Cardiology in the Young

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Cognitive function in adults with Fontan palliation versus acyanotic CHD patients and association with health-related quality of life

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Original Article

Cite this article: Remmele J, Pringsheim M, Nagdyman N, Oberhoffer-Fritz R, and Ewert P (2023) Cognitive function in adults with Fontan palliation versus acyanotic CHD patients and association with health-related quality of life. *Cardiology in the Young* **33**: 1956–1961. doi: 10.1017/S1047951122003390

Received: 13 August 2022
Revised: 6 October 2022
Accepted: 13 October 2022
First published online: 25 November 2022

Keywords:
adult CHD; cognitive function; Fontan patients; health-related quality of life

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Abstract

Background: Impairments and developmental delay are often reported in infants and young children with CHD. However, currently, there is no data regarding cognitive abilities assessed by standardised intelligence tests in adults with CHD. This study assesses the cognitive function in Fontan patients compared with acyanotic CHD patients whether restrictions in cognitive function are present in adulthood and its association with health-related quality of life. *Methods:* Forty-four adult CHD (female n = 21 (47.7%); mean age 34.7 ± 11.9 years), 22 with Fontan circulation and 22 with acyanotic CHD, underwent the Wechsler Intelligence Scale for adults as patients during routine follow-up in 2018. The Medical Outcomes Study Questionnaire Short-Form 36 Health Survey (SF-36) assessed health-related quality of life. *Results:* Fontan patients showed significantly better results in the FSIQ (p = 0.020) and perceptual reasoning (p = 0.017) in comparison with patients with acyanotic CHD. All adult CHD patients showed normal IQ in subscales and full-scale IQ (FSIQ). In health-related quality of life, no association with cognitive function was found and no significant difference between both CHD groups, but trends to reduced values in acyanotic adult CHD. *Conclusions:* Interestingly, our study results in adult Fontan patients showed that it is possible to live an adult life with normal cognitive function and good health-related quality of life with a univentricular heart. Thus, this study could be a guidepost for more in-depth studies on cognitive function in Fontan survivors. In addition, the focus should be on health-related quality of life of adult CHD with simple CHD in particular, since a reduced health-related quality of life is not only medically based.

Introduction

During the last years, mortality in children and adolescents with CHD has rapidly decreased.[1,2] Life expectancy is increasing due to the significant advances in paediatric cardiology, cardiac surgery, and aftercare in the last decades.[3–5] For this growing adult congenital heart disease population, it is a question of how to prevent, reduce, or delay them in terms of comorbidities, as they are known to have a generally increased risk of morbidities, including neurologically acquired diagnoses in particular.[1] Regarding the close interaction of the heart and the brain focus shifts on the heart–brain axis as an important neurodevelopmental factor in the CHD population.[6] Some studies in neonates, infants, and children show structural brain abnormalities such as reduced brain volume, white matter, and grey matter lesions, and outer and inner liquor space enlargement.[7–12] All of these studies pointed out a significant association of these brain-related findings with developmental delay in young children with most of them having complex CHD.

That leads to the assumption patients with complex CHD do have lifelong problems due to their CHD. So far, most of the studies investigated children and fewer adolescents, which means right now there was not enough follow-up time for children with CHD to find out the relevance when they reach adulthood.

However, less is known about cognitive function assessed by standardised intelligence tests in adult CHD patients. Since cognitive function causes individual life perspectives and plans and their health-related quality of life,[13] this study aimed to assess and compare adult CHD patients with Fontan circulation and adult CHD patients with acyanotic CHD in terms of cognitive function and associations with health-related quality of life.

Patients and Methods

Study subjects

In 2018, patients with all kinds of CHD were routinely asked to complete an intelligence test and fill in the SF-36 questionnaire during their routine appointment at the German Heart Center Munich. Forty-four adult CHD patients (female n = 21 (47.7%); mean age at assessment 34.7 ± 11.9 years) were included in this subgroup analysis. Inclusion criteria were an age of at least 18 years and no interventional treatment or surgery during the past 6 months which potentially affects their cognition. Acyanotic CHD was defined based on the underlying leading CHD diagnosis,[14] and none of the included patients had already developed a cyanotic condition (e.g., Eisenmenger syndrome). The severity class of CHD was categorised as simple, moderate, and complex based on the American College of Cardiology (ACC) definition.[15] The variable cyanosis duration was defined from the day of birth to the day of completion of the Fontan circulation. The study was following the Declaration of Helsinki (revision 2013). Approval from the local ethics board was obtained (Project Number 350/18 S). Patients voluntarily agreed to participate and to the anonymous publication of their data by giving their written informed consent.

Cognitive function

Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV)[16] was administered to all patients. This worldwide established test was validated in 2013 for the German norm population of 1664 participants.[17] These national test norms serve the comparison in this study. It is the most commonly used test to assess cognitive function in adolescents and adults from 16 to 90 years. It includes 10 core subtests to calculate the Full-Scale Intelligence Quotient (FSIQ) with four specific domains of intelligence; Verbal Comprehension (VC), Perceptual Reasoning (PR), Processing Speed (PS), and Working Memory (WM) each of them also calculated into IQ points. In this test, impairment is defined as an intelligence quotient (IQ) achieved which is below more than one standard deviation (SD) of the norm (100 IQ points ± 1SD). The versions for children and adolescents have been frequently used in paediatric cardiology populations as well.[18]

Health-related quality of life (SF-36)

The Medical Outcomes Study Questionnaire Short-Form 36 Health Survey (SF-36) is a set, subdivided into eight sections (vitality, physical function, bodily pain, general health perceptions, physical role functioning, emotional role function, social role function, and mental health) of generic health-related quality-of-life measures.[19] Out of each section scaled scores with a range from 0 (negative health) to 100 (positive health) represent the weighted sums of the Likert-scaled questions. The SF-36 relies upon patient self-reporting within a 4-week window. It is quite well established in various health care sections to assess or monitor adult patient outcomes. The German version was validated by Bullinger and Kirchberger[19] and was deployed in this study. The SF-36 is used to evaluate individual patients' health status and monitor and compare disease burden with an acceptable internal consistency[20]; therefore, it is a worldwide used well-established questionnaire. It was used in this study as it was the most recent normal value for Germany taken from a 2013 survey.[21] The norm data were assigned to our participants according to age and sex.

Data analyses

Descriptive statistics were calculated in absolute and relative frequencies (%) for categorical variables, and means and SD for numerical variables. Shapiro–Wilk test was performed to prove normal distribution. The Student's t-test was used for group comparison as well as regression and correlation models to find associations between measurements and patients' data. The analysis was made with adjustments for age and sex. All analyses were performed using the software SPSS V.20 (SPSS Inc., Chicago, Illinois, United States of America) or R software V. 3.3.1. Pirate plots were used for visualisation of the data which represent the mean, confidence interval, raw data, and density distribution. The level of statistical significance was determined two-sided and with a p-value < 0.05.

Results

Both groups show the same number of patients with more male adult CHD (64%) in the Fontan group and more female adult CHD in the acyanotic group (59%). Most of the Fontan patients were palliated with total cavopulmonary connection with about 55% followed by the Fontan Björk procedure with about 34%. In four cases, the Fontan patients had the right ventricle as their systemic ventricle (Table 1).

Fontan-specific data on oxygen saturation, blood pressure, and body composition at the date of the test are given in Table 2. Additionally, detailed information on the underlying cardiac diagnosis in Fontan patients is in Table 3.

All adult CHD patients showed normal IQ scores in subscales and full-scale score. Fontan patients showed significantly better results in the full-scale IQ as well as in subscale perceptual reasoning in comparison with patients with acyanotic CHD. Figure 1 shows the IQ results of the subscales of both groups.

The significant difference between groups in FSIQ is shown in Figure 2 by pirate plots serving detailed information on the results of each group. There were no significant associations found in terms of sex differences, number of surgeries or catheter interventions, or cyanosis duration with the IQ score.

In terms of health-related quality of life, no significant difference was found between both CHD groups, but partly obviously trends to reduced values in the acyanotic CHD group (Fig 3). Furthermore, no significant association between IQ scores and health-related quality of life was found.

Discussion

Cognitive function

Since there is a close connection of an abnormal cognitive function with overall quality of life, employment opportunities as well as educational attainments, it is important to follow this in patients with CHD into adulthood.[13] Neonates and infants are most often reported with neurodevelopmental delays, especially in patients with complex CHD.[22–25] Hypoxaemia during pregnancy, perioperative as well as postoperative, haemodynamic changes, and early surgeries are related to adverse effects on brain development and neurodevelopment.[26] For example, because of the enormous advantages in medicine and surgical procedures, surgeries with cardiopulmonary bypass have become a widespread, low-risk standard procedure; in Germany alone, around 3852 children (newborns up to the age <18 years) underwent heart surgery with cardiopulmonary bypass in 2019.[27] In addition to the benefits,

https://doi.org/10.1017/S1047951122003390 Published online by Cambridge University Press

Table 1. Group characteristics.

Variables	Fontan patients n = 22	Acyanotic CHD patients n = 22
Age (years)	32.9 ± 9.3	36.5 ± 14.1
Sex	8 ♀ / 14 ♂ (36.4% / 63.6%)	13 ♀ / 9 ♂ (59.1% / 40.9%)
Fontan type/CHD type	7 Björk (33.8%) 2 Linz (9.1%) 12 TCPC (54.5%) 1 Modified Fontan (4.5%)	7 atrial septum defects (31.8%) 3 aortic valve stenosis (13.6%) 3 coarctation of the aorta (13.6%) 2 ventricular septum defects (9.1%) 2 EBS (9.1%) 5 Other (22.7%)
Systemic ventricle	18 left ventricle (81.9%) 4 right ventricle (18.1%)	22 left ventricle (100%)
TCPC type	Extra cardiac tunnel (58.3%) Intra atrial tunnel (25%) Atrial fenestration (16.7%)	
Cyanosis duration (month)	99.4 ± 73.1	
Surgeries	3.55 ± 2.1	1.10 ± 1.3
catheter intervention	1.86 ± 1.4	0.75 ± 0.8
Age at first intervention (years)*	2.1 ± 3.7	21.1 ± 22.4

*Surgery or catheter intervention.
Cn = number; TCPC = total cavopulmonary connection; EBS = Ebstein's anomaly

Table 2. Fontan patients.

Fontan type	Age at first surgery (years)	Age at Fontan completion (years)	Oxygen saturation	RRsys (mmHg)	RRdia (mmHg)	Hight (cm)	Weight (kg)	BMI
Linz	8.9 ± 10.9	12.3 ± 6.1	92.0 ± 0	123.0 ± 0	71.5 ± 3.5	166.5 ± 0.7	67.5 ± 6.4	24.4 ± 2.5
Björk	1.7 ± 1.7	8.5 ± 6.2	94.0 ± 1.5	121.6 ± 12.0	67.9 ± 7.4	172 ± 11.4	67.4 ± 15.7	22.6 ± 4.2
TCPC l	0.7 ± 1.7	7.0 ± 8.0	94.1 ± 3.0	123.9 ± 13.1	68.8 ± 10.0	174.3 ± 10.7	70.3 ± 11.1	23.0 ± 1.8
TCPC r	3.0 ± 2.5	9.6 ± 1.3	91.8 ± 1.3	126.8 ± 3.2	78.3 ± 7.4	177.8 ± 10.6	86.8 ± 15.8	28.2 ± 8.8
Mod Fontan (n = 1)	0.2	4.9	94%	142	78	168	113	40.4

RRsys = Riva-Rocci systolic blood pressure; RRdia = Riva-Rocci diastolic blood pressure; BMI = body mass index; TCPC l = total cavopulmonary connection with left systemic ventricle; TCPC r = total cavopulmonary connection with right systemic ventricle.

Table 3. Detailed cardiac diagnosis in Fontan patients.

Cardiac diagnosis in Fontan patients	Number of patients
Dysbalanced atrioventricular septal defect	2 (9.1%)
Double-inlet left ventricle	5 (22.7%)
Tricuspid atresia	11 (50%)
Double-inlet left ventricle, L-TGA	1 (4.6%)
Hypoplastic left ventricle	1 (4.6%)
TGA, hypoplastic right ventricle	1 (4.6%)
TGA, severe sub- and valvular pulmonary stenosis	1 (4.6%)

TGA = transposition of the great arteries; L-TGA = corrected transposition of the great arteries.

however, there are also side effects that can affect the lungs, kidneys, liver, or brain. Studies from the early 2000s reported neurological deficits in up to 80% of adults after heart surgery with cardiopulmonary bypass.[28–31] This does not seem to apply to children with CHD, Gunn et al. investigated the neurodevelopmental status after early heart surgery of 130 children at the age of 2 years in a direct comparison of CHD surgery with cardiopulmonary bypass and surgery without cardiopulmonary bypass. They found no significant differences in terms of the cardiopulmonary bypass use or aortic clamp on its own but reported repeated surgeries as a high-risk factor for neurodevelopment impairments.[32] In our study, number of surgeries or interventions did not show a relation with cognitive function in adulthood. Our study population of adult CHD patients showed no impairment in cognitive function compared with the german norms. Interestingly, Fontan patients had partly significant higher scores than patients with acyanotic CHD, although the control group had the first intervention or surgery at a significantly later time, that is, after the critical developmental age. Our results are not in line with other studies, but since most of them focus on younger CHD patients it is hardly comparable. Based on advances, different technics came to use to get an improved knowledge of the developing brain and its relations to CHD. More recent studies focus on neurodevelopmental outcomes combined with brain imaging using MRI to identify differences that can explain the neurodevelopmental delay in neonates and young CHD patients. They reported a high incidence of white

https://doi.org/10.1017/S1047951122003390 Published online by Cambridge University Press

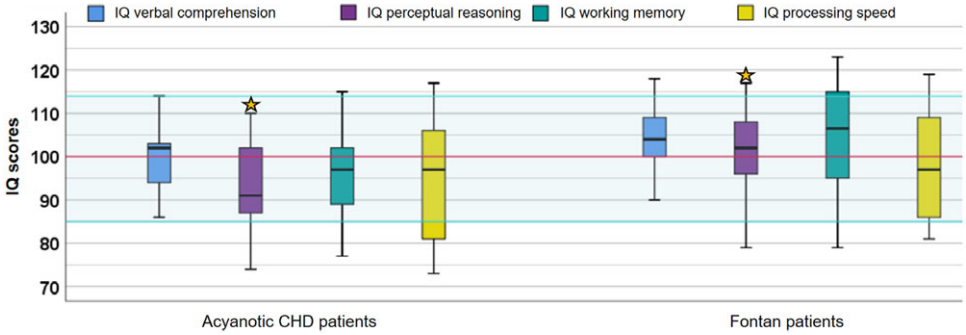

Figure 1. Subscale scores of the Wechsler Intelligence Test. IQ: Intelligence quotient; * significant difference between the groups with a level of significance $p < 0.05$.

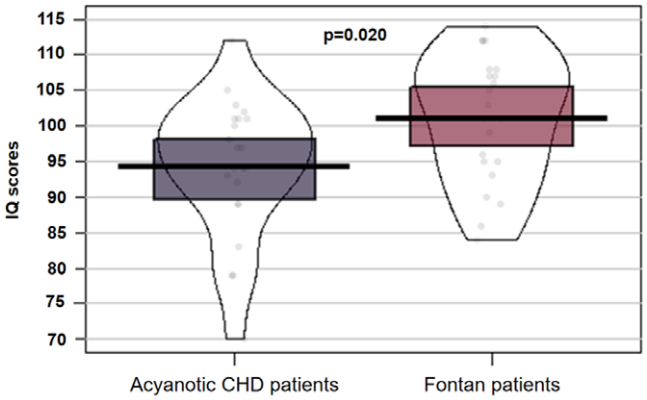

Figure 2. The FSIQ in comparison depicted with pirate plots. IQ: Intelligence quotient; level of significance $p < 0.05$.

matter lesions.[9,33–36] Additionally, Claessens et al. reported impaired cortical volume and brain gyrification in patients with univentricular heart circulation and white matter development resembling premature birth[10,37] changes that can predict developmental problems. Most of the studies in adolescents with CHD reported on executive function problems with reduced working memory and additionally, Fontes et al. on volume changes of the hippocampus with a structure–function relation of hippocampal subfields in this context in adolescents with complex CHD.[38] In another study, functional MRI was used which brought out a reduced prefrontal inhibition in patients with CHD compared to a healthy control group and a correlation with executive functioning.[39] However, besides all these advanced findings resulting from technical possibilities, it remains unclear what this means for our growing group of adult CHD. It remains unclear what impact the differences/abnormalities found will ultimately have on the function of the mature brain in adult CHD, due to the enormous neuroplasticity of the developing child's brain.[40]

In our study cohort, there was no impairment in cognitive function, and one reason might be that none of the patients in this study had been diagnosed with neuro events like ischaemic stroke. Of course, that does not mean they do not exist but it seems the brain found adaption mechanisms to enable normal cognitive function. It would be most interesting to do MRI with our Fontan cohort to find out whether there are still existing changes or undiagnosed lesions. On the one hand, it can be discussed whether MRI findings in neonates and young children with CHD present some kind of pathophysiology due to less oxygen or changes in the blood flow. For example, reported in the literature is liquor space enlargements associated with neurodevelopmental delay,[7,8] which may be due to a higher rate of ultrafiltration in the brain to prevent oxygen deficiency in the growing brain. On the other hand, a recently published work by Ehlert et al. reported reduced fractional anisotropy of the brain in both patients with cyanotic CHD and with acyanotic CHD as well in comparison with healthy controls in adolescents, especially in the frontal lobe which is associated with working memory.[41] It would be interesting if these changes of the brain still exist in older ages of our adult survivors or what kind of adaption mechanism leads the brain to normal function. MRI studies on adult CHD survivors may promise an improvement in understanding brain adaptions due to the underlying CHD.

Health-related quality of life

The adult CHD patients of both groups showed normal to good self-reported health-related quality of life measured with the SF-36 in this study without significant differences between both groups. This is in line with a recent study reporting on a large cohort of about 4000 patients with all kinds of adult CHD.[42] They also pointed out that health-related quality of life is not dependent on the complexity of the underlying CHD. With a closer look at the descriptive data (Fig 3), there were differences, without statistical significance but of interest, in the dimensions of physical role functioning, physical function, and bodily pain with worse results in patients with simple to moderate CHD, especially in comparison with normal data. Since patients with complex CHD usually have to be treated surgically postnatally and are now more often diagnosed during pregnancy than in previous decades, families have time to cope with the diagnosis. Furthermore, the need for repeated surgeries in the case of Fotan patients leads to those patients having to live with CHD from the beginning. They had to find coping strategies within their family as well as for their own, which leads to a higher sense of coherence with more mindfulness.[43] In a recently published study, Moons et al. reported on the positive association of sense of coherence with QoL in a large study with 15 enrolled countries and concluded strategies to improve SOC may improve QoL.[44] However, the enhanced sense of coherence develops during childhood through the successful application of generalised resistance resources.[45] This implies that when patients experience new, life-altering situations due to CHD later in life, we need to accompany them to help them develop their coping strategies and improve their health-related quality of life. Further studies on adult CHD patients, especially those underinvestigated with a simple CHD, should be invited to get more knowledge about their needs and worries since they do not have regular appointments like patients with moderate or complex CHD. Once this has been done, the next step is to develop

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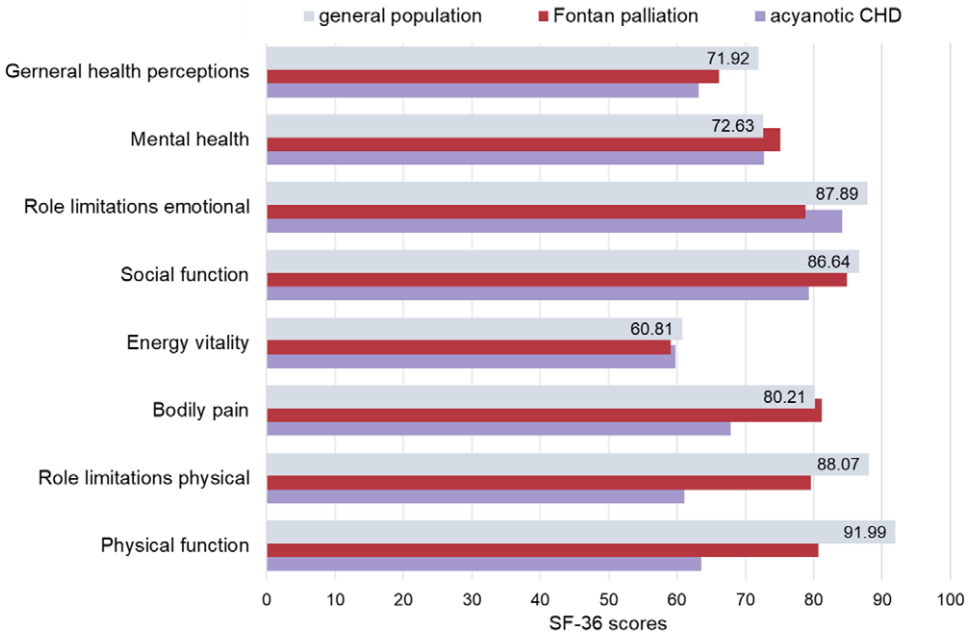

Figure 3. HrQoL scores in comparison.

programmes that support and strengthen patients in dealing with their CHD.

Conclusion

This study in adult Fontan patients showed that it is possible to live an adult life with normal cognitive function and good health-related quality of life with a univentricular heart. Thus, this study could be a guidepost for more in-depth studies on cognitive function in Fontan survivors. Since these results are not in line with other studies on Fontan patients at younger ages, further studies are needed on older Fontan survivors or long-term studies that follow the newborn patients into older ages. Additionally, various newer MRI or functional MRI techniques should be increasingly used in studies in adult CHD to understand the adaptive mechanisms that take place to allow the brain to function and to compare them with neonatal findings.

In addition, the focus should be on health-related quality of life of adult CHD with simple CHD in particular, since a reduced health-related quality of life is not only medically based. However, when the acyanotic group was compared with the norm values, the results were partly significant worse in the acyanotic CHD group, which necessitates further studies on the health-related quality of life of patients with acyanotic CHD.

Limitations

The significant differences between both groups must be interpreted with caution, since both groups showed normal results within the frame of normative data. The evaluation of the detailed surgery data is not feasible as complete data are not available for all patients, since not all of the surgeries were performed at the same hospital or in the same country. In addition, this is a single-centre experience; even though the sample size is small, it is a considerable sample of Fontan patients at this age.

Ethics and dissemination. Approval from the local ethics board of the Technical University of Munich was obtained (Project Number 350/18 S). The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding. No funding.

Contributors. Conception and design: JR, NN, and MP
Administrative support: ROF and PE
Provision of study materials or patients: JR, NN, and MP
Collection and assembly of data: JR, NN, and MP
Data analysis and interpretation: JR
Manuscript writing: All authors
Final approval of manuscript: All authors

Declaration of Conflicting Interests. The authors have no conflicts of interest to declare.

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https://doi.org/10.1017/S1047951122003390 Published online by Cambridge University Press