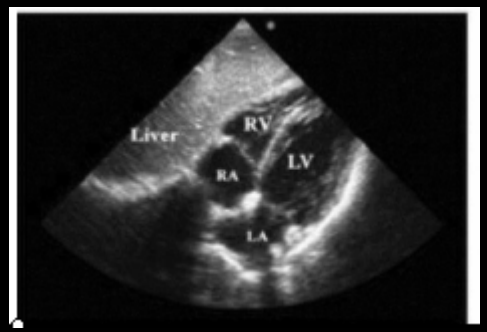
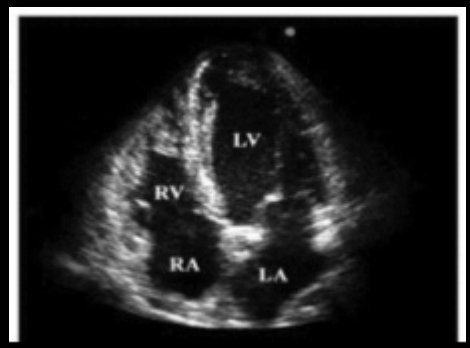
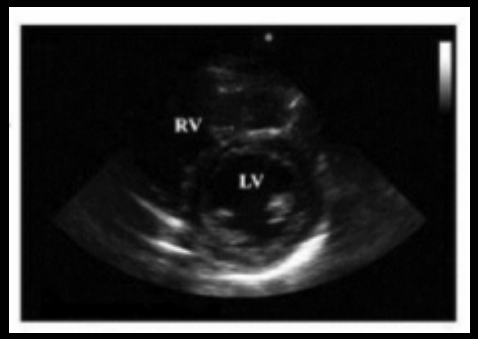
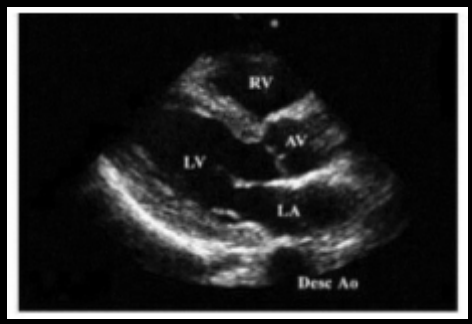
Physiologic Aspects of the Preterm Circulation









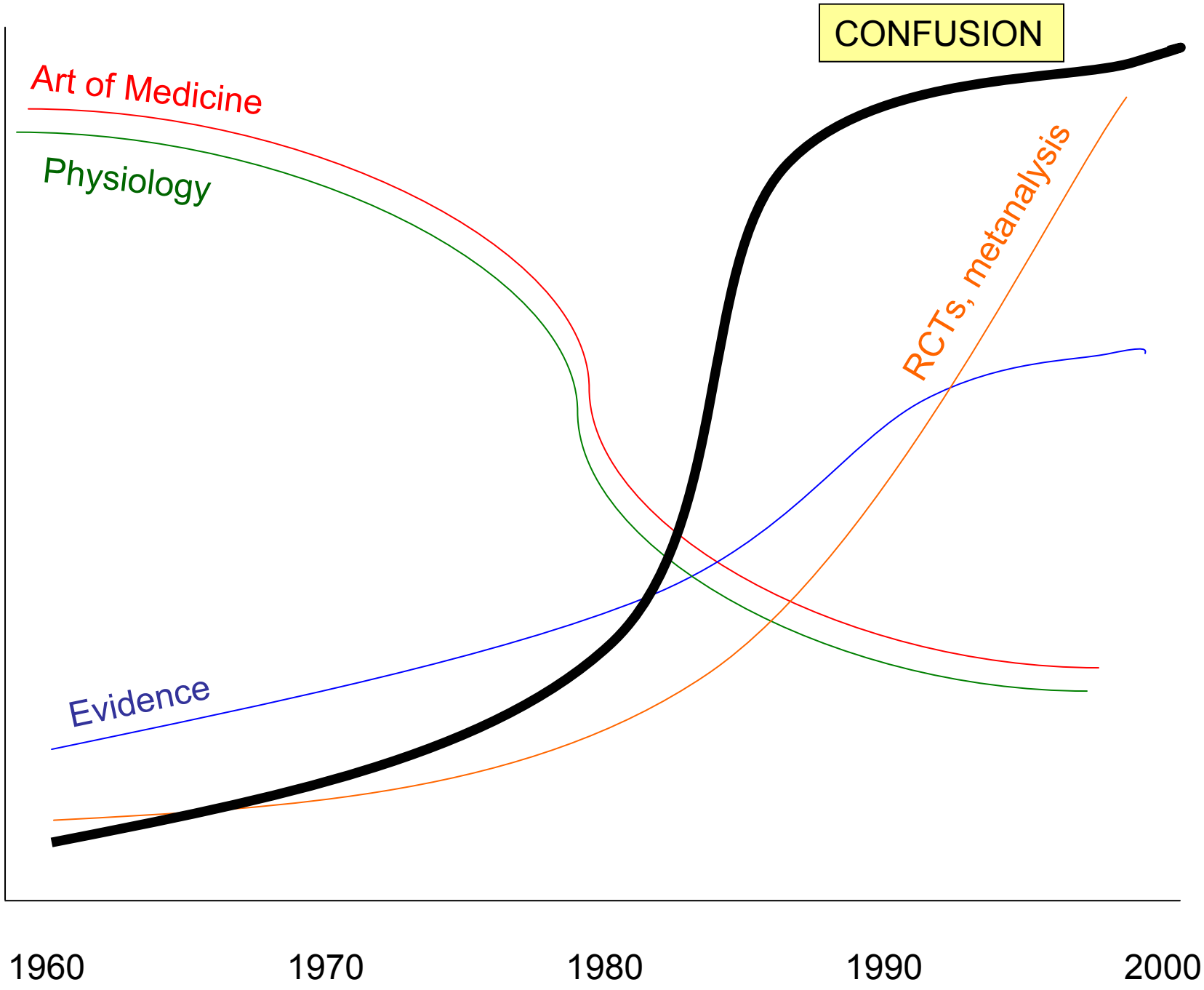
Patrick McNamara

Associate Professor of Pediatrics, University of Toronto

Staff Neonatologist, Hospital for Sick Children, Toronto

The Vulnerable Neonate

How will you ensure cardiovascular stability?


CONFUSION
Art of Medicine
Physiology
RCTs, metanalysis
Evidence
1960
1970
1980
1990
2000

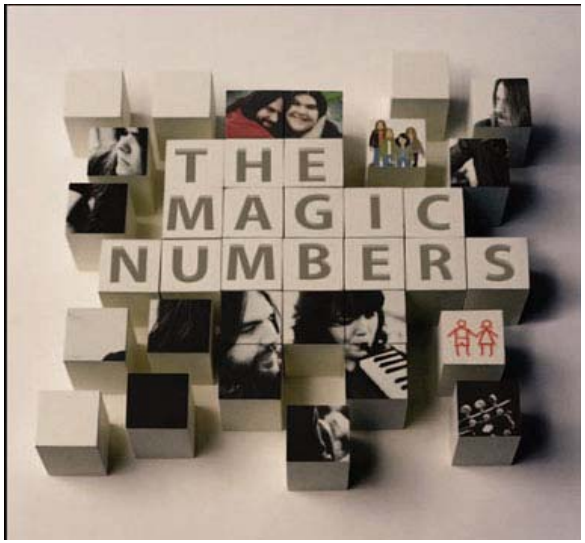
Myths

&

Magical numbers

&

Cook books



	Case I	Case II
26 week (650 g) preterm – 3 hours old		
Vitals	BP 30 / 18 (22) Heart rate 160	BP 38 / 26 (32) heart rate 160
Investigations	pH 7.19, CO_2 34, Bxs -11 Lactate 5.2 mmol/l	pH 7.19, CO_2 34, Bxs -11 Lactate 5.2 mmol/l
Likelihood of cardiotrope	High	Low

Myths of the Modern Era

“Numerical Hypotension”
(mean blood pressure < GA)
is problematic?

- Must have strong scientific validity
- Must have strong link to abnormal outcome
- Must be a reliable surrogate of systemic blood flow

Origin of Mean BP > GA

Development of audit measures and guidelines for good practice in the management of neonatal respiratory distress syndrome

CARDIOVASCULAR STABILISATION

It is essential to monitor blood pressure so that hypotension can be promptly recognised, its cause assessed, and appropriate treatment offered. Facilities for intravascular blood pressure monitoring should be available, but non-invasive blood pressure measurement using the Doppler technique may give a reliable estimate of systolic pressure. Further studies of the normal range of blood pressure in very premature infants are needed, but at the present time the working group agrees that a mean arterial blood pressure equivalent to the gestational age in weeks is adequate as a minimum value (C).

Hypotension should be treated initially with colloid or blood if there is the possibility of hypovolaemia (C). The effectiveness of inotrope infusion in the preterm newborn has not been proved, but a starting dose of dopamine 10 μg/kg/min may be needed in the preterm neonate as they are relatively resistant to this form of treatment. Its use must be avoided in the presence of hypovolaemia.

20 UK Paediatricans

(n=2 neonatologists)

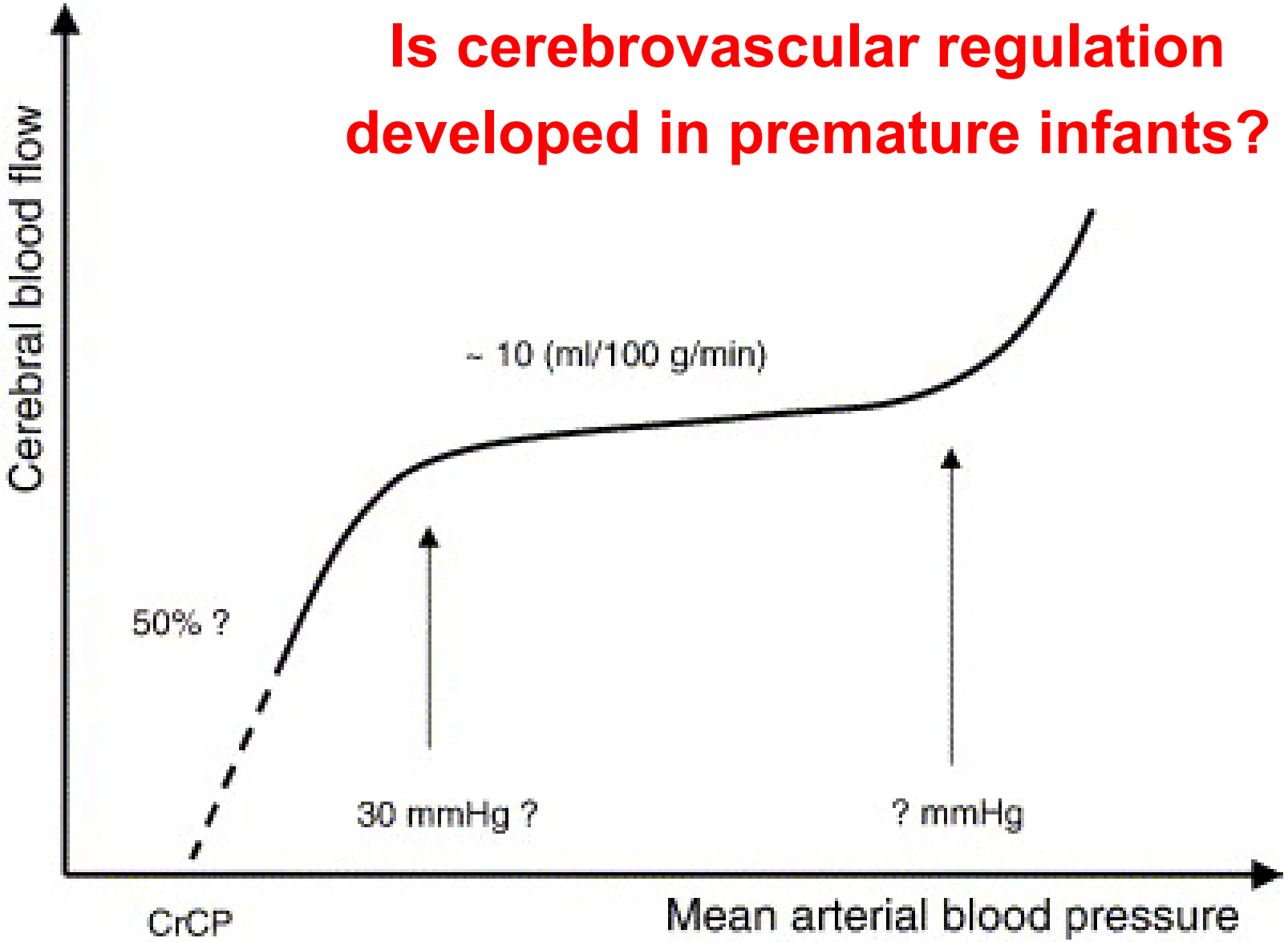
BPA report 1992 Arch Dis Child

Low Blood Pressure leads to adverse neurodevelopmental sequelae?

Cerebrovascular autoregulation is compromised in premature infants?

Griesen 2005 EHD

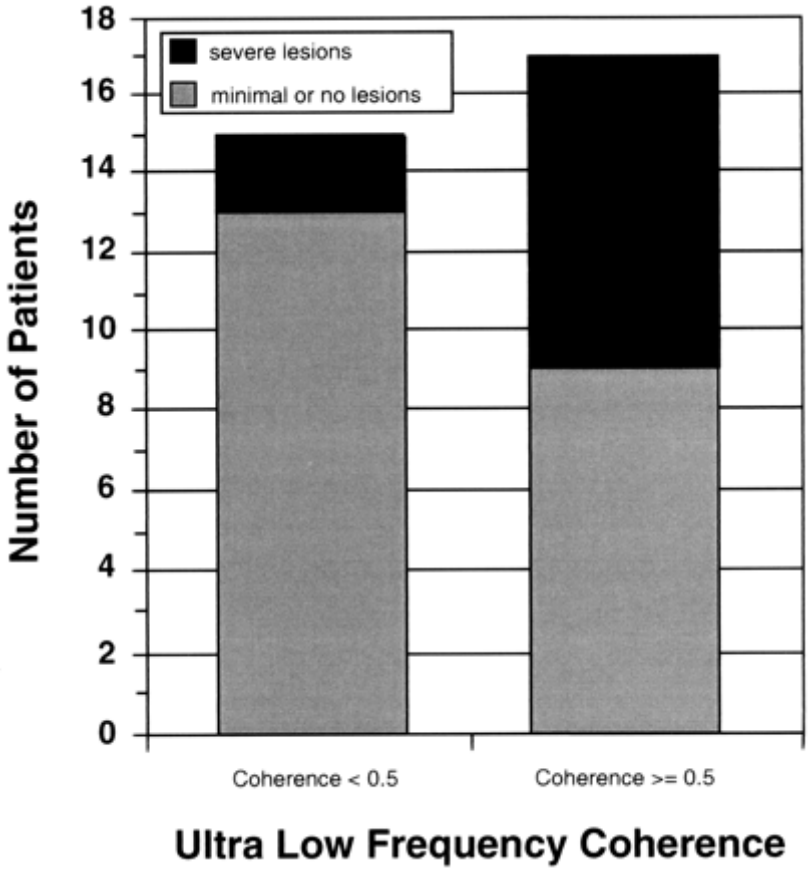
Is cerebrovascular regulation developed in premature infants?



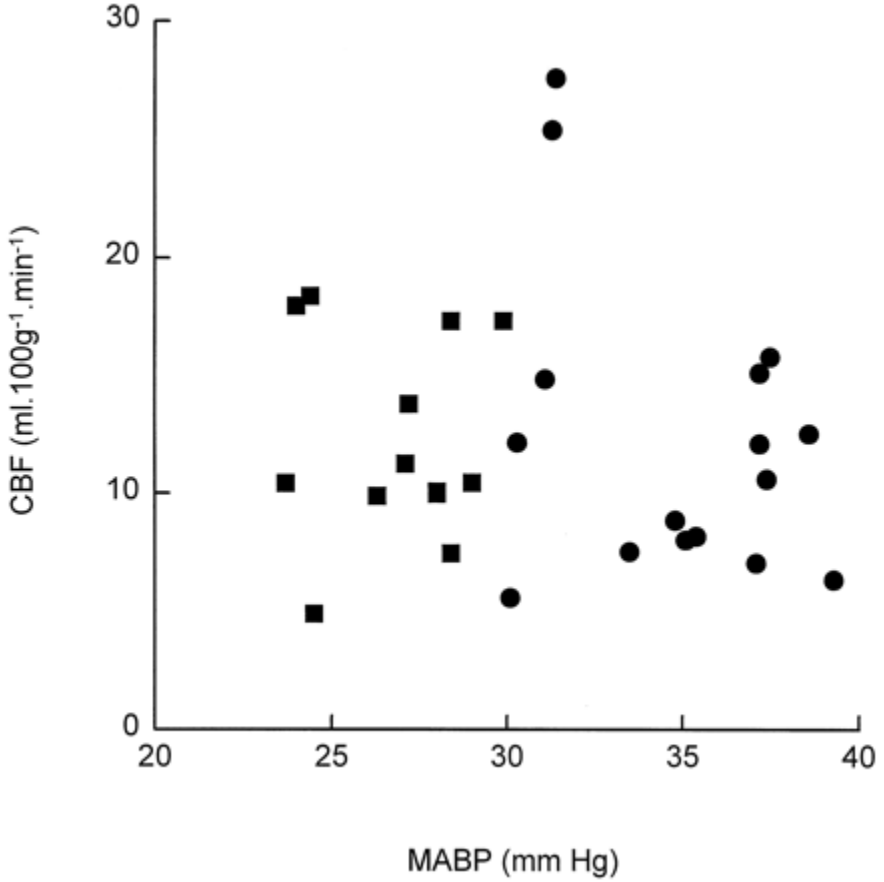
Altered by hypoxaemia x 4-7 hrs (neonatal ovine model)

Tweed 1986 Ped Red

BP & Cerebral Perfusion



Tsuji 2000 Pediatr



Tyszcuk 1998 Paediatrics

White matter Injury and Hypotension

YES	
Weindling (n=86)	1985
Miall-Allen (n=131)	1987
Watkins (n=33)	1989
Low (n=98)	1993

NO	
De Vries (n=51)	1988
Trounce (n=200)	1988
Bejar (n=127)	1992
Gronlund (n=42)	1994
D'Souza (n=34)	1995
Perlman (n=632)	1996
Wiswell (n=67)	1996
Baud (n=110)	1998
Cunn'ham (n=232)	1999
DuPlessis (n=260)	2007

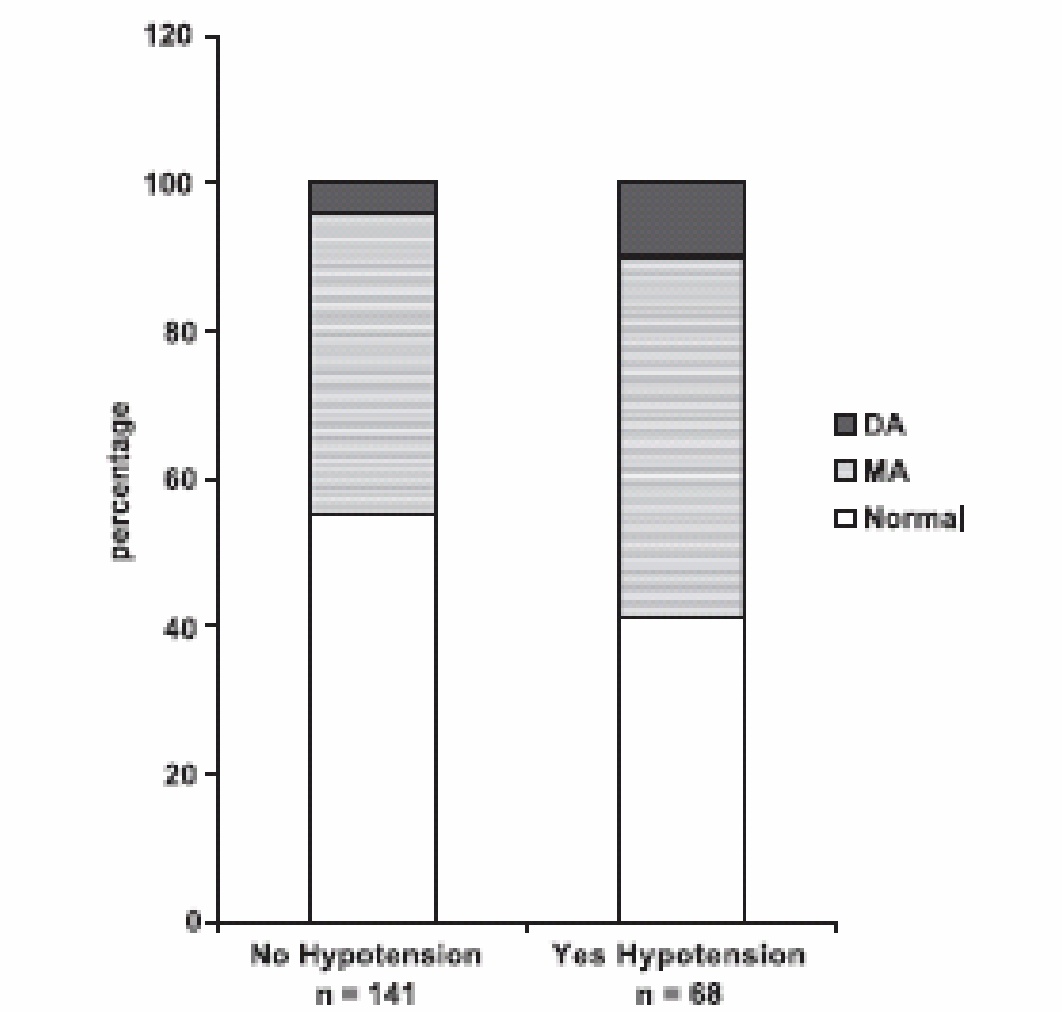
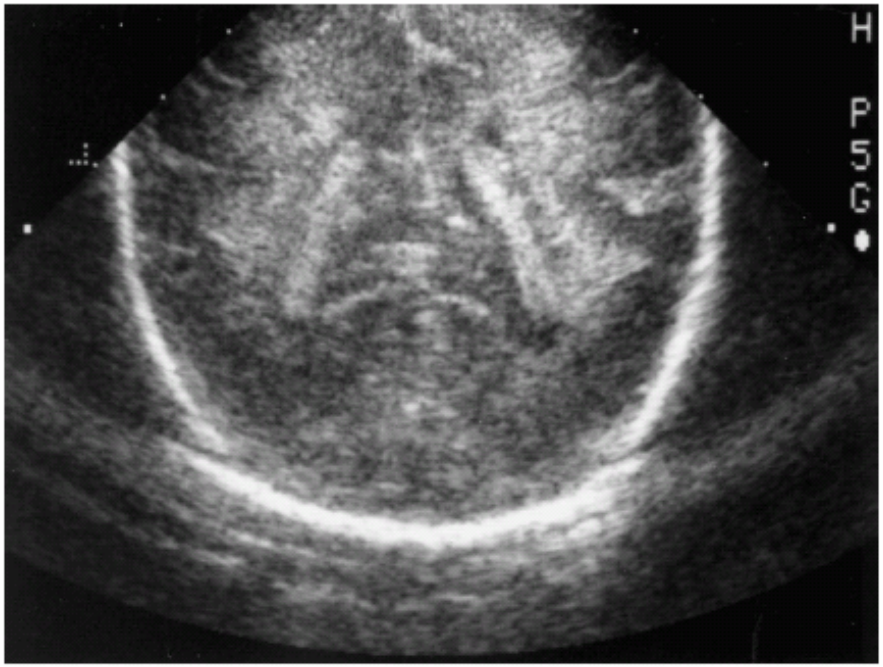


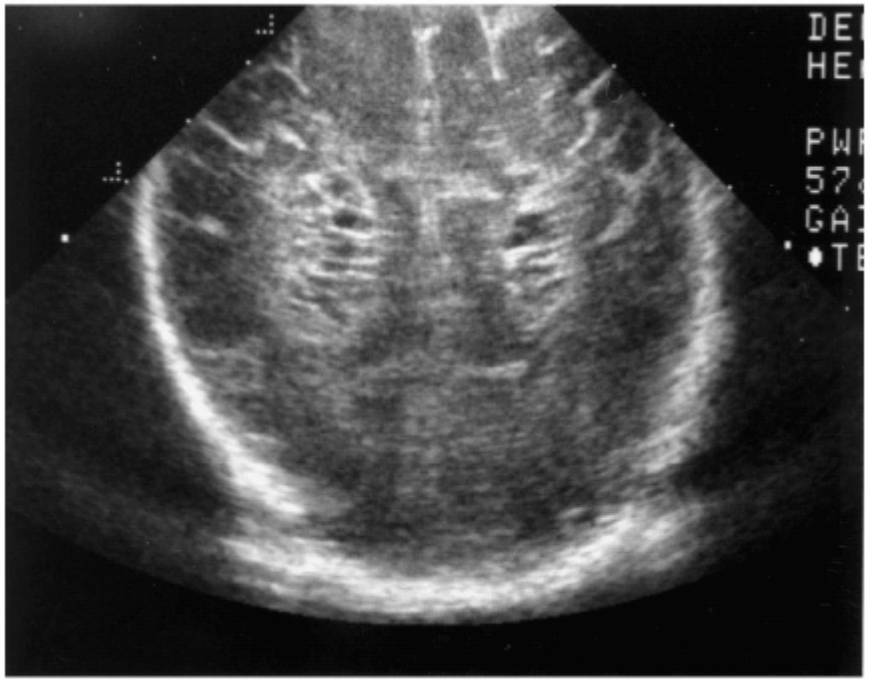
Fig. 1. Distribution of neurological morbidity at term in infants with and without hypotension.

N = 211

Higher incidence of IUGR, Postnatal steroids, BPD, Diuretic usage in hypotensive group

Martens 2003 Early Human Dev



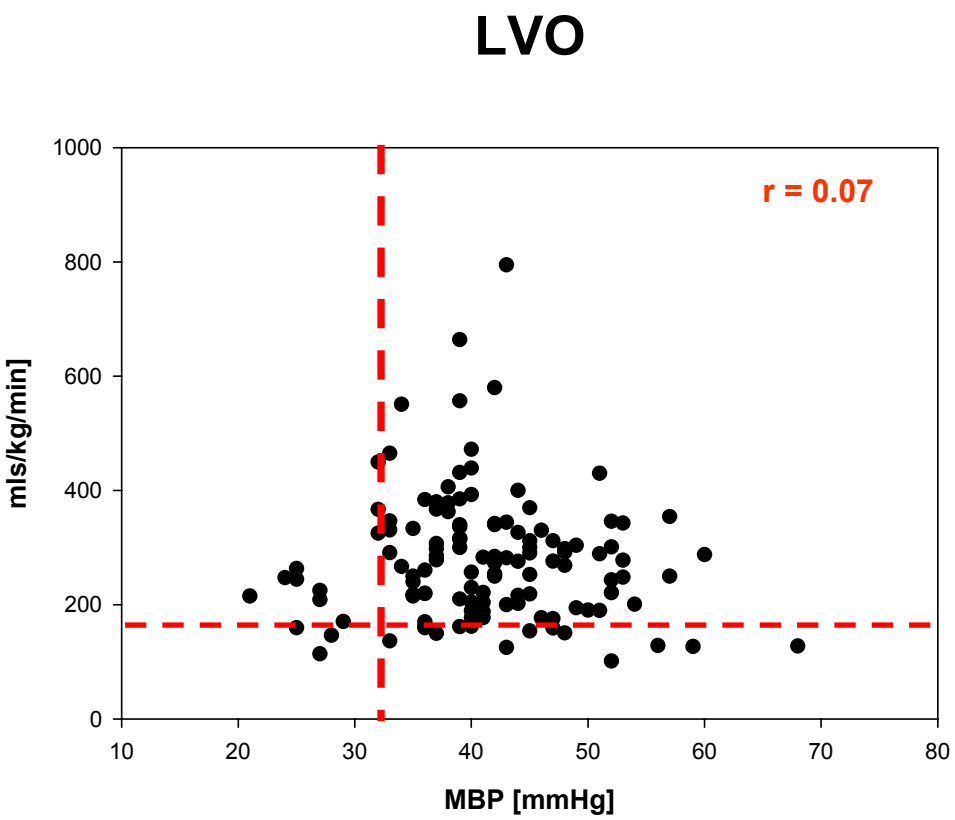


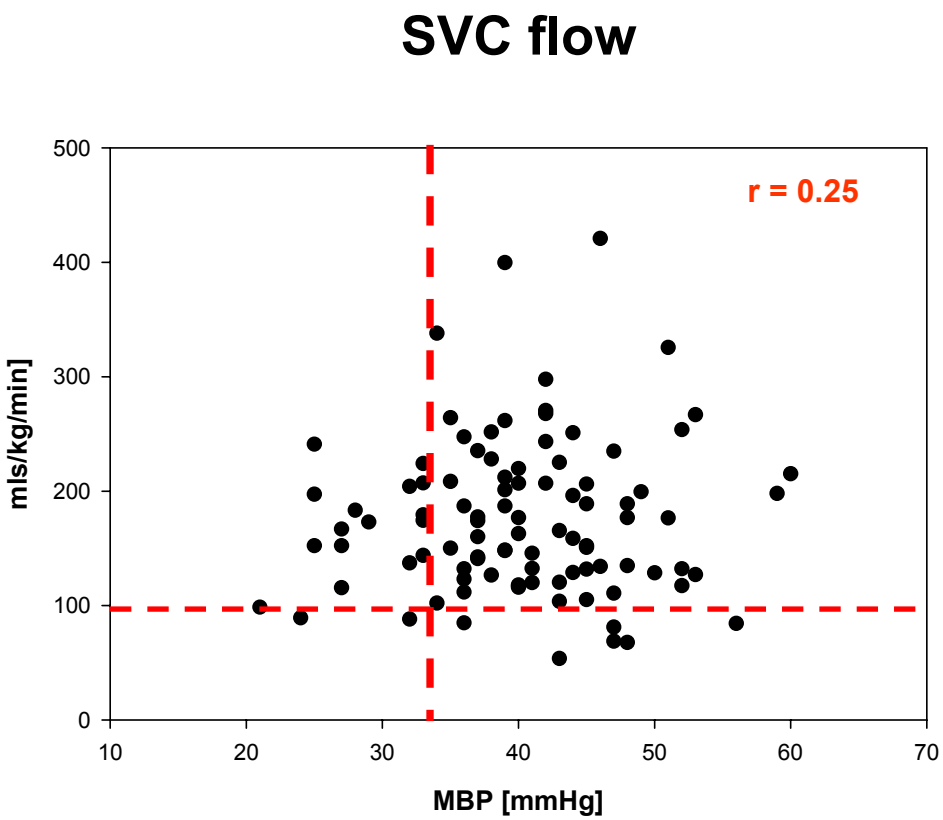
Is Hypotension an Epiphenomenon ?

A Physiologic Oversimplification

- Fail to consider systemic blood flow and tissue oxygenation
- Fail to consider the nature of the problem
- Fail to consider issues related to maturation
- Fail to consider response to treatment which may be developmentally regulated

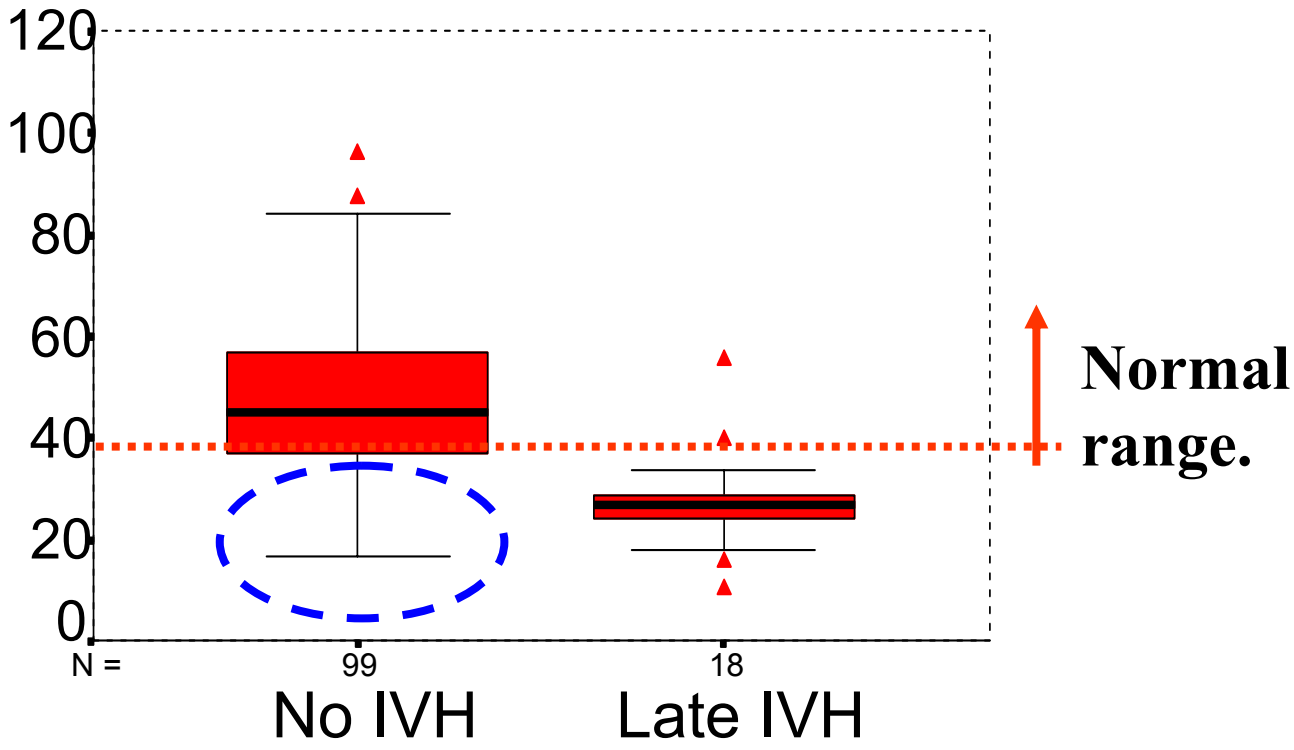
Systemic blood flow & MBP

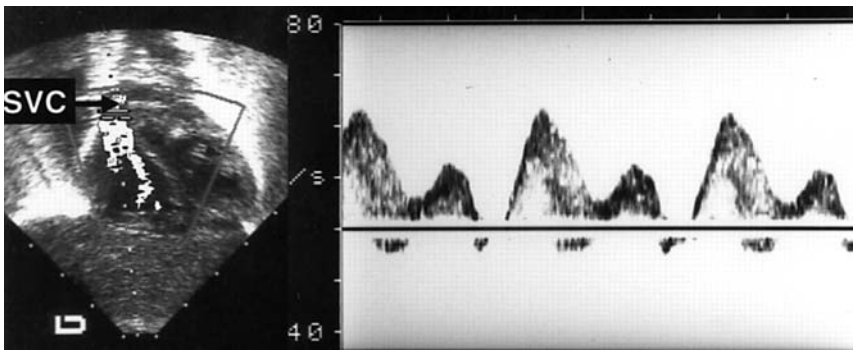




McNamara et al, 2007

Low SVC Flow and Intracranial Injury





Kluckow 2000 ADC

Therapeutic Intervention

- Identifying that there is a cadiovascular problems
- Deciding on the most appropriate intervention and when?

RECENT ADVANCES

Hypotension in the very low birthweight infant: the old, the new, and the uncertain

S J Dasgupta, A B Gill

Arch Dis Child Fetal Neonatal Ed 2003;88:F450–F454

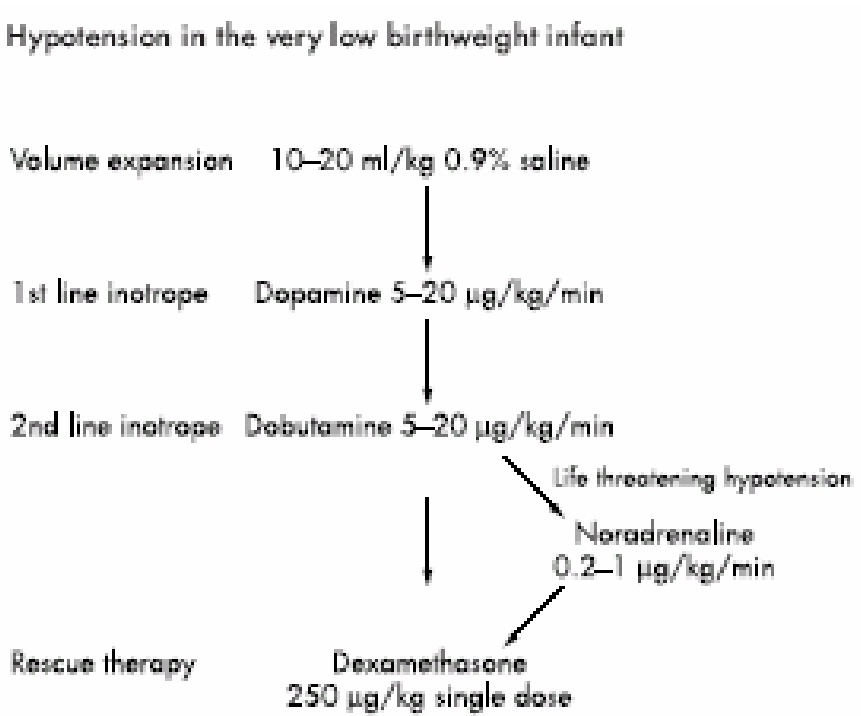
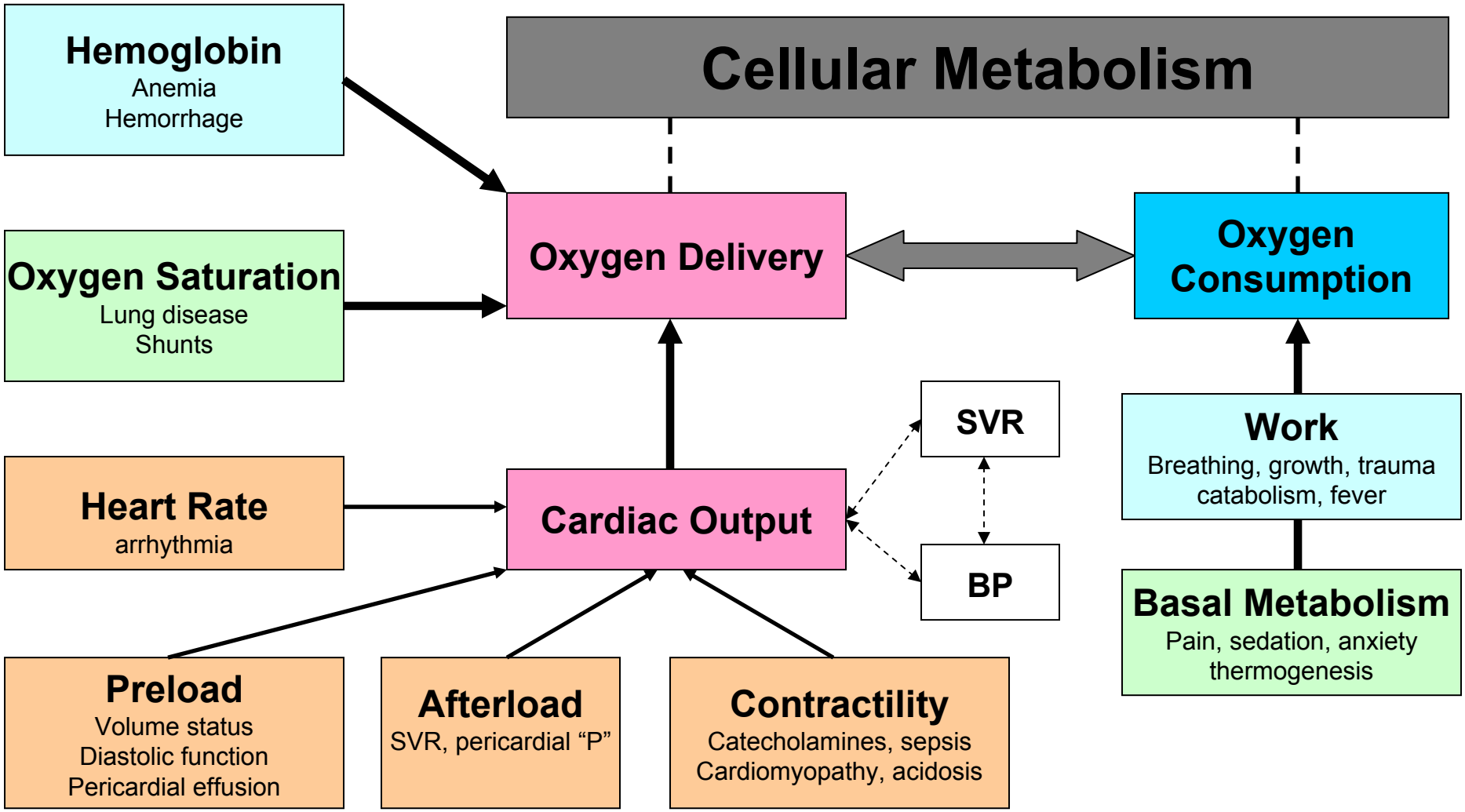


Figure 1 Flow chart for management of hypotension in the very low birthweight infant.

One rule (Pressor approach) does not fit all

- Preterm
  - PDA
  - Sepsis/NEC
- Fullterm
  - PPHN
  - Sepsis
  - HIE
  - Single ventricle physiology

Metabolic Homeostasis



Defining the Nature of the Problem

Hypovolaemia	Prematurity	< 48 hours of life	HSDA	SVT
Overinflation	Sepsis / NEC	PDA Ligation	Coarctation	Complete heart block
Adrenal suppression	Adrenal suppression	Pulmonary hypertension	HLHS	
IDM			Aortic stenosis	

Volume, preload & neonates

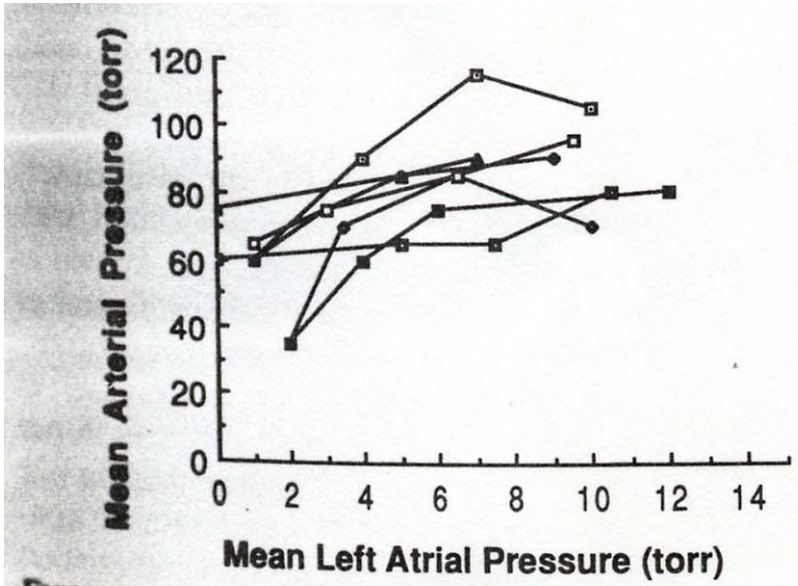


FIGURE 3. *Relation between mean left atrial pressure and mean arterial pressure before balloon inflation in each of the seven newborn lambs studied.*

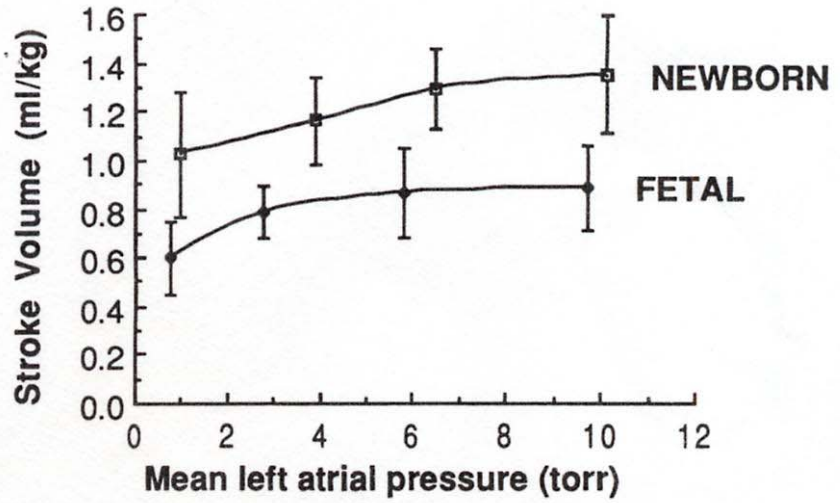


FIGURE 4. *Composite preload function curves relating mean left atrial pressure and stroke volume for all fetuses and newborns studied. (Mean values from seven newborn and 10 fetal lambs.)*

Van Hare 1990 Circ Research

Is Preload management important?

- All sick neonates (e.g. sepsis) need a CVP within normal range [5-8]
- Identifiable fluid loss e.g. gastroschisis, NEC
- Poorly compliant right ventricle i.e. Septal hypertrophy / or Hypertrophic cardiomyopathy, *TEF/HRV* [8-12]

Myocardial performance in neonates

Systolic

- Fetal/neonatal myocardium less compliant with 70 % noncontractile tissue (*Romero 1983 Ped Res*)

- Less active tension at optimal sarcomere length

Friedman 1972 Prog Card Dis

- Inotrope-responsiveness potentially less

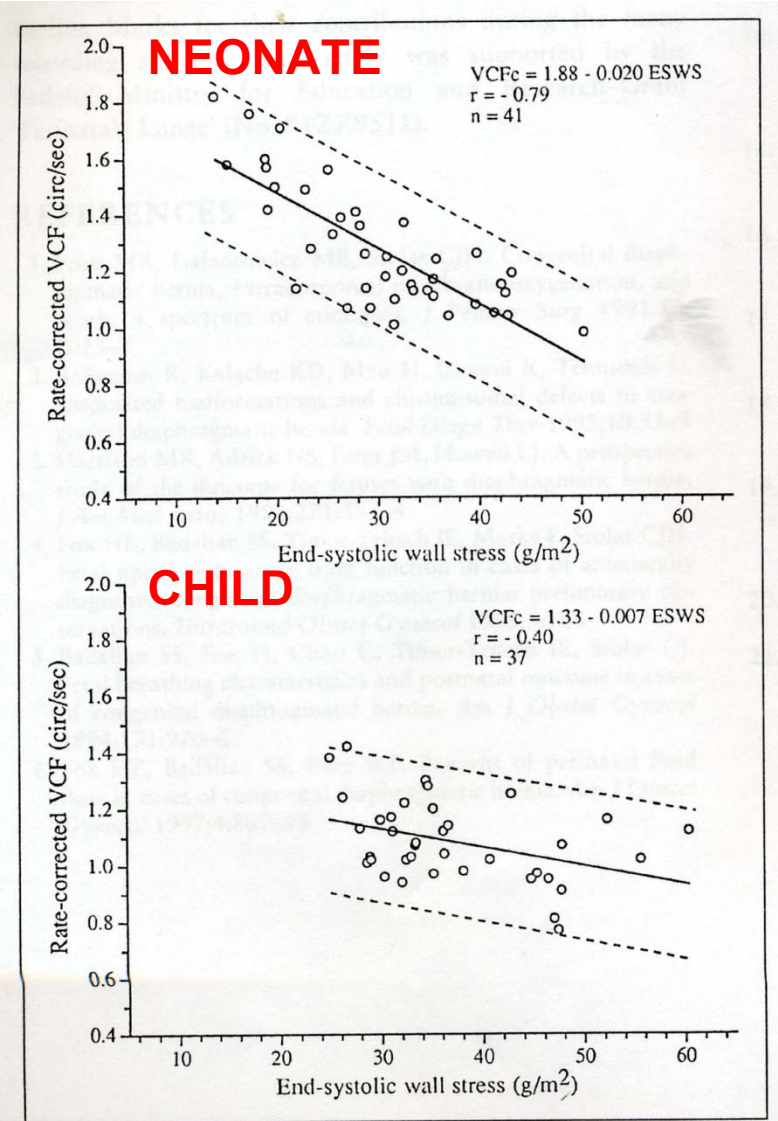
Romero 1979 Ped Res

- Diastolic vulnerability

Impaired early filling and low E waves !

Riggs 1989 JACC, Reed Circulation 1986

Stress-Velocity Relationship



Rowland 1995 Am J Card

When should Afterload be considered

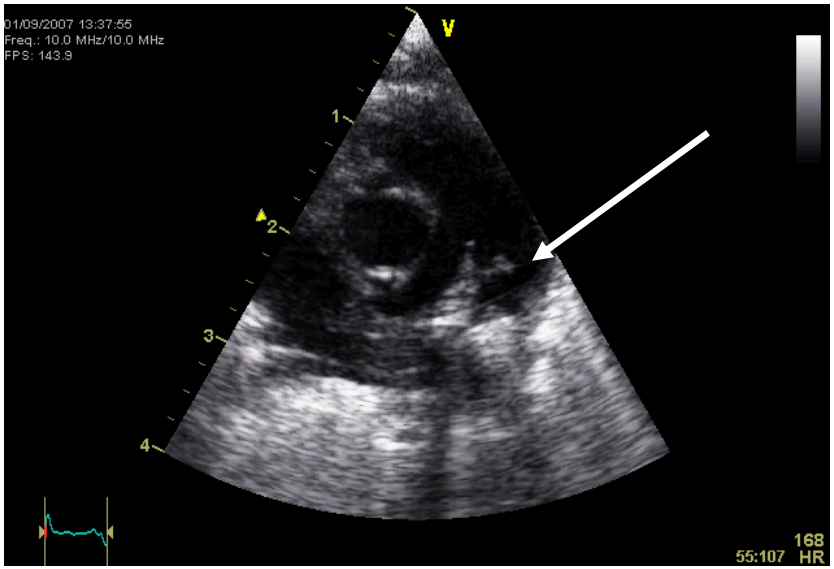
- PPHN (Pulmonary Afterload)
- Ductal Physiology
- ELBW infants with early LCOS (< 48 hours)
- Balancing Single ventricle physiology

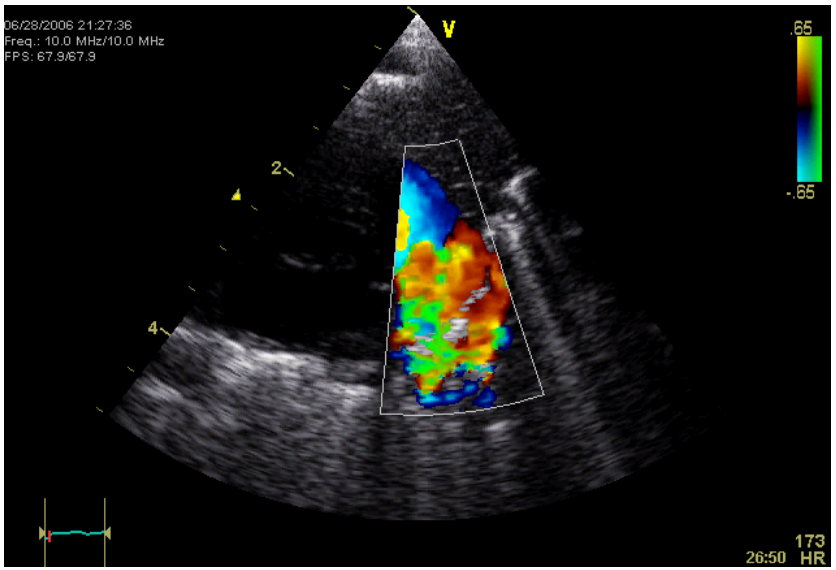
Scenario I

- 26 week premature infant 760 g (surf x 1)
- Retrieved by regional transport team
- Received 2 boluses of crystalloid (20 mls/kg) for mean blood pressure of 20 mmHg

	BP	HR	pH	Bxs	Lac	Intervention
Admit	45/22 (29)	165	7.23	-7	-	SiMV15/5, FiO_2 0.21
7 hrs	30/16 (20)	152	-	-	-	Observed 45 mins $\rightarrow$0.9% saline bolus $\rightarrow$ 35/20 (25)
12 hrs	32/16 (22)	150	7.19	-9	1.9	Dopamine 7.5μg$\rightarrow$ 38/18 (24)
15 hrs	36/14 (22)	171	-	-	-	Dopamine 10μg$\rightarrow$ 38/16 (23)
20 hrs	41/13 (22)	182	7.16	-12	3.2	Dobutamine10μg$\rightarrow$45/12 (24)

Functional USS heart





- 2.7 mm HSDA

- Left heart volume loading,

- ↓SVC flow

- absent diastolic flow in superior mesenteric artery & middle cerebral artery

Surfactant

Hypocapnia

Oxygen or Nitric oxide

Hypocapnia / Alkalosis

Pressors

Oxygen

Hypothermia

PVR

+

PDA

Ao

SVR

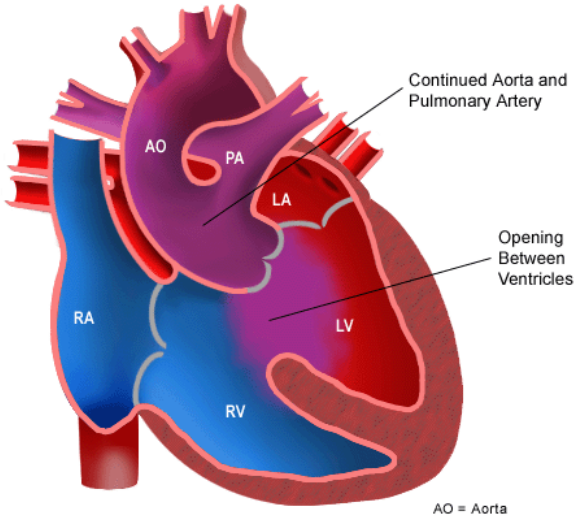
+++++

+++

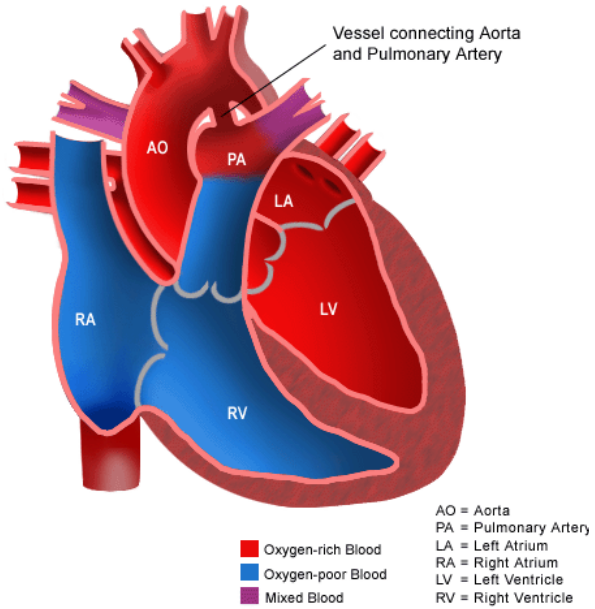
Ao

Left Ventricle

Truncus Arteriosus



Patent Ductus Arteriosus (PDA)



Dopamine

- Sympathetic amine (*Most commonly used agent*)
- Mixed β-1 & α-effects depending on dose
- Inotropic & afterload increase effects
- Improved LV performance at low dose (< 2.5 μg/kg/min)

Padbury 1986 J Pediatr

Dobutamine

- Synthetic analogue of dopamine
- Predominant β-1 effect, minimal α-effects
- Inotropic & afterload reduction effects
- Theoretical pulmonary vasodilator properties

Dopamine and Afterload

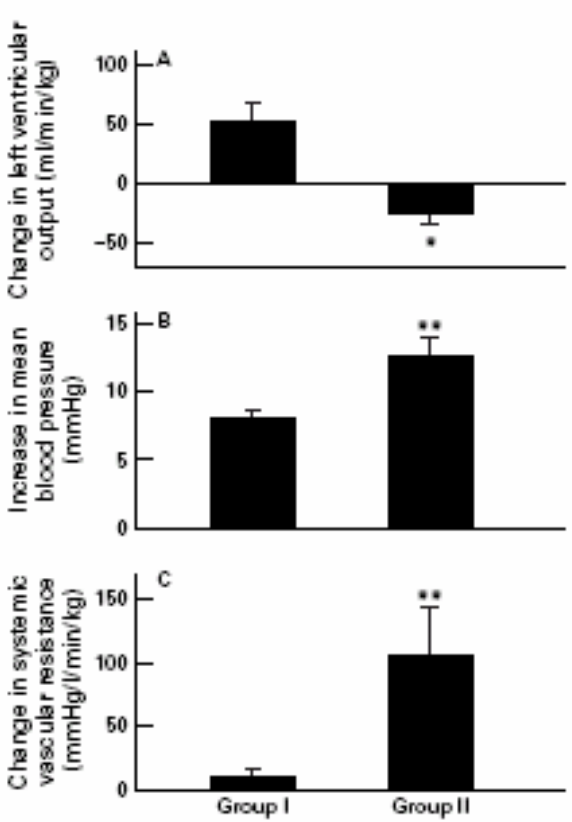


*Figure 1 Change in left ventricular output (A), mean blood pressure (B), and systemic vascular resistance (C) after dopamine treatment in groups 1 and 2 neonates. Values are expressed as mean (SE): * $p < 0.05$; ** $p < 0.01$, group 1 vs group 2*

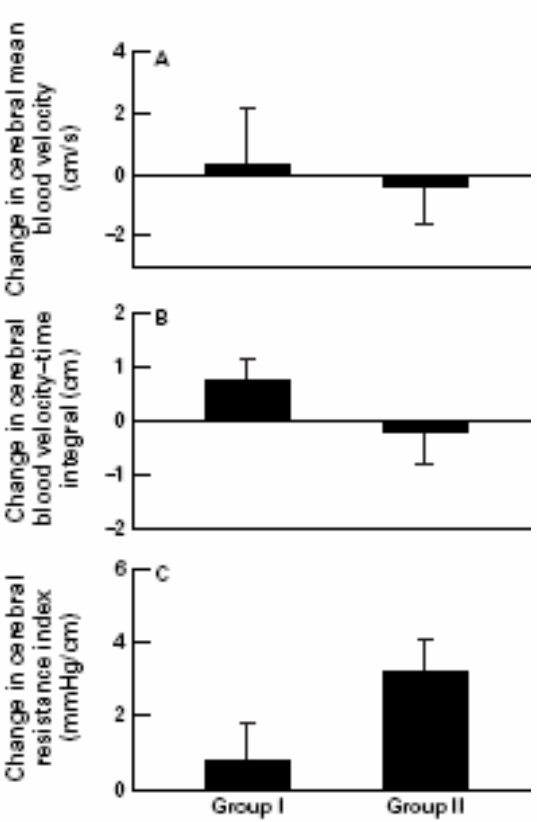


Figure 2 Changes in anterior cerebral artery mean blo velocity (A) and blood velocity–time integral (B), and cerebral vascular resistance index (C) after dopamine treatment in both groups.

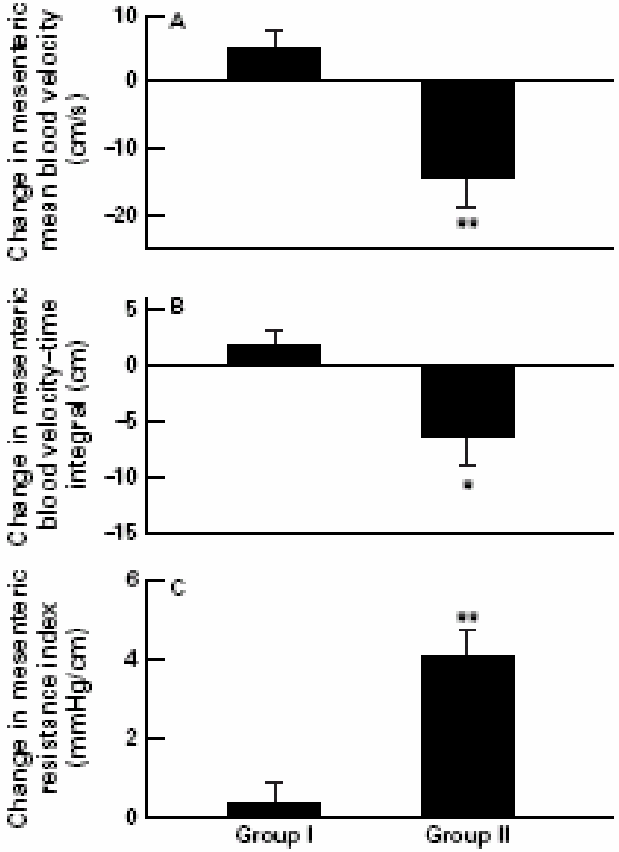


*Figure 3 Change in mesenteric artery mean blood velocity (A) and blood velocity–time integral (B) and mesenteric resistance index (C) after dopamine treatment in both groups: * $p < 0.05$; ** $p < 0.01$, group 1 vs group 2.*

Group 1 Dopamine 8 µg/kg/min

Group 2 Dopamine 6 µg/kg/min

Zhang 1999 Arch Dis Child

Circulatory instability & PDA

- Minimize oxygen exposure (SpO2 > 85%)
- Permissive acidemia pH > 7.25
- Permissive hypercapnemia pCO2 50-60 mmHg
- Increase PEEP
- Avoid excessive fluid restriction – compromises end-organ flow
- Avoid pressor agents to support the myocardium

Scenario II

Fullterm male, BWgt 4.6 Kg,
Low Apgars , Cord pH 6.9, Bxs -18.0
Mother Glycosuric, Meconium Staining at birth

Evaluation at Referral Hospital

SpO_2 85%/68% FiO_2 1.0 HR 180 / min
BP 55/25 (35) Soft ESM 2/6 localized to LLSE
Pulses weak Ventilation: 28 / 3, 70 /min
ABG: pH7.1, pCO2 65, pO2 46, BXS -12.0 Lac 5.6

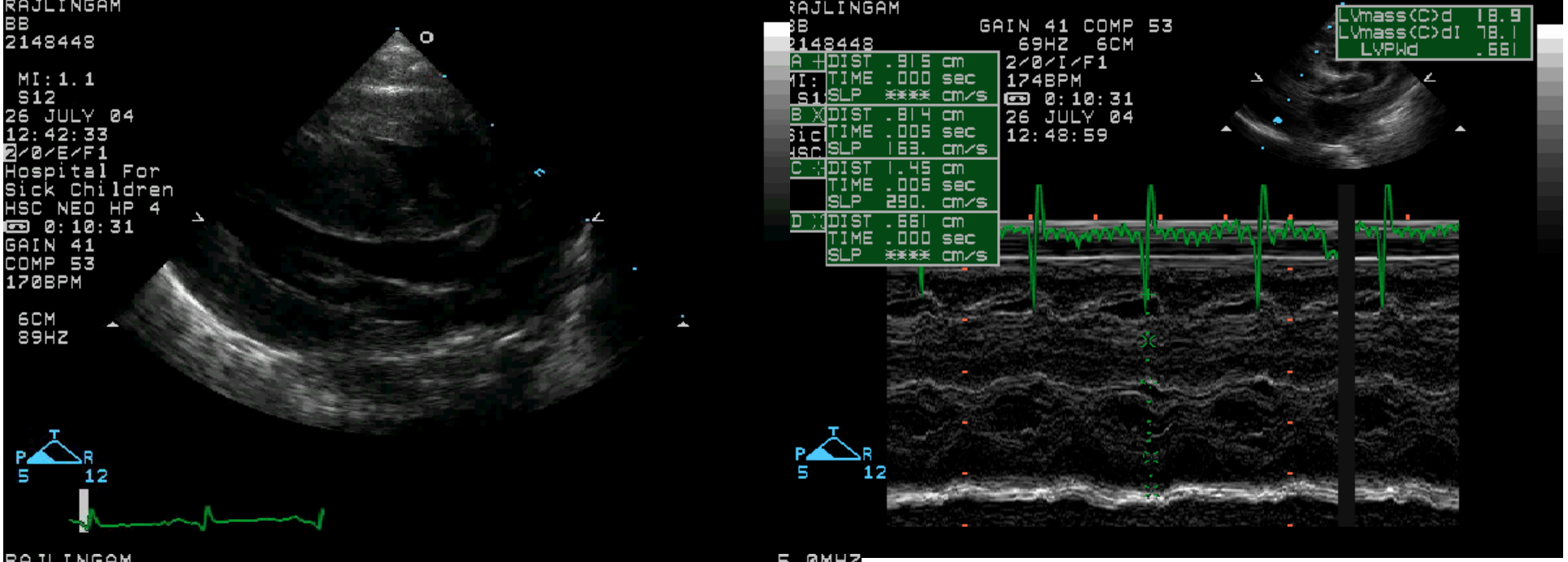
Cardiovascular Support

- Crystalloid (20 mls /kg)
- Cardiotropic Agents (dopamine 15 mcg/kg/min)
- BP 55/42 (46), HR 192, Anuric

ABG: pH 6.8, pCO2 65, paO2 45, Bxs -23 Lac 12.4

Refractory Hypotension

- Adrenal insufficiency - steroids
- Congenital heart disease – duct dependant systemic blood flow lesion (e.g. HLHS, coarctation) –PGE1
- Hypertrophic cardiomyopathy -Preload
- Tamponade (excessive ventilation, pericardial or pleural effusion, pneumothorax) - Drain


RAJLINGAM
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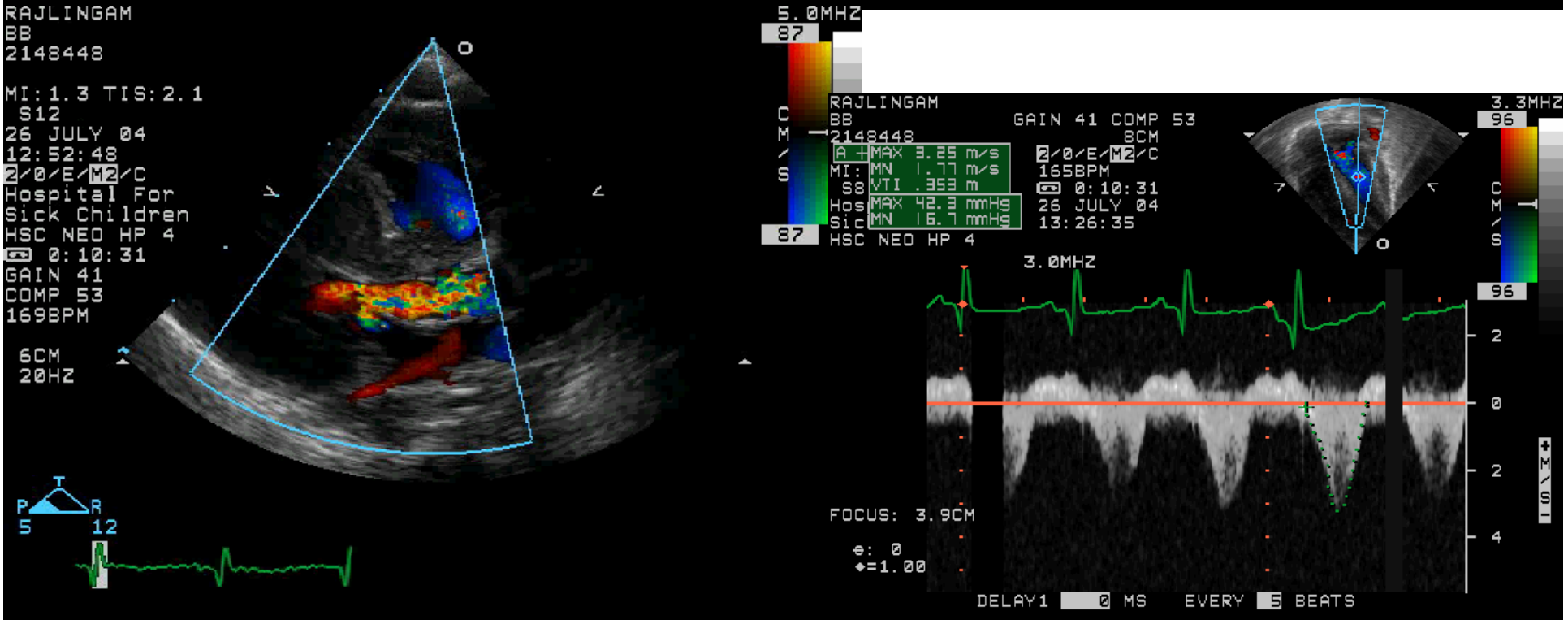
MI:1.1
S12
26 JULY 04
12:42:33
2/0/E/F1
Hospital For
Sick Children
HSC NEO HP 4
0:10:31
GAIN 41
COMP 53
170BPM
6CM
89HZ
GAIN 41 COMP 53
69HZ 6CM
2/0/I/F1
174BPM
0:10:31
26 JULY 04
12:48:59
DIST .915 cm
TIME .000 sec
SLP **** cm/s
DIST .814 cm
TIME .005 sec
SLP 163. cm/s
DIST 1.45 cm
TIME .005 sec
SLP 290. cm/s
DIST .661 cm
TIME .000 sec
SLP **** cm/s
LVmass(C)d 18.9
LVmass(C)dI 78.1
LVPWd .661
P R
S 12


RAJLINGAM
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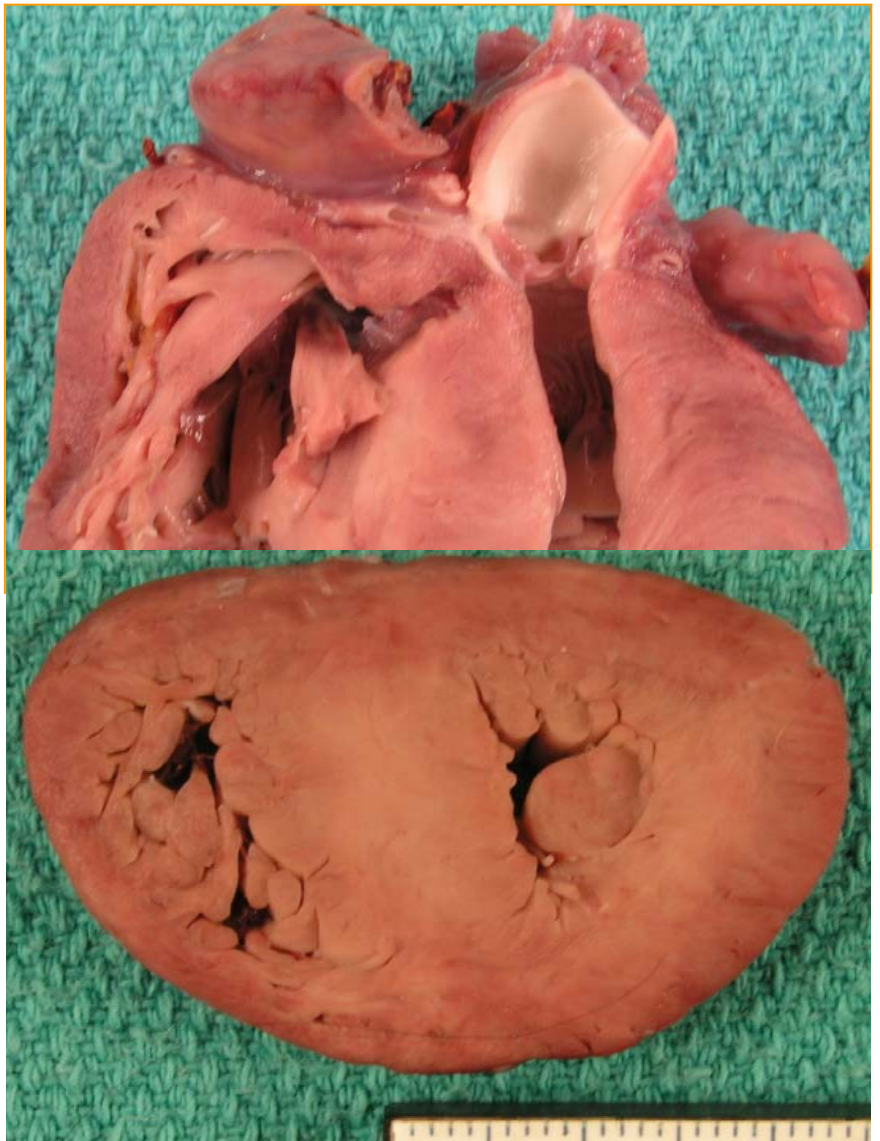
MI:1.3 TIS:2.1
S12
26 JULY 04
12:52:48
2/0/E/M2/C
Hospital For
Sick Children
HSC NEO HP 4
0:10:31
GAIN 41
COMP 53
169BPM
6CM
20HZ
5.0MHZ
87
87
RAJLINGAM
BB
2148448
GAIN 41 COMP 53
8CM
2/0/E/M2/C
165BPM
0:10:31
26 JULY 04
13:26:35
HSC NEO HP 4
MAX 3.25 m/s
MN 1.77 m/s
VTI .353 m
MAX 42.3 mmHg
MN 16.7 mmHg
3.3MHZ
96
96
3.0MHZ
FOCUS: 3.9CM
DELAY1 0 MS EVERY 5 BEATS
P R
S 12

Progression

- Inotropes weaned to off
- **PgE1** infusion commenced to support cardiac output
- **Volume** resuscitation & **Vasopressin**
- pH & Lactates normalized

Caution with Cardiotropic agents

- Tachycardia
- Increased myocardial oxygen consumption
- Compliance impaired & ↓ diastolic filling
- ⇑ Afterload



Epinephrine and Outcomes

n=91

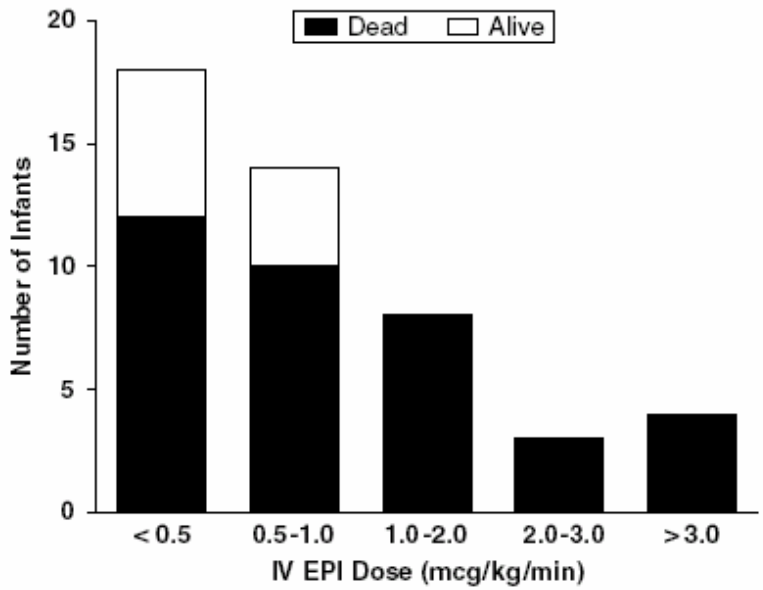


Figure 2. Outcome of infants ≤750 g birthweight in relation to maximal dose of IV epinephrine administered.

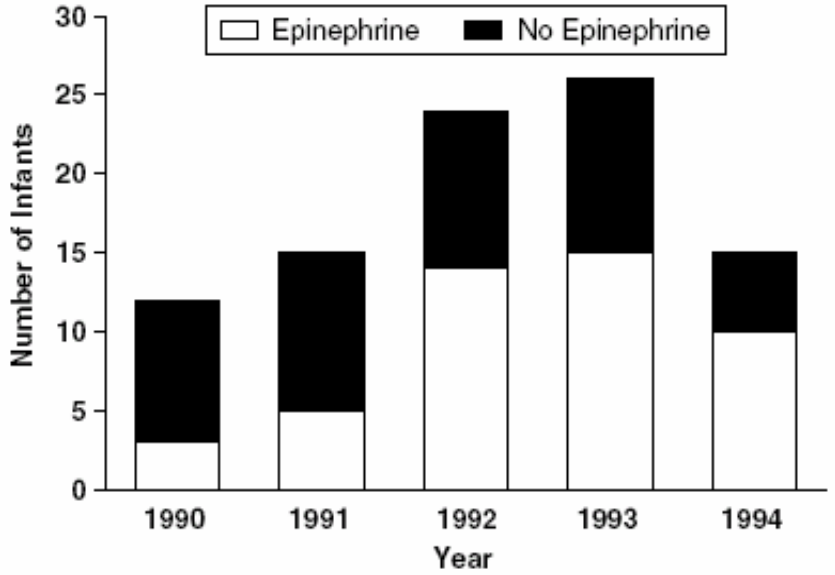


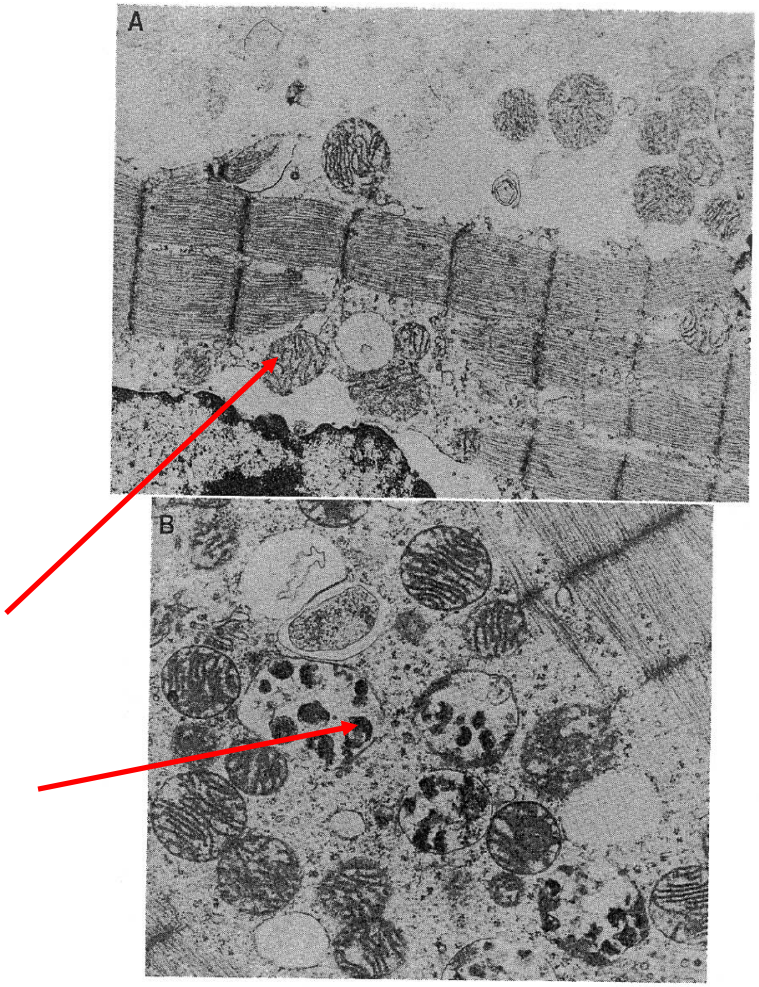
Figure 1. Use of epinephrine infusions in infants ≤750 g birthweight by year during the study period.

a tertiary NICU during the postsurfactant era. The outcome for infants ≤750 g birthweight following CPR or IV EPI in our NICU is extremely poor and suggests that extreme caution be used in applying these treatments in these infants. Current standard

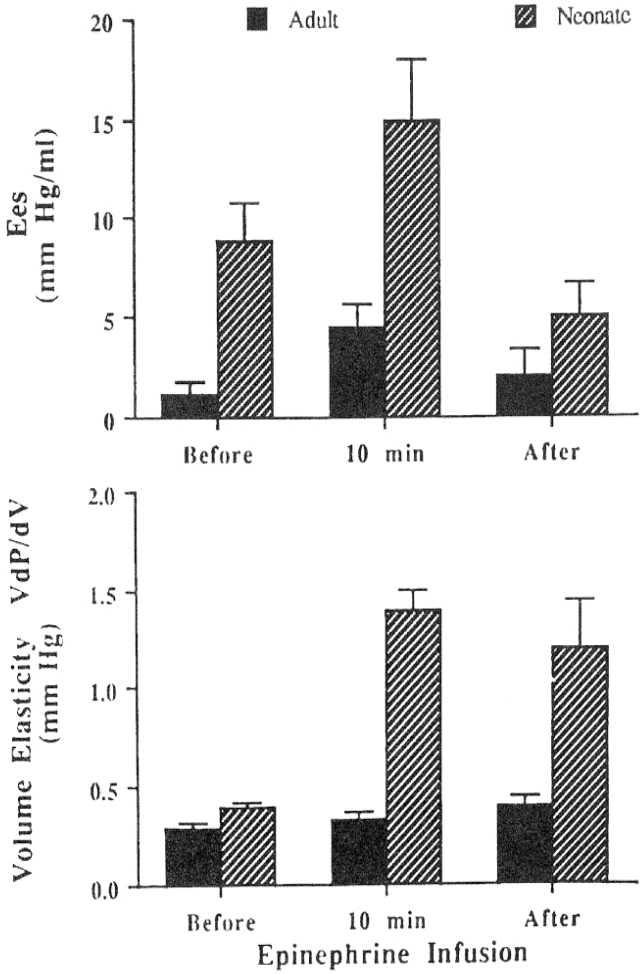
Campbell 2004 J Perin

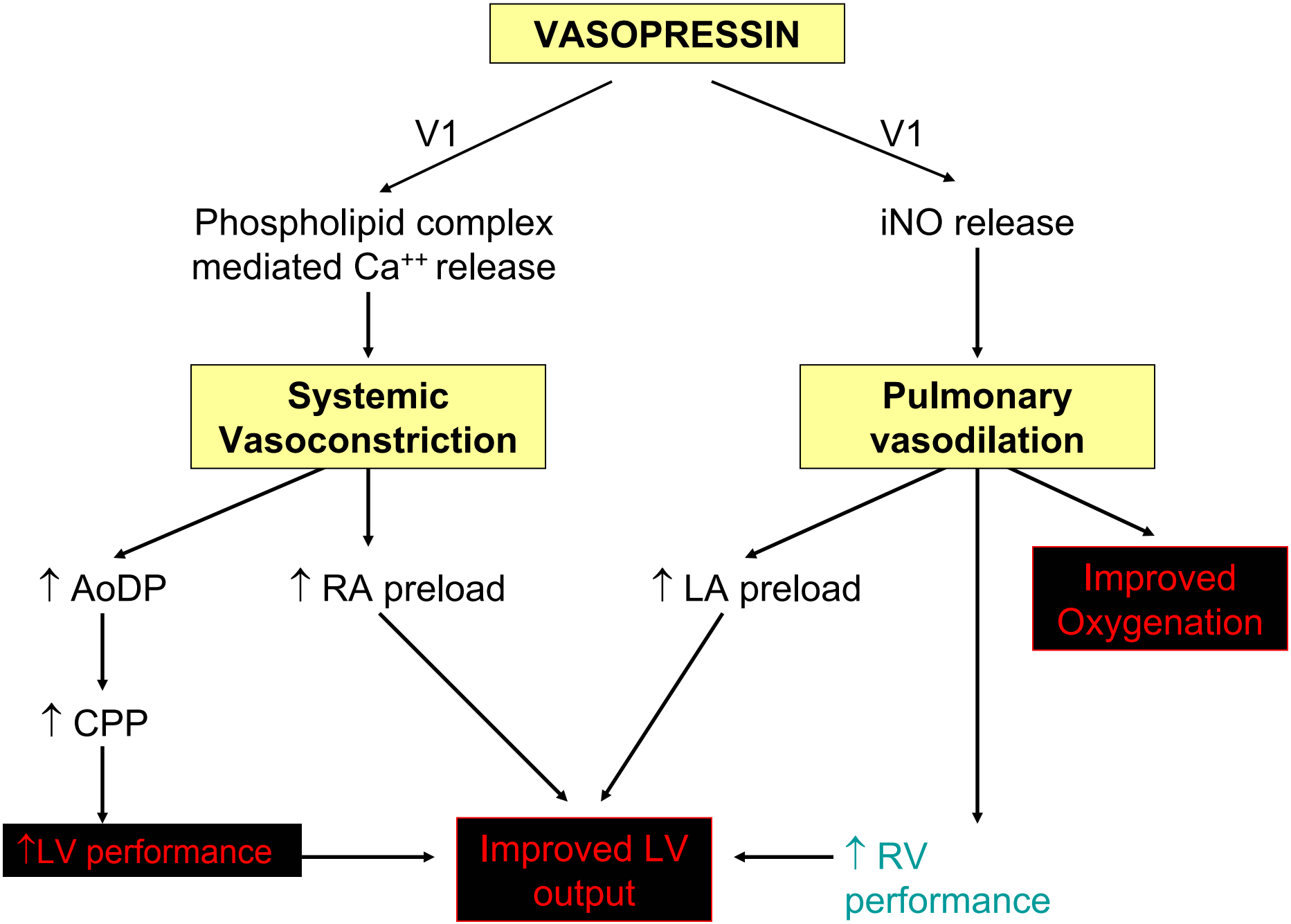
Catecholamine induced myocardial damage

Caspi J Pediatr Res 1994; 36:49-54



Caspi J et al. Circulation 1991; 84:III-394




VASOPRESSIN
V1
V1
Phospholipid complex mediated Ca++ release
iNO release
Systemic Vasoconstriction
Pulmonary vasodilation
↑ AoDP
↑ RA preload
↑ LA preload
Improved Oxygenation
↑ CPP
↑LV performance
Improved LV output
↑ RV performance

Is Vasopressin superior to epinephrine in a neonatal model of asphyxial cardiac arrest?

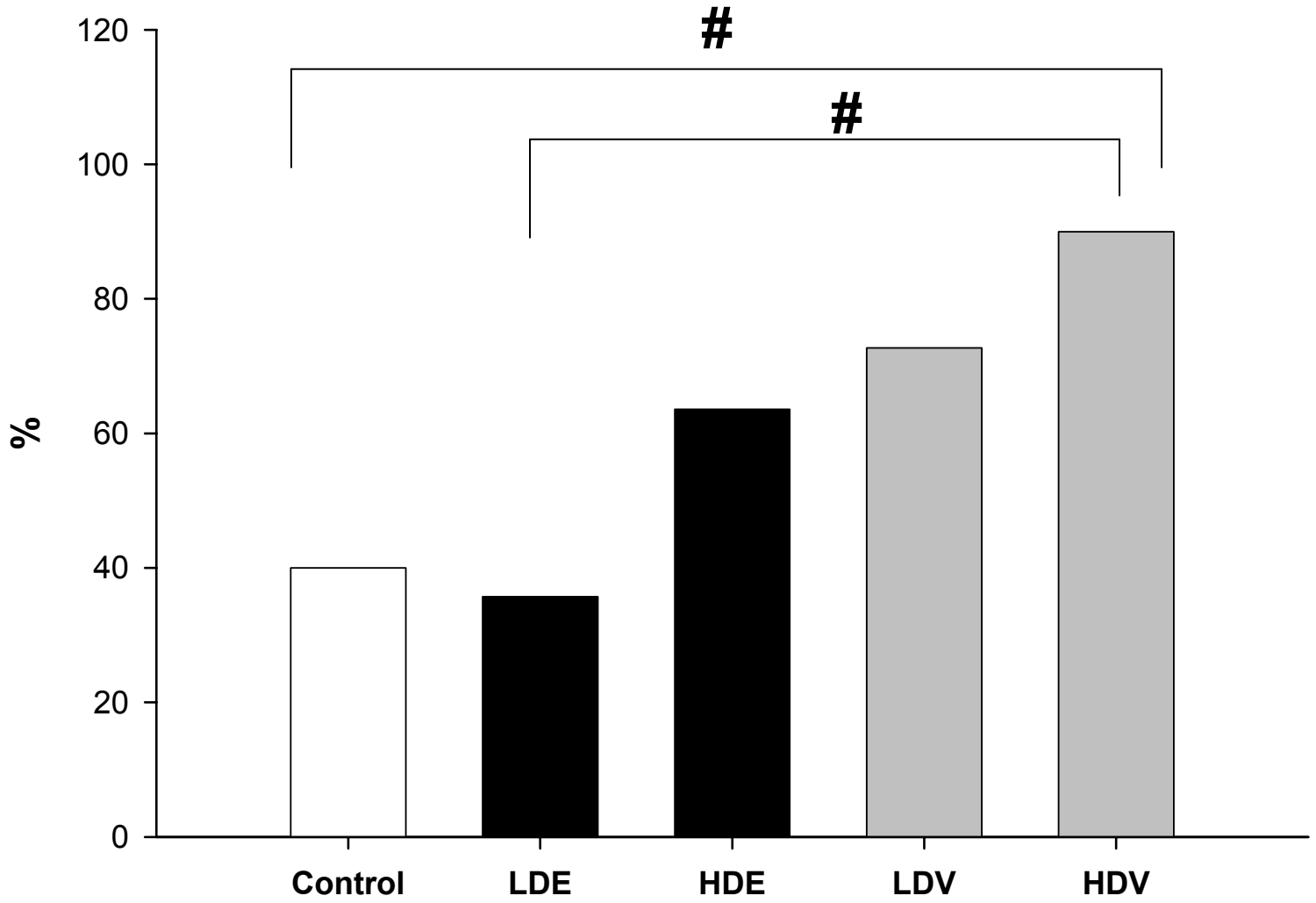
Methods: Study Design

- **Model**: Neonatal Porcine model of Asphyxial Cardiac arrest
- **Standardized Resuscitation**:
  - Single resuscitator performing chest compressions
  - Compression to ventilation rate of 5:1
- **Intervention**: Placebo controlled randomized control trial of single dose Vasopressin vs Epinephrine
  - Block randomization
  - Resuscitation medications prepared in standardized solution to ensure a consistent dose of 0.1 mls/kg administered

Interventions

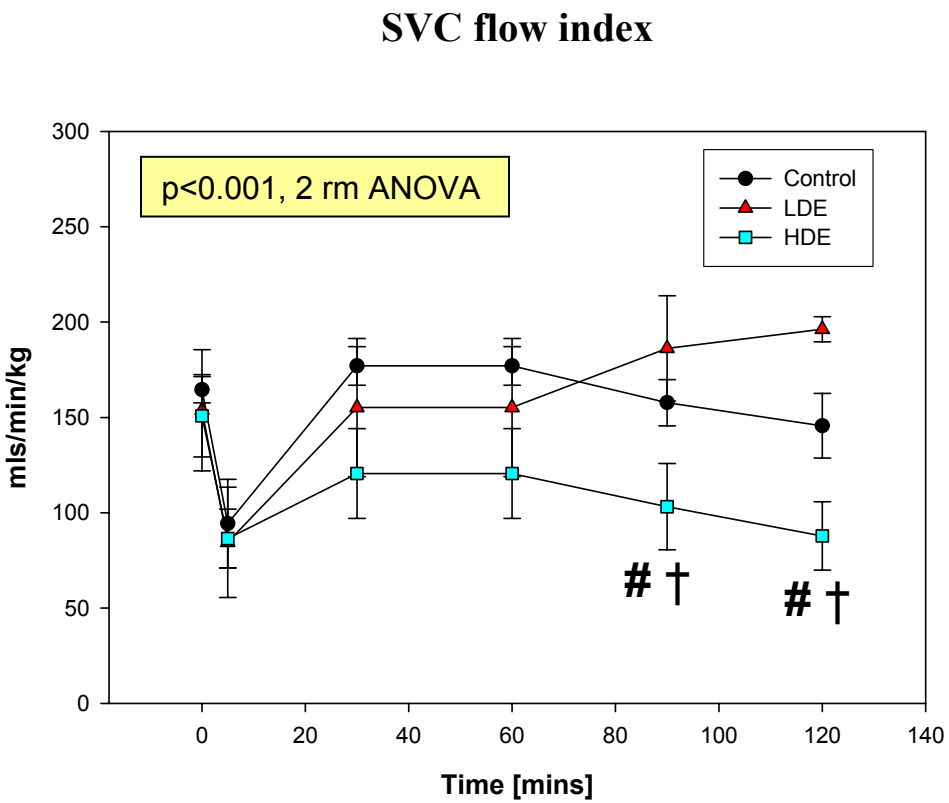
- Placebo (0.9% saline)
- Low-dose epinephrine (LDE) - 0.01 mg/kg
- High-dose epinephrine (HDE) -0.03 mg/kg
- Low-dose vasopressin (LDV) - 0.2 U/kg

Survival rate (%)

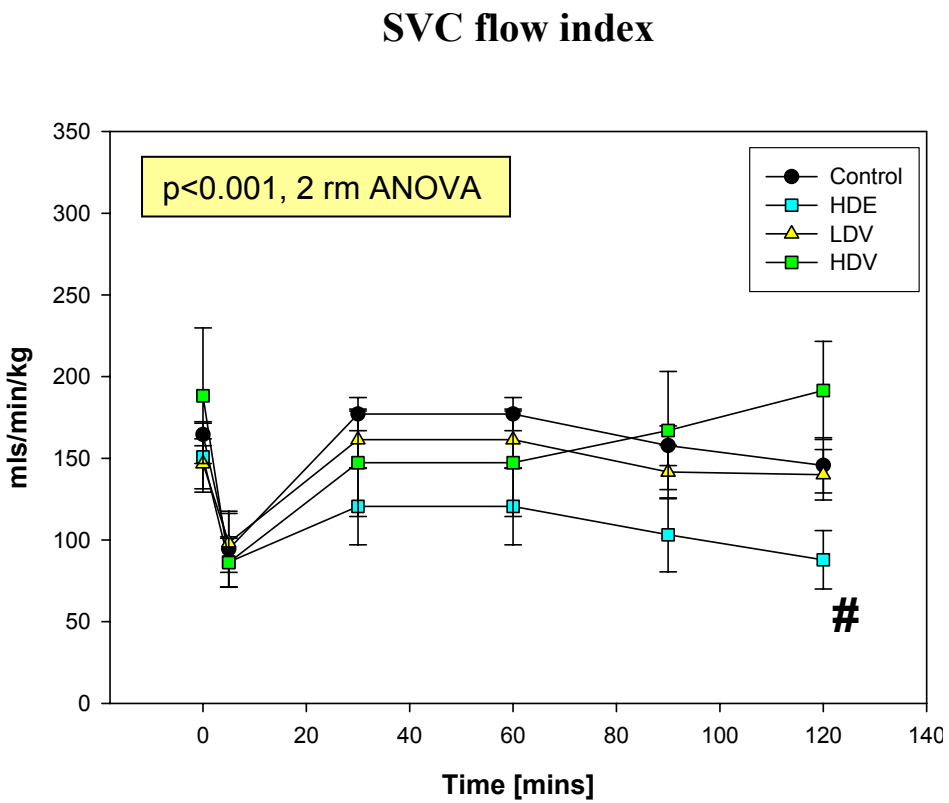


Improved survival with high-dose Vasopressin, p=0.01 ANOVA

SVC Flow



# p < 0.05 vs baseline † p< LDE

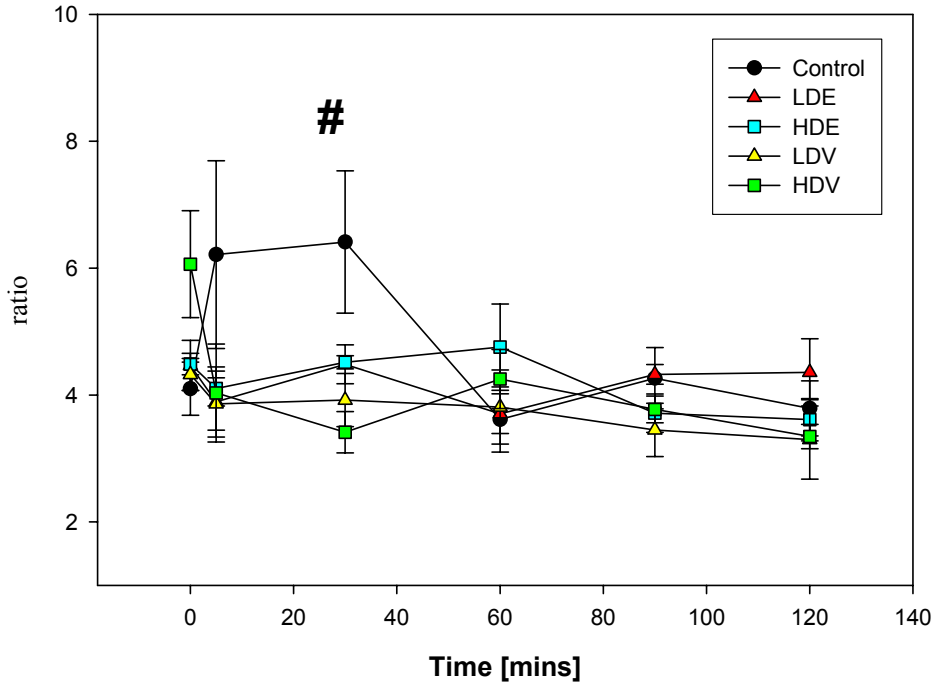


# p < 0.05 vs HDV

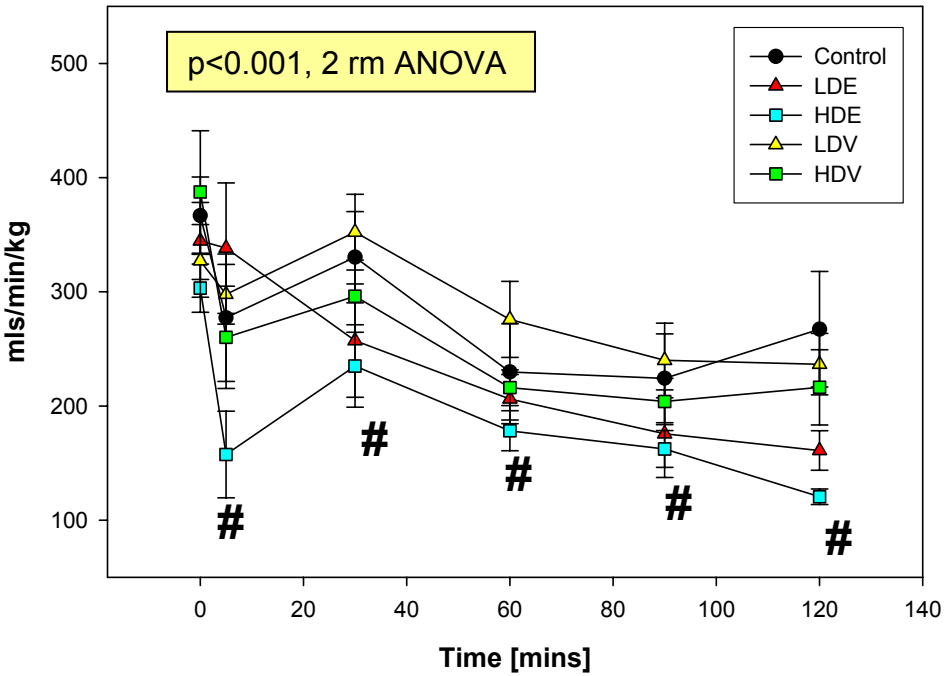
Sustained fall in SVC flow greater in HDE animals *[vs LDE, Control, and HDV (p<0.001 2rm ANOVA)]*

Pulmonary Hemodynamics

PAAT:RVET$_{inv}$



RV index

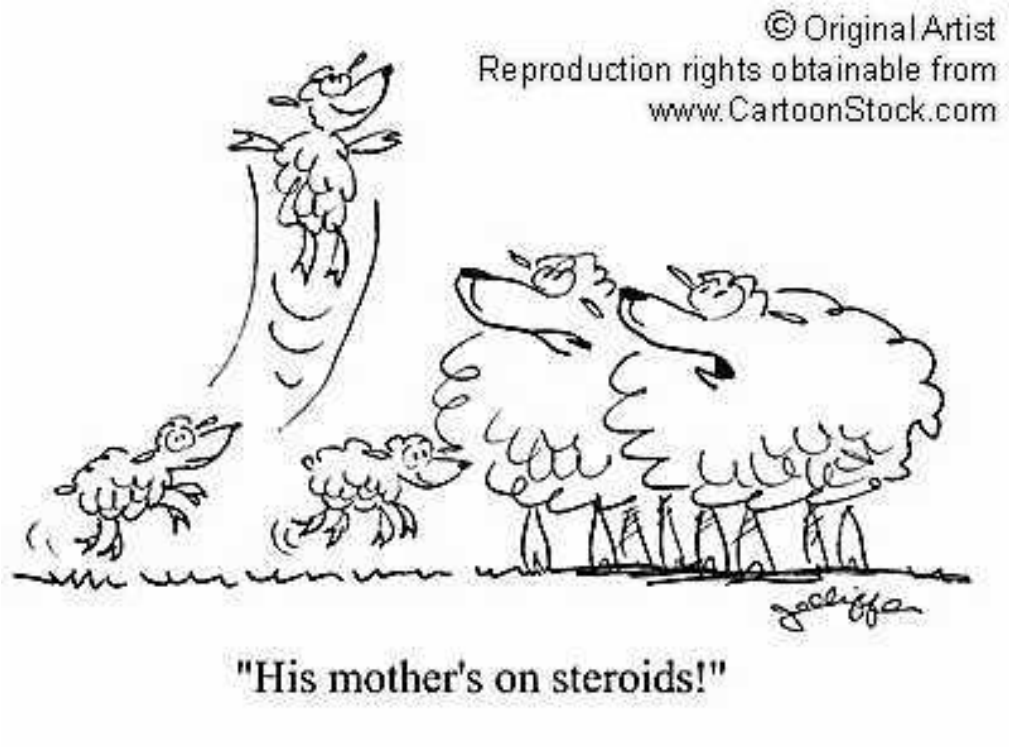


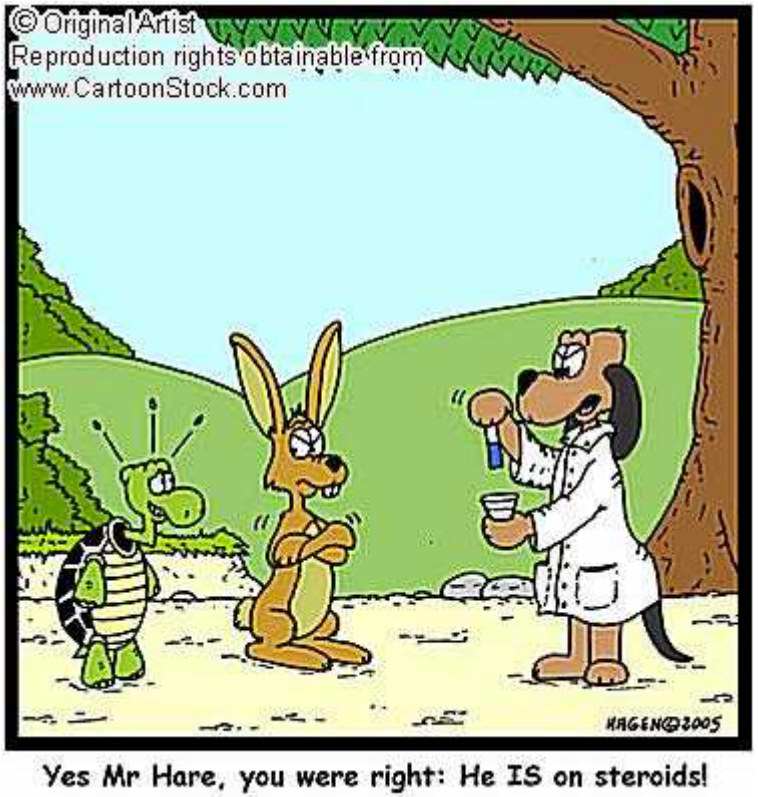
Decrease in RVI in LDE and HDE groups

Summary

- **Improved survival with High-dose Vasopressin** when compared to standard dose epinephrine
- **Epinephrine** associated with increased need for defibrillation, and greater impairment in myocardial performance or systemic blood flow
- **Vasopressin** associated with improved diastolic performance
- Role of vasopressin and defibrillation in neonatal arrest need prospective evaluation

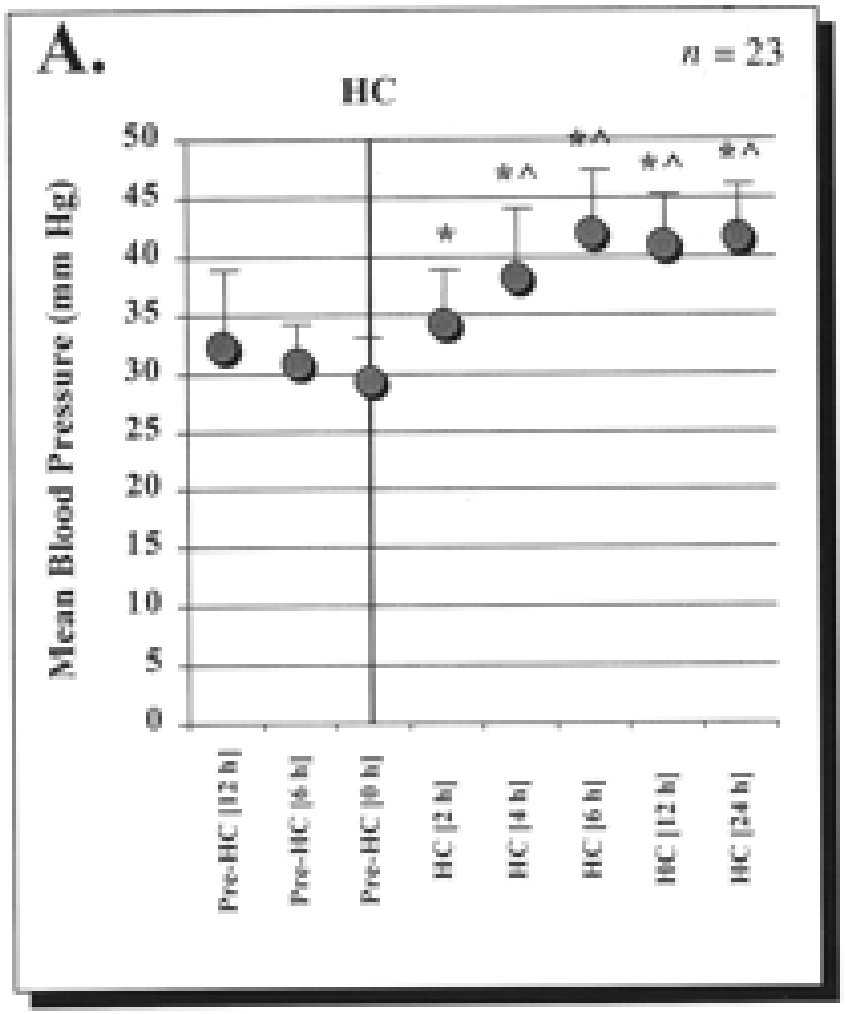
Steroids and the Neonatal Heart
The Quick Fix!

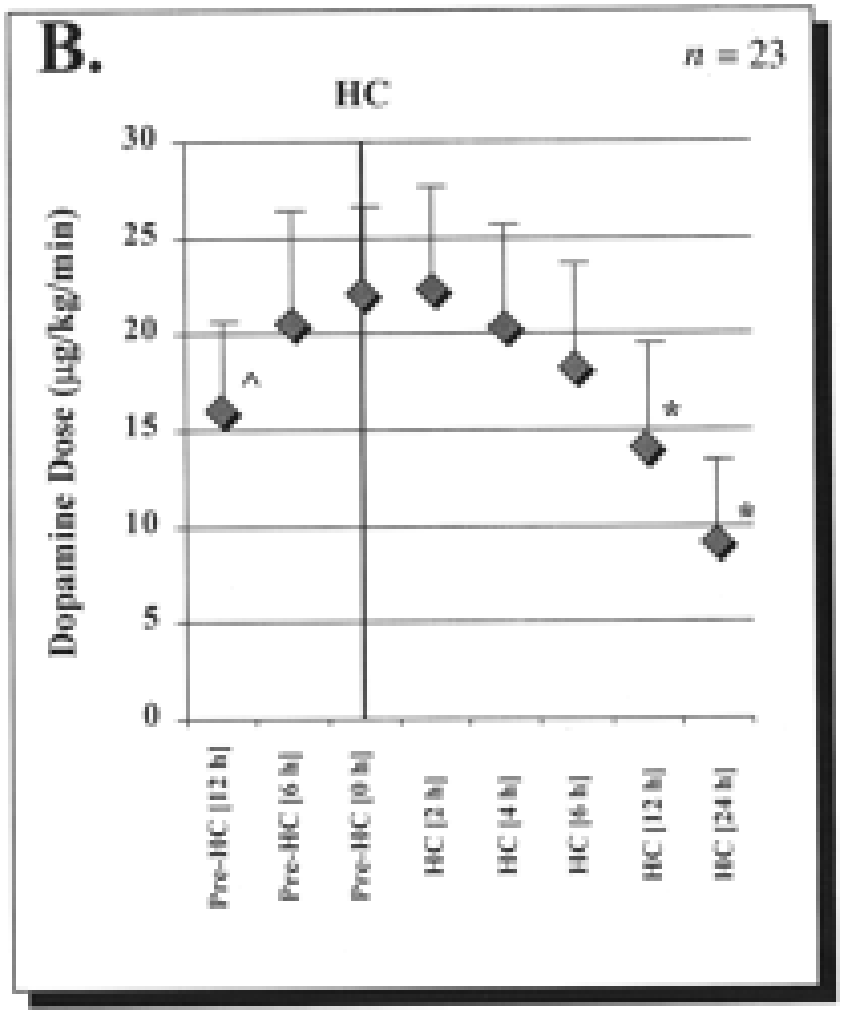




Fix the BP but MASK a low cardiac output state

Effect of hydrocortisone on mean blood pressure and the dose of dopamine during the first 24 hours of hydrocortisone treatment





Seri 2001 Pediatrics

Steroids & Cardiovascular status

- Genomic Effects (hrs)

  Up-regulation of receptors and signaling pathways

- Non-Genomic Effects (hrs)

  Hormone substitution effect
  Inhibit catecholamine metabolism
  Release of vasoactive factors
  Vascular Integrity
  Increase intracellular calcium bioavailability

Myocardial Consequences of Steroids

- Hypertrophic Cardiomyopathy

Werner 1992 Ped Res

- Hypertension

Benediktsson 1993 Lancet

- Myocardial Dysfunction

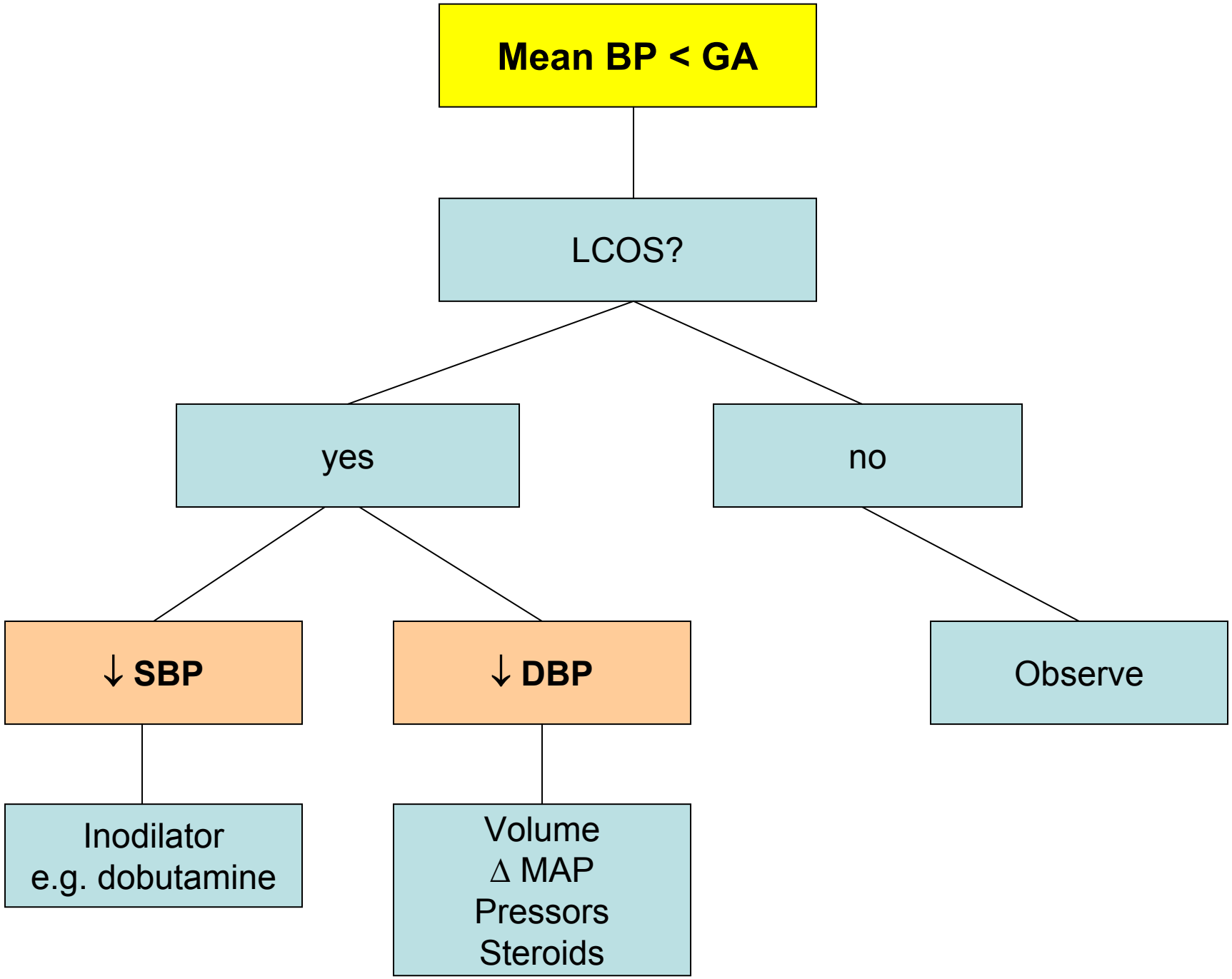
Dodic 2001 Circ Res

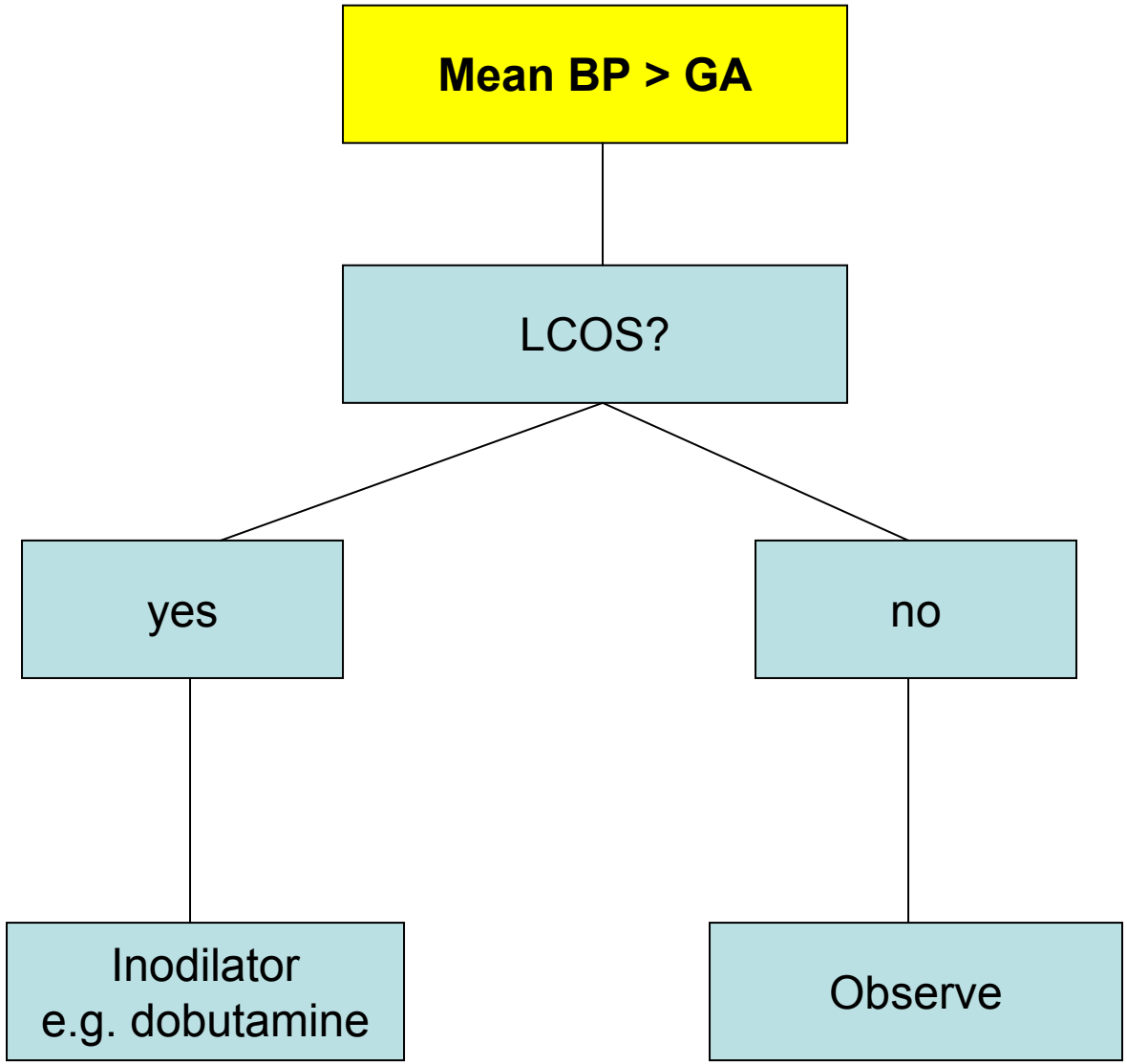
- Predisposition to arrhythmmias

Kauffmann 1994 Ped Res

Approach to the Hypotensive Infant

- Caution when treating “numerical hypotension”
- Is there evidence of suboptimal tissue oxygenation and a “low-perfusion states”
- Choose your intervention based on the nature of the problem & REASSESS
  - Is the problem preload, afterload or myocardial dysfunction
  - Is their evidence of a HSDA (NSAIDs)
  - Is their evidence of CHD (require Pgs)
- Early TnECHO may facilitate refinement of the decision making and assessing response


Mean BP < GA
LCOS?
yes
no
↓ SBP
↓ DBP
Observe
Inodilator
e.g. dobutamine
Volume
Δ MAP
Pressors
Steroids


Mean BP > GA
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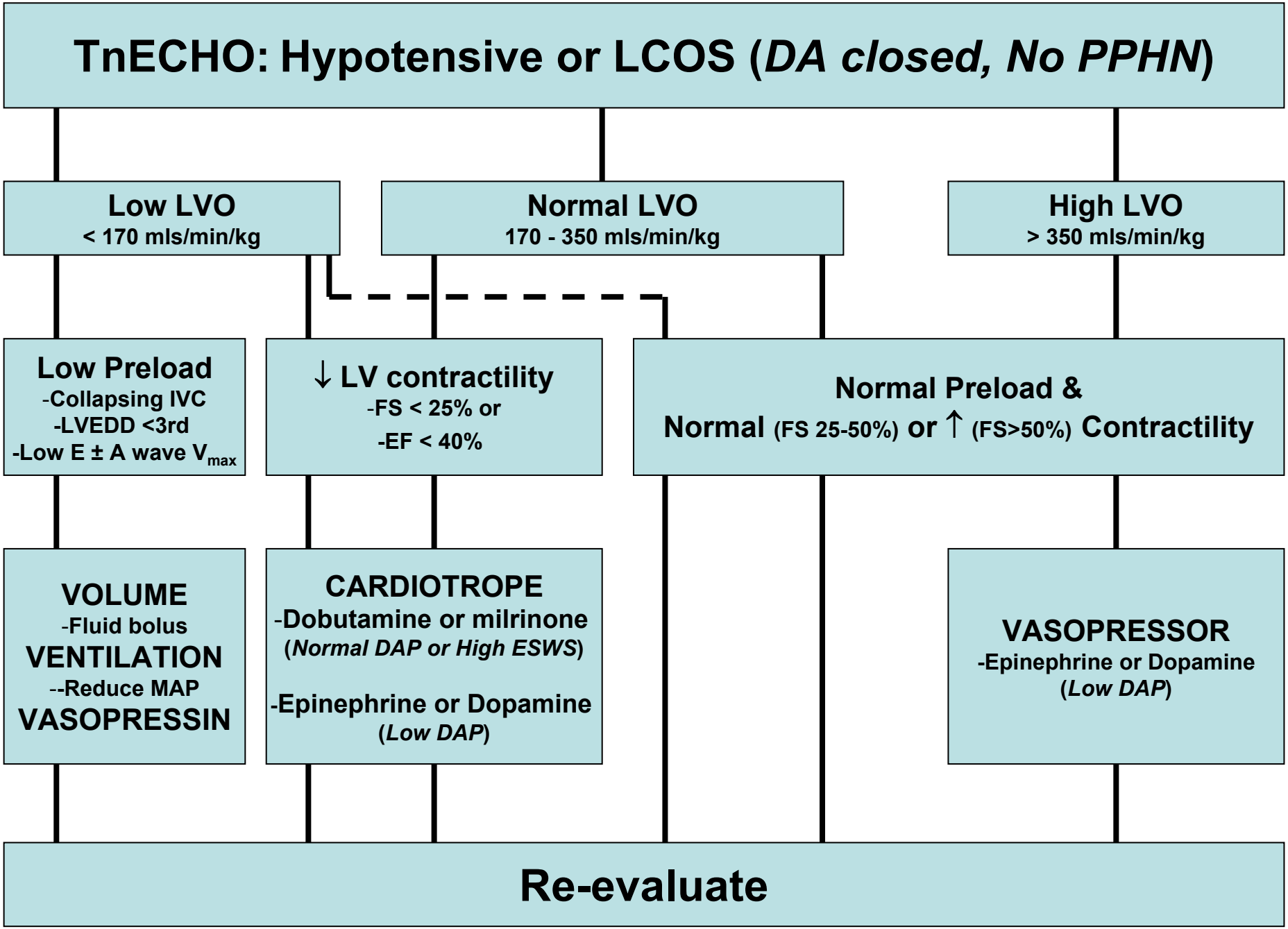
TnECHO: Hypotensive or LCOS (*DA closed, No PPHN*)
Low LVO
< 170 mls/min/kg
Normal LVO
170 - 350 mls/min/kg
High LVO
> 350 mls/min/kg
Low Preload
-Collapsing IVC
-LVEDD <3rd
-Low E ± A wave V_{max}
↓ LV contractility
-FS < 25% or
-EF < 40%
Normal Preload &
Normal (FS 25-50%) or ↑ (FS>50%) Contractility
VOLUME
-Fluid bolus
VENTILATION
--Reduce MAP
VASOPRESSIN
CARDIOTROPE
-Dobutamine or milrinone
(*Normal DAP or High ESWS*)
-Epinephrine or Dopamine
(*Low DAP*)
VASOPRESSOR
-Epinephrine or Dopamine
(*Low DAP*)
Re-evaluate

- Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided.

Philipus A. Paracelcus

German Physician and Chemist

QUESTIONS