

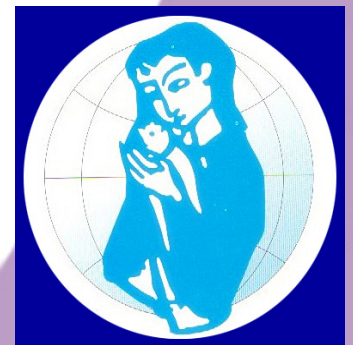
# **Cerebral Blood Flow Velocities in Mechanically Ventilated Preterm Infants**

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**The 9th IAMANEH World Congress, Cairo, November 2nd, 2006**

- IVH and PVL are significant morbidities of preterm infants
- These conditions share in their complex pathogenesis disturbances of cerebral blood flow
- Doppler ultrasound has been used to evaluate hemodynamic abnormalities that may predispose premature infants to these conditions



- low CBF has been shown to be a risk factor for IVH and PVL
- Although the critical level of CBF needed to maintain cellular integrity in very preterm infants has not yet been defined

Perlman, J. M., et al. NEJM, 1983;309: 204–209

Ellison, P., et al. Acta Paediatr Scand, 1986;75: 905–912

Meeks JH, et al. Arch Dis Child, 1999; 81: F15 –F18

Kluckow M, Evans N. Arch Dis Child,2000;82:F188-94



- Preterm infants are exposed to a variety of prenatal and postnatal factors that might influence their cardiovascular stability



# *First Successfully Ventilated Infant 1963*





- Lung mechanics may influence systemic and cerebral hemodynamics
- IPPV increases CBV and causes fluctuations in cerebral venous flow velocity
- High PiP can impair venous return to the heart and results in reversal of flow in intracranial veins

Leahy FAN et al, J Pediatr, 1982;101:984-7

Cowan F et al, Acta Pediatr Scand 1987; 76:239-47



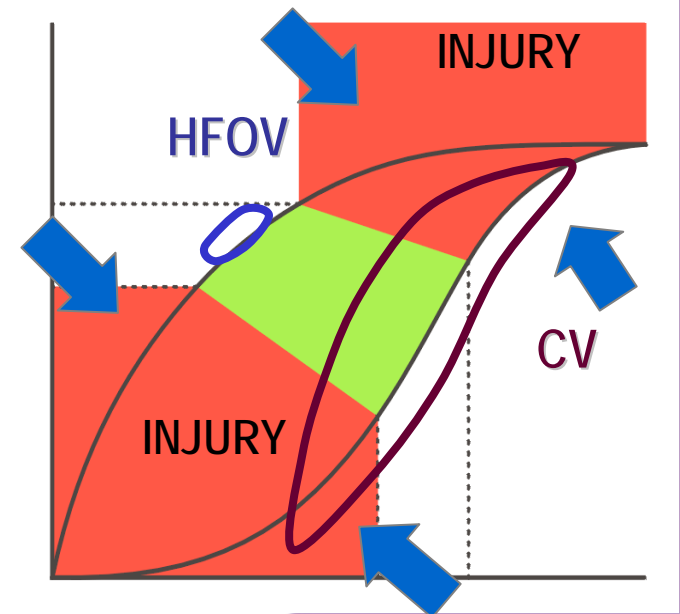
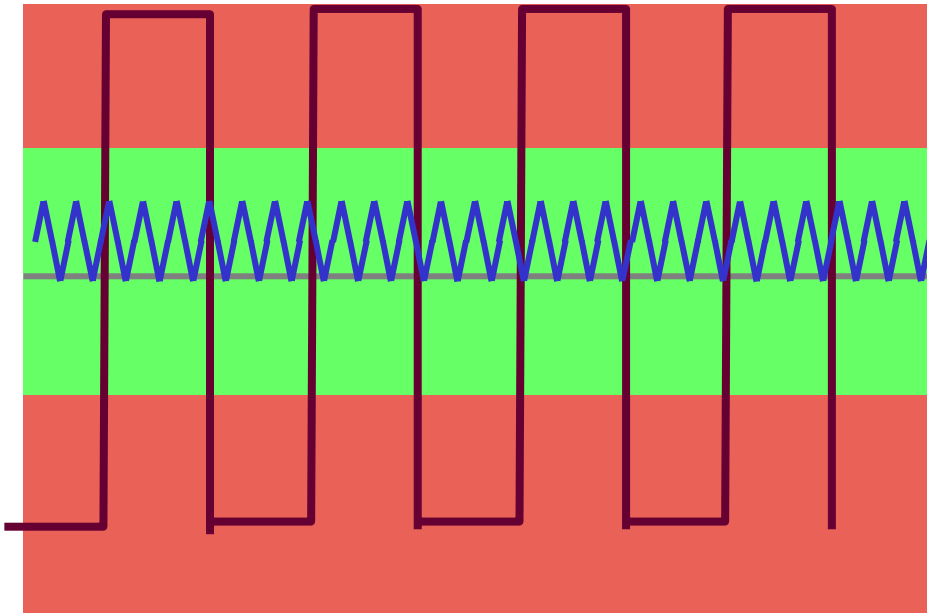
# HFOV features

- High frequency (600-900/min = 10-15 Hz)
- Very small tidal volumes (1-2 ml/kg) < dead space
- Incomplete inspiration and expiration
- Dampening of oscillations in the airways  
=> Very small intra-alveolar pressure amplitude



# HFOV

- During CV, there are swings between the zones of injury from inspiration to expiration
- During HFOV, the entire cycle operates in the “safe window” and avoids the injury zones



# HFOV vs CV in Preterm Infants

- Two uncontrolled studies in neonates showed acute alterations in cardiac performance and CBF following change from CV to HFOV

Laubscher B, et al, Arch Dis Child, 1996; 74: F172-6

Simma B, et al, Crit Care Med, 2000; 28:227-31



# HFOV vs CV in Preterm Infants

- In a more recent RCT of CV versus elective HFOV, there was no significant difference in SVC flow or RVOs in the first day after birth
- However, there were trends toward an increased incidence of borderline SVC flow and use of inotropes in these HFOV infants

Osborn DA, Evans N. J Pediatr 2003; 143: 192-8



# HFOV vs CV in Preterm Infants

- The role of elective HFOV for the treatment of RDS in preterm infants remains uncertain
- The effects of HFOV and CV on short term respiratory and neurological morbidity have been compared in several studies
- Data on long term neuro-developmental outcome were provided in three studies



# HFOV vs CV in Preterm Infants

- A major concern, which first arose with the **HIFI trial**, was the increased rates of acute (IVH, PVL) and chronic neurological injury (poor neuro-developmental outcome) that appeared to be associated with HFOV
- The nearly constant high mean airway pressure during HFOV might restrict venous return, increase intracranial venous pressure, and decrease cerebral blood flow

The HIFI Study Group. NEJM 1989; 320: 888-93



# HFOV vs CV in Preterm Infants

- In the **PROVO** study
- Similar neuro-developmental outcome at 6 years was observed between the two groups

Gerstmann DR, et al. Pediatrics 1996;98:1044–57



# HFOV vs CV in Preterm Infants

- In the **UKOS** study
- No differences in the incidence of CLD, mortality
- Developmental scores at 2 years were unaffected by mode of ventilation (RR 1.13; 95% CI: 0.78 to 1.63)

Johnson AH, et al. NEJM 2002;347:633–42

Marlow N, et al. Arch Dis Child, 2006;91:F320–6



# Systematic review of studies comparing HFOV and CV

- Eleven eligible studies on 3,275 infants were included
- There is no clear evidence that elective HFOV, as compared with CV, offers important advantages when used as the initial ventilation strategy to treat preterm babies with acute pulmonary dysfunction
- There is no evidence of a reduction in death rate



# Systematic review of studies comparing HFOV and CV

- There may be a small reduction in the rate of CLD with HFOV
- Adverse effects on short term neurological outcomes have been observed in some studies but these effects are not significant overall
- Information about effects on long term outcome is not adequate overall





# Randomized trial of HFOV versus CV: Effect on cerebral hemodynamics in preterm infants

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Children's Hospital, Mansoura, Egypt



# Objective

- To determine whether the elective use of HFOV as compared to CV in preterm infants who are mechanically ventilated for RDS influences the cerebral hemodynamics



# Setting/time

- The trial was conducted at the neonatal intensive care unit (NICU) of Mansoura University Children's Hospital
- In the period from March 2005 to June 2006



# Subjects and Methods

## *Eligibility*

- Enrollment criteria:
  - Preterm infants < 37 weeks of gestation
  - Appropriate for gestational age
  - Admitted within the first 2 hours of life
  - Having RDS
  - In need for mechanical ventilation within 12 h of birth



# Subjects and Methods

## *Eligibility*

- Exclusion criteria
  - Dysmorphic features and major congenital malformations
  - Asphyxia
  - PROM and/or chorioamnionitis
  - Exposure to maternal drugs



# Subjects and Methods

## *Randomization*

- The study was designed as a randomized controlled trial
- After enrollment, each infant was randomly assigned either HFOV or CV according to a predetermined list of random numbers
- Randomization was done by cards provided in consecutively numbered, opaque, sealed envelopes



# Subjects and Methods

## *Study end points*

- **Primary end point**
  - Mean velocities (MV) in ACA and MCA
- **Other end points:**
  - Peak systolic (PSV)
  - End diastolic velocities (EDV)
  - Resistive index (RI)  
in ACA and MCA



# Subjects and Methods

## *Sample size*

- Twenty infants in each group
- 6 cmH<sub>2</sub>O (20% difference) between the 2 groups in the MV in the ACN and MCA
- A 2-group *t* test with a significance level of 95%
- 80% power



# Subjects and Methods

- All the infants enrolled in the study were subjected to the followings:
  - Thorough perinatal history
  - Assessment of gestational age
  - Complete clinical examination



# Subjects and Methods

- Lab investigations were done prior to assessment of cerebral hemodynamics:
  - CBC
  - Blood glucose
  - Arterial blood gases and serum electrolytes
- Patients were monitored continuously for heart rate, SpO<sub>2</sub>



# Subjects and Methods

## *Radiologic investigations*

- Cranial ultrasound
- Cranial Doppler ultrasound
- Echocardiography



# Subjects and Methods

## *Cranial ultrasound*

- Cranial ultrasound was performed in day1 and day 4
- Cranial ultrasound scans were then repeated daily until 1 wk of age and then weekly until discharge from hospital
- Two dimensional imaging was performed in sagittal and coronal planes with 3-8 MHZ transducer
- Any IVH observed was classified according to Papile grading\*

\*Papile et al., J Pediatr, 1978 ;92:529-34.



# Subjects and Methods

## *Cranial Doppler ultrasound*

- Measurements of PSV, EDV, MV and RI were made in the ACA and MCA
  - Day 1 (47 Preterm infants)
  - Day 4 (26 Preterm infants)
- Examination times varied between 5 and 10 min
- A color Doppler unit by (Philips EnVisor C Ultrasound Botchell, WA 98041- 3003 USA).
- With 7.5 MHz curved linear array probe



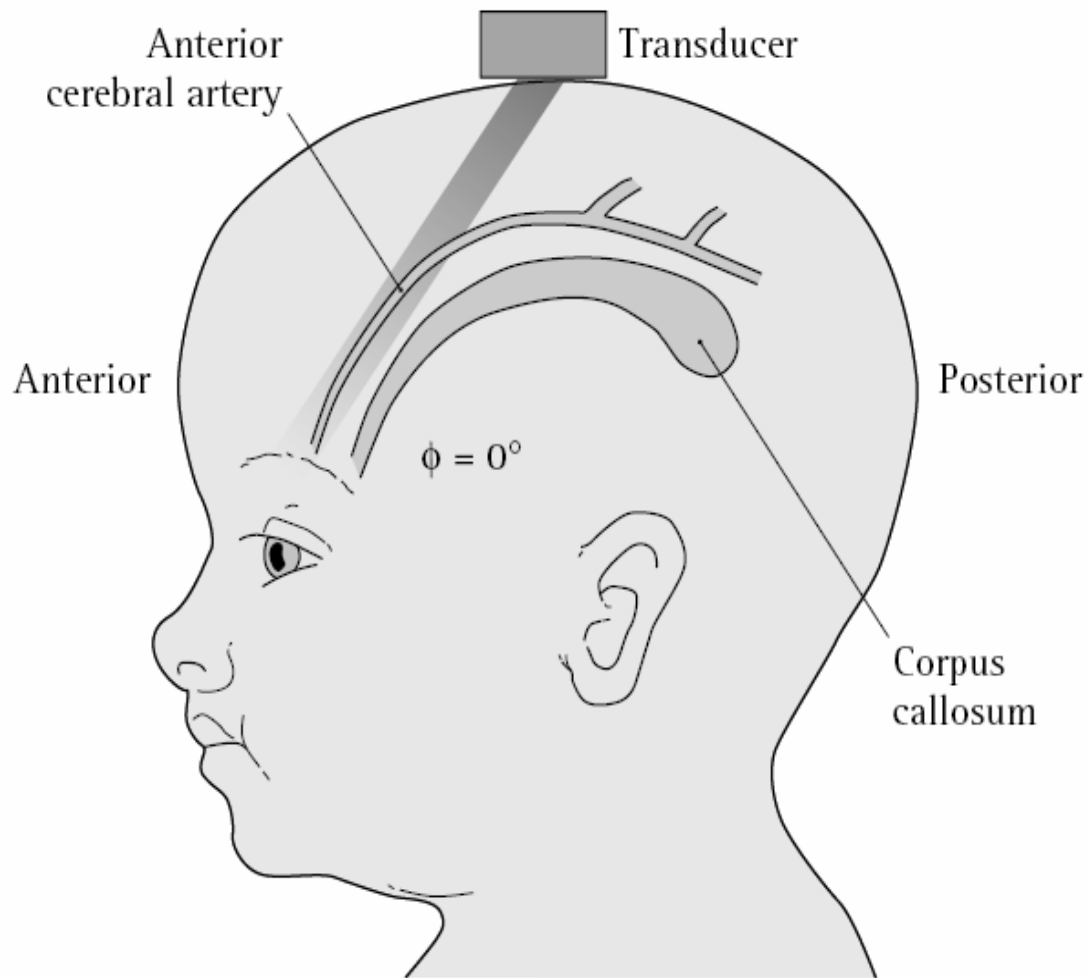
# Subjects and Methods

## *Cranial ultrasound*



(Philips EnVisor C Ultrasound scanner,  
Botchell, WA 98041- 3003 USA)





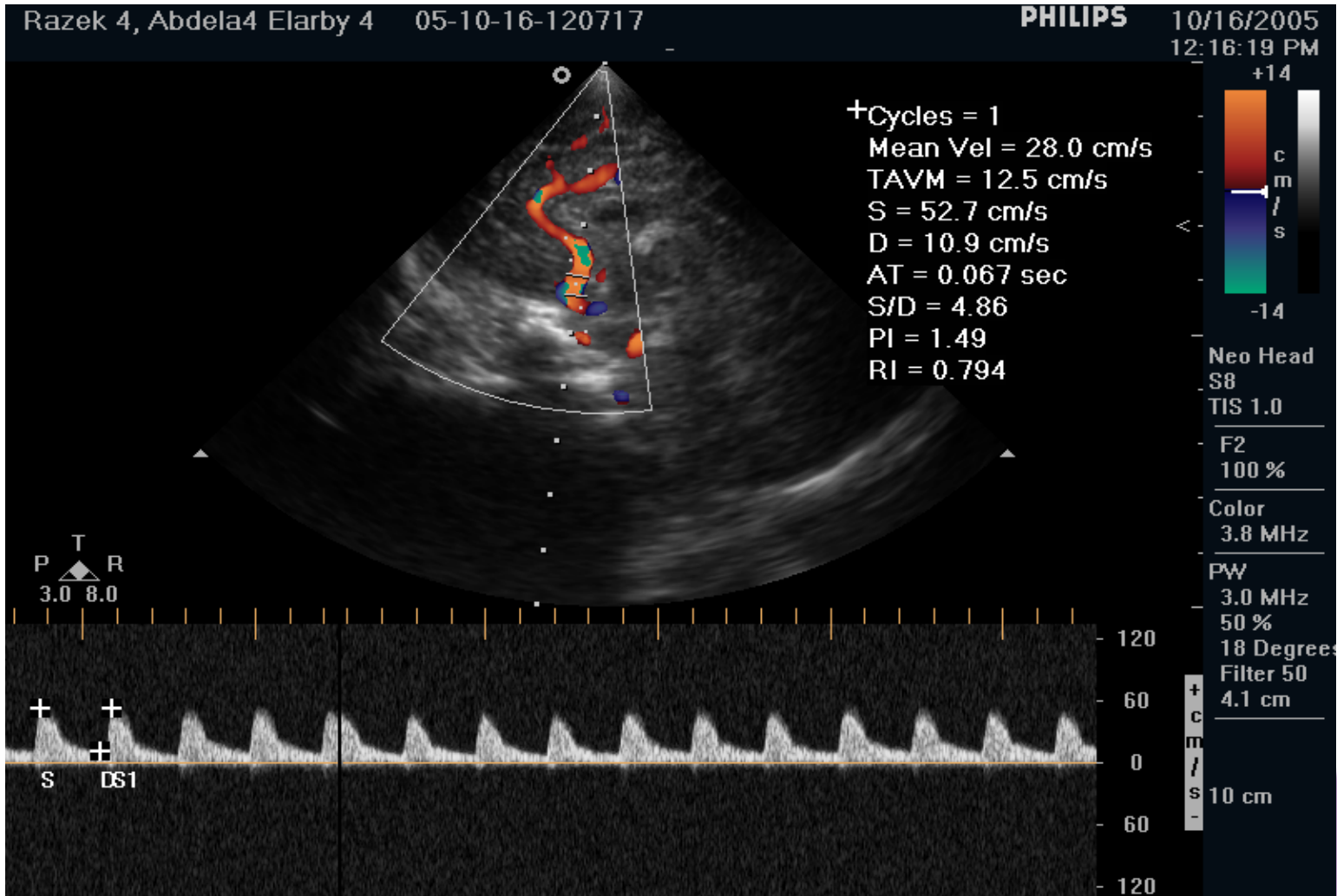
The transfontanellar approach to the anterior cerebral artery

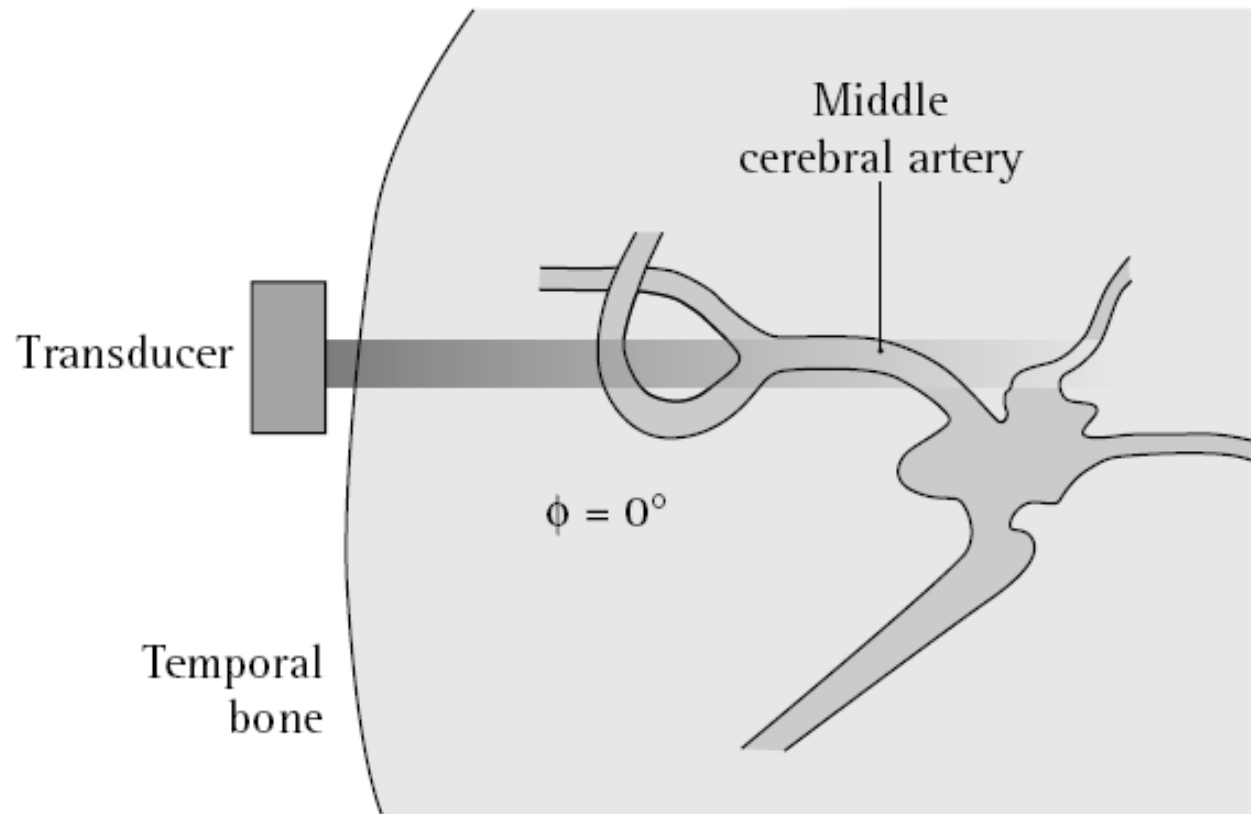
Anthony & Levene 1993



# Subjects and Methods

## *ACA Color Doppler*





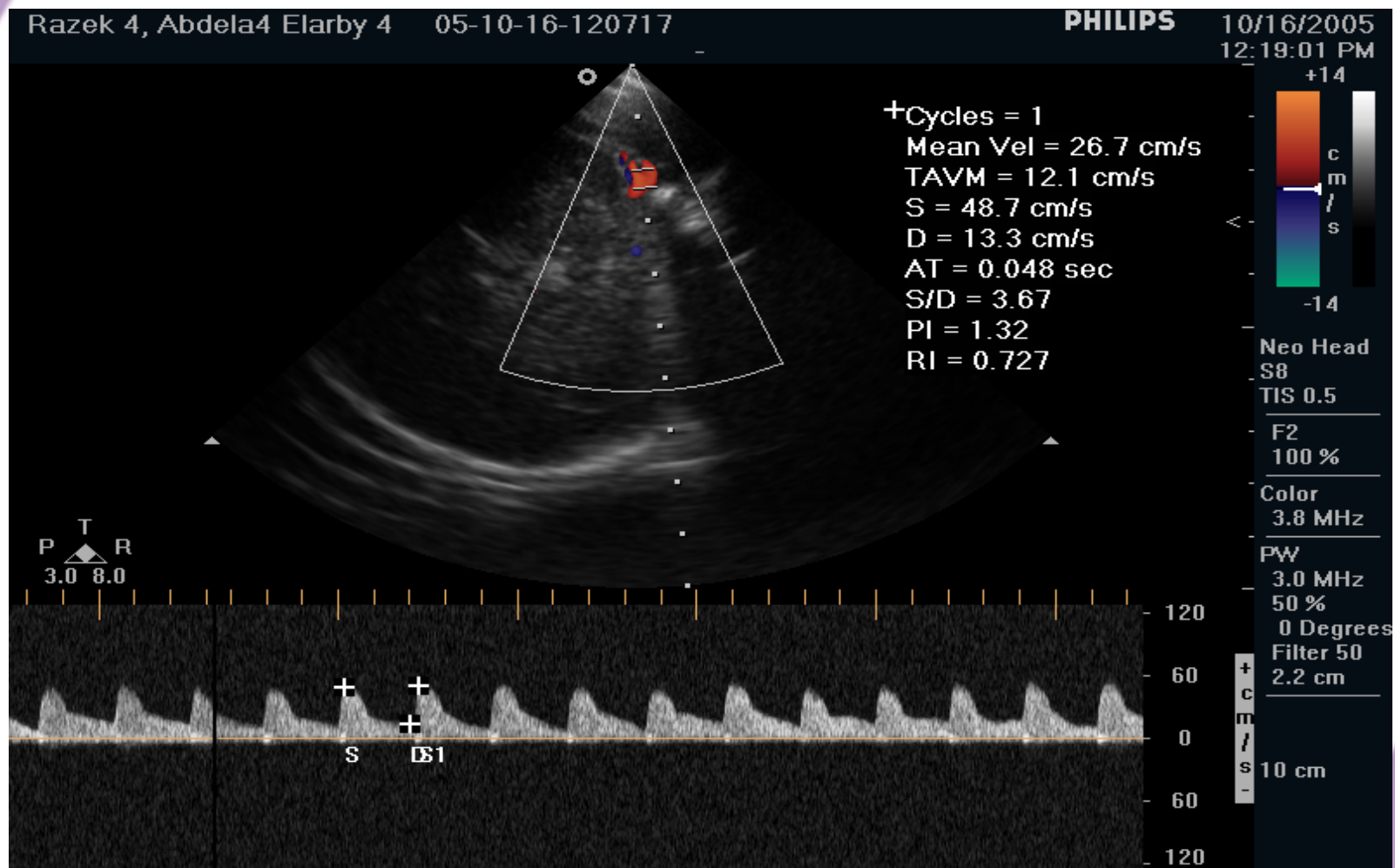
The transtemporal approach to the middle cerebral artery

**Anthony & Levene 1993**



# Subjects and Methods

## *MCA Color Doppler*



# Subjects and Methods

## *Cranial Doppler ultrasound*

- The intra-observer variability using the Doppler ultrasound machine was performed by measuring CBF in the ACA and MCA for 5 healthy preterm babies with coefficient of variance  $< 10\%$  in all measurements



# Subjects and Methods

## *Echocardiography*

- Echocardiographic monitoring was performed at the time of CBF measurements
- Significant PDA was defined as:
  - Doppler diameter of PDA  $> 2$  mm, with
  - Clinical finding of two or more of the followings:
    - Murmur of PDA
    - Tachycardia  $HR > 180$
    - Hypotension  $MBP < GA$
    - Pounding peripheral pulsations, or poor perfusion



# Subjects and Methods

## *Treatment Strategies*

- Eligible infants were randomly assigned to either HFOV, CV within 12h hour of life
- Indications for mechanical ventilation:
  - Increased FiO<sub>2</sub> requirements > 0.60
  - Respiratory acidosis (pH < 7.25)
  - Recurrent apneas
  - Early CXR consistent with severe RDS



# Subjects and Methods

## *Conventional mechanical ventilation*

- CV was delivered by using a time-cycled, pressure-limited ventilator (Drager Babylog 8000+®; Drager Medical, Lubeck, Germany)
- Initial settings:
  - A/C mode
  - Ti 0.4 seconds
  - Rate 60 BPM
  - PiP 20 cm H<sub>2</sub>O
  - PEEP 5 cm H<sub>2</sub>O



# Subjects and Methods

## *Conventional mechanical ventilation*

- The P<sub>i</sub>P and Rate were adjusted to achieve a PaCO<sub>2</sub> of 35 - 50 mm Hg
- FiO<sub>2</sub> was adjusted to maintain preductal oxygen saturation 89% to 93% with PaO<sub>2</sub> of 55 - 90 mm Hg
- Infants were changed to SIMV mode for weaning



# Subjects and Methods

## *HFOV*

- HFOV was delivered by (Drager Babylog 8000+®, Drager Medical, and Lubeck, Germany)
- Initial settings
  - MAP 6 to 8 cm H<sub>2</sub>O
  - Frequency 10 Hz
- A volume recruitment strategy was used whereby the MAP was progressively increased by 1 cmH<sub>2</sub>O every 10 to 15 minutes until the FIO<sub>2</sub> was less than 0.3



# Subjects and Methods

## *HFOV*

- CXRs were performed at least every 12 hrs, and the MAP was adjusted accordingly to achieve lung inflation at 9 posterior ribs visible above the diaphragm
- Attempts to wean MAP occurred when the FiO<sub>2</sub> was <0.3
- Once the MAP was 7 cm H<sub>2</sub>O, infants were weaned to CPAP or oxygen



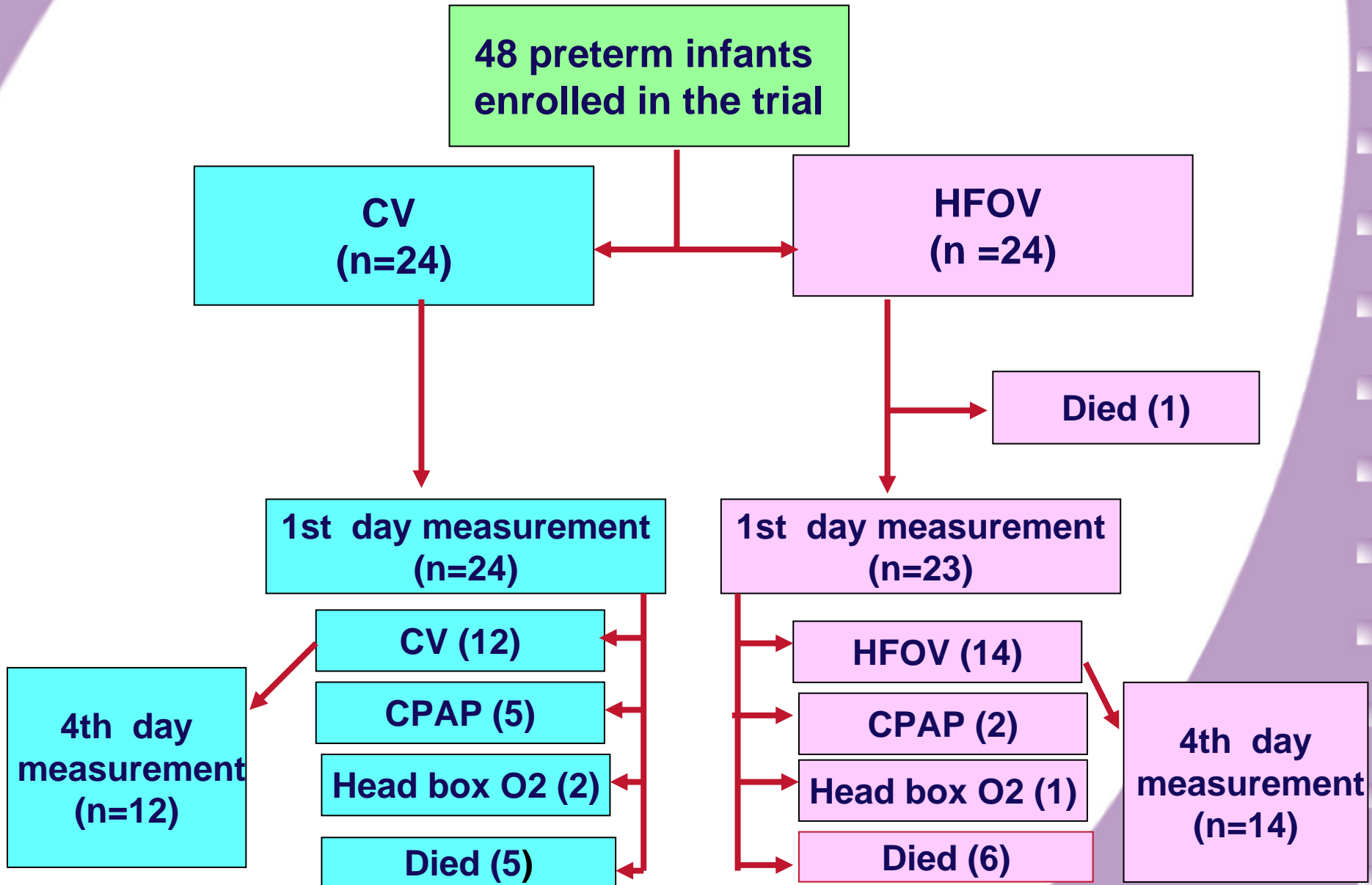
# Subjects and Methods

## *HFOV*

- The amplitude was increased until the chest was seen to be bouncing
- Subsequent adjustments to amplitude were made to achieve PaCO<sub>2</sub> 35-50 mm Hg
- Frequency was reduced only if adequate CO<sub>2</sub> elimination was not achieved
- The FiO<sub>2</sub> was adjusted to maintain preductal oxygen saturation 89% - 93% with PaO<sub>2</sub> of 55 - 90 mm Hg



# Trial Profile



# Subjects and Methods

- Surfactant
- Dopamine
- Indomethacin
- Sedation
- Phototherapy



# Subjects and Methods

## *Statistical analysis*

- Independent samples Student's t-test.
- Paired-Samples t test
- For comparisons of categorical data; Chi-square test and Fisher's exact test were used wherever applicable.
- The computer program SPSS; Release 10.0 (SPSS Inc, Chicago, Illinois, USA)
- Level of significance was set at  $p < 0.05$



# Results



# Demographic and clinical findings in the 1st day of life

	CV (n=24)	HFOV (n=23)	P Value
Birth weight (g)*	1662 ± 223	1619 ± 225	0.51
Gestational Age (wk)*	31.8 ± 1.6	31.4 ± 1.4	0.41
Male sex**	13 (54.2%)	12 (52.2%)	1.00
Cesarean delivery**	14 (58.3%)	8 (34.8%)	0.14
Antenatal steroids**	15 (62.5%)	13 (56.5%)	1.00
Dopamine***	2 (8.3%)	7 (30.4%)	0.07
Surfactant**	3 (12.5%)	4 (17.4%)	0.70
PDA**	4 (16.7%)	2 (8.7%)	0.67
IVH grade 1-2***	3 (12.5%)	2 (8.7%)	0.70
grade 3-4***	2 (8.3%)	2 (8.7%)	0.98



Independent samples T-test \*, and Chi-square test\*\* and Fisher exact test \*\*\*

# Clinical and laboratory measurements in the 1st day of life

	CV (n=24)	HFOV (n=23)	P Value*
Heart rate (BPM)	147.5 ± 15.2	155.0 ± 14.4	0.10
MABP (mmHg)	37.4 ± 1.3	36.7 ± 1.8	0.10
Hemoglobin (g/dl)	13.9 ± 1.1	14.0 ± 0.7	0.67
Blood glucose (mg/dl)	99.3 ± 21.7	92.3 ± 15.3	0.21
PaCo2 (mmHg)	38.9 ± 3.9	38.4 ± 4.1	0.65
PaO2 (mmHg)	76.3 ± 9.3	76.9 ± 9.6	0.82
MAP (cmH2O)	8.2 ± 0.7	9.2 ± 1.0	<b>&lt;0.001</b>

\*Independent samples T-test



# Clinical and laboratory measurements in the 4th day of life

	CV (n=12)	HFOV (n=14)	P Value
Heart rate (BPM)	154.2 ± 17.1	158.9 ± 16.8	0.49
MABP (mmHg)	41.3 ± 3.7	39.1 ± 3.7	0.15
Hemoglobin (g/dl)	13.9 ± 0.5	13.9 ± 0.5	0.96
Blood glucose (mg/dl)	90.3 ± 7.1	83.8 ± 12.0	0.11
PaCo <sub>2</sub> (mmHg)	40.1 ± 3.0	38.8 ± 0.8	0.06
PaO <sub>2</sub> (mmHg)	77.4 ± 6.8	74.9 ± 2.9	0.20
MAP (cmH <sub>2</sub> O)	7.8 ± 0.5	9.9 ± 1.3	<b>&lt;0.001</b>
Dopamine***	1 (8.3%)	5 (35.7%)	0.17
Theophylline***	3 (25%)	3 (21.4%)	1.00
PDA***	2 (16.7)	2 (14.2%)	0.87
IVH grade 1-2 ***	3 (25%)	1 (7.1%)	0.31

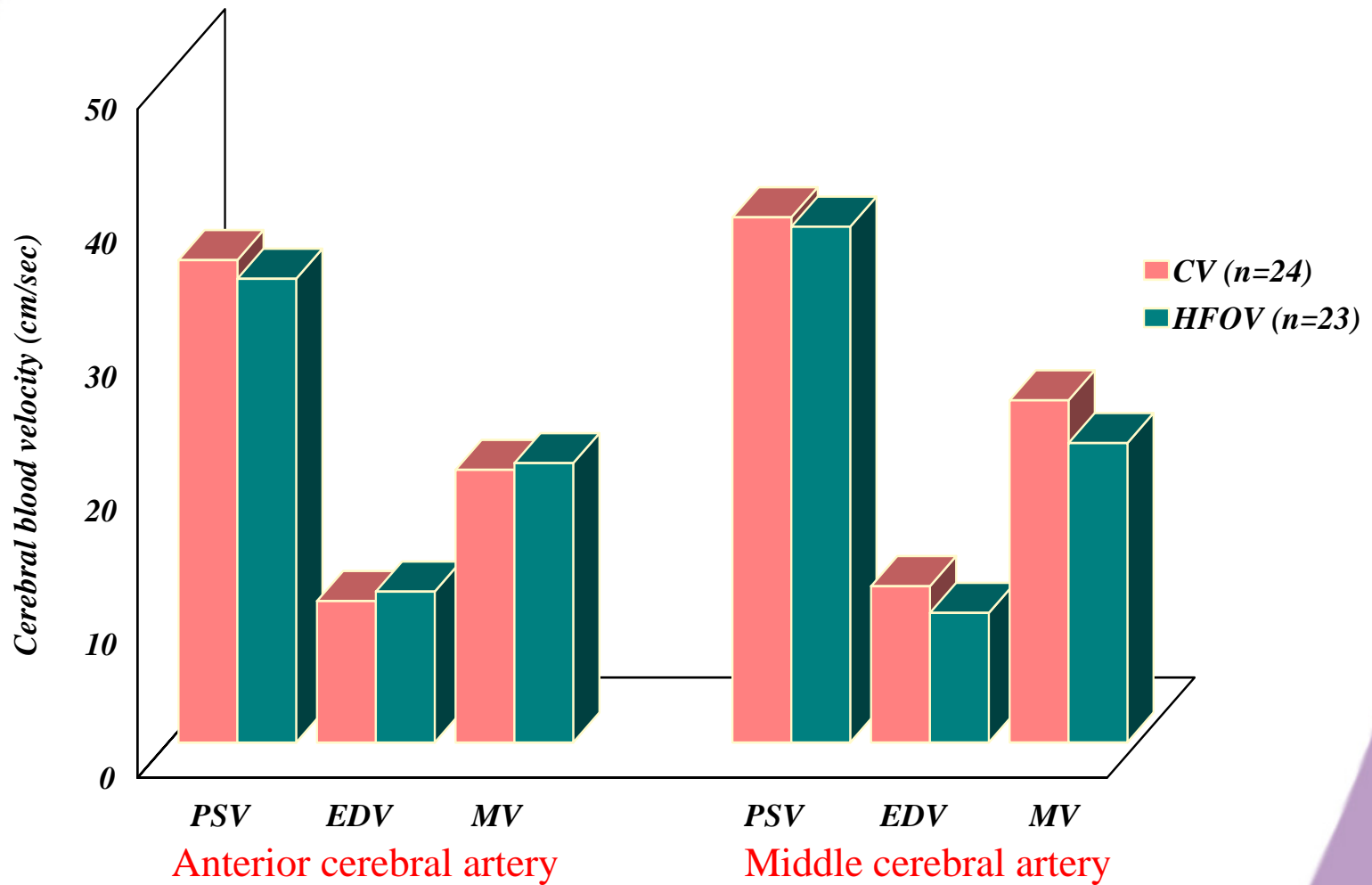


# Cerebral hemodynamic measures in the 1st day of life

	CV (n=24)	HFOV (n=23)	P Value*
<b>ACA</b>			
PSV (cm/sec)	36.1 ± 5.0	34.7 ± 3.7	0.27
EDV (cm/sec)	10.6 ± 3.4	11.3 ± 2.5	0.45
MV (cm/sec)	20.4 ± 5.1	20.9 ± 1.7	0.69
RI	0.66 ± 0.07	0.64 ± 0.1	0.39
<b>MCA</b>			
PSV (cm/sec)	39.3 ± 11.7	38.6 ± 7.7	0.80
EDV (cm/sec)	11.7 ± 4.3	9.7 ± 3.1	0.09
MV (cm/sec)	25.6 ± 6.6	22.4 ± 6.0	0.09
RI	0.69 ± 0.1	0.70 ± 0.1	0.58

Independent samples t test\*





## Cerebral hemodynamic measures in the 1st day of life

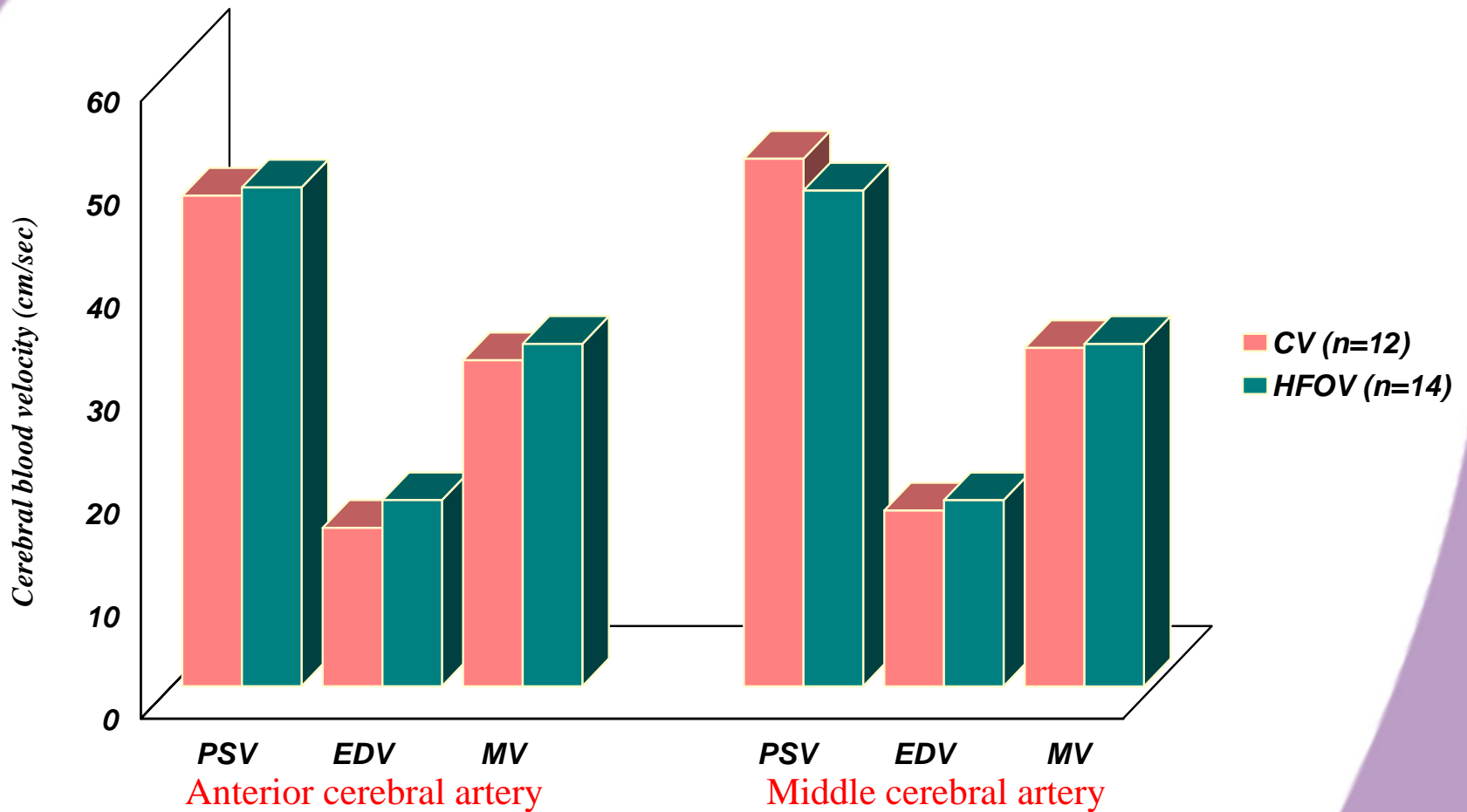


# Cerebral hemodynamic measures in the 4<sup>th</sup> day of life

	CV (n=12)	HFOV (n=14)	P Value*
<b>ACA</b>			
PSV (cm/sec)	47.7 ± 11.1	48.5 ± 7.6	0.70
EDV (cm/sec)	15.4 ± 4.0	18.1 ± 2.9	0.06
MV (cm/sec)	31.7 ± 7.2	33.3 ± 4.5	0.48
RI	0.61 ± 0.07	0.62 ± 0.07	0.80
<b>MCA</b>			
PSV (cm/sec)	51.3 ± 7.9	48.2 ± 3.7	0.20
EDV (cm/sec)	17.1 ± 5.0	18.1 ± 2.0	0.51
MV (cm/sec)	32.9 ± 7.2	33.3 ± 3.8	0.86
RI	0.60 ± 0.14	0.66 ± 0.04	0.10

Independent samples t test\*





## Cerebral hemodynamic measures in the 4th day of life

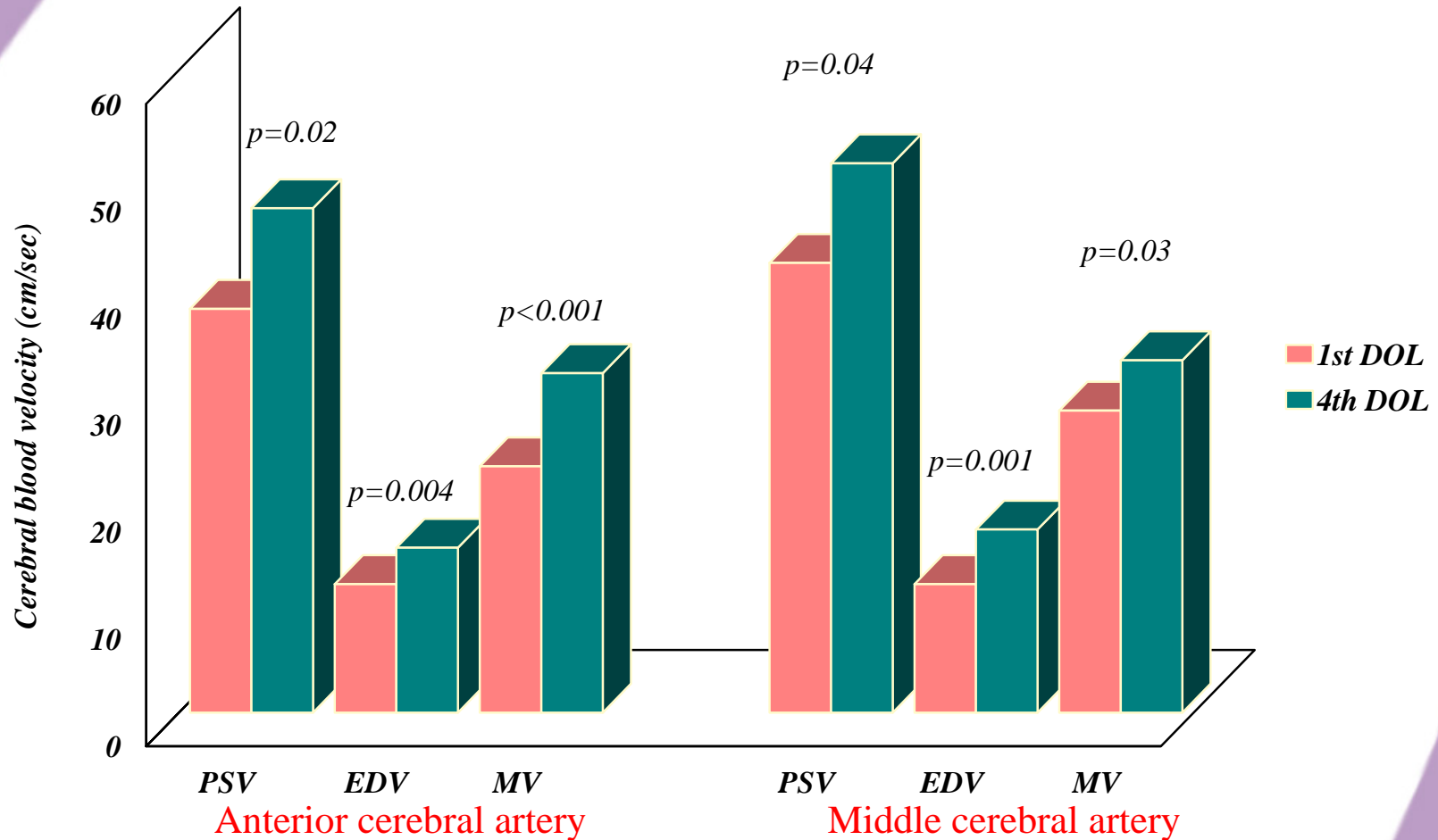


# Cerebral hemodynamic measures in 1st day and 4th day of life for babies maintained on CV (n = 12)

	1 <sup>st</sup> DOL	4 <sup>th</sup> DOL	P Value*
<b>ACA</b>			
PSV (cm/sec)	37.7 ± 5.5	47.1 ± 11.1	<b>0.02</b>
EDV (cm/sec)	12.0 ± 2.6	15.4 ± 4.0	<b>0.004</b>
MV (cm/sec)	23.0 ± 3.4	31.7 ± 7.2	<b>&lt;0.001</b>
RI	0.67 ± 0.08	0.07 ± 0.60	<b>0.002</b>
<b>MCA</b>			
PSV (cm/sec)	42.0 ± 14.1	51.3 ± 7.9	<b>0.04</b>
EDV (cm/sec)	12.0 ± 5.6	17.1 ± 5.0	<b>0.001</b>
MV (cm/sec)	28.2 ± 7.9	32.9 ± 7.2	<b>0.03</b>
RI	0.70 ± 0.11	0.61 ± 0.16	<b>0.01</b>



Paired samples t test \*



***Cerebral hemodynamic measures in 1st day and 4th day of life for babies maintained on CV (n = 12)***

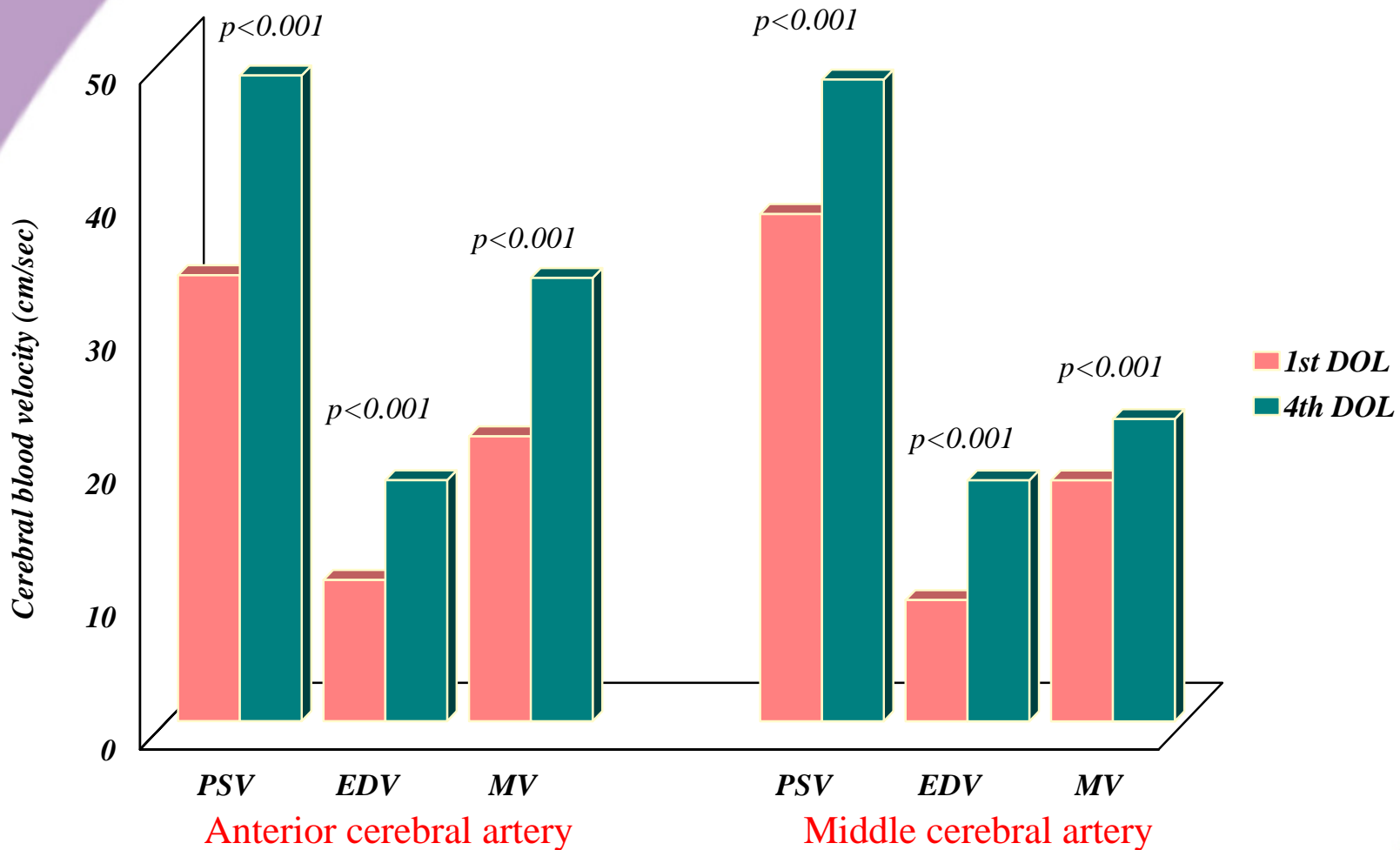


# Cerebral hemodynamic measures in 1st day and 4th day of life for babies maintained on HFOV (n = 14)

	1 <sup>st</sup> DOL	4 <sup>th</sup> DOL	P Value*
<b>ACA</b>			
PSV (cm/sec)	33.5 ± 3.9	48.5 ± 7.6	<0.001
EDV (cm/sec)	10.6 ± 1.0	18.1 ± 2.9	< 0.001
MV (cm/sec)	21.4 ± 1.7	33.3 ± 4.5	< 0.001
RI	0.65 ± 0.07	0.62 ± 0.08	0.04
<b>MCA</b>			
PSV (cm/sec)	38.1 ± 4.6	48.2 ± 3.7	<0.001
EDV (cm/sec)	9.1 ± 2.3	18.1 ± 2.0	<0.001
MV (cm/sec)	18.1 ± 2.0	22.7 ± 4.0	<0.001
RI	0.72 ± 0.07	0.66 ± 0.04	0.01

Paired samples t test\*





***Cerebral hemodynamic measures in 1st day and 4th day of life for babies maintained on HFOV (n = 14)***



# Conclusions



- This study has provided evidence that there is no difference in the effects of HFOV and CV on cerebral hemodynamics in the 1<sup>st</sup> and 4<sup>th</sup> days of life
- CBF increase progressively with increase of post-natal age in both HFOV and CV groups
- Of concern is the trend towards increased need for dopamine in infants receiving HFOV



# Recommendations



- Follow up of the babies enrolled in our study to assess the effect of different mechanical ventilation modalities on neuro-developmental outcome
- Blood pressure monitoring and appropriate volume replacement and inotrope support in infants receiving HFOV



?

## Should HFOV Be Used in the Premature Infant from Birth?

