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Expansion Thoracoplasty in Rabbit Model: Effect of Timing on Preserving Pulmonary Growth and Correcting Spine Deformity

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Abstract

Study Design—In a treatment-control animal study expansion thoracoplasty (ET) was performed in a juvenile rabbit model of thoracic insufficiency syndrome (TIS) and benefits to thoracic development and respiratory function quantified. Rabbits treated Early versus Late were compared to age matched Normal and Disease control rabbits through to skeletal maturity.

Objective—Evaluate 1) how ET changes the natural TIS disease trajectory, and 2) how timing of ET affects changes in spine growth, lung growth, and respiratory mechanics.

Summary of Background Data—Pulmonary growth potential is thought to diminish with age, thus early therapeutic intervention may increase pulmonary growth in TIS children. However, no direct empirical evidence exists to support this treatment paradigm.

Methods—Convex left scoliosis and resultant TIS was induced in 3-week-old rabbits via surgical rib-tethering. We compare the efficacy of ET performed at 7-weeks and expanded at 11-weeks (Early, n=7) versus only at 11-weeks of age (Late, n=7) in preserving lung growth and respiratory function relative to Normal (n=8) and Disease (n=10) rabbits. Sequential CT images and pulmonary function testing was performed to quantify spine curvature, lung growth, and respiratory volumes. At 28-weeks of age chest wall elastance was measured in-vivo then acinar complexity analyzed histologically via radial alveolar counts.

Results—ET performed Early or Late altered the predicted trajectory of spine deformity, pulmonary growth inhibition, and respiratory dysfunction seen in Disease rabbits. Growth was not significantly different between Early and Late rabbits and post-treatment gains remained below those of age matched Normal rabbits. Chest wall elastance was impaired by ET and more so in Early rabbits, there were no differences in pulmonary elastance.

Conclusion—ET interrupted the natural progression of deformity and pulmonary hypoplasia associated with spine curvature in Disease rabbits. However, growth benefits are only seen in cases of the most severe initial deformity and must be balanced against the further impairment to chest wall function associated with repetitive surgery.

Keywords

Rabbit model; thoracic insufficiency syndrome; early onset scoliosis; rib fusion; expansion thoracoplasty; growth-sparing treatment; pulmonary development; restrictive respiratory disease; CT-derived lung growth; radial alveolar count; chest wall mechanics

Introduction

Thoracic insufficiency syndrome (TIS) is defined as the inability of the thorax to support normal respiration and lung growth^{1, 2}. TIS is associated with prolonged deformity and dysfunction of the spine and rib cage as occurs in congenital, idiopathic, or neuromuscular scoliosis and congenital or acquired anomalies of the ribs^{1–3}. Children afflicted with TIS often present with critically failing respiratory status marked by decreased thoracic volume, increased chest wall elastance, declining vital capacity^{4–9}, and a failure to thrive determined by quality of life and expected growth^{10, 11}.

“Growth-sparing” therapies, which aim to correct spine and/or chest wall deformity without vertebral fusion¹², have shown clear success in reducing deformity while maintaining normal rates of spine growth^{13, 14} and by improving the respiratory status of critically ill patients¹⁵. However, reported increases to thoracic space available for lung growth^{16, 17}, body mass¹¹, and absolute vital capacity¹⁸ are not conclusive as there is no untreated control population available for comparison.

Furthermore, there is controversy on the importance of early therapeutic intervention. Normal pulmonary growth, defined by gains in lung parenchymal mass and alveolar multiplication, occurs primarily in the early years of life¹, although it has been shown to continue to some degree throughout adolescence¹⁹. Nevertheless, there is reasonable concern that if a TIS child misses the window of early rapid alveolarization, associated here with thoracic hypoplasia, the lost potential for lung growth may never be recuperated¹. Limited clinical data has suggested that lung function is more favorable in children treated before 2 years of age²⁰.

Previously, our group developed a rabbit model of TIS from surgically induced rib fusion producing an associated scoliosis in which extent of detriment to respiratory growth and function at maturity was highly predictable based on severity of the induced spine curve²¹. The objective currently is to use this disease model as a testing platform to evaluate respiratory development after one particular growth sparing treatment; expansion thoracoplasty (ET) distraction. After induction of TIS at 3-weeks of age, ET was initiated at Early (7-weeks) or Late (11-weeks) timepoints and evaluated with regular CT scans and pulmonary function testing until skeletal maturity at 28 weeks. Through comparison with untreated Disease and Normal control rabbits we evaluate the hypotheses that 1) thoracic development, pulmonary growth, and respiratory function is enhanced with ET treatment,

and 2) Early treatment increases potential for pulmonary growth compared to Late treatment.

Methods

Study Design

Based on somatic growth charts, a 3 week old New Zealand white rabbit is equivalent to a 3 year old child, while a 28 week old rabbit is equivalent to a mature human (18 years). The pulmonary growth rate in rabbits, determined by alveolar number, decreases monotonically from the first day of birth ²² in a manner similar to humans ^{19, 23}.

Study time points are outlined in Figure 1. Control data from 10 Disease rabbits with untreated rib fusion with scoliosis and 8 Normal rabbits was previously published ²¹.

Surgical Procedures

Rib-tethering surgery—Rib tethering was performed on Disease control, Early treatment, and Late treatment rabbits at 3 weeks of age. This was previously described in detail ²¹.

Expansion Thoracoplasty (ET)—ET was performed at age 7-weeks in Early treatment rabbits and at 11-weeks in Late treatment rabbits. Anesthetized, intubated rabbits on controlled ventilation were positioned prone, and sterilely prepped. A longitudinal incision was made along the posterior angle of the right rib mass to the intercostal muscles, which were retracted to expose the rib mass (Figure 2A). The midline of the mass was verified through fluoroscopy, and a thoracostomy performed with a high speed dental burr (Figure 2B). The thoracostomy was expanded to the maximal extent tolerated by the ribs, or until the lateral spine curve was minimized, using a laminar spreader. A custom expandable PEEK plastic implant with opposing hooks connected to a 3.5mm diameter rod was interposed into the thoracostomy to maintain expansion (Figure 2C). The incision was closed in layers over the thoracostomy and implant; an 18 gauge IV catheter served as a chest tube to prevent pneumothorax. The rabbit recovered in a high oxygen environment with the chest tube for up to 24 hours.

Early treatment rabbits underwent further lengthening of the implant at 11 weeks of age to keep up with natural growth. Rabbits were prepped as in the previous surgery and likewise the rib mass with implant exposed. Distraction was performed with a rod distractor, the incision closed and post-operative care provided as before.

CT Imaging and Analyses

Serial CT scans (Aquilion 64 scanner, Toshiba America, Tustin, CA) of the thorax were acquired at 6, 10, 14, and 28 weeks of age on sedated rabbits (Figure 3). Rabbits were positioned prone and 2 scans acquired during respiratory breath-holds of 0 and 25 cm H₂O pressure, these scans are representative of functional residual capacity (FRC) and total lung capacity (TLC) respectively. Maximal spine deformity angle (θ_M), thoracic rotation angle (TRA), left and right lung aerated volume at FRC and TLC, left and right lung mass, and

fractional tissue volume (FTV) were measured as previously described²¹. For ET rabbits, the length of the distraction between hooks was also measured from CT.

Respiratory Mechanics

Forced vital capacity (FVC) was determined at 28 weeks using the raised volume rapid thoracoabdominal compression technique, as previously described^{21, 24}. Elastance was measured dynamically under controlled ventilation using a Scireq FlexiventTM test ventilator (Scireq, Montreal, Canada). Respiratory elastance was calculated at 10, 14, and 28 weeks of age immediately after CT scans in Early and Late treatment, and Normal control rabbits; comparable data on Disease control rabbits was unavailable. Additionally, at 28 weeks an esophageal balloon was placed to partition the chest wall and lung elastance. Procedural details for elastance measures are provided in supplemental online text.

Histology

At 28 weeks of age, rabbit lungs were excised and pressure fixated with formaldehyde via the trachea under 25 cmH₂O pressure. Sections of each lobe were embedded in paraffin, sectioned, stained, and evaluated with the radial alveolar count (RAC) to measure acinar complexity^{25, 26} as previously described²¹.

Statistical Evaluation

At each time point data were compared between all groups (Early and Late treatment, Disease, and Normal) via ANOVA. At pre-treatment time-points Early and Late treatment rabbits were grouped with Disease rabbits. All data from 28 weeks is presented and earlier time points only when noteworthy.

At 28 weeks outcomes for Early and Late treatment, and Disease groups were correlated to the juvenile spine deformity angle (at 6 weeks: $\theta_{M,6wk}$). The coefficient of determination (R^2) and direction of correlation is presented. Previously we demonstrated in Disease rabbits that lung growth and spine deformity at 28 weeks correlated strongly with $\theta_{M,6wk}$, consequently these outcomes were compared between Early and Late treatment rabbits, and Disease rabbits via ANCOVA analysis with $\theta_{M,6wk}$ as the co-variate or predictor; here differences in slope and then intercept were compared²⁷.

Statistics were calculated with Prism 6 software (Graphpad Software, La Jolla, CA). Bonferroni post-hoc analysis was employed for ANOVA models. Statistically significant results are indicated at $p < 0.05$. All individual data points are provided in supplemental online spreadsheet.

Results

Deformity Induction

Rib-tethering of the right hemithorax produced an immediate convex left scoliosis ($\theta_s > 40^\circ$) in all rabbits, measured by post-op fluoroscopy. At 6 weeks of age several rabbits exhibited broken or dislocated ribs around the tethering site reducing the severity and consistency of the induced deformity. Here juvenile deformity, $\theta_{M,6wk}$, ranged from 21° – 66° in Early

treatment rabbits, 10°–41° in Late treatment rabbits, and 20°–71° in Disease control rabbits. Body weight at this time point was less than Normal for Disease and treatment rabbits in-toto, 87% (10%) $p<0.01$, however by 28 weeks there was no mean difference in any group. There was a strong negative correlation between $\theta_{M,6wk}$ and body weight at 28 weeks in Disease rabbits, $p<0.001$ ²¹.

All outcomes between groups at maturity are compared in Table 1. Juvenile deformity correlated with outcomes at maturity are shown in Table 2.

Treatment Response

Four rabbits were lost after ET surgery due to persistent pneumothorax. Two developed an apparent pneumonia following ET, diagnosed upon CT examination, that resolved shortly after treatment with antibiotics. Data acquired from rabbits while afflicted with pneumonia was discarded. Surgical trauma affected all rabbits adversely: at age 14 weeks, body weight was less than Normal in Early, 84% (9%) $p<0.01$, and Late, 87% (11%) $p<0.05$, treatment rabbits however there was no difference by 28 weeks.

Distraction length is shown in Table 3. Total distraction in Early treatment was greater than Late treatment, $p<0.001$. Distraction length did not correlate with any growth or functional outcome.

Spine Deformity—Expansion thoracoplasty interrupted the progressive spine curvature in Disease rabbits; for both treatment groups the θ_M angle at 28 weeks was similar to Normal and the slope significantly less than Disease ($p<0.01$), TRA however was similar to Disease (Figures 4 and S1).

Pulmonary Growth—Left lung mass and volume were not significantly different from Normal for any groups at any time, whereas right lung mass and TLC at maturity were significantly reduced in all groups (Table 1).

Juvenile deformity in Disease rabbits was highly predictive of total and right lung mass at maturity. With treatment (Late or Early rabbits) there was no such association (Figures 5 and S2) although values remained below Normal. Slope in the right lung of Early treatment was flat compared to Disease control ($p<0.05$).

Post-mortem—Occasional pleural adhesions between the lung and rib cage were present in Disease and treatment rabbits at sacrifice. Histology showed no evidence of pulmonary edema or congestion, indicated by the absence of hemosiderin or alveolar transudate. Results of RAC analysis reflected those of lung mass at 28 weeks; juvenile deformity was highly predictive of total and right lung RAC in Disease rabbits but not in treatment rabbits (Figures 6 and S3).

Respiratory Mechanics

FVC measured at 28 weeks was decreased in treatment groups and Disease rabbits (Table 1), however FVC was not associated with juvenile deformity in any groups.

Respiratory elastance in Early and Late treatment rabbits was greater than Normal at all post-treatment time points. Partitioned elastance at maturity shows the increase in respiratory elastance as due to the chest wall with no discernible difference in pulmonary elastance (Figure 7).

Discussion

We previously developed a rabbit model representing TIS from fused ribs and scoliosis by surgically tethering right ribs 3–9 in juvenile rabbits ²¹. This produced a progressive thoracic spine curve with variable but predictable severity at maturity (30°–126°) associated with impaired growth of the right lung and inhibited chest wall mechanics. The extent of inhibition in lung growth at maturity for these untreated Disease rabbits was largely predictable from the deformity angle measured at youth ($\theta_{M,6wk}$), Table 2. Additionally, rabbits with severe deformity ($\theta_{M,6wk} > 50^\circ$) presented significant reductions of FVC (25%), body weight (11%), lung mass (30%), TLC (21%), and RAC (26%) as compared to Normal controls. Currently, we use this rabbit TIS model as a platform to evaluate outcomes from ET intervention and specifically the hypotheses that 1) ET surgery on the constricted chest wall will reorient the thorax toward Normal to improve thoracic development, pulmonary growth, and respiratory function, and 2) the extent to which ET improves pulmonary growth is proportional to the growth potential remaining, and thus the age of the rabbit at the time of intervention.

In support of hypothesis 1, we demonstrate a sustained correction in spine curvature after ET, although no lasting improvement to thoracic rotation. Probable benefits to pulmonary growth, measured by lung mass and acinar complexity, were proportional to severity of the initial deformity with a “tipping point” occurring near 43° above which lung growth tended to improve from that of similarly deformed Disease control rabbits. Conversely, chest wall mechanics were aggravated following ET surgery, by comparison to age matched Normal control rabbits, and all treatment rabbits showed lung growth less than expected for Normals.

In support of hypothesis 2, we demonstrate a trend towards improved lung growth in Early treatment rabbits with the most severe initial deformity. This trend was not apparent in Late treatment rabbits; although statistical power was lacking in this group. Conversely, Early treatment rabbits showed a greater impediment to respiratory function than Late treatment rabbits as increased chest wall elastance.

ET with the VEPTR™ distracting implant (Vertical Expandable Prosthetic Titanium Rib, DePuy Synthes, Raynham, MA) was FDA approved in 2004 citing evidence of improved ventilator support status in TIS children. The nature of any respiratory changes have not been confirmed in subsequent studies due to the lack of an untreated control population. Reports of lung volume gains of 219% at 2 years follow up ¹⁶, and conversely a decrease in predicted FVC (–18%) and impaired respiratory mechanics shown as decreased weight normal tidal compliance (–39%) at 6 year follow up ²⁸ are suggestive. This rabbit study largely confirms these suggestions; in comparison to a Disease control cohort, ET improved lung growth in the most severely impaired rabbits (11% predicted improvement in the most

severe case) and age-normal respiratory mechanics were impaired over the span of each treatment operation (by 27% after ET and 7% after lengthening). Interestingly, FVC is of the most commonly reported clinical measure of respiratory performance^{4-6, 18, 28-30} and though it was greatly reduced compared to Normal in all experimental rabbits, it did not vary with severity of disease (Table 2) and was unresponsive to ET treatment.

Thoracic deformity from diverse origins are historically quantified by length and orientation of the spine. Adolescents with untreated early onset scoliosis (EOS) show a mild correlation between Cobb angle and FVC⁴, however no relation was found in young children evaluated pre-treatment and similarly improvements in Cobb angle did not correlate with improvements in FVC on treated children²⁹. In our studies, spine curvature was a strong predictor of lung growth in Disease control rabbits, however in ET rabbits the improvements in spine curvature and the final curvature had no impact on respiratory outcomes (Table 2). Persistent structural imperfections after ET intervention likely overwhelm any benefit from improved spine orientation in our rabbits (*e.g.* chest wall concavity, thoracic rotation, diaphragm mal-alignment). Similarly, a clinical study found minimal correlation between thoracic height or maximal chest width to respiratory function³⁰. Better understanding on the relation of structural manipulations to functional outcomes would guide improved treatment protocols.

This study is the first controlled study to evaluate timing of ET on respiratory development. By most accounts normal pulmonary alveolarization is largely complete by 8 years of age¹, thus it is assumed that growth potential decreases with age. Research on pulmonary resection in dogs suggests that alveolarization is stimulated by the strain of an expanding thoracic cavity and while adult dogs are capable of regenerative septation, a greater stimulus is required than in younger dogs^{31, 32}. Clinical examples of untreated EOS are rare; in one available post-mortem examination of an adult with untreated EOS extreme alveolar hypoplasia was readily apparent³³. There remains no clinical evidence to how surgical thoracic modulation may reverse or prevent such hypoplasia. In our treatment rabbits lung growth was reduced from Normal but not associated with the severity of initial deformity, thus ultimate growth was influenced by the treatment state and not the initial disease state. Additionally, timing of intervention had no significant effect on lung growth. Growth greater than expected only occurred in rabbits with the poorest initial prognosis. Furthermore, in those treated rabbits with improved lung growth, it is unlikely that ET excited lung growth outside of its natural age-constrained potential; the gains in lung mass during the post-treatment period did not exceed those of age matched Normal control rabbits over the same age span.

Thus this study has several limitations. Rib-tethering created a variable degree of deformity and there were few treated rabbits with severe initial deformity to make statistical conclusions on the benefits of intervention in a significantly impaired population. Additionally, induction of deformity and Early treatment in our rabbits likely occurred too late to represent what is considered “early treatment” in children, often defined as treatment provided less than 3 years of age when a progressive growth deficiency would be more impactful. Lastly, a direct evaluation of respiratory performance was not performed as

through the measurement of gas diffusing capacity³⁴ or active function of the muscles of respiration.

We developed a rabbit model of TIS treated with ET to evaluate the effects of surgical reconstruction on thoracic development and respiratory function. Our findings show that ET reliably corrected spine curvature, but provided only slight benefit to pulmonary growth, and only in the most severely deformed rabbits. Respiratory mechanics were further degraded with each surgical intervention. Differences in lung growth due to timing of intervention were not apparent due to both the limited number of subjects with the most severe disease deformity and the partially irreversible rib fusion. Further investigation will be required to understand the limits of timing of intervention and lung development. Future controlled studies investigating the particular structural anomalies most associated with respiratory impairment could provide useful clinical insight.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The manuscript submitted does not contain information about medical device(s)/drug(s).

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Figure 1. Study Overview
Timing of surgeries, CT scans, and pulmonary function testing relative to postnatal age in each group.

Figure 2. Expansion Thoracoplasty Surgery

(A) Exposure of right rib mass; (B) Anterior to posterior fluoroscopy identifying apex of deformity; (C) Thoracostomy with distraction of interposed PEEK device.

Figure 3. CT Reconstructions

Posterior projections of spine, lungs and PEEK device (yellow) comparing Disease control (left) and Early treatment (right) rabbits at 28 weeks of age.

Figure 4. Progression of Spine Deformity

Maximal spine curvature (left) and thoracic rotation (right) at maturity in relation to severity of juvenile spine curvature ($\theta_{M,6wk}$) for each experimental group. Linear regression is displayed for each group; treatment group means are shown by dashed lines and Disease group mean and 95% prediction bounds by unbroken lines. See online supplement Figure S2 for Disease group data points. Tx = treatment.

Figure 5. Lung mass

Total, left, and right lung mass at maturity for all experimental rabbits in relation to severity of juvenile spine curvature, correlation values are indicated. Average Normal values are indicated by the dotted horizontal line. Linear regression is displayed for each group; treatment group means are shown by dashed lines and Disease group mean and 95% prediction bounds by unbroken lines. See online supplement Figure S3 for Disease group data points. Tx = treatment.

Figure 6. Lung RAC

Total, left, and right lung RAC at maturity for all experimental rabbits in relation to severity of juvenile spine curvature, correlation values are indicated. Average Normal values are indicated by the dotted horizontal line. Linear regression is displayed for each group; treatment group means are shown by dashed lines and Disease group mean and 95% prediction bounds by unbroken lines. See online supplement Figure S4 for Disease group data points. Tx = treatment.

Figure 7. Respiratory Elastance

Progression of respiratory elastance (left) and Partitioned elastance at 28 weeks of age (right) for Normal and treated rabbits. Significant differences are indicated with p-values: *p<0.05, **p<0.01, ***p<0.001.

Outcomes at maturity (28 weeks) for each group. Asymmetry units are as labelled, for all other data experimental group values are reported as percent Normal and Normal value units are as labelled.

Table 1

	Early Tx	Late Tx	Disease	Significance (ANOVA)					Normal
				E. Tx vs Disease	L. Tx vs Disease	E. Tx vs Normal	L. Tx v Normal	Disease v Normal	
Body mass	96% (13)	103% (7)	98% (10)						4.2 kg (0.24)
Asymmetry									
θ _M	38° (16)	21° (13)	73° (31)	*	***			***	21° (3)
R:L lung vol.	1.0 (0.1)	0.9 (0.2)	0.9 (0.1)			***	***	***	1.4 (0.1)
TRA	13° (15)	12° (11)	25° (24)					*	3 ° (4)
Lung vol.									
FRC	88% (21)	70% (29)	99% (35)						24 mL (5)
- Left	119% (26)	101% (43)	145% (46)						10 mL (3)
- Right	66% (20)	49% (22)	66% (30)						14 mL (3)
TLC	81% (7)	79% (17)	85% (11)			*	**		123 mL (17)
- Left	96% (9)	100% (25)	106% (11)						52 mL (7)
- Right	70% (7)	64% (13)	70% (13)			*	**	*	71 mL (10)
Lung growth									
Lung mass	84% (6)	91% (9)	81% (15)			*		**	20.6 g (1.5)
- Left	95% (8)	107% (12)	93% (13)						8.7 g (0.7)
- Right	76% (8)	79% (11)	73% (18)			**	**	***	11.9 g (0.9)
FTV	103% (6)	115% (21)	95% (10)						0.14 (0.01)
-Left	98% (8)	109% (23)	88% (10)						0.14 (0.01)
-Right	107% (5)	121% (19)	103% (10)				**		0.14 (0.01)
RAC	90% (8)	93% (10)	85% (15)					*	12.0 (0.9)
- Left	91% (9)	99% (7)	84% (16)					*	12.3 (0.9)
- Right	87% (11)	87% (9)	83% (15)					*	11.8 (1.8)
Resp. mech.									

	Early Tx	Late Tx	Disease	Significance (ANOVA)					Normal
				E. Tx vs Disease	L. Tx vs Disease	E. Tx v Normal	L. Tx v Normal	Disease v Normal	
FVC						*			125 mL (21)

Significant differences between groups are indicated with p-values:

*
p<0.05,
**
p<0.01,

p<0.001.
Tx = treatment group.

Table 2

Disease trajectory for each group: Juvenile deformity ($\theta_{M,6wk}$) vs. all outcomes at 28 weeks. Coefficient of determination (R^2) is given with the direction of correlation indicated by + or – in parentheses.

	Early	Late	Disease
Body mass	(+) 0.67 *	(–) 0.11	(–) 0.83 ***
Asymmetry			
θ_M	(–) 0.00	(+) 0.10	(+) 0.88 ***
TRA	(+) 0.50	(+) 0.69 *	(+) 0.67 **
R:L lung vol.	(+) 0.19	(–) 0.78 **	(–) 0.48 *
Lung Vol.			
FRC	(–) 0.03	(+) 0.05	(+) 0.01
- Left	(–) 0.06	(+) 0.19	(+) 0.04
- Right	(–) 0.01	(–) 0.00	(+) 0.00
TLC	(–) 0.01	(+) 0.27	(–) 0.50
- Left	(–) 0.09	(+) 0.50	(–) 0.11
- Right	(+) 0.02	(+) 0.04	(–) 0.64 **
Lung Growth			
Mass	(–) 0.11	(–) 0.10	(–) 0.76 **
- Left	(–) 0.35	(+) 0.07	(–) 0.61 **
- Right	(–) 0.00	(–) 0.41	(–) 0.80 ***
FTV	(–) 0.05	(–) 0.68 *	(–) 0.38
- Left	(–) 0.04	(–) 0.68 *	(–) 0.31
- Right	(–) 0.05	(–) 0.61 *	(–) 0.36
RAC	(+) 0.07	(–) 0.50	(–) 0.68 **
- Left	(+) 0.00	(–) 0.75 *	(–) 0.63 **
- Right	(+) 0.26	(–) 0.25	(–) 0.60 **
Mechanics			
FVC	(–) 0.01	(+) 0.00	(–) 0.17

Statistically non-zero slopes are indicated with p-values

*
p<0.05,

**
p<0.01,

p<0.001.

Table 3

ET surgery distraction lengths in cm. Average with SD in parentheses.

Distraction at age:	7 weeks (cm)	11 weeks	Total
Early Treatment	2.04 (0.27)	0.69 (0.24)	2.72 (0.35)
Late Treatment	---	2.03 (0.18)	2.03 (0.18)