Epidemiology of viral respiratory infections in children undergoing heart surgery

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ABSTRACT

Background: Acute viral respiratory infections (VRI) are the most common diseases in humans and are associated with high morbidity and mortality in infants and the elderly. Children with congenital heart disease (CHD) are more susceptible to get severe forms of VRI due to their altered lung mechanics, leading to several complications, such as increased hospital stay, longer mechanical ventilation, and higher mortality. This study aimed to identify the frequency of VRI in children with CHD undergoing cardiac surgery, and to compare the major outcomes according to the presence or absence of a VRI.
Methods: This was a longitudinal, observational cohort study. Nasopharyngeal secretion samples were collected pre- and postoperatively for patients undergoing cardiac surgery, from May 2013 to May 2014. Respiratory viruses were detected using CLART Pneumovir®.
Results: Forty-eight patients were enrolled. We found a VRI preoperatively in 16 children with CHD before surgery (33.3%), and the frequency of new infections was 8.3% (4 patients). However, in this study, in univariate analyses, the two groups did not differ in any of the studied outcomes. In the multivariate regression models, adjusting for age and STAT category, the presence of a VRI did not show a significant effect on the major outcomes.
Conclusions: In conclusion, VRI was frequent in children undergoing open-heart surgery, but the presence of a VRI did not impact on major outcomes in this cohort.

1. Introduction

Viral respiratory infections (VRI) are one of the leading causes of hospitalization during the first year of life [1]. The most prevalent viruses are respiratory syncytial virus (RSV), rhinovirus, bocavirus and others [2,3]. Some strategies are used in selected children, including those with congenital heart disease (CHD), to prevent VRI-related hospitalizations, like palivizumab [4,5].

Children with CHD have altered lung mechanics, decreased lung compliance and increased pulmonary vascular resistance. Therefore, they are more susceptible to complications of VRI, especially when they undergo open-heart surgery [5,6].

Clinical detection of a VRI in children after open-heart surgery is a challenging task, and potentially lead to unnecessary use of antibiotics. Depending on the magnitude of the problem, more aggressive intervention towards VRI prevention may be needed.

The frequency of VRI and the most prevalent agents in children with CHD undergoing heart surgery at our hospital are not known. Our hypothesis is that VRI are highly prevalent in our patients and that they are associated with poorer outcomes. We aimed to determine the frequency of VRI in children submitted to heart surgery for CHD, and to estimate their impact on major outcomes: duration of mechanical ventilation, length of hospital and ICU stay, and mortality.

2. Patients and Methods

This was a longitudinal, observational, cohort study. All patients scheduled for heart surgery for CHD at our institution, a tertiary-care university hospital, between May 2013 and May 2014, were eligible. Patients were routinely assessed for respiratory symptoms the day before surgery. Since only patients without respiratory symptoms are operated, only these were included. The study was approved by the

local institutional review board (#270.409) and signed informed consent was required for enrollment.

The study consisted of collection of respiratory secretion samples, extraction of nucleic acids, PCR amplification, and microarray detection and reading. Collection of respiratory secretion samples was performed as follows: the day before surgery, three days after surgery, and seven days after surgery. All patients were tested at the three moments. Virus detection tests were done only after the study was finished; therefore, results were not timely available to affect medical decisions. We used an automated method (CLART Pneumovir®, Genomica, Madrid, Spain). This method can qualitatively detect up to 18 different respiratory viruses: RSV A and B, parainfluenza 1, 2, 3, 4A and 4B, coronavirus 229E, metapneumovirus A and B, adenovirus, enterovirus B, rhinovirus, influenza A (including H1N1), B, and C, and bocavirus, with specificity of > 99% for all viruses. Demographic and surgical data, and outcomes were collected from medical charts. Surgical complexity was categorized using STAT (STS–EACTS Congenital Heart Surgery Mortality Category) [7].

Patients with a first-sample (preoperative) positive result were considered home-infected if they were admitted for < 48 h, and hospital-infected if they were admitted for 48 h or more prior to sample collection. A hospital-acquired VRI was defined by a positive result any time after an initial (within 48 h from admission) negative result for viruses.

Pulmonary complications such as congestion and atelectasis were diagnosed by agreement between respiratory therapists and at least three medical staff looking at chest radiographs in light of clinical data.

2.1. Statistical Analysis

We used IBM SPSS 20.0 (Chicago, IL). Results were expressed as mean (standard deviation), median (range), or counts (proportions), according to data type and distribution. The frequency of VRI was calculated by dividing the number of cases of VRI by the number of patients. For comparison between groups (with and without VRI), we used Fisher's exact test, Student's *t*-test, or Mann-Whitney's *U* test, as appropriate. Multivariate logistic or linear regression models were used, for binary or continuous outcomes, respectively, to identify the influence of a VRI on the major outcomes. Independent variables were: presence of VRI, age, and STAT category. Effect sizes were estimated by parameter estimates and significance of these associations were assessed by 95% confidence intervals. A significance level of 0.05 was adopted.

3. Results

Sixty-one patients were operated in the time frame, but only 48 patients were included in the study. Among the non-included patients, four underwent emergency surgery, and nine did not consent. Twenty-three patients (47.9%) were male, and 14 (29.1%) died. Tables 1, 2 and 3 present demographic and surgical data, and outcomes, respectively, according to the presence of VRI.

Although patients with VRI were more likely to have lower STAT categories, neither STAT nor age at surgery were significantly different between patients with and without VRI.

All patients were admitted in the pediatric intensive care unit (PICU) after surgery, mechanically ventilated. Forty patients (83%) were extubated at least once, and 15 of them (37.5%) have had at least one extubation failure. Tracheostomy was needed in 3 patients.

Regarding postoperative pulmonary complications, we found pulmonary congestion in 42 patients (87.5%), pleural effusions in 21 patients (43.7%), and atelectasis in 20 patients (41.6%). Twenty-four patients (50%) have had two or more of these pulmonary complications. VRI was present preoperatively in 16 patients (33.3% of total), while 4 patients acquired a VRI during hospital stay (8.3% of total) in this cohort, with a total frequency of 41.6%. The number and type of

Table 1
Demographic and surgical data according to the presence of any viral respiratory infection (VRI).

	VRI present (n = 20)	VRI absent (n = 28)	p
Age at surgery	10 months (9 days, 16.5 years)	7.3 months (2 days, 12 years)	0.237
STAT category			0.245
1	2 (10%)	4 (14%)	
2	6 (30%)	2 (7%)	
3	6 (30%)	9 (32%)	
4	5 (25%)	8 (28%)	
5	1 (5%)	5 (17%)	
CPB duration (minutes)	110 (40, 190)	132.5 (45, 325)	0.194
XAo duration (minutes)	69 (25, 114)	94 (20,170)	0.227

Legend: VRI, viral respiratory infection; STAT, STS–EACTS Congenital Heart Surgery Mortality Category; CPB, cardiopulmonary bypass; XAo, aortic cross-clamping. Values are expressed as median (range) or count (proportion).

viruses we found are shown in Fig. 1. Among children with a VRI, association of two viruses were found in four patients: two had enterovirus B plus influenza A H1N1, one had adenovirus plus rhinovirus and one had enterovirus B plus rhinovirus. VRI were more frequent during winter (55%) than in fall (20%) and in spring and summer (10%). Immunoprophylaxis against RSV was given to seven patients before surgery. Of these, four have had a VRI, but not caused by RSV.

3.1. VRI and Outcomes

In univariate analyses, the two groups did not differ in any of the studied outcomes: duration of mechanical ventilation (p = 0.09), arteriovenous oxygen difference (p = 0.71), vasoactive-inotropic score (p = 0.85), extubation failure (p = 0.47), PICU and hospital length-of-stay (p = 0.10 and 0.16, respectively). Surprisingly, mortality was lower in patients with VRI (20 *vs.* 35%, p = 0.33), although not statistically significant due to the small number of patients.

To better understand these apparently similar outcomes in patients with and without VRI, multivariate regression models were used to adjust for age and STAT categories (1–3 *versus* 4–5). In multivariate logistic regression models, the odds-ratio (OR) for death was strongly influenced by age at surgery, but not by STAT ≥4 or the presence of a VRI. The OR for extubation failure was not influenced by any of the predictors. In multivariate general linear models, arterial-venous oxygen difference [D (A-V) O_2] and the vasoactive-inotropic score (VIS) were not influenced by any of the predictors. Length of mechanical ventilation was only influenced by STAT ≥4, and not by age at surgery or the presence of a VRI. Length of ventilatory support (invasive and non-invasive) and hospital stay were influenced by age at surgery and STAT ≥4, but not by the presence of a VRI. Finally, PICU length-of-stay was influenced only by age at surgery, but not by STAT ≥4 or the presence of a VRI. Overall, the presence of a VRI did not affect the major outcomes. These results are depicted in Tables 4 and 5.

In this cohort, 27 patients (56%) were given antibiotics because of suspected postoperative bacterial infection. Of these, five patients were positive for VRI but had negative cultures for bacteria.

4. Comment

We found a high frequency of children with a VRI undergoing open-heart surgery in our hospital (41.6%), with a frequency of hospital-acquired VRI of 8.3%. The most prevalent respiratory viruses found in our study were: rhinovirus, bocavirus, enterovirus B, influenza A (H1N1), influenza C, adenovirus, RSV A, and coronavirus. In our study, since these results were available only long after the surgery, none was cancelled or postponed because of it.

Table 2
Anatomic diagnosis of patients.

Anatomic diagnosis	N	Procedures performed
Pulmonary valve atresia or stenosis	10	Aortopulmonary shunt (n = 6), right ventricle to pulmonary artery conduit placement (n = 4)
Atrioventricular canal (total)	9	Atrioventricular canal repair (n = 9)
ASD, VSD, or both	7	ASD primary closure (n = 3), VSD patch repair (n = 4), both (n = 1)
Tetralogy of fallot	7	Aortopulmonary shunt (n = 4), VSD closure, myomectomy and transannular patch (total repair, n = 3)
Hypoplastic left heart syndrome	4	Norwood procedure (n = 3), pulmonary artery banding (n = 1)
Tricuspid atresia	2	Aortopulmonary shunt (n = 2)
Total or partial anomalous pulmonary vein connection	2	Anastomosis of anomalous veins to the left atrium (total repair, n = 2)
Mitral stenosis	2	Mitral valve plasty (n = 2)
Coarctation of the aorta	1	Coarctation repair (n = 1)
Subaortic stenosis	1	Aortic valve plasty (n = 1)
Anomalous origin of left coronary artery	1	Reimplantation of anomalous artery (n = 1)
Patent ductus arteriosus	1	Ligation (n = 1)
Transposition of great arteries	1	Arterial switch operation (n = 1)

Legend: ASD, atrial septal defect; VSD, ventricular septal defect.

Table 3
Postoperative outcomes according to the presence of viral respiratory infection.

Outcome	VRI present (n = 20)	VRI absent (n = 28)	p
D (A-V) O_2 (%)	26.7 ± 10.6	27.8 ± 9.6	0.716
VIS	5 (0, 30)	6 (0, 62)	0.853
Extubation failure	3 (17.6%)	7 (30.4%)	0.471
Duration of invasive ventilatory support (days)	1 (0, 44)	7 (0, 44)	0.094
Duration of both invasive and non-invasive ventilatory support (days)	4.5 (0, 63)	11 (0, 63)	0.166
Length of PICU stay (days)	6.5 (1, 73)	15.5 (1, 73)	0.109
Length of hospital stay (days)	11 (4, 164)	27 (4, 164)	0.160
Mortality	4 (20%)	10 (35.7%)	0.338

Legend: VRI, viral respiratory infection, D (A-V) O_2; arterial-venous oxygen difference; VIS, vasoactive-inotropic score; PICU, pediatric intensive care unit. Values are expressed as mean ± standard deviation, median (range), or count (proportion).
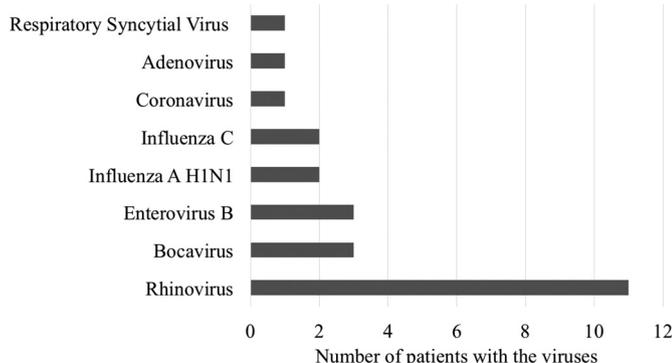

Fig. 1. Number and type of viruses detected in all patients. Legend: RSV, respiratory syncytial virus.

Table 4
Summary of variables independently associated with the main continuous outcomes in multivariate linear regression models, with corresponding parameter estimates (β) and 95% confidence intervals (95%CI).

Continuous outcome	Age (in days)	STAT ≥4	VRI present
D (A-V) O_2	0.002 (−0.001, 0.004)	−1.527 (−8.205, 5.150)	−1.223 (−7.544, 5.098)
VIS	0.001 (−0.002, 0.004)	5.577 (−2.106, 13.261)	0.542 (−6.751, 7.834)
Duration of invasive ventilatory support	−0.003 (−0.007, 0.000)	**11.542** (**0.671, 22.413**)	−4.037 (−14.294, 6.220)
Duration of both invasive and non-invasive ventilatory support	−0.006 (−0.011, −0.001)	**16.421** (**1.667, 31.174**)	−8.093 (−22.069, 5.884)
Length of PICU stay	−0.007 (−0.013, −0.001)	16.351 (−0.403, 33.105)	−9.615 (−25.549, 6.320)
Length of hospital stay	−0.015 (−0.028, −0.002)	**43.044** (**4.207, 81.881**)	−20.887 (−57.825, 16.050)

Legend: STAT, STS–EACTS Congenital Heart Surgery Mortality Category; VRI, viral respiratory infection; D (A-V) O_2, arterial-venous oxygen difference; VIS, vasoactive-inotropic score; PICU, pediatric intensive care unit. Bold means a significant effect at p < 0.05.

Table 5
Summary of variables independently associated with the main categorical outcomes in multivariate logistic regression models, with corresponding odds-ratios (OR) and 95% confidence intervals (95%CI).

Categorical outcome	Age (in days)	STAT ≥4	VRI present
Extubation failure	0.997 (0.992, 1.001)	0.271 (0.234, 7.345)	0.796 (0.085, 2.393)
Mortality	**0.990** (**0.982, 0.997**)	0.738 (0.133, 4.099)	0.833 (0.146, 4.751)

Legend: STAT, STS–EACTS Congenital Heart Surgery Mortality Category; VRI, viral respiratory infection. Bold means a significant effect at p < 0.05.

Bicer et al. studied incidence and etiology of viral infections among hospitalized children with VRI symptoms. They found a prevalence of 66.5%, and the most prevalent viruses were RSV, adenovirus, parainfluenza, and rhinovirus [8]. In our study, the frequency was lower, probably because we studied asymptomatic children, and the types of viruses were also different.

In our study, we used a polymerase chain reaction (PCR)-based, commercially-available, automated method that can detect 18 different viruses at once. Kanashito et al. compared three different methods of detecting VRI in humans: direct immunofluorescence, single-, and multiplex-PCR. In 39 nasopharyngeal samples from children with congenital heart disease, they found a VRI prevalence of 64.1%. Multiplex

PCR performed better than the other methods [9]. Krause et al. highlighted the usefulness of multiplex PCR tests to distinguish VRI from bacterial infections in children [10]. VRI can lead to unnecessary use of antibiotics. In our study, this may have occurred in five patients.

In our study, the presence of VRI was not associated with major outcomes after open-heart surgery in children. These findings did not confirm those reported by other investigators. Delgado-Corcoran et al. investigated the prevalence of rhinovirus in children submitted to heart surgery, and showed that patients with VRI had longer duration of

mechanical ventilation, more extubation failures, frequent use of bronchodilators, and longer hospital stay [11]. In another study, children submitted to open-heart surgery that had VRI experienced longer hospital and PICU length-of-stay, compared with matched controls [12]. Altman et al. studied the impact of RSV infection in children with CHD, and they found that these patients had more significant morbidity and higher mortality, with higher healthcare-associated costs [6]. We speculate that our results were negative because of: (a) limited power, given the small sample size, and (b) detection of viruses in asymptomatic children, since the ones with symptoms of VRI were rescheduled. In the study by Delgado-Corcoran et al. [11], children were considered infected when they had symptoms of VRI, while in the study by Spaeder et al. [12], infection was defined as the presence of viruses in nasopharyngeal or endotracheal specimens. Although there is evidence that a symptomatic VRI will negatively impact outcomes [12], it is not clear whether asymptomatic presence of a virus in the respiratory system will affect the outcomes. Therefore, the usefulness and the cost-effectiveness of screening all children scheduled for congenital heart surgery regarding the presence of respiratory viruses need clarification.

In Brazil, RSV is the most common cause of VRI requiring hospitalization in children [13]. In a systematic review of 20 published studies, Homaira et al. showed that patients who most benefit from passive immunization against RSV were preterm infants ($<$ 33 weeks), children with chronic lung disease and children with congenital heart disease [14]. However, the most frequent virus in our patients was rhinovirus, and RSV was detected in a single patient. This finding cannot be attributed to the use of passive immunization against RSV, since only a few of our patients were given it.

Some authors recommend screening for rhinovirus among patients scheduled for congenital heart surgery, especially infants and toddlers with respiratory symptoms, and that surgery should be postponed if positive; they, however, acknowledge that cost-effectiveness is unknown [11]. Simsic et al. adopted preoperative testing for respiratory virus by PCR before cardiac surgery for all patients with single-ventricle and, if the test is positive, surgery is rescheduled for 6 weeks, pending a negative follow-up viral PCR [15]. There are some rapid tests for VRI in the market, like the Abbott TESTPACK RSV (Abbott Diagnostics, Santa Clara, CA), the QuickVue RSV Test (Quidel Corp., San Diego, CA) or the RAMP® RSV TEST (Response Biomedical Corp., Vancouver, Canada), which are rapid enzyme immunoassay for the direct detection of RSV antigen in nasopharyngeal swab specimens [16]. The clinical value of these rapid tests in children with CHD is unknown. In children admitted to an emergency department, bedside testing for RSV, if immediately available, could have changed medical management in 64% of cases, reduced the number of tests ordered, antibiotics prescribed, and saved an average of USD 669 per patient [17]. Another issue that may be considered is the lack of preventive strategies for most of the viruses that cause VRI in these patients, besides RSV. New vaccines for these viruses could bring benefit to many patients in similar situations.

In our hospital, screening for VRI is not routine. Patients scheduled for congenital heart surgery undergo only clinical evaluation, and surgery is postponed for a few weeks if the patient has symptoms of a VRI. Our findings are important because they bring awareness to the high frequency of asymptomatic VRI in patients with CHD scheduled for open heart surgery, although, here, not associated with poorer outcomes. Although the screening test is non-invasive and technically simple, on the other hand, it is expensive. Besides, identification of a respiratory virus does not necessarily mean an active infection, since respiratory viruses can be detected weeks after a VRI. Nevertheless, despite the limitations of this study, our results suggest that screening asymptomatic children for VRI before open-heart surgery is not cost-effective, since there was no difference in outcomes.

Limitations of this study include: (a) heterogeneity of patients

regarding anatomic diagnoses, (b) the wide range of ages at surgery, and (c) higher mortality than that of centers from developed countries. Therefore, our results may not apply for resource-rich centers in developed countries, they do, at least in part, for limited-resource centers from developing countries.

In conclusion, VRI was frequent in children undergoing open-heart surgery, but the presence of a VRI did not impact on major outcomes in this cohort.

Conflict of Interest

Compliance with Ethical Standards

Acknowledgments

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