Early onset scoliosis (EOS) represents a unique group of congenital and acquired conditions that affect the growth and development of the spine in young children leading to spinal deformity. Besides affecting the height, posture, and functional mobility of affected children, the resultant spinal deformity has significant impact on the overall health of these children by limiting the volume of the thorax for the lungs to grow. Pulmonary function depends on the action of the diaphragm and respiratory expansion of the rib cage. In early onset scoliosis the disease process is not just a spine deformity, but is rather a serious three-dimensional malformation directly affecting the volume, symmetry, and function of the thorax and indirectly affecting lung growth. This workshop will educate researchers and clinicians on the latest basic and translational scientific advances regarding the etiology and pathophysiology of EOS. In addition, the workshop will foster potential collaborations between the clinicians caring for these patients and scientists investigating the molecular and biologic processes that contribute to EOS phenotype to develop novel treatment strategies beyond the insertion of rigid rod systems that straighten the spine and/or rib cage.
The vertebrae develop from the somitic mesoderm. The pre-somitic mesoderm commits to a somitic fate before mesoderm becomes capable of forming somites, but the cells within the mesoderm have sufficient plasticity to differentiate to a variety of cell types. The somites eventually form dermis (dermatome), skeletal muscle (myotome), sclerotome (cartilage, tendons), and endothelial cells. The sclerotome differentiates before the other the dermatome, in somite patterning. The sclerotome also forms the vertebrae and the rib cartilage; the myotome forms the musculature of the back, the ribs and the limbs; the dermatome forms the skin on the back. In addition, the somites specify the migration paths of neural crest cells and spinal nerve axons. It is easy to imagine how somite development play a critical role in the axial skeleton patterning.

Somitogenesis depends on a clock mechanism, or the the clock and wavefront model. Oscillating Notch and Wnt signals provide the clock. The wave is a gradient of the FGF protein that is rostral to caudal (nose to tail gradient). Somites form one after the other down the length of the embryo from the head to the tail, with each new somite forming on the caudal (tail) side of those already in existing somites. Different species have different interval timing. In the chick embryo somites are formed every 90 minutes. In the mouse the interval is variable.

One can easily imagine how a perturbation in the clock or waveform can cause a vertebral malformation, and indeed, mutations in a Notch signaling pathway member, delta-like-3, was identified in patients with Spondylocostal dysplasia, a condition with multiple vertebral anomalies, inherited in an autosomal recessive manner, and also simialr to the phenotype of the ‘pudgy’ mouse.
Spondylocostal dysplasia caused by a mutation in delta-like-3

This information was then used in the mouse to determine how mutations in Notch signaling pathway members, such as delta-like-3, regulate the clock and wave during somite development. Using a Notch reporter mouse, it was demonstrated that mutations in delta-like-3 also disrupt the normal, patterning of Notch activation.

Most congenital scoliosis curves do not seem to be inherited, and usually involve only one or at most a small number of vertebrae. Using mice expressing only one mutant delta-like-3 allele, it was found that hypoxia also predisposes to disruption of the clock, and there patients with single vertebra abnormalities have a high incidence of mutations in one allele of a gene regulating the clock. Thus, demonstrating an environmental-gene interaction causing congenital scoliosis.

Patients with congenital scoliosis also have a higher than anticipated rate of relatives with "idiopathic" scoliosis, raising the possibility that like the environmental genetic predisposition to small segment anomalies, there may be a similar occurrence, or multifactorial genetic etiology causing some cases of idiopathic scoliosis.
Signaling pathways important in regulating the clock and waveform, also regulate the development of other organs, such as the heart, kidney, and lungs. This explains the association of renal and cardiac anomalies with congenital vertebral malformations. Intriguingly, signaling pathways such as Notch are critical for normal lung development and growth. This data may be important in the concept of optimizing pulmonary function in early onset scoliosis, as it may be that the underlying cause of early onset scoliosis also alters the way the lungs develop and function.

References:


The interdisciplinary relationship between the thorax and the lung: The impact of thoracic deformity on respiratory function

Olson JC, Snyder BD
Center for Advanced Orthopaedic Studies, Beth Israel Deaconess Medical Center; Dept. of Bioengineering, Boston University School of Engineering; Dept. of Orthopaedic Surgery, Children’s Hospital; Harvard Medical School, Boston MA

Anomalies affecting the growth and development of the spine and/or ribs in growing children severely impact respiratory function, however the relationship between respiratory function and structural deformities of the thorax during growth is not well understood. The objective of this study was to create an animal model that develops severe thoracic deformity early in life so as to evaluate the resulting influence on the growth, structure and function of the spine, thorax and lungs. Therefore we tethered the right rib cage of 3½-week-old rabbits to provoke progressive constriction of the thorax during skeletal growth to limit the space available for the lung to grow, distort the spine and diaphragm, and alter chest wall compliance (Fig 1).

We tested the hypotheses: 1) structural deformities that limit the growth of the spine and thorax during development of the lung, spine and rib cage provoke mechanical inhibition of respiration and induce postnatal pulmonary hypoplasia sufficient to degrade respiratory function at skeletal maturity; 2) the extent of deformity of the spine and thorax during growth predicts respiratory function at skeletal maturity.

To accomplish our aims, computed tomography (CT) imaging of the thorax was performed at regular intervals throughout growth until maturity to monitor progressive deformity of the spine and rib cage and measure aerated lung volumes at known inspiratory pressures. From reconstructed 3D CT images of the entire thorax, the functional residual capacity (FRC), total lung capacity (TLC), and elastance of the lung and thorax were determined. By comparing static changes in thoracic anatomy and dynamic changes in respiratory mechanics measured in rabbits with a tethered hemithorax vs. normal control rabbits, we demonstrated that deformities of the spine and thorax acquired at an early age mechanically inhibited lung growth and restricted respiratory function, supporting our first hypothesis (Fig 2). Additionally we demonstrated that the extent of spinal deformity present during growth (at 6 weeks of age) predicted the extent of thoracic deformity and degradation in respiratory function at adulthood (28 weeks), supporting our second hypothesis.
These results lend credence to the clinical concept that early treatment of spinal deformity in children will prevent pulmonary complications in adulthood. To our knowledge this is the first animal model created to simulate early onset thoracic deformity for the purpose of serially evaluating pulmonary growth and function.

Table 1: Spine Deformity @ 6 wks of age (child) highly and inversely correlated with pulmonary function @ 28 wks of age (adulthood)

<table>
<thead>
<tr>
<th>Deformity (6 wks) vs.</th>
<th>Outcomes (28 wks)</th>
<th>r</th>
<th>R^2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lung Mass</td>
<td>-0.87</td>
<td>0.76**</td>
</tr>
<tr>
<td></td>
<td>- Right lung</td>
<td>-0.89</td>
<td>0.80***</td>
</tr>
<tr>
<td></td>
<td>- Left lung</td>
<td>-0.78</td>
<td>0.61**</td>
</tr>
<tr>
<td></td>
<td>Functional Residual Capacity</td>
<td>-0.85</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>Total Lung Capacity</td>
<td>-0.70</td>
<td>0.50*</td>
</tr>
<tr>
<td></td>
<td>- Right lung</td>
<td>-0.80</td>
<td>0.64**</td>
</tr>
<tr>
<td></td>
<td>- Left lung</td>
<td>-0.33</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Resp. Elastance</td>
<td>0.91</td>
<td>0.83***</td>
</tr>
<tr>
<td></td>
<td>Forced Vital Capacity</td>
<td>-0.56</td>
<td>0.31*</td>
</tr>
<tr>
<td></td>
<td>Diaphragm S.A.</td>
<td>-0.89</td>
<td>0.80***</td>
</tr>
</tbody>
</table>

Significance:  *-p<0.05,  **-p<0.01,  ***-p<0.001
Evolving treatment options for EOS - is growth modulation of the spine the answer?

Peter O. Newton, MD,
Pediatric Orthopedic & Scoliosis Center
Rady Children’s Hospital San Diego, University of California, San Diego

Spinal Growth Modulation Rationale

- Limit spinal column growth asymmetrically
- Maintain motion
- Maintain disc physiology
- Prevent need for spinal fusion for scoliosis

Nitinol Staples to Modulate Growth

- Caprine Model – Modest effect on growth
- Porcine Model – Less effective than tether

Off-label Clinical use

- Curves less than 35 degrees

Animal Data Supporting Spinal Growth Modulation via Tether

- Bovine model – anterolateral vertebral body screw-cable system
  - Fixation important to prevent screw plow
  - Coronal>Sagittal growth effect
  - asymmetric effect on physeal cartilage thickness

- Porcine model – anterolateral vertebral pronged washer-screw-tether system
  - Slower growth than bovine, faster than human
  - Consistent growth effect
  - Disc physiology maintained, but disc height less

Off Label Human Tether Use

- Indications remain to be defined
  - Primary thoracic scoliosis 35-60 degrees

Figure 1 Nitinol staples

Figure 2 Coronal Deformity after Tethering

Figure 3 CT and MRI after tethering growth
2-3+ years of remaining growth
Near certainty of impending spinal fusion indication if untreated/failing brace
Hypokyphosis
Compensatory lumbar or upper thoracic curves < 30-40 degrees

Surgical Technique
Thoracoscopic minimally invasive approach/exposure
Insertion of transverse vertebral body screws
Insertion of the tethering cord and tensioning
Post op and Peri op management

Post op Correction
Desired degree of intra op correction unknown, suggest to correct to bend film
Expect standing correction to be less then supine correction
The growth rate and tension determines the when additional growth based correction will be first appreciated, may take 6-12 months
Too much growth potential, too much initial correction, too many instrumented segments may lead to overcorrection

Questions for the future

How much growth is required per degree of correction desired?
Should the device be removed at skeletal maturity?
How should over correction be managed?
How much data should be collected before widespread adoption?
Will the human experience regarding disc physiology mirror that of the animals?

References:


