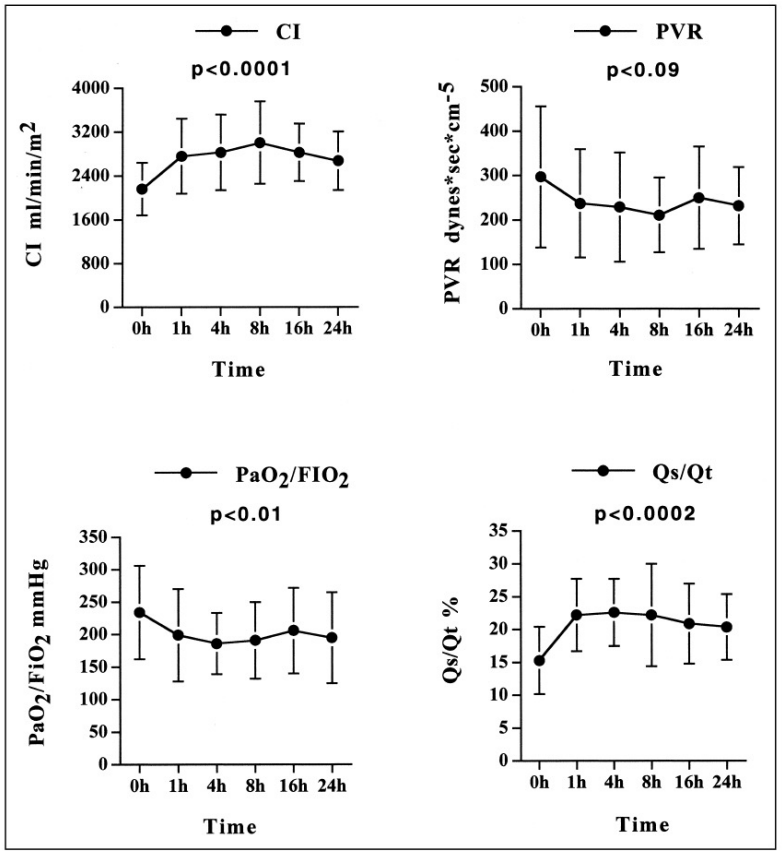


FIGURE 1. Cardiac index (CI), pulmonary vascular resistance (PVR), arterial oxygen tension-to-inspired oxygen fraction ratio (PaO_2/FiO_2), and pulmonary shunt (Qs/Qt) over 24 hours of continuous milrinone therapy.

Hemodynamic and Gas Exchange Effects of Sildenafil in Patients with Chronic Obstructive Pulmonary Disease and Pulmonary Hypertension

Isabel Blanco[1], Elena Gimeno[1], Phillip A. Munoz[2], Sandra Pizarro[1], Concepción Gistau[1], Robert Rodriguez-Roisin[1,2], Josep Roca[1,2], and Joan Albert Barberà[1,2]

[1]Department of Pulmonary Medicine, Hospital Clínic–Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona; and [2]Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Spain

TABLE 3. EFFECTS OF SILDENAFIL ON RESPIRATORY GAS MEASUREMENTS AND AND DURING EXERCISE

	Rest	
	Before Sildenafil (*Mean ± SD*)	Change after Sildenafil [*Mean (95% CI)*]
Pa_{O_2}, mm Hg	64 ± 11	−6 (−8 to −4)*
Pa_{CO_2}, mm Hg	42 ± 6	−2 (−3 to −1)*
$P(A–a)_{O_2}$, mm Hg	32 ± 9	7 (5 to 9)*
$P\bar{v}_{O_2}$, mm Hg	34 ± 2	−1.1 (−1.8 to −0.4)*
V_E, L	8.0 ± 1.2	0.6 (−0.1 to 1.2)

Crit Care Med. 1997 Nov;25(11):1807-12.

Effect of antihypertensive agents on the arterial partial pressure of oxygen and venous admixture after cardiac surgery.

Wood G[1].

⊕ Author information

Abstract

OBJECTIVE: To determine whether stopping nitroglycerin and sodium nitroprusside (both vasodilators) infusions in hypertensive, postcardiac surgical patients requiring a high FIO2 improves PaO2 and venous admixture.

DESIGN: Prospective, clinical trial.

SETTING: Intensive care unit in a university-affiliated hospital.

PATIENTS: Thirty postcardiac surgical patients who, because of high FIO2 requirements, did not meet the criteria for weaning from mechanical ventilation and who were receiving infusions of nitroglycerin and/or sodium nitroprusside to control blood pressure.

INTERVENTIONS: PaO2, venous admixture, and oxygen transport data were determined at baseline using arterial and mixed venous blood gas samples and hemodynamic values from a pulmonary artery catheter. The nitroglycerin and sodium nitroprusside infusions were stopped, and intravenous boluses of labetalol were administered to maintain a target blood pressure. After the vasodilator infusions were stopped, the baseline measurements were repeated to redetermine PaO2, venous admixture, and oxygen transport values.

MEASUREMENTS AND MAIN RESULTS: Results included a mean increase in PaO2 from 79.3 +/- 15 torr (10.5 +/- 2.0 kPa) to 118.3 +/- 38 torr (15.7 +/- 5.1 kPa) and a mean decrease in venous admixture from 26.4 +/- 5.8% to 17.6 +/- 5.6% when the vasodilators were stopped. All 30 patients had an increase in PaO2 and a decrease in venous admixture. Because of the improvement in oxygenation, 28 of the 30 patients met the criteria for weaning from mechanical ventilation once nitroglycerin and sodium nitroprusside were stopped or decreased. Labetalol was well tolerated in this group of patients who had preserved ventricular function.

CONCLUSIONS: Substituting labetalol for nitroglycerin and sodium nitroprusside improves arterial oxygenation and venous admixture in hypertensive postcardiac surgical patients who require a high FIO2. This change in therapy may allow patients to be weaned from mechanical ventilation sooner.

REVIEW ARTICLE

Efficacy of milrinone and dobutamine in low cardiac output states: Systematic review and meta-analysis

Rebecca Mathew, MD[1,2]
Goncalo M. Santos[3]
Sarah M. Visintini, MLIS[4]
F. Daniel F. Ramirez, MD[1,2,5]
Pietro DiSanto, MD[1,2]
Trevor Simard, MD[1,2,6]
Marino Labinaz, MD[1,2]
Benjamin M. Hibbert, MD, PhD[1,2,6,7]

[1] Division of Cardiology, University of Ottawa Heart Institute
[2] CAPITAL Research Group, University of Ottawa Heart Institute
[3] Faculty of Medicine, University of Ottawa
[4] Berkman Library, University of Ottawa Heart Institute
[5] School of Epidemiology and Public Health, University of Ottawa
[6] Vascular Biology and Experimental Medicine Laboratory, University of Ottawa Heart Institute
[7] Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada

Manuscript submitted 3rd November, 2018
Manuscript accepted 18th February, 2019

Clin Invest Med 2019; 42 (2): E26-32.

Abstract

Purpose: Patients in cardiac intensive care units (ICU) are admitted with increasingly higher disease acuity and a larger burden of non-cardiac critical illness. Accordingly, positive inotropes are being used with increased frequency and little comparative data to support drug selection. We compared the effectiveness and safety of dobutamine and milrinone in low cardiac output states (LCOS) and/or cardiogenic shock (CS).

Methods: We performed a systematic review comparing dobutamine to milrinone on all-cause mortality, length of stay in the ICU (LOS-ICU), length of stay in hospital (LOS-H) and significant arrhythmias in hospitalized patients with LCOS and/or CS.

Results: We identified 11 studies that meet eligibility requirements and which were published between 2001 and 2016 and included 23,056 patients. Only one randomized clinical trial was identified, with the remaining studies comprising observational cohort studies. The primary outcome, all-cause mortality, trended towards a benefit with milrinone but did not meet pre-specified significance (OR 1.13, 95% CI 1.00-1.29, p=0.06). While LOS-ICU (mean difference -0.72, 95% CI -1.10- -0.34, p=0.0002) was shorter with dobutamine, there was no difference in LOS-H (mean difference -1.22, 95% CI -4.68 – 2.24, p=0.49). Significant arrhythmias, specifically symptomatic and/or requiring anti-arrhythmic therapy, were no different between the groups (OR 1.78, 95% CI 0.85-3.76, p=0.13).

Conclusions: Currently available data comparing milrinone to dobutamine in patients requiring inotropic support is limited. Dobutamine may be associated with a shorter LOS in the ICU, with a worrisome signal of increased risk of all-cause mortality. Randomized data are needed to guide inotrope selection in patients with LCOS and/or CS.

Nielsen et al. Critical Care (2018) 22:51
https://doi.org/10.1186/s13054-018-1969-1

Critical Care

RESEARCH Open Access

Intraoperative milrinone versus dobutamine in cardiac surgery patients: a retrospective cohort study on mortality

Dorthe Viemose Nielsen[1*], Christian Torp-Pedersen[2], Regitze Kuhr Skals[3], Thomas A. Gerds[4], Zidryne Karaliunaite[1] and Carl-Johan Jakobsen[1]

Abstract

Background: Several choices of inotropic therapy are available and used in relation to cardiac surgery. Comparisons are necessary to select optimal therapy. In Denmark, dobutamine and milrinone are the two inotropic agents most commonly used to treat post-bypass low cardiac output syndrome. This study compares all-cause mortality with these drugs.

Methods: In a retrospective observational study we investigated 10,700 consecutive patients undergoing cardiac surgery from 1 April 2006 to 31 December 2013 at Aarhus and Aalborg University Hospitals in the Central and Northern Denmark Region. Prospectively entered data in the Western Danish Heart Registry on intraoperative use of inotropes were used to identify 952 patients treated with milrinone, 418 patients treated with dobutamine, and 82 patients receiving a combination of the two inotropes. All-cause mortality among patients receiving dobutamine was compared to all-cause mortality among milrinone receivers.
Multiple logistic regression analyses including preoperative and intraoperative variables along with g-formula analyses were used to model 30-day and 1-year mortality risks. Reported were standardized mortality risk differences between the treatment groups.

Results: Among patients receiving intraoperative dobutamine, 18 (4.3%) died within 30 days and 49 (11.7%) within 1 year. Corresponding 30-day and 1-year mortality for milrinone receivers were 81 (8.5%) and 170 (17.9%). Risk of death within 30 days and 1 year was increased for intraoperative milrinone compared to dobutamine with a standardized risk difference of 4.06% (confidence interval (CI) 1.23; 6.89, $p = 0.005$) and 4.77% (CI 0.39; 9.15, $p = 0.033$), respectively. Sensitivity analyses including adjustment for milrinone preference, hemodynamic instability prior to cardiopulmonary bypass, and separate analyses on hospital level all confirmed a sign toward increased mortality among milrinone receivers.

Conclusions: Intraoperative use of milrinone in cardiac surgery may be associated with an increase in all-cause mortality compared to use of dobutamine.

Keywords: Cardiac surgery, Intraoperative, Milrinone, Dobutamine, Mortality, Retrospective cohort study, g-formula, Standardized mortality risk

Meta-analysis of Randomized Trials of Effect of Milrinone on Mortality in Cardiac Surgery: An Update

David T. Majure, MD, MPH,* Teresa Greco, MSc, MStat,† Massimiliano Greco, MD,† Martin Ponschab, MD,‡ Giuseppe Biondi-Zoccai, MD,§ Alberto Zangrillo, MD,† and Giovanni Landoni, MD†

Objective: **The long-term use of milrinone is associated with increased mortality in chronic heart failure. A recent meta-analysis suggested that it might increase mortality in patients undergoing cardiac surgery. The authors conducted an updated meta-analysis of randomized trials in patients undergoing cardiac surgery to determine if milrinone impacted survival.**

Design: **A meta-analysis.**

Setting: **Hospitals.**

Participants: **One thousand thirty-seven patients from 20 randomized trials.**

Interventions: **None.**

Measurements and Main Results: **Biomed, Central, PubMed, EMBASE, the Cochrane central register of clinical trials, and conference proceedings were searched for randomized trials that compared milrinone versus placebo or any other control in adult and pediatric patients undergoing cardiac surgery. Authors of trials that did not include mortality data were contacted. Only trials for which mortality data were available were included. Overall analysis showed no difference in mortality between patients receiving milrinone versus control (12/554 [2.2%] in the milrinone group *v* 10/483 [2.1%] in the control arm; relative risk [RR] = 1.15; 95% confidence interval [CI], 0.55-2.43; $p = 0.7$) or in analysis restricted to adults (11/364 [3%] in the milrinone group *v* 9/371 [2.4%] in the control arm; RR = 1.17; 95% CI, 0.54-2.53; $p = 0.7$). Sensitivity analyses in trials with a low risk of bias showed a trend toward an increase in mortality with milrinone (8/153 [5.2%] in the milrinone arm *v* 2/152 [1.3%] in the control arm; RR = 2.71; 95% CI, 0.82-9; *p* for effect = 0.10).**

Conclusions: **Despite theoretic concerns for increased mortality with intravenous milrinone in patients undergoing cardiac surgery, the authors were unable to confirm an adverse effect on survival. However, sensitivity analysis of high-quality trials showed a trend toward increased mortality with milrinone.**

© *2013 Elsevier Inc. All rights reserved.*

KEY WORDS: ***milrinone, inotropic agents, cardiac surgery, coronary artery bypass graft surgery, anesthesia, heart failure, outcomes, mortality, intensive care***

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock

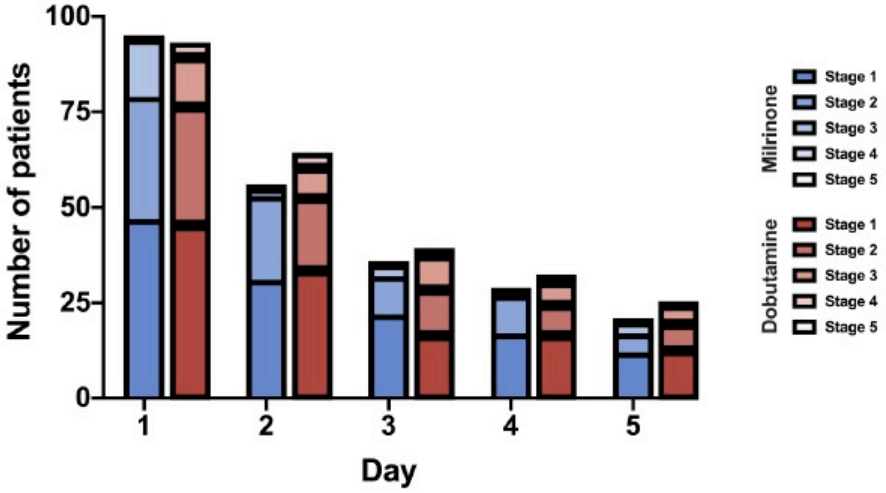
Rebecca Mathew, M.D., Pietro Di Santo, M.D., Richard G. Jung, Ph.D., Jeffrey A. Marbach, M.B., B.S., Jordan Hutson, M.D., Trevor Simard, M.D., F. Daniel Ramirez, M.D., David T. Harnett, M.D., Anas Merdad, M.B., B.S., Aws Almufleh, M.B., B.S., Willy Weng, M.D., Omar Abdel-Razek, M.D., Shannon M. Fernando, M.D., Kwadwo Kyeremanteng, M.D., M.H.A., Jordan Bernick, M.Sc., George A. Wells, Ph.D., Vincent Chan, M.D., Michael Froeschl, M.D., C.M., Marino Labinaz, M.D., Michel R. Le May, M.D., Juan J. Russo, M.D., and Benjamin Hibbert, M.D., Ph.D.

- 192 patients choc cardiogénique
- Milri: 0,125 – 0,25 – 0,375 – 0,5 - >0,5 mcg/kg/min
- Dobu: 2,5 – 5 – 7,5 – 10 - >10 mcg/kg/min
- Issue primaire composée: mort, arrêt cardiaque, transplantation, support mécanique, infarctus, ICT/AVC, dialyse
- À la randomisation:
  - 50% sous beta-bloqueurs dans les 24h
  - Dobu: 50% sous vasopresseurs, 29% intubés
  - Milri: 39% sous vasopresseurs, 13% intubés

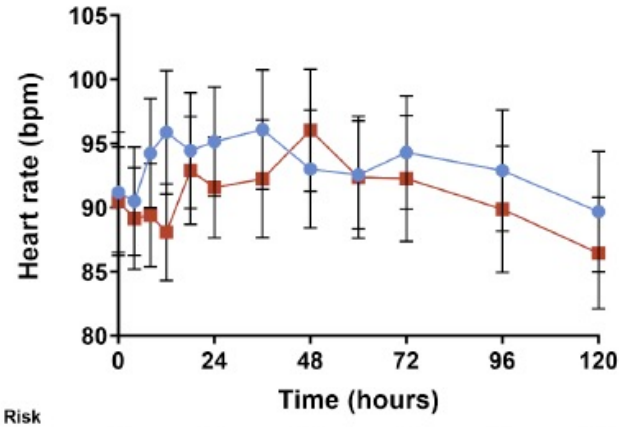
Table 2. Primary and Secondary Outcomes.*

Outcome	Milrinone (N=96)	Dobutamine (N=96)	Relative Risk or Hazard Ratio (95% CI)†	P Value‡
Primary outcome: composite of in-hospital death from any cause, resuscitated cardiac arrest, receipt of cardiac transplant or mechanical circulatory support, nonfatal myocardial infarction, transient ischemic attack or stroke diagnosed by a neurologist, or initiation of renal replacement therapy — no. (%)	47 (49)	52 (54)	0.90 (0.69–1.19)	0.47
Secondary outcomes				
In-hospital death from any cause — no. (%)	35 (37)	41 (43)	0.85 (0.60–1.21)	
Resuscitated cardiac arrest — no. (%)	7 (7)	9 (9)	0.78 (0.29–2.07)§	
Receipt of cardiac transplant or mechanical circulatory support — no. (%)	11 (12)	14 (15)	0.78 (0.36–1.71)§	
Nonfatal myocardial infarction — no. (%)	1 (1)	0	—	
Transient ischemic attack or stroke — no. (%)	1 (1)	2 (2)	0.50 (0.05–5.50)§	
Initiation of renal replacement therapy — no. (%)¶	21 (22)	16 (17)	1.39 (0.73–2.67)§	
Median cardiac ICU length of stay (IQR) — days‖	4.5 (2.0–7.0)	5.5 (3.0–10.0)	—	
Cardiac ICU length of stay ≥7 days — no. (%)‖	31 (32)	42 (44)	0.74 (0.51–1.07)	
Median hospital length of stay (IQR) — days‖	16 (6–28)	15 (6–27)	—	
Median total time receiving inotropes (IQR) — hr‖	36 (18–79)	39 (19–64)	—	
Receipt of noninvasive or invasive mechanical ventilation after randomization — no. (%)	6 (6)	7 (7)	0.86 (0.30–2.46)	
Median total time receiving noninvasive or invasive mechanical ventilation (IQR) — hr‖	48 (6–120)	48 (12–120)	—	
Acute kidney injury — no. (%)¶	86 (92)	85 (90)	1.02 (0.94–1.12)	
Normalization of lactate level — no. (%)**	33 (46)	36 (56)	0.80 (0.56–1.15)	
Arrhythmia leading to medical team intervention — no. (%)‡	48 (50)	44 (46)	1.19 (0.85–1.57)	

Figure S4. Inotrope Stage and Titration

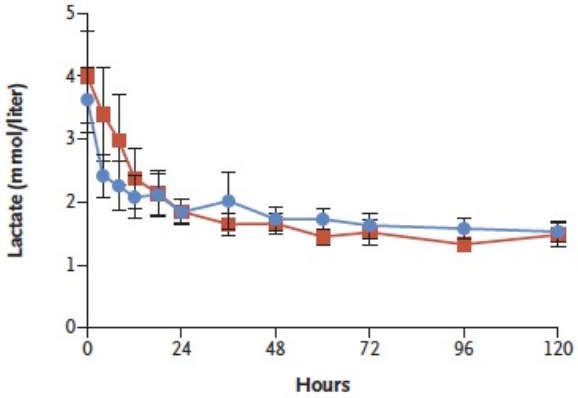


B



No. at Risk						
Milrinone	96	86	76	67	63	55
Dobutamine	96	80	75	62	60	56

D



No. at Risk						
Milrinone	94	81	72	59	51	40
Dobutamine	92	76	67	54	55	46

Comparison of the Hemodynamic Effects of Milrinone With Dobutamine in Patients After Cardiac Surgery

Robert O. Feneck, FRCA, Kathy M. Sherry, FRCA, P. Stuart Withington, FRCA, Amo Oduro-Dominah, FRCA, and the European Milrinone Multicenter Trial Group

Objective: **To compare the hemodynamic effects, efficacy, and safety of intravenous milrinone (M), 50 μg/kg during 10 minutes followed by 0.5 μg/kg/min, with intravenous dobutamine (D), 10 to 20 μg/kg/min, in patients with low cardiac output after cardiac surgery.**

Design: **Randomized, open-label, multicenter study.**

Setting: **Cardiothoracic surgery departments, operating rooms, and intensive care units in 6 university hospitals.**

Participants: **Patients (n = 120; 60 per group) after elective cardiac surgery.**

Interventions: **None.**

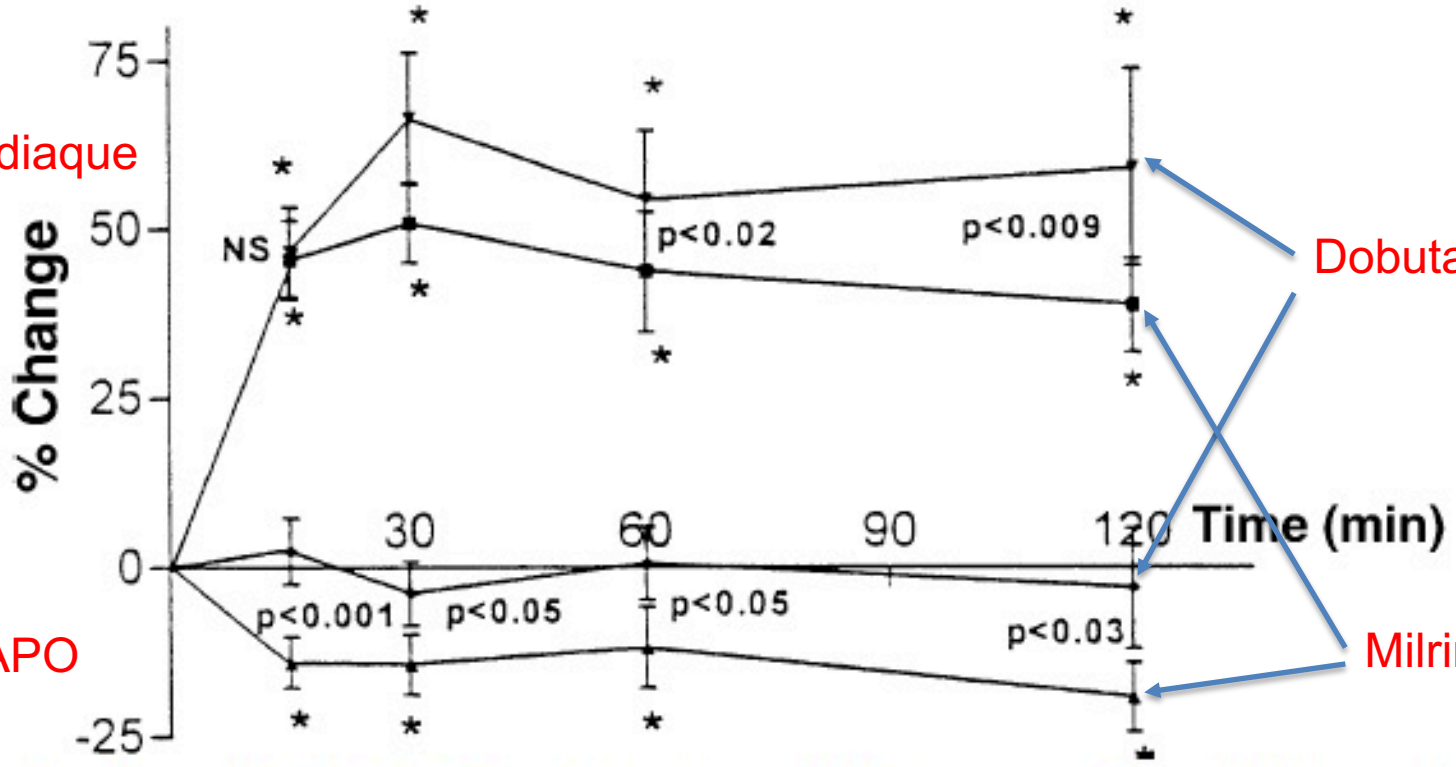
Measurements and Main Results: **Analysis compared the hemodynamics at baseline and the percentage change from baseline during 4 hours of the drug infusion. The incidence of adverse events was recorded. Both groups had low mean (± SEM) cardiac indices (M, 1.6 ([0.03] L/min/m^2; D, 1.7 [0.03] L/min/m^2) in association with adequate mean pulmonary capillary wedge pressures (M, 13.7 [1.3] mmHg; D, 12.7 [1.9] mmHg) at baseline. Group M had significantly higher systemic arterial pressures and systemic vascular resistances compared with group D; otherwise, the hemodynamics in both groups were comparable. During the study, hemodynamic responses included the following: group D had greater increases in cardiac index (at 1 hour, D = 55%, M = 36%; $p < 0.01$), heart rate (at 1 hour, D = 35%, M = 10%; $p < 0.001$), arterial pressures (mean arterial pressure at 1 hour, D = 31%, M = 7%; $p < 0.001$), and left ventricular stroke work index (at 1 hour, D = 75%, M = 45%; $p < 0.05$). Group M had greater decreases in mean pulmonary capillary wedge pressure (at 1 hour, D = −3%, M = −14%; $p < 0.05$). Comparisons of adverse events showed that dobutamine was associated with a higher incidence of hypertension (D = 40%, M = 13%; $p < 0.02$) and change of rhythm from sinus to atrial fibrillation (D = 18%, M = 5%; $p < 0.04$). Milrinone was associated with a higher incidence of sinus bradycardia (D = 2%, M = 13%; $p < 0.03$).**

Conclusions: **Milrinone and dobutamine are appropriate and comparable for the pharmacologic treatment of the low-output syndrome after cardiopulmonary bypass.**

Copyright © 2001 by W.B. Saunders Company

KEY WORDS: milrinone, dobutamine, cardiac surgery

Index cardiaque



PAPO

Dobutamine

Milrinone

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.)

Rev Bras Anestesiol
2010; 60: 3: 237-246

Comparison of the Effects of Dobutamine and Milrinone on Hemodynamic Parameters and Oxygen Supply in Patients Undergoing Cardiac Surgery with Low Cardiac Output after Anesthetic Induction

Maria José Carvalho Carmona, TSA [1], Laura Mariana Martins [2], Matheus Fachini Vane [2], Breno Altero Longo [2], Lemuel Silva Paredes [3], Luiz Marcelo Sá Malbouisson, TSA [4]

Summary: Carmona MJC, Martins LM, Vane MF, Longo BA, Paredes LS, Malbouisson LMS – Comparison of the Effects of Dobutamine and Milrinone on Hemodynamic Parameters and Oxygen Supply in Patients Undergoing Cardiac Surgery with Low Cardiac Output after Anesthetic Induction.

Background and objectives: Several classes of inotropic drugs with different hemodynamic effects are used in the treatment of low cardiac output in patients with diastolic dysfunction undergoing cardiac surgery. The objective of the present study was to compare the effects of dobutamine and milrinone on hemodynamic parameters and oxygen supply in this population of patients.

Methods: After approval by the Ethics Committee of the institution and signing of the informed consent, 20 patients undergoing cardiac surgery with cardiac index < 2 $L.min^{-1}.m^2$ after anesthetic induction and placement of a pulmonary artery catheter were randomly divided to receive dobutamine 5 $\mu g.kg^{-1}.min^{-1}$ (n = 10), or milrinone 0.5 $\mu g.kg^{-1}.min^{-1}$ (n = 10). Hemodynamic parameters were measured after anesthetic induction and after 30 and 60 minutes, and arterial and venous blood gases were measured at baseline and 60 minutes. Non-paired Student t test or two-way ANOVA for repeated measurements was used to compare the data.

Results: Dobutamine and milrinone promoted significant increases in cardiac index (56% and 47%) and oxygen supply (53% and 45%), and reduction in systemic (33% and 36%) and pulmonary (34% and 19%) vascular resistance, respectively. However, statistically significant differences were not observed between both drugs.

Conclusions: Both inotropic drugs were similarly effective in restoring tissue blood flow and oxygen supply to adequate levels in patients with low cardiac output undergoing cardiac surgery.

Keywords: ANESTHESIA, General; COMPLICATIONS: low cardiac output; DRUGS, Vasodilators: dobutamine, milrinone; SURGERY, Cardiac: myocardial revascularization.

[Rev Bras Anestesiol 2010;60(3): 237-246] ©Elsevier Editora Ltda. Este é um artigo Open Access sob a licença de CC BY-NC-ND

Table III – Hemodynamic Parameters During the Study

	Group	basal	30 minutes	60 minutes	p group factor	p time factor	p interaction
CF	dobutamine	54 ± 11	65 ± 12!	67 ± 13!	NS	< 0.001	NS
(bpm)	milrinone	61 ± 18	88 ± 18!	67 ± 12!			
MAP	dobutamine	70 ± 14	65 ± 7	65 ± 7	NS	NS	NS
(mmHg)	milrinone	66 ± 8	67 ± 6	65 ± 7			
mean PAP	dobutamine	31 ± 6	28 ± 7	26 ± 5	NS	NS	NS
(mmHg)	milrinone	31 ± 11	32 ± 9	34 ± 7			
CVO	dobutamine	17 ± 4	14 ± 3	16 ± 4	NS	NS	NS
(mmHg)	milrinone	15 ± 4	17 ± 3	17 ± 3			
POAP	dobutamine	22 ± 5	18 ± 4	18 ± 4	NS	NS	NS
(mmHg)	milrinone	22 ± 7	22 ± 5	22 ±5			
CI	dobutamine	1.59 ± 0.20	2.49 ± 0.521!	2.86 ± 0.76!	NS	< 0.001	NS
($Mmin^{-1}.m^{2}$)	milrinone	1.44 ± 0.38	2.12 ± 0.48!	2.32 ± 0.47!			
SVRI	dobutamine	2577 ± 630	1718 ± 517!	1480 ± 488!	NS	< 0.001	NS
($dyns^{-1}.cm^{-5}.m^{-2}$)	milrinone	3107 ± 1008	1993 ± 470!	1921 ± 449!			
IRVO	dobutamine	499 ± 184	309 ± 149!	270 ± 125!	NS	< 0.001	NS
(dyns-1.$cm^{-5}.m^{-2}$)	milrinone	507 ± 259	411 ± 303!	398 ± 232!			
ITSVE	dobutamine	29 ± 10	34 ± 5!	36 ±9!	NS	< 0.001	NS
($kg\text{-}min^{-1}.m^{-2}$)	milrinone	22 ± 8	29 ± 8!	32 ± 10!			
RVWI	dobutamine	12 ± 12	13 ± 4!	15 ± 4!*	NS	< 0.001	NS
($kg.min^{-1}.m^{-2}$)	milrinone	10 ± 4	13 ± 4!	16 ± 5!*			

HR = heart rate; MAP = mean arterial pressure; mean PAP = mean pulmonary artery pressure; CVP = central venous pressure; POWP = pulmonary capillary wedge pressure; CI = cardiac index; SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index; LVWI = left ventricular work index; RVWI = right ventricular work index. ! means $p < 0.05$ when compared to baseline. * means $p < 0.05$ when compared with levels at 30 minutes.

Prevention of Low Cardiac Output Syndrome After Pediatric Cardiac Surgery: A Double-Blind Randomized Clinical Pilot Study Comparing Dobutamine and Milrinone*

Anna Cavigelli-Brunner, MD[1,2]; Maja I. Hug, MD[2,3]; Hitendu Dave, MD[2,4]; Oskar Baenziger, MD[2,3]; Christoph Buerki, MD[2,5]; Dominique Bettex, MD[6]; Vincenzo Cannizzaro, MD, PhD[2,3]; Christian Balmer, MD[1,2]

Objectives: Dobutamine and milrinone are commonly used after open-heart surgery to prevent or treat low cardiac output syndrome. We sought to compare efficacy and safety of these drugs in pediatric patients.

Design: Prospective, single-center, double-blinded, randomized clinical pilot study.

Setting: Tertiary-care university children's hospital postoperative pediatric cardiac ICU.

Patients: After written consent, 50 consecutive patients (age, 0.2–14.2 yr; median, 1.2 yr) undergoing open-heart surgery for congenital malformations were included.

Interventions: After cardiopulmonary bypass, a continuous infusion of either dobutamine or milrinone was administered for the first 36 postoperative hours. Maximum dose: dobutamine 6 μg/kg/min, milrinone 0.75 μg/kg/min.

Measurements and Main Results: There were no significant differences in demographic data, complexity of surgery, and intraoperative characteristics between the two study groups (dobutamine vs milrinone). Efficacy was defined as need for additional vasoactive support, which did not differ between groups (dobutamine 61% vs milrinone 67%; $p = 0.71$). Sodium nitroprusside was used more often in the dobutamine group (42% vs 13%; $p = 0.019$). Systolic blood pressure showed a trend toward higher values in the dobutamine group, whereas both drugs increased heart rate early postoperatively. Echocardiography demonstrated a consistently good cardiac function in both groups. Central venous oxygen saturation, serum lactate levels, urine output, time to chest tube removal, length of mechanical ventilation, ICU, and hospital stay were similar in both groups. Both drugs were well tolerated, no serious adverse events occurred.

Surgery

Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: A prospective, randomized trial

Juan M. Aranda, Jr, MD, Richard S. Schofield, MD, Daniel F. Pauly, MD, PhD, Timothy S. Cleeton, ARNP, Tracy C. Walker, ARNP, V. Steven Monroe, Jr, MD, Dana Leach, RN, Larry M. Lopez, Pharm D, and James A. Hill, MD, MS *Gainesville, Fla*

Background The use of dobutamine or milrinone for inotropic support in patients with heart failure awaiting cardiac transplantation is largely arbitrary and based on institutional preference. The costs and effectiveness of these drugs have yet to be compared in a prospective, randomized study.

Methods We compared clinical outcomes and costs associated with the use of dobutamine or milrinone in 36 hospitalized patients awaiting cardiac transplantation. Patients were randomly assigned to receive either dobutamine or milrinone at the time of initial hospitalization and were followed until death, transplantation, or placement of mechanical cardiac support (intra-aortic balloon pump or left ventricular assist device).

Results Seventeen patients were randomly assigned to receive dobutamine (mean dose 4.1 ± 1.4 μg/kg/min) and 19 patients received milrinone (mean dose 0.39 ± 1.0 μg/kg/min). Therapy lasted 50 ± 46 days for those in the dobutamine group and 63 ± 45 days in the milrinone group. We did not detect differences between the 2 groups in right heart hemodynamics, death, need for additional vasodilator/inotropic therapy, or need for mechanical cardiac support before transplantation. Ventricular arrhythmias requiring increased antiarrhythmic therapy occurred frequently in both groups. Total acquisition cost of milrinone was significantly higher than that of dobutamine ($16,270 ± 1334 vs $380 ± 533 $P < .00001$).

Conclusions Both dobutamine and milrinone can be used successfully as pharmacologic therapy for a bridge to heart transplantation. Despite similar clinical outcomes, treatment with milrinone incurs greater cost. (Am Heart J 2003; 145:324-9.)

Journal of Cardiovascular Pharmacology and Therapeutics
1-9
© The Author(s) 2018
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1074248418797357
journals.sagepub.com/home/cpt
SAGE

Comparative Effectiveness and Safety Between Milrinone or Dobutamine as Initial Inotrope Therapy in Cardiogenic Shock

Tyler C. Lewis, PharmD[1], Caitlin Aberle, PharmD[2], Diana Altshuler, PharmD[1], Greta L. Piper, MD[3], and John Papadopoulos, BS, PharmD[4]

Abstract

Inotropes are an integral component of the early stabilization of the patient presenting with cardiogenic shock. Despite years of clinical experience with the 2 most commonly used inotropes, dobutamine and milrinone, there remains limited data comparing outcomes between the two. We conducted a retrospective review to compare the effectiveness and safety of milrinone or dobutamine for the initial management of cardiogenic shock. Adult patients with cardiogenic shock regardless of etiology who received initial inotrope therapy with either milrinone (n = 50) or dobutamine (n = 50) and did not receive mechanical circulatory support were included. The primary end point was the time to resolution of cardiogenic shock. Changes in hemodynamic parameters from baseline and adverse events were also assessed. Resolution of shock was achieved in similar numbers in both the groups (milrinone 76% vs dobutamine 70%, $P = .50$). The median time to resolution of shock was 24 hours in both groups ($P = .75$). There were no differences in hemodynamic changes during inotrope therapy, although dobutamine trended toward a greater increase in cardiac index. Arrhythmias were more common in patients treated with dobutamine than milrinone, respectively (62.9% vs 32.8%, $P < .01$), whereas hypotension occurred to a similar extent in both groups (milrinone 49.2% vs dobutamine 40.3%, $P = .32$). The use of concomitant vasoactive medications, dosage required, and duration of therapy did not differ between groups. There was no difference in the overall rate of discontinuation due to adverse event; however, milrinone was more commonly discontinued due to hypotension (13.1% vs 0%, $P < .01$) and dobutamine was more commonly discontinued due to arrhythmia (0% vs 11.3%, $P < .01$). Milrinone and dobutamine demonstrated similar effectiveness and safety profiles but with differences in adverse events. The choice of milrinone or dobutamine as initial inotrope therapy for cardiogenic shock may depend more on tolerability of adverse events.

Table 2. Clinical Outcomes.[a]

	Milrinone (n = 50)	Dobutamine (n = 50)	*P* Value
Resolution of shock, n (%)	38 (76)	35 (70)	.50
Dose of inotrope at resolution, µg/kg/min	0.25 (0.25-0.375)	3 (2.5-5)	n/a

Table 4. Safety Outcomes.

	Milrinone (n = 61)	Dobutamine (n = 62)	*P* Value
Arrhythmia, n (%)	20 (32.8)	39 (62.9)	<.01
Atrial fibrillation	12 (60)	15 (38.5)	.55
Sinus tachycardia	5 (25)	15 (38.5)	.02
Other	3 (15)	9 (23)	.13
Time to arrhythmia, hours[a]	12.5 (1.5-20)	12.5 (4-30.5)	.59

Milrinone vs dobu

- Dobu:
  - Effet rapide, courte action, facile à titrer
  - Insuffisance rénale
  - Hypoxémie
  - Vasoplégie importante
  - Besoin de chronotropie
  - Sepsis?
- Milrinone
  - Beta-bloqueurs, défaillant chronique
  - HTAP / dysfonction VD
  - Synergie avec dobu
  - Thérapie prolongée
  - Résistances périphériques hautes
  - Patient tachycarde

Dobutamine is the preferred inotrope for acutely unstable patients in cardiogenic shock because its short half-life (less than 2 minutes) and quick onset allow prompt improvements in CO and rapid titration.[2] Dobutamine is recommended to

Journal of Cardiovascular Pharmacology and Therapeutics 20(3)

Cochrane Library

Cochrane Database of Systematic Reviews

Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome (Review)

Uhlig K, Efremov L, Tongers J, Frantz S, Mikolajczyk R, Sedding D, Schumann J

Authors' conclusions

At present, there are no convincing data supporting any specific inotropic or vasodilating therapy to reduce mortality in haemodynamically unstable patients with CS or LCOS.

Considering the limited evidence derived from the present data due to a high risk of bias and imprecision, it should be emphasised that there is an unmet need for large-scale, well-designed randomised trials on this topic to close the gap between daily practice in critical care of cardiovascular patients and the available evidence. In light of the uncertainties in the field, partially due to the underlying methodological flaws in existing studies, future RCTs should be carefully designed to potentially overcome given limitations and ultimately define the role of inotropic agents and vasodilator strategies in CS and LCOS.

Cochrane Database of Systematic Reviews 2020, Issue 11. Art. No.: CD009669.

ESC
European Society of Cardiology
European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

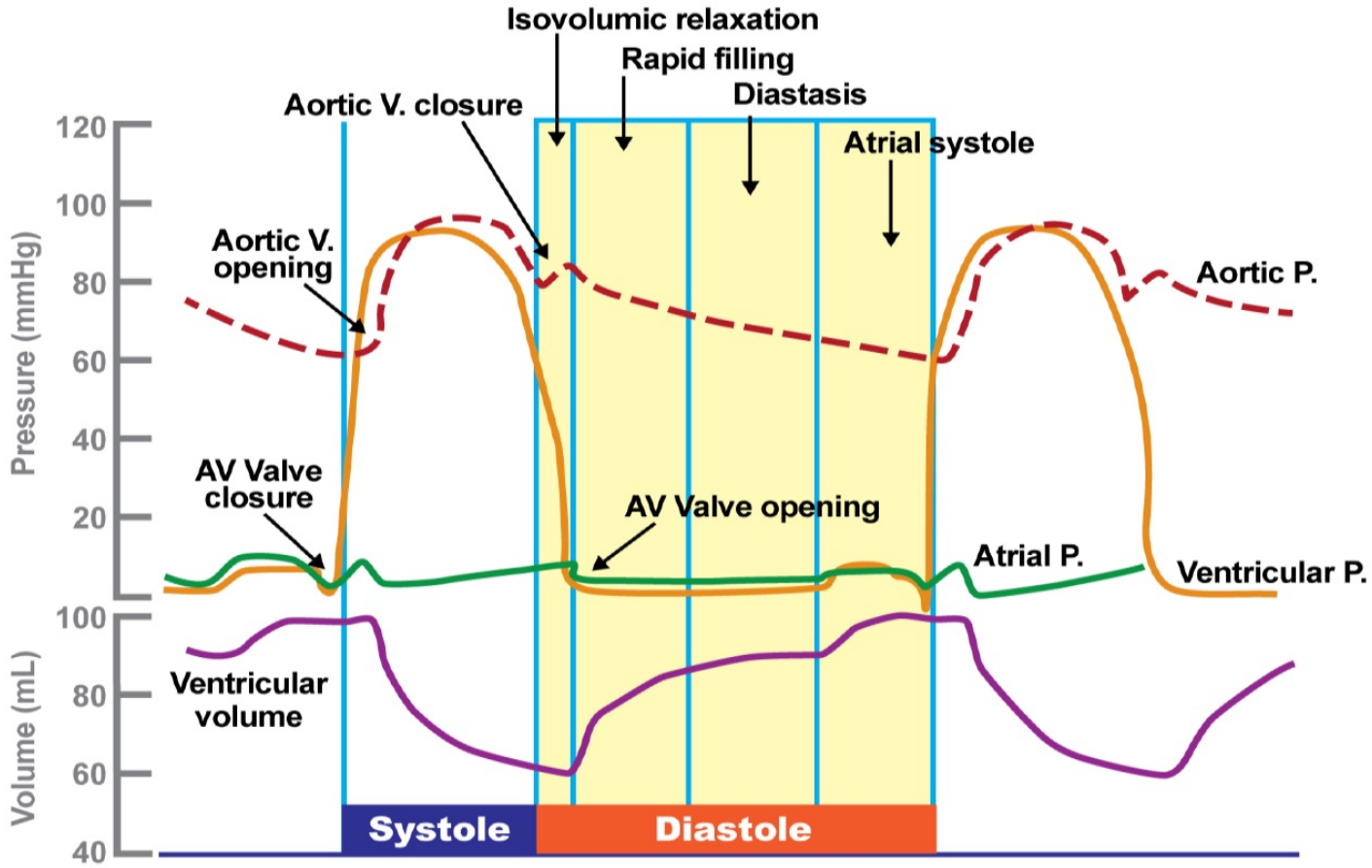
Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Inotropic agents		
Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function.[387]	IIb	C
Inotropic agents are not recommended routinely, due to safety concerns, unless the patient has symptomatic hypotension and evidence of hypoperfusion.[387,467,478]	III	C
Vasopressors		
A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion.[485–487]	IIb	B

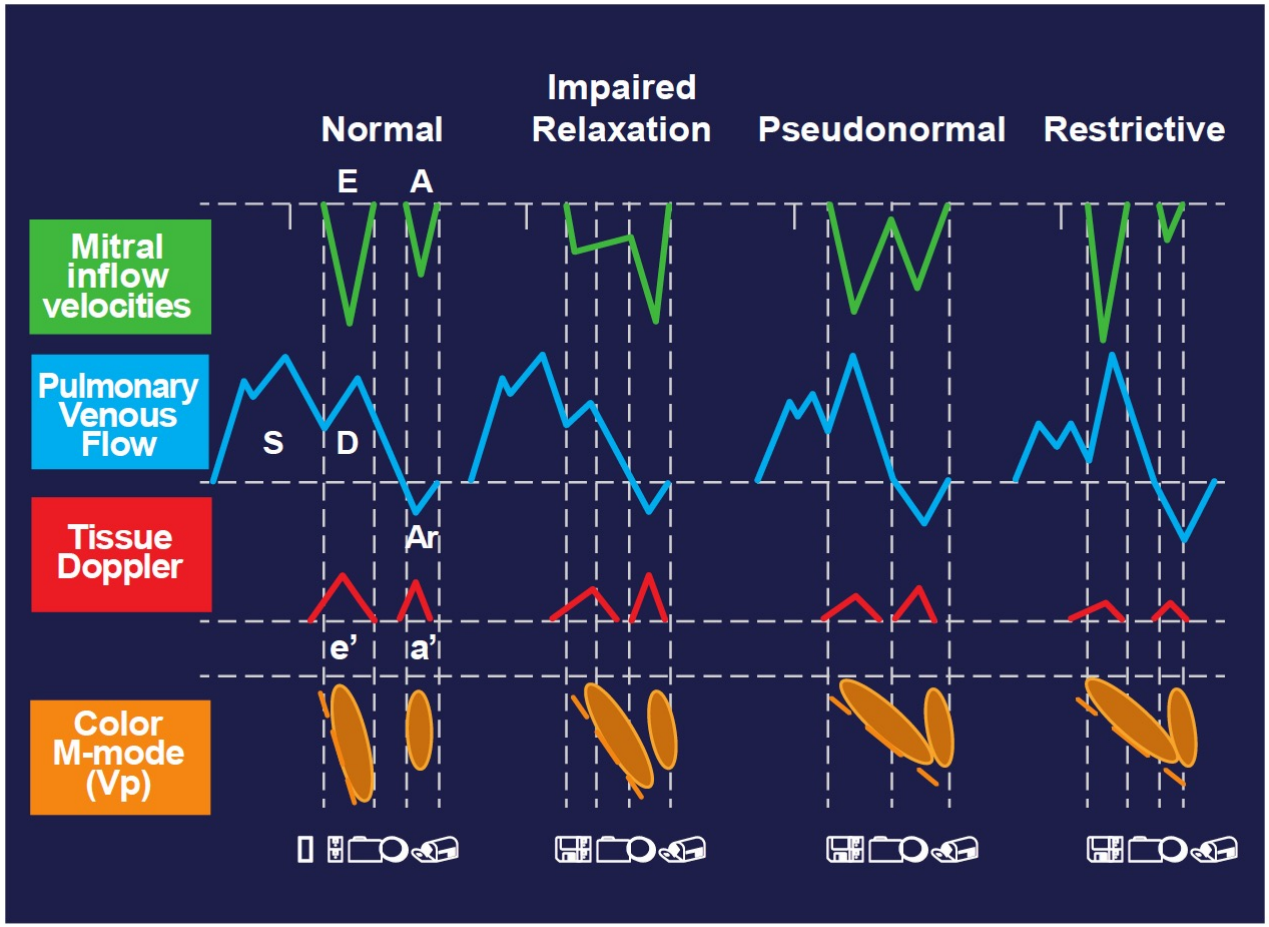
Fonction diastolique

- Quel est le meilleur inotrope pour la dysfonction diastolique?

Fonction diastolique



Fonction diastolique



Reports of Original Investigation

Milrinone enhances systolic, but not diastolic function during coronary artery bypass grafting surgery

[La milrinone améliore la fonction systolique mais non la fonction diastolique pendant la chirurgie de pontage aortocoronarien]

Pierre Couture MD FRCPC,* André Y. Denault MD FRCPC,* Michel Pellerin MD FRCPS,†
Jean-Claude Tardif MD FRCPC‡

Purpose: To evaluate the effect of milrinone on diastolic function during coronary artery bypass grafting surgery (CABG).

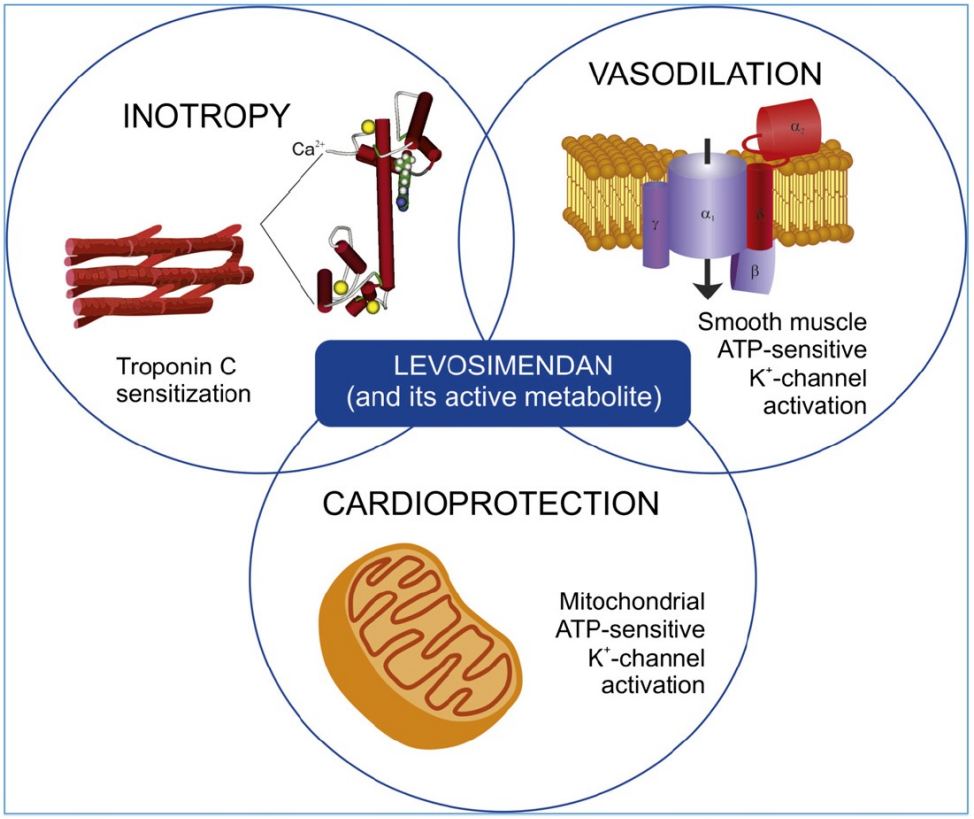
CAN J ANESTH 2007 / 54: 7 / pp 509–522

Fonction diastolique

- Tous les inotropes ont un effet lusitrope
- Chronotropie peut nuire ou aider selon:
  - Anomalie de relaxation seule
  - Restriction importante
- Attention au risque arrythmique, souvent mal toléré

Levosimendan

- Augmente sensibilité des myofilaments au calcium
- Inotropie sans aug AMPc (moins arrythmies)
- Fonction diastolique non affectée re: liaison [Ca]-dépendante (meilleure à l'écho vs dobu)
- Pas effet sur FC (moins consom O2)
- Effet inh PDE 3 aussi
- VD périphérique via ATP-sensitive K+ channels (+ effet a/n mitochondrie cardioprotecteurs)
- Anti-oxydant?
- Anti-inflammatoire?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis

A.C. Gordon, G.D. Perkins, M. Singer, D.F. McAuley, R.M.L. Orme, S. Santhakumaran, A.J. Mason, M. Cross, F. Al-Beidh, J. Best-Lane, D. Brealey, C.L. Nutt, J.J. McNamee, H. Reschreiter, A. Breen, K.D. Liu, and D. Ashby

Levosimendan in Patients with Left Ventricular Dysfunction Undergoing Cardiac Surgery

R.H. Mehta, J.D. Leimberger, S. van Diepen, J. Meza, A. Wang, R. Jankowich, R.W. Harrison, D. Hay, S. Fremes, A. Duncan, E.G. Soltesz, J. Luber, S. Park, M. Argenziano, E. Murphy, R. Marcel, D. Kalavrouziotis, D. Nagpal, J. Bozinovski, W. Toller, M. Heringlake, S.G. Goodman, J.H. Levy, R.A. Harrington, K.J. Anstrom, and J.H. Alexander, for the LEVO-CTS Investigators*

Levosimendan for Hemodynamic Support after Cardiac Surgery

G. Landoni, V.V. Lomivorotov, G. Alvaro, R. Lobreglio, A. Pisano, F. Guarracino, M.G. Calabrò, E.V. Grigoryev, V.V. Likhvantsev, M.F. Salgado-Filho, A. Bianchi, V.V. Pasyuga, M. Baiocchi, F. Pappalardo, F. Monaco, V.A. Boboshko, M.N. Abubakirov, B. Amantea, R. Lembo, L. Brazzi, L. Verniero, P. Bertini, A.M. Scandroglio, T. Bove, A. Belletti, M.G. Michienzi, D.L. Shukevich, T.S. Zabelina, R. Bellomo, and A. Zangrillo, for the CHEETAH Study Group*

Levosimendan

- Métabolite actif, ½ vie 96h
- Bolus 10-12 mcg/kg puis perf 0,1 pour 24h
- Effet protecteur rein?
- Légère augmentation FA
- Pas de tachyphylaxie
- Dim activation sympathique
- Dim cytokines

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 14, 2021 VOL. 384 NO. 2

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure

J.R. Teerlink, R. Diaz, G.M. Felker, J.J.V. McMurray, M. Metra, S.D. Solomon, K.F. Adams, I. Anand, A. Arias-Mendoza, T. Biering-Sørensen, M. Böhm, D. Bonderman, J.G.F. Cleland, R. Corbalan, M.G. Crespo-Leiro, U. Dahlström, L.E. Echeverria, J.C. Fang, G. Filippatos, C. Fonseca, E. Goncalvesova, A.R. Goudev, J.G. Howlett, D.E. Lanfear, J. Li, M. Lund, P. Macdonald, V. Mareev, S. Momomura, E. O'Meara, A. Parkhomenko, P. Ponikowski, F.J.A. Ramires, P. Serpytis, K. Sliwa, J. Spinar, T.M. Suter, J. Tomcsanyi, H. Vandekerckhove, D. Vinereanu, A.A. Voors, M.B. Yilmaz, F. Zannad, L. Sharpsten, J.C. Legg, C. Varin, N. Honarpour, S.A. Abbasi, F.I. Malik, and C.E. Kurtz, for the GALACTIC-HF Investigators*

ABSTRACT

BACKGROUND

The selective cardiac myosin activator omecamtiv mecarbil has been shown to improve cardiac function in patients with heart failure with a reduced ejection fraction. Its effect on cardiovascular outcomes is unknown.

METHODS

We randomly assigned 8256 patients (inpatients and outpatients) with symptomatic chronic heart failure and an ejection fraction of 35% or less to receive omecamtiv mecarbil (using pharmacokinetic-guided doses of 25 mg, 37.5 mg, or 50 mg twice daily) or placebo, in addition to standard heart-failure therapy. The primary outcome was a composite of a first heart-failure event (hospitalization or urgent visit for heart failure) or death from cardiovascular causes.

RESULTS

During a median of 21.8 months, a primary-outcome event occurred in 1523 of 4120 patients (37.0%) in the omecamtiv mecarbil group and in 1607 of 4112 patients (39.1%) in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.86 to 0.99; P=0.03). A total of 808 patients (19.6%) and 798 patients (19.4%), respectively, died from cardiovascular causes (hazard ratio, 1.01; 95% CI, 0.92 to 1.11). There was no significant difference between groups in the change from baseline on the Kansas City Cardiomyopathy Questionnaire total symptom score. At week 24, the change from baseline for the median N-terminal pro–B-type natriuretic peptide level was 10% lower in the omecamtiv mecarbil group than in the placebo group; the median cardiac troponin I level was 4 ng per liter higher. The frequency of cardiac ischemic and ventricular arrhythmia events was similar in the two groups.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Teerlink at San Francisco Veterans Affairs Medical Center, Cardiology, 111C, Bldg. 203, Rm. 2A-49, 4150 Clement St., San Francisco, CA 94121, or at john.teerlink@ucsf.edu.

*A complete list of GALACTIC-HF committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on November 13, 2020, at NEJM.org.

N Engl J Med 2021;384:105-16.
DOI: 10.1056/NEJMoa2025797
Copyright © 2020 Massachusetts Medical Society.

ESC European Society of Cardiology

European Journal of Heart Failure (2020) 22, 1684–1693
doi:10.1002/ejhf.1743

RESEARCH ARTICLE

Treatment with 24 hour istaroxime infusion in patients hospitalised for acute heart failure: a randomised, placebo-controlled trial

Valentina Carubelli[1*†], Yuhui Zhang[2†], Marco Metra[1], Carlo Lombardi[1], G. Michael Felker[3], Gerasimos Filippatos[4,5], Christopher M. O'Connor[6], John R. Teerlink[7,8], Phillip Simmons[9], Robert Segal[9], Gabriella Malfatto[10], Maria Teresa La Rovere[11], Dianfu Li[12], Xiumin Han[13], Zuyi Yuan[14], Yali Yao[15], Benjamin Li[16], Lit Fui Lau[17], Giuseppe Bianchi[9], and Jian Zhang[2*], on behalf of the Istaroxime ADHF Trial Group

[1]Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University and Civil Hospital of Brescia, Brescia, Italy; [2]Heart Failure Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Beijing, China; [3]Duke University School of Medicine and Duke Clinical Research Institute, Durham, NC, USA; [4]National and Kapodistrian University of Athens, Athens, Greece; [5]Medical School, University of Cyprus, Nicosia, Cyprus; [6]Inova Heart and Vascular Institute, Falls Church, VA, USA; [7]Section of Cardiology, San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA; [8]School of Medicine, University of California, San Francisco, CA, USA; [9]Windtree Therapeutics, Inc., Warrington, PA, USA; [10]IRCCS Istituto Auxologico Italiano, Department of Cardiovascular, Neural and Metabolic Sciences, S. Luca Hospital, Milan, Italy; [11]Istituti Clinici Scientifici Maugeri IRCCS, Department of Cardiology, Institute of Montescano, Pavia, Italy; [12]Jiangsu Provincial People's Hospital, First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [13]The General Hospital of Shenyang Military Region of Chinese People's Liberation Arm, Shenyang, China; [14]The First Affiliated Hospital of Xi'An Jiaotong University, Xi'an, China; [15]The First Hospital of Lanzhou University, Lanzhou, China; [16]Lee's Pharmaceutical Limited, Taipei, Taiwan; and [17]CVie Therapeutics Limited, Taipei, Taiwan

Received 17 September 2019; revised 22 December 2019; accepted 22 December 2019; online published-ahead-of-print 23 January 2020

Aim Istaroxime is a first-in-class agent which acts through inhibition of the sarcolemmal Na^+/K^+ pump and activation of the SERCA2a pump. This study assessed the effects of a 24 h infusion of istaroxime in patients hospitalised for acute heart failure (AHF).

Methods and results We included patients hospitalised for AHF with left ventricular ejection fraction ≤40% and E/e' > 10. Patients were randomised to a 24 h intravenous infusion of placebo or istaroxime at doses of 0.5 μg/kg/min (cohort 1: placebo $n = 19$; istaroxime $n = 41$) or 1.0 μg/kg/min (cohort 2: placebo $n = 20$, istaroxime $n = 40$). The primary endpoint of change in E/e' ratio from baseline to 24 h decreased with istaroxime vs. placebo (cohort 1: -4.55 ± 4.75 istaroxime 0.5 μg/kg/min vs. -1.55 ± 4.11 placebo, $P = 0.029$; cohort 2: -3.16 ± 2.59 istaroxime 1.0 μg/kg/min vs. -1.08 ± 2.72 placebo, $P = 0.009$). Both istaroxime doses significantly increased stroke volume index and decreased heart rate. Systolic blood pressure increased with istaroxime, achieving significance with the high dose. Self-reported dyspnoea and N-terminal pro-brain natriuretic peptide improved in all groups without significant differences between istaroxime and placebo. No significant differences in cardiac troponin absolute values or clinically relevant arrhythmias were observed during or after istaroxime infusion. Serious cardiac adverse events (including arrhythmias and hypotension) did not differ between placebo and istaroxime groups. The most common adverse events were injection site reactions and gastrointestinal events, the latter primarily with istaroxime 1.0 μg/kg/min.

Phenylephrine

- Agoniste alpha pur (10-20:1 vs levo)
- Aug résistances artérielles et diminution capacitance veineuse
  - D.C. variable selon état volémique / cardiaque
  - FC diminuée par baroréflexe
- Moins de tachyarrythmies
- Durée action 15-20 minutes re: résistance COMT
- Indic: Sténose Ao, IHSS, perte tonus sympathique, choc distributif réfractaire, tachyarrythmies
- Métaraminol: direct + indirect, effets semblables

SHOCK, Vol. 29, No. 4, pp. 446–451, 2008

SHORT-TERM EFFECTS OF PHENYLEPHRINE ON SYSTEMIC AND REGIONAL HEMODYNAMICS IN PATIENTS WITH SEPTIC SHOCK: A CROSSOVER PILOT STUDY

Andrea Morelli,[*] Matthias Lange,[†] Christian Ertmer,[†] Martin Dünser,[‡] Sebastian Rehberg,[†] Alessandra Bachetoni,[§] Mariadomenica D'Alessandro,[§] Hugo Van Aken,[†] Fabio Guarracino,[‖] Paolo Pietropaoli,[*] Daniel L. Traber,[¶] and Martin Westphal[†]

[*]Department of Anesthesiology and Intensive Care, University of Rome, "La Sapienza," Rome, Italy; [†]Department of Anesthesiology and Intensive Care, University Hospital of Muenster, Muenster, Germany; [‡]Department of Intensive Care Medicine, University of Bern, Bern, Switzerland; [§]Laboratory of Clinical Pathology, Department of Surgery, University of Rome, "La Sapienza," Rome; [‖]Department of Cardiothoracic Anesthesia and Intensive Care Unit, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; and [¶]Investigational Intensive Care Unit, University of Texas Medical Branch, Galveston, Texas

Received 9 Jul 2007; first review completed 20 Jul 2007; accepted in final form 2 Aug 2007

ABSTRACT—Clinical studies evaluating the use of phenylephrine in septic shock are lacking. The present study was designed as a prospective, crossover pilot study to compare the effects of norepinephrine (NE) and phenylephrine on systemic and regional hemodynamics in patients with catecholamine-dependent septic shock. In 15 septic shock patients, NE (0.82 ± 0.69 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was replaced with phenylephrine (4.39 ± 5.23 $\mu g \cdot kg^{-1} \cdot min^{-1}$) titrated to maintain MAP between 65 and 75 mmHg. After 8 h of phenylephrine infusion treatment was switched back to NE. Data from right heart catheterization, acid-base balance, thermo-dye dilution catheter, gastric tonometry, and renal function were obtained before, during, and after replacing NE with phenylephrine. Variables of systemic hemodynamics, global oxygen transport, and acid-base balance remained unchanged after replacing NE with phenylephrine except for a significant decrease in heart rate (phenylephrine, 89 ± 18 vs. NE, 93 ± 18 bpm; $P < 0.05$). However, plasma disappearance rate (phenylephrine, 13.5 ± 7.1 vs. NE, 16.4 ± 8.7 %·min^{-1}) and clearance of indocyanine green (phenylephrine, 330 ± 197 vs. NE, 380 ± 227 mL·min^{-1}·m^{-2}), as well as creatinine clearance (phenylephrine, 81.3 ± 78.4 vs. NE, 94.3 ± 93.5 mL·min^{-1}) were significantly decreased by phenylephrine infusion (each $P < 0.05$). In addition, phenylephrine increased arterial lactate concentrations as compared with NE infusion (1.7 ± 1.0 vs. 1.4 ± 1.1 mM; $P < 0.05$). After switching back to NE, all variables returned to values obtained before phenylephrine infusion except creatinine clearance and gastric tonometry values. Our results suggest that for the same MAP, phenylephrine causes a more pronounced hepatosplanchnic vasoconstriction as compared with NE.

KEYWORDS—Catecholamines, phenylephrine, norepinephrine, sepsis, septic shock

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock

Emily Vail, MD; Hayley B. Gershengorn, MD; May Hua, MD, MSc; Allan J. Walkey, MD, MSc; Gordon Rubenfeld, MD, MSc; Hannah Wunsch, MD, MSc

Ephedrine

- Effet direct + indirect
  - Compétition reuptake noradré
  - Effet Beta
- Tachyphylaxie si norad déplétée
- Durée ad 3-6h re: résistance COMT
- Indication: vasoplégie post induction

Femme enceinte

- Peu d'autorégulation a/n placentaire
- Récepteurs alpha

- Acidose fétale avec ephedrine? Plus de nausées. Plus de transfert transplacentaire.
- Plus de bradycardie avec phényl
- Noradrénaline?

Anaesthesia 2018, 73, 71–92 doi:10.1111/anae.14080

Guidelines

International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia

S. M. Kinsella,[1] B. Carvalho,[2] R. A. Dyer,[3] R. Fernando,[4] N. McDonnell,[5] F. J. Mercier,[6] A. Palanisamy,[7] A. T. H. Sia,[8] M. Van de Velde[9,10], A. Vercueil[11] and the Consensus Statement Collaborators

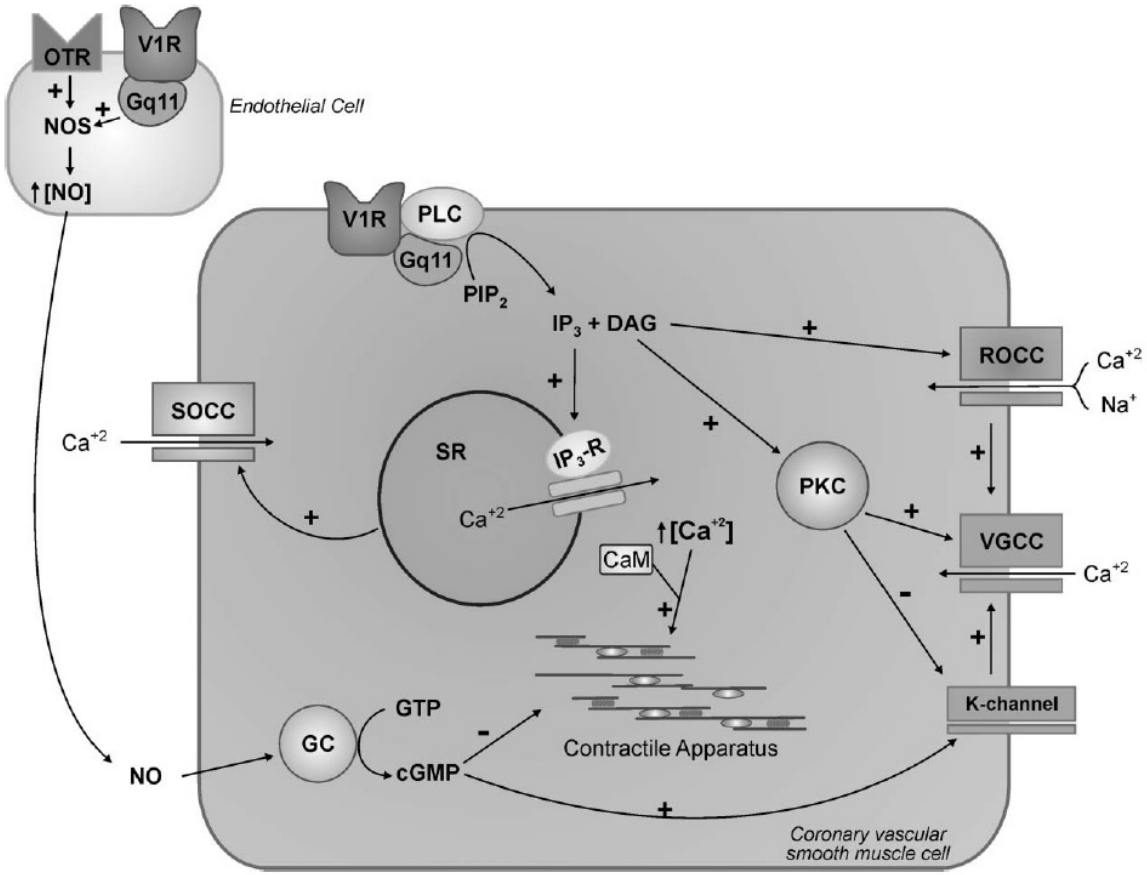
3 α-agonist drugs are the most appropriate agents to treat or prevent hypotension following spinal anaesthesia. Although those with a small amount of β-agonist activity may have the best profile (noradrenaline (norepinephrine), metaraminol), phenylephrine is currently recommended due to the amount of supporting data. Single-dilution techniques, and/or prefilled syringes should be considered.

7 When using an α-agonist as the first-line vasopressor, small doses of ephedrine are suitable to manage SAP < 90% of baseline combined with a low heart rate. For bradycardia with hypotension, an anticholinergic drug (glycopyrronium (glycopyrrolate) or atropine) may be required. Adrenaline (epinephrine) should be used for circulatory collapse.

Vasopressine

- Hormone anti-diurétique, hypophyse postérieure
- Récepteurs
  - V1 (AVPR1a): vasoconstriction
  - V2 (AVPR2): tubule distal nephron (aquaporine) + plaquettes (relâche vWF) + vasodilatation?
  - V3 (AVPR1b): sécrétion ACTH?
  - Oxytocine + purinergique (vasodilat via eNOS?)
- Réserves épuisables

Vasopressin



Pelletier et al. J CV Pharm 2014

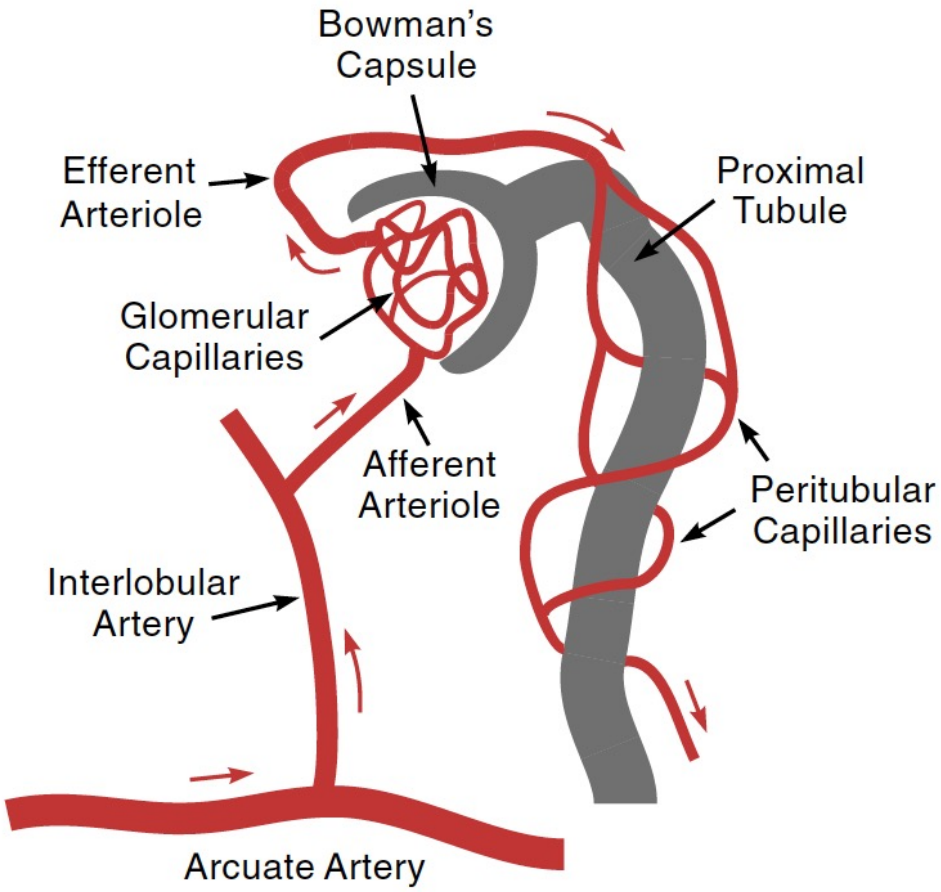
Vasopressine

- Chez patient avec TA normale, peu d'effet (ex: SiADH)
- En choc, vasoconstricteur artériel
- Hémodynamie:
  - D.C.: diminué
    - Surtout si fonction anormale ou hypovolémie
  - FC: diminuée
  - SVR: augmentée
  - PAM: augmentée

Vasopressine

- Hémodynamie, lits vasculaires:
  - VC splanchnique
  - VC coronaire à haute dose
  - VC cutanée, digitale
  - VC efférente rénale (augmentation diurèse si choc distributif, vs SiADH si TA normale)
  - VD pulmonaire? (dim PVR/SVR vs levo?)
- Moins de FA vs levo

Vasopressine



Vasopressine

- ½ vie 15-30 minutes
  - Vasopressinase foie/rein
- Plus résistante à hypoxie ou acidose?
- Effets immuns
- Relâche vWF: aug aggrégation plaquettaire?
  - Thrombopénie? Effet net sur coag en sepsis?
- Peut donner hyponatrémie
- Dose 1.8 – 3.6 U/h

Vasopressine

- Indications:
  - Choc septique
  - Vasoplégie post CEC
  - Mort cérébrale
  - Hépato-rénal? Dysfonction VD isolée?
  - Arrêt cardiaque
- Attention!
  - SCA, dysfonction cardiaque, ischémie périphérique, ischémie mésentérique, TBI ou autre insulte neuro, hypoNa,…

Vaso vs Levo

- VASST
  - 6229 patients évalués, 802 randomisés, 2001 à 2006
    - Plus de 600 exclus re: recevaient déjà vaso
    - La moitié avait moins de 15 mcg/min de levo, MAP 73 mmHg
    - Environ la moitié n'avaient pas les critères actuels de choc
    - Dose 0.6 à 1.8 U/h
  - 12h post critères d'inclusion
  - Puissance mal calculée (mortalité 37% vs 60%)
  - Exclusions: ischémie mésentérique, SCA, insuf cardiaque, hypoNa, TBI, Raynaud, sclerodermie

Vaso vs Levo

- Effets secondaires idem
- Trend chez choc moins sévère (< 15 mcg/min)

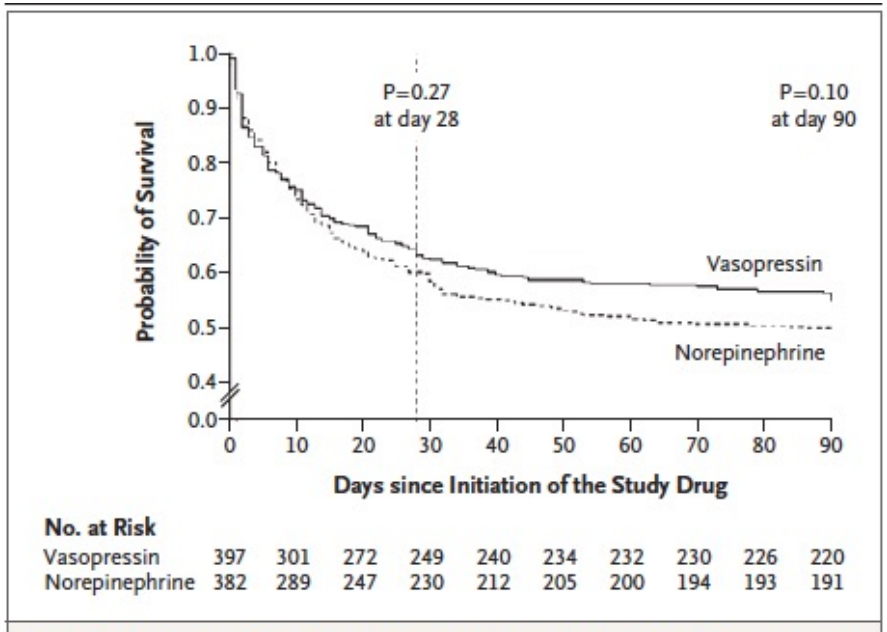


Figure 2. Kaplan–Meier Survival Curves for Patients Who Underwent Randomization and Infusion.

The dashed vertical line marks day 28. P values were calculated with the use of the log-rank test.

Vaso vs Levo

Post-hoc subgroups		NOREPINEPHRINE GROUP N / total N (%)	VASOPRESSIN GROUP N / total N (%)	P VALUE*	INTERACTION STATISTIC P VALUE**
Treatment by lactate Quartile	First lactate quartile (≤1.4mmol/L)	26/77 (33.8)	17/90 (18.9)	0.03	0.04
	Second lactate quartile (1.5 – 2.3 mmol/L)	36/87 (41.4)	35/85 (41.2)	0.98	0.65
	Third lactate quartile (2.4 – 4.4 mmol/L)	30/77 (39.0)	31/85 (36.5)	0.74	0.51
	Fourth lactate quartile (>4.4mmol/L)	47/83 (56.6)	49/80 (61.3)	0.55	-

CHEST

Original Research

CRITICAL CARE

The Cardiopulmonary Effects of Vasopressin Compared With Norepinephrine in Septic Shock

Anthony C. Gordon, MD; Nan Wang, PhD; Keith R. Walley, MD; Deborah Ashby, PhD; and James A. Russell, MD

Table 4—*Detailed Cardiopulmonary Variables Over Time Comparing Vasopressin vs Norepinephrine in Patients Who Had a PA Catheter (n = 241)*

Variable	0 h	6 h	12 h	24 h	36 h	48 h	60 h	72 h	84 h	96 h	*P* Value[a]
Svo_2, %											
NE	68.6 ± 14.4	69.5 ± 14.3	68.4 ± 13.8	69.8 ± 15.6	66.9 ± 14.2	66.4 ± 15.9	62.9 ± 17.4	63.3 ± 17.7	65.3 ± 17.1	62.3 ± 17.4	.92
AVP	67.0 ± 15.7	64.0 ± 17.0	68.3 ± 13.8	66.2 ± 14.6	67.7 ± 15.8	67.3 ± 13.0	65.0 ± 16.8	65.4 ± 14.4	64.2 ± 14.8	65.7 ± 15.0	…
Cardiac index, L/min per m²											
NE	3.95 ± 1.26	3.92 ± 1.22	3.70 ± 1.14	3.67 ± 1.02	3.61 ± 1.23	3.62 ± 1.27	3.46 ± 1.18	3.82 ± 1.40	3.49 ± 1.15	3.53 ± 1.10	.87
AVP	3.82 ± 1.31	3.51 ± 1.39	3.46 ± 1.29	3.70 ± 1.57	3.46 ± 1.45	3.65 ± 1.45	3.52 ± 1.46	3.59 ± 1.39	3.47 ± 1.48	3.65 ± 1.61	…
SVI, mL/min per m²											
NE	39.8 ± 14.3	39.9 ± 11.9	37.8 ± 11.7	40.2 ± 11.9	37.5 ± 11.9	39.9 ± 14.0	38.4 ± 12.9	40.4 ± 13.6	39.6 ± 11.8	39.8 ± 11.9	.53
AVP	37.5 ± 12.5	37.2 ± 14.3	36.3 ± 12.7	39.0 ± 14.6	37.5 ± 14.9	39.1 ± 14.8	38.9 ± 15.1	39.5 ± 13.7	38.7 ± 13.0	40.0 ± 13.5	…
LVSWI, g/m²											
NE	28.5 ± 11.7	31.2 ± 11.9	29.8 ± 12.5	31.7 ± 12.2	29.4 ± 12.4	31.3 ± 12.8	32.5 ± 13.4	33.2 ± 13.2	32.0 ± 11.5	34.8 ± 12.3	.72
AVP	26.6 ± 10.3	28.8 ± 11.9	27.7 ± 11.7	30.2 ± 14.0	29.3 ± 13.6	31.5 ± 14.7	31.4 ± 15.3	31.5 ± 14.2	31.6 ± 10.9	32.0 ± 12.5	…
PAOP, mm Hg											
NE	17.3 ± 5.7	17.9 ± 5.3	17.7 ± 4.8	18.9 ± 6.1	18.7 ± 5.7	19.4 ± 7.2	17.9 ± 5.3	18.7 ± 6.4	19.2 ± 8.3	18.9 ± 5.2	.32
AVP	20.6 ± 5.9	19.2 ± 5.0	19.6 ± 6.7	20.2 ± 6.0	19.0 ± 5.8	19.1 ± 5.9	19.5 ± 6.4	19.5 ± 6.8	19.4 ± 5.6	19.5 ± 6.3	…
MPAP, mm Hg											
NE	28.0 ± 6.7	29.4 ± 6.3	29.0 ± 5.9	29.4 ± 8.7	29.4 ± 6.6	29.8 ± 7.1	28.6 ± 6.9	30.0 ± 7.7	28.9 ± 7.8	30.4 ± 7.3	.82
AVP	30.3 ± 6.7	30.2 ± 8.2	29.9 ± 8.2	29.7 ± 6.3	29.8 ± 8.0	30.1 ± 7.1	29.8 ± 7.8	29.9 ± 7.3	28.7 ± 6.3	29.8 ± 7.4	…

Data are presented as mean ± SD. LVSWI = left ventricular stroke work index; MPAP = mean pulmonary arterial pressure; PAOP = pulmonary artery occlusion pressure; SVI = stroke volume index; Svo_2 = mixed venous oxygen saturation. See Table 1 and 2 legends for expansion of other abbreviations.

[a]*P* value comparing difference over time between treatment groups.

JAMA | Original Investigation

Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock

The VANISH Randomized Clinical Trial

Anthony C. Gordon, MD; Alexina J. Mason, PhD; Neeraja Thirunavukkarasu, MSc; Gavin D. Perkins, MD; Maurizio Cecconi, MD; Magda Cepkova, MD; David G. Pogson, MB BCh; Hollmann D. Aya, MD; Aisha Anjum, BSc; Gregory J. Frazier, MSc; Shalini Santhakumaran, MSc; Deborah Ashby, PhD; Stephen J. Brett, MD; for the VANISH Investigators

- Vaso ad 0.06 U/min vs levo
- RCT multicentrique 409 patients
- 2 X 2 avec corticos ou non

JAMA 2016

Table 2. Outcome Data in the 4 Treatment Groups and Comparison of the Vasopressin Group With the Norepinephrine Group

	Vasopressin			Norepinephrine			Vasopressin vs Norepinephrine, Absolute Difference (95% CI)[b]
	Hydrocortisone[a]	Placebo	Total[a]	Hydrocortisone	Placebo	Total	
28-d Survivors who never developed kidney failure, No./total (%)[c]	46/81 (56.8)	48/84 (57.1)	94/165 (57.0)	46/77 (59.7)	47/80 (58.8)	93/157 (59.2)	−2.3 (−13.0 to 8.5)[d]
Kidney failure–free days in other patients, median (IQR), d[a]	5 (0-23)	12 (1-25)	9 (1-24)	13 (0-25)	14 (1-24)	13 (1-25)	−4 (−11 to 5)[d]
28-d Mortality, No./total (%)	33/100 (33.0)	30/104 (28.8)	63/204 (30.9)	29/101 (28.7)	27/103 (26.2)	56/204 (27.5)	3.4 (−5.4 to 12.3)
ICU mortality, No./total (%)	32/100 (32.0)	26/104 (25.0)	58/204 (28.4)	24/101 (23.8)	27/103 (26.2)	51/204 (25.0)	3.4 (−5.2 to 12.0)
Hospital mortality, No./total (%)	35/100 (35.0)	33/104 (31.7)	68/204 (33.3)	31/101 (30.7)	29/103 (28.2)	60/204 (29.4)	3.9 (−5.1 to 12.9)
Kidney failure, No./total (%)	41/101 (40.6)	46/104 (44.2)	87/205 (42.4)	46/101 (45.5)	51/103 (49.5)	97/204 (47.5)	−5.1 (−15.2 to 5.0)
Survivors	21/67 (31.3)	26/74 (35.1)	47/141 (33.3)	26/72 (36.1)	29/76 (38.2)	55/148 (37.2)	−3.8 (−15.5 to 7.9)
Nonsurvivors	20/33 (60.6)	20/30 (66.7)	40/63 (63.5)	20/29 (69)	22/27 (81.5)	42/56 (75)	−11.5 (−29.6 to 6.6)
Duration of kidney failure, median (IQR), d	4 (1 to 7)	2 (1 to 6)	3 (1 to 7)	3 (2 to 6)	4 (2 to 8)	4 (2 to 8)	−1 (2 to 0)
Survivors	4 (2 to 7)	3 (2 to 8)	4 (2 to 8)	4 (2 to 8)	4 (3 to 8)	4 (2 to 8)	0 (−3 to 2)
Nonsurvivors	2 (1 to 7)	2 (1 to 3)	2 (1 to 7)	3 (2 to 5)	2 (1 to 8)	3 (2 to 7)	−1 (−3 to 0)
Use of RRT, No./total (%)	29/101 (28.7)	23/104 (22.1)	52/205 (25.4)	32/101 (31.7)	40/103 (38.8)	72/204 (35.3)	−9.9 (−19.3 to −0.6)
Survivors	15/67 (22.4)	13/74 (17.6)	28/141 (19.9)	15/72 (20.8)	18/76 (23.7)	33/148 (22.3)	−2.4 (−12.5 to 7.7)
Nonsurvivors	14/33 (42.4)	10/30 (33.3)	24/63 (38.1)	17/29 (58.6)	22/27 (81.5)	39/56 (69.6)	−31.5 (−50.2 to −12.9)

Vasopressine et chirurgie cardiaque

- Vasoplégie post CEC: I.C. > 2.5, patients en choc éliminés, surtout contexte IECA ou post LVAD
  - Résultats: diminue les besoins de lévo…
- Par contre:
  - Moins bonne perfusion splanchnique sous CEC
  - Moins bons flots dans la mammaire vs levo

Vasopressin *versus* Norepinephrine in Patients with Vasoplegic Shock After Cardiac Surgery

The VANCS Randomized Controlled Trial

Ludhmila Abrahao Hajjar, M.D., Ph.D., Jean Louis Vincent, M.D., Ph.D.,

- RCT monocentrique 300 patients
- Vaso ad 0.06 U/min vs levo
- Hypotension après chx cardiaque avec IC > 2.2
- Exclus: ischémie mésentérique, SCA, Raynaud…

Anesthesiology 2016

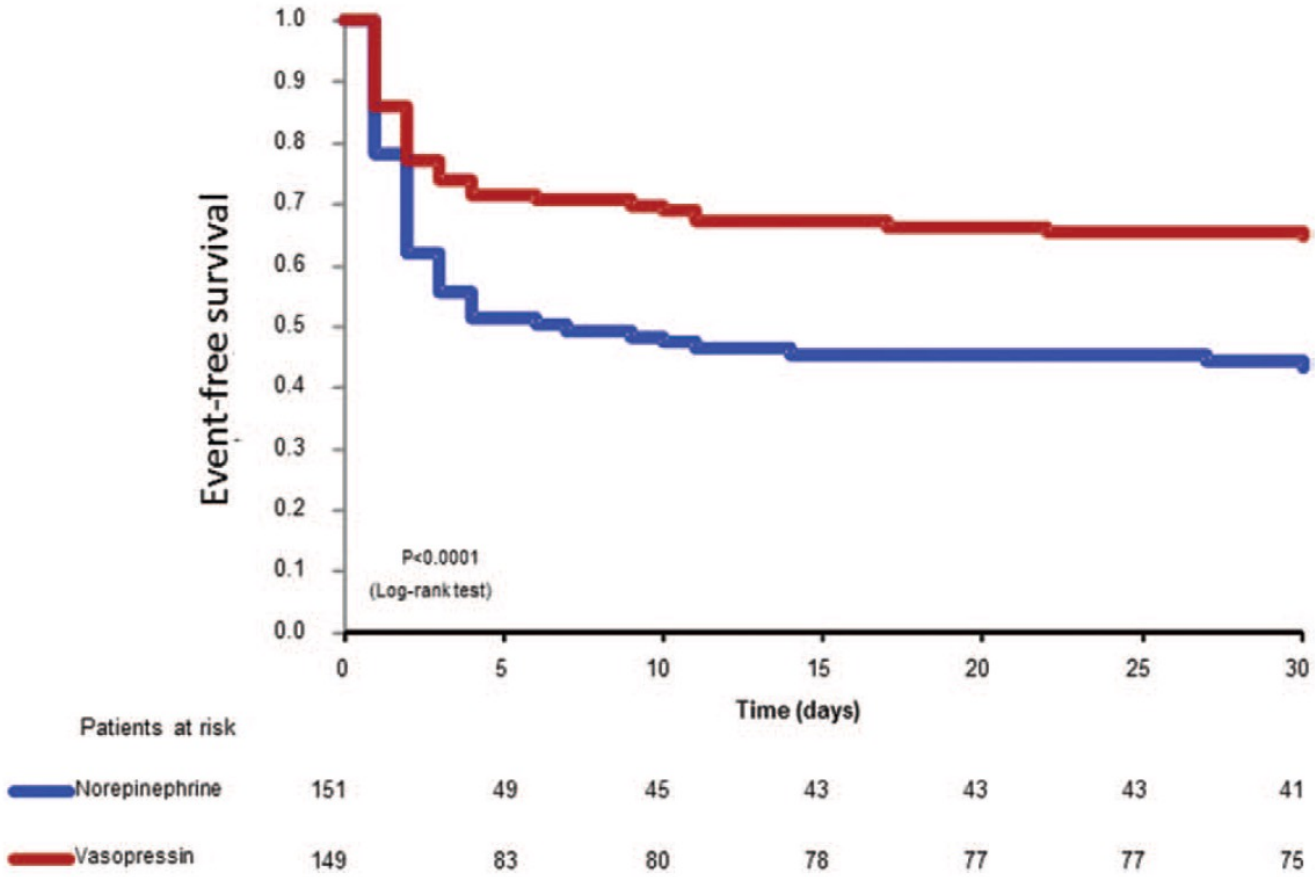


Fig. 2. Kaplan–Meier curves showing the 30-day event-free—primary outcome—survival in patients randomized to norepinephrine or vasopressin infusion. Primary outcome refers to the composite endpoint of mortality or severe complications within 30 days after randomization, including stroke, requirement of mechanical ventilation for longer than 48 h, deep sternal wound infection, reoperation, or acute renal failure.

ELSEVIER

European Journal of Cardio-thoracic Surgery 29 (2006) 952–956

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

www.elsevier.com/locate/ejcts

Comparative hemodynamic effects of vasopressin and norepinephrine after milrinone-induced hypotension in off-pump coronary artery bypass surgical patients

Yunseok Jeon [1], Jung Hee Ryu [1], Young Jin Lim [*], Chong Sung Kim, Jae-Hyon Bahk, Seung Zhoo Yoon, Ju Youn Choi

Department of Anesthesiology, Seoul National University Hospital, Seoul, Republic of Korea

Received 9 November 2005; received in revised form 14 February 2006; accepted 16 February 2006; Available online 3 May 2006

Table 2
Hemodynamic variables in the patients with milrinine–vasopressin and milrinine–norepinephrine infusion

Variables	VP group ($n = 25$)			NE group ($n = 25$)		
	Baseline	Milrinone	Milrinone + VP	Baseline	Milrinone	Milrinone + NE
HR (beats/min)	70 ± 10	73 ± 8	75 ± 10	68 ± 11	69 ± 14	69 ± 11
MAP (mmHg)	74 ± 2	65 ± 5*	78 ± 7#	78 ± 8	69 ± 6*	89 ± 10#
MPAP (mmHg)	15 ± 3	15 ± 4	16 ± 4	17 ± 5	16 ± 4	19 ± 5
PCWP (mmHg)	12 ± 3	11 ± 3	13 ± 4#	11 ± 2	11 ± 2	11 ± 4
CVP (mmHg)	7 ± 1	8 ± 2	7 ± 2	7 ± 2	6 ± 2	7 ± 3
CO (l/min)	4.7 ± 0.9	5.5 ± 0.9*	5.4 ± 0.8	4.4 ± 0.7	5.2 ± 1.1*	5.1 ± 1.4
SVR (dyne s/cm^5)	1218 ± 299	838 ± 209*	1100 ± 244#	1345 ± 299	1011 ± 195*	1446 ± 681#
PVR (dyne s/cm^5)	95 ± 34	72 ± 30*	84 ± 18#	119 ± 85	87 ± 33*	139 ± 97#
PVR/SVR	0.09 ± 0.02	0.10 ± 0.03*	0.08 ± 0.03#	0.08 ± 0.02	0.09 ± 0.02*	0.09 ± 0.02

Values are mean ± SD. VP: vasopressin; NE: norepinephrine; HR: heart rate; MAP: mean arterial pressure; MPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; CVP: central venous pressure; CO: cardiac output; SVR: systemic vascular resistance; PVR: pulmonary vascular resistance.

* $p < 0.05$: compared with baseline.

# $p < 0.05$: compared with milrinone infusion.

Intensive Care Med (2019) 45:844–855
https://doi.org/10.1007/s00134-019-05620-2

SYSTEMATIC REVIEW

Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials

Myura Nagendran[1], James A. Russell[2], Keith R. Walley[2], Stephen J. Brett[1,3], Gavin D. Perkins[4], Ludhmila Hajjar[5], Alexina J. Mason[6], Deborah Ashby[7] and Anthony C. Gordon[1,3*]

© 2019 Springer-Verlag GmbH Germany, part of Springer Nature

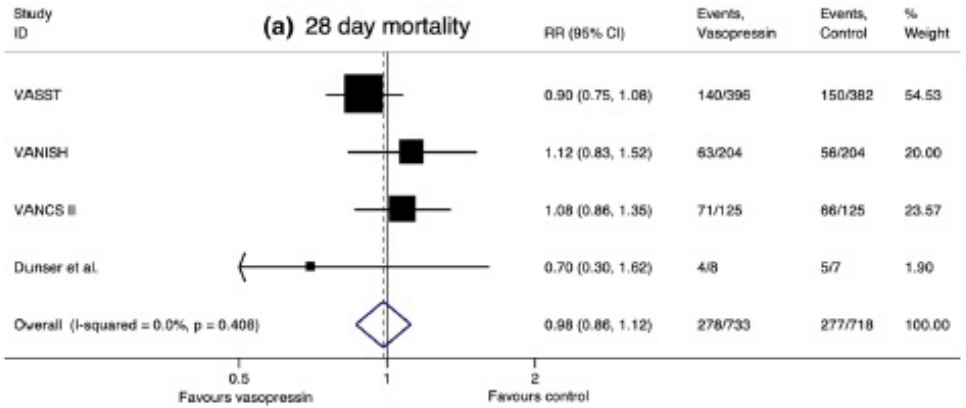


Table 3 Serious adverse events

Outcome	Vasopressin	Norepinephrine	ARD[a] (95% CI)
Serious adverse events, no./total (%)	124/735 (16.9)	120/718 (16.7)	0.2 (−3.7 to 4.0)
Digital ischaemia	21/735 (2.9)	8/718 (1.1)	1.7 (0.3–3.2)
Mesenteric ischaemia[b]	14/727 (1.9)	18/711 (2.5)	−0.6 (−2.1 to 0.9)
Acute coronary syndrome	18/735 (2.5)	17/718 (2.4)	0.1 (−1.5 to 1.7)
Arrhythmia	39/735 (5.3)	58/718 (8.1)	−2.8 (−0.2 to −5.3)

[a] Percentage absolute risk difference

[b] The reduced denominator for mesenteric ischaemia is due to no available data on this serious adverse event in the trial by Dunser et al.

Vaso ou pas...

- À favoriser en choc distributif pur:
  - Arrythmies supra-ventriculaires / tachycardie
  - Atteinte rénale ou à risque de
  - Obstruction chambre de chasse
  - Dysfonction VD isolée?
  - Mort cérébrale, acidose importante, synd hepato-rénal
- Contre-indiqué ou non étudié:
  - Choc cardiogénique ou défaillance cardiaque
  - Possibilité d'ischémie mésentérique
    - Choc réfractaire?
  - Ischémie digitale
  - Ischémie coronarienne

Terlipressine

- Terlipressine = agoniste AVPR1 sélectif
  - ½ vie plus longue
  - VC pulmonaire
  - Hépato-rénal, hémorragie varicielle
- Selepressine
  - AVPR1 sélectif mais plus courte ½ vie
  - Réduction de la perméabilité capillaire?

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock The SEPSIS-ACT Randomized Clinical Trial

Pierre-Francois Laterre, MD; Scott M. Berry, PhD; Allan Blemings, MS; Jan E. Carlsen, MD; Bruno François, MD; Todd Graves, PhD; Karsten Jacobsen, MD; Roger J. Lewis, MD, PhD; Steven M. Opal, MD; Anders Perner, MD, PhD; Peter Pickkers, MD, PhD; James A. Russell, MD; Nis A. Windeløv, MD, PhD; Donald M. Yealy, MD; Pierre Asfar, MD; Morten H. Bestle, MD, PhD; Grégoire Muller, MD; Cédric Bruel, MD; Noëlle Brulé, MD; Johan Decruyenaere, MD; Alain-Michel Dive, MD, PhD; Thierry Dugernier, MD, PhD; Kenneth Krell, MD; Jean-Yves Lefrant, MD; Bruno Megarbane, MD, PhD; Emmanuelle Mercier, MD; Jean-Paul Mira, MD, PhD; Jean-Pierre Quenot, MD; Bodil Steen Rasmussen, MD, PhD; Hans-Christian Thorsen-Meyer, MD; Margot Vander Laenen, MD; Marianne Lauridsen Vang, MD; Philippe Vignon, MD, PhD; Isabelle Vinatier, MD; Sine Wichmann, MD, PhD; Xavier Wittebole, MD; Anne Louise Kjølbye, MS, PhD; Derek C. Angus, MD, MPH; for the SEPSIS-ACT Investigators

IMPORTANCE Norepinephrine, the first-line vasopressor for septic shock, is not always effective and has important catecholaminergic adverse effects. Selepressin, a selective vasopressin V1a receptor agonist, is a noncatecholaminergic vasopressor that may mitigate sepsis-induced vasodilatation, vascular leakage, and edema, with fewer adverse effects.

OBJECTIVE To test whether selepressin improves outcome in septic shock.

DESIGN, SETTING, AND PARTICIPANTS An adaptive phase 2b/3 randomized clinical trial comprising 2 parts that included adult patients (n = 868) with septic shock requiring more than 5 µg/min of norepinephrine. Part 1 used a Bayesian algorithm to adjust randomization probabilities to alternative selepressin dosing regimens and to trigger transition to part 2, which would compare the best-performing regimen with placebo. The trial was conducted between July 2015 and August 2017 in 63 hospitals in Belgium, Denmark, France, the Netherlands, and the United States, and follow-up was completed by May 2018.

INTERVENTIONS Random assignment to 1 of 3 dosing regimens of selepressin (starting infusion rates of 1.7, 2.5, and 3.5 ng/kg/min; n = 585) or to placebo (n = 283), all administered as continuous infusions titrated according to hemodynamic parameters.

MAIN OUTCOMES AND MEASURES Primary end point was ventilator- and vasopressor-free days within 30 days (deaths assigned zero days) of commencing study drug. Key secondary end points were 90-day mortality, kidney replacement therapy–free days, and ICU-free days.

RESULTS Among 868 randomized patients, 828 received study drug (mean age, 66.3 years; 341 [41.2%] women) and comprised the primary analysis cohort, of whom 562 received 1 of 3 selepressin regimens, 266 received placebo, and 817 (98.7%) completed the trial. The trial was stopped for futility at the end of part 1. Median study drug duration was 37.8 hours (IQR, 17.8-72.4). There were no significant differences in the primary end point (ventilator- and vasopressor-free days: 15.0 vs 14.5 in the selepressin and placebo groups; difference, 0.6 [95% CI, −1.3 to 2.4]; $P = .30$) or key secondary end points (90-day mortality, 40.6% vs 39.4%; difference, 1.1% [95% CI, −6.5% to 8.8%]; $P = .77$; kidney replacement therapy–free days: 18.5 vs 18.2; difference, 0.3 [95% CI, −2.1 to 2.6]; $P = .85$; ICU-free days: 12.6 vs 12.2; difference, 0.5 [95% CI, −1.2 to 2.2]; $P = .41$). Adverse event rates included cardiac arrhythmias (27.9% vs 25.2% of patients), cardiac ischemia (6.6% vs 5.6%), mesenteric ischemia (3.2% vs 2.6%), and peripheral ischemia (2.3% vs 2.3%).

CONCLUSIONS AND RELEVANCE Among patients with septic shock receiving norepinephrine, administration of selepressin, compared with placebo, did not result in improvement in vasopressor- and ventilator-free days within 30 days. Further research would be needed to evaluate the potential role of selepressin for other patient-centered outcomes in septic shock.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02508649

JAMA. 2019;322(15):1476-1485. doi:10.1001/jama.2019.14607
Published online October 2, 2019. Corrected on October 15, 2019.

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: See Supplement 2 for a full list of the Selepressin Evaluation Program for Sepsis-Induced Shock–Adaptive Clinical Trial (SEPSIS-ACT) Investigators.

Corresponding Author: Derek C. Angus, MD, MPH, University of Pittsburgh, 3550 Terrace St, 614 Scaife Hall, Pittsburgh, PA 15261 (angusdc@upmc.edu).

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 3, 2017 VOL. 377 NO. 5

Angiotensin II for the Treatment of Vasodilatory Shock

Ashish Khanna, M.D., Shane W. English, M.D., Xueyuan S. Wang, M.D., Kealy Ham, M.D., James Tumlin, M.D., Harold Szerlip, M.D., Laurence W. Busse, M.D., Laith Altaweel, M.D., Timothy E. Albertson, M.D., M.P.H., Ph.D., Caleb Mackey, M.D., Michael T. McCurdy, M.D., David W. Boldt, M.D., Stefan Chock, M.D., Paul J. Young, M.B., Ch.B., Ph.D., Kenneth Krell, M.D., Richard G. Wunderink, M.D., Marlies Ostermann, M.D., Ph.D. Raghavan Murugan, M.D., Michelle N. Gong, M.D., Rakshit Panwar, M.D., Johanna Hästbacka, M.D., Ph.D., Raphael Favory, M.D., Ph.D., Balasubramanian Venkatesh, M.D., B. Taylor Thompson, M.D., Rinaldo Bellomo, M.D., Jeffrey Jensen, B.S., Stew Kroll, M.A., Lakhmir S. Chawla, M.D., George F. Tidmarsh, M.D., Ph.D., and Adam M. Deane, M.D., for the ATHOS-3 Investigators*

Bleu de méthylène

- Inhibiteur iNOS et guanylate cyclase
- Augmente SVR et PAM, diminue vasopresseurs
- Effet cardiaque léger (mais diminue D.C. au total)
- Coloration bleutée, interfère avec oxymètre
- Diminution flots coronaires, mésentériques, rénaux?
- Post CEC, sepsis, anaphylaxie, intox réfractaire, transplantation hépatique

Bleu de méthylène

- Risque de syndrome sérotoninergique
- Anémie hémolytique (G6PD)
- Méthémoglobinémie à haute dose
- Augmentation PAP, diminution VC hypoxémique
- Peu d'études solides
- Bolus 1-2 mg/kg IV et/ou perfusion 0,5 mg/kg/h pour quelques heures

Hydroxocobalamine

Use of Hydroxocobalamin (Vitamin B12a) in Patients With Vasopressor Refractory Hypotension After Cardiopulmonary Bypass: A Case Series

Sarah Armour, MD,* Trygve K. Armour, MD,* William R. Joppa, PharmD, RPh,†
Simon Maltais, MD, PhD,‡ James A. Nelson, MBBS,* and Erica Wittwer, MD, PhD*

Hydroxocobalamin (vitamin B12a) is an emerging treatment for vasoplegic syndrome (VS) associated with cardiopulmonary bypass (CPB). Given its cost and scarcity, an institutional guideline for its use as a rescue treatment in cases of suspected VS was developed. Hemodynamic variables and vasopressor requirements were reviewed for a series of 24 post-CPB patients who received B12a. Favorable changes in hemodynamic parameters and vasopressor requirements were seen after B12a administration although guideline criteria for VS were inconsistently met. These findings support the continued study of B12a in patients with CPB-associated VS. (Anesth Analg XXX;XXX:00–00)

5g IV en 10-15 minutes, répétable X 1 30-60 minutes plus tard
Néphrotoxicité

Choc distributif réfractaire

Canule fémorale!

TABLE 2] Potential Rescue Therapies for Refractory Shock

Therapy	Dose	Mechanism of Action	Adverse Effects
Hydrocortisone	Bolus: 50 mg every 6 h or 100 mg every 8 h Infusion: 10 mg/h	Increased vascular catecholamine response	Secondary infection Hyperglycemia Hypernatremia
Calcium chloride	Bolus: 1-2 g Infusion: 20-50 mg/kg/h	Increased vascular calcium signaling	Hypercalcemia Inhibition of β-adrenergic effects
Sodium bicarbonate	1-2 mEq/kg	Reversal of metabolic acidosis	Hypernatremia Ionized hypocalcemia Respiratory acidosis
THAM	9 mL/kg (324 mg/kg or 2.7 mEq/kg) up to 500 mg/kg/dose over 60 min	Reversal of metabolic acidosis	Hyperkalemia Fluid overload
Methylene blue	Bolus: 1-2 mg/kg every 4-6 h Infusion: 0.25-1 mg/kg/h	Inhibition of NOS	Serotonin syndrome Hypoxia Pulmonary hypertension
Hydroxocobalamin	5 g	Scavenging of NO	Interference with hemodialysis sensors
Ascorbic acid	25 mg/kg every 6 h or 1.5 g every 6 h	Increased catecholamine and vasopressin synthesis	Minimal
Thiamine	200 mg every 12 h	Improved lactate clearance	Minimal
Terlipressin (not available in the United States)	Bolus: 1 mg every 6 h Infusion: 1.3 μg/kg/h	Activation of vasopressin-V_{1a} receptors	Reduced cardiac output Increased pulmonary vascular resistance
Angiotensin II	Starting: 2-10 ng/kg/min Maximum: 20-40 ng/kg/min	Angiotensin II receptor activation	Hypertension Metabolic alkalosis

NO = nitric oxide; NOS = nitric oxide synthase; THAM = tris-hydroxymethyl-aminomethane (tromethamine).

Jentzer et Al.
CHEST Aug 2018

ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami, A. Cariou, X. Forceville, C. Schwebel, C. Martin, J.-F. Timsit, B. Misset, M. Ali Benali, G. Colin, B. Souweine, K. Asehnoune, E. Mercier, L. Chimot, C. Charpentier, B. François, T. Boulain, F. Petitpas, J.-M. Constantin, G. Dhonneur, F. Baudin, A. Combes, J. Bohé, J.-F. Loriferne, R. Amathieu, F. Cook, M. Slama, O. Leroy, G. Capellier, A. Dargent, T. Hissem, V. Maxime, and E. Bellissant, for the CRICS-TRIGGERSEP Network*

ABSTRACT

BACKGROUND

Septic shock is characterized by dysregulation of the host response to infection, with circulatory, cellular, and metabolic abnormalities. We hypothesized that therapy with hydrocortisone plus fludrocortisone or with drotrecogin alfa (activated), which can modulate the host response, would improve the clinical outcomes of patients with septic shock.

METHODS

In this multicenter, double-blind, randomized trial with a 2-by-2 factorial design, we evaluated the effect of hydrocortisone-plus-fludrocortisone therapy, drotrecogin alfa (activated), the combination of the three drugs, or their respective placebos. The primary outcome was 90-day all-cause mortality. Secondary outcomes included mortality at intensive care unit (ICU) discharge and hospital discharge and at day 28 and day 180 and the number of days alive and free of vasopressors, mechanical ventilation, or organ failure. After drotrecogin alfa (activated) was withdrawn from the market, the trial continued with a two-group parallel design. The analysis compared patients who received hydrocortisone plus fludrocortisone with those who did not (placebo group).

RESULTS

Among the 1241 patients included in the trial, the 90-day mortality was 43.0% (264 of 614 patients) in the hydrocortisone-plus-fludrocortisone group and 49.1% (308 of 627 patients) in the placebo group (P=0.03). The relative risk of death in the hydrocortisone-plus-fludrocortisone group was 0.88 (95% confidence interval, 0.78 to 0.99). Mortality was significantly lower in the hydrocortisone-plus-fludrocortisone group than in the placebo group at ICU discharge (35.4% vs. 41.0%, P=0.04), hospital discharge (39.0% vs. 45.3%, P=0.02), and day 180 (46.6% vs. 52.5%, P=0.04) but not at day 28 (33.7% and 38.9%, respectively; P=0.06). The number of vasopressor-free days to day 28 was significantly higher in the hydrocortisone-plus-fludrocortisone group than in the placebo group (17 vs. 15 days, P<0.001), as was the number of organ-failure–free days (14 vs. 12 days, P=0.003). The number of ventilator-free days was similar in the two groups (11 days in the hydrocortisone-plus-fludrocortisone group and 10 in the placebo group, P=0.07). The rate of serious adverse events did not differ significantly between the two groups, but hyperglycemia was more common in hydrocortisone-plus-fludrocortisone group.

CONCLUSIONS

In this trial involving patients with septic shock, 90-day all-cause mortality was lower among those who received hydrocortisone plus fludrocortisone than among those who received placebo. (Funded by Programme Hospitalier de Recherche Clinique 2007 of the French Ministry of Social Affairs and Health; APROCCHSS ClinicalTrials.gov number, NCT00625209.)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 1, 2018 VOL. 378 NO. 9

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

ABSTRACT

BACKGROUND

Whether hydrocortisone reduces mortality among patients with septic shock is unclear.

METHODS

We randomly assigned patients with septic shock who were undergoing mechanical ventilation to receive hydrocortisone (at a dose of 200 mg per day) or placebo for 7 days or until death or discharge from the intensive care unit (ICU), whichever came first. The primary outcome was death from any cause at 90 days.

RESULTS

From March 2013 through April 2017, a total of 3800 patients underwent randomization. Status with respect to the primary outcome was ascertained in 3658 patients (1832 of whom had been assigned to the hydrocortisone group and 1826 to the placebo group). At 90 days, 511 patients (27.9%) in the hydrocortisone group and 526 (28.8%) in the placebo group had died (odds ratio, 0.95; 95% confidence interval [CI], 0.82 to 1.10; P=0.50). The effect of the trial regimen was similar in six prespecified subgroups. Patients who had been assigned to receive hydrocortisone had faster resolution of shock than those assigned to the placebo group (median duration, 3 days [interquartile range, 2 to 5] vs. 4 days [interquartile range, 2 to 9]; hazard ratio, 1.32; 95% CI, 1.23 to 1.41; P<0.001). Patients in the hydrocortisone group had a shorter duration of the initial episode of mechanical ventilation than those in the placebo group (median, 6 days [interquartile range, 3 to 18] vs. 7 days [interquartile range, 3 to 24]; hazard ratio, 1.13; 95% CI, 1.05 to 1.22; P<0.001), but taking into account episodes of recurrence of ventilation, there were no significant differences in the number of days alive and free from mechanical ventilation. Fewer patients in the hydrocortisone group than in the placebo group received a blood transfusion (37.0% vs. 41.7%; odds ratio, 0.82; 95% CI, 0.72 to 0.94; P=0.004). There were no significant between-group differences with respect to mortality at 28 days, the rate of recurrence of shock, the number of days alive and out of the ICU, the number of days alive and out of the hospital, the recurrence of mechanical ventilation, the rate of renal-replacement therapy, and the incidence of new-onset bacteremia or fungemia.

CONCLUSIONS

Among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not result in lower 90-day mortality than placebo. (Funded by the National Health and Medical Research Council of Australia and others; ADRENAL ClinicalTrials.gov number, NCT01448109.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Venkatesh at the Department of Intensive Care, Wesley Hospital, 451 Coronation Dr., Auchenflower, Brisbane, QLD 4066, Australia, or at bvenkatesh@georgeinstitute.org.au.

*A full list of investigators in the ADRENAL Trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on January 19, 2018, at NEJM.org.

N Engl J Med 2018;378:797-808.
DOI: 10.1056/NEJMoa1705835
Copyright © 2018 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org at UNIVERSITE DE MONTREAL on April 5, 2018. For personal use only. No other uses without permission.
Copyright © 2018 Massachusetts Medical Society. All rights reserved.

Vasopresseurs et cerveau

TABLE 1. Cerebrovascular Adrenergic Receptor (α, β) Distribution and Effects of Vasopressors in Awake or Anesthetized Subjects Without Cerebral Pathology

Extracranial Arteries (eg, ICA)		Intracranial Arteries (eg, MCA)		Cerebral Pial Arterioles			Cerebral Parenchymal Arterioles		
$\alpha_1 > > > \alpha_2 > \beta$		$\alpha_1 > > \alpha_2 > \beta$		$\alpha_1 > \alpha_2 > \beta$			$B > \alpha_1 > \alpha_2$		
Drug	**Mechanism**	**α Agonist**	**β Agonist**	**CBF**	**MCA Flow Velocity**	**CPP**	**CO**	**$SctO_2$**	**$CMRO_2$**	**OEF**
Phenylephrine[14–16]	Alpha-1 receptor agonist	+++	−	NA	↑	↑	↓	↓	NA	NA
Ephedrine[14,17]	Mixed alpha/beta-1-receptor agonist	++	++	NA	→	↑	↑→	↑→	NA	NA
Norepinephrine[15,18–23]	Mixed alpha/beta-1-receptor agonist	+++	+++	↓→	↑→	↑	→	→↓	→	NA
Dopamine[24–28]	Dose-dependent agonist: beta and alpha receptors	+	++	↑↓	NA	↑	↑↓	NA	→	NA

↑Increase in parameter; ↓Decrease in parameter; →No change in parameter. For each drug, references, preferably from human studies, are provided for the indicated cerebrovascular effects.

Data concerning the distribution of adrenergic receptors in the cerebral vasculature are from Brassard et al[10]; α-receptor reactivity reduces progressively from extracranial arteries to parenchymal arterioles where the activity is nearly absent.[10] Of note, the effects of vasopressors on $SctO_2$ should be interpreted with caution, as a given effect on $SctO_2$ may be secondary to changes in cardiac output, cerebral arterial to venous blood volume ratio, and/or extracranial skin perfusion.

CBF indicates cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen; CO, cardiac output; CPP, cerebral perfusion pressure; ICA, Internal carotid artery; MCA, middle cerebral artery; NA, no data available (to our knowledge); OEF, oxygen extraction fraction; $SctO_2$, brain tissue oxygenation.

Bolus de vasopresseurs

EPINEPHephrine 10 mcg/mL Syringe Preparation:

1. Draw up 9 mL of normal saline into a 10 mL syringe (DO NOT use 10ml IV line "flush" syringes)
2. Into this syringe, draw up 1 mL of EPINEPHphrine 0.1 mg/mL (1 mg/10ml) from a cardiac syringe
3. Label syringe

Phenylephrine 100 mcg/mL Syringe Preparation:

1. Draw up 1 mL of phenylephrine from a 10 mg/mL vial into a 3 mL syringe
2. Inject this into a 100 mL bag of normal saline. Label bag; safely discard when finished
3. Draw up 10 mL into a 10 mL syringe
4. Label syringe
5.

ePHEDrine 5 mg/mL Syringe Preparation:

1. Draw up 9 mL of normal saline into a 10 mL syringe (DO NOT use 10ml IV line "flush" syringes)
2. Into this syringe, draw up 1 mL of ePHEDrine from a 50 mg/mL vial
3. Label syringe

Figure 2. Instructions for ad hoc preparation of bolus-dose vasopressors (adapted from Weingart[6] and Cocchio[9]).

- Lévo 8mg/250ml: diluer 1 ml dans 9 ml de NS
  - 3 mcg/ml

Cochrane Library

Cochrane Database of Systematic Reviews

Vasopressors for hypotensive shock (Review)

Gamper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M, Herkner H

Authors' conclusions

We found no evidence of substantial differences in total mortality between several vasopressors. Dopamine increases the risk of arrhythmia compared with norepinephrine and might increase mortality. Otherwise, evidence of any other differences between any of the six vasopressors examined is insufficient. We identified low risk of bias and high-quality evidence for the comparison of norepinephrine versus dopamine and moderate to very low-quality evidence for all other comparisons, mainly because single comparisons occasionally were based on only a few participants. Increasing evidence indicates that the treatment goals most often employed are of limited clinical value. Our findings suggest that major changes in clinical practice are not needed, but that selection of vasopressors could be better individualised and could be based on clinical variables reflecting hypoperfusion.

Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD003709.

Surviving Sepsis Guidelines

- Noradrenaline 1er choix (strong recom, mod evid)
- Ajout vaso (ad 1.8 U/h) (faible rec, mod evid) ou adrenaline (faible recom, faible evid) si PAM non atteinte
- Ajout vaso (ad 1,8 U/h) pour diminuer norad (faible recom, mod evid)
- Dopa chez patient ultrasélectionné seulement (faible recom, faible evid)
- Dobutamine si hypoperfusion malgré volume et vasopresseurs (faible recom, faible evid)

Autres

- Calcium
- Glucagon: adenylyl cyclase sans récepteur
- Insuline
- Hormones thyroïdiennes
- Midodrine: agoniste alpha1, pic à 1h
- Amphétamines, cocaïne, caffeine, théophylline, …

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension

A Randomized Clinical Trial

François Lamontagne, MD; Alvin Richards-Belle, BSc; Karen Thomas, MSc; David A. Harrison, PhD; M. Zia Sadique, PhD; Richard D. Grieve, PhD; Julie Camsooksai, BSc; Robert Darnell, BA; Anthony C. Gordon, MD; Doreen Henry, MSc; Nicholas Hudson, BA; Alexina J. Mason, PhD; Michelle Saull, BSc; Chris Whitman, BSc; J. Duncan Young, DM; Kathryn M. Rowan, PhD; Paul R. Mouncey, MSc; for the 65 trial investigators

IMPORTANCE Vasopressors are commonly administered to intensive care unit (ICU) patients to raise blood pressure. Balancing risks and benefits of vasopressors is a challenge, particularly in older patients.

OBJECTIVE To determine whether reducing exposure to vasopressors through permissive hypotension (mean arterial pressure [MAP] target, 60-65 mm Hg) reduces mortality at 90 days in ICU patients aged 65 years or older with vasodilatory hypotension.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, pragmatic, randomized clinical trial was conducted in 65 ICUs in the United Kingdom and included 2600 randomized patients aged 65 years or older with vasodilatory hypotension (assessed by treating clinician). The study was conducted from July 2017 to March 2019, and follow-up was completed in August 2019.

INTERVENTIONS Patients were randomized 1:1 to vasopressors guided either by MAP target (60-65 mm Hg, permissive hypotension) (n = 1291) or according to usual care (at the discretion of treating clinicians) (n = 1307).

MAIN OUTCOME AND MEASURES The primary clinical outcome was all-cause mortality at 90 days.

RESULTS Of 2600 randomized patients, after removal of those who declined or had withdrawn consent, 2463 (95%) were included in the analysis of the primary outcome (mean [SD] age 75 years [7 years]; 1387 [57%] men). Patients randomized to the permissive hypotension group had lower exposure to vasopressors compared with those in the usual care group (median duration 33 hours vs 38 hours; difference in medians, −5.0; 95% CI, −7.8 to −2.2 hours; total dose in norepinephrine equivalents median, 17.7 mg vs 26.4 mg; difference in medians, −8.7 mg; 95% CI, −12.8 to −4.6 mg). At 90 days, 500 of 1221 (41.0%) in the permissive hypotension compared with 544 of 1242 (43.8%) in the usual care group had died (absolute risk difference, −2.85%; 95% CI, −6.75 to 1.05; P = .15) (unadjusted relative risk, 0.93; 95% CI, 0.85-1.03). When adjusted for prespecified baseline variables, the odds ratio for 90-day mortality was 0.82 (95% CI, 0.68 to 0.98). Serious adverse events were reported for 79 patients (6.2%) in the permissive care group and 75 patients (5.8%) in the usual care group. The most common serious adverse events were acute renal failure (41 [3.2%] vs 33 [2.5%]) and supraventricular cardiac arrhythmia (12 [0.9%] vs 13 [1.0%]).

CONCLUSIONS AND RELEVANCE Among patients 65 years or older receiving vasopressors for vasodilatory hypotension, permissive hypotension compared with usual care did not result in a statistically significant reduction in mortality at 90 days. However, the confidence interval around the point estimate for the primary outcome should be considered when interpreting the clinical importance of the study.

TRIAL REGISTRATION isrctn.org Identifier: ISRCTN10580502

Visual Abstract

Editorial page 931

Video and Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: 65 Trial investigators are listed at the end of the article.

JAMA. 2020;323(10):938-949.

Vasodilatateurs inhalés

- NO: gaz inhalé 1-40 PPM
- Prostacyclines (Flolan): nébulisé
  - En continu 4-12 ml/h (10 mcg/ml)
- Milrinone: nébulisé 5 mg q 4h

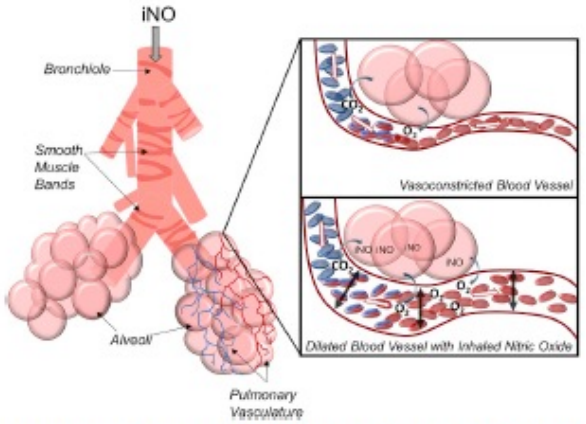


Fig. 3. Representative image of inhaled nitric oxide inducing dilation of pulmonary arteries in the lungs leading to increased oxygen exchange in a patient.

- Améliorer le match ventilation-perfusion
  - Fonctionne mais ne change pas le devenir clinique
- Diminuer les résistances pulmonaires (environ 20-25%)
  - Amélioration des paramètres hémodynamiques
  - Peu d'effets vasodilatateurs systémiques

Free Radical Biology and Medicine 152 (2020) 422–431

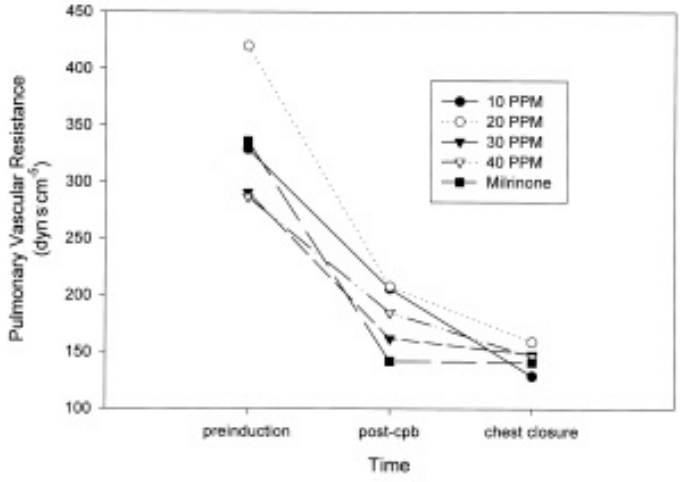
Vasodilatateurs inhalés

- NO:
  - Formation de superoxydes à haute FiO2
  - En méta-analyse, plus d'insuffisance rénale
  - Courte demi-vie. Rebond à l'arrêt (faire sevrage prog.)
  - Effet antiplaquettaire
  - Titrer vu possible détérioration PaO2/FiO2 à haute dose
  - Neuroprotection?
- Flolan
  - Effet antiplaquettaire
  - Courte demi-vie
  - Effet anti-inflammatoire?

Dose Response to Nitric Oxide in Adult Cardiac Surgery Patients

Alann R. Solina, MD,* Steven H. Ginsberg, MD,† Denes Papp, MD,† William R. Grubb, MD,† Peter M. Scholz, MD,‡ Enrique J. Pantin, MD,† Ronald P. Cody, EdD,§ Tyrone J. Krause, MD‖

Department of Anesthesiology and Department of Surgery, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, Piscataway, NJ



Journal of Clinical Anesthesia 13:281–286, 2001

Table 2
Studies Comparing iNO to $iPGI_2$ in Cardiac Surgical Patients with Pulmonary Hypertension

Study	Group	n	ΔPAP	ΔPVR	ΔCI	ΔCO	ΔRVEF	ΔCVP	ΔSVO_2
Fattouch	iNO	19	-13	-150	+1.3	-	+10	-	-
2006[a]	$iPGI_2$	21	-11	-180	+1.2	-	+11	-	-
Winterhalter	iNO	23	-10	-195	-	+1.0	-	0	+3
2008[b]	$iPGI_2$	23	-8	-247	-	+2.7	-	-1	+2
Khan	iNO	14	-6	-	+0.5	-	-	-3	+8
2009[c]	$iPGI_2$	11	-9	-	+0.4	-	-	-3	+5

*Fattouch K, et al. J Cardiovasc Med 2006;7:119. Values are differences compared with control group (n = 18) 1 hour prior to arrival to the intensive care unit after mitral valve operations for mitral stenosis.

†Winterhalter M, et al. J Cardiothorac Vasc Anesth 2008;22:406. Values are change from preoperative baseline before treatment in cardiac surgical patients with pulmonary hypertension upon arrival in the intensive care unit after operation.

‡Khan TA, et al. J Thorac Cardiovasc Surg 2009;138:1417. Values are change in response to treatment after cardiopulmonary bypass in a crossover study of patients undergoing heart (n = 6) or lung (n = 19) transplantation.

Abbreviations: ΔCI, change in cardiac index in $L/min/m^2$ body surface area; ΔCO, change in cardiac output in L/min; ΔCVP, change in central venous pressure in mmHg; ΔPAP, change in mean pulmonary artery pressure in mmHg; ΔPVR = change in pulmonary vascular resistance in $dynes \bullet sec \bullet cm^{-5}$; ΔRVEF, change in right ventricular area ejection fraction in %; ΔSVO_2, change in mixed venous oxygen saturation in %.

A Comparison of Inhaled Nitric Oxide and Milrinone for the Treatment of Pulmonary Hypertension in Adult Cardiac Surgery Patients

Alann Solina, MD, Denes Papp, MD, Steven Ginsberg, MD, Tyrone Krause, MD, William Grubb, MD, Peter Scholz, MD, Leini-Luck Pena, MD, and Ronald Cody, EdD

Objective: To investigate the relative effects of milrinone and nitric oxide on pulmonary and systemic hemodynamic responses in cardiac surgery patients with a history of pulmonary hypertension.

Design: Prospective and randomized.

Setting: University hospital.

Participants: Forty-five adult cardiac surgery patients.

Interventions: Cardiac surgery patients with pulmonary hypertension were randomly assigned to one of three study groups: Group 1 patients ($n = 15$) were treated with intravenous milrinone on separation from cardiopulmonary bypass, group 2 patients ($n = 15$) with 20 ppm of inhaled nitric oxide, and group 3 patients ($n = 15$) with 40 ppm of inhaled nitric oxide. Heart rate, right ventricular ejection fraction, and pulmonary vascular resistance were measured throughout the perioperative period at specific data points.

Measurements and Main Results: There were no significant differences in demographics, anesthesia, surgery, or baseline hemodynamics among the groups. The group receiving 40 ppm nitric oxide had a significantly higher ($p < 0.05$) right ventricular ejection fraction on arrival in the intensive care unit (40% *v* 30% for the milrinone group and 33% for the nitric oxide 20 ppm group). The milrinone group required significantly more phenylephrine in the intensive care unit ($p < 0.05$).

Conclusions: Treatment of pulmonary hypertension in adult cardiac surgery patients with inhaled nitric oxide compared with milrinone is associated with lower heart rates, higher right ventricular ejection fraction, and a lower requirement for treatment with vasopressor agents.

Copyright © 2000 by W.B. Saunders Company

KEY WORDS: *pulmonary hypertension, cardiac surgery, nitric oxide*

Journal of Cardiothoracic and Vascular Anesthesia 32 (2018) 2130–2138

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Pharmacokinetics and Pharmacodynamics of Nebulized and Intratracheal Milrinone in a Swine Model of Hypercapnia Pulmonary Hypertension

Paul Gavra, PhD*, André Y. Denault, MD, PhD†, Yves Théoret, BPharm, PhD‡, Louis P. Perrault, MD, PhD§, France Varin, BPharm, PhD*,1

*Faculty of Pharmacy, Université de Montréal, Montréal, Canada
†Department of Anesthesiology, Montreal Heart Institute, Montréal, Canada
‡Unité de Pharmacologie Clinique, CHU Ste-Justine, Montréal, Canada
§Department of Surgery, Montreal Heart Institute, Montréal, Canada

Objectives: Milrinone pulmonary administration is used currently for the treatment of pulmonary hypertension. Several methods are available: simple jet nebulization, vibrating mesh nebulization, intratracheal instillation, and intratracheal atomization. The aim of this study was to explore the concentration-effect relationship of milrinone for each of these methods.

Design: Observational open-label pharmacokinetic/pharmacodynamics cohort study.

Setting: Single-center, hospital animal laboratory.

Participants: Twelve swine.

Interventions: After hypercapnia pulmonary hypertension, swine were administered equivalent inhaled milrinone doses of 15 or 50 μg/kg through simple jet nebulization, vibrating mesh nebulization, intratracheal instillation, and intratracheal atomization.

Measurements and Main Results: Blood and urine samples were taken up to 360 minutes postadministration. The ratio of mean systemic arterial pressure to mean pulmonary arterial pressure was monitored continuously. Right heart echographies were taken before and after hypercapnia and after drug administration. Mean elimination half-lives were similar for the 4 administrations. Mean percent changes in the ratio were of 37 (60%), 18 (31%), 17 (36%), and 20 (20%), for simple jet nebulization, vibrating mesh nebulization, intratracheal instillation, and intratracheal atomization, respectively. Mean maximum plasma concentrations for intratracheal administrations were reached at 8 and 45 min for atomization and instillation, respectively. Significant increases in right atrial diameter and right ventricular end-diastolic area were witnessed during pulmonary hypertension as well as a return to baseline values after milrinone administration.

Conclusions: The intratracheal methods, particularly intratracheal atomization, showed less hemodynamic effect than nebulizations and, in the case of intratracheal instillation, unpredictable drug exposure. Nebulization methods on the other hand, especially simple jet nebulization, suggest better efficacy and sensitivity but are less fit for emergency situations.

© 2018 Elsevier Inc. All rights reserved.

Can J Anesth/J Can Anesth (2016) 63:1140–1153
DOI 10.1007/s12630-016-0709-8

REPORTS OF ORIGINAL INVESTIGATIONS

A multicentre randomized-controlled trial of inhaled milrinone in high-risk cardiac surgical patients

Une étude randomisée contrôlée multicentrique sur la milrinone inhalée chez les patients de chirurgie cardiaque à risque élevé

André Y. Denault, MD, PhD · Jean S. Bussières, MD · Ramiro Arellano, MD · Barry Finegan, MD · Paul Gavra, PhD · François Haddad, MD · Anne Q. N. Nguyen, PhD · France Varin, PhD · Annik Fortier, MSc · Sylvie Levesque, MSc · Yanfen Shi, MD · Malısa Elmi-Sarabi, MSc · Jean-Claude Tardif, MD · Louis P. Perrault, MD, PhD · Jean Lambert, PhD

Received: 23 February 2016 / Revised: 2 May 2016 / Accepted: 15 July 2016 / Published online: 28 July 2016
© Canadian Anesthesiologists' Society 2016

Journal of Cardiothoracic and Vascular Anesthesia 33 (2019) 663–673

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Intravenous and Inhaled Milrinone in Adult Cardiac Surgery Patients: A Pairwise and Network Meta-Analysis

Lisa Q. Rong, MD[*,†], Mohamed Rahouma, MD[†], Ahmed Abouarab, MD[†], Antonino Di Franco[†], Nicole M. Calautti[*], Meghann M. Fitzgerald, MD[*], Mohammed J. Arisha[*], Dina A. Ibrahim[*], Leonard N. Girardi, MD[†], Kane O. Pryor, MD[*], Mario Gaudino, MD[†]

[*]*Department of Anesthesiology, Weill Cornell Medicine, New York, NY*
[†]*Department of Cardio-Thoracic Surgery, Weill Cornell Medicine, New York, NY*

Objective: To summarize the evidence on the hemodynamic, echocardiographic, and clinical effects of inhaled and intravenous milrinone (iMil and IvMil) in adult cardiac surgery patients.

Design: Systematic review, pairwise and network meta-analysis.

Setting: Multi-institutional.

Participants: Adult cardiac surgery patients.

Interventions: Comparison between iMil and IvMil versus other agents or placebo.

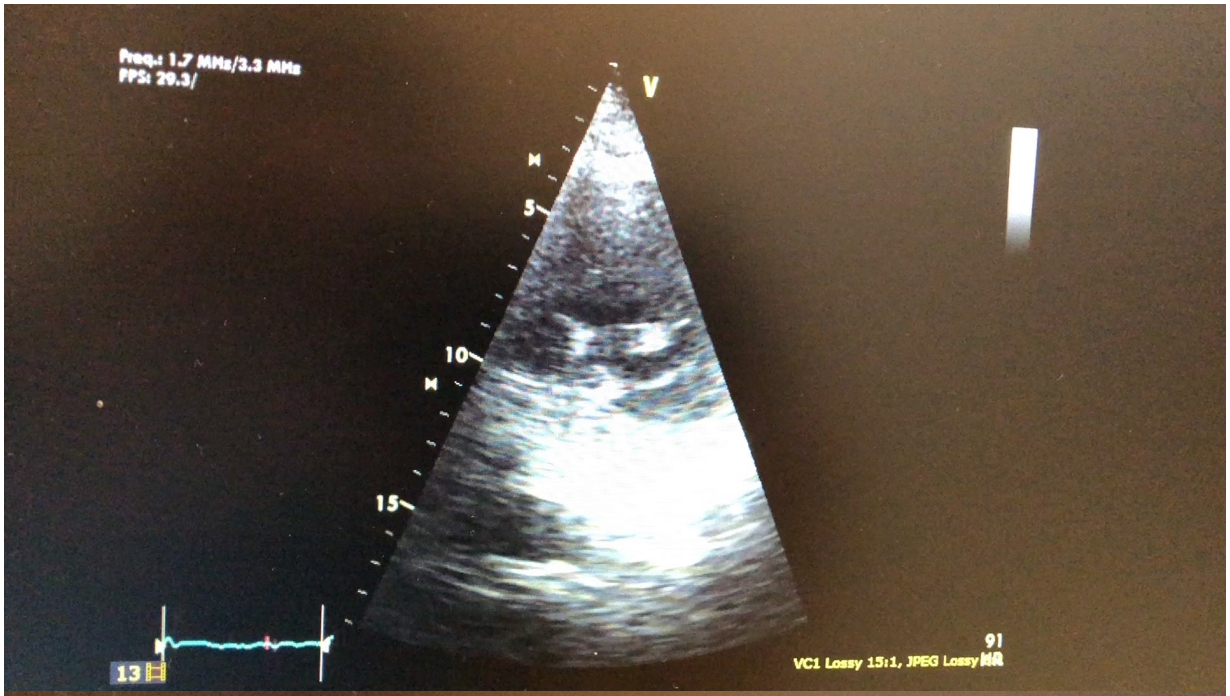
Measurements and Main Results: The primary endpoints were mean pulmonary artery pressure (MPAP) and peripheral vascular resistance (PVR). Secondary endpoints included the following: (1) mean arterial pressure, heart rate, and cardiac index (CI); (2) echocardiographic data; and (3) clinical outcomes. Random model, leave-one-out-analysis, and meta-regression were used. Thirty studies (6 iMil and 24 IvMil) were included for a total of 1,438 patients (194 iMil and 521 IvMil). IvMil was associated with a lower MPAP, lower PVR, and higher CI compared to placebo (standardized mean difference [SMD] = −0.22 [95% CI = −0.48 to 0.05], SMD = −0.49 [95% CI = −0.71 to −0.27], and SMD = 0.94 [95% CI = 0.51 to 1.37]). No difference in any outcome was found between iMil and placebo. At network meta-analysis, significantly lower PVR and shorter hospital length of stay were found for IvMil compared to iMil (SMD = −0.82 [95% CI = −1.53 to −0.10] and SMD = −0.50 [95% CI = −0.95 to −0.05], respectively).

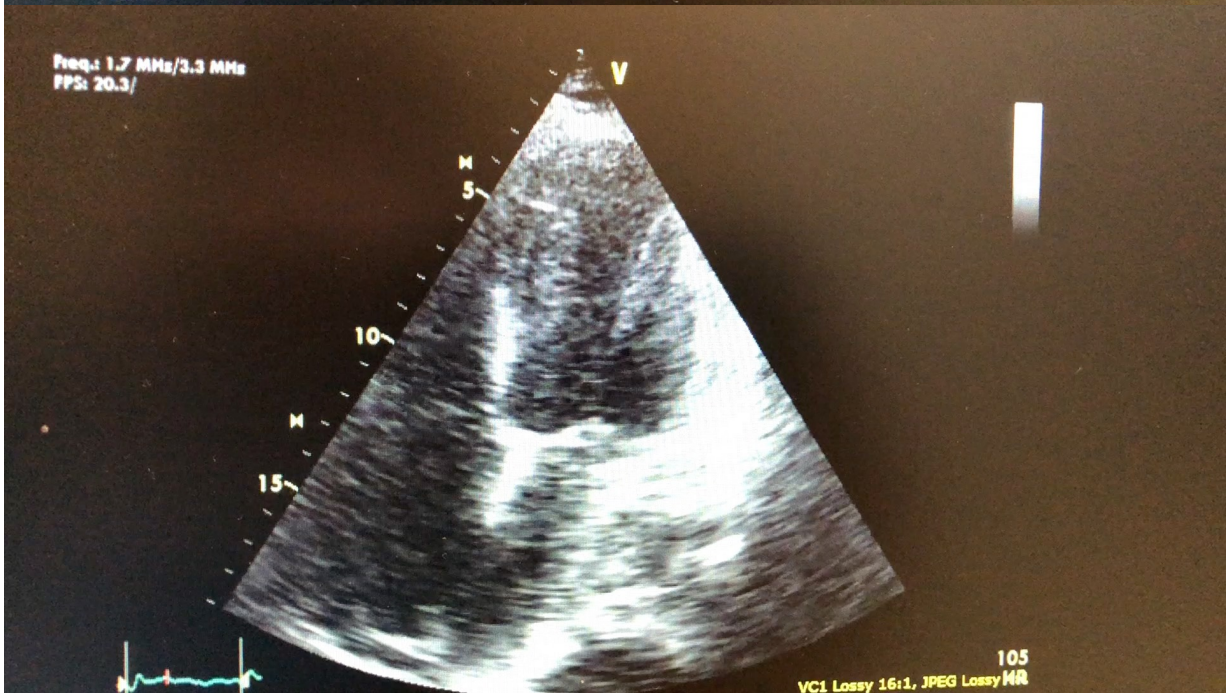
Conclusion: These results support the clinical use of IvMil in cardiac surgery patients. No evidence at present supports the adoption of iMil.

© 2018 Elsevier Inc. All rights reserved.

Cas clinique #4

- Patient 78 ans, J1 PAC-PMC, connu FeVG 35%
  - Repris dans la nuit pour tamponnade
  - En choc depuis, anurique, lactates 10
- Sous:
  - BIA 1:2
  - Pacé 90, amio
  - Milrinone 0,375 mcg/kg/min
  - Adré 10 mcg/min
  - Lévo 80 mcg/min
  - Vaso 2.4 U/h


Freq.: 1.7 MHz/3.3 MHz
FPS: 29.3/
V
5
10
15
13
91
VC1 Lossy 15:1, JPEG Lossy HR


Freq.: 1.7 MHz/3.3 MHz
FPS: 20.3/
V
5
10
15
105
VC1 Lossy 16:1, JPEG Lossy HR

Cas clinique #5

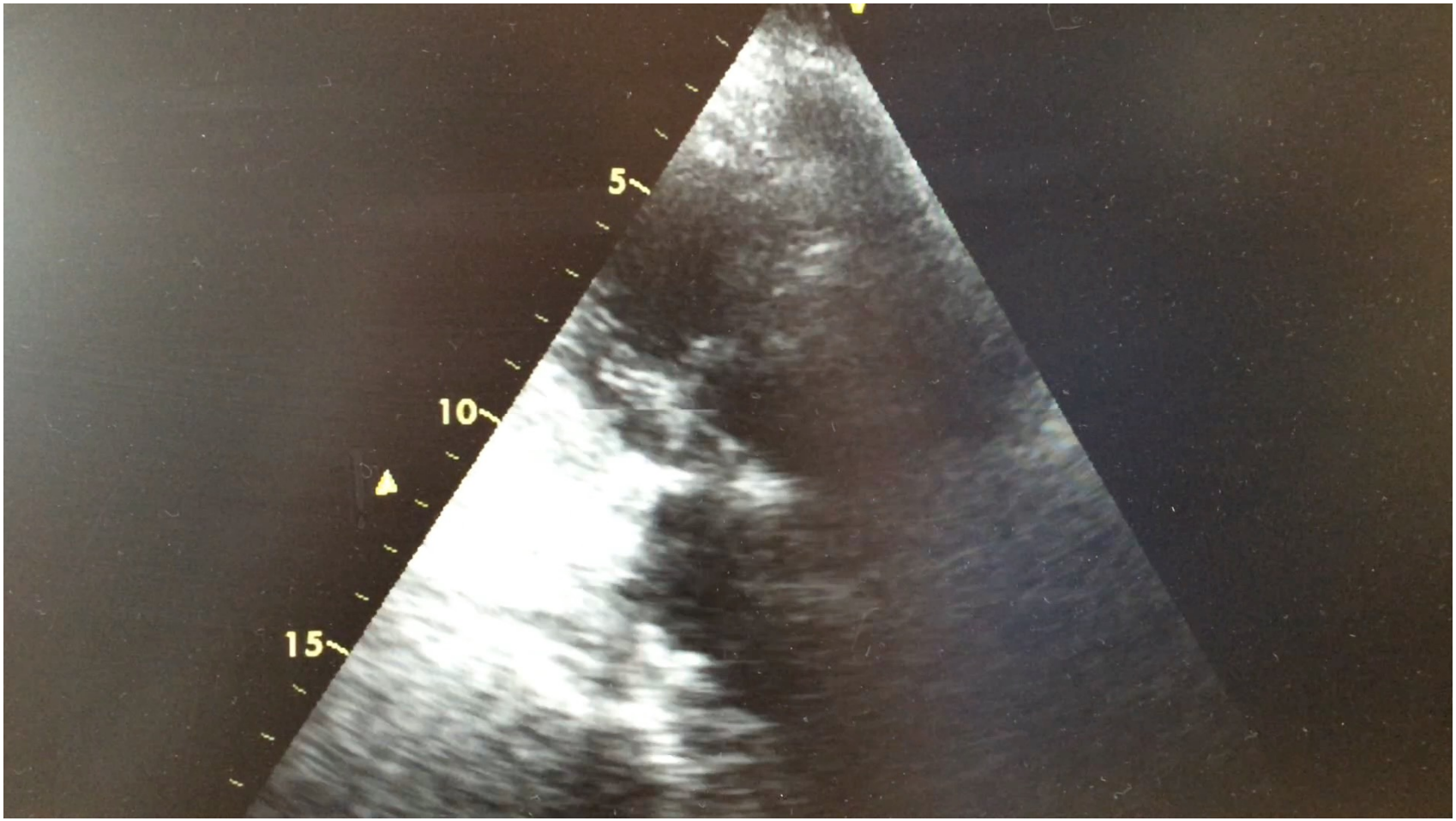
- Patient de 70 ans CU (1/2 colectomie), CMP ischémique FeVG 30-35%
  - Admis pour urosepsis obstructif, JJ installé, HC + à BGN
- Lévo 40 mcg/min post-op
  - Bolus albumine 5% 500 ml: lévo 60 mcg/min
  - Oligo-anurique
  - Lactates 4, puis 5 au contrôle
  - FeVG 20%, VD OK

Cas clinique #5

- Votre conduite?
  - 1. Ajout vaso
  - 2. Ajout dobu
  - 3. Ajout adré
  - 4. Ajout milrinone
  - 5. Garder lévo seulement

Cas clinique #6

- Patiente 50 ans, PVM minimalement invasif
  - Arrêt cardiaque per-op sur saignement massif au retrait de la canule jugulaire
  - Choc sévère post-op
    - Dysfonction VD sévère
    - Dysfonction VG modérée à sévère avec tako-tsubo
    - Obstruction dynamique de la chambre de chasse
      - Gradient fin de systole 100 mmHg
- Sous BIA 1:1, lévo 100 mcg/min, dobu 5 mcg/kg/min


5
10
15

Vasodilatateurs

- IV
  - Labetalol / esmolol
  - Nitro / Nitroprussiate
  - Nicardipine / Clevedipine
  - Hydralazine
  - Enalaprilat
  - Phentolamine
  - Sulfate de magnésium
  - Propofol / sédation?
- PO courte action

Labetalol

- Effet beta-bloqueur > alpha (5 à 7:1)
- Beta-bloqueur NON spécifique
  - Risque d'hyperréactivité bronchique
- Chronotrope et inotrope négatif
- 10-80 mg IV q 10 min
- Début d'action: 5 minutes
- Durée d'action: 2-4 heures
  - ATTENTION si perfusion: bolus vs dose fixe
- Moins efficace que les autres
- Attention si phéo, cocaïne, …

Esmolol

- Beta-bloqueur plus sélectif Beta1
- Début action: 1-2 minutes
- Durée action: 10-30 minutes
- 50-300 mcg/kg/min IV, bolus possible
- Faible antihypertenseur mais utile pour dP/dT ou si on veut tester l'effet d'un beta-bloqueur

- Metoprolol serait une alternative si non disponible (durée 4-6h)

Nitroprussiate

- Générateur de NO
- Vasodilatateur artériel et veineux
- Effet imprévisible
- Début action: 1 minute
- Durée action: 10 minutes
- 0,3-2 mcg/kg/min IV perfusion
  - Max 2 mcg/kg/min si prolongé
- Risque intox cyanure ou thiocyanate
  - Insuffisance rénale
  - Tx prolongé > 24-48h

Nitroprussiate

- Tachycardie
- Diminution flot coronaire, cérébral et rénal
- Perte de l'autorégulation cérébrale, HTIC
- Augmentation de la mortalité dans ECLIPSE vs clevedipine (post-op chirurgie cardiaque)
- Contrindication relative chez femme enceinte

Nitro

- Veinodilatateur > artériel
- Peu efficace
- Indications: ischémie coronarienne ou hypervolémie
- Méthémoglobinémie
- Tachyphylaxie

Nicardipine

- BCC dihydropyridine
- Excellent en neuro:
  - Particulièrement efficace dans les zones ischémiques ou si vasospasme
  - Dilate artérioles de résistance seulement alors pas d'augmentation de la PIC
- Balance oxygène myocarde favorable
- Début action 5-15 minutes
- Durée action 1.5-4 heures
- 2.5-15 mg/h IV perfusion
- Plus efficace et rapide que labetalol

Clevedipine

- BCC dihydropyridine
- Début action: 2-4 minutes
- Durée action: 5-15 minutes (estérases sang)
- 1-16 mg/h IV perfusion
- Même bénéfices théoriques que nicardipine
- Dans une émulsion lipidiques
  - Pas si allergie soya ou oeuf (comme propofol)

Enalaprilate

- IECA
- Effet imprévisible (selon volémie et niveau de rénine)
- 1.25 à 5 mg
- Début action 15 minutes
- Durée jusqu'à 12-24h
- Contrindication chez la femme enceinte, insuffisance rénale, hyperkaliémie,…

Hydralazine

- Vasodilatateur artériolaire
- Tachycardie réflexe
- Effet imprévisible
- 5-20 mg IV q 4-6h
- Début action 10-30 minutes
- Durée action 2-6 heures
- Peut augmenter HTIC
- Possible vol coronarien

Phentolamine

- Bloqueur alpha pur
- Début action rapide
- Durée 15 minutes
- Bolus 1-5 mg IV
- Pour phéo, IMAO + tyrosine, cocaïne…
- Infiltration SC de vasopresseurs
- Tachycardie et risque d’angine

Sulfate de magnésium

- Effet bloqueur calcique
- Phéo, éclampsie
- 40-60 mg/kg bolus puis perfusion 2g/h

Table 1.

Agents for Treating Hypertensive Emergencies with Comorbidities[1,5,8,12,14,17,51,64,66,91,a]

Comorbidity	Preferred Agent(s)
Acute aortic dissection	Esmolol[b]
Acute congestive heart failure	Nesiritide,[c] nitroglycerin, nitroprusside
Acute intracerebral hemorrhage	Labetalol, nicardipine
Acute ischemic stroke	Labetalol, nicardipine
Acute myocardial infarction	Clevidipine,[d] esmolol, labetalol, nicardipine,[d] nitroglycerin
Acute pulmonary edema	Nesiritide,[c] nitroglycerin, nitroprusside
Acute renal failure	Clevidipine, fenoldopam, nicardipine
Eclampsia or preeclampsia	Hydralazine, labetalol, nicardipine
Perioperative hypertension	Clevidipine, esmolol, nicardipine, nitroglycerin, nitroprusside
Sympathetic crisis or catecholamine toxicity	Clevidipine, fenoldopam, nicardipine, phentolamine

Médication PO

- Clonidine
- Prazosin
- Hydralazine
- CDZ courte action
- Metoprolol > bisoprolol
- Captopril
- Amlodipine (norvasc)
  - Début action ad 6-12h
  - ½ vie 30-50 heures; équilibre à 1 semaine…

Conclusion

- Pensez aux récepteurs que vous voulez stimuler et leurs effets plus qu'au médicament lui-même
- Mesurer les effets si vous changer d'agent pour individualiser votre thérapie