Original Research Article

Influence of congenital heart defect types over cardiopulmonary bypass, aortic cross-clamping, and ICU length of stay

ABSTRACT

Aim: Surgical correction of congenital heart defects (CHD) often requires interruption of blood flow through cardiopulmonary bypass (CPB) and aortic cross-clamping (ACC), for which duration(s) are considered to be prognostic factors, along with intensive care unit (ICU) length of stay (ICULOS). The aim of this study was to evaluate these surgical prognostic factors in pediatric patients with different types of CHD regarding their type of lesion and associated genetic factors.
Study design: Cross-sectional cohort study with 307 pediatric patients.
Place and Duration of Study: Pediatric Intensive Care Unit (ICU) of *Hospital da Criança Santo Antônio*, in Porto Alegre/RS, Brazil, from 2006-2009 (3 years)
Methodology: We studied intraoperative factors and dysmorphological/cytogenetic examinations in 266 pediatric patients admitted for the first time in a reference pediatric ICU from Southern Brazil following cardiac surgery. Prognostic factors such as duration of CPB, ACC and ICULOS, in addition to dysmorphological and cytogenetic examinations were compiled and analyzed. P-values of <0.05 were considered significant.
Results: CPB time was associated to four outflow tract defects (Tetralogy of Fallot [ToF], transposition of the great arteries [TGA], double outlet right ventricle, and truncus arteriosus [TA]), atrioventricular septal defect, and hypoplastic left heart syndrome (HLHS) ($p<0.001$). ACC duration was associated to three outflow tract defects (ToF, TGA, and TA) and HLHS ($p<0.001$). Moreover, CPB and ACC times showed an association with cyanotic and complex heart defects, as well as prolonged ICULOS ($p<0.001$). There was no relationship between these prognostic factors and syndromic aspects or cytogenetic findings.
Conclusions: CHD type has an impact over CPB and ACC duration and ICULOS, whereas genetic factors are not associated with those prognostic factors.

Keywords: congenital heart defects, cardiopulmonary bypass, aortic cross-clamping, high resolution karyotype, fluorescent in situ hybridization, prognostic factors

1. INTRODUCTION

Congenital heart defects (CHDs) are the major cause of birth malformations, accounting for approximately 0.9% of all live births, having a profound impact on children's morbimortality and repercussions on health care costs. The individualization of this wide spectrum of structural abnormalities through genetic assessment is an important factor for adequate clinical diagnosis likewise surgical management and treatment.

Surgical intervention remains one of the main treatment options, usually combined with cardiopulmonary bypass (CPB) and/or aortic cross-clamping (ACC). Although these techniques may enable better surgical repair strategies, they are also associated with an increased risk for morbidity and mortality, especially with regard to intraoperative factors such as prolonged CPB and ACC times during cardiac procedures (1–3). Furthermore, the

duration of CPB and ACC are associated with increased intensive care unit length of stay (ICULOS) following cardiac surgery, assuming a linear relationship between these factors (4). CPB time has also been classified as a risk factor for ICULOS in children (5,6) and adults (3).

One of the many pathways by which CPB exerts harmful systemic effects is through the artificial conditions of the bypass circuit, which induces cellular activation and subsequent inflammatory response, resulting in mechanical shear stress, tissue ischemia, and reperfusion lesions (7,8). Individual factors from the systemic inflammatory response to CPB ultimately combine by redundancy and through amplifier cascades to finally produce characteristic post-CPB damage, culminating in endothelial lesions, capillary leakage, and systemic organ dysfunction (9,10). Clinical manifestations of these effects may be reflected as multiorgan postoperative complications, such as renal failure, neurological events, and pulmonary dysfunction, resulting in prolonged mechanical ventilation and ICULOS and, in a broader spectrum, delaying the recovery of patients.

Consequently, intrinsic characteristics of each genetic diagnosis and the physiological repercussions of their distinct defects may somehow impact surgical outcomes. Hence, the aim of this study was to evaluate different types of CHD and associated genetic factors with surgical prognostic factors, such as CPB, ACC and ICULOS at a reference cardiac pediatric hospital in Southern Brazil.

2. METHODOLOGY

A retrospective cohort study over a three-year period of patients with CHD admitted for the first time to the Pediatric ICU of *Hospital da Criança Santo Antônio*, in Porto Alegre/RS, Brazil, was performed. The only inclusion criteria was admission in the Pediatric ICU for cardiac reasons, while patients with non-cardiac motives were excluded. These patients were also previously described in other studies (11–14). This study was approved by the Ethics Committee of all applicable institutions. Data used to perform this classification consisted of echocardiographic results, reports of cardiac catheterization and surgery. Thus, CHDs were classified as described by Botto et al. (15) into 11 different categories, in which defects at the top of this list were postulated to occur earlier in embryogenesis than those further down (the exception being the group of “other major defects,” which, although listed last, precedes in coding the category of patent ductus arteriosus). Clinical and surgical information, including the duration of CPB and ACC, as well as ICULOS, were individually collected from electronic medical records and patient charts from the hospital’s main data archives. Surgical cardiac diagnosis was also matched with genetic examinations, that consisted of dysmorphological physical examination performed by a clinical geneticist, classifying patients in syndromic or not, considering dysmorphia number and types. Cytogenetic evaluation was also performed through high-resolution GTG-Banding karyotype and fluorescence *in situ* hybridization (FISH) test for detection of 22q11.2 microdeletion, previously described (11,13–14). Data from both sources were then compared for disparities, with no divergence found.

Statistical analysis of quantitative variables included descriptive parameters, such as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were described as absolute and relative frequencies. Student’s t-test or analysis of variance (ANOVA) complemented by Tukey were applied to compare means between groups. In case of asymmetry, the Mann-Whitney test or Kruskal-Wallis test complemented by Dunn’s test were applied. Spearman’s correlation test was used to assess the relationship between

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numerical variables. Differences with $p<0.05$ were considered to be statistically significant. Analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA).

3. RESULTS AND DISCUSSION

During the study period, 307 patients with CHD were hospitalized for the first time in the ICU. From them, 266 (86.6%) underwent heart surgery and, thus, fulfilled the inclusion criteria, being included in the study analysis after parental consent. The remaining 41 (13.4%) required ICU admission for non-surgical cardiac reasons (clinical and/or catheterization) and were thusly excluded from the analysis.

Almost one-half of the entire sample were male (52.4%) and the major part (80.5%) had a Caucasian ethnicity. The overall median age at the time of surgery was 272 days (IQR 109–1047 days). The largest proportion of CHDs consisted of tetralogy of Fallot (11.4%), atrioventricular septal defect (11.1%), and isolated atrial or ventricular septal defects (each 14.7%), together accounting for almost one-half of the entire sample (51.9% [n = 159]), as summarized in Table 1. Most CHDs were acyanotic (65.1% [n = 200]) and non-complex (65.8% [n = 202]).

Table 1. Distribution of sample by defect type

Defect type	n (%)
Heterotaxias (A)	6 (2.3)
Corrected L-transposition (B)	1 (0.4)
Outflow tract defects	
Tetralogy of Fallot (C)	32 (12.0)
D-transposition of the great arteries (D)	21 (7.9)
Double outlet right ventricle (E)	5 (1.9)
Truncus arteriosus (F)	3 (1.1)
Atrioventricular septal defect (G)	34 (12.8)
Total anomalous pulmonary venous return (H)	7 (2.6)
Ebstein anomaly (I)	3 (1.1)
Right obstructive defects	
Tricuspid atresia (J)	6 (2.3)
Pulmonary atresia (intact septum) (K)	6 (2.3)
Pulmonic stenosis/atresia (L)	14 (5.3)
Peripheral pulmonary stenosis (M)	-
Left obstructive defects	
Hypoplastic left heart (N)	12 (452)
Coarctation of the aorta (O)	22 (8.3)
Aortic arch atresia or hypoplasia (P)	-
Aortic valve stenosis (Q)	3 (1.1)

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Septal defects	
Ventricular septal defect (R)	41 (15.4)
Atrial septal defect (S)	38 (14.3)
Patent ductus arteriosus (T)	3 (1.1)
Other major heart defects (U)	9 (3.4)
Total	266 (100.0)

Two hundred and thirty-six surgeries (88.7%) were performed with CBP support and 222 (83.4%) with ACC requirement. Analysis revealed that the overall median duration of CPB was 54.5 min (IQR 33–85.5 min). Regarding the type of defect, results revealed that all outflow tract defects (tetralogy of Fallot, D-transposition of the great arteries, double outlet right ventricle, and truncus arteriosus), atrioventricular septal defects, and hypoplastic left heart syndrome were among the groups with longer CPB times ($P < .001$) (Fig 1a). After multiple comparisons among the types of defects, statistical analysis revealed that these six groups were significantly higher compared to a single right obstructive defect (tricuspid atresia) — a single left obstructive defect (coarctation of the aorta), along the atrial septal defect ($P < .001$).

The median duration of ACC was 28.5 min (IQR 14–56 min). Similar to CPB, multivariate analysis revealed that ACC times were associated with some outflow tract defects (tetralogy of Fallot, D-transposition of the great arteries, and truncus arteriosus only), along with hypoplastic left heart syndrome ($P < .001$), as shown in Figure 1b. After multiple comparisons among the types of lesions, statistical analysis revealed that these four congenital heart defects presented significantly higher ACC times than the right obstructive defects (tricuspid atresia and pulmonary atresia), a single left obstructive defect (coarctation of the aorta), and atrial septal defect ($P < .001$).

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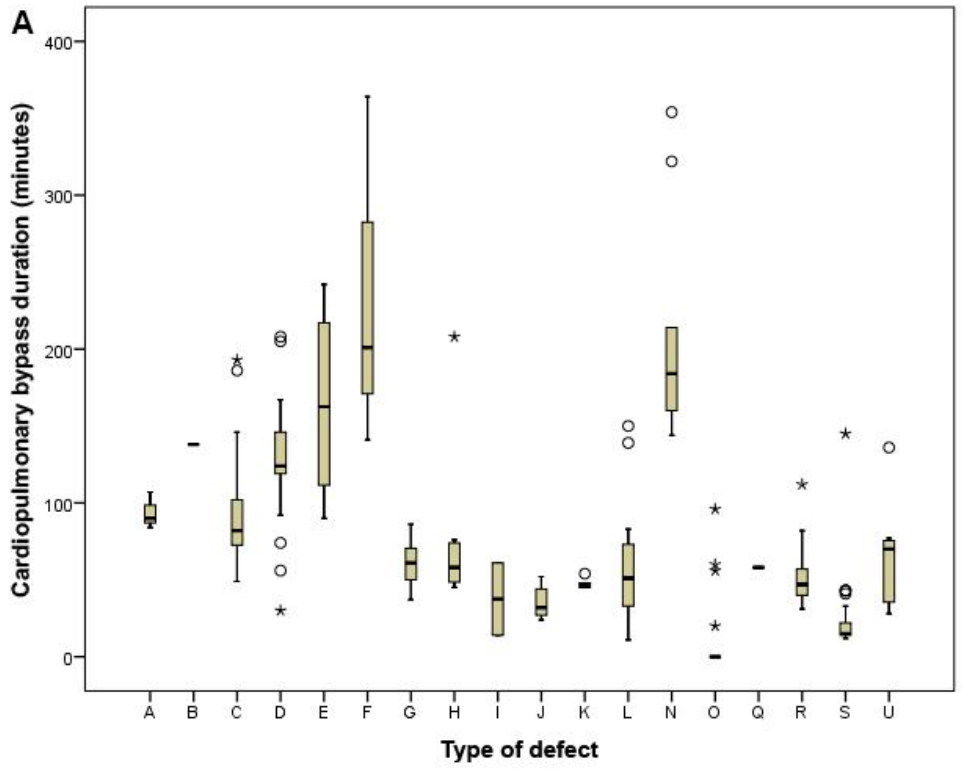
A
Cardiopulmonary bypass duration (minutes)
400
300
200
100
0
A B C D E F G H I J K L N O Q R S U
Type of defect

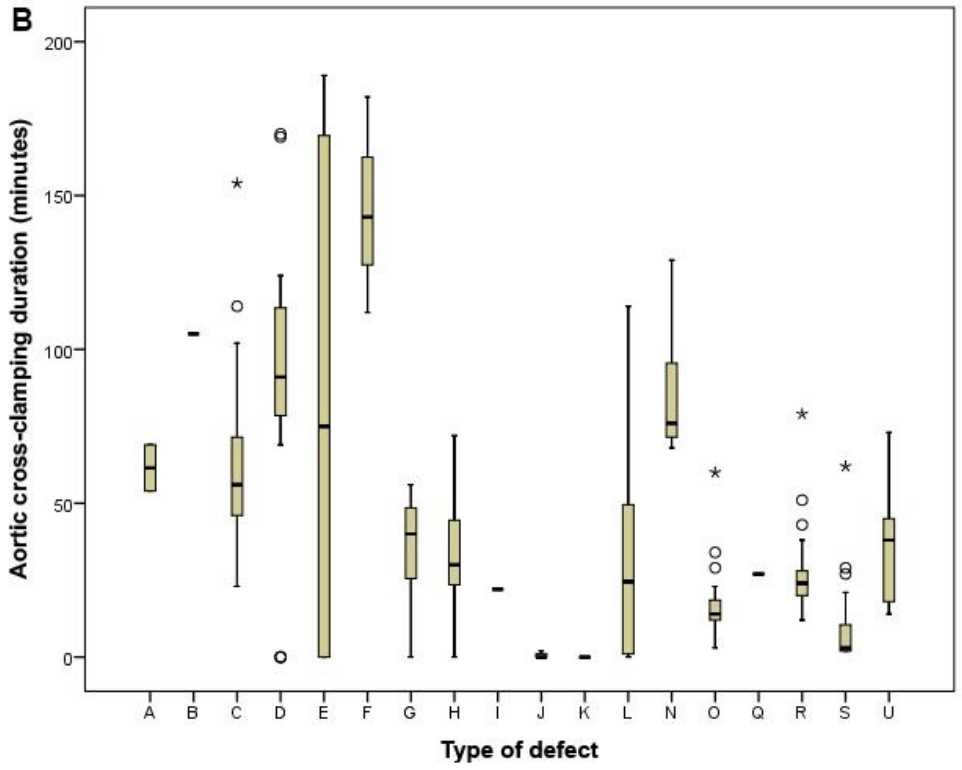
B
Aortic cross-clamping duration (minutes)
200
150
100
50
0
A B C D E F G H I J K L N O Q R S U
Type of defect

Fig. 1. Cardiopulmonary bypass (A) and aortic cross-clamp (B) duration in minutes and types of congenital heart defects
A: Heterotaxia; B: Corrected L-transposition; C: Tetralogy of Fallot; D: D-Transposition of the great arteries; E: Double outlet right ventricle; F: Truncus arteriosus; G: Atrioventricular septal defect; H: Total anomalous pulmonary venous return; I: Ebstein anomaly; J: Tricuspid atresia; K: Pulmonary atresia; L: Pulmonic stenosis; M: Peripheral pulmonary stenosis; N: Hypoplastic left heart; O: Coarctation of the aorta; P: Aortic arch atresia/hypoplasia; Q: Aortic valve stenosis; R: Ventricular septal defect; S: Atrial septal defect; T: Patent ductus arteriosus; U: Other major heart defects

CPB and ACC times were also significantly longer in patients with cyanotic and complex defects ($P < .001$), indicating that the resulting severity of the defect's physiopathology may also influence the duration of CPB and/or ACC.

As for genetic evaluation of surgical patients, 69 patients (25.9%) were considered syndromic by the dysmorphological physical examination. Cytogenetic evaluation through the high resolution GTG-Banding karyotype revealed that 41 patients (15.4%) were carriers of a chromosomal anomaly. The FISH test detected only 4 patients (1.5%) with a 22q11.2 microdeletion. Our results were not able to determine a significant association of these genetic findings with the duration of either CPB or ACC. Therefore, despite the importance that genetic examinations play on the diagnosis of CHDs, none of them seem to influence the duration of CPB and/or ACC.

Finally, the individual Spearman correlation between CPB ($\rho=0.372$; $P < .001$) and ACC ($\rho=0.311$; $P < .001$) times and ICULOS was also significant, indicating that, regardless of cardiac defect or type of surgical procedure, patients with longer CPB and ACC times were more likely to experience prolonged ICULOS.

Diagnosis and management of fetal cardiac abnormalities provide valuable information which can affect before and after delivery plans, and furthermore surgical correction of CHD (16). Considering the vast spectrum of these defects, we demonstrated that some types of cardiac lesions may also impact surgical prognostic factors, such as CPB and ACC. All outflow tract defects, including tetralogy of Fallot, D-transposition of the great arteries, double outlet right ventricle, and truncus arteriosus, were significantly associated with longer CPB times, also related to the severity of obstruction within the subpulmonary right ventricular outflow tract, leading to more complex surgical repair in these types of defects. This level of surgical complexity is observed when the aortic arch has to be approached or enlarged and redirected to reconstruct intracardiac defects, such as ventricular septal defects, valvuloplasty involving the use of pericardial flaps or synthetic material for reconstruction and expansion of the outflow tract (as in tetralogy of Fallot), dilatation and preservation of the valve ring, implantation of valve prosthesis, use of extra cardiac organic or inorganic tubes (valved or not), or even reimplantation of the coronary arteries. The same association was observed in patients with hypoplastic left heart syndrome, in which atresia of the mitral and aortic valves contribute to the malformation of the left ventricle causing an obstructive lesion. On the other hand, children with atrioventricular septal defects present with left-to-right shunts, which divert blood flow from the systemic arterial to the pulmonary circulation and, despite not being an obstructive defect, are equally associated with longer CBP time. The diameters of the defects and the characteristics of the common atrioventricular valve will also influence the duration of the surgical correction, which is also a consequence of the complexity of the technical difficulty involved in the repair. Clinical intraoperative evolution might present different degrees of pulmonary hypertension and

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ventricular dysfunction, eventually requiring the use of either nitric oxide or even extracorporeal membrane oxygenation (ECMO).

Regarding ACC, hypoplastic left heart syndrome and the same outflow tract defects (tetralogy of Fallot, transposition of the great arteries, and truncus arteriosus) were also significantly associated with longer ACC time. In contrast to CBP, the double outlet right ventricle, as well as the atrioventricular septal defect, were not associated with prolonged ACC time.

Pediatric patients have a small circulating plasma volume, and circulatory changes caused by extracorporeal circulation are profoundly greater than those in adults. The systemic inflammatory response caused by CPB involves the activation of cellular and humoral cascades, which can be more severe due to higher metabolic demands, reactive pulmonary vasculature, and immature organ systems with altered homeostasis (7). In addition, both CPB and ACC cause direct damage due to ischemia and reperfusion injury, adding significant morbidity to the direct surgical trauma itself (8,17,18). Accordingly, our data revealed that the majority of corrective surgeries for CHD performed in our hospital were performed under CPB, worthy noting that this information leads to better surgical planning which is ultimately crucial for further development and expansion of hospital practices and logistics regarding pediatric cardiac surgeries.

Moreover, we observed a strong association between complex defects and cyanotic patterns with either CPB or ACC duration. Complex heart defects have a greater negative impact on physiology due to the severity of morphological malformations, causing harsh hemodynamic repercussions and culminating in greater morbidity. Similarly, defects with cyanotic patterns lead to pulmonary hypoflow, stimulating the compensatory production of erythrocytes, increasing haemoglobin and haematocrit values, inducing changes in blood viscosity and, consequently, increasing the risk for thrombotic events. All these defect-related hemodynamic changes could potentiate the effects of the systemic inflammatory response to CPB in patients undergoing cardiac surgical procedures. For this reason, estimation of CPB and ACC times must be a part of preoperative evaluation of these patients to optimize the use of CPB and improve the management of cardiac surgery itself.

Nowadays, the use of molecular approaches as screening models to establish the genetic basis of CHD etiology has facilitated not only early diagnosis, but therapeutic planning as well, helping to plan better surgical strategies and improving clinical care and outcomes (13). Alicandro et al. (19) postulated that genetic studies have enhanced knowledge and the ability to care for patients with CHDs in three fields: reverse medicine, including genotype-phenotype correlations and new diagnostic criteria for classification of CHD based on genetic assessment; predictive medicine, shifting toward a genotype-prognosis paradigm to establish specific diagnostic and surgical protocols to improve outcome(s); and preventive medicine, for which genetic studies will help prevent defects or reduce their severity and complications.

Whilst the prevalence of genetic alterations found in our study is in accordance with previous studies (11,20–22), we were not able to find an association between the duration of either CPB and/or ACC with the syndromic aspect of CHD patients, determined through a dysmorphological clinical examination by a clinical geneticist, or even with the presence of chromosomal anomalies detected through high resolution GTG-Banding karyotype and FISH test for 22q11.2 microdeletion. Nonetheless, it is noteworthy the rarity of studies that analyzed the association of these genetic findings and surgical variables, such as CPB and ACC, whose relevance and usefulness as prognostic factors of influence remains questionable.

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Prolonged ICU hospitalization is also a major problem in pediatric patients following cardiac surgical procedures. Without considering the general consequences of prolonged ICULOS, such as costs, risk(s) for secondary infections, and quality of health care, our results demonstrated that prolonged CPB and ACC times may also predict prolonged ICU hospitalization. Our findings are consistent with several previously published studies that highlight the role of CPB and ACC as crucial predictors of postoperative events, such as prolonged ICULOS, and renal, pulmonary, and neurological complications (7,23–25). In the same manner, our results highlight the close relation between surgical therapeutics and later intensive care post-operative management, being an important key to development of hospital policies aiming for better overall outcomes related to CHD treatments.

4. CONCLUSION

Finally, we postulate that the idiosyncrasies inherent to each type of CHD may impact the duration of CPB, ACC and ICULOS and consequent inflammatory response. In-depth knowledge of the embryology, anatomy, and pathophysiology of each defect, as well as a case-by-case study and mapping, help in clinical-surgical planning to improve surgical strategies and, thus, improve surgical times, in an attempt to minimize damage and postoperative effects in the correction of CHD, notably the most complex. Subsequently, more studies are still necessary to better understand the role of the genetic status over these surgical prognostic factors.

CONSENT AND ETHICAL APPROVAL

This study was approved by the Ethics Committee of all national applicable institutions.
All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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