Intraoperative isoflurane exposure predicts reduced frontal lobe connectivity compared to dexmedetomidine in neonates with congenital heart disease

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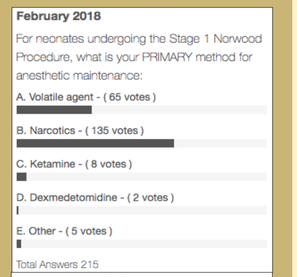
INTRODUCTION

The GAS and PANDA studies showed a single anesthetic exposure of short duration does not adversely affect neurocognitive outcomes in children [1-2], however the MASK study showed an association between multiple anesthetic exposures and decreases in cognitive ability [3]. Unfortunately, babies born with critical congenital heart disease (CHD) often require numerous, lengthy anesthetics during infancy. Interestingly, dexmedetomidine (DEX) mitigates neuronal death caused by other anesthetics [4].

Advanced MRI techniques have shown good prognostic capability for predicting neurodevelopmental outcomes [5]. This study examined the hypothesis that longer volatile anesthetic (ISO) duration and lower DEX/ISO ratio would result in impaired brain structural and functional connectivity as determined by postoperative functional MRI (fMRI).



65/215 (30%) of respondents use volatile agent as primary anesthetic

KEY BACKGROUND POINTS

- **Lengthy or multiple exposures to volatile anesthetics may impact neurocognitive outcomes**
- **Dexmedetomidine has been shown to mitigate neuronal damage caused by volatile anesthetics**
- **Advanced MRI techniques show good prognostic capabilities for predicting neurodevelopmental outcomes**

METHODS

Prospective observational study examining neonates with complex CHD requiring neonatal intervention. The effects from ISO duration (min), total ISO exposure (ml) (estimated as product of averages of V_E, Et_{ISO}, and $Duration_{ISO}$), total DEX dose (mcg/kg), and DEX/ISO ratio during cardiac surgery were investigated using manual tractography (MT), voxel-based morphometry (VBM), diffusion tensor imaging (DTI), and resting blood-oxygen-level dependent (BOLD) postoperative fMRI modalities.

RESULTS

Table 1. Perioperative variables

	Median	IQR
Age (d)	8	6 - 16
Weight (kg)	3.1	2.7-3.4
BSA (m^2)	0.21	0.19-0.22
CPB (min)	94	64-129
MAP (mm Hg)	45	41-47
Anes duration (hr)	3.8	2.8-4.6
ISO exposure (ml)†	454	287-732
ISO MAC•hrs	0.65	0.43-0.98
Total DEX (mcg)	5.6	4.6-7.8
DEX : duration	1.5	1.2-1.8
DEX : ISO MAC·hrs ratio	8.14	5.36-12.37
DEX : ISO ml ratio	0.012	0.008 - 0.018

IQR – interquartile range

†ISO exposure *estimated* as V_E*Et_{ISO}*$Duration_{ISO}$

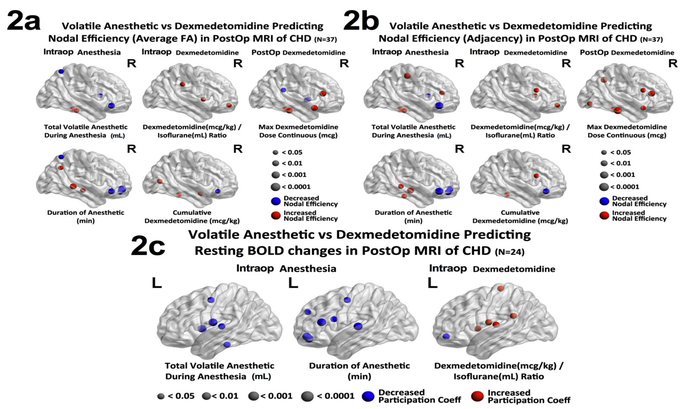


Figure 2. Postoperative graph analysis. DTI using (a) Average FA and (b) Adjacency methods shows reduced nodal efficiency with increased ISO and opposite effects with increased DEX and DEX/ISO ratio. (c) Resting BOLD showing reduced connectivity with increased ISO and opposite effect with increased DEX/ISO ratio

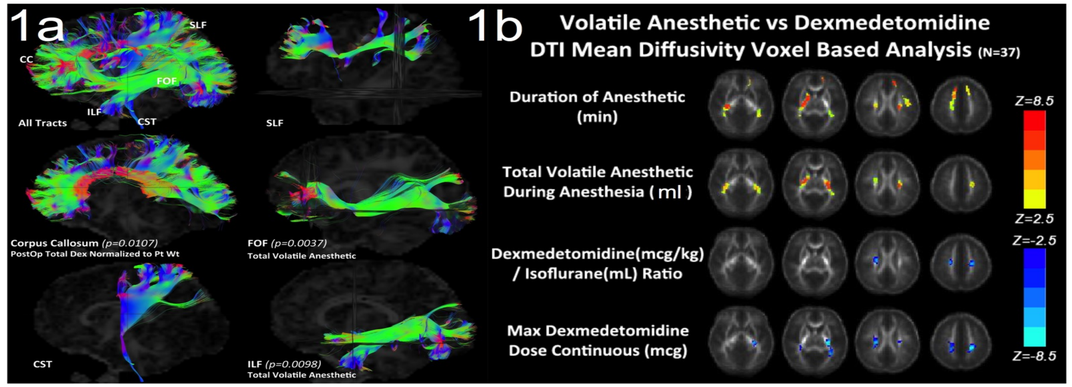


Figure 1. Manual tractography (a) showing reduced structural connectivity in FOF and ILF associated with increased ISO and voxel-based morphometry (b) showing increased diffusivity associated with increased ISO and opposite effects with increased DEX and DEX/ISO ratio

SUMMARY

- Higher ISO exposure is associated with reduced frontal brain connectivity in CHD neonates using multiple fMRI approaches
- DEX exposure was associated with metrics of improved brain connectivity using the same analytical approaches.
- Higher DEX in relation to ISO exposure confers improved brain connectivity in CHD neonates.

Significance

Complex CHD patients often require numerous, lengthy anesthetics, suggesting all efforts for neuroprotection should be employed.

Given FOF and ILF abnormalities have been observed in patients with ADHD [6], our novel observations may help explain the behavioral abnormalities identified by Hu, *et al* [3].

REFERENCES

1. Davidson AJ, Disma N, de Graaff JC, GAS consortium. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet 2016;387(10015):239-50.
2. Sun LS, Li G, Miller TL, et al. Association Between a Single General Anesthesia Exposure Before Age 36 Months and Neurocognitive Outcomes in Later Childhood. JAMA 2016;315(21):2312-20.
3. Hu D, Flick RP, Zaccariello MJ, et al. Association between Exposure of Young Children to Procedures Requiring General Anesthesia and Learning and Behavioral Outcomes in a Population-based Birth Cohort. Anesthesiology 2017;127(2):227-240.
4. Alam A, Suen KC, Hana Z, et al. Neuroprotection and neurotoxicity in the developing brain: an update on the effects of dexmedetomidine and xenon. Neurotoxicol Teratol 2017;60:102-116.
5. Parikh, NA. Advanced neuroimaging and its role in predicting neurodevelopmental outcomes in very preterm infants. Semin Perinatol. 2016;40(8):530-541.
6. Cortese S, Imperati D, Zhou J, et al. White Matter Alterations at 33-Year Follow-Up in Adults with Childhood Attention-Deficit/Hyperactivity Disorder. Biological psychiatry. 2013;74(8):591-598.

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