

# The neurodevelopmental and mental health outcomes in children with single ventricle physiology and Fontan circulation: a state-of-the-art review and future directions

Enrico Piccinelli<sup>1,2</sup>, Gianfranco Butera<sup>1</sup>, Mara Pilati<sup>1</sup>, Micol Rebonato<sup>1</sup>, Roberto Formigari<sup>1</sup>, Marin Verrengia<sup>1</sup>, Alberto Testa<sup>1</sup>, Gianluigi Perri<sup>1</sup>, Umberto Morbiducci<sup>2</sup>, Marco Deriu<sup>2</sup> and Lorenzo Galletti<sup>1</sup>

<sup>1</sup> Paediatric Cardiology Department, Ospedale Pediatrico Bambino Gesù, Roma, Italy

<sup>2</sup> PolitoBIOMed Lab, Department of Mechanical and Aerospace Engineering, Politecnico di Torino, Italy

## Abstract

The survival of patients with single ventricle circulation undergoing Fontan operation has significantly improved in the last decades. However, the neurodevelopmental outcome of these patients is still not satisfying and far below the healthy controls. The aetiology of neurodevelopment disability and mental health disorders is multifactorial and has a cumulative and synergic trend over the years. Genetic factors, abnormal fetal circulation, peri and intra-operative care, multiple hospitalizations and socioeconomic status play a crucial role in this process. Due to the heterogeneity of anatomies and different treatment possibilities there is a need for a personalized, multidisciplinary and translational approach focused on the patient. The introduction of new technologies driven by artificial intelligence and the continuous integration of in vivo data and biomedical simulations into medicine promises significant improvements in pathologies diagnosis and treatment thus enhancing the quality of life of patients and their families.

## Keywords

Neurodevelopmental outcomes, Single ventricle physiology, Fontan circulation, Future directions, Bioengineering

## 1. Introduction

The Fontan procedure is the final stage of three operations performed to palliate children born with single ventricle physiology. In these patients, due to the complex heart anatomy it is impossible to repair the heart re-creating the physiologic biventricular circulation. The original operation was described in 1968 by Francis Fontan in patients with tricuspid atresia [1]. Various modifications have been developed in the following decades and the extracardiac total cavo-pulmonary connection (TCPC), is now the most widely used [2]. In this operation, the systemic venous blood coming from the inferior vena cava (IVC) is diverted through an extracardiac conduit connecting to the pulmonary arteries (PAs), completing the previous performed Glenn connection of the superior vena cava (SVC) to the PAs. In recent years, the survival of patients with single ventricle circulation has significantly improved due to the advancements in fetal diagnosis, perioperative management and medical care [3,4]. Therefore, all the efforts are focused on reducing the long-term morbidity and improving quality of life and neuropsychological outcomes [5,6,7,8]. The literature regarding the neurodevelopmental outcomes in children with single ventricle physiology is redundant and often controversial and no large randomized trials have been conducted. For this reason, we aim to provide a state-of-the-art review of the neurodevelopment and mental health outcomes of children with single ventricle physiology undergoing Fontan operation in the modern era and to give insight into future directions and tools for neurodevelopment impairment prediction, including artificial intelligence (AI).

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\*Corresponding author.

email: dottor.piccinelli@gmail.com (E. Piccinelli); gianfranco.butera@opbg.net (G. Butera); marco.deri@polito.it (M. Deriu); lorenzo.galletti@opbg.net (L. Galletti)

orcid: 0000-0001-6987-2745 (E. Piccinelli)



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## 2. Material and methods

Relevant studies were identified by PubMed, Embase and Cochrane. No language restrictions were used. The first search from PubMed, Embase and Cochrane was performed by the first author of this review and double-checked by the other corresponding authors. The following keywords were used: (neurodevelopment outcome OR mental health OR neurodevelopment disability OR artificial intelligence OR computational models) AND (congenital heart disease OR single ventricle OR hypoplastic left heart syndrome OR Fontan circulation). We included only papers from January 2000 up to August 2022. Older papers were excluded, with the exceptions of papers explaining concepts, surgical techniques or to compare the neurodevelopment outcome early after the introduction of the Fontan operation.

## 3. Etiology and risk factors of neurodevelopmental disability

The aetiology of neurodevelopmental disability in patients with single ventricle physiology is multifactorial and has a cumulative and synergic trend over the years. In many patients with congenital heart disease (CHD) there is a predisposition to extracardiac and brain congenital anomalies [9]. Indeed, an exome sequencing of 1213 CHD parent-offspring trios identified shared genetic contributions to CHD and neurodevelopmental disabilities [10]. Moreover, the abnormal fetal circulation typical of univentricular physiologies is often related to brain dismaturation. Fetuses with hypoplastic left heart syndrome (HLHS) have altered cerebral perfusion and oxygenation due to intracardiac mixing and the retrograde brain perfusion through the ductus arteriosus and the hypoplastic aorta. This abnormal perfusion has a dramatic effect on brain growth and maturation. In fact, even term infants with HLHS have smaller and less mature brains than controls [11]. Fetal brain magnetic resonance imaging (MRI) of patients with CHD at 25–35 weeks of gestation demonstrated significantly lower maturation scores compared to healthy controls. In particular germinal matrix, myelination and superior temporal sulcus scores were significantly delayed in this population [12]. Moreover, a comprehensive neuropathologic evaluation of 11 electively aborted HLHS fetuses revealed chronic diffuse white matter injury (WMI) [13]. This brain dysmaturity represents the substrate for further brain injuries during and after surgery. Stegeman et al. described the pre- and post-operative spectrum of brain MRI of patients with critical CHD, including patients with HLHS. Interestingly, 348 MRI scans confirmed that the most affected area involved before and after surgery is the white matter in 25% and 30% of infants, respectively. They also noted that 6% of these patients presented with arterial ischemic stroke even before surgery. Finally, not only thrombotic lesions were reported but also hemorrhagic injuries especially intraparenchymal cerebral haemorrhage, cerebellar haemorrhage, intraventricular haemorrhage and subdural haemorrhage [14]. Interestingly, this punctate WMI typical of patients with CHD, share a similar injury pattern to preterm infants [15]. Guo et al. analysed 216 term-born CHD neonates and WMI was identified in 86 of them [16]. The comparison between WMI and preterm neonates highlighted that WMI in patients with CHD has a specific topology with a preference for anterior and posterior lesions. Indeed, the central areas are less vulnerable in comparison to the preterm neonates, reflecting the expected maturation of pre-oligodendrocytes [16]. Despite the improvements in surgical techniques and post-operative intensive care, deep hypothermic circulatory arrest (DHCA) negatively impacts on the neurologic outcome. In many centers, regional low-flow cerebral perfusion (RLFP) is used instead of DHCA to reduce the time of cerebral ischemia. A recent study comparing brain MRI before and after Norwood operation highlighted the presence of new or worsened ischemic lesions in 73% of infants, especially periventricular leukomalacia and focal ischemic lesions [17]. Furthermore, a randomized, controlled trial comparing new cerebral injuries on MRI after surgery using DHCA or antegrade cerebral perfusion in neonates with complex aortic arch obstructions including HLHS showed no significant difference between these techniques [18]. When analyzing early neurodevelopmental outcomes after cardiac surgery, these operative factors may be even less important than pre- and post-operative factors such as longer postoperative stay in intensive care, which are associated with lower psychomotor and mental development index [19]. Also socioeconomic status (SES) should be accounted for, because it emerged that children with single ventricle physiology and lower SES have reduced functional status and fine motor, problem-solving, adaptive behaviour and communication skills at the age of 6 years in comparison to patients with higher SES [20]. Finally, these children usually experience multiple

hospitalizations, catheterization and eventually further surgeries. Every additional procedure increases the risk of brain injuries due to anaesthesia, cardiac bypass and cardiac thromboembolism. These patients are naturally predisposed to thromboembolic events and stroke due to liver dysfunction or protein-losing enteropathy, which plays a role in the coagulation-fibrinolysis balance [21]. The common findings of high haematocrit and pro-inflammatory status also increase the thromboembolic risk. Finally, the blood mix and direct venous-arterial connection through interatrial communication, single ventricle and Fontan fenestration in the different stages raise the risk of stroke [22].

#### **4. Neurodevelopmental outcomes in Childhood**

In the last decades, the neurodevelopmental outcome of children with single ventricle physiology has improved. However, despite substantial progress in care, this population still presents with cognitive, motor, social and psychological deficits. In the late '80s around 64% of patients with HLHS presented major developmental disabilities at some point in their stage-palliation [23]. More recent studies and reviews bring different and controversial results [24]. Goldberg et al. assessed the neurodevelopmental outcome of 51 preschool children with HLHS and other single ventricle physiologies palliated with the Fontan procedure, reporting no significant difference in Wechsler Intelligence scale from the healthy population [25]. On the contrary, a recent nationwide Finnish prospective study of 23 patients with HLHS, 13 with other univentricular physiology, and 40 healthy controls followed until 5 years old demonstrated a significantly lower median full-scale IQ at preschool age, in the first two groups in comparison to the healthy controls. This study also confirmed a high rate of brain MRI abnormalities, mainly ischemic in 82% of the patients with HLHS and in 56% of children with other single ventricle anatomies [26]. When a broad range of neuropsychological outcome variables was extended from children to young adults with single ventricle physiology, they scored significantly lower compared to the general population. Indeed, they obtained lower intelligence test scores, decreased motor function, impaired visuospatial abilities and more marked behavioral disorders [27]. Promising data are coming from the recent introduction of hybrid approaches for initial palliation of HLHS, that has shown more favourable neurodevelopment outcomes and quality of life at 2–3 years of age, with cognitive, language and motor composite scores on the Bayley-III not significantly different from healthy peers [28].

Interestingly, when compared to preschool children with CHD undergoing biventricular repair, patients with single ventricle following the Fontan pathway presented with similar neurodevelopmental outcomes and full-scale IQ. However, the Fontan group performed worse in terms of processing speed, attention, and impulsivity [29]. Even more controversial is the sub-analysis of the HLHS group versus other functional single ventricle anatomies. According to Goldberg et al. the HLHS group had significantly lower Wechsler Intelligence scores than the non-HLHS group but no significant difference in the behavioural scores [25], while Gaynor et al. found no significant difference in the neurodevelopmental outcomes among the two groups [29].

Finally, a studies focusing on specific neurocognitive aspects,, analysing the deficits in visual-perceptive skills and executive function highlighted that the Fontan group didn't differ significantly from the control group for the Test of Visual-Perceptual Skills summary but had worse results on all scales of both the copy and immediate recall trials of the Rey–Osterrieth Complex Figure [30,31]. Regarding the executive function, patients with single ventricle physiology displayed deficits in flexibility and problem-solving [31].

#### **5. Mental health and psychiatric disorders**

Children and adolescents with CHD have a higher risk of developing mental health disorders due to multiple hospitalizations and interventions, stressful life events, social and cultural factors [32-34]. A recent large comparative cross-sectional study from the Texas Children's Hospital including 1164 patients with CHD from 4 to 17 years old highlighted that 18.2% of this population had a diagnosis or medication for anxiety or depression, significantly higher than healthy peers. In particular children with complex single ventricle hearts had around 7 times higher odds of developing anxiety and/or depression [35]. DeMaso et al. from Boston Children's Hospital confirmed that adolescents with single ventricle CHD who underwent the Fontan procedure have higher odds to receive a psychiatric diagnosis compared with healthy peers (65% vs. 22%). Specifically, they presented with increased risk of anxiety disorders and Attention deficit hyperactivity disorder (ADHD) [36]. The same group also highlighted that early-term-born adolescents with single

ventricle anatomy (born between 37 and 38 weeks gestation) were more likely to develop ADHD during their life when compared to full-term birth peers with the same physiology [37]. Depressive symptoms are also common in patients with single ventricle physiology, as shown by Pike et al. who correlated this condition to signs of chronic injury at MRI in specific brain areas controlling cognition, anxiety, and depression [38].

However, despite all the neurodevelopmental and psychiatric issues and the multiple operations and interventions, the quality of life (QoL) of these patients is self-perceived normal, even when compared to healthy controls [39,40]. Similar conclusions come from a more recent study highlighting that a higher level of education and full-time occupation positively influences patients' quality of life [41].

## 6. Biomedical technologies and future directions

Considering the anatomical inter-variability and the plethora of possible treatment strategies for patients with single ventricle physiology, the way forward to obtain better outcomes and longer life expectancy is a multidisciplinary and integrated approach tailored on the single patient: personalised surgical approach as well as ad-hoc peri and post-operative care, combined with affordable short and long-term prediction tools is the future challenge. A translational approach, combining biomedical engineering methodologies and advanced imaging technologies may address this topic, improving the surgical results and the neurodevelopmental outcomes. In this regard, Computational Fluid Dynamics (CFD) to simulate the hemodynamics in patients with single ventricle physiology models has been already applied successfully e.g. to predict the best surgical solution in the different palliation stages [42-46]. More in detail, CFD was largely adopted to assess the flow efficiency of the systemic-pulmonary shunt, at the ventricular and neo-aortic level and in the Fontan circulation quantifying energy losses and how the latter correlate with the clinical outcome. The capability of exploring different hemodynamic scenarios adopting patient-specific computational models where virtual surgical connections can be pre-operatively tested can be extremely useful for surgical and clinical decision-making. The availability of *in silico* but also *in vitro* models of possible surgical options supports the identification of the best surgical pathway, stressing the differences in the local hemodynamics, e.g. analyzing the impact that competitive flows might have in terms of energetics of the system. For instance, in Norwood I operation, a model-based approach may support the patient-specific selection between the two most commonly used shunts: the Blalock-Taussig shunt and the Sano shunt. In fact, different variables contribute to the performance of these shunts, e.g. their size, length and positions, affecting the fine balance between systemic and pulmonary blood flow [47,48]. This is an important issue among surgeons and paediatric cardiologists as there is still debate about performing one or the other shunt considering that the transplantation-free survival at 12 months is significantly better with the Sano shunt but there is no significant difference after one year between the two groups [49,50].

Moreover, biomedical simulations may predict the possibility of thrombus formation in the Fontan circulation eventually responsible for stroke in case of conduit fenestration [51]. The analysis of the different flow conditions, flow stagnation and graft size may anticipate the need for more strict anticoagulation to avoid cerebral accidents. The advantage of these technologies is not only in terms of optimization and personalization of treatment for these patients but will also allow a better resource distribution that can be invested in other aspects of their complex care.

On the other side, a strict follow-up of these patients would guarantee the prompt recognition of neurocognitive impairment and mental health disorders, allowing the early start of the neurodevelopmental interventions and psychological and educational support [52]. Numerous tools to improve executive function have been proposed for patients with ADHD and children with learning disabilities, with promising results [53,54]. Nevertheless, there is insufficient experience in the field of CHD. A preliminary experience with the Cogged intervention, consisting of home-based 45-minutes training sessions for 5-8 weeks, demonstrated to improve the self-regulatory control abilities of adolescents with CHD, but with no effects on other executive functions or behavioral outcomes [55].

Finally, AI is expanding in the medical field, and in CHD as well. From the viewpoint of the clinician, artificial intelligence can be seen as a diagnostic and therapeutic technology that enabling the analysis of very large pools of data, allows the discovery of patterns not immediately obvious [56]. Among the AI applications of specific interest here we mention its integration with fetal echocardiography for the extraction of undiscovered image features, a promising approach which can markedly improve image acquisition and optimization, automated measurements, classification of diagnoses etc [57]. This is of relevance because prenatal diagnosis of CHD is crucial in parents' decision-making regarding the

continuation of pregnancy, based on the consolidated knowledge that neonates with postnatally diagnosed CHD have increased mortality and worse neurodevelopment outcomes before and after surgery [58-60]. Within AI, machine learning models can be as important in predicting the adverse outcomes for congenital heart surgery as in improving social interaction and supportive education in patients with worse neurodevelopmental outcome after surgery [61,62].

## 7. Conclusion

More than 50 years after the introduction of the Fontan procedure, surgical and perioperative care developments have improved medium and long-term survival of patients with single ventricle physiology. Nevertheless, the neurodevelopmental and mental health outcome is still not satisfying, despite a clear understanding of potential risk factors. The way forward is a personalized, multidisciplinary and translational approach with the integration of imaging technologies with biomedical simulations (such as the already employed CFD models) and AI (applied e.g. for image segmentation, geometry sampling and even generation of synthetic data). It is expected that such a multidisciplinary framework will lead to a significant improvement in the objective quality of life of these patients and their families.

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