

## Cardiovascular Risk Factors in Children and Adolescents with Fontan Circulation

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### Abstract

**Background:** Long-term outcomes of patients with Fontan circulation are uncertain regarding the prevalence and role of risk factors (RFs) such as increased body mass index (BMI), arterial hypertension, and hypercholesterolemia.

**Objectives:** To describe the prevalence of RFs in patients with univentricular heart, with variable follow-up times.

**Methods:** This mixed cohort study was performed with 66 patients, who underwent blood count, fasting blood glucose, C-reactive protein (CRP), and lipid profile tests; systolic/diastolic blood pressure (SBP/DBP) measurements; and anthropometric and sociodemographic data collection. Cardiovascular RFs among first-degree relatives and physical activity habits were also assessed. Prevalence was described using proportions, with a 95% confidence interval. Continuous variables (height, weight, age, SBP, DBP) were described as means and standard deviations (m±SD). Associations between RFs were assessed using chi-squared or Fisher's exact tests. Spearman's correlation was used for analyzing CRP and the presence of 2 or more RFs. The Shapiro-Wilk test was used to check for data normality. Statistical significance considered  $p < 0.05$ .

**Results:** In our population, 19.7% were overweight, mean SBP was  $89.44 \pm 37.4$ , and mean DBP was  $60.0 \pm 26.08$ . The most prevalent diseases in the interviewees' families were systemic arterial hypertension (30.3%), obesity (16.7%), and 2 or more cardiovascular RFs among first-degree relatives (13.8%). We observed a trend towards significance between the presence of 2 familial RFs and overweight, as well as a risk profile for cardiovascular disease. There was an association between the BMI percentile, the presence of 2 or more RFs ( $p < 0.05$ ), and CRP ( $p < 0.01$ ).

**Conclusions:** Overweight is common in patients with univentricular heart, being related to more than 2 cardiovascular RFs among first-degree relatives; physical inactivity and changes in lipid profiles are also frequent.

**Keywords:** Child, Adolescent; Fontan Procedure/methods; Cardiovascular Diseases; Heart Defects, Congenital/surgery; Risk Factors; Obesity; Physical Inactivity.

### Introduction

Univentricular heart, also known as functionally single ventricle, is a complex group of heterogeneous congenital heart defects, comprising multiple pathological subtypes. This may occur either with ventricular hypoplasia, double-inlet atrioventricular connections, or mitral or tricuspid valve atresia. Surgical

correction is represented by the Fontan procedure, which is used to bypass the ventricular mass. When unsuccessful, cardiac transplant is an alternative.<sup>1</sup>

Previous studies have shown that obesity is associated with symptomatic heart failure and mortality in patients with Fontan palliation.<sup>2</sup> The prevalence of overweight and obesity increases with the age of patients undergoing Fontan conversion, with

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36% being overweight and 14% being obese after the age of 30 years.<sup>3</sup>

Nevertheless, the available data on the prevalence and role of risk factors (RFs) such as increased body mass index (BMI), arterial hypertension, and hypercholesterolemia with regard to long-term outcomes are insufficient. Additional studies are needed to determine factors causing geographic and racial differences in outcomes.

Therefore, the aim of this report is to describe the prevalence of major RFs in patients with univentricular heart.

## Methods

Four hundred and forty-one patients with congenital heart disease were recruited to participate in this mixed cohort study that occurred between September 2010 and March 2016. They were aged between 2 and 18 years and had been attending the Pediatric Cardiology Unit of a reference center in southern Brazil.

This group of patients attended regular follow-up visits based on the severity of each patient's illness. The follow-ups were conducted by the unit's pediatric cardiologist. All the information obtained with the applied questionnaires was further recorded in a database.

Out of this group, 66 patients with univentricular heart who attended the follow-ups consistently were selected to participate in this study. Exclusion criteria consisted of genetic syndromes, conditions that precluded the patients from providing an anthropometric measurement (such as patients in wheelchairs or with underdeveloped limbs), and unwillingness to participate.

The unit's schedule was revised weekly to select patients who met the criteria and had appointments with the doctor on that specific week. The patient and their legal guardian were then contacted by telephone and were invited to take part on the study on the day the appointment had been set. Those who agreed to participate were required to fast for at least 12 hours before the appointment for laboratory tests. If telephone contact failed, patients were still offered to participate right before the doctor's appointment and the laboratory exams were postponed.

Written informed consent was obtained from all participants and legal guardians after they had been explained the process. A fasting venous blood sample was then drawn for laboratory testing, which included

blood count, glucose, lipid profile, and C-reactive protein (CRP) tests. In addition, anthropometric measurements, blood pressure (BP), sociodemographic factors, physical activity habits, family history, and the presence of RFs among first-degree relatives (diabetes, systemic arterial hypertension [SAH], obesity, and dyslipidemia) were investigated.

The nutritional state of patients was evaluated through the BMI, which was calculated and classified using the World Health Organization (WHO) Anthro and Anthro Plus software. The WHO 2006/2007 BMI cut-off criteria were: overweight (> 85<sup>th</sup> percentile and < 97<sup>th</sup> percentile) and obesity (> 97<sup>th</sup> percentile).<sup>4</sup>

BP was measured with properly calibrated aneroid sphygmomanometers that could measure up to 300mmHg. These values were analyzed according to the Report of the Second Task Force on Blood Pressure Control in Children.<sup>5</sup>

The patient's level of physical activity was assessed through the International Physical Activity Questionnaire (IPAC) in its short version, which had been previously validated and culturally adapted to the Brazilian reality. The self-administered questionnaire was filled in during the doctor's appointment. IPAC scores were then calculated, and individuals were classified as: very active, active, irregularly active, and sedentary.<sup>6</sup>

Blood samples were collected through a peripheral venous puncture after 12 hours of fasting. Blood serum was separated after the blood was centrifuged. Serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were analyzed by enzymatic methods in an automatic analyzer (Selectra E, Vital Scientific, USA). The reagent kits and protocols used for the enzymatic methods were in accordance with the operating instructions manual. Serum CRP levels were determined by nephelometry using a Behring Nephelometer 100 Analyzer (Dade Behring, USA). Blood samples collected with ethylenediaminetetraacetic acid (EDTA) were used for determining hematocrit and hemoglobin levels using an automatic analyzer (Coulter Act, Coulter, USA).

Reference ranges for the laboratory tests were in accordance with Brazilian (2005) and American (2011) guidelines for the reduction of cardiovascular risk in children: total cholesterol > 170mg/dl; LDL cholesterol > 110mg/dl; HDL cholesterol < 45mg/dl; triglycerides > 75mg/dl (2 to 9 years old) or > 90mg/dl (10 to 18 years old); fasting plasma glucose > 100mg/dl; CRP > 0.3mg/dl; hematocrit (HCT) < 35%; hemoglobin (HGB) < 11g/dl;

systolic blood pressure (SBP) and diastolic blood pressure (DBP) > 90<sup>th</sup> percentile.<sup>7</sup>

All data in this study were collected by professionals who had been trained to properly fill in the study questionnaires on at least 2 different days.

### Statistical analysis

Prevalences were described as proportions, with an appropriate 95% confidence interval. Continuous variables (height, weight, age, SBP, DBP) were described as means and standard deviations ( $m \pm SD$ ). The chi-squared or Fisher's exact tests were used with categorical variables (dyslipidemia, hypertension, sex, blood glucose, BMI percentile, and sedentary lifestyle) and for verifying the association between RFs. Spearman's correlation was used for CRP values and the presence of two or more RFs; the Shapiro-Wilk test was used to verify the normality of the data. The "CRP" and "RFs family" variables were not normally distributed and were described using medians and interquartile ranges. Statistical significance considered  $p \leq 0.05$ . All data were analyzed and stored using SPSS, version 17.0. Patients with altered results were promptly referred to a deeper investigation by a specialized unit. This study was approved by the Ethics Committee of the Institute of Cardiology, number 4470/2010.

### Results

The study comprised 66 children and adolescents, mostly male (65.2%), White (83.9%), with a mean age of  $10.18 \pm 4.6$  years. According to the interviews, 19.7% of them were overweight and more than 20% had increased BP, with a mean SBP of  $89.44 \pm 37.4$  and a mean DBP of  $60.0 \pm 26.08$ . Most of the patients had had corrective surgery early in life (93.4%) and of these, 36.1% presented an extracorporeal circulation time greater than 80min. Regarding their birth, 78.5% had been born at term. The characteristics of the study cohort are shown in Table 1.

Table 2 shows the cohort's laboratory profile: 34.8% of the patients presented low HDL levels and 30.3% presented increased triglycerides. Moreover, 6.1% of the patients presented low hematocrit levels.

Reports of hypertension (30.3%), obesity (16.7%), and 2 or more RFs among first-degree relatives (13.8%) were the most prevalent diseases in the families of the interviewed patients (Table 3). By associating nutritional state with risk profile, we identified a greater prevalence

of elevated cholesterol (23%), low HDL (46%), high LDL (23%), elevated triglycerides (46%), elevated CRP (23%), and the presence of 2 or more cardiovascular RFs (33%) in overweight patients when compared to eutrophic patients. However, statistical significance has not been found for these associations.

When associating overweight patients and cardiovascular risk profile, none of the variables showed significance, except for the "presence of 2 or more RFs" variable, which showed a trend towards statistical significance ( $p = 0.05$ ).

The non-parametric correlation (Spearman's test) between the BMI percentile and the presence of 2 or more RFs resulted in a coefficient of 0.30 ( $p < 0.05$ ) (Chart 1). When using the same test to correlate the BMI percentile with CRP values, we found a coefficient of 0.35 ( $p < 0.01$ ).

### Discussion

The current study describes a pediatric population with univentricular heart; most of them underwent the Fontan procedure to correct this congenital heart disease in the past. The analysis of data collected from the cohort has shown a 19.7% prevalence of overweight (> 97<sup>th</sup> BMI percentile) and the presence of at least 2 RFs among first-degree relatives.

This single ventricle population represents 15% of all children and adolescents with congenital heart disease examined between 2010 and 2016 in a medium-sized hospital in southern Brazil. This percentage is much higher than those found in Germany (9.4%) and in the United States (3.7%).<sup>8,9</sup> We believe that Brazilian policies prohibiting the interruption of pregnancy when this heart disease is detected early may have an impact on the prevalence of this disease in our country.

Previous studies have shown prevalence rates of 15.9% and 13.4% for overweight and obesity, respectively, in children and adolescents who underwent a palliative Fontan procedure; this is in line with our results.<sup>10,11</sup> Patients with congenital heart disease who underwent cardiac surgery in the past have an increased risk of developing cardiovascular disease when overweight and obesity are associated. Fogel et al.,<sup>12</sup> analyzed the cardiovascular effects of obesity in ventricular function and mass in patients who underwent a Fallot procedure, showing that obese patients had increased heart rates and decreased systolic and diastolic volumes in both ventricles when compared to normal-weight patients.<sup>12</sup> Therefore, weight control and overweight prevention are

**Table 1 – Characteristics of the population (n = 66)**

Variables	n (%)
Sex	
Male	43 (65.2)
Female	23 (34.8)
White ethnicity	52 (83.9)
Weight (kg) (m±SD)	35.64 ± 17.55
Height (cm) (m±SD)	137 ± 24.32
Age (m±SD)	10.18 ± 4.6
BMI	
Eutrophic	47 (71.2)
Overweight	13 (19.7)
Obesity	6 (9.1)
SBP (m±SD)	89.44 ± 37.4
DBP (m±SD)	60.0 ± 26.08
Born at term	51 (78.5)
Birth weight (m±SD)	2.97 ± 0.64
Birth length (m±SD)	48.07 ± 4.25
Gestational hypertension	11 (18.3)
Gestational diabetes	5 (8.3)

*m: mean; SD: standard deviation; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; n (%): absolute and relative numbers, respectively.*

**Table 2 – Laboratory profile of the cohort (n = 66)**

Variables	n (%)
Low HDL	23 (34.8)
Elevated triglycerides	20 (30.3)
Elevated total cholesterol	13 (19.7)
Elevated CRP	8 (12.1)
Elevated LDL	8 (12.1)
Hyperglycemia	7 (10.6)
Low hematocrit	4 (6.1)
CRP (median IQR)	0.09 (0.04-0.18)
RFs family (median IQR)	0 (0-1)

*n (%): absolute and relative numbers, respectively; CRP: C-reactive protein; RFs family: risk factors in the family.*

**Table 3 – Cardiovascular risk factors among first-degree relatives.**

Variables	n (%)
Hypertension	20 (30.3)
Obesity	11 (16.7)
Dyslipidemia	6 (9.2)
Diabetes	4 (6.2)
Presence of 2 or more RFs	9 (13.8)

*n (%)*: absolute and relative numbers, respectively; RFs: risk factors among first-degree relatives.

very important for these patients because they may avoid surgical and non-surgical interventions in the long term.

Stefen et al.,<sup>13</sup> reported an 8-year follow-up of 110 children with congenital heart disease, in which the BMI was carefully analyzed throughout the years. There was an increase in BMI of 10 points in the cohort at the eighth year, whereas an increase of 21.6 points was observed in the group of children with exercise intolerance, and an increase of 27.3 points was seen in the group of children with physical activity restrictions.<sup>13</sup> It is important to note that physical activity restrictions are one of the main causes of overweight in children with congenital heart disease, whilst it is also an important RF for cardiovascular diseases and other complications of the underlying disease. A study with overweight children who had undergone Fontan's showed the fragility of this population, mostly because they are susceptible to impairments of the pulmonary artery and endothelial function, as well as to increased pulmonary arterial resistance in the long term, all of which are aggravated by excess weight.<sup>10</sup>

Fuenmayor et al.,<sup>14</sup> analyzed the prevalence of dyslipidemia in a pediatric population of 52 patients with congenital heart disease and verified that 13.4% of them presented elevated LDL levels, which was similar to our findings (12.1%).<sup>14</sup> However, when analyzing a population of 476 children free of congenital heart disease, 13.27% of them presented elevated LDL levels. These findings, which are in line with our results, thus suggest that the presence of congenital heart disease is not a RF for elevated LDL. Nonetheless, it is long known that elevated LDL levels are a RF for the development of atherosclerosis and long-term cardiovascular events.

The presence of HTN and/or more than 2 cardiovascular RFs among first-degree relatives were prevalent in

this sample. A study by Borges et al.,<sup>15</sup> investigated cardiovascular RFs in 155 parents/caregivers of children with heart disease and observed that obesity and hypertension were among the most prevalent RFs, which was similar to our results.<sup>15</sup> Farias et al.,<sup>16</sup> by identifying the predetermining factors in the prevention of cardiovascular disease in adolescents, showed that the occurrence of HTN and diabetes mellitus among the interviewees' relatives was high.<sup>16</sup> Importantly, both studies suggest that interventions are highly recommended, in view of the great impact the family has on shaping the long-term habits and lifestyle of children and adolescents.

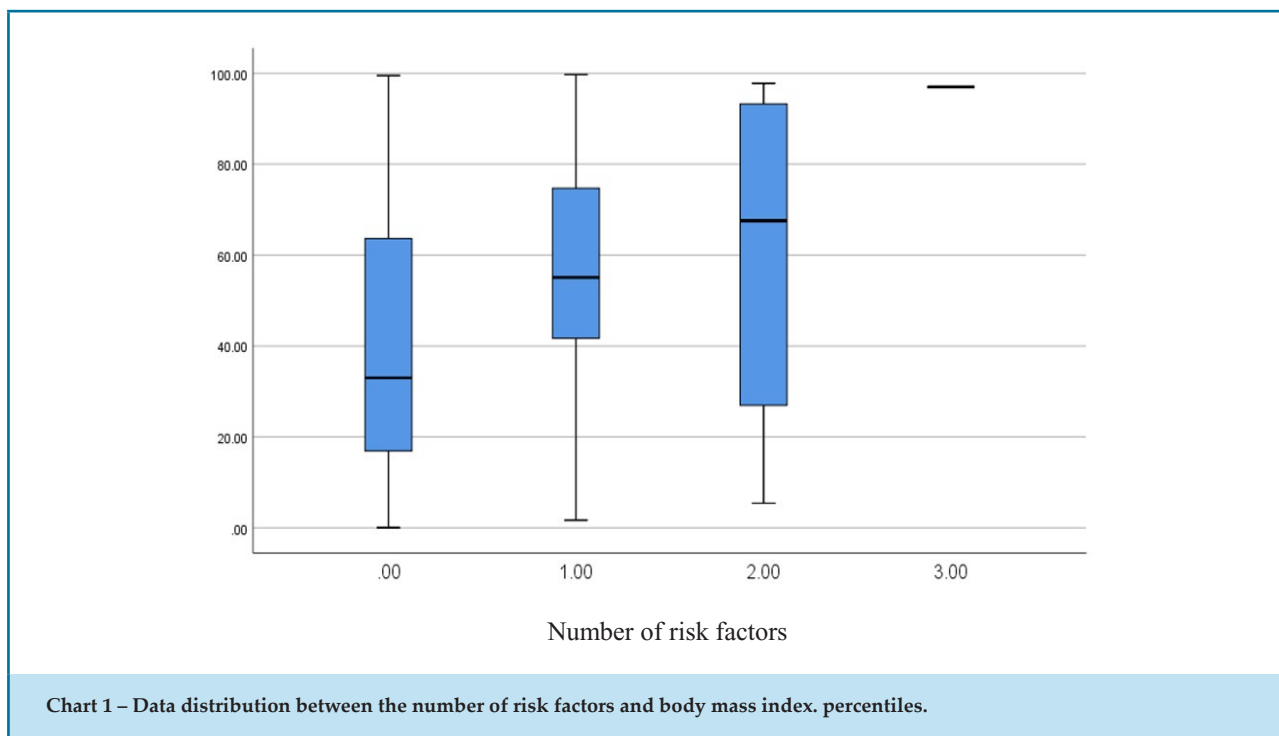
## Conclusion

This study suggests that overweight is frequent in patients with univentricular heart and can be related to the presence of more than 2 cardiovascular RFs among first-degree relatives. Furthermore, physical activity habits and alterations of the lipid profile are also important characteristics of the studied population. We recommend that future studies assess the prevalence of cardiovascular RFs in patients with a single ventricle who have had a Fontan procedure, as well as the nutritional profile and energetic metabolism of these patients.

## Author contributions

Conception and design of the research: Barbiero SM, Pellanda LC. Acquisition of data: Barbiero SM, Carloto RB, Schwantes GC, Guimarães MM, Goulart MR, Schuh DS. Analysis and interpretation of the data: Barbiero SM, Carloto RB, Pereira DS, Goulart MR, Schuh DS, Pellanda LC. Obtaining financing: Barbiero SM, Pellanda LC. Writing of the manuscript: Barbiero SM, Carloto RB,





Pereira DS, Schwantes GC, Guimarães MM, Pellanda LC. Critical revision of the manuscript for intellectual content: Pellanda LC. Project coordination: Pellanda LC.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

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### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto de Cardiologia (RS) under the protocol number 4470. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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