UCDAVIS
CHILDREN'S HOSPITAL

Neonatal Resuscitation: Scientific Basis

MIAMI NEONATOLOGY 2019

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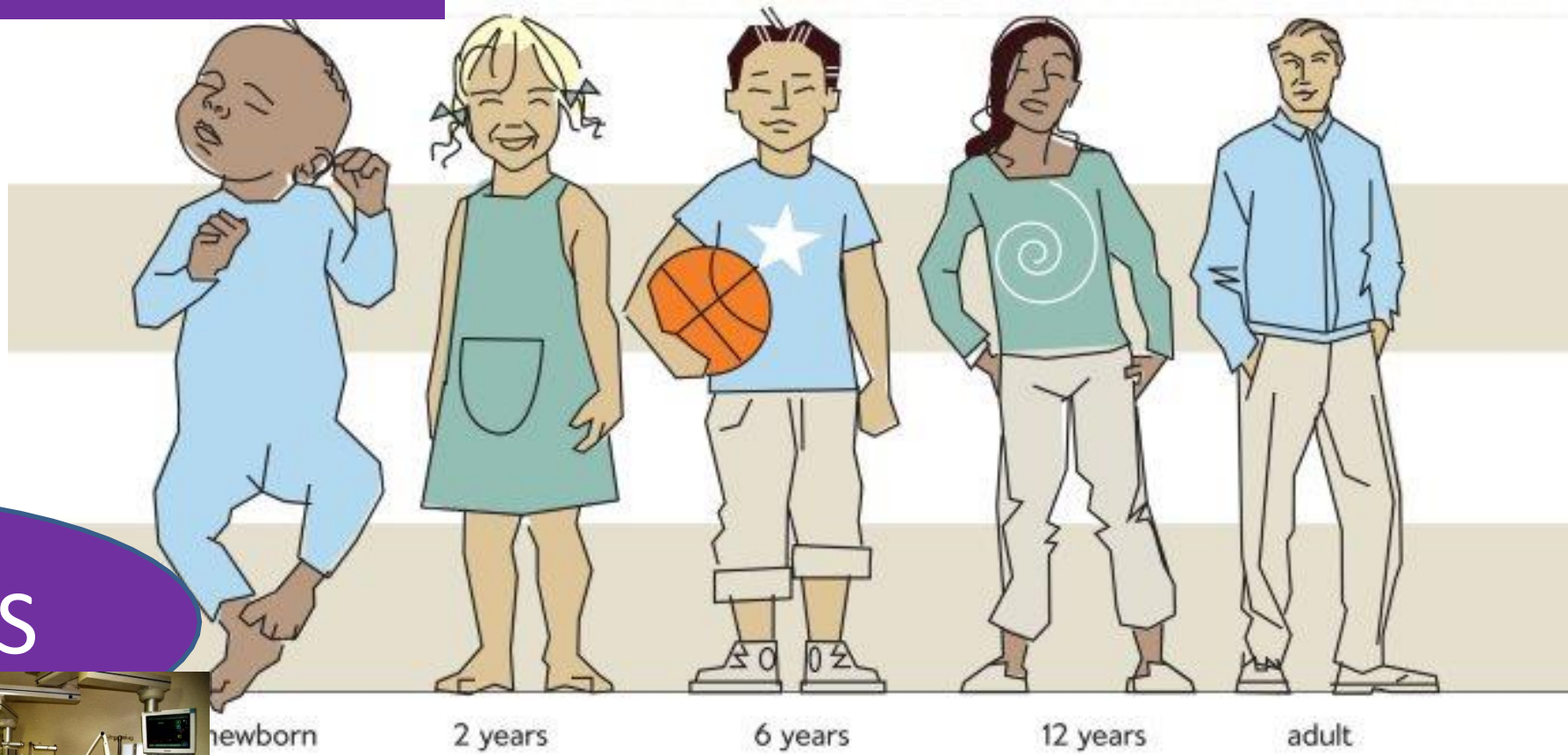
All images courtesy of Satyan Lakshminrusimha, MD.

Children are Not Small Adults

Extremely preterm neonates are not small term babies

Micropreemies

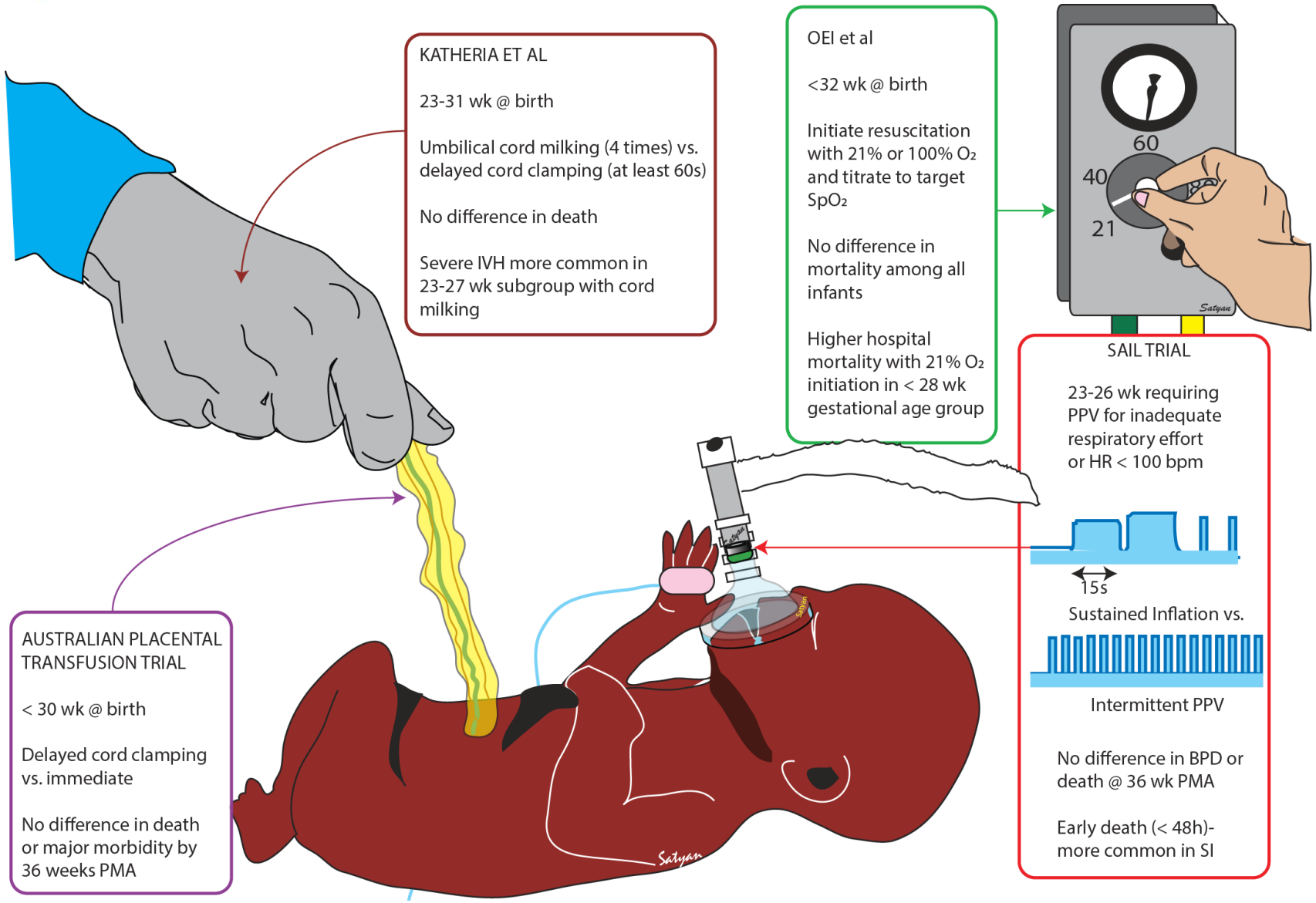
Babies are not small children



Credit: Martin Gradén/Volvo Car Corporation.
Source: Burdi AR, et al. *J Biomech*. 1969;2:267-280.

NRP vs. PALS

Evidence-Based Medicine vs. Physiologic Approach in Micro-preemies



KATHERIA ET AL

23-31 wk @ birth

Umbilical cord milking (4 times) vs. delayed cord clamping (at least 60s)

No difference in death

Severe IVH more common in 23-27 wk subgroup with cord milking

OEI et al

<32 wk @ birth

Initiate resuscitation with 21% or 100% O_2 and titrate to target SpO_2

No difference in mortality among all infants

Higher hospital mortality with 21% O_2 initiation in < 28 wk gestational age group

SAIL TRIAL

23-26 wk requiring PPV for inadequate respiratory effort or HR < 100 bpm

Sustained Inflation vs.

Intermittent PPV

No difference in BPD or death @ 36 wk PMA

Early death (< 48h)- more common in SI

AUSTRALIAN PLACENTAL TRANSFUSION TRIAL

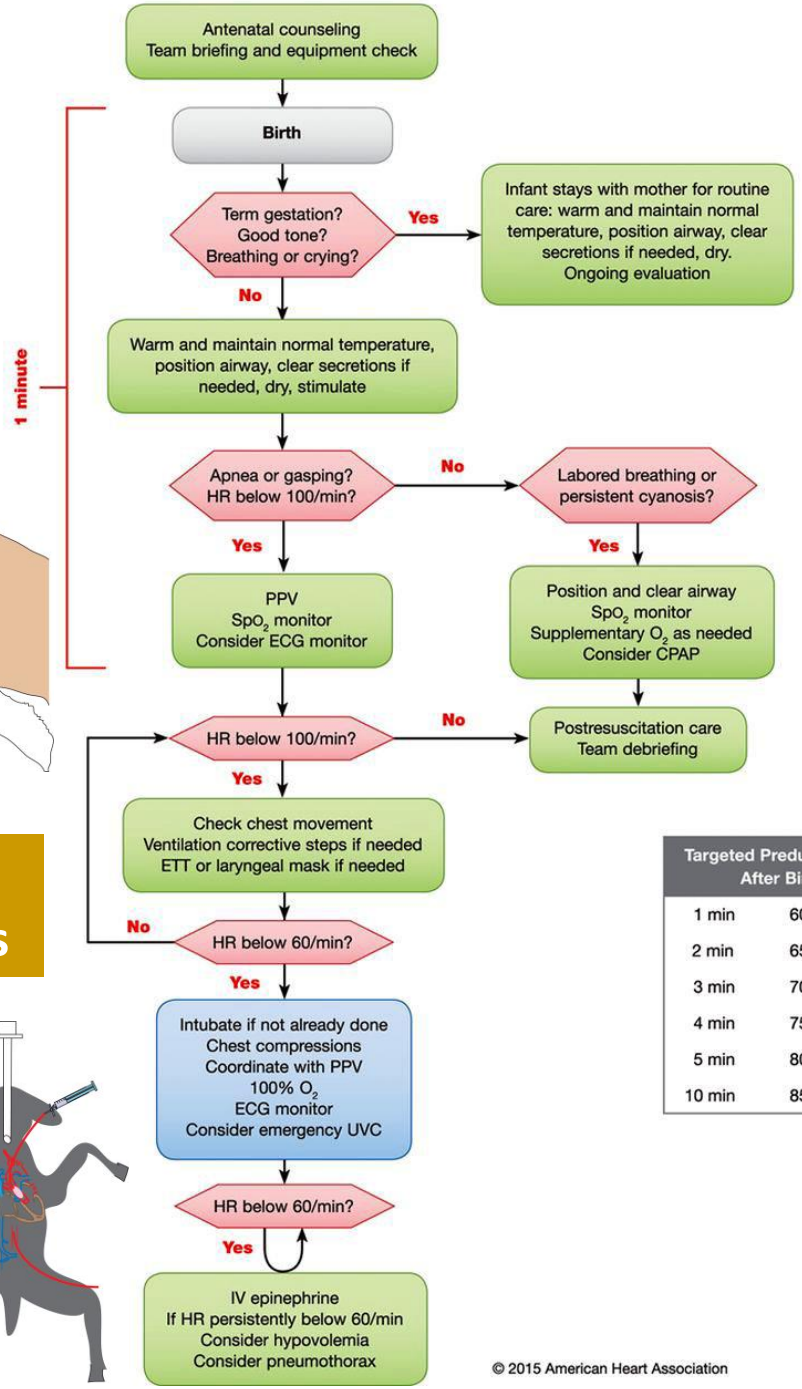
< 30 wk @ birth

Delayed cord clamping vs. immediate

No difference in death or major morbidity by 36 weeks PMA

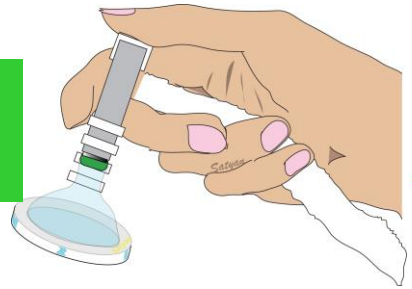
Physiology of Asphyxia

Neonatal Resuscitation Algorithm—2015 Update

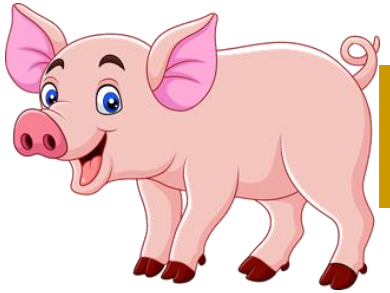


Approach to Meconium Stained Amniotic Fluid (MSAF)

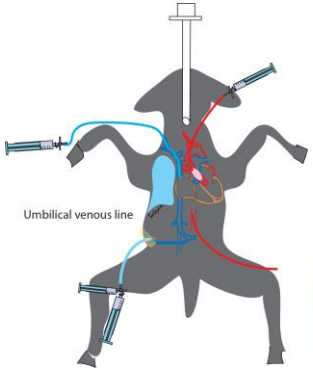
Mask ventilation



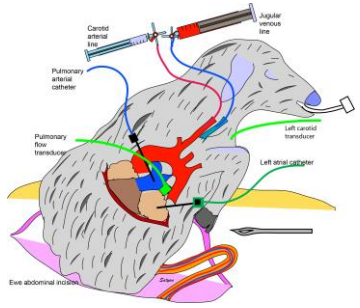
Room air vs. oxygen – term and preterm



Chest compressions



Targeted Preductal SpO_2 After Birth	
1 min	60%-65%
2 min	65%-70%
3 min	70%-75%
4 min	75%-80%
5 min	80%-85%
10 min	85%-95%



Targeted SpO_2 with titrated FiO_2

Epinephrine

Initial Questions to the Delivering Team

- **C**ord Management
- **L**ength of gestation (or Last Menstrual Period – LMP or EDD)
- **A**mniotic Fluid (Meconium, blood stained or clear)
- **S**ingle / Multiple gestation
- **P**redisposing factors
  - Maternal diabetes
  - Hypertension

Placental Transfusion - Delayed vs. Physiologic Cord Clamping

Late-preterm and term infants, vaginal delivery non-breathing despite drying and stimulation for 30 s

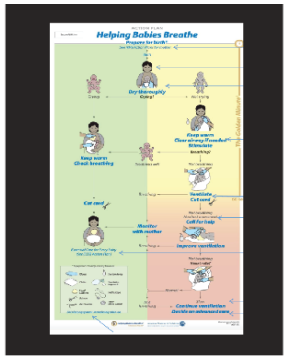
↓

Randomization

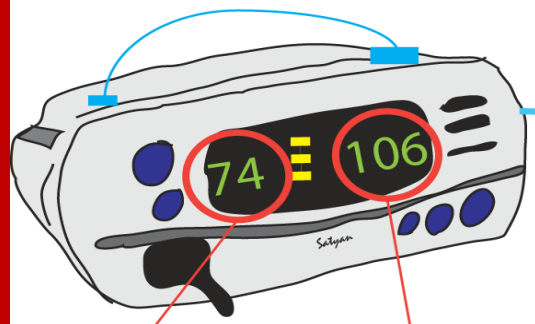
Early cord clamp (< 60s)

Delay cord clamp (≥ 180s)

Nepcord III (Andersson et al MHNP (2019) 5:15



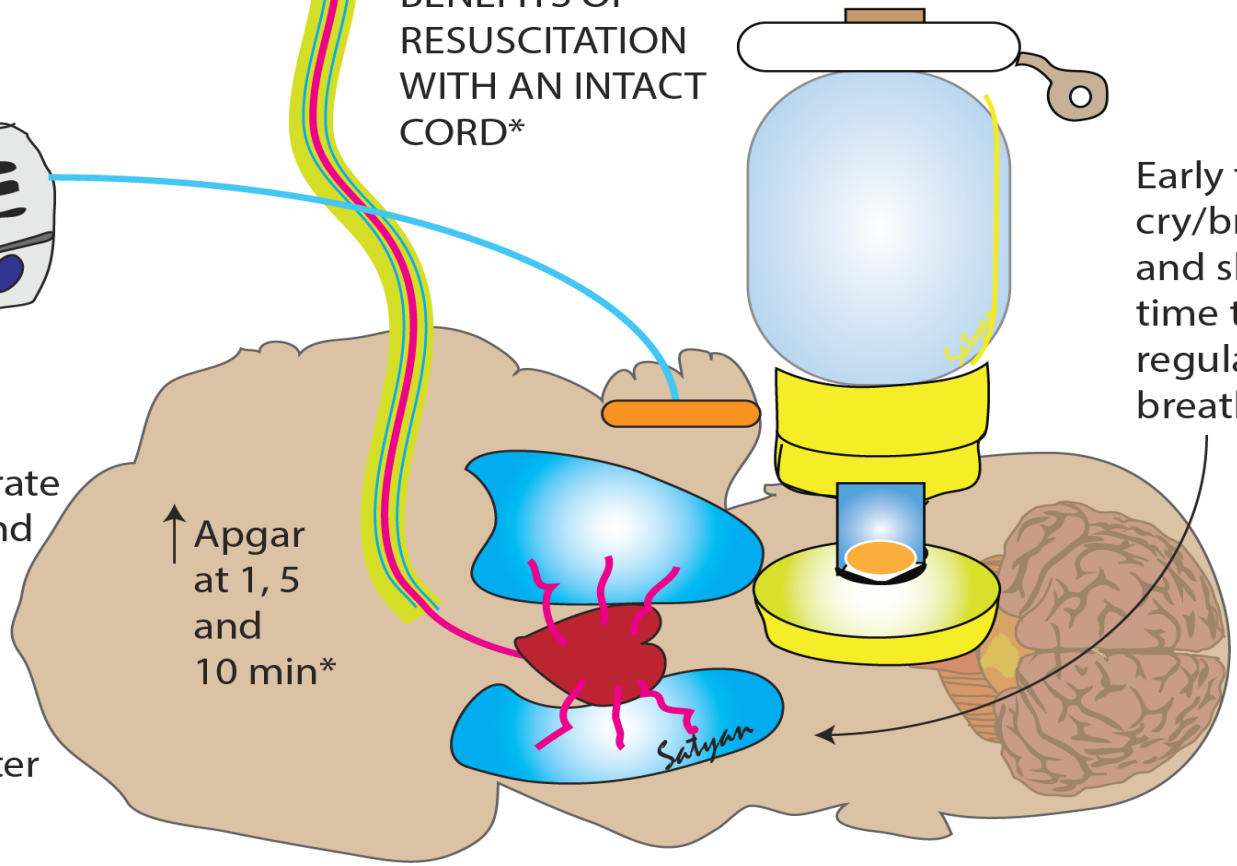
Nurse-midwives trained in Helping Babies Breathe algorithm



↑ SpO_2 at 1, 5 and 10 min*

↓ Heart rate at 1, and 5 min*

BENEFITS OF RESUSCITATION WITH AN INTACT CORD*

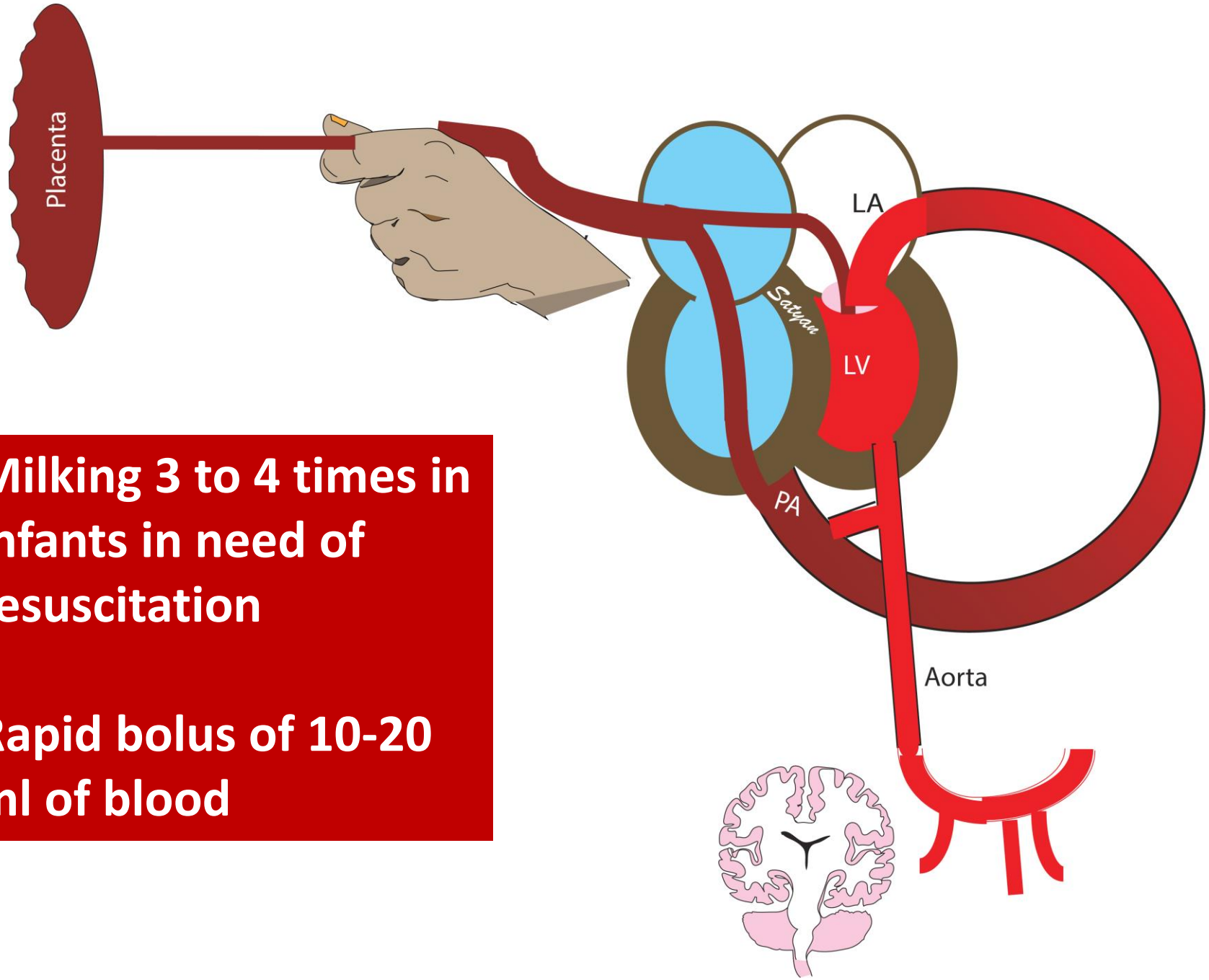


↑ Apgar at 1, 5 and 10 min*

Early first cry/breath and shorter time to regular breathing*

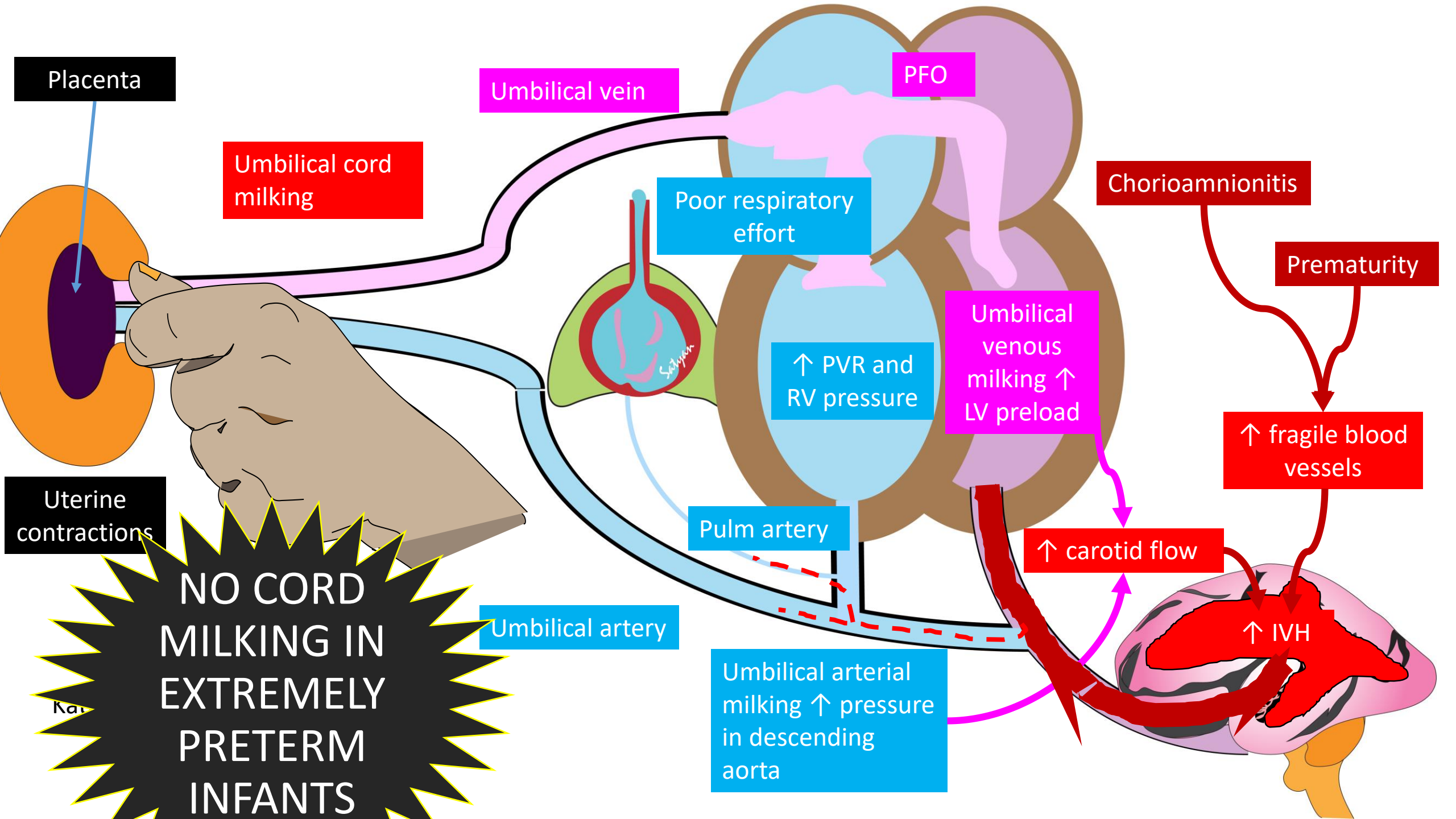
No difference in baby's temperature after resuscitation or bilirubin at discharge

Placental Transfusion Intact cord milking

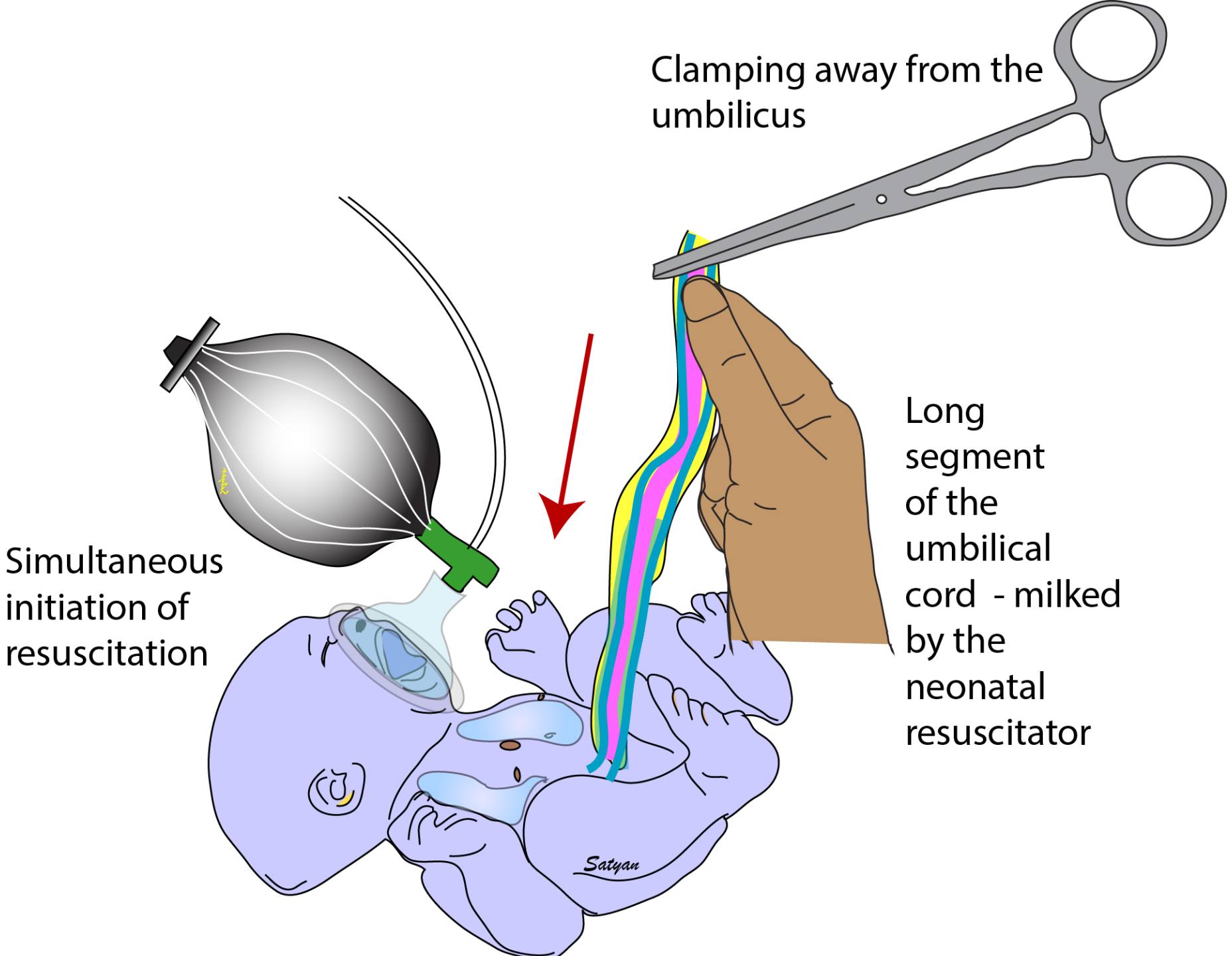


Milking 3 to 4 times in infants in need of resuscitation

Rapid bolus of 10-20 ml of blood


Placenta
Umbilical vein
PFO
Umbilical cord milking
Poor respiratory effort
Chorioamnionitis
Prematurity
↑ PVR and RV pressure
Umbilical venous milking ↑ LV preload
↑ fragile blood vessels
Uterine contractions
Pulm artery
↑ carotid flow
NO CORD MILKING IN EXTREMELY PRETERM INFANTS
Umbilical artery
↑ IVH
Umbilical arterial milking ↑ pressure in descending aorta

Placental Transfusion Cut cord milking



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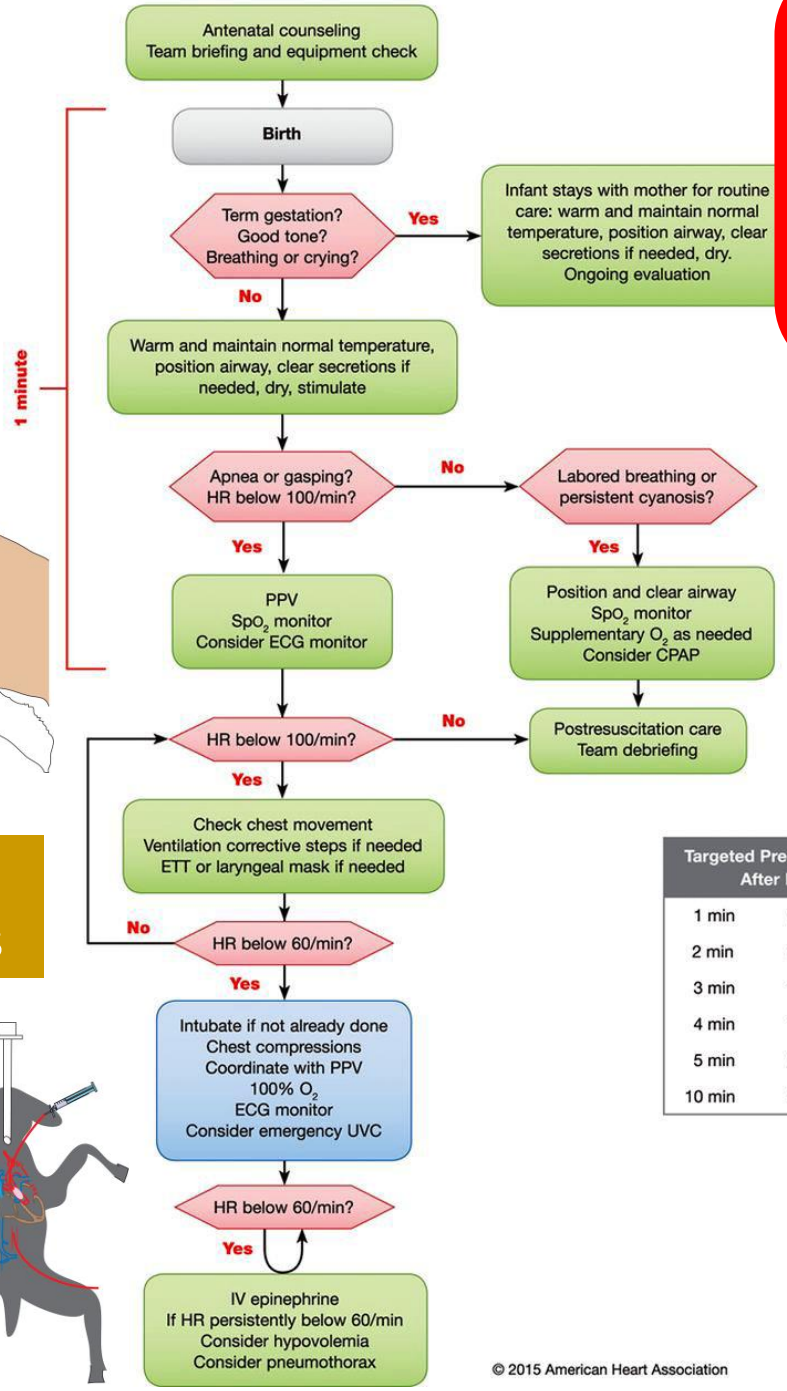

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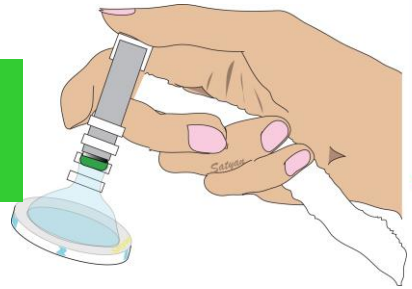

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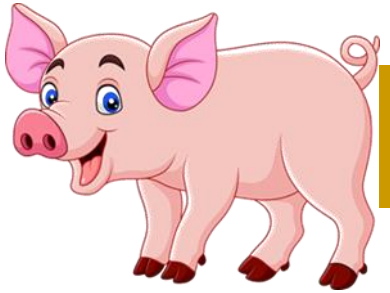

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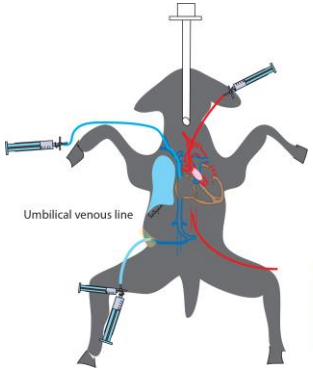

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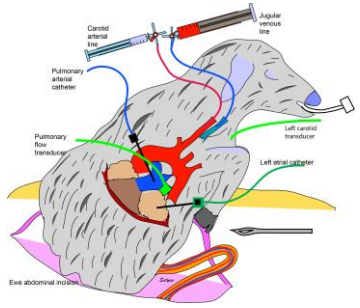


Targeted SpO_2 with titrated FiO_2

Epinephrine

Changing Guidelines:
Suction Meconium – Vigorous vs. Non-vigorous

Amnioinfusion

Frazer NEJM 2005 n=1998

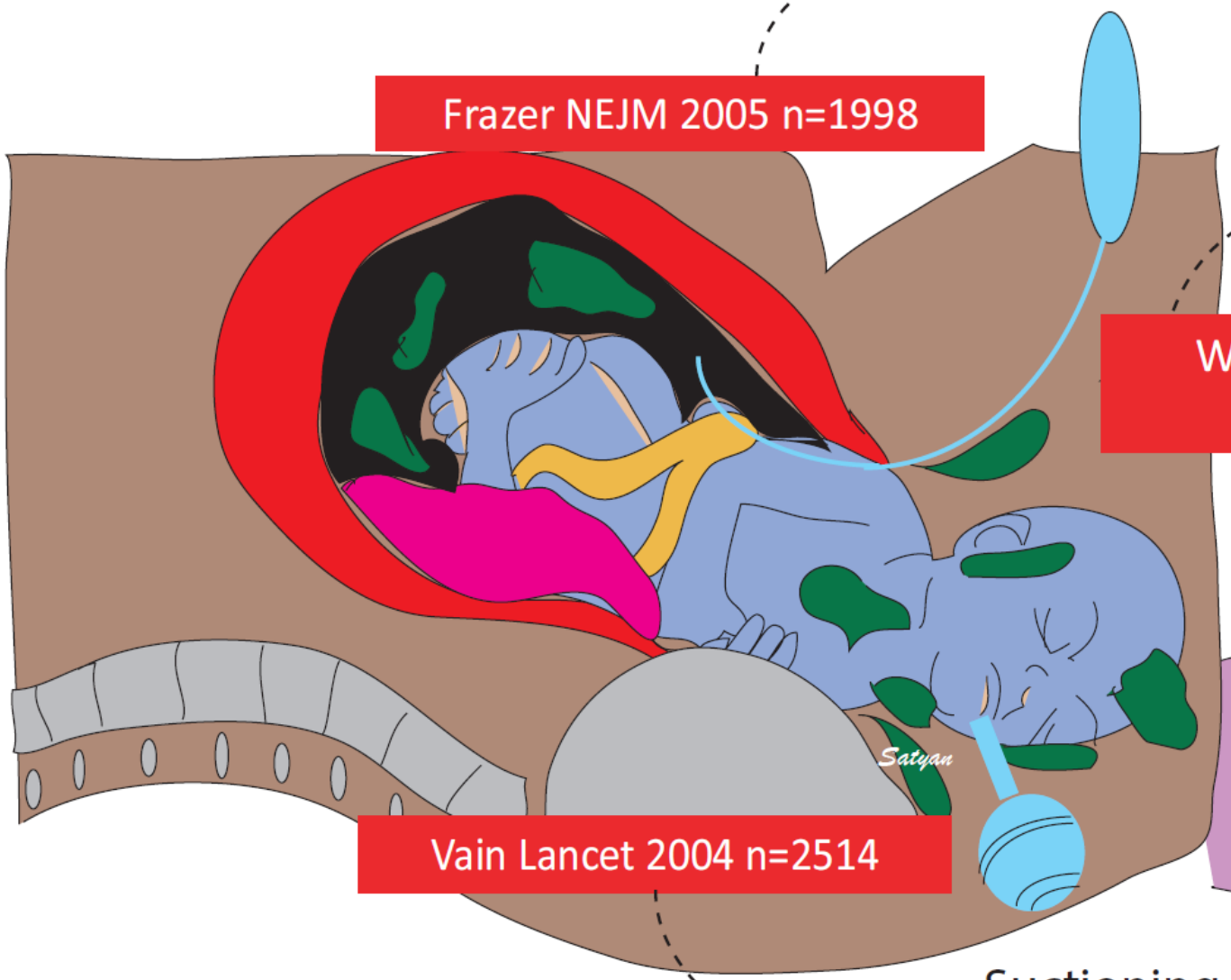
Chiruvolu et al Pediatrics 2018 n=232
Wiswell - Editorial

Tracheal Suctioning

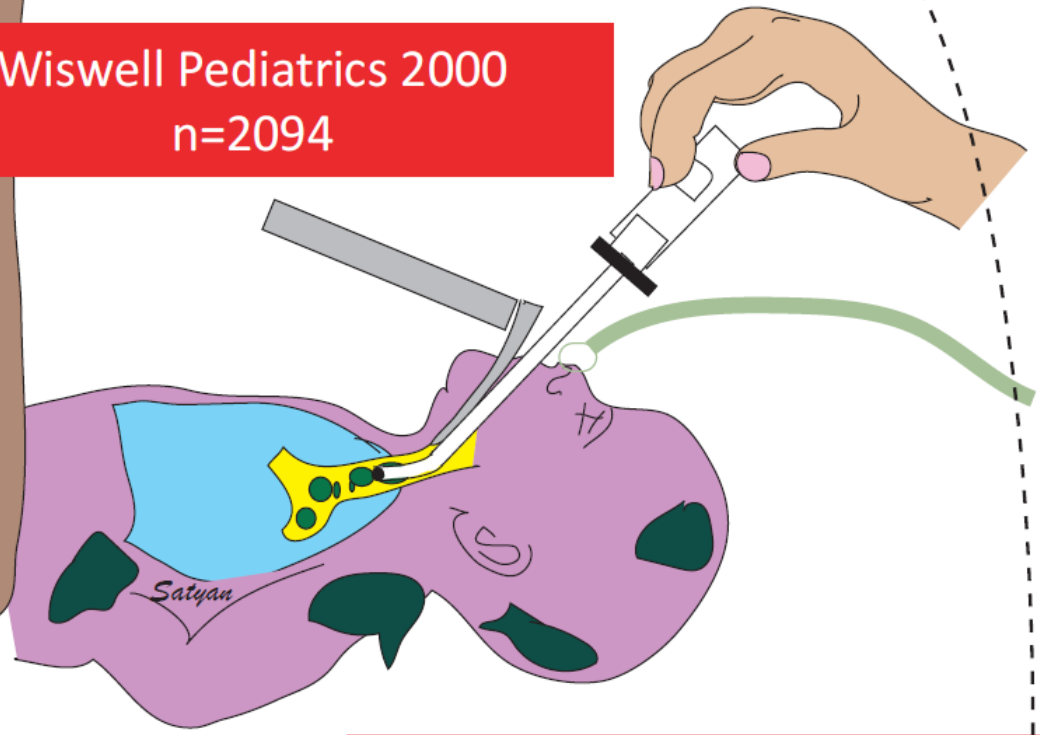
Vigorous

Non-vigorous

Wiswell Pediatrics 2000
n=2094



Vain Lancet 2004 n=2514



Suctioning
at delivery
of head

Chettri J Pediatrics 2015 n=122
Nangia Resuscitation 2016 n=175

Singh Clin Epi Global H 2018 n=152
Kumar et al Eur J Ped 2019 n = 132

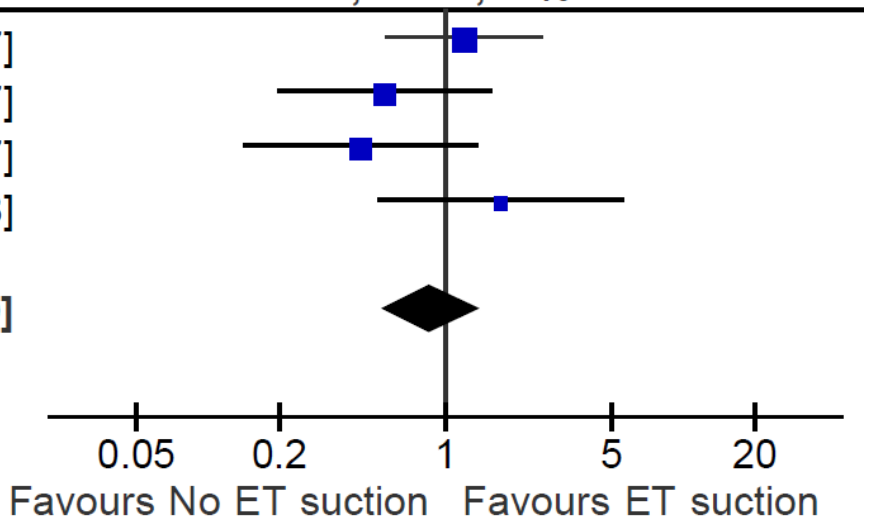
Metaanalysis – No Difference in Mortality/MAS

1.1 Mortality

Study or Subgroup	No ET suction Events	Total	ET suction Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chettri et al	12	61	10	61	31.1%	1.20 [0.56, 2.57]
Kumar et al.	5	66	9	66	28.0%	0.56 [0.20, 1.57]
Nangia et al	4	88	9	87	28.2%	0.44 [0.14, 1.37]
Singh et al.	7	77	4	75	12.6%	1.70 [0.52, 5.58]
Total (95% CI)		**292**		**289**	**100.0%**	**0.87 [0.54, 1.40]**
Total events	28		32			

Heterogeneity: Chi² = 4.02, df = 3 (P = 0.26); I² = 25%

Test for overall effect: Z = 0.58 (P = 0.56)



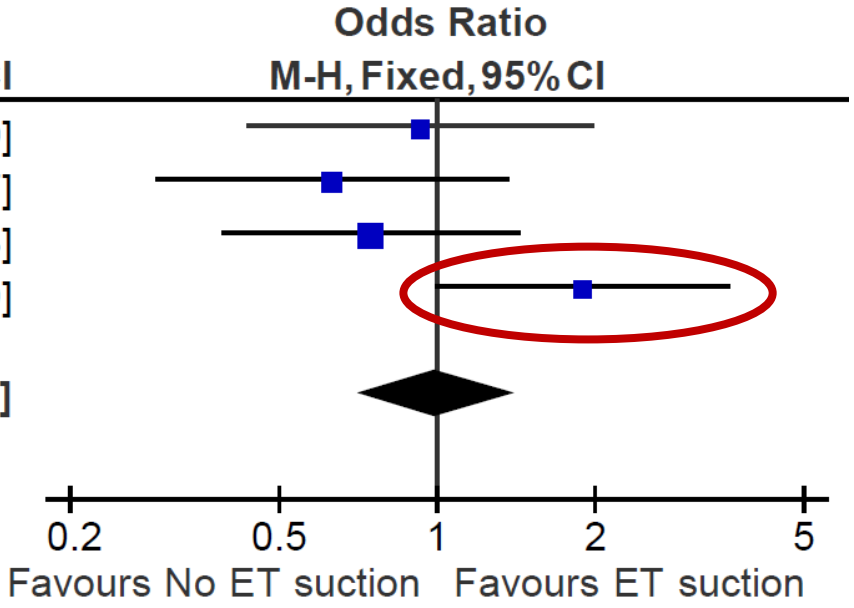
Metaanalysis – No Difference in Mortality/MAS

1.2 Meconium aspiration syndrome

Study or Subgroup	No ET suction Events	Total	ET suction Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chettri et al	19	61	20	61	21.4%	0.93 [0.43, 1.99]
Kumar et al.	15	66	21	66	25.3%	0.63 [0.29, 1.37]
Nangia et al	23	88	28	87	32.4%	0.75 [0.39, 1.43]
Singh et al.	44	77	31	75	20.9%	1.89 [0.99, 3.60]
Total (95% CI)		**292**		**289**	**100.0%**	**1.00 [0.70, 1.41]**
Total events	101		100			

Heterogeneity: Chi² = 5.94, df = 3 (P = 0.11); I² = 50%

Test for overall effect: Z = 0.02 (P = 0.98)



↑ NICU Respiratory Admissions with No Routine Suction

TABLE 3 Neonatal Therapy and Outcomes

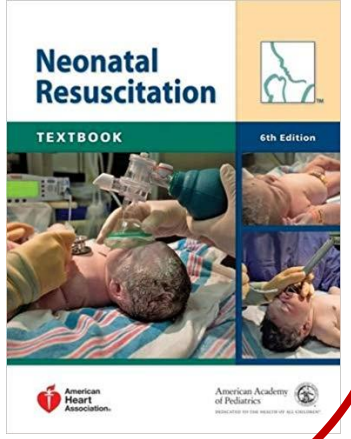
Denominator – non-vigorous babies with MSAF

	Retrospective ($N = 130$)	Prospective ($N = 101$)	OR (95% CI)[a]
	Routine Tracheal Suction	No Routine Tracheal Suction	
NICU respiratory admissions[b]	29 (22)	40 (40)	2.2 (1.2–3.9)
Oxygen therapy[b]	24 (19)	37 (37)	2.5 (1.2–4.5)
Mechanical ventilation[b]	11 (9)	19 (19)	2.6 (1.1–5.8)
Surfactant therapy[b]	3 (2)	10 (10)	5.8 (1.5–21.8)
Inhaled nitric oxide therapy	3 (2)	6 (6)	2.9 (0.71–12)
Hypothermia therapy	4 (3)	5 (5)	1.8 (0.55–5.4)
MAS	7 (5)	11 (11)	2.3 (0.83–6.2)
HIE	5 (4)	6 (6)	1.4 (0.39–4.9)
Transfer for ECMO	2 (2)	1 (1)	0.69 (0.06–7.8)

[a] Adjusted for late preterm, postterm, and deliveries with fetal distress.

[b] $P < .05$.

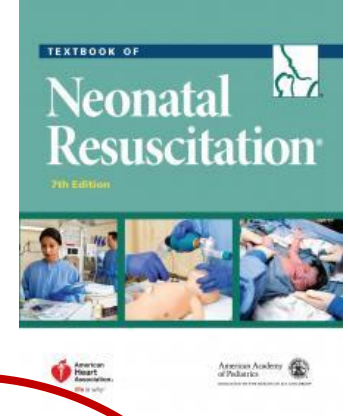
Chiruvolu et al Pediatrics 2018



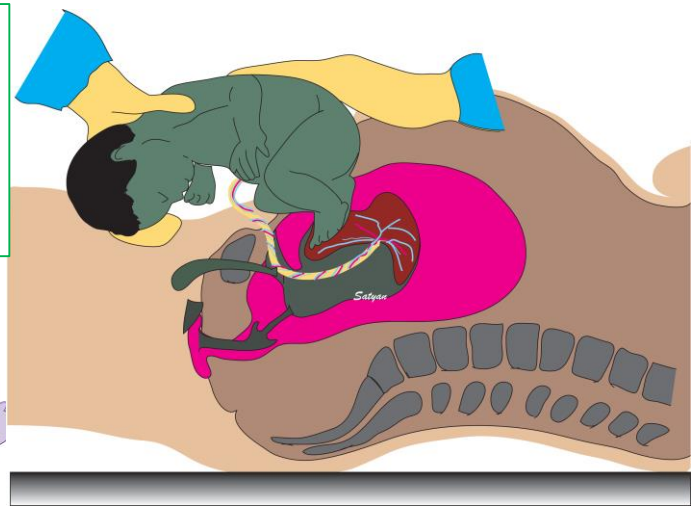
6th ED

Meconium stained amniotic fluid
10-15% of deliveries

7th ED

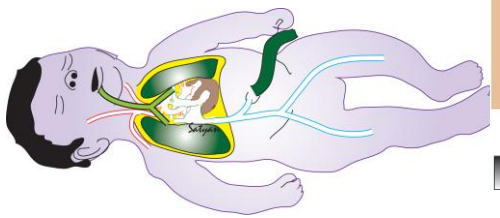


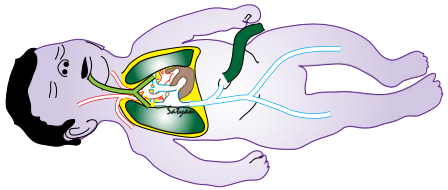
No stimulation of all 'visibly appearing'* non-vigorous newborns (10-20%)



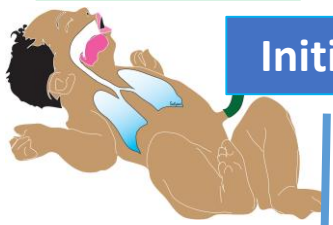
Dry and stimulation of all newborns by obstetric or neonatal providers

Vigorous without stimulation

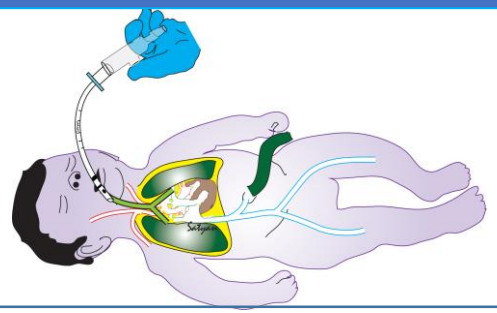




Vigorous following stimulation*

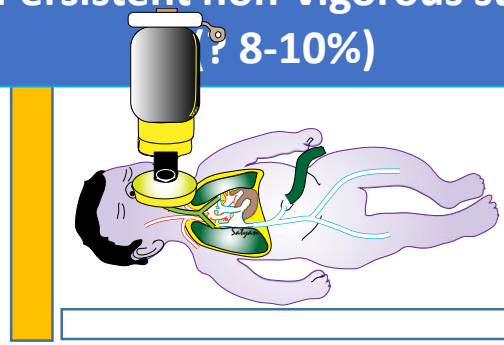


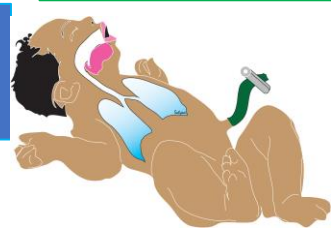
Initial non-vigorous state (10-20%)



How can we measure incidence of Meconium Aspiration Syndrome (MAS)?

Persistent non-vigorous state (? 8-10%)





*May include newborns who briefly visibly appeared non-vigorous

Routine tracheal intubation and suction

Move to positive pressure ventilation (PPV)

Problems of decreasing denominators

Larger denominator with some well newborns

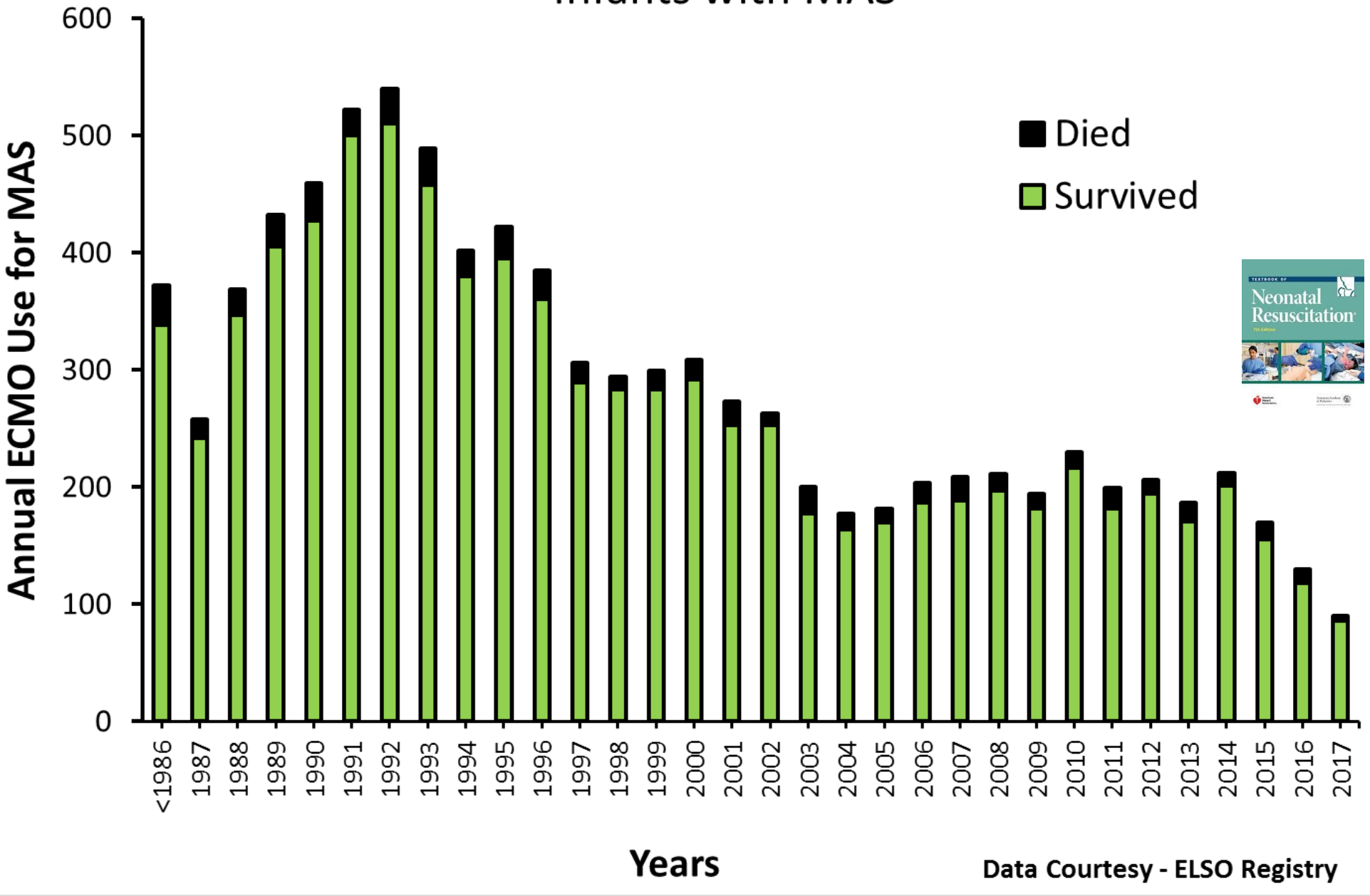
Smaller denominator with sicker newborns

Vermont Oxford Network - ≥ 35 w GA + Meconium Aspiration syndrome + Apgar Score < 3 at 1 min

	2013-15	2017	RR (95% CI)
Total Births	N=222,438	N=78,712	
MAS with Apgar < 3 at 1 min	N=1586	N=362	
Endotracheal suctioning, %	82.4	52.1	0.63 (0.56, 0.71)
Conventional or high frequency ventilation, %	57.4	61.9	1.08 (0.97, 1.20)
Inhaled nitric oxide, %	16.2	21.9	1.35 (1.08, 1.69)
ECMO, %	1.8	2.3	1.23 (0.47, 3.19)
Surfactant at any time, %	27.7	36.0	1.30 (1.09, 1.55)
Outcomes			
Death, %	5.3	7.2	1.38 (0.88, 2.16)
Pneumothorax, %	10.3	11.5	1.11 (0.80, 1.55)
Moderate/severe hypoxic-ischemic encephalopathy, %	12.1	20.1	1.67 (1.27, 2.19)

Edwards E et al Children 2019

International Trends of ECMO Use and Outcomes in Infants with MAS



The current "no routine suction" recommendation has not led to increased ECMO for MAS

Treatment Recommendations – ILCOR 2019 (**Consensus on Science with Treatment Recommendations (CoSTR)**)

- For non-vigorous newborns delivered through meconium-stained amniotic fluid, we suggest against routine immediate direct laryngoscopy after delivery with or without tracheal suctioning when compared to immediate resuscitation without direct laryngoscopy.
- Meconium-stained amniotic fluid remains a significant risk factor for receiving advanced resuscitation in the delivery room.
- A provider may perform intubation and tracheal suctioning to relieve airway obstruction.

Physiology of Asphyxia

Neonatal Resuscitation Algorithm—2015 Update

Antenatal counseling
Team briefing and equipment check

Birth

Term gestation?
Good tone?
Breathing or crying?
- Yes → Infant stays with mother for routine care: warm and maintain normal temperature, position airway, clear secretions if needed, dry. Ongoing evaluation
- No → Warm and maintain normal temperature, position airway, clear secretions if needed, dry, stimulate

1 minute

Apnea or gasping?
HR below 100/min?
- No → Labored breathing or persistent cyanosis?
  - Yes → Position and clear airway; SpO_2 monitor; Supplementary O_2 as needed; Consider CPAP
- Yes → PPV; SpO_2 monitor; Consider ECG monitor

HR below 100/min?
- No → Postresuscitation care; Team debriefing
- Yes → Check chest movement; Ventilation corrective steps if needed; ETT or laryngeal mask if needed

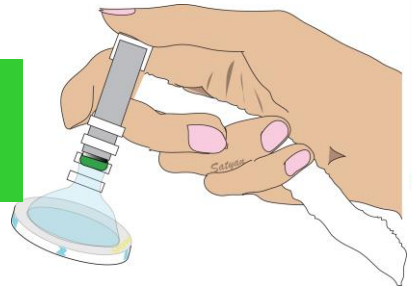
HR below 60/min?
- Yes → Intubate if not already done; Chest compressions; Coordinate with PPV; 100% O_2; ECG monitor; Consider emergency UVC

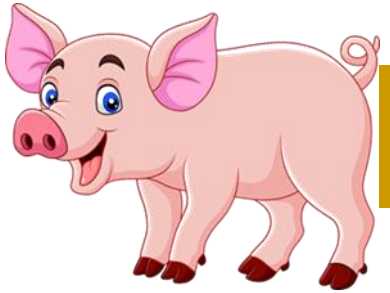
HR below 60/min?
- Yes → IV epinephrine; If HR persistently below 60/min; Consider hypovolemia; Consider pneumothorax

Approach to Meconium Stained Amniotic Fluid (MSAF)

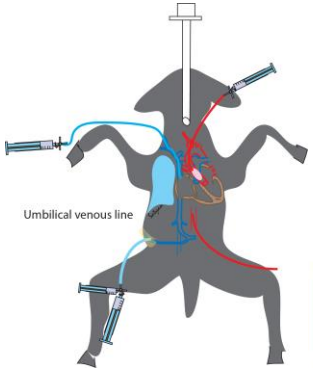
Room air vs. oxygen – term and preterm

Mask ventilation





Chest compressions



Epinephrine

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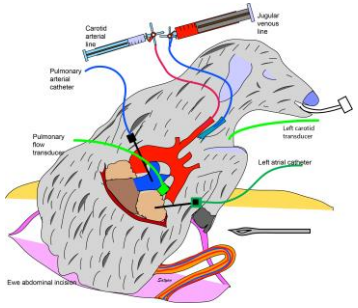


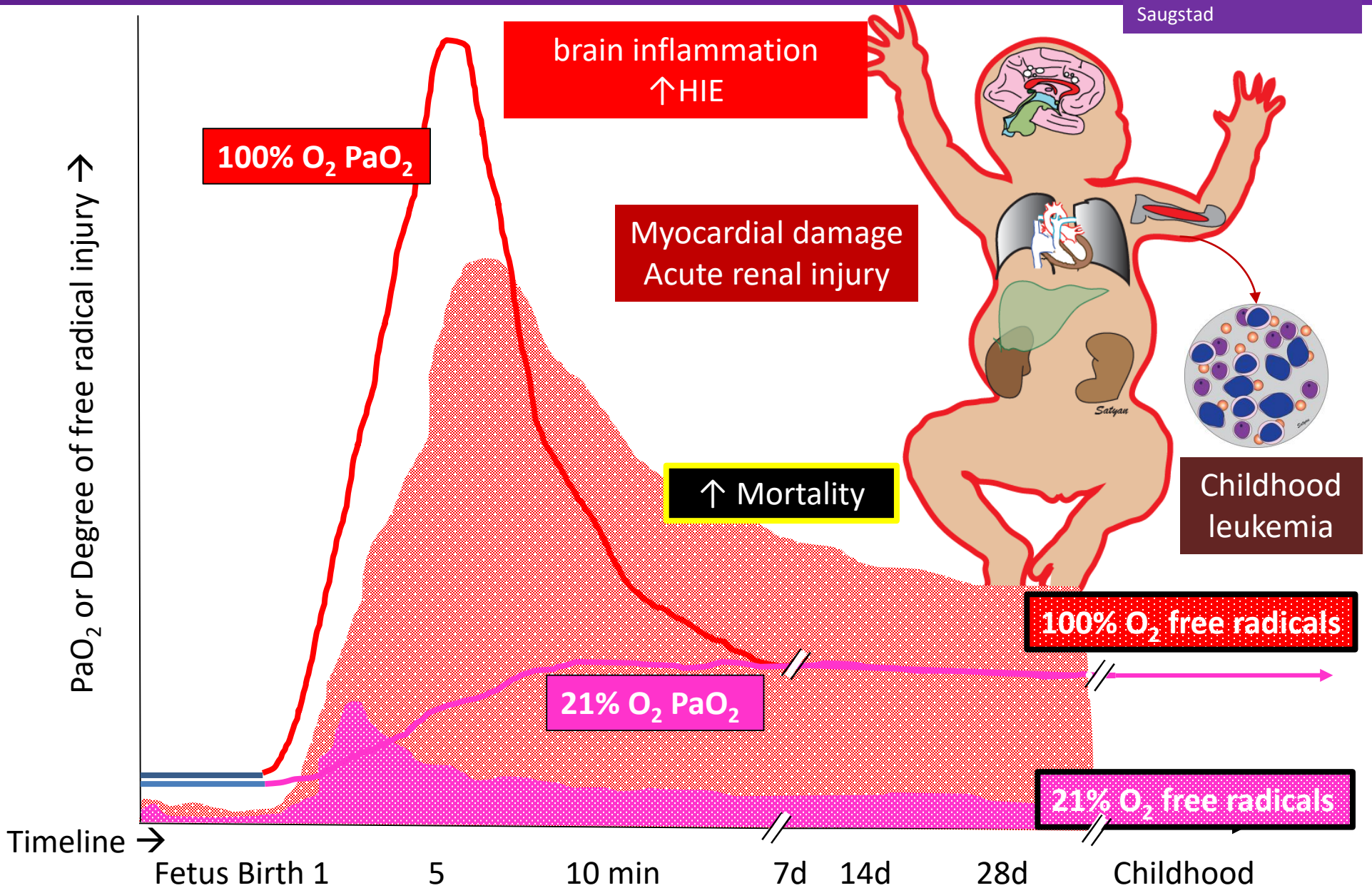
Targeted SpO_2 with titrated FiO_2

What is Optimal Oxygenation in the Delivery Room?

Term: Effects of Resuscitation with 100% O_2

Diagrammatic Representation

Slide courtesy-Dr. Saugstad

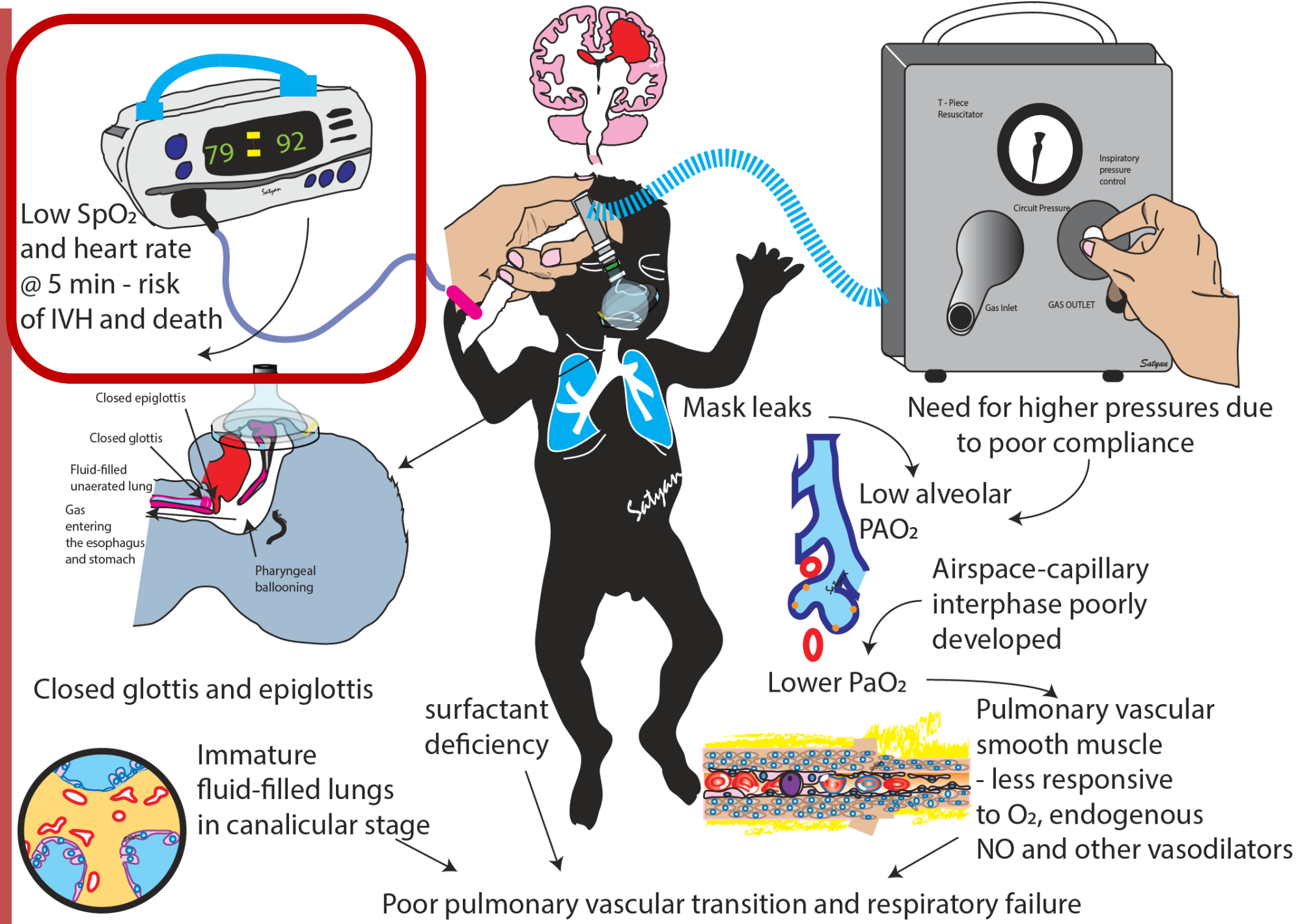


What about Preterm Infants?

Saugstad et al Pediatric Research 2018

Oei JL et al Arch Dis Child Fet Neonatal Ed 2018

Crawshaw JR, Kitchen MJ, Binder-Heschl C, et al. Arch Dis Child Fetal Neonatal Ed 2018;**103**:F112–F119.



What is Optimal Oxygenation in the Delivery Room?

Delivery room
> 31 weeks: air
28-31 weeks: air or 30 %
< 28 weeks: 30%
At 5 min: SpO_2≥80 % and HR > 100 bpm

ILCOR – CoSTAR treatment guidelines:

We suggest starting with a lower oxygen concentration (21-30%) compared to higher oxygen concentration (60-100%) for preterm (<35 weeks gestation) newborns who receive respiratory support at birth with subsequent titration of oxygen concentration using pulse oximetry (weak recommendation, very low certainty of evidence).

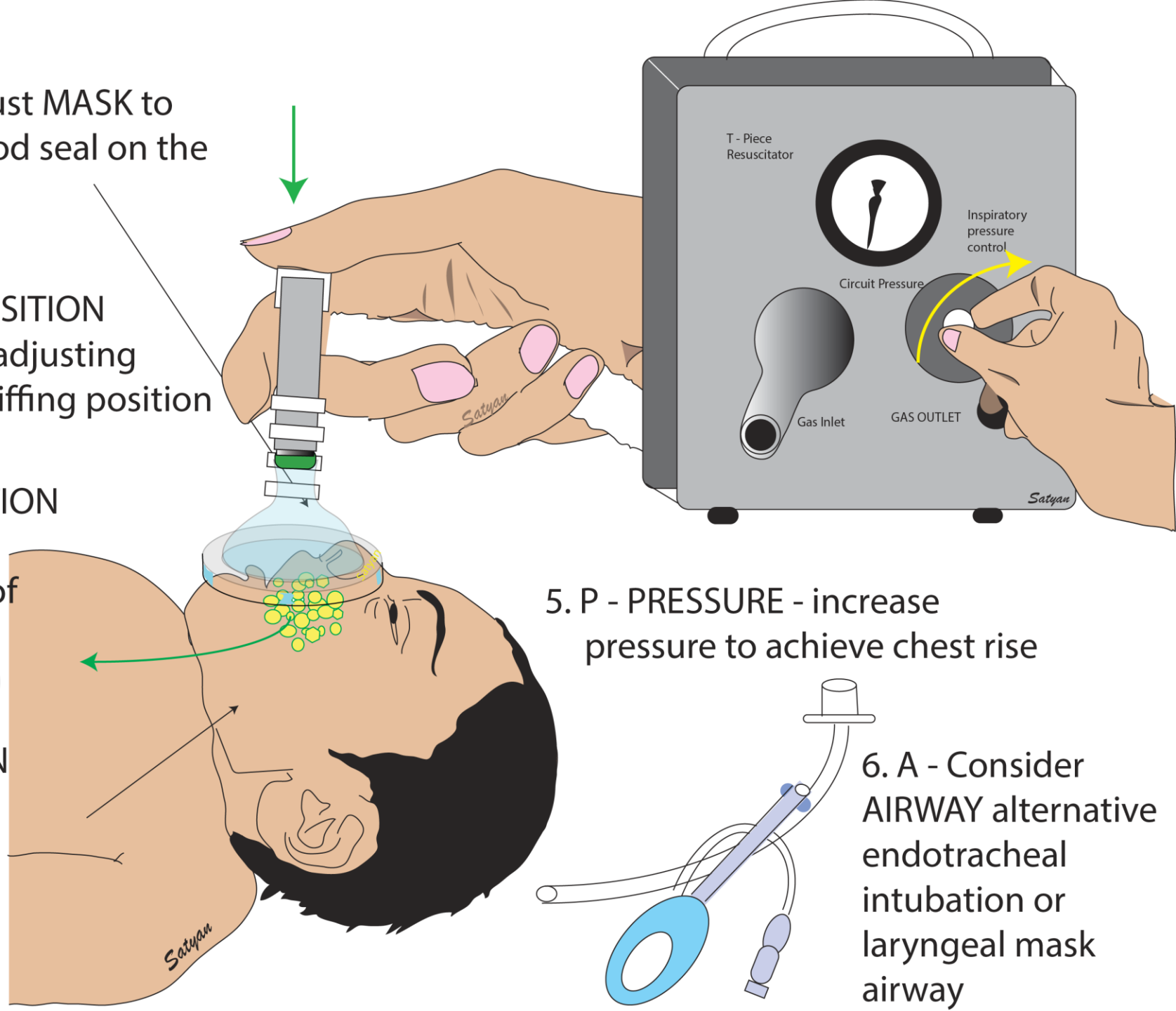
Corrective Steps – MRSOPA

1. M - Adjust MASK to assure good seal on the face

2. R - REPOSITION airway by adjusting head to sniffing position

3. S - SUCTION mouth and nose of secretions (if present)

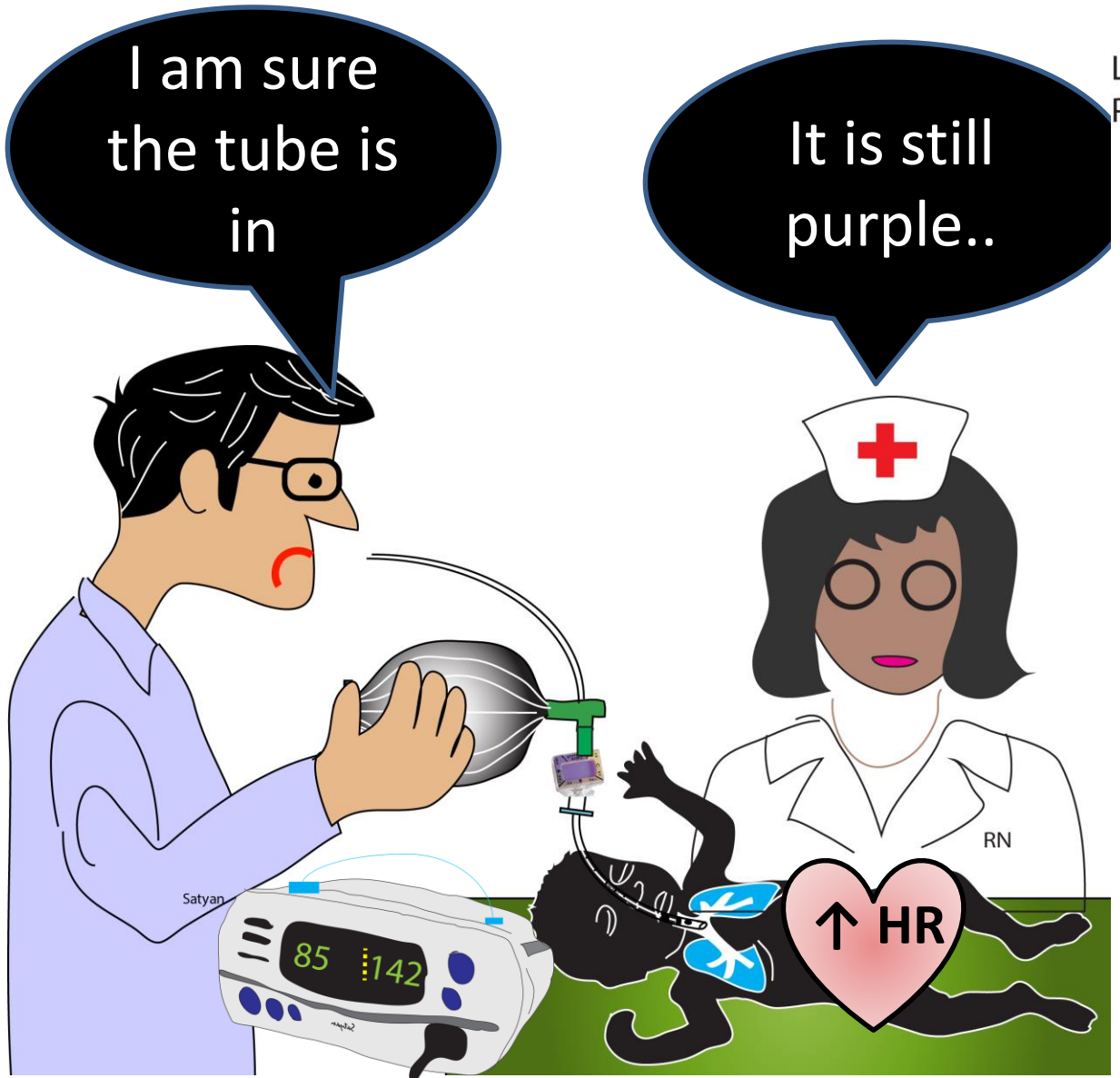
4. O - OPEN mouth slightly and move jaw forward

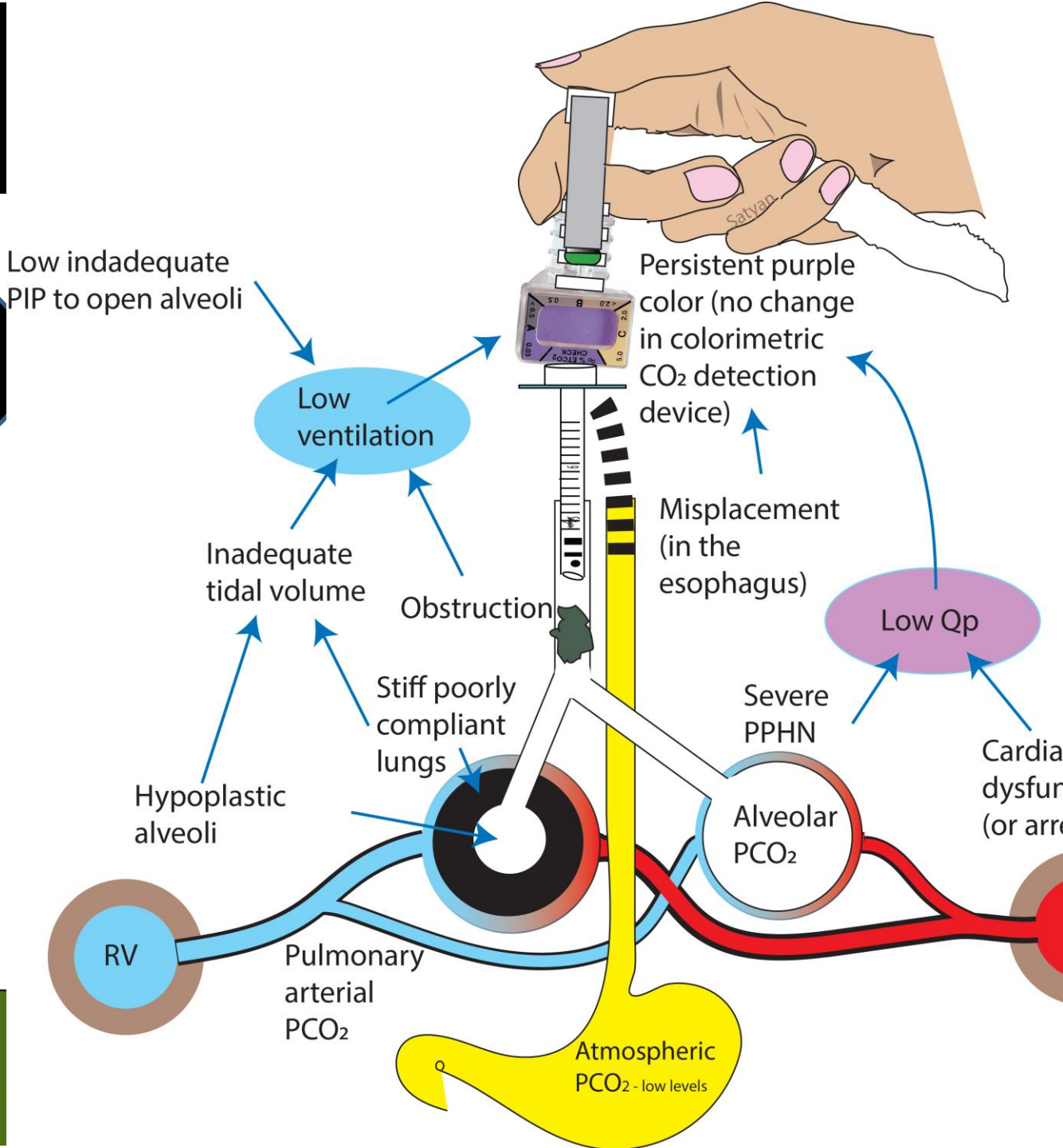


5. P - PRESSURE - increase pressure to achieve chest rise

6. A - Consider AIRWAY alternative endotracheal intubation or laryngeal mask airway

Intubation - ETT





Physiology of Asphyxia

Neonatal Resuscitation Algorithm—2015 Update

Antenatal counseling
Team briefing and equipment check

Birth

Term gestation?
Good tone?
Breathing or crying?
- Yes → Infant stays with mother for routine care: warm and maintain normal temperature, position airway, clear secretions if needed, dry. Ongoing evaluation
- No → Warm and maintain normal temperature, position airway, clear secretions if needed, dry, stimulate

1 minute

Apnea or gasping?
HR below 100/min?
- No → Labored breathing or persistent cyanosis?
  - Yes → Position and clear airway; SpO_2 monitor; Supplementary O_2 as needed; Consider CPAP
- Yes → PPV; SpO_2 monitor; Consider ECG monitor

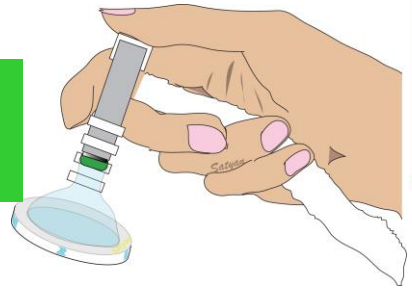
HR below 100/min?
- No → Postresuscitation care; Team debriefing
- Yes → Check chest movement; Ventilation corrective steps if needed; ETT or laryngeal mask if needed

HR below 60/min?
- Yes → Intubate if not already done; Chest compressions; Coordinate with PPV; 100% O_2; ECG monitor; Consider emergency UVC

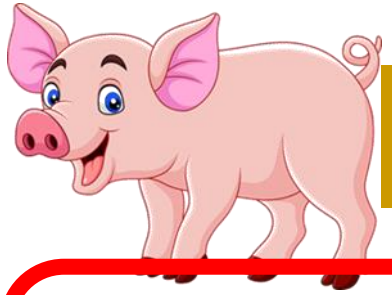
HR below 60/min?
- Yes → IV epinephrine; If HR persistently below 60/min; Consider hypovolemia; Consider pneumothorax

Approach to Meconium Stained Amniotic Fluid (MSAF)

Mask ventilation

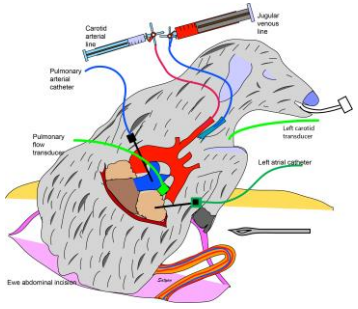


Room air vs. oxygen – term and preterm



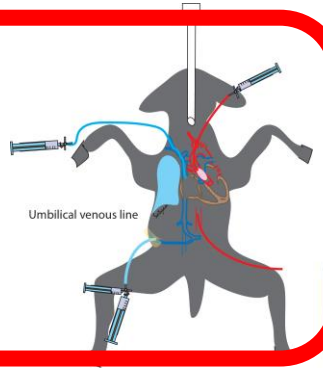
Chest compressions

Targeted Preductal SpO_2 After Birth	
1 min	60%-65%
2 min	65%-70%
3 min	70%-75%
4 min	75%-80%
5 min	80%-85%
10 min	85%-95%



Targeted SpO_2 with titrated FiO_2

Epinephrine

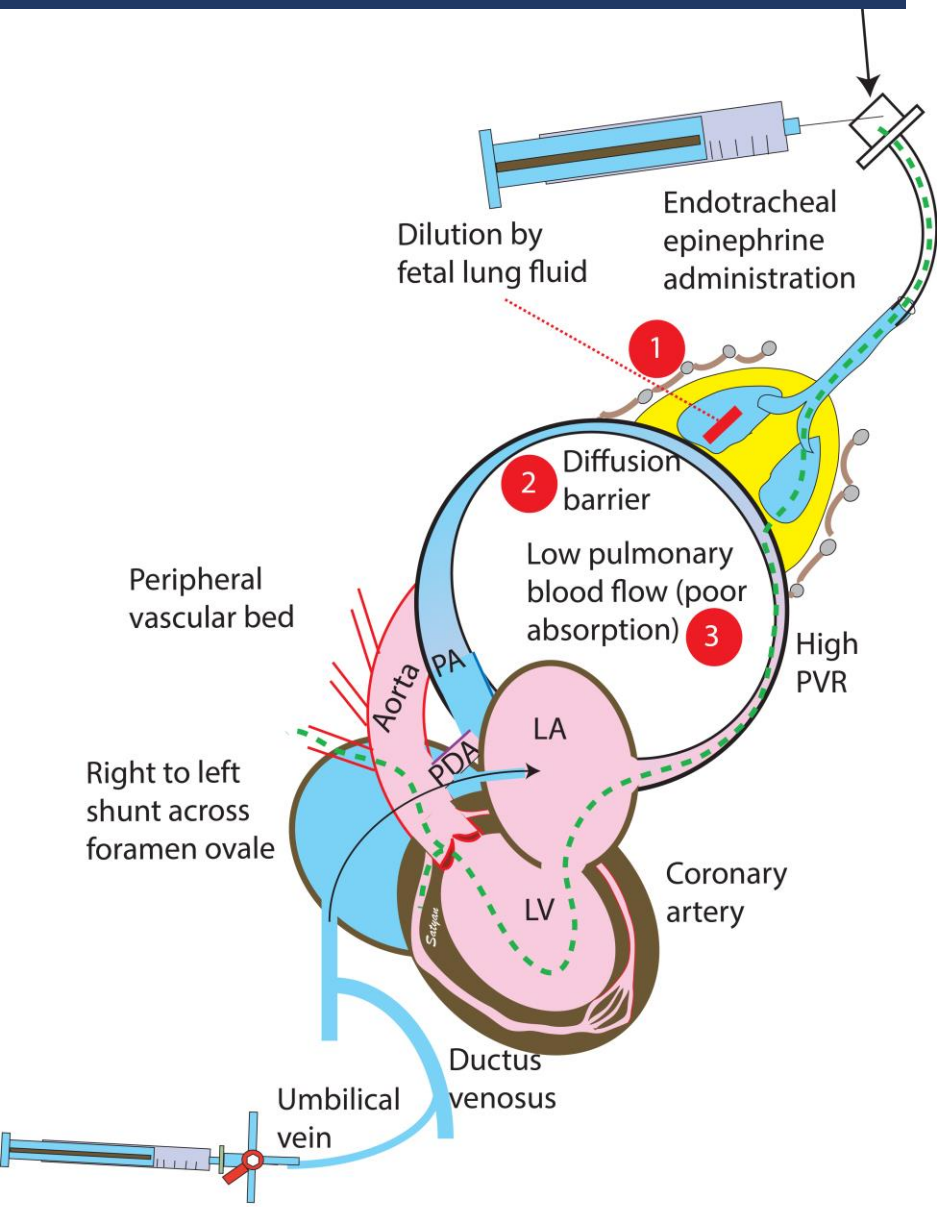


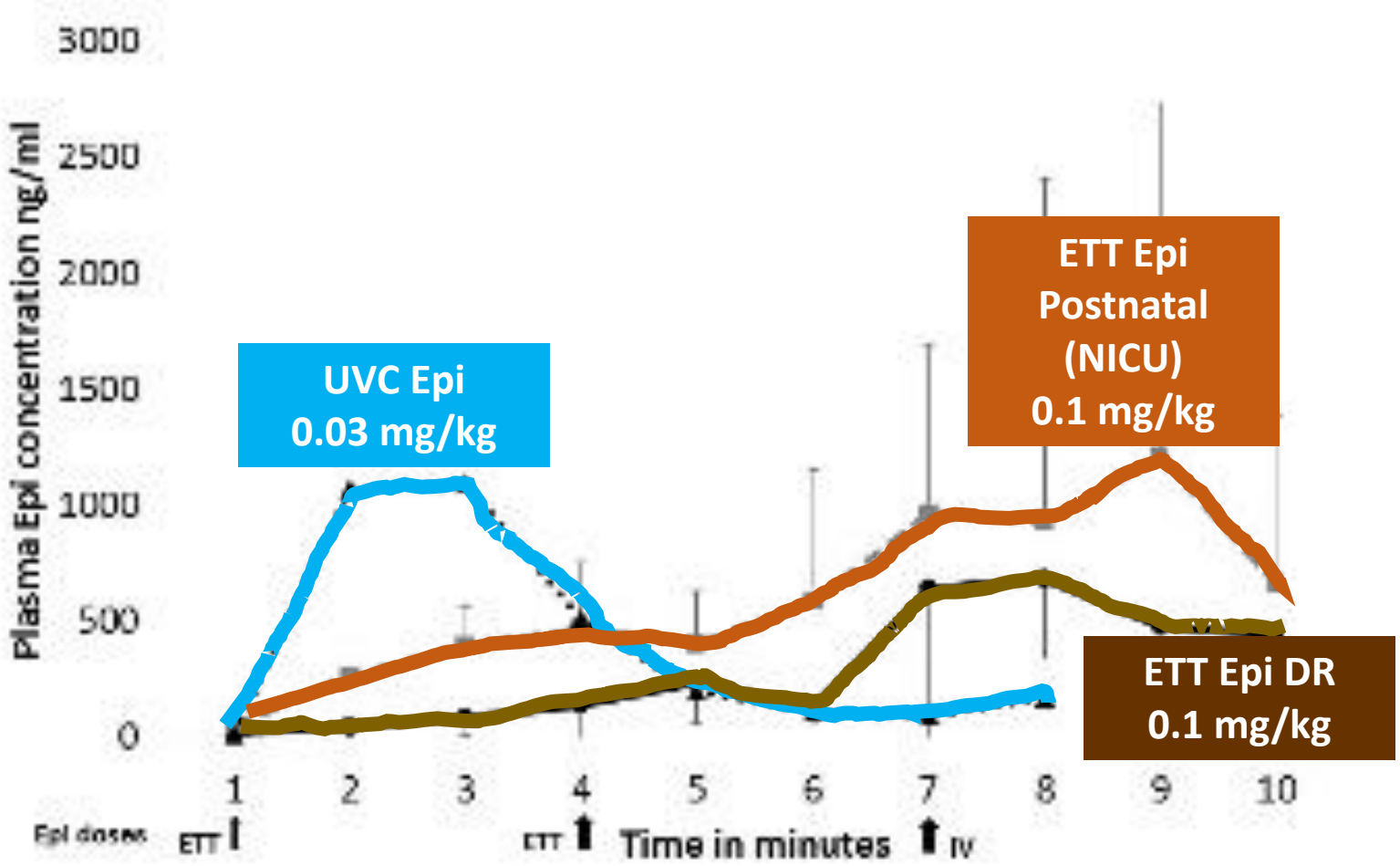
Resuscitation - Epinephrine

- Intravenous (UV) administration of epinephrine may be considered at a dose of 0.01 to 0.03 mg/kg of 1:10,000 epinephrine followed by 0.5 to 1 ml of flush.

- If an endotracheal administration route is attempted while intravenous access is being established, higher dosing will be needed at 0.05 to 0.1 mg/kg.

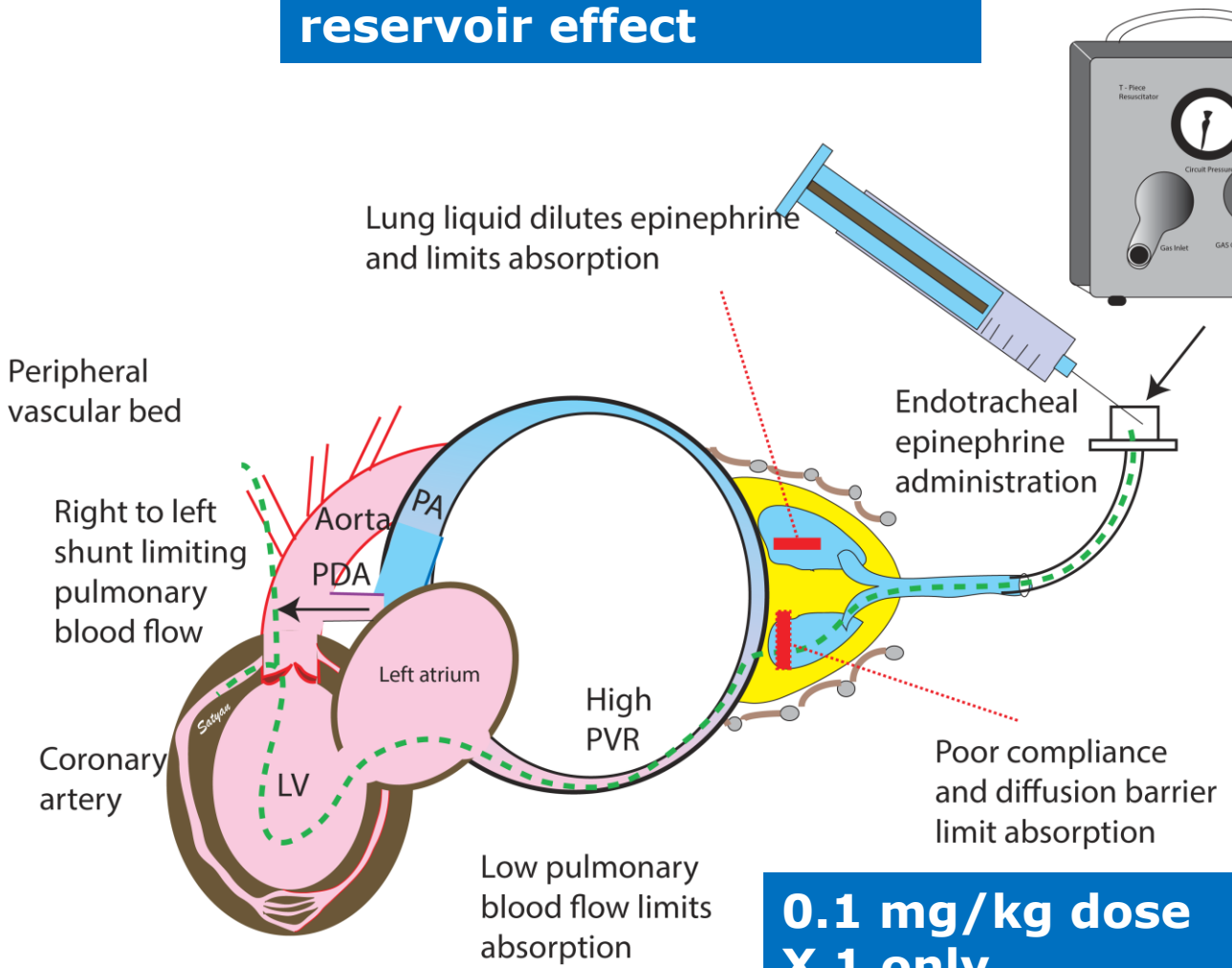
ETT Epinephrine





Nair et al Early Hum Dev 2019

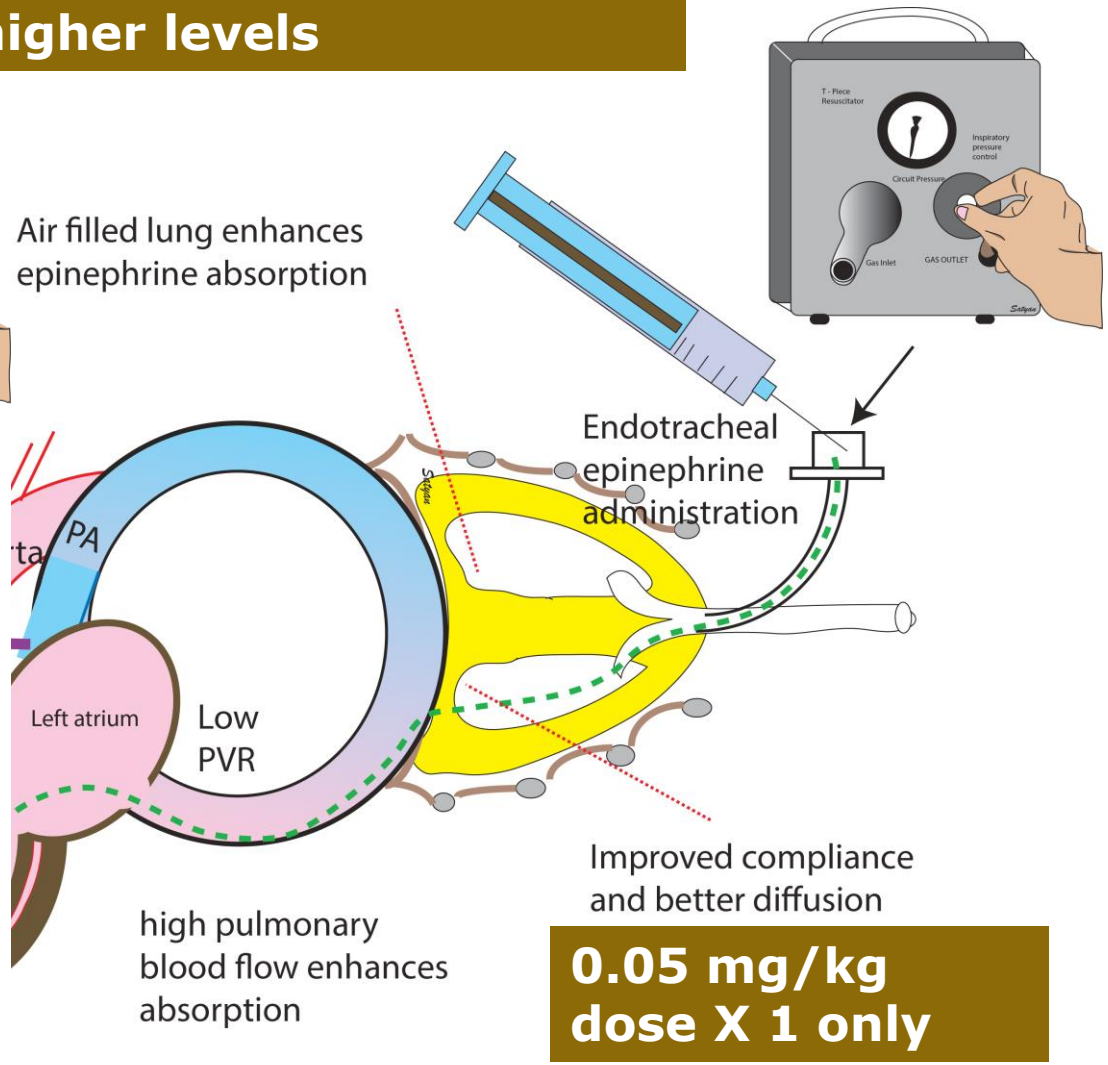
Newly born in the DR Slow absorption – reservoir effect



0.1 mg/kg dose X 1 only

Nair et al Early Hum Dev 2019

Postnatal in the NICU– higher levels

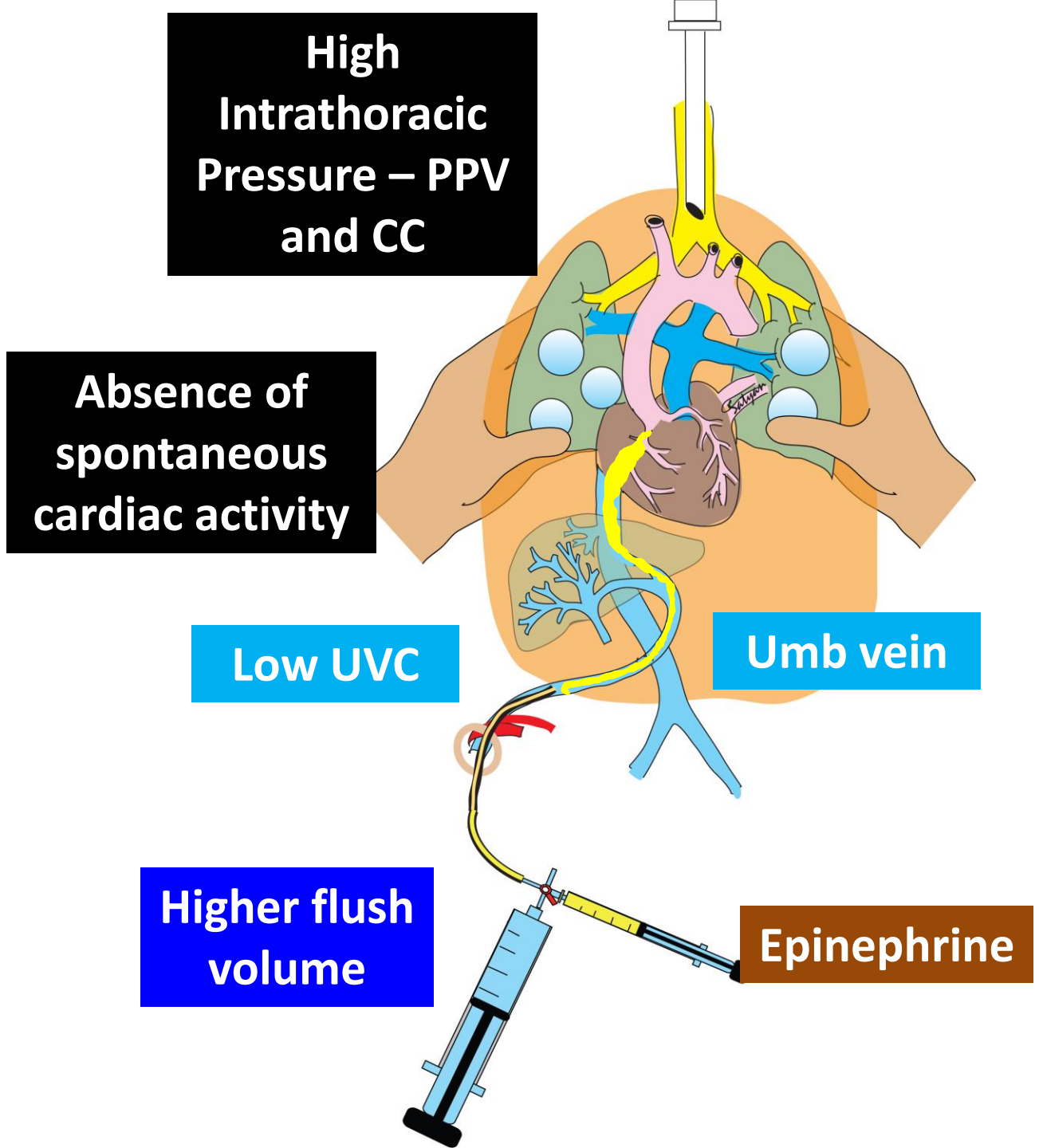


0.05 mg/kg dose X 1 only

Current Recommended Flush – 0.5 to 1 ml

Volume of a 5 Fr single lumen UVC is 0.56 ml

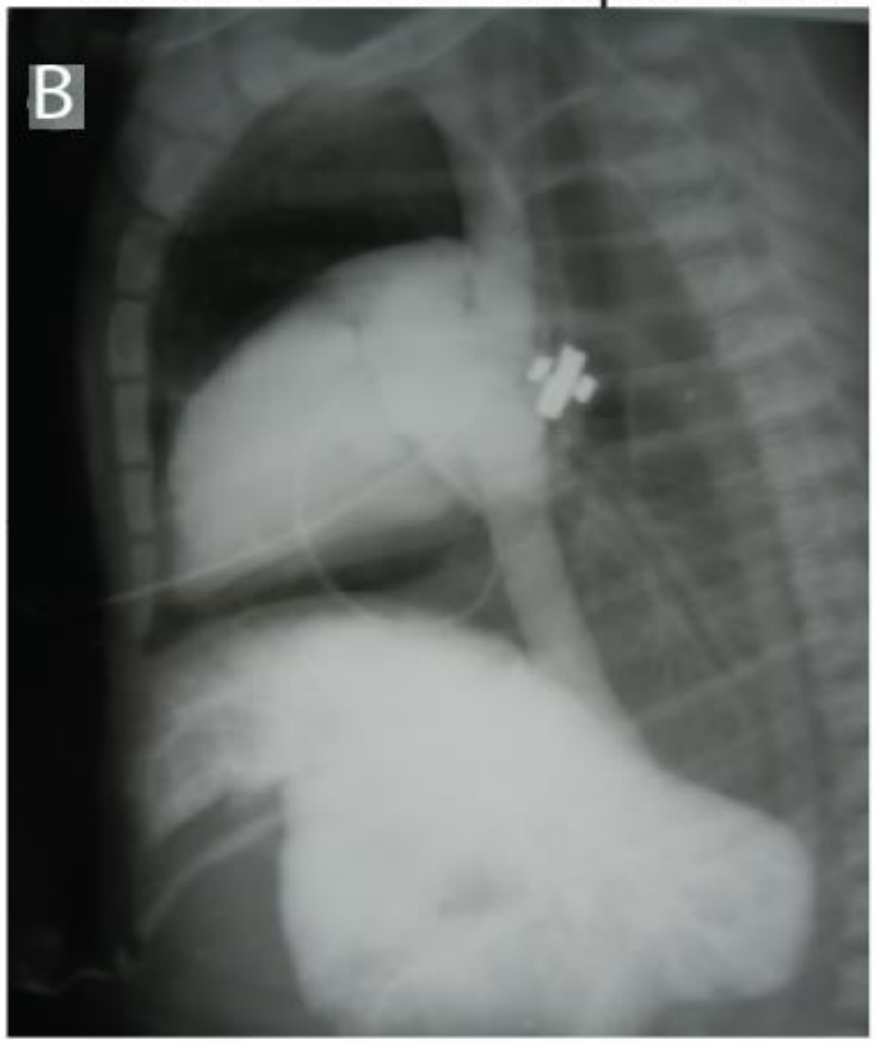
Potential Benefit Of Higher Flush Volume



Distribution Of Epinephrine

A. Epinephrine followed by 1 ml contrast (Omnipaque) flush + 30 sec of chest compressions

B. Epinephrine followed by 10 ml contrast (Omnipaque) flush + 30 sec of chest compressions



Vali et al Children journal 2019

Parameter	Low dose (0.01 mg/kg)n=11		High dose (0.03 mg/kg)n=12	
	Low flush(6)	High flush(5)	Low flush(7)	High flush(5)
ROSC achieved n(%)	2 (33%)	2 (40%)	5 (71%)	5 (100%)
ROSC with 1st dose of epi	1 (16.7%)	2 (40%)	3 (42%)	4 (80%)†
Median time to ROSC from PPV (sec)	697 (536-858)^	397 (396-398)	480 (372-600)	420 (360-420)
Median time to ROSC from epi & flush (sec)	127 (101-153)^	47 (41-53)	90 (60-120)	36 (30-60)

ROSC: Return of Spontaneous Circulation

^ p<0.05 low dose low flush vs high dose high flush. (unpaired t test)

†p<0.05 high dose high flush vs low dose low flush

Sankaran et al PAS 2019

Parameter	03 mg/kg)n=12
	igh flush(5)
ROSC achie	%)
ROSC w epi	
Me from	
Media from e	)

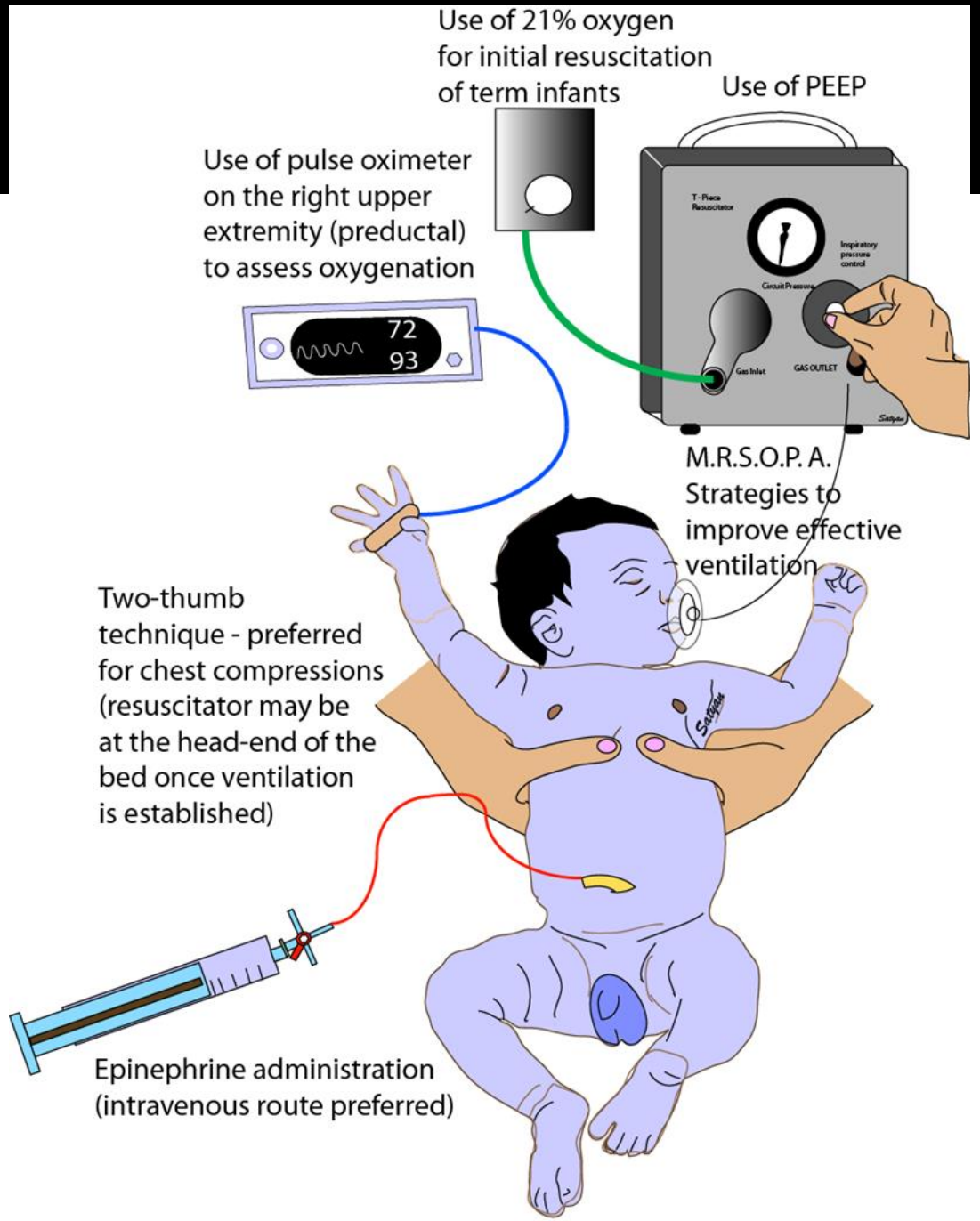
Dose – 0.03 mg/kg or
0.3 ml/kg 1:10,000
↓
Flush – 3 ml/kg
(~10 ml in Term)

ROSC: Return
^ p<0.05 low dose low
†p<0.05 high dose high

Sankaran et al PAS 2019

Summary

- Ventilation of the lungs is the key to neonatal resuscitation
- Increasing heart rate is the most important sign of effective resuscitation
- Avoid cord milking in extremely preterm infants
- 21% oxygen may not be adequate for initial resuscitation of extremely preterm infants
- Epinephrine: avoid multiple ET doses
- UVC epinephrine: 0.03mg/kg → 3 ml/kg flush



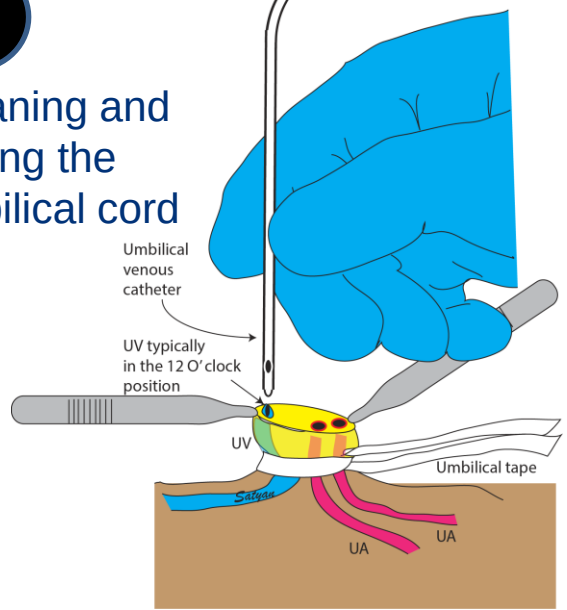
UVC EPI

4 Umbilical venous catheter flushed with normal saline to propel epinephrine to the neonate's heart

2 Sterile, flushed umbilical venous catheter inserted after dilating the umbilical vein

3 Syringe with appropriate dose of epinephrine administered through the umbilical venous catheter

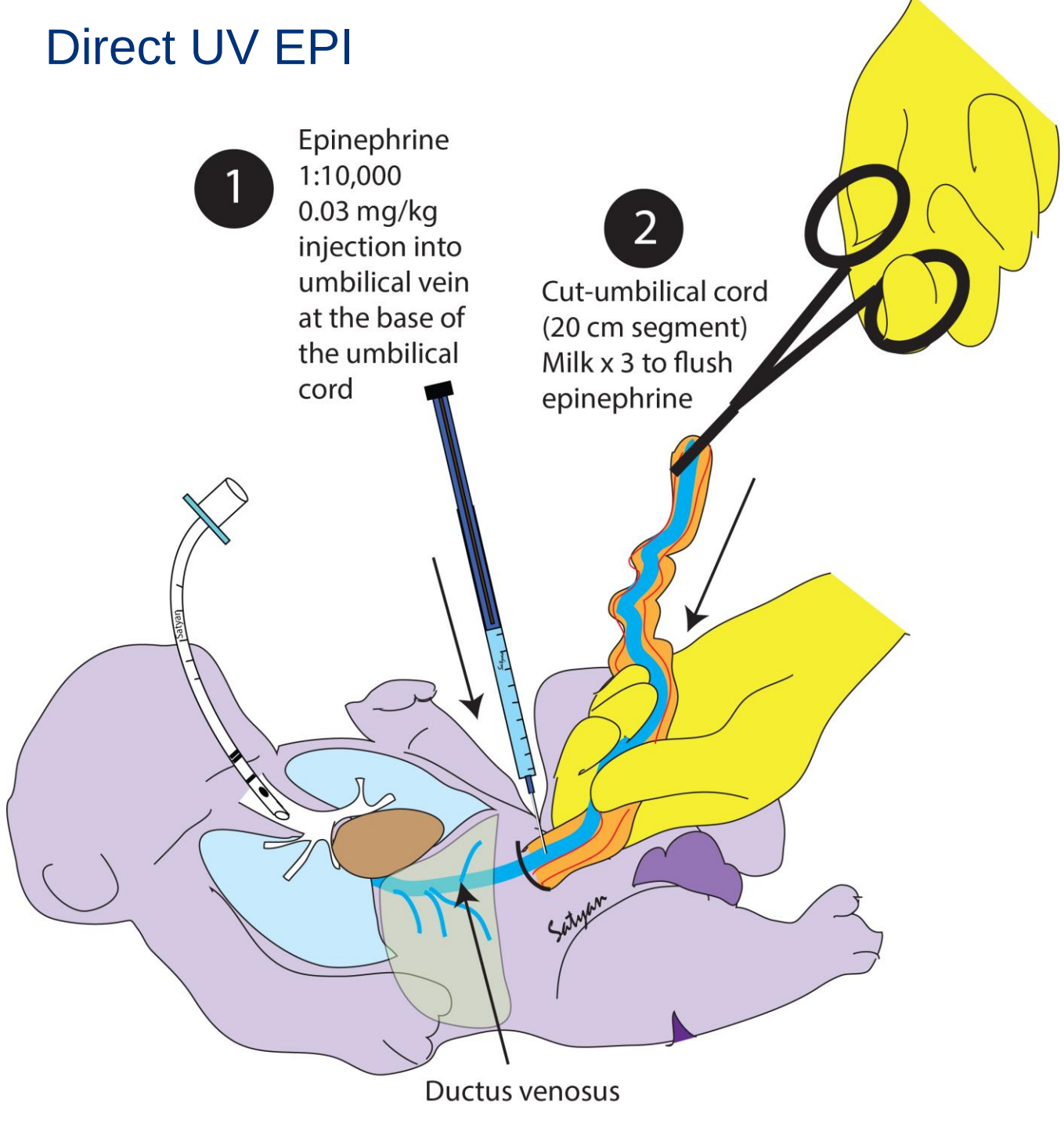
1 Cleaning and cutting the umbilical cord



Direct UV EPI

1 Epinephrine 1:10,000 0.03 mg/kg injection into umbilical vein at the base of the umbilical cord

2 Cut-umbilical cord (20 cm segment) Milk x 3 to flush epinephrine



All images courtesy of Satyan Lakshminrusimha, MD.