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Does hypothermia impair cerebrovascular autoregulation in neonates during cardiopulmonary bypass?

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What is known: Studies of cerebral blood flow during neonatal cardiopulmonary bypass have historically reported that hypothermia ablates the pressure autoregulation mechanism that constrains blood flow in the brain. These studies did not control for arterial blood pressure.

What this study adds: This is the first study to show that hypotension is collinear with hypothermia during neonatal bypass, raising the possibility that hypotension, not hypothermia is the cause for impaired autoregulation during cold bypass.

Abstract

Background

Autoregulation monitoring has been proposed as a means to identify optimal arterial blood pressure goals during cardiopulmonary bypass, but it has been observed that cerebral blood flow is pressure passive during hypothermic bypass. When neonates cooled during cardiopulmonary bypass are managed with vasodilators and controlled hypotension, it is not clear whether hypothermia or hypotension were the cause of impaired autoregulation.

Aim

We sought to measure the effect of both arterial blood pressure and hypothermia on autoregulation in a cohort of infants cooled for bypass, hypothesizing a collinear relationship between hypothermia, hypotension, and dysautoregulation.

Methods

Cardiopulmonary bypass was performed on 72 Infants at Texas Children's Hospital during 2015 and 2016 with automated physiologic data capture, including arterial blood pressure, nasopharyngeal temperature, cerebral oximetry, and a cerebral blood volume index derived from near infrared spectroscopy.

Cooling to 18°C, 24°C, and 30°C was performed on 33, 12, and 22 subjects, respectively. The hemoglobin volume index was calculated as a moving correlation coefficient between mean arterial blood pressure and the cerebral blood volume index. Positive values of the hemoglobin volume index indicate impaired autoregulation. Relationships between variables were assessed utililzing a generalized estimating equation approach.

Results

Hypothermia was associated with hypotension ~~(p<0.0001)~~, dysautoregulation ~~(p<0.0001)~~, and increased cerebral oximetry ~~(p<0.0001)~~. Comparing the baseline temperature of 36°C with 18°C, arterial blood pressure was 44 mmHg [39 – 52] vs. 25 mmHg [21 – 31]; the hemoglobin volume index was 0.0 [-0.02 to 0.004] vs. 0.5 [0.4 – 0.7] and cerebral oximetry was 59% [57 – 61] vs. 88% [80 – 92] (Median, 95% CI of median; P<0.0001 for all 3 associations by linear regression with generalized estimation of equations with data from all temperatures measured).

Conclusions

Arterial blood pressure, temperature, and cerebral autoregulation were collinear in this cohort. The conclusion that hypothermia causes impaired autoregulation is thus confounded. The effect of temperature on autoregulation should be delineated before clinical deployment of autoregulation monitors to prevent erroneous determination of optimal arterial blood pressure. Showing the effect of temperature on autoregulation will require a normotensive hypothermic model.

Neonates who require cardiac surgery with cardiopulmonary bypass suffer neurologic injuries documented by MRI with an incidence of 35% to 75%.(1-3) The majority of lesions are located in the white matter, which suggests an ischemic mechanism related to low systemic oxygen delivery. Controlled hypotension is used for neonatal cardiac surgery, as vasodilation promotes even cooling and rewarming, prevents acidosis, and reduces afterload related strain on the infant heart when separating from bypass.(4, 5) Aggressive afterload reduction has been temporally associated with improved systemic oxygen delivery and survival.(6) However, the brain is uniquely perfused in a pressure-dependent fashion, independent of systemic blood flow.(7) It is not known if hypotension during neonatal bypass exceeds the limits of autoregulatory mechanisms of the cerebral vasculature and increases the ischemic burden on the neonatal brain.

Real-time monitoring of autoregulation has been proposed as a means to define patient-specific arterial blood pressure goals in both the pediatric and adult settings.(8-11) In theory, delineating the lower limit of autoregulation as an arterial blood pressure target for neonatal bypass would prevent hypoperfusion due to hypotension. This concept has been challenged by the historic observation of pressure passive cerebral circulation in neonates that is believed to be caused by hypothermia.(12, 13) If hypothermia ablates the autoregulatory mechanism, then a monitor designed to detect the lower limit of autoregulation would be confounded by reporting impaired autoregulation at any arterial blood pressure. However, studies showing impaired neonatal autoregulation during hypothermia did not account for the arterial blood pressure, so it is not known if the impaired autoregulation was due to hypotension, or hypothermia.

We hypothesized that hypothermia, hypotension, and dysautoregulation are highly co-linear during neonatal cardiopulmonary bypass due to pharmacologic vasodilation, precluding the conclusion that hypothermia ablates autoregulation. We tested this hypothesis in a retrospective cohort of neonates who required surgery with cardiopulmonary bypass in the first month of life. The result of this study has implications for the deployment of autoregulation monitoring in a clinical environment. If hypothermia is associated with disturbed autoregulation at normotension, then autoregulation monitoring during hypothermia would not be helpful to find optimal arterial blood pressure. If hypothermia and hypotension are strongly co-linear, then a study of hypothermia with normotension is indicated to confirm that an autoregulation monitor can still identify optimal arterial blood pressure for cerebrovascular reactivity.

Methods

This study is an observational, retrospective analysis of high resolution physiologic data that is collected at Texas Children's Hospital using an FDA-cleared, secure data warehouse (Sickbay™; Medical Informatics, Houston TX). Approval from the institutional review board was obtained prior to extracting, de-identifying, and analyzing the subject data. Eligible subjects were neonates under 30 days of life at the time of surgery for congenital heart disease at Texas Children's Hospital with the requisite physiologic recordings, who underwent any degree of hypothermia less than 34°C. Signals required to analyze autoregulation with the hemoglobin volume index include continuous invasive arterial blood pressure and continuous reflectance spectroscopy with 805 nm wavelength near infrared light to trend cerebral blood volume. Further, it was required that a continuous nasal temperature was recorded into the same time-stamped file for each subject. Eligible subjects were identified from records dating from January 2015, when clinical cerebral oximetry was added to the data warehouse, to March 2016, when the study was performed. Signals extracted from the entire duration of anesthesia and surgery included: arterial blood pressure at 240 Hz from a line contiguous with the cerebral circulation (ie: not isolated from the carotid circulation by a cross-clamp), bilateral regional cerebral oxygen saturation (rSO_2) at 0.5 Hz, bilateral optical density of 805nm light from the cerebral oximetry monitoring at 0.5 Hz, and nasopharyngeal temperature at 240 Hz.

Anesthesia, cardiopulmonary bypass, and surgery

The protocol for anesthesia and cardiopulmonary bypass at Texas Children's Hospital has been described previously.(3, 14) A primarily ~~narcotic~~opiod-based anesthetic is used for neonates with doses of fentanyl ranging from 100 µg/kg to 400 µg/kg, supplemented with midazolam 0.25 mg/kg to 3 mg/kg, and isoflurane up to 1% end-tidal concentration and up to 3% inspired sweep gas during cardiopulmonary bypass. Paralysis is maintained with intermittent vecuronium. ε-Aminocaproic acid is used for all bypass cases. Bypass is initiated with a circuit containing 1 unit of packed red blood cells and 1 unit of fresh frozen plasma. The standard flow rate for neonatal bypass is 150ml~~cc~~/kg/min, and phentolamine is given in increments of 0.05 mg/kg (range 0.1 – 0.5 mg total dose) until the arterial blood pressure is between 30 and 35 mmHg at full flow. pH-stat blood gas management is used for hypothermic bypass, and ultrafiltration is used throughout the bypass period. Hematocrit is maintained between 30% and 35% during cooling, and between 40% and 45% at separation from bypass. When aortic arch surgery is required, selective cerebral perfusion is used as previously described.(14) Any time period with either circulatory arrest or selective cerebral perfusion were deleted from analysis as autoregulation analysis has no meaning during circulatory arrest, and the effect of isolated cerebral perfusion on autoregulation has not been clarified.

Quantifying cerebrovascular autoregulation

The autoregulatory function was quantified for each subject as a continuous variable in time throughout the recorded operation using the hemoglobin volume index.(15) First, the blood volume index is obtained by mathematical inversion of the optical density of 805 nm light from the reflectance spectroscopy monitor (1-OD 805nm). The arterial blood pressure and time-synchronized blood volume indices are then low pass filtered as 10-second averages to remove rapid fluctuations that exceed the frequency response of autoregulatory function.(16) 30 consecutive paired samples of arterial blood pressure and blood volume indices (300 second epoch) are included in a Pearson's correlation coefficient to render the hemoglobin volume index, which is updated in a moving, overlapped window

every 60 seconds. Positive values of the hemoglobin volume index indicate passive cerebral vasculature and impaired autoregulation. Negative values of the hemoglobin volume index indicate reactive cerebral vasculature and intact autoregulation.

Data analysis

Recordings extracted from the data warehouse were analyzed using ICM+ (Cambridge Enterprises, Cambridge UK). By inspection, artifact was negligible, so only periods of circulatory arrest and selective perfusion were deleted from analysis. All study variables (arterial blood pressure, nasopharyngeal temperature, and hemoglobin volume index) were averaged in one-minute intervals to a single time-stamped file. Although not a study variable, rSO_2 was added as a fourth variable into the same time-stamped file. Individual subject characteristics and data ~~was~~ were binned by averaging in an even-partitioned array of nasopharyngeal temperature: 18°C (<21.5°C); 24°C (21.5 – 27.4°C); 30°C (27.5°C – 33.4°C); and 36°C (≥33.5°C). Binning by temperature for each individual subject thus produced up to four repeated measures of each study variable (ABP, HVx, rSO_2) for each subject, depending on the range of temperatures experienced by that subject. Inconsistently repeated measures due to variations in temperatures observed dictated sequential univariate analyses comparing ABP, HVx, rSO_2, and temperature using linear regression with generalized estimation of equations.(17) Co-linearity between the study variables precludes multivariate analysis.

Results

Seventy-two eligible subjects were identified and all were included in the analysis. Deep hypothermic circulatory arrest and/or selective cerebral perfusion was used for 33 (48%) of subjects. Patient characteristics, including diagnostic categories and surgical procedures are shown in Table 1. Subjects requiring the lowest temperatures on cardiopulmonary bypass were younger at the time of surgery and had diagnostic categories that required early correction, such as infradiaphragmatic anomalous pulmonary venous return, or had aortic arch abnormalities requiring selective antegrade cerebral perfusion for arch reconstruction. The longest cardiopulmonary bypass times, and aortic cross clamp times occurred in subjects with moderate hypothermia during bypass, accounted for by the lengthy arterial switch operation for subjects with transposition of the great arteries.

Univariate correlations between temperature, ABP, HVx, and rSO_2 are shown in table 2 along with estimates from the generalized estimation of equations model and 95% CI of these estimates. As previously observed, hypothermia was correlated with a more positive HVx, indicating dysautoregulation ~~(p<0.0001)~~. In addition, hypotension was correlated with a more positive HVx, indicating dysautoregulation ~~(p<0.0001)~~. Arterial blood pressure was also correlated with temperature, such that hypothermia was accompanied by hypotension ~~(p<0.0001)~~. Comparing the baseline temperature of 36°C with 18°C, arterial blood pressure was 44 mmHg [39 – 52] vs. 25 mmHg [21 – 31] and the hemoglobin volume index was 0.0 [-0.02 to 0.004] vs. 0.5 [0.4 – 0.7] (Median, 95% CI of median; P<0.0001 for both associations). These co-linearities preclude a multivariate analysis to determine whether hypothermia or hypotension are independently associated with dysautoregulation. The hypothermic, hypotensive, dysautoregulated state was also correlated with a higher rSO_2, as rSO_2 was negatively correlated with temperature and arterial blood pressure, and positively correlated with HVx on univariate analyses ~~(p<0.0001 for all 3 associations)~~using the same statistical model. These correlations are more easily visualized in Figure 1, ~~showing~~ which shows ~~hemoglobin volume index~~HVx, arterial blood pressure, and rSO_2 as a function of binned temperature.

Discussion

The findings of this study question a common understanding of neonatal bypass physiology. Two prior studies have both shown that neonatal hypothermic bypass is associated with pressure passive cerebral vasculature.(12, 13) Both studies used intermittent measures of cerebral blood flow or flow velocity, plotted across arterial blood pressure for the entire cohort to quantify the correlation between cerebral blood flow and arterial blood pressure as a marker of autoregulation. The present study adds temporal granularity with continuous autoregulation measurements using the HVx, and the ability to assess within subjects for changes in autoregulation across temperature and across arterial blood pressure. The finding of impaired autoregulation during hypothermia was confirmed by the present study, but the causal assignment is questioned when arterial blood pressure is included in the analysis. Low arterial blood pressure was (not surprisingly) associated with impaired autoregulation, but hypotension was also associated with hypothermia, such that multivariate analysis to determine the independent effect of temperature on autoregulation is precluded.

The presented results show that during hypothermic bypass, the neonate is in a state of hypotension and dysautoregulation with an rSO_2 that is elevated from baseline. The use of pH stat blood gas management in this cohort may explain the universal elevation in rSO_2 seen during hypothermia. Further, data from Greeley *et al* have documented impairment of neurovascular coupling by showing a reduction in cerebral oxygen metabolism greater than cerebral blood flow reduction during neonatal hypothermic bypass.(18) This so-called state of luxury flow would explain an elevation of rSO_2 during hypothermia. Neurovascular coupling is also referred to as *metabolic* autoregulation, which can be confused with *pressure* autoregulation, but the two mechanisms are distinct.(19) The HVx measures vascular reactivity in response to arterial blood pressure changes, not changes in metabolism. One might reasonably ask why a disturbance of pressure autoregulation matters if the brain is protected by flow exceeding metabolism. Two considerations apply to this question.

First, the entire neonatal bypass strategy is a low-pressure high-flow state, including both hypothermic and normothermic bypass. During normothermia, the brain is not protected from hypoperfusion by reduced metabolism. It is believed that the high bypass flow rate afforded by vasodilation (and associated hypotension) results in adequate cerebral blood flow. Animal models have shown that the vasculature of the brain is pressure-dependent, and not output-dependent. Specifically, if the arterial blood pressure is greater than the lower limit of pressure autoregulation, then cerebral blood flow is unaffected by changes in pump flow rates.(7) If the neonatal cerebral vasculature has the same pressure dependence, then hypotension below the lower limit of autoregulation during normothermia may contribute to the current high rate of white matter injury. Knowing the neonatal lower limit of autoregulation would then be helpful to prevent injurious hypotension.

Second, the monitoring of autoregulation to identify the lower limit of autoregulation and target optimal arterial blood pressure for the brain would be confounded if hypothermia causes dysautoregulation. In that case, autoregulation data obtained during hypothermia should not be included to identify optimal perfusion pressures used during normothermia. If, however, hypothermia does not impair pressure autoregulation then autoregulation monitoring from the entire bypass period can be used to delineate the lower limit of autoregulation.

The main limitation of this study is inability to show that hypothermia does or does not cause dysautoregulation. An association between hypothermia and dysautoregulation independent of

hypotension would have to be done with normotensive bypass, and the temporal link between survival and the current bypass strategy precludes such a study at our center.

Conclusion

Neonatal Hypothermic cardiopulmonary bypass is associated with impaired cerebrovascular autoregulation. Although this association has been thought to be a causal link, the present study demonstrates that hypothermic neonatal bypass with the current, high-flow low-resistance strategy is also associated with hypotension, which is itself associated with dysautoregulation. Whether or not hypothermia is associated with dysautoregulation in neonatal bypass should be determined in a normotensive bypass model before clinical deployment of autoregulation monitoring.

Disclosures

ETHICS - Approval for this study was obtained from the institutional review board at the Baylor College of Medicine, (H-40207 and H-28829; last renewals 1/13/2016 and H-28829)
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DISCLOSURES - Dr. Rusin discloses that he has a financial interest in Medical Informatics Corp, which has been disclosed and managed by the COI policy of Baylor College of Medicine.

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Table 1: Subject characteristics are shown as a function of lowest temperature achieved during cardiopulmonary bypass.

Demographics					
Lowest temp	18 C (n = 36)	24 C (n = 9)	30 C (n = 17)	32 C (n = 2)	Total (n = 64)
Age (days)	8 [4 - 14]	10 [8 - 21]	9 [6 - 16]	23 [15 - 30]	9 [4 - 15]
Weight (kg)	3.3 [2.6-3.5]	3.5 [3.2-3.9]	3.4 [3.0-3.6]	3.0 [3.0-3.1]	3.3 [3.0-3.6]
Male sex (%)	23 (60%)	5 (50%)	13 (70%)	2 (100%)	43 (60%)
genetic synd. (%)	8 (21%)	0	2	1	11 (16%)
Diagnosis					
	18 C	24 C	30 C	>30 C	total
HLHS	12	0	0	0	12
TGA	3	7	15	0	25
CoA, IAA	13	0	0	0	13
TAPVR	7	1	0	0	8
Truncus/DORV	1	1	2	0	4
PA-MAPCAS	0	0	0	1	1
VSD	0	0	0	1	1
Procedure					
	18 C	24 C	30 C	>30 C	total
Norwood	13	0	0	0	13
ASO	2	7	15	0	24
CoA/IAA repair	13	0	0	0	13
TAPVR repair	7	1	0	0	8
Truncus/Rastelli	0	1	2	1	4
OHT	1	0	0	0	1
VSD closure	0	0	0	1	1
Procedure data					
	18 C	24 C	30 C	>30 C	total cohort
Duration (min)	397 [338 - 431]	508 [387 - 542]	502 [383 - 546]	261 [204 - 317]	414 [354 - 516]
CPB time (min)	187 [147 - 223]	324 [280 - 355]	276 [229 - 324]	123 [77 - 169]	214 [163 - 289]
ACC time (min)	106 [77 - 131]	175 [145 - 186]	159 [124 - 209]	67 [36 - 97]	119 [93 - 167]
DHCA (%)	25 (63%)	3 (33%)	0	0	28 (41%)
DHCA time (min)	15 [9 - 23]	15 [13 - 19]	n/a	n/a	15 [9-23]
SACP (%)	33 (87%)	0	0	0	33 (48%)
SACP time (min)	42 [21 - 73]	n/a	n/a	n/a	41.5 [21 - 73]
lowest Hb (g/dL)	31 [29 - 32]	32 [29 - 34]	32 [29 - 32]	30 [28 - 32]	31 [29 - 32]

HLHS: hypoplastic left heart syndrome. TGA: transposition of the great arteries. CoA: coarctation of the aorta. IAA: interrupted aortic arch. TAPVR: total anomalous pulmonary venous return. Truncus: truncus arteriosus. DORV: double outlet right ventricle. PA-MAPCAS: pulmonary atresia with major aortopulmonary collateral arteries. VSD: ventricular septal defect. Norwood: Norwood operation including Blalock-Taussig shunt, Sano shunt with Brawn modification and/or Damus-Kaye-Stansel procedure. ASO: arterial switch operation. OHT: orthotopic heart transplant. CPB: cardiopulmonary bypass. ACC: aortic cross clamp: DHCA: deep hypothermic circulatory arrest. SACP: selective antegrade

cerebral perfusion. Hb: hemoglobin. ~~p-values determined by Kruskal-Wallis or Fisher's exact tests.~~ Continuous variables are shown as median and interquartile range.

Table 2. Estimates from the generalized estimation of equations models of relationships between temperature, arterial blood pressure, hemoglobin volume index, and cerebral oximetry.

	ABP B (95% CI)	HVX B (95% CI)	RSO_2 B (95% CI)
TEMPERATURE	0.999 (0.881 - 1.12) p < 0.0001	-7.97 (-10.39 - -5.55) p < 0.0001	-0.270 (-0.317 - -0.222) p < 0.0001
ABP		-12.28 (-15.6 - -9.00) p < 0.0001	-0.348 (-0.419 - -0.277) p < 0.0001
HVX			0.007 (0.00392 – 0.010) p < 0.0001

GEE: generalized estimating equations, ABP: arterial blood pressure, HVx: hemoglobin volume index, rSO_2: regional oxygen saturation. The GEE model results show that decreased temperature was associated with lower ABP, higher HVx (dysautoregulation), and higher rSO_2. Lower ABP was associated with higher HVx (dysautoregulation), and higher rSO_2. Higher HVx (dysautoregulation) was associated with higher rSO_2.

Figure Legends

Figure 1: Hypothermia during infant cardiopulmonary bypass was associated with A) dysautoregulation demonstrated by an increase in the hemoglobin volume index (HVx; p<0.0001), B) hypotension demonstrated by decreased mean arterial blood pressure (ABP; p<0.0001), and C) luxury perfusion, demonstrated by marked increases in cerebral oximetry (rSO_2; p<0.0001). Box-Whisker plots show median, interquartile range, 10^{th} and 90^{th} percentiles.

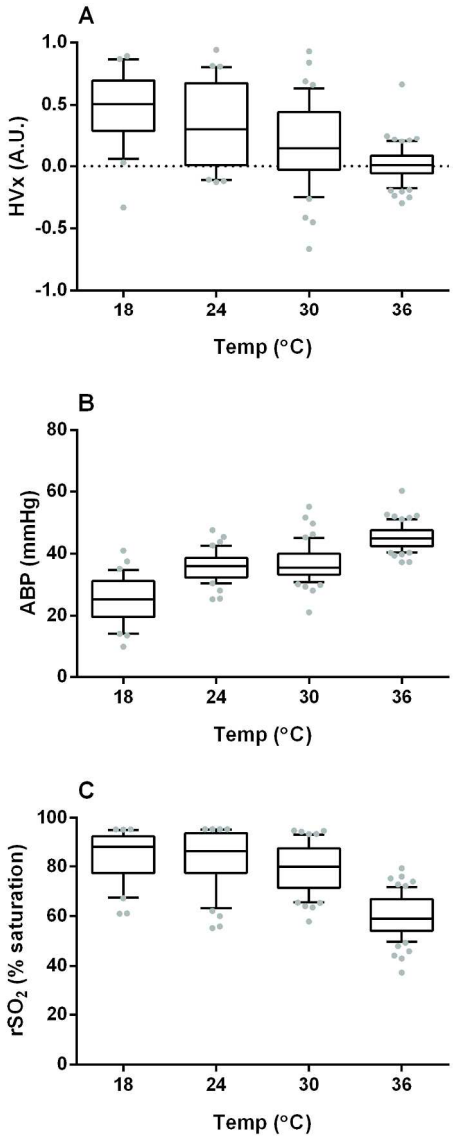

Figure 1: Hypothermia during infant cardiopulmonary bypass was associated with A) dysautoregulation demonstrated by an increase in the hemoglobin volume index (HVx; $p<0.0001$), B) hypotension demonstrated by decreased mean arterial blood pressure (ABP; $p<0.0001$), and C) luxury perfusion, demonstrated by marked increases in cerebral oximetry (rSO2; $p<0.0001$). Box-Whisker plots show median, interquartile range, 10th and 90th percentiles.

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