Tracheomegaly in Infants with Severe Congenital Diaphragmatic Hernia Treated with Fetal Endoluminal Tracheal Occlusion

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Objective To measure and evaluate the effects of tracheal dimensions on survival and ventilation in a large series of infants with congenital diaphragmatic hernia (CDH) treated antenatally with fetal endoluminal tracheal occlusion (FETO).

Study design Tracheal dimensions on chest radiograph (CR) were measured by 2 blinded radiologists. Survival, day 1 best oxygenation index and duration of ventilation, continuous positive airway pressure, and hospital stay were recorded. Survivors with a minimum 12-month follow-up were longitudinally compared for incidence of gastroesophageal reflux, chest infections, chest deformities, and hernia recurrence.

Results Seventy infants with CDH (41 who underwent FETO) were treated between 2004 and 2010. Hernia repair was performed in 26 infants without FETO (8 with patch repair) and 35 infants with FETO (26 with patch repair; $P = .0015$). Infants with FETO had a wider trachea than those without FETO at T1 ($P < .0001$) and between T1 and the carina ($P < .0001$). Tracheal diameter was similar in survivors and nonsurvivors in the FETO group. Tracheal size was not correlated with day 1 best oxygenation index in the FETO group ($R^2 = 0.17$) or the non-FETO group ($R^2 = 0.07$). There were no between-group differences in duration of mechanical ventilation ($P = .30$), continuous positive airway pressure ($P = .20$), or hospital stay ($P = .30$). In the longitudinal study, tracheal widths were larger on the last CR than on preoperative CR in patients without FETO (T1, $P = .02$; widest point, $P = .001$; carina, $P = .0001$), and for patients with FETO at the widest point ($P < .0001$) and at the carina ($P < .0001$), but not at T1 ($P = .12$). There were no differences in clinical variables between the FETO and non-FETO groups.

Conclusion FETO has a significant impact on tracheal size of infants with CDH; however, tracheal size does not affect survival or the requirement for early respiratory support. *(J Pediatr 2014;164:1311-5)*.

Congenital diaphragmatic hernia (CDH) is a complex anomaly with significant risk of mortality, due mainly to pulmonary hypoplasia.[1] Intrauterine tracheal occlusion appears to ameliorate and even reverse impaired lung growth in experimental models[2] and in the human condition.[3] The technique appears to work by preventing the egress of liquid from the lung, increasing airway pressure, causing cellular proliferation, and increasing alveolar airspace and maturation of pulmonary vasculature.[4] In many centers in Europe and Brazil,[5,6] intratracheal placement of a detachable balloon, known as fetal endoluminal tracheal occlusion (FETO), has replaced the earlier method of external tracheal clipping.

The FETO Task Force initiated a clinical program in which this technique was performed on fetuses with CDH and a poor prognosis, with a "liver-up" position and a lung-to-head ratio ≤1.0.[5] According to stratified data from the Antenatal CDH Registry, FETO increased survival in severe cases with left-sided CDH by up to 49% and in cases with right-sided CDH by up to 35%.[7]

The most common complication associated with FETO is premature rupture of the membranes, with an incidence of 17% within 3 weeks after the procedure.[7] The resultant preterm labor and delivery in this subset of fetuses with CDH is associated with higher mortality. A more recently reported side effect of FETO is tracheomegaly, although animal studies initially suggested that the balloon does not cause significant tracheal damage.[8-12]

King's College Hospital (KCH), London is part of the European FETO Task Force and currently the sole center in the United Kingdom that performs FETO, which has been performed on fetuses with CDH and a poor prognosis since 2002. A collaborative study with the University Hospital Brugmann compared the presence of tracheomegaly in a cohort of infants who underwent FETO and a cohort of infants with no congenital lung abnormalities.[13]

CDH	Congenital diaphragmatic hernia
CPAP	Continuous positive airway pressure
CR	Chest radiograph
CT	Computed tomography
d1-BOI	Day 1 best oxygenation index
FETO	Fetal endoluminal tracheal occlusion
KCH	King's College Hospital
WTP	Widest tracheal point

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The aim of the present study was to determine whether any such effects are more common in infants with CDH who underwent FETO compared with those who did not undergo FETO. We also examined possible implications for clinical outcomes in a large cohort of infants with CDH by relating tracheal size to outcome in infants with FETO and those without FETO in the newborn period and at follow-up.

Methods

We conducted a review of all neonates born with CDH at KCH between January 2004 and December 2010. The study was approved by the KCH Institutional Review Board (approval no. 2938). A proportion of the neonates had been diagnosed antenatally with severe CDH (defined as a lung-to-head ratio ≤1.0 and a "liver-up" position[5,7]) and had undergone FETO at KCH's Harris Birthright Research Centre for Fetal Medicine. We excluded infants who underwent FETO at KCH but were then delivered at other centers. Demographic data for the patients included in this study were retrieved from the clinical notes. The patients were divided into 2 groups: FETO and non-FETO (internal control).

Tracheal Size

Tracheal size and clinical outcome were assessed at 2 separate time points, in the neonatal period and at last follow-up. Tracheal size was assessed by 2 pediatric radiologists (M.S. and P.A.), who blindly reviewed the chest radiographs (CRs) of the entire cohort. Images were viewed on GE-PACS workstations (GE Healthcare, Buckinghamshire, United Kingdom) with high-definition monitors. Tracheal measurements were obtained at 3 levels: T1 vertebral body, carina, and widest tracheal point (WTP). Tracheal measurements were evaluated in more depth in patients who also had undergone a chest computed tomography (CT) scan during the study period. The results on CT were compared with those on the CRs obtained at the date closest to the CT scan.

Neonatal Cross-Sectional Study

The FETO and non-FETO groups were compared in terms of tracheal measurements, days of mechanical ventilation (including continuous positive airway pressure [CPAP]), and length of hospital stay. In addition, each patient's WTP was correlated to day 1 best oxygenation index (d1-BOI) and duration of mechanical ventilation, CPAP, and hospital stay using linear regression analysis. The d1-BOI was calculated as described previously, as fraction of inspired oxygen times mean airway pressure, divided by the partial pressure of oxygen in arterial blood; the best (ie, lowest) value on day 1 of life is the d1-BOI.[14]

Longitudinal Study

This aspect of the study focused on patients with CDH born and treated at KCH between January 2006 and December 2009. This population comprises survivors with imaging data available on KCH's high-specification picture archiving and communications system (PACS) with at least a 12-month follow-up. Tracheal measurements at T1, the carina and the WTP on CRs from birth to the last review of infants with and without FETO were compared using logistic regression analysis (slope difference and deviation from zero). The location of the WTP at the last follow-up was also recorded and compared with that at birth.

In addition, data on severe gastroesophageal reflux requiring fundoplication, severe chest infections prompting hospital admission, severe chest wall deformities, and diaphragmatic hernia recurrence were compared in the FETO and non-FETO groups.

Statistical Analyses

Data are expressed as median (range) or mean ± SEM as appropriate, following determination of normality with the D'Agostino-Pearson test. Categorical data were compared using the χ^2 or Fisher exact test. Ordinal data were compared with 2-tailed parametric tests (eg, *t* test) or nonparametric tests (eg, Mann-Whitney test) as appropriate. Nonparametric data correlation is expressed as Spearman rank correlation coefficient (*r*). Linear regression analysis was used to study the correlation between tracheal size and clinical variables in the neonatal study and the progression of tracheal growth over the years in the longitudinal study. $P < .05$ was considered to indicate statistical significance.

Results

Neonatal Cross-Sectional Study

During the study period, 70 infants with CDH were born and treated at KCH. Of these, 41 (59%) had undergone FETO in utero (**Table**). The FETO group had an earlier median gestational age compared with the non-FETO group (35 weeks [range, 31-40 weeks] vs 38 weeks [range, 29-41 weeks]; $P < .0001$). Six infants in the FETO group (15%) and 3 infants in the non-FETO group (11%) died before undergoing surgical repair ($P = .73$).

On CR review, the trachea was wider at T1 (8.6 ± 0.3 mm vs 6.4 ± 0.2 mm; $P < .0001$) and at the WTP (8.9 ± 0.4 mm vs 6.9 ± 0.3 mm; $P < .0001$) in the FETO group compared with the non-FETO group (**Figure 1**). However, there was no between-group difference in tracheal width at the level of the carina (6.4 ± 0.2 vs 6.0 ± 0.2 mm; $P = .26$) (**Figure 1**). The WTP was most commonly at the level of T1 (75%) and less commonly at the level of T4 (8%), T2 (7%), T3 (7%), or C7 (3%) (**Figure 2**).

There was no difference in tracheal width between survivors and nonsurvivors in the FETO group at all 3 points (T1: 8.4 ± 0.4 vs 9.4 ± 0.7 mm, $P = .15$; WTP: 8.8 ± 0.4 vs 9.5 ± 0.7 mm, $P = .19$; carina: 6.4 ± 0.2 vs 6.6 ± 0.5 mm, $P = .60$).

Tracheal size did not correlate with d1-BOI ($r = 0.004$; $P = .98$). This was confirmed in an independent test of the correlation between tracheal size and d1-BOI in the FETO group ($r = 0.017$; $P = .52$) and non-FETO group ($r = 0.07$; $P = .52$).

A chest CT scan was performed in 3 infants (2 in the FETO group) for diagnostic purposes, to exclude congenital airway

Table. Demographic data for the study cohort (n = 70)

	FETO (n = 41; 59%)	Non-FETO (n = 29; 41%)	*P* value
Male sex, n (%)	25 (61)	18 (62)	.92
Preterm (<36/40 wk), n (%)	26 (63)	3 (10)	<.0001
Birth weight, g, median (range)	2510 (1356-3820)	2922 (1670-3630)	.0049
Surgical repair, n (%)	35 (85)	26 (89)	.73
Patch requirement, n (%)	26 (74)	8 (31)	.0015
Age at surgery, d, median (range)	4 (1-9)	4 (2-21)	.45

malformations in 2 infants and to evaluate a mediastinal mass in 1 infant. There were no differences between the CR and CT views of tracheal size at T1 (7.7 ± 1.2 vs 7.9 ± 1.6; $P = .80$), the WTP (8.1 ± 1.1 vs 8.5 ± 1.4; $P = .31$), or the carina (7.0 ± 0.6 vs 7.3 ± 0.9; $P = .44$).

There was no difference in median length of hospital stay between the FETO and non-FETO groups (36 days [range, 11-157 days] vs 24 days [range, 14-324 days]; $P = .30$), and no correlation between tracheal size and length of hospital stay ($R^2 = 0.006$; $P = .59$).

The median duration of mechanical ventilation was 15 days (range, 4-45 days) in the FETO group and 12 days (range, 5-31 days) in the non-FETO group ($P = .32$). There was no correlation between tracheal size and days on mechanical ventilation ($R^2 = .001$; $P = .55$). Similarly, there was no between-group difference in the median duration of CPAP (FETO group: 4 days [range, <24 hours to 28 days]; non-FETO group: 2 days [range, <24 hours to 21 days]; $P = .18$), and there was no correlation between tracheal size and duration of CPAP ($R^2 = 0.04$; $P = .22$).

Longitudinal Study

A total of 169 CRs (median, 4 CR per patient; range, 2-8) of 38 consecutive patients (24 FETO and 14 non-FETO) from birth to last outpatient review were evaluated. In both groups, tracheas grew progressively at a similar rate of increase (slope difference at T1, $P = .38$; at the WTP, $P = .96$; at the carina, $P = .58$) (Figure 2, A-C). Tracheal width was significantly larger on the last CR compared with the preoperative CR in the non-FETO group at all levels (T1, $P = .02$; WTP, $P = .001$; carina, $P = .0001$) and for the FETO group at the WTP ($P < .0001$) and the carina ($P < .0001$), but not at T1 ($P = .12$) (Figure 2, A-C). In the FETO group, the WTP was most frequently at the level of T3 (42%) and less frequently at T2 (25%), T4 (17%), T1 (12%), or T5 (4%) (Figure 2, D).

At a median follow-up of 36 months (range, 12-87 months), 2 patients in the FETO group (10%) and 1 patient in the non-FETO group (8%) underwent fundoplication for severe gastroesophageal reflux ($P = 1$). Severe chest infections necessitated hospital admission in 6 infants in the FETO group (30%) and in 3 infants in the non-FETO group (25%) ($P = 1$). In addition, 7 infants in the FETO group (35%) and 2 infants in the non-FETO group (17%) had significant chest wall deformities ($P = .40$), including pectus excavatum, pectus carinatum, and asymmetry. Finally, diaphragmatic hernia recurred in 6 patients in the FETO group (30%) and in 1 patient in the non-FETO group (8%) ($P = .20$).

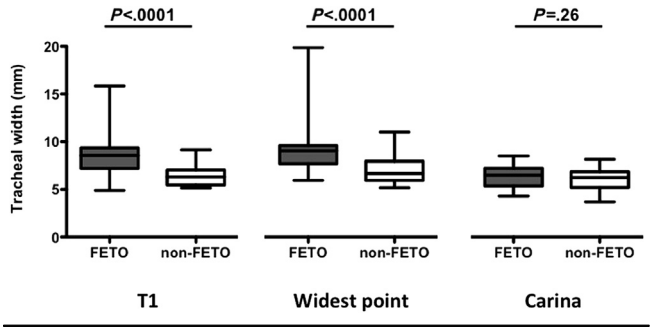

Figure 1. Neonatal cross-sectional study of tracheal width in the FETO and non-FETO groups, measured on CR at 3 levels (T1, WTP, and carina).

Discussion

Tracheomegaly is a recently recognized complication of infants with CDH treated with FETO. In 2010, McHugh et al[9] reported 5 infants who presented with features of respiratory distress shortly after birth and were found to have marked tracheomegaly. That report highlighted the potential risk of mechanical damage induced by in utero balloon occlusion. The presence of tracheomegaly in survivors who underwent FETO was also found in a cross-sectional study of 7 infants with CDH using CT scans.[10] Enlargement of the tracheal width, perimeter, and area was reported in all patients who underwent FETO compared with patients who did not undergo FETO; however, none of the 7 patients exhibited tracheomegaly-related respiratory symptoms at longer follow-up. More recent studies have shown that in some cases, dilation of the airway also involves the main bronchi, as reported in a case of bronchial dilatation successfully managed by bronchial stenting[11] and in a series of 7 children followed for 2 years.[12]

Our present results confirm previous reports.[9-12] Tracheal diameters were wider at birth in our cohort of patients with CDH treated with FETO compared with those who did not undergo FETO. However, postnatally and at follow-up, we found no correlation between tracheal size and degree of respiratory support required. Similar findings were reported in a collaborative study comparing infants who underwent FETO with infants without congenital anomalies.[13] In the present study, we compared infants who underwent FETO with infants who did not, who seemed to be the best control group for assessing whether changes in tracheal diameter influence clinical outcomes. In accordance with the protocol of the FETO Task Force,[5,7] only those infants with a predicted risk of mortality of >90% were selected for intervention, clearly establishing a

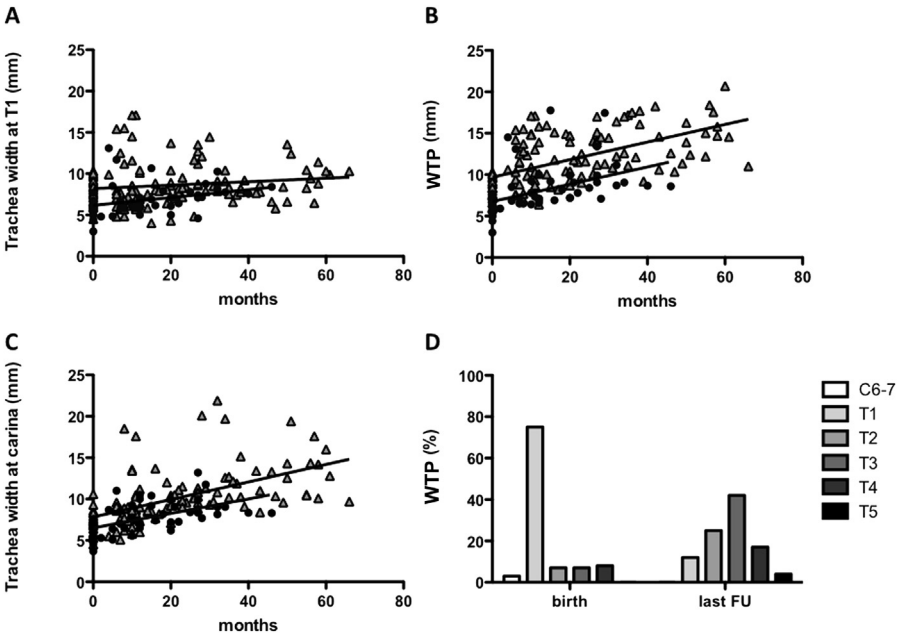

Figure 2. **A-C,** Longitudinal study of tracheal growth at T1, the WTP, and the carina. *Triangles* represent the FETO group; *circles*, the non-FETO group. **D,** Location of the WTP at birth and at the latest follow-up CR. *FU,* follow-up.

selection bias. However, outcome indices in these infants were broadly similar to those in infants who did not undergo FETO. In contrast, the infants who underwent FETO were less mature, smaller, and more likely to require a patch closure of the diaphragmatic defect (**Table**).

We retrospectively reviewed our patients' perinatal and follow-up CRs to study the tracheal anatomy. Yearly (minimum) follow-up at the clinic with a CR is part of our protocol, allowing assessment of parenchymal and bony anatomy and detection of asymptomatic recurrence. Although CT provides a more accurate definition of thoracic anatomy,[9-12] the trachea is easily visualized and can be measured accurately on a simple CR. To minimize exposure to ionizing radiation, CT is used selectively in our practice. Nonetheless, in the infants who underwent chest CT for other reasons, we confirmed the correlation of tracheal diameters with those measured on CR. Radiologic correlation between these 2 imaging modalities has been reported previously.[15]

Although no major bronchial abnormalities were detected in this series, we recognize that bronchial anatomy is less consistently, and less clearly, demonstrated by plain radiography.

Tracheomegaly was detected in the majority of CRs obtained before CDH closure in infants in the FETO group. Tracheal enlargement did not appear to have a deleterious effect during the neonatal period, however. In the FETO group, survivors and nonsurvivors had similar tracheal measurements. There was no difference in d1-BOI between the FETO and non-FETO groups.

Tracheomegaly did not emerge as a factor affecting perinatal morbidity. In the 2 groups, infants with large tracheas spent comparable amounts of time on mechanical ventilation, CPAP, and overall in the hospital. Tracheomegaly may be associated with tracheomalacia, and it is possible that some of the infants in the FETO group had tracheomalacia. We did not routinely perform a bronchoscopy examination, and we could not assess the collapsibility of the trachea based on our radiologic evaluation.

We are not aware of any studies in the literature detailing the evolution of tracheal morphology in children who underwent FETO. In the present study, the tracheas of both groups of patients grew progressively, with similar rates of increase at T1, the WTP, and the carina. This implies that FETO did not affect the ability of the trachea to grow. Tracheas with and without FETO grew progressively in a manner similar to that reported by Wailoo and Emery[16] in a quantitative necropsy study of the trachea in 452 children ranging in age from 28 weeks gestation to 14 years. That study found tracheal growth in relation to crown-rump length mainly during the first 4 years of life and around puberty. In our present longitudinal study, tracheas were larger in the FETO group compared with the non-FETO group at long-term follow-up as well.

The tracheal width at T1 was significantly larger on the last CR compared with the preoperative CR in the non-FETO group, but similar on both CRs in the FETO group. This finding is in keeping with the necropsy study of Wailoo and Emery,[16] which found that in normal infants, the trachea is funnel-shaped in the neonatal period and becomes cylindrical with increasing age. In our study, in the non-FETO group, tracheal size increased significantly with increasing age at T1, but to a lesser degree than at the WTP and the carina. Conversely, in the FETO group, the proximal portion of tracheas that were very dilated at birth plateaued over 5 years of

follow-up. Moreover, whereas in the present study, the WTP was at T1 in the vast majority of neonatal CRs in the FETO group, in the long-term study the WTP was at T3 in the majority of patients. This is a significant finding, demonstrating tracheal remodeling post-FETO. We speculate that this is consistent with craniocaudal tracheal growth cessation, usually proximal to the carina. Borrowing from terminology hitherto associated with the anatomy of choledochal cysts,[17] we propose the terms "cystic tracheomegaly" to distinguish morphology evident in the postnatal period from "fusiform tracheomegaly," into which it evolves at follow-up. The exact pathophysiological mechanism for the development of tracheomegaly remains unclear. On one hand, it can be speculated that tracheomegaly is the direct result of a molding effect of the balloon left in situ over a period of weeks. On the other hand, a more attractive theory may be dilatation of the immature trachea proximal to the obstructing FETO balloon.

Our investigation of whether tracheomegaly post-FETO affected long-term clinical outcome revealed no major differences in this subgroup compared with patients in the non-FETO group. The proportions of children who required hospital admission for significant respiratory tract infections were comparable. This aspect of the data requires qualification, however; the frequency and severity of infections and long-term lung function tests have not been formally evaluated and await further study.

In conclusion, FETO has a significant impact on tracheal size in infants with CDH. The degree of tracheomegaly does not appear to impact survival or early respiratory support in these infants who undergo FETO compared with those who do not. The proportion of children with long-term respiratory infections at current follow-up appears to be similar in the 2 groups; however, frequency and severity require further evaluation. As the cohort of children who have undergone FETO approach the age at which formal pulmonary function tests are feasible, detailed assessment will be an important part of subsequent investigations. ■

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