The Lower Limits of Neonatal Cerebral Autoregulation During Congenital Cardiac Surgery

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ABSTRACT

Background: An estimated 50% of neonates who have heart surgery develop neurological injury due to inadequate or excessive perfusion. The neonatal brain is vulnerable to perturbations in cerebral blood flow, particularly during congenital cardiac surgery. Hypoperfusion with low blood pressure or hyperperfusion with elevated blood pressure can lead to neurologic injury. Consequently, blood pressure management is challenging. With this retrospective study, we sought to characterize neonatal cerebral autoregulation during congenital heart surgery in a tertiary pediatric heart center. Our goal was to generate autoregulation curves in this susceptible population to determine the lower limit of autoregulation (LLA) as it relates to age. The hemoglobin volume index (HVx) is a metric of autoregulation where negative values correspond to instances of intact autoregulation and positive values correspond to instances of impaired autoregulation. We hypothesized that autoregulation curves utilizing HVx could be derived during neonatal cardiac surgery, and the LLA increases with age.

Methods: From Jan 2013 to May 2018, all subjects less than 1 month of age undergoing congenital heart surgery at Texas Children's Hospital were identified. To be included in the analysis, subjects must have had the requisite signals to generate an autoregulation curve: arterial blood pressure (ABP), cerebral oximetry (rSO2), and cerebral hemoglobin volume index (HVx) derived from near infrared spectroscopy (805 nm). Intraoperative signals were collected by an automated, high resolution (>120 Hz) data collection system. HVx was calculated as a moving correlation coefficient between mean ABP and the cerebral blood volume index using Matlab (R2016b, MathWorks, Natick, MA). The LLA was defined as the corresponding ABP below the optimal ABP when the HVx is 0.2. Linear regression was utilized to examine the relationship between the LLA and age. Time was quantified when the patient blood pressure was below the LLA.

Results: Autoregulation curves were generated in 145 of 169 patients (86%), representing over 1095 hours of recorded intraoperative data (figure 4). When autoregulation curves could not be generated, it was due to poor signal quality or marginal blood pressure range causing the algorithm to be ineffective in delineating the LLA. In the linear regression model, age explained 15% of the variance ($r^2 = 0.15$, $F(1,78) = 13.4$, $p < 0.0005$), and each 1 day increase in age corresponded to a 0.32 mmHg increase in the LLA ($\beta = 0.32$, $p < 0.0001$, figure 5). The average percent time spent below the LLA was 17% (figure 6), and the mean "dose" severity of hypotension quantified by the mmHg below the LLA x time below the LLA was 22937 ± 29146 mmHg*s (figure 7).

Conclusions: This is the largest study examining autoregulation in the neonatal population undergoing cardiac surgery. Though the overall lower limit of autoregulation does increase with age, data not only indicate that the metrics of autoregulation are variable among individuals, but also that neonates spend a substantial amount of time where blood pressure is below the LLA. With an increasing amount of time where blood pressure is below an individual neonate's LLA, the risk for neurologic injury increases. The results support the need for real-time, individualized autoregulation monitoring as a means to identify optimal patient blood pressure goals for the practicing anesthesiologist.

BACKGROUND

Cerebral autoregulation[1]:

- Maintenance of constant cerebral blood flow (CBF):
  - Myogenic control of arteriolar resistance
  - Neurovascular coupling
  - Pressure autoregulation
- Outside limits of autoregulation:
  - CBF passively dependent on CPP
  - Small changes in blood pressure lead to cerebral ischemia / edema
- Limits of autoregulation not defined for neonates[2]:
  - 50% have neurologic injury after cardiac surgery

Measurement of autoregulation[3,4]:

- Can be measured using pressure reactivity index (PRx) or hemoglobin volume index (HVx)
- Correlation (<0.5 Hz)
  - Arterial blood pressure
  - Intracranial pressure (PRx) or near-infrared spectroscopy (805 nm) (HVx)
- Intact autoregulation = negative values
- Impaired autoregulation = positive values

For congenital cardiac surgery, the lower limits of autoregulation have not been defined in the neonatal population

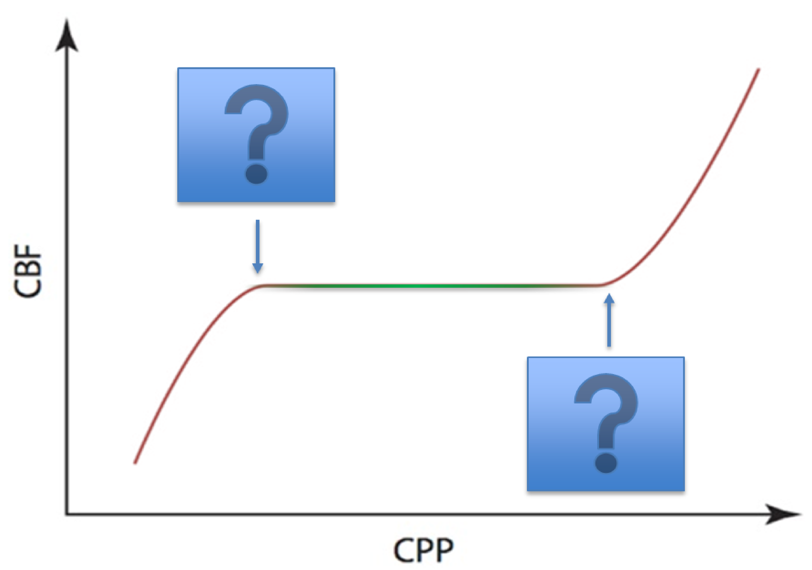

Figure 1. Conceptual autoregulation curve. Constant cerebral blood flow (green) and impaired autoregulation (red). CBF = cerebral blood flow. CPP: cerebral perfusion pressure

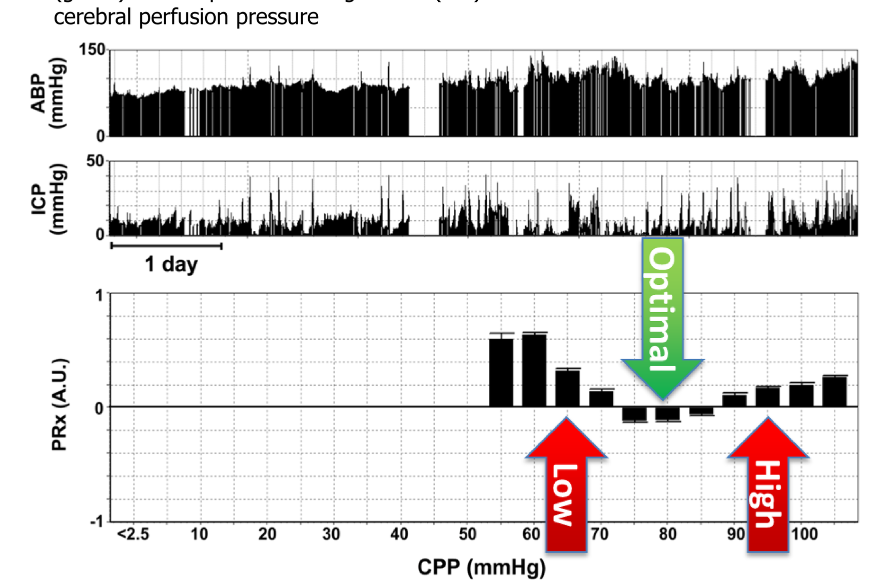

Figure 2. Pressure reactivity index delineating impaired and intact autoregulation in head-injured patients. ABP = arterial blood pressure. ICP = intracranial pressure. PRx = pressure reactivity index. CPP = cerebral perfusion pressure.

METHODS

Study Design:

Neonates (< 1 month) undergoing congenital heart surgery at Texas Children's Hospital (1/2013 – 5/2018) (n = 563)

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Arterial blood pressure (240 Hz)
Near infrared spectroscopy: 805 nm (0.25 Hz)

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Patients with available signals for analysis (n = 169)

Figure 3. Flowchart of study design. Signals collected using Sickbay™ (Medical Informatics Corp., Houston, TX).

Analysis:

- Cerebral hemoglobin volume index (HVx) calculated from moving correlation coefficient (<0.5 Hz)[5]
  - Mean arterial blood pressure
  - Cerebral blood volume index measured and calculated from near-infrared spectroscopy (NIRS) (805 nm)
- Calculations and derivation of cerebral autoregulation curves performed with Matlab (R2016b, MathWorks, Natick, MA)
- Lower limit of autoregulation (LLA) defined as ABP when HVx = 0.2
- Linear regression of LLA and age performed (Stata, StataCorp, College Station, TX)

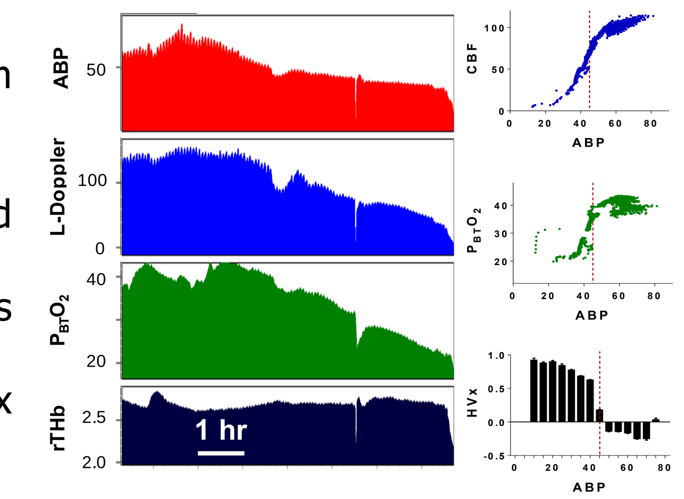

Figure 3. Derivation of cerebral autoregulation curve utilizing relative total hemoglobin and hemoglobin volume index (HVx).

RESULTS

Descriptive Statistics:

Table 1. Patient population characteristics and diagnosis category (n = 145*).

Characteristic	Value
Age (d)	12.7 ± 8.4
Weight (kg)	3.2 ± 0.62
Height (cm)	38.3 ± 2.0
CPB case	93 (64%)

Diagnosis category	Value
Single ventricle (hypoplastic left or variant)	30 (20%)
Single ventricle (hypoplastic right or variant)	26 (18%)
d-Transposition of great arteries	27 (19%)
Distal aortic arch obstruction	42 (29%)
Other	15 (11%)
Normal morphology	5 (3%)

Values are mean ± standard deviation or frequency (percentage). CPB = cardiopulmonary bypass. *145 out of 169 subjects (85.8%) with available signals to generate an autoregulation curve.

Autoregulation Curve by Age:

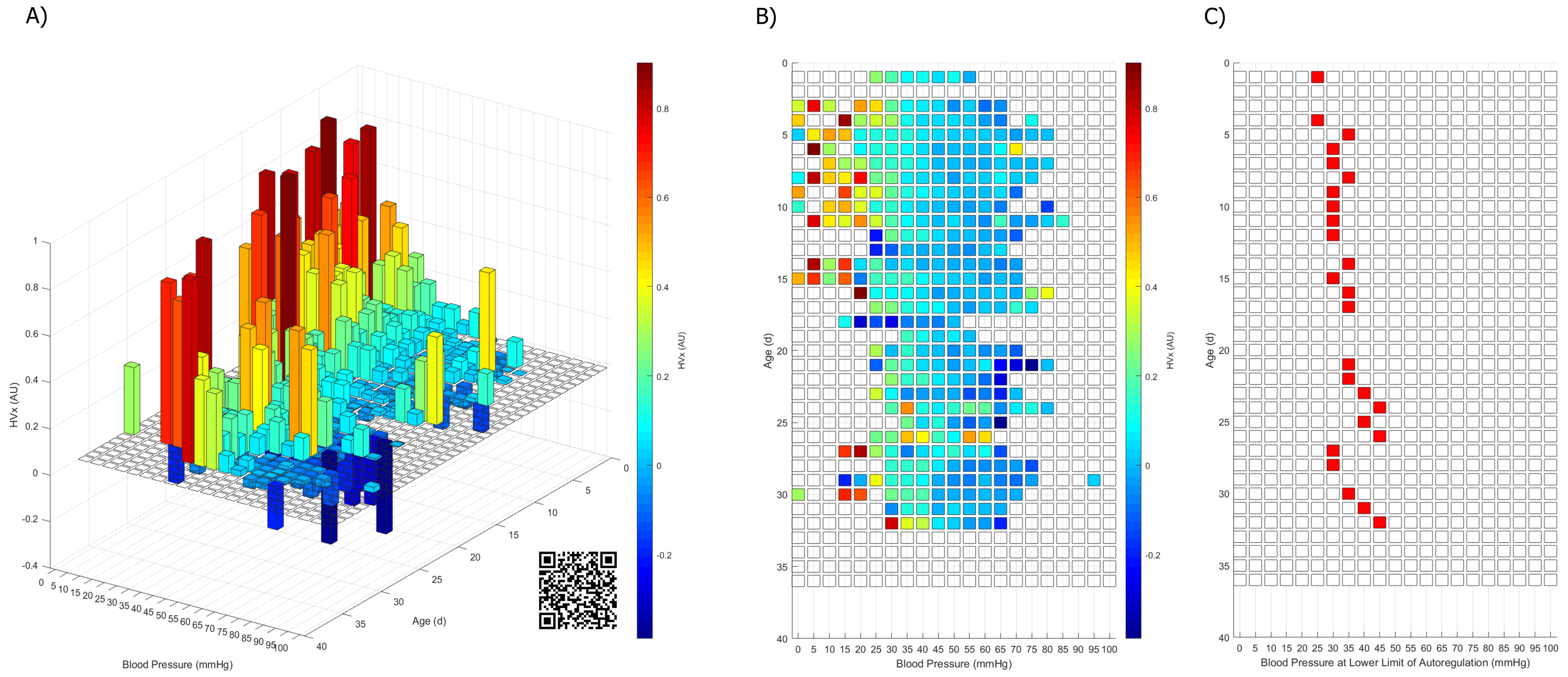

Figure 4. Neonatal autoregulation curves during cardiac surgery (n = 145). A) 3-dimensional view of HVx, mean arterial blood pressure, and age. QR code to access video of plot available via Internet. B) 2-dimensional colormap view of autoregulation curve by age. C) Lower limit of autoregulation by age across population defined as HVx = 0.2. HVx = hemoglobin volume index.

RESULTS

Linear Regression:

- Linear regression of lower limit of autoregulation (LLA) (mmHg) by age (days)
  - LLA ranged from 30 – 40 mmHg
  - Each 1 day increase in age corresponded to 0.32 mmHg increase in LLA ($p < 0.0001$)
  - Though positive trend exists, large amount of variance in data and weak correlation ($r^2 = 0.15$, $p < 0.0005$)

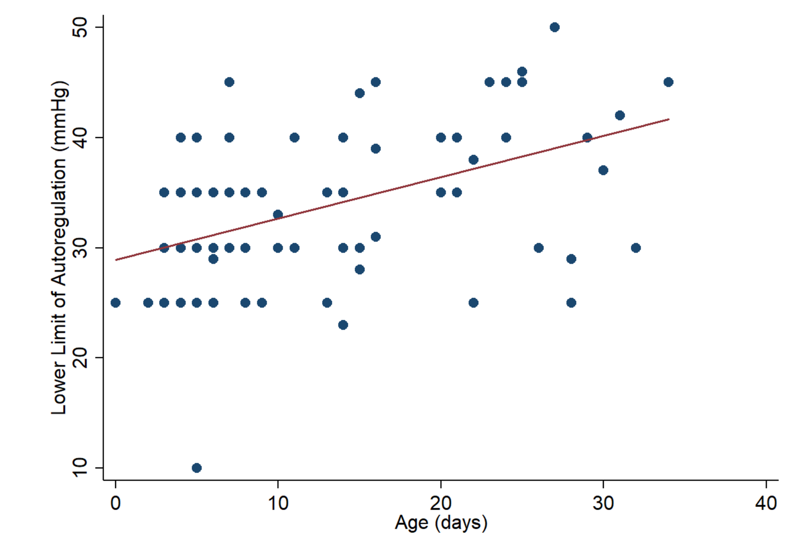

Figure 5. Lower limit of autoregulation by age. ($r^2 = 0.15$, $F(1.78) = 13.4$, $\beta = 0.32$, $p < 0.0005$)

Characterization of Time Below Lower Limit of Autoregulation:

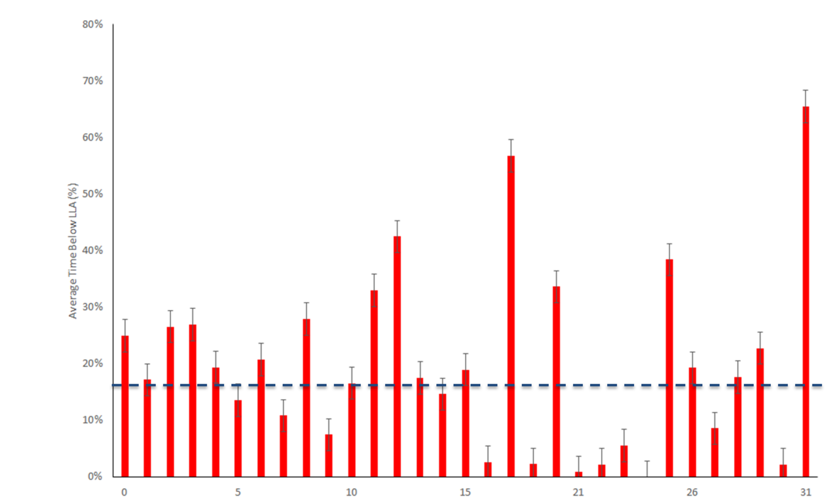

Figure 6. Average percent time spent below lower limit of autoregulation (LLA) by age. Overall mean time spent below LLA was 17%.

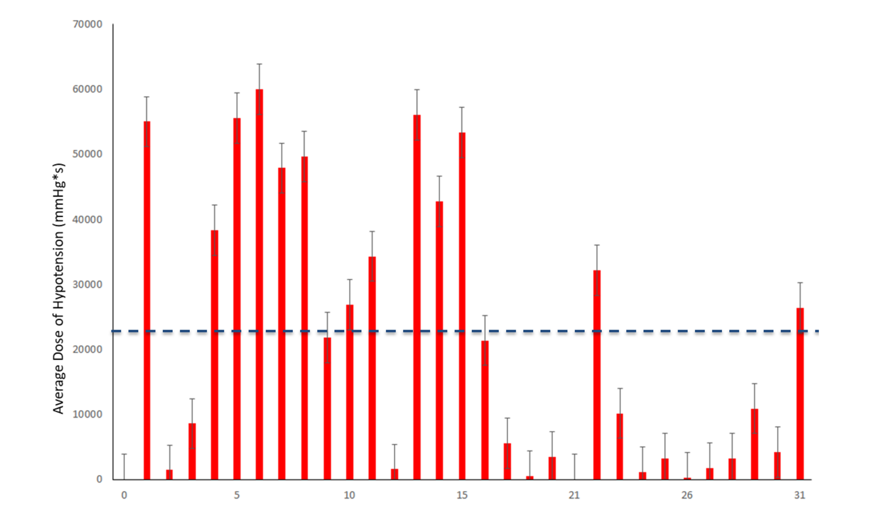

Figure 7. Severity of hypotension calculated by time spent below lower limit of autoregulation (LLA) * mmHg below LLA (mmHg*s) by age. Overall mean dose of hypotension was 22937 mmHg*s.

During the intraoperative period, the blood pressure was below the lower limit of autoregulation was 17% of the time

CONCLUSIONS

Retrospective analysis creating cerebral autoregulation curves for all neonates in the cardiac operating rooms utilizing arterial blood pressure and cerebral near-infrared spectroscopy was achieved:

- 17% of time, neonates had mean arterial blood pressures below lower limit of autoregulation
- Severity of hypotension was increased at younger age (< 15 days)
- Wide variation in lower limits of autoregulation exist
- Suggests need for individualized autoregulation monitoring for accurate hemodynamic goals

Limitations:

- Incomplete or missing signals
- Heterogeneity of cases and cardiopulmonary bypass techniques

Future:

- Correlate autoregulation metrics with outcome data (neurodevelopmental outcomes)
- Develop individualized, real-time, cerebral autoregulation monitoring

With individualized cerebral autoregulation monitoring, targeted cerebral perfusion pressures can be performed on a patient-by-patient basis

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