# Inotropes/inodilators in AHF /cardiogenic shock

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CEEA Kosice 2016


The DIK-OK-W Pyramid
"Wisdom"
Research
Operational knowledge
Knowledge
Information
Data

# Conflicts of interest

- Have long term collaborations with
  - ORION Pharma (manufacturer of levosimendan)
  - BAXTER (manufacturer of esmolol)

# Goals

- Personal view on teaching
- Physiology/Pathophysiology
- Pharmacology
- Therepeutics
- Clinical reasoning for individual patients

# Personal view on teaching/education

# The DIK-OK-W Pyramid

# The DIK-OK-W Pyramid

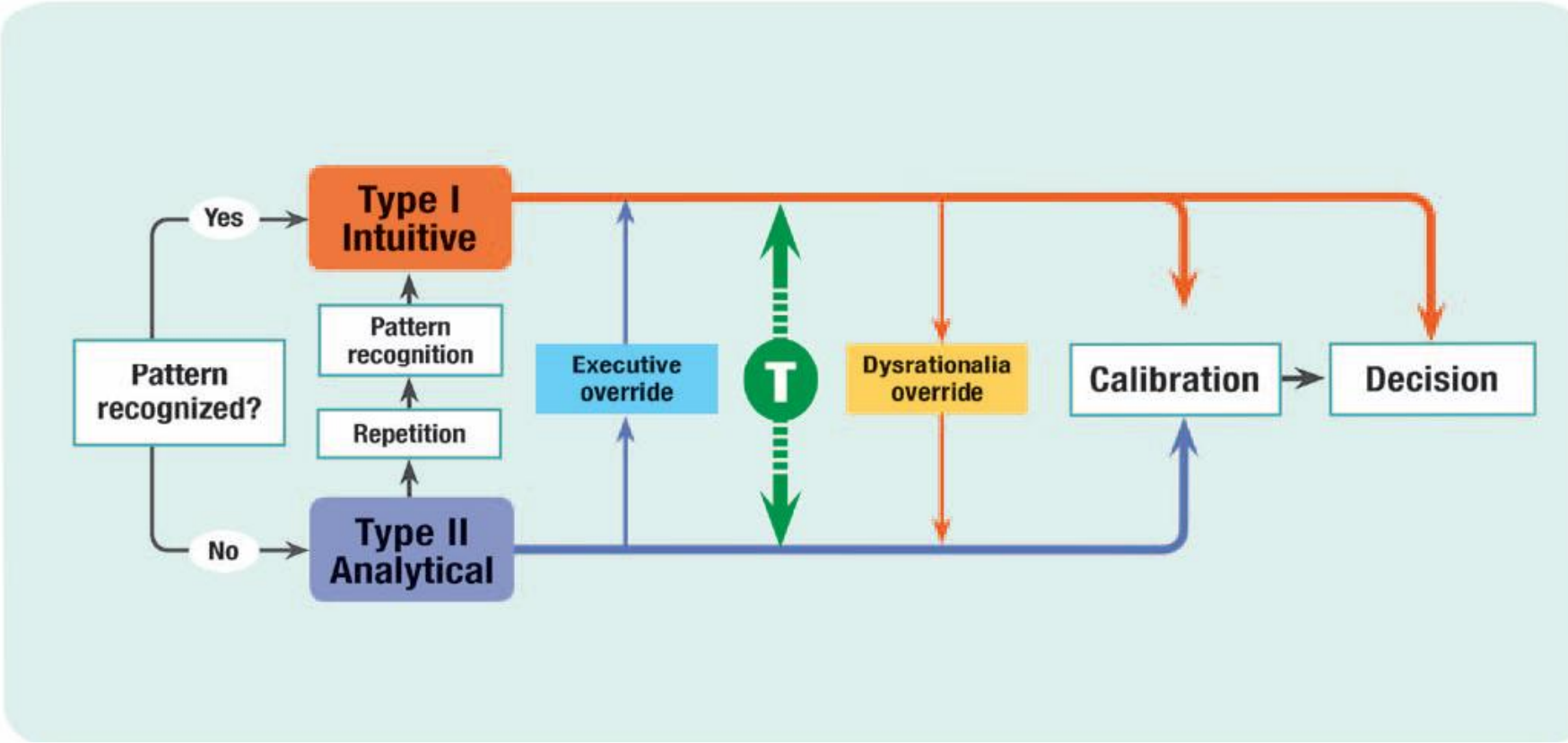
REVIEW ARTICLE

*David S. Warner, M.D., Editor*

# Cognitive Processes in Anesthesiology Decision Making

Marjorie Podraza Stiegler, M.D., Avery Tung, M.D., F.C.C.M.

Anesthesiology 2014; 120:204-17




Anesthesiology 2014; 120:204-17

*Open access, freely available online*

Essay

# Why Most Published Research Findings Are False

John P. A. Ioannidis

PLoS Medicine | www.plosmedicine.org
ugust 2005 | Volume 2 | Issue 8 | e124

# Why Most Published Research Findings Are False: Problems in the Analysis

**Steven Goodman, Sander Greenland**

April 2007 | Volume 4 | Issue 4 | e165 | e168

# Physiology/pathophysiology

# Why is the cardiovascular system necessary for a complex vertebrate ?

- Provide O2 (nutrients) and remove CO2 to/from the cells
- Provide a functional reserve if necessary
  - Flight/fight
  - The maximum capacity of physical effort depends also on lung/skeletal muscle/vessels/capillaries/Hb….
    - Functional reserve at nearly all levels

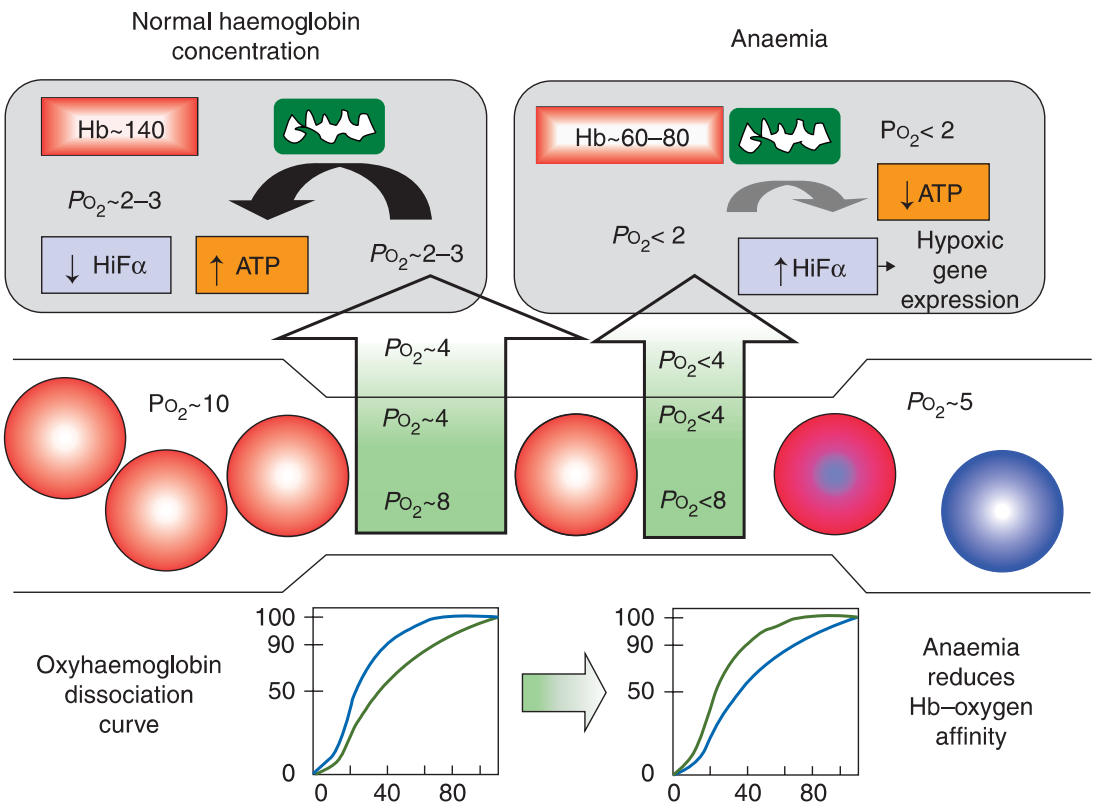



**Fig 1** Comparison of oxygen transport from the microcirculation at physiological Hb concentrations and during anaemia.[40–45] ATP, adenosine triphosphate; Hb, haemoglobin in g litre$^{-1}$; HIFα, hypoxia-inducible factor alpha; $P_{O_2}$, partial pressure of oxygen in kPa.

British Journal of Anaesthesia 107 (S1): i41–i59 (2011)

**The Role of Venous Return in Critical Illness and Shock—Part I: Physiology**

Duane J. Funk, MD[1,2]; Eric Jacobsohn, MD[1,2]; Anand Kumar, MD[1,3]

CO = EV x HR

$$CO = \frac{MAP - P_{RA}}{SVR}$$

Inotrope

Inodilator/
Vasodilator (arterial)

# The cardiocentric view of haemodynamics

## Consider a patient with cardiogenic shock following myocardial infarction. How would you evaluate the efficacy of positive inotropic drug ?

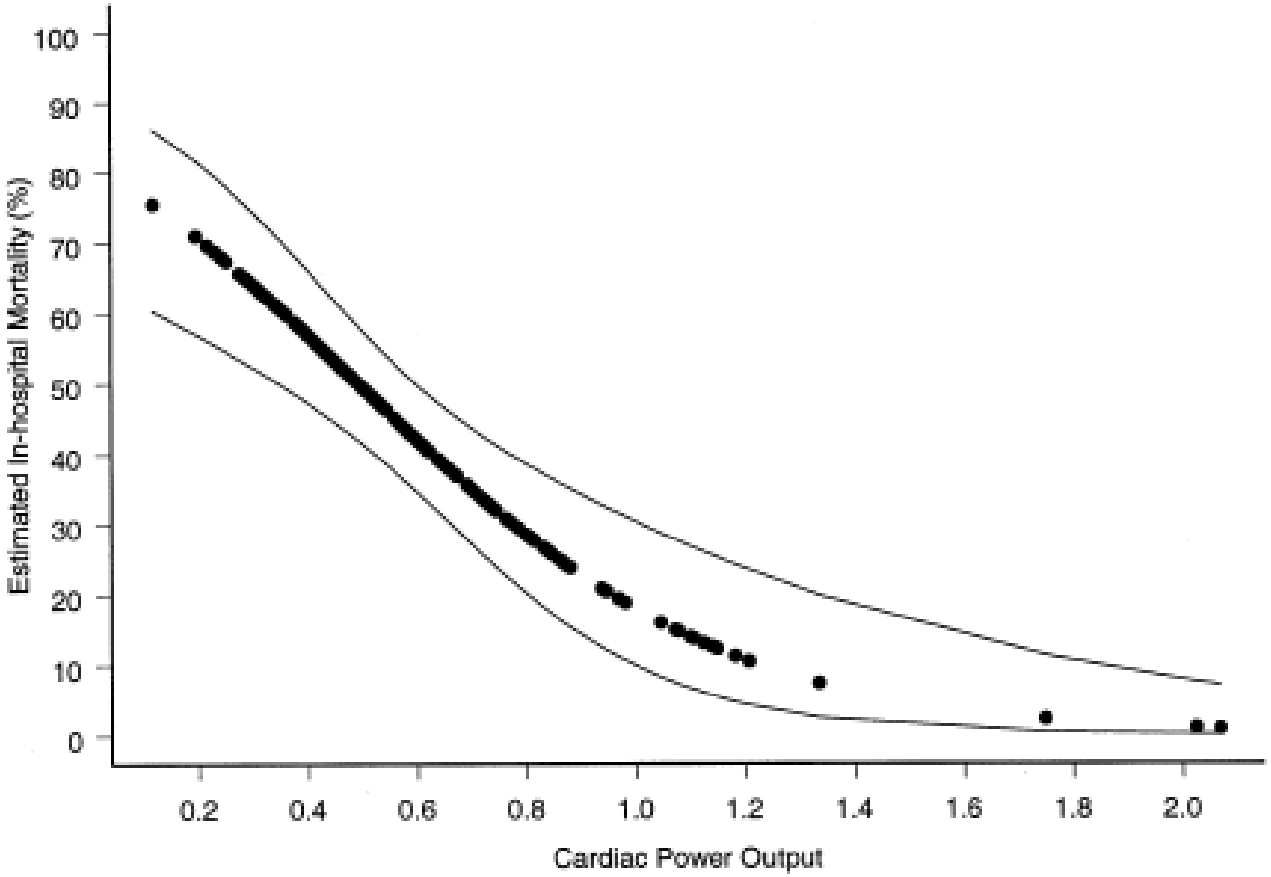
- Haemodynamic criteria (CI, PCWP, PAP, RAP, iEV, iLVSW, iRVSW, function curves of LV/RV)
- $O_2$ extraction
- Organ function (kidney, liver, skin…)
- Different time constants
- When would you define the failure of the positive inotrope ?
- When would you indicate an ventricular assist device ?

# Cardiac Power Is the Strongest Hemodynamic Correlate of Mortality in Cardiogenic Shock: A Report From the SHOCK Trial Registry

Rupert Fincke, MD,* Judith S. Hochman, MD, FACC,† April M. Lowe, MS,‡
Venu Menon, MD, FACC,§ James N. Slater, MD, FACC,† John G. Webb, MD, FACC,‖
Thierry H. LeJemtel, MD, FACC,¶ Gad Cotter, MD, FACC,# for the SHOCK Investigators
*New York and Bronx, New York; Watertown, Massachusetts; Chapel Hill and Durham, North Carolina; and Vancouver, Canada*

J Am Coll Cardiol 2004;44:340–8

CPO = MAP x DC / 451 (W)




J Am Coll Cardiol 2004;44:340–8

# In the cardiocentric view

- There is the confounding effect of HR in CO
  - Increases in HR can compensate for decreased EV
    - It is energetically not good for the heart
    - May explain the lack of beneficial effects of catecholamines on an acute/semi-chronic basis in heart failure
    - No studies have addressed this issue….. properly

STATE-OF-THE-ART PAPER

# Resting Heart Rate in Cardiovascular Disease

Kim Fox, MD, FESC,* Jeffrey S. Borer, MD, FACC,† A. John Camm, MD, FESC, FACC,‡
Nicolas Danchin, MD, FESC,§ Roberto Ferrari, MD, FESC,‖
Jose L. Lopez Sendon, MD, FESC, FACC,¶ Philippe Gabriel Steg, MD, FESC, FACC,#
Jean-Claude Tardif, MD, FACC, FRCPC,** Luigi Tavazzi, MD, FESC, FACC,††
Michal Tendera, MD, FESC, FACC,‡‡ for the Heart Rate Working Group

*London, England; New York, New York; Paris, France; Ferrara and Pavia, Italy; Madrid, Spain; Montreal, Canada; and Katowice, Poland*

J Am Coll Cardiol 2007;50:823–30

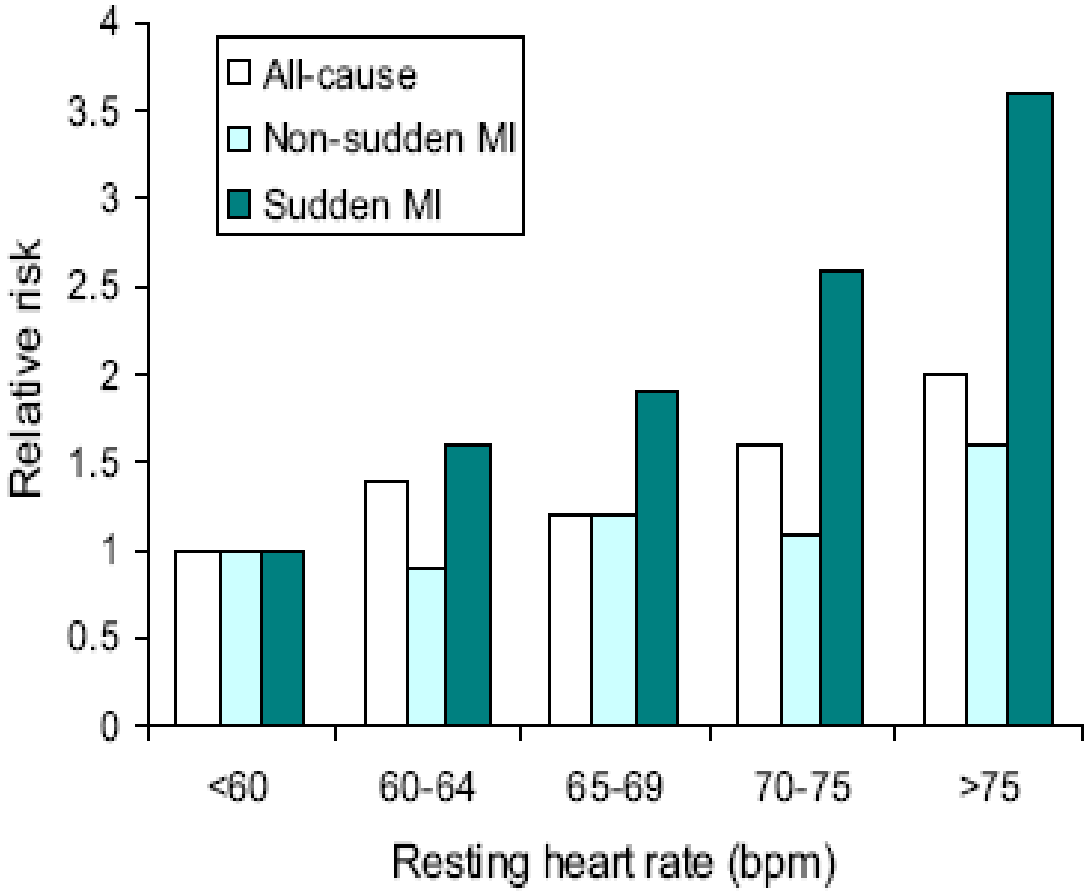



**Figure 1** **Heart Rate and Mortality in Healthy Men**

J Am Coll Cardiol 2007;50:823–30

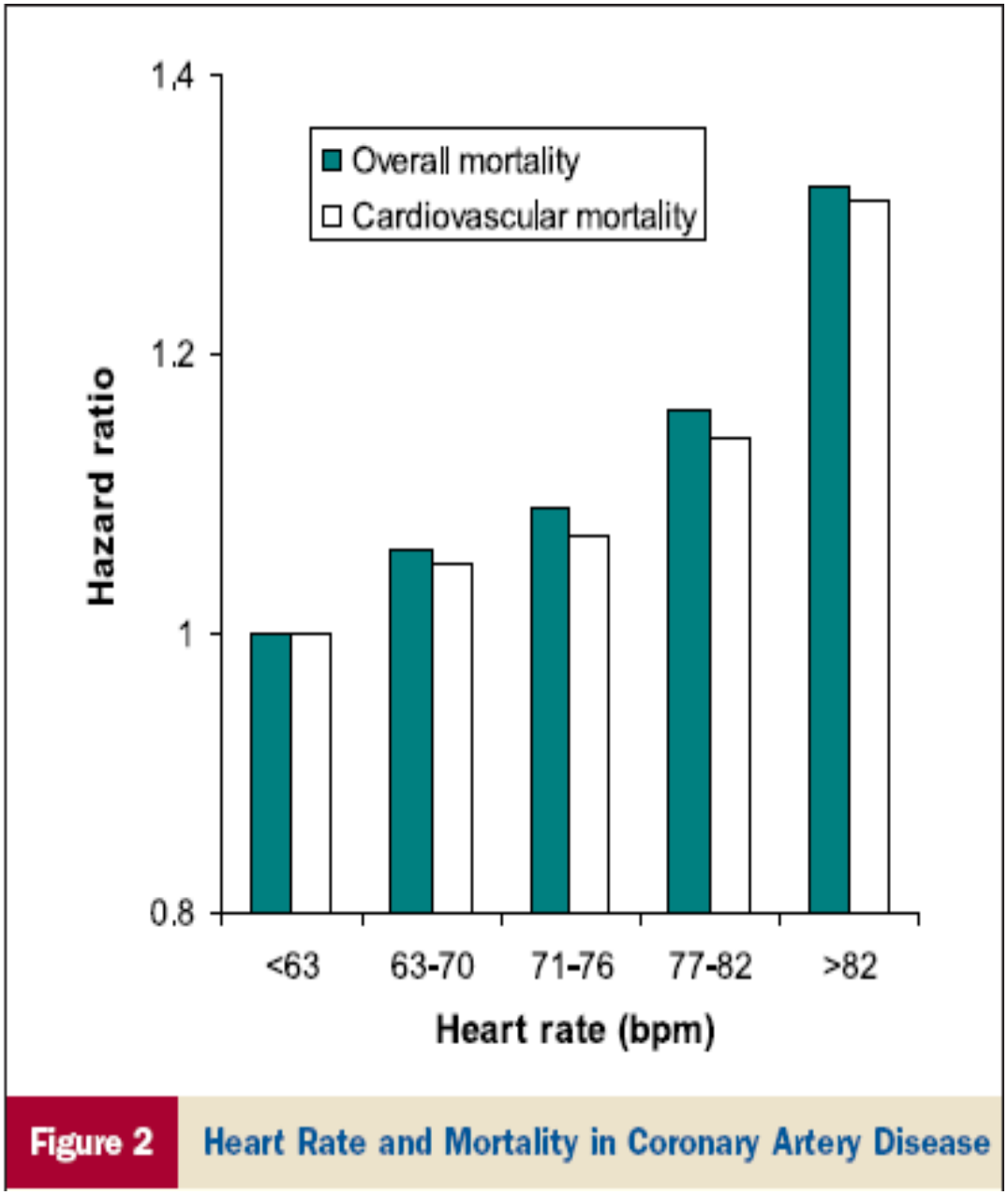



**Figure 2** Heart Rate and Mortality in Coronary Artery Disease

J Am Coll Cardiol 2007;50:823–30

# Integrated

- Venous component of the circulation
  - Congestion
- Interactions RV/LV
- Cardiorespiratory interactions
- Ventricular-large artery coupling
- Intra-organ haemondynamics
  - The waterfall

# Why would vasodilators improve outcome more than inotropes/inodilators ?

## Why would an inodilator *not* improve outcome in patients with heart failure or cardiac dysfunction?

***Dan Longrois[1,2] and Xavier Norel[2]***

[1]Department of Anesthesia and Intensive Care, Hôpital Bichat-Claude Bernard, Assistance Publique-Hôpitaux de Paris, Université Paris Diderot and
[2]Unité INSERM U698, Paris, France

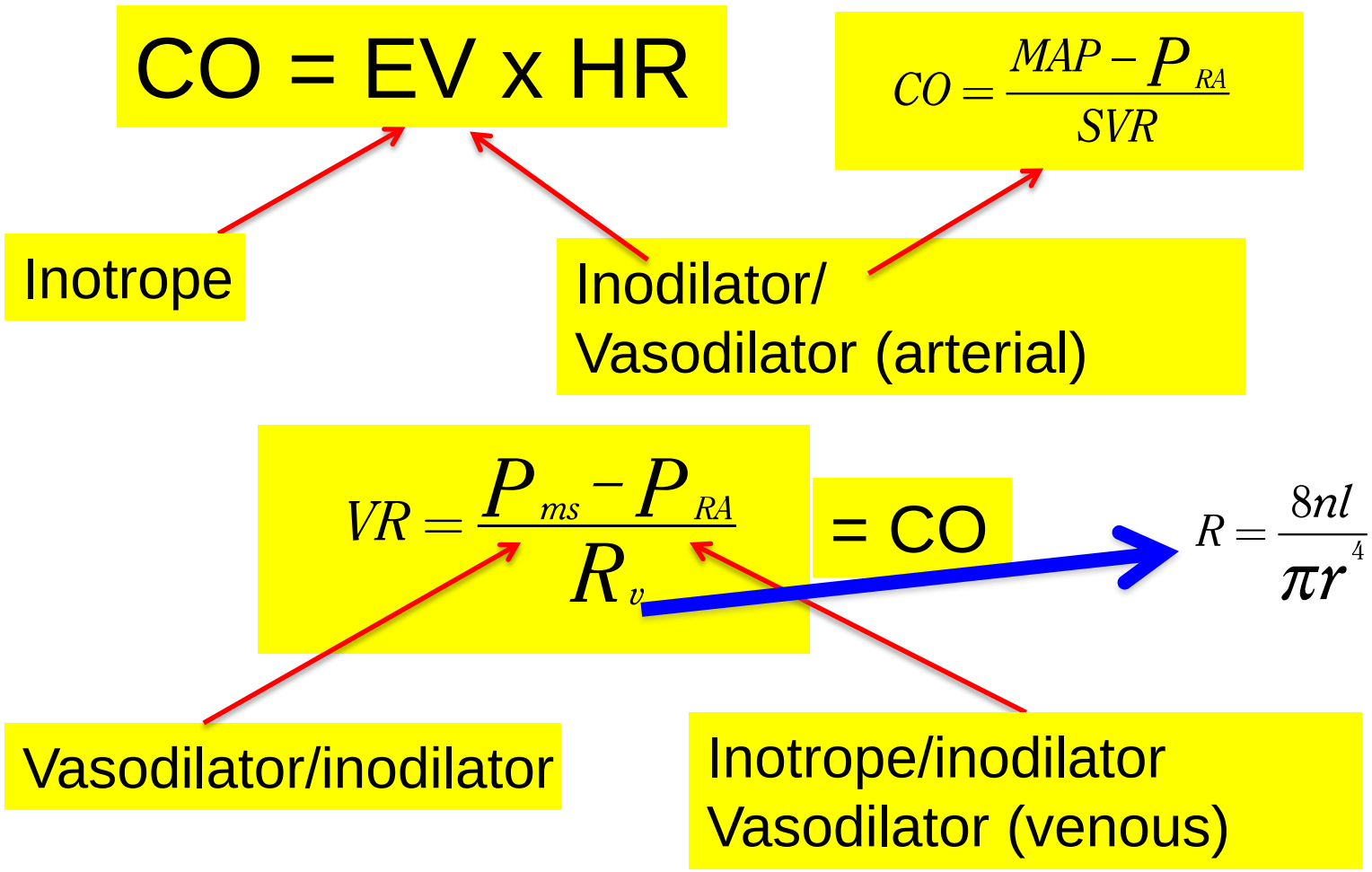
www. Intensetimes.eu

The reshape of paradigm:

From “cardiocentric” to intergrated

# The Role of Venous Return in Critical Illness and Shock—Part I: Physiology

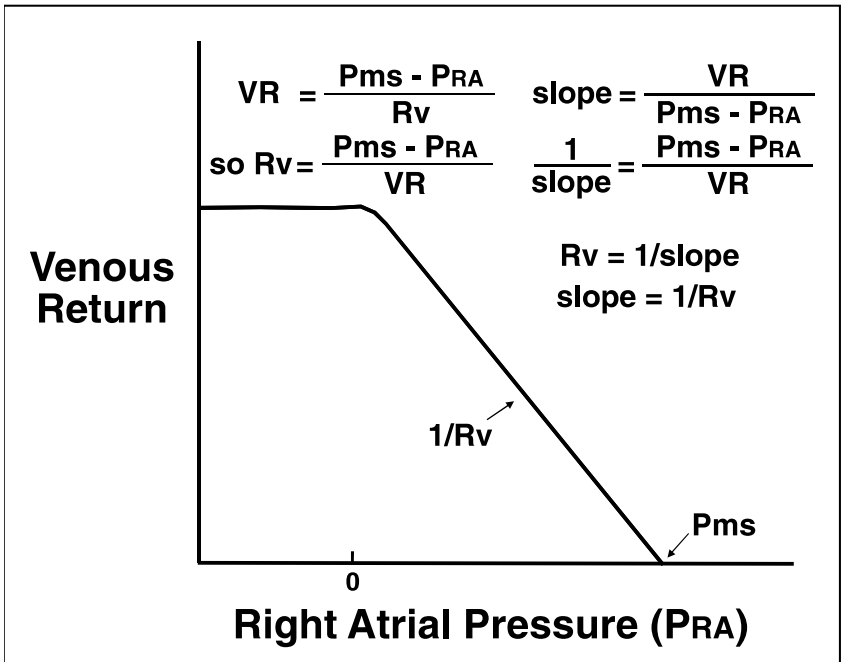
Duane J. Funk, MD[1,2]; Eric Jacobsohn, MD[1,2]; Anand Kumar, MD[1,3]

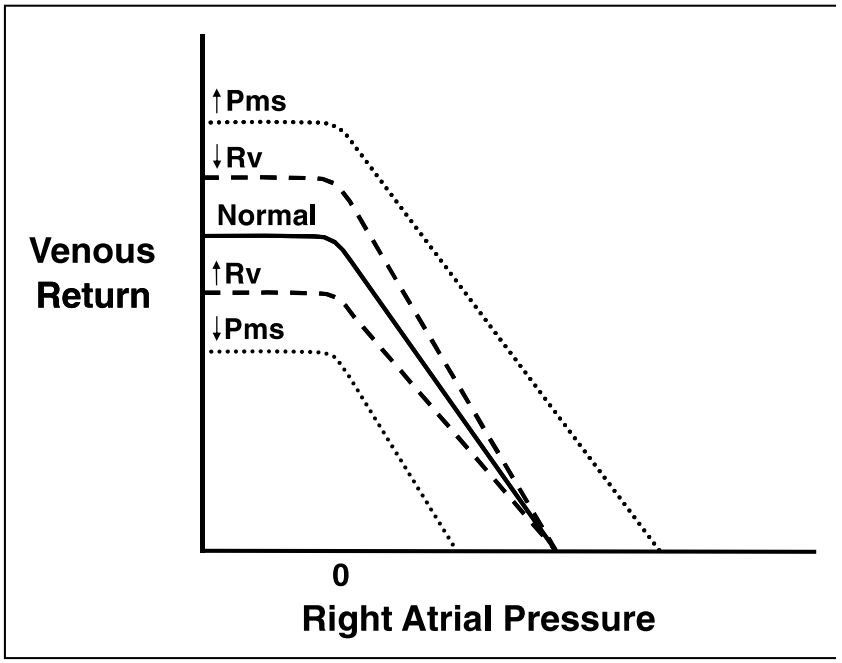



Crit Care Med 2013; 41:255–262

# The Role of Venous Return in Critical Illness and Shock—Part I: Physiology

Duane J. Funk, MD[1,2]; Eric Jacobsohn, MD[1,2]; Anand Kumar, MD[1,3]




Crit Care Med 2013; 41:255–262

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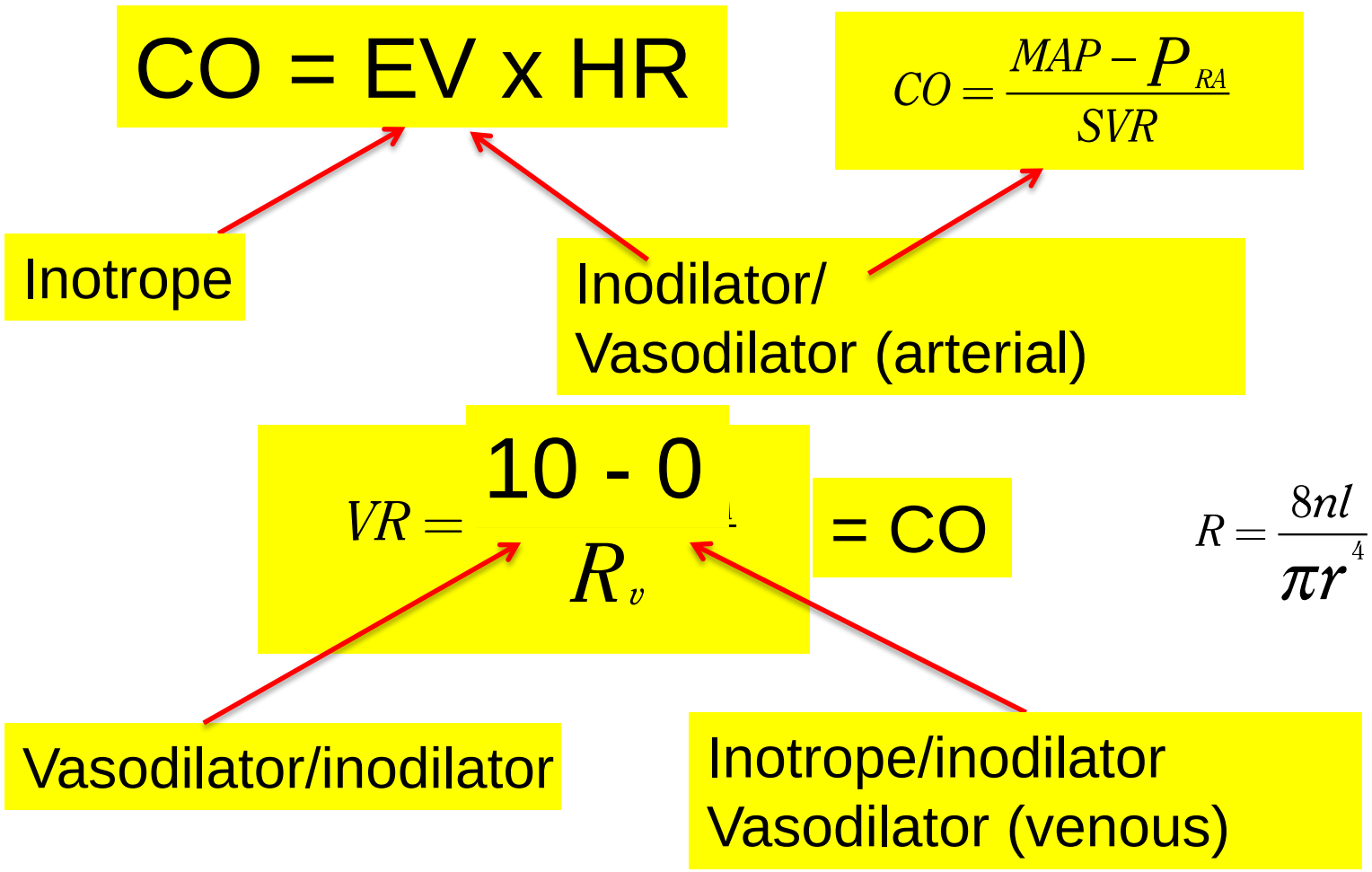



Crit Care Med 2013; 41:255–262

# The Role of Venous Return in Critical Illness and Shock—Part I: Physiology

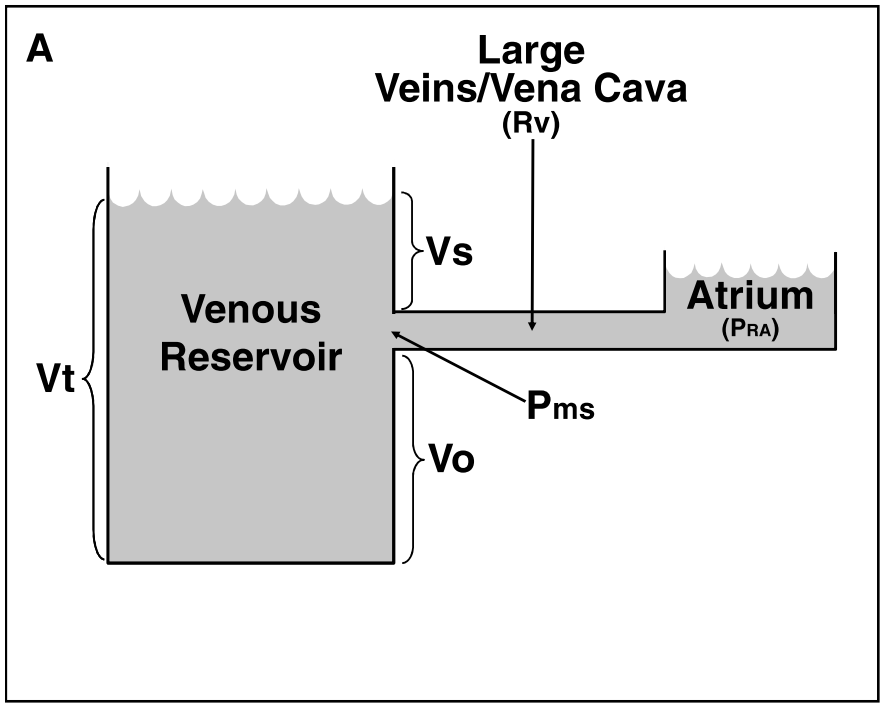
Duane J. Funk, MD[1,2]; Eric Jacobsohn, MD[1,2]; Anand Kumar, MD[1,3]

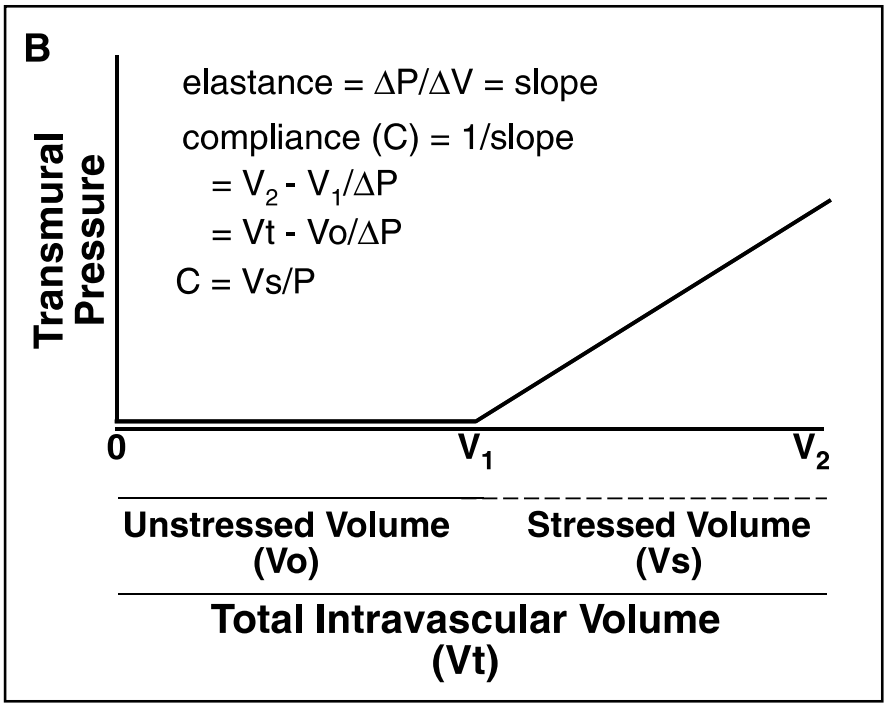
| Structure | Percentage of Total Blood Volume |
|---|---|
| Systemic venous system | 64 |
| Systemic arterial system | 13 |
| Capillaries | 7 |
| Pulmonary circuit | 9 |
| Heart | 7 |

Crit Care Med 2013; 41:255–262

# The Role of Venous Return in Critical Illness and Shock—Part I: Physiology

Duane J. Funk, MD[1,2]; Eric Jacobsohn, MD[1,2]; Anand Kumar, MD[1,3]




Crit Care Med 2013; 41:255–262

# The Role of Venous Return in Critical Illness and Shock—Part I: Physiology

Duane J. Funk, MD[1,2]; Eric Jacobsohn, MD[1,2]; Anand Kumar, MD[1,3]

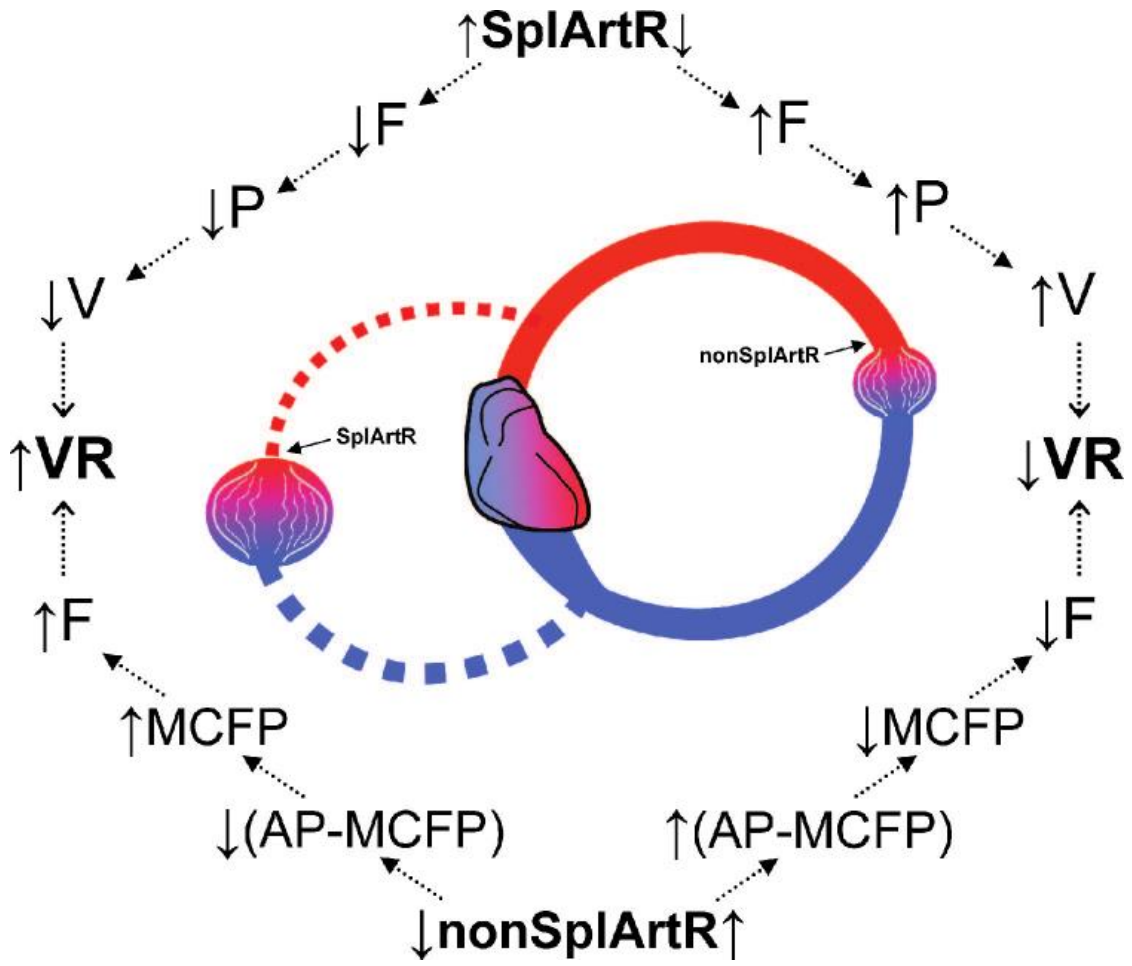
$$P_{ms} = Vs/Csw$$

Vs is stressed blood volume and C is systemic compliance (mean compliance of the cardiovascular circuit). The latter approximates the compliance of the venous reservoir

$$P_{ms} = \frac{V_t - V_o}{C}$$

This equation suggests that $P_{ms}$ can be altered through two basic mechanisms: (1) a change in the total volume in the reservoir (Vt); or (2) a change in the proportion of Vo and Vs (5). Under ideal circumstances, adding or removing volume should increase and decrease Vt and Vs, respectively, without altering Vo. An alteration of autonomic tone, catecholamine stress responses, or infusion of exogenous vasoactive substances will alter the ratio of Vs to Vo without a change in C

Crit Care Med 2013; 41:255–262




Anesthesiology 2008; 108:735– 48

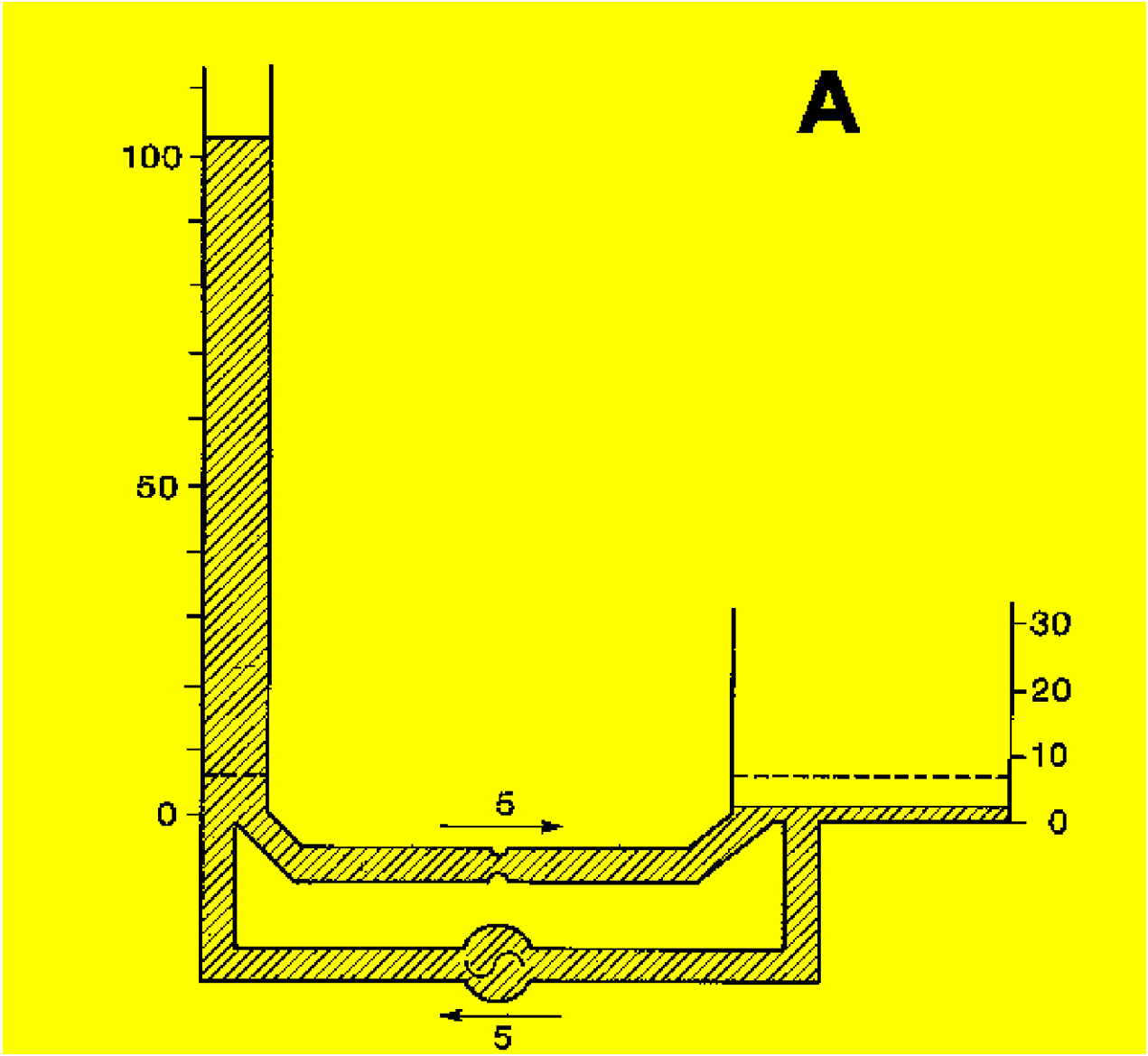
Pflugers Arch - Eur J Physiol (2002) 445:10–17
DOI 10.1007/s00424-002-0922-x

INVITED REVIEW

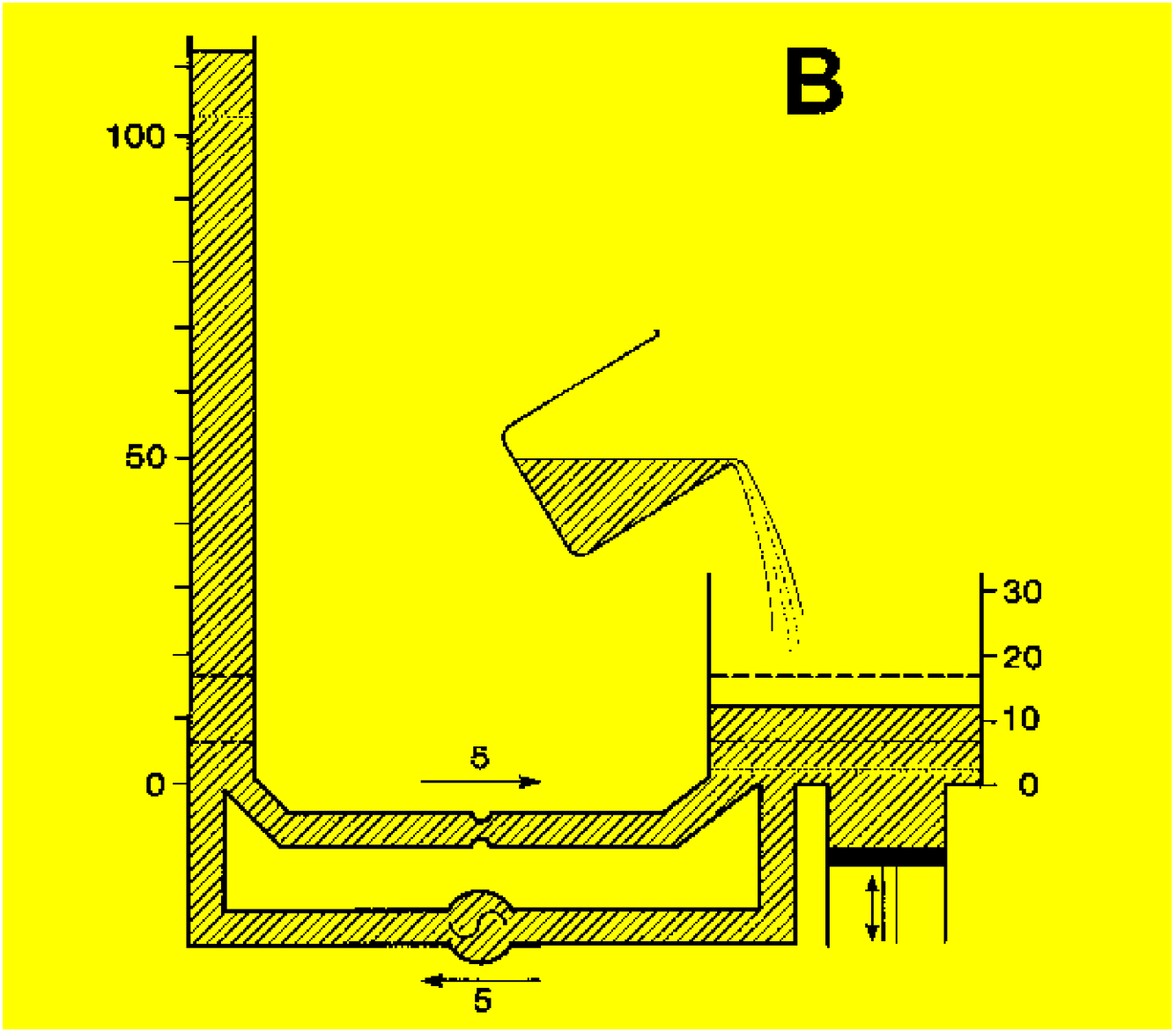
**John V. Tyberg**

# How changes in venous capacitance modulate cardiac output

Pflugers Arch - Eur J Physiol (2002) 445:10–17




Pflugers Arch - Eur J Physiol (2002) 445:10–17




Pflugers Arch - Eur J Physiol (2002) 445:10–17

# Normal SNS activation

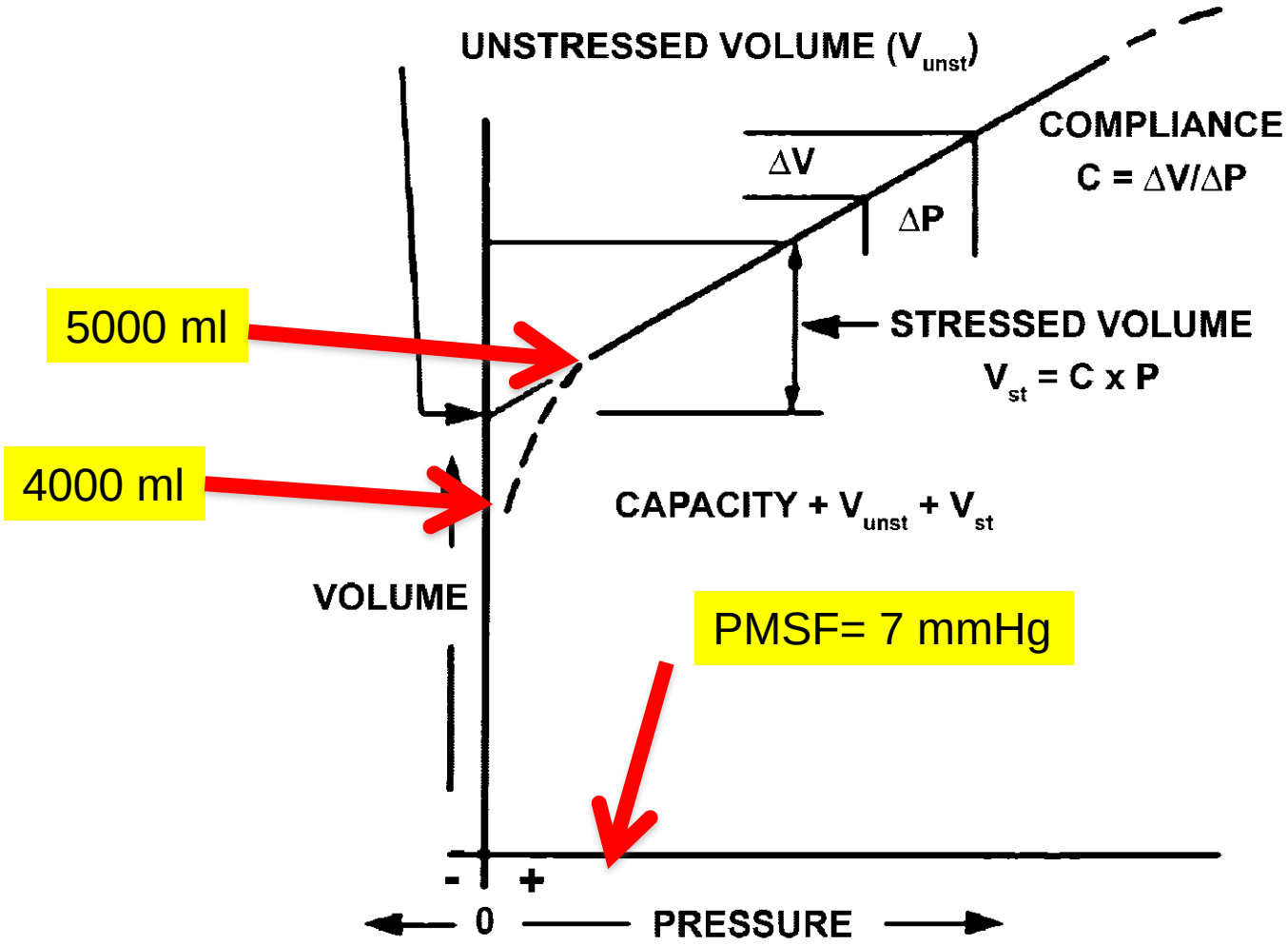
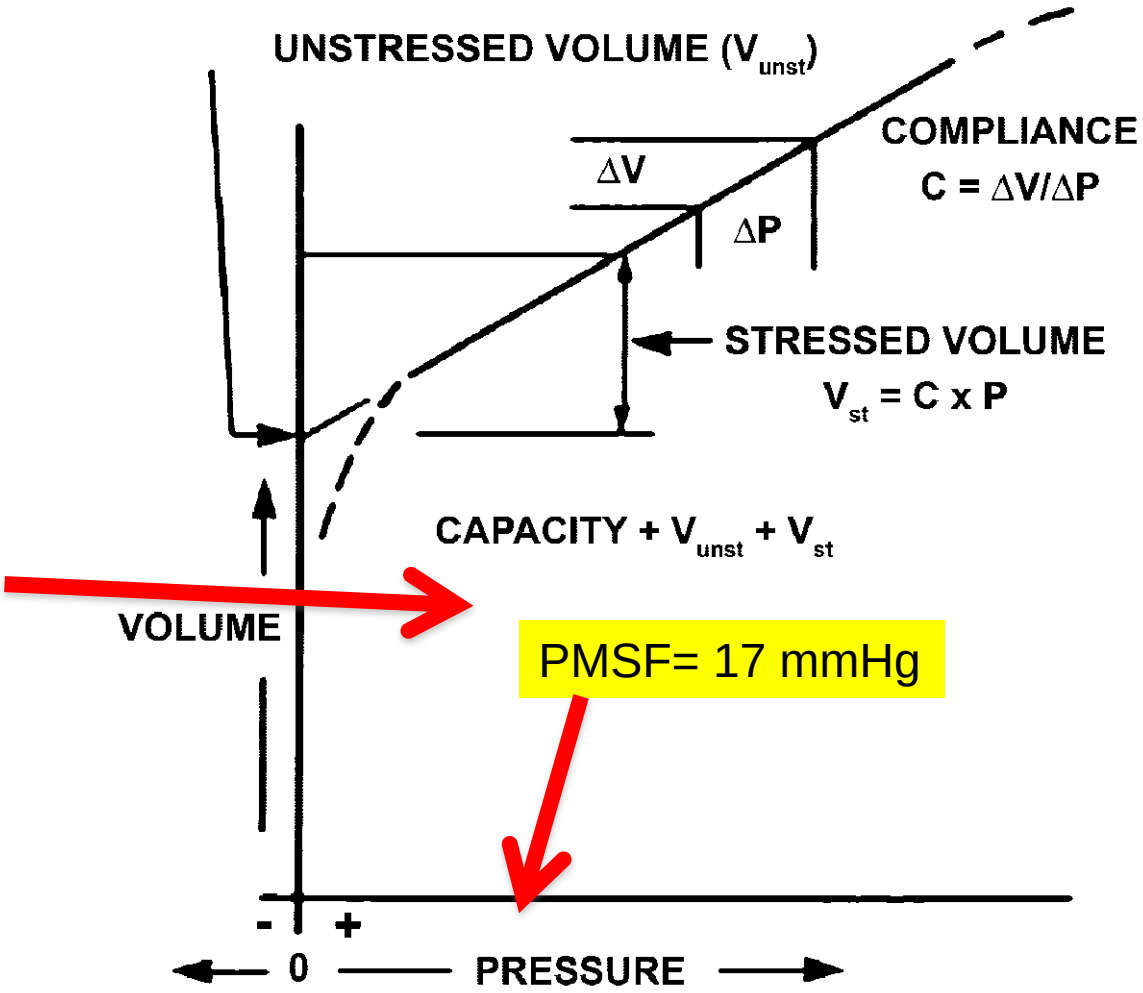



Fig. 1. Vascular capacitance definitions. Reprinted from *Encyclopedia of Human Biology,* Volume 8, page 626, 1997, with permission from Elsevier.

# Maximal SNS activation




3400 ml

PMSF= 17 mmHg

Fig. 1. Vascular capacitance definitions. Reprinted from *Encyclopedia of Human Biology,* Volume 8, page 626, 1997, with permission from Elsevier.

# Minimal SNS activation (anesthesia ? )

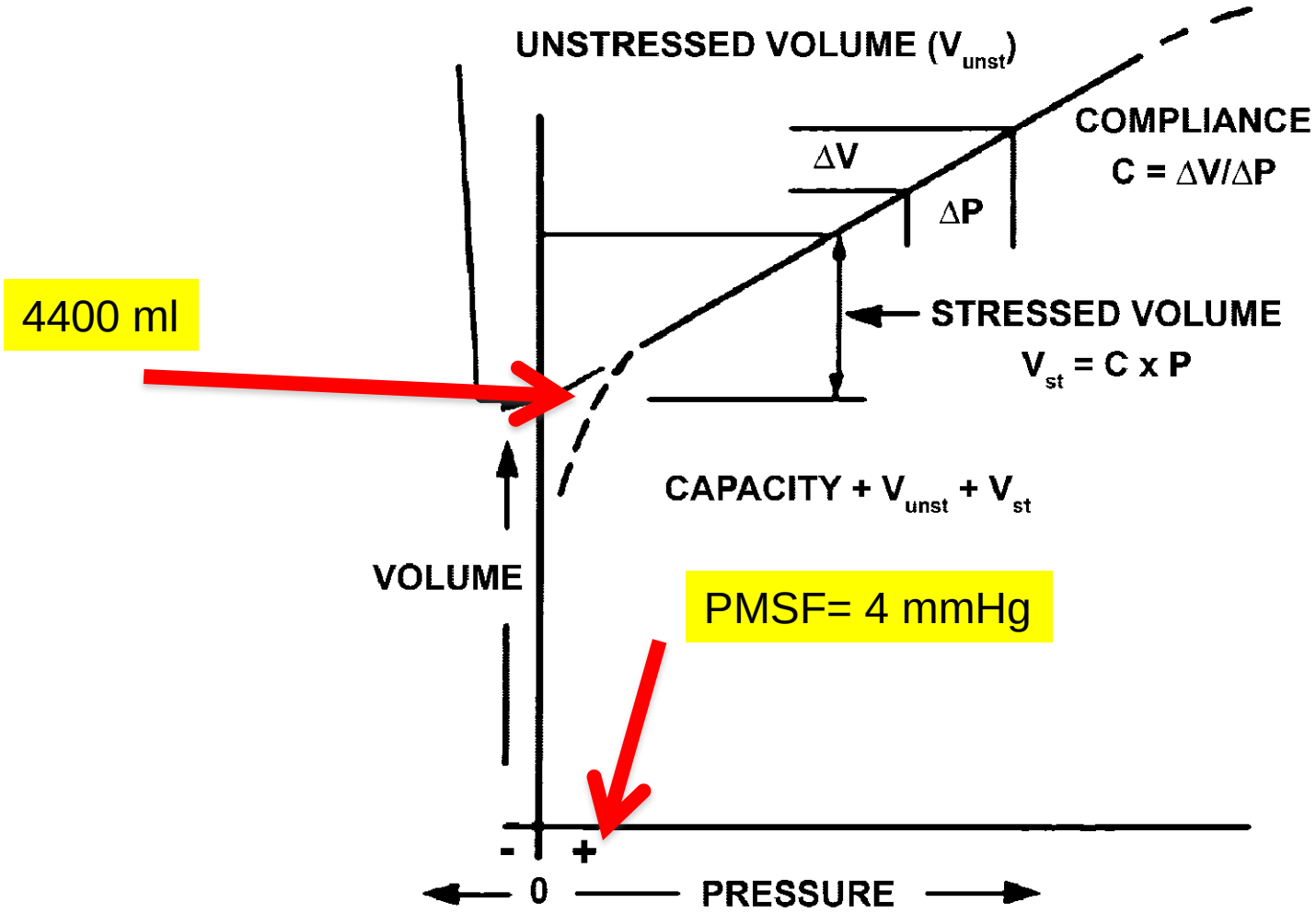



Fig. 1. Vascular capacitance definitions. Reprinted from *Encyclopedia of Human Biology,* Volume 8, page 626, 1997, with permission from Elsevier.

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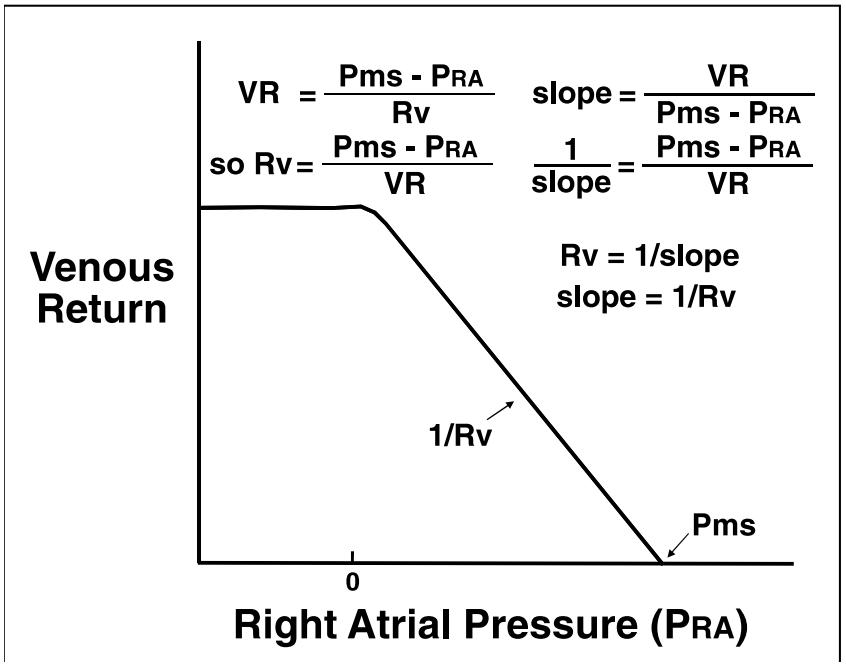
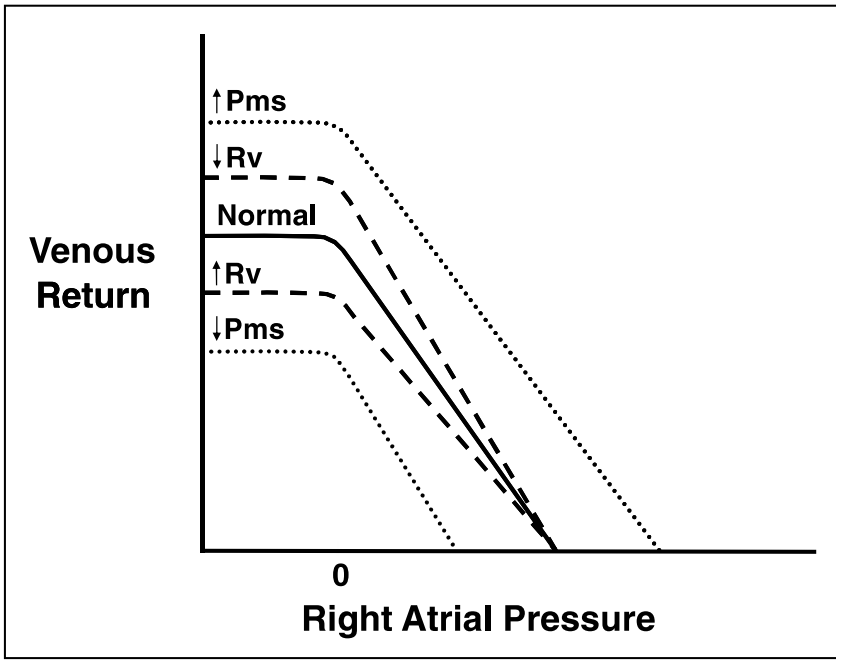



Crit Care Med 2013; 41:255–262

ELSEVIER

Pharmacology & Therapeutics 90 (2001) 179–230

Pharmacology & Therapeutics

# Autonomic control of the venous system in health and disease
## Effects of drugs

Catherine C.Y. Pang*

*Department of Pharmacology and Therapeutics, Faculty of Medicine, The University of British Columbia, 2176 Health Sciences Mall, Vancouver, B.C., Canada, V6T 1Z3*

C.C.Y. Pang / Pharmacology & Therapeutics 90 (2001) 179–230

# KEY MESSAGES (1)

- Mean venous pressure in humans
  - 10 to 15 mm Hg in small venules
  - 4 to 8 mm Hg in peripheral veins
  - 1 to 2 mm Hg in the vena cavae
- THE GRADIENT THAT IS RESPONSIBLE for venous return (cardiac output) is less than 10 mmHg
- Given the very high compliance of the venous system, an increase in CVP is much more likely to be due to decreased venous compliance and not to increased intravascular volume.
- Plus retrograde increase in CVP due to HF ?

C.C.Y. Pang / Pharmacology & Therapeutics 90 (2001) 179–230

# Who would attempt to define congestion ?

(in heart failure for instance)

Circulation
Heart Failure
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

**Sympathetically Mediated Changes in Capacitance : Redistribution of the Venous Reservoir as a Cause of Decompensation**

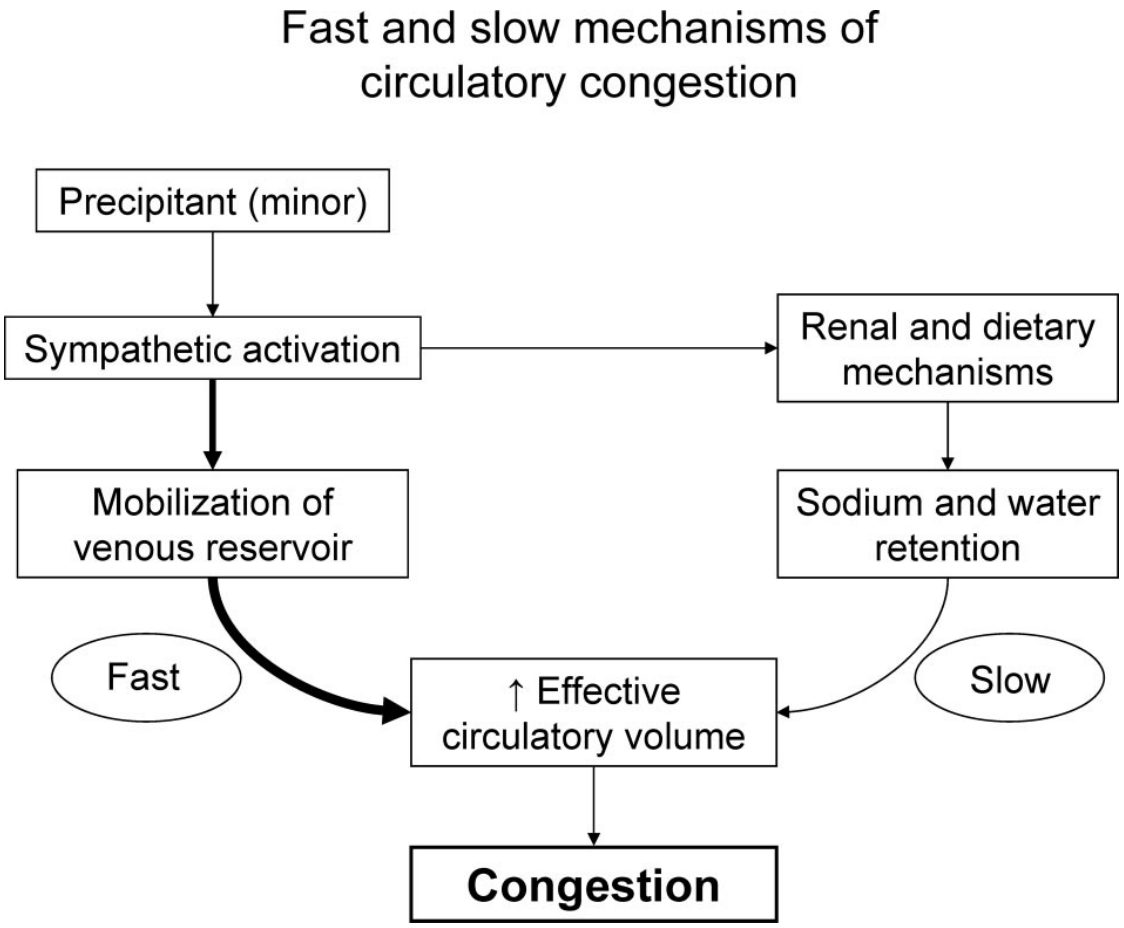
Catherine Fallick, Paul A. Sobotka and Mark E. Dunlap

*Circ Heart Fail* 2011;4;669-675;
DOI: 10.1161/CIRCHEARTFAILURE.111.961789
Circulation: Heart Failure is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-3289. Online ISSN: 1941-3297

*"To be accepted as a paradigm, a theory must seem better than its competitors, but it need not, and in fact never does, explain all the facts with which it can be confronted."*

—Thomas Kuhn, *The Structure of Scientific Revolutions*

## Heard on Rounds




**Increased Volume Is Neither Necessary Nor Sufficient to Cause Congestion**

*Circ Heart Fail* 2011;4;669-675;

European Journal of Heart Failure (2010) 12, 423–433
doi:10.1093/eurjhf/hfq045

REVIEW

# Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine

Mihai Gheorghiade[1], Ferenc Follath[2], Piotr Ponikowski[3], Jeffrey H. Barsuk[4], John E.A. Blair[5], John G. Cleland[6], Kenneth Dickstein[7,8], Mark H. Drazner[9], Gregg C. Fonarow[10], Tiny Jaarsma[11], Guillaume Jondeau[12], Jose Lopez Sendon[13], Alexander Mebazaa[14,15], Marco Metra[16], Markku Nieminen[17], Peter S. Pang[18], Petar Seferovic[19], Lynne W. Stevenson[20], Dirk J. van Veldhuisen[21], Faiez Zannad[22], Stefan D. Anker[22], Andrew Rhodes[23], John J.V. McMurray[24], and Gerasimos Filippatos[25]*

European Journal of Heart Failure (2010) 12, 423–433

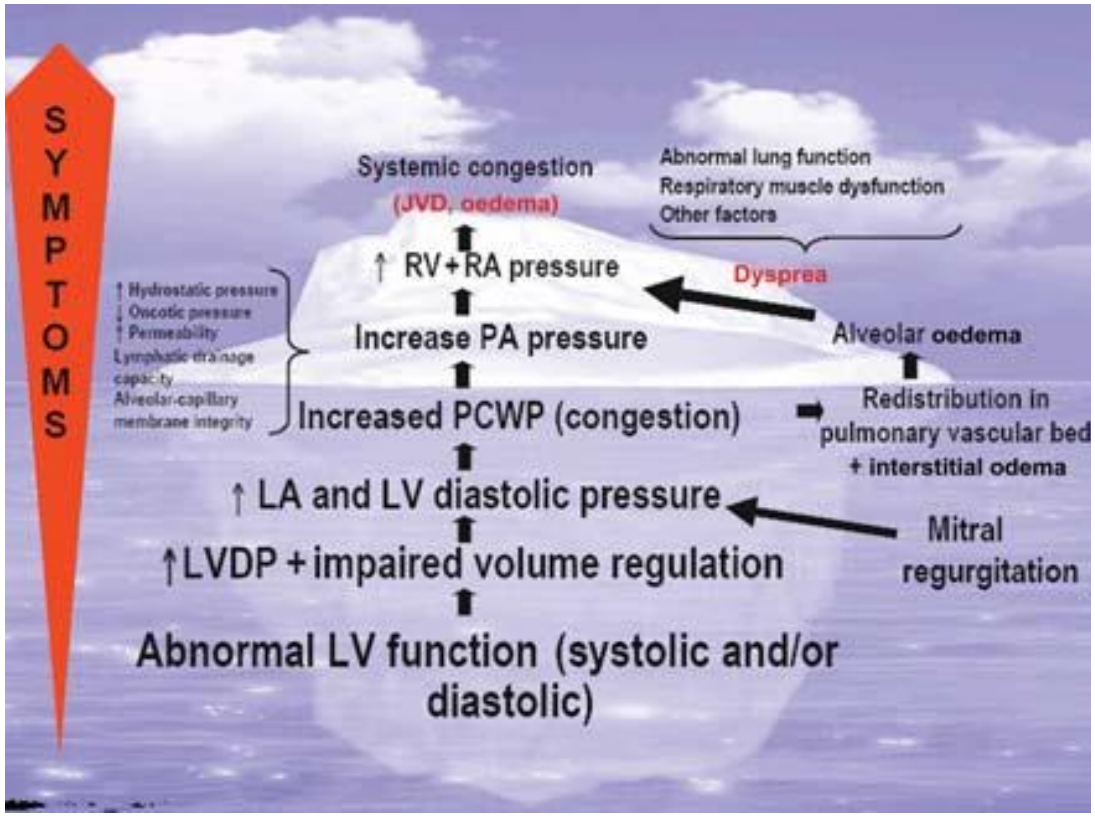



**Figure 1** Pathophysiology of congestion. RV, right ventricular; RA, right atrial; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; LA, left atrial; LV, left ventricular; LVDP, left ventricular diastolic pressure; JVD, jugular venous distension.

Increased LVEDP
("left side" congestion)

Increased RVEDP
("right side" congestion)
-Isolated
-Secondary to Increased LVEDP

European Journal of Heart Failure (2010) 12, 423–433

**Table 1 Diagnostic value of clinical markers of congestion**

| Sign or symptom | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| Dyspnoea on exertion | 66 | 52 | 45 | 27 |
| Orthopnoea | 66 | 47 | 61 | 37 |
| Oedema | 46 | 73 | 79 | 46 |
| Resting JVD | 70 | 79 | 85 | 62 |
| S3 | 73 | 42 | 66 | 44 |
| Chest X-ray | | | | |
| Cardiomegaly | 97 | 10 | 61 | — |
| Redistribution | 60 | 68 | 75 | 52 |
| Interstitial oedema | 60 | 73 | 78 | 53 |
| Pleural effusion | 43 | 79 | 76 | 47 |

European Journal of Heart Failure (2010) 12, 423–433

# Gheorghiade de al. conclude

- Congestion is a very frequent clinical problem in AHF/ADHF syndromes
- Is probably also a problem (with differences) in ICU patients
- Diagnosis is difficult
- Evaluation is complex
- Is associated with worse outcome initially and at distance

European Journal of Heart Failure (2010) 12, 423–433

# The questions raised by the article of Gheorghiade et al.

- Increased LVEDP/ RVEDP may be a problem of:
  - Systolic RV/LV dysfunction
  - Diastolic RV/LV dysfunction
  - Increased volemia
  - Normo-/ hypovolemia and decreased venous (pulmonary and systemic) compliance
    - Secondary to activation of the SNS
- Does not clearly state that congestion and volume overload are not similar
  - In routine clinical practice this results in the fact that diuretics are the (only) solution to congestion

European Journal of Heart Failure (2010) 12, 423–433

# A few considerations on “left side congestion”

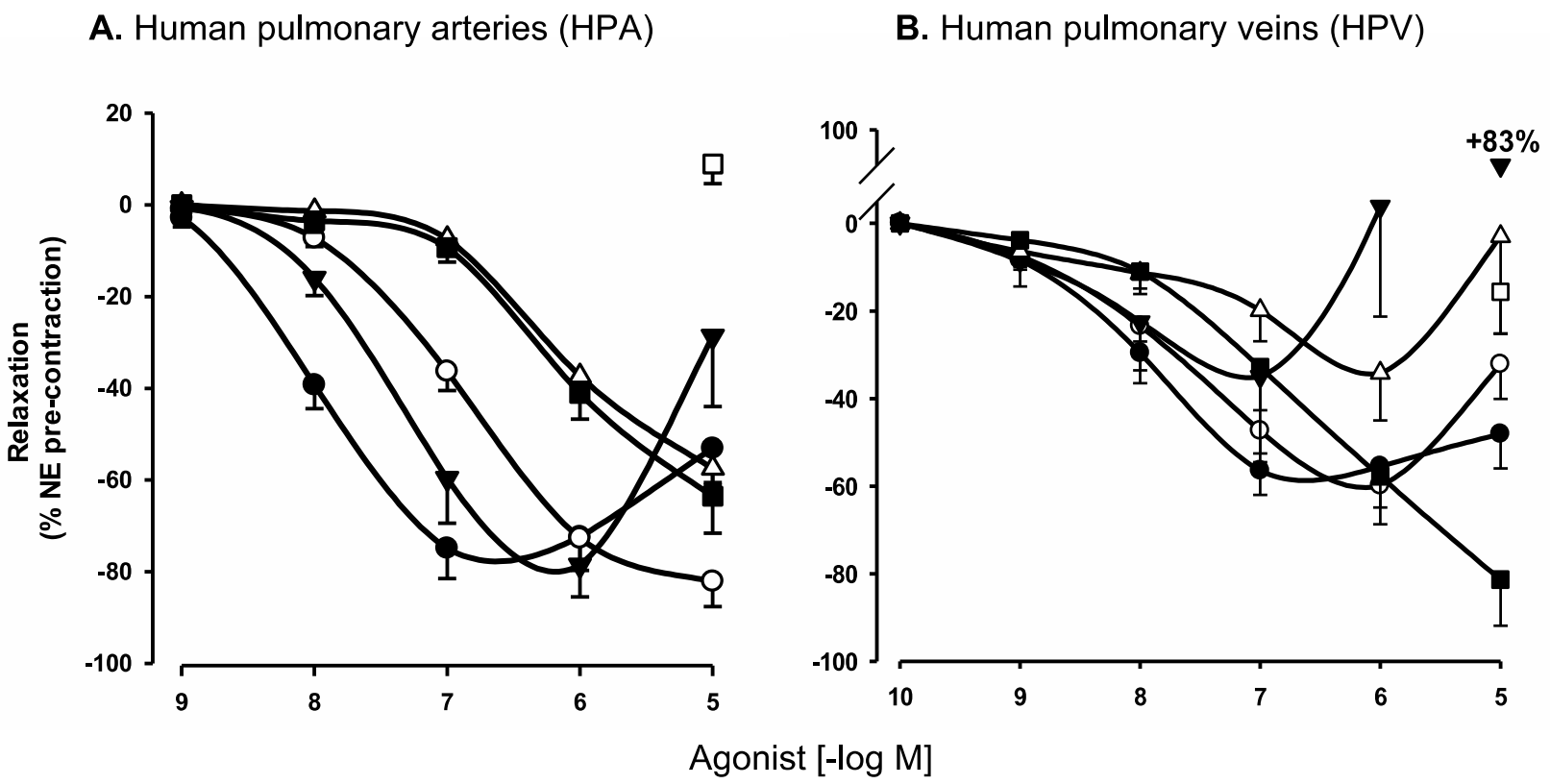
What is the role of pulmonary veins in the transpulmonary vascular resistance ?

A comparative study of $PGI_2$ mimetics used clinically on the vasorelaxation of human pulmonary arteries and veins, role of the DP-receptor

Chabha Benyahia[a,b], Kamel Boukais[a,c], Ingrid Gomez[a,b], Adam Silverstein[d], Lucie Clapp[e], Aurélie Fabre[f], Claire Danel[f], Guy Leséche[f], Dan Longrois[a,b,f], Xavier Norel[a,b,*]

[a] *INSERM U698, CHU X. Bichat, 46 rue H. Huchard, Paris 75018, France*
[b] *Paris Nord University, Sorbonne Paris Cité, UMR-S698, Paris F-75018, France*
[c] *Paris Descartes University, Sorbonne Paris Cité, UMR-S698, Paris F-75018, France*
[d] *United Therapeutics, Research Triangle Park, NC 27709, USA*
[e] *Department of Medicine, University College London, London WC1E 6JF, UK*
[f] *CHU X. Bichat, Assistance Publique-Hôpitaux de Paris, Paris Diderot University, Sorbonne Paris Cité, UMR-S698, Paris F-75018, France*

Prostaglandins & other Lipid Mediators 107 (2013) 48–55




●Iloprost (n = 23-19), ○Treprostinil (n = 33-28), ▼ Beraprost (n = 7-5), Δ $PGI_2$ (n = 5-4), ■ MRE-269 (n = 15-9), □Time Control (n = 7-3).

Prostaglandins & other Lipid Mediators 107 (2013) 48–55

# Ventricular-large artery coupling

LV-Ao

RV-PA

Nephrol Dial Transplant (2010) 25: 3815–3823
doi: 10.1093/ndt/gfq614
Advance Access publication 14 October 2010

*Editorial Reviews*

NDT
Nephrology Dialysis Transplantation

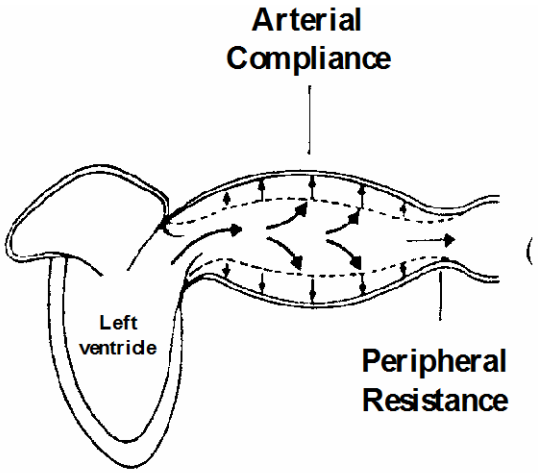
# Arterial functions: how to interpret the complex physiology

Gerard M. London and Bruno Pannier

Nephrol Dial Transplant (2010) 25: 3815–3823

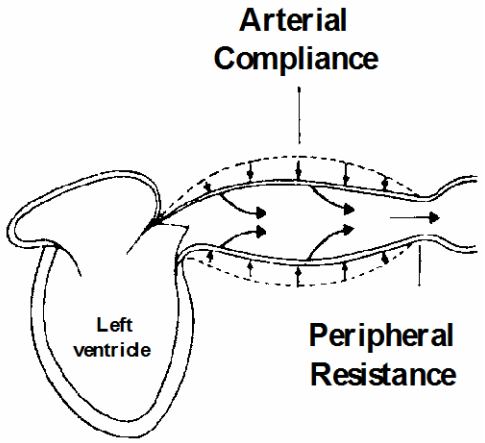
## A. Systole

In normally compliant arterial system important part of the stroke volume is stored in the arteries during ventricular systole stretching the arterial walls




## B. Diastole

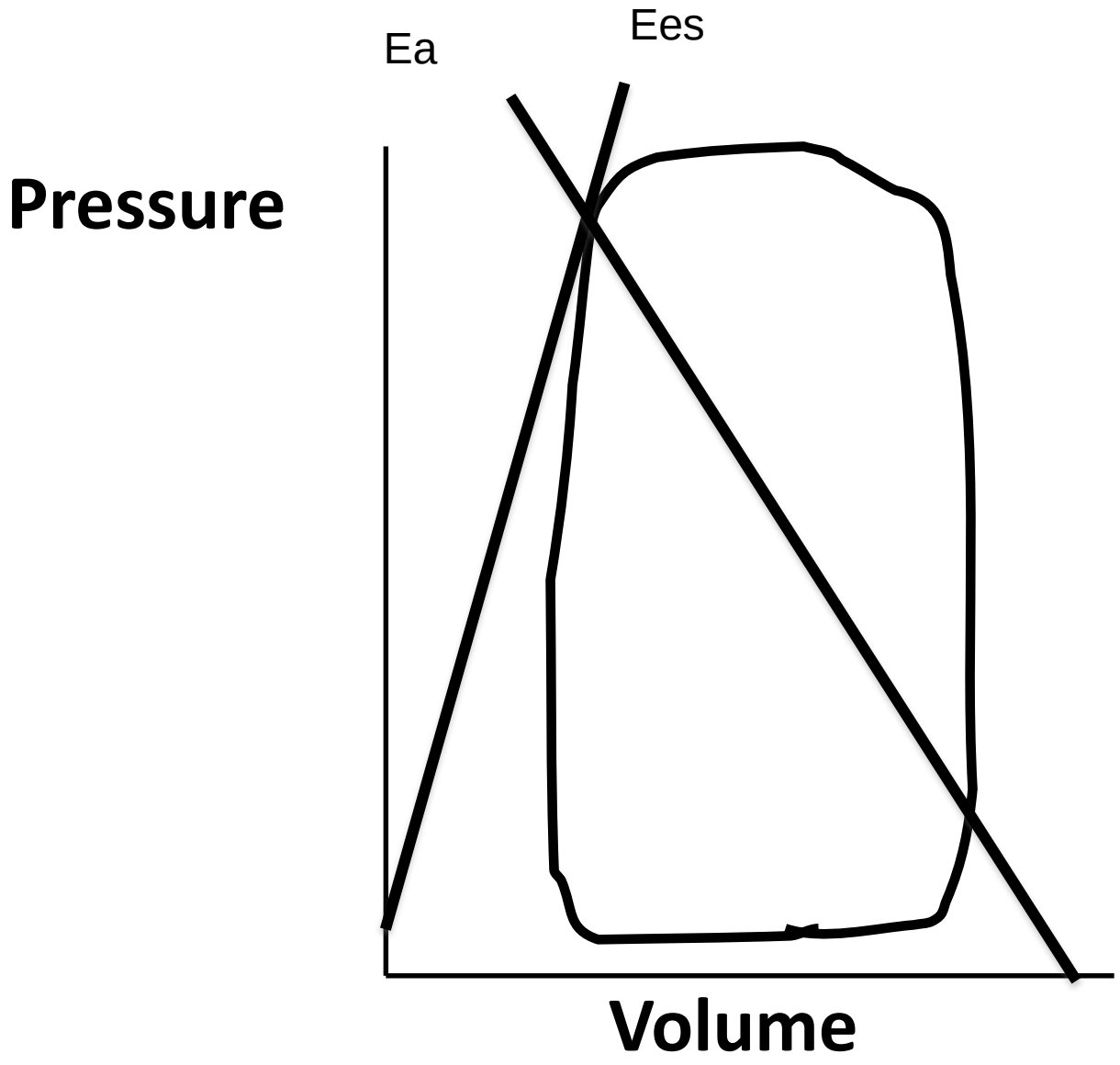
During ventricular diastole the previously stretched arterial walls recoils with the stored volume insuring continuous perfusion of tissues and organs



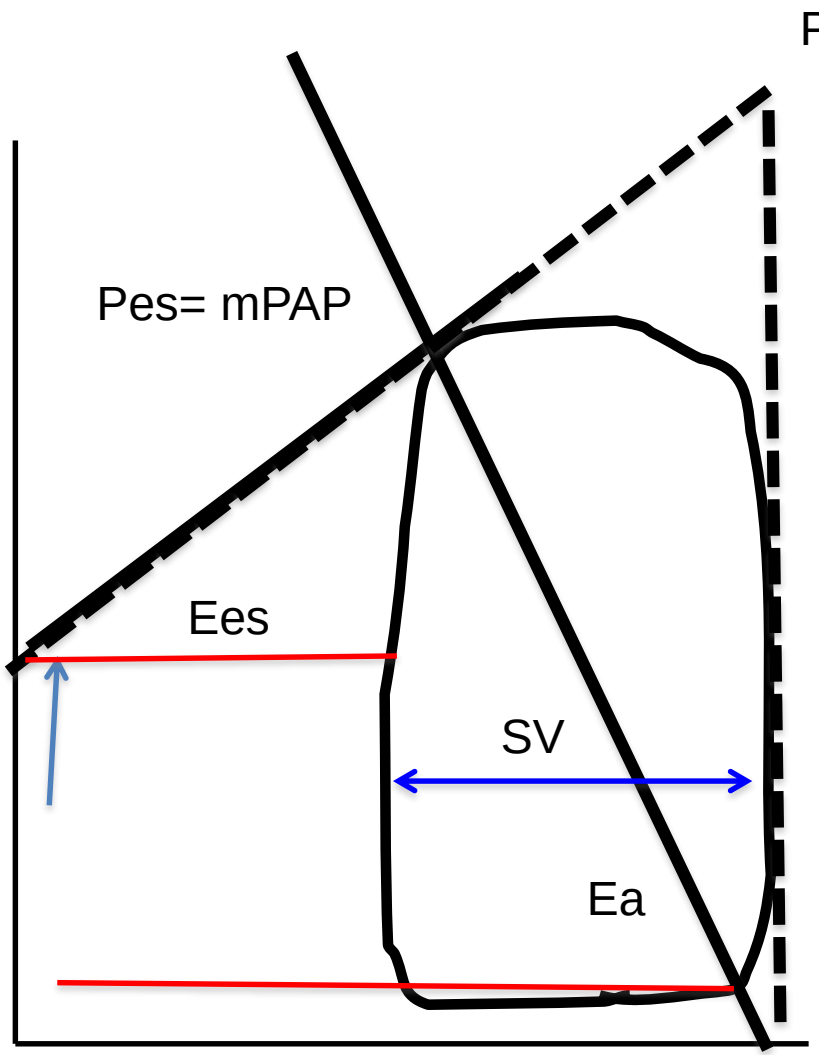

Nephrol Dial Transplant (2010) 25: 3815–3823

# THE message

- SVR/PVR (non pulsatile) are not the only determinant of the ventricular afterload
- Mechanical properties of the AO/PA are the pulsatile component of the afterload and are very important
  - Chronic and acute basis


Ea
Ees
Pressure
Volume

**RV Pressure**



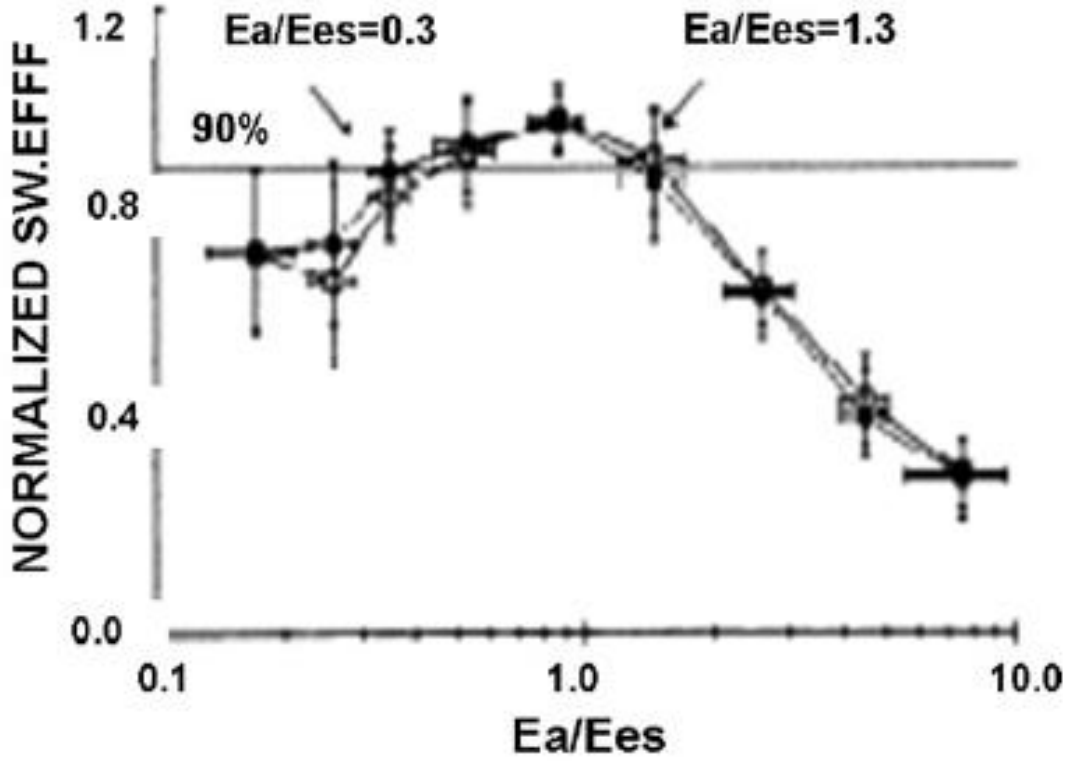

**RV Volume**

$$Ees = \frac{Pmax - mPAP}{SV}$$

$$Ea = \frac{mPAP}{SV}$$

De Tombe et al. Am J Physiol 264:H1817-H18248 1993

# Ventricular-arterial coupling

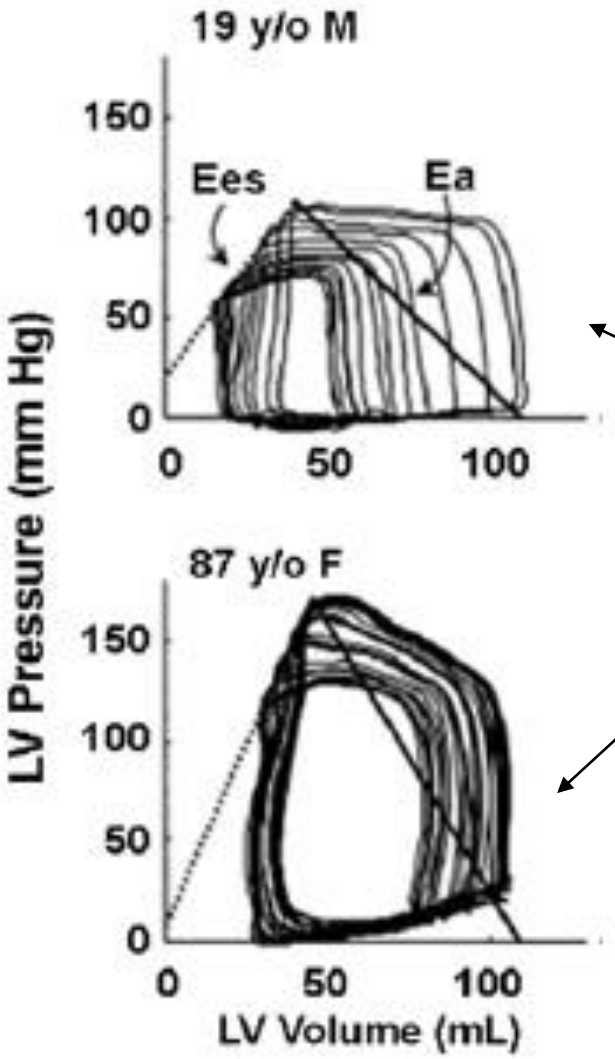



Ea is a measure of impedance (being influenced by static and pulsatile afterload and by heart rate) and is calculated as
the ratio of systolic pressure/stroke volume
Ees is the slope of the end-systolic pressure-volume relation..

# Ea/ Ees ratio

- Physiologic increase of Ea with age
  - Stiffening of large arteries
- Physiologic increase of Ees with age
  - Ea/Ees ratio in healthy elderly patients is maintained close to 1.
- In normal subjects
  - 0.7-1
- In CHF patients
  - Up to 4
    - Decreased Ees (decreased systolic function)
    - Increased Ea (increased systemic vascular resistance)

A

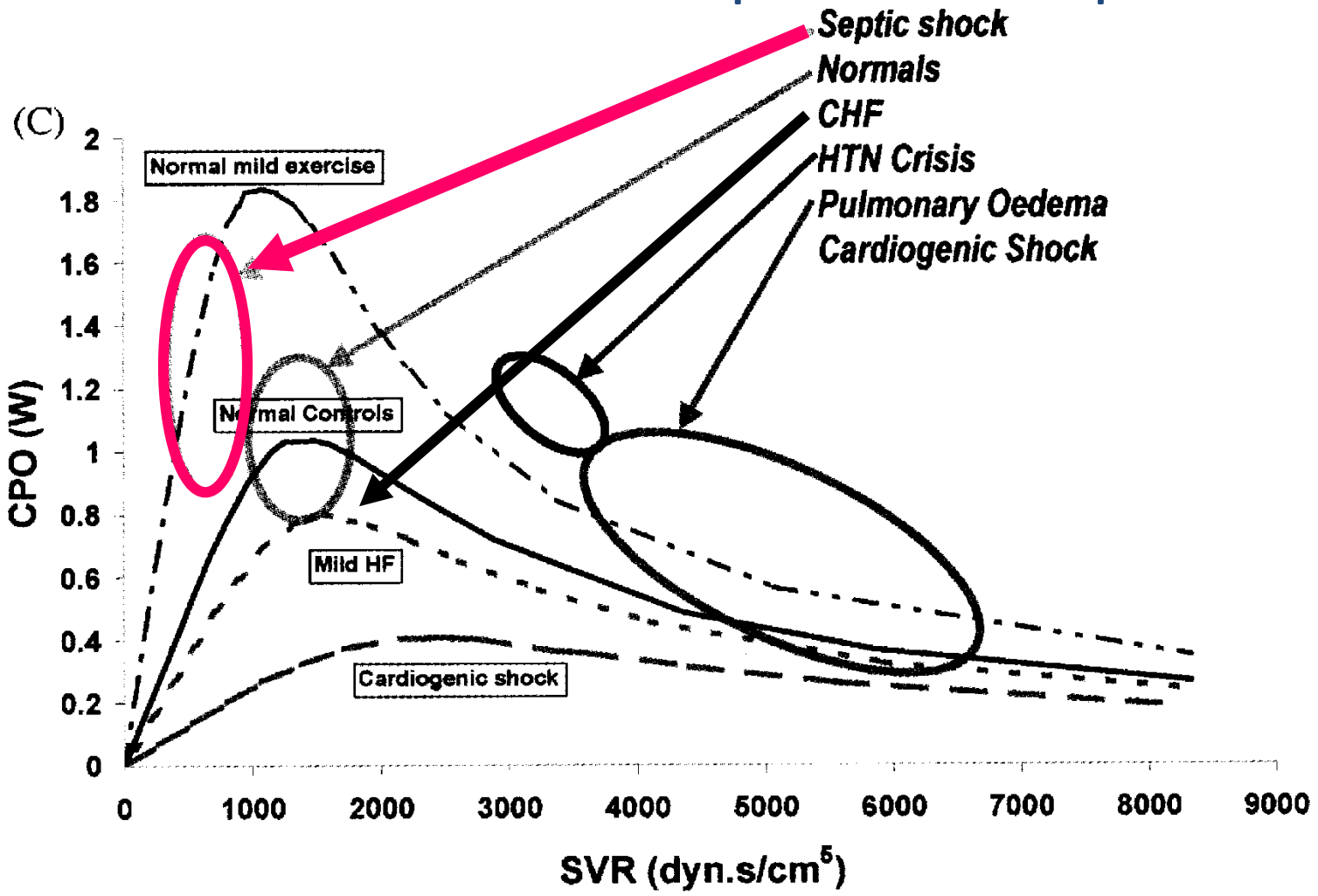



Slopes of volume vs pressure different despite similar Ea/Ees values

Greater variability of pressure with changes in central volume in the elderly patients

J Am Coll Cardiol 32:1221-1227, 1998

# Interactions cardiac output-arterial pressure




The role of cardiac power and systemic vascular resistance in the pathophysiology and diagnosis of patients with acute congestive heart failure. Cotter et al. Eur. J. Heart Fail. 2003;5: 443-415 + **Editoria**l

# Nitroprusside in Critically Ill Patients with Left Ventricular Dysfunction and Aortic Stenosis

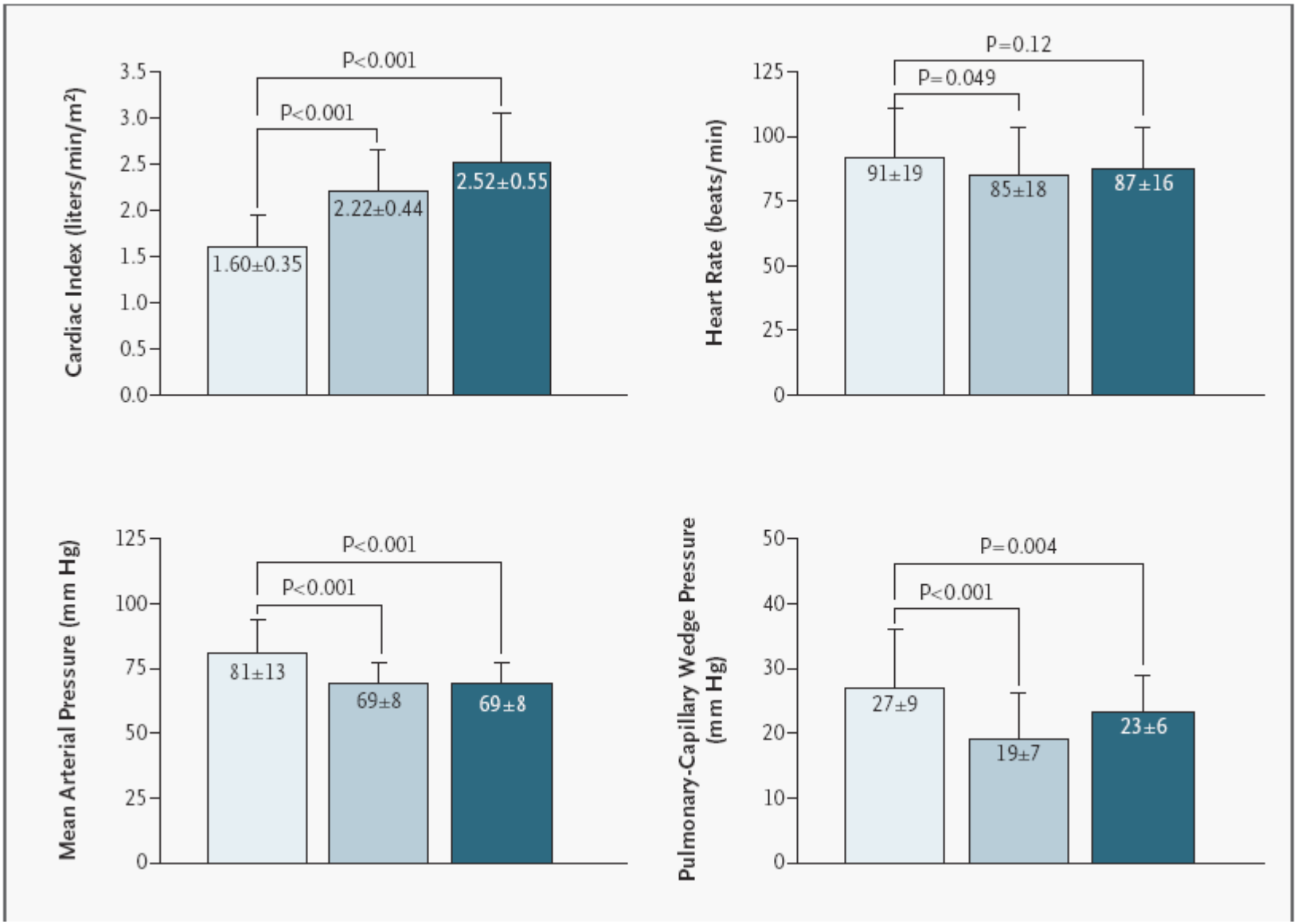
Umesh N. Khot, M.D., Gian M. Novaro, M.D., Zoran B. Popović, M.D., Roger M. Mills, M.D., James D. Thomas, M.D., E. Murat Tuzcu, M.D., Donald Hammer, M.D., Steven E. Nissen, M.D., and Gary S. Francis, M.D.

**N Engl J Med 2003;348:1756-63.**

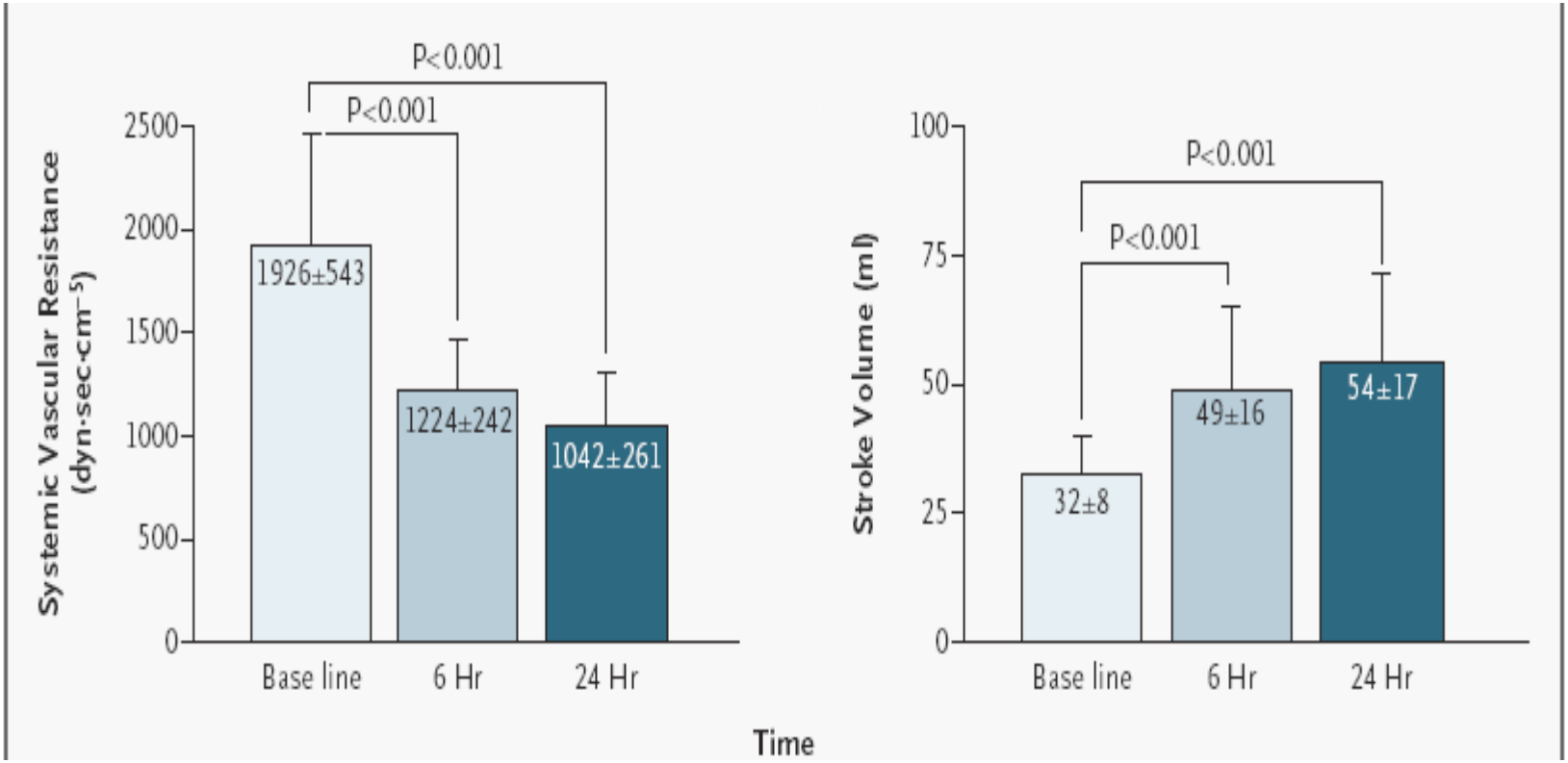
**Table 1. Base-Line Characteristics of the 25 Patients.***

| Characteristic | Value |
|---|---|
| Age — yr | 73±15 |
| Male sex — no. (%) | 16 (64) |
| Myocardial infarction >7 days earlier — no. (%) | 17 (68) |
| History of coronary-artery bypass grafting — no. (%) | 9 (36) |
| Recent unstable angina or myocardial infarction — no. (%)† | 10 (40) |
| Unstable angina | 2 (8) |
| Myocardial infarction without ST-segment elevation | 6 (24) |
| Myocardial infarction with ST-segment elevation | 2 (8) |
| Serum creatinine >2.0 mg/dl (>177 μmol/liter) — no. (%) | 8 (32) |
| Ejection fraction | 0.21±0.08 |
| Aortic-valve area — $cm^2$ | 0.6±0.2 |
| Dimensionless index | 0.19±0.08 |
| Dimensionless index ≤0.25 — no. (%) | 21 (88)‡ |
| Aortic-valve pressure gradient — mm Hg | |
| Mean | 39±23 |
| Peak | 65±37 |
| Mitral regurgitation ≥3+ — no. (%)§ | 5 (20) |
| Aortic regurgitation ≥3+ — no. (%)§ | 3 (12) |
| Cardiac index — liters/min/$m^2$ | 1.60±0.35 |

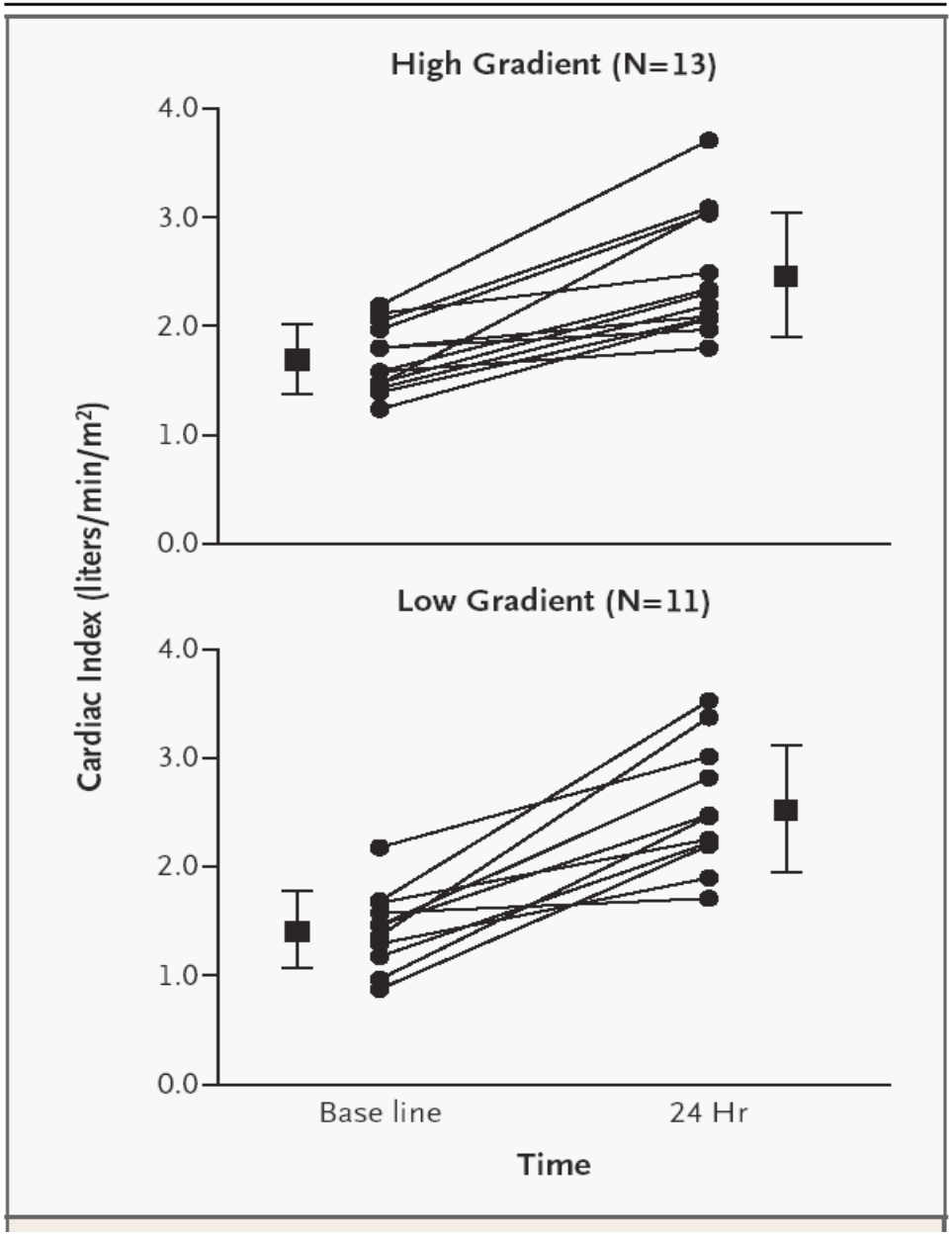
N Engl J Med 2003;348:1756-63.




N Engl J Med 2003;348:1756-63.




N Engl J Med 2003;348:1756-63.


High Gradient (N=13)
Low Gradient (N=11)
Cardiac Index (liters/min/m²)
4.0
3.0
2.0
1.0
0.0
Base line
24 Hr
Time

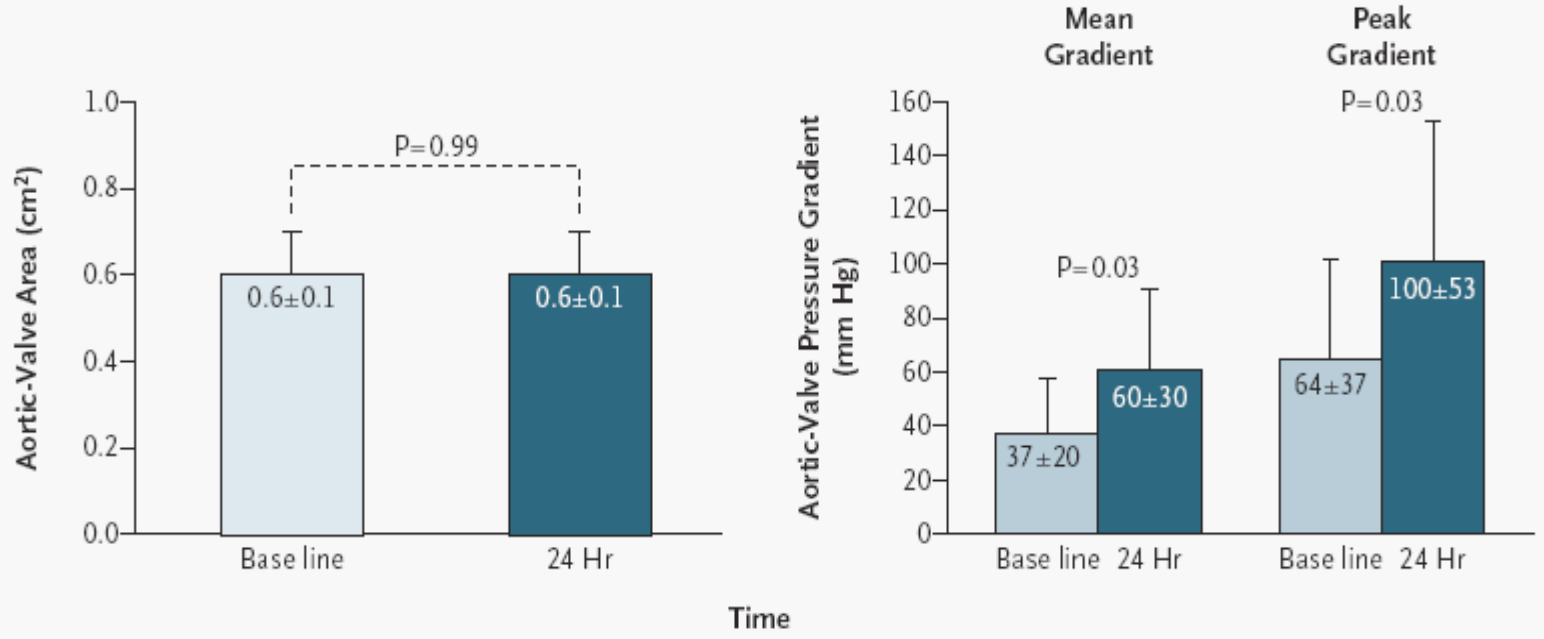


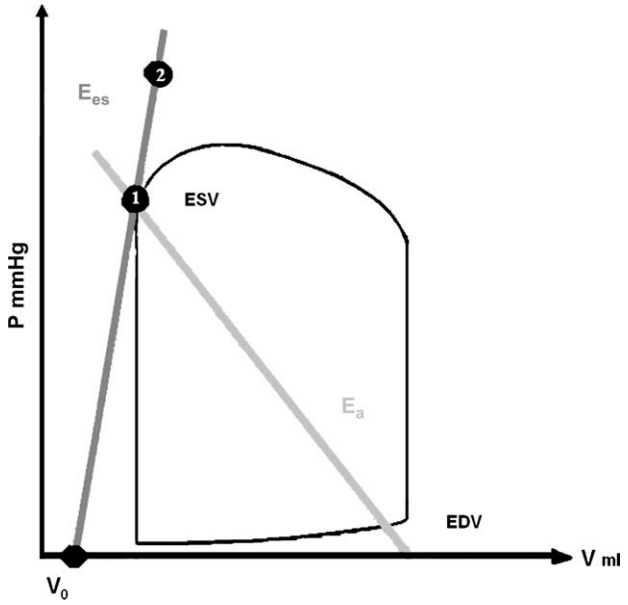

**Figure 3. Effect of Nitroprusside on Aortic-Valve Area and Mean and Peak Aortic-Valve Pressure Gradients in a Subgroup of Six Patients.**

In these patients, nitroprusside increased the stroke volume from 34±10 to 58±23 ml (P=0.03). The area of the aortic valve was calculated with the use of the continuity equation. The error bars represent standard deviations.

**N Engl J Med 2003;348:1756-63.**

# Effect of levosimendan on ventriculo-arterial coupling in patients with ischemic cardiomyopathy

F. Guarracino, C. Cariello, A. Danella, L. Doroni, F. Lapolla, M. Stefani, R. Baldassarri and C. Vullo
*Cardiothoracic Anaesthesia and Intensive Care Unit, Cardiothoracic Department, University Hospital of Pisa, Italy*




Acta Anaesthesiol Scand 2007; 51: 1217–1224

Individual and mean values for parameters of cardiovascular performance.

| Patient no. | | HR (beats/min) | PCWP (mmHg) | SVRI (dyne/cm$^5$/m$^2$) | CI (l/min/m$^2$) |
|---|---|---|---|---|---|
| Mean ± SD | pre-Levo | 70 ± 15 | 21 ± 5 | 997 ± 341 | 1.9 ± 0.4 |
| Mean ± SD | post-Levo | 73 ± 16 | 18 ± 5 | 855 ± 324 | 2.1 ± 0.4 |
| | | $P = 0.004$ | $P = 0.002$ | $P = 0.0002$ | $P = 0.0004$ |

pre-Levo
post-Levo

Individual and mean values for parameters of cardiovascular performance.

| Patient no. | ESVI (ml/m$^2$) | | EDVI (ml/m$^2$) | | EF (%) | | SVI (ml/m$^2$) | | MAP (mmHg) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | pre-M | post-M | pre-M | post-M | pre-M | post-M | pre-M | post-M | pre-M | post-M |
| Mean ± SD | 48 ± 15 | 56 ± 16 | 69 ± 18 | 77 ± 20 | 31 ± 6 | 28 ± 7 | 21 ± 6 | 21 ± 8 | 83 ± 10 | 98 ± 8 |
| Mean ± SD | 38 ± 14 | 43 ± 8 | 63 ± 18 | 69 ± 21 | 40 ± 9 | 37 ± 8 | 25 ± 8 | 25 ± 7 | 72 ± 5 | 93 ± 10 |
| | $P = 0.07$ | $P = 0.02$ | $P = 0.018$ | $P = 0.14$ | $P = 0.001$ | $P = 0.0002$ | $P = 0.03$ | $P = 0.015$ | $P = 0.016$ | $P = 0.01$ |

pre-Levo
post-Levo

Pre-M and post-M: before and after metaraminol administration
Required for calculation of Ees

Acta Anaesthesiol Scand 2007; 51: 1217–1224

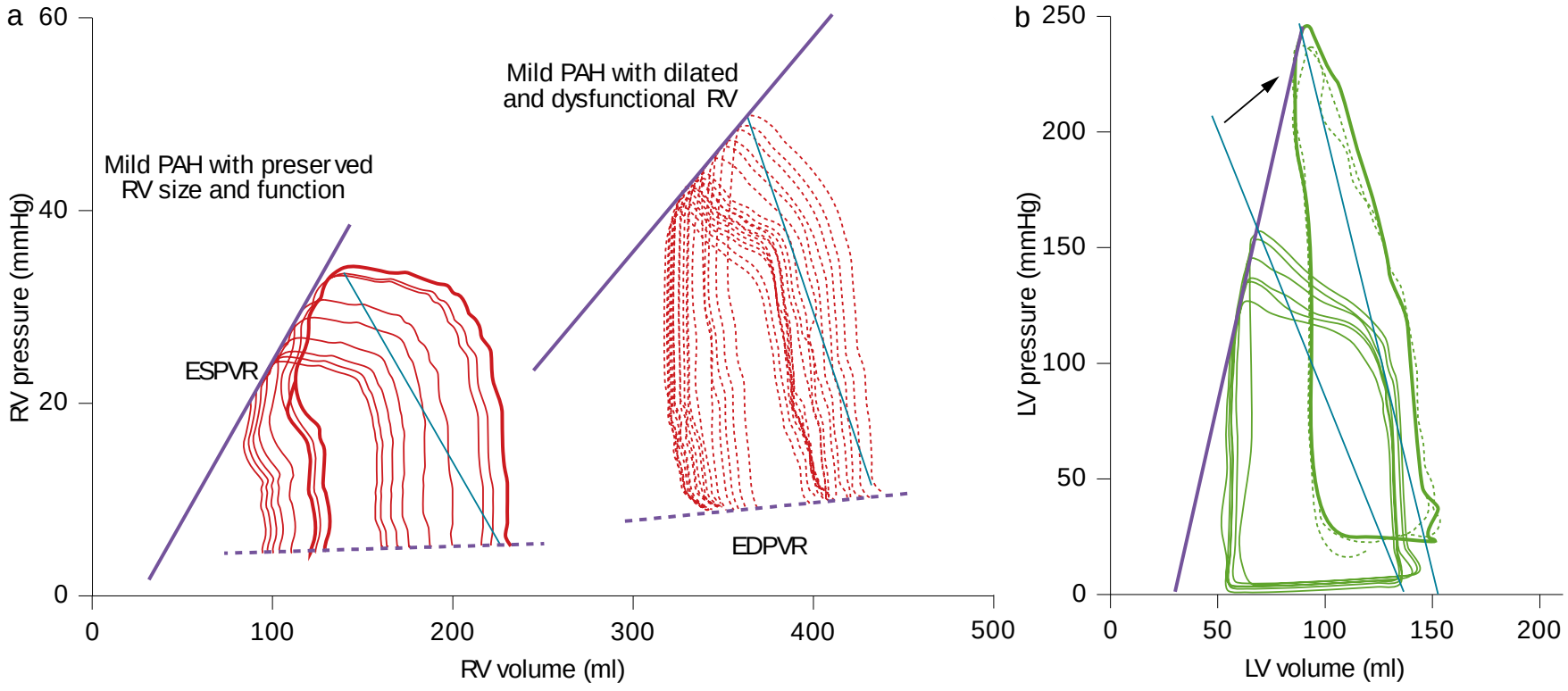
Individual and mean values for parameters of ventriculo-arterial coupling.

| | Patient no. | $E_{es}$ mmHg/ml/m$^2$ | $E_a$ mmHg/ml/m$^2$ | $E_a/E_{es}$ |
|---|---|---|---|---|
| pre-Levo | Mean $\pm$ SD | 2.8 $\pm$ 1 | 4.3 $\pm$ 1 | 1.76 $\pm$ 1 |
| post-Levo | | 4.4 $\pm$ 2 | 3.2 $\pm$ 1 | 0.83 $\pm$ 0.2 |
| | | $P = 0.05$ | $P = 0.005$ | $P = 0.002$ |

# Assessment and treatment of right ventricular failure

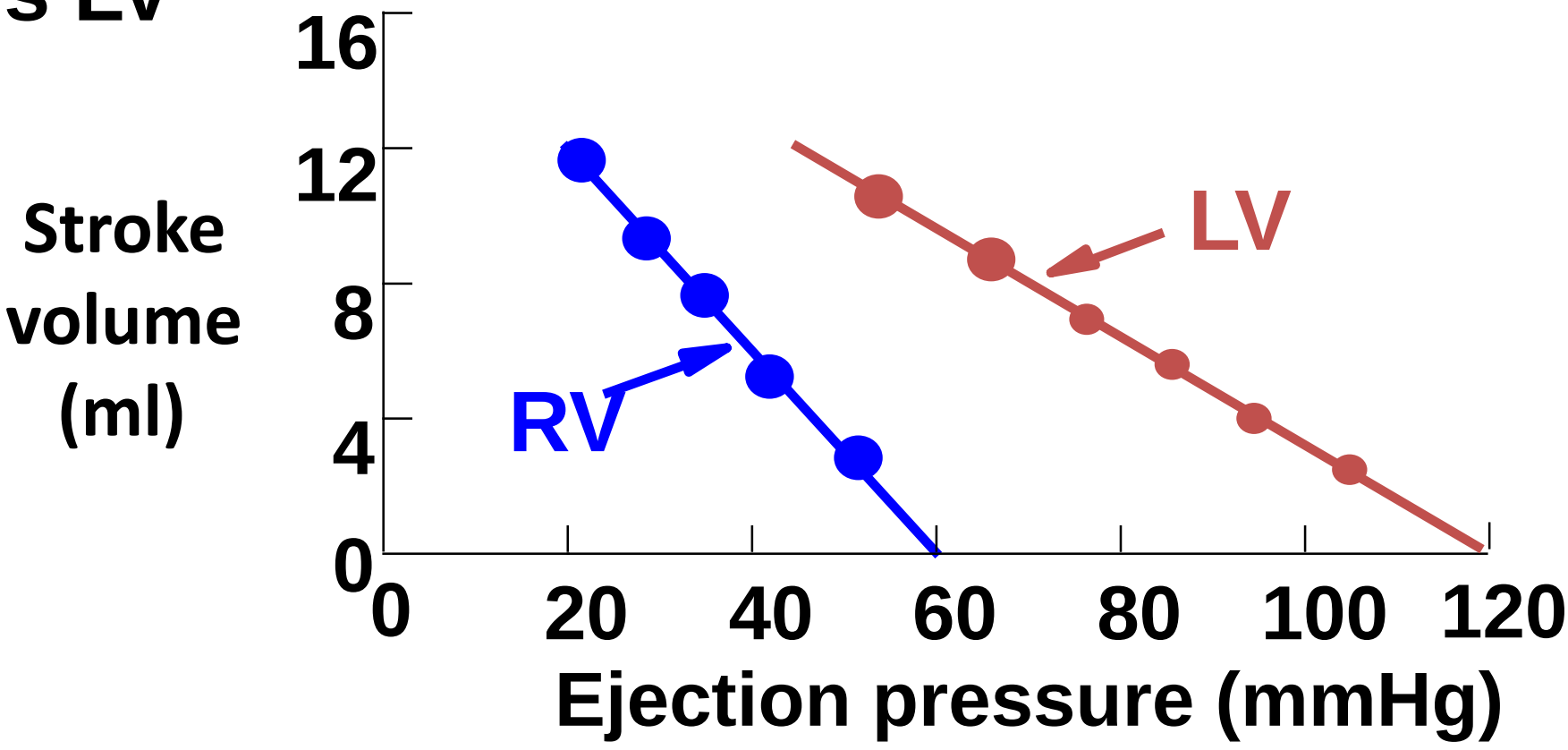
Marc A. Simon

Simon, M. A. Nat. Rev. Cardiol. 10, 204–218 (2013)




Simon, M. A. Nat. Rev. Cardiol. 10, 204–218 (2013)

# Effect of afterload on pump function: RV vs LV




Weber et al. Am J Cardiol 1981; 47: 686-695

# Early right ventriculo-arterial uncoupling in borderline pulmonary hypertension on experimental heart failure

**Alberto Pagnamenta, Céline Dewachter, Kathleen McEntee, Pierre Fesler, Serge Brimioulle and Robert Naeije**

*J Appl Physiol* 109:1080-1085, 2010. First published 5 August 2010;
doi: 10.1152/japplphysiol.00467.2010

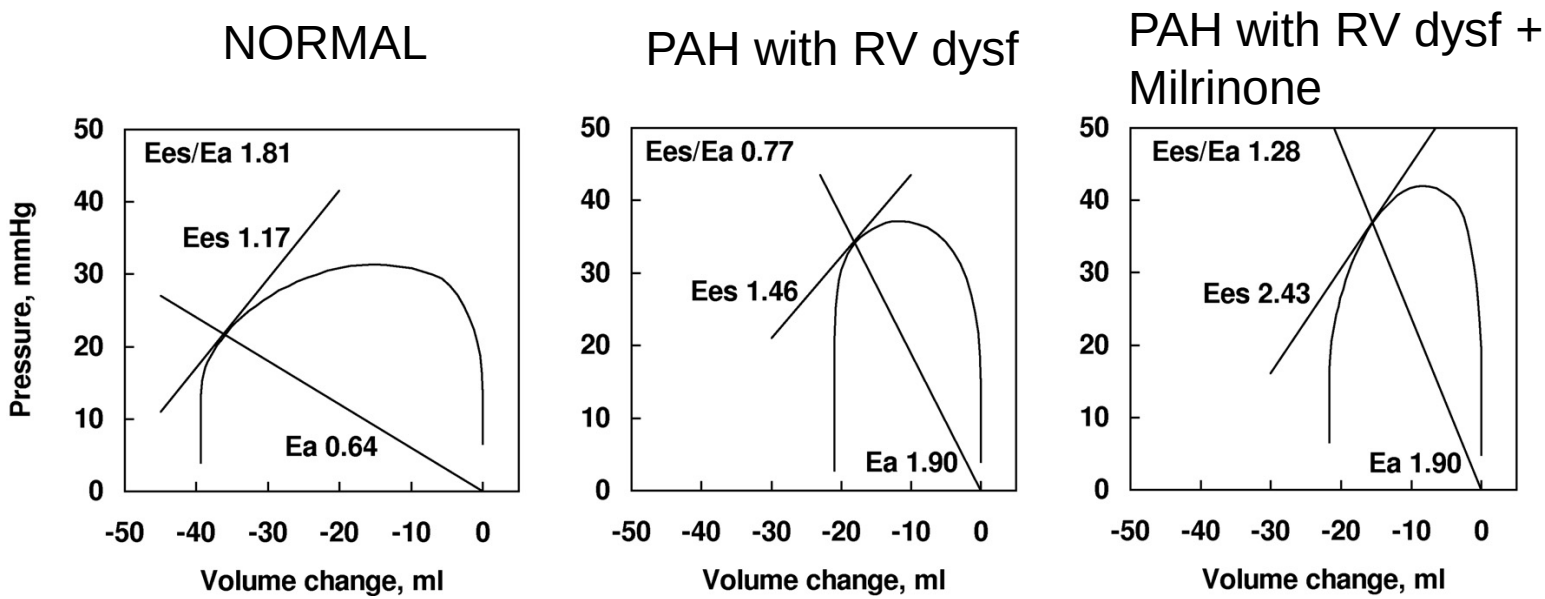



Fig. 1. Typical pulmonary vascular impedance (PVZ) spectra and pressure-volume relationships in a control dog (*left*) and in a dog with heart failure before and after administration of milrinone (*middle* and *right*). Heart failure was associated with an upward shift of the PVZ spectrum at all frequencies and an increase of pulmonary arterial elastance (Ea) with right ventricular (RV)-arterial uncoupling. Administration of milrinone shifted the PVZ spectrum downward at all frequencies and improved RV-arterial coupling because of an improvement in end-systolic elastance (Ees). Zc, characteristic impedance.

*J Appl Physiol* 109:1080-1085, 2010

# Effects of levosimendan versus dobutamine on pressure load-induced right ventricular failure*

François Kerbaul, MD, PhD; Benoît Rondelet, MD; Jean-Paul Demester; Pierre Fesler, MD; Sandrine Huez, MD; Robert Naeije, MD, PhD; Serge Brimioulle, MD, PhD

Crit Care Med 2006; 34:2814–2819

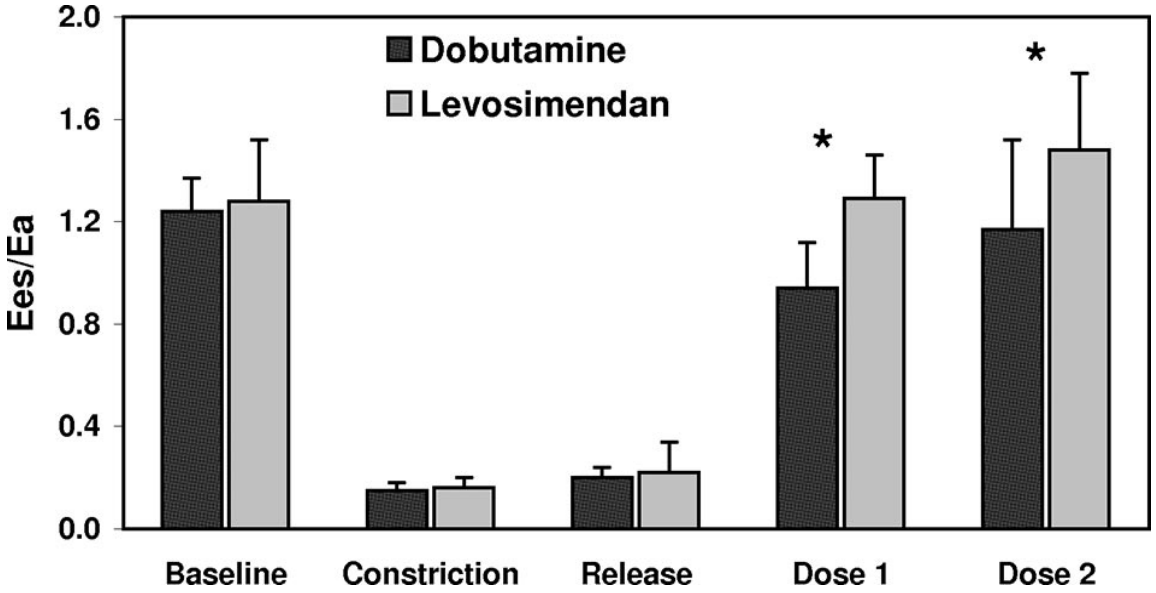



**Figure 5.** Right ventricular-pulmonary arterial (PA) coupling efficiency assessed as the ratio of ventricular end-systolic elastance (*Ees*) to effective arterial elastance (*Ea*) at baseline, during PA constriction, and 30, 60, and 90 mins after PA release, in the dobutamine and levosimendan groups (mean ± SE). PA constriction markedly and persistently decreased coupling efficiency. Levosimendan restored coupling efficiency better than dobutamine ($p < .05$).

Crit Care Med 2006; 34:2814–2819

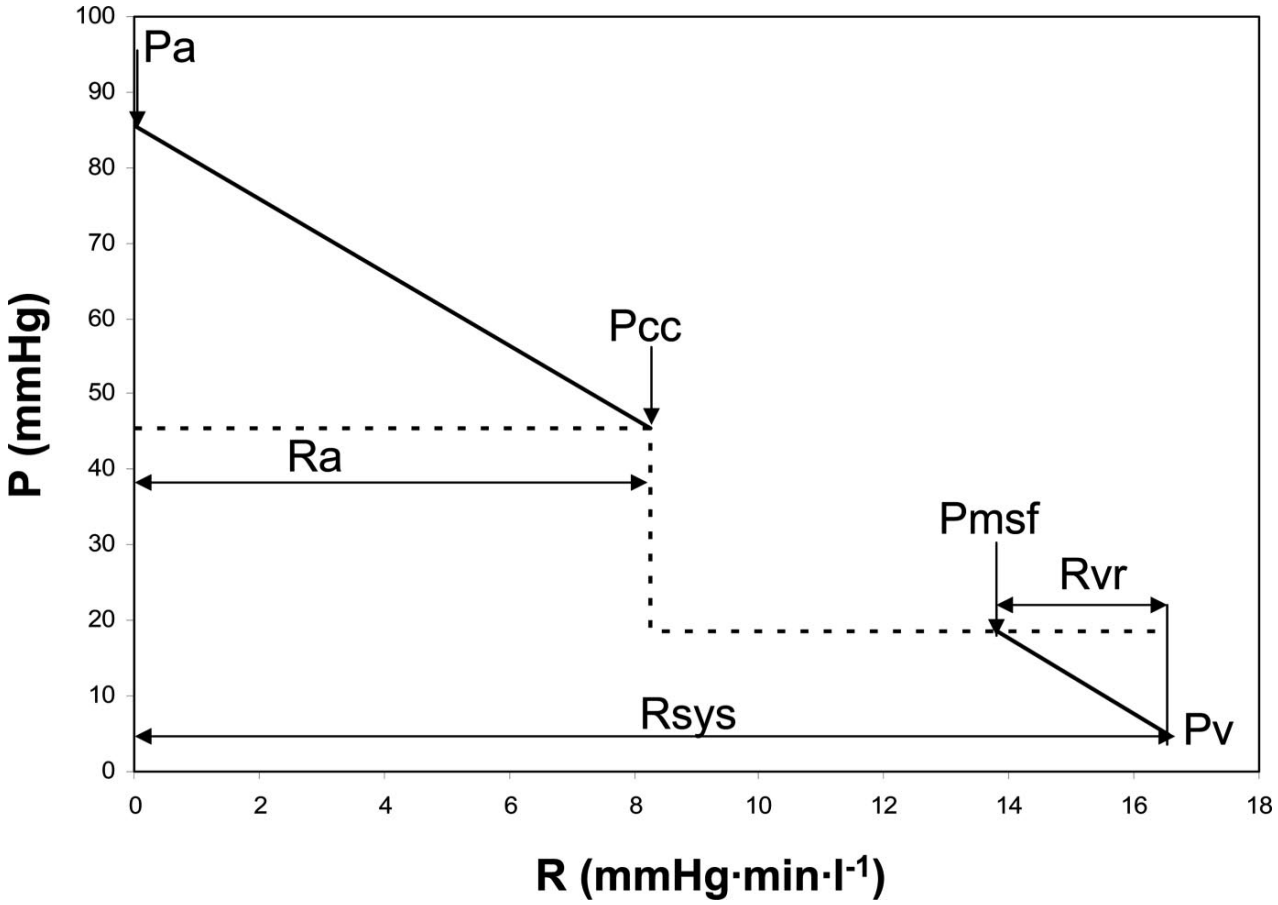
# Intra-organ haemodynamics

The “waterfall”

# Determination of Vascular Waterfall Phenomenon by Bedside Measurement of Mean Systemic Filling Pressure and Critical Closing Pressure in the Intensive Care Unit

Jacinta J. Maas, MD,* Rob B. de Wilde, PhD,* Leon P. Aarts, MD, PhD,†
Michael R. Pinsky, MD, Dr hc, FCCM,‡ and Jos R. Jansen, PhD*

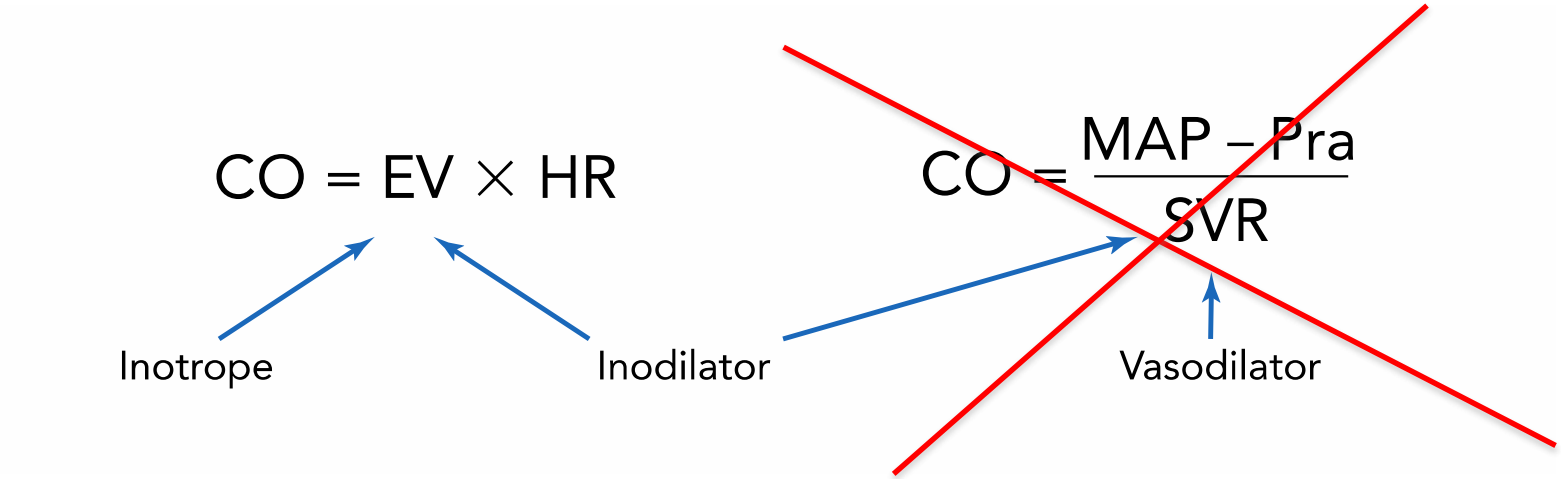
Anesth Analg 2012;114:803–10)




Anesth Analg 2012;114:803–10)

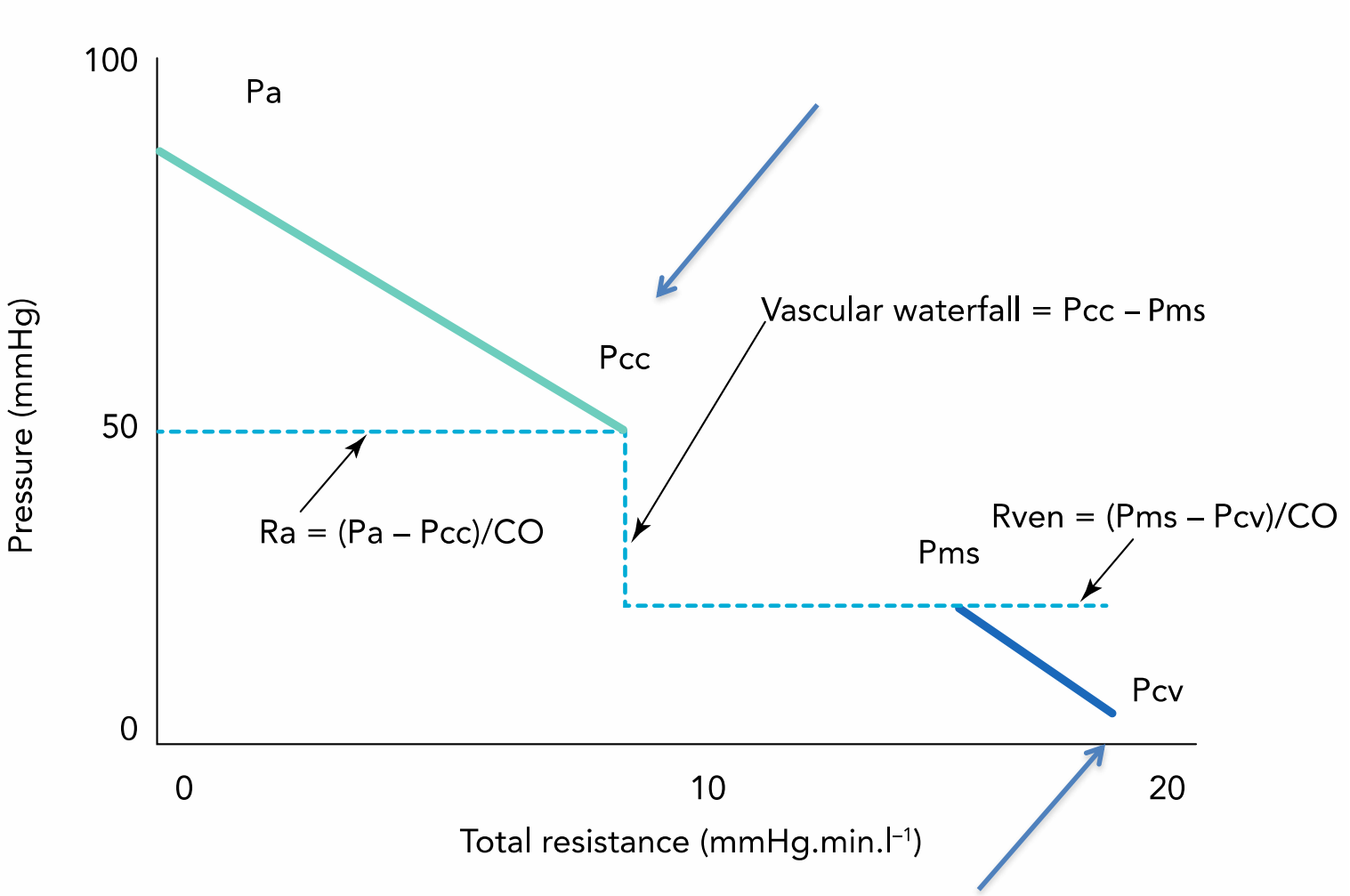
# Determination of Vascular Waterfall Phenomenon by Bedside Measurement of Mean Systemic Filling Pressure and Critical Closing Pressure in the Intensive Care Unit

Jacinta J. Maas, MD,* Rob B. de Wilde, PhD,* Leon P. Aarts, MD, PhD,†
Michael R. Pinsky, MD, Dr hc, FCCM,‡ and Jos R. Jansen, PhD*




Anesth Analg 2012;114:803–10)

# The arterial and venous resistances are regulated separately and differently !




This pressure changes with vasoconstrictors and vasodilators

# Pharmacology

# Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update

Steven M. Hollenberg, MD; Tom S. Ahrens, DNS, RN, CCRN, CS; Djillali Annane, MD, PhD;
Mark E. Astiz, MD, FCCM; Donald B. Chalfin, MD, MS, FCCM, FCCP; Joseph F. Dasta, MSc, FCCM;
Stephen O. Heard, MD, FCCM; Claude Martin, MD, FCCM; Lena M. Napolitano, MD, FCCM;
Gregory M. Susla, PharmD, FCCM; Richard Totaro, MB, BS, FRACP, FJFICM;
Jean-Louis Vincent, MD, PhD, FCCM; Sergio Zanotti-Cavazzoni, MD

**(Crit Care Med 2004; 32:1928 –1948**

| Drug | Dose Range, $\mu g \cdot kg^{-1} \cdot m^{-1}$ | Heart Rate | Cardiac Index | Stroke Volume Index | SVRI | LVSWI |
|---|---|---|---|---|---|---|
| Isoproterenol | 1.5 to 18 μg/min | 11 to 20 | 47 to 119 | 22 to 89 | −24 to −44 | 74 to 157 |
| Dopamine | 2 to 55 | 1 to 23 | 4 to 44 | 7 to 32 | −6 to 18 | 5 to 91 |
| Epinephrine | 0.06 to 0.47 | −6 to 27 | 24 to 54 | 12 | −7 to 34 | 32 to 95 |
| Norepinephrine | 0.03 to 3.3 | −6 to 8 | −3 to 21 | 5 to 15 | 13 to 111 | 42 to 142 |
| Dobutamine | 2 to 28 | 9 to 23 | 12 to 61 | 15 | −6 to −21 | 23 to 58 |
| Milrinone[a] | 0.5 | 1 | 41 to 49 | 47 | −30 to −35 | 51 to 56 |

Mebazaa *et al*. *Critical Care* 2010, **14**:201
http://ccforum.com/content/14/2/201

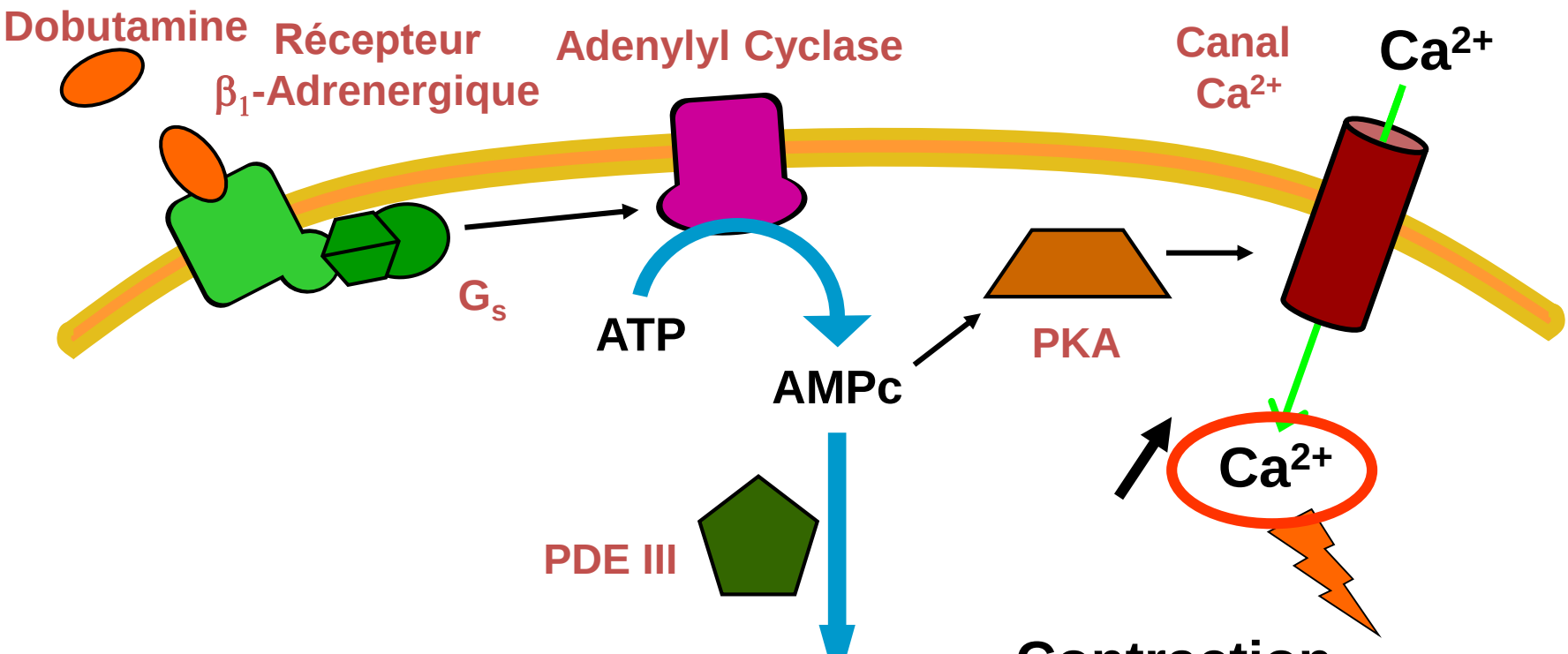
CRITICAL CARE

REVIEW

# Clinical review: Practical recommendations on the management of perioperative heart failure in cardiac surgery

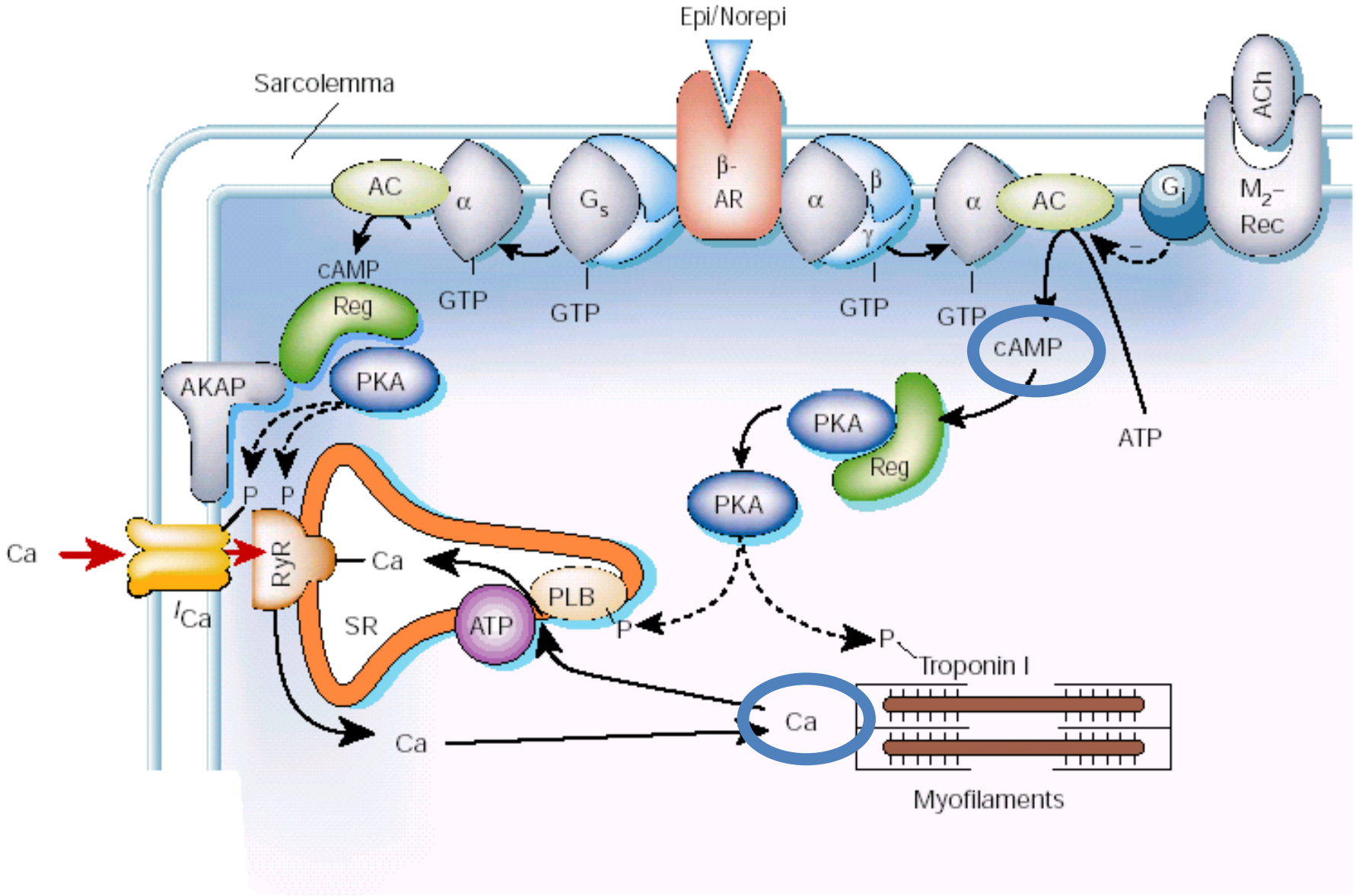
Alexandre Mebazaa[1], Antonis A Pitsis[2], Alain Rudiger[3], Wolfgang Toller[4], Dan Longrois[5], Sven-Erik Ricksten[6], Ilona Bobek[7], Stefan De Hert[8], Georg Wieselthaler[9], Uwe Schirmer[10], Ludwig K von Segesser[11], Michael Sander[12], Don Poldermans[13], Marco Ranucci[14], Peter CJ Karpati[15], Patrick Wouters[16], Manfred Seeberger[17], Edith R Schmid[18], Walter Weder[19] and Ferenc Follath[20]

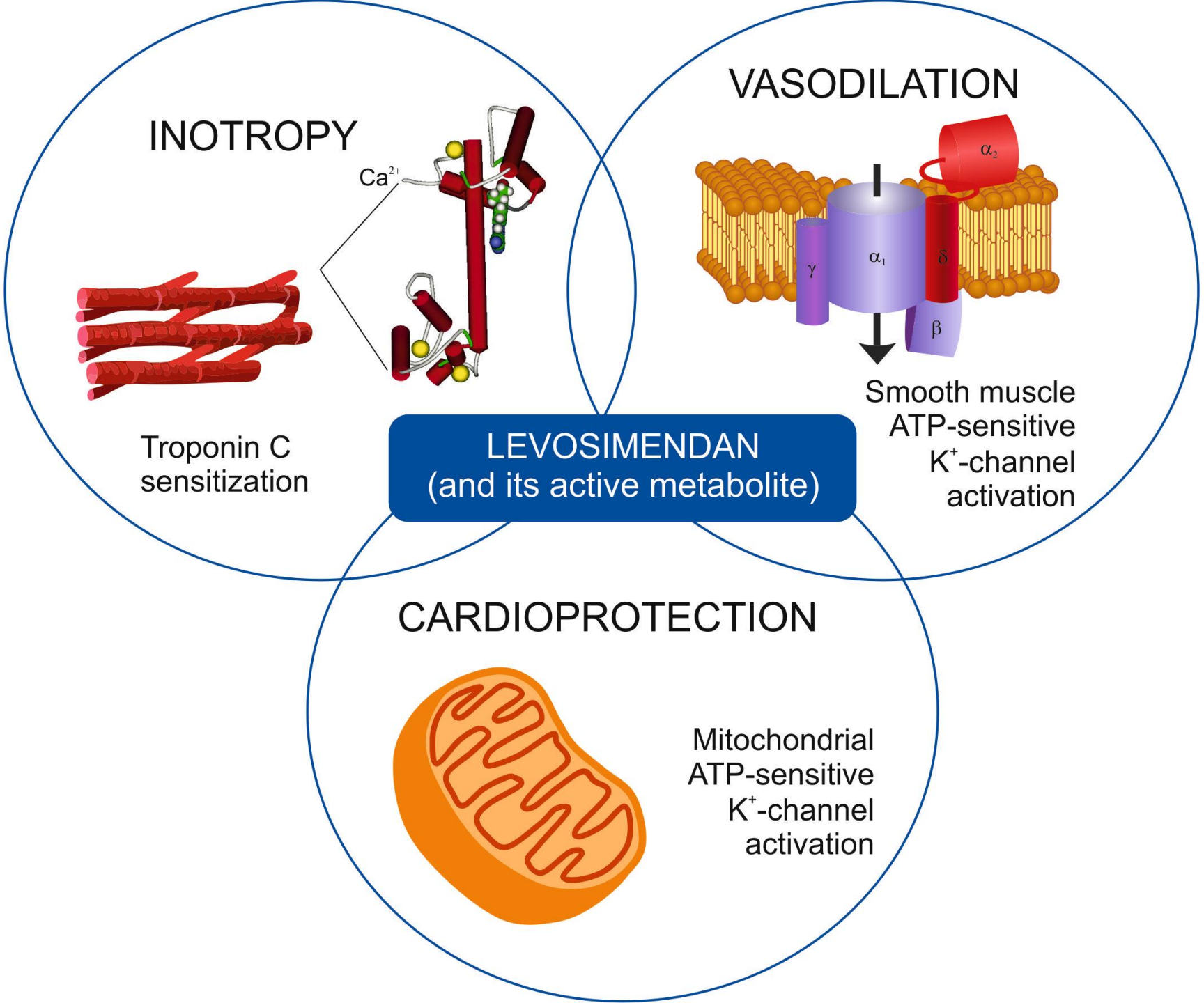
# Mécanismes d'action des inotropes



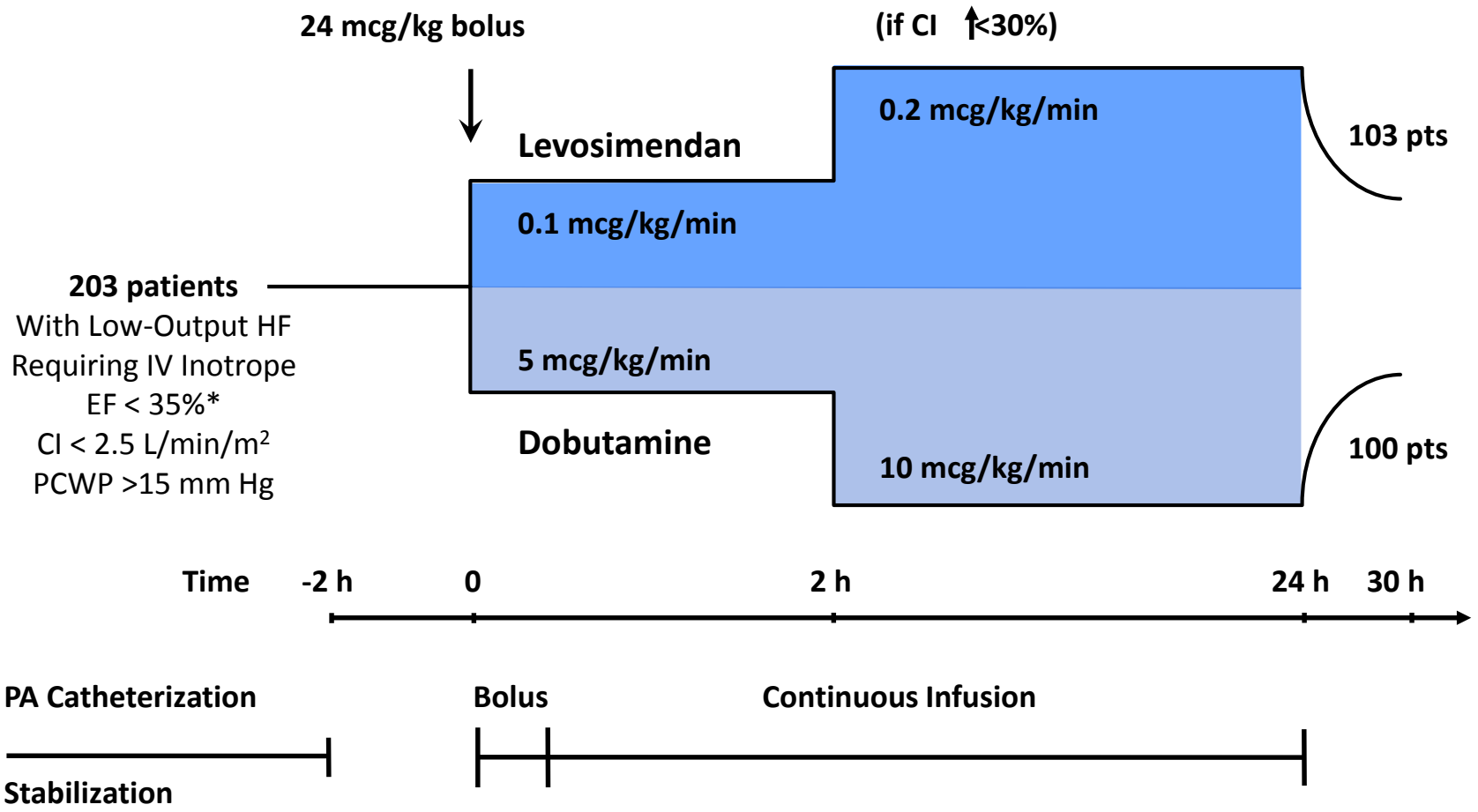


Bers DM. *Nature.* 2002;415:198-205.
Movsesian MA. *J Card Fail.* 2003;9:475-480.
McBride BF, et al. *Pharmacotherapy.* 2003;23:997-1020.


Epi/Norepi
Sarcolemma
ACh
AC
α
$G_s$
β-
AR
α
β
γ
α
AC
$G_i$
$M_2$–
Rec
cAMP
Reg
GTP
GTP
GTP
GTP
cAMP
AKAP
PKA
PKA
Reg
ATP
PKA
P
P
Ca
RyR
Ca
PLB
$I_{Ca}$
SR
ATP
P
P
Troponin I
Ca
Ca
Myofilaments


INOTROPY
Ca2+
Troponin C
sensitization
VASODILATION
α2
α1
γ
δ
β
Smooth muscle
ATP-sensitive
K+-channel
activation
LEVOSIMENDAN
(and its active metabolite)
CARDIOPROTECTION
Mitochondrial
ATP-sensitive
K+-channel
activation

# LIDO Study Design

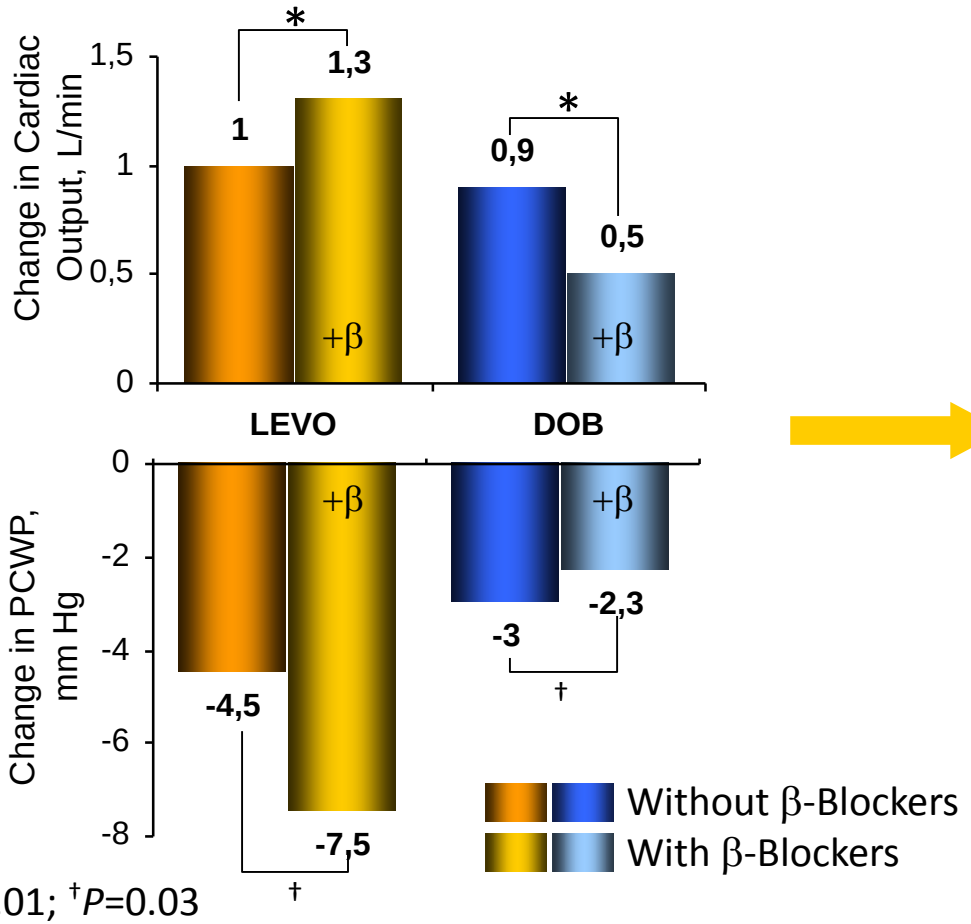



*Within one month of enrollment.

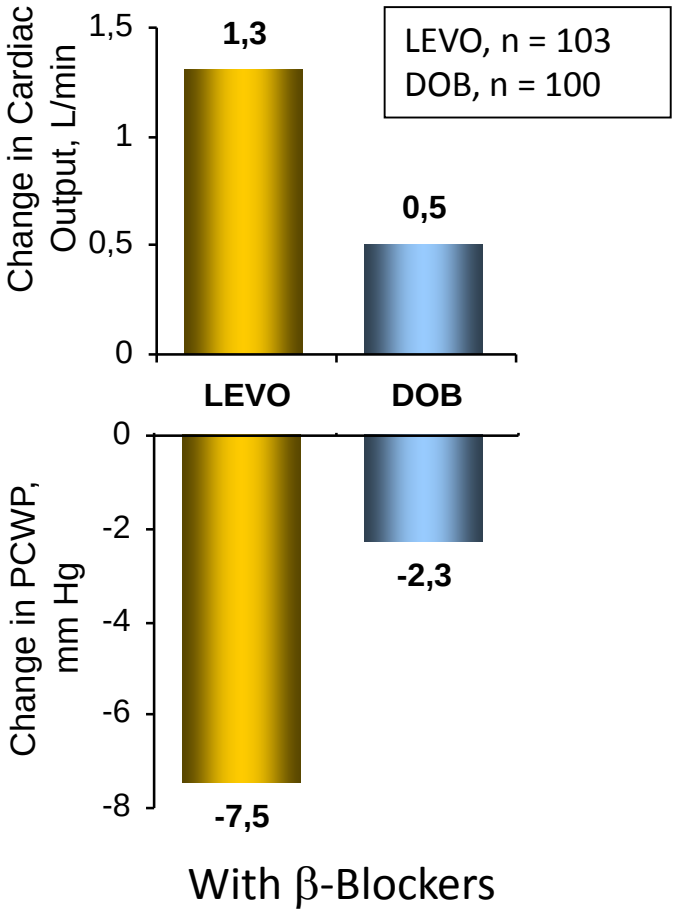
Follath F, et al. *Lancet*. 2002;360:196-202.

# LIDO: Effect of β-Blockers

Subset Analysis of Patients Enrolled in the LIDO Study




*P=0.01; †P=0.03




With β-Blockers

Follath F, et al. *Lancet*. 2002;360:196-202.

Journal of the American College of Cardiology
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Vol. 54, No. 19, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.05.015

**STATE-OF-THE-ART PAPER**

# The Sympathetic Nervous System in Heart Failure

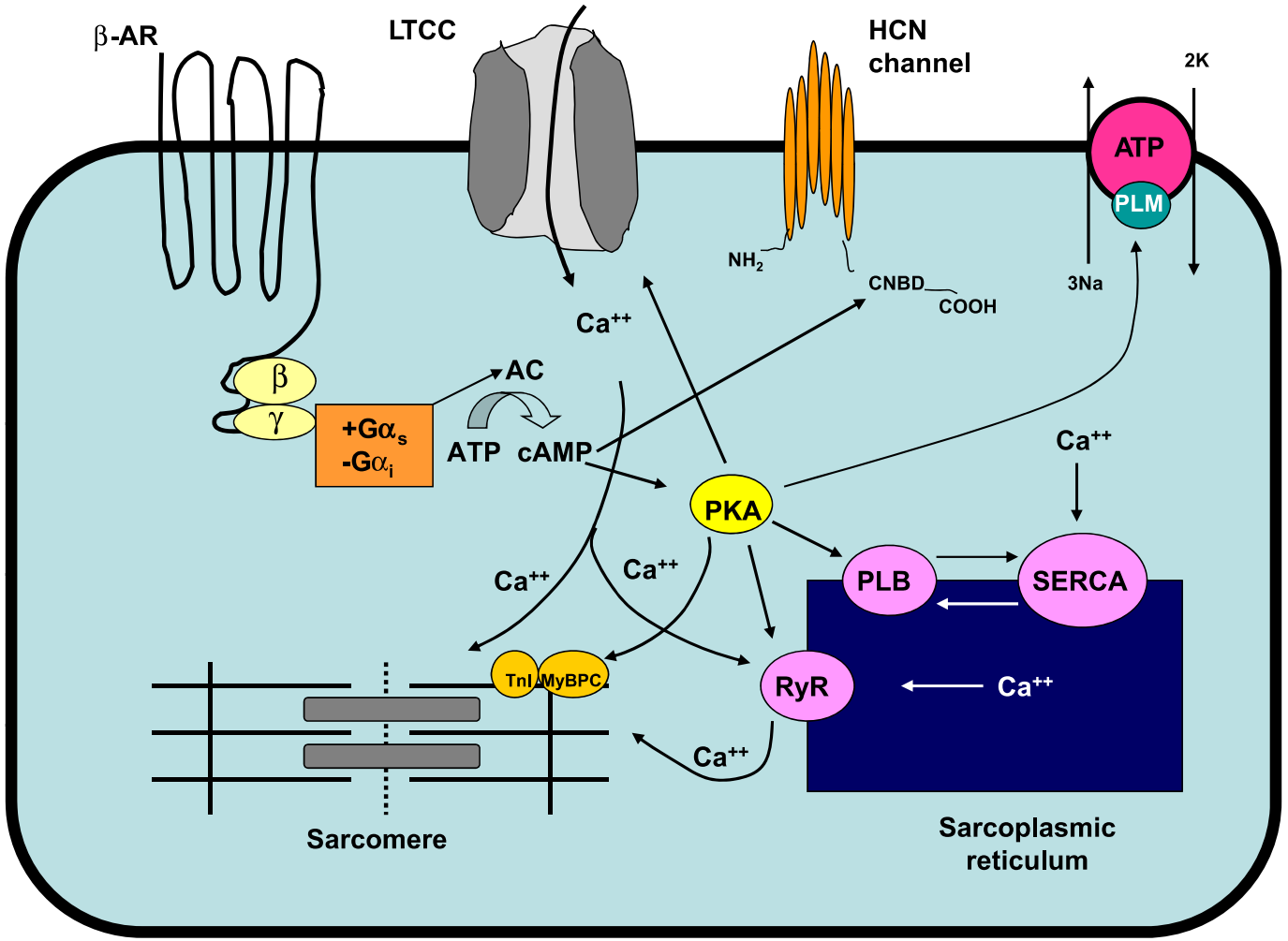
## Physiology, Pathophysiology, and Clinical Implications

Filippos Triposkiadis, MD,* George Karayannis, MD,* Grigorios Giamouzis, MD,*‡
John Skoularigis, MD,* George Louridas, MD,† Javed Butler, MD, MPH‡

*Larissa and Thessaloniki, Greece; and Atlanta, Georgia*

J Am Coll Cardiol 2009;54:1747–62

In CHF : Desensitization/downregulation B1 / Resensitization if beta-blockers chronically
Preserved beta-2/ alpha 1 receptor numbers/signaling




J Am Coll Cardiol 2009;54:1747–62

**Figure 2** **Beta-AR Signaling**

The major intracellular effect of the sympathetic transmitters norepinephrine and epinephrine is mediated by formation of 3′,5′-cyclic monophosphate (cAMP), which increases the activity of the cAMP-dependent protein kinase A (PKA). PKA mediates a series of phosphorylations in diverse intracellular substrates, including the L-type $Ca^{++}$ channels (LTTC), hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, sarcoplasmic ryanodine receptors (RyR), phospholamban (PLB), myofibrillar proteins troponin I (TnI), cardiac myosin-binding protein C (MyBPC), and phospholemman (PLM). AC = adenylyl cyclase; AR = adrenergic receptor; ATP = adenosine triphosphate; CNBD = cyclic nucleotide-binding domain; $G_{alpha\,i}$ and $G_{alpha\,s}$ = G protein alpha-subunit subtypes; SERCA = sarcoendoplasmic reticulum.

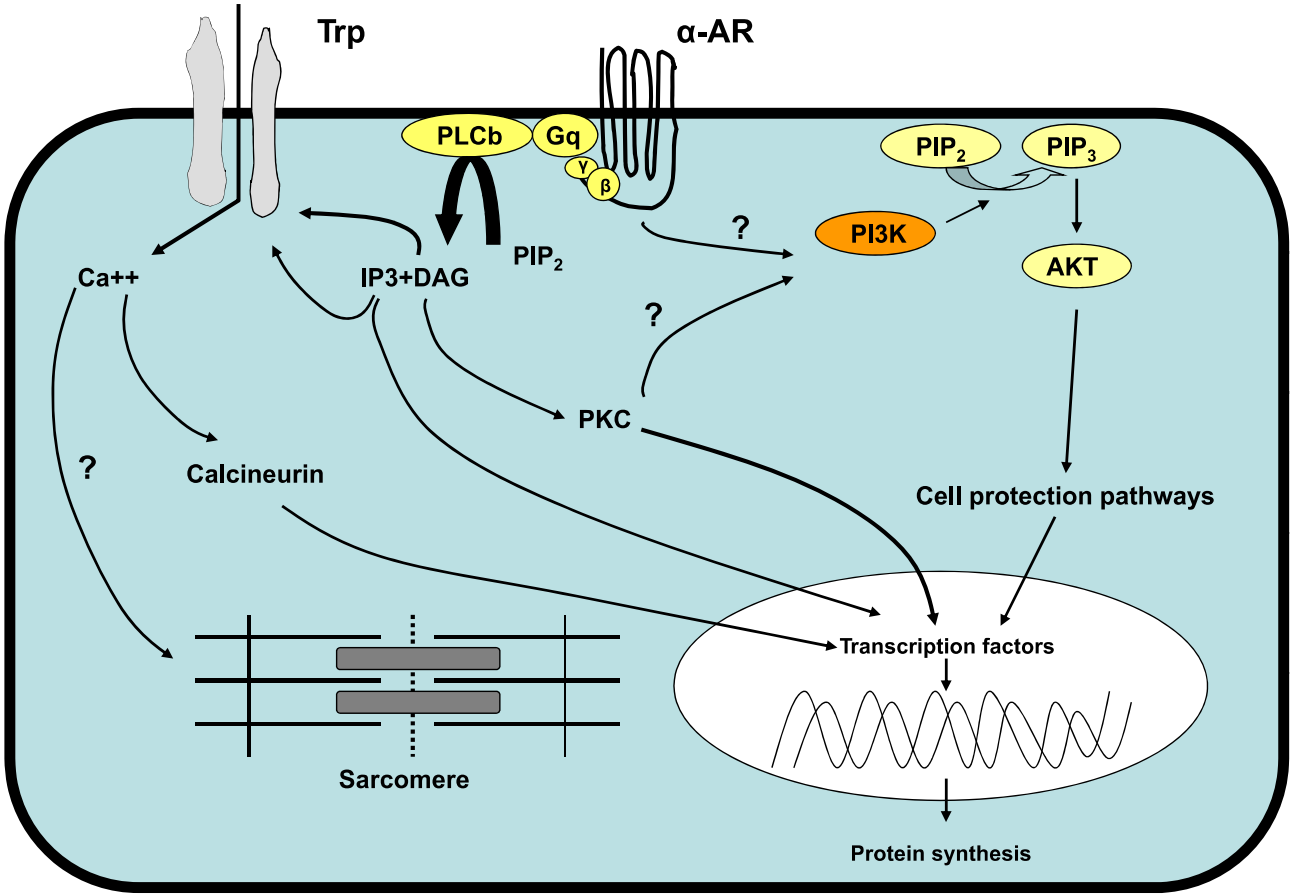



**Figure 3** **Alpha$_1$-AR Signaling**

J Am Coll Cardiol 2009;54:1747–62

Agonist-induced stimulation of alpha$_1$-ARs activates $G_q$ and phospholipase $C_b$ ($PLC_b$), resulting in hydrolysis of phosphatidylinositol bisphosphate ($PIP_2$), to generate inositol trisphosphate ($IP_3$) and diacylglycerol (DAG). DAG, in turn, activates protein kinase C (PKC) to initiate a series of phosphorylations that alter channel activity and induce transcriptional changes. Moreover, $IP_3$ interacts with perinuclear inositol trisphosphate receptors ($IP_3R$) disinhibiting growth-related gene transcription. Both $PIP_2$ and DAG increase the permeability of the transient receptor potential (Trp) channel to $Ca^{2+}$, which enters the cell and activates calcineurin to initiate downstream growth signaling pathways. $Ca^{2+}$ entry through transient receptor potential channels may also act on myofilaments enhancing contractile responses. The alpha$_1$-AR also transactivates epithelial growth factor receptors, resulting in formation of phosphoinositide 3-kinase ($PI_3K$) and phosphatidylinositol trisphosphate ($PIP_3$), activation of the Akt pathway, and initiation of cell-survival signaling pathways. Abbreviations as in Figure 2.

# One of the first explanations why VD would save lives

- Inotropes do not save lives or even increase mortality
  - CHF patients
  - ADHF patients
  - AHF patients
  - Many types of ICU patients
    - Cardiac surgery
    - Patients with severe sepsis
- Mechanisms of the deleterious effects of inotropes ?
  - MvO2 ?
  - Heart rate ?

# Therapeutic approach of inotropes/inodilators/vasodilators

# Meta-analyses for dobutamine/milrinone/levosimendan

- Heterogenous groups of patients
- Statistical associations with outcomes:
  - Neutral/deleterious for dobutamine/milrinone

Intensive Care Med (2012) 38:359–367

Journal of Cardiothoracic and Vascular Anesthesia, Vol 26, No 1 (February), 2012: pp 70-77

  - Beneficial for levosimendan ?

Journal of Cardiothoracic and Vascular Anesthesia, Vol 26, No 1 (February), 2012: pp 70-77

Critical Care 2011, 15:R140

*Acta Anaesthesiol Scand* 2013; **57:** *431–442*
*Printed in Singapore.* 

**ACTA ANAESTHESIOLOGICA SCANDINAVICA**
doi: 10.1111/aas.12056

# Association between inotrope treatment and 90-day mortality in patients with septic shock

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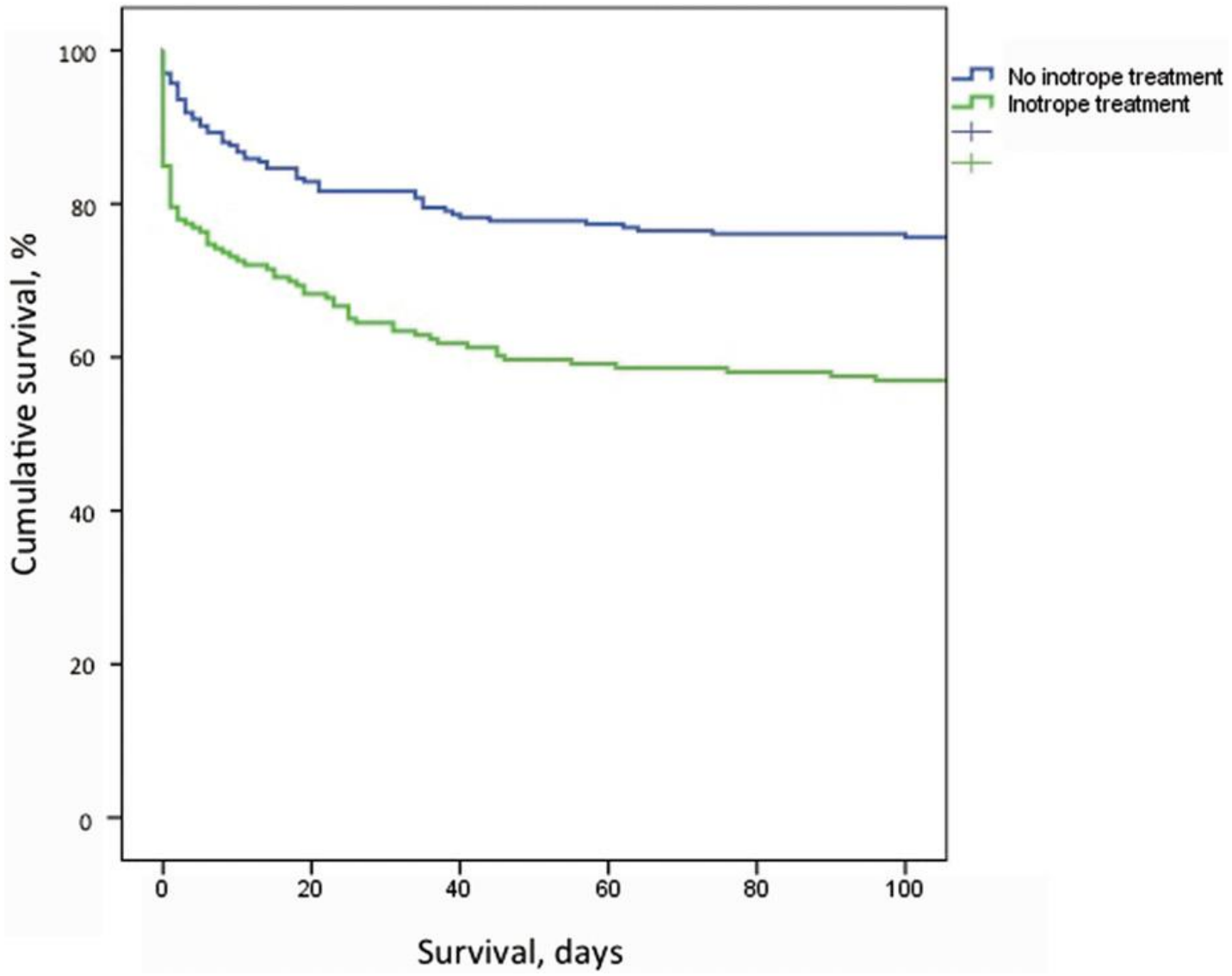
[1]*Department of Surgery, Intensive Care Units, Division of Anaesthesia and Intensive Care Medicine, Helsinki, Finland* and [2]*Department of Internal Medicine, Division of Cardiology, Helsinki University Central Hospital, Helsinki, Finland*

Acta Anaesthesiol Scand 2013; 57: 431–442




Acta Anaesthesiol Scand 2013; 57: 431–442

Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

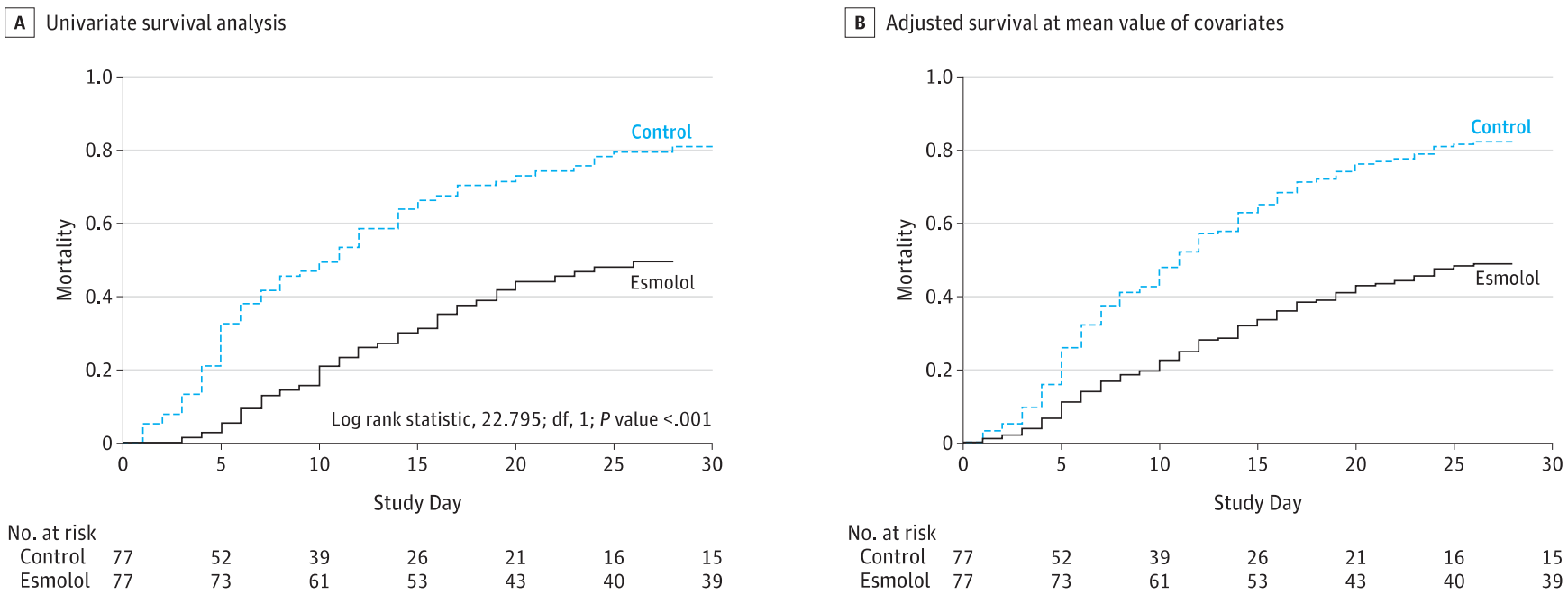
# Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock

## A Randomized Clinical Trial

Andrea Morelli, MD; Christian Ertmer, MD; Martin Westphal, MD; Sebastian Rehberg, MD; Tim Kampmeier, MD; Sandra Ligges, PhD; Alessandra Orecchioni, MD; Annalia D'Egidio, MD; Fiorella D'Ippoliti, MD; Cristina Raffone, MD; Mario Venditti, MD; Fabio Guarracino, MD; Massimo Girardis, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Alexander Mebazaa, MD; Mervyn Singer, MD, FRCP

JAMA. doi:10.1001/jama.2013.278477
October 2013

## Figure 5. Survival Analysis of Study Patients




A, unadjusted survival plots (Kaplan-Meier) of patients. B, multivariable adjusted survival (Cox) at mean values of Simplified Acute Physiology Score II. Ordinate axis is scaled as "1-survival" to depict the 0 intersection without breaking the axis.

JAMA. doi:10.1001/jama.2013.278477
October 2013

# Second reasons why VD would improve survival

- Because of intrinsic beneficial effects
- Why ?
  - How documentation of these mechanisms could contribute widen the use of VD ?

Alexandre Mebazaa
John Parissis
Raphael Porcher
Etienne Gayat
Maria Nikolaou
Fabio Vilas Boas
J. F. Delgado
Ferenc Follath

# Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods

Intensive Care Med (2011) 37:290–301

# NOT a prospective study

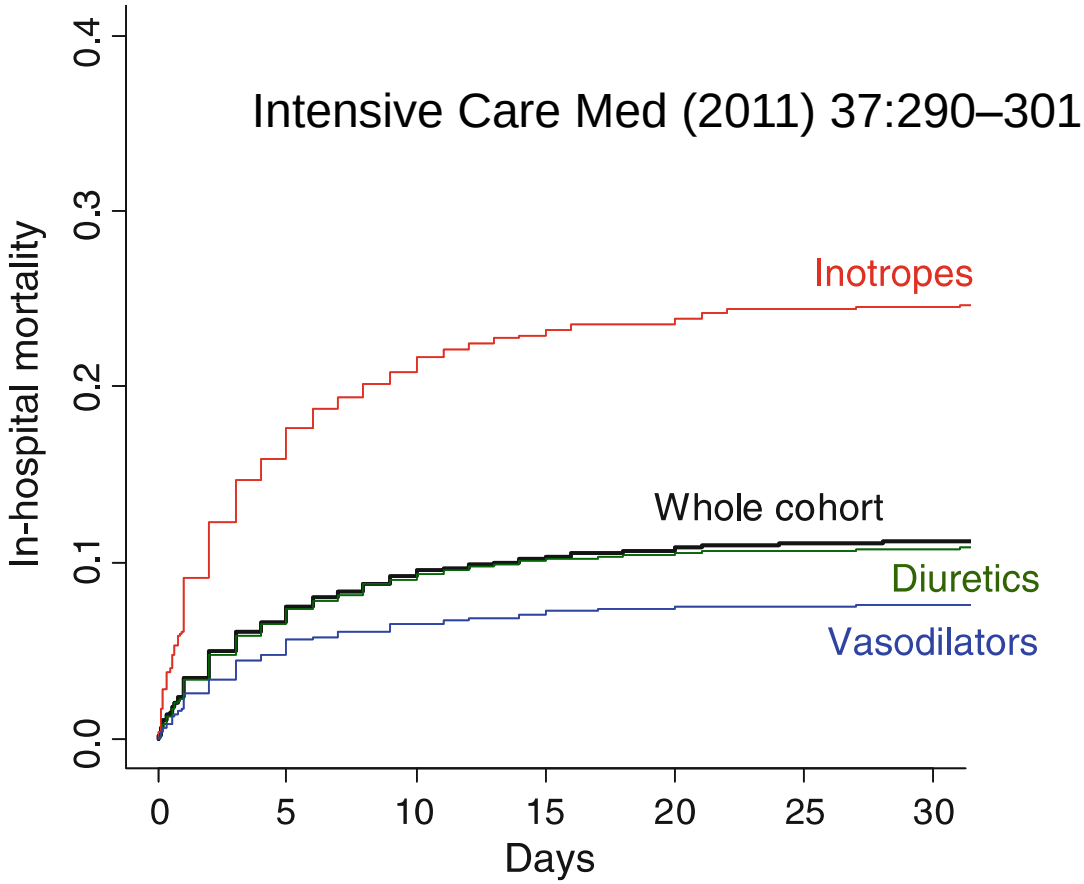
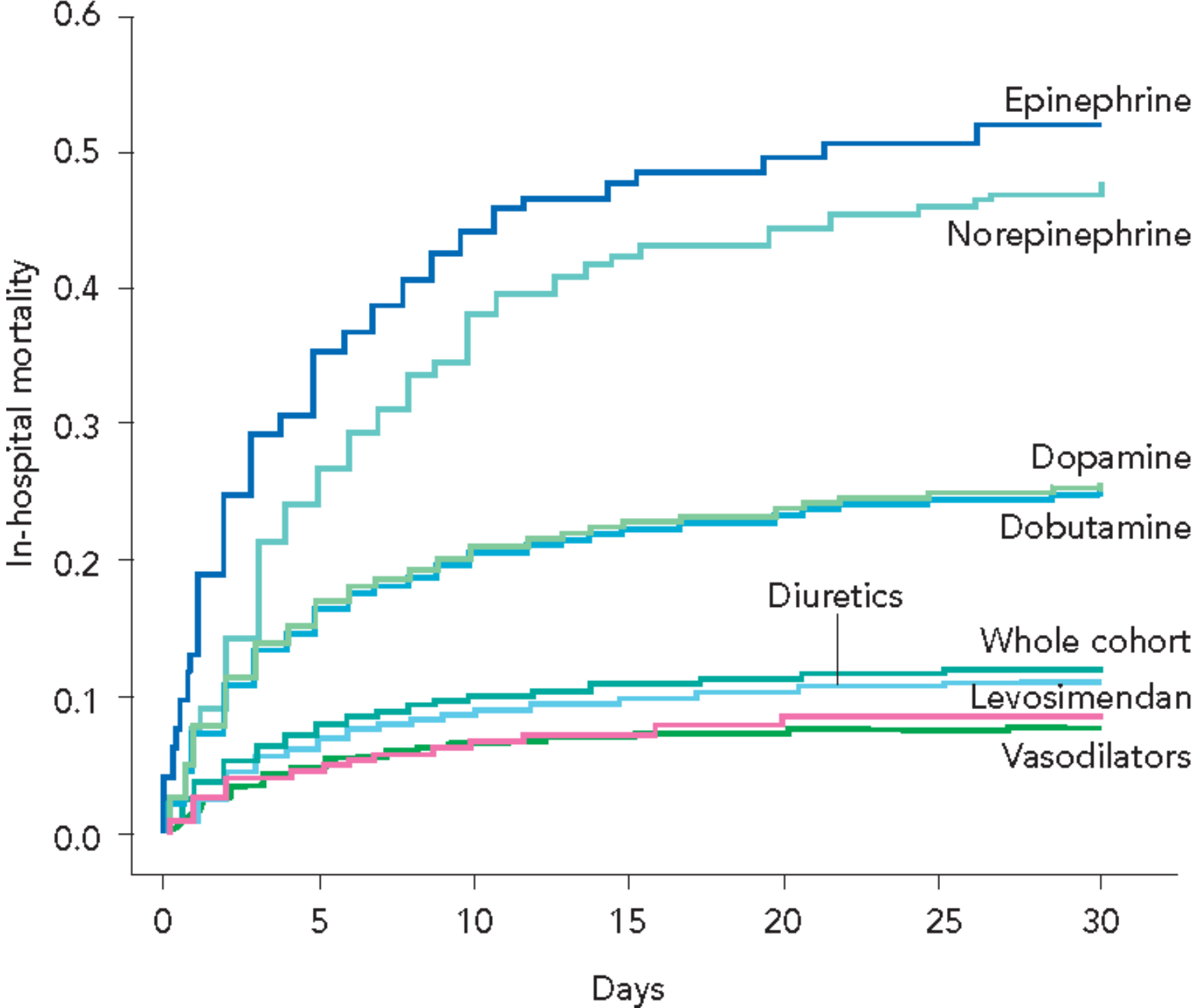
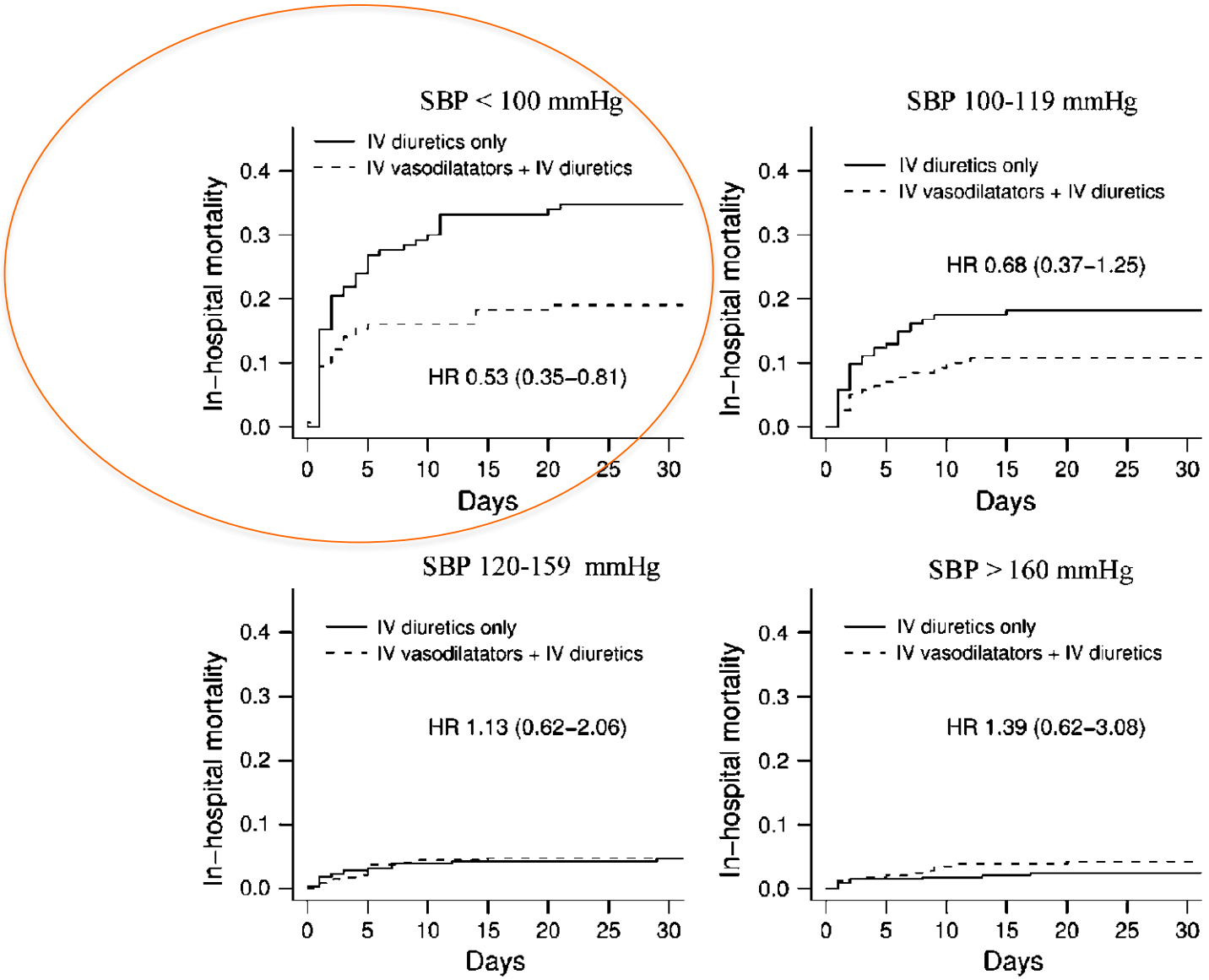



**Fig. 1** Effect of the main intravenous (IV) drugs administered during first 48 h in acute heart failure (AHF) patients on in-hospital mortality. Whole cohort ($n = 4{,}953$), IV diuretics ($n = 4{,}167$), IV vasodilators (mostly nitrates, $n = 1{,}930$), IV inotropes and/or IV vasopressors ($n = 1{,}617$)


0.6
0.5
0.4
0.3
0.2
0.1
0.0
In-hospital mortality
Epinephrine
Norepinephrine
Dopamine
Dobutamine
Diuretics
Whole cohort
Levosimendan
Vasodilators
0
5
10
15
20
25
30
Days




Intensive Care Med (2011) 37:290–301

# From the most (but also less) recent literature

- The goals of HS for ICU patients (mortality)
  - AHF/ADHF
  - Cardiac surgery
  - Septic shock patients
  - Other pathologies
- Are not obvious anymore
  - Classical approaches (inotropes/vasoconstrictors) do not improve survival
  - “Counter-intuitive” interventions (vasodilators, b-blockers) are under new scrutiny

# Clinically unused determinants of heart function

- LV-aorta coupling
- RV-pulmonary artery coupling
- P artery to P veins coupling +++
  - Mechanisms of dyspnea ?
- Critical closing pressure within vital organs
  - Brain, heart, kidney lower than in other organs
- Arterial and venous resistances regulated differently

# Why would vasodilators improve outcome more than inotropes/inodilators ?

## Why would an inodilator *not* improve outcome in patients with heart failure or cardiac dysfunction?

***Dan Longrois[1,2] and Xavier Norel[2]***

[1]Department of Anesthesia and Intensive Care, Hôpital Bichat-Claude Bernard, Assistance Publique-Hôpitaux de Paris, Université Paris Diderot and
[2]Unité INSERM U698, Paris, France

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The reshape of paradigm:

From “cardiocentric” to intergrated

# The Role of Venous Return in Critical Illness and Shock—Part I: Physiology

Duane J. Funk, MD[1,2]; Eric Jacobsohn, MD[1,2]; Anand Kumar, MD[1,3]

$$CO = EV \times HR$$

$$CO = \frac{MAP - P_{RA}}{SVR}$$

Inotrope

Inodilator/
Vasodilator

$$VR = \frac{P_{ms} - P_{RA}}{R_v} = CO$$

$$R = \frac{8nl}{\pi r^4}$$

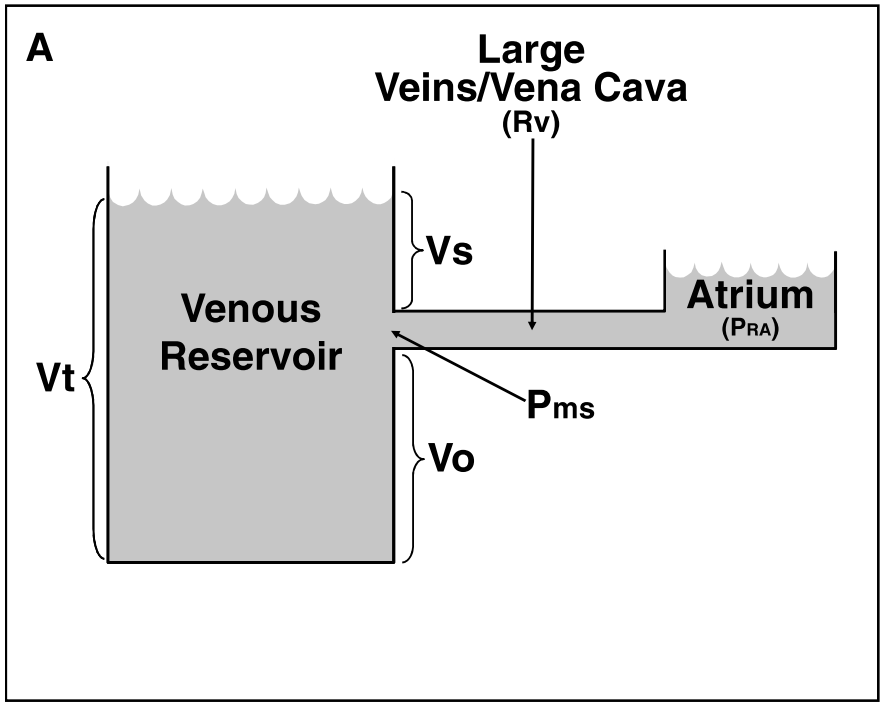
Vasodilator/inodilator

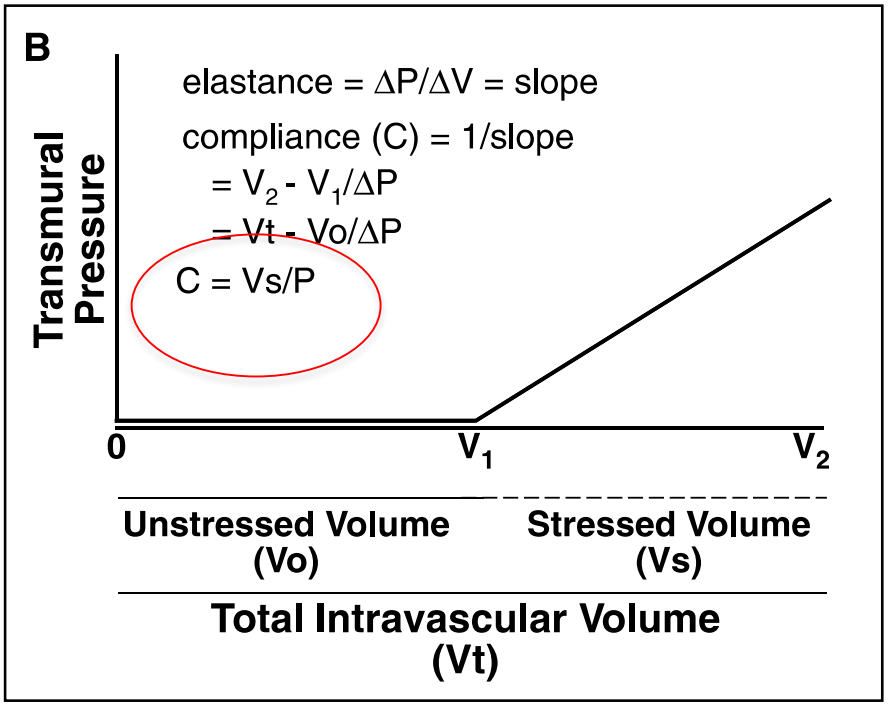
Inotrope/inodilator
Vasodilator

Crit Care Med 2013; 41:255–262

# The Role of Venous Return in Critical Illness and Shock—Part I: Physiology

Duane J. Funk, MD[1,2]; Eric Jacobsohn, MD[1,2]; Anand Kumar, MD[1,3]



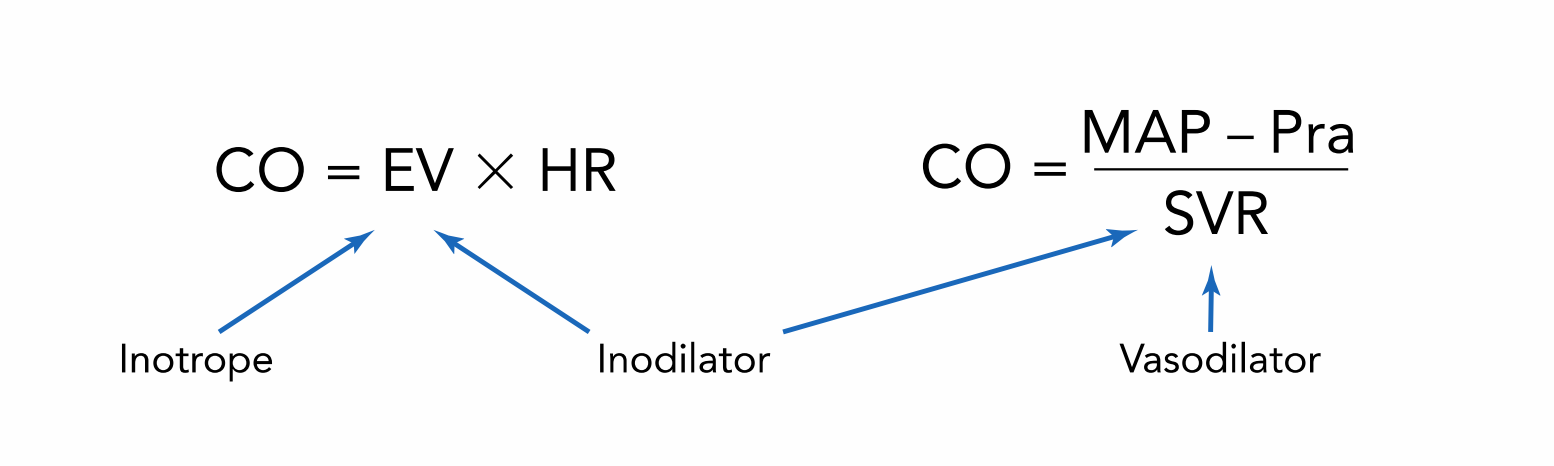




The venous circulation should be approached by bearing in mind not only pressures but mainly compliance +++++++

Crit Care Med 2013; 41:255–262

# Determination of Vascular Waterfall Phenomenon by Bedside Measurement of Mean Systemic Filling Pressure and Critical Closing Pressure in the Intensive Care Unit

Jacinta J. Maas, MD,* Rob B. de Wilde, PhD,* Leon P. Aarts, MD, PhD,†
Michael R. Pinsky, MD, Dr hc, FCCM,‡ and Jos R. Jansen, PhD*

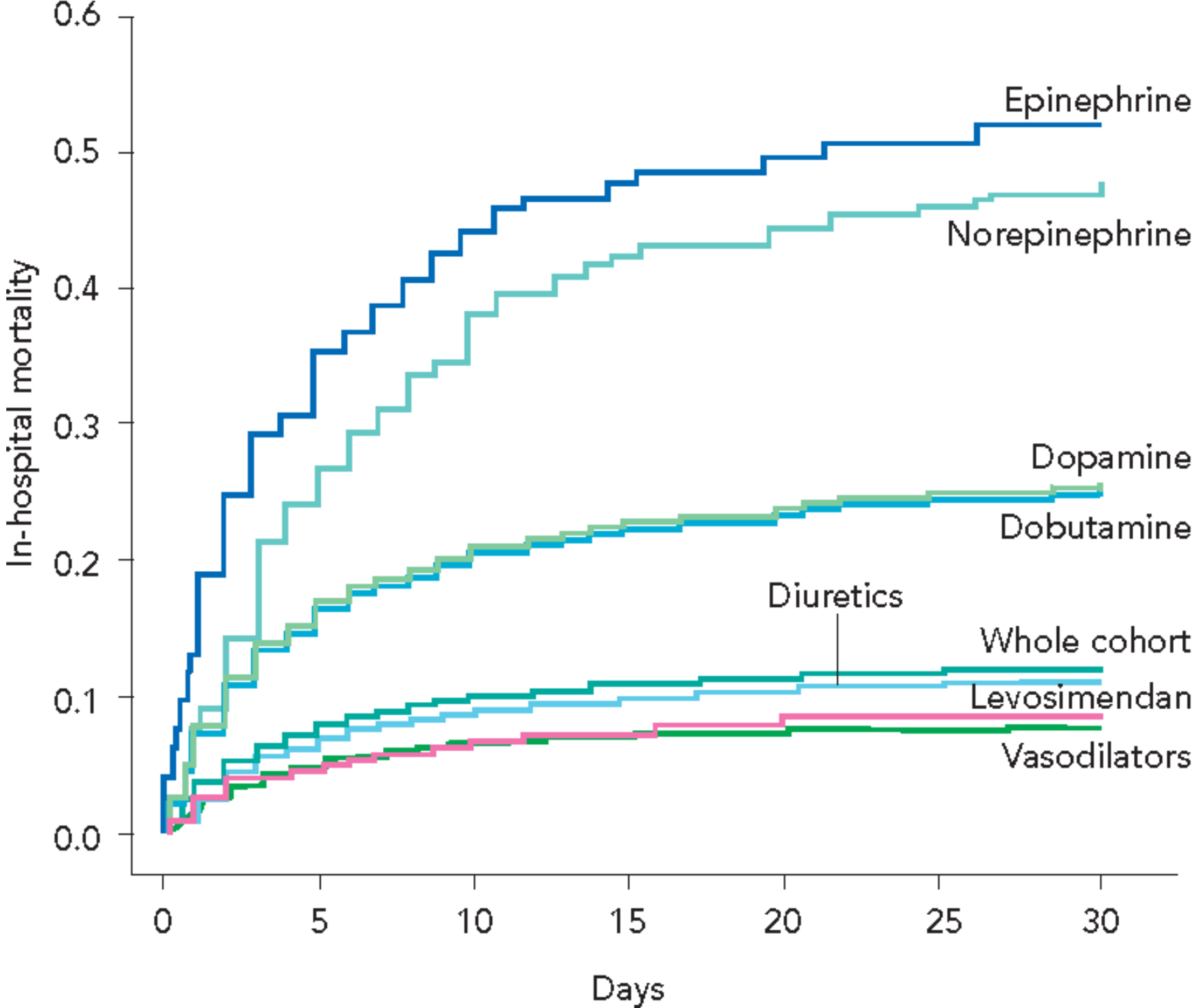



Anesth Analg 2012;114:803–10)

# KEY MESSAGES (2)

- Veins, relative to arterioles, are less affected by locally released metabolic vasodilator factors but are more dominated by sympathetic activity and probably pharmacological interventions (catecholamines)

C.C.Y. Pang / Pharmacology & Therapeutics 90 (2001) 179–230


0.6
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In-hospital mortality
Epinephrine
Norepinephrine
Dopamine
Dobutamine
Diuretics
Whole cohort
Levosimendan
Vasodilators
0
5
10
15
20
25
30
Days

# In many situations

- AHF
- ADHF
- ICU patients

The patients have “normal” arterial circulatory function

BUT are “congestive” because of decreased venous compliance (either with hyper or with normovolemia or even hypovolemia)

“right side” and “left side” decreases in venous compliance

The main credible explanation for the deleterious effects of inotropes/ vasoconstrictors versus (ino)dilators is that vasodilators improve compliance

-venous side (systemic and pulmonary)

- arterial side (ventricle/large artery coupling)

# Right ventricular dysfunction predicts renal dysfunction after cardiac surgery: a possible role for venous congestion

P-G Guinot[1], MD; O Abou Arab[1], MD; D Longrois[2], MD, PhD; H Dupont[1, 3] MD, PhD.

Presented at ESICM 2013, Paris,
Manuscript submitted

# TTE evaluation of RV function

- RVEF: biplane Simpson's method on a four-chamber view.
- The systolic tricuspid annular motion at the lateral wall (Sr(t))
- M-mode annular systolic excursion plane (tricuspid annular systolic plane excursion (TAPSE)) were measured by placing the tissue-Doppler pulse wave and M-mode sample volume at the level of the basal RV free wall.
- Qualitative measure of right ventricular dilatation was estimated from multiple views and graded as no dilation or dilatation.
- Inferior vena cava (IVC) diameter was measured on a subcostal view
- CVP

# Definition of RV dysfunction

- Due to the complex geometry and lack of accepted standards for echocardiographic evaluation of RV function, RV dysfunction (RVd) was defined as ≥ 2 echocardiographic variables of significant RV dysfunction from among the following RV parameters: RVEF, TAPSE, Sr(t) (all in the lowest quartile) and RV dilatation

# Correlation between haemodynamic, right ventricular and left ventricular echocardiographic variables (all measured upon ICU admission) and POD1 sCr variation

| | Univariate | |
|---|---|---|
| | r ($CI_{95\%}$) | *p* value |
| RVEF | -0.36 (-0.54- -0.14) | 0.004 |
| TAPSE | -0.33 (-0.52- -0.11) | 0.004 |
| Systolic lateral tricuspid annular motion velocity | -0.03 (-0.26-0.19) | 0.07 |
| IVC diameter | 0.31 (0.09-0.5) | 0.007 |
| CVP | 0.36 (0.14-0.54) | 0.001 |
| LVEF | 0.03 (-0.19-0.26) | 0.78 |
| MAP | 0.16 (-0.23-0.23) | 0.91 |
| Cardiac index | -0.09 (-0.32- 0.14) | 0.43 |
| Postoperative fluid balance | -0.11 (-0.33-0.12) | 0.35 |
| CPB duration | 0.16 (-0.09-0.36) | 0.17 |

# Factors associated with AKI

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR ($CI_{95\%}$) | *p* value | OR ($CI_{95\%}$) | *p* value |
| Right ventricular dysfunction | 17.7 (3.7-83.9) | 0.0001 | 12.7 (2.6-63.4) | 0.02 |
| Diuretic treatment | 7.9 (2.5-24.9) | 0.0001 | 5.2 (1.5-18.3) | 0.01 |
| Norepinephrine treatment | 4.9 (1.8-13.4) | 0.002 | | |
| Postoperative transfusion | 5 (1.5-16.9) | 0.01 | | |

# Mechanisms of RV dysfunction ?

# Cross-Talk Between Cardiac Muscle and Coronary Vasculature

NICO WESTERHOF, CHRISTA BOER, REGIS R. LAMBERTS, AND PIETER SIPKEMA

*Laboratory for Physiology and Department of Anesthesiology, Institute for Cardiovascular Research Vrije Universiteit, VU University Medical Center, Amsterdam, The Netherlands*

Physiol Rev 86: 1263–1308, 2006;

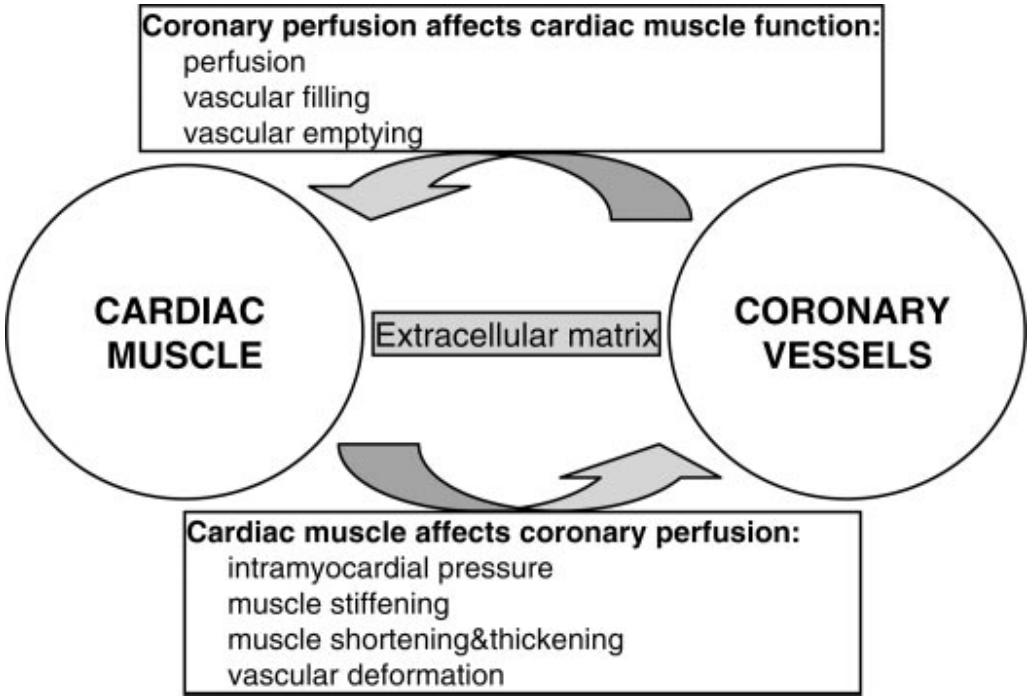



FIG. 38. Summary of the major mechanisms of mechanical cross-talk.

Physiol Rev 86: 1263–1308, 2006;

# Improvement of Donor Myocardial Function after Treatment of Autonomic Storm During Brain Death

*Gérard Audibert,[1,2] Claire Charpentier,[1] Carole Seguin-Devaux,[2] Pierre-Alain Charretier,[1] Hélène Grégoire,[3] Yvan Devaux,[2] Jean-François Perrier,[1] Dan Longrois,[1,2] and Paul-Michel Mertes[1,2,4]*

**TABLE 3.** Cardiac graft evaluation according to the occurrence of autonomic storm and its treatment

| | No AS | AS-nT | AS-T | *P* value |
|---|---|---|---|---|
| N | 17 | 17 | 12 | |
| CK-MB/CK >10% (%) | 23.5 | 8.3 | 20.0 | 0.565 |
| c-Troponin I (mean ng/ml±SD) | 2.5±3.8 | 1.8±2.3 | 1.7±4.4 | 0.709 |
| LVEF (mean %±SD) | 55.4±13.4 | 49.0±18.8 | 63.9±10.3[a] | 0.049 |
| Cardiac transplantation (%) | 10 (58.8) | 7 (41.2) | 11 (91.7)[b] | 0.023 |
| Patient survival at 2 months (%) | 8 (80) | 3 (43) | 11 (100)[b] | <0.001 |

[a] $P < 0.05$ versus AS-nT group.
[b] $P < 0.01$ versus AS-nT group.
No AS, no autonomic storm; AS, autonomic storm; AS-nT, untreated autonomic storm; AS-T, treated autonomic storm; LVEF, left ventricular ejection fraction.

Transplantation 2006;82: 1031–1036

**TABLE 5.** Independent prognostic factors of good myocardial function (LVEF >50%)

| Parameter | N | Odds ratio | 95% CI | *P* value |
|---|---|---|---|---|
| Autonomic storm treatment | | | | |
| AS-nT | 14 | 1 | — | — |
| No AS | 16 | 2.7 | 0.52; 14.08 | — |
| AS-T | 12 | 15.2 | 1.25; 185.50 | 0.034 |
| CK-MB/CK | | | | |
| ≤10% | 36 | 1 | — | — |
| >10% | 6 | 0.13 | 0.01; 1.13 | 0.043 |

Multiple logistic regression adjusted on age and sex (n=42).

No AS, no autonomic storm; AS, autonomic storm; AS-nT, untreated autonomic storm; AS-T, treated autonomic storm; LVEF, left ventricular ejection fraction.

Transplantation 2006;82: 1031–1036

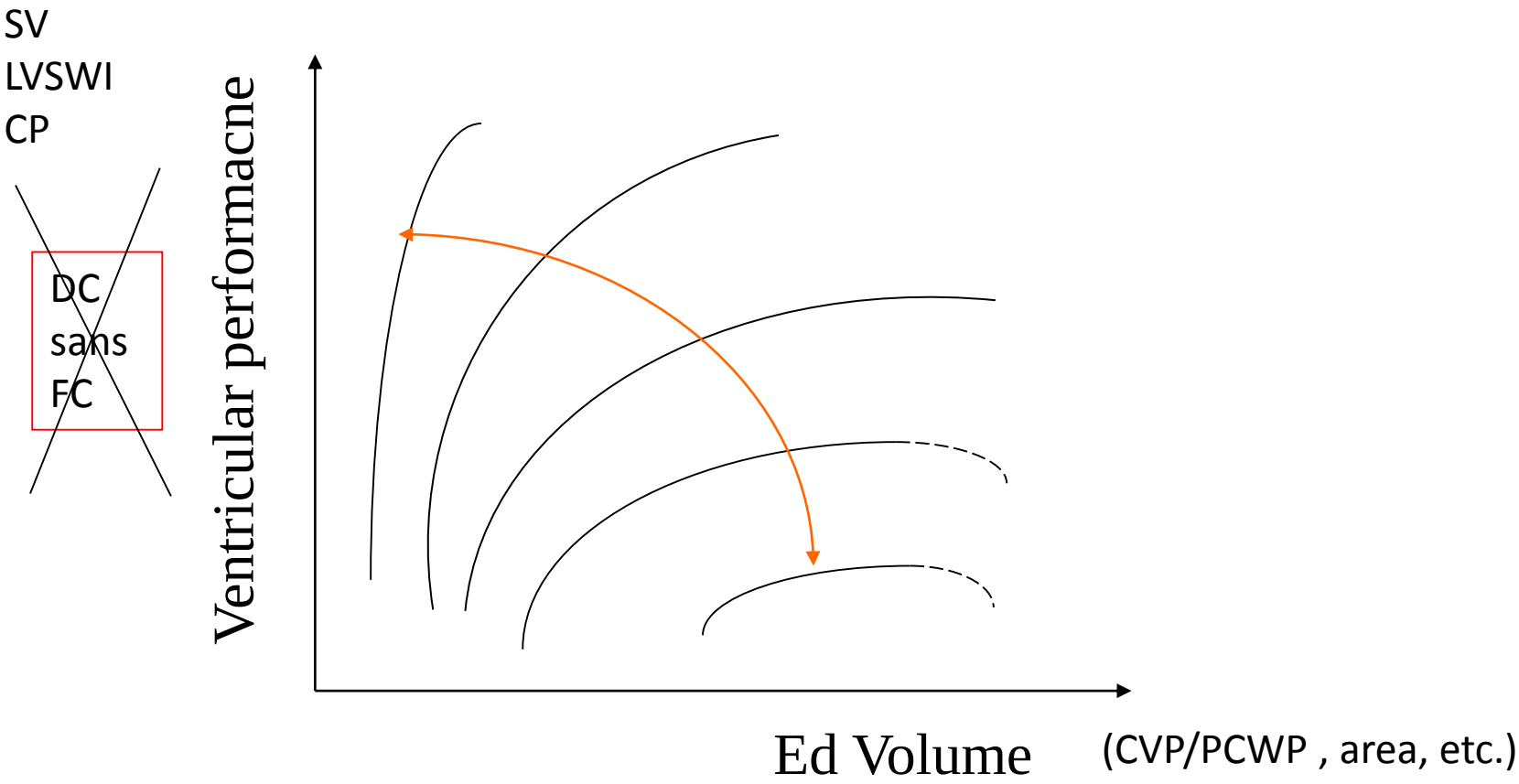
# My conclusions (2)

- When designing clinical trials on vasodilators one should have a (validated) hemodynamic model with
  - Monitoring tools that can be used in clinical practice +++++
  - Defined therapeutic goals
- The present-day hemodynamic model is WRONG

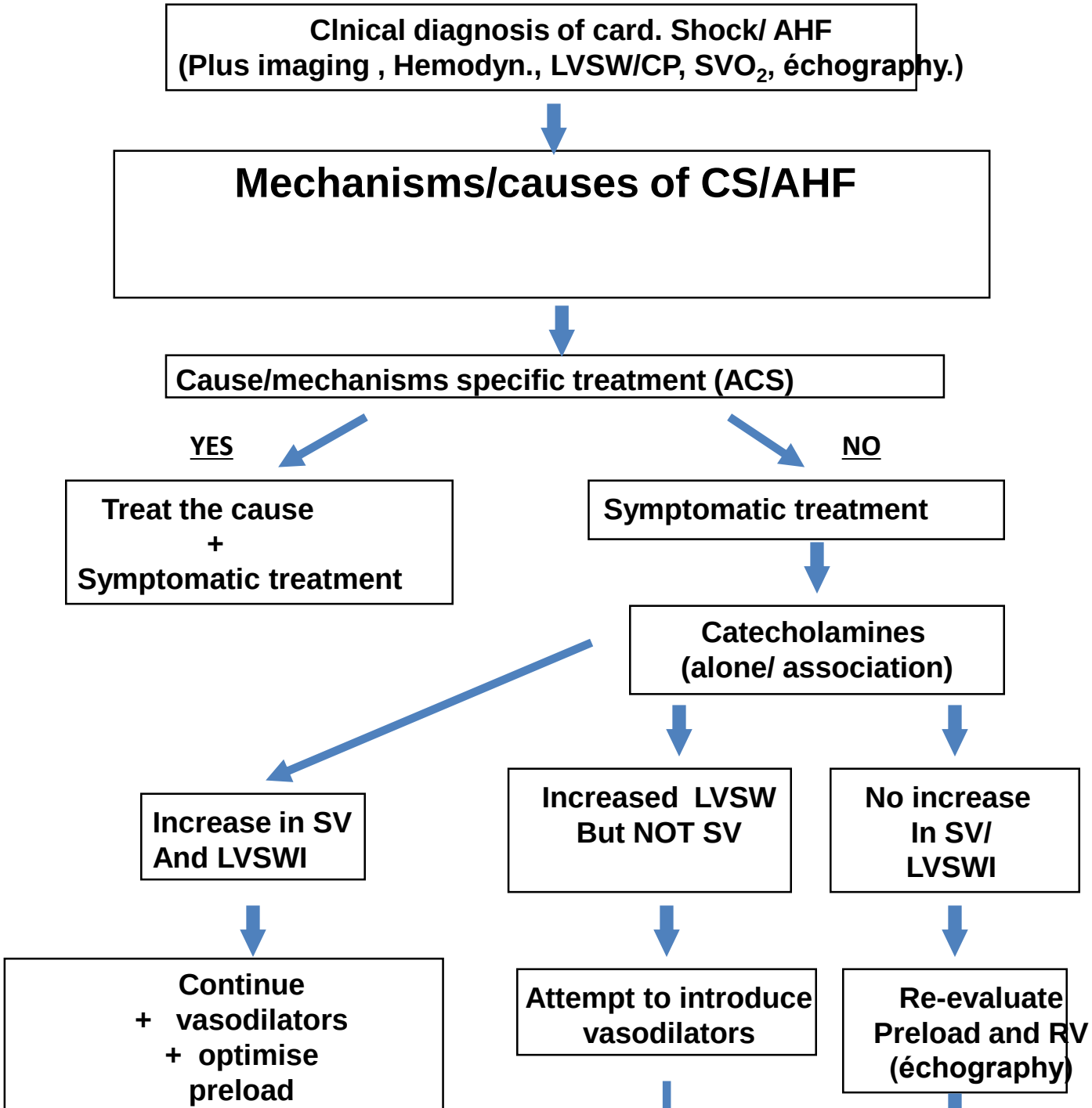
# Clinical reasoning

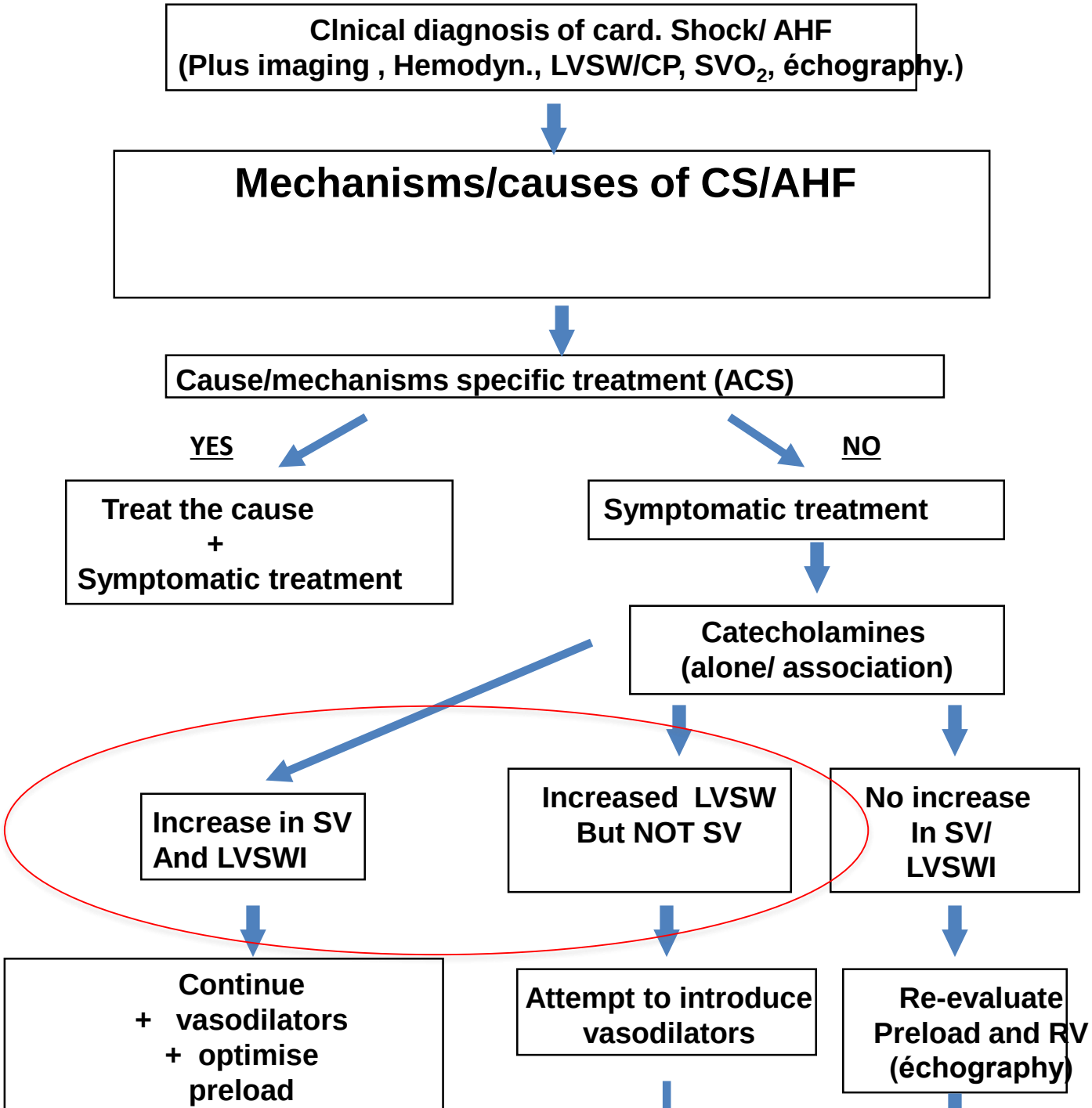
How do you evaluate the efficacy/side effects of inotropic drugs/interventions ?

# Evaluation of clinical efficacy of inotropic interventions




E. Braunwald, 1992


Clnical diagnosis of card. Shock/ AHF
(Plus imaging , Hemodyn., LVSW/CP, SVO2, échography.)
Mechanisms/causes of CS/AHF
Cause/mechanisms specific treatment (ACS)
YES
NO
Treat the cause
+
Symptomatic treatment
Symptomatic treatment
Catecholamines
(alone/ association)
Increase in SV
And LVSWI
Increased LVSW
But NOT SV
No increase
In SV/
LVSWI
Continue
+ vasodilators
+ optimise
preload
Attempt to introduce
vasodilators
Re-evaluate
Preload and RV
(échography)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Continue
+ vasodilators
+ optimise
preload
Attempt to introduce
vasodilators
Re-evaluate
Preload and RV
(échography)

# Examples

- HR= 90 bpm; SV= 35 ml; CO = 3.15 l/min
  - SvO2 = 55 %; Lactate 2.9 mmol/L; SBP : 92 mmHg
- Inotropes (dobutamine)
  - Scenario 1: HR = 95; SV= 42 ml; CO= 3.99 l/min
    - Sv02= 65 %; Lactate ?; SBP 100 mmHg
  - Scenario 2: HR= 120; SV= 32; C0= 3.84 l/min
    - SvO2= 62 %, Lactate ? ; SBP 100 mmHg
  - Scenario 3: HR= 140; SV= 20; CO = 2.8 l/min
    - SvO2= 40; Lactate ?; SBP 70 mmHg
    - Possible causes ?

# Possible causes of scenario 3

- Obstructive CM
  - SAM ++++
- Atrial fibrillation
- Myocardial ischemia
- Hypovolemia
- Acute RV dilatation
  - Why with dobutamine ?

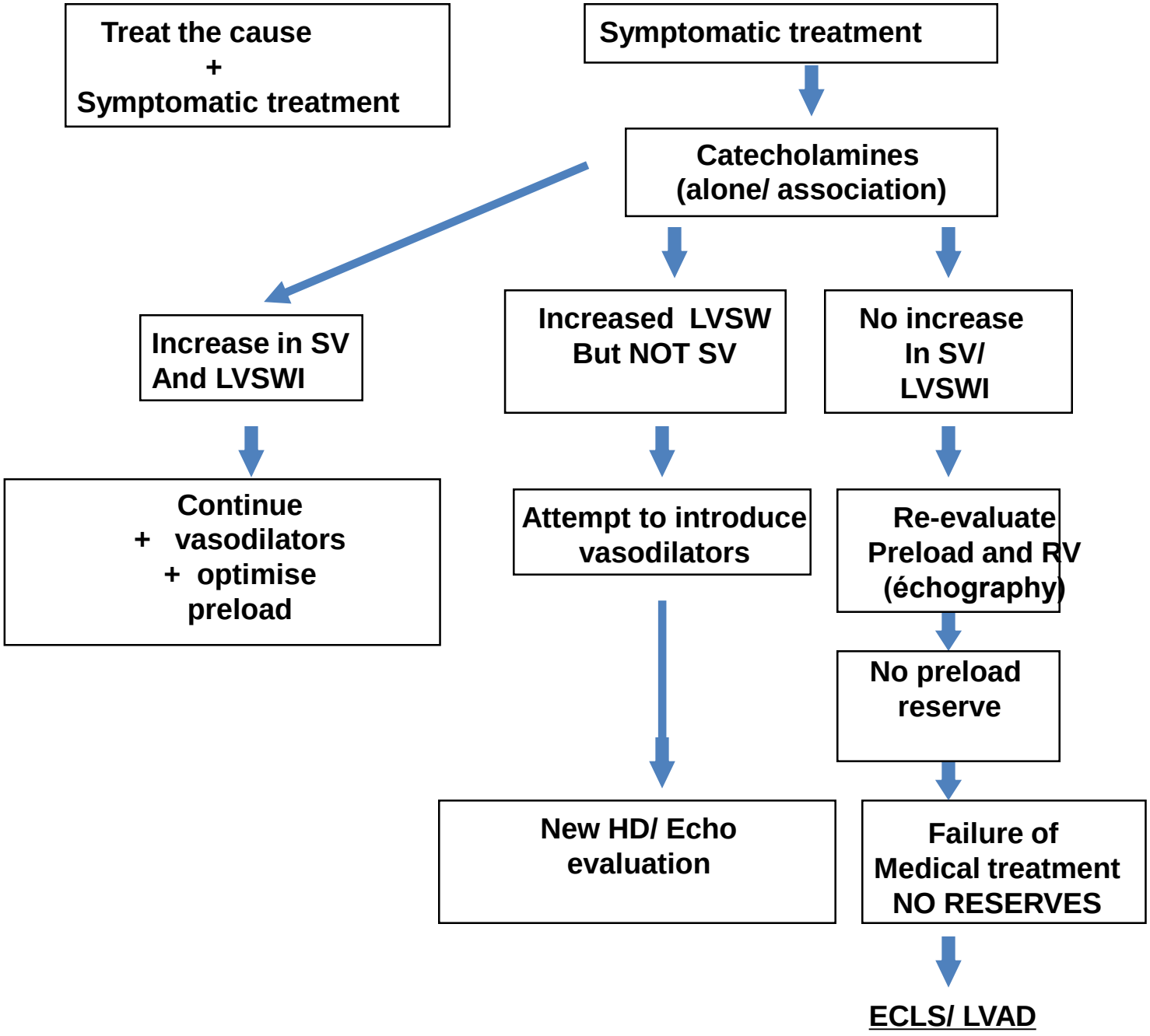
REVIEWS

# Update on hypertrophic cardiomyopathy and a guide to the guidelines

*Srijita Sen-Chowdhry[1,2], Daniel Jacoby[3], James C. Moon[1,4] and William J. McKenna[5]*

NATURE REVIEWS | CARDIOLOGY

VOLUME 13 | NOVEMBER 2016 | 651


Treat the cause
+
Symptomatic treatment
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Catecholamines
(alone/ association)
Increase in SV
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Increased LVSW
But NOT SV
No increase
In SV/
LVSWI
Continue
+ vasodilators
+ optimise
preload
Attempt to introduce
vasodilators
Re-evaluate
Preload and RV
(échography)
No preload
reserve
New HD/ Echo
evaluation
Failure of
Medical treatment
NO RESERVES
ECLS/ LVAD

# Conclusions (1)

- Inotropes/vasodilators may have complex effects
- The most important issues are:
  - Understanding physiology/pathophysiology
  - Measuring
    - Hemodynamics +++++
      - Heart, heart vessels/interactions, organ hemodynamics
    - Echocardiography ++++++++++++++++++++++++++
    - Biology

# Conclusions (2)

- In chronic/acute settings, a pharmacological intervention can modify the system
  - One can become pre-load dependent even if one has CHF/ AHF +++++
- Essential to understand/use an algorithm to define the failure of pharmacological interventions rapidly (< 6 hours)
- Possibility to mechanically assit the heart
  - ECLS/LVAD/VAD