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Serial Perfusion Study Depicts Pulmonary Vascular Growth in the Survivors of Non-Extracorporeal Membrane Oxygenation-Treated Congenital Diaphragmatic Hernia

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Key Words
Congenital diaphragmatic hernia · Lung perfusion · Vascular growth

Abstract

Background: Pulmonary growth in the survivors of congenital diaphragmatic hernia (CDH) still remains an intriguing issue. In the literature there are conflicting reports on pulmonary vascular growth in CDH. ***Objective:*** In a cohort of CDH patients treated without extracorporeal membrane oxygenation (ECMO), serial perfusion studies were conducted prospectively to follow the growth of pulmonary vasculature. ***Material and Methods:*** Survivors of CDH repair between January 2000 and January 2003 were studied prospectively. Patient demography, time of presentation, arterioalveolar oxygen gradient (A-aDO_2), time to complete lung expansion, and respiratory symptoms were noted. Lung perfusion studies were done at 3 months, 9 months, and 6 years of follow-up. ***Results:*** 24 neonates completed the study. Mean presentation was 6.9 h, and preoperative A-aDO_2 was 288.8. 16/24 were managed by conventional ventilation and 8/24 required high-frequency ventilation and nitric oxide therapy (none were treated with ECMO). Mean duration of preoperative stabilization was 26.5 h, time to full lung expansion was 2.8 days, and postoperative ventilation was 3.7 days. Mean perfusion (%) of ipsilateral lung was 33.7% at 3 months, 43.2% at 9 months, and 46.8% at 6 years. Perfusion of ipsilateral lung improved by 9.4% from 3 to 9 months ($p < 0.001$), 13.1% from 3 months to 6 years ($p < 0.001$), and 3.7% from 9 months to 6 years postoperatively ($p < 0.001$). Respiratory symptoms were seen in 45% (11/24) of survivors at 3 months, 14% (4/24) at 9 months, and 12.5% (3/24) at 6 years postoperatively. ***Conclusions:*** There was reduced perfusion of affected lung at 3 months which improved significantly at 9 months and at 6 years. Recovery of pulmonary vascular function correlated with amelioration of respiratory symptoms. The majority of survivors showing a significant vascular growth lead a symptom-free life.

Introduction

Pulmonary morbidity among the survivors of congenital diaphragmatic hernia (CDH) remains the prime area of concern. Clinical series have documented varying incidences of reactive [1, 2], obstructive [3, 4] or restrictive airways [5, 6], structural thoracic sequel and hypomotility of repaired diaphragm in the long-term survivors. Objective assessments of ventilatory function and perfusion studies have shown conflicting reports on pulmonary growth. It is largely believed that alveolar function shows rapid improvement whereas vascular growth lags behind

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significantly [4, 7–9]. However, marked clinical improvement in respiratory symptoms, absence of significant ventilation-perfusion mismatch and its sequel in the form of pulmonary hypertension in the majority of survivors contradicts this finding [5, 10, 11]. Only a few studies have shown improved vascular remodeling parallel with the alveolar growth of hypoplastic lung in CDH survivors [12–14]. We conducted a prospective study to follow the vascular growth of the lung by serial perfusion scintigraphy in a subset of CDH patients who were managed without extracorporeal membrane oxygenation (ECMO).

Material and Methods

Survivors of CDH repair between January 2000 and January 2003 were included in this prospective study after approval from the Institutional Review Board and clearance from the Ethical Committee. Informed consent was obtained from the parents of each child for the study.

Patient demographics, side of defect, time of presentation, time to stabilization and surgical intervention, preoperative A-aDO_2 (arterial-alveolar oxygen difference), type of ventilator requirement, postoperative time to full lung expansion, and duration of postoperative ventilator support were recorded. Recording of respiratory symptoms and perfusion scintigraphy were done at 3 months, 9 months, and 6 years of follow-up. We have used the principle of permissive hypercapnia and reduced pressure ventilatory strategy (high-frequency ventilation and nitric oxide therapy) while treating our CDH neonates.

Lung Perfusion Scintigraphy

Lung perfusion scintigraphy was performed as per the guidelines of the Society of Nuclear Medicine [15]. A chest radiograph was obtained within a day prior to the test to note any consolidation, atelectasis or mass lesion. An intravenous cannula was introduced and the child sedated with pethidine (1 mg/kg i.v.). The radiopharmaceutical was prepared by tagging macroaggregated albumin (MAA) particles with ^{99}Tc, with a dose of 50,000–100,000 particles [15] and activity of 0.5–2.0 MBq/kg (20–80 μCi). It has a half-life of 1.5–3 h within the lungs. ^{99}Tc-MAA was injected slowly during 3–5 respiratory cycles, with the patient lying supine. Planar images were obtained in anterior, posterior and lateral projections. The percentage function of individual lungs was calculated. Quality control and radiochemical purity and particle size determination of ^{99}Tc-MAA were performed as per the Society of Nuclear Medicine guidelines [15].

Results

During the 3-year study period, 35 neonates with CDH were presented. Four had expired prior to surgery due to intractable pulmonary hypertension and associated anomalies (rachischisis in 1, complex congenital heart disease in 1). Out of remaining 31 neonates who underwent surgery, 28 (90%) survived. 24 survivors of CDH repair completed this prospective study with a minimum of 6 (range 6–8) years of follow-up. There were 15 males and 9 females (ratio 1.6:1). The mean duration of presentation was 6.9 ± 7.2 h. There were 22 left-sided and 2 right-sided defects. Mean preoperative A-aDO_2 was 288.8 ± 176.8. All patients were managed by conventional ventilation initially and 8/24 required high-frequency ventilation and nitric oxide therapy subsequently (table 1). None of the patients were treated with ECMO. The time required for stabilization of physiological parameters and surgical intervention was 26.5 ± 11.5 h. All had primary repair with 6 large defects requiring flap/patch repair. Postoperatively, time to full expansion of lung on plain chest X-ray was 2.8 ± 1.7 days with a mean postoperative duration of ventilator support of 3.7 ± 2.9 days.

Mean percentages of perfusion of ipsilateral lung were 33.7 ± 4.1% at 3 months, 43.2 ± 3.4% at 9 months, and 46.8 ± 2.8% at 6 years. The mean increase of percentage perfusion of ipsilateral lung was 9.4% from 3 months to 9 months postoperatively ($p < 0.001$), 13.1% from 3 months to 6 years postoperatively ($p < 0.001$), and 3.7% from 9 months to 6 years postoperatively ($p < 0.001$).

Respiratory symptoms were seen in 45% (11/24) of survivors at 3 months, 14% (4/24) at 9 months, and finally 12.5% (3/24) remained symptomatic 6 years postoperatively. All 3 children were diagnosed as having reactive airways managed by regular bronchodilators, none being oxygen-dependent.

Modest versus Severe Hypoplasia Groups

There were 16 survivors who were managed by conventional ventilation and 8 survivors were managed by high-frequency ventilation and nitric oxide therapy (out of which 6 had required a patchplasty for their diaphragmatic defect). We believe the former group (non-patch group) would represent a modest degree of pulmonary hypoplasia compared to the latter group, i.e. patch group (for the sake of comparison, we would call this group a patch group although 6 of them actually had patchplasty) (table 1).

Comparison between the two groups (table 2) revealed that the patch group had earlier presentation (2.0 vs. 8.0 h, $p = 0.42$), a higher A-aDO_2 (478.5 vs. 166, $p = 0.0002$), a longer period of preoperative stabilization (36 vs. 24 h, $p = 0.012$), delayed postoperative lung expansion

Table 1. Patient profile

Sl No.	Sex	Side of CDH	Time of presentation, h	Pre-operative A-aDO2	Time to surgery HRS	Time to full lung expansion on X-ray days	Duration of postoperative ventilation days	Perfusion-affected lung			Respiratory symptoms		
								3 months	9 months	6 years	3 months	9 months	6 years
1	M	L	0	300	20	3	2	40	46	48	+	–	–
2	M	L	0	400	36	4	4	30	42	46	+	–	–
3	M	L	6	350	28	3	3	32	44	48	–	–	–
4	F	L	8	300	20	5	3	35	42	48	+	+	–
5	M	R	24	250	6	1	1	40	46	51	–	–	–
6*	M	L	4	500	36	5	7	28	35	42	+	+	+
7*	F	L	6	320	0	4	5	30	42	48	+	–	–
8	F	L	8	126	16	1	1	35	44	52	–	–	–
9	M	L	5	90	16	1	1	40	48	46	–	–	–
10	F	R	28	50	32	1	1	36	40	44	–	–	–
11*	F	L	0	605	48	7	9	28	36	42	+	+	+
12	M	L	10	130	24	3	4	33	44	48	+	–	–
13*	M	L	6	270	28	3	5	36	46	48	–	–	–
14*	F	L	8	573	36	4	10	28	38	42	+	+	+
15	M	L	4	144	16	1	2	32	43	46	–	–	–
16	M	L	16	50	24	1	1	42	48	51	–	–	–
17	F	L	12	90	26	2	2	36	44	48	–	–	–
18*	M	L	0	457	38	4	7	30	42	44	+	–	–
19	M	L	6	193	24	2	2	32	42	51	–	–	–
20	F	L	0	356	32	1	1	35	44	48	–	–	–
21	M	L	8	188	24	1	1	36	48	46	–	–	–
22*	M	L	0	456	32	3	5	30	44	46	+	–	–
23	F	L	8	126	24	2	3	36	46	48	–	–	–
24*	M	L	0	608	50	5	10	30	42	44	+	–	–

* Survivors with high frequency/NO ± patch (patch group). Remaining = Survivors without patch, on conventional ventilation (non-patch group).

(4 vs. 1.5 days, p = 0.0018) and a longer period of postoperative ventilation (7 vs. 2 days, p = 0.0001).

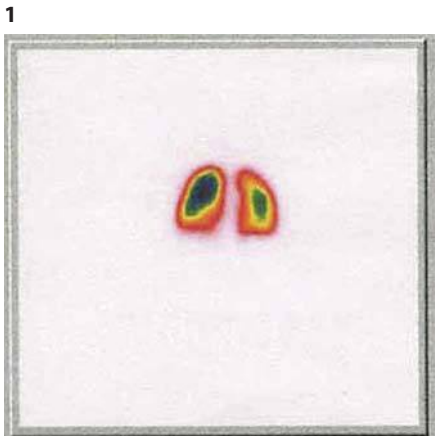
Mean perfusion (%) of ipsilateral lung was also significantly lower among the patch group compared to the non-patch group at 3 months (30.0 vs. 35.5, p = 0.0005), 9 months (42 vs. 44, p = 0.023) and at 6 years (44 vs. 48, p = 0.009) post-repair follow-up (table 3).

Intra-group analysis revealed that perfusion of ipsilateral lung improved consistently and significantly from the 3rd month to 9 months and to 6 years of follow-up in the non-patch group, whereas in the patch group, perfusion showed initial improvement at the 9th month with marginal but insignificant improvement at 6 years compared to that at 9 months (table 4).

Discussion

Pulmonary Vasculature in CDH

Herniation of intestinal contents into developing thoracic cavity affects the airway and vascular development of ipsilateral as well as contralateral lungs known as pulmonary hypoplasia. The pulmonary vasculature shows a decreased number of pulmonary arteries per unit lung volume and an increase in the medial, adventitial and total wall thickness of all arteries [12]. Failure of vascular remodeling, muscularization of pulmonary arterioles and susceptibility to hypoxemia and acidosis leads to pulmonary hypertension in the neonatal period [13, 16–19]. However, with increasing age the natural history of vascular remodeling and alveolar growth has been docu-



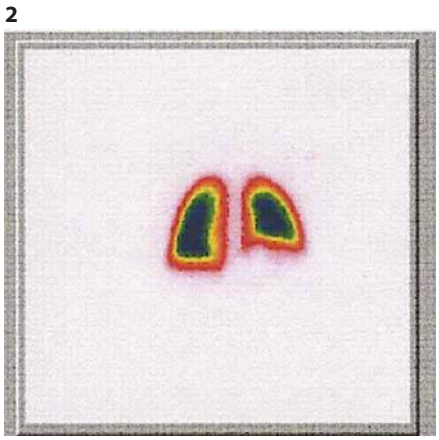


Fig. 1. Perfusion scintigraphy of left CDH survivor (case No. 2) at 3 months showing 30% perfusion in the affected site.
Fig. 2. Perfusion scintigraphy of left CDH survivor (case No. 2) at 9 months showing 42% perfusion in the affected site.

Table 2. Comparison between non-patch (n = 16) and patch (n = 8) survivors

	Median	SD	p value
Presentation since birth, h			
Non-patch	8.0	7.9	0.042
Patch	2.0	3.3	
A-aDO2			
Non-patch	166	144.7	0.0002
Patch	478.5	126.2	
Preoperative stabilization, h			
Non-patch	24	7.4	0.012
Patch	36	15.4	
Postoperative expansion of lung, days			
Non-patch	1.5	1.2	0.0018
Patch	4.0	1.3	
Postoperative ventilation, days			
Non-patch	2.0	1.0	0.0001
Patch	7.0	2.1	

Table 3. Comparison of perfusion, % of ipsilateral lung between non-patch and patch groups

	Non-patch group (n = 16)	Patch group (n = 8)	p value
Perfusion at 3 months	35.5 ± 3.4	30 ± 2.6	0.0005
Perfusion at 9 months	44 ± 2.3	42 ± 3.8	0.023
Perfusion at 6 years	48 ± 2.2	44 ± 2.5	0.009

Table 4. Comparison of mean of perfusion, % change in the ipsilateral lung within non-patch group and patch group

	Non-patch group, mean of % change	Patch group, mean of % change
Perfusion change at:		
9 vs. 3 months	8.8 ($p < 0.001$)	10.6 ($p < 0.001$)
6 years vs. 9 months	3.6 ($p < 0.01$)	3.8 ($p > 0.05$, ns)
6 years vs. 3 months	12.4 ($p < 0.001$)	14.5 ($p < 0.001$)

ns = Not significant.

mented by few authors in the follow-up of these patients including those with a severe degree of hypoplasia requiring ECMO [3, 12–14]. These results are consistent with amelioration of pulmonary hypertension and pulmonary symptoms with time. Beals et al. [12] have shown fewer numbers of arteries with increased muscular thickness and a lower percentage of muscularization of arteries in deceased infants with CDH.

Lung Perfusion Study

Several perfusion studies in CDH survivors have demonstrated a reduced mean perfusion in the affected and contralateral lung compared to healthy neonates in the early postoperative period [1, 4, 6, 7, 20–22]. In the subsequent follow-up, ventilation was shown to improve with age. However, perfusion has been reported to remain the same or worsen [1, 4, 6–9, 21, 22]. These studies consist of small sample sizes and non-uniform patient characteristics and study protocols. Most of the experimental studies also only address the issue of pulmonary hypoplasia in fetal life and early neonatal period [23].

On the contrary, we have found a significant improvement in the percentage of affected side perfusion at 9 months and continued improvement at 6 years of age. Arena et al. [3] have shown a similar observation in their series with a 9.7% increase in the ipsilateral lung perfusion

(p = 0.015) at 1 year and stabilization of perfusion in the mid-term (4.5 ± 1.8 years) and long-term (21 ± 5.7 years) follow-up. However, their subgroups of patients were operated during different eras (long-term group = 1972–1997, mid-term group = 1997–2002). Ours is the first report with a uniform cohort of survivors (operated during the recent and short era) undergoing systematic prospective evaluation. We believe that the natural history of growth and development of lungs do happen in CDH survivors treated without ECMO. Vascular musculature does undergo significant remodeling along with alveolar growth, thereby preventing ventilation-perfusion mismatch and its clinical consequences in the majority.

Modest versus Severe Hypoplasia Groups

Comparison between the patch and non-patch subgroups highlights two significant findings, one that patients with modest hypoplasia fare significantly better in all areas such as delayed presentation, lower A-aDO2, early preoperative stabilization, early postoperative lung expansion and shorter postoperative ventilation compared to the severe hypoplasia group. Perfusion of affected lung showed consistent early improvement in both groups. The modest group continued to show improvement in lung perfusion up to 6 years of follow-up, whereas the severe hypoplasia group showed no significant improvement in the latter part of follow-up with final perfusion at 6 years being significantly below the normal/modest group.

Respiratory Sequelae

At early follow-up the incidence of respiratory symptoms had subsided from 45% at 3 months to 14% at 9 months (fig. 1, 2). At 6–8 years of follow-up, only 12.5% had a chronic respiratory complaint. These children were diagnosed as having a reactive airway requiring bronchodilator and were stabilized by 6–8 years of follow-up, none being dependent on oxygen. Some children were even engaged in school sports.

Conclusions

Lung perfusion is reduced in the affected side at 3 months postoperatively in the CDH survivors. However, in the subset of CDH managed without ECMO, the perfusion status improved at 9 months and also continued to improve at 6 years of age indicating significant improvement in the vasculature of the hypoplastic lung. The respiratory symptoms also showed a similar trend with only a minority (12.5%) suffering from reactive airway disease at 6 years of follow-up, none requiring oxygen therapy for sustenance. Further long-term experimental and clinical studies are required among the CDH survivors to understand the extent of vascular growth and remodeling in the postoperative period as well as factors responsible for it.

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