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Research paper

Respiratory morbidity in children with congenital heart disease

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ABSTRACT

Objective: To evaluate the respiratory outcome in children with congenital heart disease (CHD), considering recent management procedures and the CHD pathophysiology.
Design and Setting: Clinical and functional respiratory outcome were evaluated in 8-year-old children with isolated CHD followed up from birth in the prospective population-based EPICARD cohort.
Patients: Children were assigned to two groups, based on the pathophysiology of the CHD: CHDs with left-to-right shunt (n = 212) and CHDs with right outflow tract obstruction (n = 113).
Results: Current wheezing episodes were observed in 15% of the children with isolated CHD and left-to-right shunt, and 11% of the children with isolated CHD and right outflow tract obstruction (not significant). Total lung capacity (TLC) was the only respiratory function parameter that significantly differed between the two groups. It was lower in children with left-to-right shunt (88.72 ± 0.65% predicted) than in those with right outflow tract obstruction (91.84 ± 0.96, p = 0.006). In multivariate analysis, CHD with left-to-right shunt (coeff. [95% CI]: -3.17 [-5.45; -0.89]) and surgery before the age of 2 months (-6.52 [-10.90; -2.15]) were identified as independent factors associated with significantly lower TLC values.
Conclusion: Lower TLC remains a long-term complication in CHD, particularly in cases with left-to-right shunt and in patients requiring early repair. These findings suggest that an increase in pulmonary blood flow may directly impair lung development.

Short title: Respiratory outcome in children with CHD

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1. Introduction

Congenital heart diseases (CHDs) are the most common congenital abnormalities with a worldwide prevalence of about 9/1000 birth [1]. Their surgical and medical management has improved considerably in recent years, transforming their prognosis and potentially decreasing the likelihood of long-term complications [2].

CHD has been associated with long-term restrictive pulmonary disease [3–5]. Extrinsic pulmonary causes, including a restrictive thoracic cage due to multiple thoracotomies or spinal deformities, diaphragmatic weakness or paralysis, and skeletal muscle weakness, were thought to make a major contribution to this restrictive disease [6]. The higher prevalence of a restrictive syndrome in patients with tetralogy of Fallot also suggested a role for intrinsic factors, such as alterations to lung development due to a reduction of pulmonary blood flow (PBF) associated with this disease [6]. Consistent with this hypothesis, the frequency of pulmonary hypoplasia has been shown to be higher in fetuses with right outflow obstruction [7].

The postnatal hemodynamic changes observed in CHDs could also have consequences for lung development, as alveolarization occurs mostly after birth. Indeed, a restrictive pulmonary disease has also been detected in 36–47% of patients with CHD and left-to-right shunts [4,8,9]. A direct impact of hemodynamic changes on lung function was strongly suggested by the significantly greater decrease in forced vital capacity in patients with ventricular septal defect (VSD) not undergoing surgery than in those undergoing surgery [10]. In infants with left-to-right shunt, surgery and shunt closure increase lung volume and improve respiratory mechanics rather than impairing respiratory function [11]. In order to better understand the functional respiratory outcome of children with CHD, considering recent management procedures, and the pathophysiology of the CHD, we evaluated clinical and functional respiratory outcomes in 8-year-old children with CHD followed up from birth in the prospective population-based EPICARD cohort [12].

2. Methods

2.1. Data source

We used data from a population-based, prospective cohort study of children with CHD born in the Greater Paris area (Paris and its suburbs) and from the EPICARD study. This study included all cases (live births, pregnancy terminations due to fetal abnormalities, fetal deaths) diagnosed in the prenatal period or up to the age of 1 year in birth cohorts from May 1, 2005 to April 30, 2008. Major abnormalities and a sample of minor VSDs were prospectively followed up through assessments at the ages of 3 (only cardiological assessment) and 8 years (cardiological and respiratory assessment). Written informed consent was obtained from study participants, and the study was approved by the French Ethics Committee *Comité de Protection des Personnes* (CPP) Ile-de-France II (No. 2013-02-06, Ref. P121201).

2.2. Study population

We assessed 981 of the children eligible for follow-up in the EPICARD cohort at the age of 3 years, and 753 at the age of 8 years. The characteristics of the children assessed at the age of ei8ght years and of the children lost to follow-up are indicated in Appendix 1.

Of the 753 children assessed at the age of 8 years, we excluded 153 children with a chromosomal or other associated congenital abnormality, and 135 with isolated CHD but equivocal physiology or postoperative changes in PBF (Fig. 1). In total, 465 children were eligible for inclusion in the study and underwent a complete clinical evaluation, lung function tests, and an echocardiogram, performed in each case by the same experienced pediatric cardiologist. The main outcome measure was total lung capacity (TLC).

No lung function test (LFT) results were obtained from 140 of these children (four failed to perform LFTs properly and no LFTs were performed for the others), who were excluded.

Thus, 325 children were considered for the final analysis. They were assigned to two subgroups, based on the pathophysiology of the CHD. All cases were reviewed by two trained pediatric cardiologists, and were classified as CHD with left-to-right shunt or CHD with a right outflow tract obstruction:

- CHD associated with left-to-right shunt (n = 212), including 167 atrial and/or ventricular septal defects, 11 atrial and/or ventricular septal defects associated with aortic coarctation, and 23 other complex CHDs.
- CHD associated with a right outflow tract obstruction (n = 113), including 21 cases of tetralogy of Fallot, 87 of pulmonary valvular stenosis, and 38 other complex CHDs.

Passive smoking at home was coded according to the parents' report. Clinical characteristics (prematurity [gestational age <37 weeks], hypotrophy [birth weight <10th percentile], prenatal diagnosis, type of CHD, CHD management until the age of 8 years, including sternotomy) were extracted from the EPICARD database, and completed by evaluation at the age of 8 years. CHD status at 8 years of age was coded in five classes: (1) spontaneous resolution, (2) minor, nonoperated CHD, (3) repaired CHD with the first intervention (surgery or cardiac catheterization) performed before the age of 2 months, (4) repaired CHD with the first intervention performed between the ages of 2 and 5 months, and (5) repaired CHD with the first intervention performed after the age of 6 months. Asthma symptoms were evaluated with the standardized ISAAC questionnaire, completed by the parents: asthma ever during the patient's lifetime, wheezing during the last 12 months, and wheezing ever during the patient's lifetime. Hospitalization for respiratory causes (lower respiratory tract infection, wheezing exacerbation, acute dyspnea, etc.) before and after the age of 3 years was reported by parents.

2.3. Functional evaluation

The lung function tests (LFTs) performed were spirometry and plethysmography, which were carried out in accordance with the recommendations of the American Thoracic Society/European Respiratory Society task force [13]. GLI 2012 lung function regression equations from the Global Lungs Initiative/ERS Task Force 2012 were used to calculate the percentage of predicted value for age and height and Z-score values of spirometric indices (FVC, FEV_1), and the Utrecht dataset [14] was used to calculate the percentage of the predicted

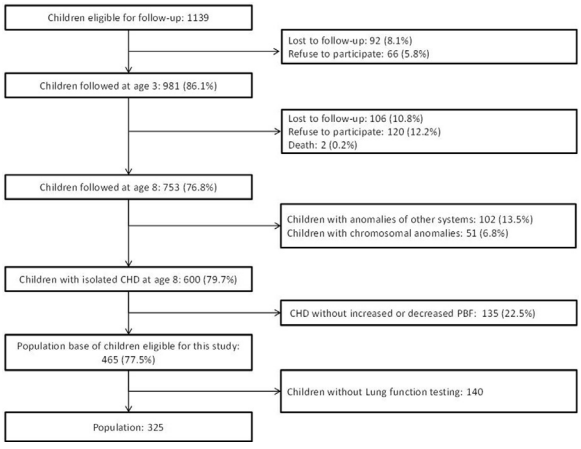

Fig. 1. Study flow-chart
CHD: congenital heart disease.

value for TLC, the main outcome measure in this study. The restriction threshold was defined by a TLC value below 80% of predicted value for age and height.

2.4. Statistical analysis

Data are expressed as mean ± SEM. We compared the distribution of sociodemographic and clinical characteristics, and the results of pulmonary function tests (FEV_1 pre-bronchodilator, FVC, FEV_1/FVC and TLC) in the two groups, with the usual tests (χ^2 or Fisher's exact test for categorical variables and *t* tests or ANOVA for continuous variables). For TLC, we obtained unadjusted and adjusted estimates of the effect of type of PBF, through simple and multiple linear regression analyses. In addition to the subgroup of CHD, the multiple regression analysis included the following potentially confounding variables: CHD status at 8 years of age, sternotomy, exposure to passive smoking in the last 12 months, and prematurity. The choice of variables for inclusion in the multiple regression model was based on published findings and assumptions about the variables. Estimates from the regression models are reported with regression (β) coefficients, corresponding to the effect of a one-unit change in each variable relative to its reference category, and the 95% confidence interval (CI). All analyses were performed with Stata v14 (StataCorp, College Station, TX, USA). A p value less than 0.05 was considered to be statistically significant.

3. Results

3.1. Population description

The characteristics of the study population are presented in Table 1. No significant difference was observed between the subgroup of children who performed LFTs and the subgroup of children who did not (Appendix 2).

The mean age of the patients was 8.2 years; 46% were male and 18.5% were born preterm. There was no significant difference between subgroups of CHD for age, sex ratio, term at birth, and tobacco exposure. Cardiac echography at the age of 8 years showed that 48% of all CHDs resolved spontaneously, and that 14% of patients had a minor but persistent CHD that had never required treatment. At least one therapeutic procedure had been performed on 100 children (30.8%). These procedures included surgical repair with sternotomy (n = 93) or catheterization (n = 7). Mean age at first procedure was 8.2 months, with no significant difference between groups.

3.2. Clinical respiratory outcome

Clinical respiratory outcome did not significantly differ between the two subgroups of CHD (Table 1). More than one third of the population had experienced at least one wheezing episode at some time in their lives, 14% were still wheezing during the last 12 months, and 7% still required long-term daily respiratory treatment. The percentage of children hospitalized for a respiratory cause between birth and 3 years of age was slightly higher in the group with CHD and left-to-right shunt (20%) than in the group with CHD and right outflow tract obstruction (12%), but this difference was not statistically significant.

3.3. Lung function outcome

FEV_1 and FEV_1/FVC measurements showed no obstructive pattern and no difference between subgroups (Table 2). By contrast, TLC was significantly lower in children with CHD and left-to-right shunt than in children with CHD and right outflow tract obstruction (Table 2, p = 0.006). However, only 32 children with left-to-right shunt (15%) had a TLC below 80% of the predicted value, whereas this was the case for 12 children with right outflow tract obstruction (11%; p = 0.236). No difference between the subgroups was observed for other LFT parameters (Appendix 3).

Multivariate analysis confirmed that CHD with left-to-right shunt was an independent factor associated with significantly lower predictive values for TLC coefficient (−3.17; 95% CI: −5.45; −0.89) (Table 3). Undergoing surgery before the age of 2 months was also an independent worsening factor associated with significantly lower predictive values for the TLC coefficient (−6.52 [−10.90; −2.15]) (Table 3, Fig. 2).

Repair by median sternotomy was significantly associated with TLC values in univariate analysis, but not in multivariate analysis.

We also conducted a sensitivity analysis with multiple imputations of TLC data for children without LFT, and of missing data for passive smoking (n = 6) and prematurity (n = 1), which yielded similar results (Appendix 4).

Table 1
Characteristics of the study population.

	Total (N = 325)	CHD with left-to-right shunt (N = 212)	CHD with right outflow tract obstruction (N = 113)	p
Age (years)	8.2 ± 0.01	8.2 ± 0.01	8.2 ± 0.01	0.233
Sex ratio (male)	150 (46.2)	104 (49.1)	46 (40.7)	0.150
Prematurity	60 (18.5)	37 (17.5)	23 (20.5)	0.462
Asthma (ever)	62 (19.2)	39 (18.5)	23 (20.5)	0.656
Wheezing during the last 12 months	44 (13.6)	32 (15.2)	12 (10.6)	0.255
Wheezing (ever)	123 (37.9)	84 (39.6)	39 (34.5)	0.366
At least 1 hospitalization age 0–3*	56 (17.2)	42 (19.8)	14 (12.4)	0.092
At least 1 hospitalization age 3–8*	16 (4.9)	12 (5.7)	4 (3.5)	0.591
Pulmonary treatment during the last 12 months	21 (6.6)	16 (7.8)	5 (4.5)	0.265
Passive smoking during the last 12 months	97 (28.9)	60 (28.3)	37 (32.7)	0.405
Thoracic surgery	100 (30.8)	73 (34.4)	27 (23.9)	0.050
Sternotomy	93 (28.6)	66 (31.1)	27 (23.9)	0.169
Age at first thoracic surgery (months)	8.2 ± 1.4	7.9 ± 1.7	8.5 ± 2.3	0.825
CHD management				0.485
Spontaneous resolution	157 (48.3)	108 (50.9)	49 (43.4)	
Minor CHD, not operated	45 (13.9)	30 (14.2)	15 (13.3)	
Repaired CHD, first intervention <2 months	41 (12.6)	27 (12.7)	14 (12.4)	
Repaired CHD, first intervention 2–5 months	49 (15.1)	27 (12.7)	22(19.5)	
Repaired CHD; first intervention ≥6 months	33 (10.2)	20 (9.4)	13 (11.5)	

Data are mean ± SEM or N (%).
* Hospitalization rate is for respiratory illness. CHD: congenital heart disease.

Table 2
Pulmonary function tests.

	Total (*N* = 325)	CHD with left-to-right shunt (*N* = 212)	CHD with right outflow tract obstruction (*N* = 113)	*p*
FEV_1 (Z-score) mean±SEM	0.07 ± 0.07	0.00 ± 0.09	0.19 ± 0.11	0.195
FVC (% predicted)	103.07 ± 0.80	102.01 ± 1.04	105.05 ± 1.18	0.068
FEV_1/FVC (%)	86.96 ± 0.42	87.07 ± 0.50	86.77 ± 0.76	0.736
TLC (% predicted)	89.82 ± 0.55	88.72 ± 0.65	91.84 ± 0.96	0.006
TLC < 80% (N,%)	44 (13.5)	32 (15)	12 (11)	0.236
TLC according to CHD management				
Spontaneous closure	91.40 ± 0.73	90.50 ± 0.87	93.37 ± 1.31	0.068
Minor residual shunt, not operated	89.78 ± 1.24	88.35 ± 1.20	92.63 ± 2.79	0.105
Repaired CHD, first intervention <2 months	83.70 ± 1.52	81.87 ± 1.73	87.09 ± 2.81	0.102
Repaired CHD, first intervention 2–5 months	88.73 ± 1.68	85.76 ± 2.39	92.12 ± 2.19	0.058
Repaired CHD; first intervention ≥6 months	91.41 ± 1.72	92.47 ± 1.78	89.85 ± 3.39	0.462

Data are mean ± SEM.FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; CHD: congenital heart disease; TLC: total lung capacity.

Table 3
Factors associated with total lung capacity (TLC).

		Univariate			Multivariate		
TLC	*N*	Coef.	95% CI	*p*	Coef.	95% CI	*p*
CHD management							
Spontaneous closure	157	Ref		<0.0001	Ref		0.005
Minor residual shunt, not operated	45	−1.62	−4.79; 1.55		−1.79	−4.93; 1.36	
Repaired CHD, first intervention <2 months	40	−7.70	−11.02; −4.38		−6.52	−10.90; −2.15	
Repaired CHD, first intervention 2–5 months	47	−2.66	−5.78; 0.46		−1.36	−6.25; 3.54	
Repaired CHD, first intervention ≥6 months	32	0.10	−3.63; 3.65		1.08	−3.58; 5.75	
Type							
All CHD with right outflow tract obstruction	113	Ref		0.006	Ref		0.007
All CHD with left-to-right shunt	208	−3.12	−5.35; −0.89		−3.17	−5.45; −0.89	
Sternotomy							
No	231	Ref		0.001	Ref		0.307
Yes	90	−3.91	−6.27; −1.54		−2.20	−6.41; 2.03	
Passive smoking 12 months							
No	224	Ref		0.866	Ref		0.508
Yes	97	−0.20	−2.55; 2.15		−0.77	−3.04; 1.51	
Prematurity							
No	261	Ref		0.895	Ref		0.546
Yes	59	−0.19	−2.97; 2.60		−0.83	−3.52; 1.87	

CHD: congenital heart disease; CI: confidence interval.

4. Discussion

The aim of this study was to describe clinical and functional respiratory outcomes for a large population-based cohort of patients with CHD and to identify main contributors to respiratory outcome.

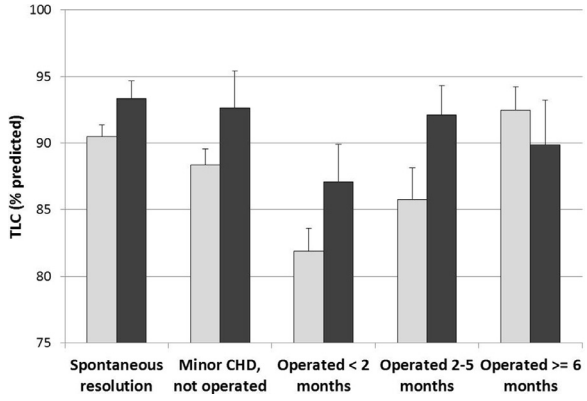

Fig. 2. Total lung capacity (TLC) values according to management of the congenital heart disease (CHD)

Gray columns: CHDs with left-to-right shunts; black columns: CHDs with right outflow tract obstruction. Values are mean ± SE.

No significant difference was found in the prevalence of wheezing or asthma between children with CHD and left-to-right shunt and those with CHD and right outflow tract obstruction, thus not confirming previous studies that suggested the prevalence of obstructive respiratory illness was higher in left-to-right shunt CHDs [15]. In our study, the proportion of children with wheezing in the last 12 months was very similar to that reported for the French general population. The most recent French school surveys of children at the age of 10 years have reported a prevalence of 11% for wheezing in the last 12 months [16]. The proportion of children receiving regular respiratory treatment was low in our population (7%), but slightly higher than the most recent estimates of 4.2% for the French general population of children aged 5–9 years [17]. Our finding is very close to the 7% of children with daily inhaled treatments reported in a previous cohort of 1188 children with CHD [3].

In accordance with our results for clinical symptoms, we detected no functional obstruction in our population. The FEV_1/FVC ratio was normal in both subgroups. Similarly, a normal FEV_1/FVC ratio was obtained in most previous series, including those with patients with a left-to-right shunt [3,8,18].

A decrease in TLC was observed in our population, and was significantly more marked in children with CHD and left-to-right shunt. This decrease was sometimes important, with TLCs lower than 80% of the predicted values for 13.5% of the population in our study. We can hypothesize that the clinical impact of the decrease in TLC was

greater for these children, but one of the limitations of our study was the absence of dyspnea sensation. Long-term restrictive lung disease in CHD had already been reported in several cohort studies, but was mostly related to CHDs with right outflow tract obstruction, such as tetralogy of Fallot [6]. Nevertheless, the association between CHD with left-to-right shunt and low TLC values has been reported in previous series. In a population evaluated at a median age of 11.3 years, a restriction of lung function was observed in 47% of patients with VSD, and 43% with ASD [9]. In adults with a history of CHD (various diagnoses), restrictive lung disease was found in 36% of patients with history of VSD, ASD, or atrioventricular septal defect [8]. Finally, FEV_1 was found to be significantly lower in 182 consecutive patients with surgical VSD closure than in controls, with no difference in FEV_1/FVC ratio [18].

Mechanical extrapulmonary factors are unlikely to have made a significant contribution to the decline in TLC in our population. Sternotomy was not identified as an independent factor contributing to TLC in multivariate analysis, and only one child had marked scoliosis. Intrinsic developmental factors are also thought to contribute to restrictive lung disease [6]. Assuming that the cases of CHD with the most severe hemodynamic alterations were also those that underwent surgery the soonest after birth, our results suggest that these hemodynamic alterations had a highly significant long-term impact on lung development. Such an interaction between hemodynamic alterations and pulmonary development has already been demonstrated, as early as the fetal period, for CHD with a decrease in PBF. Indeed, partial pulmonary artery ligature has been shown experimentally to impair lung development in sheep fetuses [19]. In human fetuses with CHD, pulmonary hypoplasia has been shown to be significantly associated with right outflow tract obstruction [7]. Our results indicate that postnatal hemodynamic changes probably also influence lung development, particularly in patients with left-to-right shunt and a presumed increase in PBF. Indeed, CHD with a left-to-right shunt would not be expected to affect PBF before birth [20]. Instead, PBF increases shortly after birth, this increase being paralleled by a drop in pulmonary vascular resistance. Our demonstration of a deleterious additive effect of left-to-right shunt and the magnitude of the hemodynamic changes, as demonstrated by the young age at surgery of these patients, supports the hypothesis of a direct effect of increases in pulmonary blood flow on early pulmonary development.

Several previous studies support our hypothesis. Altered lung compliance was measured in babies with CHD and a left-to-right shunt before surgery, with significant improvement after surgical shunt closure [11,21]. Persistent ductus arteriosus in preterm newborns is a known risk factor for impaired lung development and the occurrence of bronchopulmonary dysplasia [22]. Persistent ductus arteriosus has been shown to have a direct impact on alveolar development in animal models [23]. The main limitation for this hypothesis is the presumption of alterations to pulmonary blood flow based on CHD anatomy. The presumed effect is generally correct, but may not necessarily be constant over time, from birth to the date of the study. Our results therefore call for prospective studies including a better documentation of the natural course of changes in pulmonary flow in patients with CHD. However, this limitation is unlikely to call into question our demonstration of a deleterious effect on respiratory function of left-to-right shunts with largest hemodynamic consequences. More careful long-term follow-up of these children is therefore required, in collaboration with pediatric cardiologist. Plethysmography should be performed at school age to identify patients who need additional respiratory follow-up and care.

5. Conclusion

The results of this study confirm that low TLC remains a long-term complication in children with CHD, particularly those with left-to-right shunts, and those requiring early repair, which suggests that an increase in PBF can directly impair lung development.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcped.2021.07.003.

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