Pulmonary hypertension and right ventricular failure

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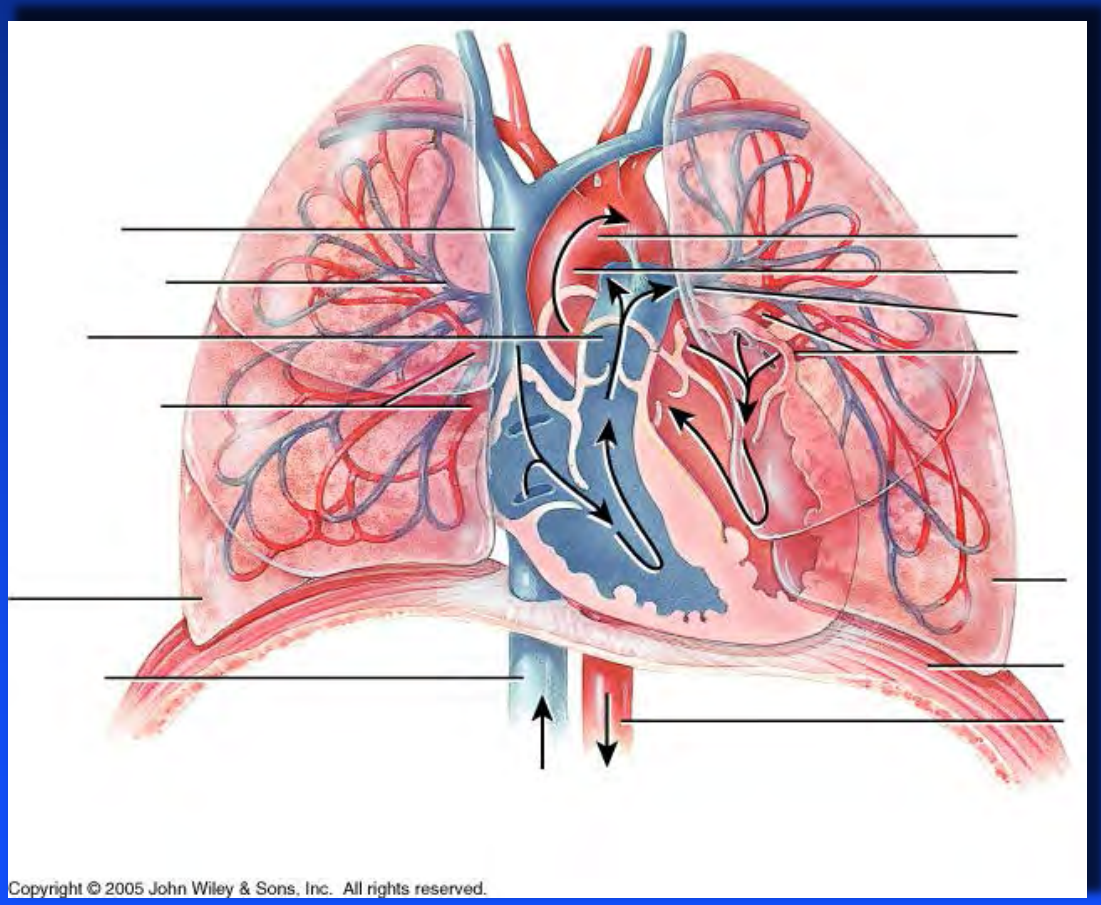
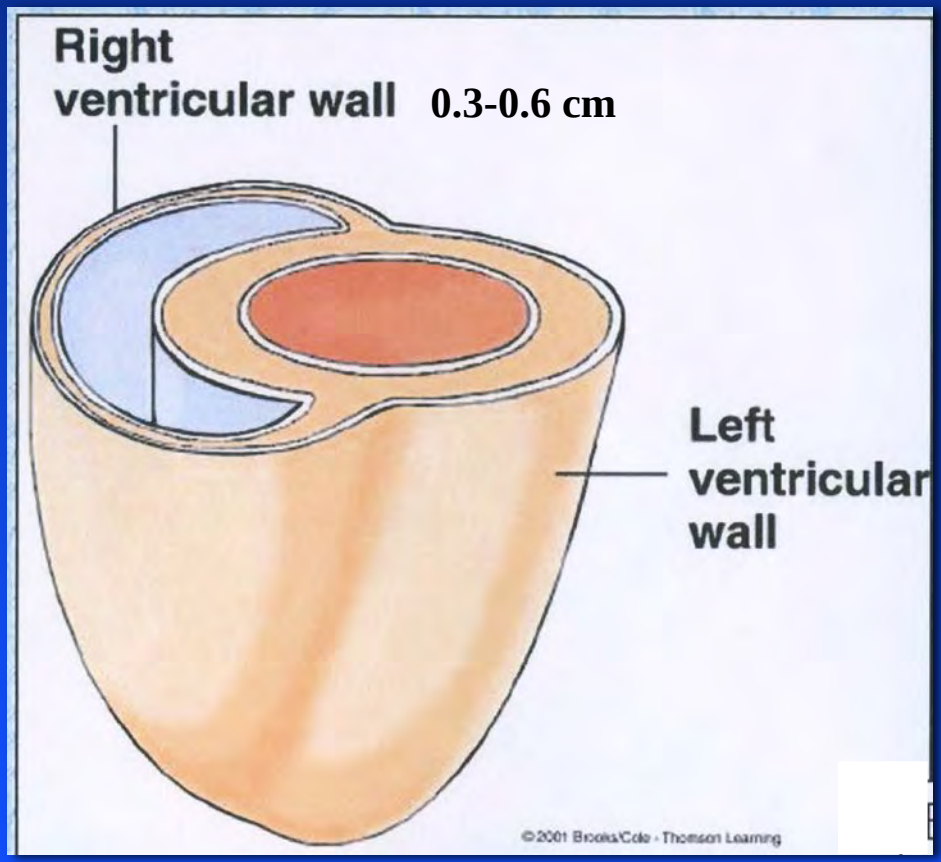
Pulmonary circulation and the right ventricle (RV)

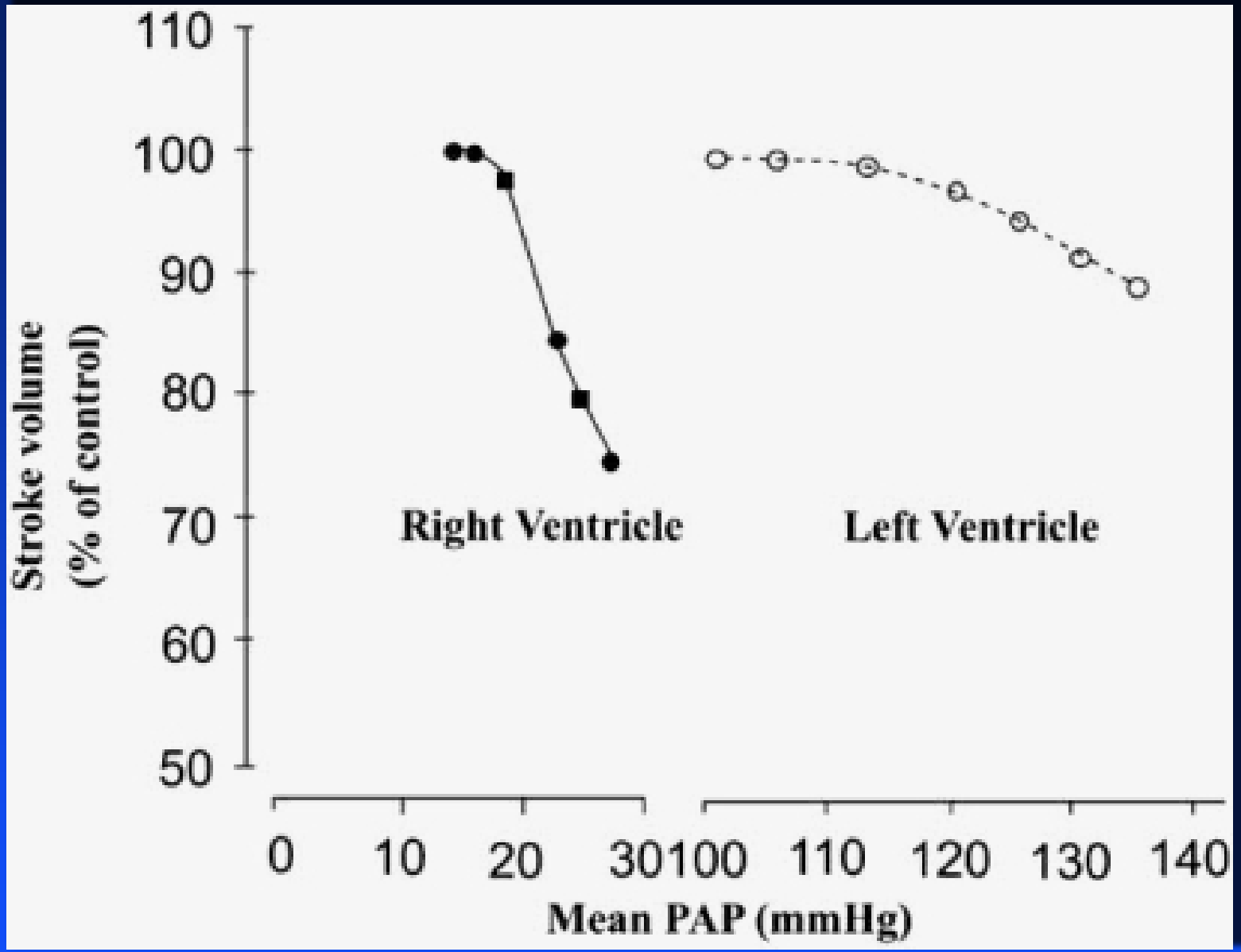
- Low resistance, low pressure, high capacitance circuit
- 3-4 fold increase in RV stroke volume with no major change in pulmonary artery pressure



Pulmonary circulation and the right ventricle (RV)

- RV stroke work is 1/6 of the LV
- Crescent-shaped geometry with a high compliance
- Poor tolerance to an increase in RV afterload





Matthews and McLaughlin Current Cardiology Reviews 2008;4:49-59

Pulmonary hypertension

- MPAP > 25 mmHg or SPAP > 55 mmHg
- RV hypertrophy/failure
- Classification:

-Pulmonary arterial hypertension

-primary, idiopatic pulmonary hypertension (sporadic, familial)

-related to collagen diseases (sclerodermi, lupus, RA)

-portopulmonary hypertension

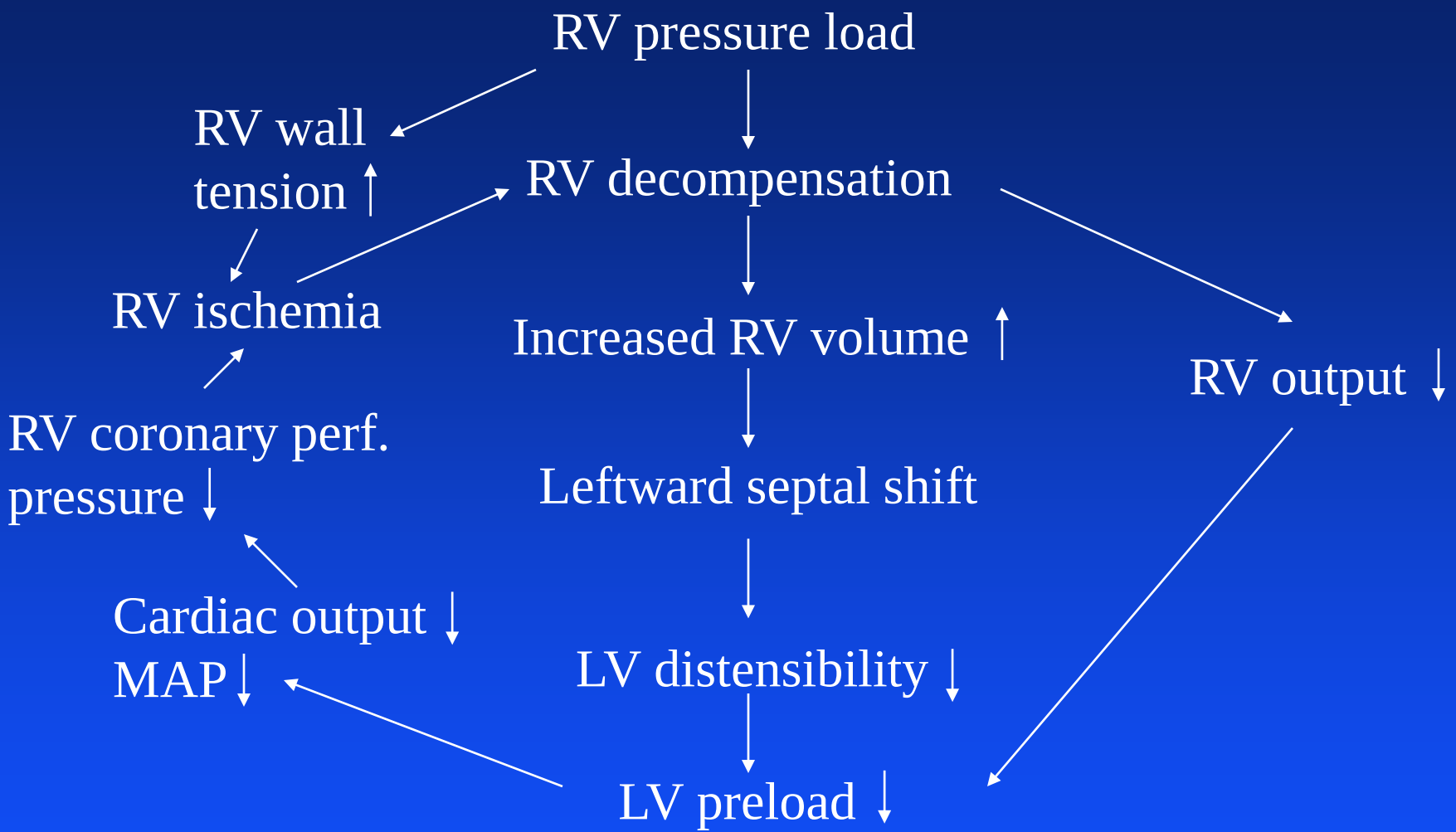
-Pulmonary venous hypertension (LV failure, valve disease)

-Pulmonary hypertension assoc. with lung disease

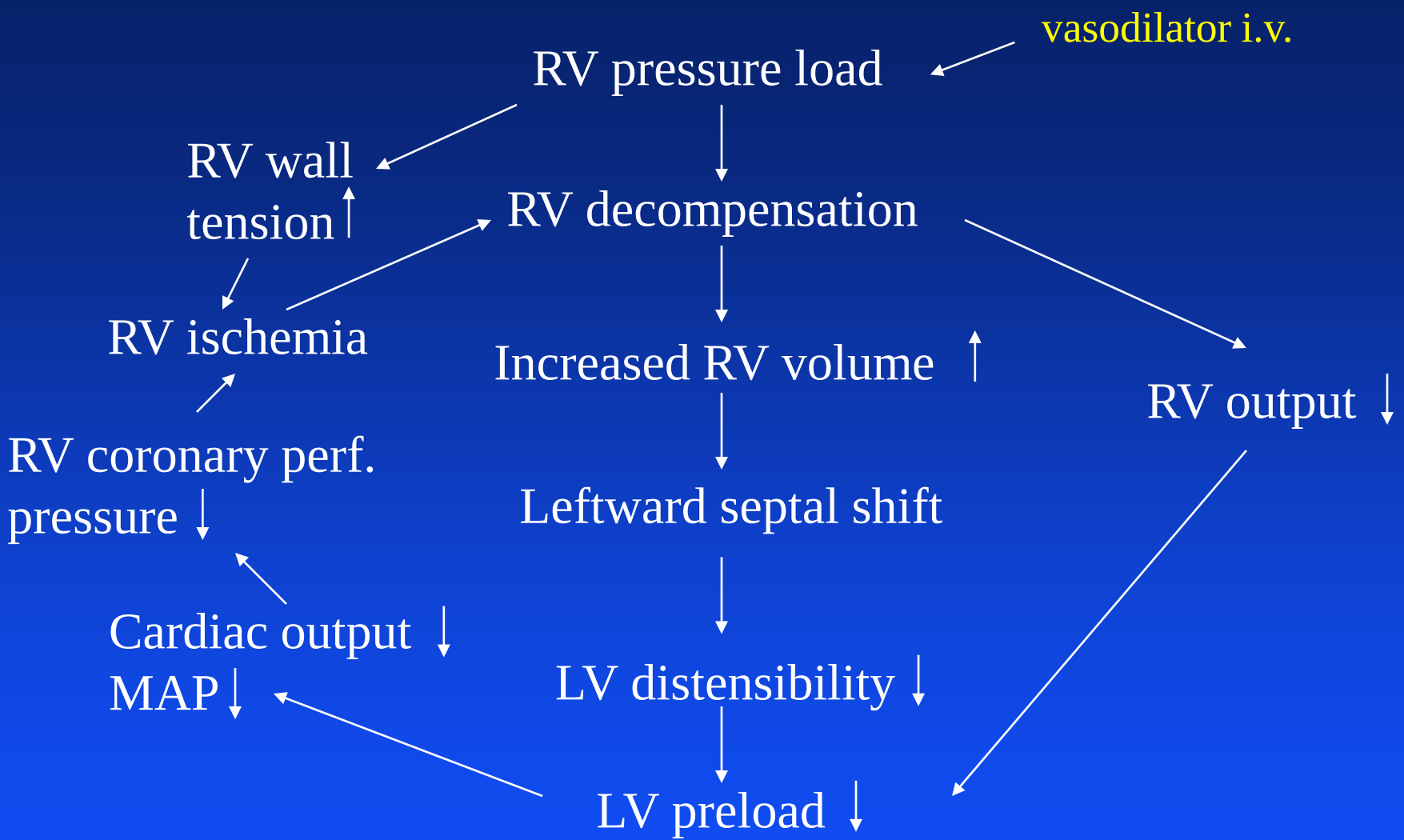
-Pulmonary hypertension caused by thromboembolic disease

$$(MPAP - PCWP) = CO \times PVR$$

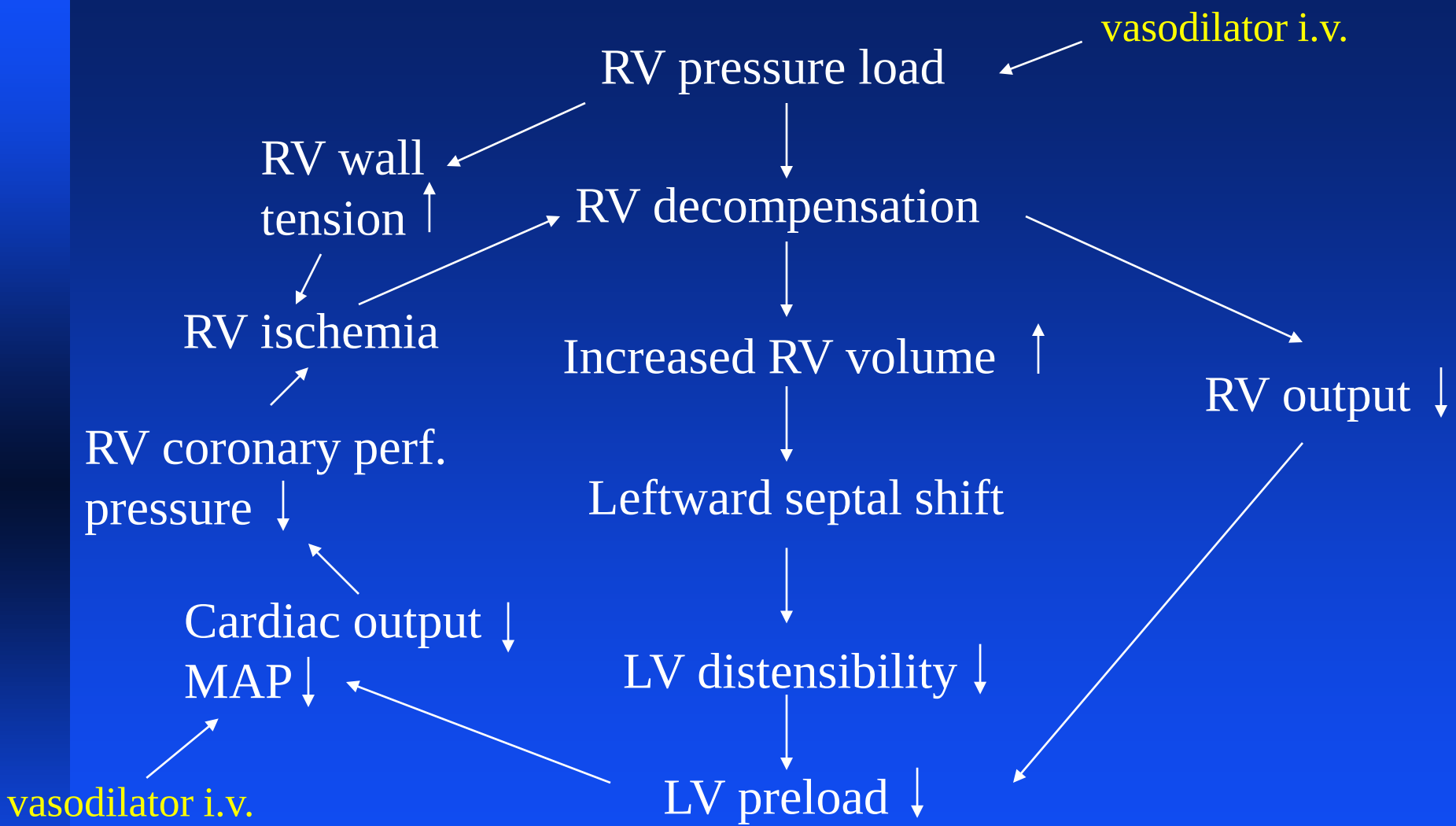
$$MPAP = PCWP + (CO \times PVR)$$



The pathophysiology of acute right ventricular failure in pulmonary hypertension

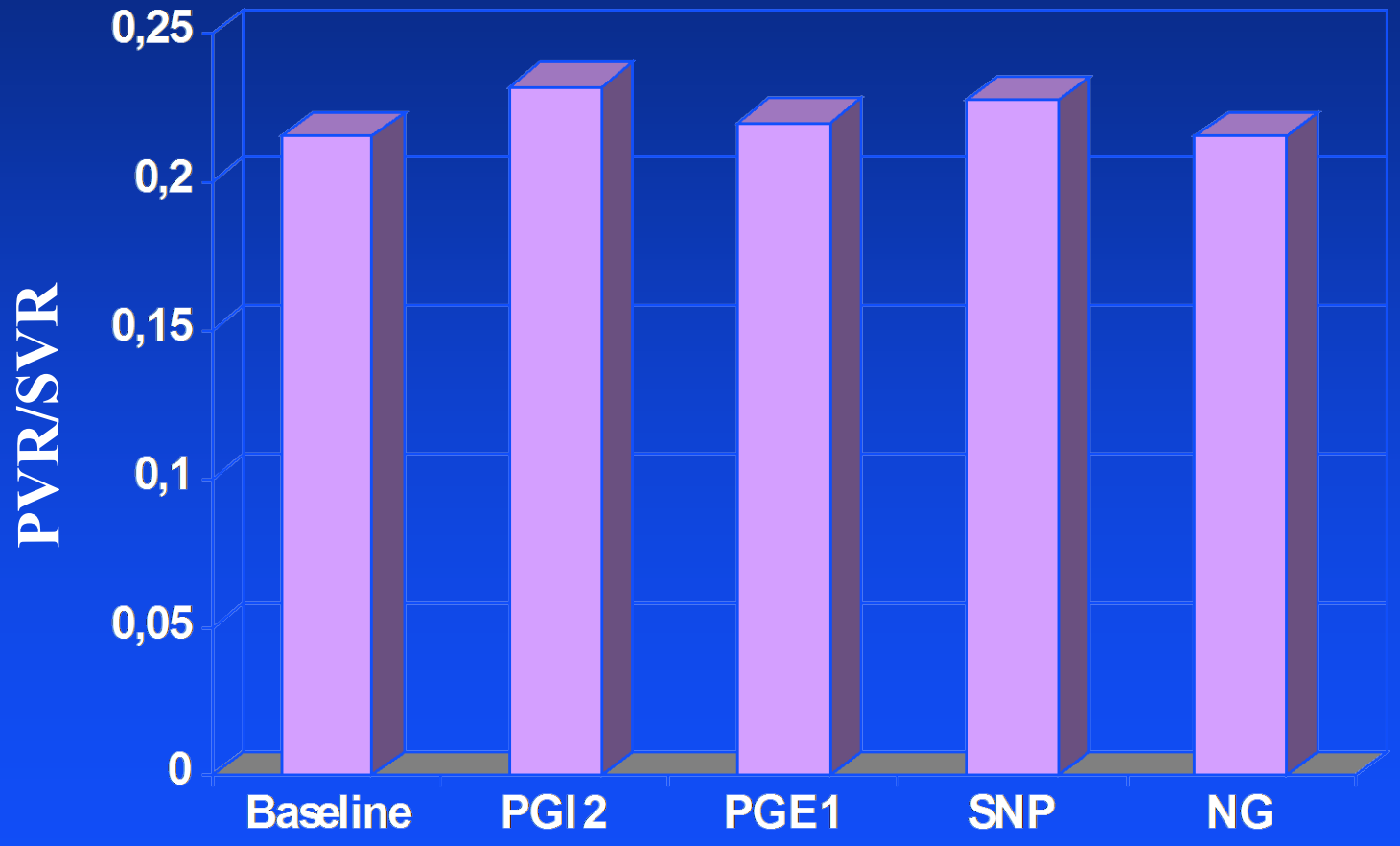


The pathophysiology of pulmonary hypertension
acute right ventricular failure



The pathophysiology of pulmonary hypertension
acute right ventricular failure

Intravenous vasodilators and pulmonary selectivity (PVR/SVR ratio)



Kieler-Jensen et al J Heart Lung Transplant 1995;14:436

The Nobel Prize in Physiology or Medicine 1998

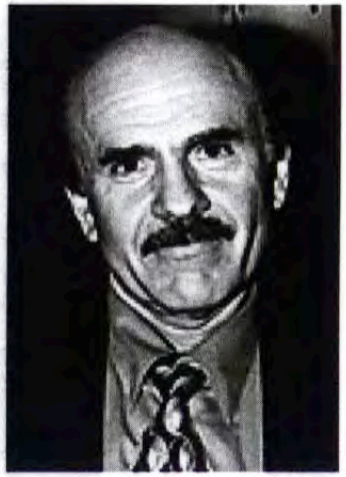
"for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system"

Robert F. Furchgott

1/3 of the prize

USA

SUNY Health Science Center
Brooklyn, NY, USA



Louis J. Ignarro

1/3 of the prize

USA

UCLA School of Medicine
Los Angeles, CA, USA

Ferid Murad

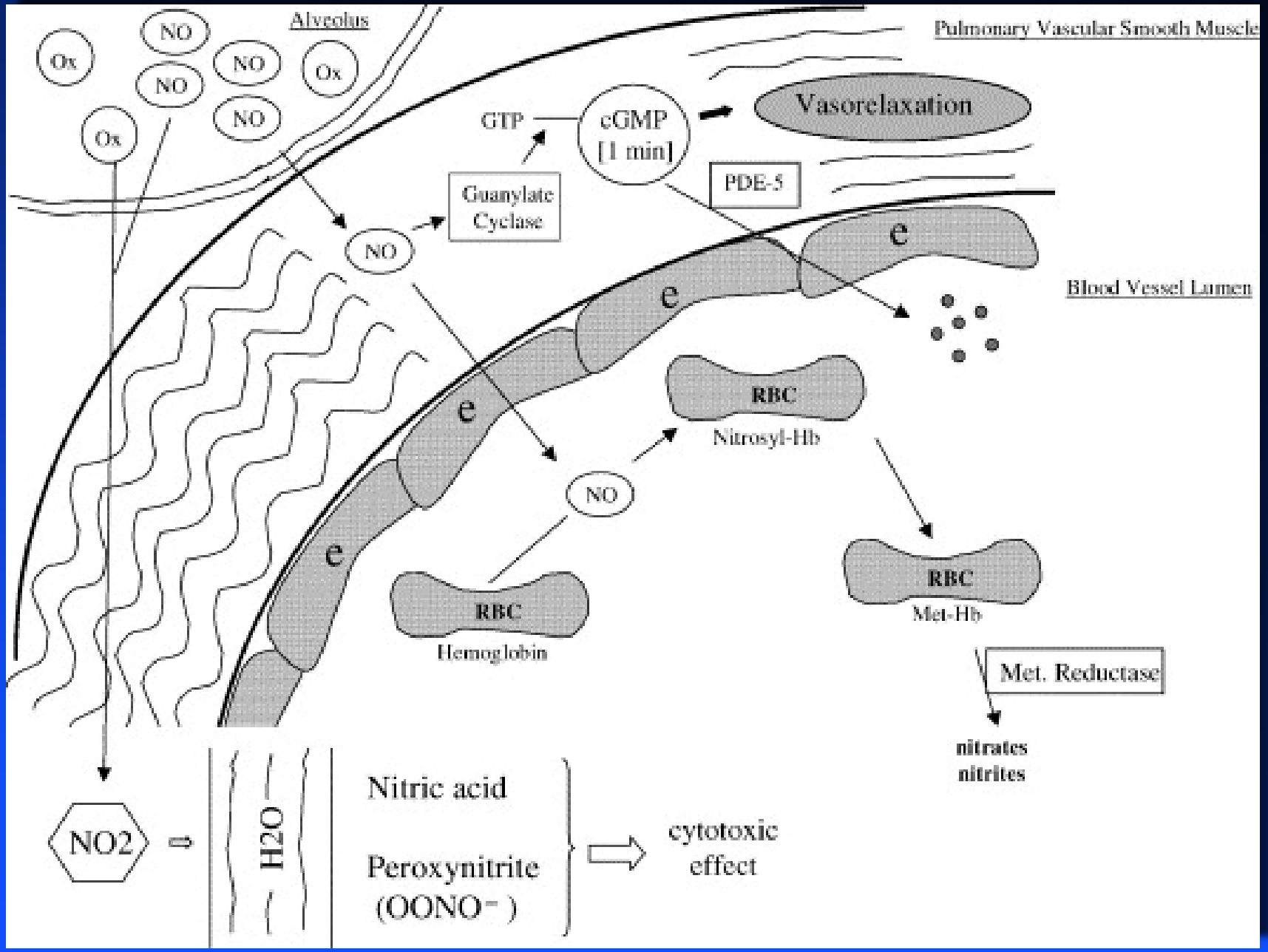
1/3 of the prize

USA

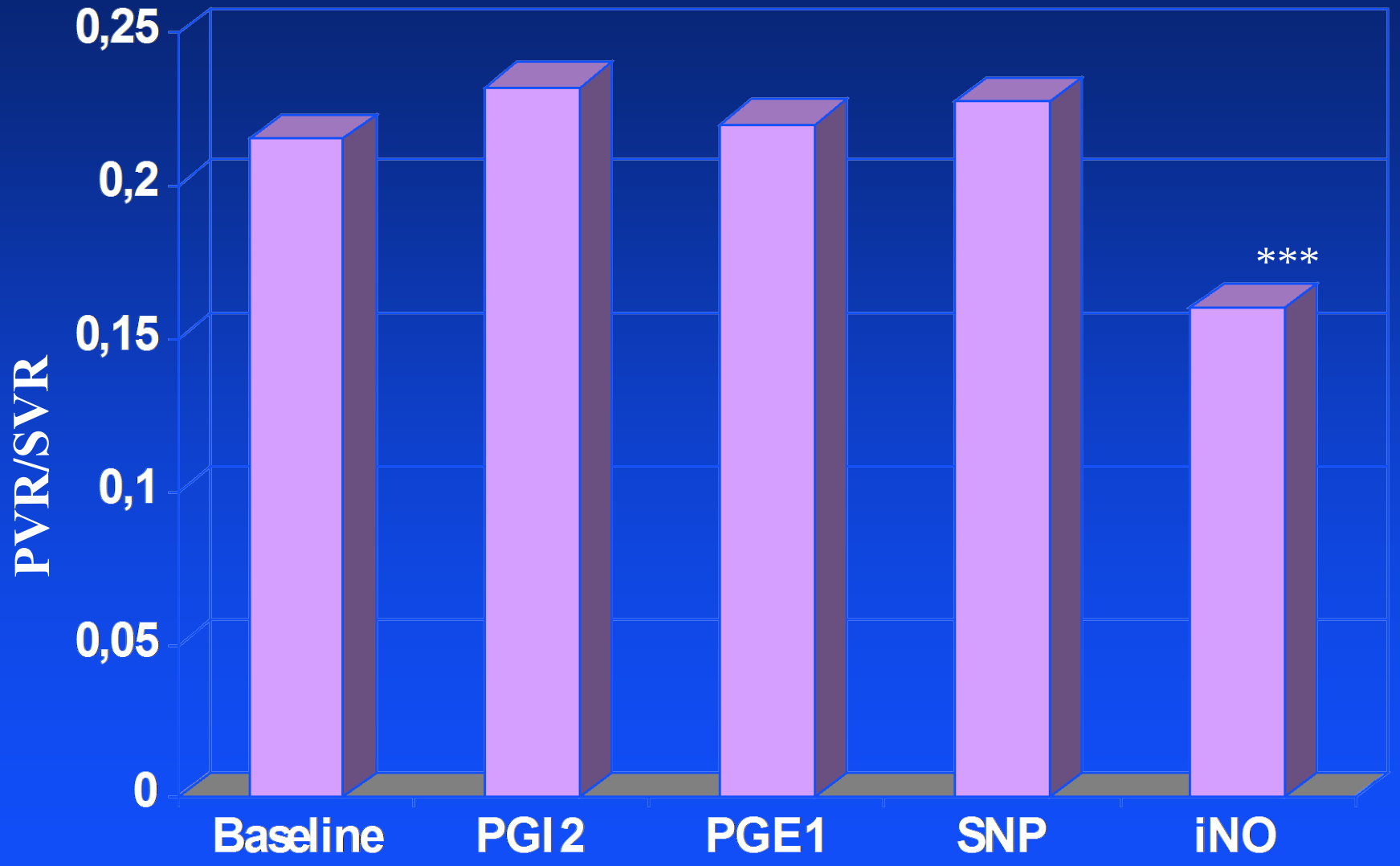
University of Texas Medical School at Houston
Houston, TX, USA

EDRF = NO

Inhaled NO – mechanisms of action



Effects of inhaled NO on the PVR/SVR ratio



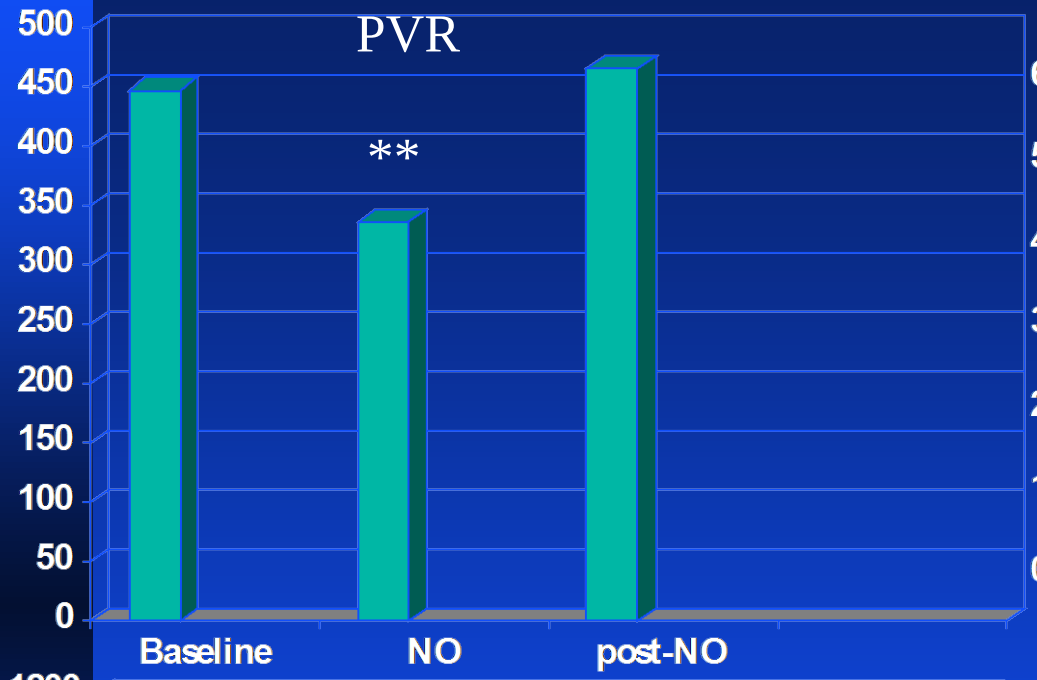
Kieler-Jensen et al J Heart Lung Transplant 1995;14:436

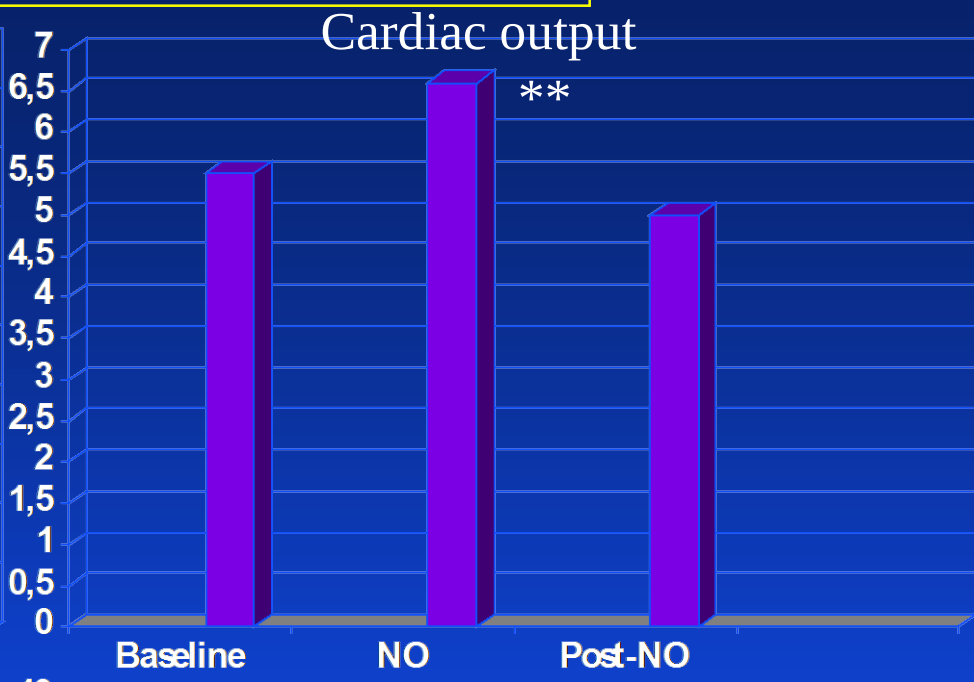
Inhaled NO in ARDS-induced RVF

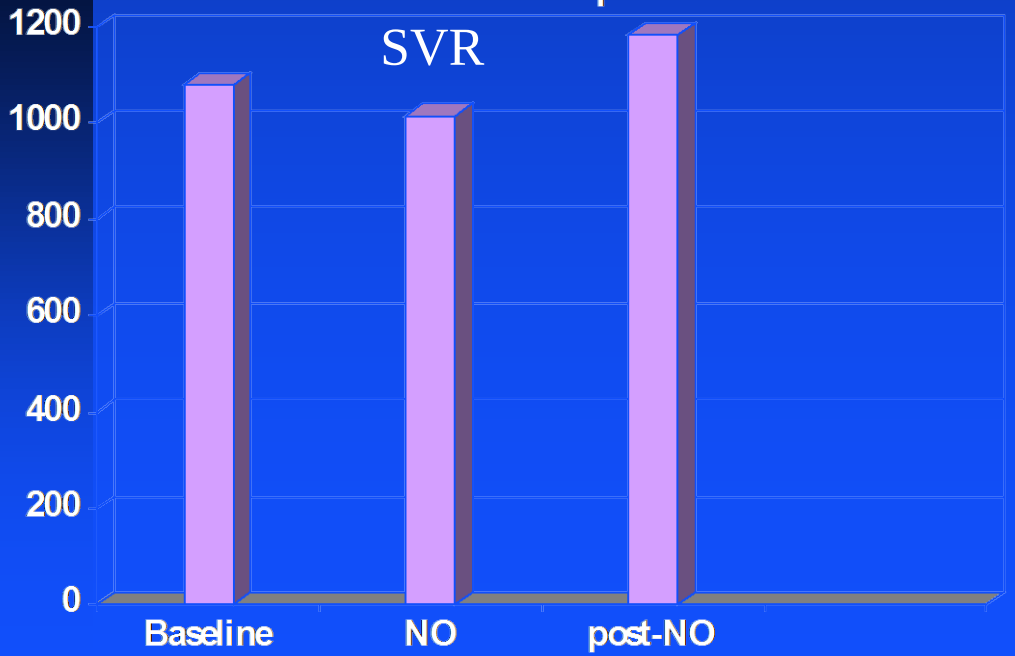
- Twenty-six patients with RVF because of ARDS
- Incremental concentrations of inhaled NO (mean 35 ppm)

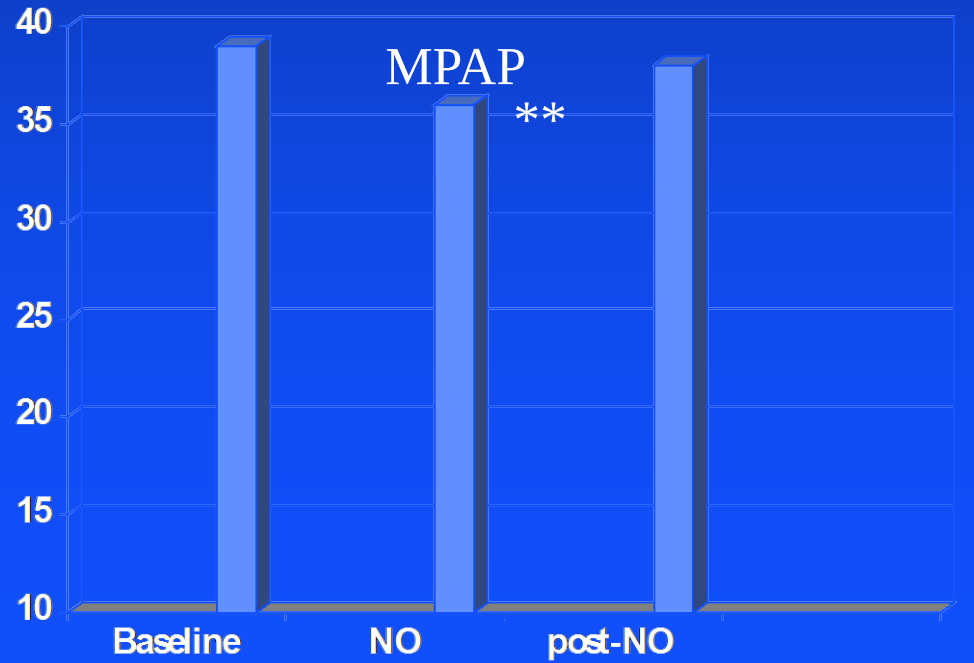
Bhorade et al Am J Respir Crit Care Med 1999;159:571-579

Inhaled NO in ARDS-induced RVF





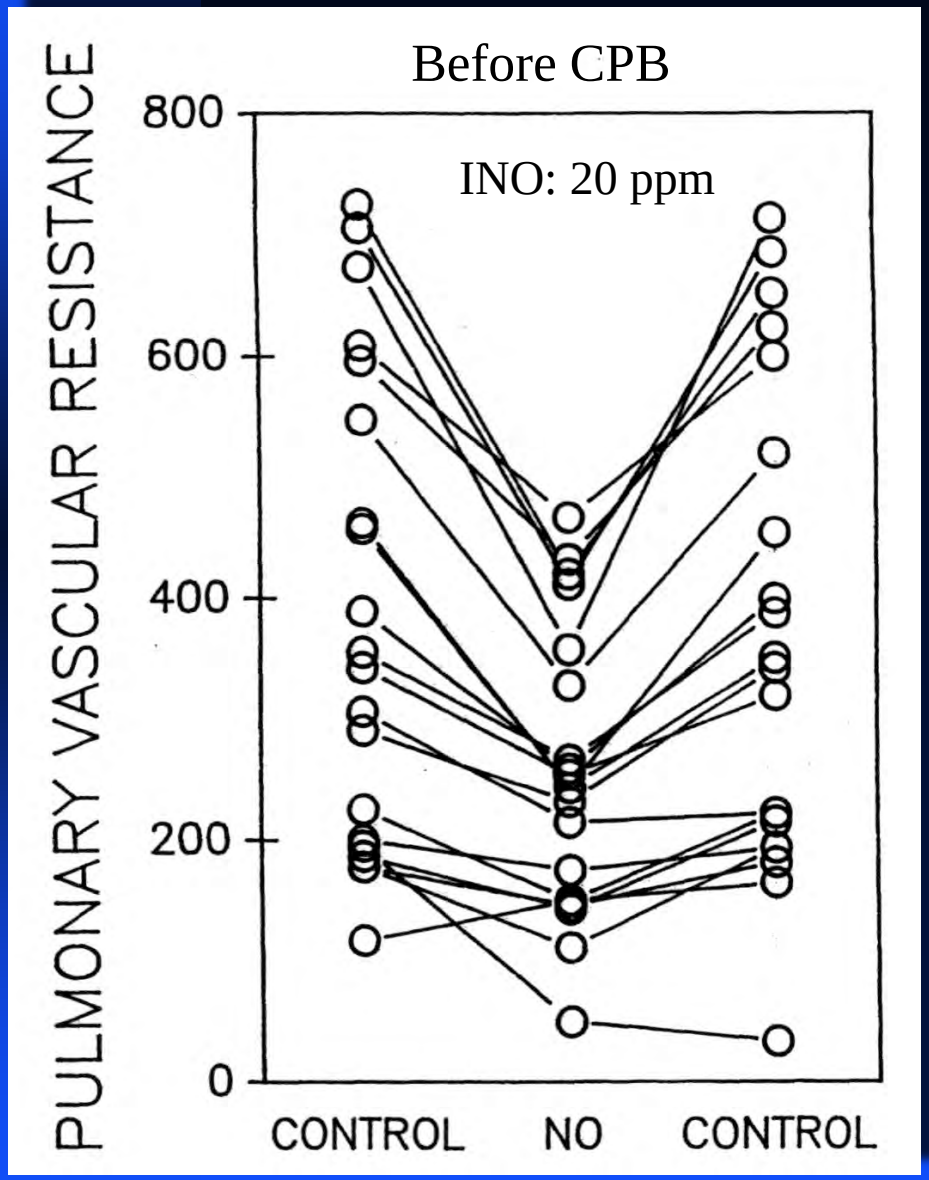


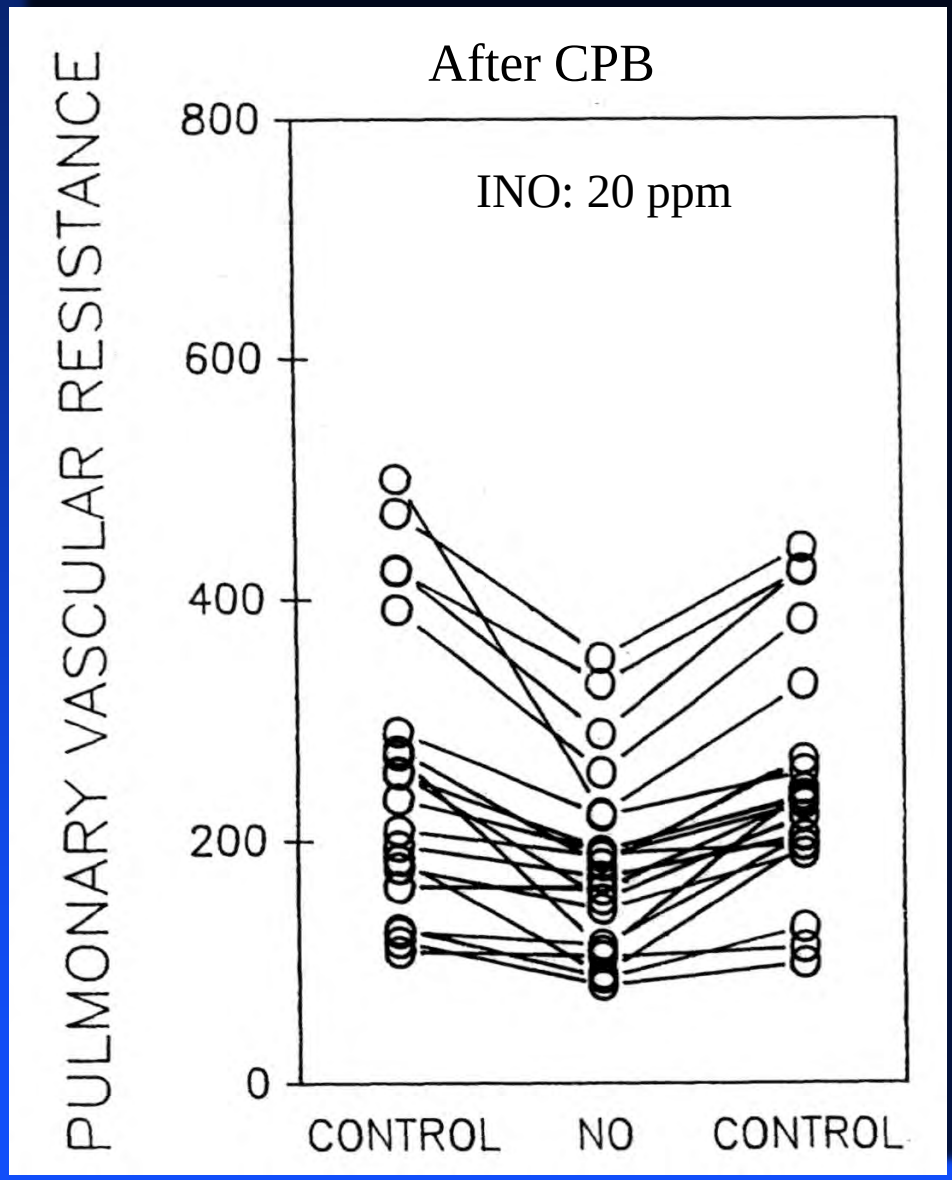


Inhaled NO in cardiac surgery

- High preoperative PVR in valvular heart disease
- Endothelial dysfunction after cardiopulmonary bypass

Inhaled NO before and after MVR or CABG



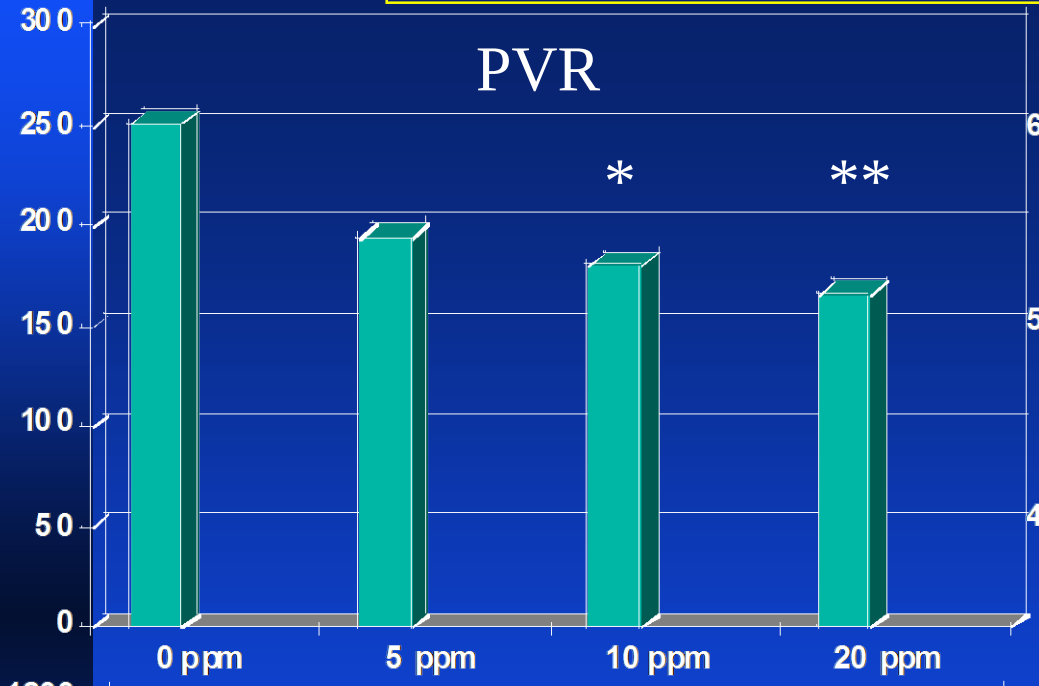


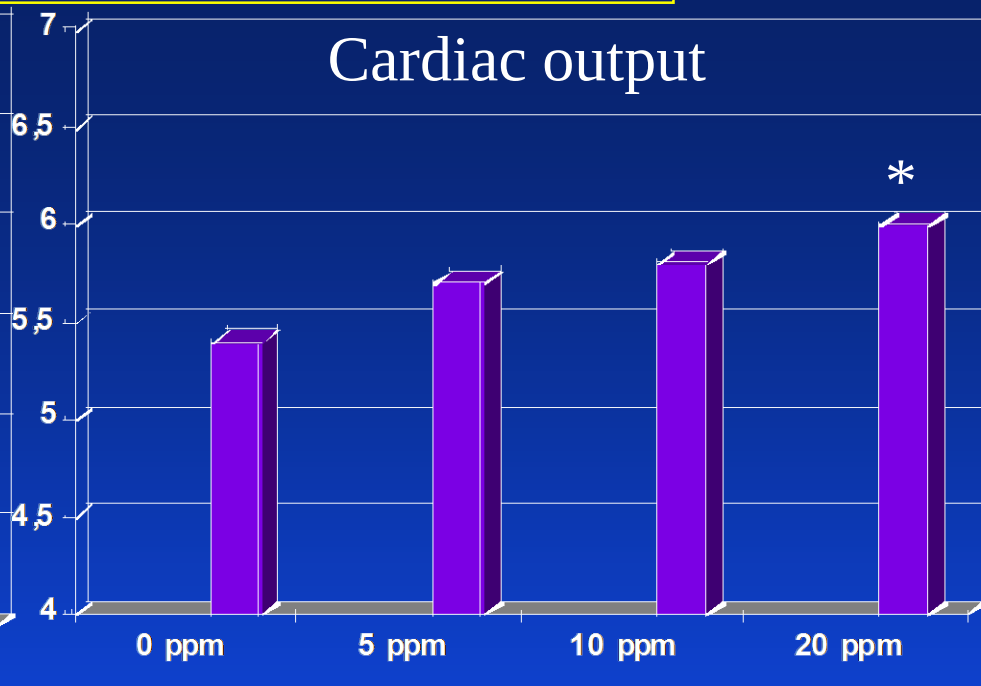
Rich et al Anesthesiology 1993;78:1028

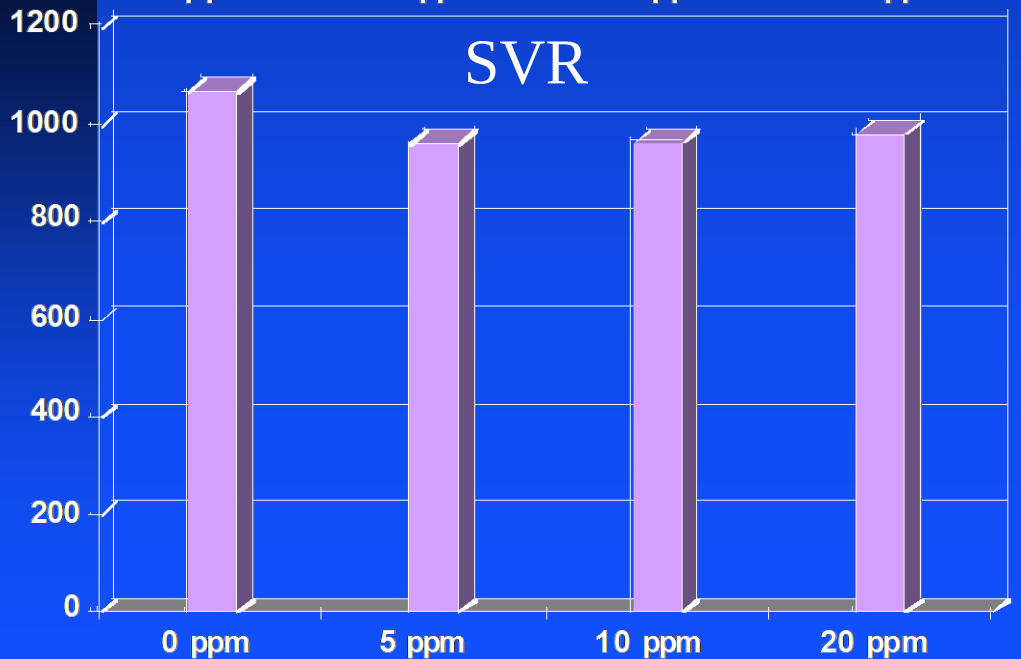
Inhaled NO in heart transplantation

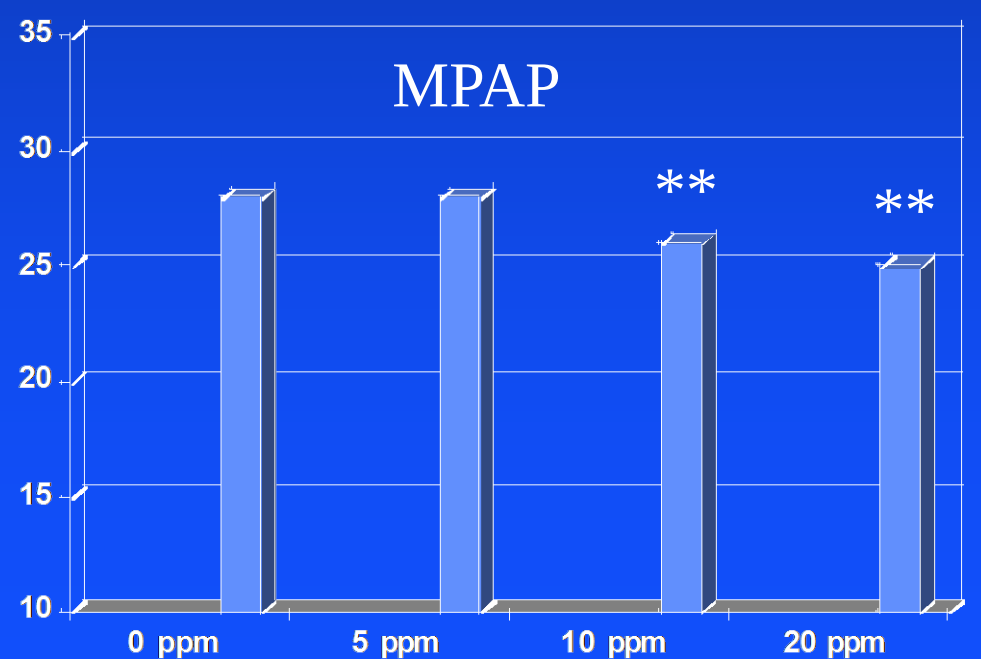
Kieler-Jensen et al J Heart Lung Transplant 1995;14:436-443

Inhaled NO in heart transplantation

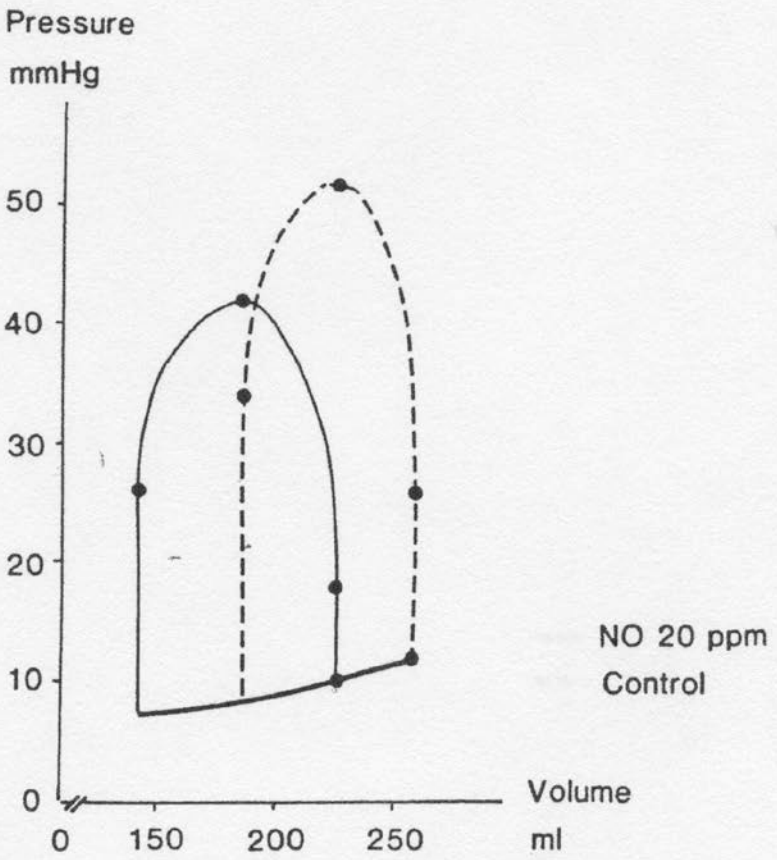








RV pressure-volume curve after heart transplantation - effects of inhaled NO (20ppm)

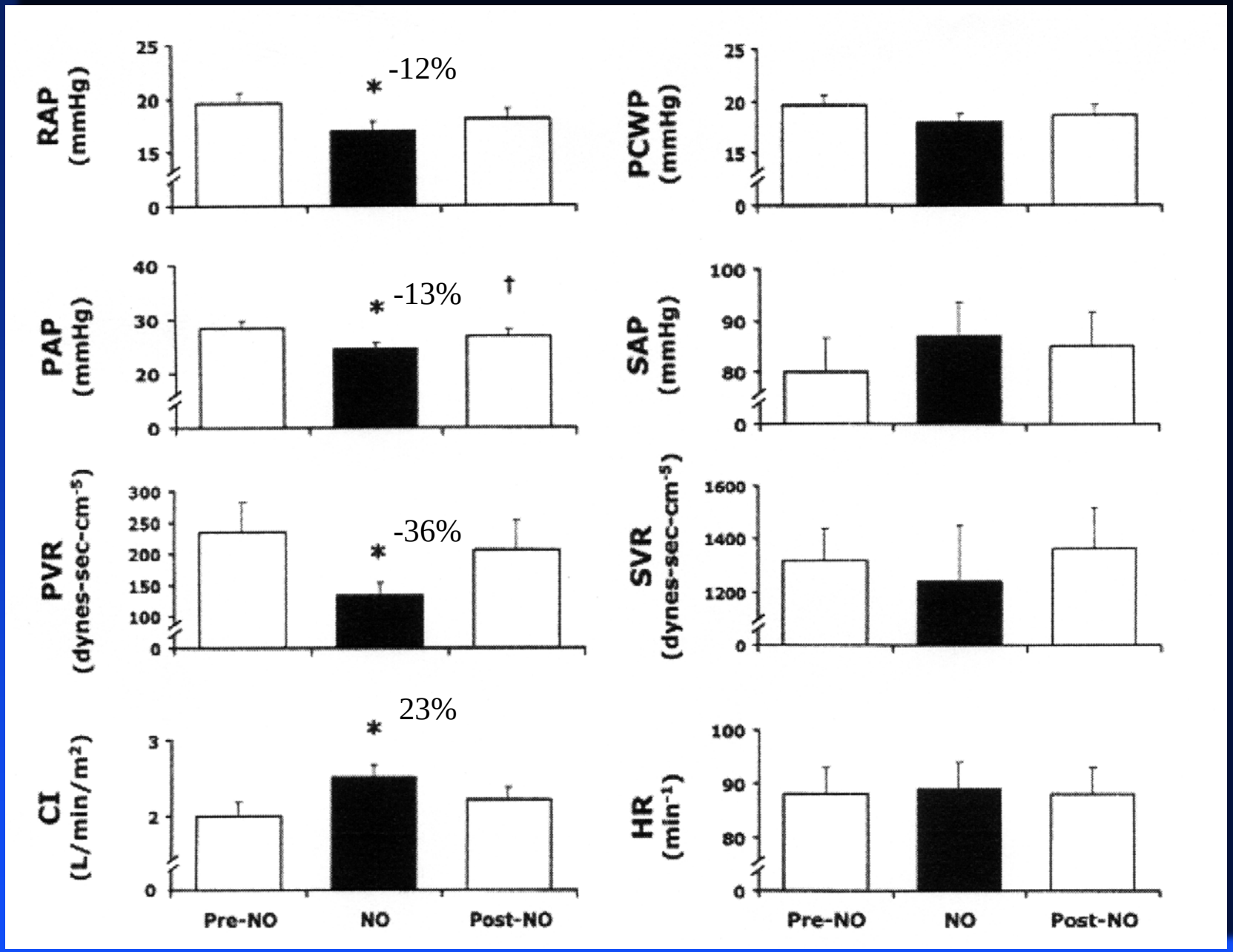


PVR: 254 to 178 dynes x sec x cm-5
SV: 72 to 83 ml
RVEF: 28% to 37%
RVEDV: 258 to 225 ml

Inhaled NO in RVF after posterior AMI

- Thirteen patients with RV infarction and cardiogenic shock
- Inhalation of NO (80 ppm)

Inglessis et al J Am Coll Cardiol 2004;44:793-798



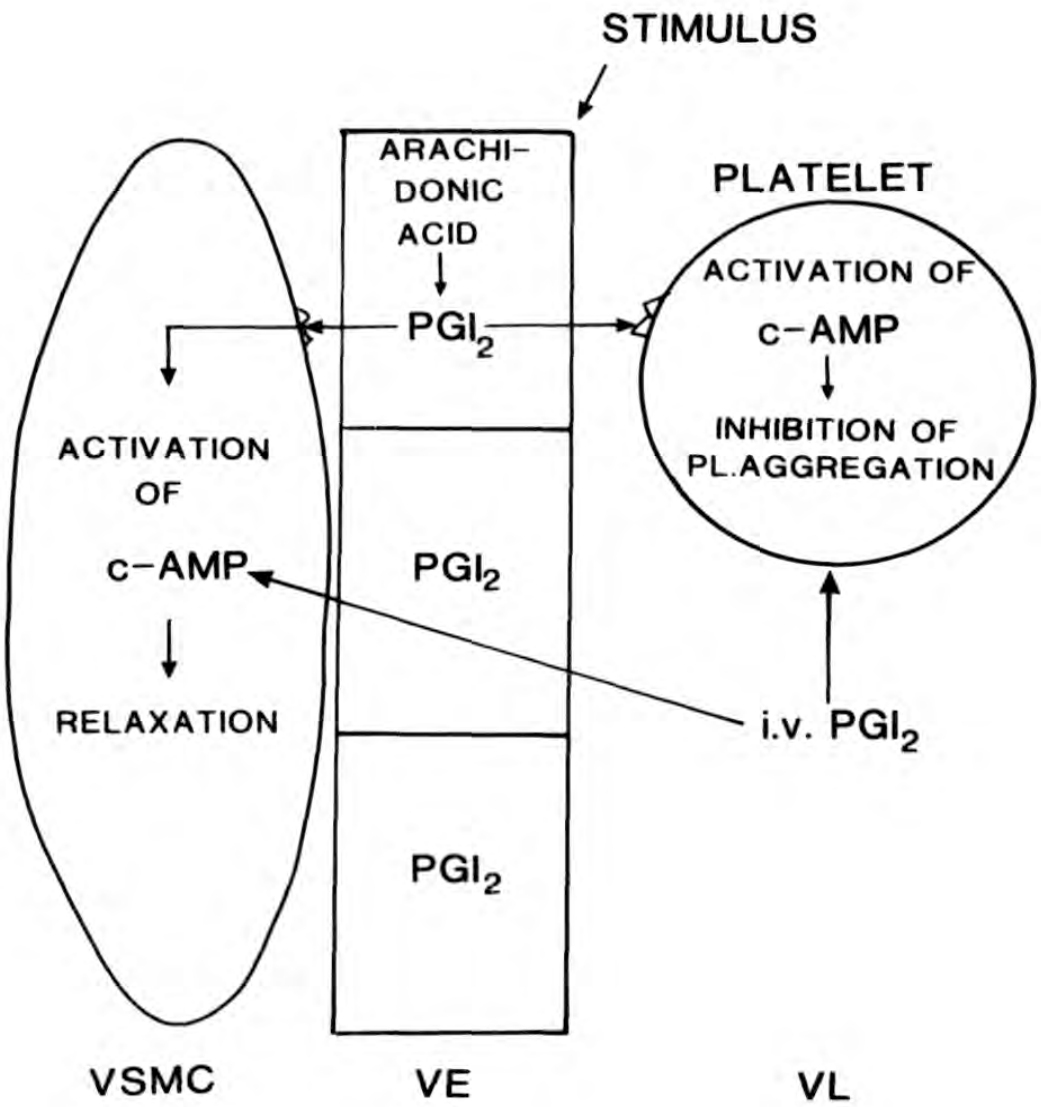
Inglessis et al J Am Coll Cardiol 2004;44:793-798

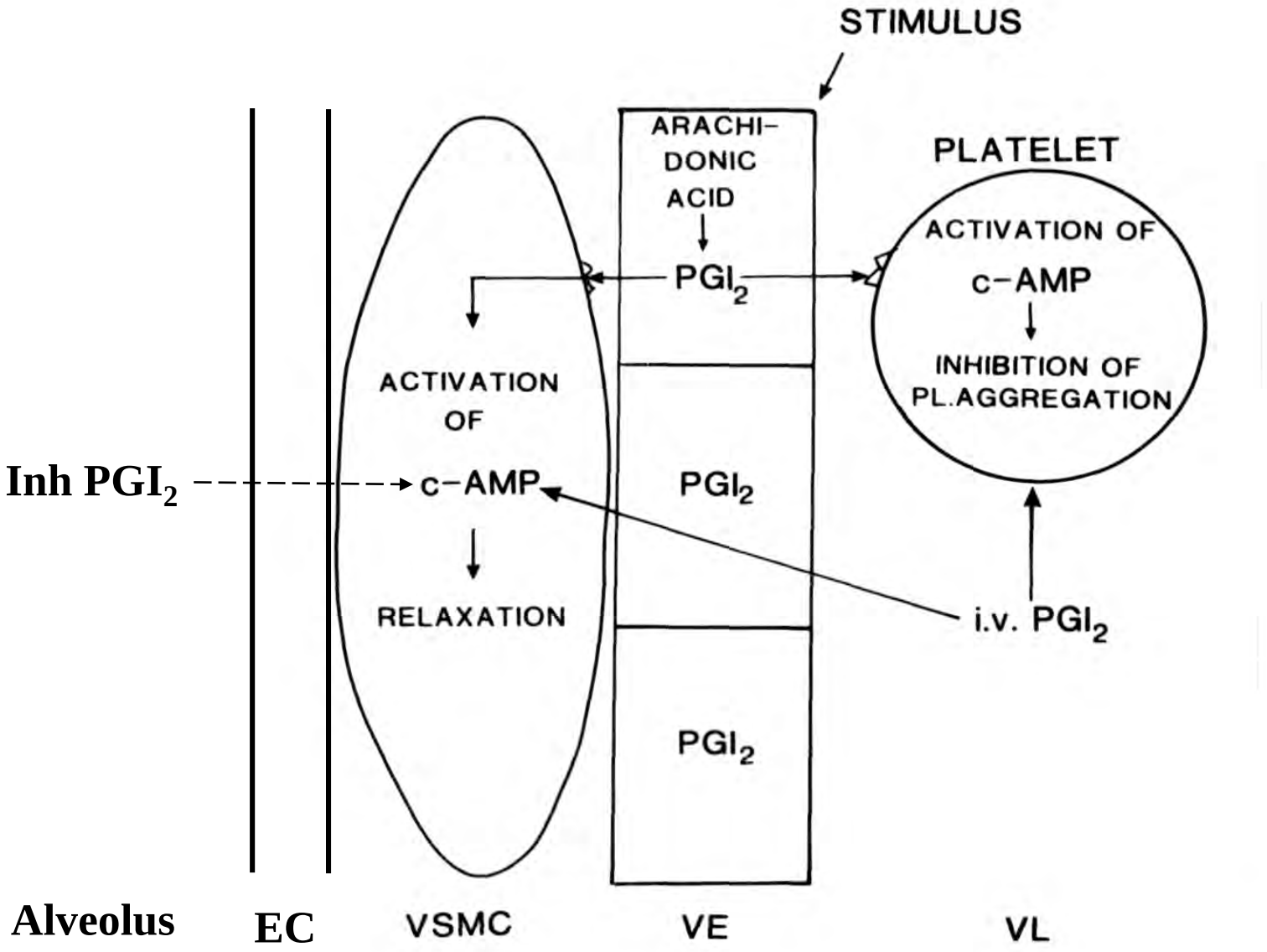
Limitations with NO for inhaled therapy of postoperative pulmonary hypertension

- Rebound pulmonary hypertension
- Toxicity: NO_2, methemoglobinemia
- Equipment
- Cost

Inhaled alternatives to NO?

Inhaled prostacyclin (PGI_2) for the treatment of RVF


STIMULUS
ARACHI-
DONIC
ACID
PGI2
PLATELET
ACTIVATION OF
c-AMP
INHIBITION OF
PL.AGGREGATION
ACTIVATION
OF
c-AMP
RELAXATION
PGI2
PGI2
i.v. PGI2
VSMC
VE
VL


STIMULUS
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RELAXATION
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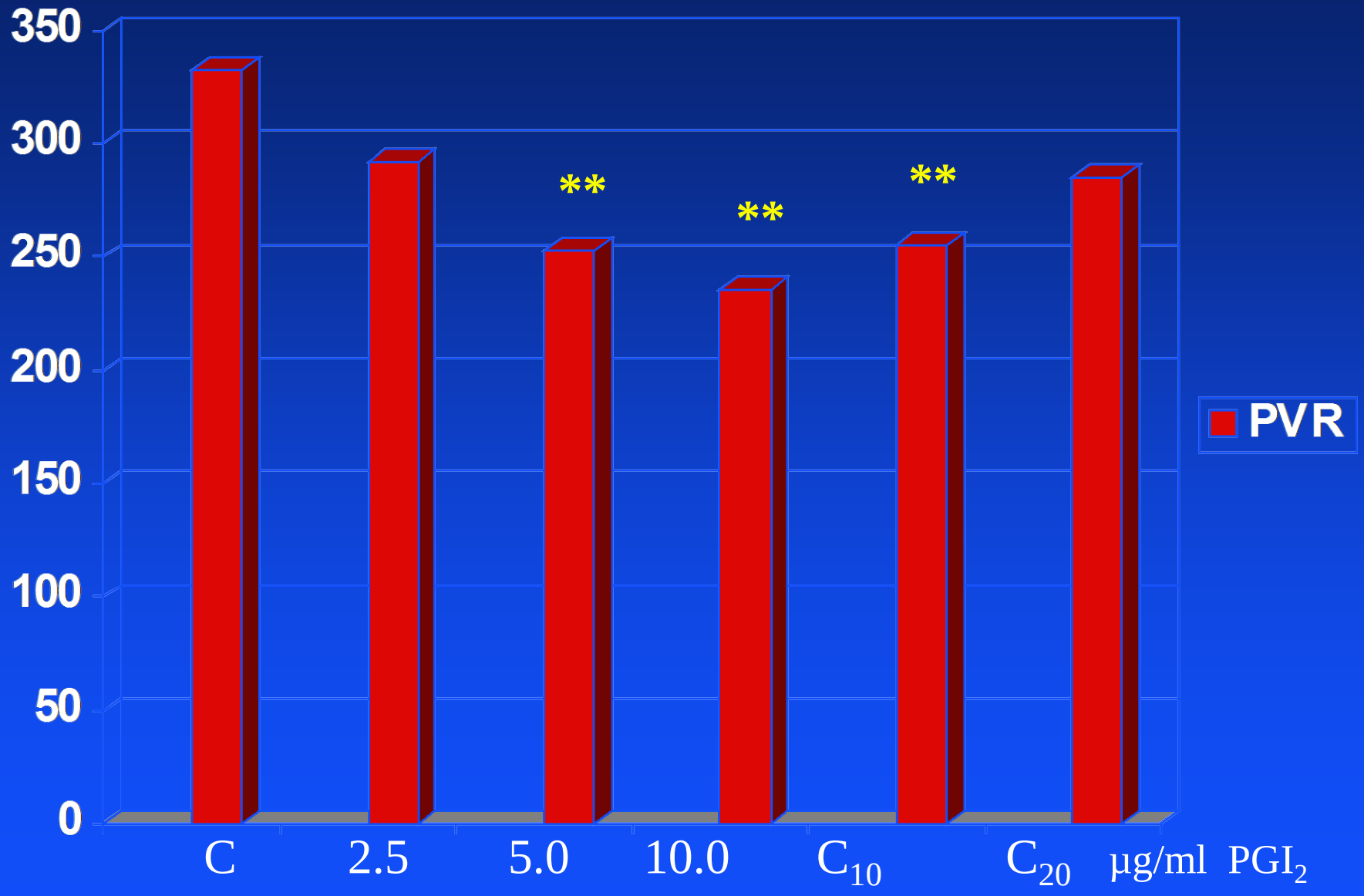
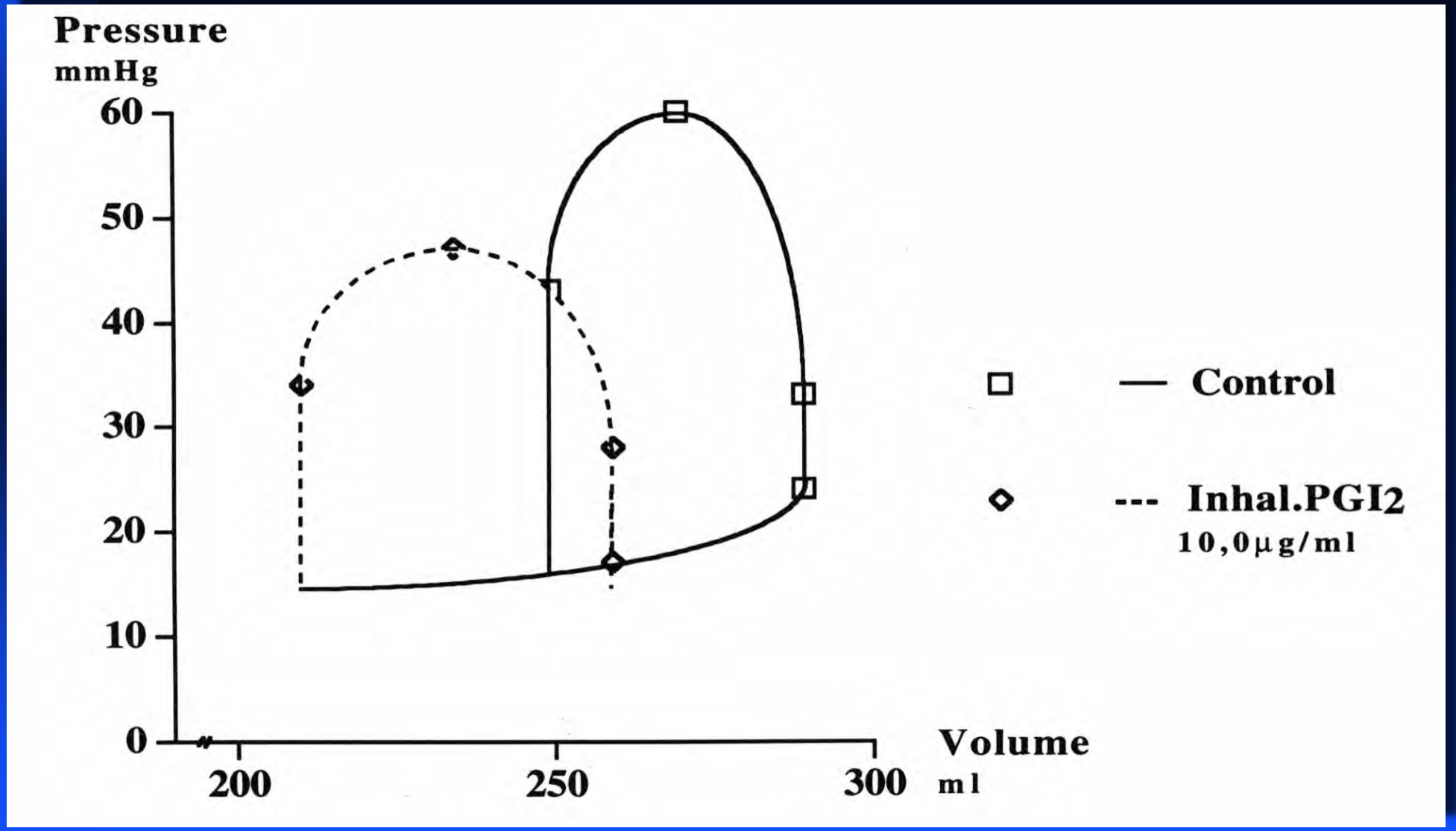
PGI2
i.v. PGI2
Alveolus
EC
VSMC
VE
VL

Effects of aerosolized PGI_2 on PVR after cardiac surgery

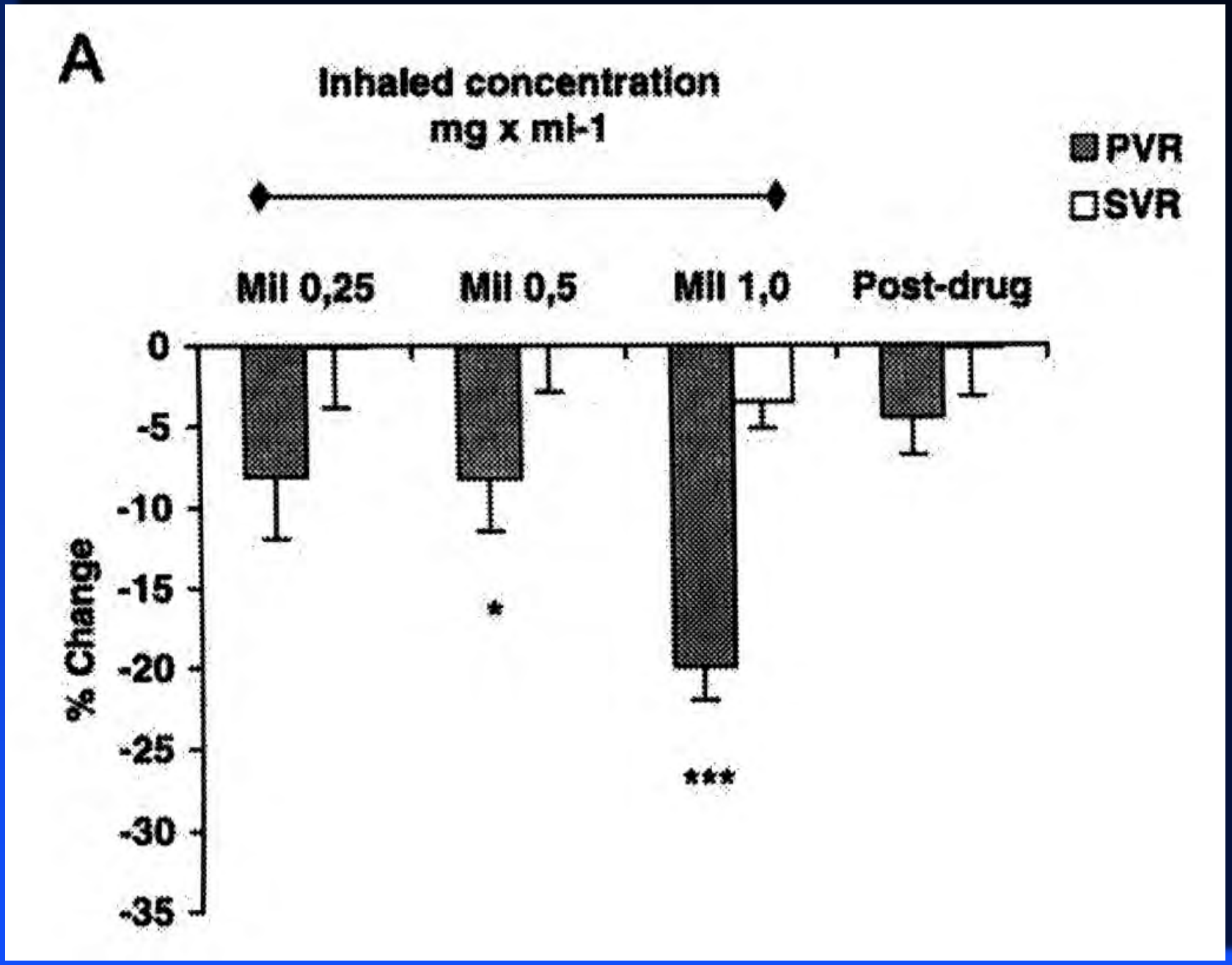


Haraldsson et al J Cardiothoracic Vasc Anesth 1996;10:864-868

Inhaled PGI_2 in one patient with RVF after heart transplantation



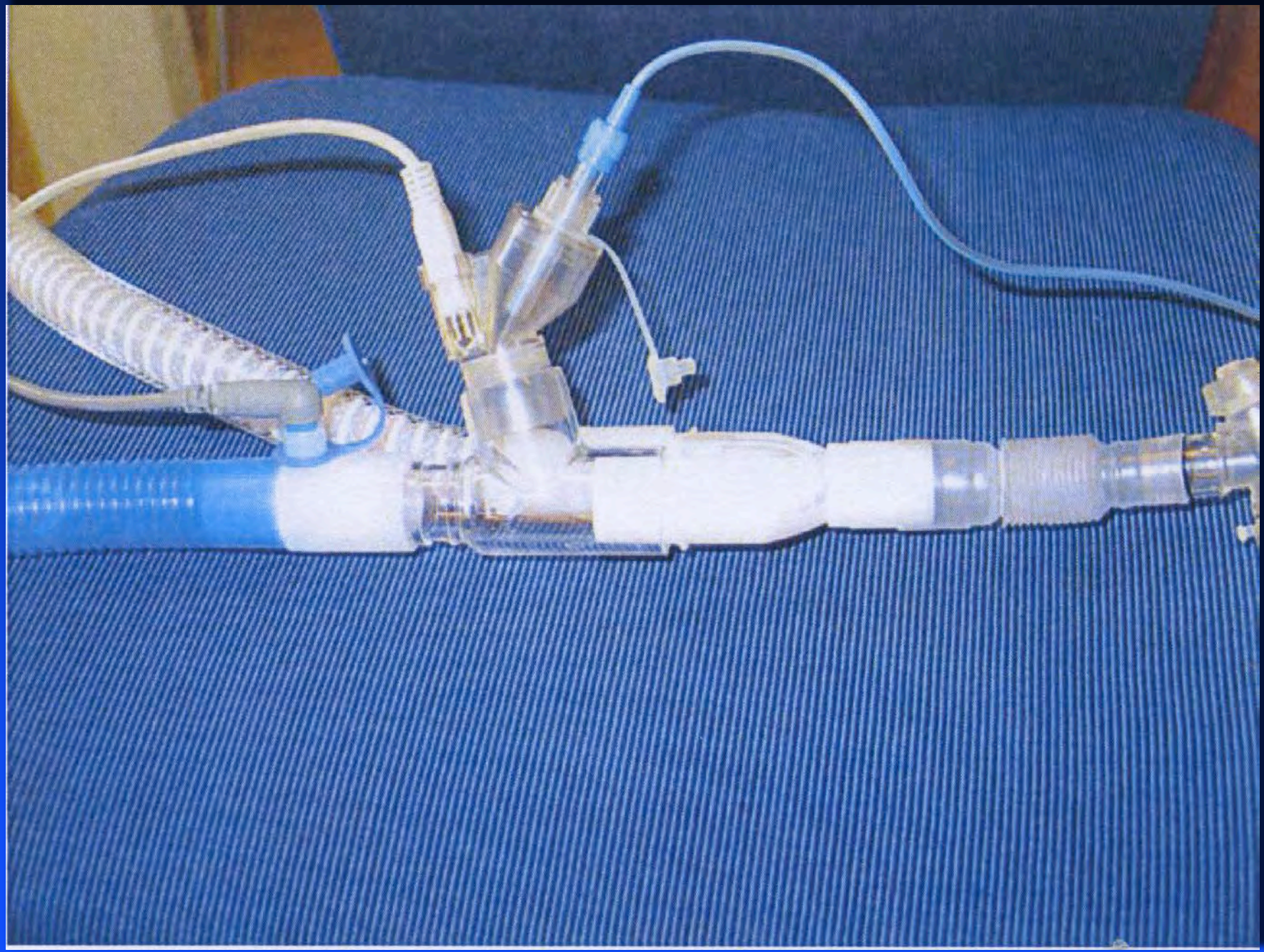
Inhaled milrinone for treatment of pulmonary hypertension and RV failure

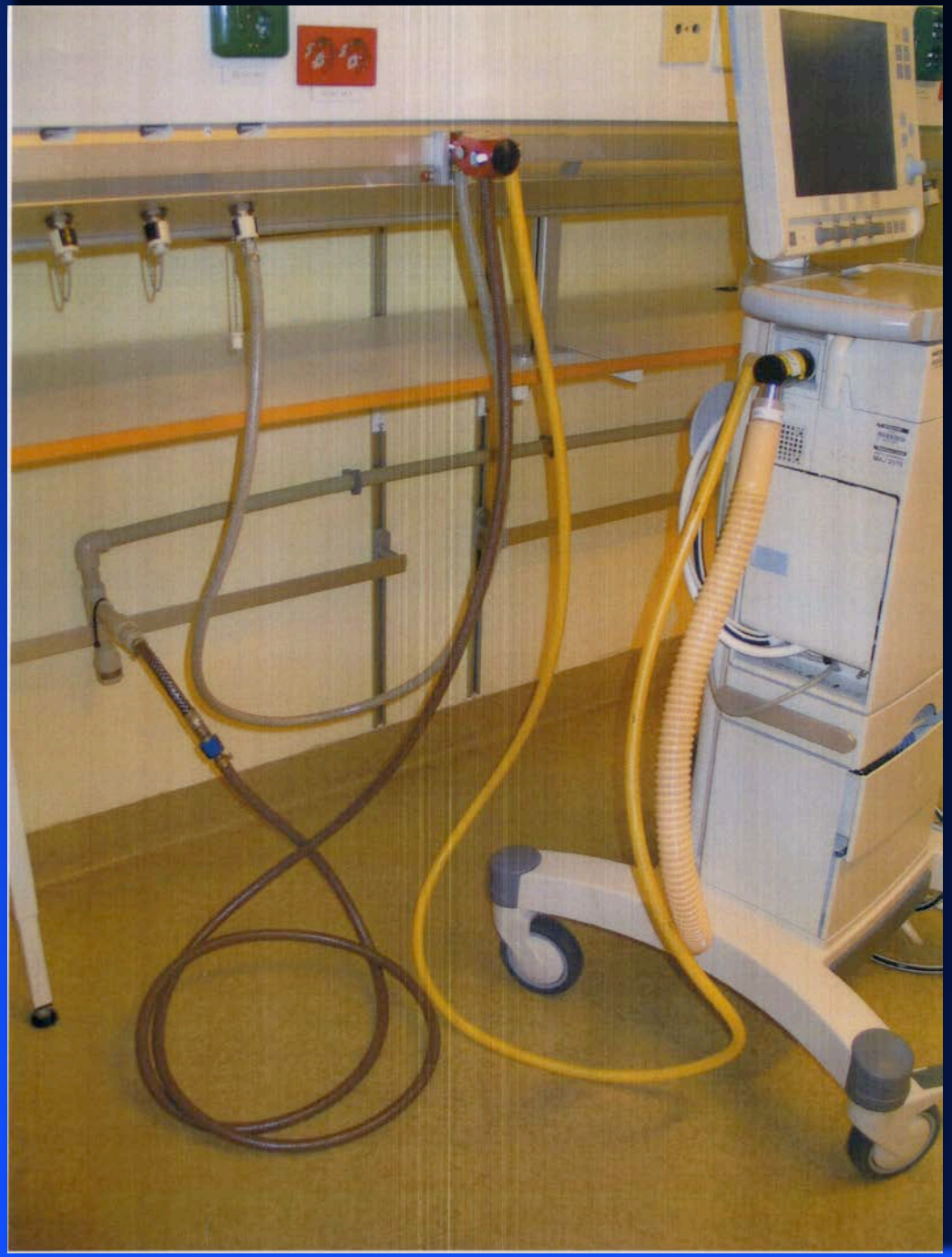


Haraldsson et al Anesth Analg 2001,93:1439

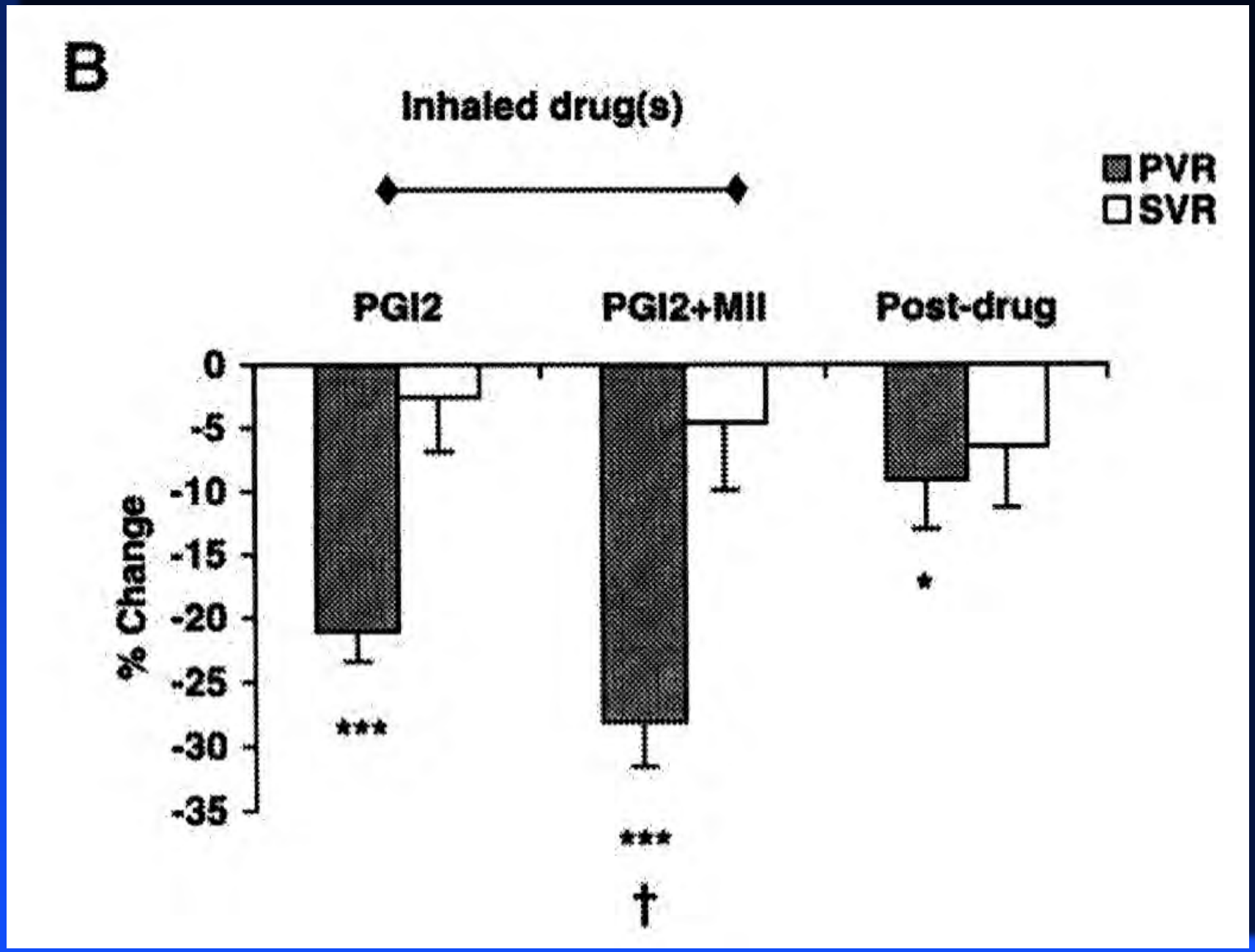
Inhaled prostaglandins and milrinone - doses

- Prostacyclin /Flolan®): 10 µg/ml, 5-10 ml/h
- Iloprost (Ilomedin®): 10 µg/ml, 2.5-5 µg x 6-9
- Treprostinil (Remodulin®): 30-50 µg x 4
- Milrinone: 1 mg/ml, 5-10 ml/h

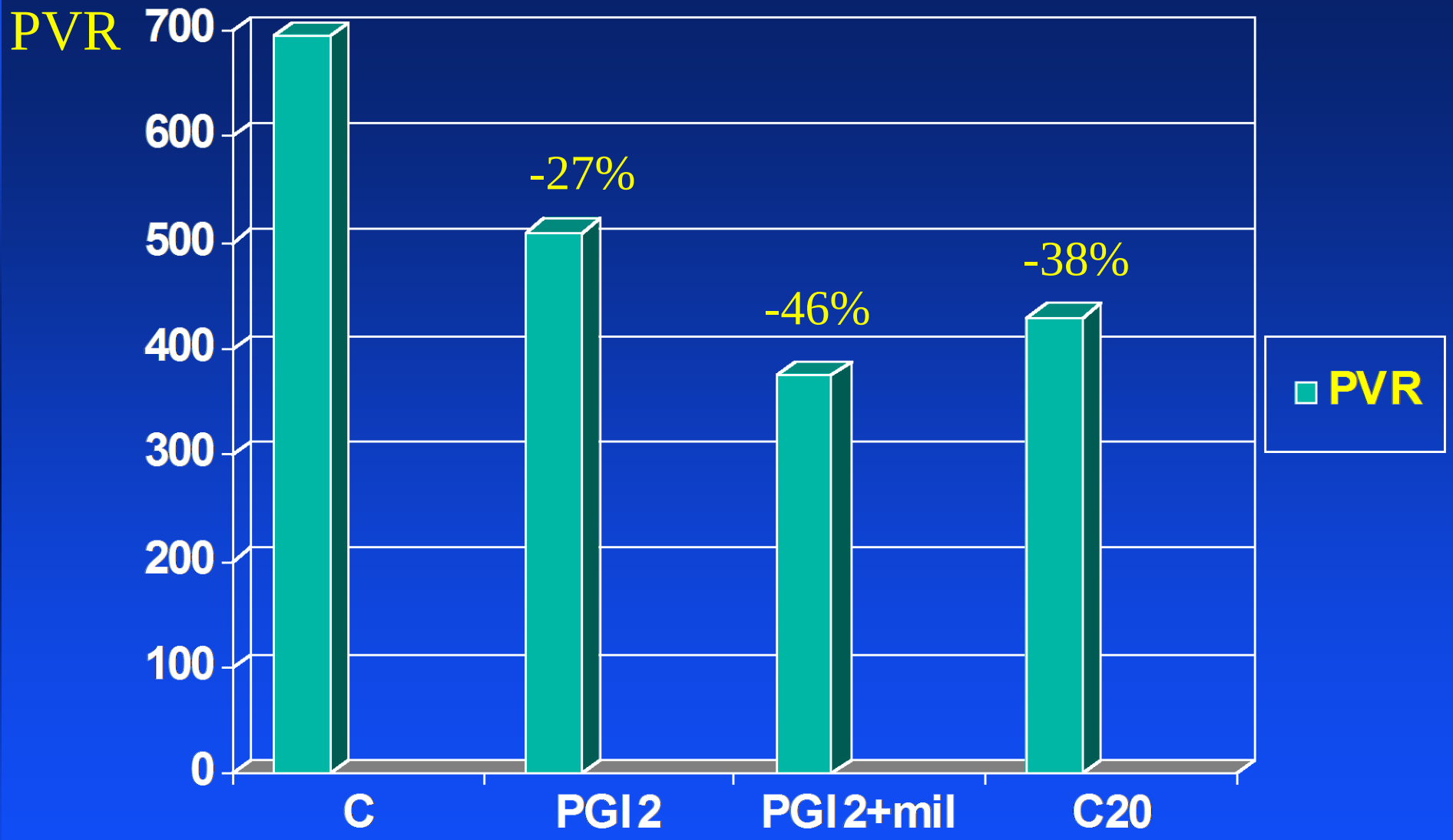




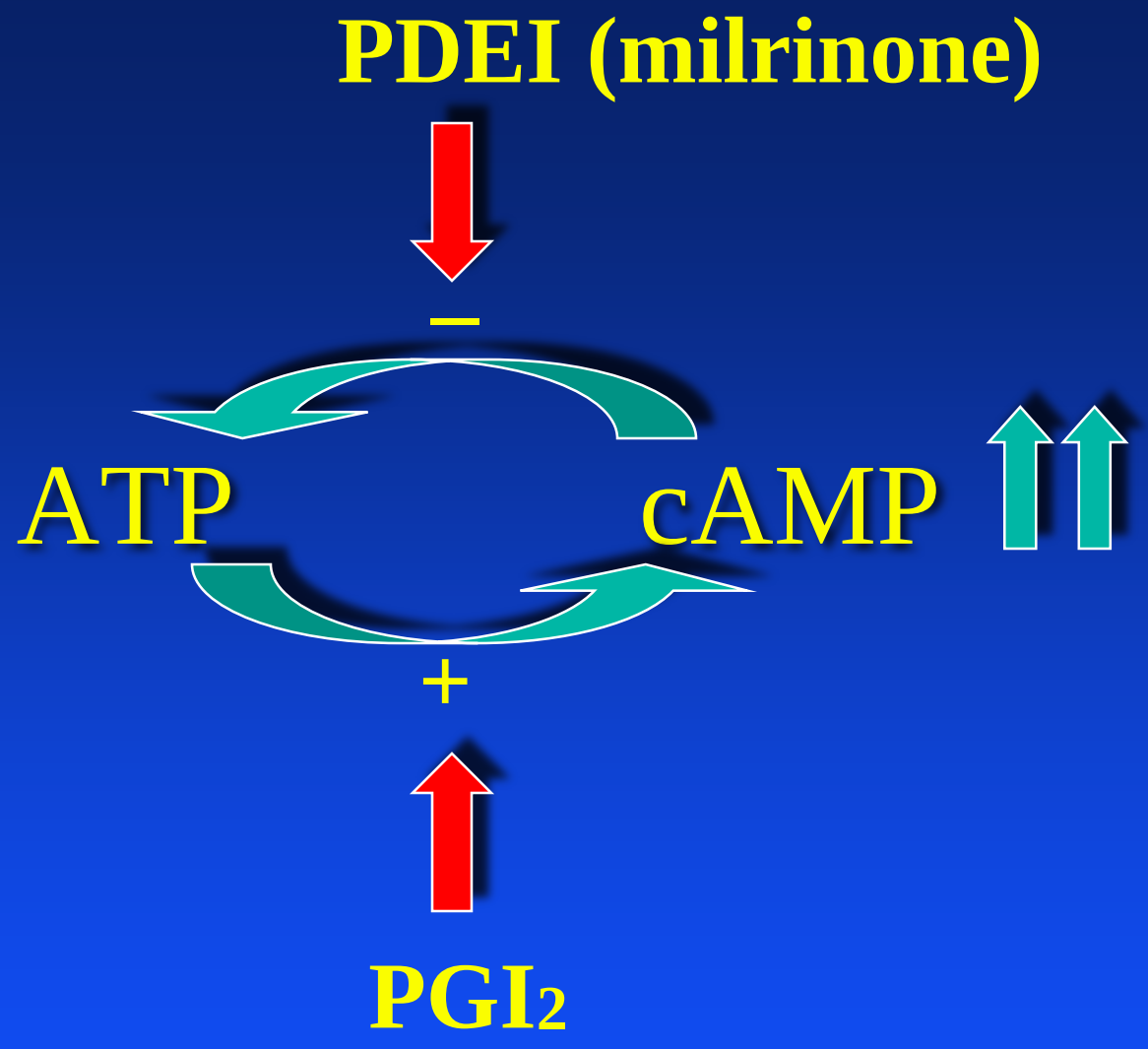
Combined treatment of RVF with inhaled PGI_2 plus inhaled milrinone



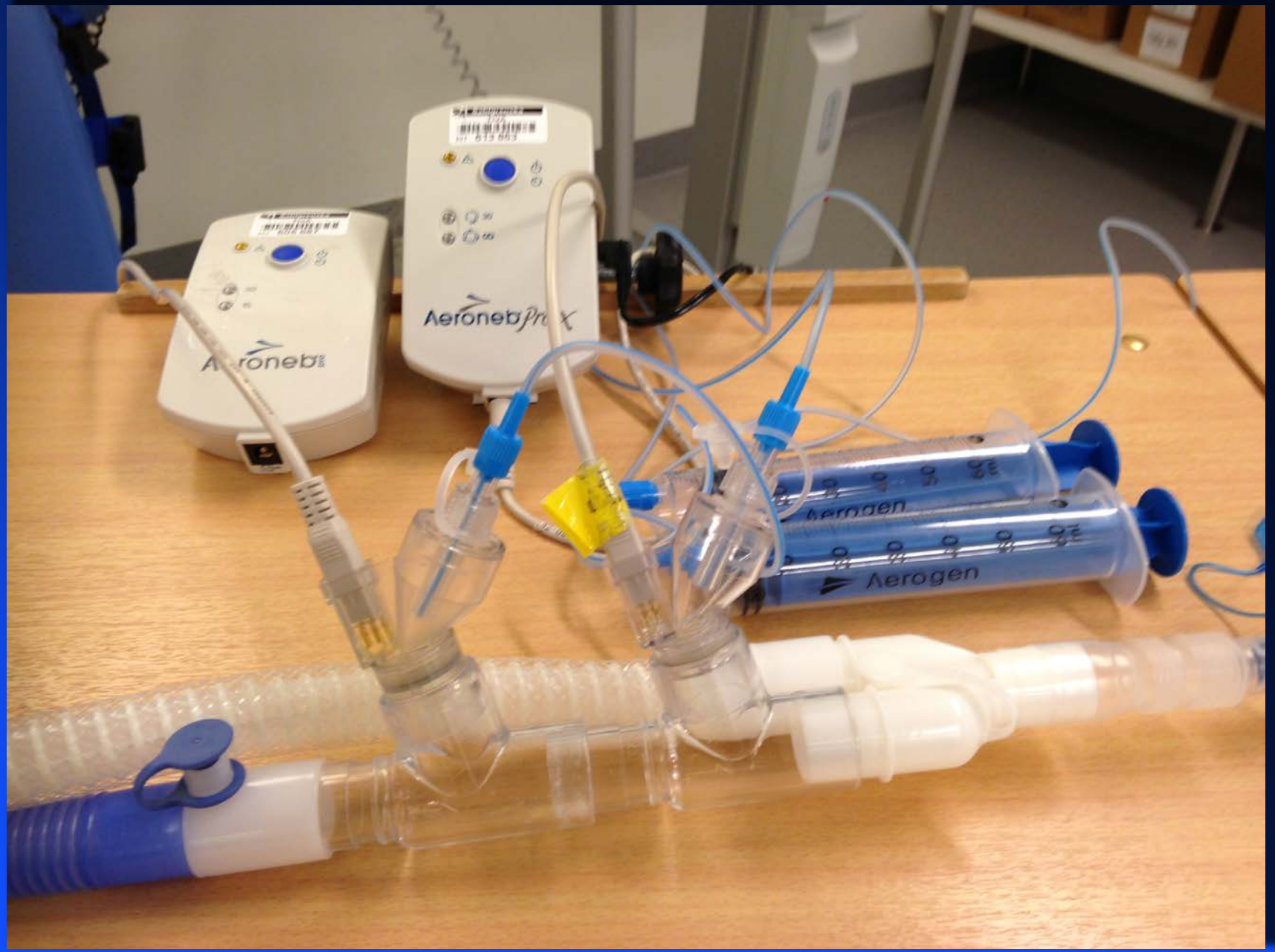
Haraldsson et al Anesth Analg 2001,93:1439



Effects of combined inhalation with PGI_2 and milrinone in one patient with severe pulmonary hypertension and RVF.



The rationale for the use of combined inhalation with PGI_2 and a phosphodiesterase inhibitor (PDEI)


Aerogen
Aerogen

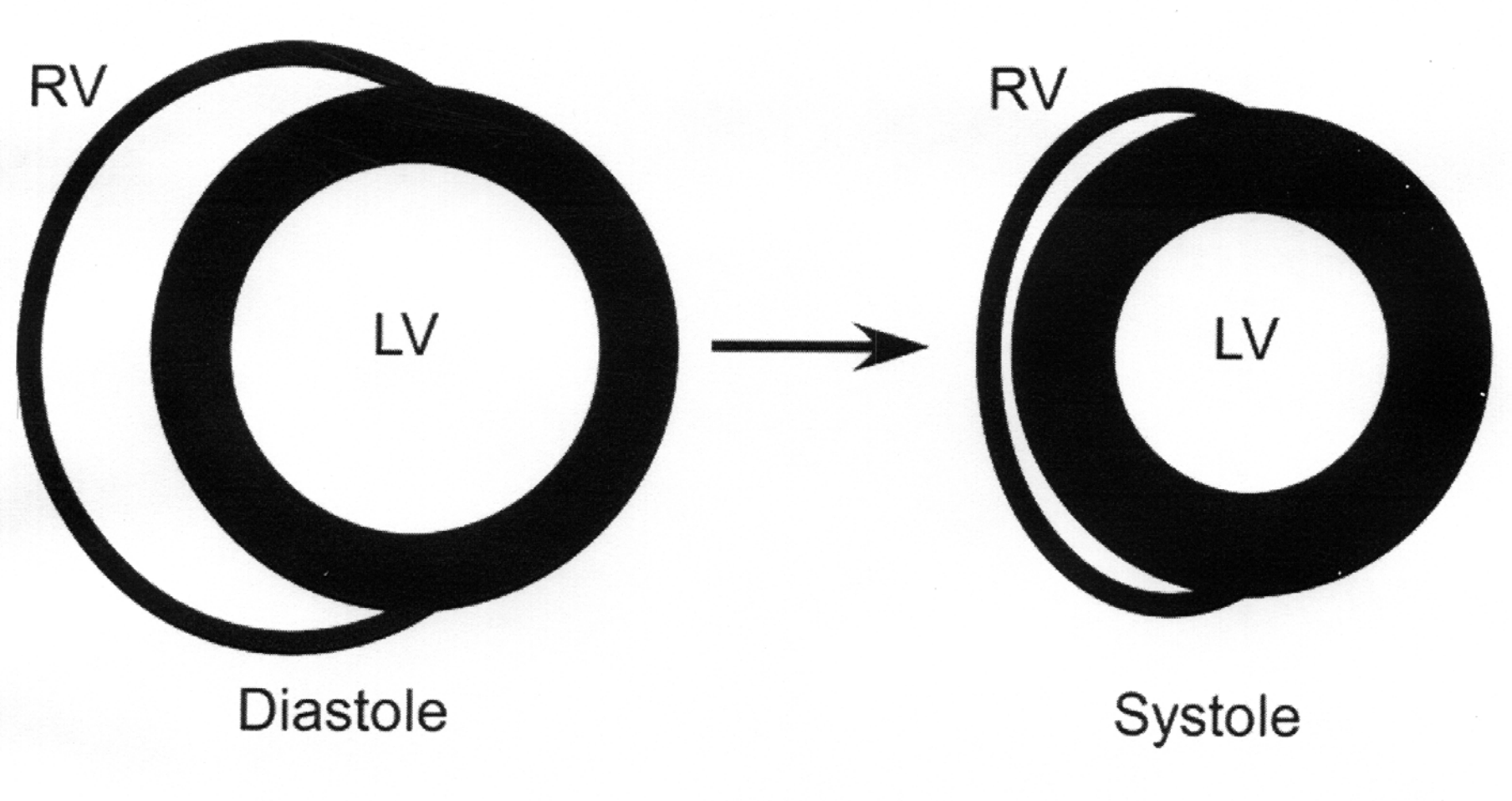
Inhaled therapies in RVF – correlates for success

- High PVR (> 250 dynes x sec x cm^{-5})
- Reversible, not fixed high PVR
- Isolated RVF
- LV failure or biventricular is a contraindication!!

More aspects on the management of isolated RVF

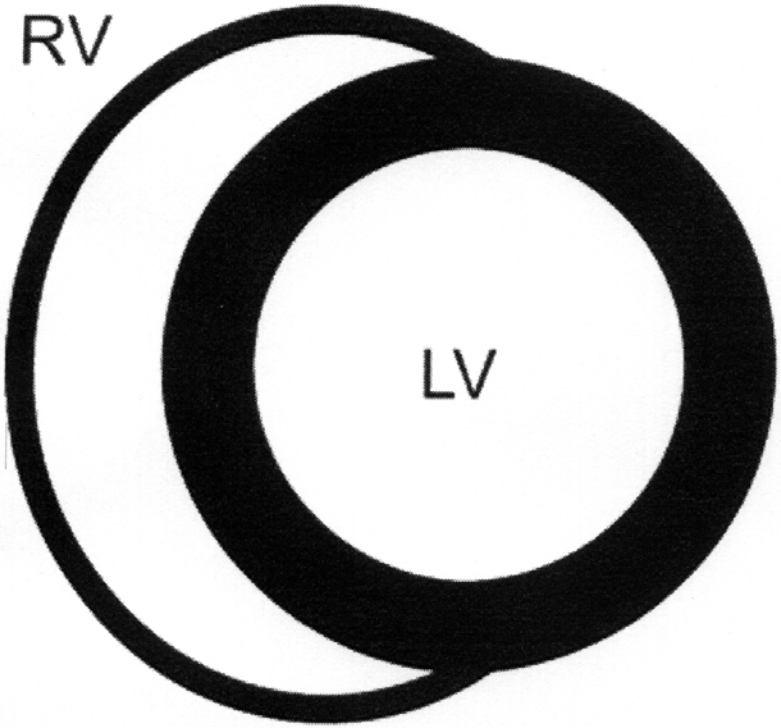
- Selective pulmonary vasodilation (inhaled NO, PGI_2, milrinone
- Optimise RV preload (CVP 10-15 mmHg)
- High systemic pressure improves RV perfusion and LV assist - norepinephrine

Systolic ventricular interaction

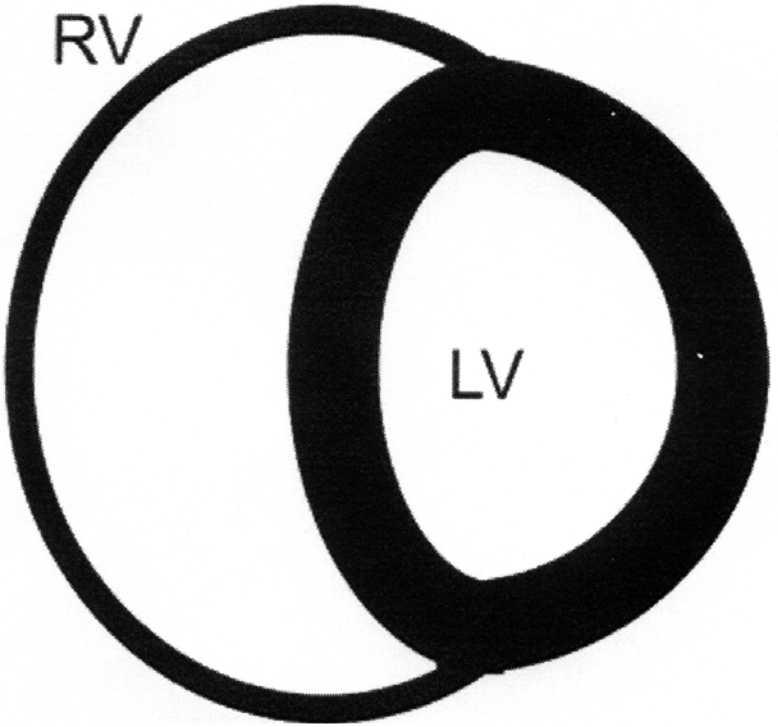


LV contributes with ≈ 60% of RV pressure and stroke volume

Diastolic ventricular interaction in RVF

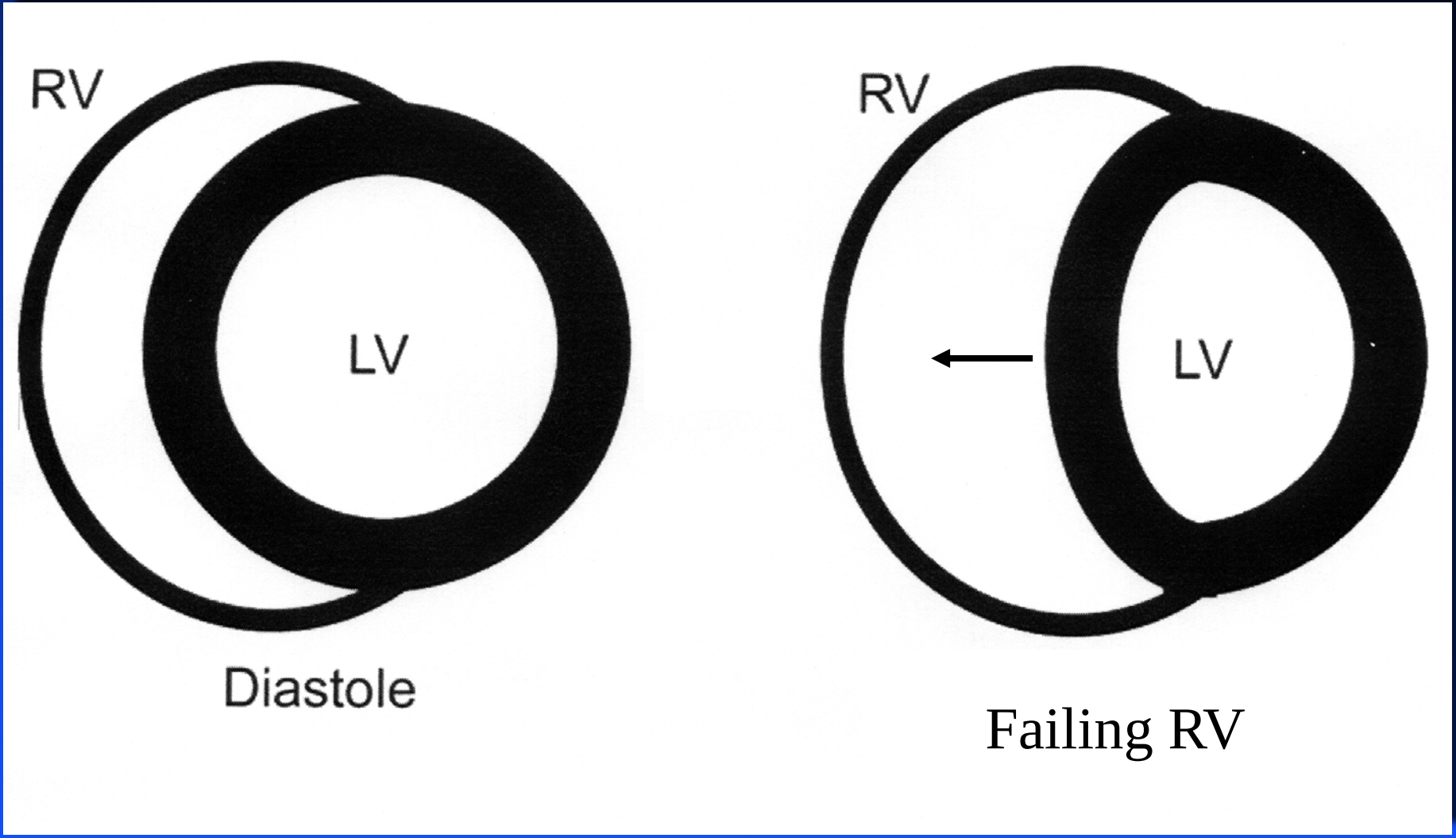


Diastole



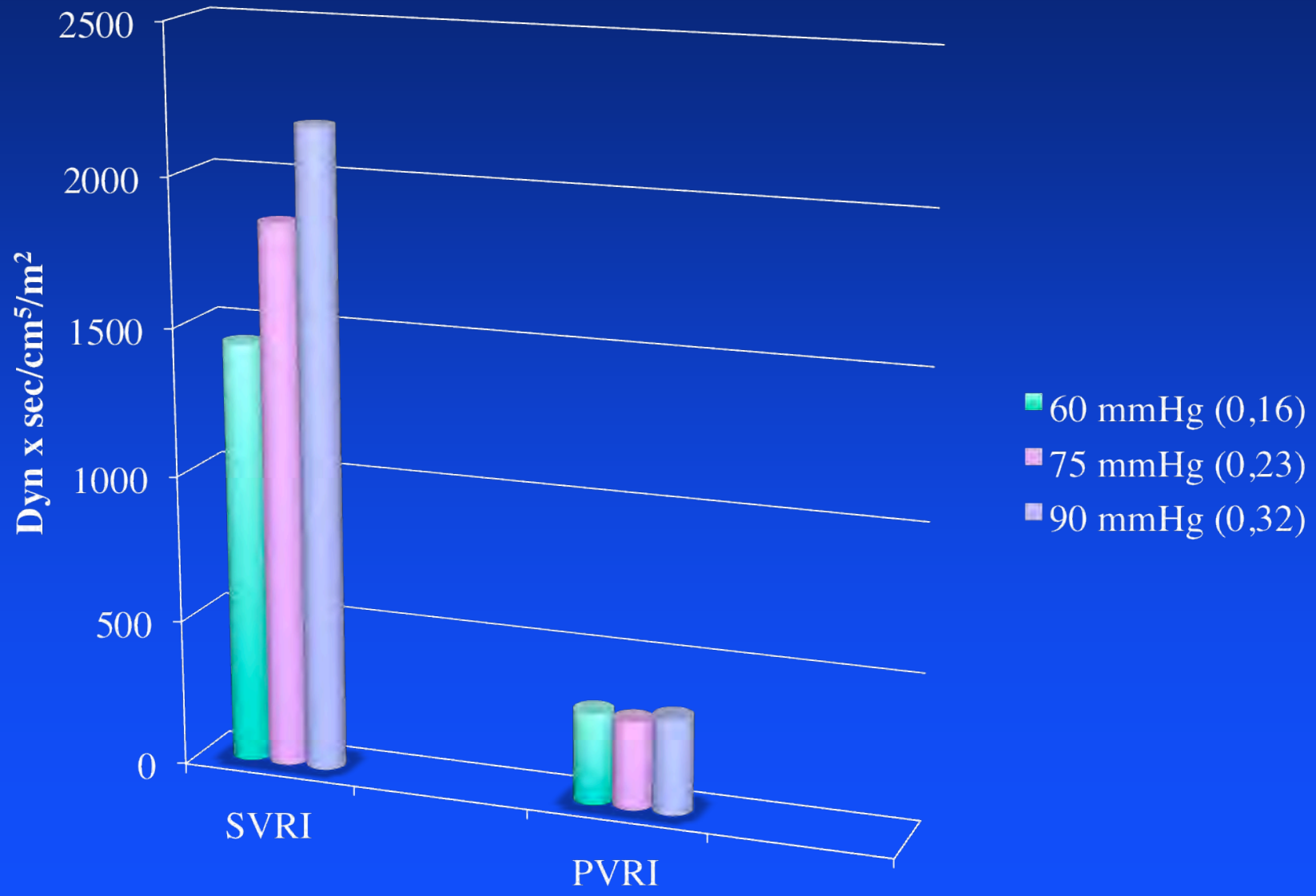
Failing RV

Systolic ventricular interaction - RVF



- Left ventricular

Effects of norepinephrine on systemic and pulmonary vascular resistance



More aspects on the management of isolated RVF

- Selective pulmonary vasodilation (inhaled NO, PGI_2, milrinone
- Optimise RV preload (CVP 10-15 mmHg)
- High systemic pressure improves LV assist and RV perfusion - norepinephrine
- Inotropic support

Inotropic agents

- Norepinephrine
- Epinephrine
- Dopamine
- Dobutamine
- Dopexamine
- Isoprenalin
- Levosimendan
- Milrinone

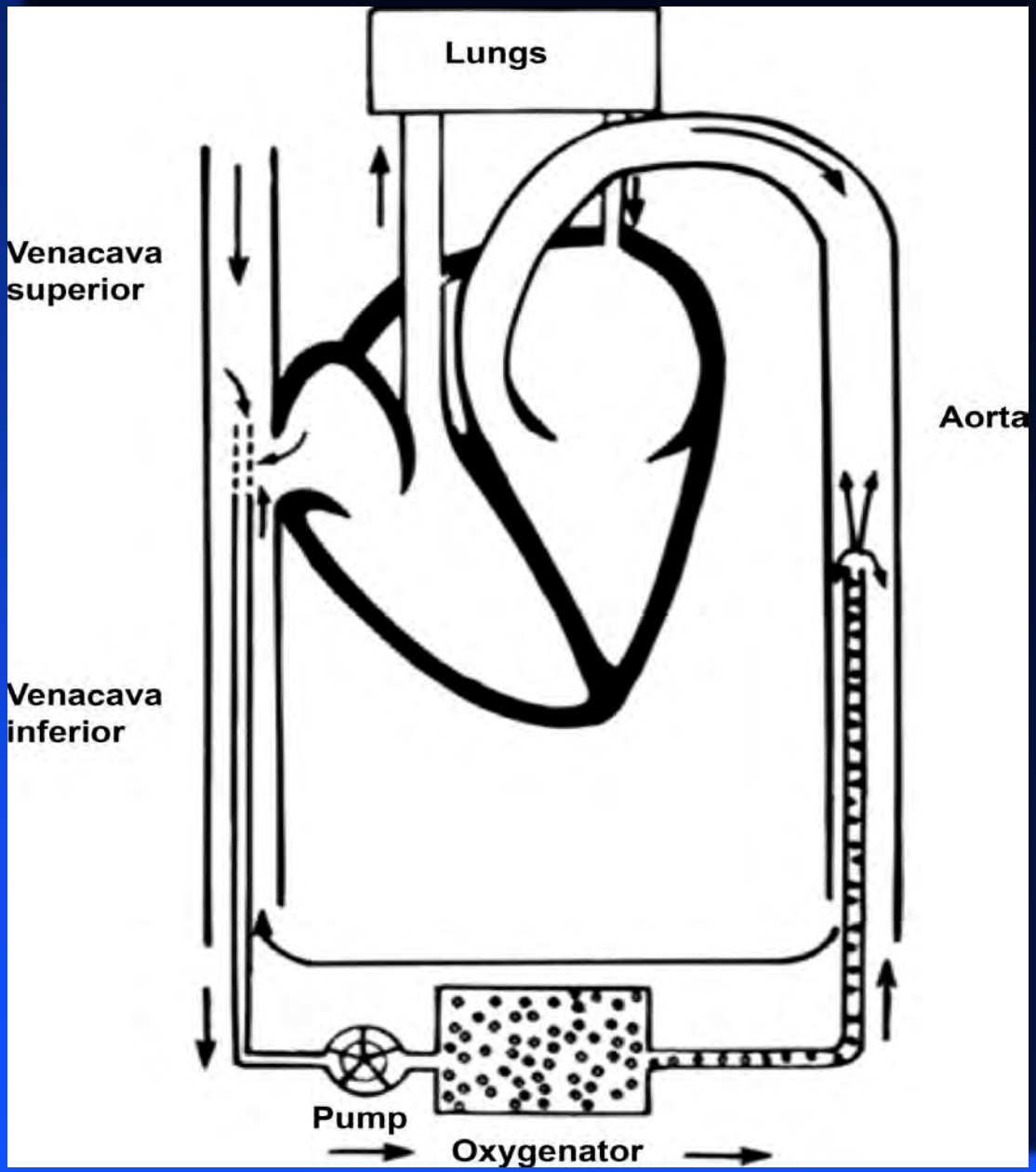
vasoconstriction

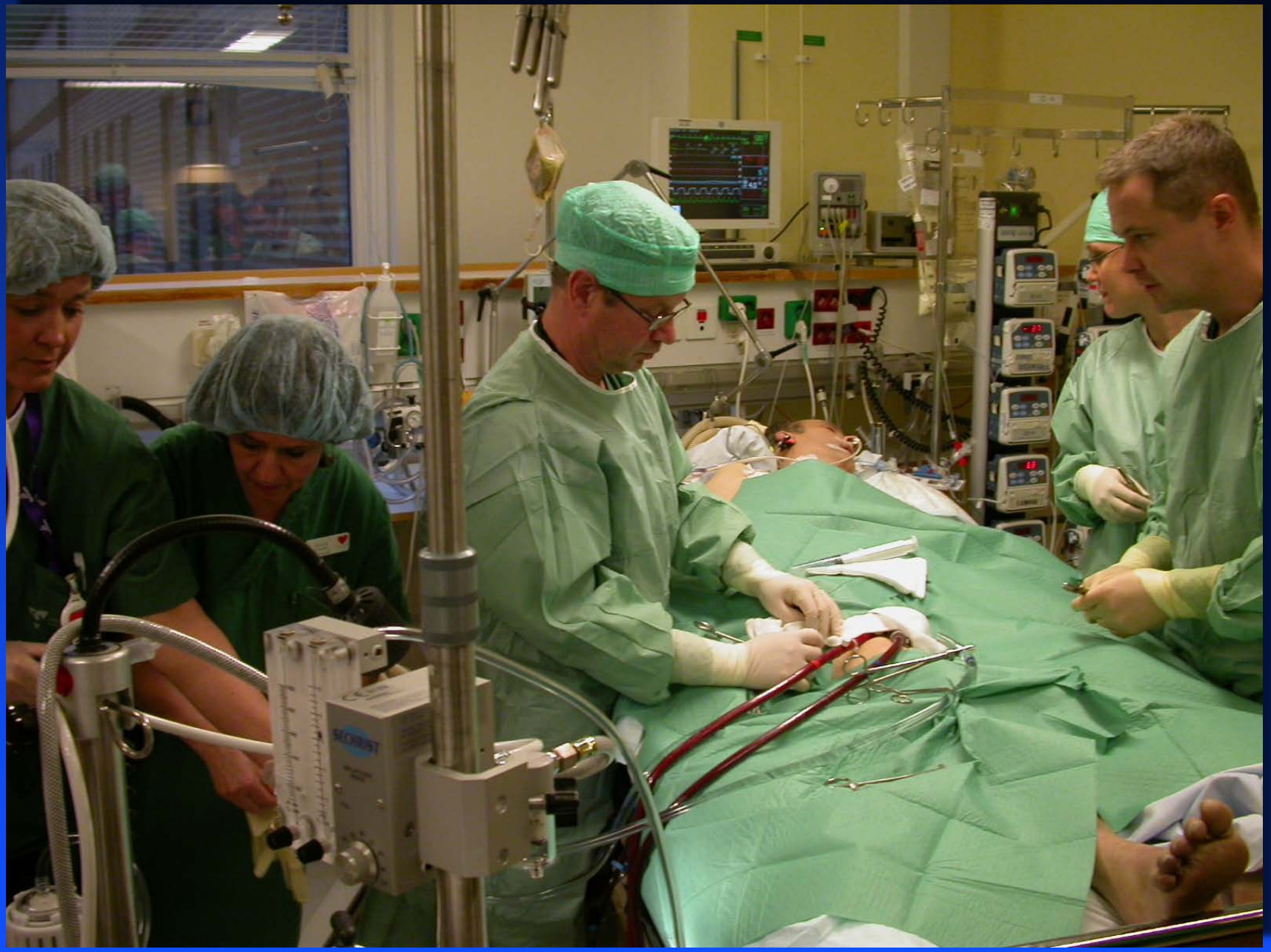
vasodilation

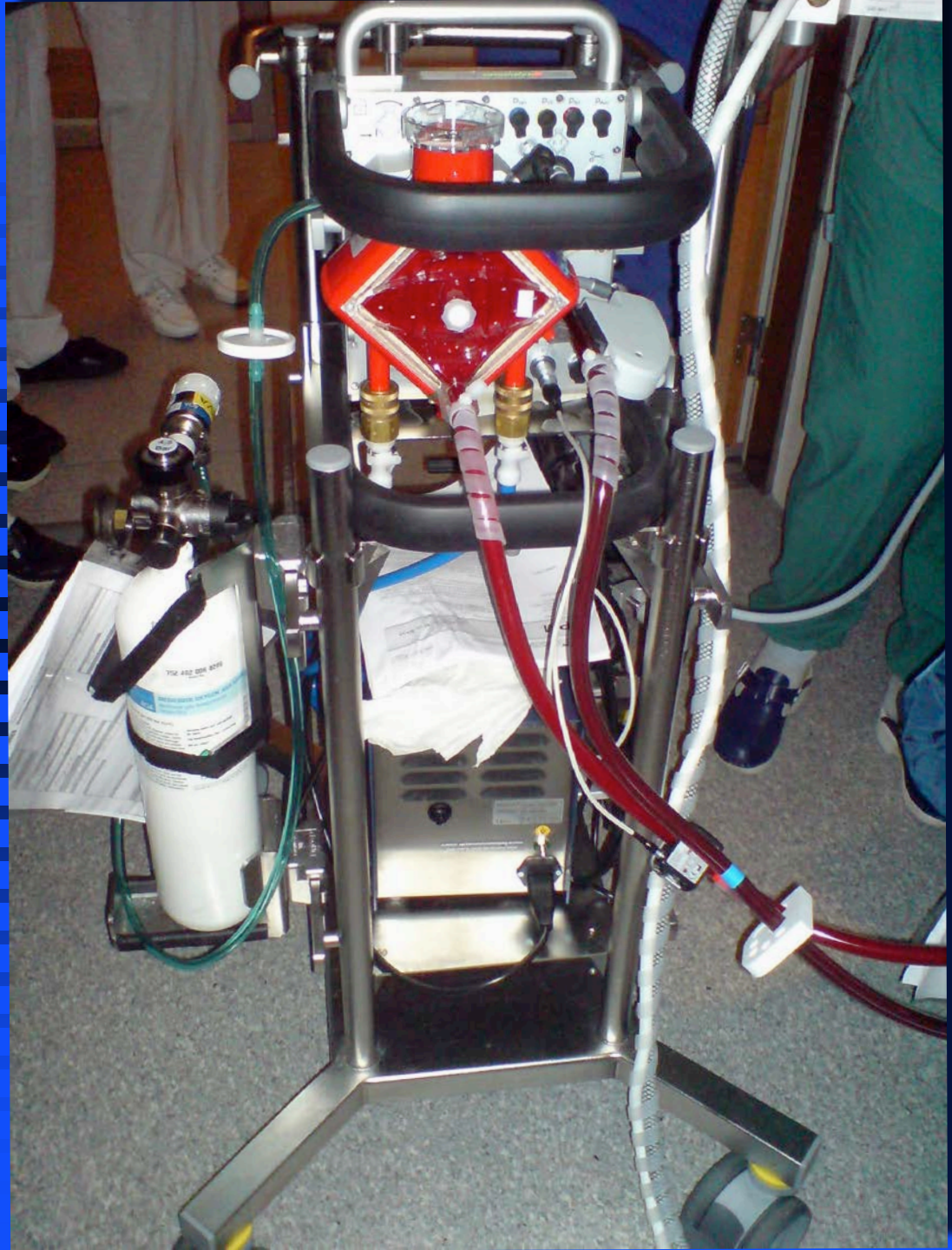
More aspects on the management of isolated RVF

- Optimise RV preload (CVP 10-15 mmHg)
- High systemic pressure improves LV assist and RV perfusion
- Selective pulmonary vasodilation (inhaled NO, PGI_2, milrinone
- Inotropic support (dopamine, milrinone, noradrenaline)
- ECMO/RVAD

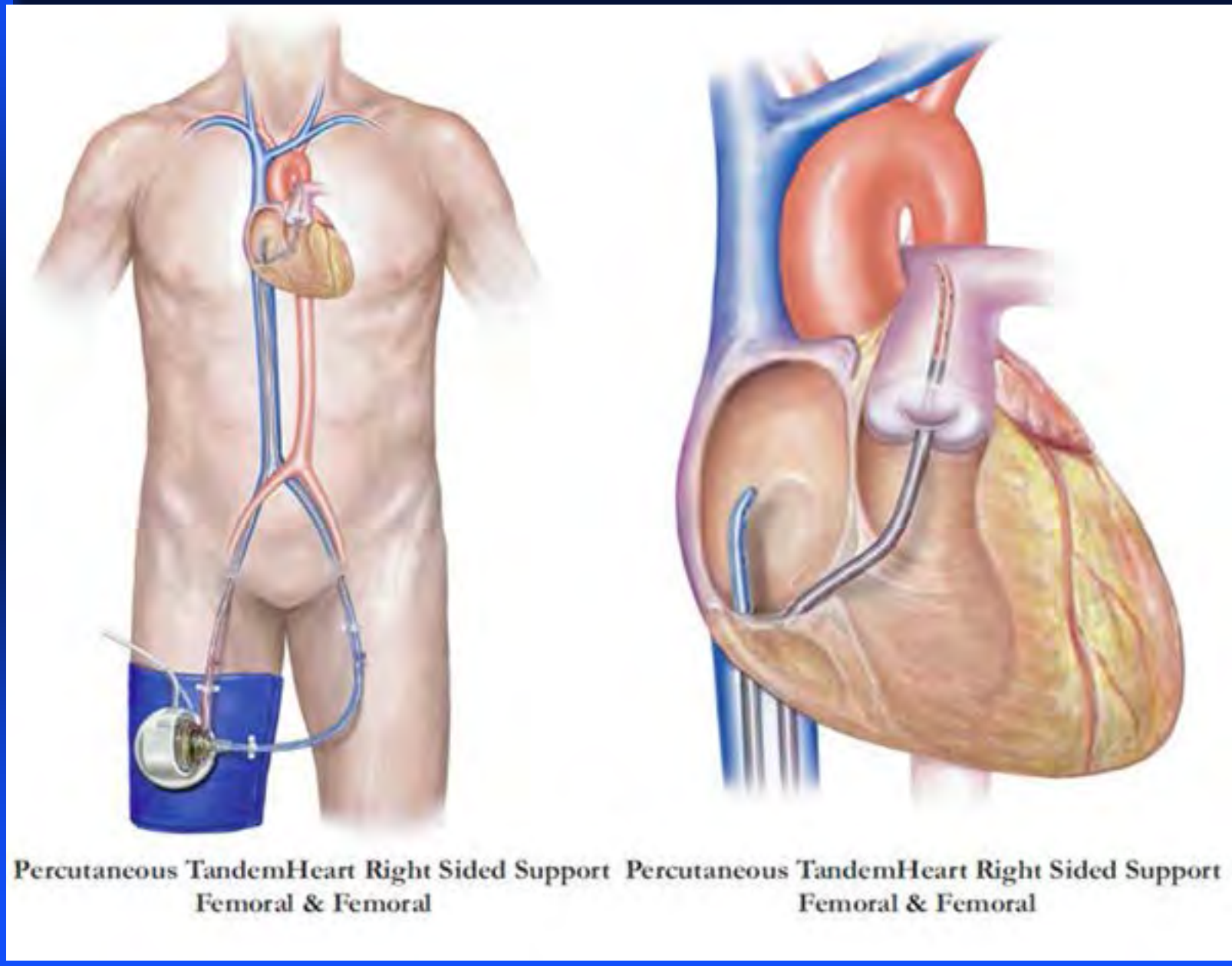
Extracorporeal circulatory support





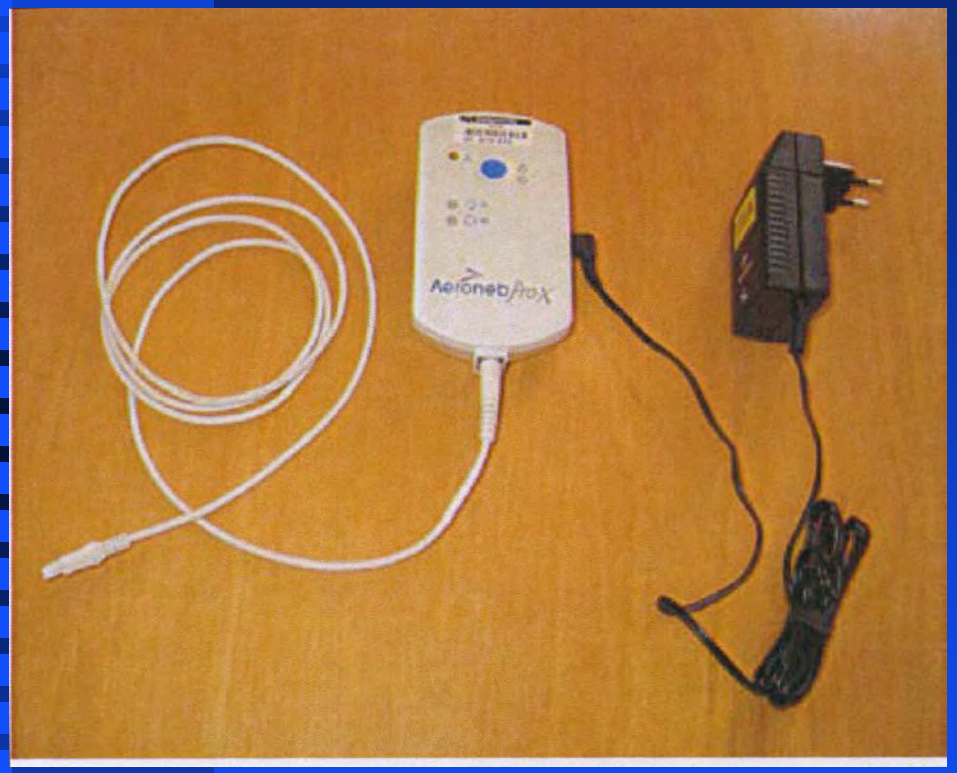


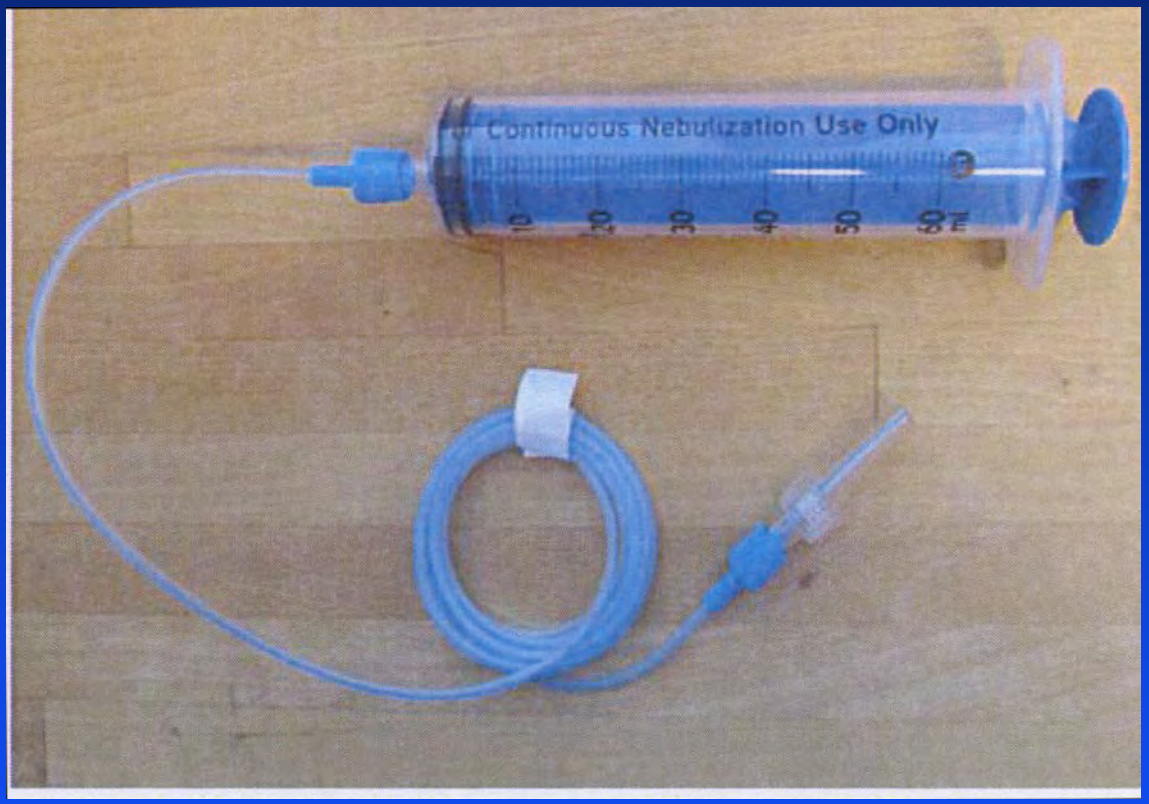
Perkutaneous RVAD, TandemHeart®

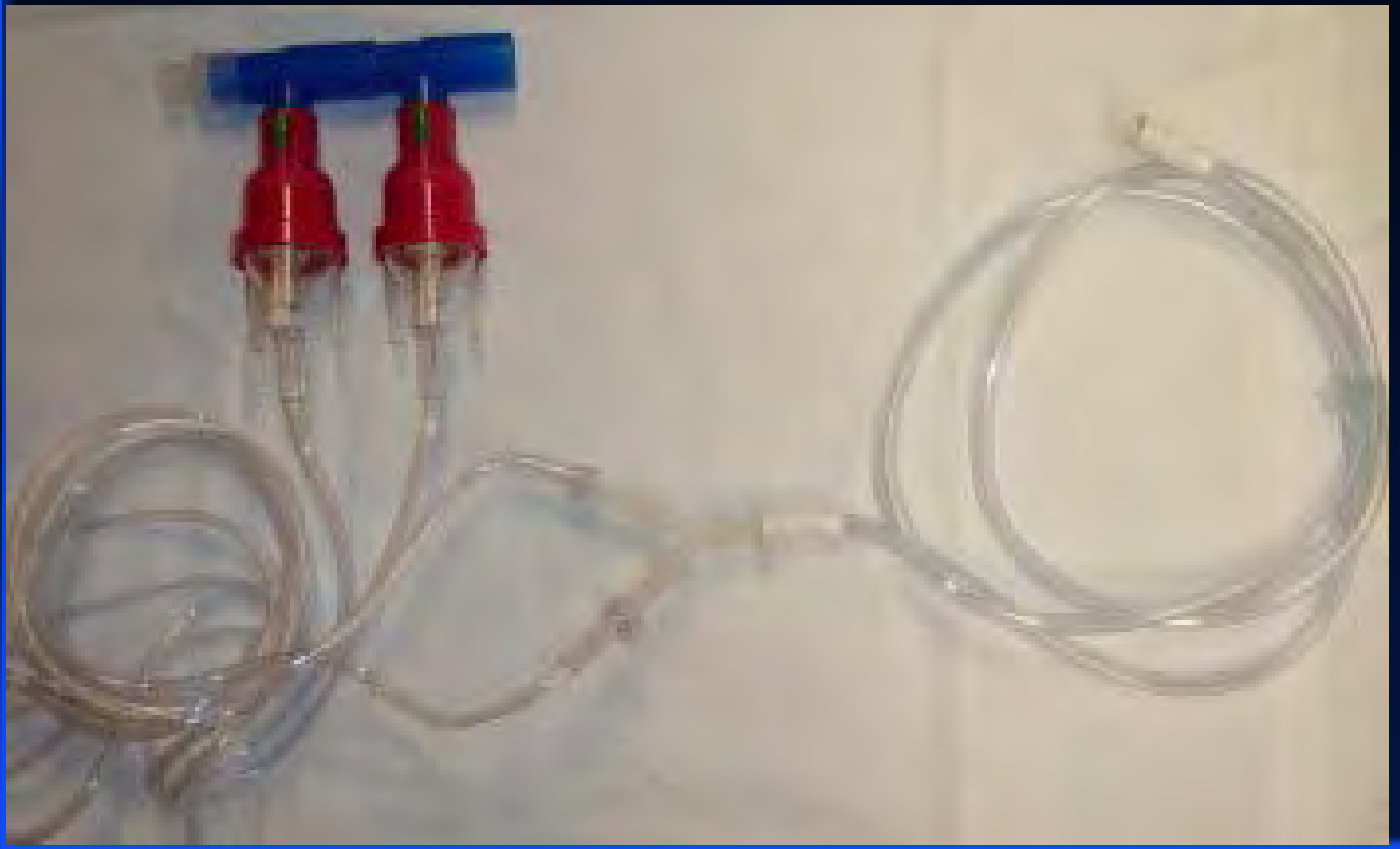


Percutaneous TandemHeart Right Sided Support
Femoral & Femoral

Percutaneous TandemHeart Right Sided Support
Femoral & Femoral


AeronebProX


Continuous Nebulization Use Only



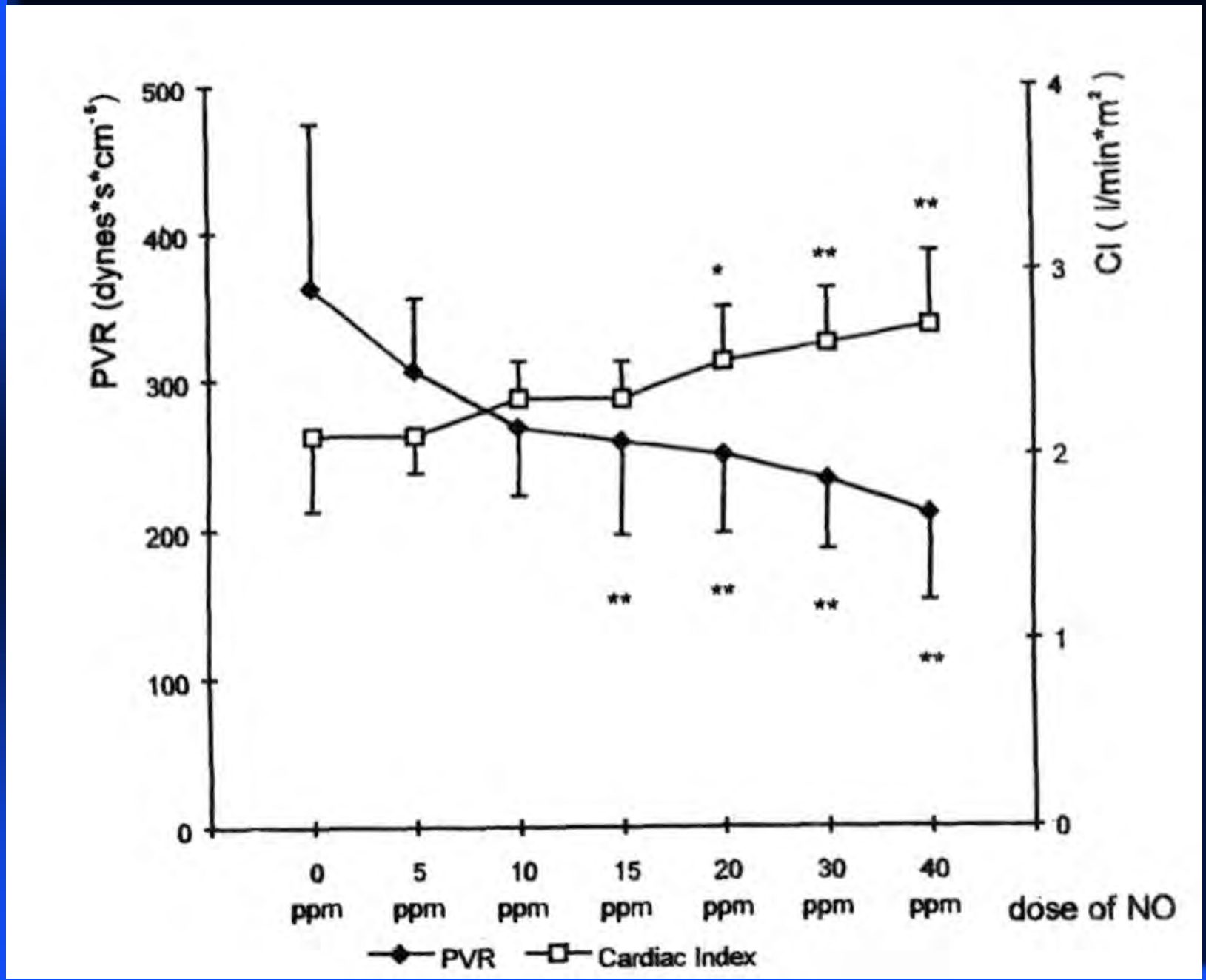
Inhaled NO in patients receiving LVAD

Nitric Oxide Inhalation in the Treatment of Right Ventricular Dysfunction Following Left Ventricular Assist Device Implantation

Frank Wagner, MD; Michael Dandel, MD; Grischa Günther; Matthias Loebe, MD;
Ingram Schulze-Neick, MD; Ullrich Laucke, MD; Rainer Kuhly, MD;
Yuguo Weng, MD; Roland Hetzer, MD

Circulation 1997;96:291

- 8 patients with RV dysfunction;
  - -CI < 2.5 l/min/m2
  - -MPAP > 25 mmHg,
  - -RVEF < 30%
- Catecholamines, PDE-3 inhibitors, nitrates, PGI_2
- Inhaled NO 5-40 ppm



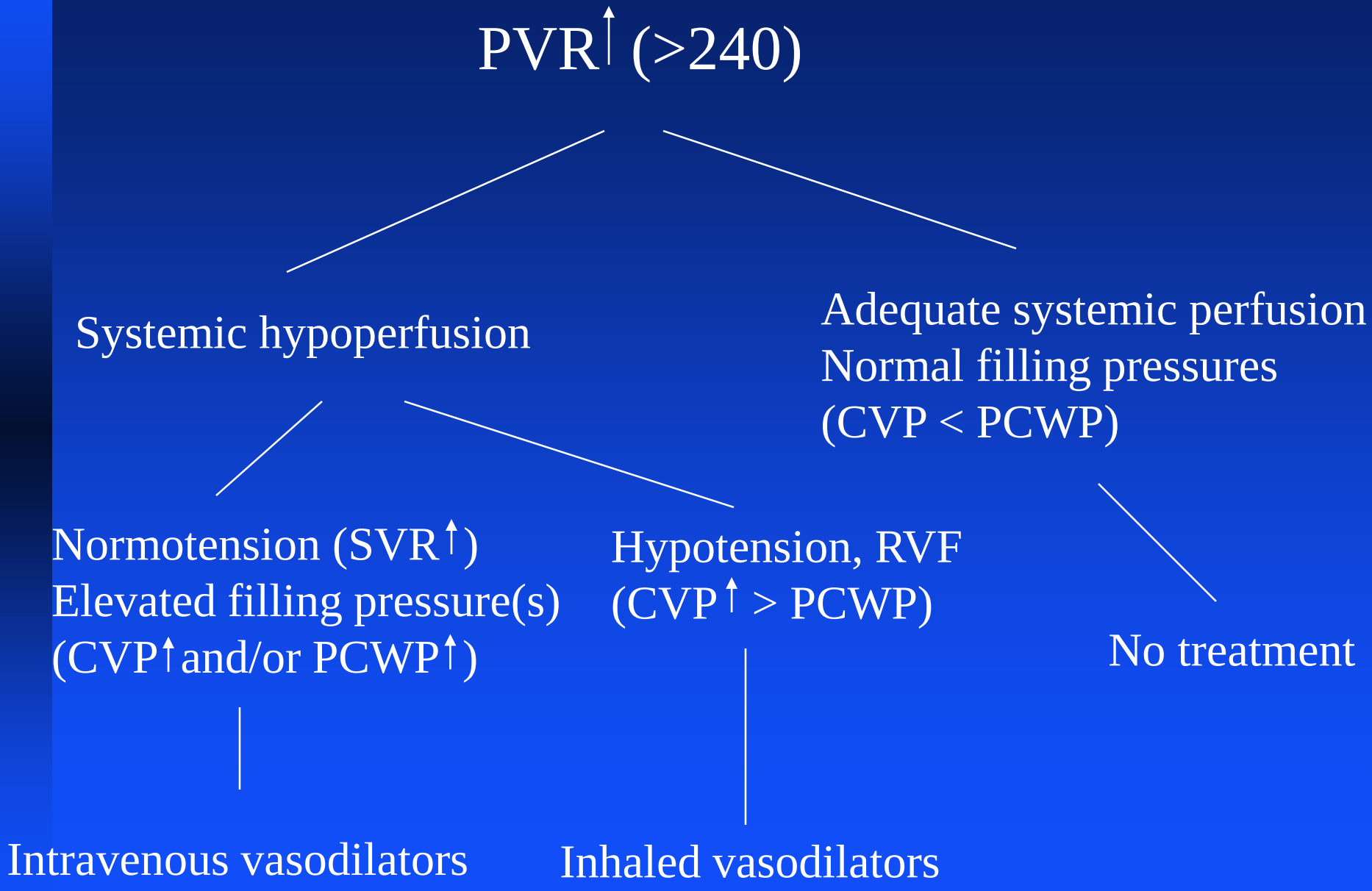
Wagner et al Circulation 1997;96:291

Prerequisites for a succesful treatment of RV failure with an inhaled vasodilator

- Pulmonary hypertension caused by a high PVR (> 240)
- PVR should not be fixed
- Isolated RV failure

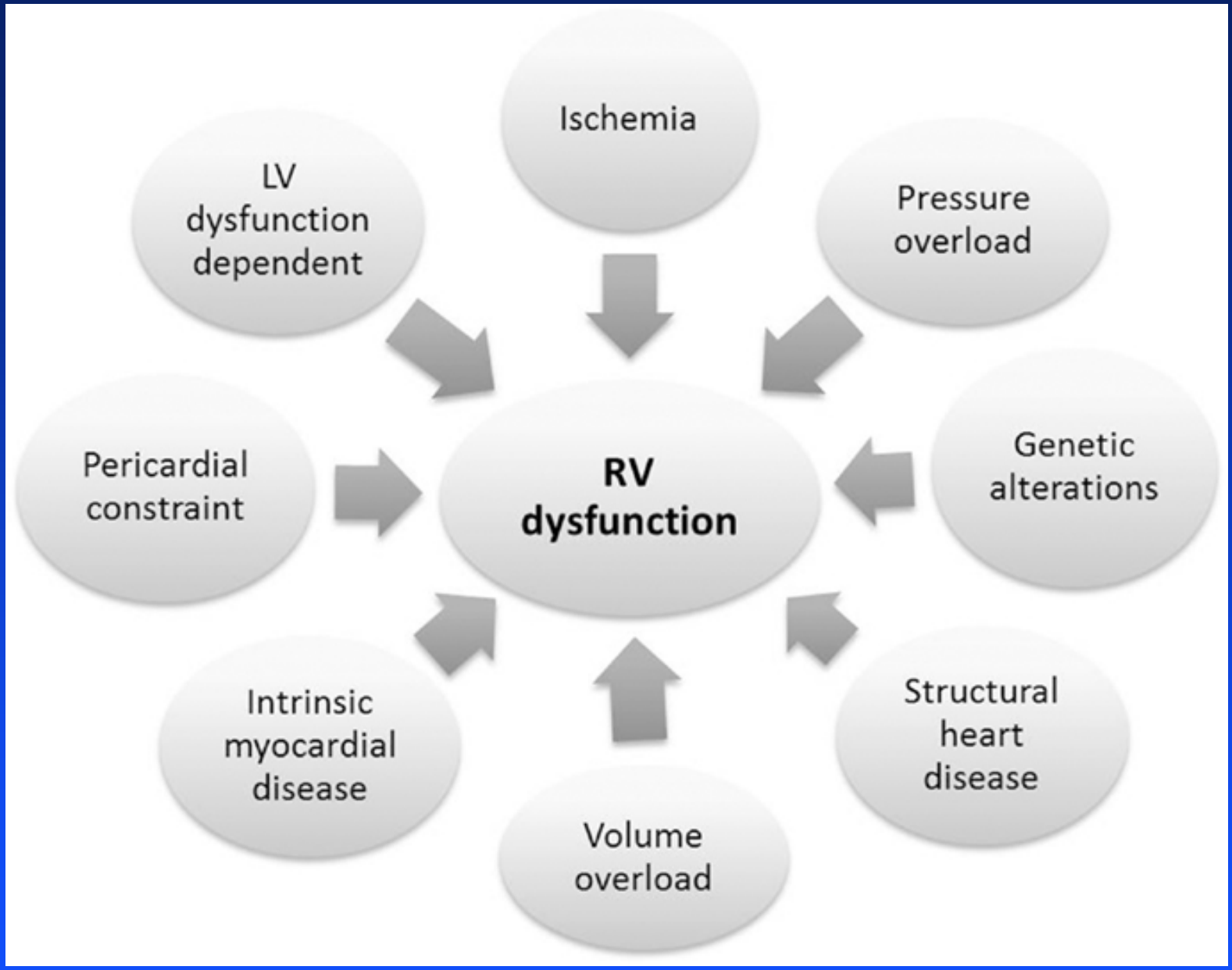
$$(MPAP - PCWP) = CO \times PVR$$

$$MPAP = PCWP + (CO \times PVR)$$


PVR↑ (>240)
Systemic hypoperfusion
Adequate systemic perfusion
Normal filling pressures
(CVP < PCWP)
Normotension (SVR↑)
Elevated filling pressure(s)
(CVP↑and/or PCWP↑)
Hypotension, RVF
(CVP↑ > PCWP)
No treatment
Intravenous vasodilators
Inhaled vasodilators

Inhaled NO should be used in the *treatment* of postoperative pulmonary hypertension if:

- Pulmonary vascular resistance is high and reversible *plus*
- Systemic hypoperfusion is present *plus*
- Isolated RV failure
- Graft dysfunction after lung transplantation

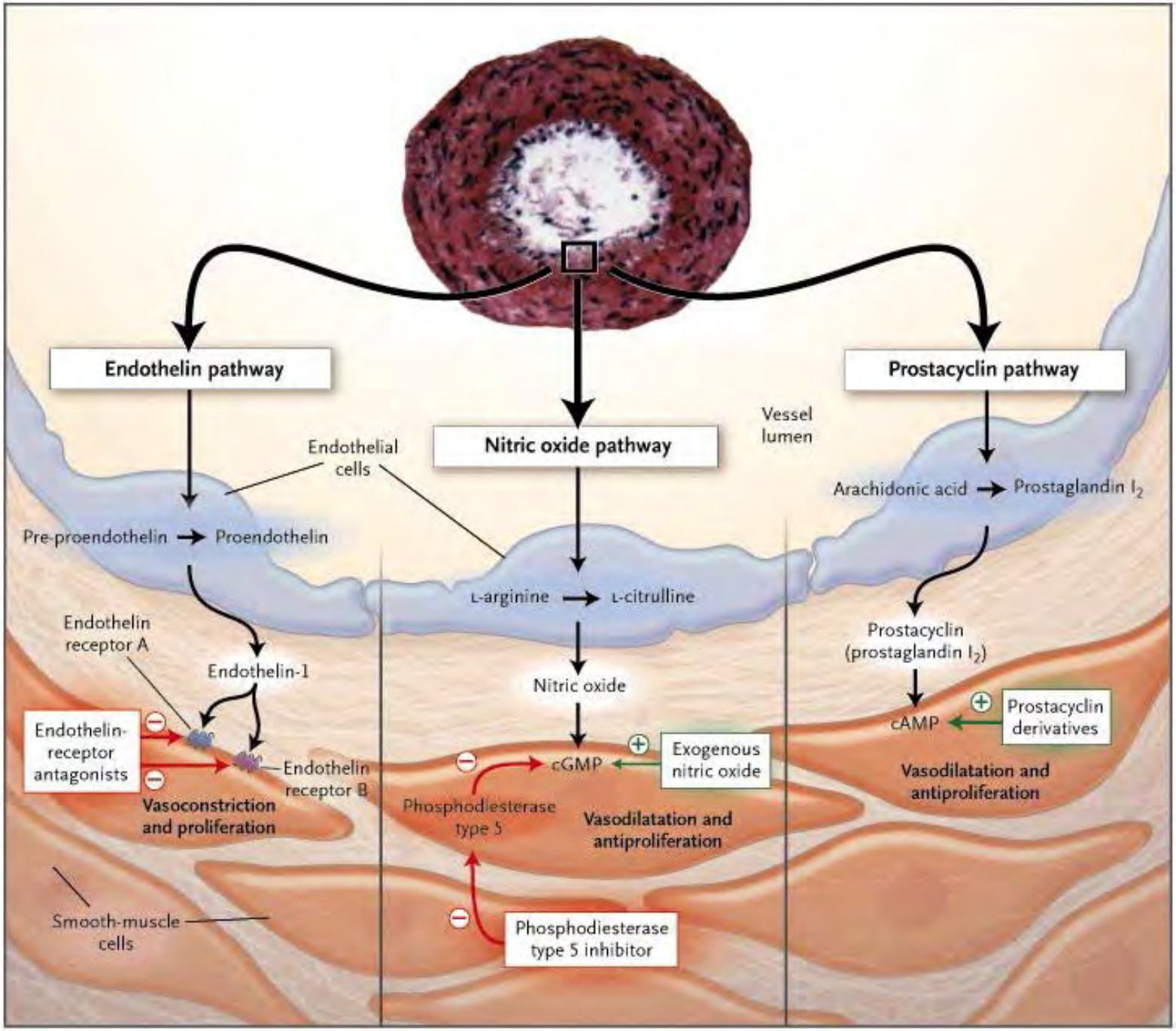

Ischemia
LV dysfunction dependent
Pressure overload
Pericardial constraint
RV dysfunction
Genetic alterations
Intrinsic myocardial disease
Volume overload
Structural heart disease

Righ ventricular failure (RVF)

- Lung disease (RVF:1/2000 COPD, ARDS)
- Sepsis
- Pulmonary embolism (RVF independent risk factor)
- Cardiomyopathy (ischemic, dilatative) (RVF independent risk factor)
- Heart transplantation/heart surgery (RVF leading cause of death)
- Primary pulmonary hypertension
- Coronary artery disease (RV infarction + RVF, 8-fold increase in mortality) 50% of patients with posterior-AMI develop RVF
- Valvular heart disease

Why should we treat pulmonary hypertension in cardiac surgery?

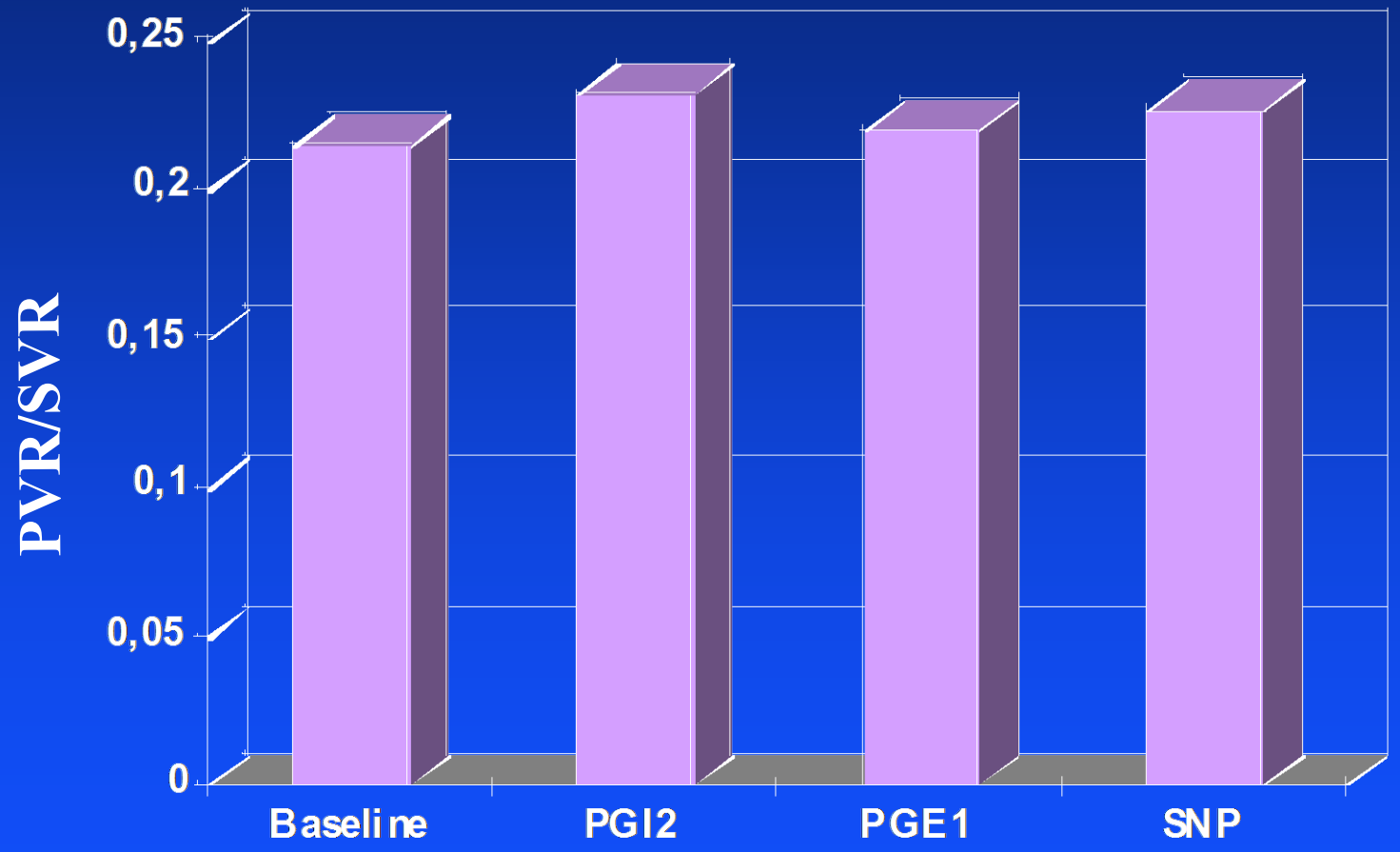
- Preoperative pulmonary hypertension is an independent predictor of postoperative mortality
- Cardiac surgery with CPB may induce pulmonary vasoconstriction:
  - -protamine - heparin
  - -endothelial dysfunction


Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Vessel lumen
Endothelial cells
Pre-proendothelin
Proendothelin
Arachidonic acid
Prostaglandin I_2
L-arginine
L-citrulline
Endothelin receptor A
Endothelin-1
Nitric oxide
Prostacyclin (prostaglandin I_2)
Endothelin-receptor antagonists
Endothelin receptor B
Vasoconstriction and proliferation
cGMP
Exogenous nitric oxide
cAMP
Prostacyclin derivatives
Vasodilatation and antiproliferation
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Smooth-muscle cells
Phosphodiesterase type 5 inhibitor

Why should we treat pulmonary hypertension in cardiac surgery?

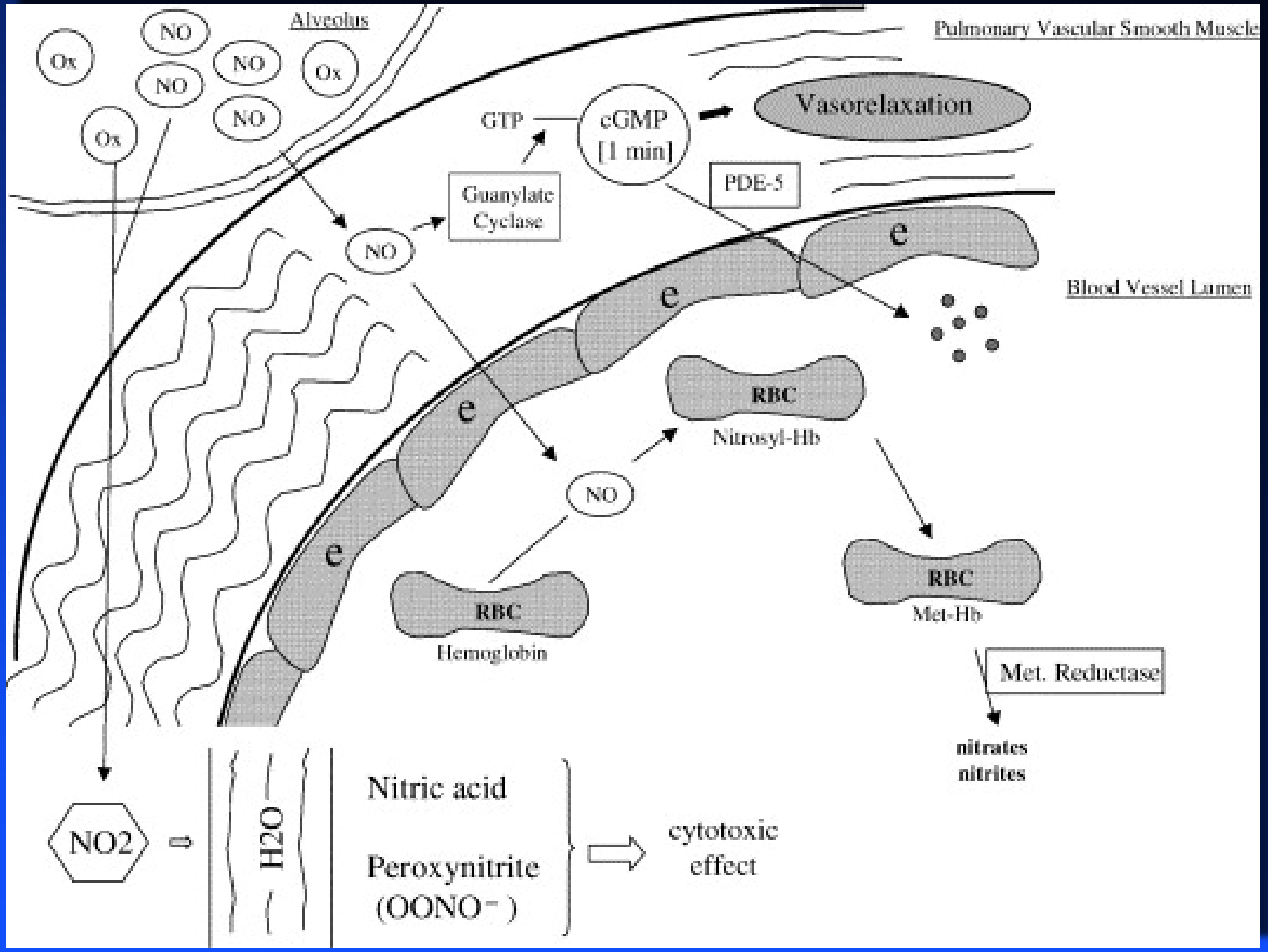
- Perioperative pulmonary hypertension is an independent predictor of postoperative mortality
- Cardiac surgery with CPB may induce pulmonary vasoconstriction:
  - -protamine - heparin
  - -endothelial dysfunction
- Perioperative pulmonary hypertension may cause refractory right ventricular failure (RVF) with a mortality of 40-60%
- Incidence of severe refractory RVF:
  - -heart transplantation 2-3%
  - -LVAD 20-30%

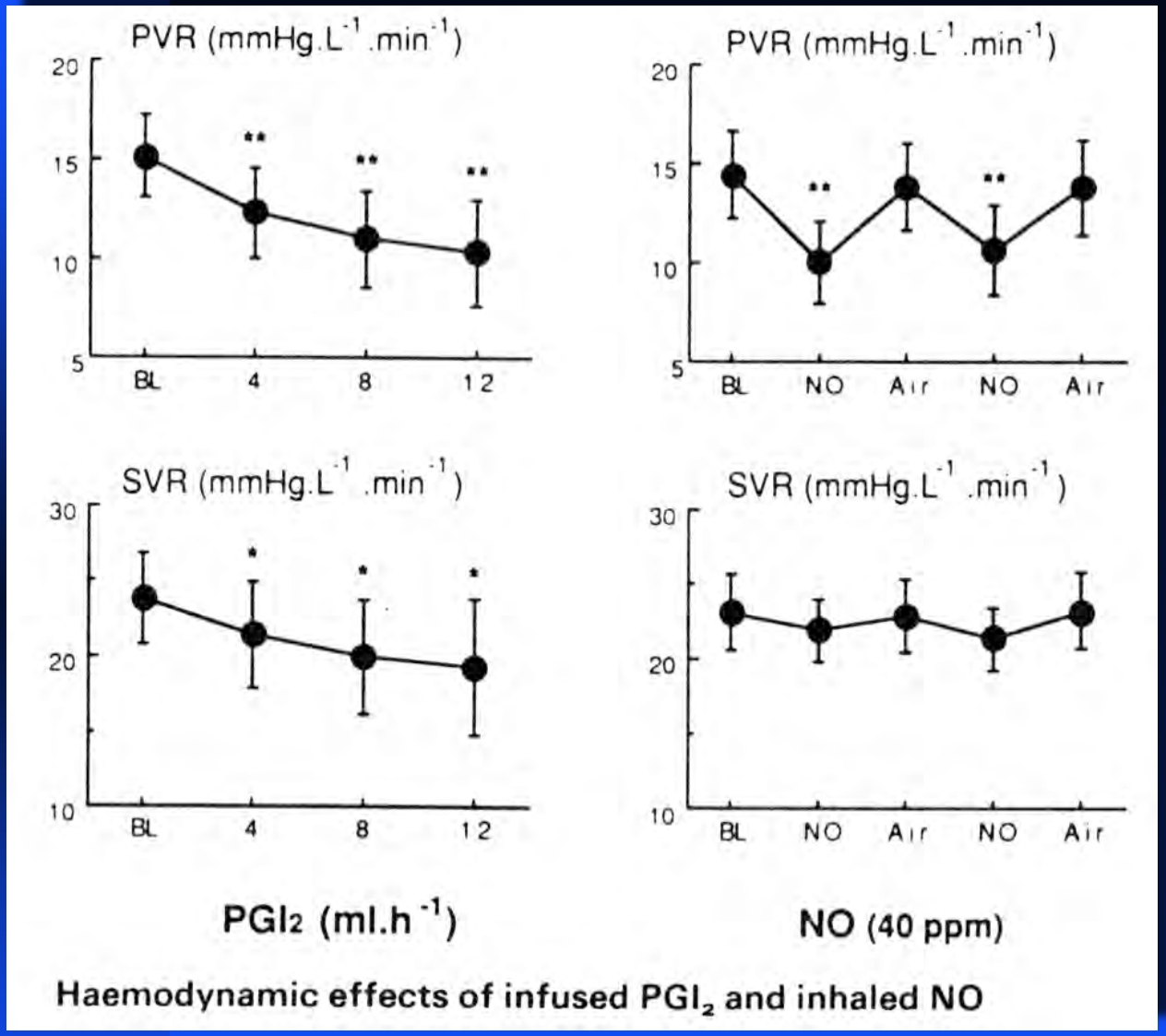
The pulmonary selectivity of intravenous vasodilators (PVR/SVR ratio)



Kieler-Jensen et al J Heart Lung Transplant 1995;14:436

Inhaled NO – mechanisms of action





Haemodynamic effects of infused PGI_2 and inhaled NO

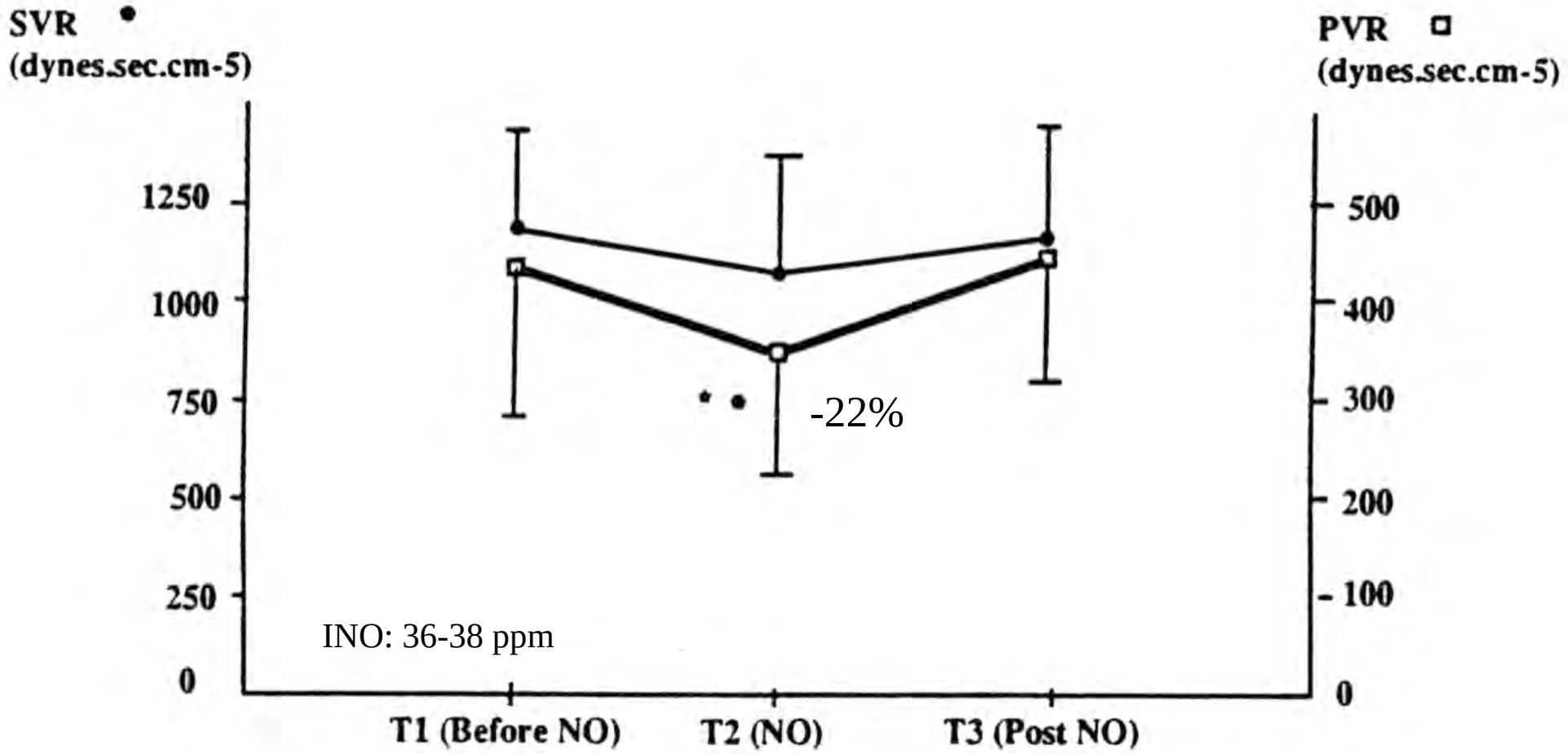
Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension

JOANNA PEPKE-ZABA
TIMOTHY W. HIGENBOTTAM
A. TUAN DINH-XUAN DAVID STONE
JOHN WALLWORK

Lancet 1991;338:1173

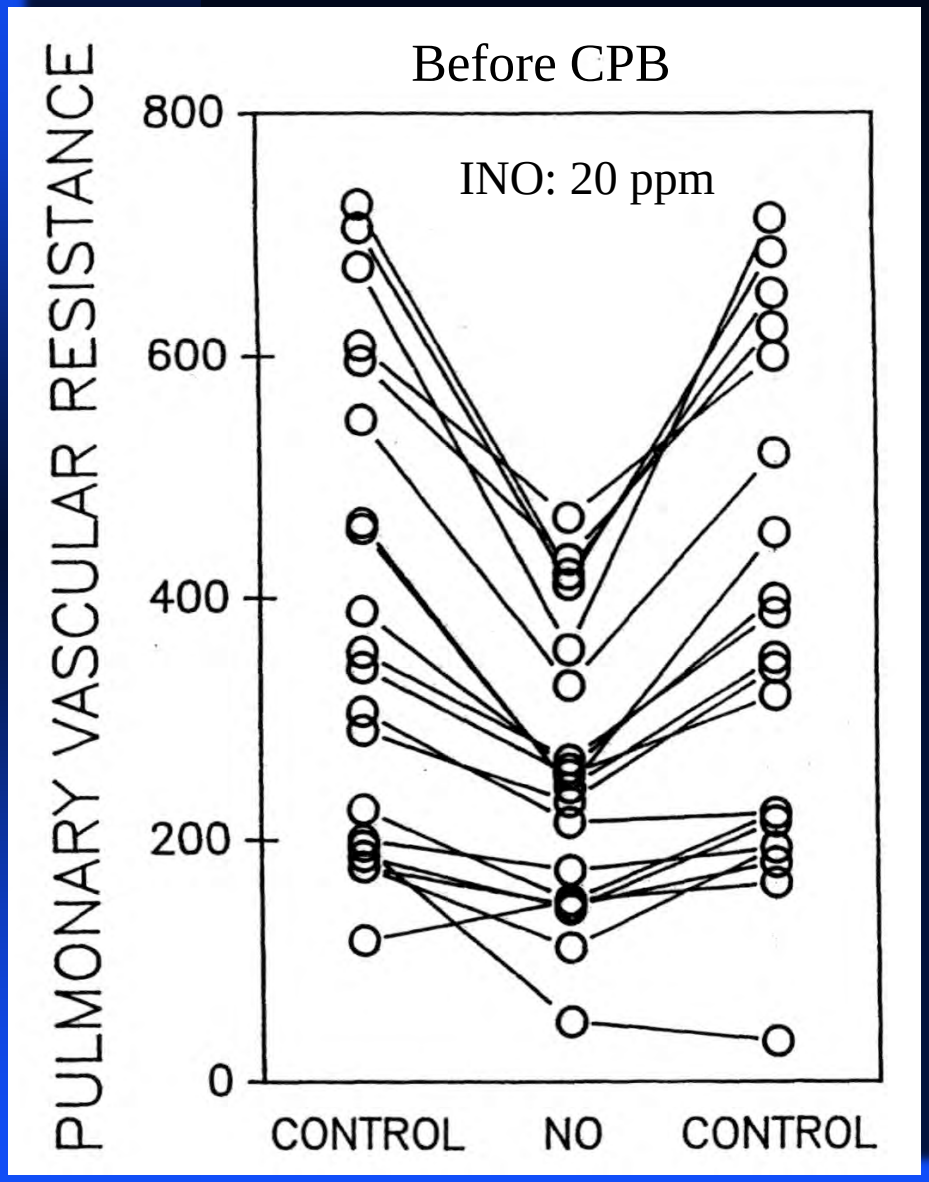
Inhaled NO in cardiac surgery

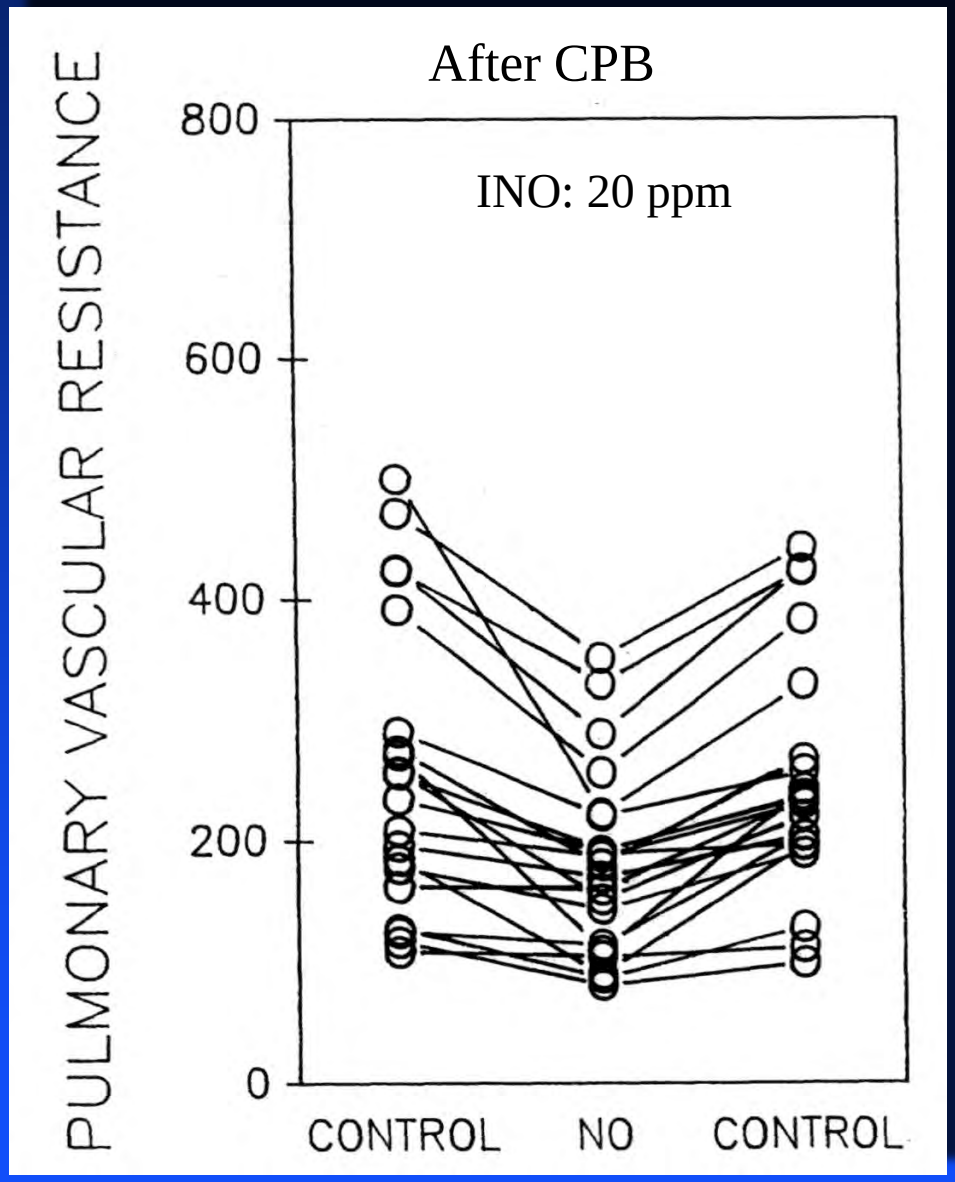
Inhaled NO after mitral valve replacement (MVR)



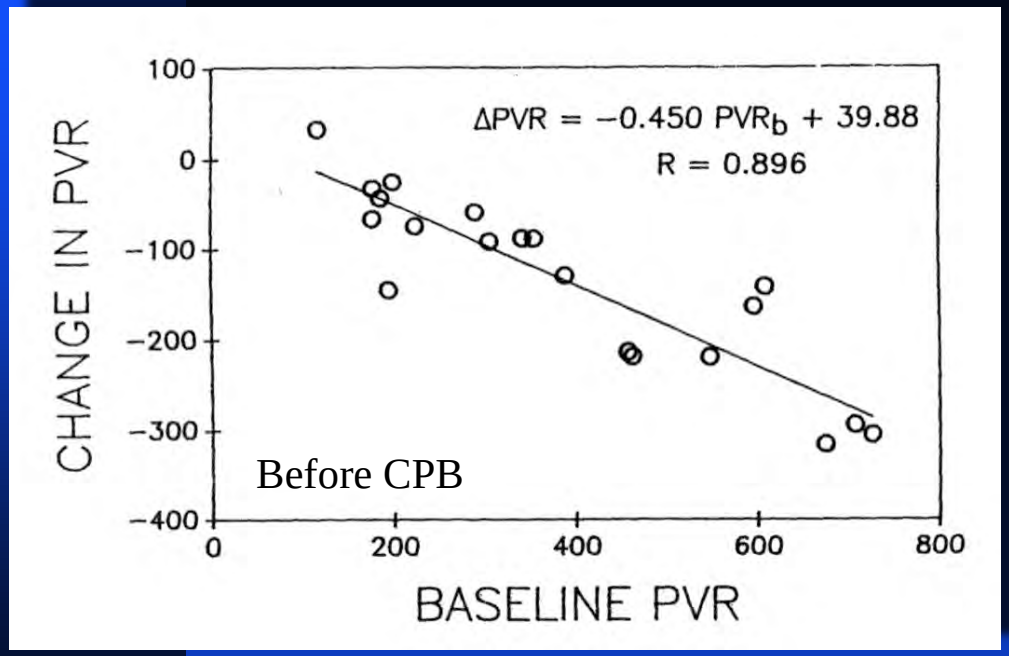
Girard et al Anesthesiology 1992;77:880

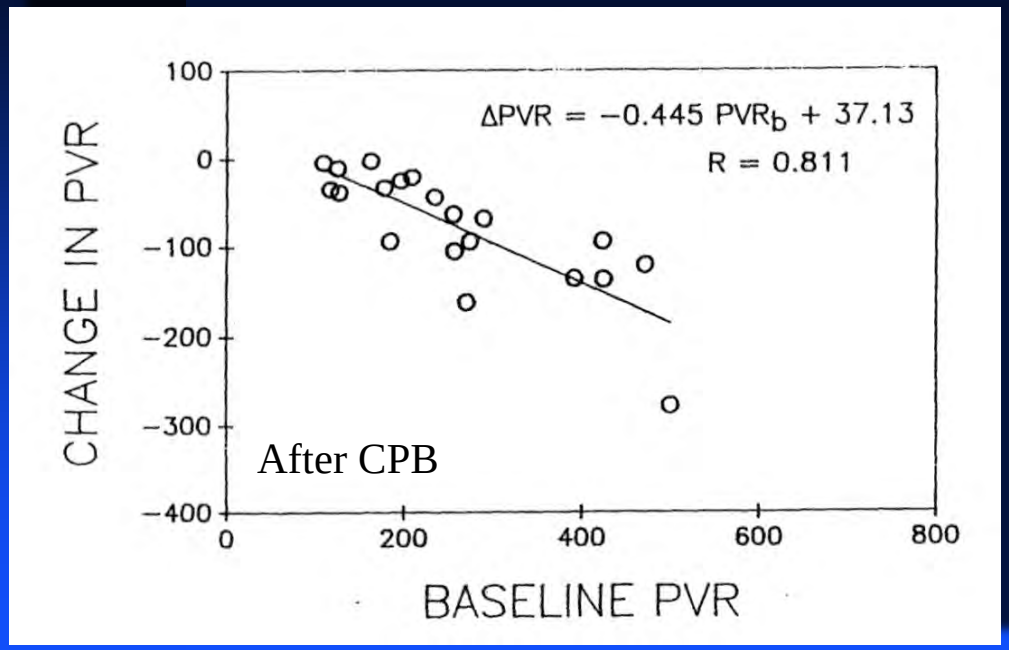
Inhaled NO before and after MVR or CABG

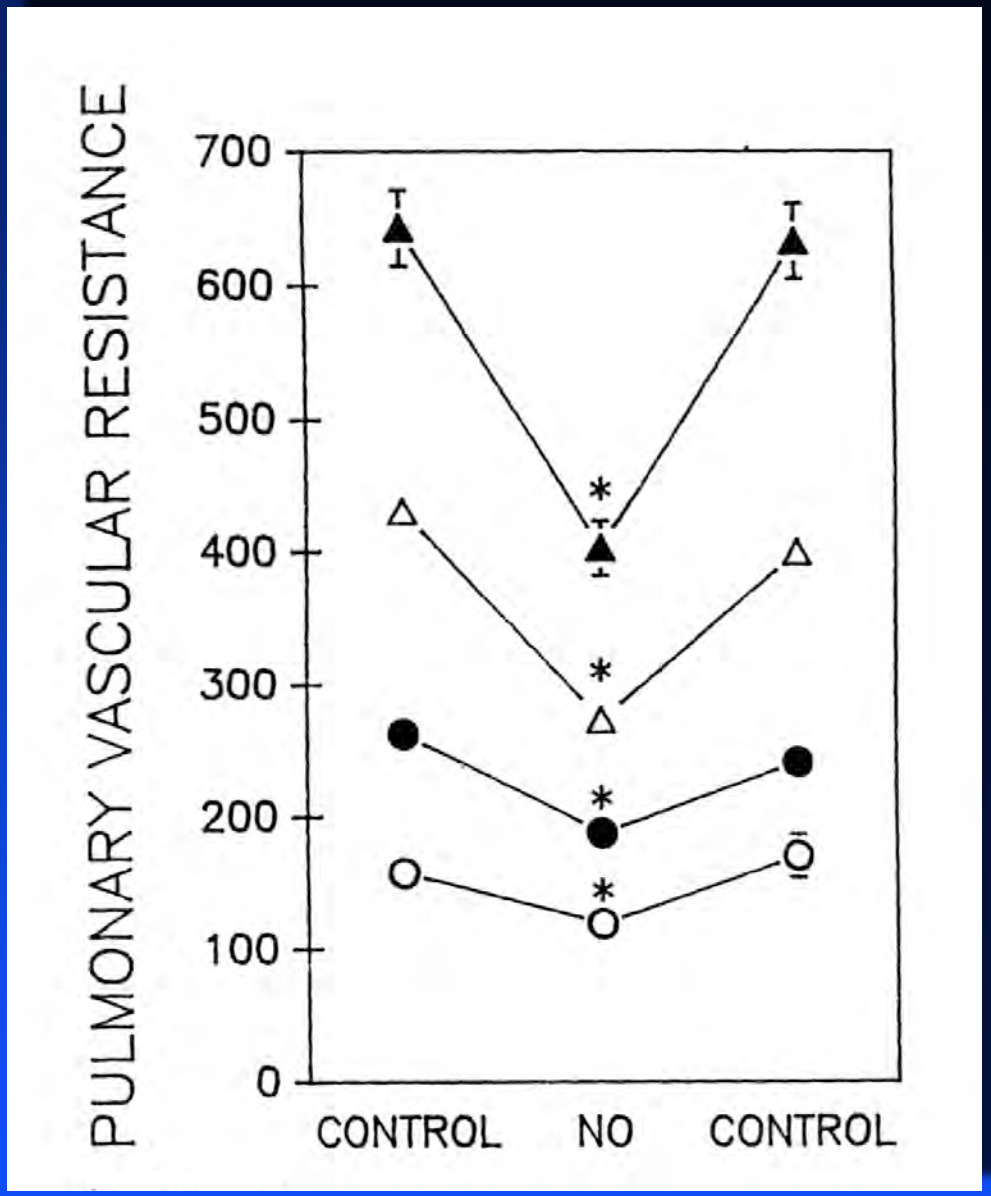




Rich et al Anesthesiology 1993;78:1028

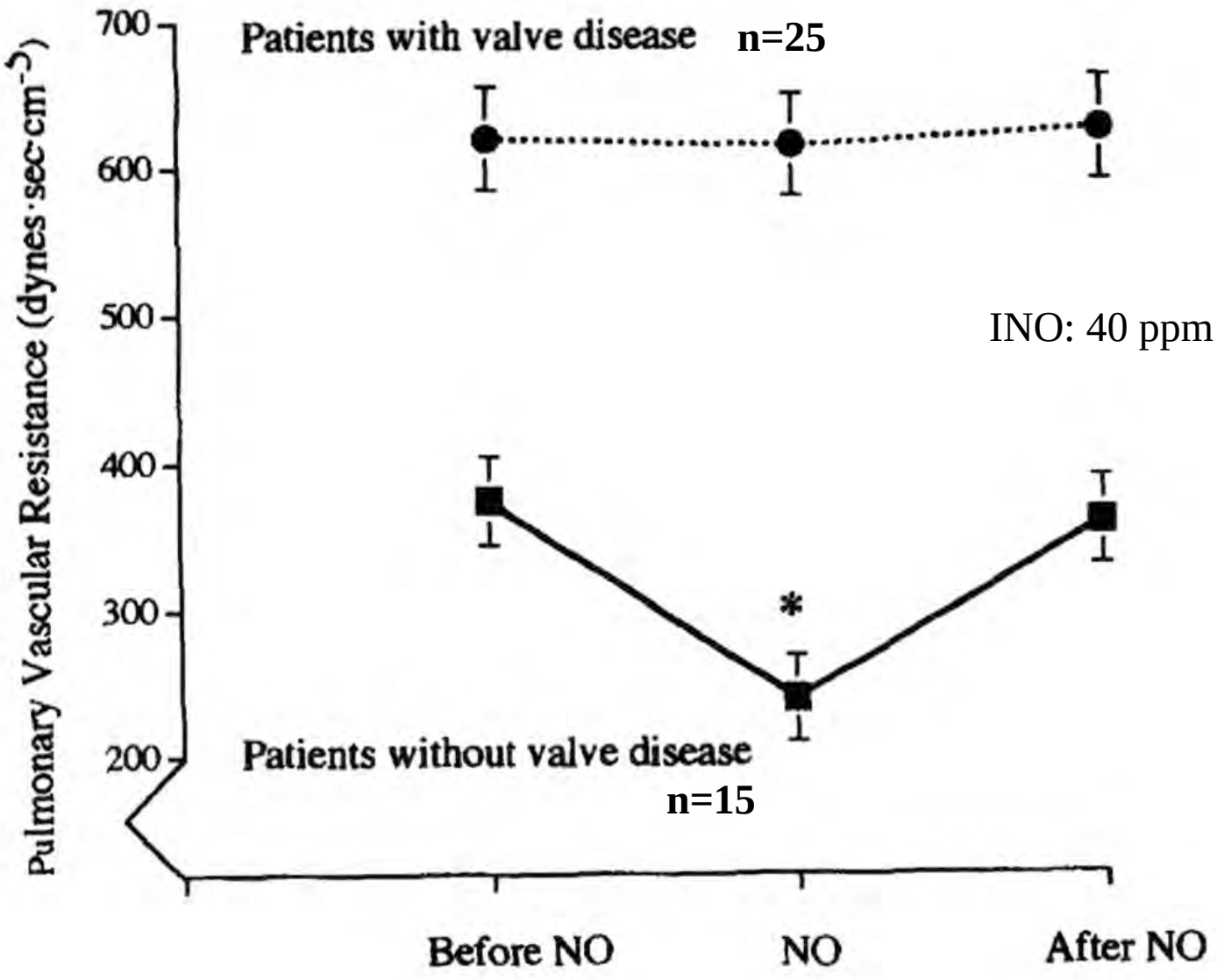






Rich et al Anesthesiology 1993;78:1028

Inhaled NO after MVR or CABG



Fullerton et al Ann Thorac Surg 1997;63:1251

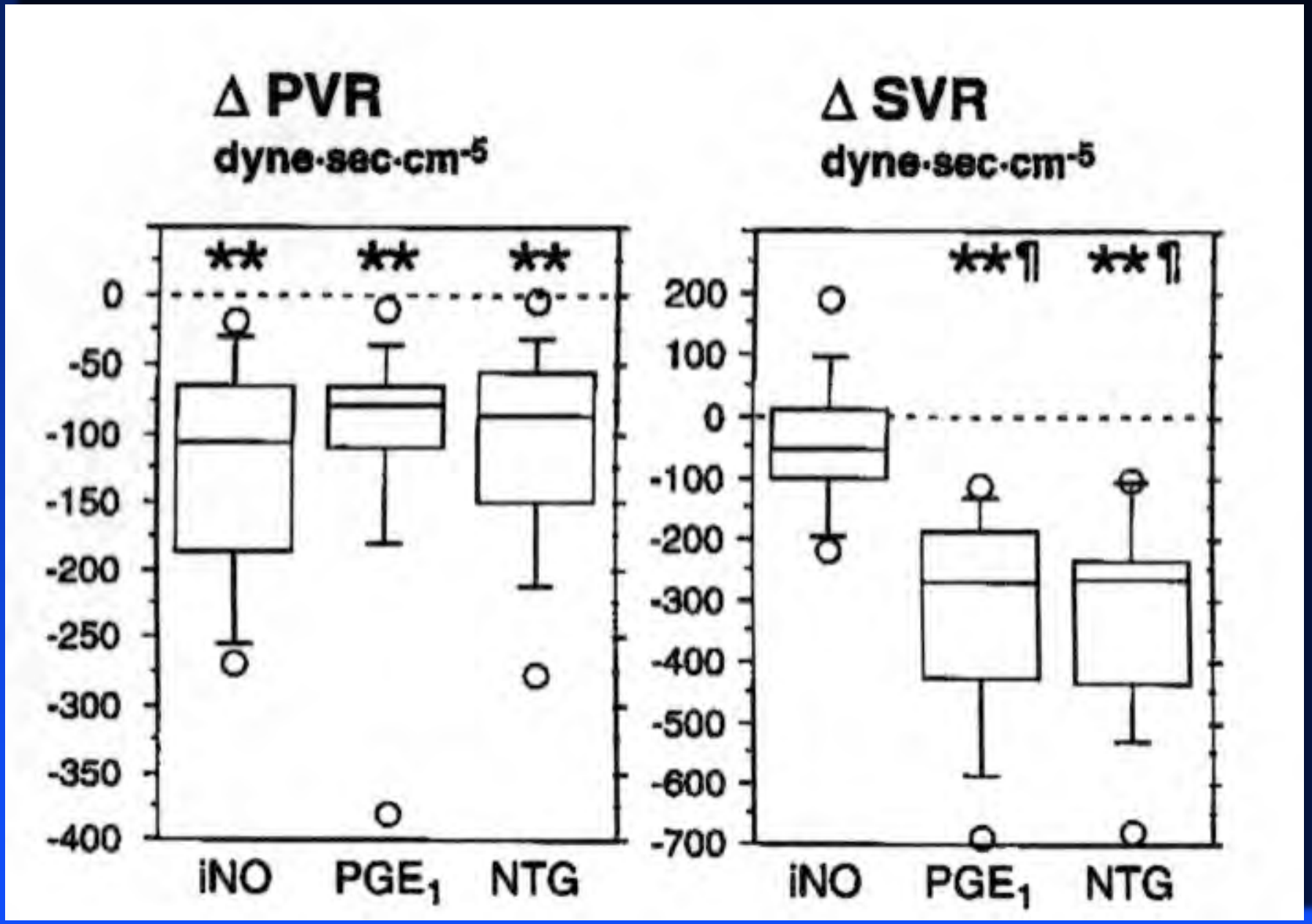
Inhaled Nitric Oxide Versus Intravenous Vasodilators in Severe Pulmonary Hypertension After Cardiac Surgery

Edith R. Schmid, MD*, Christoph Bürki, MD*, Markus H. C. Engel, MD*, Daniel Schmidlin, MD*, Mico Tornic, MD*, and Burkhardt Seifert, PhD†

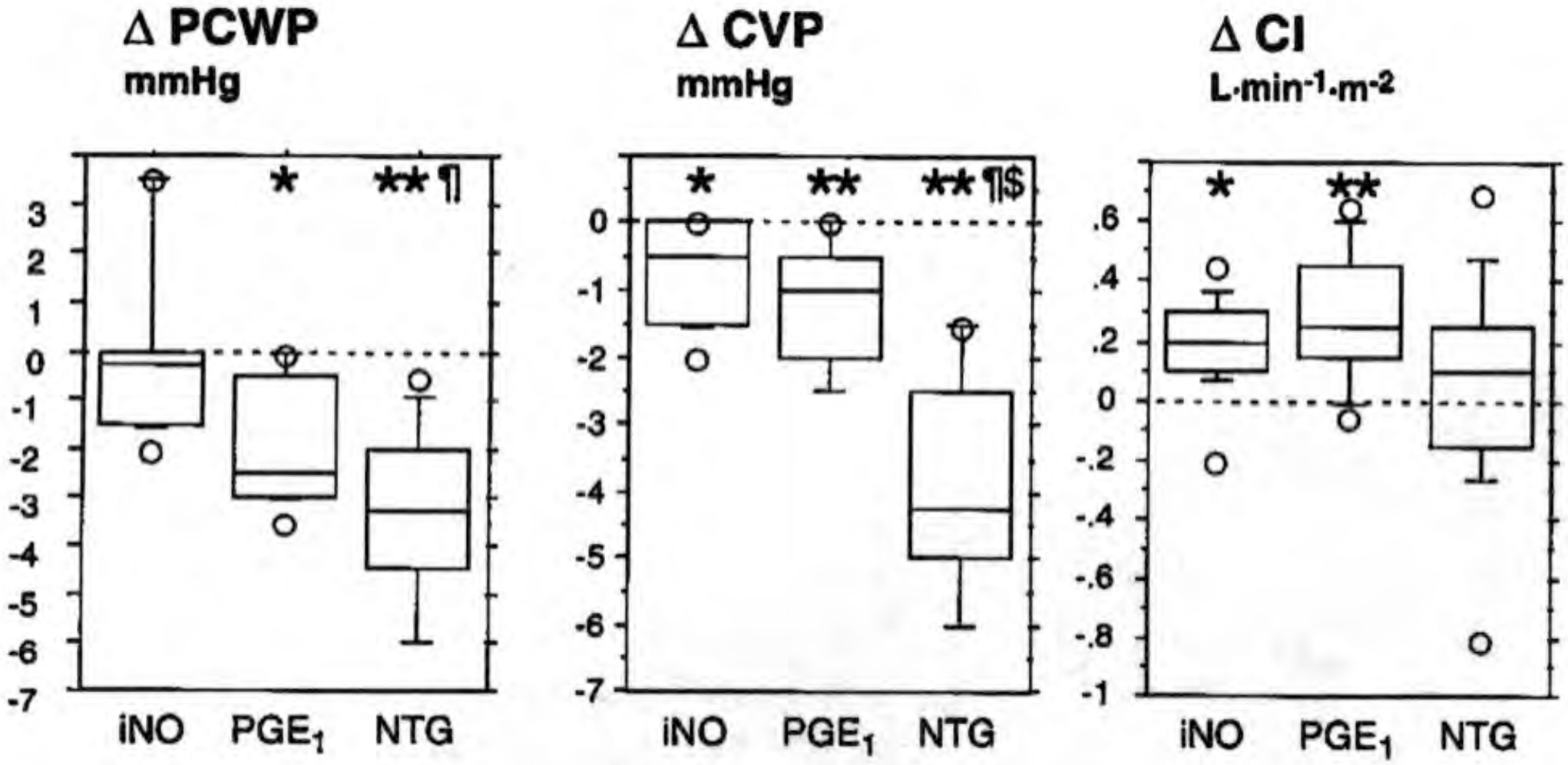
*Division of Cardiovascular Anesthesia, Institute of Anesthesiology, University Hospital of Zurich; and †Department of Biostatistics, University of Zurich, Zurich, Switzerland

Anesth Analg 1999,89:1108

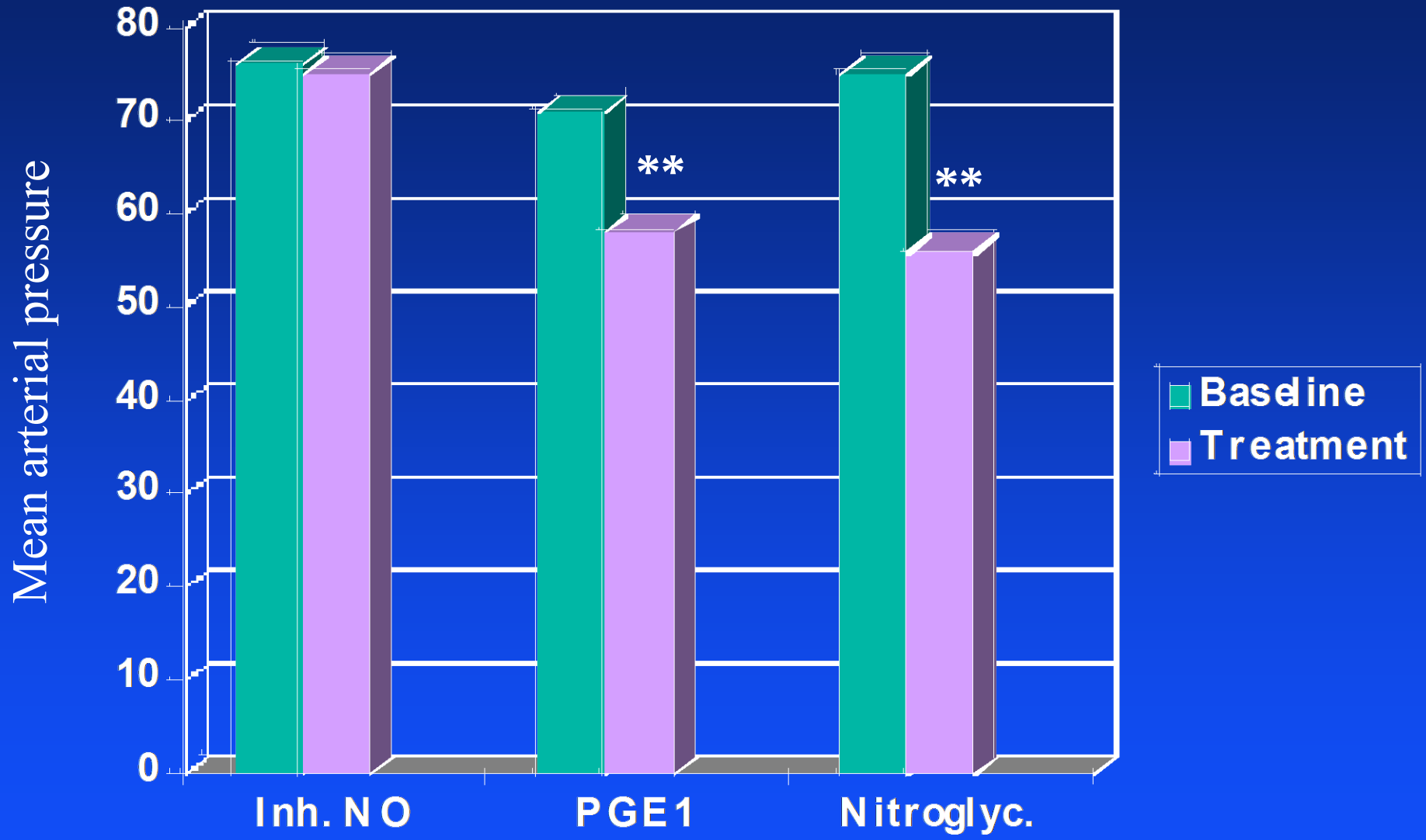
- Severe postoperative pulmonary hypertension (n=14)
- Dobutamine/dopamine ± norepinephrine
- Maintained RV function
- Randomized crossover design:
  - -Inhaled NO (40 ppm)
  - -PGE1 (0,1µg/kg/min)
  - -Nitroglycerin (3-5 µg/kg/min)



Schmid et al Anesth Analg 1999,89:1108

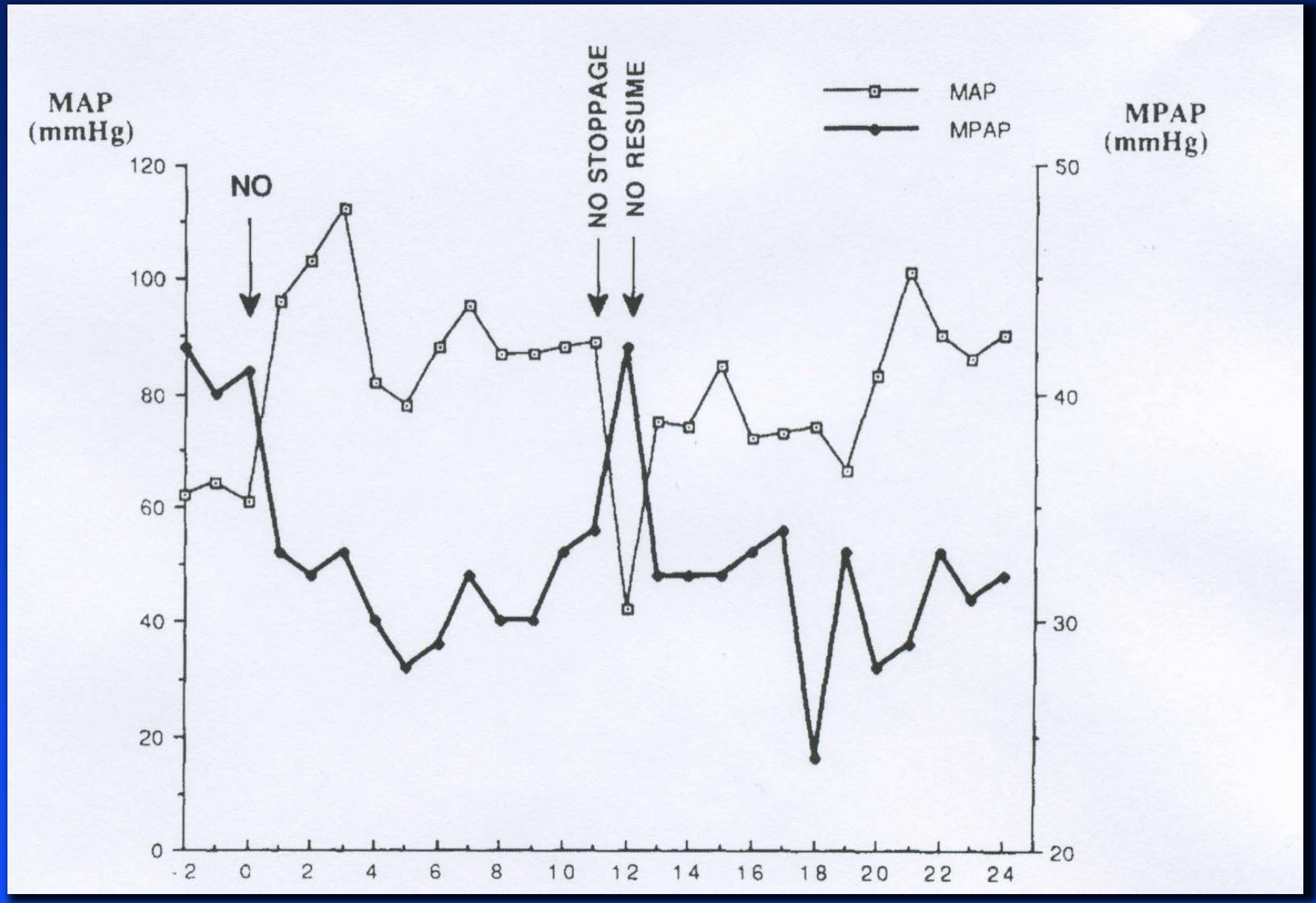


Schmid et al Anesth Analg 1999,89:1108



Schmid et al Anesth Analg 1999,89:1108

Inhaled NO in heart transplantation



Girard et al J Cardiothoracic Vasc Anesth 1993;7: 481

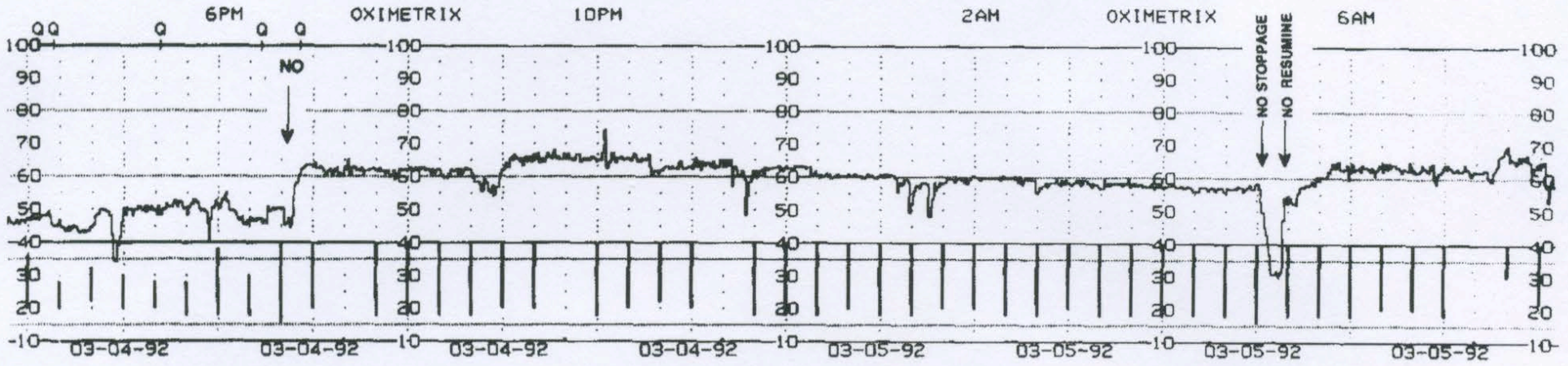
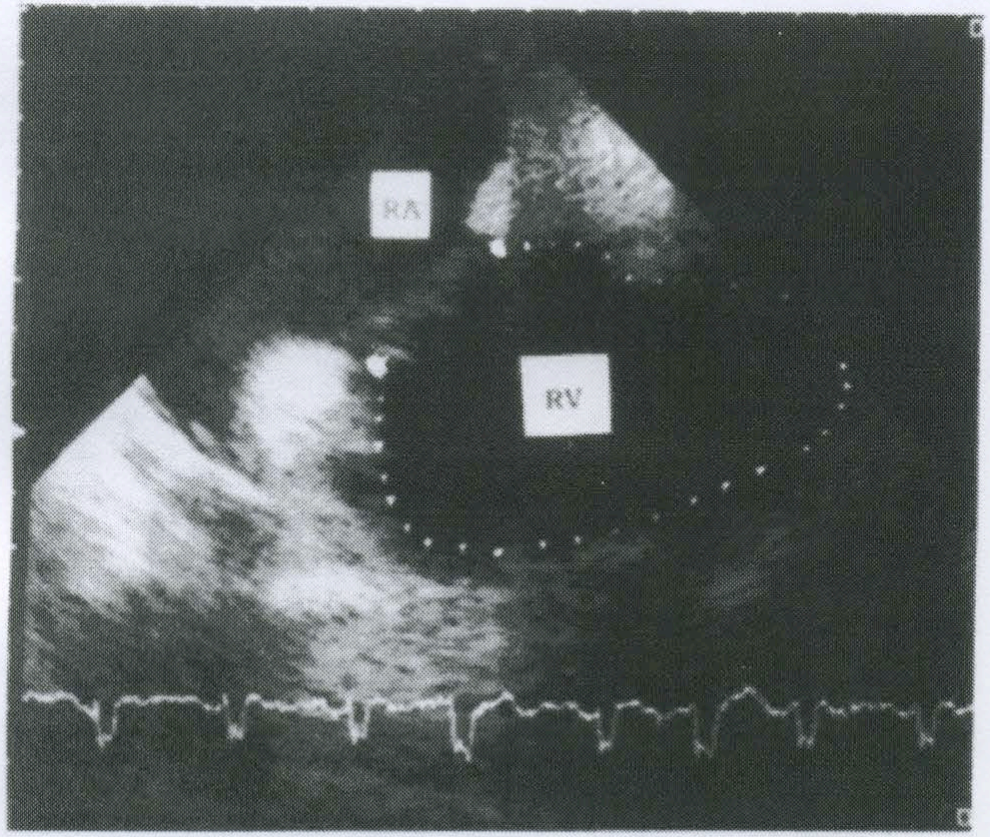


Fig 2. Changes in SvO_2 during NO

Girard et al J Cardiothoracic Vasc Anesth 1993;7: 481



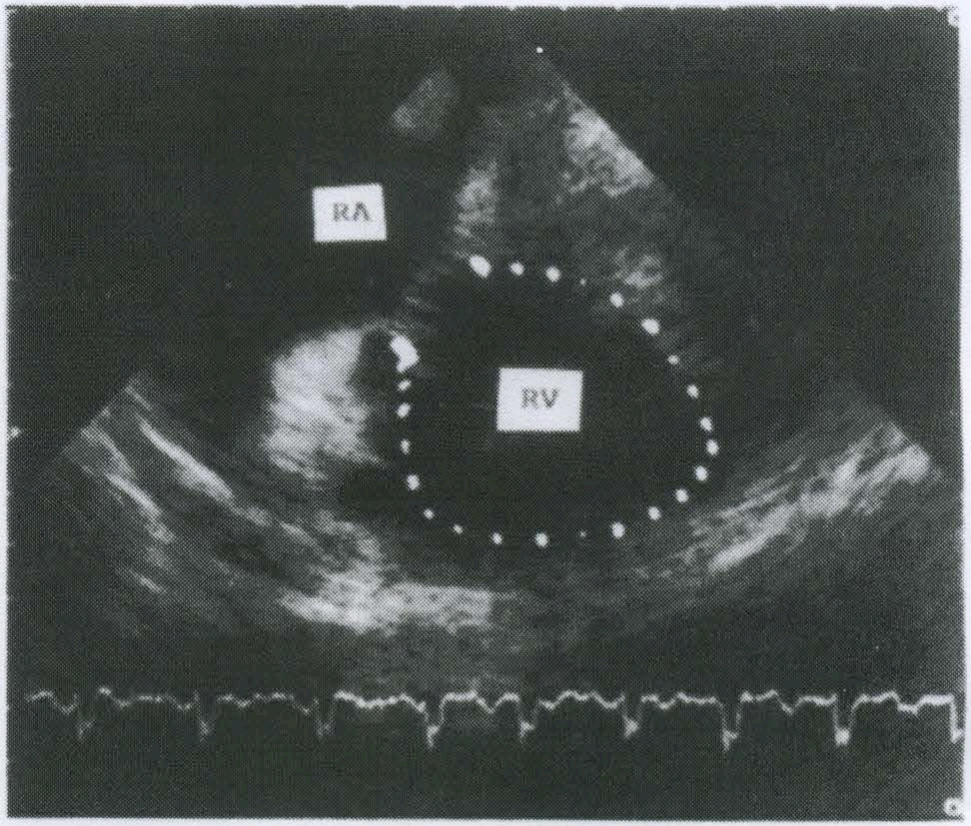


Fig 3. Ultrasonographic pictures (left without NO; right with NO) of the right ventricle. NO introduction brought about three remarkable findings: a reduction in size of the ventricle, an attenuation of the septum shift, and a reduction in the size of the tricuspid annulus.

Girard et al J Cardiothoracic Vasc Anesth 1993;7: 481

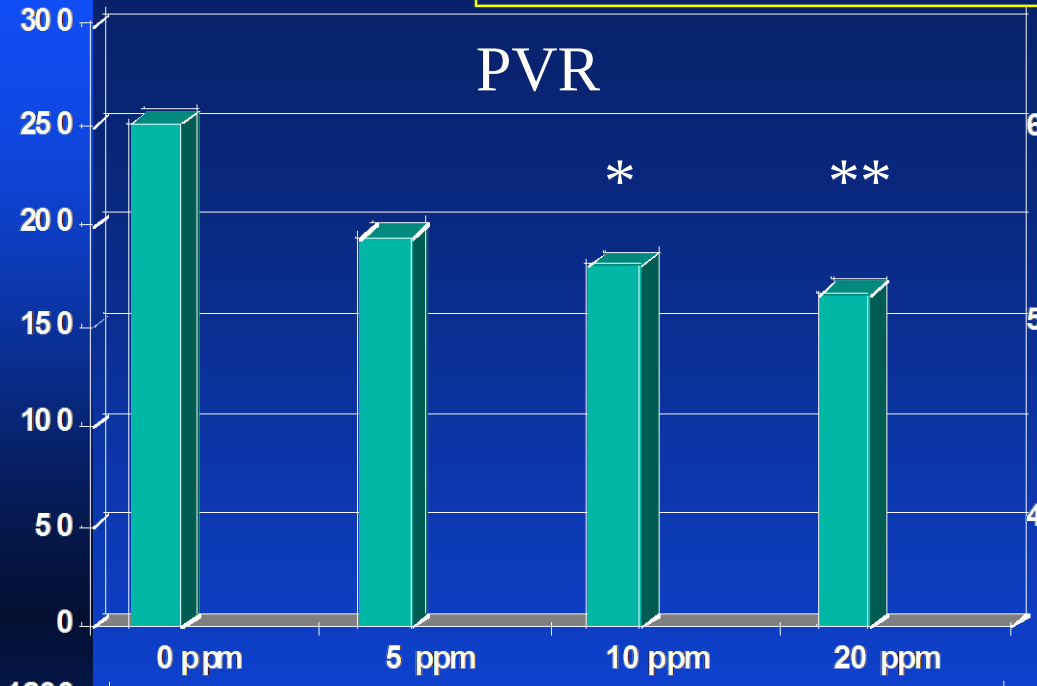
Vasodilator Therapy after Heart Transplantation: Effects of Inhaled Nitric Oxide and Intravenous Prostacyclin, Prostaglandin E_1, and Sodium Nitroprusside

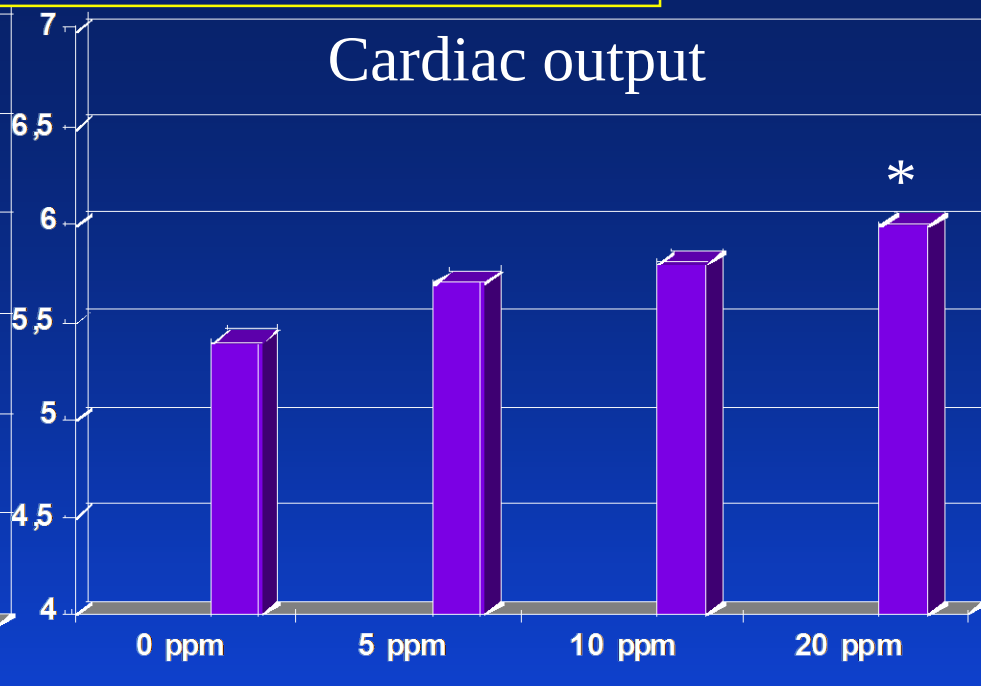
Niels Kieler-Jensen, MD, PhD, Stefan Lundin, MD, PhD,
Sven-Erik Ricksten, MD, PhD

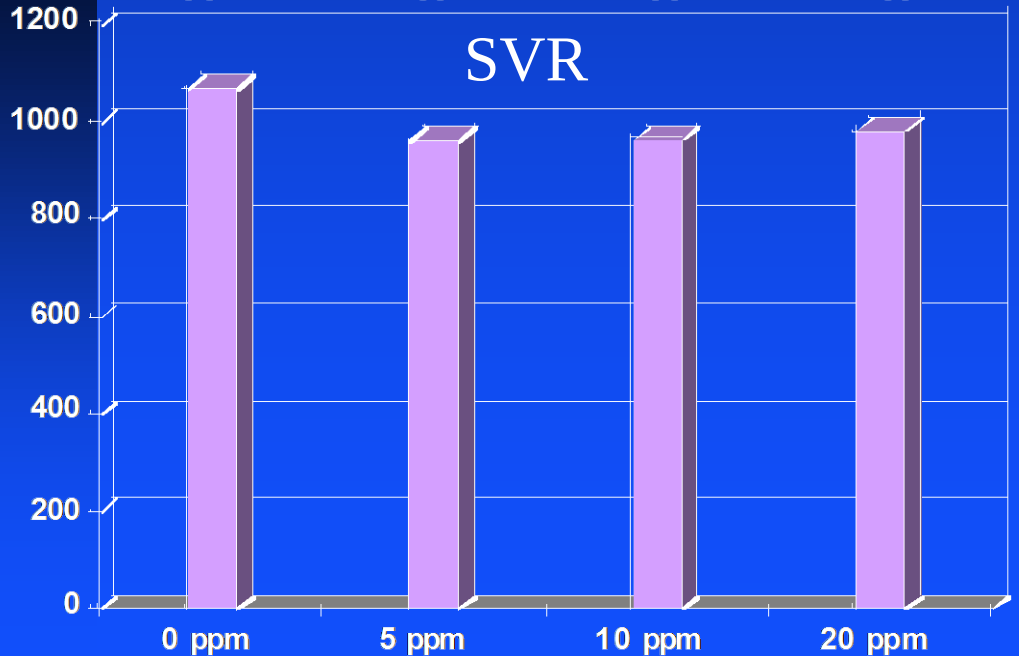
J Heart lung Transplant 1995;14:436

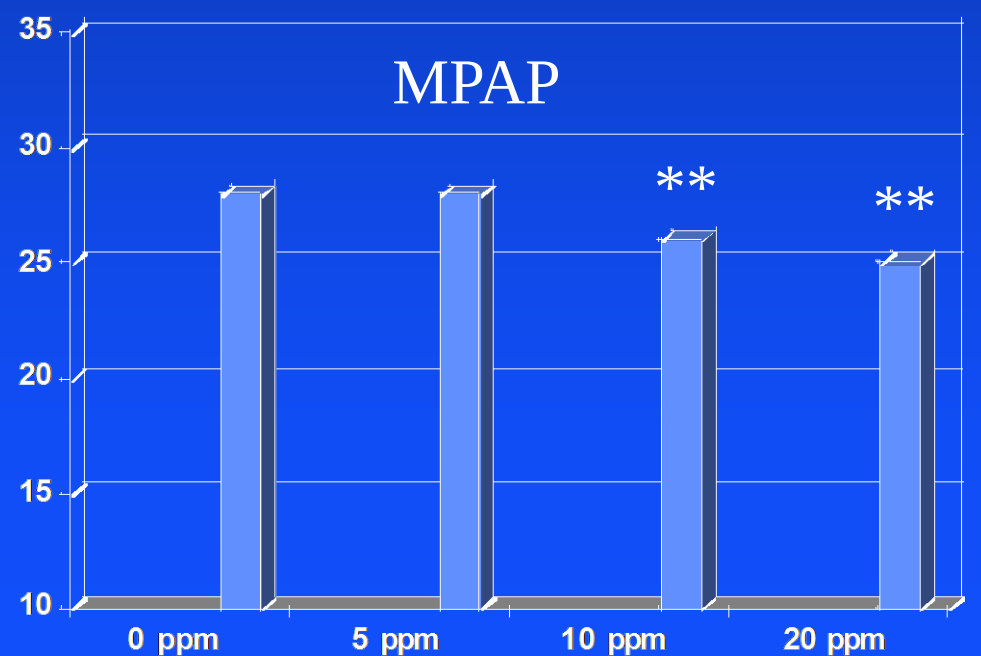
- Uncomplicated heart transplantation (n=9)
- Preoperative PVR: (144-472), TPG: (6-20 mmHg)
- NO inhalation: 5, 10 and 20 ppm
- Intravenous PGI_2, PGE_1 and sodium nitroprusside (SNP) to decrease MAP from 90 to 75 mmHg

Inhaled NO in heart transplantation

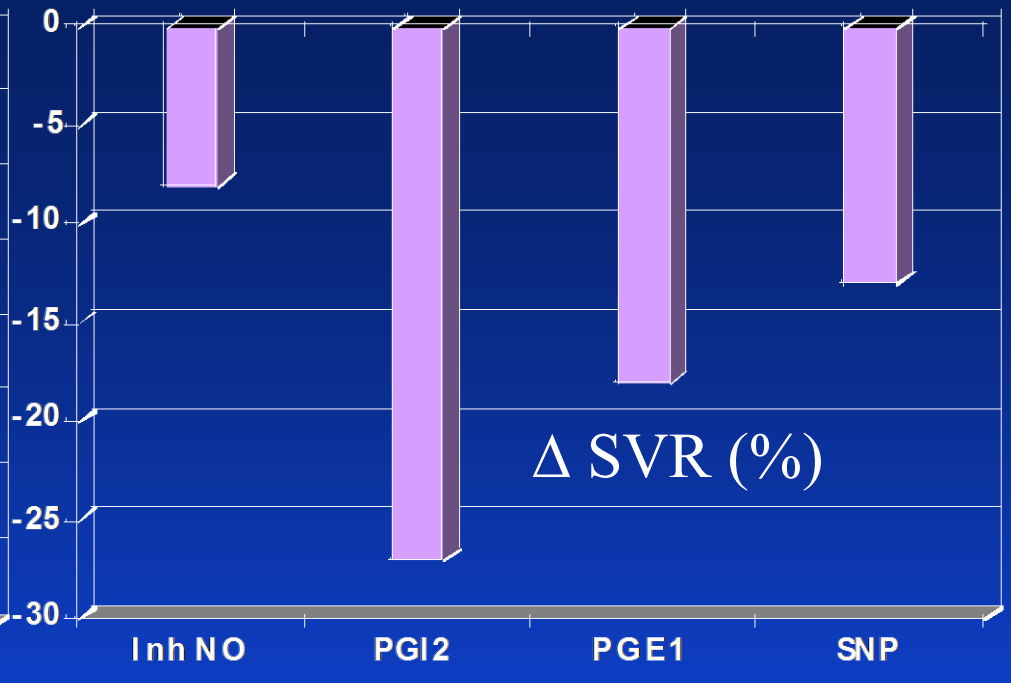


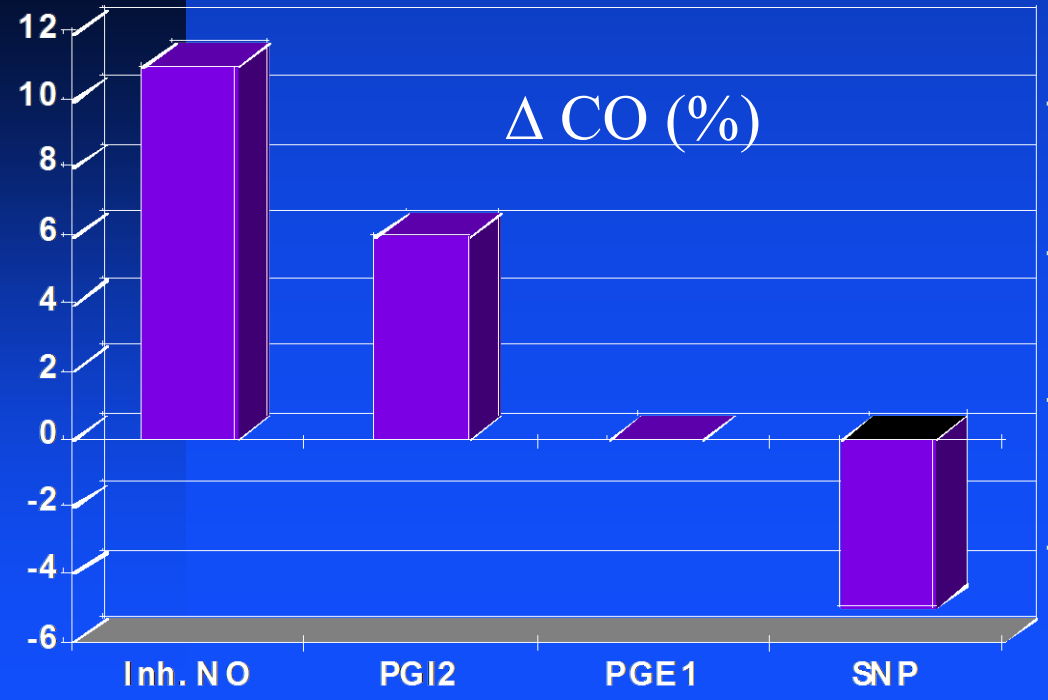


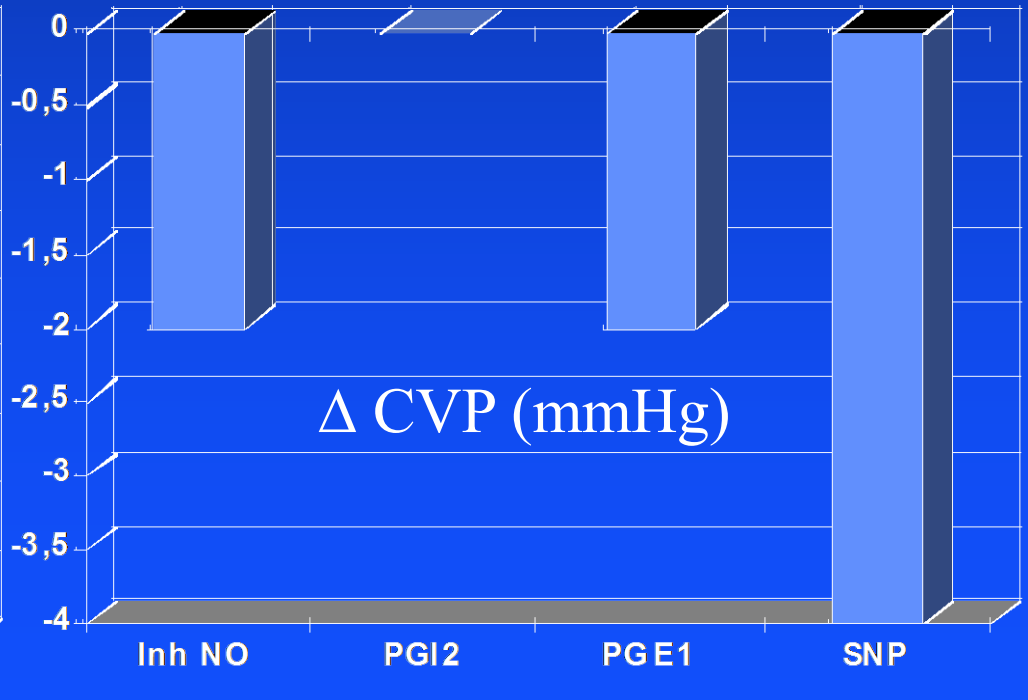




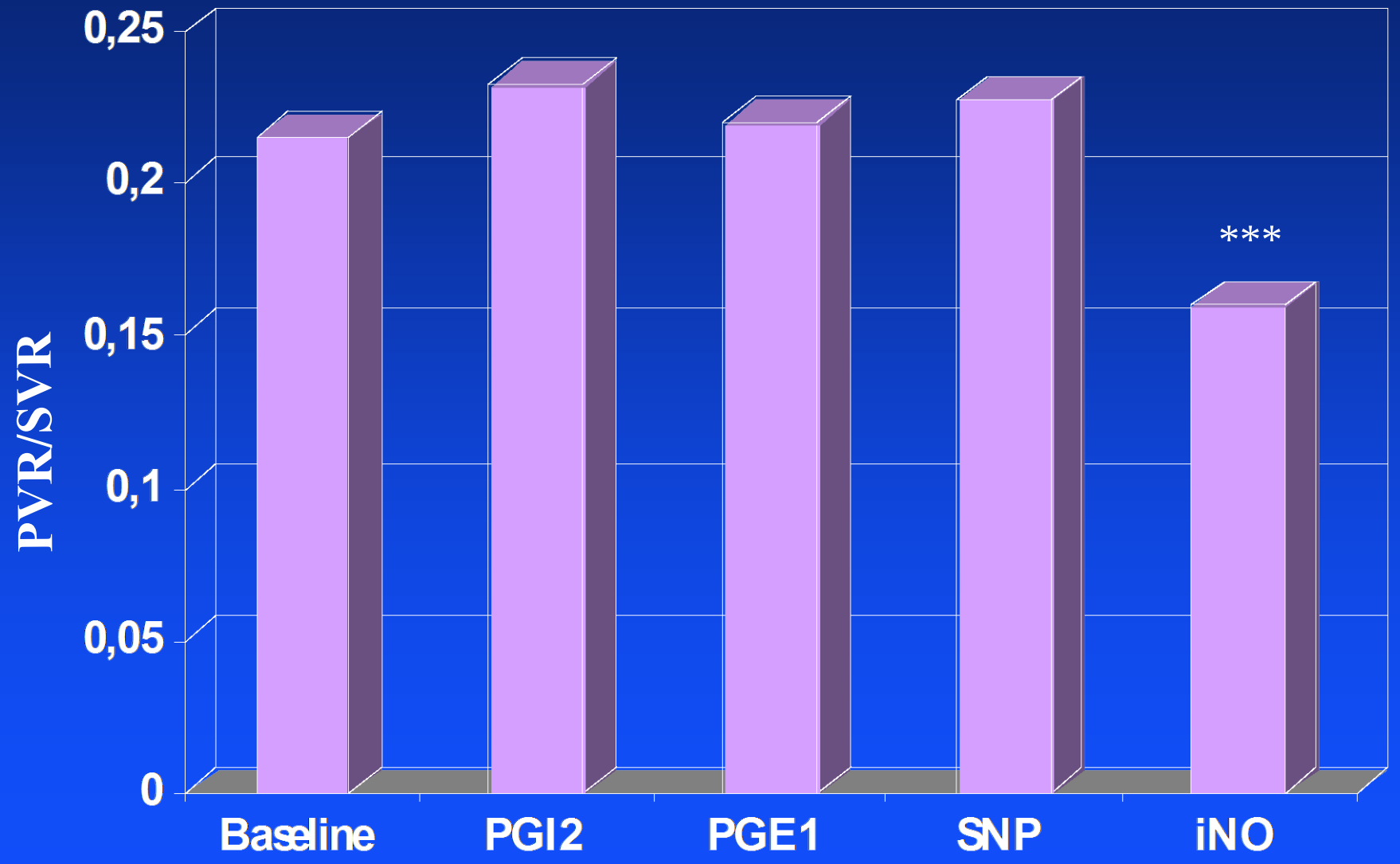

0
-5
-10
-15
-20
-25
-30
-35
-40
Δ PVR (%)
Inh. NO
PGI2
PGE1
SNP


0
-5
-10
-15
-20
-25
-30
Δ SVR (%)
Inh NO
PGI2
PGE1
SNP


12
10
8
6
4
2
0
-2
-4
-6
Δ CO (%)
Inh. NO
PGI2
PGE1
SNP


0
-0,5
-1
-1,5
-2
-2,5
-3
-3,5
-4
Δ CVP (mmHg)
Inh NO
PGI2
PGE1
SNP

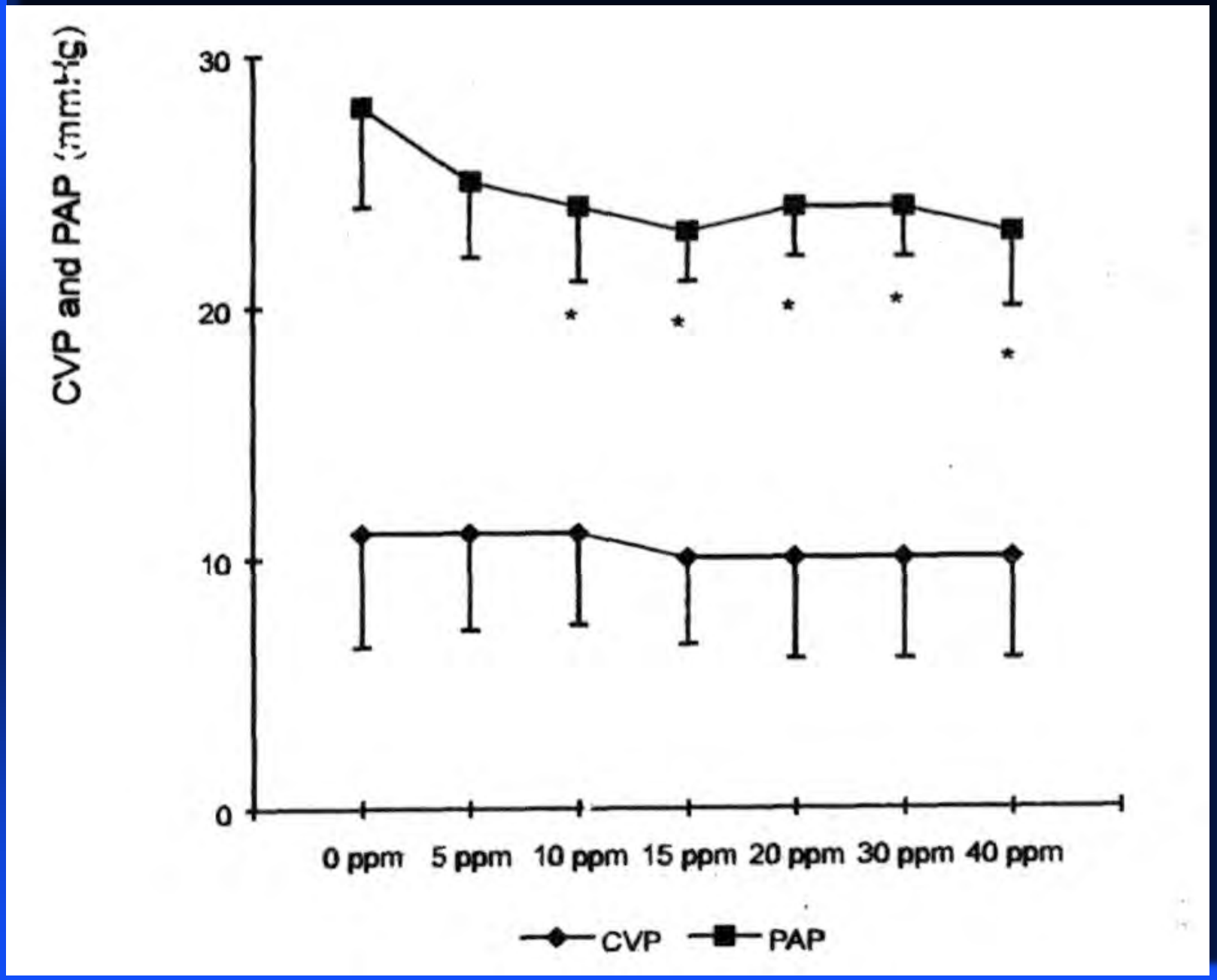
Effects of inhaled NO on the PVR/SVR ratio



Kieler-Jensen et al J Heart Lung Transplant 1995;14:436

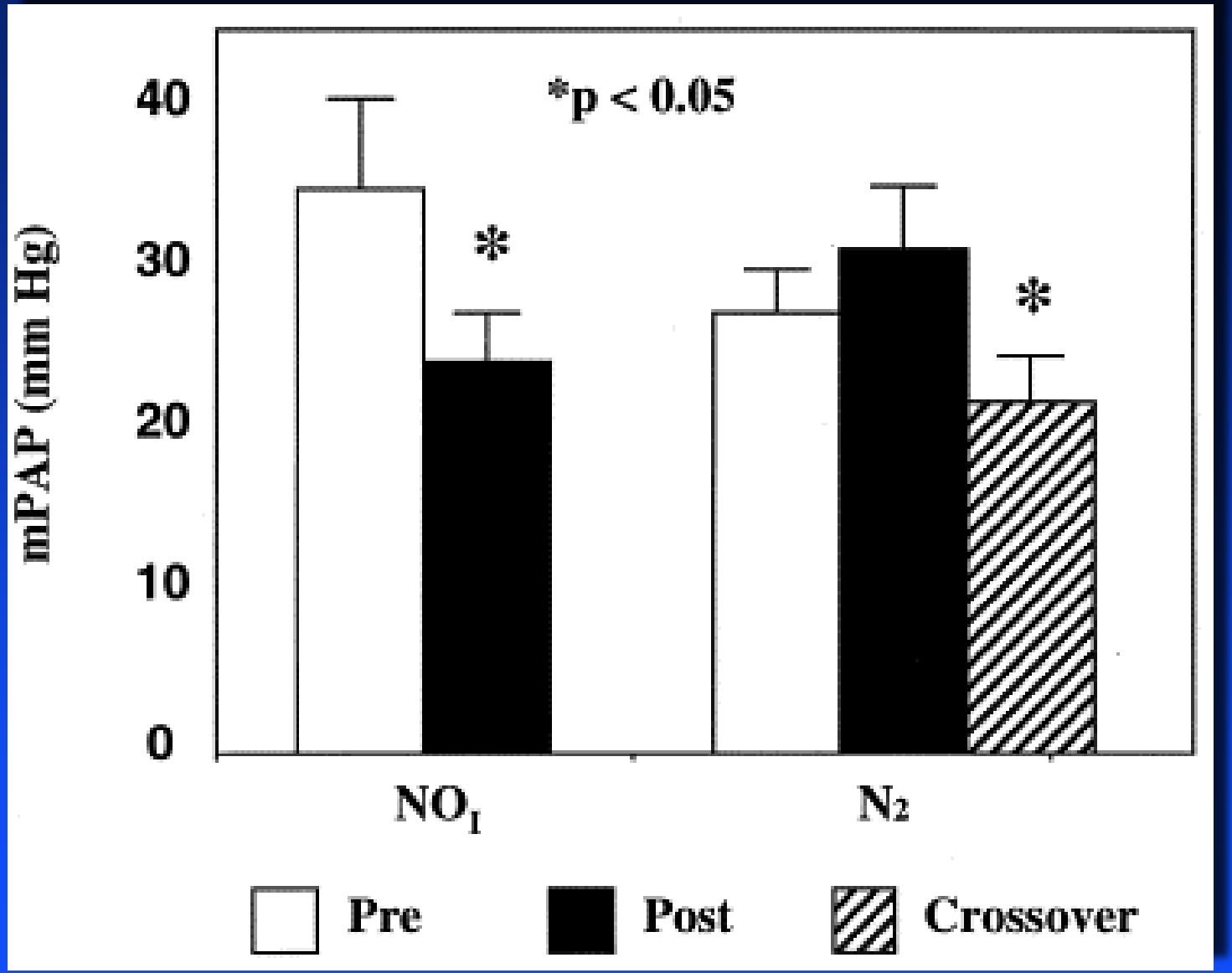
Inhaled NO in heart transplant recipients

Author	Year	Dose NO (PPM)	PVR	MPAP	CVP	CO	MAP	SVR
Kieler-Jensen	1995	20	-35%	-11%	-15%	11%	ns	ns
Auler	1996	20	-39%	ns	ns	17%	ns	-16%
Ardehali	2001	20	-26%	-16%	ns	ns	ns	ns
Khan	2009	20	?	-19%	-21%	20%	ns	?



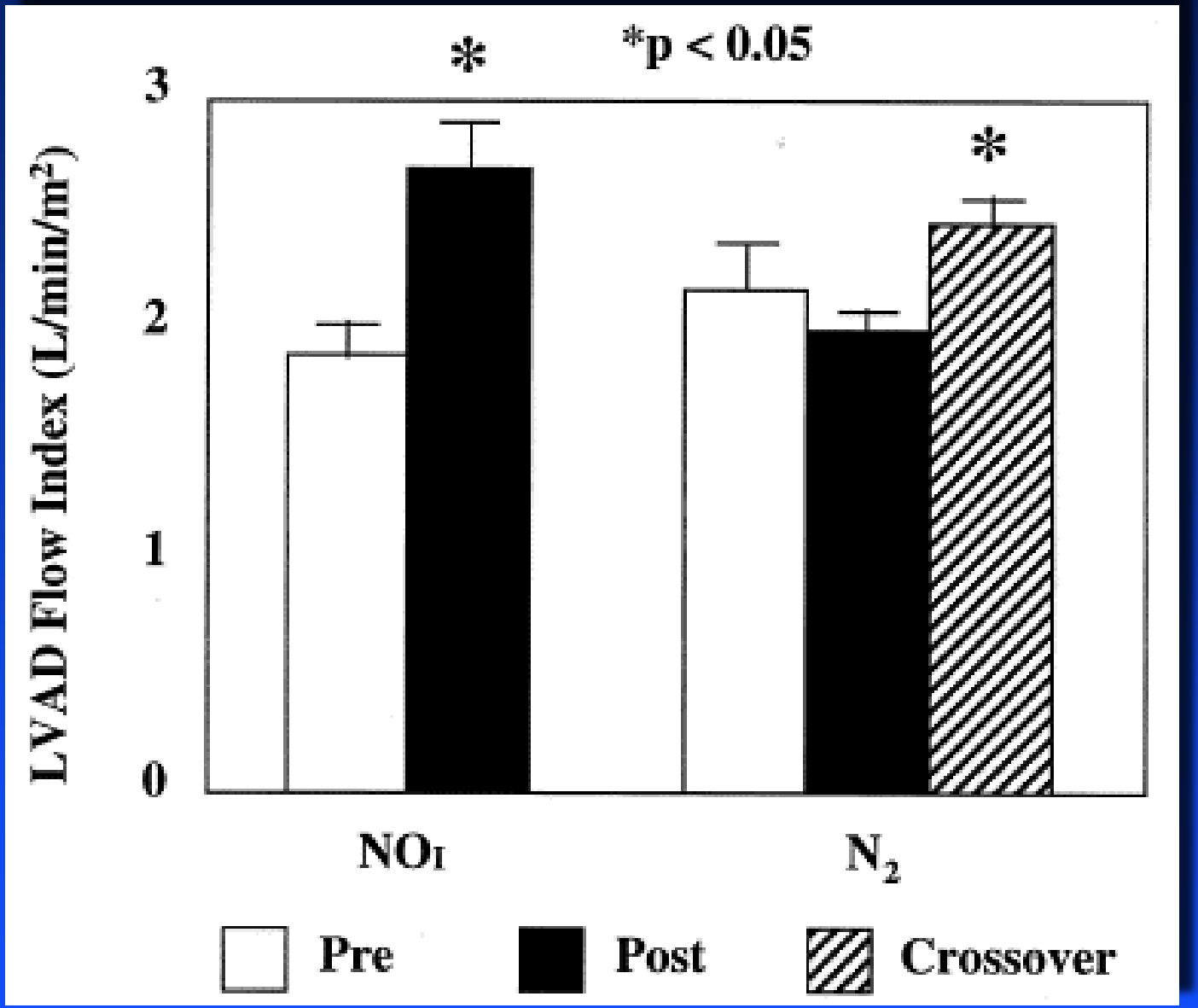
Wagner et al Circulation 1997;96:291

Inhaled NO vs N_2 in LVAD recipients - a randomised study



Argenziano et al Ann Thoracic Surg 1998; 65:340

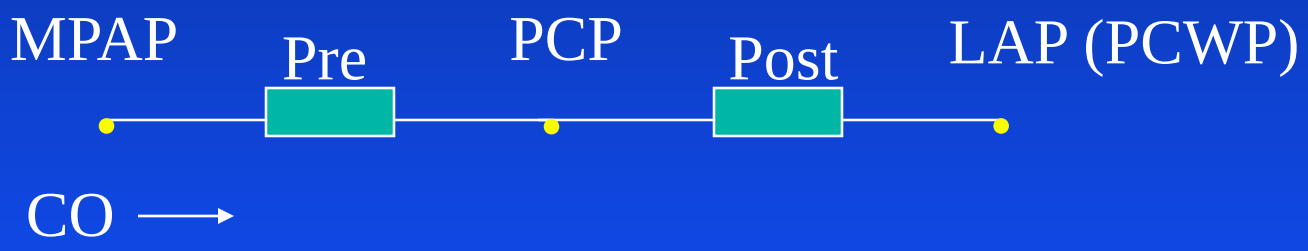
Inhaled vs N_2 in LVAD recipients - a randomised study



Argenziano et al Ann Thoracic Surg 1998; 65:340

What are the effects of inhaled NO on pulmonary serial vascular resistances?

Pulmonary serial vascular resistances



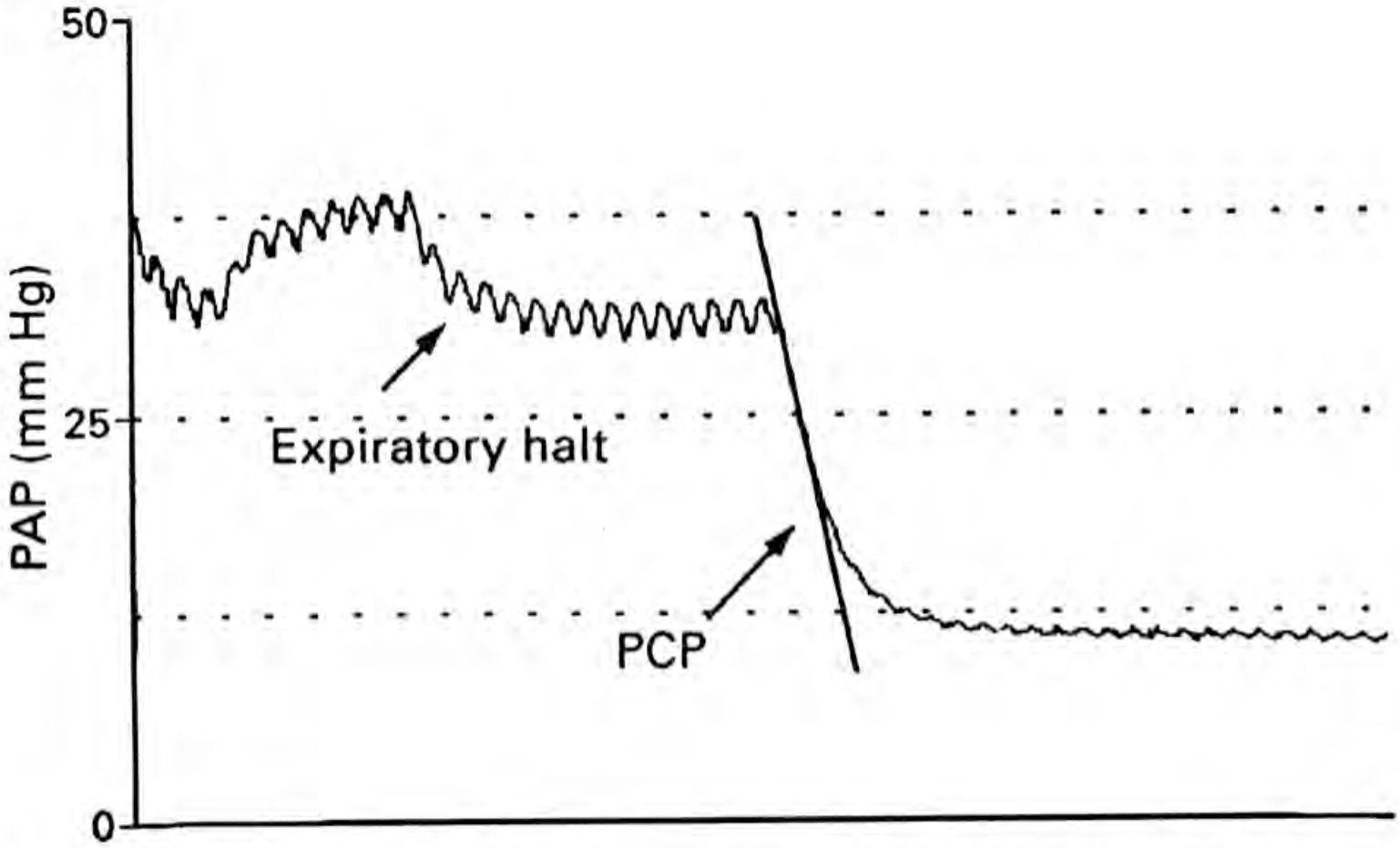
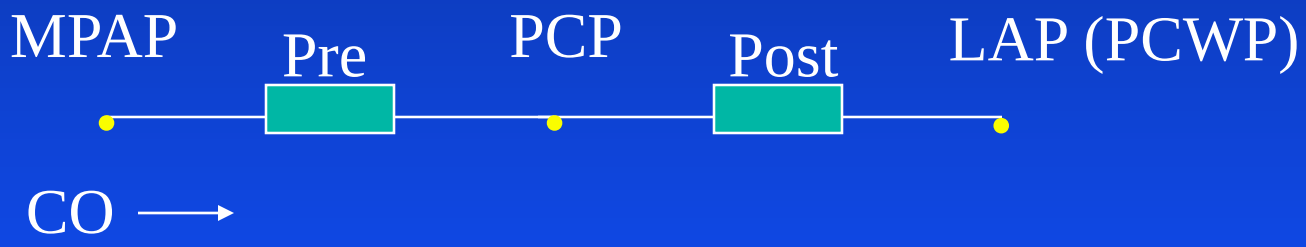


Figure 1 Registration of pressure decay after inflation of the pulmonary artery catheter balloon. Pulmonary capillary pressure (PCP) was estimated as the inflexion point of the pressure decay curve.

Benzing and Geiger Acta Anaesthesiol Scand 1994; 38:640

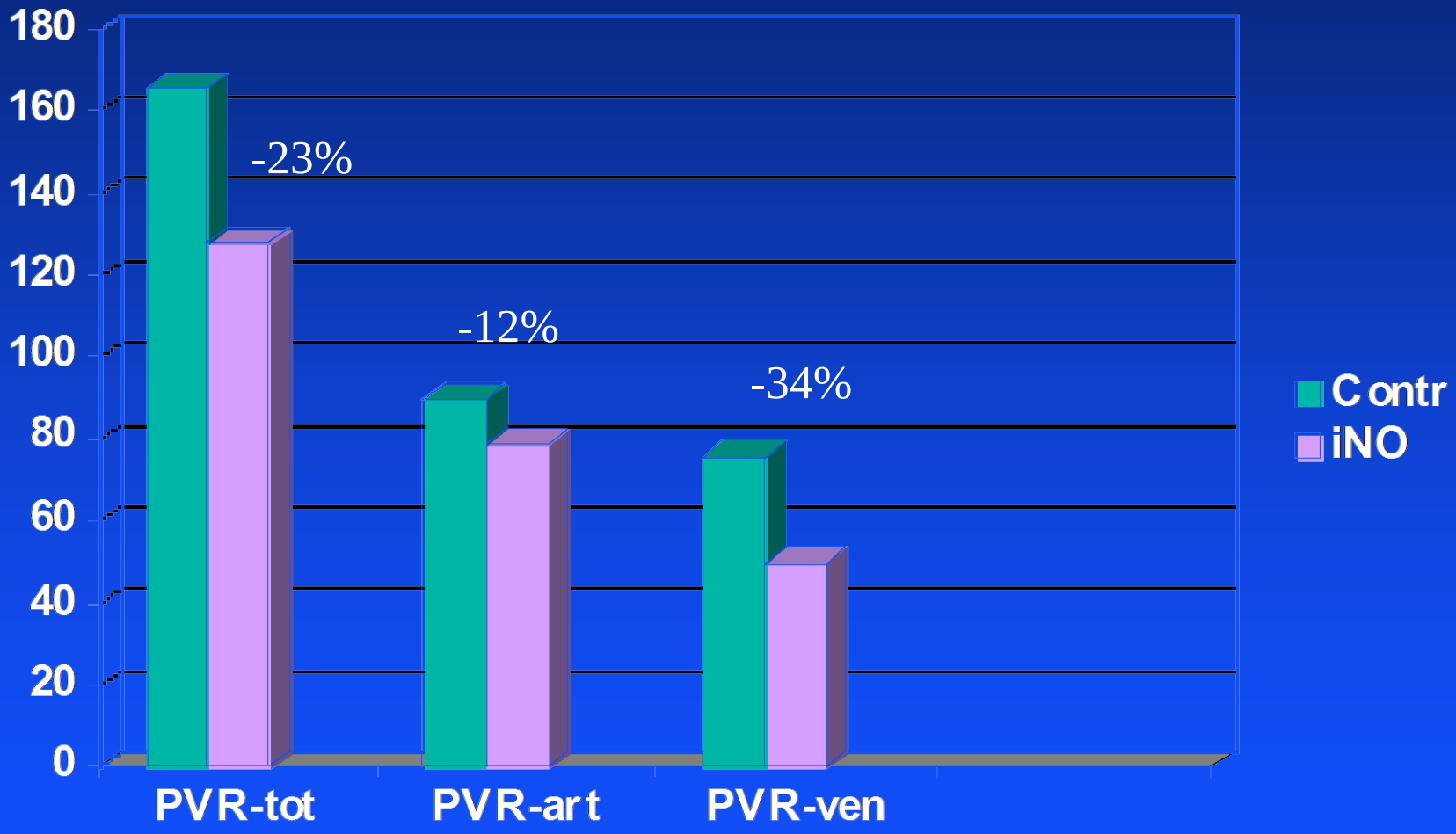
Pulmonary serial vascular resistances



$$\text{Pre} = \frac{\text{MPAP - PCP}}{\text{CO}} \qquad \text{Post} = \frac{\text{PCP - PCWP}}{\text{CO}}$$

$$\text{PVR} = \text{Pre} + \text{Post}$$

Effects of inhaled NO on longitudinal distribution of pulmonary vascular resistance in ARDS



Benzing Geiger 1994 Acta Anaesthesiol Scand; 38:640

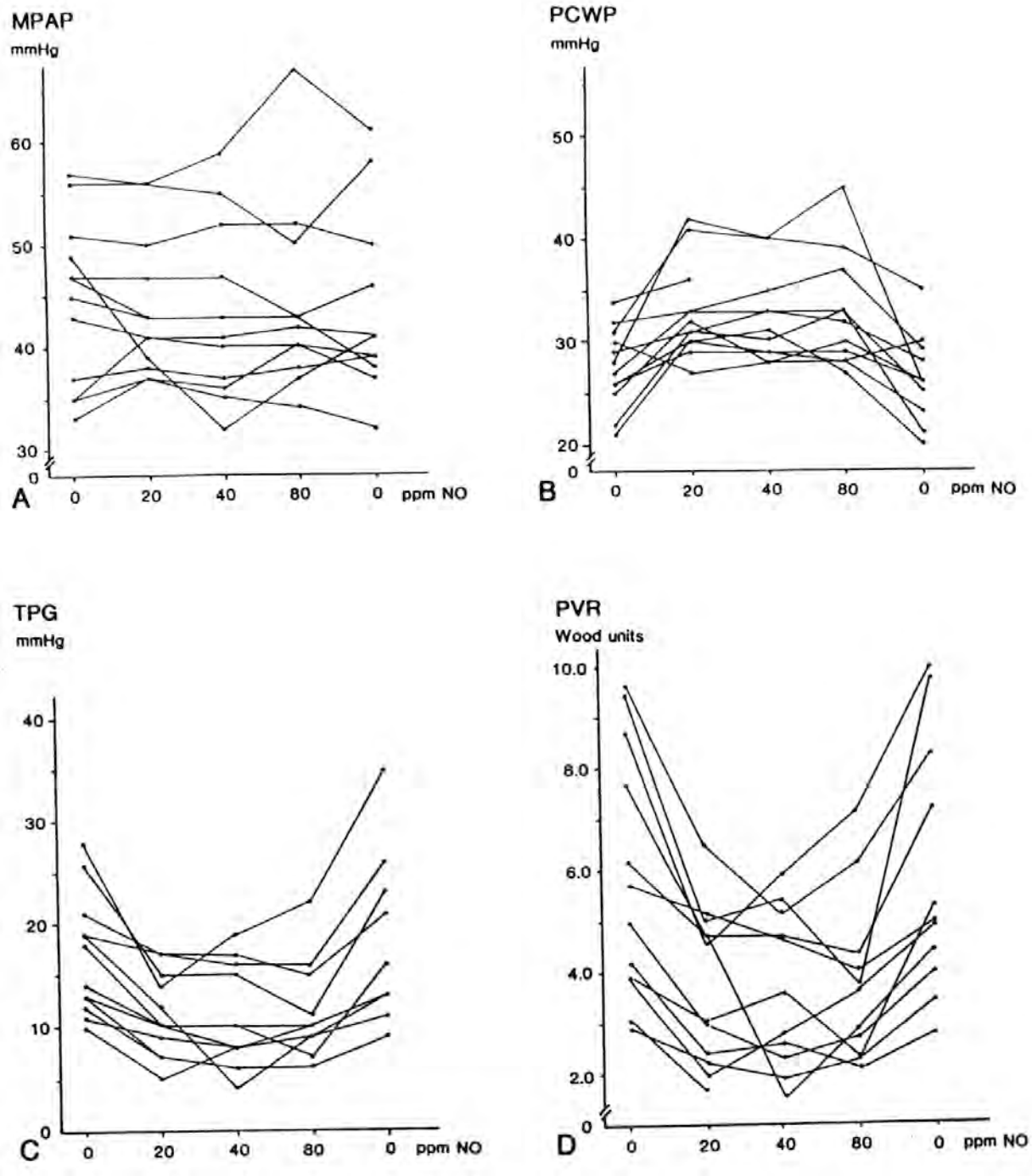
Inhaled NO in heart transplant candidates with elevated pulmonary vascular resistance

Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance

Niels Kieler-Jensen, MD,[a] Sven-Erik Ricksten, MD, PhD,[a] Ola Stenqvist, MD, PhD,[a] Claes-Håkan Bergh, MD, PhD,[b] Björn Lindelöv, MD,[b] Åke Wennmalm, MD, PhD,[c] Finn Waagstein, MD, PhD,[b] and Stefan Lundin, MD, PhD[a]

- 12 heart transplant candidates
- PVR > 200 dynes x sec x cm^{-5}
- Inhaled NO: 20, 40, 80 ppm

Kieler Jensen et al J Heart Lung Transplant 1994;13:366

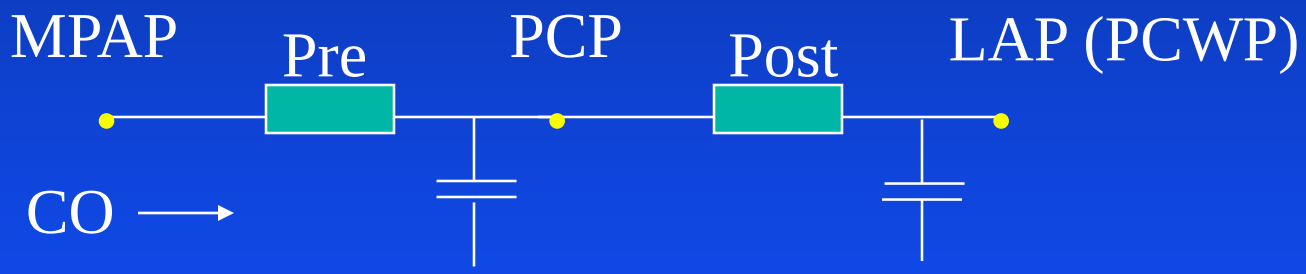


Kieler Jensen et al
J Heart Lung Transplant
1994;13:366

Inhaled NO in heart transplant candidates with high PVR

Author	Year	Dose NO (PPM)	PVR	MPAP	PCWP	TPG	CO
Kieler-Jensen	1994	80	-36%	ns	18%	-34%	ns
Semigran	1994	80	-46%	ns	28%	-36%	ns
Loh	1994	80	-31%	ns	23%	-35%	ns
Haraldsson	1998	40	-43%	-7%	21%	-42%	ns
Sablotzki A	2002	30	-19%	-15%	ns	-17%	ns

Pulmonary serial vascular resistances and capacitances



NO has a predominant vasodilating effect on the pulmonary venous vasculature.

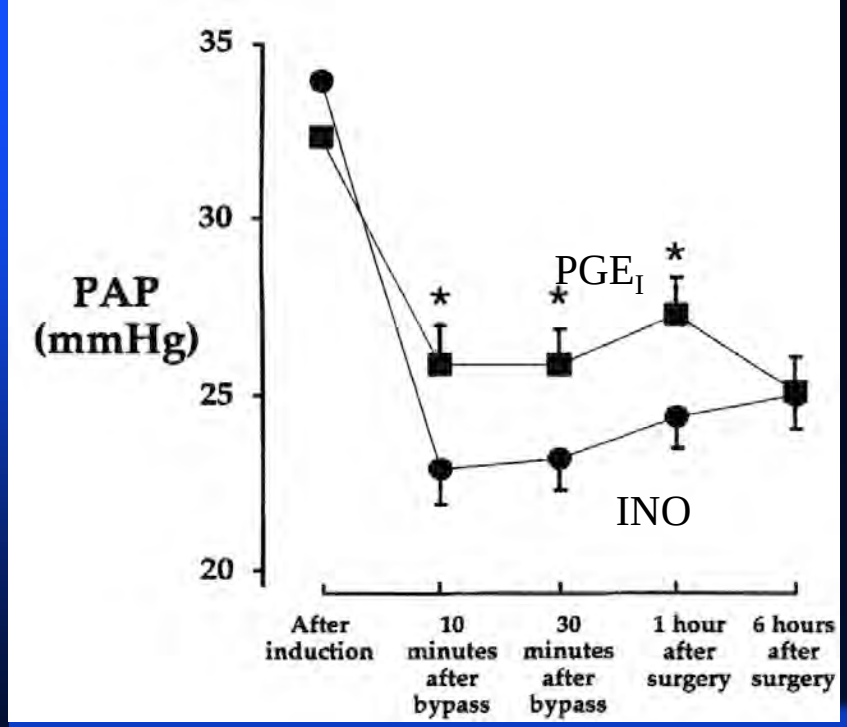
- decreases pulmonary capillary pressure
- shifts blood volume from the arterial to venous capacitance vessels

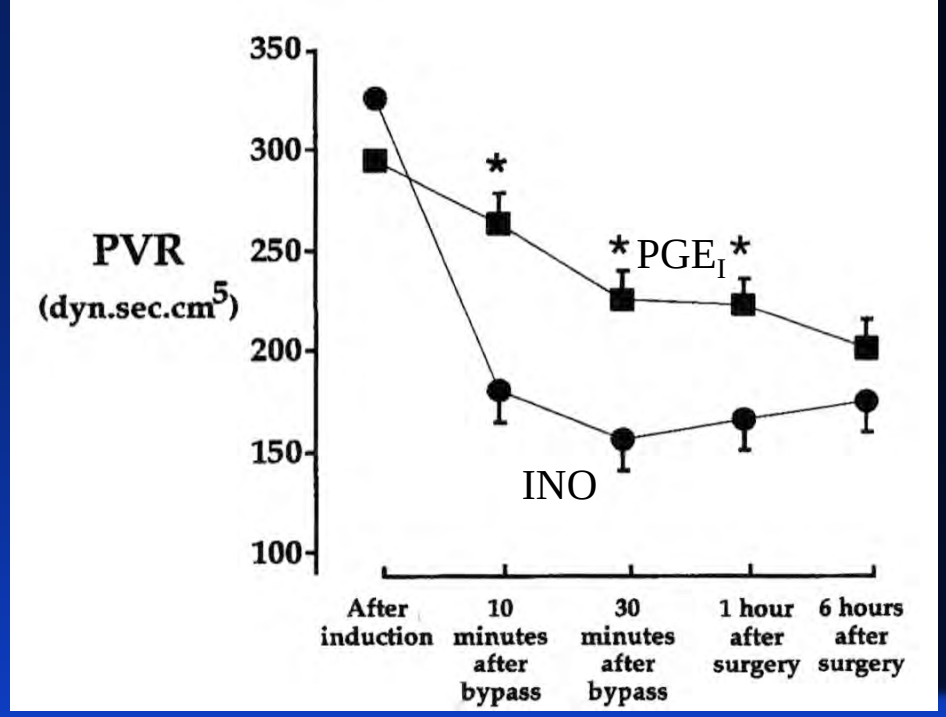
Does inhaled NO affect outcome in cardiac surgery or heart transplantation?

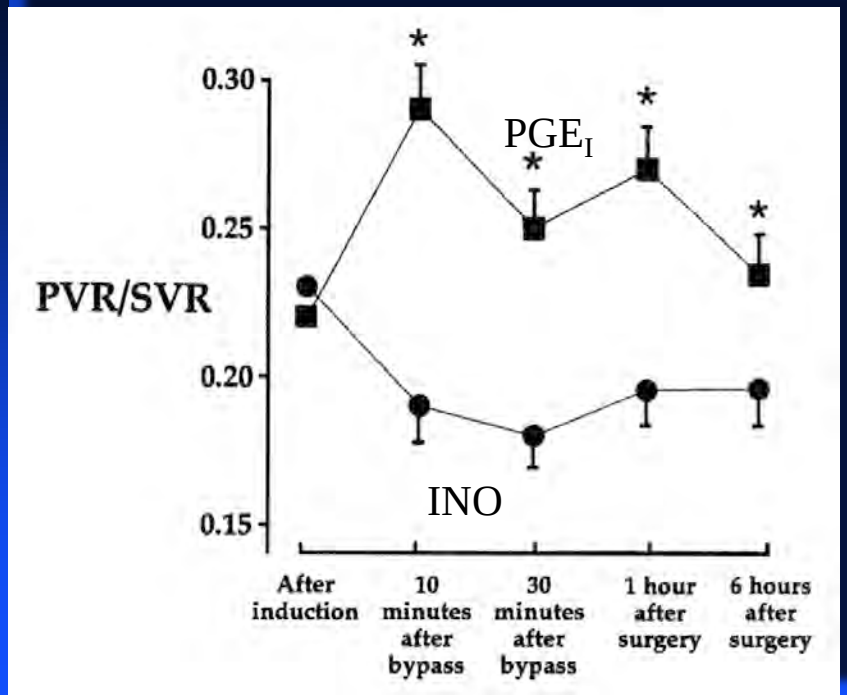
Inhaled NO vs. i.v PGE_1 during weaning from CPB after heart transplantation

- Seventy patients randomised to:
  - -Inhaled NO, n=35 (4-24 ppm)
  - -PGE_1 iv, n=35 (8-24 ng/kg/min)
- Treatment started immediately prior to weaning from CPB
- MPAP maintained < 25 mmHg
- Measurements: after induction, 10´, 30´, 1 h, 6h after weaning
- Isoprenalin 0.02 µg/kg/min and epinephrine/ norepinephrine if MAP < 65 mmHg

Rajek et al Anesth Analg 2000;90:523







Failed weaning from CPB:
-Inhaled NO, n=0
-Intravenous PGE1, n=6
$p<0.03$

Rajek et al Anesth Analg 2000;90:523

Inhaled NO after LVAD implantation: a randomised double-blind placebo-controlled trial

- 150 patients undergoing LVAD implantation
- PVR ≥ 200 dyne/sec/cm-5
- Randomised to:
  - -iNO (40 ppm)
  - -iN_2
- Inhalation for:
  - -48 hours, until extubation, study-defined RVD
- Cross-over to open label iNO was allowed < 48 h, if RVD criteria were met

Potapov et al J heart Lung Tranplant 2011;30.870

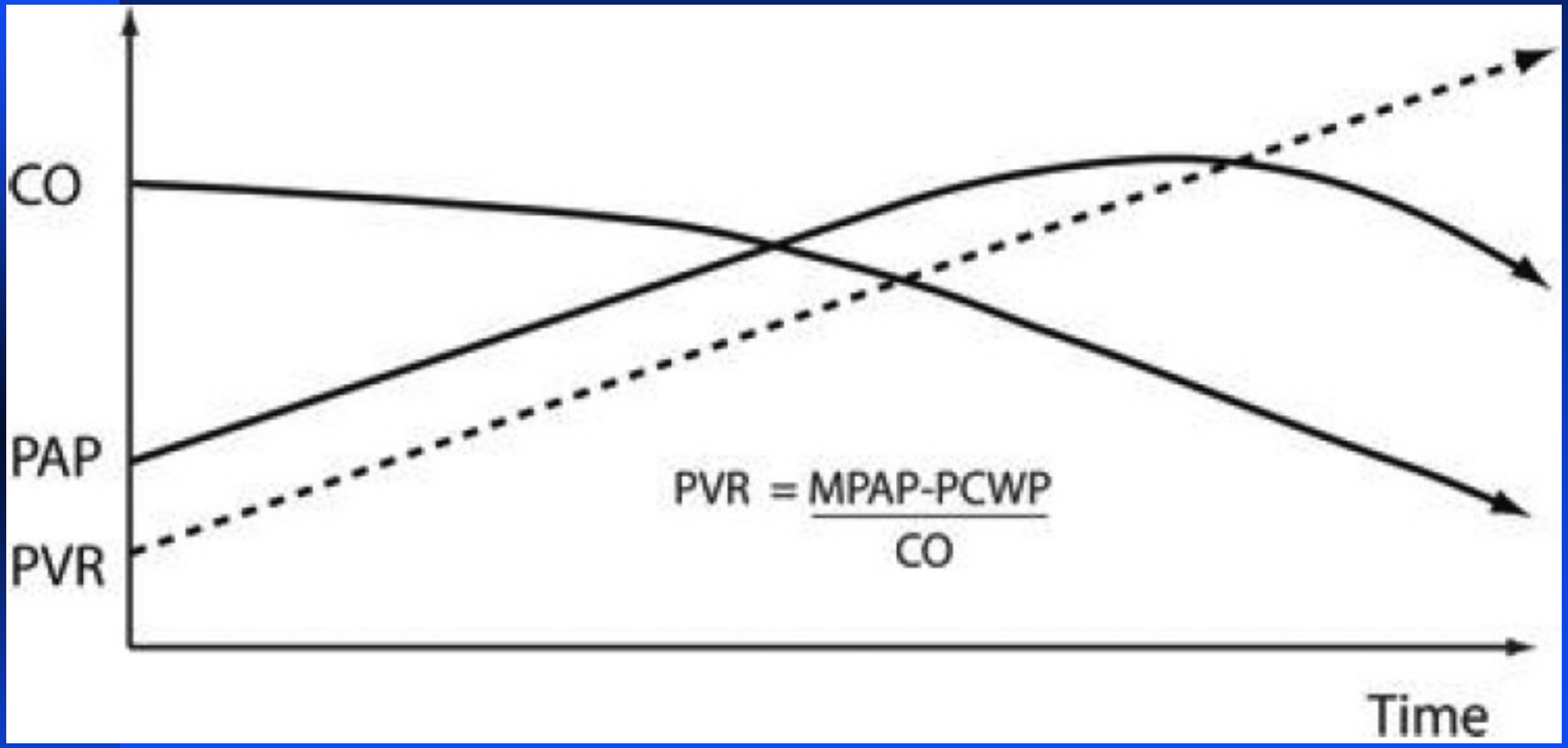
Inhaled NO after LVAD implantation: a randomised double-blind placebo-controlled trial

- RVD criteria
  - -iNO: 9.6%
  - -placebo: 15.6% (p=0.330)
- Median time on mechanical ventilation
  - -iNO 2 days
  - -placebo 3 days (p=0.077)
- 35 patients crossed-over to open label iNO
  - -iNO: n=15 (21%)
  - -placebo: n=20 (26%)
- 18 patients crossed-over before RVD criteria were met

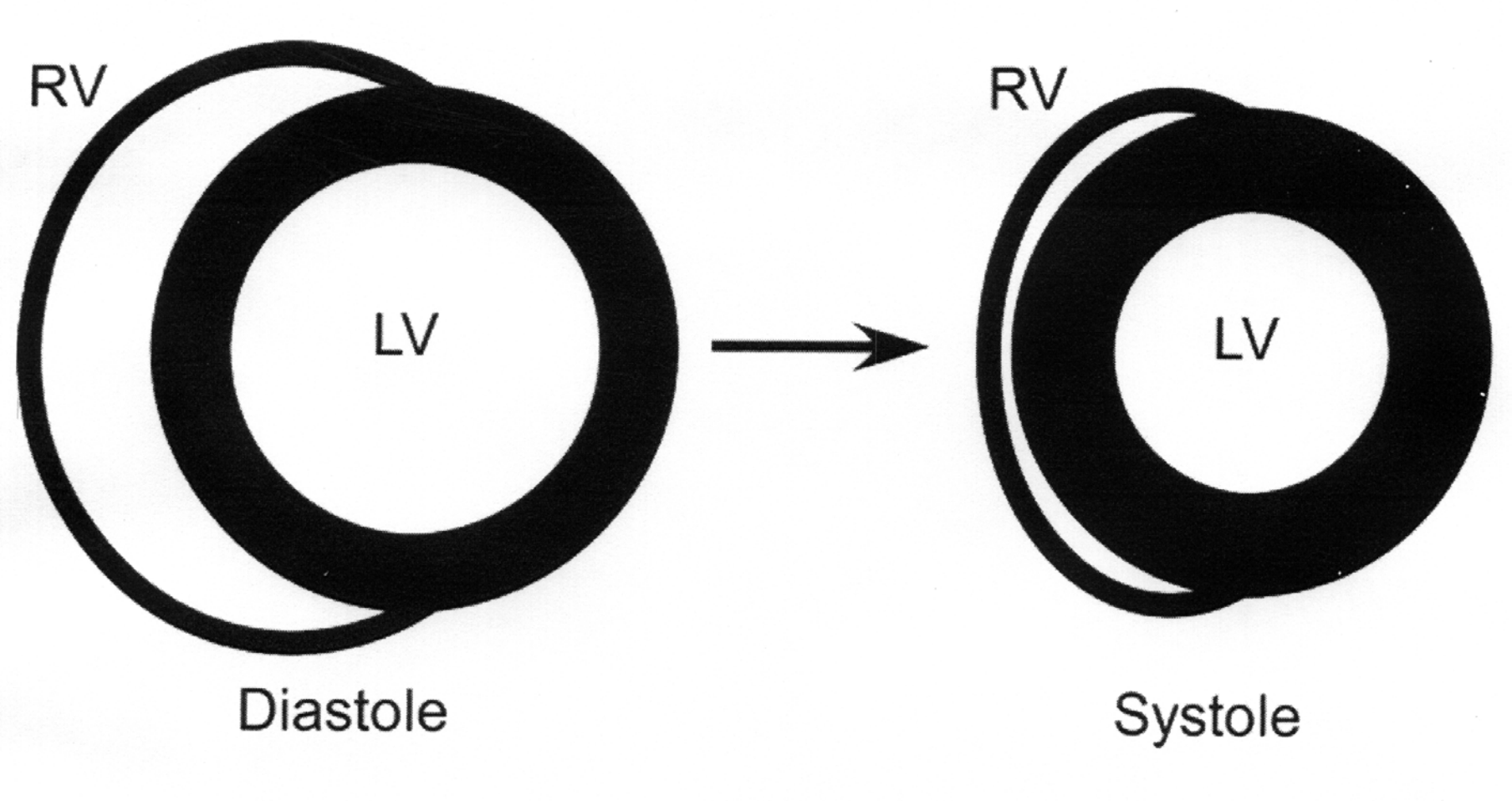
Potapov et al J heart Lung Tranplant 2011;30.870

Conclusions on iNO in cardiac surgery patients :

- Induces a selective pulmonary vasodilation
- Has a predominant vasodilating effect on the venous vasculature
- Improves RV function in patients with high, reversible PVR and RV failure
- Facilitates weaning from CPB in heart transplantation
- Prevents RV failure in LVAD insertion?
- Useful in the evaluation of heart transplant candidates with high PVR


CO
PAP
PVR
PVR = MPAP-PCWP / CO
Time

Systolic ventricular interaction

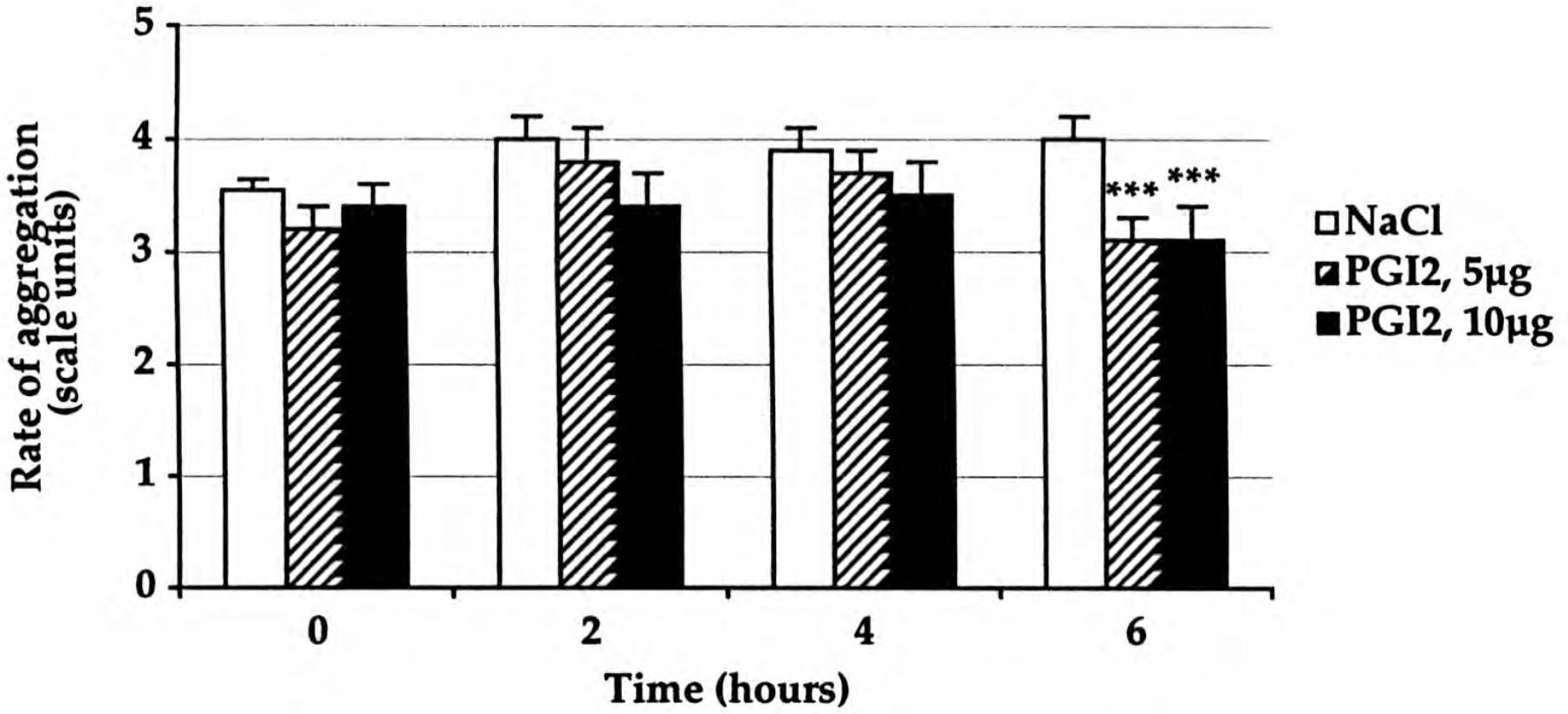


LV contributes with ≈ 60% of RV pressure and stroke volume

Treatment of RVF

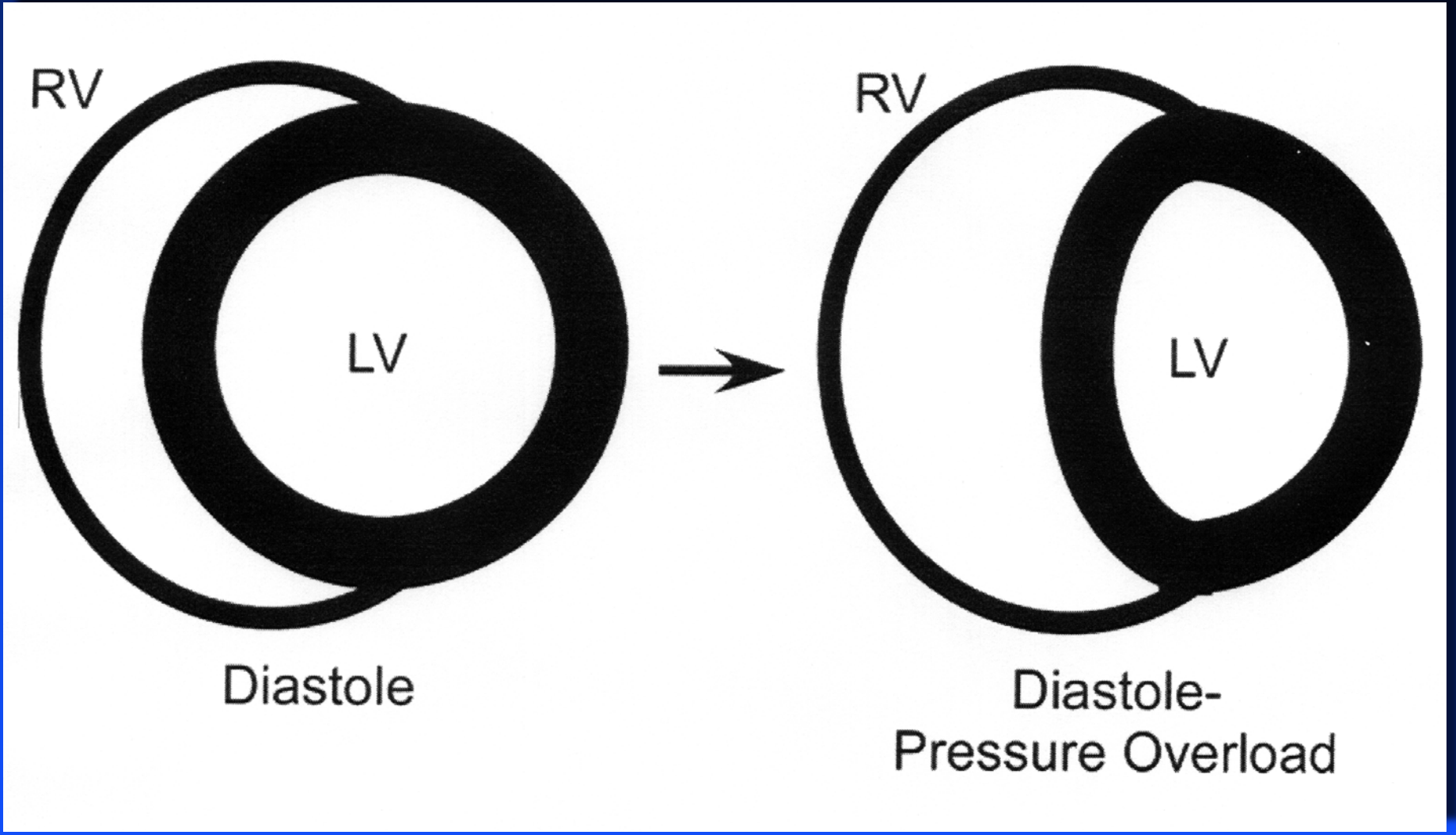
- Optimise RV preload (CVP 10-15 mmHg)
- High systemic pressure improves RV perfusion and LV assist - norepinephrine

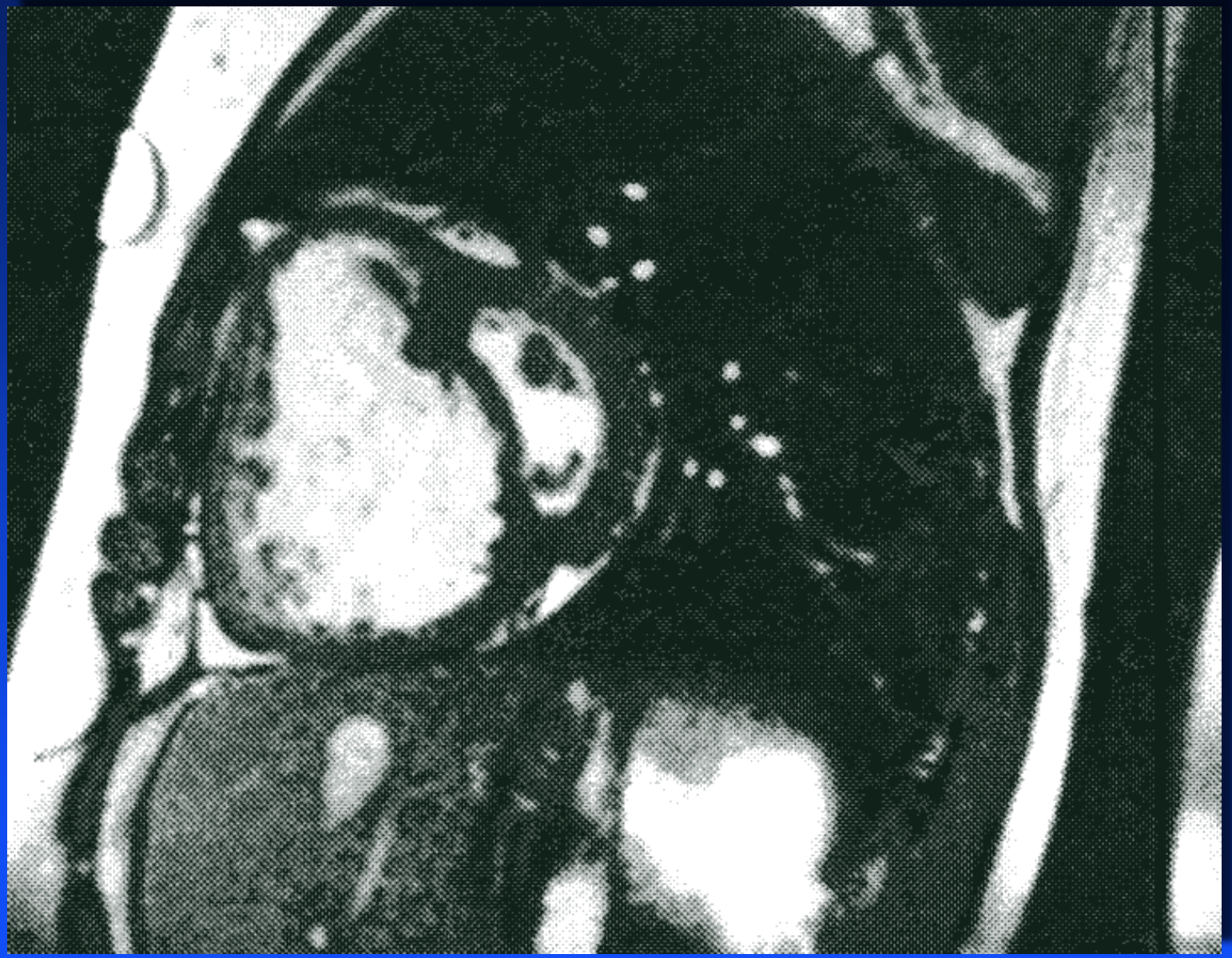
Effects of inhaled PGI2 on rate of platelet aggregation in vitro



Haraldsson et al Intensive Care Medicine 2000;26:188-194

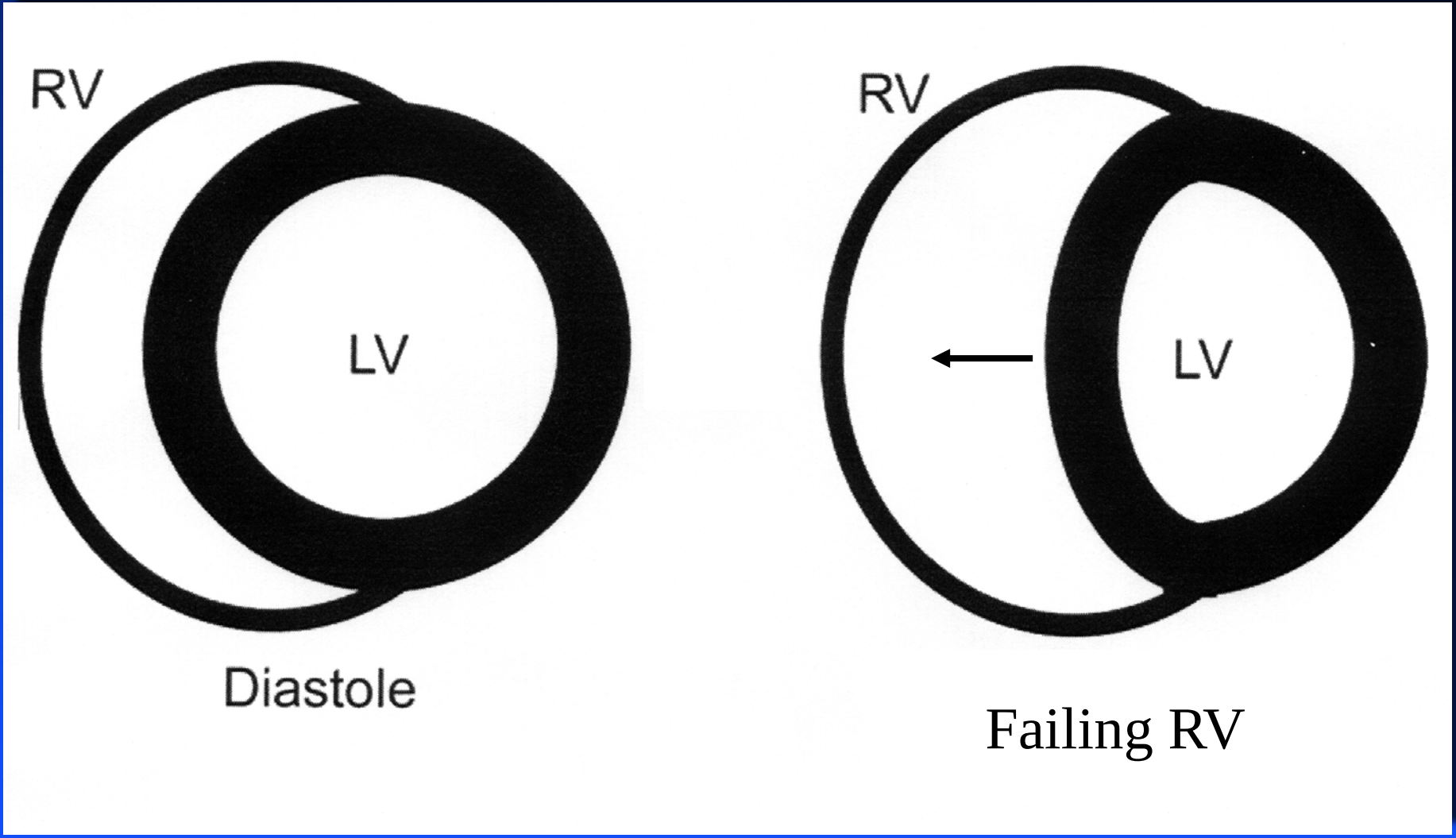
Diastolic ventricular interaction





Roeleveld et al Radiology 2005;234:710-717

Systolic ventricular interaction - RVF



- Left ventricular

Effects of aerosolized PGI_2 on central hemodynamics

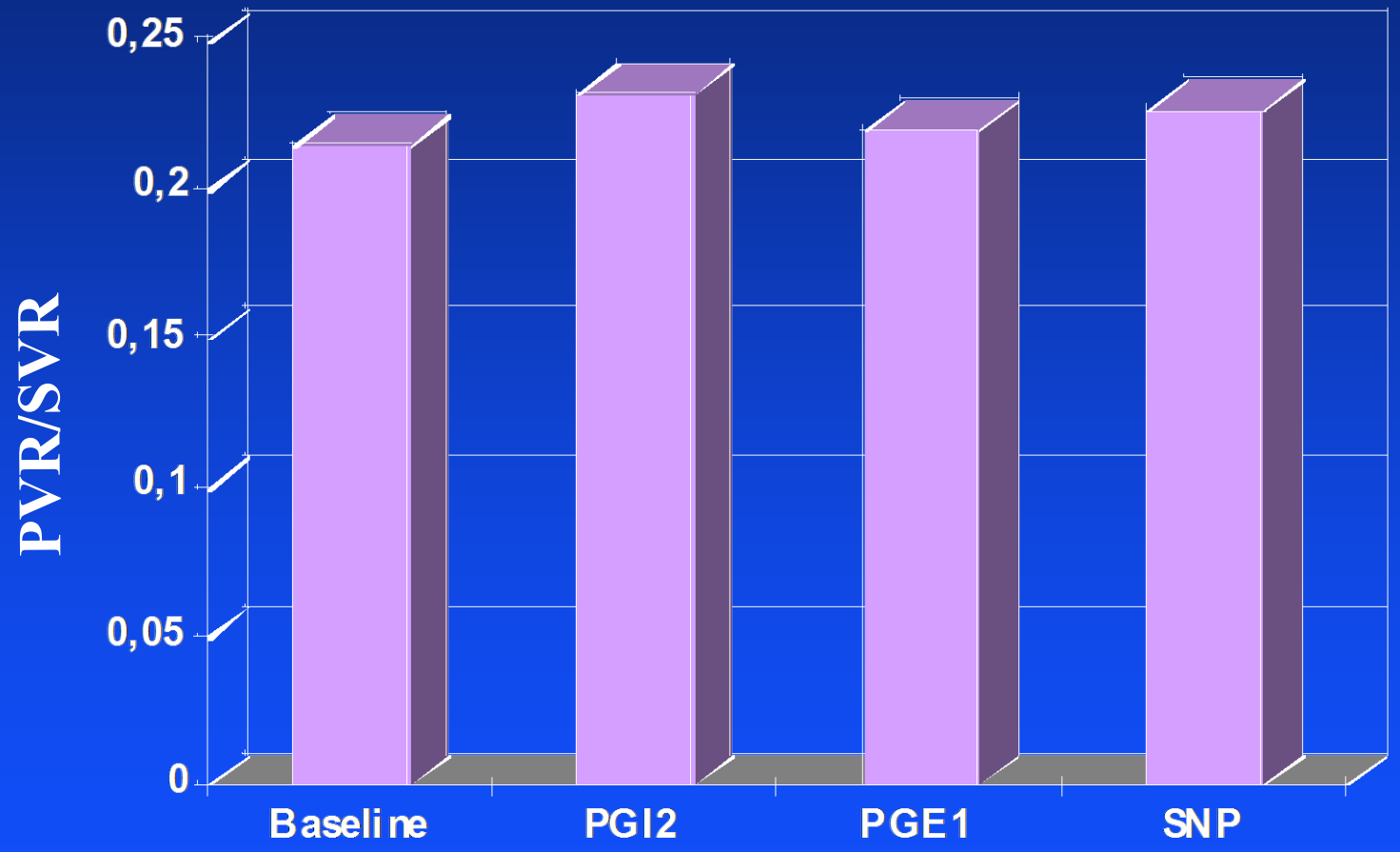
	C	2.5	5.0	10.0	C_{10}	C_{20}
MAP (mmHg)	88	89	87	85	84	84
PCWP (mmHg)	19	20	21	18	19	19
CVP (mmHg)	15	14	14	13**	14	16
SV (ml)	48	47	47	47	47	47
PVR/SVR	0.26	0.23	0.20**	0.19**	0.23*	0.26
TPG (mmHg)	19	17*	15**	14**	16**	18
SVR	1310	1303	1278	1234	1559	1184

Haraldsson et al J Cardiothoracic Vasc Anesth 1996;10:864-868

Inhaled therapies for RVF

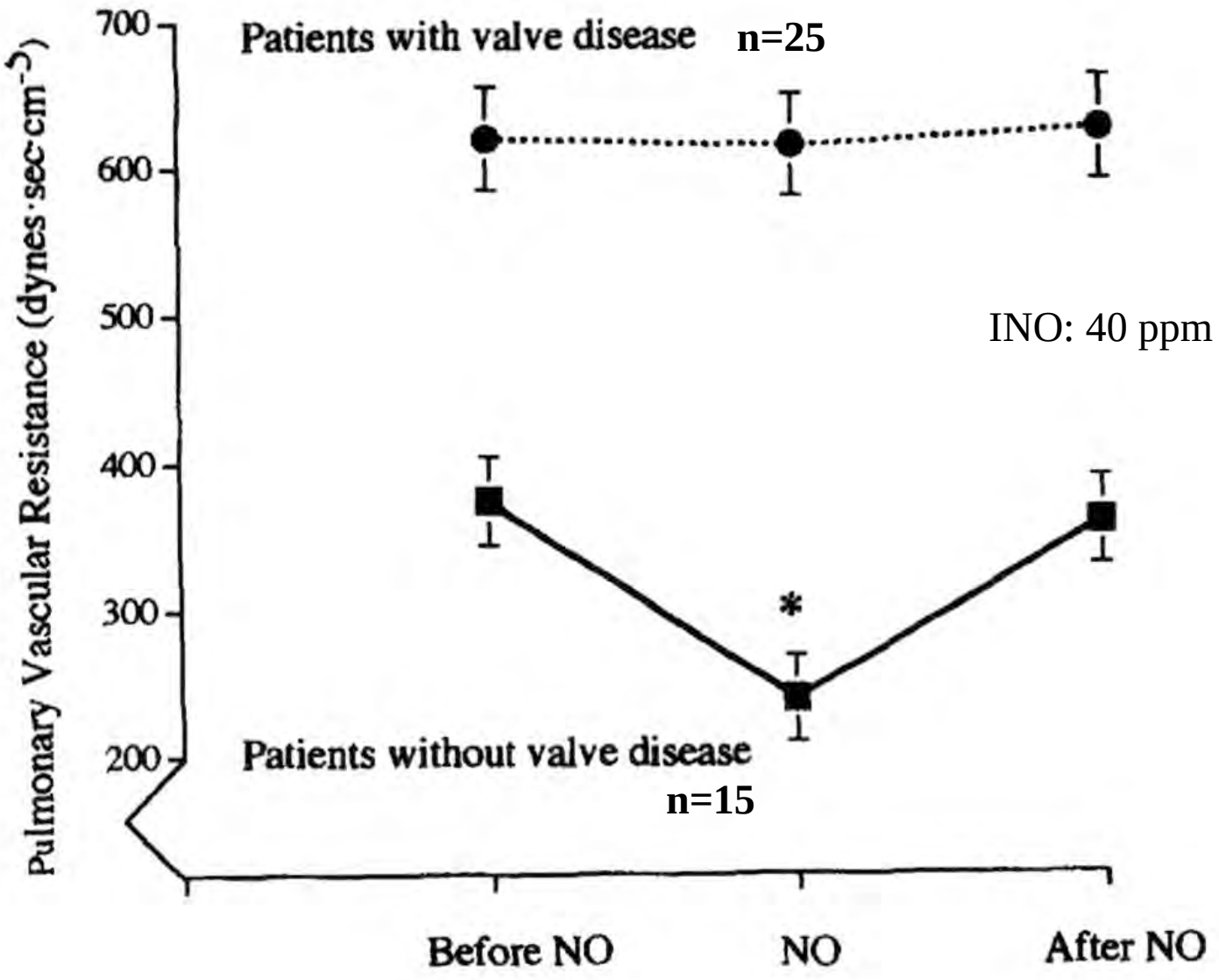
- Inhaled prostacyclin (PGI_2)
- Inhaled iloprost
- Inhaled treprostinil
- Inhaled milrinone
- Inhaled sildenafil

The pulmonary selectivity of intravenous vasodilators (PVR/SVR ratio)

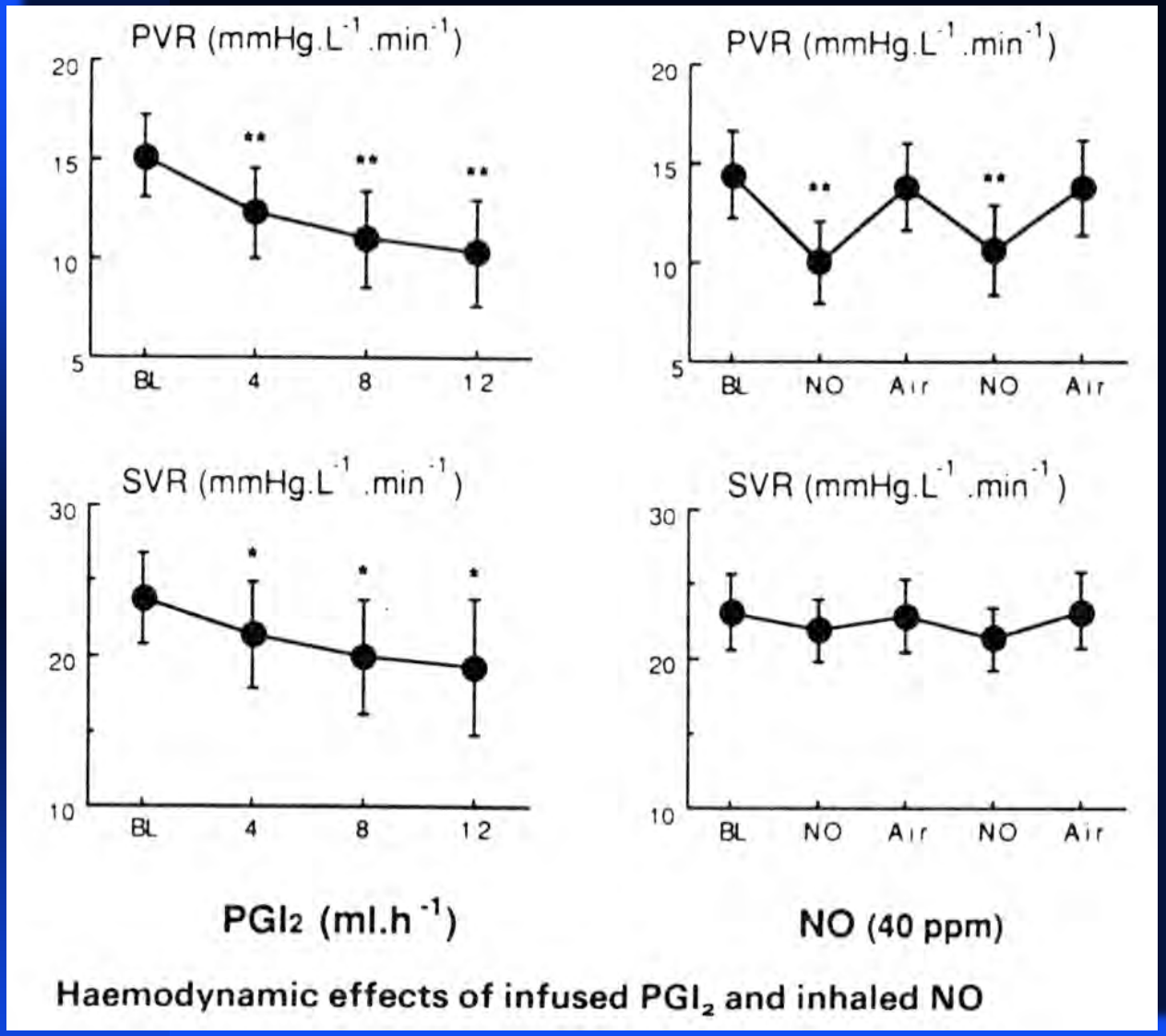


Kieler-Jensen et al J Heart Lung Transplant 1995;14:436

Inhaled NO after MVR or CABG



Fullerton et al Ann Thorac Surg 1997;63:1251



Haemodynamic effects of infused PGI_2 and inhaled NO

Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension

JOANNA PEPKE-ZABA
TIMOTHY W. HIGENBOTTAM
A. TUAN DINH-XUAN DAVID STONE
JOHN WALLWORK

Lancet 1991;338:1173

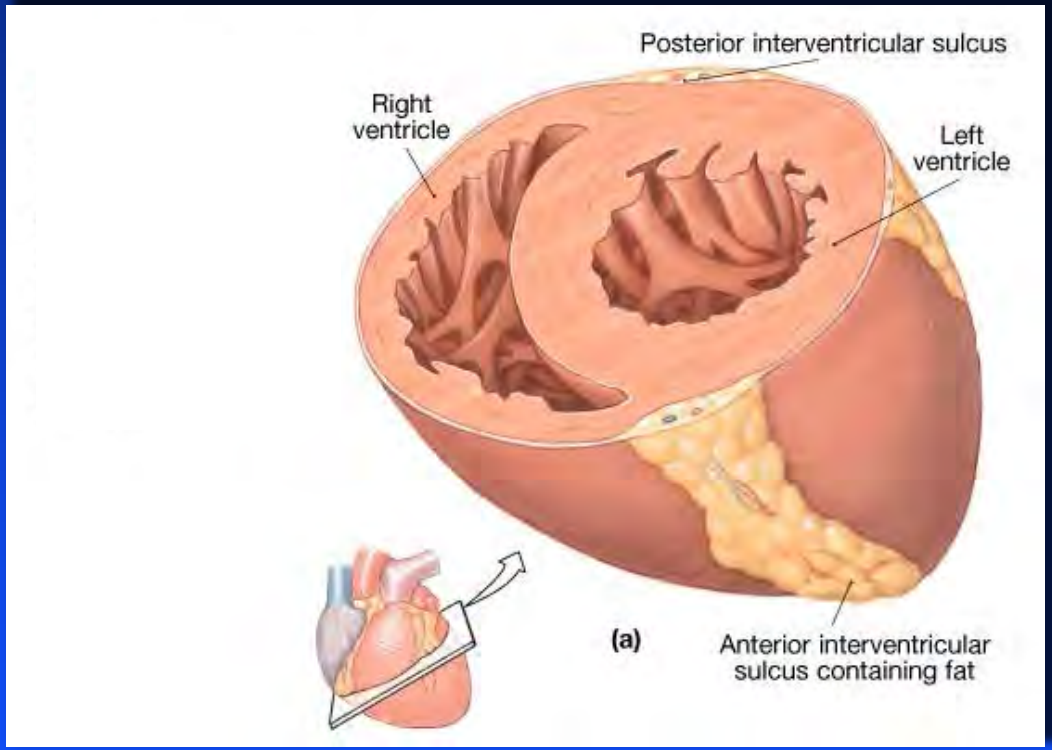
Inhaled NO in RVF after heart transplantation

Pulmonary circulation and the right ventricle (RV)

- Low resistance, low pressure, high capacitance circuit
- 3-4 fold increase in RV stroke volume with no change in pulmonary artery pressure
- RV stroke work is 1/6 of the LV
- RV wall thickness < 0.6 cm
- Crescent shaped geometry with a high compliance
- Poor tolerance to an increase in RV afterload

Pulmonary circulation and the right ventricle (RV)

- RV stroke work is 1/6 of the LV
- RV wall thickness < 0.5 cm
- Crescent shaped geometry with a high compliance
- Poor tolerance to an increase in RV afterload

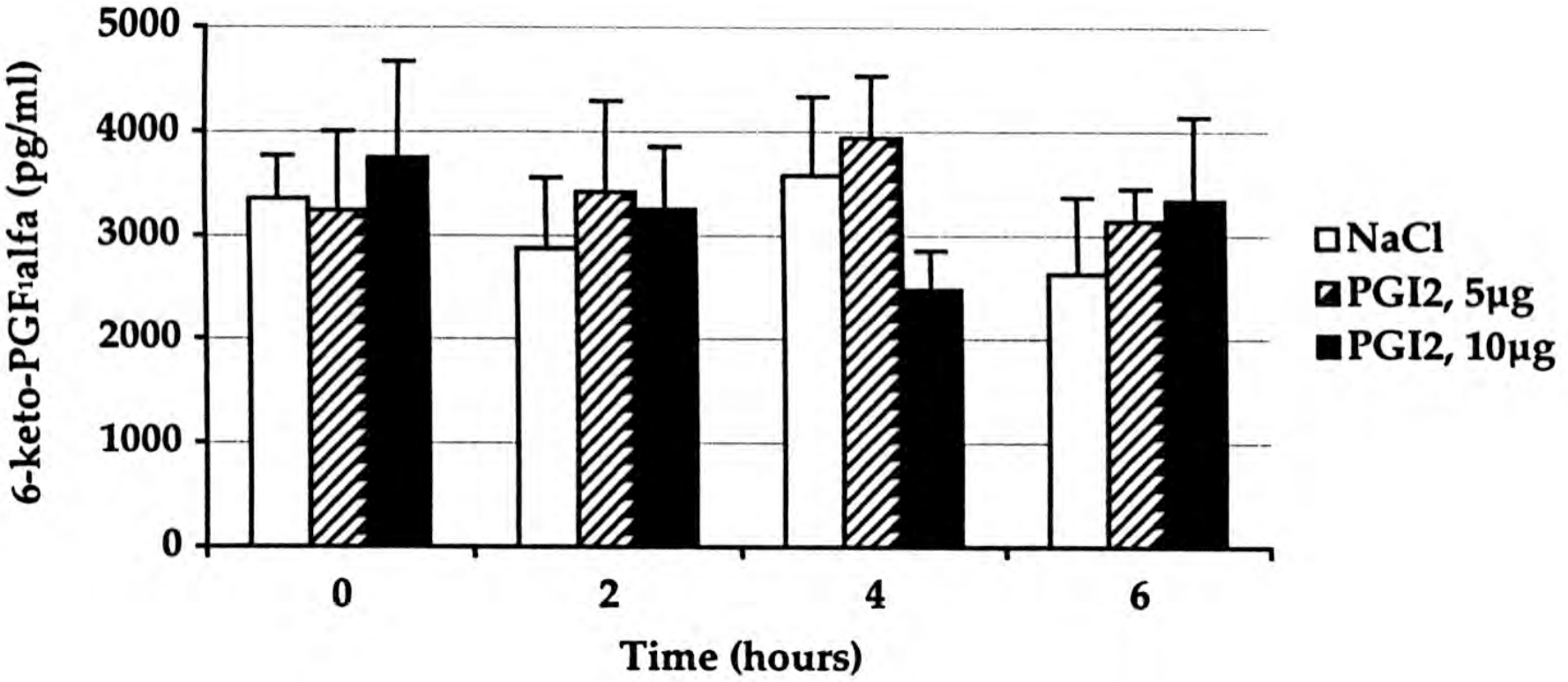


Inhaled NO causes a selective pulmonary vasodilation and improves RV function in:

- ARDS
- Cardiac surgery (CABG, MVR, AVR)
- Heart transplantation
- Right ventricular myocardial infarction
- Left ventricular assist device (LVAD)
- Lung transplantation (one-lung ventilation)
- Porto-pulmonary hypertension

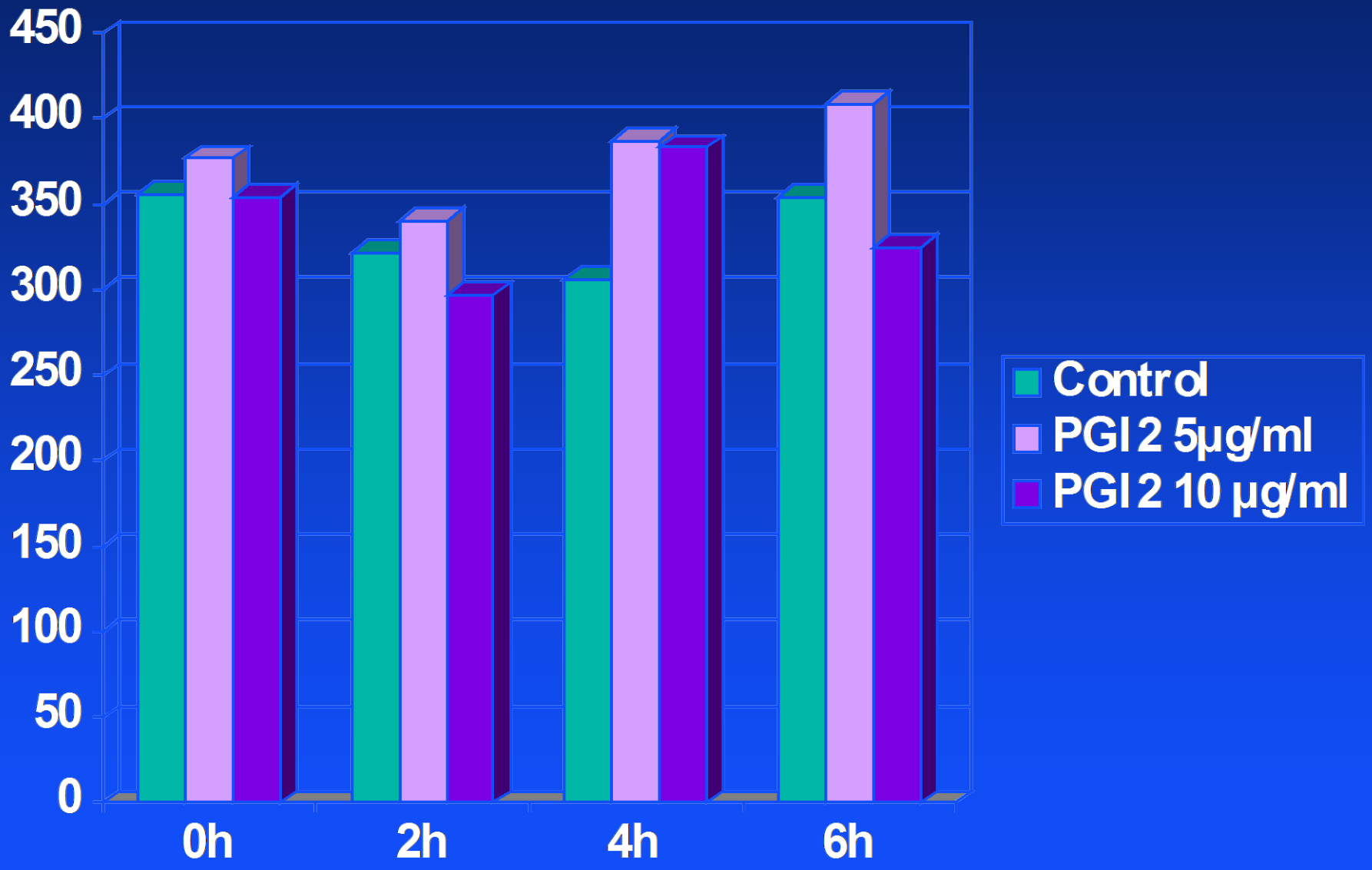
Is there a ”spill-over” of PGI_2 to the systemic circulation when inhaled?

Fig. 2



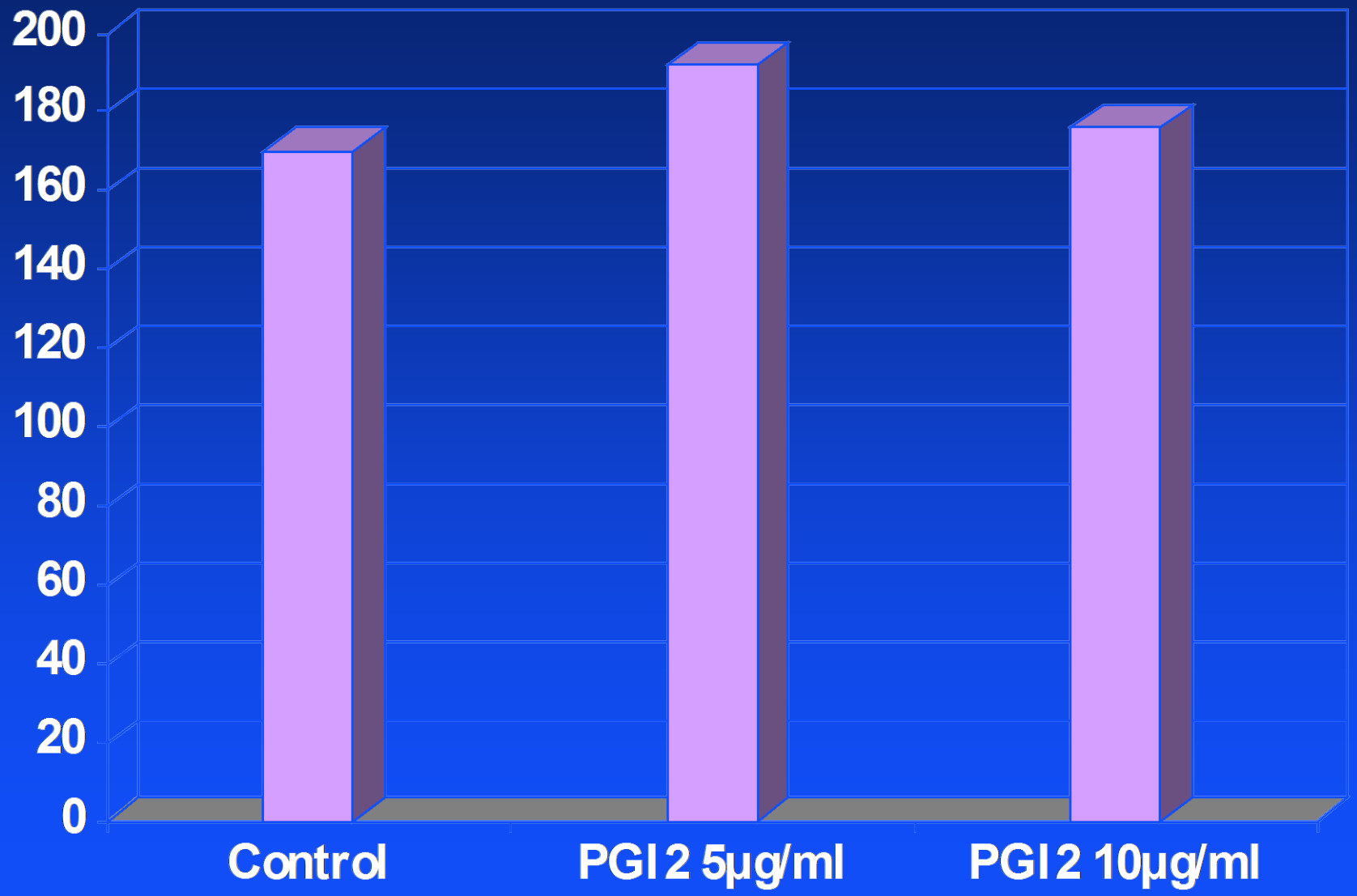
Haraldsson et al Intensive Care Medicine 2000;26:188-194

Inhaled PGI_2 on bleeding time after CPB



Haraldsson et al Intensive Care Medicine 2000;26:188-194

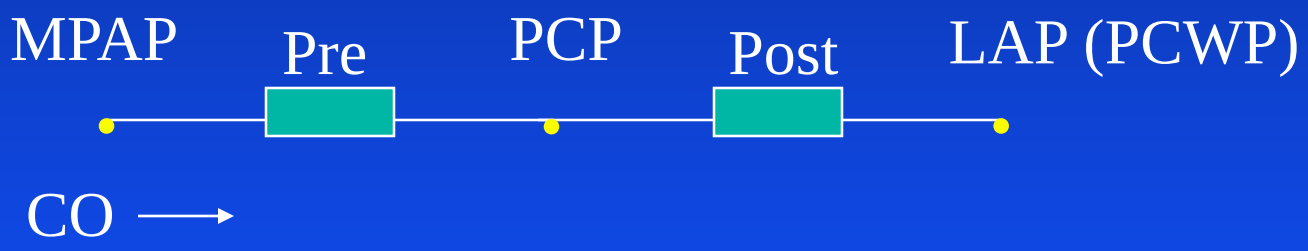
Inhaled PGI_2 on 6 h chest tube drainage



Haraldsson et al Intensive Care Medicine 2000;26:188-194

What are the effects of inhaled NO on pulmonary serial vascular resistances?

Pulmonary serial vascular resistances



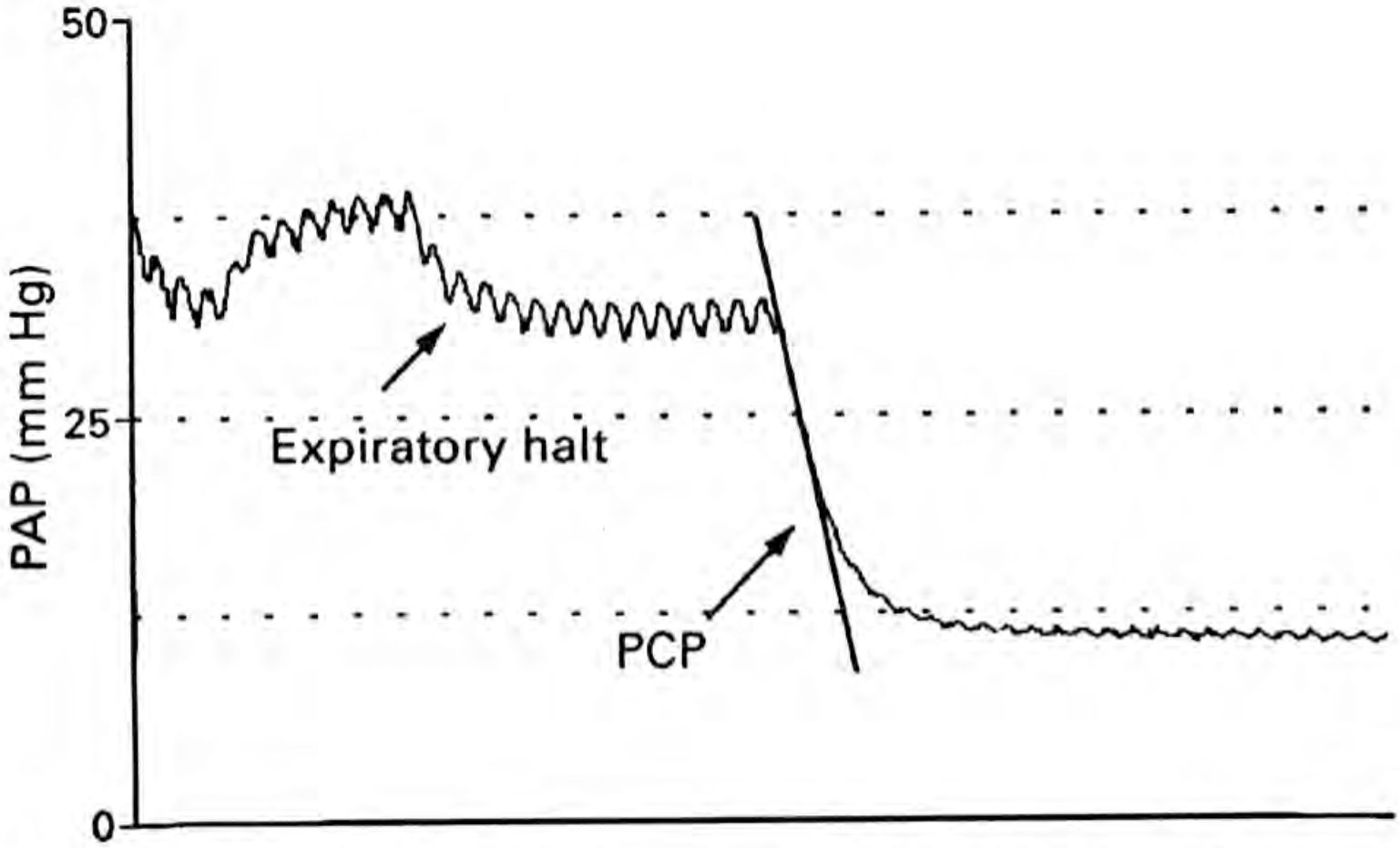
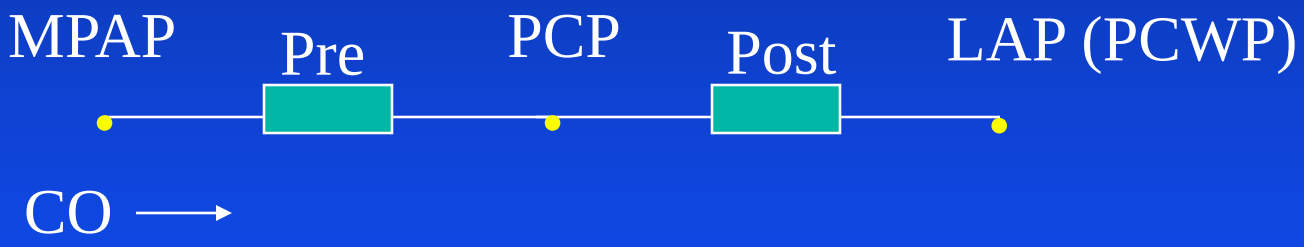


Figure 1 Registration of pressure decay after inflation of the pulmonary artery catheter balloon. Pulmonary capillary pressure (PCP) was estimated as the inflexion point of the pressure decay curve.

Benzing and Geiger Acta Anaesthesiol Scand 1994; 38:640

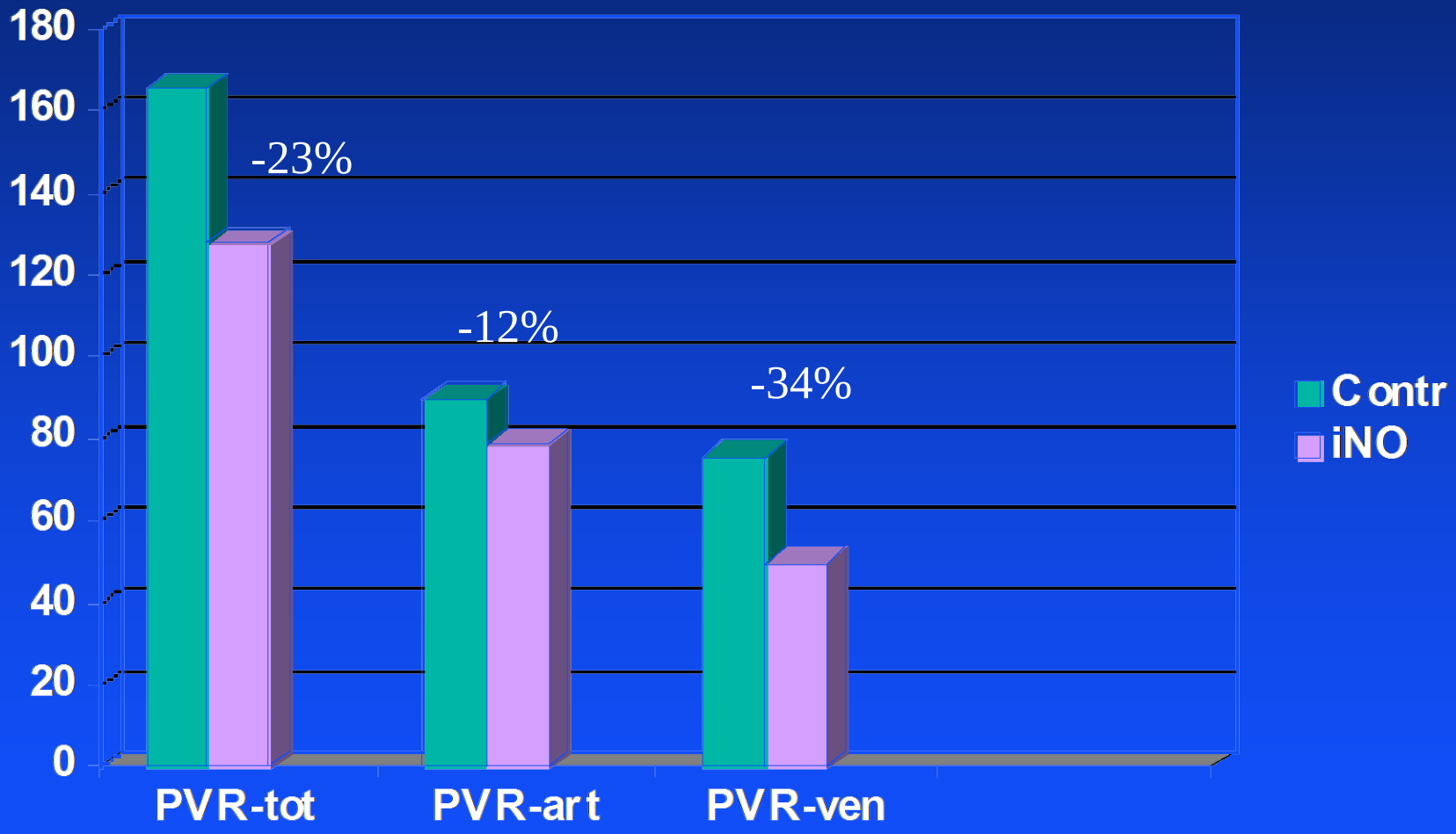
Pulmonary serial vascular resistances



$$\text{Pre} = \frac{\text{MPAP} - \text{PCP}}{\text{CO}} \qquad \text{Post} = \frac{\text{PCP} - \text{PCWP}}{\text{CO}}$$

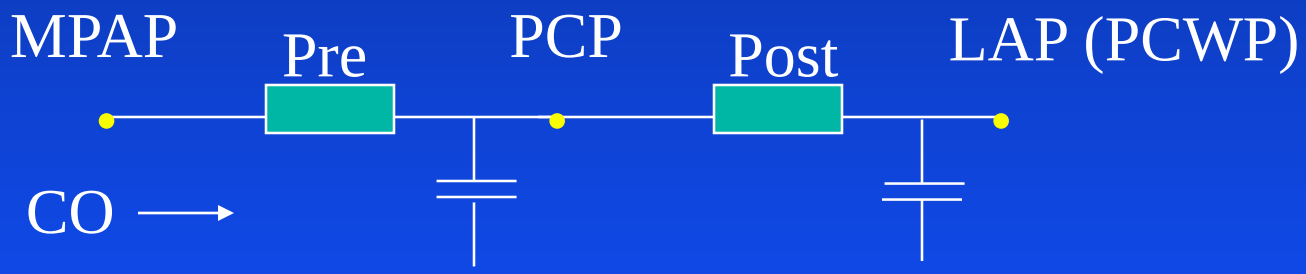
$$\text{PVR} = \text{Pre} + \text{Post}$$

Effects of inhaled NO on longitudinal distribution of pulmonary vascular resistance in ARDS



Benzing Geiger 1994 Acta Anaesthesiol Scand; 38:640

Pulmonary serial vascular resistances and capacitances



NO has a predominant vasodilating effect on the pulmonary venous vasculature.

- decreases pulmonary capillary pressure
- shifts blood volume from the arterial to venous capacitance vessels

Management of patients with right ventricular failure

Right ventricular failure (RVF)

Cardiac conditions

- Coronary artery disease (RV infarction)
- Valvular heart disease
- Cardiomyopathy (ischemic, dilatative)
- Heart surgery (CABG, AVR, MVR)
- Heart transplantation
- Post-LVAD

Extra-cardiac conditions

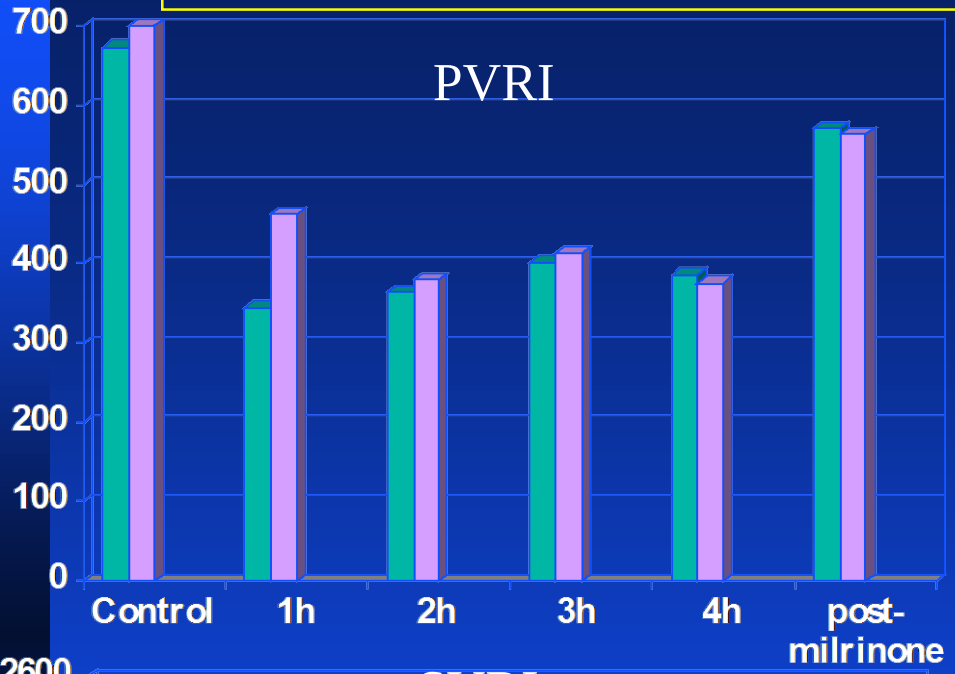
- Pulmonary embolism
- Lung disease (COPD, ARDS)
- Primary pulmonary hypertension
- Sepsis
- Lung transplantation
- Post-thromboendarterectomy

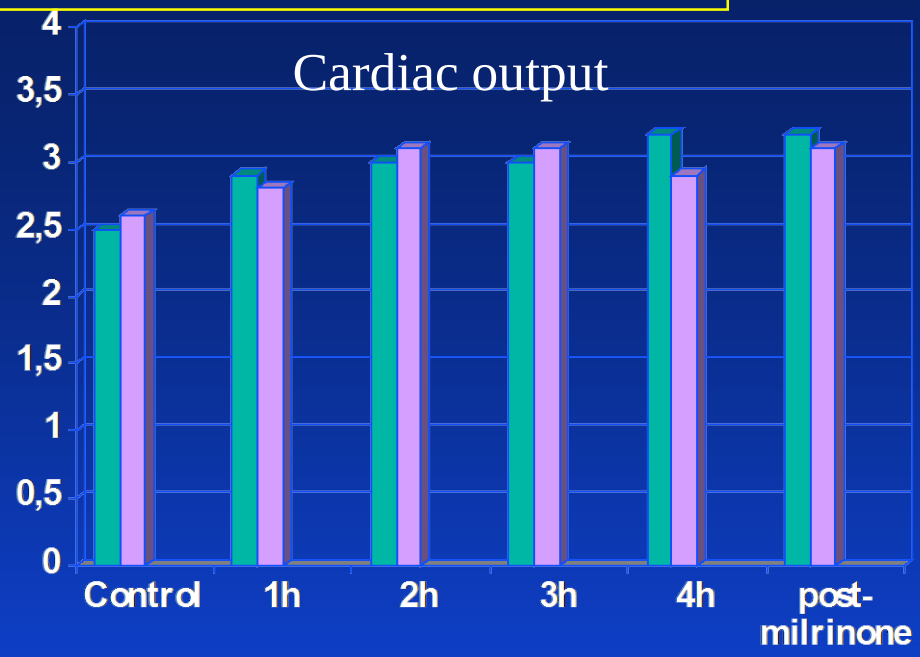
RVF rarely occurs in the setting of normal pulmonary vascular resistance!

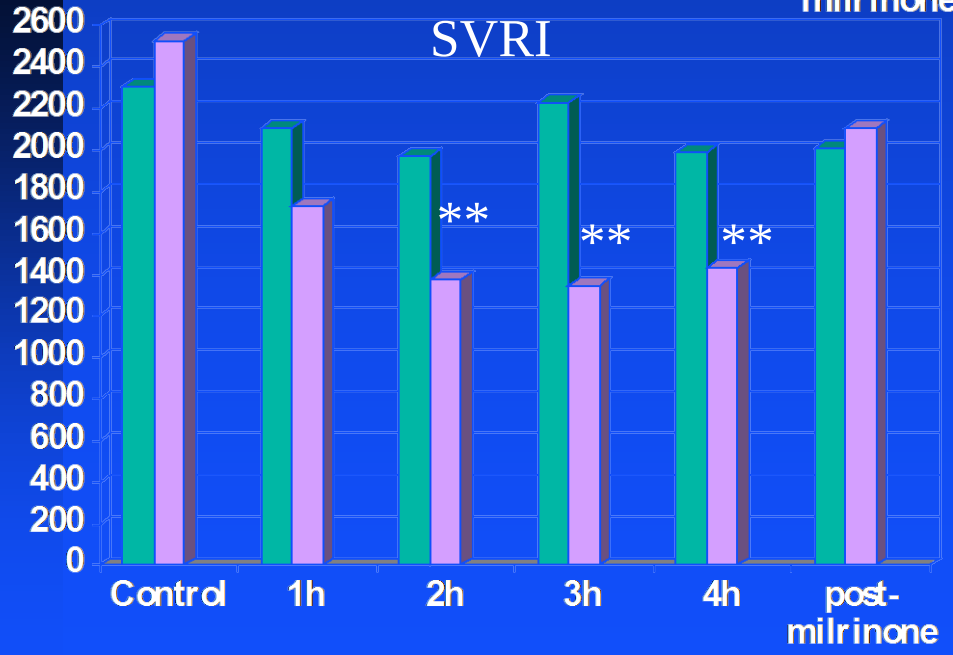
Treatment of severe cor pulmonale with inhaled iloprost (5 µg x 6)

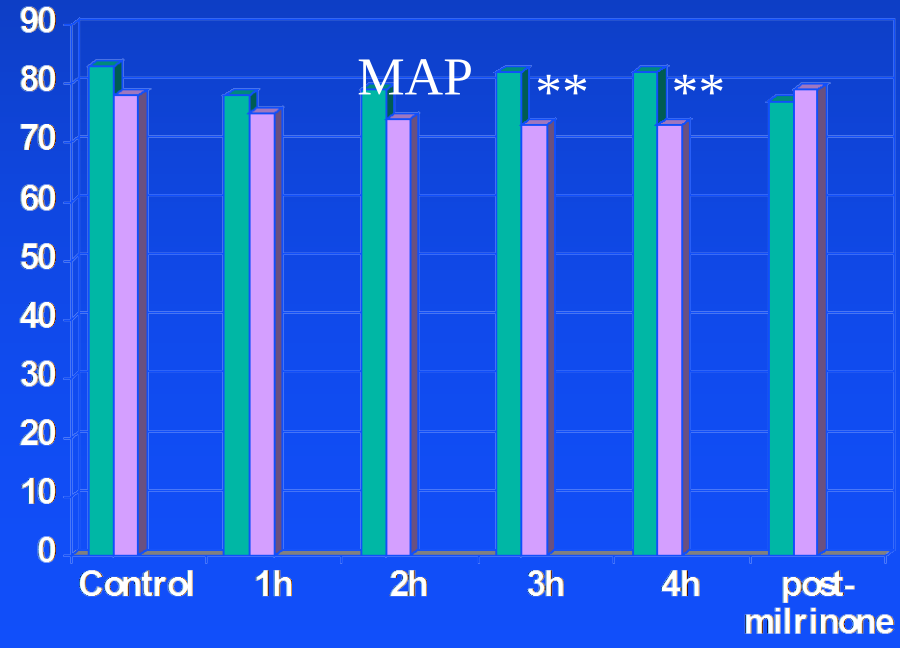
	Baseline treatment	3-days
SPAP (mmHg)	70	36
Tricuspid annulus (mm)	53	31
RA area (cm^2)	30	21
Inferior cava (mm)	29	18
NT-proBNP (pg/ml)	2938	921
TAPSE (mm)	14	18

Inhaled vs i.v. milrinone after mitral valve surgery

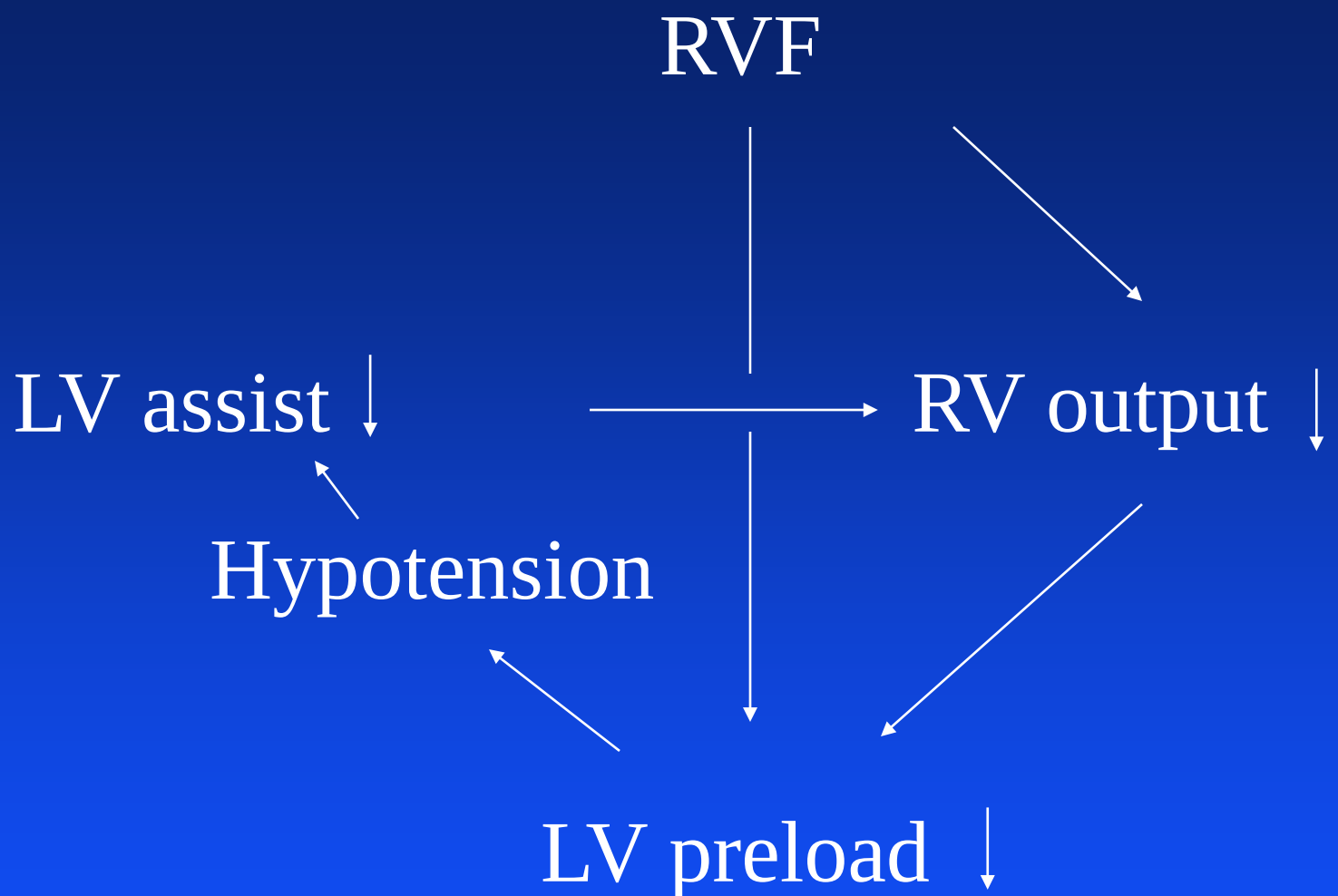






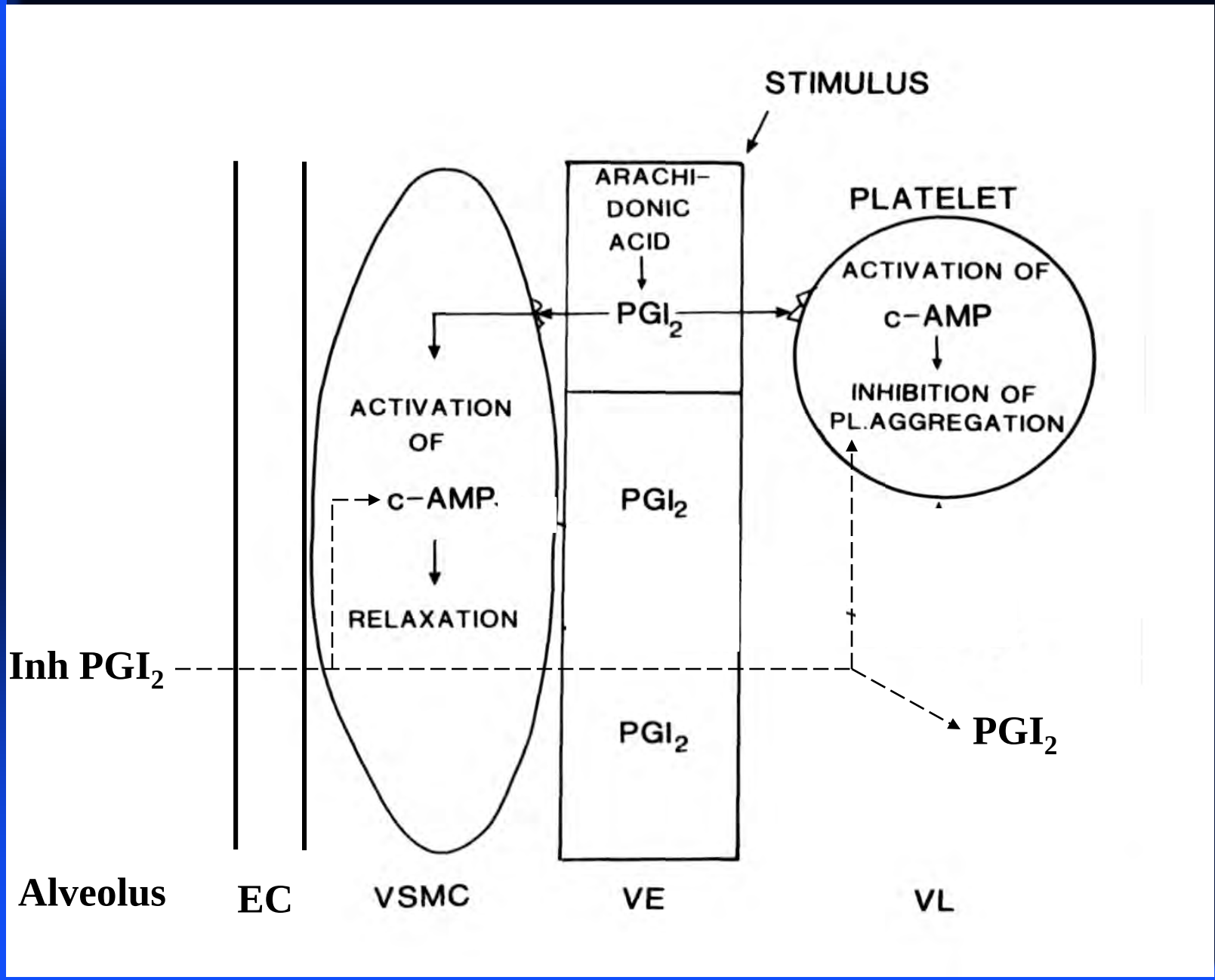


Wang et al Adv Ther 2009;26:462-468


RVF
LV assist ↓
RV output ↓
Hypotension
LV preload ↓

Inhaled prostaglandins - doses

- Prostacyclin: 10 µg/ml, 5-10 ml/ h
- Iloprost: 10 µg/ml, 2.5-5 µg x 6-9
- Treprostinil: 30-50 µg x 4


STIMULUS
ARACHI-
DONIC
ACID
PLATELET
ACTIVATION OF
c-AMP
INHIBITION OF
PL.AGGREGATION
PGI2
ACTIVATION
OF
c-AMP
RELAXATION
PGI2
PGI2
Inh PGI2
PGI2
Alveolus
EC
VSMC
VE
VL

Six hours of PGI_2 inhalation (10 µg/ml) after cardiac surgery:

- No increase in systemic levels of 6-keto-PGF_1-α
- No increase in bleeding time
- No increase in bleeding

Haraldsson et al Intensive Care Medicine 2000;26:188-194