Persistent Pulmonary Hypertension of the newborn (PPHN)

Persistent Fetal Circulation (PFC)

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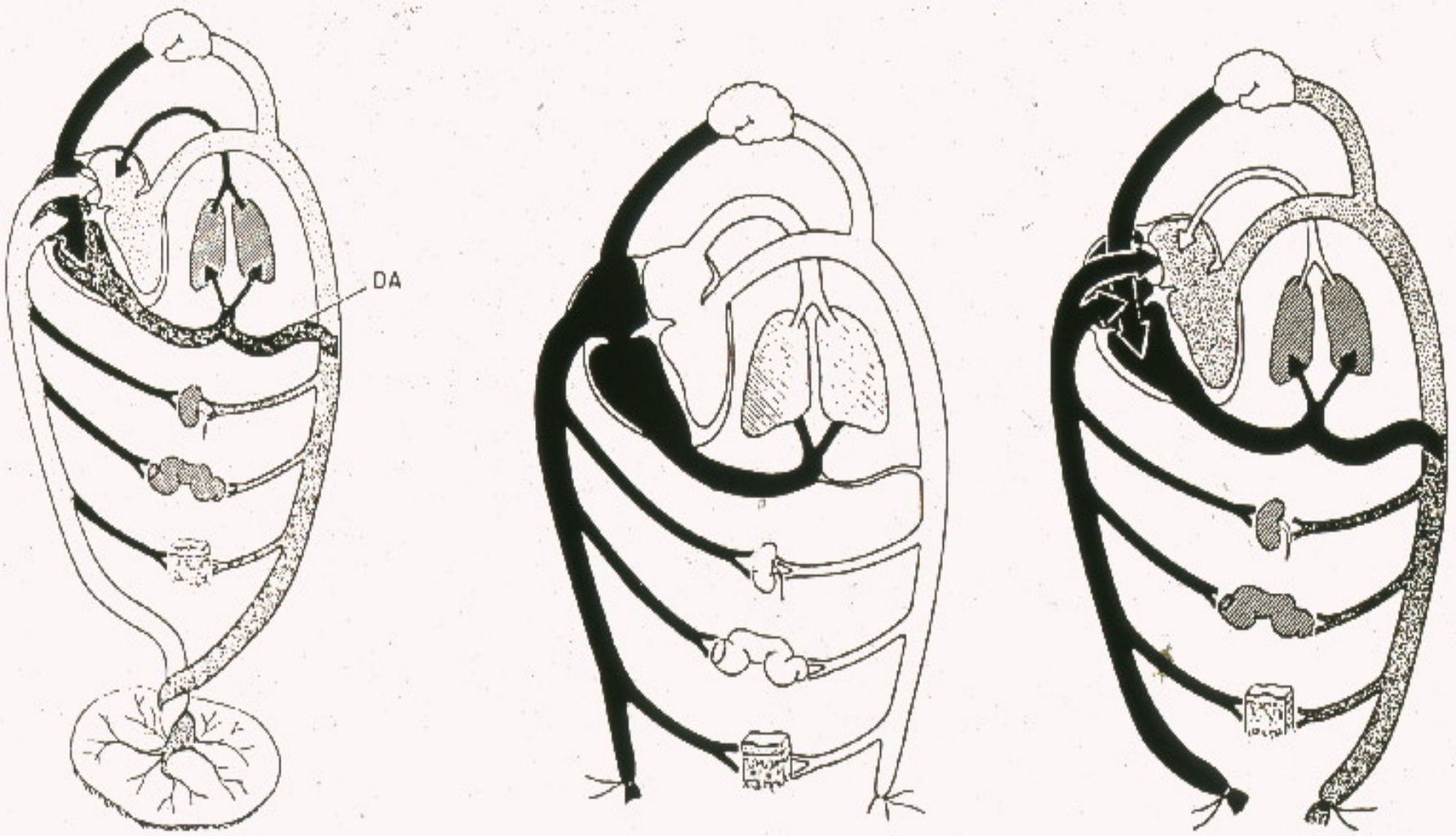
Professor of Pediatrics
Columbia University Medical Center



Fetal Circulation ***Normal Newborn Circulation*** ***PFC***

(Modified from Avery GB (ed): Neonatology. JB Lippincott 1987: 213-14.

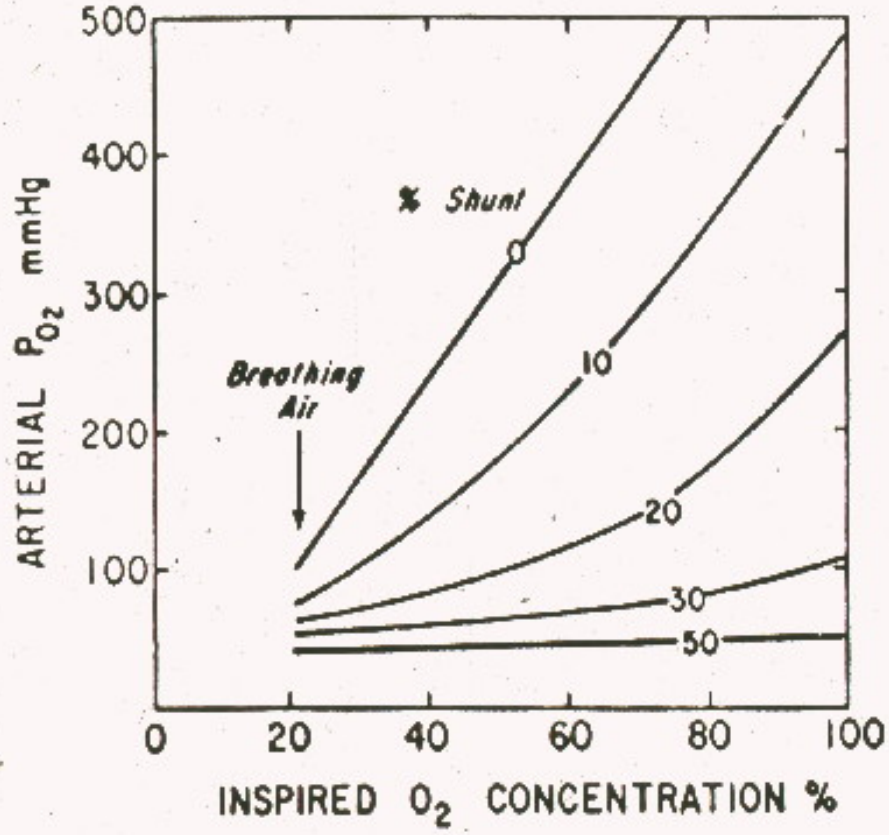
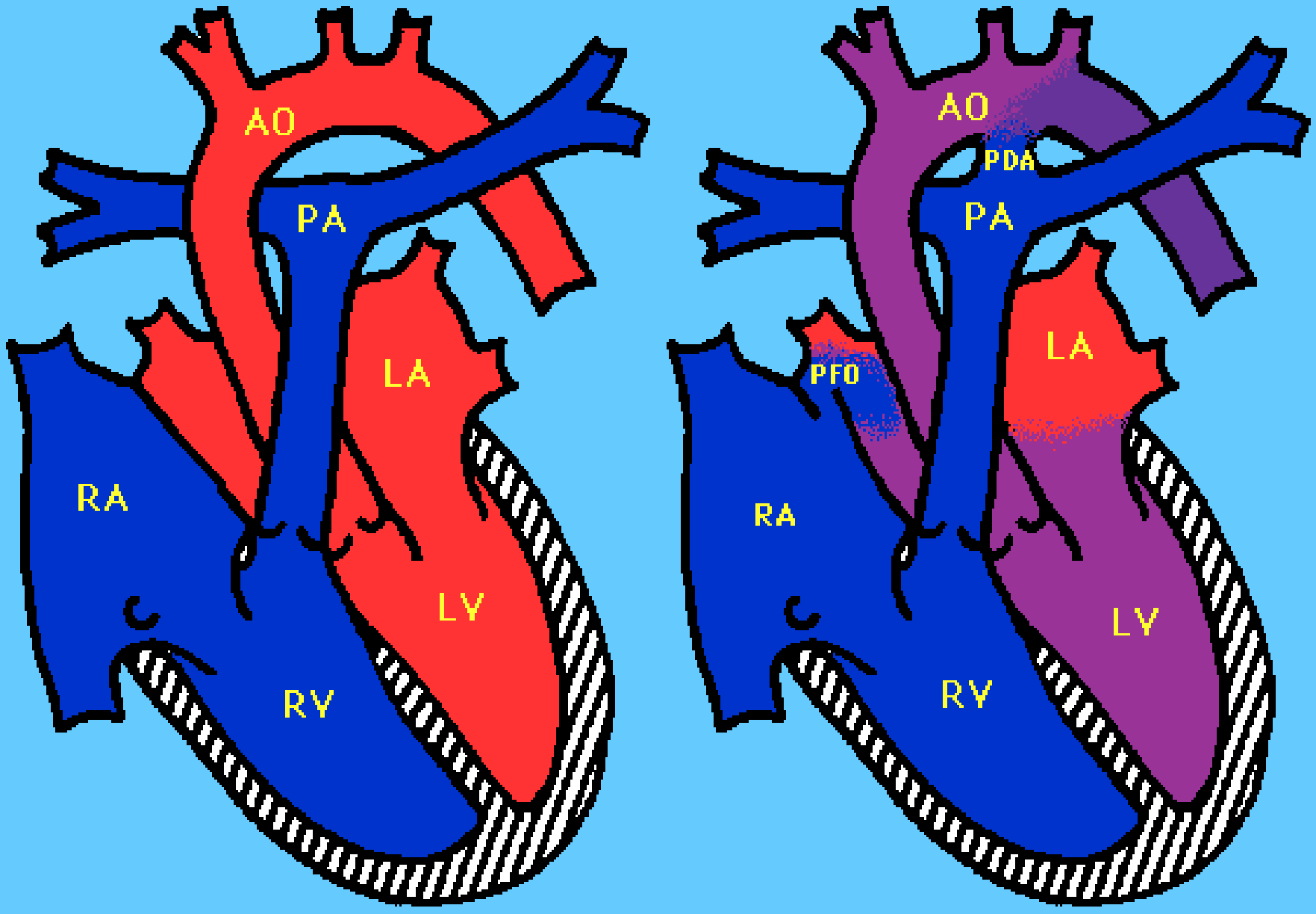


Fig. 78. Response of the arterial P_{O_2} to increased inspired oxygen concentrations in a lung with various amounts of shunt. Note that the P_{O_2} remains a long way below the normal level for 100% oxygen. Nevertheless, useful gains in oxygenation occur even with severe degrees of shunting. (This diagram shows typical values only; changes in cardiac output, oxygen uptake, etc., will affect the position of the lines).

Persistance of the Fetal Circulation



Normal

Persistance of the Fetal Circulation

PPHN - Causes

- Perinatal asphyxia, MAS
- Congenital heart diseases
- Pulmonary hypoplasia, CDH, Oligohydramion
- RDS
- GBS or other sepsis
- Premature ductal closure secondary to maternal drug therapy (NSAIDs)
- Maternal use of selective serotonin-reuptake inhibitor (SSRI, fluoxetine) in late pregnancy
- Alveolar capillary dysplasia (Misaligment of PVs)
- Idiopathic
- Iatrogenic

Diagnosis of Pulmonary Hypertension

- History
- Oxygen requirment out of proportion to the severity of lung disease
- Pre-/ Post- Oxygen Saturation
- EKG (RV hypertrophy)
- Echocariography
- Cardiac Catheterization - Gold standard
- Biochemical Marker: B-type natriuretic peptide (BNP),and N-terminal proBNP(NT-proBNP)

Echocardiographic Estimation of PA presssure

- TR jet flow

  Modified Bernouli equation: Systolic PAP = 4 × (TR peak jet velocity)^2 + RA pressure

- Septal flattenning, Interventricular septum at end-systole

  RV pressure/Systemic pressure: round <50%
  Flat = 50-100%, Bowing to LV ≥100%

- RA enlargement, RV hypertrophy / dilation, RV wall thickness, Dilated PA, ↑ velocity PV regurgitation, ↓ acceleration time of RV ejection to PA

PPHN
Management in 1980's

"Full Artillery" Approach

1. FiO_2 100%
2. IMV 50 – 100/min.
   PIP 25 – 45 cm H_2O to achieve $PaCO_2$ < 25 mmHg
3. Muscle relaxant
4. Tolazoline
5. Dopamine 2-20 μg/kg/min
   Dobutamine 5-30 μg/kg/min
   to achieve mean BP 45 – 50 mmHg
6. $NaHCO_3$ 1 meg/kg/hr to keep pH > 7.55

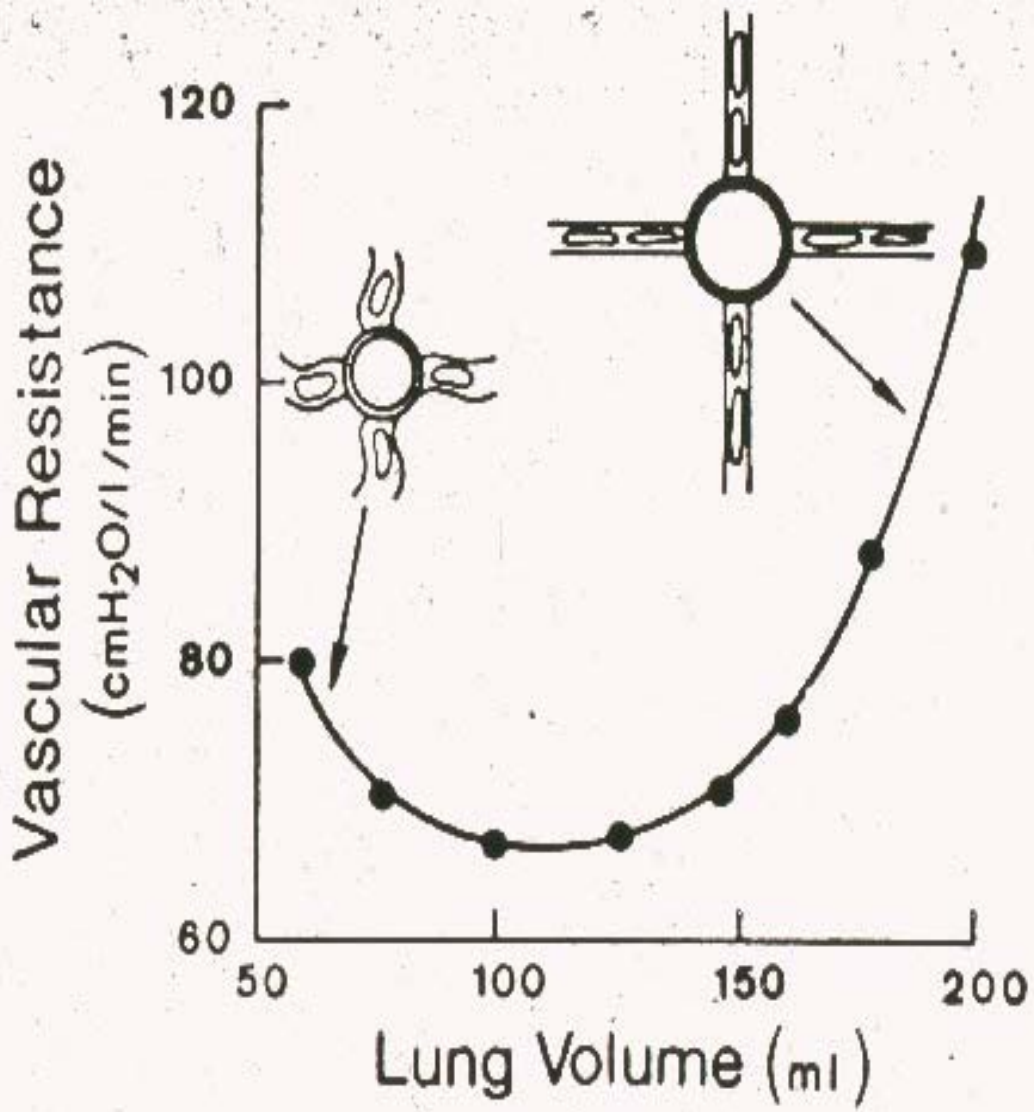


Figure 27. Effect of lung volume on pulmonary vascular resistance when the transmural pressure of the capillaries is held constant. At low lung volumes, resistance is high because the extra-alveolar vessels become narrow. At high volumes, the capillaries are stretched and their caliber is reduced. (Data from a dog lobe preparation.)

Hyperventilation

- Overventilation impedes venous return, decreases pulmonary blood flow, oxygenation, cardiac output and blood pressure
- Increases pulmonary vascular resistance. The capillaries are stretched and their caliber is reduced
- Increases lung injury (barotrauma, volutrauma, and biotrauma).
- Shifts O_2-hemoglobin dissociation curve to the left due to alkalosis
- Decreases cerebral blood flow.
- Causes hearing loss.

Management of PPHN

Columbia Approach

- Treating the underlying disease
- Continuously monitoring of pre- & post-ductal O_2 saturation
- Mechanical Ventilation: 1. Conventional ventilation 2. PTV (SIMV, A/C) 3. HFPPV 4. HFV (HFO)
- No hyperventilation, induction of alkalosis or neuromuscular blockade
- Pulmonary vasodilator-- INO (for pre-ductal oxygen saturation < 90%). If no response, milrinone, inhaled iloprost or I.V. sidenafil may be added.
- ECMO as last resort

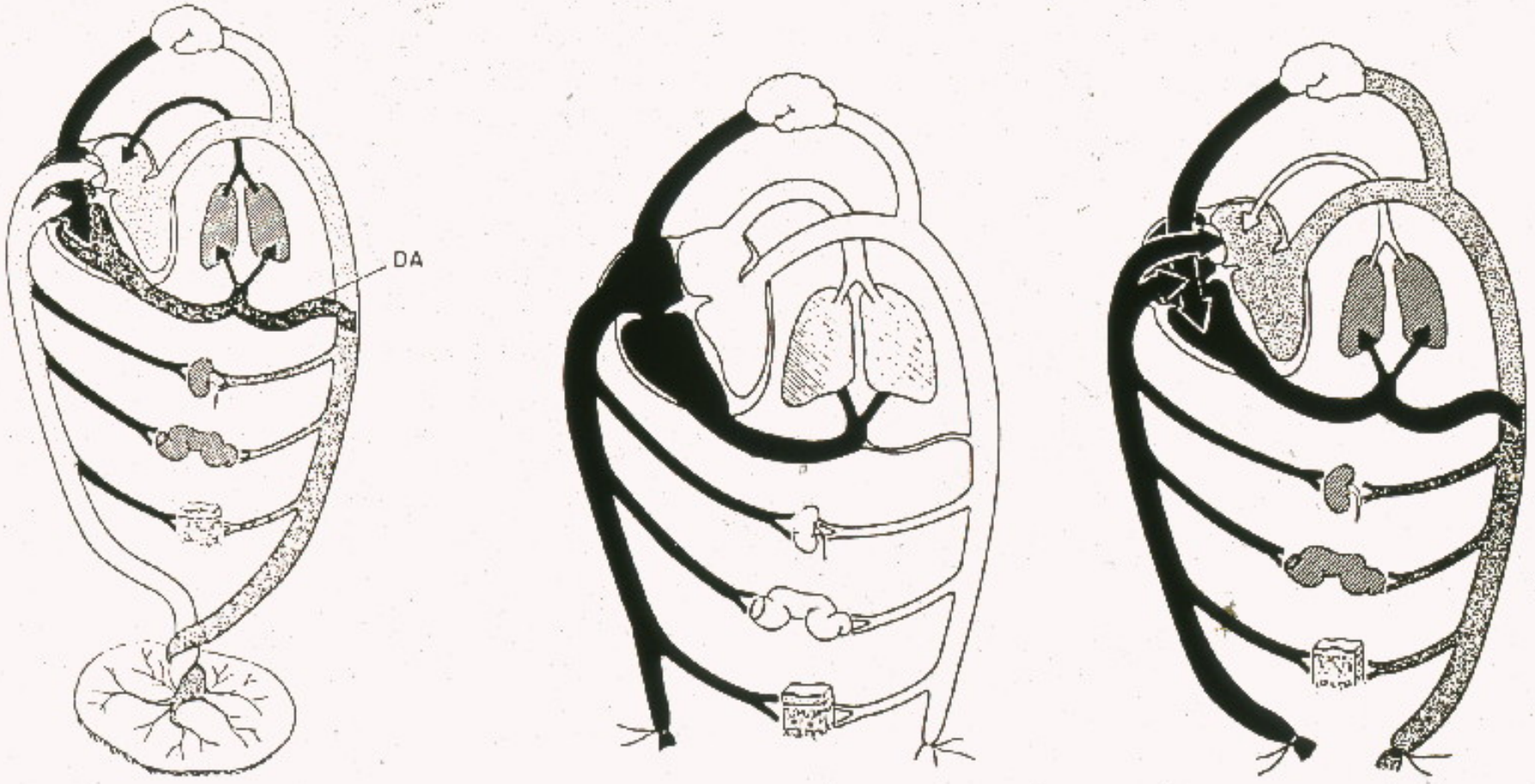
P P H N

Vasodilator Therapy

- tolazoline (priscoline)
- epinephrine (0.1 ug/kg/min)
- prostaglandin E_1 (0.1 ug/kg/min)
- magnesium sulfate
- inhaled nitric oxide (after 5/1994)
- milrinone I.V.
- sidenafil P.O., or I.V
- inhaled iloprost

P P H N
tolazoline (priscoline)

- Infuse into upper extremity or scalp vein
- Test dose: 1 mg/kg
- Maintenance: 1mg/kg/hr



Fetal Circulation ***Normal Newborn Circulation*** ***PFC***

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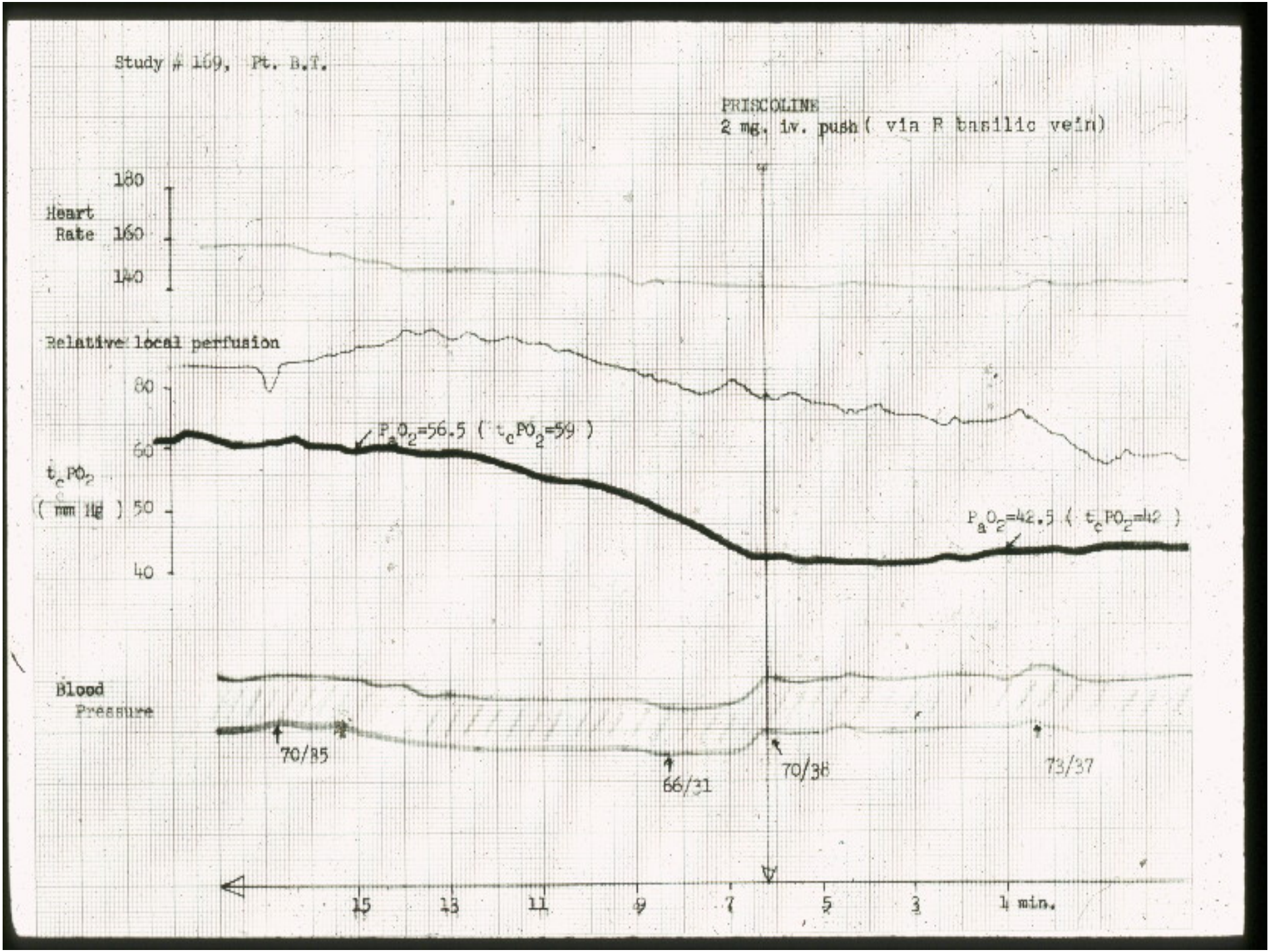
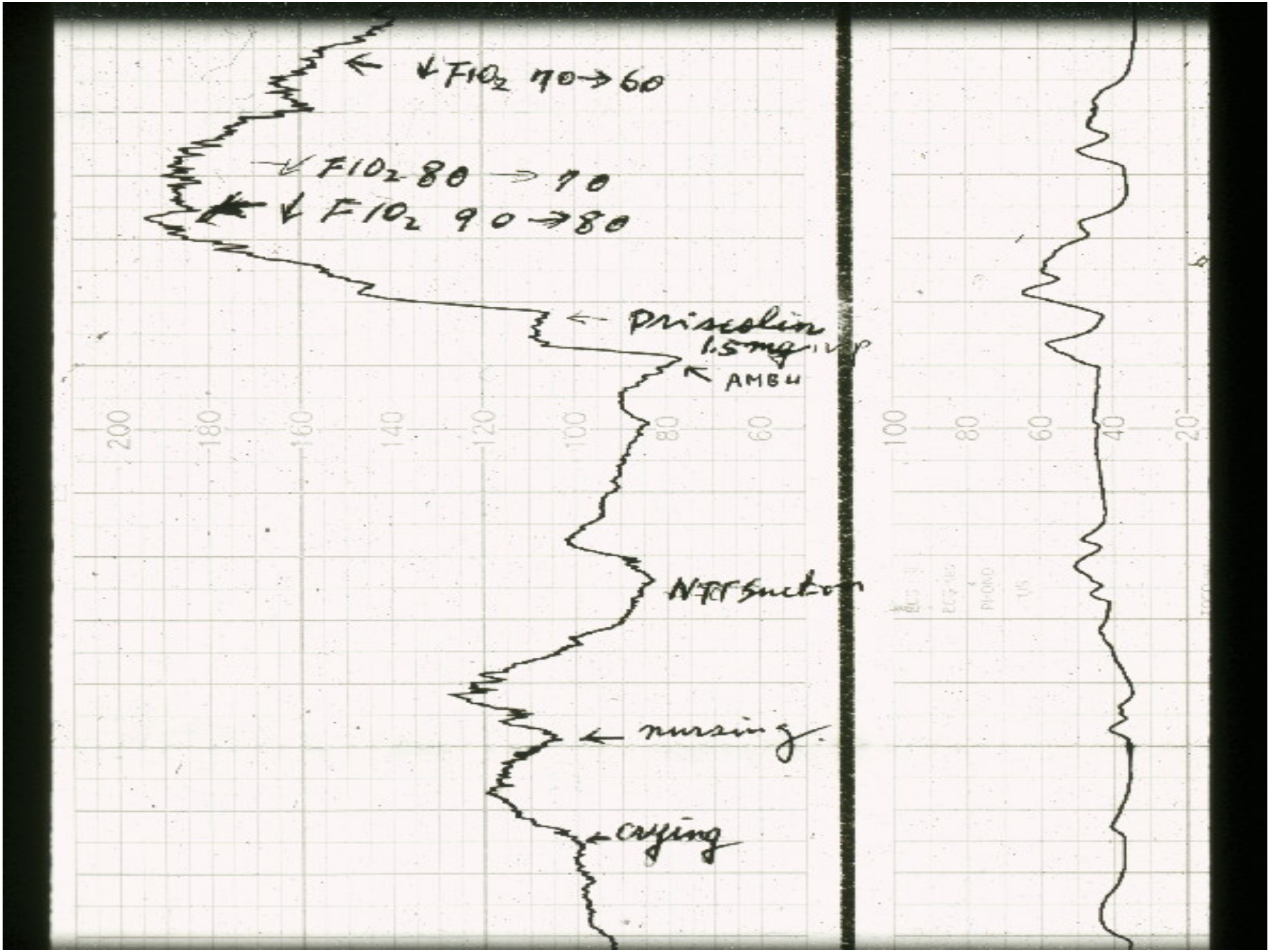
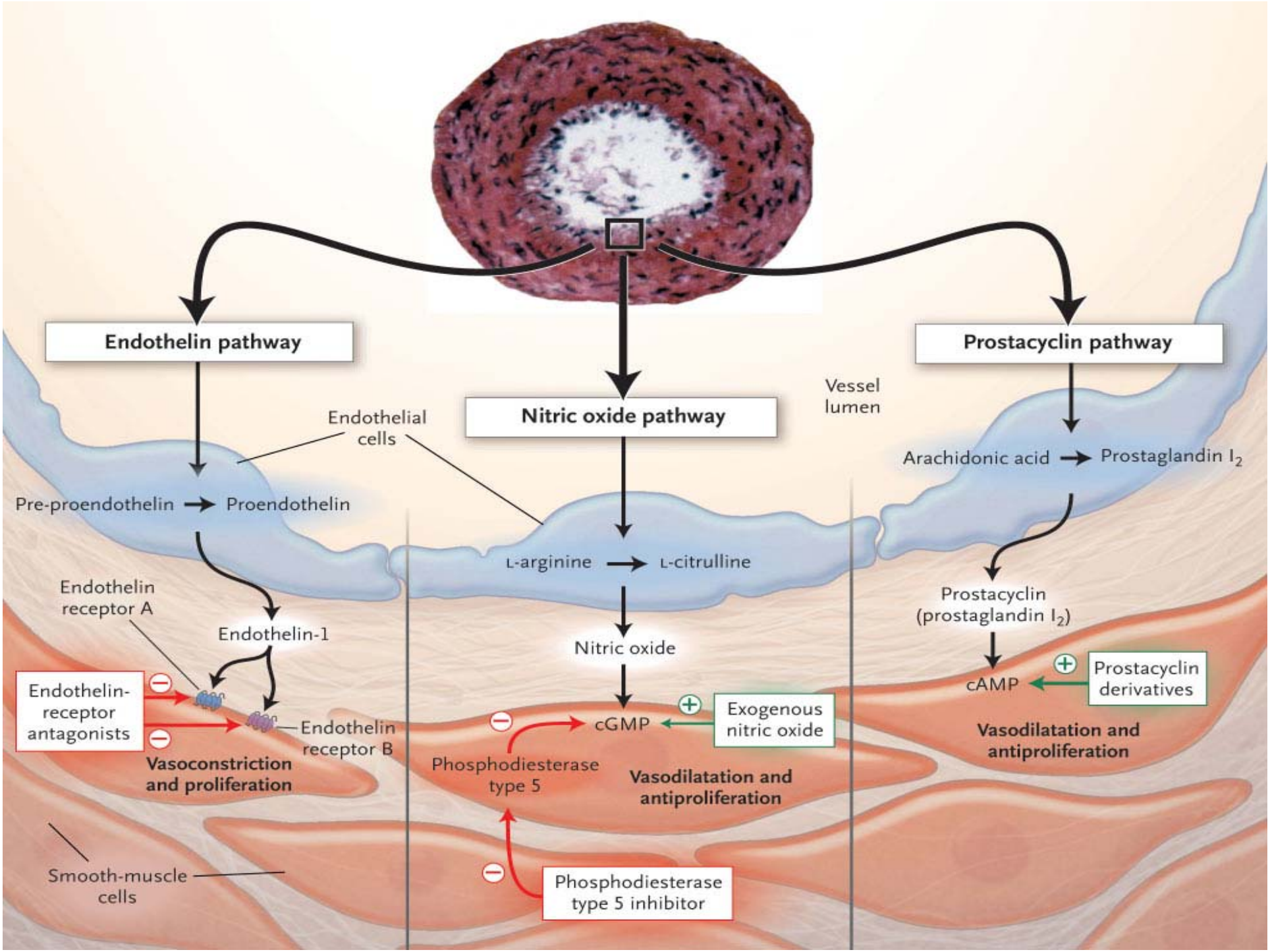

Study # 169, Pt. B.T.
PRISCOLINE
2 mg. iv. push (via R basilic vein)
180
Heart
Rate 160
140
Relative local perfusion
80
60
t_cPO_2
(mm Hg) 50
40
P_aO_2=56.5 (t_cPO_2=59)
P_aO_2=42.5 (t_cPO_2=42)
Blood
Pressure
70/85
66/31
70/38
73/37
15
13
11
9
7
5
3
1 min.


FIO2 70→60
FIO2 80 → 70
FIO2 90→80
Priscolin
1.5mg
AMBU
NTT Suction
nursing.
crying
200
180
160
140
120
100
80
60
100
80
60
40
20


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

Vasodilator Therapy

Inhaled Nitric Oxide

Phosphodiesterase type 5 inhibitor (PDE5):

- sildenafil

Prostacycline:

- inhaled iloprost
- inhaled treprostinil (lasting >3 hrs)
- flolan

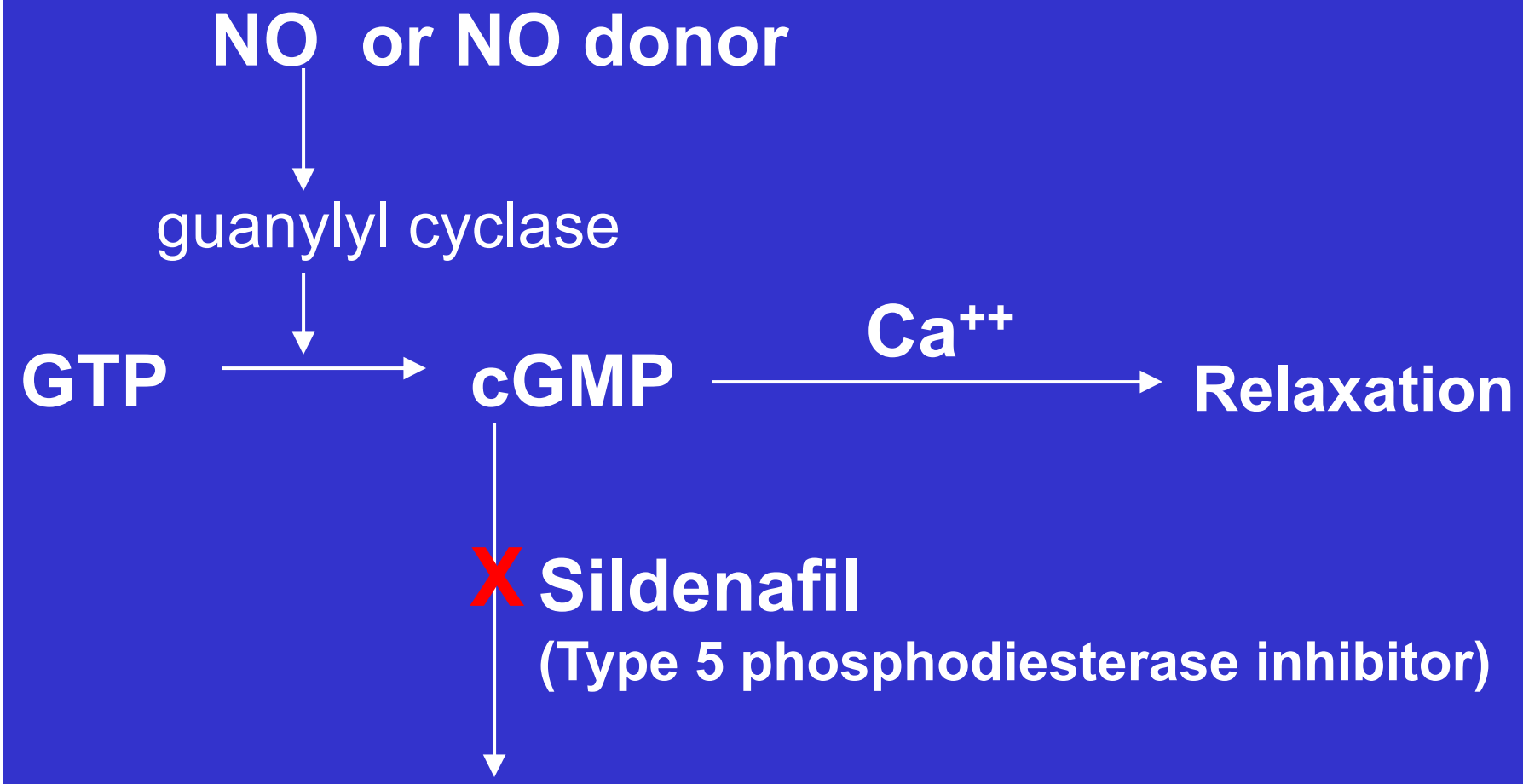
Phosphodiesterase type 3 inhibitor (PDE3):

- milrinone

Endothelin receptor antagonist:

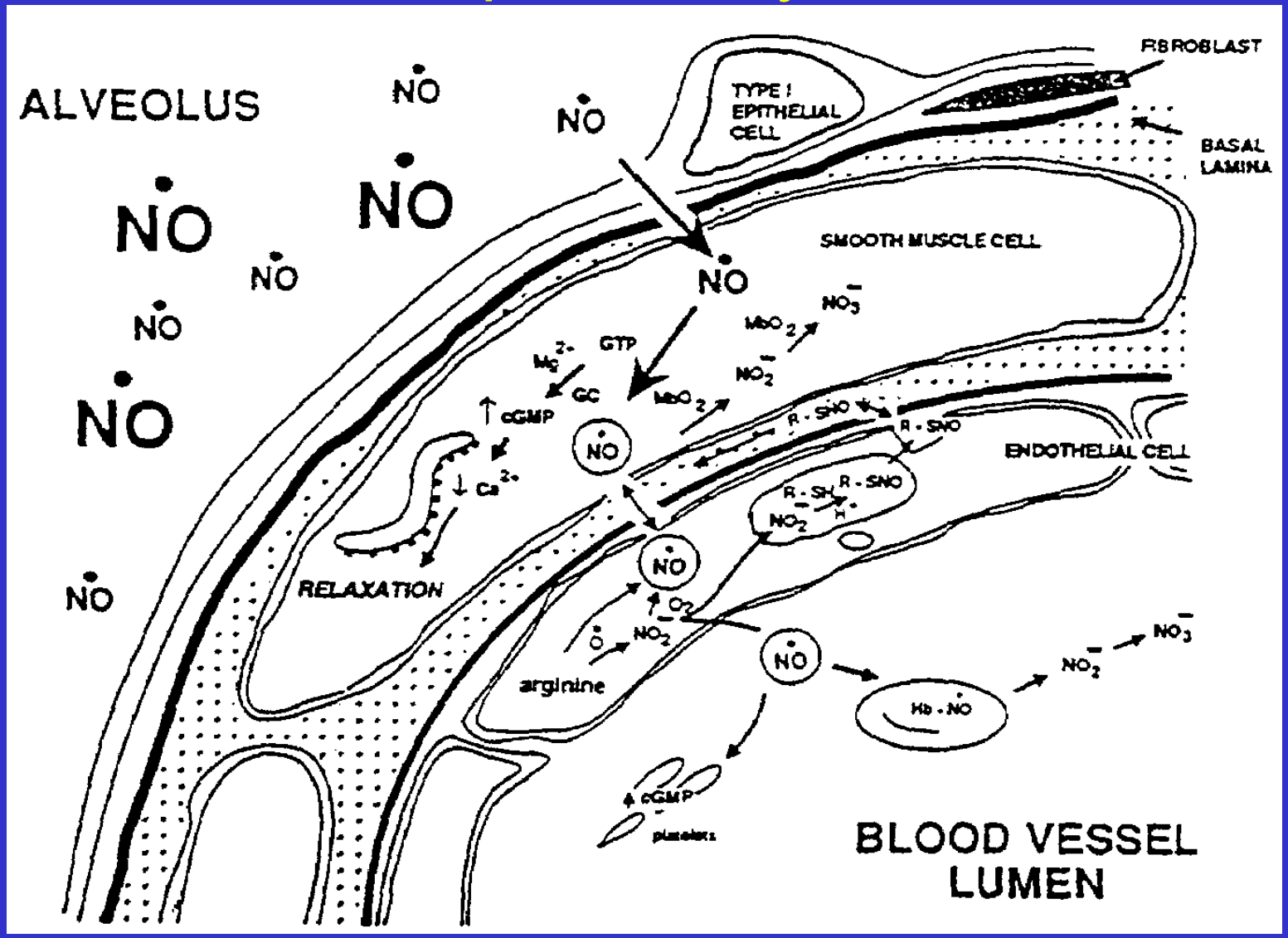
- bosentan
- Ambrisentan

Nitric Oxide Pathway

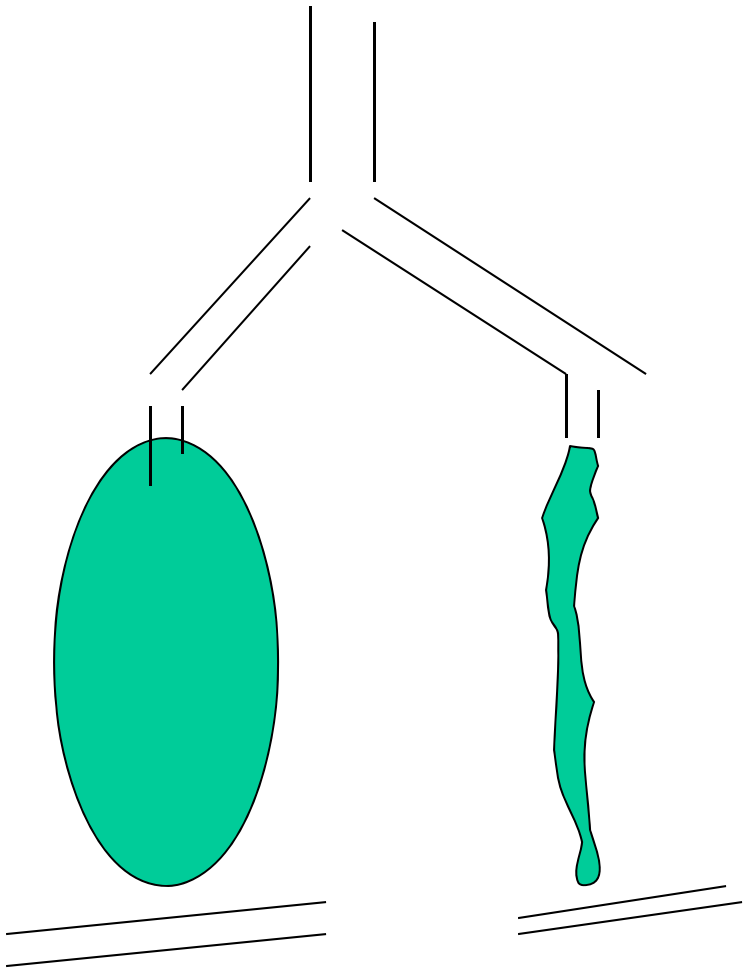


1992

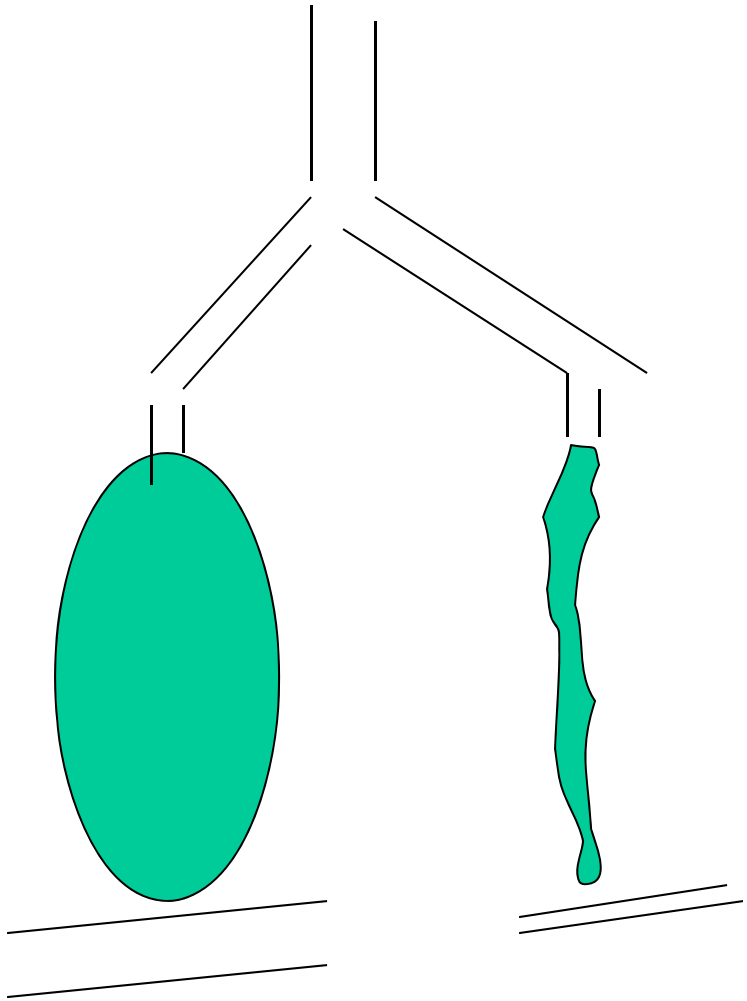
Schematic of NO uptake and mechanism for pulmonary vasodilatation



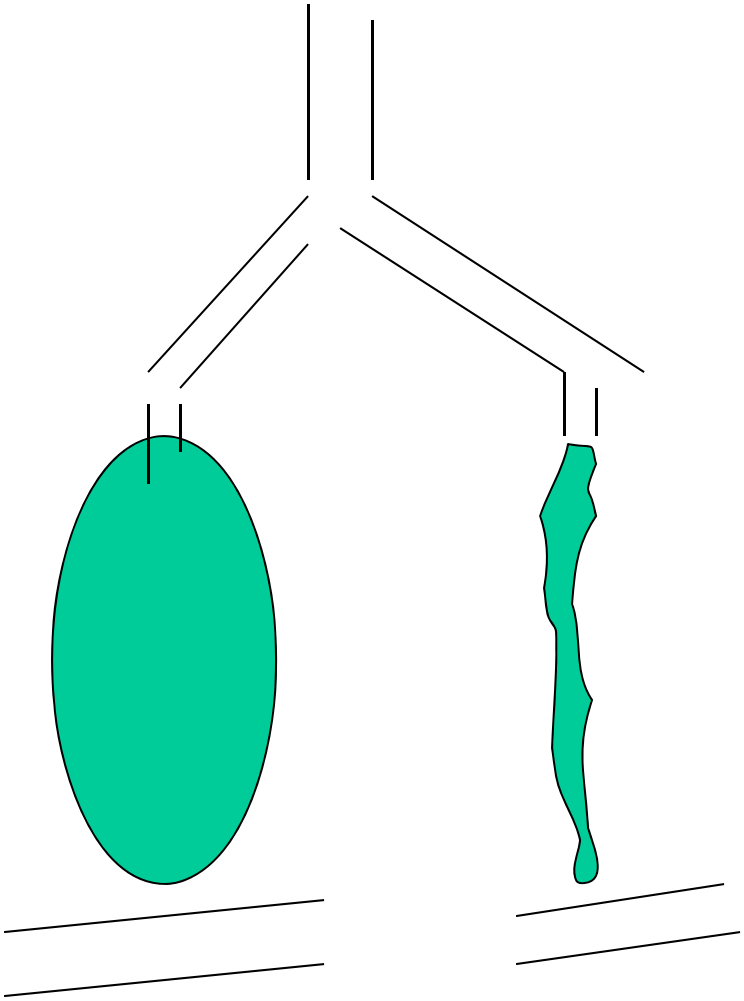
PPHN



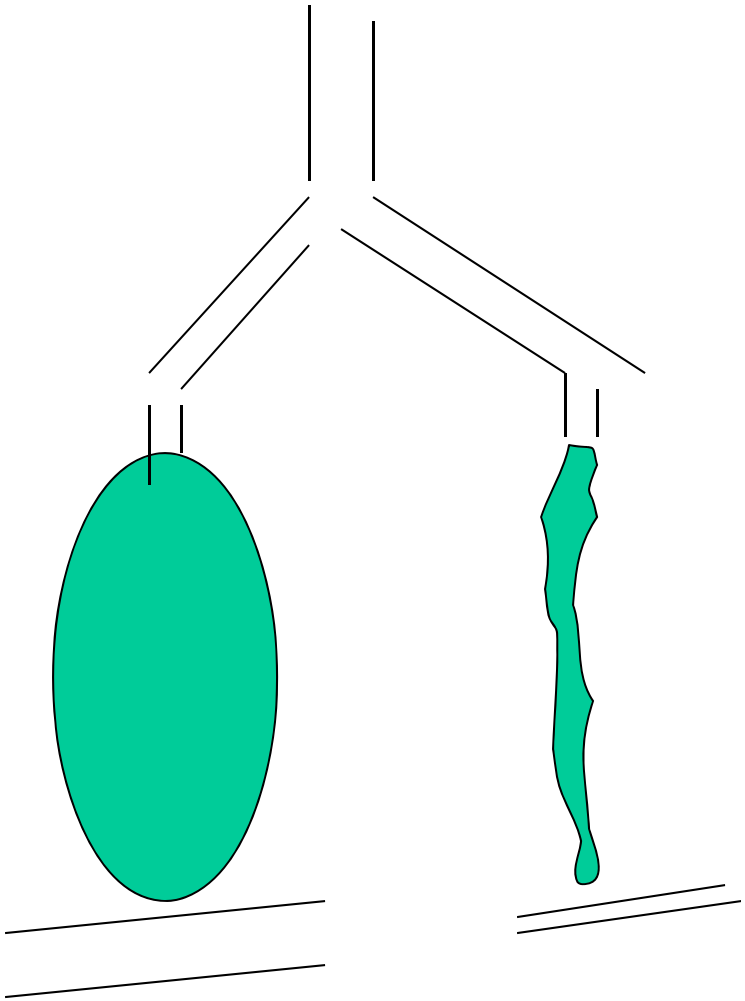
PPHN + INO



PPHN + Nipride



PPHN + INO



Inhaled Nitric Oxide

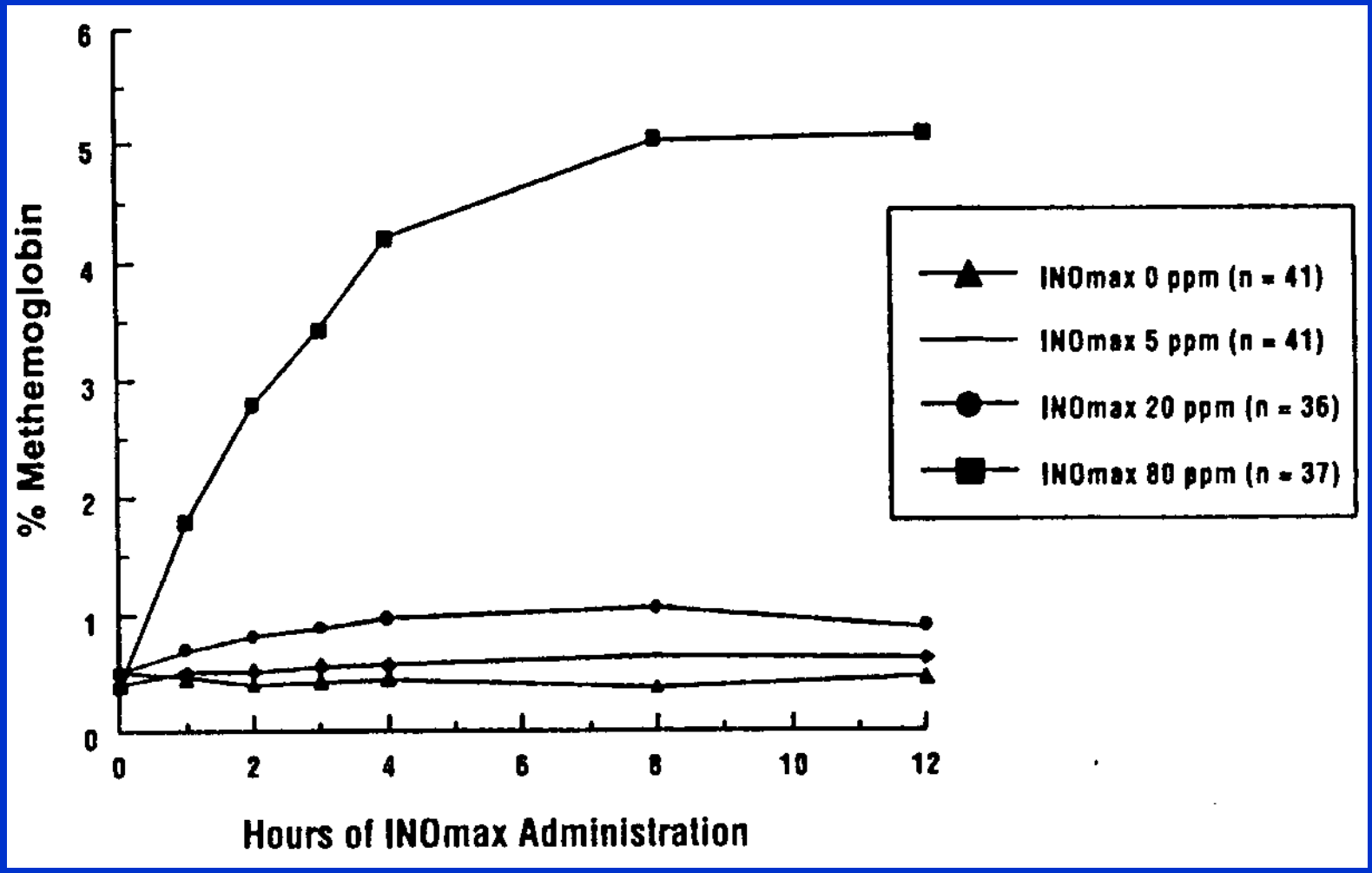
- Selective pulmonary vasodilator
- The gold standard therapy for PPHN

INOmax™
Dosage

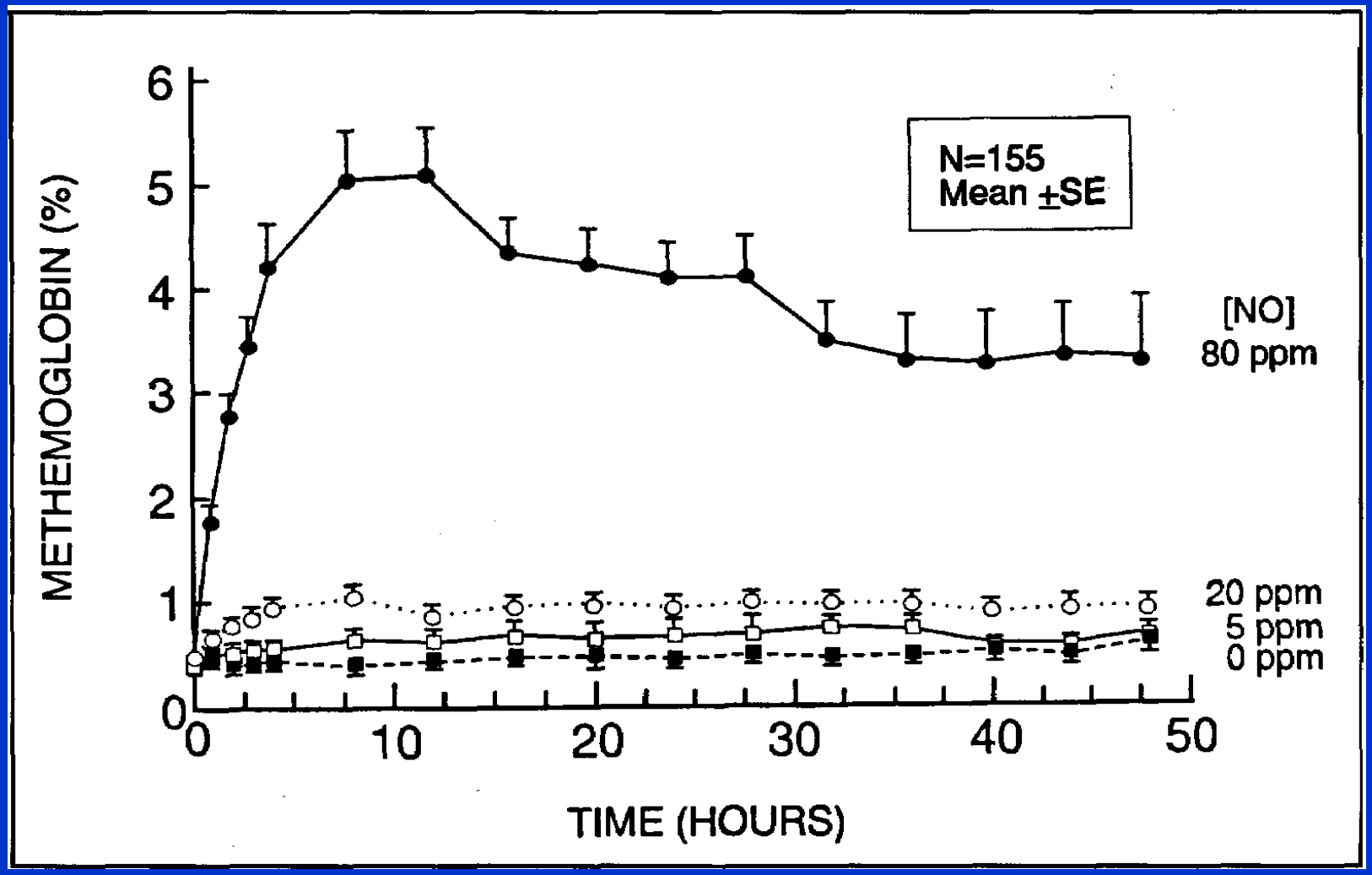
- The recommended initial dose is 20 ppm.
- Dose reduced as tolerated to 5 ppm after a sustained improvement in oxygenation (24 to 48 hours).
- Duration is usually 2 to 6 days

Methemoglobin Concentration-Time Profiles

Neonates Inhaling 0, 5, 20 or 80 ppm INOmax™

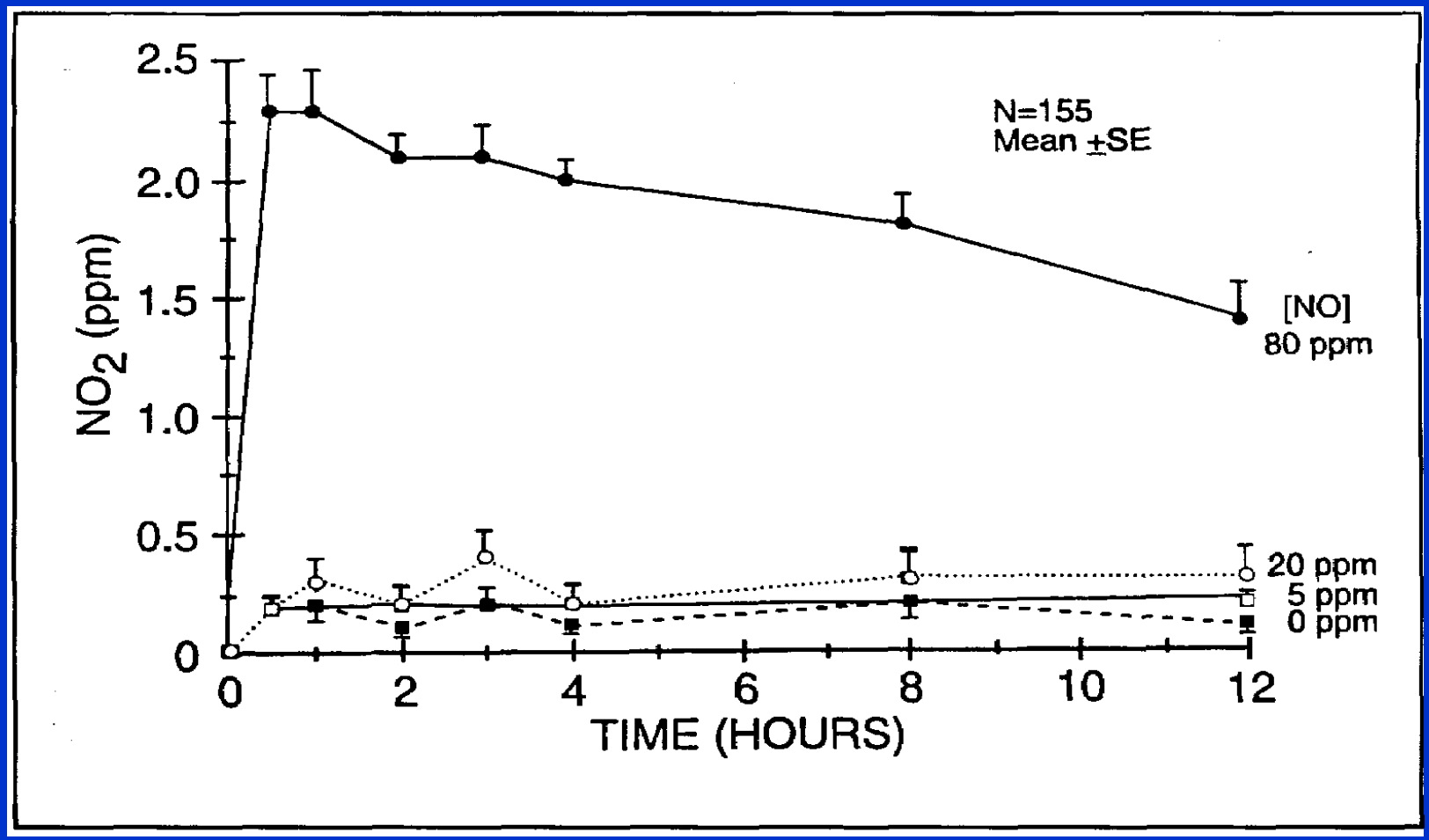


Methemoglobin Concentration - Time Profile



Davidson et al. Pediatrics 1998;101:325-334

Inspired NO_2 level - Time Profile



Davidson et al. Pediatrics 1998;101:325-334

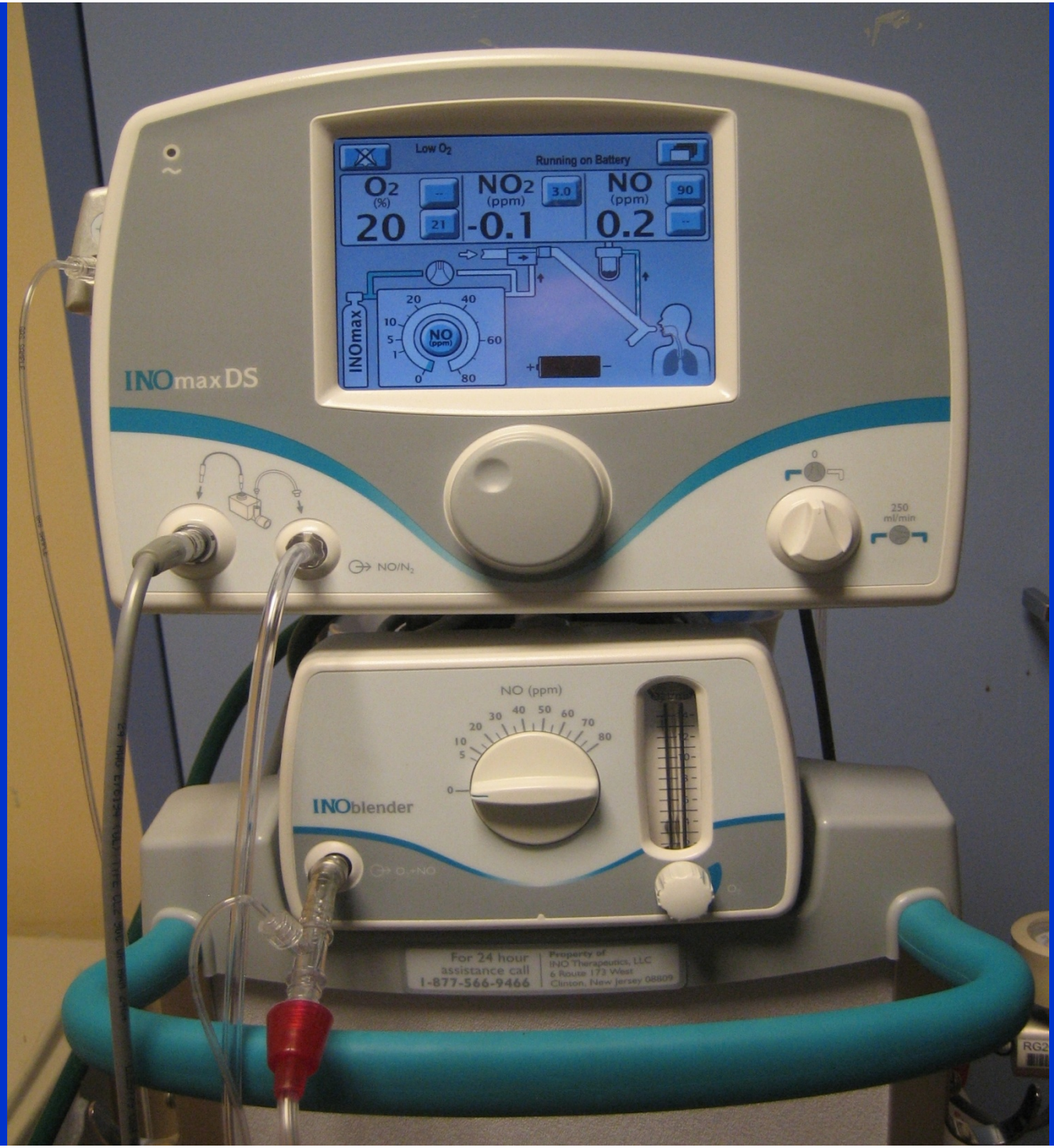
INOmax™
Administration

- INOvent™ system or other systems
- Precise monitoring of inspired NO and NO_2 should be instituted
- Monitoring for PaO_2 and pre- & post-ductal O_2 saturation
- Monitoring MetHb (baseline, 6 hours and then every 12 hours).

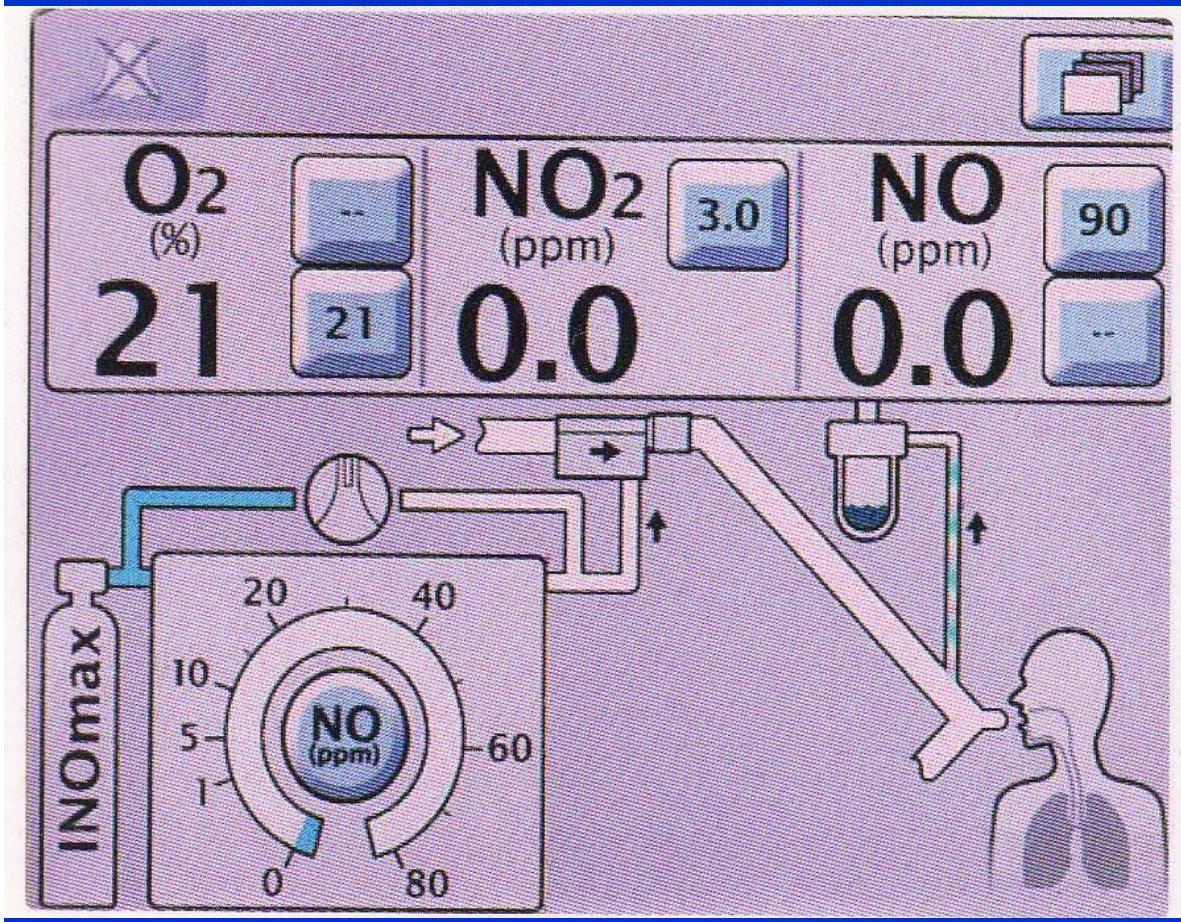
INOmaxtm DS Transport System

INO max DS

INOblender


Low O2
Running on Battery
O2 (%)
20
21
NO2 (ppm)
-0.1
3.0
NO (ppm)
0.2
90
INOmax
NO (ppm)
INOmaxDS
NO/N2
250 ml/min
NO (ppm)
INOblender
For 24 hour assistance call 1-877-566-9466
Property of INO Therapeutics, LLC 6 Route 173 West Clinton, New Jersey 08809

INO max DS



Alarm area

Monitoring area

Graphics area

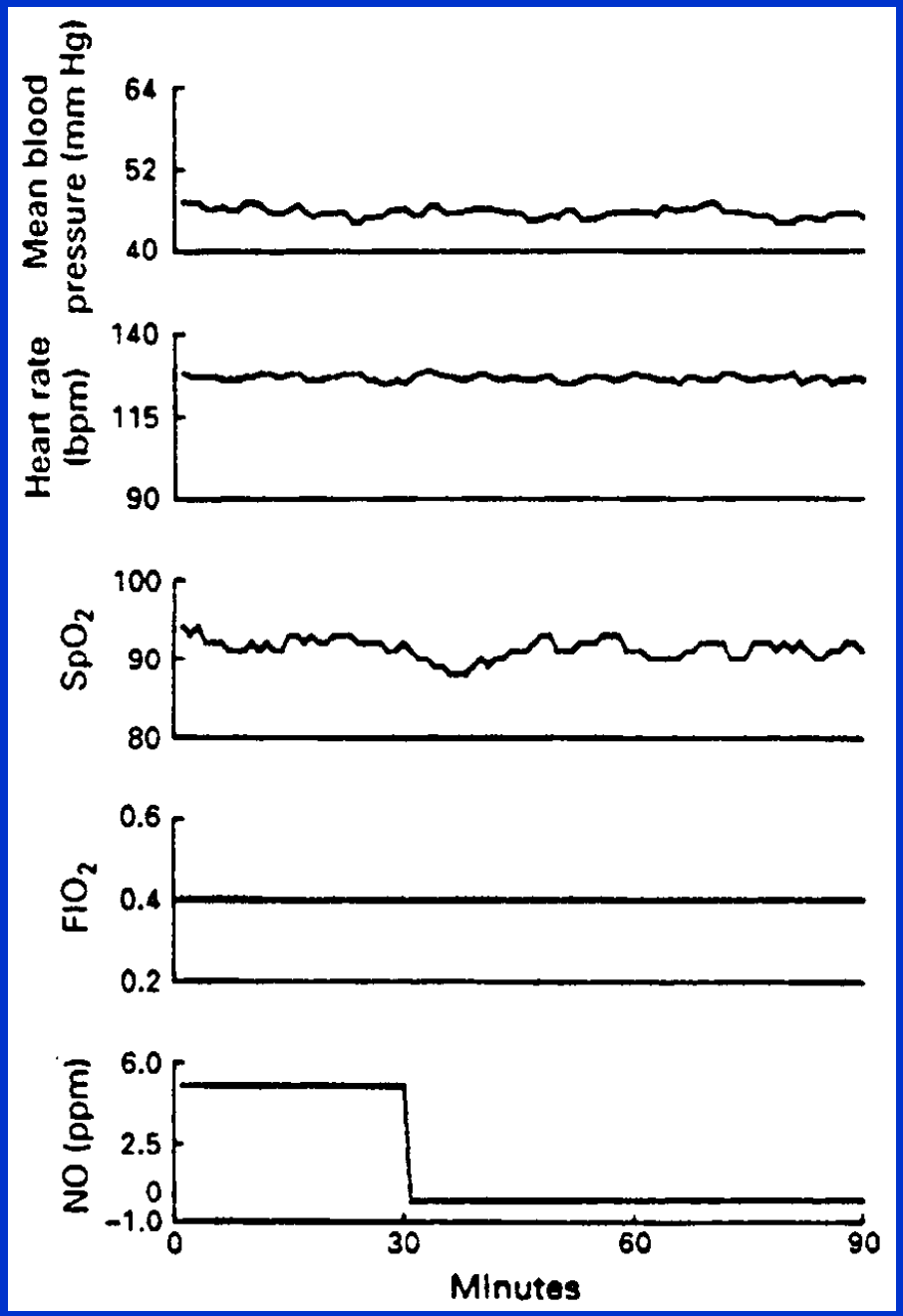
INOmax™
Weaning

20ppm → 15ppm → 10 ppm →
5 ppm → (4 --->3 -->2 -->1) → 0

INOmax™
Discontinuation

- INOmaxTM discontinued when the infant is stable on 5 ppm, and FiO2 <60%

- About half of patients require an increase of FiO2 (20 - 40%) for a few hours after weaning off INOmaxTM

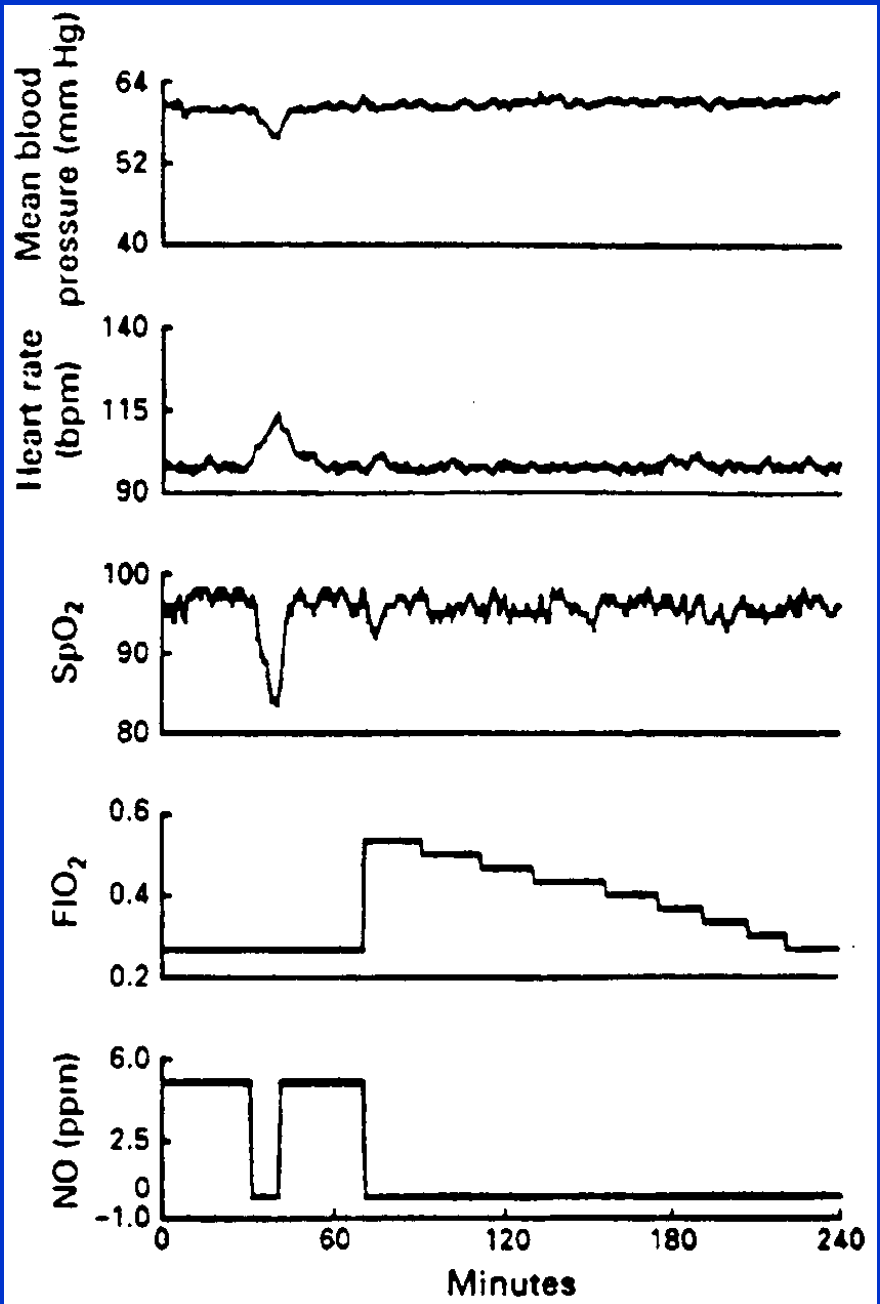


Discontinuation of INO (1)

Note the stability of mean blood pressure, heart rate, and SPO_2 with the same FiO_2 as INO is withdrawn.

Aly H, Sahni R, Wung JT

Arch Dis Child 1997;76:

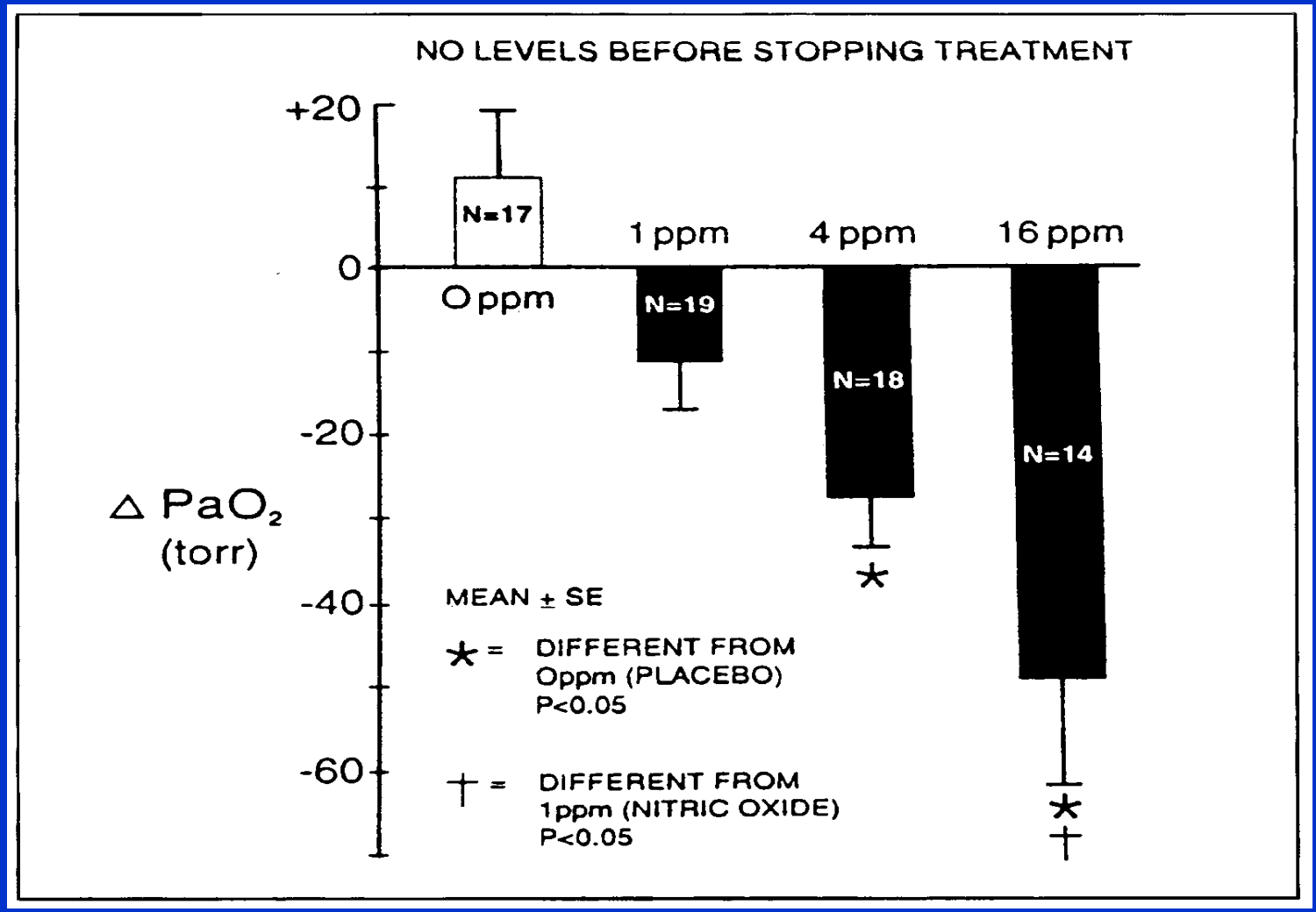


Discontinuation of INO (2)

Acute deterioration of mean blood pressure, heart rate, and SPO_2 with the same FiO2 followed the initial attempt at weaning. FiO2 was increased and the weaning was successful. Note how quickly FiO2 was reduced following successful weaning.

Aly H, Sahni R, Wung JT
Arch Dis Child 1997;76:

Changes in PaO_2 30 minutes after discontinuing INO treatment gases



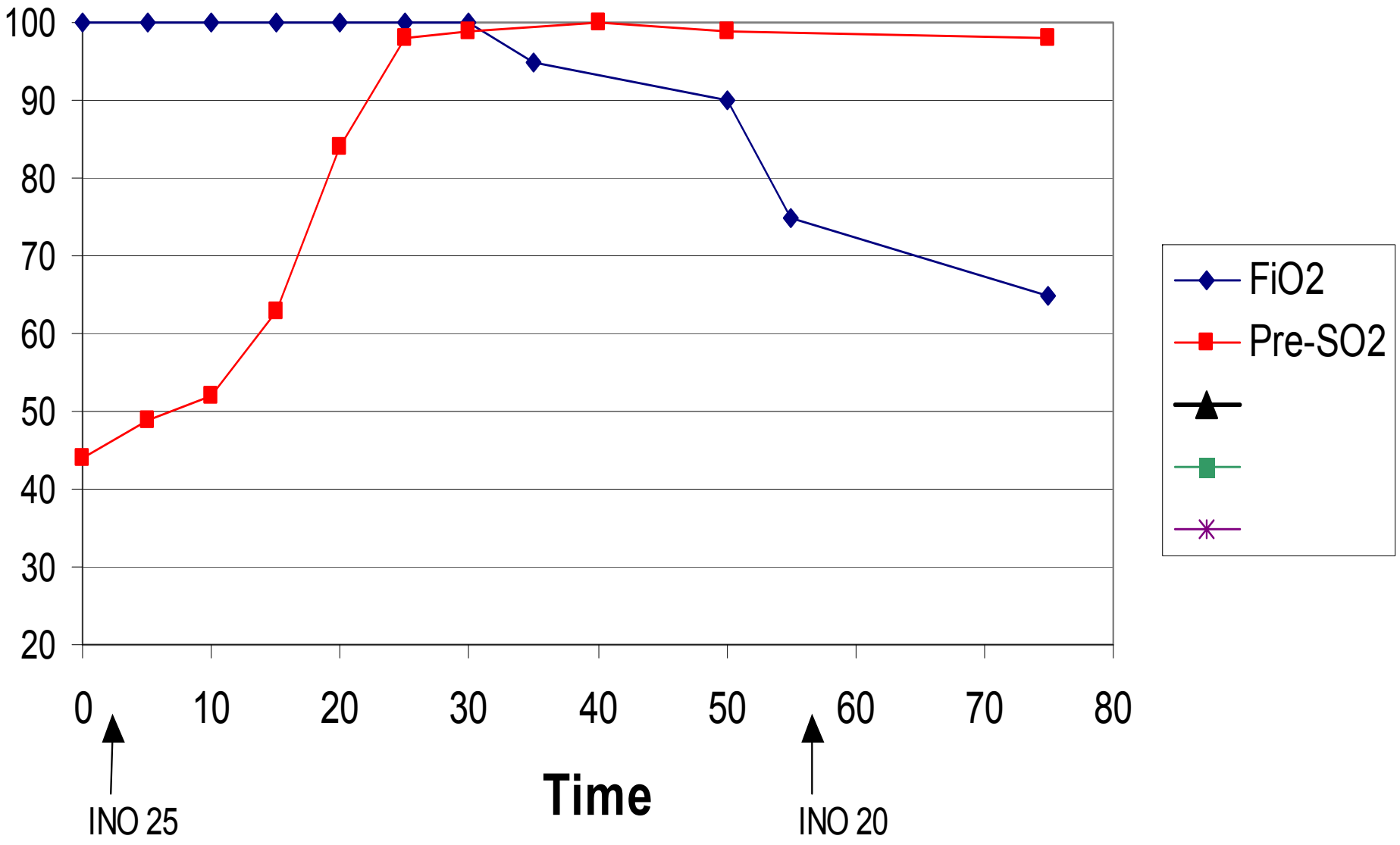
PPHN Case #8 (1)

- 4250g B/M 40 wk. gestation
- 35y.o. G5 P4 gestational D.M. on Insulin Variable deceleration, vaginal delivery, cord around neck x 2
- In nursery - tachypnea & acrocyanosis
- 2hrs - oxyhood FiO_2 90% VBG 7.31/54/55
- Endotracheal intubation
- 28.5 hrs - arrived CHONY
- 29.1hrs - INO 25 PPM started
- 56hrs - INO discontinued
- 3d - extubated, 7d - off CPAP

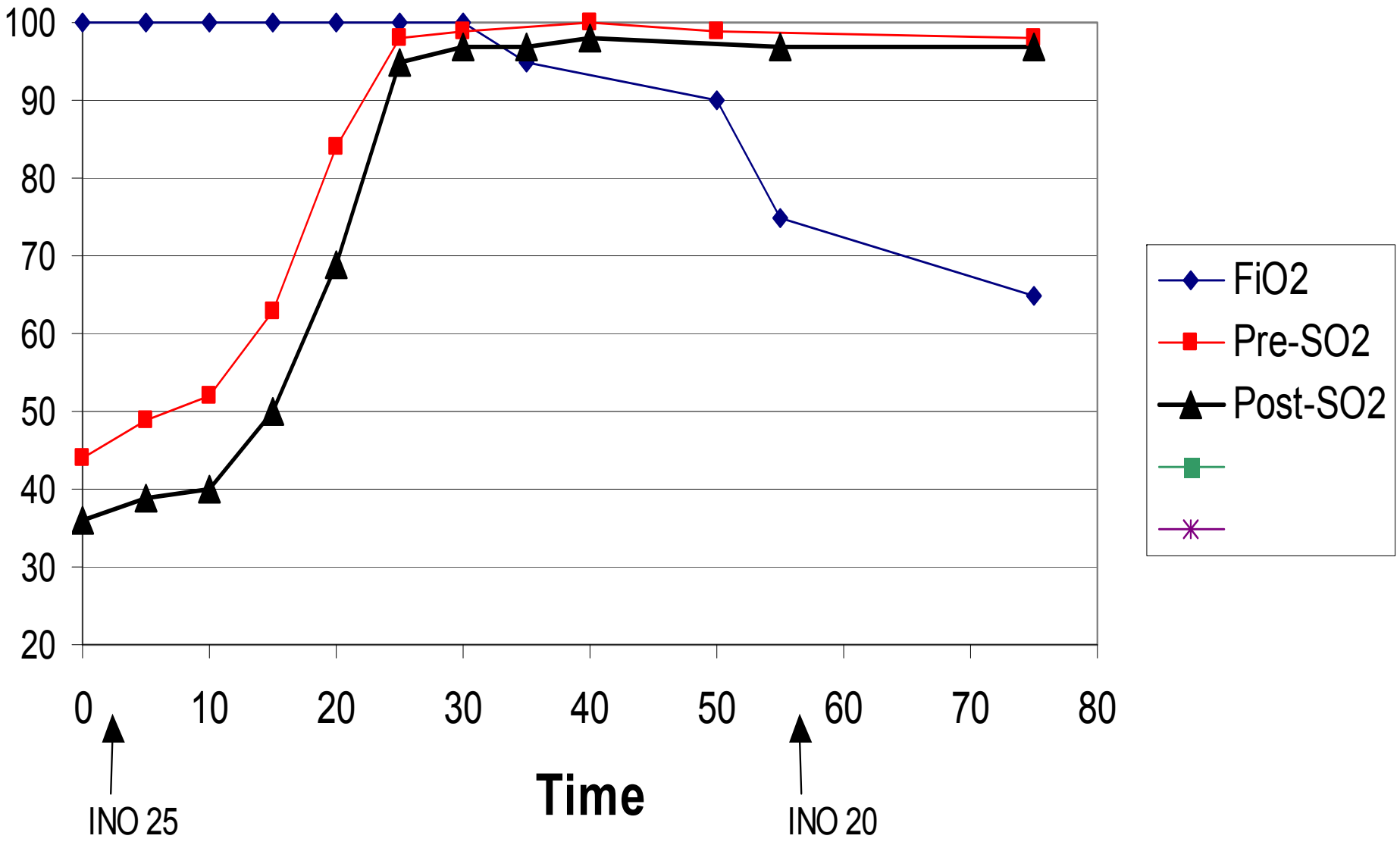
PPHN Case #8 (2)

Hrs	IMV	P	Ti	FiO_2	pH	PCO_2	PO_2
8	40	25/5	0.35	100	7.44	31	150
9					7.50	27	127
12					7.48	21	150
17					7.32	39	57
19	60	35/5	0.48	100	7.45	25	81
19.1					7.44	28	58
21	86	22/3	0.25		7.49	26	81
24	80	24/4	0.35		7.37	37	52
28.5	Arrived at CHONY						
29	100	25/0	0.3	100	7.21	56	16
29.1	INO 25 ppm started						
30	100	22/0	0.3	65	7.45	33	99

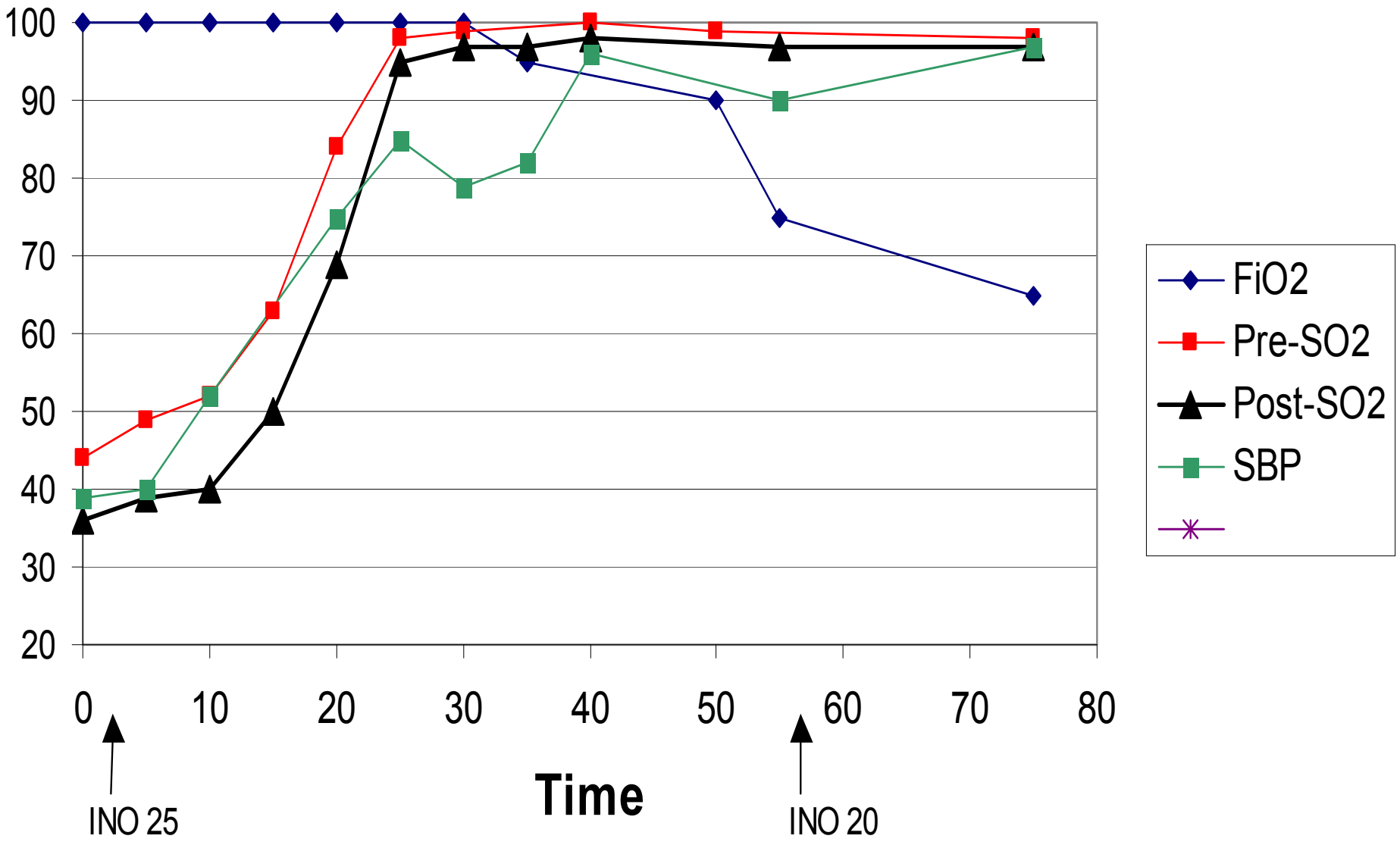
PPHN 4250g IMV 100 P25/0 Ti 0.3



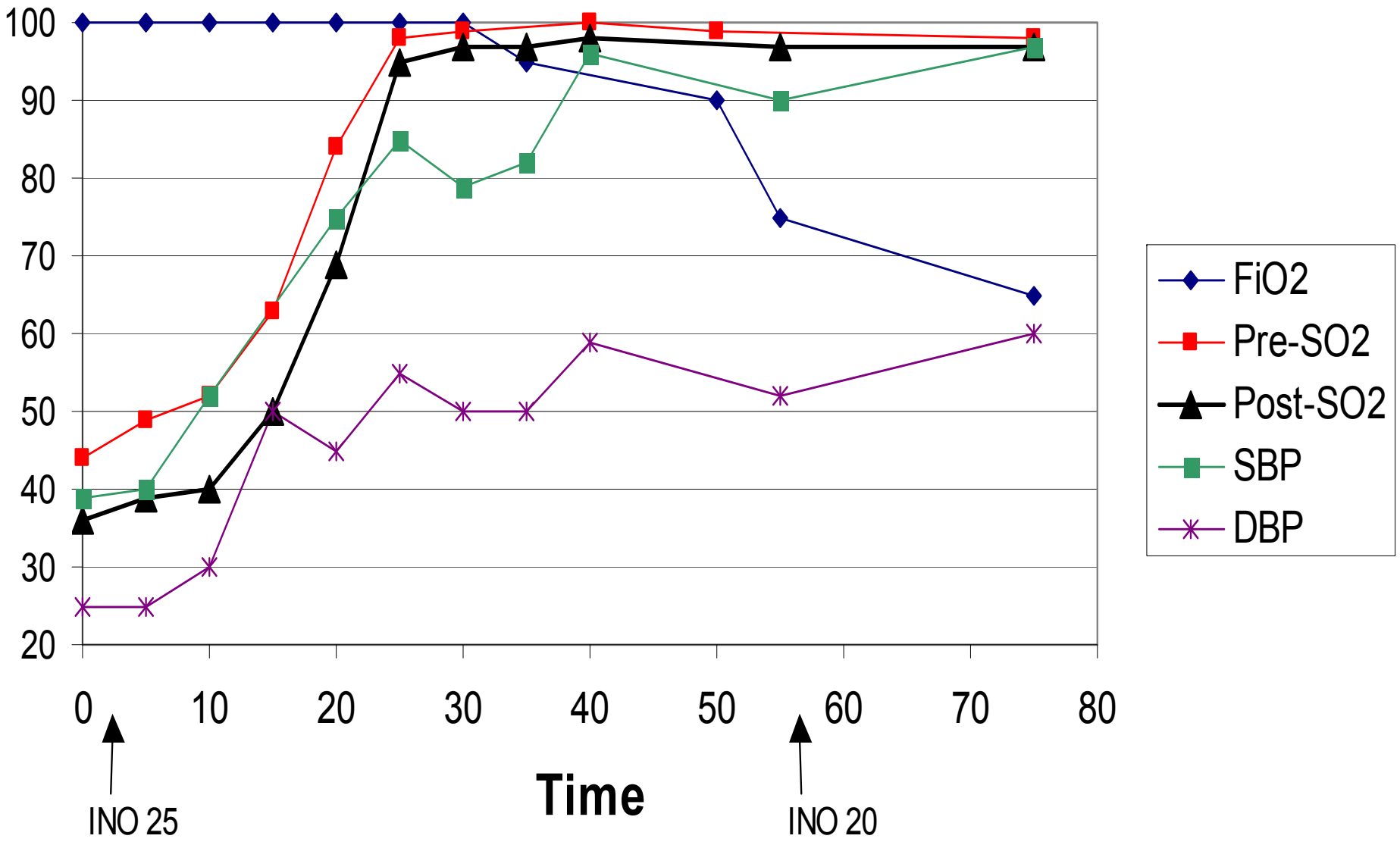
PPHN 4250g IMV 100 P25/0 Ti 0.3



PPHN 4250g IMV 100 P25/0 Ti 0.3

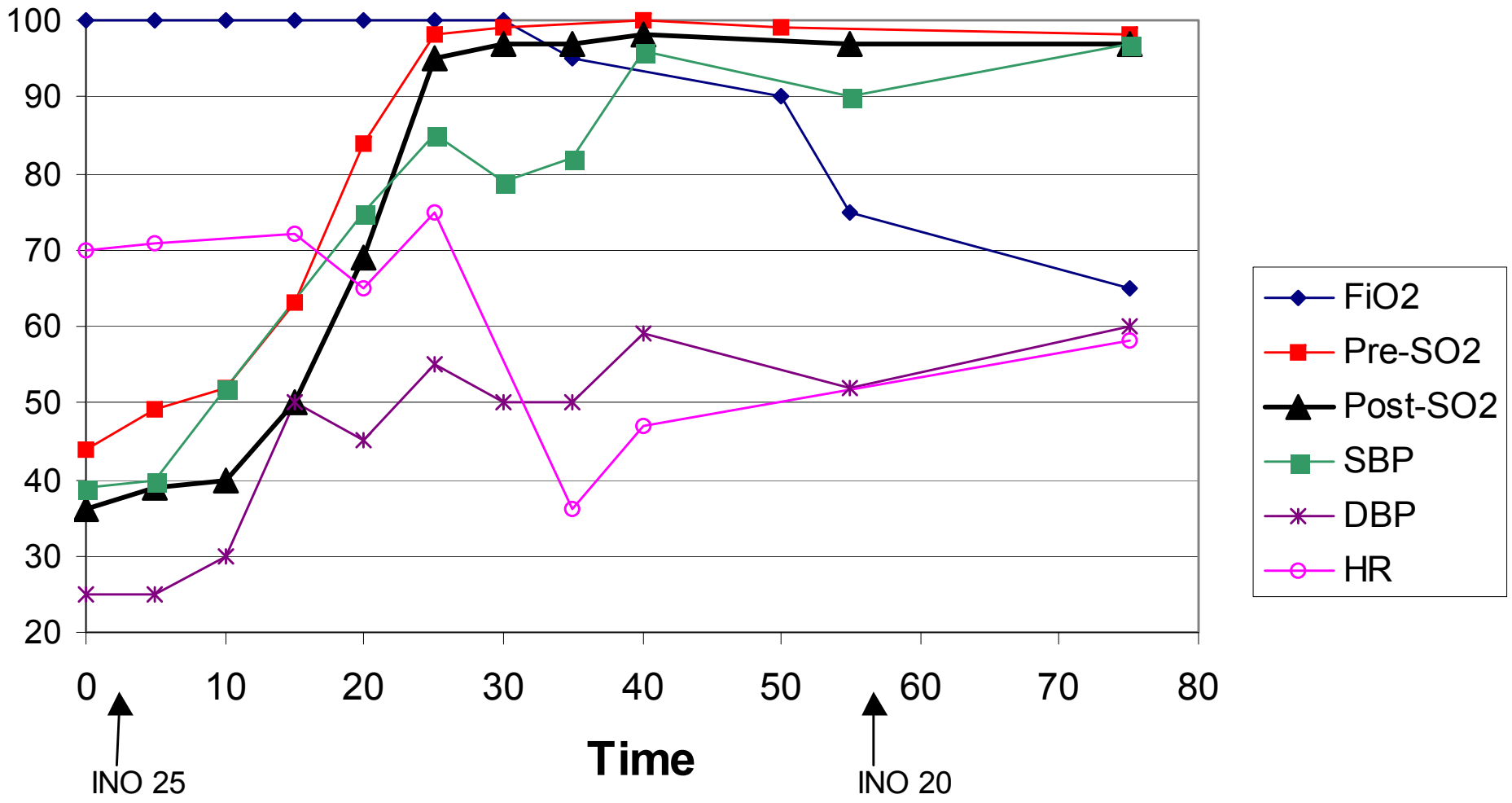


PPHN 4250g IMV 100 P25/0 Ti 0.3



Case #8 –(3), on IMV 100, P 25/0, Ti 0.3

O_2 saturation and BP response to INO,



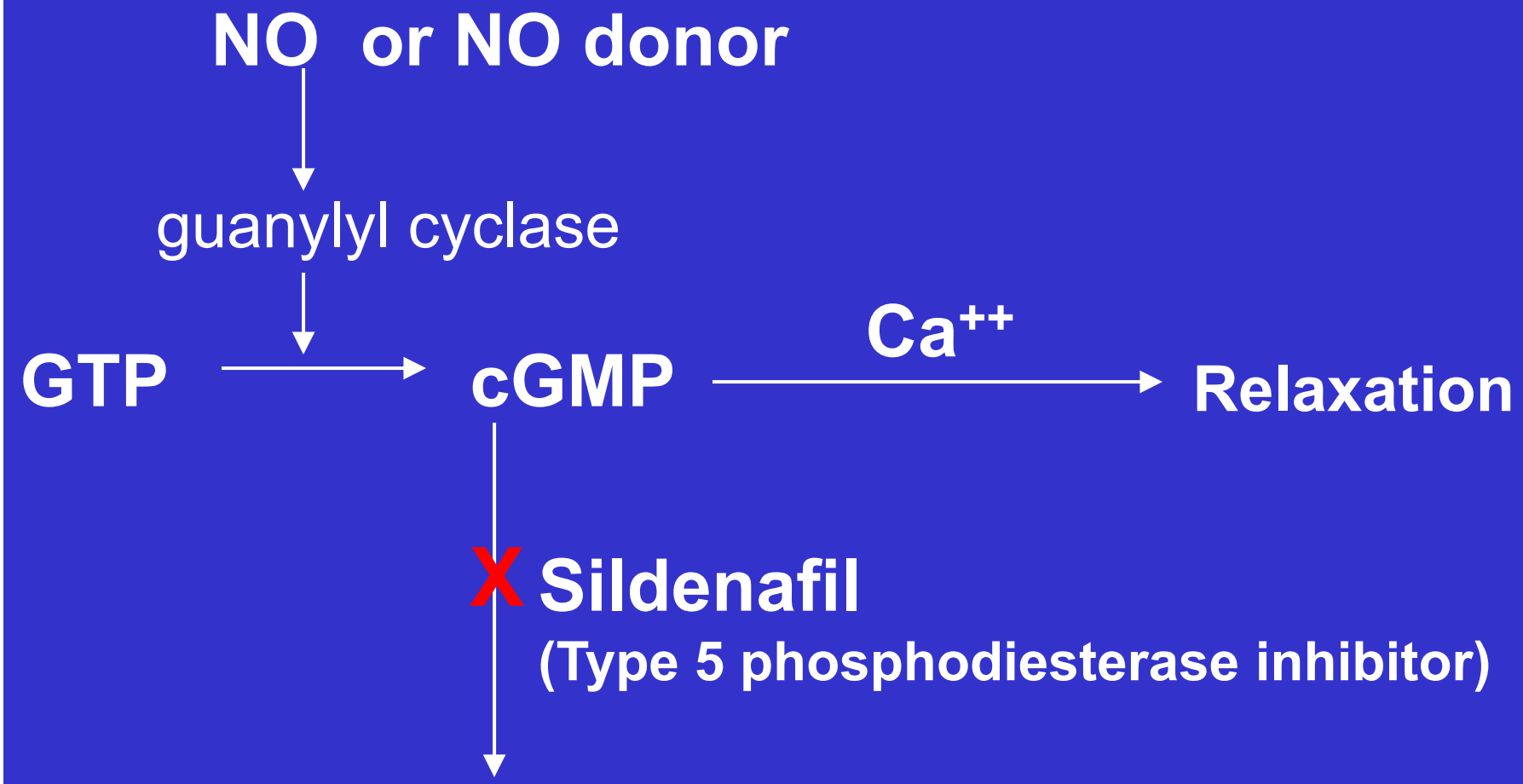
- Understand the nature of the disease
- Watch for trending
- Be patience

- 735 gm, 26 wks,PROM x7 days, oligohydramions
- Stat c-section for preterm labor, variable deceleration, breech presentation, cord prolapse,
- Apgar score 7/1', 8/5'
- CPAP $FiO_2$40%, Deteriorated during transport from TN to NICU, $FiO_2$60%,→ NTT → $FiO_2$100%,IMV rate 40, P 20/5, O_2 sat. 50's→Curosurf → O_2 sat. transiently ↑to 90's for 5 min. and then ↓to <20's
- ECHO revealed PPHN
- INO 20ppm started with slowly ↑ O_2 sat.
- INO x 3days, IMV x 4days, CPAP x 85 days, Discharged at DOL#100

30% of PPHN fail to respond to iNO

It is not the single magic bullet for the complex pathophysiology of PPHN

Nitic Oxide Pathway

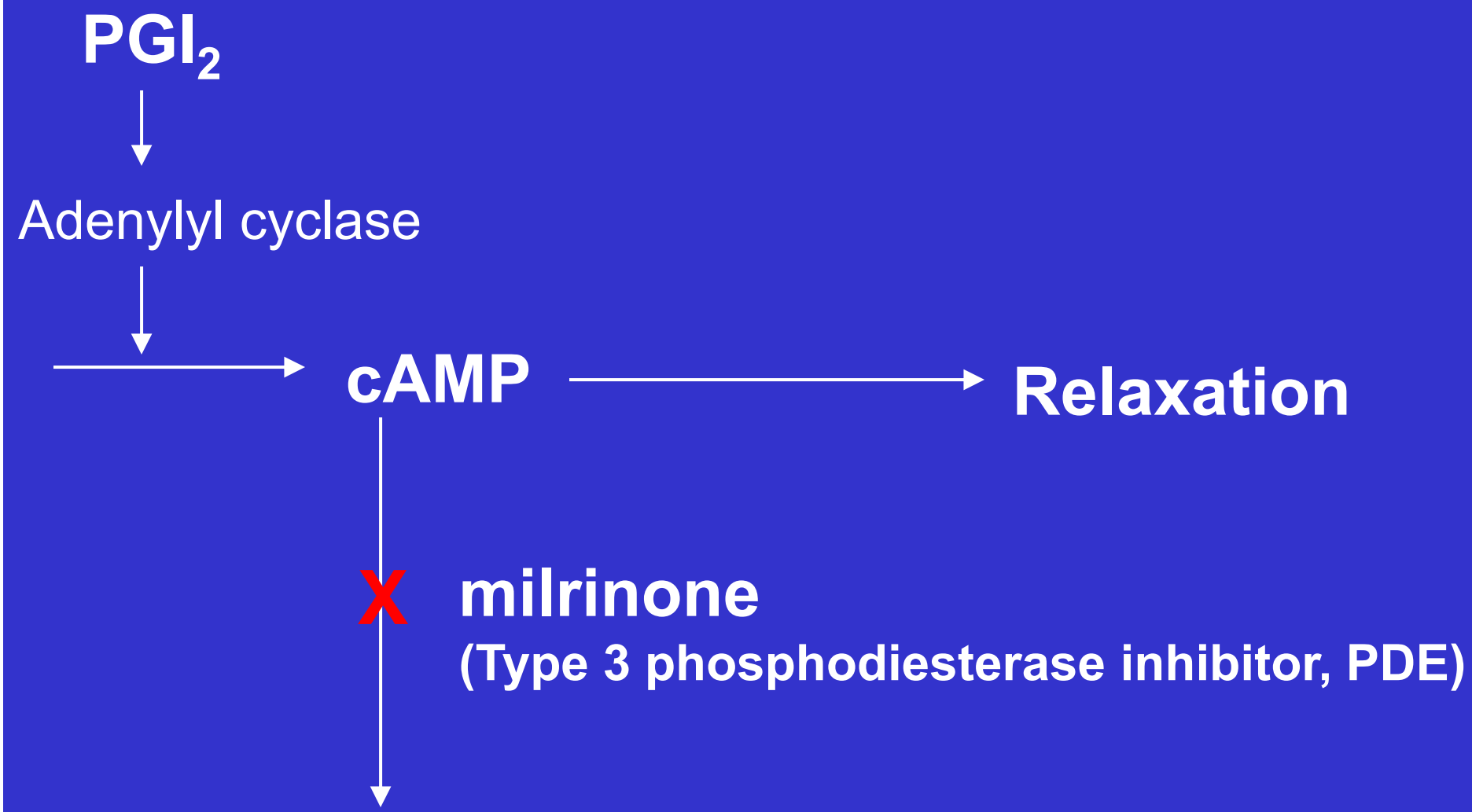


Intravenous Sildenafil for PPHN

- Loading dose: 0.4mg/kg over 3 hours
- Maitenance infusion: 1.6mg/kg/day

Steinhorn et al, J Pediatr, 2009

Prostacycline Pathway



Inhaled Nitric Oxide

Phosphodiesterase type 5 inhibitor (PDE5):

sildenafil

Prostacycline:

ventavis (iloprost) inhalation

treprostinil (remodulin) I.V. or S.C.

(tyvaso) oral inhalation (>18 yr. old)

epoprostenol (flolan) I.V.2ng/kg/min, ↑2 ng q8h

Phosphodiesterase type 3 inhibitor (PDE3):

milrinone

Endothelin receptor antagonist:

bosentan, Ambrisentan

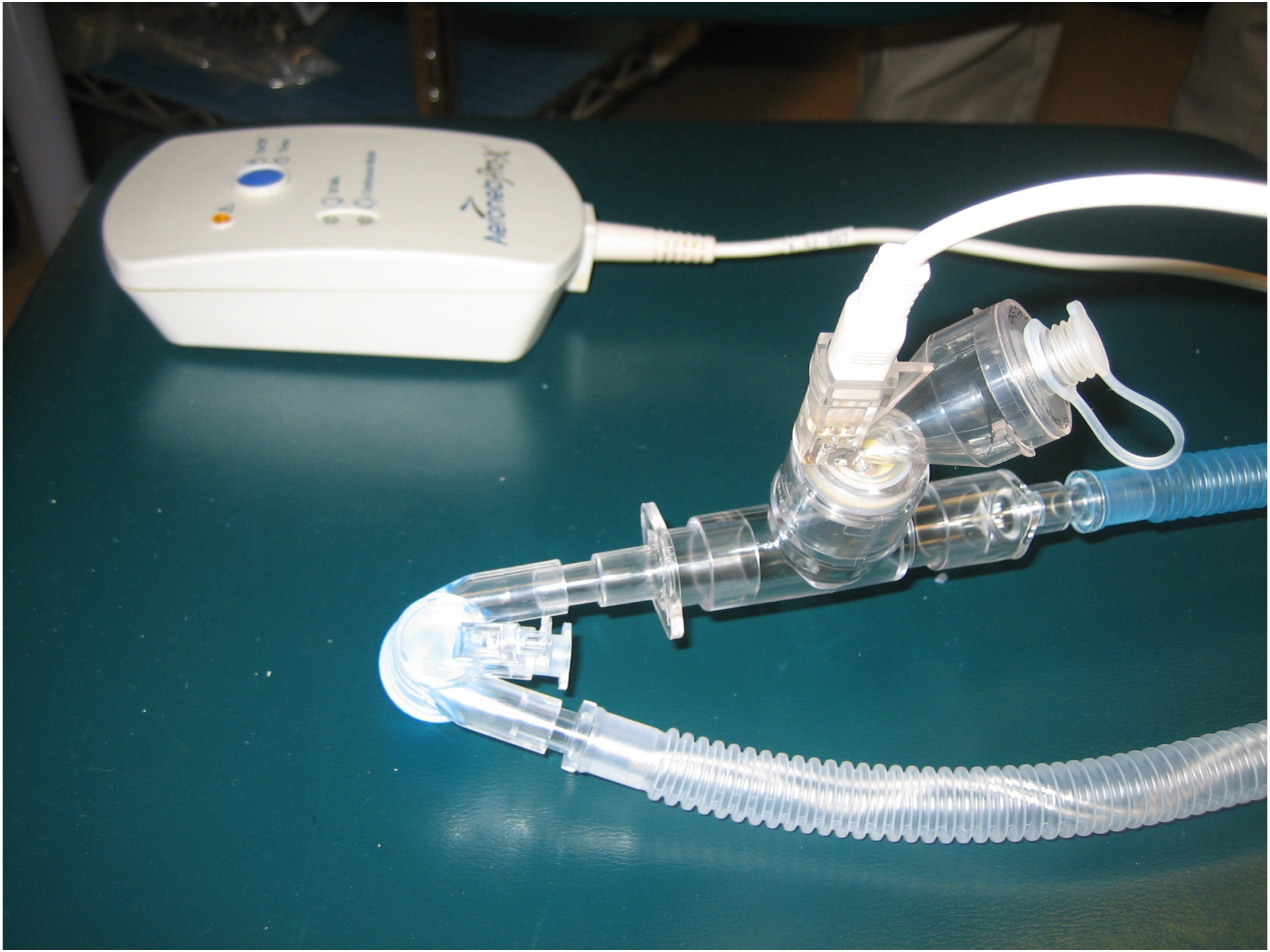
Inhaled prostacyclin for term infants with PPHN refractory to iNO

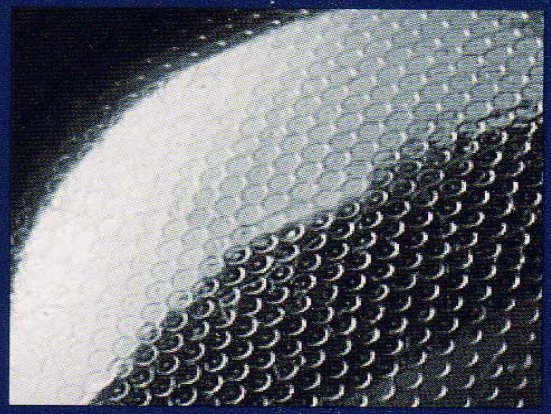
Four infants with severe PPHN unresponsive to iNO show improvement with inhaled PGI_2. The intravenous form of PGI_2 was aerosolized in an alkaline solution through the respiratory circuit. Age at initiation of PGI_2 ranged from 1 day to 16 days old and was preceded with iNO for at least 3 hours (range 3hr to 14 days). Within 1 hour of initiation of PGI_2, mean PaO_2 increased from 57 to 100 ($p = 0.06$) and within 2 hours, mean OI decreased from 29 to 19 ($p<0.05$). 3 MAS survived, 1 ACD with transient response and died 6 days later.

The journal of Pediatrics 2002;141:830-2, Kelly LK et. al.

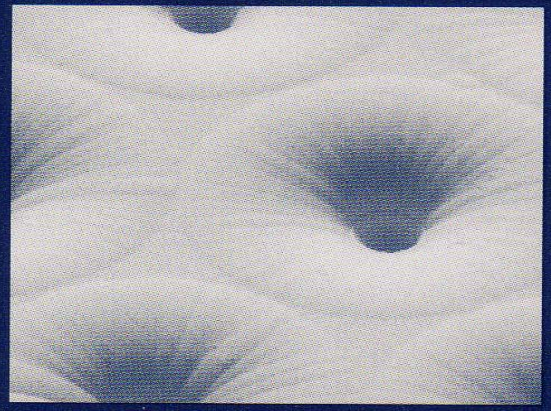
iloprost (Ventavis) inhaled

- 2.5 - 5mcg (10 mcg/ml) diluted with Glycine solution or normal saline to make total volume 2 ml to be inhaled over 15 min.
- Nebulization using Aeroneb (electronic micropump) q3hr. 6 - 9 times/day
- (Half-life 20 – 30 min.)
- For severe acute PPHN, q 45 - 60 min
- Continuously nebulization: 10 mcg diluted in 9 ml N/S to run 2-3 ml/hr, after 2.5 - 5 mcg in 2 ml N/S to show improvement.
- Monitor vital signs and O_2 saturations


AeroEclipse

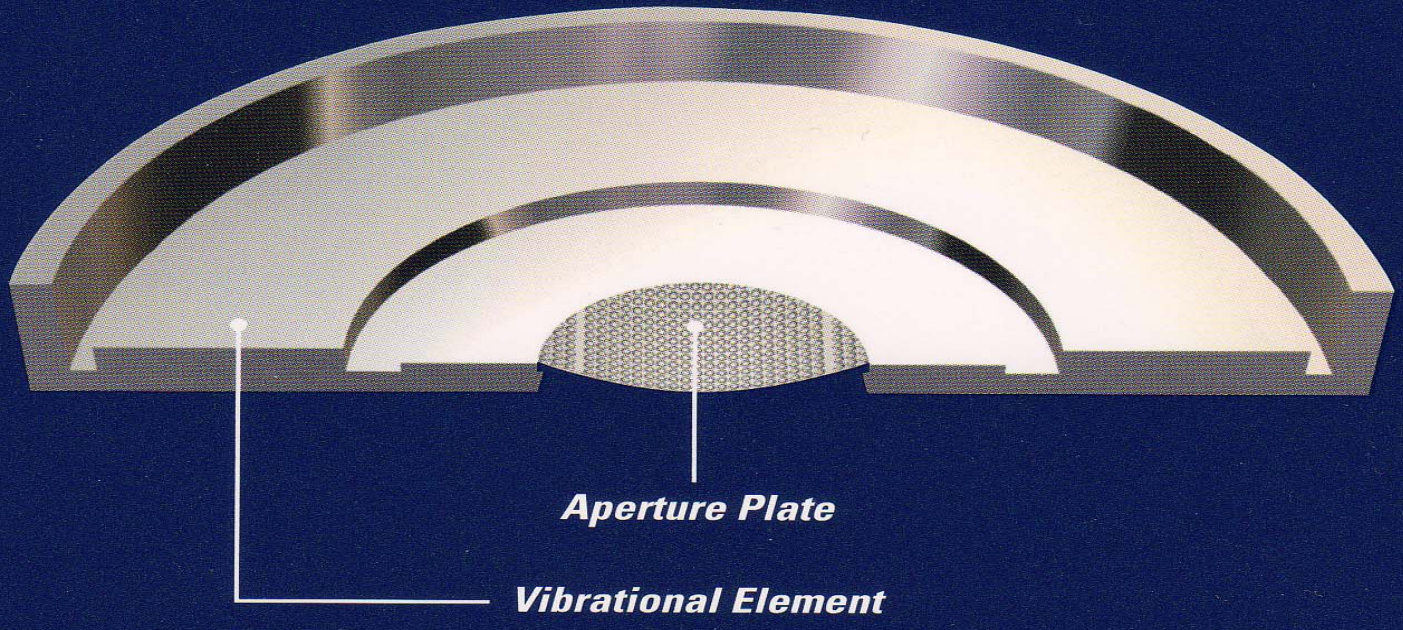


Aperture Plate

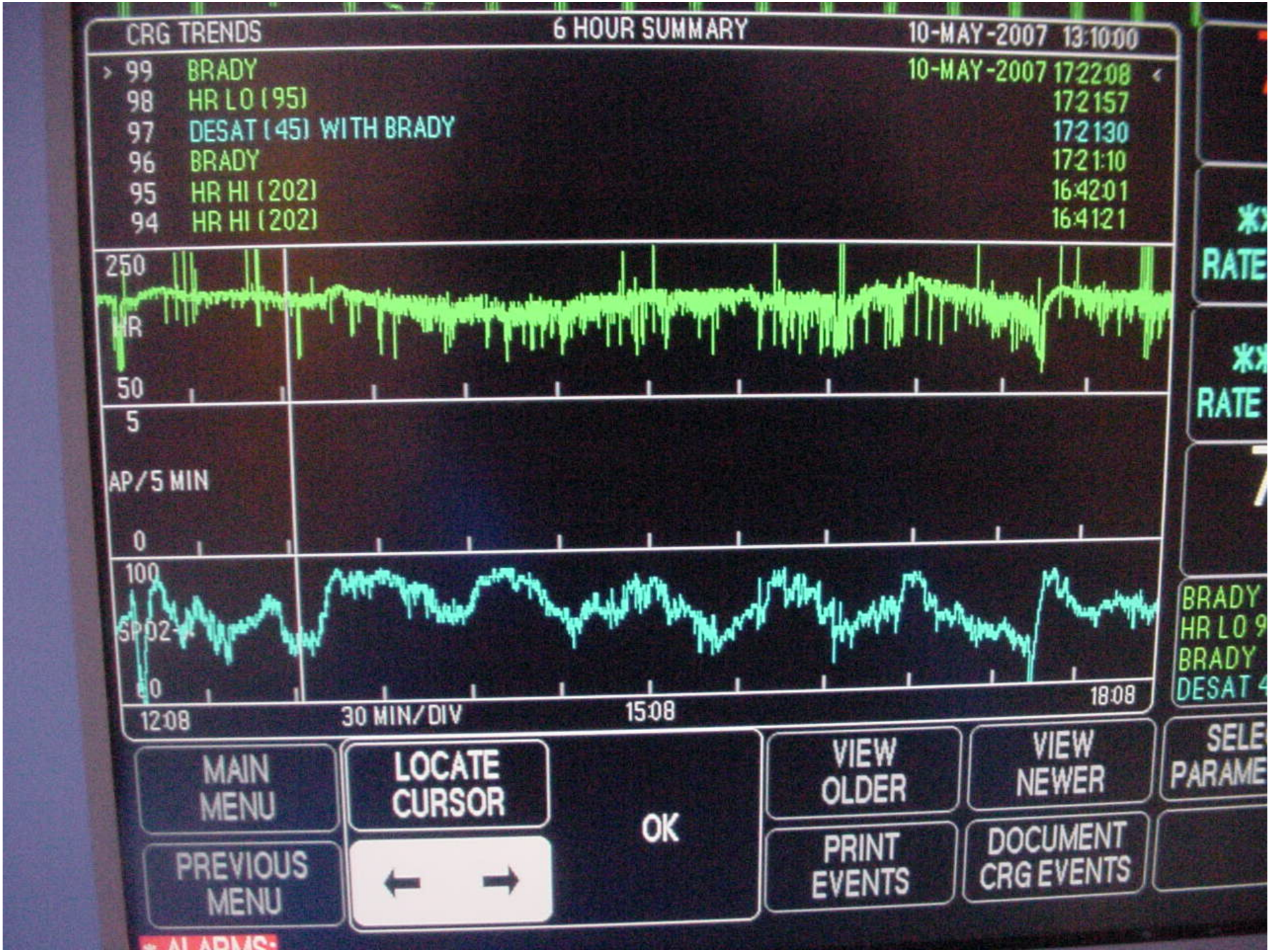


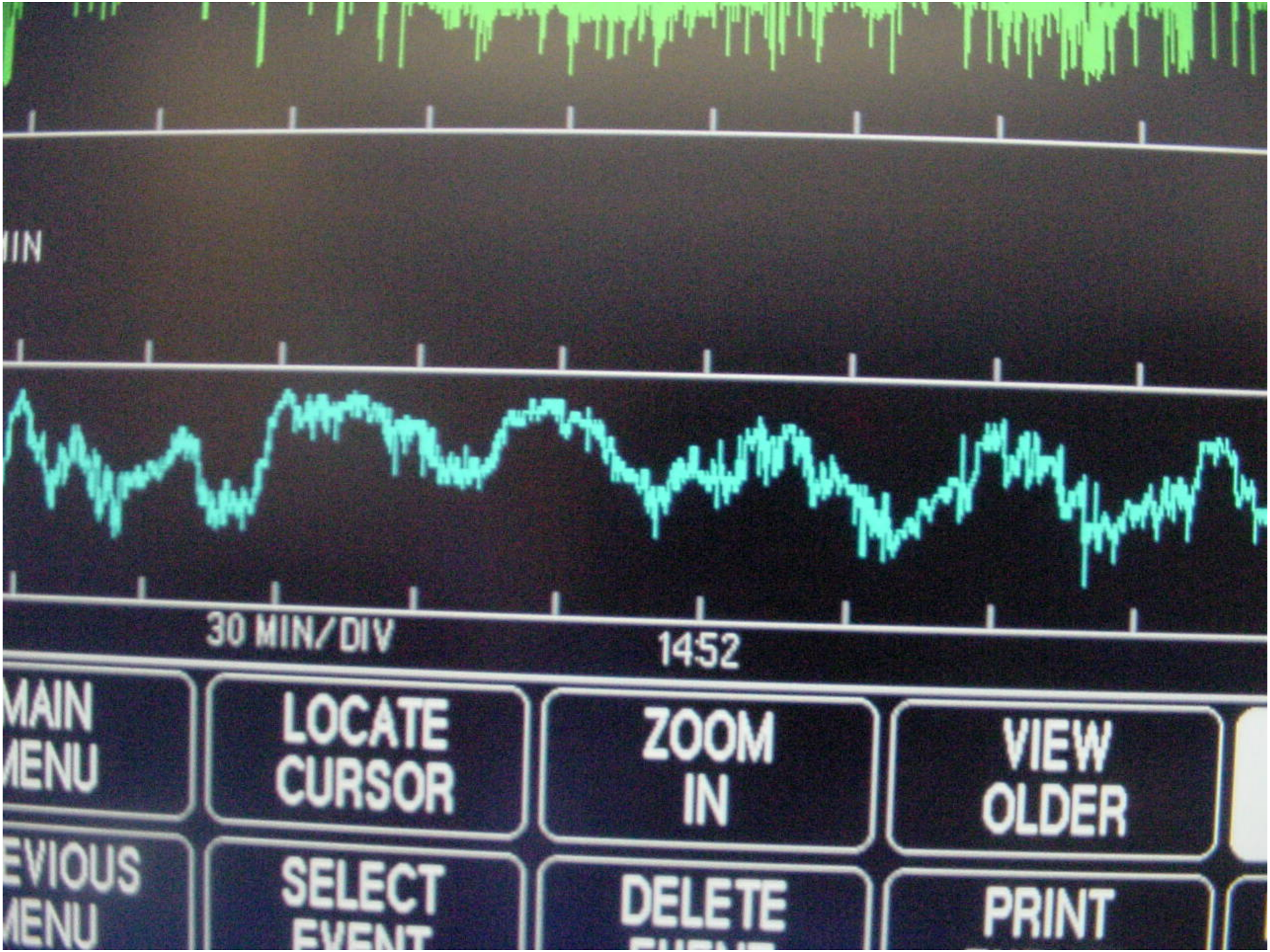
Aperture Plate
(enlarged 250X)

Electronic Micropump
Aerosol Generation

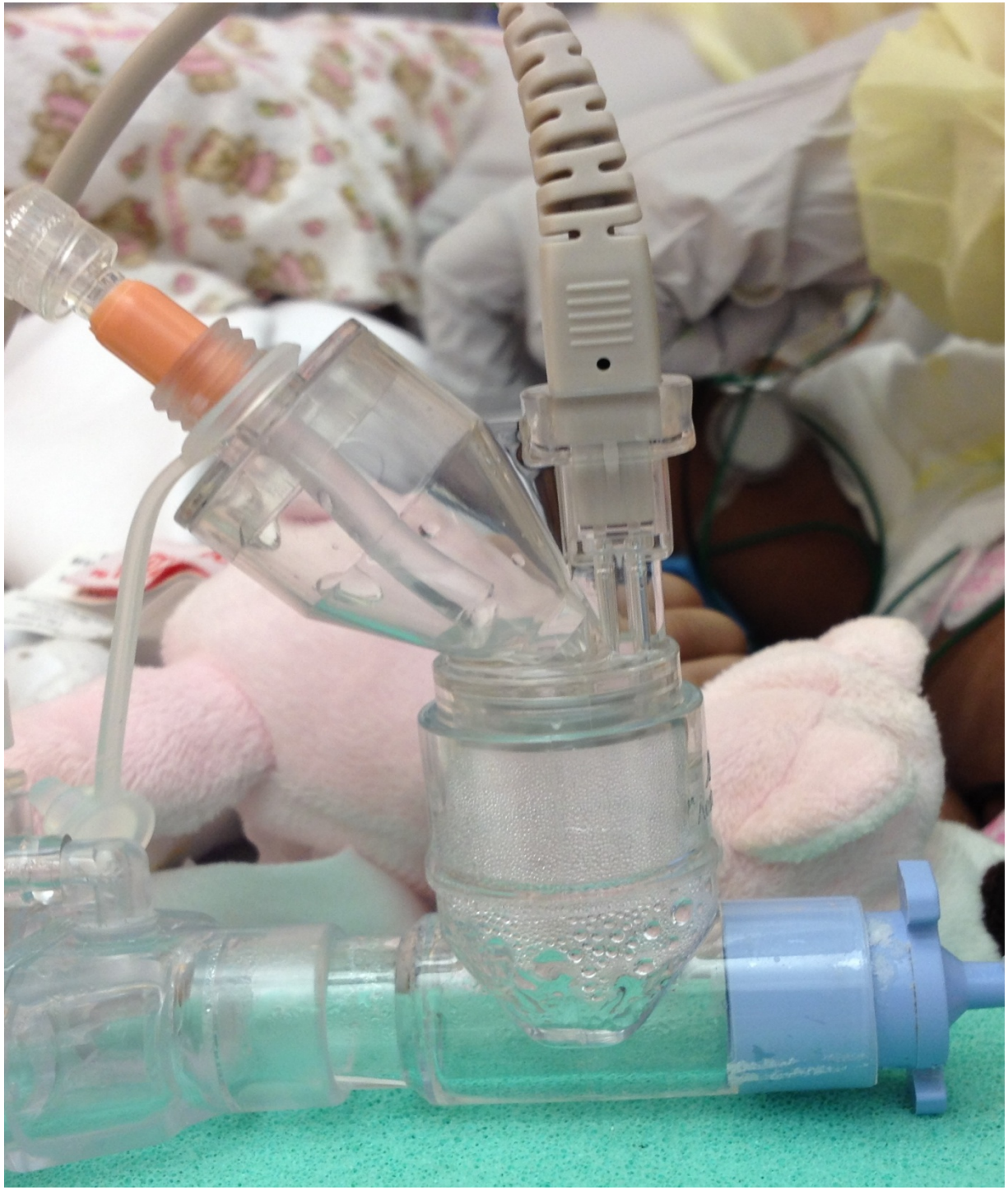


On/Off
Timer
30 Min.
Continuous Mode
Biomedical Engineering
Pro-X
AeroChamber Plus

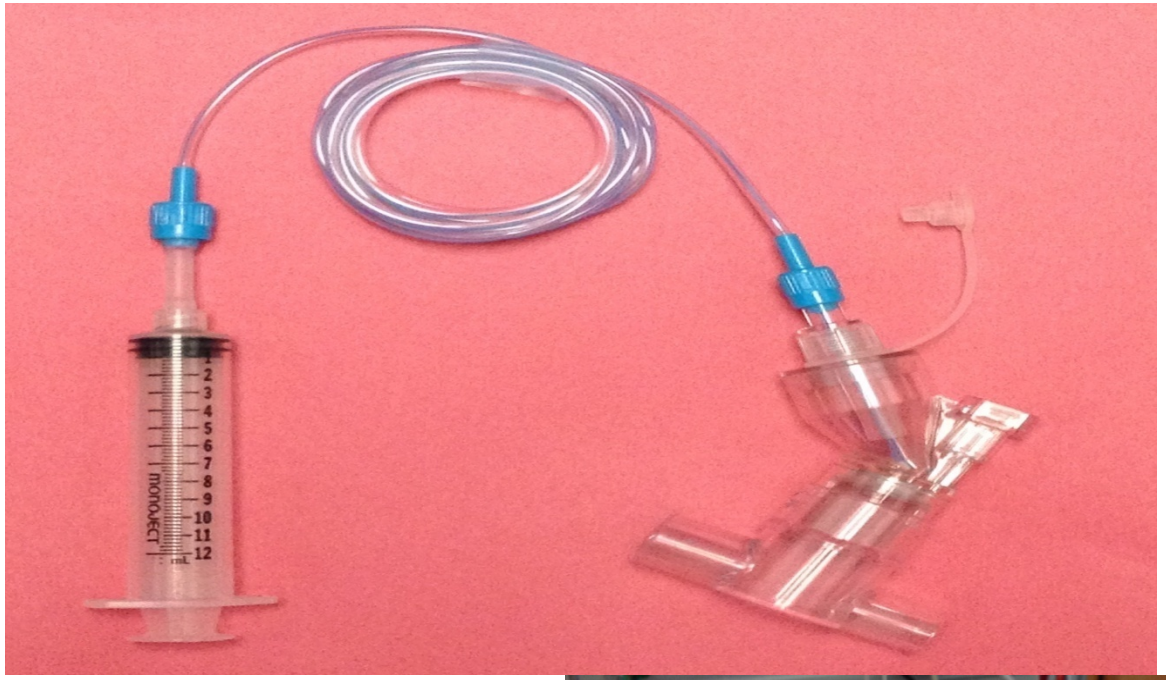

CRG TRENDS
6 HOUR SUMMARY
10-MAY-2007 13:10:00
99 BRADY
98 HR LO (95)
97 DESAT (45) WITH BRADY
96 BRADY
95 HR HI (202)
94 HR HI (202)
10-MAY-2007 17:22:08
17:21:57
17:21:30
17:21:10
16:42:01
16:41:21
250
HR
50
5
AP/5 MIN
0
100
SPO2
0
12:08
30 MIN/DIV
15:08
18:08
RATE
RATE
BRADY
HR LO 9
BRADY
DESAT 4
MAIN MENU
LOCATE CURSOR
OK
VIEW OLDER
VIEW NEWER
PREVIOUS MENU
PRINT EVENTS
DOCUMENT CRG EVENTS


IN
30 MIN/DIV
1452
MAIN MENU
LOCATE CURSOR
ZOOM IN
VIEW OLDER
EVIOUS MENU
SELECT EVENT
DELETE
PRINT

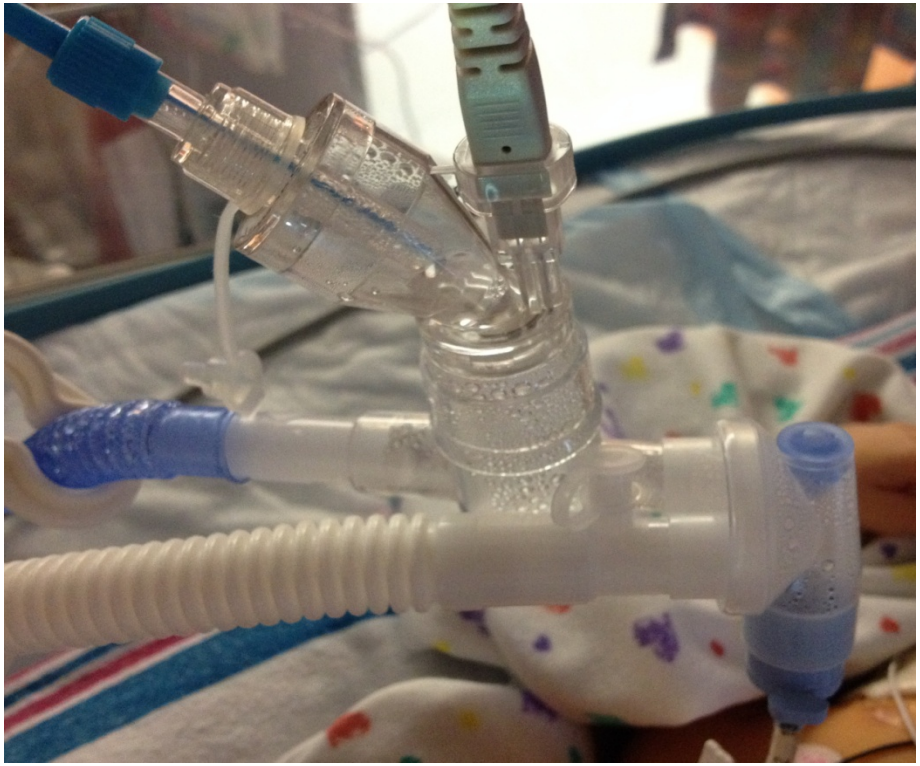
Ilopost inhaled continuously



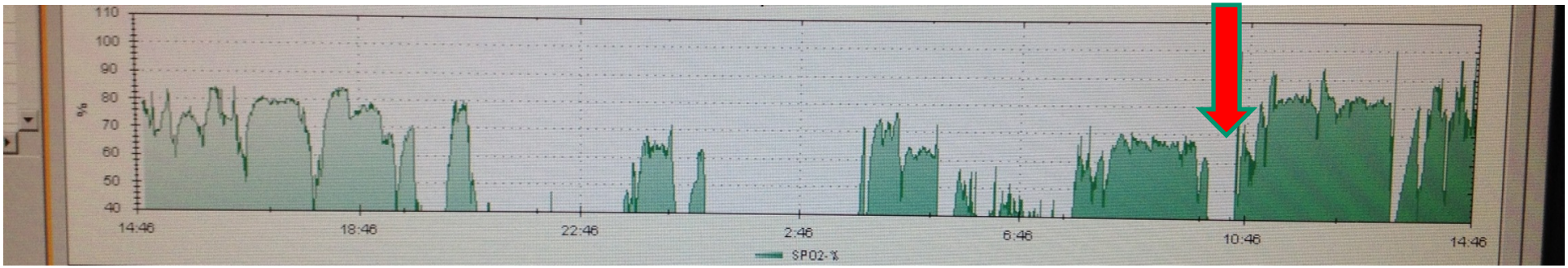
SIMV

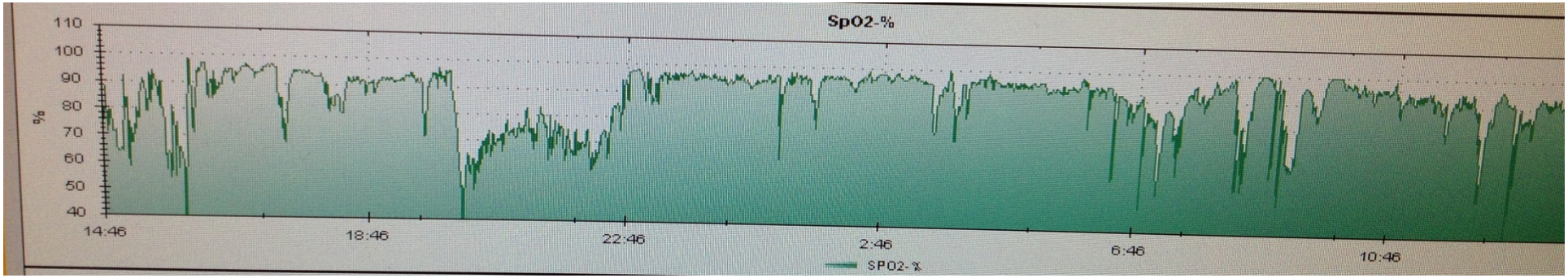


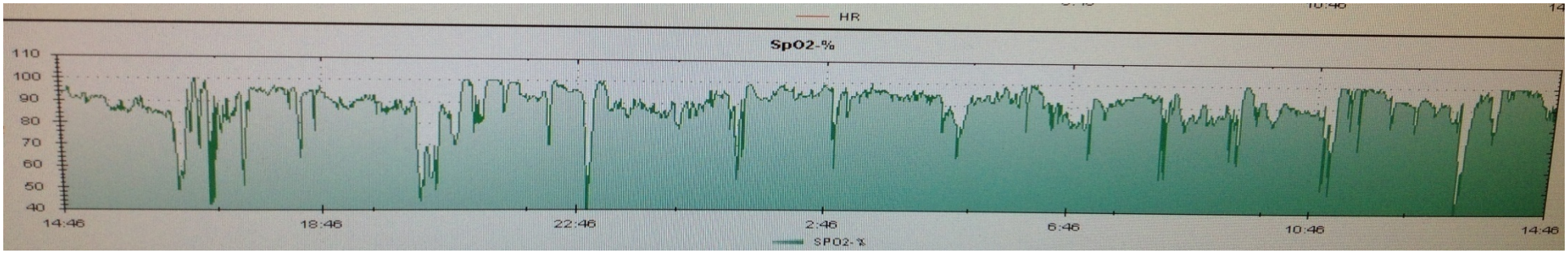
HFO

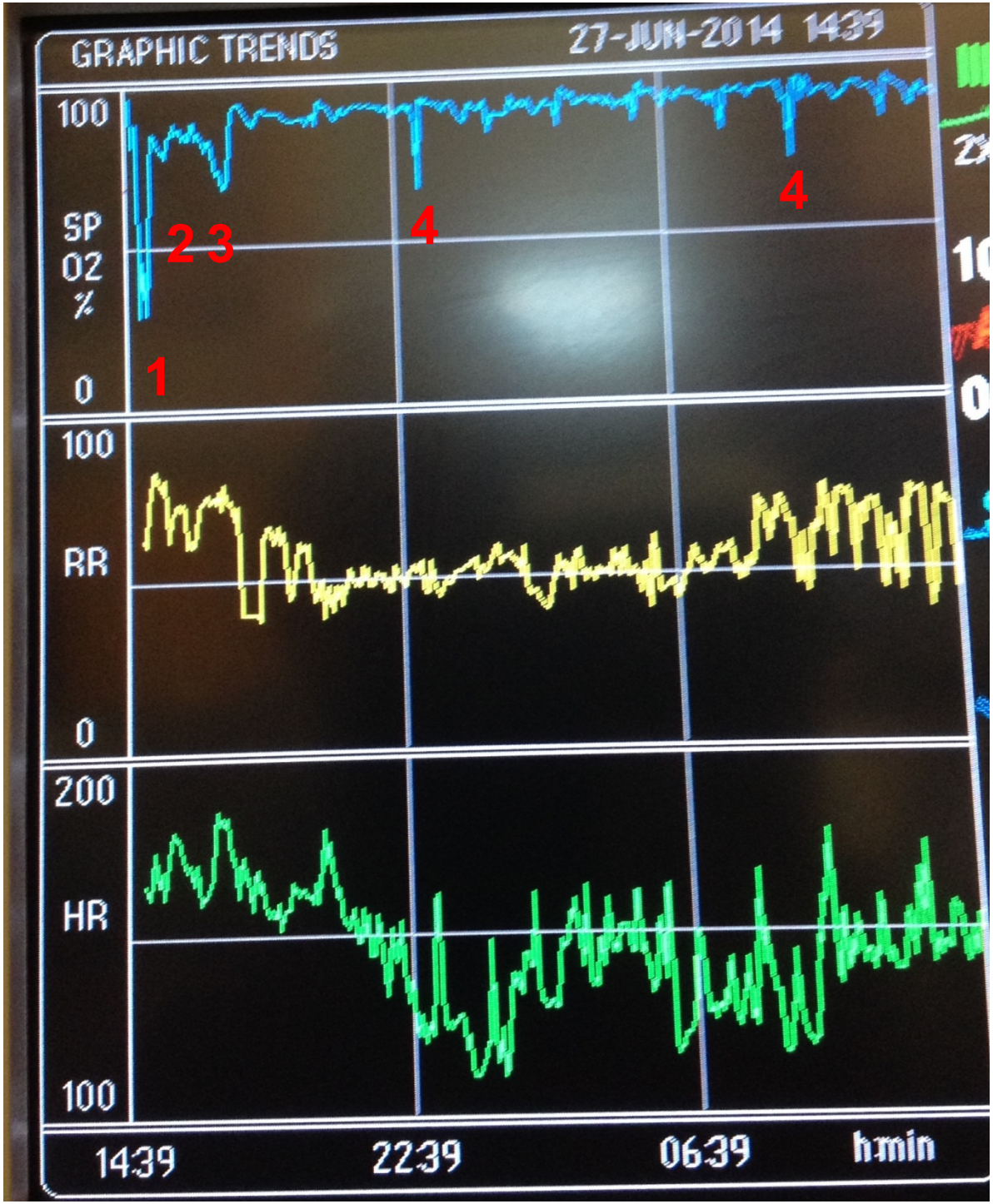


flolan I.V. infusion
→inhaled ilopost continuously







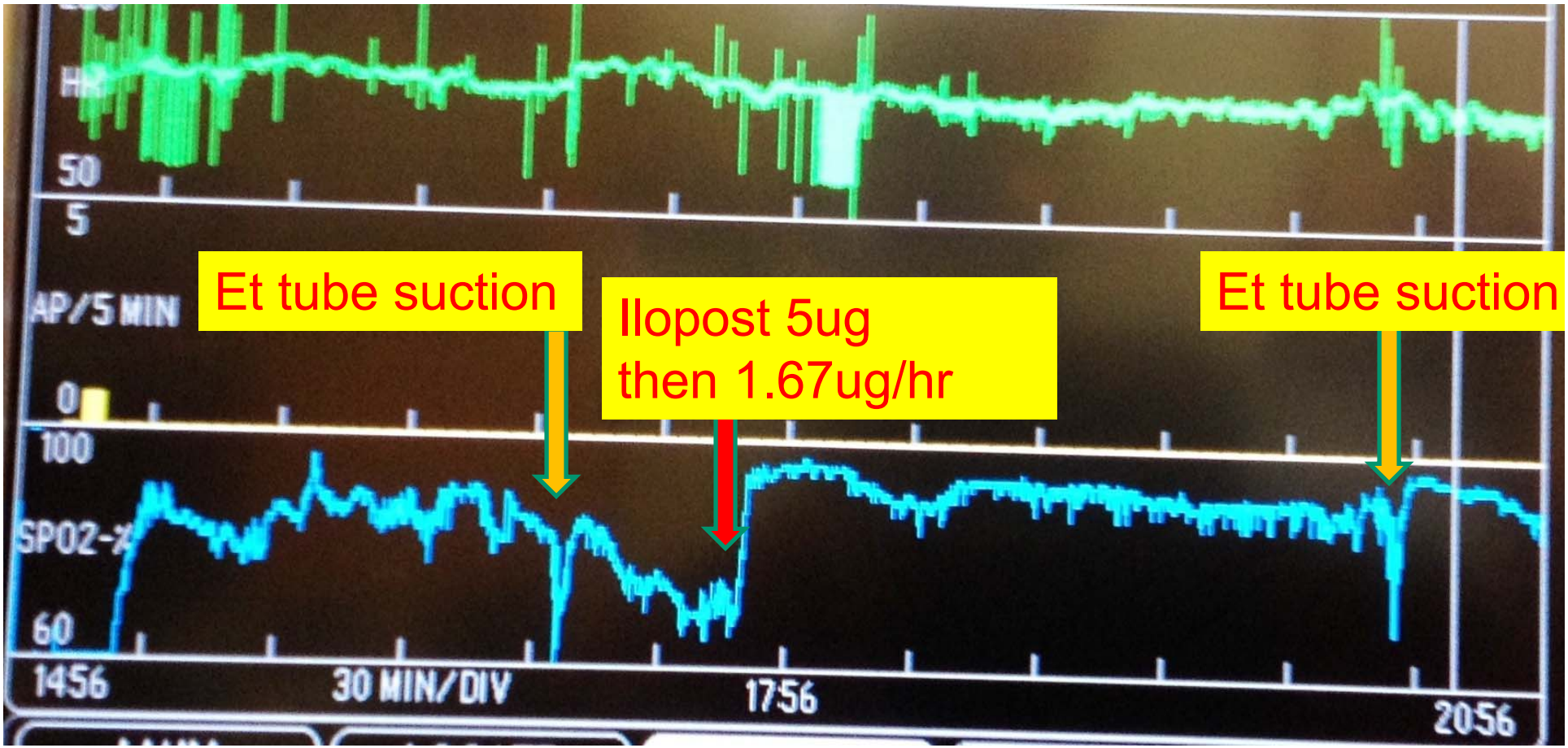


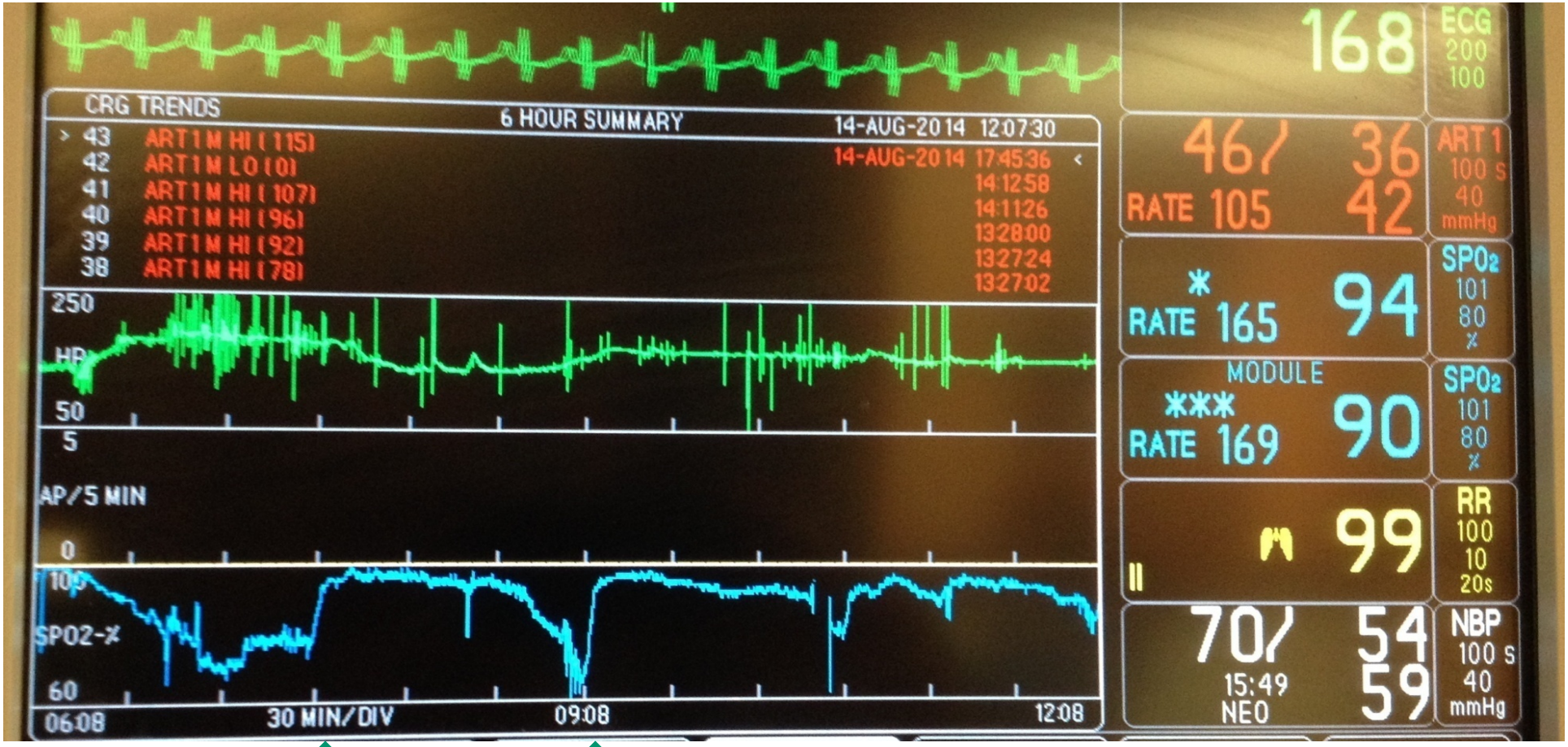
1.HFO

2.A/C

3. Iloprost 5 ug (in 2 ml saline) nebulization followed by continous nebulization 1.67ug (in 2 ml saline)/hr

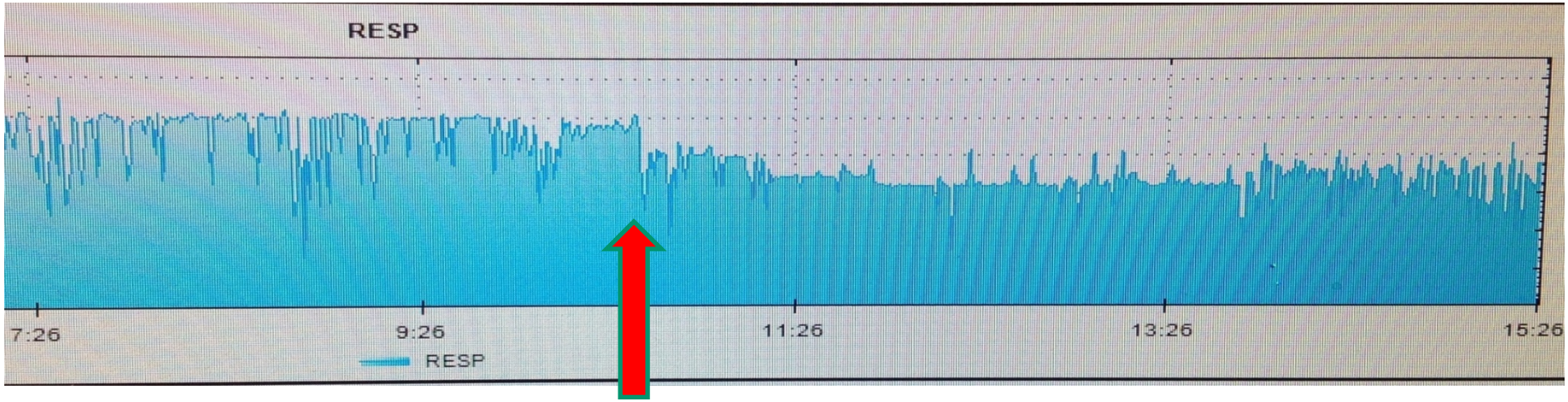
4. Et tube suction


50
5
AP/5 MIN
0
100
SPO2-%
60
1456
30 MIN/DIV
1756
2056
Et tube suction
Ilopost 5ug
then 1.67ug/hr
Et tube suction

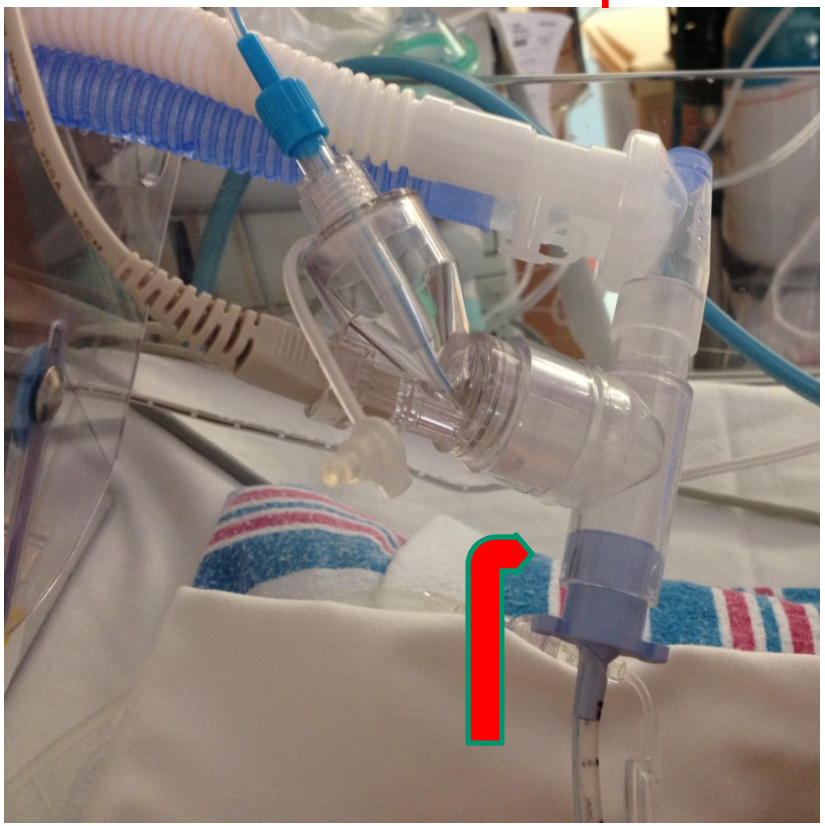


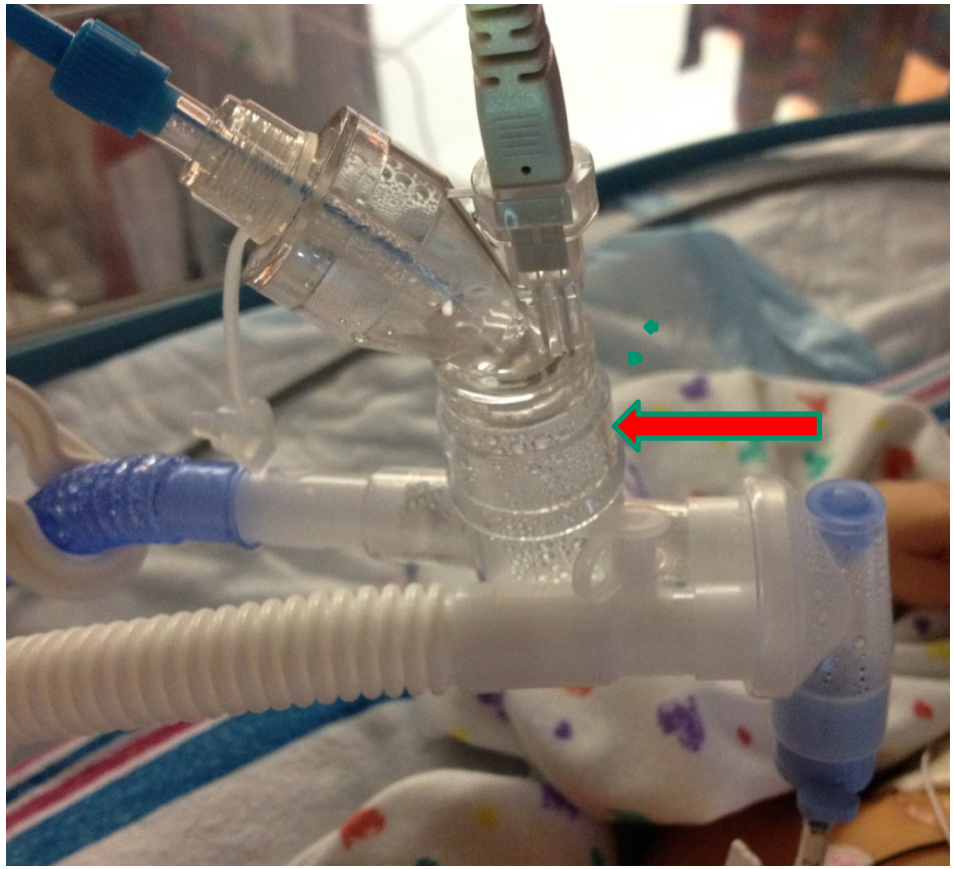
Ilopost 2.5ug in 2 ml N/S bolus

Ilopost 2.5ug in 2 ml N/S bolus then Ilopost 10ug in 11 ml N/S to run 2ml/hr

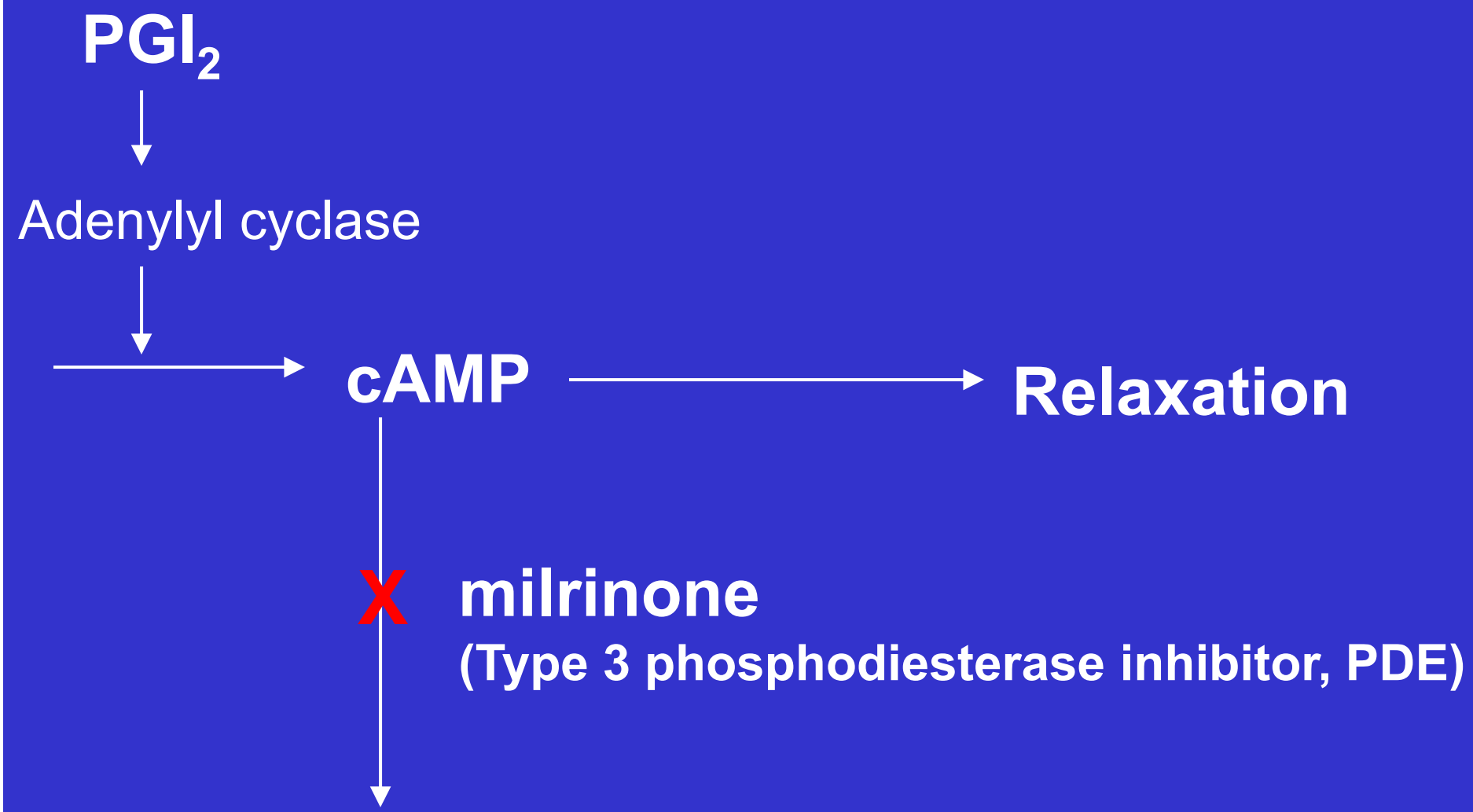


Increased deadspace





Prosacycline Pathway



Inhaled Nitric Oxide

Phosphodiesterase type 5 inhibitor (PDE5):

sildenafil

Prostacycline:

ventavis (iloprost) inhalation

treprostinil (Remodulin) I.V. or S.C.

epoprostenol (flolan) I.V.2ng/kg/min, ↑2 ng q8h

Phosphodiesterase type 3 inhibitor (PDE3):

milrinone (0.3 ug/kg/min → 0.5ug/kg/min)

Endothelin receptor antagonist:

bosentan ,Ambrisentan

Inhaled Nitric Oxide

Phosphodiesterase type 5 inhibitor (PDE5):

sildenafil

Prostacycline:

ventavis (iloprost) inhalation

treprostinil (Remodulin) I.V. or S.C.

epoprostenol (flolan) I.V.2ng/kg/min, ↑2 ng q8h

Phosphodiesterase type 3 inhibitor (PDE3):

milrinone

Endothelin receptor antagonist:

bosentan (ETA & ETB antagonist, 1.5mg/kg/d q12h → 3mg/kg/d q12h, P.O.)

ambrisentan (selective ETA antagonist)

Endothelin receptor antagonists

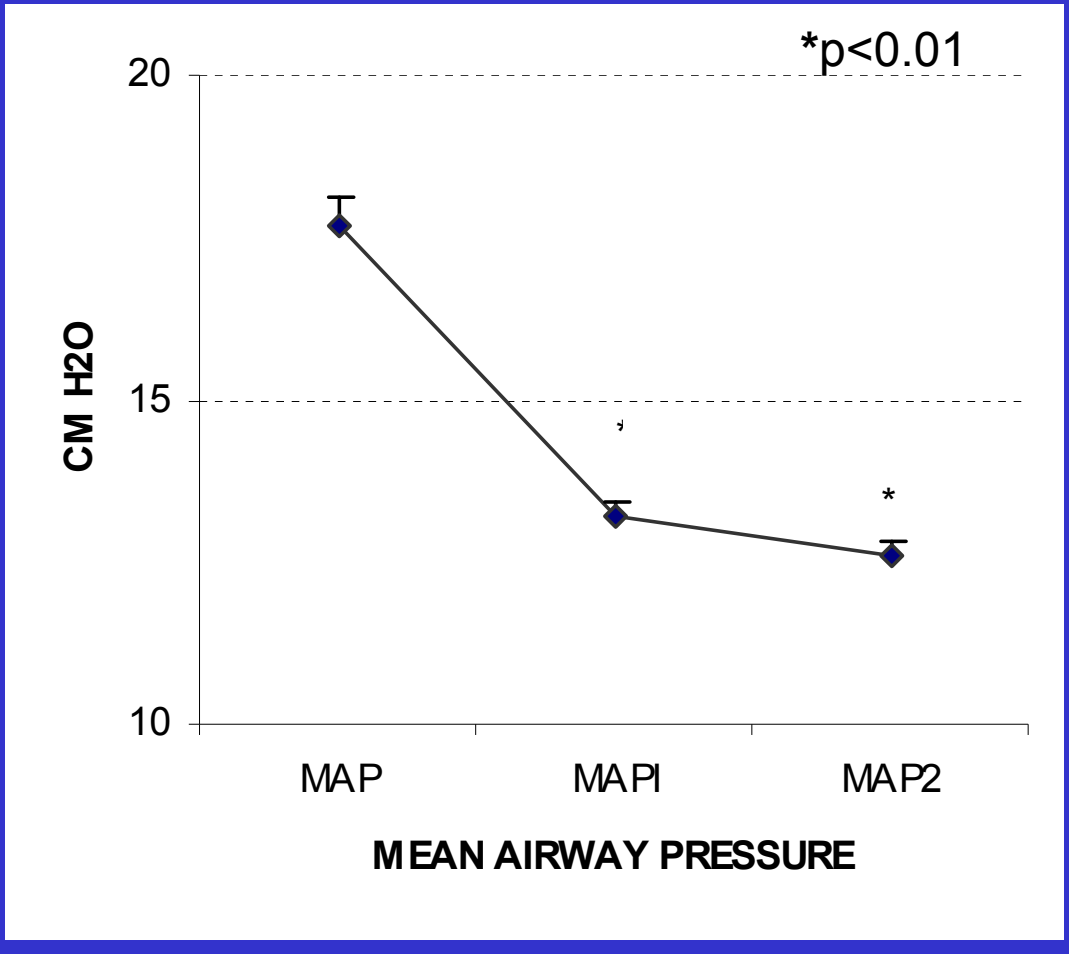
- bosentan and sitaxsentan

  have been reported to be effective in treating pulmonary hypertension. It remains to be seen if they are safer, more effective or even complementary to sildenafil.


Thank You for your attention
Wishing you a truly fabulous day

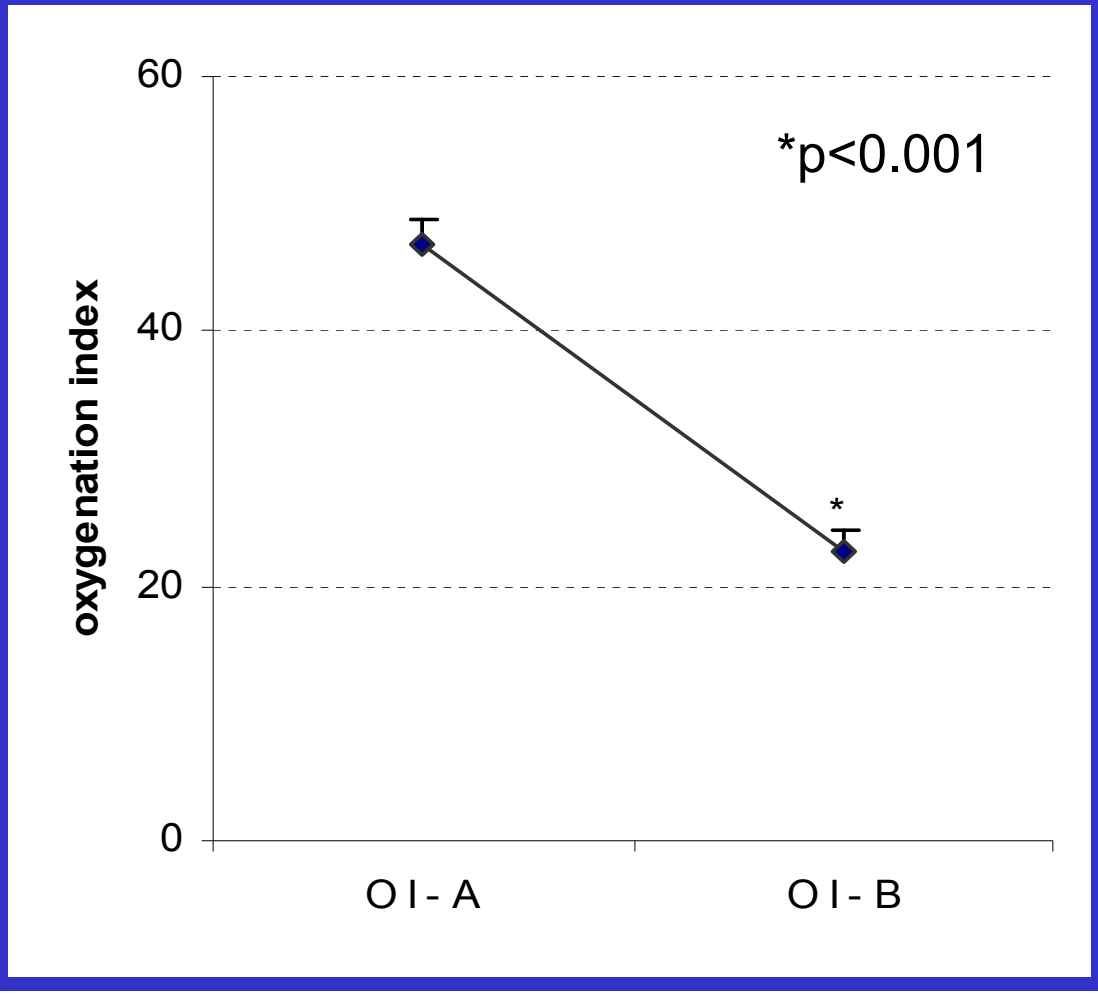
MAP: MAP at referral hospital, **MAP1:** baseline MAP following admission and before INO therapy, **MAP2:** MAP within 24 hours of INO therapy

Journal of Perinatology 2002; 22: 435



Oxygenation index before (OI-A), and after starting INO therapy (OI-B)

Journal of Perinatology 2002; 22: 435



	CHONY	Kinsella	NINOS	Davidson	Clark
N	112	107	114	114	126
Gestation (wks)	40 (med)	>34	>34	>37	>34
Baseline O.I.	50.7 ± 2.6	49.3 ± 3.4	43.0 ± 17.6	24 ± 9	37+24
PaO2 (mm Hg)	32.7 ± 1.3	40.3 ± 1.7	46.8 ± 15.5	59 ± 16	72+64
PH	7.26 ± 0.2	7.41 ± 0.02	NA	7.50 ± 0.11	7.45+0.1
$PaCO_2$ (mm Hg)	51.9 ± 2.2	35.5 ± 1.3	NA	30 ± 9	35+13
INO (hours)	45 (med)	75.5 ± 1.1	40 (med)	58 ±	<96
Ventilator days	6.69 ± 0.3	9 ± 1	11.6 ± 7	9.2 ± 7.4	11+7
Nonresponders (ECMO+deaths)	25%	30-60%	46%	29.8%	40%
ECMO	17.9%		39%		38%
Mortality	8%	15%	14%	8%	8%