

# Painful Procedures Correlate With Markers of Hypoxia, Oxidative Stress and Intestinal Injury in Premature Neonates

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## Original Paper

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# Eight Years Later, Are We Still Hurting Newborn Infants?

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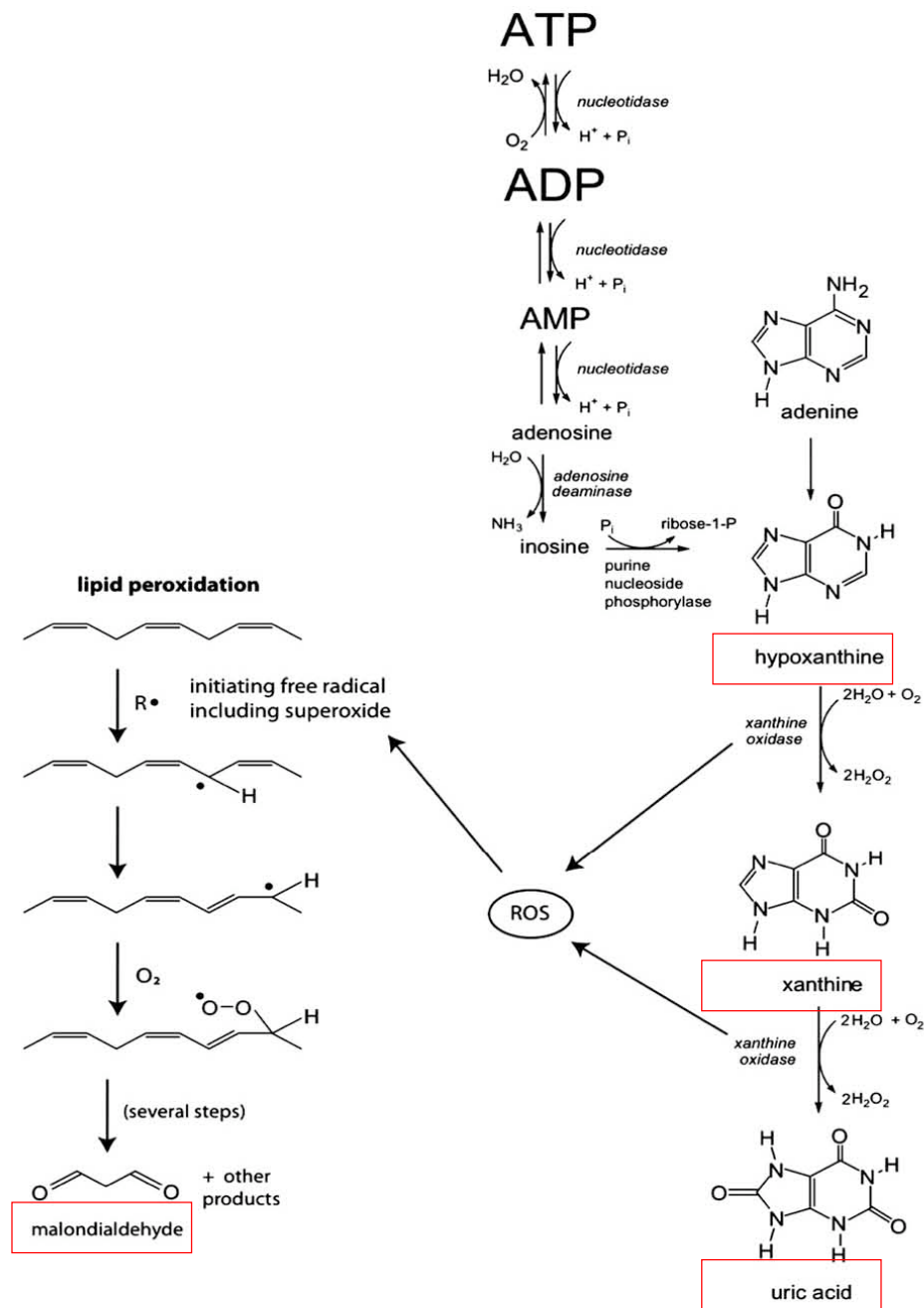
**Table 2.** Incidences of procedures in 2001 and 2009, with frequencies per infant per day and p values comparing frequencies

| Procedure                                 | Percent of total procedures |                   | Frequency per infant per day (mean $\pm$ SD) |                 | SDM  | p value |
|-------------------------------------------|-----------------------------|-------------------|----------------------------------------------|-----------------|------|---------|
|                                           | 2001<br>(n = 151)           | 2009<br>(n = 175) | 2001                                         | 2009            |      |         |
| Nasal suctioning                          | 31.2                        | 31.6              | 4.5 $\pm$ 2.3                                | 3.4 $\pm$ 2.2   | 0.49 | <0.001  |
| Endotracheal suctioning                   | 23.0                        | 23.0              | 3.3 $\pm$ 4.0                                | 2.5 $\pm$ 3.5   | 0.21 | 0.06    |
| NPT suctioning                            | 9.4                         | 5.7               | 1.3 $\pm$ 2.4                                | 0.6 $\pm$ 1.2   | 0.37 | <0.001  |
| Heel lancing                              | 7.1                         | 10.7              | 1.0 $\pm$ 1.6                                | 1.5 $\pm$ 1.1   | 0.36 | 0.001   |
| Intravenous cannula insertion             | 3.8                         | 3.2               | 0.5 $\pm$ 0.6                                | 0.4 $\pm$ 0.3   | 0.21 | 0.06    |
| Nasogastric tube insertion                | 3.8                         | 1.9               | 0.5 $\pm$ 0.6                                | 0.2 $\pm$ 0.1   | 0.70 | <0.001  |
| Intravenous cannula removal               | 3.2                         | 2.2               | 0.5 $\pm$ 0.7                                | 0.3 $\pm$ 0.2   | 0.39 | <0.001  |
| Nasogastric tube removal                  | 3.1                         | 1.0               | 0.4 $\pm$ 0.5                                | 0.1 $\pm$ 0.1   | 0.83 | <0.001  |
| X-ray                                     |                             |                   |                                              |                 | 0.15 | 0.17    |
| NPT insertion                             |                             |                   |                                              |                 | 0.20 | 0.08    |
| Failed intravenous cannula insert         |                             |                   |                                              |                 | 0    | 1.0     |
| Laxative or enema                         | 1.2                         | 1.1               | 0.2 $\pm$ 0.5                                | 0.1 $\pm$ 0.1   | 0.28 | 0.01    |
| Nasal oxygen cannula insertion            | 1.0                         | 1.0               | 0.2 $\pm$ 0.4                                | 0.1 $\pm$ 0.2   | 0.32 | 0.004   |
| Intubation                                | 0.9                         | 0.6               | 0.1 $\pm$ 0.4                                | 0.08 $\pm$ 0.08 | 0.07 | 0.52    |
| Peripheral arterial line insertion        | 0.8                         | 0.4               | 0.1 $\pm$ 0.3                                | 0.05 $\pm$ 0.07 | 0.23 | 0.04    |
| Extubation                                | 0.7                         | 0.5               | 0.1 $\pm$ 0.3                                | 0.06 $\pm$ 0.08 | 0.18 | 0.09    |
| Peripheral arterial line removal          | 0.6                         | 0.3               | <0.1 $\pm$ 0.3                               | <0.1 $\pm$ 0.06 |      |         |
| Failed peripheral arterial line insertion | 0.5                         | 0.8               | <0.1 $\pm$ 0.5                               | <0.1 $\pm$ 0.06 |      |         |
| Venipuncture                              | 0.4                         | 0.2               | <0.1 $\pm$ 0.3                               | <0.1 $\pm$ 0.1  |      |         |
| Insertion umbilical line                  | 0.4                         | 0.3               | <0.1 $\pm$ 0.2                               | <0.1 $\pm$ 0.05 |      |         |
| Removal umbilical line                    | 0.3                         | 0.4               | <0.1 $\pm$ 0.2                               | 0.1 $\pm$ 0.1   |      |         |
| Failed umbilical line insertion           | 0.2                         | 0.2               | <0.1 $\pm$ 0.2                               | <0.1 $\pm$ 0.06 |      |         |
| Insertion central line                    | 0.2                         | 0.4               | <0.1 $\pm$ 0.2                               | <0.1 $\pm$ 0.05 |      |         |
| Insertion chest tube                      | 0.1                         | 0.2               | <0.1 $\pm$ 0.2                               | <0.1 $\pm$ 0.1  |      |         |
| Failed central line insertion             | 0.1                         | 0.2               | <0.1 $\pm$ 0.2                               | <0.1 $\pm$ 0.09 |      |         |
| Venipuncture attempt                      | 0.1                         | 0.02              | <0.1 $\pm$ 0.2                               | <0.1 $\pm$ 0.03 |      |         |
| Removal central line                      | 0.1                         | 0.2               | <0.1 $\pm$ 0.1                               | <0.1 $\pm$ 0.05 |      |         |
| Removal chest tube                        | 0.1                         | 0.07              | <0.1 $\pm$ 0.1                               | <0.1 $\pm$ 0.04 |      |         |

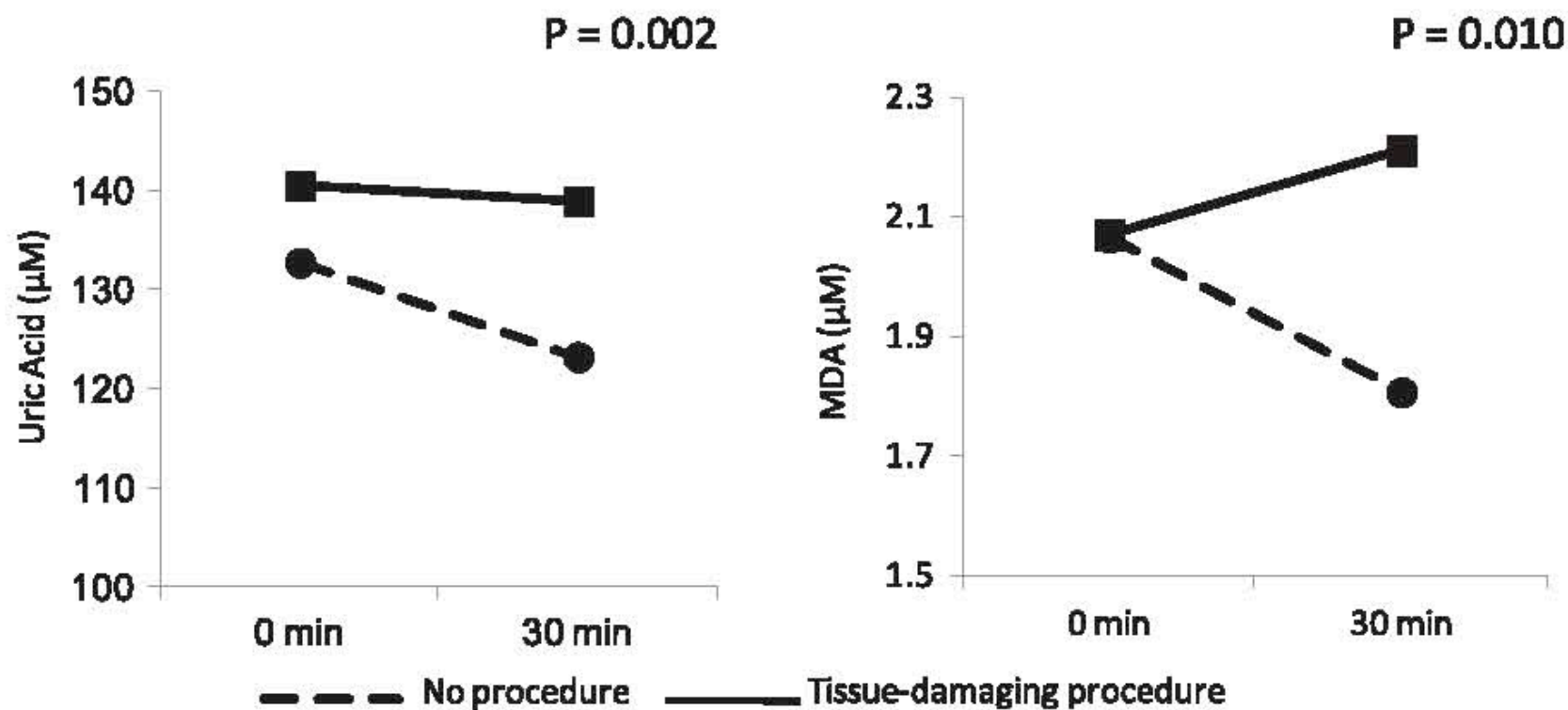
11.4 $\pm$  5.7 per day

NPT = Nasopharyngeal tube; SDM = standardized mean difference.





**Figure 1.** Pathway from ATP to UA and MDA.



**Figure 2.** Plasma [UA] and [MDA] at baseline and 30 minutes post-TDP.



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## Procedural Pain and Oxidative Stress in Premature Neonates

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## Research Team

- Co-investigators: Elba Fayard MD, Danilo Boskovic PhD, Andrew Hopper MD, NICU physicians
- Research Nurses: Laurel Slater, Erin Hoch, Valerie Mag-akat, Priscilla Pegis, Dorothy Forde
- Research Technicians: Yayesh Asmerom MS
- PhD students: Teleka Patrick MD, PhD, Megan Holden PhD, **John Tan, PhD**
- LLU Children's hospital nurses doctors



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|                               | On Room Air<br>(n=19)                                                                                                 | Receiving Oxygen<br>(n=23)                                                                                             | P value <sup>#</sup> |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------|
| Birthweight (g)               | 1220 ± 426                                                                                                            | 886 ± 279                                                                                                              | 0.004                |
| Birthweight @Exam<br>time     | 2352 ± 724                                                                                                            | 1804 ± 575                                                                                                             | 0.009                |
| Gestational Age (wks)         | 29.5 ± 2.2                                                                                                            | 27.1 ± 2.1                                                                                                             | 0.001                |
| Gestational Age@ Exam<br>time | 36.5 ± 2.6                                                                                                            | 34.6 ± 2.8                                                                                                             | 0.030                |
| Apgar-1 min                   | 4.8 ± 1.9                                                                                                             | 3.9 ± 2.5                                                                                                              | 0.157                |
| Apgar-5 min                   | 7.1 ± 1.2                                                                                                             | 6.5 ± 2.1                                                                                                              | 0.300                |
| Gender                        | Female: 9<br>Male: 10                                                                                                 | Female: 8<br>Male: 15                                                                                                  | 0.408 <sup>+</sup>   |
| SNAPPE_II                     | 15.1 ± 10.9                                                                                                           | 22.9 ± 15.2                                                                                                            | 0.06                 |
| Ethnicity                     | African-American: 6<br>Asian: 2<br>Hispanic/Latino: 1<br>Caucasian: 6<br>Other/More than<br>one race: 0<br>Unknown: 2 | African-American: 1<br>Asian: 1<br>Hispanic/Latino: 2<br>Caucasian: 14<br>Other/More than one<br>race: 4<br>Unknown: 1 | 0.29 <sup>+</sup>    |
| #ROP exam                     | 2.2 ± 1.7                                                                                                             | 2.3 ± 1.6                                                                                                              | 0.909                |
| Mode of oxygen<br>support     | Spontaneous room<br>air = 19                                                                                          | CPAP: 4<br>HFNC:11<br>Nasal cannula: 3<br>NAVA: 2<br>NCPAP: 1<br>NIMV: 1<br>NIPPV: 1                                   | < 0.001 <sup>+</sup> |



## Adverse effects of ROP exam

- Conflicting findings
  - No differences in apnea, bradycardia or oxygen desaturation 24-72 hours after the exam (Reid et al, 2017; Klein et al, 2008)
  - Increased apnea events (Mitchell et al, 2016; Reid et al, 2017)
  - Decreased gastric emptying (Bonthala et al, 2000)
  - Transient ileus (Degirmencioglu et al, 2014;



## Effect on HR

Figure 1. Individual PR values across eyedrop and procedure phases.

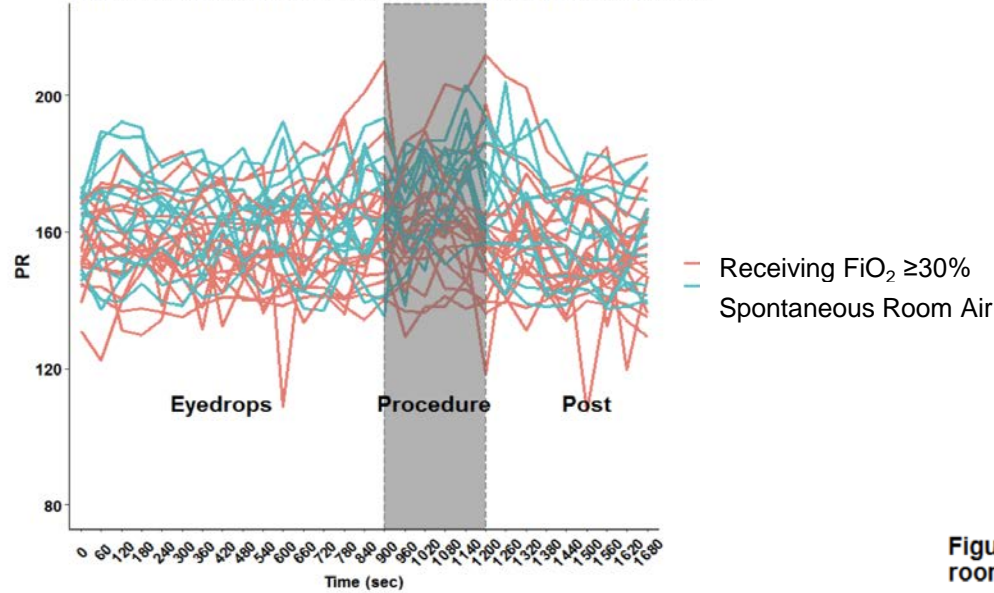
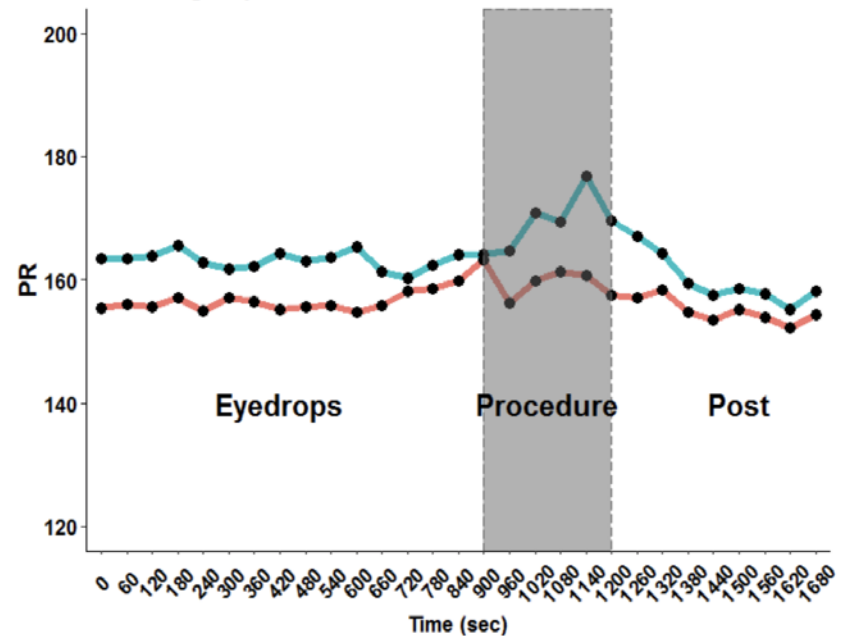


Figure 2. Average PR values across eyedrop and procedure phases by room air group.





## Effect on SPO<sub>2</sub>

Figure 1. Individual SpO<sub>2</sub> values across eyedrop and procedure phases.

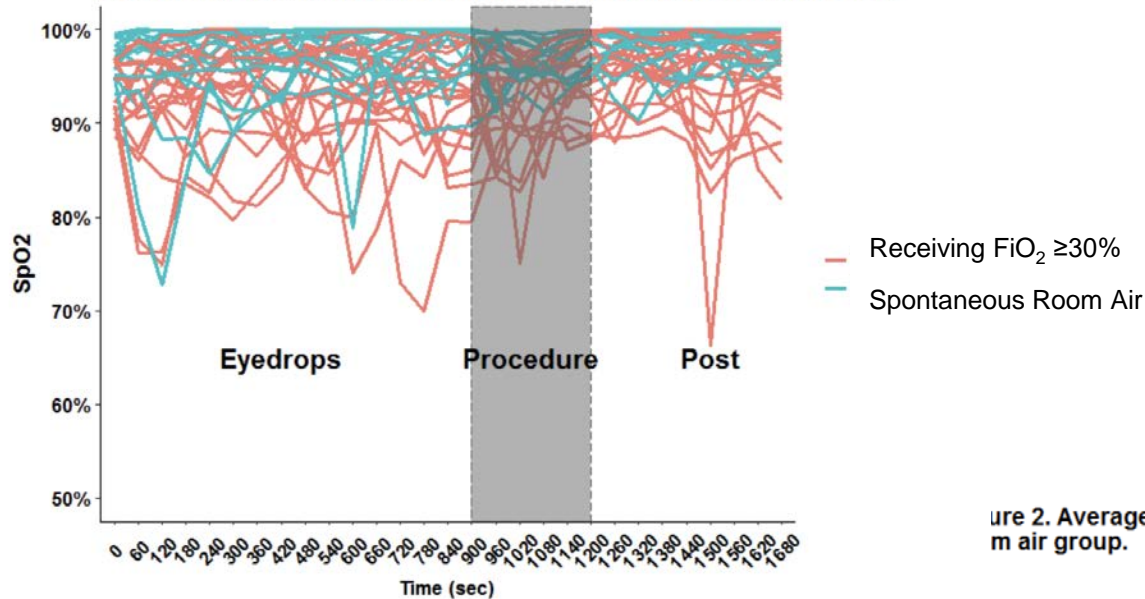
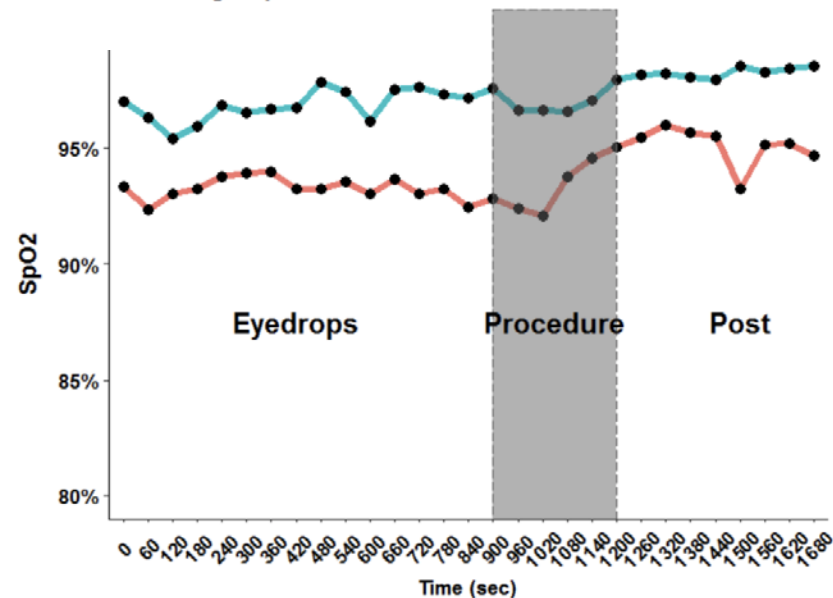


Figure 2. Average SpO<sub>2</sub> values across eyedrop and procedure phases by room air group.





## Effect on StO<sub>2</sub>

Figure 1. Individual StO<sub>2</sub> values across eyedrop and procedure phases.

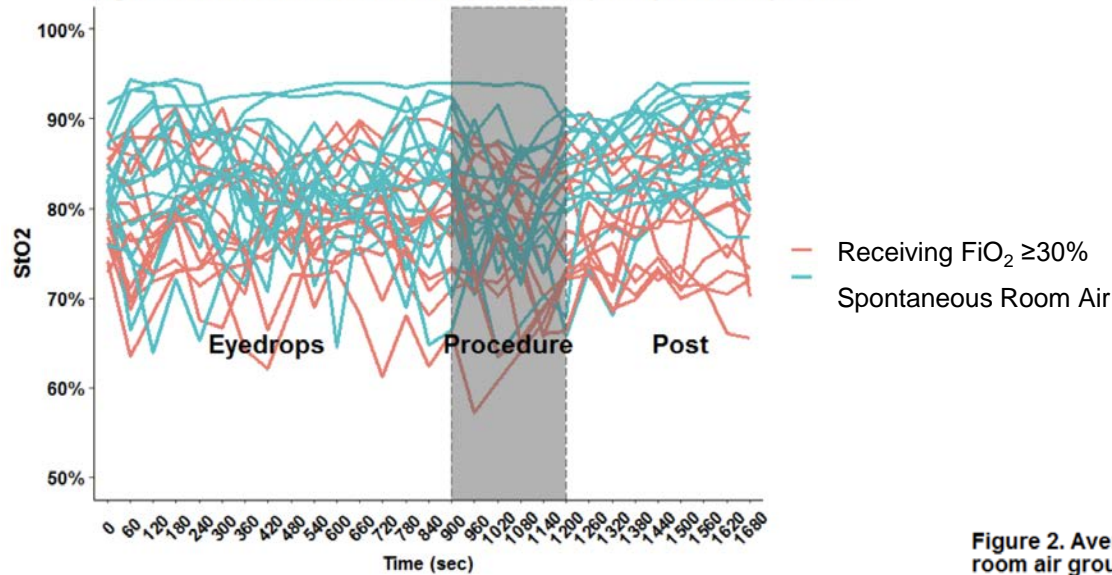
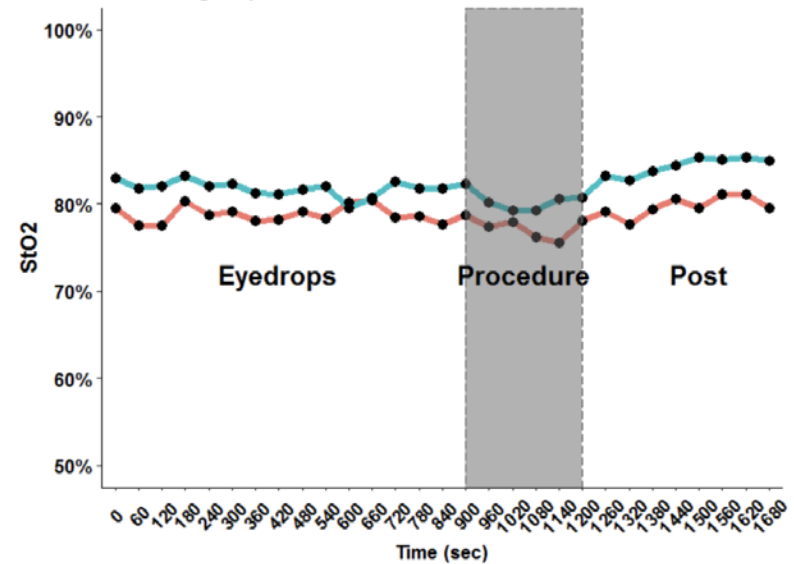
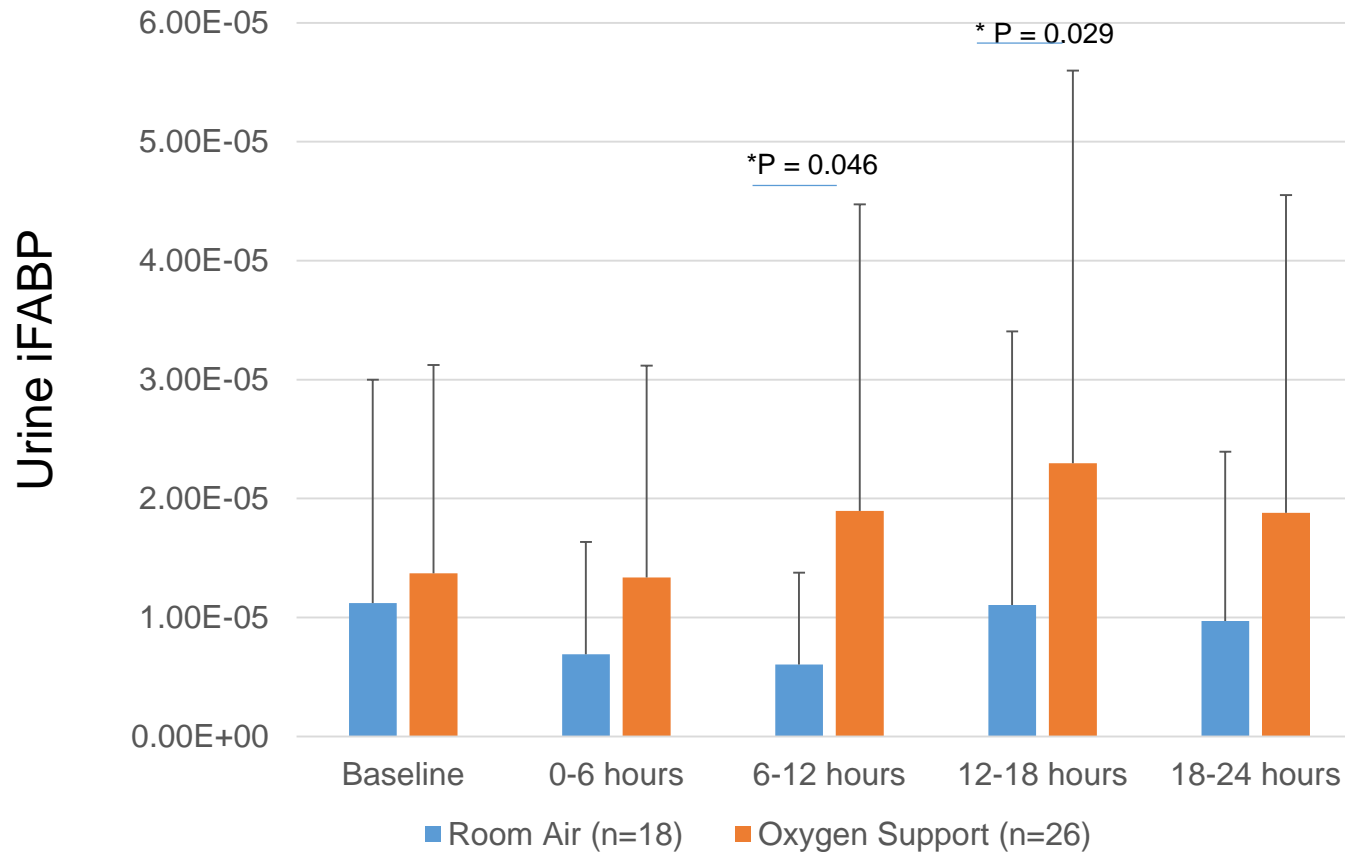


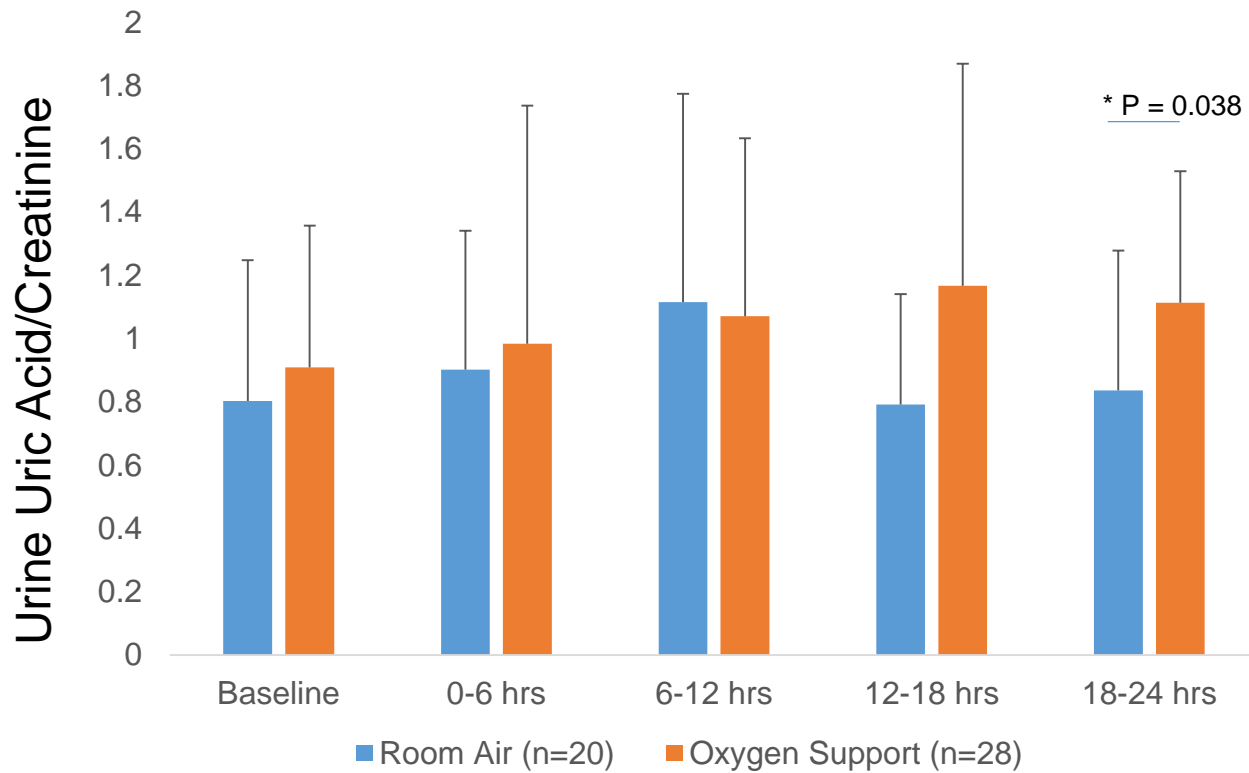
Figure 2. Average StO<sub>2</sub> values across eyedrop and procedure phases by room air group.



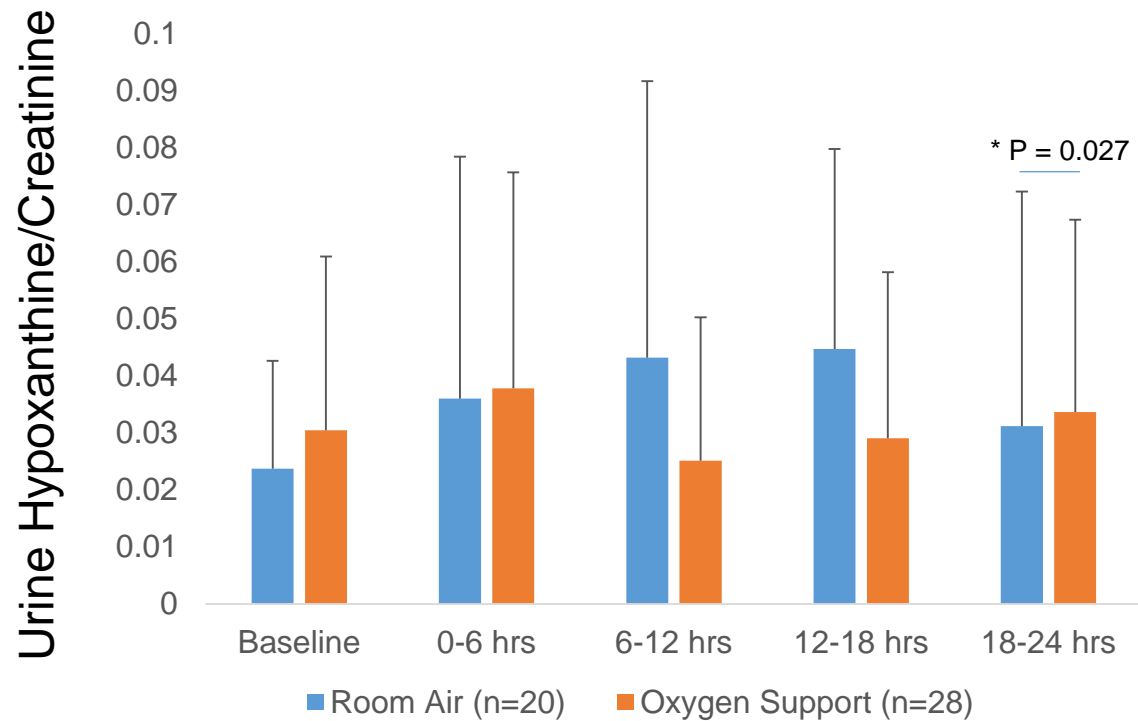




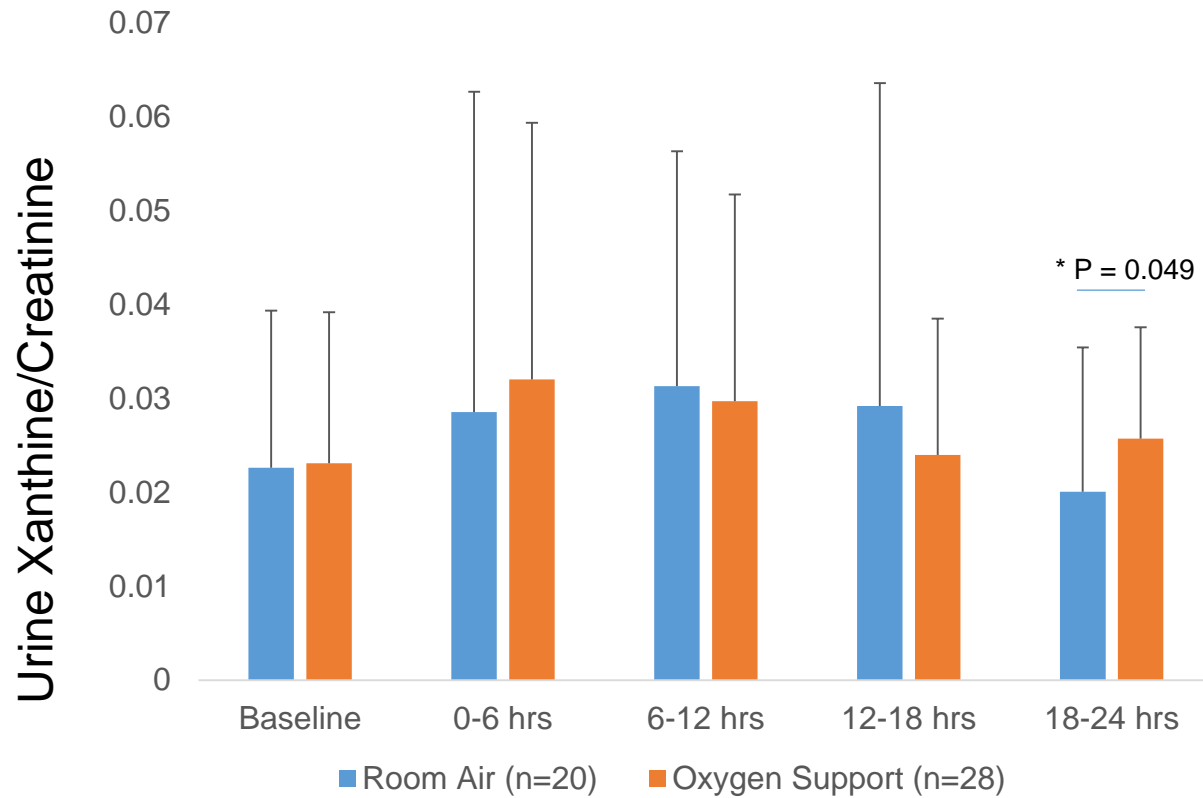
\* Mann-Whitney



\* Mann-Whitney



\* Mann-Whitney



\* Mann-Whitney



## Next step?

- Examine mechanism of injury in neonates on oxygen
- Determine minimum mydriatic dosage, specifically for neonates on oxygen
- Examine current feeding protocols
- Perform a study with larger sample size