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Long-term neurodevelopmental effects of intraoperative blood pressure during surgical closure of a septal defect in infancy or early childhood

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Abstract

Background: Many children born with congenital heart defects are faced with cognitive deficits and psychological challenges later in life. The mechanisms behind are suggested to be multifactorial and are explained as an interplay between innate and modifiable risk factors. The aim was to assess whether there is a relationship between mean arterial pressure during surgery of a septal defect in infancy or early childhood and intelligence quotient scores in adulthood. *Methods:* In a retrospective study, patients were included if they underwent surgical closure of a ventricular septal defect or an atrial septal defect in childhood between 1988 and 2002. Every patient completed an intelligence assessment upon inclusion, 14–27 years after surgery, using the Wechsler Adult Intelligence Scale Version IV. *Results:* A total of 58 patients met the eligibility criteria and were included in the analyses. No statistically significant correlation was found between blood pressure during cardiopulmonary bypass and intelligence quotient scores in adulthood ($r = 0.138$; 95% CI −0.133–0.389). Although amongst patients with mean arterial pressure < 40 mmHg during cardiopulmonary bypass, intelligence quotient scores were significantly lower (91.4; 95% CI 86.9–95.9) compared to those with mean arterial pressure > 40 mmHg (99.8; 95% CI 94.7–104.9). *Conclusions:* Mean arterial pressure during surgery of ventricular septal defects or atrial septal defects in childhood does not correlate linearly with intelligence quotient scores in adulthood. Although there may exist a specific cut-off value at which low blood pressure becomes harmful. Larger studies are warranted in order to confirm this, as it holds the potential of partly relieving CHD patients of their cognitive deficits.

Neurodevelopmental impairment is common in patients with congenital heart defects and is potentially the most damaging complication.[1] Post-operatively, these patients are challenged with impairment of cognition, language, and motor functions during infancy.[2] Upon school entry, they are faced with deficits impacting the quality of life[3] and have a higher prevalence of psychiatric diagnoses compared to their healthy peers.[4,5]

The aetiology behind neurodevelopmental impairment in patients with CHDs has been the focus of numerous research efforts over the past decades. Factors mediating the risk of neurodevelopmental impairment can generally be divided into innate and modifiable risk factors. The interplay between these two components is suggested to induce neurodevelopmental impairment amongst CHD patients. These factors include, but are not limited to, exposure to volatile anaesthetic agents, length of ICU stay,[2] duration of cardiopulmonary bypass,[7] and specific patient characteristics such as the presence of a genetic syndrome, low birth weight, and presence of APOE ϵ2 allele.[8]

However, no studies have, to our knowledge, evaluated the association between mean arterial pressure during surgery and neurodevelopmental impairment in a population of atrial septal defect and ventricular septal defect patients. This is particularly interesting, as CHD patients are suggested to have an inherent vulnerability to intraoperative haemodynamic instability.[9] Therefore, we hypothesised that a low intraoperative blood pressure, especially when operated at a young age, has a negative impact on neurocognitive development. Thus, the aim of this long-term retrospective study was to describe the relationship between blood pressure during septal defect closure in infancy or early childhood and full-scale intelligence quotient scores in adulthood.

Methods

This study was approved by the Regional Committee on Biomedical Research Ethics of the Central Denmark Region (1-10-72-233-17) and the Danish Data Protection Agency (2012-58-006) and complies with the World Medical Association's Declaration of Helsinki. All patients provided written informed consent prior to enrolment. This study was conducted as a substudy of a previously published study assessing intelligence quotient scores in patients with septal defects and healthy controls.[10] This manuscript adheres to the applicable Equator guidelines.

Design and study population

In this retrospective study, inclusion criteria were (1) surgical closure of isolated atrial septal defect between 1988 and 1999 or (2) surgical closure of isolated ventricular septal defect between 1990 and 2002 at Aarhus University Hospital, Denmark. Exclusion criteria were (1) associated syndromes, (2) recent head trauma, (3) lack of Danish language skills, (4) diagnosis of coronary artery disease or other congenital cardiac abnormalities, (5) age at inclusion below 18 years, and (6) age at surgery above 1 standard deviation from mean age at surgery, as blood pressure was considered incomparable across wide ranges of age. The exclusion criteria 1–5 were applied primarily in the original study, whereas exclusion criteria 6 was applied secondarily for this substudy only. Patients were invited via electronic mail, and according to Danish law, patients were asked to express their interests prior to receiving the more comprehensive study material. Patients, who agreed to participate, received an email with practical information including the date and time of examination. In order to ensure that the number of patients included was in accordance with the conducted sample size calculation, patients were contacted in blocks of 50–100 patients at a time, and upon reaching the aimed number of patients, no further invitations were sent out.

Stratification of patients

In a subanalysis, patients were divided into two groups based on their mean arterial pressure during cardiopulmonary bypass. A threshold of 40 mmHg was set according to the guidelines from the European Resuscitation Council 2015 for a 1-year-old child.[11]

Additional stratifications were performed in order to account for possible differences in intelligence scores at the extremities of bypass time and age at surgery. Long bypass time was defined as 75 minutes or above (1SD above mean value), whereas low age at surgery was defined as 0.7 years or below (1SD below mean value). All cut-off values used in the stratification of patients were set in advance prior to data analyses.

Data acquisition

Data related to the surgical intervention were retrospectively collected from reviewing the following charts: patient notes, anaesthesia records, and ICU charts. This included information on demographics, medical history, type of anaesthetic agents used during surgery, surgical technique, vital parameters (e.g. mean arterial pressure), and blood sample analyses. Throughout an operation, an anaesthesiologist or anaesthetic nurse manually noted the blood pressures with 5-minute intervals on the patient's anaesthesia record. For each patient, an average mean arterial pressure was obtained for each of the three intraoperative phases (pre-, intra-, and post-cardiopulmonary bypass), by averaging all measurements in the respective phase.

Outcome data were prospectively collected and included neuropsychological testing and information on educational attainment. The neuropsychological test battery has been previously described in detail.[10] Retrospective data collection was conducted in the period from September, 2019 to January, 2020, whereas prospective data collection was performed in the period from March, 2018 to November, 2018.

Neuropsychological testing

Intelligence and cognitive abilities were obtained using the Wechsler Adult Intelligence Scale Version IV. The Wechsler Adult Intelligence Scale Version IV comprises four subdomains representing major components of intelligence (1) verbal comprehension, (2) perceptual reasoning, (3) working memory, and (4) processing speed. Full-scale intelligence quotient scores and the four subdomains, all with a scaled score mean of 100 (SD ± 15), were calculated according to the manual. A higher score indicated a better performance. The neuropsychological testing was conducted by trained research assistants under the supervision of an experienced research neuropsychologist (L.E). Testing personnel was blinded to the cardiac diagnosis.

Surgical technique

In brief, surgical closure was performed on cardiopulmonary bypass via a median sternotomy. Every patient was supported on the same standard cardiopulmonary bypass setup, which included (1) maintenance of hypothermia between 28 and 35°C, (2) priming with a combination of blood, Ringer's lactate, bicarbonate, albumin, and heparin, (3) cardioplegic induction with St. Thomas solution, (4) blood flow target of 2.4 L/min/m^2, and (5) haematocrit target of 25–30%. The defect was accessed through the right atrium, or for a ventricular septal defect occasionally the right ventricle and closed with either direct suture or insertion of a patch of artificial material or pericardium. All procedures were performed by one of the seven experienced paediatric cardiac surgeons at Aarhus University Hospital, Denmark.

Anaesthetic technique

The choice of anaesthetic technique was at the discretion of the attending paediatric anaesthesiologist. For all patients, intraoperative monitoring included intra-arterial blood pressures in the right radial artery, ECG, and peripheral oxygen saturation, whereas no anaesthetic depth monitoring was performed. Intraoperative arterial blood samples were analysed, and also at the discretion of the attending anaesthesiologist.

In general, a volatile anaesthetic agent was used for induction and maintenance in combination with one or more intravenous anaesthetic agents. For analgesia, intravenous opioids were used including mainly fentanyl, but also morphine and sufentanil. Intraoperative muscle relaxation with pancuronium, atracurium, or cisatracurium was used in all patients. Lastly, the majority of the patients were given either dopamine or dobutamine to increase inotropy.

Outcomes

Our primary outcome was full-scale intelligence quotient scores, whereas the index scores verbal comprehension, perceptual reasoning, working memory, and processing speed were secondary outcomes. Other secondary outcomes were educational attainment, which included educational level (assessed by the International Standard Classification of Education 2011), dyslexia, dyscalculia, special needs teaching, and educational psychologist counselling, which were all obtained through a personal interview by an experienced research nurse.

Statistical analyses

Data are reported as means ± standard deviations, absolute numbers with percentages of patients, or as medians with total range, as appropriate. Continuous data were compared using student's t-tests or Wilcoxon rank-sum tests, as appropriate for normally and non-normally distributed data, respectively. Binary data were compared using chi-squared tests. A Spearman's correlation was performed to test for a correlation between mean arterial pressure during cardiopulmonary bypass and full-scale intelligence quotient scores. Similarly, Spearman's correlations were performed to assess whether cardiopulmonary bypass time and age at surgery correlated with full-scale intelligence quotient scores. P-values < 0.05 were considered statistically significant for our primary outcome, whereas only p-values < 0.01 were considered statistically significant for our secondary outcomes. All p-values are two-sided. The current study was conducted as a substudy of a previously published study, for which a sample size calculation was performed.[10] Furthermore, maximum and minimum values were identified for each blood parameter to evaluate possible predictors of lower neurodevelopmental outcomes. Data were stored in RedCap (Denmark), statistical analyses were conducted on a blinded dataset using Stata/SE 15.1 (Stata Corp., TX, United States of America), and data were graphically described in GraphPad Prism 8 (GraphPad Software, La Jolla, CA, United States of America).

Results

A total of 66 patients, who underwent surgical correction of either atrial septal defect or ventricular septal defect at Aarhus University Hospital between 1988 and 2002, gave their informed consent to participate in the original study. For this substudy, 1 patient was excluded due to missing anaesthetic chart and 7 patients were secondarily excluded due to high age at the time of surgery leaving 58 patients eligible for analyses (atrial septal defect: n = 27, ventricular septal defect: n = 31), as displayed in detail in Figure 1. Data collection was complete for all patients.

For the entire population, mean age at time of surgery was 2.8 ± 2.2 years with a median age of 2.2 years and total range from 0.2 to 8.2 years. Mean age at time of neurodevelopmental assessment was 24.5 ± 4.0 years with a median age of 24.5 years and total range from 18 to 32 years. Median times of post-operative stay at the ICU and hospital were 1 day (1–5 days) and 9 days (2–27 days), respectively. Mean arterial pressure was 66.4 mmHg before cardiopulmonary bypass, 41.0 mmHg during cardiopulmonary bypass, and 60.4 mmHg after cardiopulmonary bypass. No statistically significant correlation was found between blood pressure during cardiopulmonary bypass and full-scale intelligence quotient score in adulthood (r = 0.138; 95% CI −0.133–0.389, p = 0.303) (Fig 2).

Upon stratification of patients based on mean arterial pressure during cardiopulmonary bypass, the distributions were as follows; 33 patients had a mean arterial pressure < 40 mmHg and 25 patients had a mean arterial pressure > 40 mmHg. Patient characteristics of the entire population are shown in Table 1, whereas

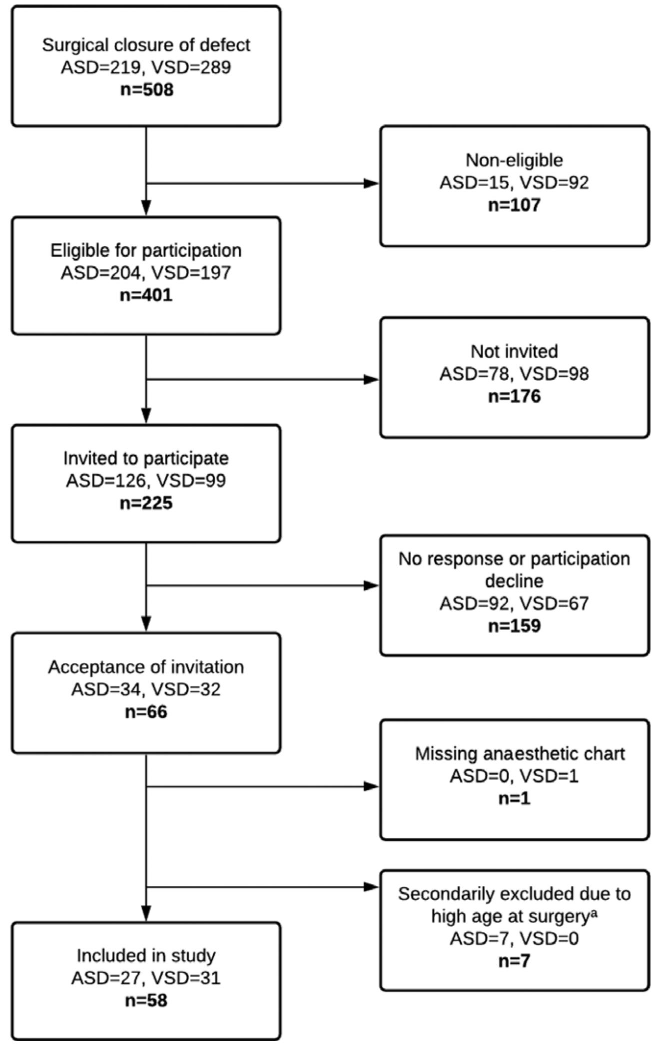

Figure 1. Flowchart of inclusion process. ASD=Atrial septal defect; VSD=Ventricular septal defect.
[a]High age at surgery was defined as age at surgery above 1SD from mean age at surgery.

characteristics of the stratified groups are shown in Supplementary Table S1.

Intelligence quotient scores and educational attainment

Intelligence quotient tests were performed in the period between March, 2018 and November, 2018. In the study population, mean full-scale intelligence quotient score was 95.0 ± 15.8, verbal comprehension was 90.9 ± 13.5, perceptual reasoning was 95.7 ± 15.8, working memory was 93.1 ± 12.9, and processing speed was 106.3 ± 16.5. Data on educational attainment are shown in Table 2.

For the stratified groups, full-scale intelligence quotient scores were lower amongst patients with mean arterial pressure < 40 mmHg (91.4 ± 12.6) compared to patients with mean arterial pressure > 40 mmHg (99.8 ± 12.4), p = 0.014. The lower full-scale intelligence quotient scores amongst patients with mean arterial pressure < 40 mmHg were primarily driven by a significantly lower perceptual reasoning index score, whereas the other three subdomains; verbal comprehension, working memory,

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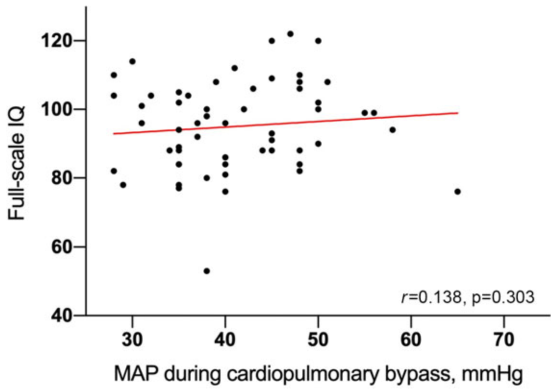

Figure 2. Spearman's correlation between full-scale intelligence quotient scores and MAP during cardiopulmonary bypass in patients operated for ASD or VSD. ASD=Atrial septal defect; MAP=Mean arterial pressure; VSD=Ventricular septal defect.

and processing speed analyses revealed only a tendency towards lower scores amongst patients with mean arterial pressure < 40 mmHg compared to patients with mean arterial pressure > 40 mmHg. Although mean full-scale intelligence quotient scores were within the expected population range (85–115), 33% of patients with mean arterial blood pressure < 40 mmHg had a full-scale intelligence quotient score below the expected population range compared to 12% amongst patients with mean arterial pressure > 40 mmHg, p = 0.060. Also, for the subdomains perceptual reasoning and verbal comprehension, we found significantly higher proportions of patients with scores below 85 amongst patients with mean arterial pressure < 40 mmHg compared to those with mean arterial pressure > 40 mmHg (33% versus 4%, p = 0.006, and 42% versus 12%, p = 0.012, respectively). Intelligence quotient scores and educational attainment distributions for the stratified groups are shown in Table 3 and Supplementary Table S2, respectively.

Anaesthetic agents and arterial blood samples during surgery

Anaesthetic agents used during surgery are presented in Table 4 and for the stratified groups in Supplementary Table S3. As shown, volatile anaesthetic agents were used in 100% of the patients, whereas inotropes were used in 76% of the patients. Intraoperative blood samples are displayed in Supplementary Table S4.

Supplementary analyses

Additional analyses were performed in order to identify potential confounding factors. First, a comparison of full-scale intelligence quotient scores between atrial septal defect and ventricular septal defect patients was performed and showed no statistically significant differences between the two groups (full-scale intelligence quotient score = 94.2 ± 12.5 and full-scale intelligence quotient score = 95.7 ± 13.7, respectively), p = 0.670. Additionally, no correlation between cardiopulmonary bypass time and full-scale intelligence quotient score was present (r = 0.076, 95% CI −0.201–0.342, p = 0.581). Furthermore, patients were divided into arbitrary subgroups based on cardiopulmonary bypass time under or above 75 minutes. No statistically significant differences in full-scale intelligence quotient scores were present between the group with short cardiopulmonary bypass time and the group with long cardiopulmonary bypass time (full-scale intelligence quotient score = 95.2 ± 13.5 and full-scale intelligence quotient score = 93.8 ± 10.7, respectively), p = 0.771.

In addition to surgical defect closure, a subgroup of patients underwent prior pulmonary artery banding and/or cardiac catheterisation. In total, 14 patients underwent cardiac catheterisation, and out of those, 3 patients also had pulmonary artery banding performed prior to the final ventricular septal defect repair. No statistically significant differences in full-scale intelligence quotient scores were found between patients who had undergone cardiac

Table 1. Characteristics of patients undergoing surgery for ASD or VSD

	N=*58*
Demographics	
Age at surgery, years	2.8 ± 2.2
Age at IQ testing, years	24.5 ± 4.0
Male sex, n (%)	19 (39)
BMI, kg/m^2	24.5 ± 4.3
Height, cm	170.3 ± 11.7
Defect characteristics	
VSD, n (%)	31 (53)
Perimembranous, n (%)	17 (55)
Muscular, n (%)	14 (45)
ASD, n (%)	27 (47)
Primum, n (%)	2 (7)
Secundum, n (%)	25 (93)
Defect size, mm	11.6 ± 7.9
Pulmonary-to-systemic blood flow (Qp/Qs)	2.8 ± 1.0
Previous pulmonary artery banding, n (%)	3 (5)
Preoperative catheterisation, n (%)	14 (24)
Perioperative information	
Weight, kg	11.9 ± 5.3
Height, cm	90.2 ± 20.4
BMI, kg/m^2	13.9 ± 1.5
Total bypass time, min.	53 ± 22
Cross-clamp time, min.	24 ± 14
VSD closure, n (%)	
Patch, n (%)	20 (65)
Direct suture, n (%)	11 (35)
ASD closure, n (%)	
Patch, n (%)	16 (59)
Direct closure, n (%)	11 (41)
Hospital stay > 14 days, n (%)	3 (5)
Hospital stay, days (range)	9 (2–27)
ICU stay > 1 day, n (%)	15 (26)
ICU stay, days (range)	1 (1–5)

Data are reported as mean ± standard deviation, absolute numbers, and percentages of patients or median with total range.
ASD = Atrial septal defect; ICU = intensive care unit; VSD = Ventricular septal defect.

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Table 2. Educational attainment

	N = 58
Educational attainment	
ISCED primary education, n (%)	2 (3)
ISCED secondary education, n (%)	45 (78)
ISCED tertiary education, n (%)	11 (19)
Dyslexia, n (%)	10 (17)
Dyscalculia, n (%)	3 (5)
Special needs teaching [a], n (%)	26 (45)
Educational Psychologist Counselling [b], n (%)	9 (16)

Data are reported as absolute numbers and percentages of patients.
ISCED = International Standard Classification of Education 2011.
[a]Received special needs teaching during primary or secondary school.
[b]Received educational psychologist counselling during primary or secondary school.

Table 3. Intelligence quotient testing in stratified groups

	MAP < 40 mmHg n = 33	MAP > 40 mmHg n = 25	P-value
Full-scale IQ	91.4 ± 12.6	99.8 ± 12.4	0.014
Verbal comprehension	88.1 ± 13.4	94.6 ± 13.1	0.069
Perceptual reasoning	91.5 ± 16.0	101.2 ± 14.0	0.019
Working memory	91.4 ± 13.0	95.8 ± 12.7	0.201
Processing speed	102.6 ± 16.4	111.2 ± 15.6	0.051

Data are reported as mean ± standard deviation.
IQ = intelligence quotient; MAP = mean arterial pressure.

Table 4. Intraoperatively administered drugs

	N = 58
Volatile anaesthetic agents	
Sevoflurane, n (%)	14 (24)
Isoflurane, n (%)	3 (5)
Enflurane, n (%)	1 (2)
Halothane, n (%)	38 (66)
None, n (%)	2 (3)
Intravenous anaesthetic agents	
Midazolam, n (%)	49 (84)
Ketamine, n (%)	13 (22)
Thiopental, n (%)	7 (12)
Intravenous opioid agents	
Fentanyl, n (%)	54 (93)
Morphine, n (%)	1 (2)
Sufentanil, n (%)	4 (7)
Muscle relaxants	
Suxamethonium, n (%)	12 (21)
Pancuronium, n (%)	55 (95)
Atracurium, n (%)	2 (3)
Cisatracurium, n (%)	1 (2)
Inotropes and vasoactive agents	
Dopamine, n (%)	36 (62)
Dobutamine, n (%)	8 (14)

Data are reported as absolute numbers and percentages of patients.

catheterisation and those who had not (full-scale intelligence quotient score = 91.5 ± 12.0 and full-scale intelligence quotient score = 96.1 ± 13.4, respectively), p = 0.252. Similarly, no statistically significant differences in full-scale intelligence quotient scores were found between patients who had undergone both cardiac catheterisation and pulmonary artery banding and those who had not (full-scale intelligence quotient score = 84.3 ± 8.5 and full-scale intelligence quotient score = 95.6 ± 13.1, respectively), p = 0.148.

Similarly, no correlation between age at surgery and full-scale intelligence quotient score was found (r = 0.023, 95% CI −0.244–0.287, p = 0.865). Analogously, patients were divided into arbitrary subgroups based on age at surgery under or above 0.7 years. No differences in full-scale intelligence quotient scores were present between the group with low age at surgery and the group with high age at surgery (full-scale intelligence quotient score = 96.8 ± 11.5 and full-scale intelligence quotient score = 94.8 ± 13.3, respectively), p = 0.723.

Lastly, we found no correlation between the size of the atrial septal defect or ventricular septal defect and full-scale intelligence quotient score (r = 0.041, p = 0.780), nor did we find any correlation between the pulmonary–systemic flow ratio and full-scale intelligence quotient scores (r = 0.090, p = 0.692).

Discussion

In this retrospective study, we did not find a linear correlation between mean arterial pressure during cardiopulmonary bypass and intelligence quotient scores in adults surgically treated for a septal defect in infancy or early childhood. However, in risk groups stratified by mean arterial pressure during cardiopulmonary bypass, the full-scale intelligence quotient score was found to be significantly lower amongst patients with mean arterial pressure < 40 mmHg compared to patients with mean arterial pressure > 40 mmHg. Interestingly, 33% of patients with mean arterial pressure < 40mmHg had full-scale intelligence quotient scores below 85, compared to only 12% amongst patients with mean arterial pressure > 40mmHg. In other words, a significantly larger proportion of patients with mean arterial pressure < 40mmHg had cognitive shortcomings that would be clinically recognisable and potentially disabling in their everyday life.

No previous studies have, to our knowledge, investigated the effects of blood pressure during surgery on neurodevelopmental outcomes in a population of simple CHD patients, although similar studies have been conducted on populations of complex CHD patients in an effort to identify intraoperative risk factors. The notion that cardiopulmonary bypass represents a critical phase during surgery was supported by a study showing that the duration of cardiopulmonary bypass was associated with reduced neurodevelopmental status after neonatal arterial switch operation,[12] and it has been suggested that there is a special vulnerability to haemodynamic fluctuations in this population.[13,14] This has been explained as the "*Encephalopathy of congenital heart disease*",[9,15] which may represent a major innate risk factor of intraoperative hypoxic brain injury with subsequent neurodevelopmental impairment. It is proposed that the structural and haemodynamic characteristics of CHDs lead to autoregulation mechanisms, which ultimately result in delayed maturation of oligodendrocytes, reduced myelinisation, and increased vulnerability of the brain.[16,17]

Although we did not demonstrate a linear correlation between mean arterial pressure during cardiopulmonary bypass and full-scale intelligence quotient score, there may exist an inflection point at which low blood pressures become harmful. Our result suggests that this potential cut-off value is around 40mmHg, although this was an arbitrary value chosen for this study only. Galli et al showed that hypotension in the early post-operative period significantly increased the risk of cerebral necrosis.[18] Thus, it is within reason to conceptualise that low blood pressure during surgery could have the same implications, and it has been previously shown that children with CHD are at risk of cerebral hypoperfusion before, during, and after cardiac surgery.[19] In ventricular septal defect-operated patients specifically, a study by Eichler et al[20] revealed no significant difference in intelligence quotient scores compared to healthy controls, but the mean age at testing in the study by Eichler et al was 7 years, whereas the mean age at testing in our study was 24 years. It is conceivable that testing at a higher age allows for a more nuanced assessment of the cognitive functions.

It is important to emphasise that a number of perioperative factors influence the neurodevelopmental outcomes in patients undergoing septal defect closure. Previous studies demonstrated associations between exposure to volatile anaesthetic agents and impaired neurodevelopmental outcome.[2,6] In terms of blood analyses, we found a tendency towards lower levels of arterial pCO_2 in the group with mean arterial pressure < 40mmHg. Low levels of pCO_2 are known to induce vasoconstriction and decreased cerebral blood flow,[21] but we were not able to demonstrate any correlation between pCO_2 levels during surgery and neurodevelopmental outcome.

Identification of risk factors during surgery, and subsequently avoidance thereof, could partly relieve these children of their cognitive deficits, knowing that impaired neurodevelopmental may not solely be associated with events happening in the operating room.

In this study, we included patients that were operated more than 20 years ago, and it is clear that some practices in terms of anaesthetic and surgical techniques have changed since then. In a contemporary cohort, atrial septal defect, as well as ventricular septal defect patients, are typically operated at an earlier age, total intravenous anaesthesia is more common, and patients are only rarely cooled to moderate hypothermia compared with 20 years ago. Nevertheless, at our institution, the practices used back then are generally very similar to today in terms of monitoring, surgical approach, and cardiopulmonary bypass management, including blood flow.

Limitations

Generally, it is obviously very challenging to assess a relationship between an exposure and an outcome when there are more than 20 years in between. In addition, the retrospective study design has inherent limitations, such as the inability to demonstrate causal inferences but only potential associations. It is clear that the time frame and the retrospective design make our study susceptible to confounding factors such as, for instance, multiple general anaesthesia procedures, either cardiac catheterisation or pulmonary artery banding prior to defect closure, or anaesthesia for any other reason later in life. Second, we did not have intraoperative indicators of diminished cerebral perfusion (transcranial Doppler, near-infrared spectroscopy, standard electroencephalography, or processed electroencephalography), which have previously been demonstrated to predict the occurrence of neurodevelopmental impairment.[22,23] Third, the range in age at surgery in our population is rather wide, and it is obviously difficult to compare an 8-year-old with an infant. Nevertheless, we decided not to exclude more patients than we did, as this would have seriously compromised the power of our study. Fourth, since our study population is comprised of only a subgroup of the patients operated in the eligibility period, there is a risk of selection bias. Nevertheless, there is no reason to assume that the association between mean arterial pressure during cardiopulmonary bypass and full-scale intelligence quotient score is any different between included patients and non-included patients. Lastly, very few events were registered on educational attainment, which makes it difficult to draw any specific conclusions with respect to these particular outcomes.

Conclusions

For surgical closure of an atrial septal defect or ventricular septal defect in infancy or early childhood, mean arterial pressure during cardiopulmonary bypass was not found to correlate linearly with intelligence quotient scores in adulthood. However, an inflection point may exist at which blood pressures below a specific value lead to impaired neurodevelopment. Large-scale, prospective studies are warranted in order to assess whether mean arterial pressure below a specific cut-off value predicts neurodevelopmental impairment.

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Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951121001414.

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Regional Committee on Biomedical Research Ethics of the Central Denmark Region.

References

1. Gaynor JW, Stopp C, Wypij D, et al. Neurodevelopmental outcomes after cardiac surgery in infancy. Pediatrics 2015; 135: 816–825.
2. Andropoulos DB, Ahmad HB, Haq T, et al. The association between brain injury, perioperative anesthetic exposure, and 12-month neurodevelopmental outcomes after neonatal cardiac surgery: a retrospective cohort study. Paediatr Anaest 2014; 24: 266–274.
3. Nyboe C, Udholm S, Larsen SH, et al. Risk of lifetime psychiatric morbidity in adults with atrial septal defect (from a Nation-Wide Cohort). Am J Cardiol 2020; 128: 1–6.
4. Holst LM, Kronborg JB, Idorn L, et al. Impact of congenital heart surgery on quality of life in children and adolescents with surgically corrected ventricular septal defect, tetralogy of fallot, and transposition of the great arteries. Cardiol Young 2019; 29: 1082–1087.
5. Nyboe C, Fonager K, Larsen ML, et al. Effect of atrial septal defect in adults on work participation (from a nation wide register-based follow-up study regarding work participation and use of permanent social security benefits). Am J Cardiol 2019; 124: 1775–1779.
6. Diaz LK, Gaynor JW, Koh SJ, et al. Increasing cumulative exposure to volatile anesthetic agents is associated with poorer neurodevelopmental

outcomes in children with hypoplastic left heart syndrome. Thorac Cardiovasc Surg 2016; 152: 482–489.
7. Gaynor JW, Stopp C, Wypij D, et al. Impact of operative and postoperative factors on neurodevelopmental outcomes after cardiac operations. Ann Thorac Surg 2016; 102: 843–849.
8. Gaynor JW, Wernovsky G, Jarvik GP, et al. Patient characteristics are important determinants of neurodevelopmental outcome at one year of age after neonatal and infant cardiac surgery. J Thorac Cardiovasc Surg 2007; 133: 1344–1353, 1353.e1341–1343.
9. Gaynor JW. The encephalopathy of congenital heart disease. J Thorac Cardiovasc Surg 2014; 148: 1790–1791.
10. Asschenfeldt B, Evald L, Heiberg J, et al. Neuropsychological status and structural brain imaging in adults with simple congenital heart defects closed in childhood. J Am Heart Assoc 2020; 9: e015843.
11. Maconochie IK, Bingham R, Eich C, et al. European resuscitation council guidelines for resuscitation 2015: section 6. Paediatric life support. Resuscitation 2015; 95: 223–248.
12. Hövels-Gürich HH, Seghaye MC, Schnitker R, et al. Long-term neurodevelopmental outcomes in school-aged children after neonatal arterial switch operation. J Thorac Cardiovasc Surg 2002; 124: 448–458.
13. Mahle WT. Neurologic and cognitive outcomes in children with congenital heart disease. Curr Opin Pediatr 2001; 13: 482–486.
14. Ballweg JA, Wernovsky G, Gaynor JW. Neurodevelopmental outcomes following congenital heart surgery. Pediatr Cardiol 2007; 28: 126–133.
15. Volpe JJ. Encephalopathy of congenital heart disease- destructive and developmental effects intertwined. J Pediatr 2014; 164: 962–965.
16. Donofrio MT, Duplessis AJ, Limperopoulos C. Impact of congenital heart disease on fetal brain development and injury. Curr Opin Pediatr 2011; 23: 502–511.
17. McQuillen PS, Goff DA, Licht DJ. Effects of congenital heart disease on brain development. Prog Pediatr Cardiol 2010; 29: 79–85.
18. Galli KK, Zimmerman RA, Jarvik GP, et al. Periventricular leukomalacia is common after neonatal cardiac surgery. J Thorac Cardiovasc Surg 2004; 127: 692–704.
19. du Plessis AJ. Mechanisms of brain injury during infant cardiac surgery. Semin Pediatr Neurol 1999; 6: 32–47.
20. Eichler A, Köhler-Jonas N, Stonawski V, et al. Child neurodevelopment and mental health after surgical ventricular septal defect repair: risk and protective factors. Dev Med Child Neurol 2019; 61: 152–160.
21. McCann ME, Schouten AN. Beyond survival; influences of blood pressure, cerebral perfusion and anesthesia on neurodevelopment. Paeditr Anaest 2014; 24: 68–73.
22. Kussman BD, Wypij D, Laussen PC, et al. Relationship of intraoperative cerebral oxygen saturation to neurodevelopmental outcome and brain magnetic resonance imaging at 1 year of age in infants undergoing biventricular repair. Circulation 2010; 122: 245–254.
23. Finucane E, Jooste E, Machovec KA. Neuromonitoring modalities in pediatric cardiac anesthesia: a review of the literature. J Cardiothorac Vasc Anesth 2020; 34: 3420–3428.

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