Clinical Profile of Systemic Inflammatory Response after Pediatric Cardiac Surgery with Cardiopulmonary Bypass

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Abstract

Background: The postoperative period of congenital cardiomyopathies correction is frequently accompanied by systemic inflammatory response.

Objectives: To assess the frequency of occurrence and clinical manifestations of the systemic inflammatory response syndrome after cardiopulmonary bypass (SIRS-CPB) in children submitted to cardiac surgery.

Methods: Historical cohort study including patients up to 3 years old that were submitted to elective corrective surgeries for congenital cardiopathies with cardiopulmonary bypass (CPB). A total of 101 patients were assessed by means of clinical criteria of organ dysfunction through score tests, as comparing predisponent factors and aggregated morbidity to the presence of SIRS-CPB.

Results: Twenty-two patients (21.9%) fulfilled the criteria for SIRS-CPB. The sex or type of cardiopathy did not differ between groups (p = NS). Patients diagnosed with SIRS-CPB (compared to patients without SIRS-CPB) presented lower mean age (6.8 ± 5.5 *versus* 10.8 ± 5.1 months, p < 0.05), lower weight (5.3 ± 1.9 *versus* 6.9 ± 2.0 kg, p < 0.05), and longer CPB duration (125.1 ± 49.5 *versus* 93.9 ± 33.1 minutes, p < 0.05). Longer median duration of mechanical ventilation (120.0 *versus* 13.0 hours, p < 0.05), longer stay in Intensive Care Unit (ICU) (265.0 *versus* 107.0 hours, p < 0.05) and in hospital (22.0 *versus* 10.0 days, p < 0.05) were observed. In the multivariate analysis, higher weight (OR = 0.68, p = 0.01) was identified as a protection factor.

Conclusion: The adopted clinical criteria identified a risk group for SIRS-CPB, which presented lower weight and longer CPB duration as predisponent factors. Patients with SIRS-CPB remain in mechanical ventilation, in ICU and in hospitalization for a longer period of time. (Arq Bras Cardiol 2010; 94(1) : 119-124)

Key Words: Systemic inflammatory response syndrome; thoracic surgery; cardiopulmonary bypass.

Introduction

After the introduction of cardiopulmonary bypass (CPB) as a supportive tool in cardiac surgery, the benefits to patients with congenital and acquired cardiopathies increased, as it was possible to modify these diseases' natural course and significantly increase the survival rates[1].

CPB is a modality of controlled circulation that is crucial to the majority of corrective cardiac surgeries and may, together with the tissular injury due to surgical incision, trigger a series of inflammatory processes through cellular activation and liberation of inflammatory mediators[2-4]. In this context, there is a stimulation of leukocytes, monocytes, macrophages, basophils, endothelial cells, myocytes and hepatocytes. There is an increase in the circulation of complement fractions (mainly C3a, C4a and C5a)[5,6], citokynes (mainly tumor necrosis factor-alpha, class 1, 6, 8 and 10 interleukins)[7-9], histamine[10] and *adhesion molecules*[11].

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The inflammatory cascade is then amplified and may be associated with clinical manifestations by fever occurrences[12,13], myocardial dysfunction (due to mechanical, ischemic and immunological injury)[14,15] and/or vasoplegy[16,17], with occurrence of hypotension; signs of low cardiac output with hyperperfusion and tissular hypoxia; acute renal insufficiency[18,19]; acute pulmonary lesion[20], *acute respiratory* distress *syndrome*[21]; *blood dyscrasia*[22], neurological symptoms[23,24] and liquid retention with weight gain down to endothelial lesion[25]. When present, these manifestations may prolong the period of stay in ICU and in general hospital due to aggregated morbidity. In extreme cases, multiple organs failure syndrome or even rare and severe clinical status with syndromes similar to septic shock may be observed.

Diagnosis criteria for SIRS-CPB are still in need of a consensus, and studies are made based on isolated variables or non-uniform clinical criteria. The frequency of SIRS-CPB clinical manifestations varies from 22 to 27.5%, even though it has been evaluated by means of different methods[5,6].

The present study was developed with the objective of evaluating the occurrence of SIRS-CPB clinical manifestations in pediatric patients submitted to cardiac surgery with CPB for correction of congenital cardiopathies and of relating them

to clinical outcomes. In order to do that, the study of clinical variables was proposed, for they could reflect the dysfunction of organs and subsystems in the precocious postoperative period or, in group, they could represent SIRS-CPB and become applicable to clinical recognition.

Methods

This is a historical cohort study carried out through analyses of the records of children submitted to surgical correction due to congenital cardiopathies and admitted in the intensive cardiac care unit at Hospital Infantil Pequeno Príncipe from January 1st till December 31st, 2003. The study was approved by the Humana Research *Ethics Committee of Hospital das Clínicas, Universidade Federal do Paraná, and of* Hospital Infantil Pequeno Príncipe.

Selected patients were up to 3 years old (141 individuals). The choice of younger children for the research is justified by the fact that SIRS-CPB occurs more frequently in children than in adults[5].

Forty patients were excluded from the study according to the following criteria:

a) mechanical ventilation during more than 48 hours before surgery;

b) preoperative infection;

c) death during surgical intervention or in the first 48 hours after surgery;

d) precocious postoperative infection within the first five days;

e) record with incomplete data. The exclusion criteria were applied with the purpose of eliminating other known causes of deflagration of inflammatory process, specially prolonged mechanical ventilation and other infectious processes.

After the exclusion, defined by the abovementioned criteria, data from 101 patients were assessed.

In the whole sample, mean age was 9.9 ± 5.4 months, mean weight 6.6 ± 2.1 kg. The sex distribution was homogeneous, with 50% each.

The mean CPB duration was 100.7 ± 39.2 minutes and aortic clamping duration was 68.2 ± 27.6 minutes. Median time of stay in intensive care unit (ICU) was 133.0 hours (varying from 33 to 1,162 hours) and of general hospitalization was 12.0 days (varying from 0 to 756 hours).

Clinical criteria for SIRS-CPB

Clinical variables associated with SIRS-CPB were assessed in the first five days of the postoperative period, which corresponds to a period of intense inflammatory activity: (a) fever (if higher than or equal to 38 degrees Celsius); (b) hemodynamic dysfunction (inotropic score–[26]); (c) pulmonary dysfunction (PaO_2/FiO_2 relation smaller than 300); (d) renal dysfunction (increase of more than 20% in creatinine); (e) clinical endothelial dysfunction and (f) radiologic endothelial dysfunction.

Endothelial dysfunction was evaluated in clinical and radiologic aspects. With regard to clinical aspect, the volume of liquid collected by drains that were set during surgical intervention was measured. Groups were considered as altered when drainage was above the third quartile in comparison to the whole sample. Concerning the radiologic aspect, interstitial thickness was measured by means of a radiologic index[7] in the preoperative period and in two postoperative moments: admittance of the patient in ICU and after 48 hours of permanence. Increase of 50% in interstitial thickness was considered to be significant alteration (Figure 1).

According to the quantity of altered variables (with one attributed point each), it was possible to divide the sample into two groups. In Group I were gathered the patients who presented three or more points, considered as the presence of SIRS-CPB. Group II were composed by the patients who did not present SIRS-CPB and presented up to two points.

Assessment of predisponent factors

The association between type of cardiopathy (acyanotic or cynotic), age, weight, duration of CPB and of aortic occlusion was assessed.

Assessement of hospital outcome

Hospital outcome was analyzed through a comparison between groups with regard to duration of ventilation, duration of stay in intensive care unit, total period of time of hospitalization and death.

Statistical analysis

Variables are presented as proportions (when categorical), mean and standard deviation (when continuum and normally distributed) or mean and inter-quartile interval (when continuum and asymmetric).

The predisponent factors for SIRS-CPB were compared through Pearson's chi-square test (χ^2) and Student's t-test. Additionally, relative risks with respective 95% confidence interval were calculated for categorical variables.

Logistic regression was made as considering SIRS-CPB a dependent variable.

With regard to outcomes among patients with and without SIRS-CPB, Pearson's χ^2 and Mann-Whitney tests were used.

Multiple linear models were also used for continuum outcomes, and Spearman's correlation was used for the assessment of SIRS-CPB by means of continuum score. The score was elaborated with the attribution of one point of the following altered criteria: fever, hemodynamic dysfunction, pulmonary dysfunction, renal dysfunction and endothelial dysfunction (clinical and radiologic). In this manner, the score varied from 0 to 6.

Results

Twenty-two (21,9%) patients who fulfilled the criteria indicative of SIRS-CPB were identified (Group I) during the first five days of the postoperative period.

From the whole sample, 12.9% of the patients presented fever. Hemodynamic dysfunction was present in 15.8%, pulmonary and renal dysfunction in 22.8%, interstitial edema

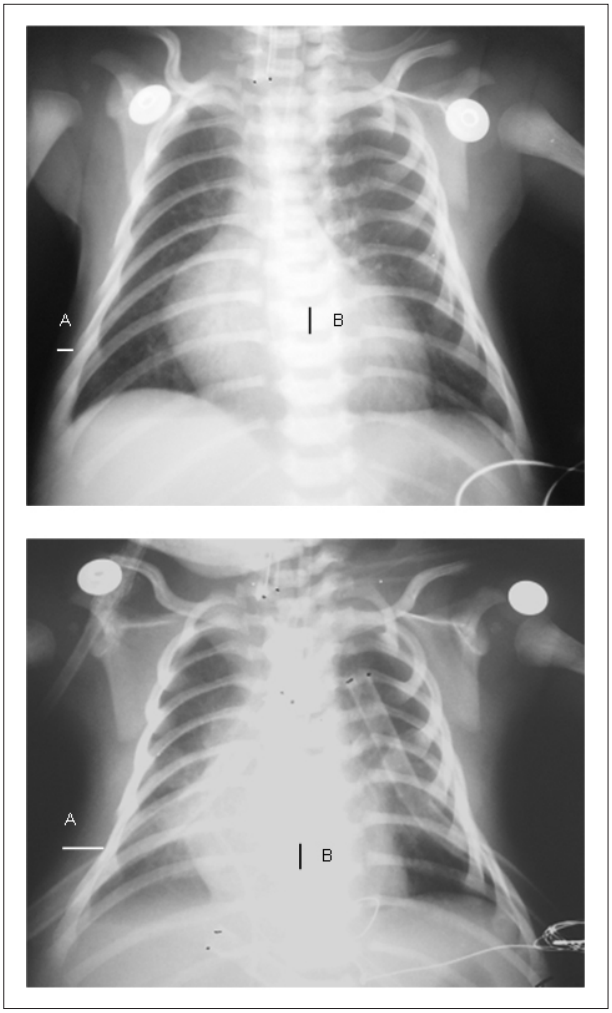

Figure 1 - Delimitation of parameters for radiologic index. In A, the thickness of the subcutaneous tissue is measured and, in B, the vertebral height, which is utilized as index factor, is measured. Preoperative interstitial thickness is compared to that of the postoperative period. These are radiographs of a patient submitted to Jatene procedure, and it is possible to observe a great increase in the thickness of soft tissues in the first postoperative hour.

in 28.7% and volume of drainage in 25.7% of the sample (Figure 2).

The presence of one isolated clinical factor (except for fever) was significantly associated with a higher frequency of identification of SIRS-CPB among these patients.

In face of the altered variable, the diagnosis for SIRS-CPB was significantly more frequent, while in the absence of alterations, the diagnosis became unprovable. When a hemodynamic dysfunction was characterized, SIRS-CPB was diagnosed in 81.3% of the patients. This diagnosis was present in 10.6% of the patients without hemodynamic dysfunction (Figure 3).

Assessment of predisponent factors

After the formation of groups based on clinical criteria, a similar frequency o SIRS-CPB was observed when the analysis was made according to sex or type of cardiopathy.

Patients of Group I had lower age (6.8 ± 5.5 *versus* 10.8 ± 5.1 months, $p < 0.05$), lower weight (5.3 ± 1.9 *versus* 6.9 ± 2.0 kg, $p < 0.05$), longer exposition to CPB (125.1 ± 49.5 *versus* 93.9 ± 33.1 minutes, $p < 0.05$) and aortic clamping (82.3 ± 34.0 *versus* 64.2 ± 24.3 minutes, $p < 0.05$), all occurrences that led to SIRS-CPB (Table 1).

Even in a multivariate model, time of CPB and weight were still considered as significant predisponent factors for SIRS-CPB. The variables weight and age, as well as time of CPB and time of aortic occlusion, are connected and interfere with each other. Therefore, only weight and time of CPB were assessed in the multivariate model.

Assessment of clinical outcomes

Patients of Group I were submitted to mechanical ventilation during longer periods of time (mean 120.0 *versus* 13.0 hours, $p < 0.05$), stayed longer in the ICU (mean 265.0 *versus* 107.0 hours, $p < 0.05$) and in hospitalization (mean 22.0 *versus* 10.0 days, $p < 0.05$) (Table 2). The difference between groups concerning death occurrences (13.6 *versus* 2.5%, respectively) was not statistically significant ($p = 0.068$).

Discussion

SIRS-CPB was present in 21.9% of the patients in a young population (up to 3 years old) submitted to elective cardiac surgery, and the majority of other predisponent preoperative causes that could provoke SIRS were excluded.

Seghaye et al[6], in 1993, found an incidence of 27.5% of SIRS in a study with children in which the diagnostic criteria was adapted from SIRS manifestations in clinical patients. The use of SIRS criteria in this case has high sensibility, however, there is still a necessity of specificity for the vital signs, neurological and laboratorial data are strongly influenced by factors that are intrinsic to the procedure or to specific care given in the ICU during the postoperative period.

In the studied sample, isolated organ dysfunction occurred with frequently between in 15.8 to 28.7% of the patients. Kirklin et al[5] studied adult and pediatric patients in 1983 and found recurrent organ failure associated with global morbidity in 22% of the sample. Cardiac (23%), pulmonary (35%), renal (21%) and haemostatic dysfunctions (18%) were present and related to high levels of C3a within three hours after the intervention as much as to age inferior to 1 year old.

With the exception of renal dysfunction, all other complications were associated with prolonged CPB.

The frequency of hemodynamic dysfunction in patients was of 16%. Among these patients, 81% presented SIRS-CPB, and such diagnosis occurred in only 11% of the patients without hemodynamic dysfunction. These facts may lead to the adoption of higher-influence criteria for the hemodynamic variable concerning the SIRS-CPB diagnosis.

Unlikely the shock in adults, the shock in children presents a singularity: in 80% of occurrences it is associated with myocardial dysfunction[27]. Postoperatively, the low cardiac output syndrome is described in approximately 24% of newborns submitted to Jatene procedure and is characterized by myocardial dysfunction and decrease in cardiac output, both associated with an increase in

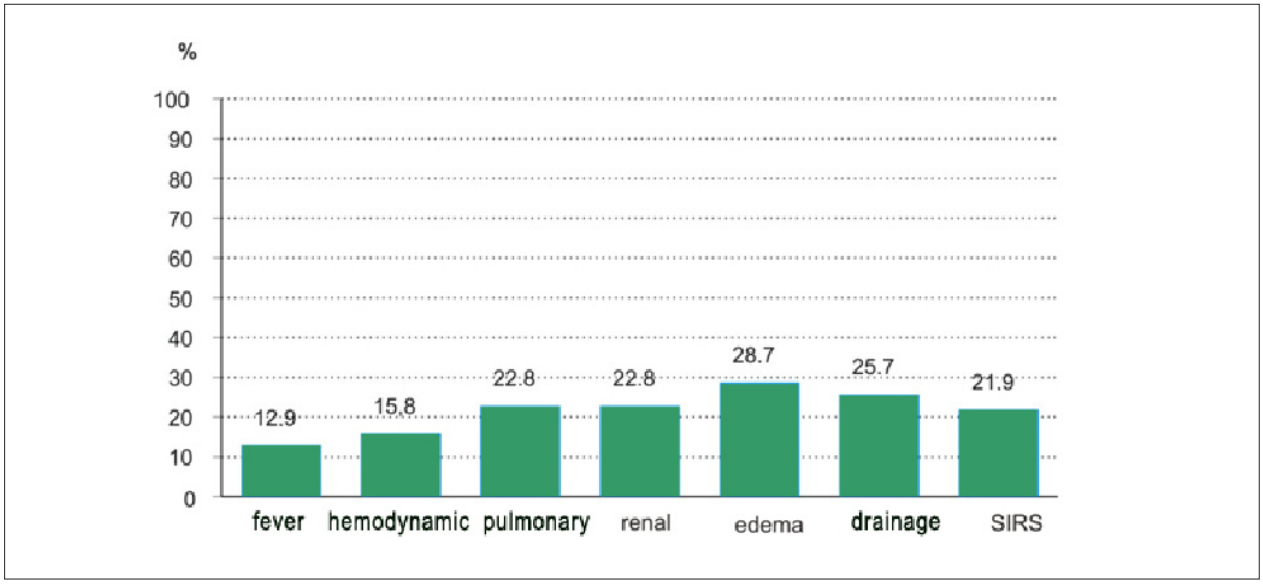

Figure 2 - Distribution of frequency of isolated clinical criteria in the whole sample and frequency of SIRS in the studied population; SIRS – systemic inflammatory response syndrome.

peripheral vascular resistence[26].

CPB is followed by acute respiratory distress in a 0.4% frequency in the adult population with associated mortality[21]. During CPB, there is activation and migration of neutrophils to the pulmonary endothelium, which may initiate a local lesion by means of a phenomenon called pulmonary *leukocyte sequestration*[5]. This may explain the acute pulmonary lesion associated with surgery for cardiac correction with CPB. In the studied patients, a frequency of 22.8% for acute pulmonary lesion was observed, but not cases of acute respiratory distress syndrome. The acute pulmonary lesion accompanied by pulmonary dysfunction and decrease in PaO_2/FiO_2 relation

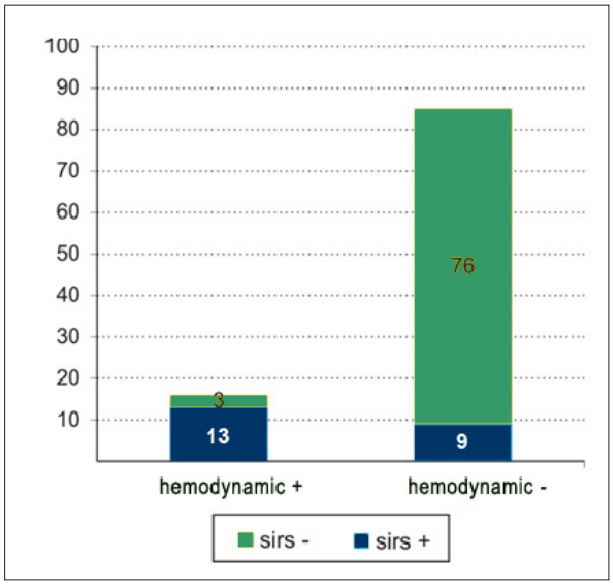

Figure 3 - SIRS-CPB frequency in patients with and without alterations in the postoperative period; SIRS – systemic inflammatory response syndrome.

may have been responsible for prolonged mechanical ventilation observed in patients diagnosed with SIRS-CPB.

The analysis of renal function after surgical procedure has been difficult with regard to the determination of frequency, for the different groups have different diagnostic criteria. In adults, Tuttle et al[28], in 2003, assessed a group of patients submitted to CPB with a renal failure criterion similar to the one herein stated (increase of 25% in creatinine) and observed a 42% incidence. In the present study, a 22.8% frequency was registered, which is an important criterion for SIRS-CPB score, because 81% of the patients with renal failure presented SIRS-CPB and only 7% of the group which had normal renal function were diagnosed with SIRS-CPB.

Through the radiologic index, it was shown that a high frequency of interstitial edema (28.7%) would identify, during the surgical procedure, the patients who would present liquid extravasations, besides intravascular space, in the immediate postoperative period. The inflammatory process after CPB has its final lesion characterized by an increase of diffuse capillary permeability with significant liquid extravasation towards the

Table 1 – Comparison between Group I and II concerning predisponent factors for the development of SIRS-CPB

Variable	Group I (SIRS) n=22 Mean ± SD	Group II (no SIRS) n=79 Mean ± SD	p
Age (months)	6,8 ± 5,5	10,8 ± 5,1	0,002
Weight (kg)	5,3 ± 1,9	6,9 ± 2,0	0,001
CPB time (min.)	125,1 ± 49,5	93,9 ± 33,1	0,001
Aortic clamping time (min.)	82,3 ± 34,0	64,2 ± 24,3	0,006

SIRS – systemic inflammatory response syndrome

Table 2 - Analysis of the comparison between Group I and II clinical outcomes. Values expressed in median and inter-quartile interval

Variable	Group I (SIRS) n=22	Q25-75	Group II (no SIRS) n=79	Q25-75	p-value
Duration of MV (hours)	120.0	43.3-288.0	13.0	4.0-24.0	<0.001
Permanence in ICU (hours)	265.0	205.0-554.8	107.0	81.0-148.0	<0.001
Hospitalization (days)	22.0	16.0-35.0	10.0	8.0-15.0	<0.001

SIRS – systemic inflammatory response syndrome; MV – mechanical ventilation; ICU – intensive care unit.

interstitial tissue[7-25]. This finding could be partially explained by the presence of what is currently called endothelial dysfunction. In these case, the endothelium is the target for the inflammatory chain and, when it expresses adhesion molecules, it also adheres and activates leukocytes, causing lesion in this barrier and permits a free liquid flow from the intra-vascular space to the interstitial tissue[3,29]. It is believed that this radiologic data may be explored in a prospective study, for it could represent a precocious diagnostic tool for SIRS-CPB in this group of patients.

Carriers of SIRS-CPB present independent lower age and weight, hence there is a protective factor when older patients are treated. The biggest surgical technique complexity in neonatal period, together with the biggest surface of relative exposition of CPB circuits, could explain the frequent occurrences of SIRS-CPB in children and its protective effect in young adults.

In this paper, mean CPB duration was significantly longer in Group I than Group II. The same result was observed with regard to time of aortic occlusion. Both groups presented Odds Ratio equal to 1.02. Kirklin et al[5], in 1983, observed that CPB's increase from 60 to 120 minutes would also increase postoperative morbidity in all age groups.

The group with SIRS-CPB patients had a worse outcome concerning the time period of hospitalization. These patients are kept for longer periods in mechanical ventilation, which could be explained by two reasons. The first one would be that CPB may unleash a pulmonary injury comprised in the inflammatory chain, in which pulmonary *leukocyte sequestration and endothelial injury happen*[5]. The second reason may be directly related to the first one, for patients who are kept for longer periods of time in mechanical ventilation are exposed to a higher risk of pneumonia and direct pulmonary injury (barotrauma, volutrauma and injury by O_2)

Despite the fact that cases of infection in the immediate postoperative period were retrospectively rejected, dosages of serum *procalcitonin could be useful for these patients as a means of excluding infections*[30,31]. These factors were minimized through a selection criterion, in which patients that underwent elective surgeries and that presented no preoperative factors that could unleash SIRS were chosen. Patients who presented clinical status compatible with infection and whose evolvement and hemoculture results confirmed these initial impression were not selected.

Recently, the hypothesis that the utilization of corticosteroids in the postoperative period would minimize the inflammatory process and that their reposition would diminish hemodynamic dysfunction, which is common in this period, have been considered, since adrenal failure is very common in severely sick patients[32,33].

The present study shows limitations in its final conclusions, for it deals with a retrospective analysis in which the clinical variables could not be controlled. There were no available quantitative data concerning measures of hemodynamic dysfunction, like invasive procedures of cardiac output, which could precisely define a situation of hemodynamic dysfunction.

Conclusions

Based on clinical criteria established for this retrospective study, it was possible to identify that patients with lower weight and prolonged CPB belong to a risk population for development of SIRS-CPB. These individuals remain for longer periods in mechanical ventilation, in intensive care units and in general hospital.

Potential Conflict of Interest

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

Sources of Funding

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Study Association

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