Treatment of Systemic Hypotension in Preterm Infants

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Definition

- mean systemic BP of less than an infant's gestational age in completed weeks
- mean BP < 10th centile with respect to birth weight and postnatal age (statistical definition)
- other reference charts

Joint Working Party BAPM and RCP. Arch Dis Child 1992;67:1221-7

Watkins et al. Early Hum Dev 1989;19:103-10

Mechanisms

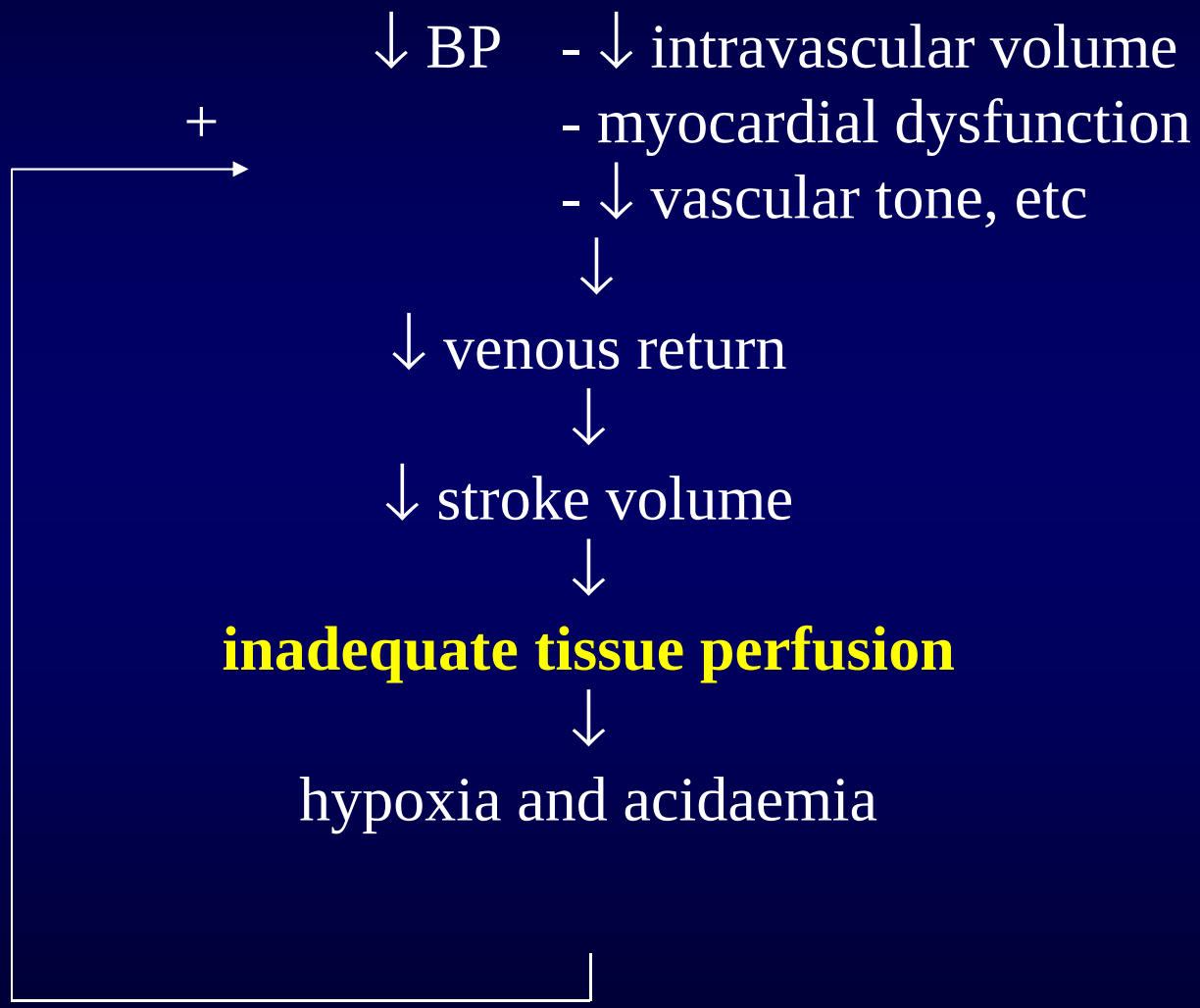
- **Low blood volume**
  - oedematous ill infants loss fluid into subcutaneous tissues or lungs
  - high transepidermal water loss
  - blood removed for biochemical and haematological analysis
  - Haemorrhage
- **Myocardial depression** (hypoxia and acidaemia → myocardial depression → ↓ cardiac output)
- **Hormonal insufficiency** - cortisol

Mechanisms

- **High positive pressure ventilation** (IPPV and HFOV)
  - compromising venous return → ↓ cardiac output
  - splinting of the heart by hyperinflated lungs (external compression)
  - obstructing pulmonary vasculature →↑ R ventricular volume → compresses on L ventricular cavity →↓ L ventricular output

- **Others**
  - hypothermia
  - birth asphyxia
  - infection
  - cardiac problems *e.g.*, PDA, hypoplastic left heart
  - vascular tone deficiency
  - ? chorioamnionitis / funistis (early-onset hypotension)
  - drugs *e.g.*, morphine

Hypotension



Adverse outcomes of hypotension

Many studies have shown that sustained hypotension and hypoxaemia in preterm infants resulted in substantial ↑ in major brain abnormalities such as:

- hyperechoic parenchymal lesions
- intraventricular haemorrhage
- ventriculomegaly

(53% in hypotensive *vs* 8% in non-hypotensive infants)

Adverse outcomes of hypotension

- retrospective review; n = 110
- ELBW (400 – 999 g) infants
- comparing infants with ‘treated hypotension’ (*i.e.*, volume expanders, inotropes and corticosteroids) at the first 72 h of life *vs* those with no hypotension
  - neurodevelopment testing and Bayley assessment
  - multivariate analysis adjusted for socioeconomic status and neonatal morbidity
- ‘treated hypotension’ infants were more likely to have delayed motor development, hearing loss and death

Fanaroff et al. Pediatrics 2006; 117:1131-5

Treatment of hypotension in preterm infants

- Volume replacement (blood, crystalloids, colloids)
- Inotropes (dopamine, dobutamine, adrenaline)
- Hormone replacement therapy (hydrocortisone or dexamethasone)

Inotropes *vs* Volume expansion

Often difficult to distinguish:

Hypovolaemia *vs* Myocardial dysfunction

(and both factors may co-exist)

Inotropes *vs* Volume expansion

- RCT, n = 39, sealed envelopes
- VLBW infants
- 20 ml/kg of plasma protein fraction (PPF) may be given for initial resuscitation
- 4.5% albumin (n = 20) *vs* dopamine (n = 19)

– 20 ml/kg over 30 min	– 5 μg/kg/min
– repeated 2nd dose after 30 min	– ↑ stepwise by 2.5 μg/kg/min every 30 min up to max 10 μg/kg/min
– 9/20 (45%) received PPF initially	– 10/19 (53%) had PPF initially
– 9/20 (45%) responded	– 17/20 (89%) responded

- because a significant proportion of patients were resuscitated with PPF, the study only demonstrated that infants who ***subsequently*** developed hypotension were likely to have myocardial dysfunction

Gill and Weindling. Arch Dis Child 1993;69:284-7

Treatment of low blood volume

Blood transfusion

- especially in infants with Hct < 0.40 or Hb < 12-13 g/dL
- packed cells (15 - 20 ml/kg, over 30-120 min depending on clinical condition)

Caution

- infants with poor cardiac function may not tolerate sudden ↑ in volume expansion
- ? hepatic iron deposition with repeated blood transfusions

Fluid volume *vs* Protein load

- RCT, n = 60
- preterm infants
- 20% albumin (n=20) *vs* FFP (n=20) *vs* 4.5% albumin (n=20)
  - 5 ml/kg - 15 ml/kg - 15 ml/kg
  - infusion rates were 5 ml/kg/h in all groups
- mean ↑ in BP 1 h after the infusion, was significantly lower in infants receiving 20% albumin (i.e. 9% ↑ in 20% albumin *vs* 19% ↑ in FFP *vs* 17% ↑ in 4.5 % albumin)
- the volume infused rather than albumin load is more important in producing a sustained ↑in BP

Emery et al. Arch Dis Child 1992;67:1185-8

Colloids *vs* Crystalloids (Adults)

- meta-analysis
- 37 RCTs with 1622 patients
- resuscitation with colloids were associated with an increased risk of mortality (4 extra deaths for every 100 patients resuscited)

Schierhout and Roberts. BMJ 1998;316:961-4

Colloids vs Crystalloids (Adults)

- meta-analysis
- 105 articles reviewed in which 17 (814 critically ill patients) were selected
- no overall differences in:
  - pulmonary oedema
  - mortality
  - duration of hospital stay
- subgroup analysis revealed that isotonic crystalloid resuscitation is associated with a lower mortality in trauma patients

Choi et al. Crit Care Med 1999;27:200-9

Colloids vs Crystalloids (All groups)

- meta-analysis
- 30 RCTs with 1419 critically ill patients
- the risk of death in the albumin treated group was higher than in the crystalloid group
- for every 100 patients treated with albumin, there are 6 additional deaths

Cochrane Injuries Group Albumin Reviewers. BMJ 1998;317:235-40

Proposed mechanisms:

- anticoagulant properties:
  - inhibiting platelets aggregation
  - enhancing inhibition of Factor Xa by antithrombin III

    may be detrimental to critically ill patients with haemorrhagic hypovolaemia

- albumin leaks across the capillary membrane into the extravascular spaces and results in worensing oedema

Colloids vs Crystalloids (Preterm infants)

- RCT, n = 63
- gestations: 23-34 wks; BW:540-1950g
- Normal saline (n = 31) *vs* 5% albumin (n = 32)
  - 10 ml/kg of the test solution
  - a total of 3 infusions (i.e. 30 ml/kg)
- no difference in outcome as assessed by:
  - no. of infants requiring subsequent inotropic support
  - chronic lung disease
  - death
- 5% albumin group
  - required significantly more volume expander to maintain a normal BP (median 27.5 ml/kg *vs* 10 ml/kg)
  - had high mean % weight gain within the first 48 h
- normal saline was as effective as 5% albumin for treating hypotension BUT it is much cheaper and caused less fluid retention

So et al. Arch Dis Child 1997;76:F43-6

Colloids *vs* Crystalloids *vs* Hydroxyethyl starch

- RCT, n = 21
- gestations: 29 (± 3) wks

	Normal saline	*vs*	5% albumin	*vs*	Hydroxyethyl starch
Mean aortic flow velocity (m/sec) after 10 min of infusion (p = 0.79)	0.03 (-0.03 to 0.12)		0.05 (-0.02 to 0.07)		0.03 (-0.04 to 0.11)
BP normalization (%) (p = 0.50)	57% (20 - 94%)		86% (60 - 100%)		71% (37 - 100%)

- no evidence that hydroxyethyl starch was superior

Liet et al. Acta Paediatr 2006;95:555-60

Dopamine *vs* Dobutamine

- case series, n = 12
- preterm infants
- all 12 infants responded when the infusion rate was 10 μg/kg/min
- dobutamine failed to raise the mean BP in 7 who relapsed
- recommended to start dopamine at a rate of 10 μg/kg/min in order to avoid delay in treatment

Miall-Allen and Whitelaw. Crit Care Med 1989;17:1166-9

Dopamine *vs* Dobutamine

- RCT, n = 40
- gestational age: 23-33 wks
- patients with hypotension despite colloid expansion
- dopamine (n = 20) *vs* dobutamine (n = 20)
  - starting dose 5 μg/kg/min
  - increased over 3 h to 15 μg/kg/min
- infants receiving dopamine had significantly higher median systolic BP (39 mmHg *vs* 34 mmHg in the dobutamine group)

Greenough and Emery. Eur J Pediatr 1993;152:925-7

Dopamine *vs* Dobutamine

- RCT, n = 20
- gestational age < 32 wks
- dopamine (n = 10) *vs* dobutamine (n = 10)
  - starting dose 5 μg/kg/min
  - increased in increment of 5 μg/kg/min
  - maximum rate of 20 μg/kg/min
- all 10 infants were successful in achieving BP ≥ 31 mmHg after treatment with dopamine, whereas 6 of 10 infants failed in the dobutamine group

Roze et al. Arch Dis Child 1993;69:59-63

Dopamine *vs* Dobutamine

- RCT, n = 63
- gestational age ≤ 34 wks with RDS
- dopamine (n = 31) *vs* dobutamine (n = 32)
  - starting dose 5 μg/kg/min
  - increased in increments of 5μg/kg/min
  - maximum rate of 20 μg/kg/min
- no infants in the dopamine group failed to maintain a BP ≤ 30 mmHg after treatment, whereas 5 of 32 infants (16%) failed in the dobutamine group
- the increase in mean arterial BP was significantly higher in the dopamine group (11.3 mmHg *vs* 6.8 mmHg)

Klarr et al. J Pediatr 1994;125:117-22

Inotropes

Dopamine has been shown to be more effective than dobutamine in raising blood pressure in neonates

Short et al. Pediatrics 2006;117:S34-9

Dopamine *vs* Adrenaline

- RCT, n = 60
- gestations < 32 weeks; BW < 1,501 g

	Dopamine (n = 28)	*vs*	Adrenaline (n = 32)
Doses:	2.5 – 10 µg/kg/min		0.125 – 0.5 µg/kg/min
Increment:	↑ stepwise every 20 min		
Treatment failure:	36%		37%
Withdrawal of inotropes:	66 (± 28) h*		38 (± 20) h
Insulin usage:	12%		45%*

- other medium term outcomes e.g. PDA, BPD, NEC, GI complications, sepsis, severe ROP and mortality were not significantly different between groups
- Conclusions: dopamine (low/moderate dose) was as effective as adrenaline (low-dose) for treatment of hypotension in VLBW infants BUT adrenaline was associated with more transient adverse effects

Valverde et al. Pediatrics 2006;117:e1213-22

BP

Pulse rate

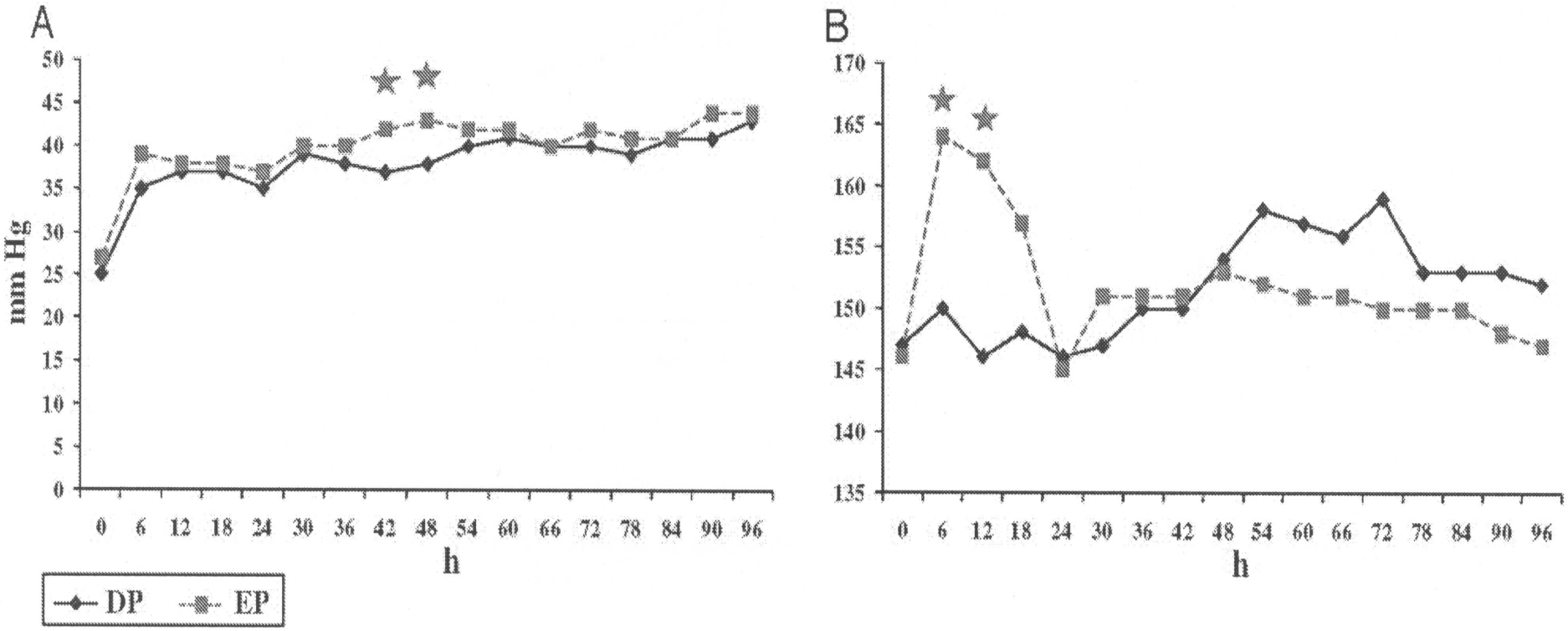


FIGURE 1

Changes in MBP (A) and heart rate (B) throughout the first 96 hours of life, evaluated from baseline, before giving the inotrope (time 0) and then every 6 hours. Only responders. Star indicates $P < .05$.

HPA axis

- hypothalamus, pituitary and adrenal glands are dynamic endocrine organs during fetal development
- adrenal glands, in particular, exhibit remarkable transformation in size, morphology and function during the perinatal and early neonatal periods

Mesiano and Jaffe. Endocr Rev 1999

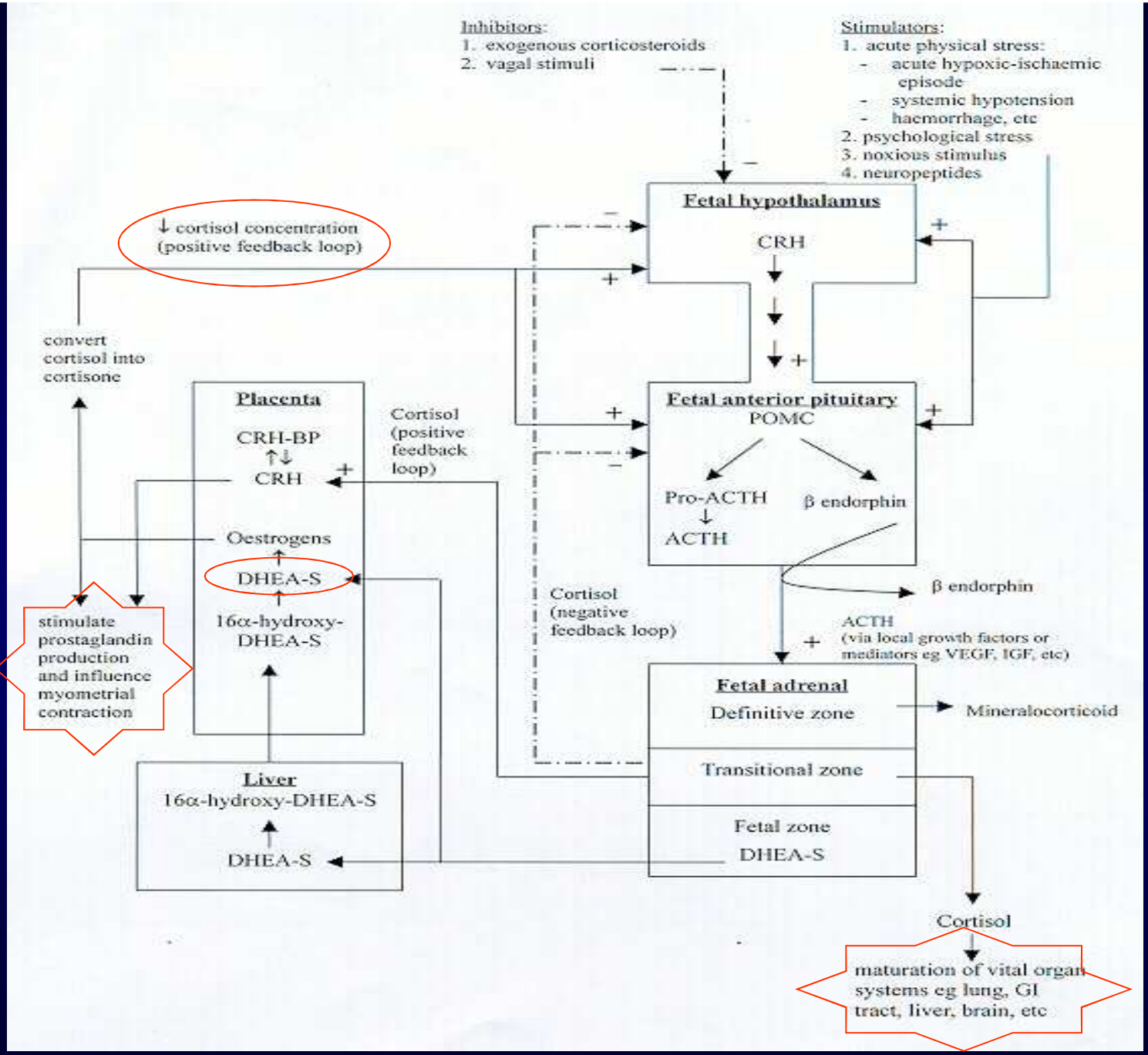
Ng. Arch Dis Child 2000

HPA axis

Normal development of the hypothalamic-pituitary-adrenal (HPA) axis is essential for:

- regulation of intrauterine homeostasis
- influences the timing of parturition
- timely differentiation and maturation of vital organ systems

Mesiano and Jaffe. Endocr Rev 1999
Ng. Arch Dis Child 2000



Ng et al. Arch Dis Child 2000

Adrenocortical insufficiency of newborns

- no evidence of clinical adrenocortical insufficiency in term infants, despite dramatic remodeling of the adrenal cortex immediately after birth

- ill and extremely premature infants (*esp*. < 1000 g) may have decreased ability to produce adequate amount of glucocorticoids

HPA axis immaturity

Elevated steroid precursors in preterm infants, including:

- ↑17-hydroxypregnenolone
- ↑17-hydroxyprogesterone (17-OHP)
- ↑dehydroepiandrosterone (DHEA)

+

low serum cortisol levels in stressed sick preterm infants

↓

indicating immaturity of adrenal enzyme activity and inadequate adrenal reserve for stress

Lee et al. J Clin Endocrinol Metab 1989

HPA axis immaturity

Sick premature infants,
< 30 weeks gestation (n = 25)
↓
markedly ↑ basal level of steroid precursors:
- 17-hydroxypregnenolone (x 7 fold)
- 17-hydroxyprogesterone (x 18 fold)
- 11-deoxycortisol (x 8 fold)
↓ ← ACTH test (36 µg/kg)
↓ poststimulation cortisol
+
↑ precursors /cortisol ratios
↓
suggests adrenal insufficiency
secondary to ↓ activity of 11β-hydroxylase

Hingre et al. J Clin Endocrinol Metab 1994

HPA axis immaturity

VLBW infants, < 32 weeks gestation (n = 67)

↓

low circulating basal ACTH and cortisol levels

↓← $^{1\text{-}24}$ ACTH test (0.1 μg/kg)

only 36% responded to ACTH stimulation

(serum cortisol < 414 nmol/L or 15 μg/dL)

↓

↑ 11-deoxycortisol /cortisol ratio

↓

suggests delayed maturation of

adrenal enzyme

(↓ 11β-hydroxylase activity)

↓

physiologically inadequate circulating cortisol

in stressed VLBW infants

Korte et al. J Pediatr 1996

Corticosteroids ***(Animal studies)***

1. significant ↑ in mean arterial pressure during cortisol infusion in preterm ovine fetuses

Wood et al. Am J Physiol 1989

2 (a) an association between early cardiovascular dysfunction and impaired urinary cortisol excretion in premature baboons, and

(b) a significant improvement in cardiovascular function 4-6 h after hydrocortisone replacement

Yoder et al. Pediatr Res 2002

Refractory hypotension in preterm infants

- very preterm (< 28 gestation weeks)
- extremely low birth weight infants (< 1000 g)
- severe hypotension
- occurs within the first week (days) of life
- refractory to conventional treatment of volume expansion and inotropic support
- responds readily to systemic corticosteroids (hydrocortisone and dexamethasone) treatment
- suspects to have 'adrenocortical insufficiency' (with intact pituitary function)

Helbock et al. Pediatrics 1993
Fauser et al. Eur J Pediatr 1993
Ng et al. Arch Dis Child 2001
Seri et al. Pediatrics 2001

Results (Adrenal)

***Cortisol* and inotropes or volume expanders**

Basal and peak serum cortisol at day 7 were ***negatively*** associated with:

- dopamine (maximum and total cumulative dose)
- dobutamine
- adrenaline
- volume of crystalloid
- duration of inotropic support

Results

Multivariate analysis (generalised additive model)

Basal and peak serum cortisol remained significantly associated with:

- the lowest systolic, mean and diastolic BP ($p < 0.0001$)
- duration of inotropic support ($p < 0.05$)

Table 3: Percentile table of serum cortisol concentrations at day 7 in preterm infants with 'normal' blood pressure (Group 1) and hypotensive infants requiring inotropic support (Group 2)

	Group 1 (n = 54)				Group 2 (n = 71)			
Percentile	**0 min**	**15 min**	**30 min**	**60 min**	**0 min**	**15 min**	**30 min**	**60 min**
3rd	99	192	270	223	43	86	131	117
10th	142	254	340	286	70	128	185	165
25th	206	338	431	366	115	191	261	235
50th	311	464	561	483	198	299	384	347
75th	470	637	730	637	343	467	564	514
90th	680	848	925	817	560	697	797	730
97th	979	1123	1168	1044	909	1034	1121	1033

Results are serum cortisol concentrations (nmol/L)

Ng et al. Arch Dis Child 2004

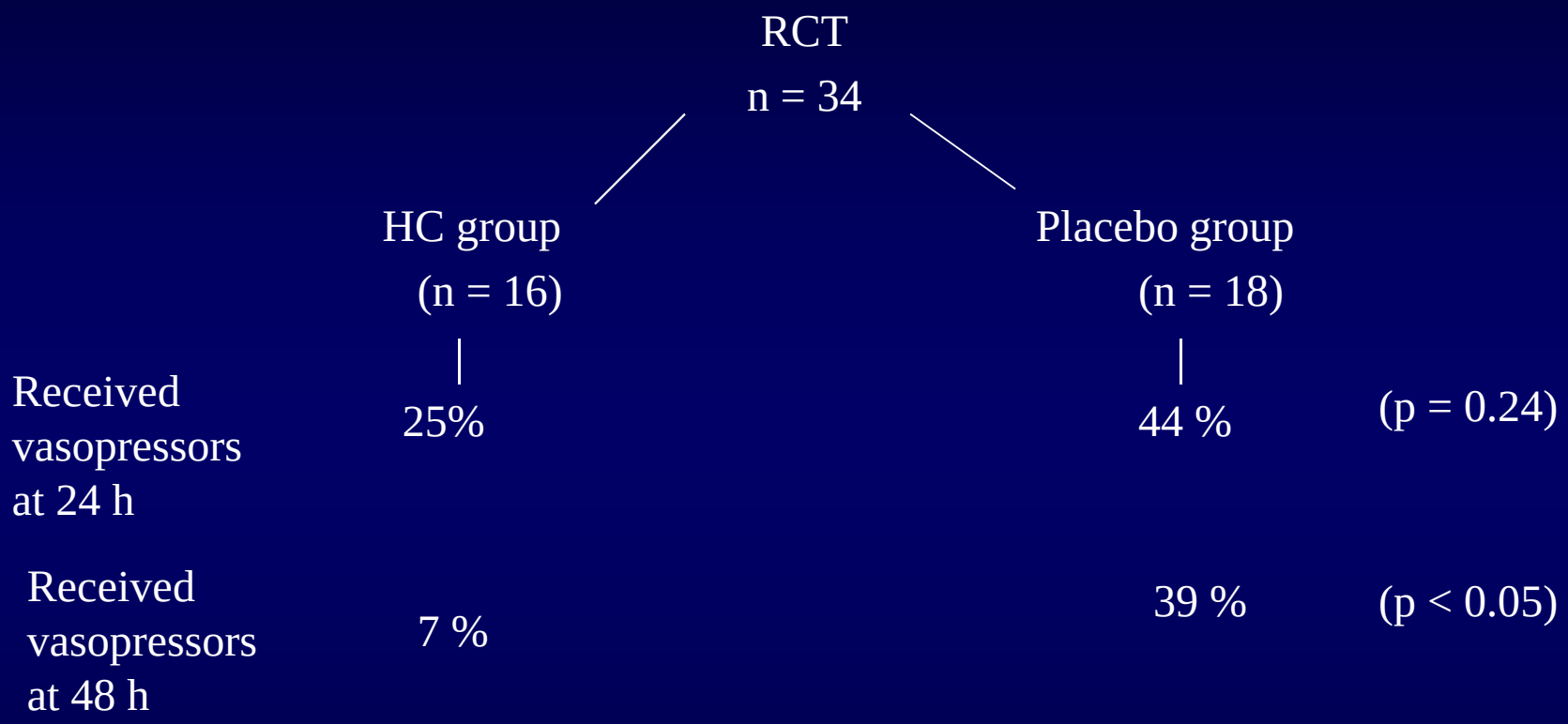
RCT

Preterm 28 weeks gestation (median),
BW 690 g (median)
severe hypotension requiring adrenaline
(on day 2)

dexamethsone (0.25 mg/kg)	saline
n = 8	n = 9
adrenaline infusion was discontinued within 12 h in:	
• 5 of 8 infants	• 1 of 9 infants
	← rescue dexamethasone
	5 of 8 infants weaned off adrenaline 1-7 h later

Gaissmaier and Pohlandt. J Pediatr 1999

RCT of prophylactic hydrocortisone for prevention of hypotension in ELBW infants



Note: 3 infants in the placebo group received dobutamine

Note: 1 infants in the HC group had gastric perforation on day 6

Conclusions: prophylactic hydrocortisone treatment reduced the use of vasopressors for treatment of hypotension

Efird et al. J Perinatol 2005

RCT of a ‘stress-dose’ of hydrocortisone for rescue treatment of refractory hypotension in preterm infants

RCT
Infants with refractory hypotension
≥ 30 ml/kg isotonic saline
≥ 10 µg/kg/min dopamine
(n = 48)

	HC group (n = 24)	Placebo group (n = 24)	
Weaned off vasopressor after 72 h of treatment	19 (79 %)	8 (33 %)	(p = 0.001)
Median duration of vasopressor support	39 (28-64) h	81 (47-136) h	(p = 0.001)
Use of ≥ 2 vasopressors	2	11	(p = 0.009)
Use of dopamine	↓↓	-	(p < 0.001)
Use of dobutamine	↓↓	-	(p = 0.002)
Use of volume expanders	↓	-	(p = 0.022)
Mean arterial BP	↑↑	-	(p = 0.001)

Note: no spontaneous gastrointestinal perforation in either group, despite 80% of patients received prophylactic indomethacin treatment, and routine prophylactic proton pump inhibitor was given to all enrolled patients

Note: median [cortisol] < 115 nmol/L (4.17 μg/dL) or < 10th percentile

Note: HC-treated infants had significantly more glycosuria ($p = 0.029$)

Conclusions:

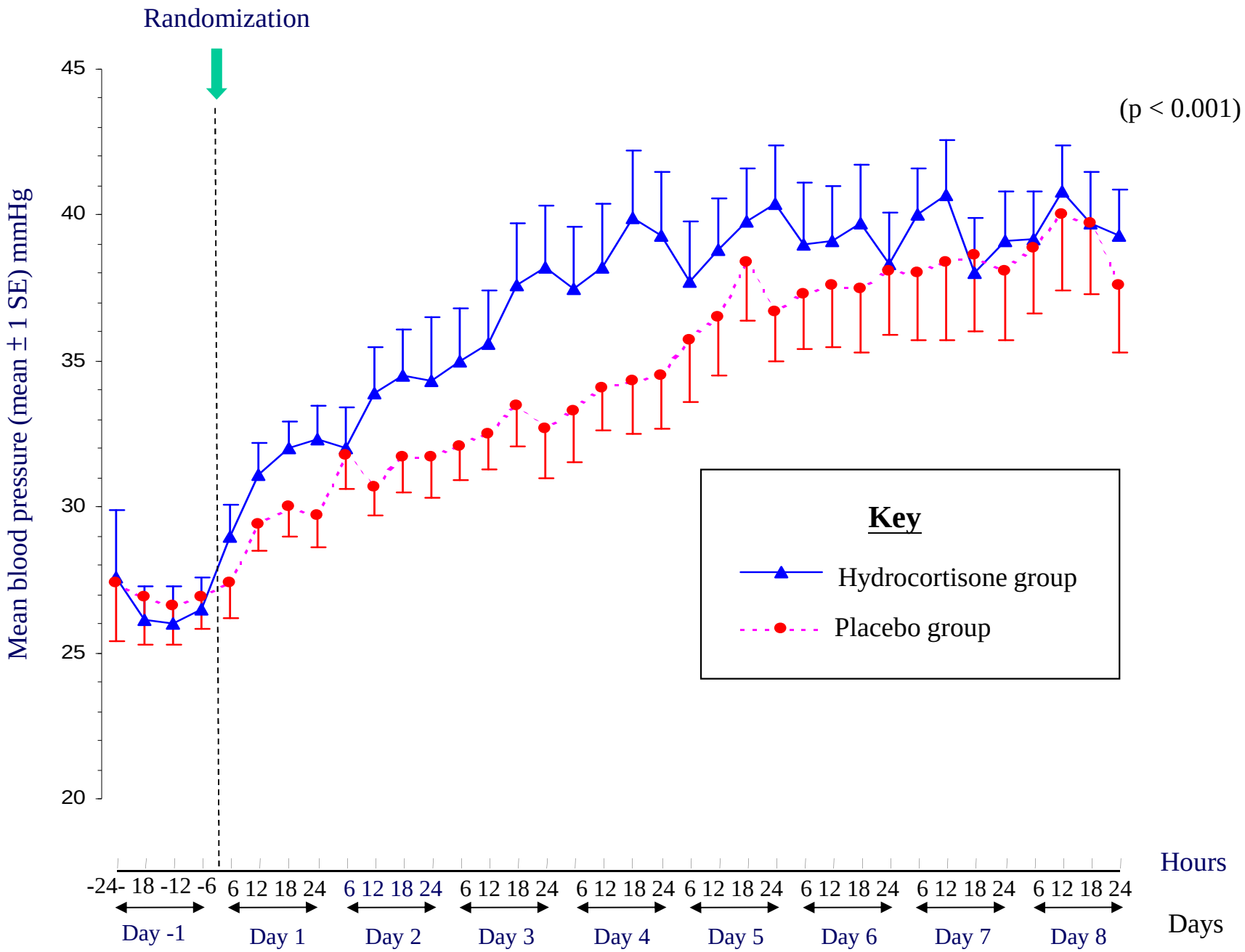
1. a 'stress-dose' of hydrocortisone was effective for treating refractory hypotension and TAP

2. decreased the use of vasopressors and volume expanders for BP support

3. ? proton pump inhibitor for prevention of GI perforation

Ng et al. Pediatrics 2006

Figure


Randomization
(p < 0.001)
Mean blood pressure (mean ± 1 SE) mmHg
45
40
35
30
25
20
Key
Hydrocortisone group
Placebo group
-24- 18 -12 -6 6 12 18 24 6 12 18 24 6 12 18 24 6 12 18 24 6 12 18 24 6 12 18 24 6 12 18 24 6 12 18 24
Hours
Day -1
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Days

Low-dose dexamethasone for treatment of refractory hypotension (retrospective study)

- retrospective study; n = 24
- gestations: 26 (23 – 34) wks; BW: 801 (457 – 1,180 g)
- refractory hypotension
  - after volume resuscitation
  - combined dopamine and dobutamine > 30 μg/kg/min
- low-dose dexamethasone:

  0.1 mg/kg → 0.05 mg/kg every 12 h for 5 doses
- Results
  - BP responded 2 h after drug administration from 30 (± 5) mmHg to 34 (± 6) mmHg
  - inotrope requirement ↓ 6 h after treatment from 34 (± 9) to 24 (± 13) μg/kg/min
  - urine output increased in the first 6 h of treatment
- Conclusions: low-dose dexamethasone rapidly ↑ BP and ↓ inotrope requirement in VLBW infants

Noori et al. Biol Neonat 2006;89:82-7

Inhaled corticosteroids on systemic BP (RCT)

RCT for RDS
(data extracted from previous RCT)
- inhaled fluticasone (500 µg every 12 h)
(n = 53)

	IF group (n = 27)	Placebo group (n = 26)	
Use of volume expanders	↓↓	-	(p = 0.001)
Use of dopamine	? ↓	-	(p = 0.10)
Post-treatment [cortisol]	↓↓	-	(p = < 0.001)

Conclusion: IF-treated infants required significantly less volume expanders (? also a trend for less inotropes usage) for BP support

Ng et al. Biol Neonate 2004

Mechanisms

- corticosteroids have the ability to ↑ the density of β-adrenergic receptors within a few hours of drug administration
- corticosteroids can reverse the desensitisation effect of prolonged catecholamine exposure on the receptors
- corticosteroids can ↑ angiotensin 2 (type 1) receptor gene expression of the myocardium

Davies and Lefkowitz. J Clin Endocrinol Metab 1980
Brodde et al. Eur Heart J 1989
Segar et al. Pediatr Res 1995

Postnatal steroid survey

- retrospective survey of cohorts
- California Perinatal Quality Care Collaborative - via Verment Oxford Network data (expanded data)
- 1,401 VLBW infants representing about one-third of the cohort

Results:

- postnatal corticosteroids were used in 19.3% of infants
  - BPD (3.6%)
  - non-BPD *e.g.*, hypotension, stridor, etc (11.8%)
  - both BPD and non-BPD indications (4%)
- postnatal corticosteroids used exclusively for hypotension had
  - ↑ IVH
  - ↑ PVL
  - ↑ mortality

  compared with those treated for BPD or did not receive the treatment

- ***Conclusions***: prospective studies evaluating **long-term benefits** are warrented

Finer et al. Pediatrics 2006;117:704-13

Conclusions (*TAP and BP)*

- characterised the endocrinological abnormalities of ‘Transient Adrenocortical insufficiency of Prematurity’ (TAP) in hypotensive preterm infants:
  - normal or exaggerated pituitary response
  - adrenocortical insufficiency (within the first week)
  - good recovery of adrenal function by day 14
- demonstrated a significant relation between serum cortisol and BP (*positive*) or inotropes/volume expanders (*negative*) at day 7
- provided percentiles for serum cortisol concentrations at day 7 in preterm infants with normal blood pressure and hypotensive infants requiring inotropic support
- a short course of corticosteroids is probably justified in patients with refractory hypotension
- long-term follow-up data are urgently needed for corticosteroids treatment of hypotension