Week 1: Clinical Trials and General Neonatology

Neonatal/Infant Resuscitation

Tuesday, June 9 2:30-4:00 pm EDT

AAP Neonatal Resuscitation Program Steering Committee (NRPSC) Highlighted Program

Moderators:
Satyan Lakshminrusimha
Tetsuya Isayama

EDT	Abstract #	Title	Presenting author
2:30 pm		Introduction & General Information	
2:35 pm	3378957	Randomized Controlled Trial of Oxygen Saturation Targets During Resuscitation of Preterm Neonates in the Delivery Room: The START Study	Vishal Kapadia
2:45 pm	3375525	Femoral occlusion during neonatal CPR – A simple technique to improve Coronary perfusion and hasten recovery in perinatal cardiac arrest	Munmun Rawat
2:55 pm	3375623	Resuscitation with an intact cord enhances pulmonary vasodilation and ventilation but reduces systemic oxygen toxicity and oxygen load in a preterm ovine model	Praveen Chandrasekharan
3:05 pm	3379017	Continuous Chest Compressions with Asynchronous Ventilations Increase Cerebral Blood Flow and Oxygen Delivery in the Perinatal Asphyxiated Cardiac Arrest Lamb Model	Payam Vali
3:15 pm	3378115	Direct Umbilical Vein Injection of Epinephrine with Cut Umbilical Cord Milking	Peggy Chen
3:25 pm	3380291	Return of Spontaneous Circulation is Associated with Excess Oxygen Delivery in Near-term Asphyxiated Lambs	Shiraz Badurdeen
3:35 pm	3362190	Cochrane update 2020: Sustained versus standard inflations during neonatal resuscitation.	Matteo Bruschettini
3:45 pm		Wrap Up	

Question Asked	**Answer Given**	Responder
i think this will affect blood flow and causes ischaemia in LL esp if long time of resuscitation is needed	We are collecting the skeletal muscle samples distal to femoral occlusion to look for ischemia, necrosis and measure creatinine kinase in both controls (No femoral occlusion) and study group (with femoral occlusion).	Munmun Rawat
How practical it is to perform femoral inclusion and insertion of the umbilical cord during resuscitation	Since the person occlusing the femorals usually stands at the foot end there's ample space for a second resuscitator to stand on the side and put a low lying UVC. The lower abdomen and umbilicus field is clear for the UVC placement.	Munmun Rawat
considered possible complications in the extremities due to hypoperfusion, necrosis?	Yes, we are collecting the skeletal muscle samples distal to femoral occlusion to look for ischemia, necrosis and measure creatinine kinase in both controls (No femoral occlusion) and study group (with femoral occlusion).	Munmun Rawat
Thanks for a very clear presentation. From which catheter were the samples for epinephrine levels taken?	Thank you. Samples were drawn from the carotid artery line.	Munmun Rawat
Very nice study! have you examined the brian to assess if there are higher brain injury rates due to the higher carotid blood flow?	Thank you. We are collecting the brain samples to look for the oxidative and reperfusion injury. We will test all the samples once the study is complete.	Munmun Rawat
Did u look at head USG?	We did not look at head USG. During dissection while collecting the samples, the brain and the ventricles were examined. We did not see any gross bleed in the ventricles so far.	Munmun Rawat
Did the femoral occlusion result in more ROSC without Epi?	Yes, 3 out of 10 lambs achieved ROSC without epinephrine whereas in the controls all the lambs needed epi. In addition, overall lambs required fewer doses of epinephrine with femoral occlusion (mean 1.9±1.8 vs 3.4±1.1)	Munmun Rawat
Any lower limb ischemia in any lamb?	We are collecting the skeletal muscle samples distal to femoral occlusion to look for ischemia, necrosis and measure creatinine kinase in both controls (No femoral occlusion) and study group (with femoral occlusion).	Munmun Rawat

DID YOU DOCUMENT ANY BRAIN INJURY IN THOSE CASES SUBJECTED TO ARTERIAL OCCLUSION?	We are collecting brain samples to evaluate oxidative stress. During dissection while collecting the samples, the brain and the ventricles were examined. We did not see any gross bleed in the ventricles so far.	Munmun Rawat
Nice presentation	Thank you.	Munmun Rawat
Did you measure adverse effects such as incidence of intraventricular hemorrhage?	During dissection while collecting the samples, the brain and the ventricles were examined. We did not see any gross bleed in the ventricles so far.	Munmun Rawat
Did you evaluate for brain hemorrhage by any chance? Can increased brain flow be associated with IVH?	After euthnasia, the brain was dissected and the ventricles were examined. We did not see any gross bleed in the ventricles so far. Even though femoral occlusion results in increase in increase in carotid blood flow, it is never higher than the baseline carotid flow.	Munmun Rawat
Is there any danger to increase carotid blood flow to the brain that fast?	After euthnasia, the brain was dissected and the ventricles were examined. We did not see any gross bleed in the ventricles so far. Even though femoral occlusion results in increase in increase in carotid blood flow, it is never higher than the baseline carotid flow.	Munmun Rawat
Doing leg elevation could increase inc abd pressure and may affect ventilation?	We did not have any issues with increase in abdominal pressure. The ventilatory parameters for similar chest rise remained the same.	Munmun Rawat
beautiful presentation	Thank you	Munmun Rawat
Was there any difference in intraventricular bleed in those two groups?	We did not see brain bleed in any of our term lambs in control or study group so far during dissection.	Munmun Rawat
do you speculate increase in IVH rates in infants exposed to femoral occlusion?	Femoral occlusion is performed only durinmg chest compressions and stopped at return of spontaneous circulation. Since carotid artery flow is always lower than the baseline level during this period, we do not anticipate a rise in IVH incidence. A clinical RCT is needed to confirm this.	Munmun Rawat
Do you think it will inceease the risk of IVH in preterm Babies?	Since our study is conducted in a term model we cannot comment on preterm infants. However we plan to perform a study in preterm lamb model as well.	Munmun Rawat

Would you need another person to do this? Would this be a problem for low-resource settings?	To perform femoral occlusion we would need an additional person but leg elevation can be performed by placing a wedge under the infants legs.	Munmun Rawat
Did you observe any incidence of IVH in these sheeps ?	Not so far.	Munmun Rawat
Would you speculate studying for the safety for Preterm infants?	Yes we plan to study in a preterm model.	Munmun Rawat
is there a way that you can study if lifting the legs impacts FRC?	We did not see any change or increase in ventilatory requirements during this maneuver.	Munmun Rawat
Assuming the epinephrine administration was through IV access already in place, can you speculate how it would be with ETT epi	In our lab we have shown reduced bioavailability of epinephrine via ETT and hence did not use that route.	Munmun Rawat
How long were the femorals occluded? How did you measure the pressure applied?	Femoral were continuously occluded throughout the chest compression phase. The same resuscitator occluded the femorals for all our experiments.	Munmun Rawat
How long do you elevate the legs?	We occlude the femorals continuously during Chest Compression phase	Munmun Rawat
at what point do you discontinue femoral arterial occulision?	At return of spontaneous circulation (sustained HR >60 bpm)	Munmun Rawat
Is until return of blood flow?	At return of spontaneous circulation (sustained HR >60 bpm)	Munmun Rawat
IS THIS APPICABLE TO PRETERM	We plan to study in a preterm model	Munmun Rawat
Very interesting! What do you suggest as the next necessary step to indeed confirm clinical effectivity of femoral occlusion in clinical practice? Are you planning a clinical study as well?	Thank you. We are planning to study in preterm model as well as clinically.	Munmun Rawat
once rosc occurs and femoral occlusion released is there higher chance of repeat arrest or bradycardia	One lamb in each group rearrested after ROSC and were counted as 'No ROSC'.	Munmun Rawat

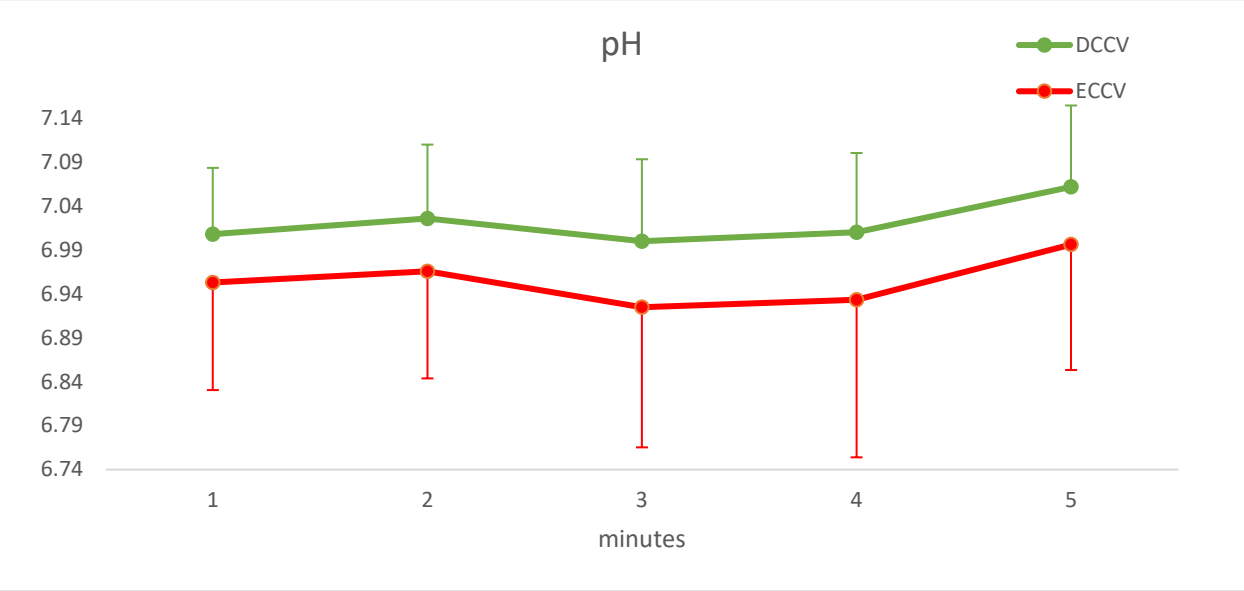
Responses from Praveen Chandrasekharan, MD

1) *Despite the lower PaO_2, there was increased pulmonary blood flow. Was blood flow in the PDA affected?*

PBF was higher in spite of the low PaO_2 blood coming from the Placenta.

What is the minimum "PaO_2" for resulting in pulmonary vasodilation?

The blood flow in the ductus remained right to left throughout the first 5 min of intervention in the asphyxiated model. We speculate that the significant difference in acidosis (as shown below), which could be secondary to significant low $PaCO_2$ and or increased perfusion secondary to uninterrupted left ventricular output, could be the reason for increased pulmonary blood flow. These findings do validate are previous observation presented in PAS 2018 (PAS 2018. Publication no 1725.4). Since lung aeration improves pulmonary blood flow, and studies have shown that a bolus of blood during ventilation have improved pulmonary blood flow (31649907) even if the ventilation remained the same, it is unclear what the optimal PaO2 is to create pulmonary vasodilation. Based on our published data, the change point for PVR (i.e. to decrease PVR) in preterm non-asphyxiated lambs with similar lung development is PaO_2 is 31±0.7 mmHg (Figure 3C, PMID: 31836427). Intact cord clamping and oxygen exposure is an unexplored area, more evidence both translational and clinical are needed to validate these findings. In the presence of an intact cord and ventilation, the minimum PaO_2 required for pulmonary vasodilation is unknown.



2) "What about resuscitation in the first 5 minutes, Not all places can do resus and delayed cord clamping"

Katheria et al. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5527831/, have shown the using a trolley with a heating mattress, CPAP could be delivered with an intact cord in apneic preterm neonates. If the HR is >60 bpm, effective ventilation with an intact cord is possible and will improve saturations as shown in NEPCORD III trial. The ABC study (Protocol published by Knol et al. 2019 https://pubmed.ncbi.nlm.nih.gov/31106181/) using another resuscitation table are conducting an RCT. If the initial assessment of the HR is <60 bpm, while the umbilical cord is intact, despite effective PPV, the cord should be immediately clamped and resuscitation be done per neonatal resuscitation protocol based on region/country.

3) For the DCC group, what do you do if cord stops pulsating before 5 min?

As far as the heart rate improves, regardless of cord pulsations, in this asphyxiated model, positive pressure ventilation was continued for 5 minutes. If the HR drops to <60 bpm during the 5 min, then the cord was clamped and resuscitation was resumed as per NRP protocol. Cord pulsations was not noticed during the experiment, but UV and UA flows with pulsations were noted later in our experiements.

4) What about shorter duration of DCC 3 minutes?

Since our study aim was to improve heart rate and saturations by 5 min in an asphyxiated preterm model, we dud 5 min of DCC with ventilation. Nepcord III did randomize to DCCV for 3 min.

5) *Did you look at deaths in the 1st 5 minutes? Nestor Vain*

Since the intervention was done once the HR was <90 bpm, ventilation lead to 100% ROSC in both ECCV and DCCV. We currently are doing studies with HR <60 bpm in preterm models.

6) *A very interesting and important subject at this moment. Are you aware of the ABC-trials (Airway, Breathing, Clamping), where delayed (physiological) cord clamping is already being studied in a large Dutch RCT using a resuscitation table in preterm infants? Do you think we should use DCC in practice?*

Thank you for your comment. Yes, we have read the published protocol https://pubmed.ncbi.nlm.nih.gov/31106181/. At this point if the heart rate is not <60 bpm if a portable resuscitation table is available which could be used even in a sterile field, effective ventilation and an intact cord, based on our observation would be helpful to stabilize a preterm neonate.

Question 1. With mask or non invasive device how will be sure of delivered pressure?
Answer 1 (Colin Morley): The only way to know the delivered pressure with a mask or non-invasive device is to measure, and display, the pressure as near to the baby as possible. However, as there is frequently a mask leak and a leak with any non-invasive device some of the delivered pressure will be lost. Clinically it is not possible measure pharyngeal pressure during a resuscitation.

Question 2. The early SLI studies suggested that it works if babies have spontaneous breathing efforts- could you comment?
Answer 2 (Colin Morley): The best way for the lungs to start to aerate is for the baby to breath, often with initial deep breaths. A tidal volume from a spontaneous breath will synergise with any delivered pressure. If there is no spontaneous breathing the applied pressure may not be enough to aerate the lungs.

Question 3. Any increase in air-leak with sustained inflation? Especially in the lower gestational ages
Answer 3 (Matteo Bruschettini): No, there was no increase in air-leak, as shown in Analysis 1.10 on page 52 of the full review (RR 0.89, 95% CI 0.57;1.4). The study by Lista and coll including infants with gestational age 25 to 28 reported 9 and 2 air-leaks in the SLI and control group, respectively (RR 4.35, 95% CI 0.96;19.78). However, The study by Kirpalani and coll including even smaller infants (gestational age 23 to 26) reported 11 and 19 air-leaks in the SLI and control group, respectively (RR 0.57, 95% CI 0.28;1.16)

Question 4. Did you look at deaths in the 1st 5 minutes? (Nestor Vain)
Answer 4 (Matteo Bruschettini): We looked at deaths in the delivery room; which was reported by five trials (479 infants). Four of these five reported no events, whereas the study by Jiravisitkul and coll reported one event in the SLI group. See Analysis 1.1.1 on page 48 of the full review (RR 2.66, 95% CI 0.11;63.4).

Question 5. Any idea about incidence of BPD in babies received SI?
Answer 5 (Matteo Bruschettini): BPD any grade was reported in four trials (735 infants: 397 and 338 in the SLI and control group, respectively). The incidence of BPD any grade was 151/397=38% in the SLI group, whereas incidence of moderate to severe BPD was 83/344=24%. As shown in Analysis 1.9 (on page 51 of the full review), BPD rates were similar in SLI and control groups.

Question 6. Is BPD higher in those groups?
Answer 6 (Matteo Bruschettini): Not sure what ”those groups” refer to. See previous answer on BPD.