Management of Congenital Heart Disease Associated with Ellis-van Creveld Short-rib Thoracic Dysplasia

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Objective To evaluate clinical outcome of patients with Ellis-van Creveld syndrome (EVC) in whom congenital heart disease (CHD) repair was delayed intentionally to reduce the risk of postoperative respiratory morbidity and mortality.

Study design This retrospective review of 51 *EVC* c.1886+5G>T homozygotes born between 2005 and 2014 focused on 18 subjects who underwent surgery for CHD, subdivided into early (mean, 1.3 months) vs delayed (mean, 50.1 months) repair.

Results Growth trajectories differed between control subjects and patients with EVC, and CHD was associated with slower weight gain. Relative to controls, infants with EVC had a 40%-75% higher respiratory rates (independent of CHD) accompanied by signs of compensated respiratory acidosis. Blood gases and respiratory rates approached normal values by age 4 years. Hemodynamically significant CHD was present in 23 children, 18 (78%) of whom underwent surgical repair. Surgery was performed at 1.3 ± 1.3 months for children born between 2005 and 2009 (n = 9) and 50.1 ± 40.2 months ($P = .009$) for children born between 2010 and 2014 (n = 9). The latter had shorter postoperative mechanical ventilation (1.1 ± 2.4 days vs 49.6 ± 57.1 days; $P = .075$), shorter intensive care duration of stay (16 ± 24 days vs 48.6 ± 44.2 days; $P = .155$), and no postoperative tracheostomies (vs 60%; $P = .028$) or deaths (vs 44%; $P = .082$).

Conclusion Among children with EVC and possibly other short-rib thoracic dysplasias, delayed surgical repair of CHD reduces postoperative morbidity and improves survival. Respiratory rate serves as a simple indicator for optimal timing of surgical repair. *(J Pediatr 2017;191:145-51).*

In 1940, Richard W. B. Ellis and Simon van Creveld described the constellation of short-limbed chondrodysplasia, polydactyly, ectodermal dysplasia, and congenital "morbus cordis" (heart disease), and coined the term *chondroectodermal* dysplasia for what is now commonly called Ellis-van Creveld syndrome (EVC; MIM# 225500).[1] McKusick et al[2] studied EVC among Old Order Amish populations during the 1960s, tracing the condition through 30 sibships and 10 generations to 1 of 4 Swiss Anabaptist founders who immigrated to the New World between 1744 and 1800. Amish pedigrees proved critical in mapping EVC to chromosome 4p16 and in 2000 the phenotype was finally linked to a homozygous splice-donor change in *EVC* (c.IVS13+5G>T).[3,4,5]

In 2015, a human phenocopy linked to *WDR35*[6] implicated aberrant sonic hedgehog (SHH) signaling in primary cilia as central to the pathogenesis of EVC.[7-13] This and other studies established EVC within the larger phenotypic series of short rib thoracic dysplasias (PS208500; SRTDs) caused by an array of genes (eg, *EVC, EVC2, WDR35, IFT172, DYNC2LI1, TTC21B, IFT80, TCTEX1D2, WDR19, NEK1, CEP120, WDR60, WDR34, DYNC2H1, KIAA0586, SRTD1, IFT140, IFT52*) that converge on the action of primary cilia and their intraflagellar transport system.[14,15] A number of these syndromes are also properly categorized as ciliary chondrodysplasias. For our purposes, we focus on the concept of the phenotypic series (ie, PS208500), because it emphasizes shared anatomic features of the shortened tubular bones, short ribs, and thoracic constriction (SRTDs) that predispose to cardiopulmonary morbidity.[16,17]

Sixty percent of neonates with EVC have congenital heart disease (CHD), especially atrioventricular septal defects, and all are born with short ribs and a long, narrow rib cage that decreases chest wall size and compliance.[2,18,19] The interplay between cardiac and respiratory pathology is the most vexing aspect of EVC and, despite advances in medical and surgical care, many affected infants still die of

CHD	Congenital heart disease
EVC	Ellis-van Creveld syndrome
Qp:Qs	Pulmonary to systemic blood flow ratio
SHH	Sonic hedgehog
SRTD	Shortened tubular bones, short ribs, and thoracic constriction

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respiratory failure.[19] In the report by McKusick et al,[2] 30 of 52 (58%) patients with EVC died from cardiopulmonary complications before age 6 months of age, two-thirds within the first 2 weeks of life. Little changed by 2010, when outcomes of 11 *EVC* c.IVS13+5G>T homozygotes born between 2004 and 2009 with hemodynamically significant CHD, 9 of whom underwent surgical repair within 5 months of life were reported.[19] Four (44%) died from respiratory failure by postoperative month 5 and 60% of survivors required tracheostomy.

There are similarities between EVC and other asphyxiating thoracic dystrophies within the SRTD family.[16,17,20] Although respiratory morbidity of SRTD is commonly attributed to mechanical aspects of the chest wall, murine data indicate that Evc protein, through downstream actions on Shh targets (eg, Gli2, Gli3, Foxf1), might also influence lung embryogenesis.[21-23] Whether such findings pertain to humans is unknown, but life-threatening respiratory complications associated with EVC and other SRTDs often dissipate with age, and evidence suggests that adults with EVC have normal pulmonary function.[24-26] To accommodate this distinctive pattern of early ribcage and lung development, we intentionally delayed thoracotomy for Amish patients with EVC born between 2010 and the present.

Methods

The Institutional Review Board of Lancaster General Hospital approved the study and parents consented in writing on behalf of their children. Over the last decade (2005-2014), 51 children homozygous for *EVC* c.IVS13+5G>T who had the characteristic phenotype were treated. We conducted a retrospective chart review of growth, pulmonary maturation, and clinical outcome. The same Clinic for Special Children nurse measured and recorded growth and respiratory indices during each outpatient encounter. Respiratory rates were recorded for a full minute in relaxed or sleeping subjects; children on chronic supplemental oxygen remained so during respiratory measurements.

Thirty children (59%) were born with CHD and 18 (35%) underwent surgical repair. The latter were divided into 2 temporal cohorts (**Figure 1**): 1 born between 2005 and 2009 (n = 9) and the second born between 2010 and 2014 (n = 9; mean age, 5.4 ± 3.1 years; range 0.9-12.5; 47% female). We used the Student *t* test and Fisher exact test (Prism 6, GraphPad, La Jolla, CA) to compare them.

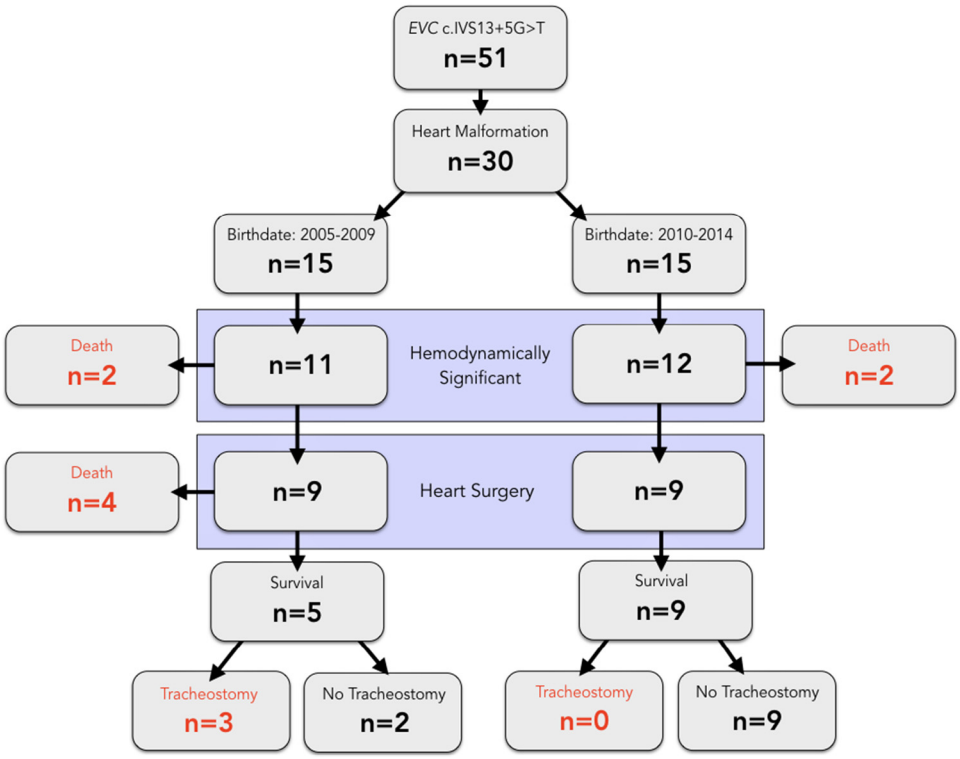

Figure 1. Fifty-one *EVC* c.IVS13+5G>T homozygotes were diagnosed at a single center (Clinic for Special Children) and divided into 2 cohorts based on the strategy for managing hemodynamically significant CHD. Affected children born between 2005 and 2009 were managed using conventional guidelines for the timing of surgical repair, which occurred at an average of 1.3 ± 1.3 months and was associated with high postoperative respiratory morbidity (78%) and mortality (44%). For affected patients born between 2010 and 2014, surgery was delayed an average of 50.1 ± 40.2 months, and there were no postoperative deaths or tracheostomies.

A lung biopsy was performed on 1 female *EVC* c.IVS13+5G>T homozygote (born 2016) who is not included within the present cohort. This is the only patient in our series who had a lung biopsy. Sections of formalin-fixed paraffin-embedded tissue stained by automation (hematoxylin-eosin, elastin, trichrome, periodic acid-Schiff) were examined by standard light microscopy. Immunohistochemistry for vimentin was performed using appropriate tissue controls.

Results

EVC c.IVS13+5G>T homozygotes had different growth trajectories than control subjects and somatic growth was more markedly delayed in EVC children (**Figure 2**). All 51 patients with EVC had short ribs, narrow thorax, chronic tachypnea, and a palpable liver. Reduced tidal volume in neonates manifested as 40%-75% higher respiratory rates, which decreased to control values between 36 and 48 months of age (**Figure 3**, A). Breathing mechanics did not differ between children with and without CHD (**Figure 3**, B) and, for individual patients, neither prenatal sonographic measurements nor postnatal chest radiographs were predictive of postnatal pulmonary function.

We analyzed a total of 243 blood gas samples (both venous and arterial) from 15 patients with EVC born with CHD between 2010 and 2014 (**Figure 1**). Blood carbon dioxide (pCO_2) and bicarbonate (HCO_3) showed compensated respiratory acidosis, which resolved by about 4 years of age in parallel to normalization of respiratory rate (**Figure 3**, C and D). Blood pCO_2 and HCO_3 were closely correlated (Pearson $r = 0.69$; $P < .0001$), as expected from the Henderson-Hasselbalch equilibrium (data not shown).

Among 15 EVC patients born with CHD between 2010 and 2014, 9 (60%) were chronically hypoxemic (arterial oxygen saturation of <90% breathing room air) and 2 (13%) suffered from paroxysms of arterial oxygen desaturation (≤70%) that could last several minutes; one of these children died during a cyanotic attack in early infancy and the other had cyanotic episodes that diminished over time and finally abated by year 2 of life.

Post mortem lung biopsies were obtained on a single female EVC c.IVS13+5G>T homozygote (born in 2016) who died of circulatory failure at day 7 of life. She was born to a 33-year-old G9P9 mother with no prenatal complications who delivered by primary caesarean at $37^{6/7}$ weeks gestation for concerns of placental abruption. Birth weight (2.76 kg) was appropriate for gestational age, Apgar scores were 5 (1 minute) and

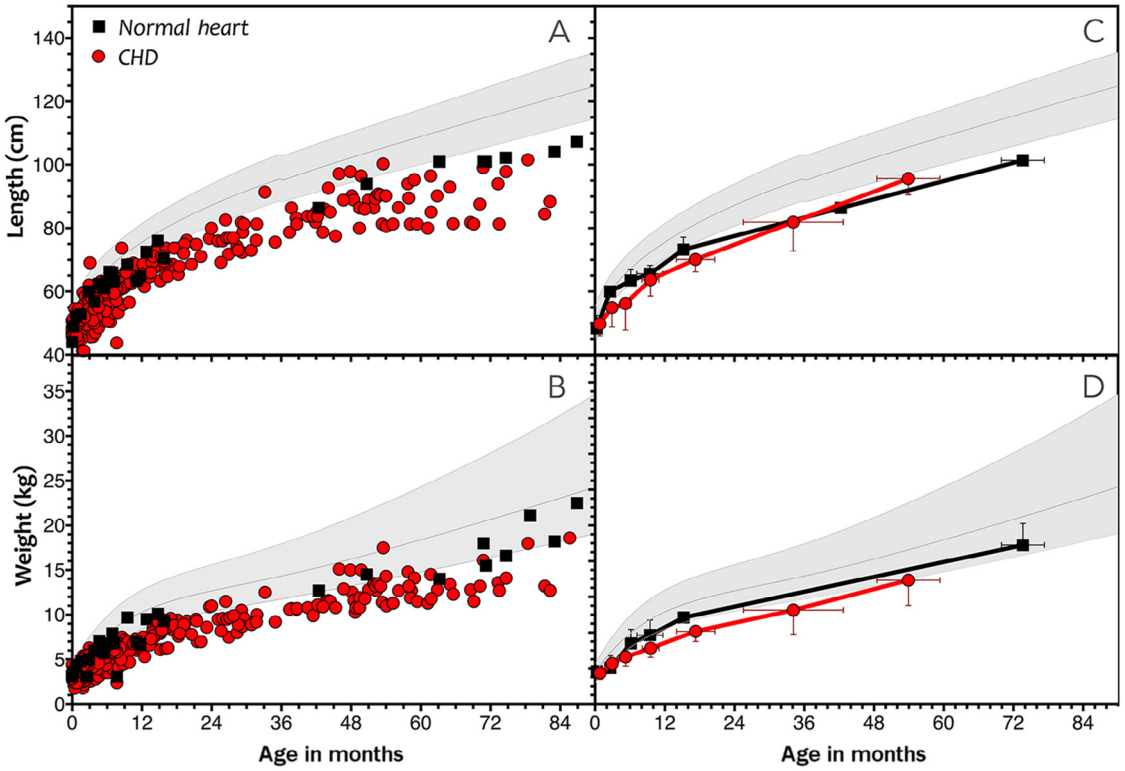

Figure 2. Growth trajectories for *EVC* **C**, IVS13+5G>T homozygotes with (*red circles*) and without (*black squares*) hemodynamically significant CHD. **A, B,** Individual measurements; data were smoothed to construct **C** and **D**. Gray shaded areas represent 3rd to 97th growth percentiles for healthy control children.

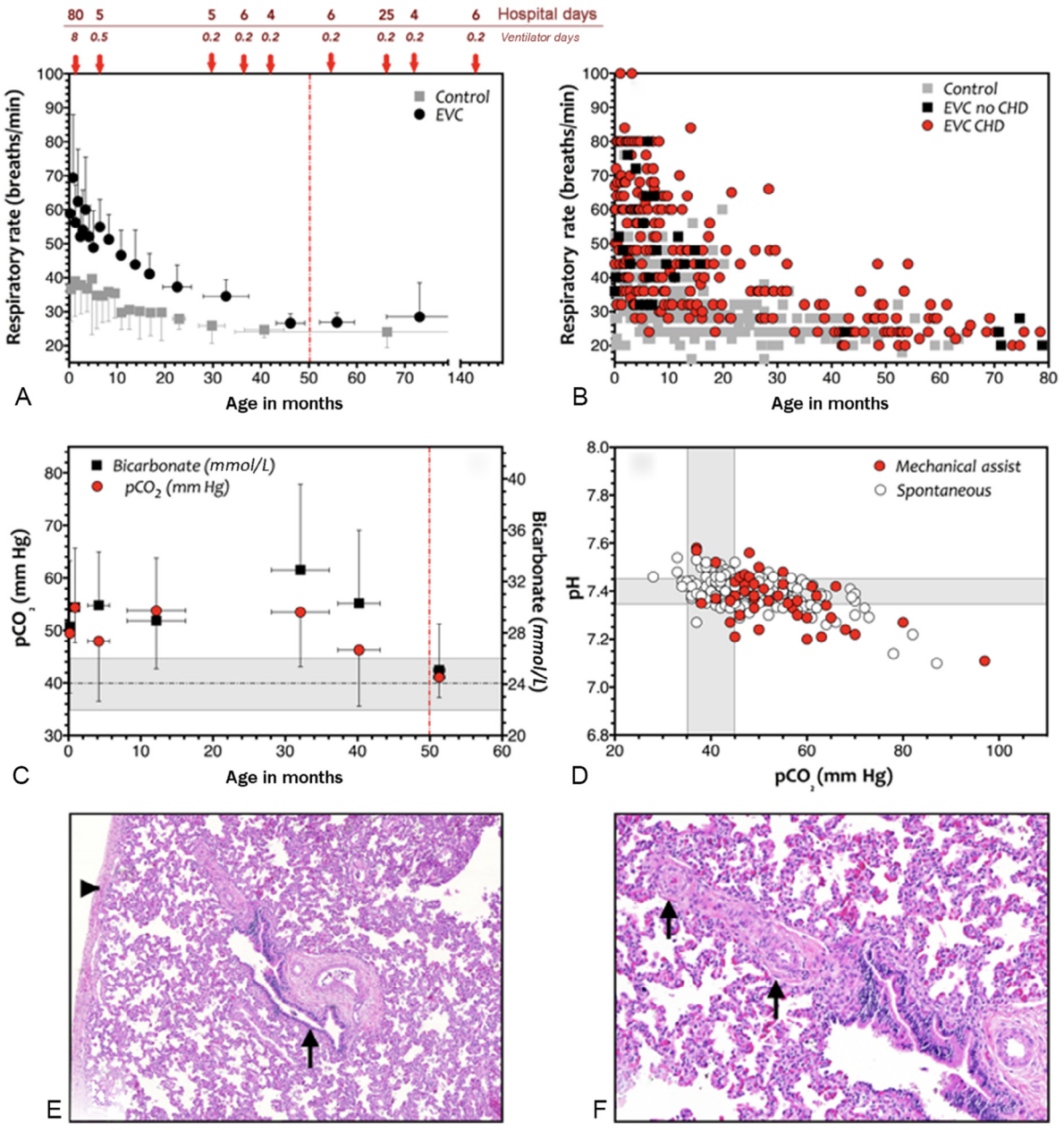

Figure 3. **A**, *EVC* IVS13+5G>T homozygotes (n = 40, *black circles*) have elevated respiratory rates relative to control children (gray squares, error bar = 1 SD) which normalize by approximately 48 months of age. Red dotted line and arrows show the average and individual timing of cardiothoracic surgery, respectively, and number of postoperative hospital (upper) and ventilator (lower) days are indicated for each patient. **B,** Respiratory rates were similar in EVC patients with (*red circles*) and without (*black squares*) CHD. **C, D,** There were 243 blood gas samples obtained from 15 subjects in the 2010-2014 cohort that showed compensated respiratory acidosis (elevated arterial and venous pCO_2 and bicarbonate, stable pH) during the first years of life in patients who were spontaneously breathing or mechanically assisted (ventilator or continuous positive airway pressure); acid-based status normalized by age 4 years, in parallel with respiratory rate. Blood pCO_2 and HCO_3 were closely correlated (Pearson r = 0.69; $P < .0001$) as expected from the Henderson-Hasselbalch equilibrium (data not shown). **E,** Histologic image of a post mortem lung biopsy viewed at low power shows lung parenchyma between the late saccular and early alveolar development, appropriate for patient age, and a normally developed bronchovascular bundle (*black arrow*). There is no evidence of alveolar capillary dysplasia, venous misalignment, or interstitial abnormalities. Pleural surface (*arrowhead*) appears unremarkable (stain: hematoxylin- and eosin; original magnification ×40). **F,** Histologic image at higher power (lower image) shows profiles of intraparenchymal arterioles with medial hypertrophy (black arrows), consistent with pulmonary hypertension (stain: hematoxylin- and eosin; original magnification ×100).

Table I. Cardiac catheterization data

Patients	Age (mo)	Diagnosis	Qp:Qs*	PVR†	Surgery	Outcome
3	36	Common atrium	2.3	1.5	Yes	Alive
2	6	Common atrium	1.6	4.8	No	Deceased
4	108	Common atrium	1.6	1.0	Yes	Alive
1	12	Common atrium	1.4	3.9	No	Alive
5	0	DORV, MV hypoplasia, coarctation	0.6	2.3	Yes	Alive
6	48	Unbalanced AV canal, pre-Fontan	0.5	1.3	Yes	Alive
Mean	35		1.3	2.4		
SD	40		0.7	1.5		

AV, atrioventricular; *DORV*, double outlet right ventricle; *MV*, mitral valve; *PVR*, pulmonary vascular resistance (expressed in Wood Units).
*Normal reference value: 1.0.
†Normal reference value: < 3.0 Wood Units.

8 (5 minutes), and prenatal ultrasonographic and postnatal signs of maturation were consistent with accurate timing of conception.

The child was born with physical stigmata characteristic of EVC. An echocardiogram on the first day of life showed an unbalanced atrioventricular canal with right ventricular predominance and a hypoplastic left ventricular outflow tract. She was started on prostaglandin and initially had balanced circulation, but on day 6 of life developed signs of pulmonary overcirculation that prompted emergent bilateral pulmonary artery banding. Loading of her single ventricle precipitated marked atrioventricular valve regurgitation and, on day of life 7, she died of circulatory shock. Soon after death, the sternum was opened at the bedside and 2 pieces of lung tissue were removed.

Wedge biopsies of lung parenchyma were obtained from the right lower ($2.5 \times 1.4 \times 0.8$ cm) and middle ($2.4 \times 1.6 \times 0.9$ cm) lobes. Histologic examination of lung parenchyma showed maturation between the late saccular and early alveolar stage of lung development (**Figure 3**, E), concordant with the child's chronological age. The number of airspace generations (ie, radial-alveolar count) was appropriate for age and there was a normal alveolar capillary network with no evidence of dysplasia or venous misalignment. The pulmonary interstitium showed no evidence of increased glycogen-containing mesenchymal cells (periodic acid-Schiff and vimentin stains, not shown) to suggest pulmonary interstitial glycogenosis. Small muscular arteries and arterioles had intimal proliferation and medial hypertrophy consistent with grade II pulmonary hypertension (**Figure 3**, F), confirmed on trichrome and elastin stains (not shown).

Six patients with EVC from the 2010-2014 cohort underwent cardiac catheterization (**Table I**). Pulmonary overcirculation was observed in 4 children with common atrium, who had pulmonary to systemic blood flow ratios (Qp:Qs) ranging from 1.4 to 2.3, as compared with the normal circulation in which pulmonary and systemic blood flow are separate and equal (ie, Qp:Qs = 1). Children with unbalanced atrioventricular canal or double outlet right ventricle (pulmonary artery band, stent in the ductus arteriosus) had low pulmonary blood flow (Qp:Qs of 0.5 and 0.6, respectively). Average pulmonary vascular resistance among all 6 subjects was 2.4 ± 1.5 Wood units (reference value, ≤3); 2 children with common atrium (ages 6 and 12 months) had mild pulmonary vascular hypertension (**Table I**).

Among 15 subjects from the 2010-2014 cohort who had CHD, 3 were lost to follow-up, 2 died of preoperative respiratory complications, and 1 did not require surgery (**Figure 1**). For the 9 remaining subjects, the main indications for corrective surgery were common atrium (n = 4) and atrioventricular canal defect (n = 3). The average age of CHD repair was 50.1 ± 40.2 months (range, 0.1 to 144.0) (**Figure 3**). Postoperative ventilator and hospital days were 1.1 ± 2.4 and 16 ± 24 days, respectively. These values were skewed by the youngest

Table II. Characteristics and survival of 2010-2014 vs 2005-2009 postoperative EVC cohorts

			Two-tailed Fisher exact test		
Birth years	2005-2009	2010-2014	*P* value	OR†	95% CI
Reference	O'Connor 2010[19]	Present			
Number of patients	9	9	1.0		
Common atrium	78%	44%	.35		
Unbalanced AV canal	22%	22%	1.0		
Preoperative gastrostomy	0%	67%	.018	35.30	1.5-805.0
Age at surgery (months)	1.3 ± 1.3	50.1 ± 40.2	.009		
Mechanical ventilator (days)	49.6 ± 57.1	1.1 ± 2.4	.075		
Intensive care (days)	48.6 ± 44.2	16 ± 24	.155		
Tracheostomy*	60%	0%	.028	0.04	0.001-0.900
Mortality	44%	0%‡	.082	0.06	0.003-1.400

*Among survivors.
†OR expressed as the 2010-2014 cohort relative to the 2005-2009 cohort.
‡Two affected infants died of respiratory complications before surgical intervention.

patient, who was mechanically ventilated 8 days and hospitalized 80 days after a ductus arteriosus stent and pulmonary artery banding procedure shortly after birth (**Figure 3**, A). Excluding this child from analysis, the 8 remaining patients with EVC were extubated within 6 ± 2 postoperative hours and 7 were discharged within 6 days. There were no postoperative deaths or serious respiratory complications (**Table II**). In contrast, postoperative mortality and tracheostomy were 44% ($P = .082$) and 60% ($P = .028$), respectively, in children from the 2005-2009 cohort who underwent CHD repair at an average age of 1.3 ± 1.3 months ($P = .009$).

Successful delay of surgery required meticulous longitudinal medical care and intensive nutritional therapy. Six children (67%) from the 2010-2014 cohort had gastrostomy tubes placed preoperatively, typically before 6 months of age, to optimize growth and medical management. In most cases, gastrostomy was accompanied by Nissen fundoplication to protect the pulmonary system from gastric refluxate.

Discussion

Cardiopulmonary disease continues to claim the lives of many young patients with EVC, particularly those who undergo thoracotomy for heart repair.[19,27] The thoracic dystrophy characteristic of EVC and other SRTDs is associated with reduced alveolar volume, shallow tachypnea, and downward displacement of the liver (pseudohepatomegaly) (**Figure 3**). In children with comorbid CHD, these signs of reduced pulmonary reserve portend significant perioperative risk and justify delay of thoracotomy. Although conceptually simple, this strategy necessitates percipient medical and nutritional care and must be balanced against risks of delayed CHD repair (eg, chronic hypoxemia, failure to thrive, pulmonary vascular disease). Nevertheless, respiratory outcome and postoperative survival markedly improve for patients with EVC in whom corrective surgery can be delayed, and this principle might extend to any child who suffers from SRTD and comorbid CHD.

In developing mice, Evc and Evc2 colocalize to cardiac tissue and multiple cartilaginous structures, including ribs and vertebrae[28] and, in the embryonic mouse heart, are expressed strongly in atrial septal mesenchyme and the secondary heart field (eg, outflow tract and dorsal mesenchymal protrusion).[28] These structures fuse with atrioventricular cushions to close the primary atrial foramen and form the atrioventricular mesenchymal complex. Not surprisingly, atrioventricular septal defects, particularly common atrium and atrioventricular canal, are most frequently observed in EVC.[29,30] Inactivating variants of either *Evc* or *Evc2* abrogate hedgehog signaling within chondrocytes, osteoblasts, and fibroblasts, connecting *EVC* and *EVC2* changes in humans to short stature (adult height, 108-161 cm), acromelic foreshortening, ectodermal dysplasia, genu valgum, and short ribs, with its attendant consequences for lung mechanics.[2,31]

The respiratory rate is inversely proportional to alveolar volume and their product, alveolar ventilation, determines CO_2 elimination under control of the central nervous system. During the first years of life, patients with EVC had higher blood CO_2 and HCO_3 levels consistent with compensated underventilation that sometimes required mechanical support (**Figure 3**). By age 4 years, the pulmonary system matures sufficiently to eliminate CO_2 at a normal respiratory rate. These observations are consistent with the normal pattern of metabolic expenditure in humans (corrected for body surface area), which shows a steep increase during the first few months of life followed by a steady decline thereafter.[32]

Reduced alveolar volume secondary to rib hypoplasia is sufficient to explain respiratory insufficiency in young patients with EVC, but to date no studies have documented lung histology associated with the condition. SHH transcripts are found throughout developing murine lung epithelium, especially in distal tips of the terminal buds where alveolar-capillary units form.[23] Three transcription factors (Gli1, Gli2, and Gli3) transduce Shh signals during murine embryogenesis. *Gli2*$^{-/-}$ mice have tracheoesophageal stenosis and hypoplastic lungs with abnormal alveolar lobulation, and haploinsufficiency or knockout of *Gli3* on this background results in a more severe lung phenotype.[21] Via its interaction with Foxf1, Shh may also mediate formation of distal pulmonary vessels to ensure their proper alignment with developing alveoli.[22] These animal data indicate that loss of EVC or EVC2 function could alter lung development through downstream effects on SHH signaling. Our histologic observations, although provisional (n = 1), neither confirm nor refute this finding. Lung hypoplasia is difficult to evaluate on biopsy material. Specifically, radial-alveolar counts are often unreliable as a means of determining the presence or absence of lung hypoplasia. A more effective post mortem method for evaluating for lung hypoplasia is that of lung volumes, which cannot be performed on biopsy material.

The clinical picture is further complicated by interactions between the pulmonary and cardiovascular systems. Although EVC heart lesions can be associated with low or high pulmonary blood flow, the latter type predominate (**Table I**). In children, pulmonary overcirculation and elevated pulmonary capillary wedge pressure (eg, as observed in common atrium and atrioventricular canal defects; **Table I**) are consistently associated with higher airway resistance,[33] reduced lung compliance and volumes, and pulmonary vascular disease.[34] These changes can evolve quickly; we observed acute grade II hypertensive pulmonary vascular changes in lung tissue within just 7 days of life, still evident 1 day after bilateral pulmonary artery banding (**Figure 3**, F).

Table I also underscores the divergence of cardiac phenotypes among *EVC* c.IVS13+5G>T homozygotes, most of which are in the family of atrioventricular septal defects. Despite the variable heart lesions observed in patients with EVC, our principle focus here is on their common respiratory phenotype and how this evolves over time in ways that affect the response to thoracotomy. Accordingly, we believe our conclusions can be generalized to a broad range of operable cardiac lesions in children with a number of different SRTDs.[20]

Whatever specific mechanical and histologic derangements contribute to respiratory vulnerability in EVC, clinical data indicate that respiratory insufficiency associated with EVC

and other STRDs improves over time and is not a chronic feature of these disorders. Thus, as the ribcage and lungs mature, matching of alveolar volume to pulmonary blood flow must be sufficient to maintain CO_2 excretion at normal respiratory rates and also accommodate the increased metabolic demands of exertion and illness.[35] These physiologic changes take place gradually in patients with EVC between birth and 48 months of age, marking the transition to stable respiratory reserve; this principle might apply to any child who suffers from SRTD and comorbid CHD. ■

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