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A Rib Construct for Severe Spinal Deformity: Clinical, Biomechanical, Animal Studies, and Commercialization

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A Rib Construct for Severe Spinal Deformity: Clinical, Biomechanical, Animal Studies, and Commercialization

Daniel James Bonthius

A dissertation submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Graduate Studies.

Molecular and Cell Biology Program

2022

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This dissertation is dedicated to my parents, Dan and Nancy Bonthius. Thank you for your incredible love and support over the years. You have always been there for me through both good and the challenging times. Whether it was assisting me with school work, seeing you at athletic events, or providing general guidance in hard moments, I always knew I could count on you. The foundation you gave me made all of this dissertation work possible.

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Dr. Yongren Wu- mechanical testing, Dr. Gregory Wright- mechanical testing, Dr. Laura Wolgamott-clinical consultant, Dr. Mohammed Alshareef- clinical consultant, Dr. Brooke Damon- Lab Manager, Shuchun Sun, PhD- mechanical testing, FE modeling, Drs. A Smith, MA McCrackin, M Wolfe, K Helke- veterinary staff animal facility.

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(**Equation 1**) $TLC =(0.163*L)+(0.189*W)-4.928$

DANIEL JAMES BONTHIUS. A Rib Construct for Severe Spinal Deformity: Clinical, Biomechanical, Animal Studies, and Commercialization. (Under the direction of HAI YAO).

Abstract

Introduction: Current treatments for early-onset spinal deformity (EOSD) have high complication rates and limited effectiveness. The rib construct (RC) is a novel technique for correcting early-onset spinal deformity. A series of hooks are used on the proximal superior ribs for proximal fixation to contour the thorax, with traditional fixation distally.

Methods: The performance of the rib construct was evaluated in *ex vivo* biomechanical testing, an *in vivo* animal model, and a clinical study. An R-FIX (Rib-FIXation) System was developed based on these studies for optimization of the technique.

Results: *Ex vivo* biomechanical testing showed that porcine spines instrumented with the rib construct were significantly less prone to proximal fixation failure and less stiff compared to pedicle screws. The porcine animal model study showed that sagittal spinal alignment improved substantially in hyperkyphotic pigs that were instrumented with the rib construct. Histological analysis at the sub-gross and cellular level reveal changes consistent with growth modulation of the spine. The clinical study showed that sagittal and coronal Cobb angles and other parameters of trunk, shoulder, neck and head alignment improved significantly in patients treated with the rib construct. Complication rates were improved compared to traditional methods, with a notable lack of proximal junctional kyphosis or neuromonitoring changes. The refined R-FIX System was tested in cadavers and spine models and functioned appropriately.

Interpretation: The rib construct is an effective treatment for early-onset spinal deformity.

Chapter 1. General Introduction

1.1 Summary

Scoliosis, hyperkyphosis, and kyphoscoliosis are deformities of the spine in the coronal plane, sagittal plane, or both planes respectively. These spinal deformities arise from multiple etiologies and can have a dramatically negative impact on patient quality of life. Early-onset spinal deformity (EOSD) begins before the age of 10 years. Treatment for early-onset spinal deformity should mitigate the deformity while promoting a well-developed thoracic cavity, improved lung volume, and improved pulmonary function with minimal complications.

1.2 Normal Spinal Anatomy and Alignment

The spine is composed of 5 regions from rostral to caudal: 1) cervical, 2) thoracic, 3) lumbar, 4) sacral, and 5) coccyx (**Figure 1A**). The cervical region comprises the neck and includes seven vertebrae C1-C7. The thoracic region supports the thoracic cavity and is composed of 12 vertebrae T1-12. The lumbar region comprises the lower back and includes five vertebrae L1-L5. The sacral and coccyx regions are fused and are comprised of five sacral bones S1-S5 and three to five coccyx bones, respectively. There is a normal degree of curvature to these spinal regions including cervical lordosis, thoracic kyphosis, and lumbar lordosis.

There are two layers of bone in each vertebra. The cortical bone is a dense layer that surrounds the outside of each vertebra and gives it strength. The trabecular bone is deep to the cortical layer and is composed of a spongy lattice structure. The trabecular bone provides structural support while keeping the bone relatively lightweight.

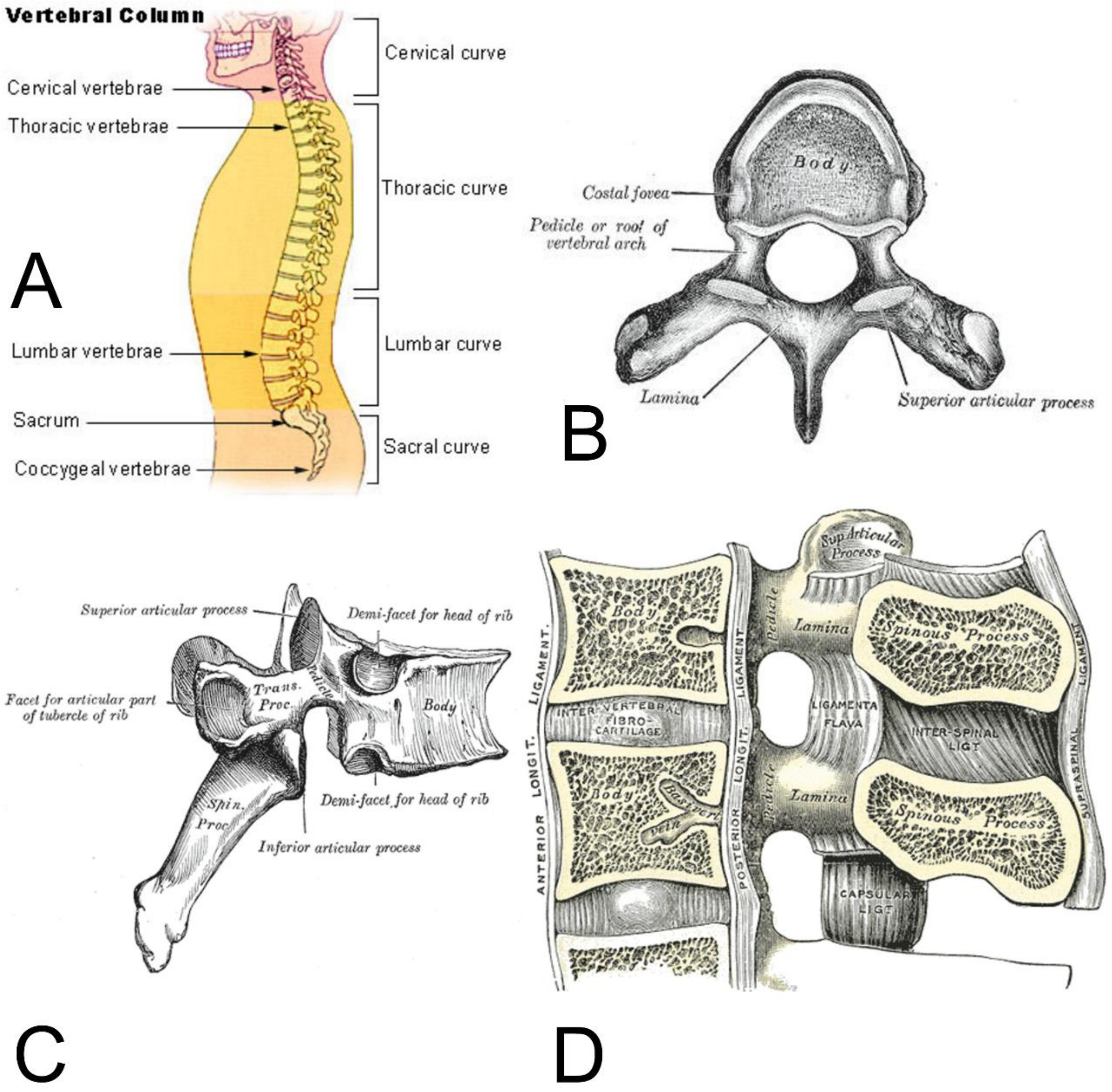


Figure 1. A) Normal anatomy and curvature of the spine showing the cervical, thoracic, lumbar, sacral, and coccyx regions. **B-C**) Anatomical features of the individual vertebra. **D**) Ligaments of the spine. Figure built from a series of public domain images from www.shutterstock.com.

Each individual vertebra is composed of a large central structure called the vertebral body. The vertebral body is connected to two pedicles, which are connected, to two lamina. Together, the vertebral body, pedicles, and lamina form a hole called the spinal canal, which houses the spinal cord (**Figure 1B-C**). Transverse processes protrude laterally from each lamina and a spinous process protrudes posteriorly. Superior and inferior articular processes also protrude from the lamina and form cartilaginous joints called the superior and inferior facets. The facets help stabilize the spine and allow motion.

Each vertebra is stacked on top of another and separated from its neighbor by an intervertebral disc (IVD) in between the vertebral bodies. The disc is composed of a fibrocartilaginous outer ring called the annulus fibrosis and a fluid filled central sack called the nucleus pulposus. The intervertebral discs serve as shock absorbers for the spine and allow motion.

Several ligaments attach to the vertebrae and help connect and stabilize each vertebra (**Figure 1D**). The anterior longitudinal ligament connects the anterior surfaces of the vertebral bodies. The posterior longitudinal ligament connects the posterior surfaces of the vertebral bodies. The ligamentum flavum connects the lamina. The interspinal and supraspinous ligaments connect the spinous process.

1.3 Introduction to Spinal Deformity and Early-Onset Spinal Deformity (EOSD)

There are four main types of spinal deformity. 1) Scoliosis is curvature of the spine in the coronal plane (**Figure 2A**). 2) Hyperkyphosis is exaggerated anterior curvature of the spine in the sagittal plane (**Figure 2B**). 3) Lordosis is exaggerated posterior curvature of the spine in the sagittal plane. 4) Rotational deformity is torsion of the spine in the axial plane. Spinal deformity frequently occurs in three dimensions, involving a combination of the above deformities. An example is kyphoscoliosis, which, as its name implies, involves a combination of curvatures in the coronal and sagittal planes. These deformities can be categorized based on etiology, including idiopathic, congenital, neuromuscular, infectious, syndromic, traumatic, degenerative, or postural.

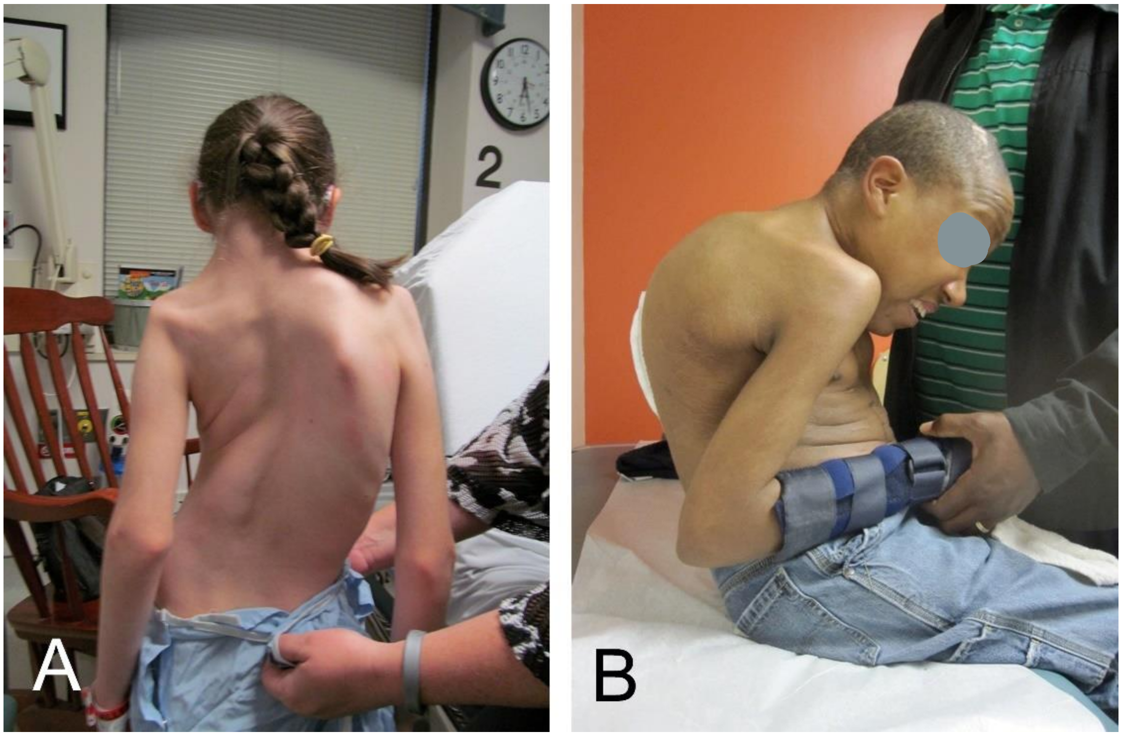


Figure 2. A) An 11-year-old girl with scoliosis and a substantial rib hump. **B**) A 20-year-old male with severe hyperkyphosis.

Scoliosis is defined as lateral curvature of the spine >10° and has an incidence of 1-3% in the worldwide population.[1] Scoliosis is further divided into four categories, based on age of onset: 1) infantile scoliosis (0-3 years), 2) juvenile scoliosis (4-9 years), adolescent scoliosis (10-16 years) and adult scoliosis (over 16 years). The term "early-onset scoliosis" (EOS) typically describes scoliosis that begins before the age of 10 years. The majority of scoliosis cases have their onset during adolescence. Early-onset scoliosis accounts for somewhere between 4-21% of pediatric spinal deformity.[1-3] While early-onset scoliosis represents only a minority of scoliosis cases, the outcome for these patients is typically more severe than in later-onset scoliosis. Infantile scoliosis may resolve without treatment within the first few years of life. However, if the scoliosis does not resolve, then the curvature may progress throughout childhood until skeletal maturity. If left untreated, the outcome of early-onset scoliosis is usually poor. The spinal curvature may progress, resulting in debilitating deformity, inhibited pulmonary development, respiratory failure, cardiac disease, and early mortality.[4-6] Early-onset scoliosis is particularly difficult to treat because surgical intervention must accommodate growth of the developing spine, as premature spinal fusion results in stunted growth and pulmonary insufficiency. Patients with early-onset scoliosis may also present with hyperkyphosis. This hyperkyphosis can range widely in magnitude and may exceed 100° in severe cases.

While early-onset scoliosis generally describes lateral curvature of the spine, hyperkyphosis (excessive anterior curvature of the spine) or other types of deformity can also be present in these patients. Thus, the general term "early-onset spinal deformity" (EOSD) is preferred to describe the spectrum of three-dimensional deformities present in these patients. The degree of curvature necessary to be considered "hyperkyphotic" in children is subject to debate. The thoracic spine has a "normal" amount of kyphosis in healthy individuals to counterbalance the lordosis of the cervical and lumbar spine. According to the Lenke Classification System, normal thoracic kyphosis ranges from 10°-40° in adolescence, with thoracic curvature >40° considered hyperkyphotic.[7] Some studies have shown average thoracic kyphosis to be within this range of 10°-40°.[8-9] Other studies have found average thoracic kyphosis to be somewhat greater.[10-12] Cil et al. found thoracic kyphosis to be 45°±11°, 48°± 11°, 46°±11°, and 53°±9° in 3-6 years, 7-9 years, 10-12 years, and 13-15 years age groups, respectively.[10] While these studies exhibited variable results for the average kyphotic curvature in patients, a general trend towards slightly increased kyphosis with age and growth has emerged across studies. Normal thoracic kyphosis is generally considered to be within 20° and 50°, with >50° considered hyperkyphotic.[7-12] The presence of hyperkyphotic deformities present unique challenges in the treatment of patients with EOSD.

1.4 Early-onset Spinal Deformity Disease State Fundamentals

Pathophysiology of Early-onset Spinal Deformity

The etiology and pathophysiology of early-onset spinal deformity, as with any form of spinal deformity, is complex. The disease can be idiopathic, congenital, neuromuscular, infectious, syndromic, traumatic, degenerative, or postural in origin.

Idiopathic Early-onset Spinal Deformity

Idiopathic early-onset spinal deformity (unknown origin) is probably the least well understood etiology.[13,14] There appears to be a strong genetic component. Hereditary characteristics are multi-factorial, and multiple genes are believed to be linked to the development of idiopathic deformity. While no specific mechanism for idiopathic deformity has been verified, there are several theories, most of which focus on the wedging of intervertebral discs (IVD).[15] One theory, termed the "vicious cycle theory," proposes that asymmetrical loading on the vertebrae leads to asymmetrical growth, thus creating the "wedge" appearance.[16] Curve progression occurs most rapidly during phases of rapid linear body growth, particularly during infancy and adolescence. The latter period may be marked by an abrupt acceleration in curve progression, with rapidly progressing curves approaching 2 degrees per month.[17] Infantile curves may either resolve or progress, with resolving curves being far more common. Ninety-five percent of juvenile idiopathic scoliosis curves are progressive.[18] The behavior of adolescent curves depends on curve patterns and magnitude. Known risk factors for rapid curve progression include larger curve magnitude, lesser maturity, and specific curve patterns.[19,20] Larger curves continue to progress in adulthood. In particular, thoracic curves greater than 50° and lumbar curves greater than 30° tend to progress. Curve progression significantly slows at the completion of linear body growth.

Congenital Early-onset Spinal Deformity

Congenital malformations of the spine are usually classified into 2 basic types: 1) failure of formation of the vertebrae, and 2) failure of segmentation of the vertebrae, with frequent mixed types. Congenital spinal deformities worsen through asymmetric growth. Spinal radiographs can provide clues regarding potential growth asymmetry, with unilateral failures of segmentation (unilateral bars) having a worse prognosis than failures of formation (hemivertebra), and the combination having the worst prognosis. In congenital hyperkyphosis, the failures of formation, being acute angular deformities, place the spinal cord at risk (**Figure 3**), whereas the hyperkyphotic failures of segmentation have a more gradual hyperkyphosis at the apex and less paralysis risk. Congenital deformities can pose significant threats to health when they become severe at a young age, with cord impingement in hyperkyphosis and pulmonary compromise in scoliosis. These spinal malformations occur early in gestation and are often associated with other parts of the VACTERL complex, which is an association of multiple congenital anatomical defects that often occur together. VACTERL stands for vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistuala, renal anomalies, and limb abnormalities.[21] For this reason, chest x-ray, echocardiogram, kidney ultrasound, and MRI scan of the spinal cord should be obtained in all cases of congenital scoliosis and kyphosis.

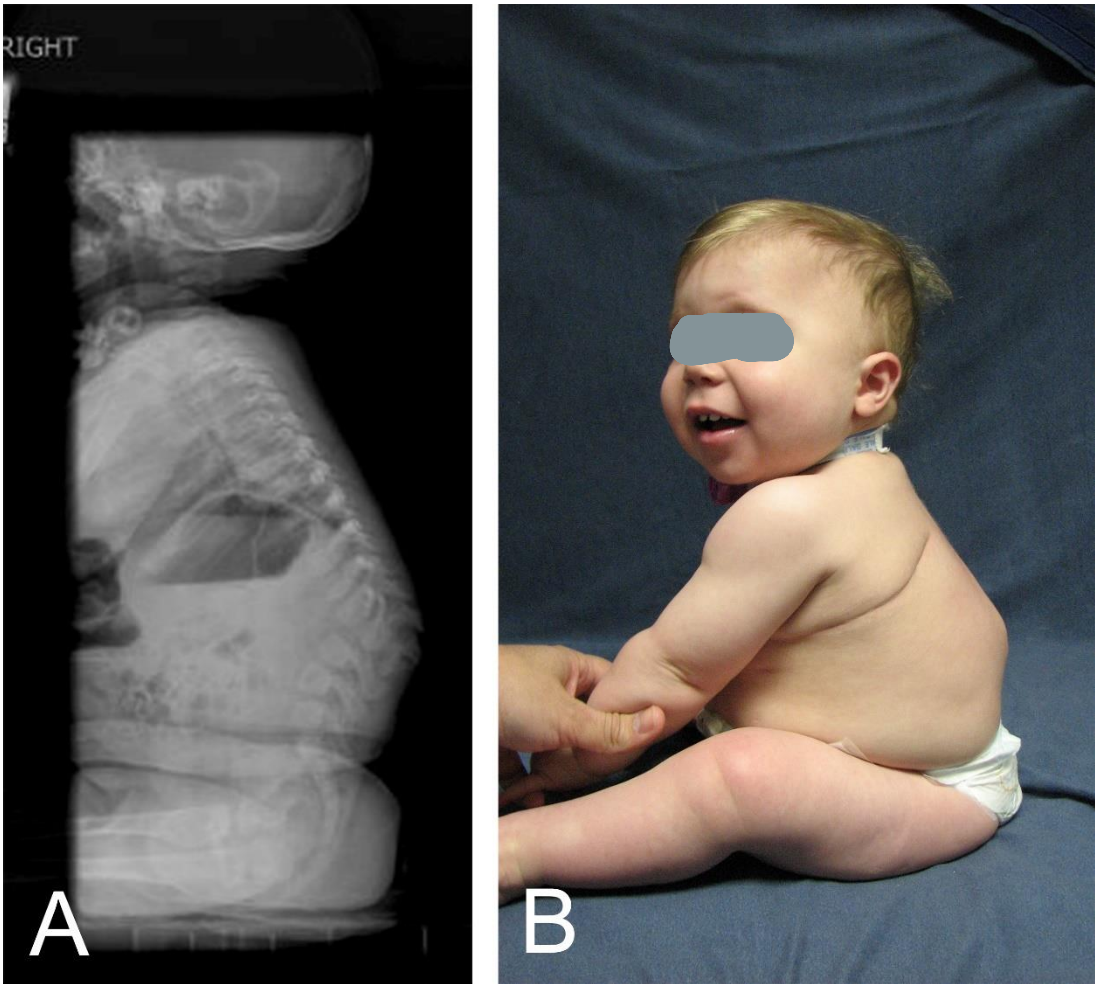


Figure 3. A 1-year-old boy with congenital hyperkyphosis due to failure of formation of one of his vertebral bodies. The boy is at risk for neurological complications due to his acute angular deformity.

Neuromuscular Early-onset Spinal Deformity

The neuromuscular etiologies include a multitude of disorders that affect nervous system control of muscle. Neuromuscular deformity is caused by poor muscle control, weakness, or paralysis of paraspinal muscles and the surrounding musculature.[22] This can be due to dysfunction at the level of the brain (cerebral palsy), spinal cord (spina bifida), motor neurons (polio), peripheral motor nerves (Charcot-Marie-Tooth disease), neuromuscular junction (myasthenia gravis), and muscle (Duchenne muscular dystrophy).

Syndromic Early-onset Spinal Deformity

Syndromic spinal deformity refers to deformity associated with chromosome or gene-based syndromes, such as Marfan syndrome, Ehlers-Danlos syndrome, Neurofibromatosis, Down syndrome, Achondroplasia, and Prader-Willi syndrome.[23] In these syndromes, abnormalities of muscle tone, strength, or bone structure lead to spinal deformities.

Adult Spinal Deformity

The previously discussed variants of spinal deformity typically arise in childhood. However, adult spinal deformity is common and can be either residual from childhood or *de novo*. *De novo* adult-onset scoliosis and kyphosis generally arise from degenerative disc disease, reduced mobility and balance, neurodegenerative disorders, or osteoporosis. It is particularly important to obtain a DEXA (dual energy x-ray absorptivity) scan to determine bone density in adults undergoing evaluation for spinal surgery.[24]

Disease progression and prognosis of EOSD

Early-onset spinal deformity can progress into severe deformity throughout growth of the child. In the most severe cases, coronal curvature may reach upwards of 120°-150°.[25] In the presence of hyperkyphosis, the patient is at greatly increased risk of spinal cord compression, which may lead to paraplegia. In a 1955 study by James et al., 21 patients were observed with kyphoscoliotic early-onset spinal deformity. Of these 21 patients, five (24%) became paraplegic.[26]

Inhibited pulmonary or cardiopulmonary development and function are well-documented complications of early-onset spinal deformity. [4-6] Lung compliance, lung volume, and alveolar growth may all be reduced in these patients. The bronchiole tree and associated alveoli are not fully developed until the age of eight years. Furthermore, thoracic volume at the age of 10 years is only 50% of expected adult volume.[27-29] Importantly, as the thorax is a 3-dimensional structure, severe hyperkyphosis worsens pulmonary complications in patients with early-onset spinal deformity. In addition to interfering with lung volume and alveolar development, early-onset spinal deformity has led to bronchial torsion and loss of inspiratory muscle function.[30-32]

1.5 Social Impact

Reduced Quality of Life

The impact of severe progressive early-onset spinal deformity on the physical, social, and emotional lives of affected children and their families is tremendous. Deformities can lead to substantial disability, pain, pulmonary disease, cardiac failure, and premature death.[1-3] Children with early-onset spinal deformity exhibit a 50% increase in mortality by age 40.[33] In addition, children with early-onset spinal deformity suffer from a substantially reduced quality of life. For these patients, the quality of life is impaired by their limitations of physical function, physical pain, need for frequent hospitalizations, and the restrictions that accompany being tethered to equipment and devices. Additionally, the quality of life is reduced in family members and caregivers, whose burdens often exceed those caring for children with other serious illnesses, such as cancer, asthma, heart disease, or epilepsy.[34,35] Furthermore, the psychological impact that results from the need for bulky instrumentation placed along the spine and repeated surgical lengthening procedures is substantial in many patients.[36]

Economic Impact

To fully appreciate the impact of early-onset spinal deformity, the economic aspects of the disease must be understood. The requirements for multiple surgical procedures, implants, hospital stays, imaging, and other healthcare expenditures can make the per-patient cost substantial. In addition, the need for unplanned surgeries to address high complication rates augments costs. Unfortunately, very few comprehensive studies examining the cost of treating early-onset spinal deformity in the United States have been published.

Growing rods are commonly used by pediatric spine surgeons to treat early-onset spinal deformity. The construct is comprised of single or dual extendible rods inserted along the length of the deformity, anchored proximally and distally by hooks or pedicle screws. Cost of initial implantation is approximately $34,000, and serial lengthening procedures average $6,327 per procedure, including both outpatient and inpatient procedures.[37,38] Serial lengthening surgeries, as well as definitive fusion, are required at the end of treatment. Furthermore, unplanned surgeries may be required for complications. Revision surgeries typically cost $10,000-$12,000. In total, a six-year course of treatment with growing rods costs approximately $149,234.

Magnetically controlled growing rods, which allow the surgeon to lengthen the rods remotely as the child grows rather than through serial invasive surgeries, are more expensive than traditional growing rods for initial implantation, but may save money over the course of the treatment by lowering the cost of lengthening procedures. The cost of the implant itself ranges from $13,125–$21,875. Cost of the entire initial implantation procedure is approximately $64,000, including the cost of the implant materials, surgeon fees, and cost of the hospital stay (compared to approximately $34,000 for traditional growing rods). MAGEC costs roughly $174 per lengthening procedure. This cost for lengthening procedures is substantially less than traditional growing rods. In total, the course of treatment for both traditional growing rods and magnetic growing rods is estimated to be roughly equal ($149,000). However, cost is widely variable, based on the number of lengthening procedures required and complication rates. One economic analysis by Su et al estimated cost savings to be upwards of $40,000 over a 5-year course of treatment with magnetic growing rods compared to traditional growing rods.[39]

VEPTR (Vertical Expandable Prosthetic Titanium Rib) is another widely used growth-sparing implant. Instead of using pedicle screws for intra-spinal fixation for growing rods, VEPTR uses rib-based fixation for proximal fixation of the device. The cost of VEPTR implantation surgery varies tremendously, but generally ranges from $80,000 to $140,000 for initial implantation.[37,38] Similar to growing rods, serial lengthening procedures, revisions, and definitive fusion are also required at the end of treatment with VEPTR.

1.6 Clinical Manifestations and Patient Workup

Patients with spinal deformities usually present in childhood or adolescence due to rib prominence or asymmetry in trunk balance, shoulder height, or extremity length. Additional physical examination findings may provide important clues to an underlying diagnosis. These may include cutaneous lesions, such as café au lait spots or axillary freckling suggestive of neurofibromatosis; spinal hairy patches, hemangiomas, or sinuses suggestive of dysraphism; elongated fingers with the “wrist sign” or “thumb sign” suggestive of Marfan syndrome; short trunk or limbs suggestive of dwarfism; and limb-size discrepancy, cavus foot, toe clawing, or equinus contractures suggestive of a plexopathy or peripheral neuropathy.

The spinal examination should include the Adams Forward Bend Test to assess trunk rotation, limb length inequality, and spinal motion (**Figure 4**).[40] The Adams Forward Bend Test looks for elevation of one side of the spine, relative to the other, as a measure of spinal column rotation. This test is conducted with the patient bending forward at the waist while standing, as if to touch his or her toes. Detection is usually by trunk asymmetry on forward bend. Limb length inequality is detected by noting a difference in the height of one hemipelvis, compared to the other, while the patient is in the standing position. Motion is assessed by evaluating the ability of the patient to bend forward, backward, and sideways. Forward and sideways bending can be quantified by measuring how far the patient’s hands can reach in each direction.[40]

Figure 4. Adams Forward Bend Test. Severe scoliosis and elevation of the right side of the spine and rib cage.

Criteria for diagnosis

In patients with suspected spinal deformity, coronal and sagittal radiographs should be obtained. Many techniques have been described for measuring spinal alignment.[41] However, the "Cobb angle" is the most clinically relevant. The Cobb angle is a measure of curvature of the spine in degrees and can be used to quantify both scoliosis and kyphosis. It is calculated by locating the most tilted vertebrae above and below the curve and drawing lines parallel to the superior and inferior vertebral end plates, respectively. The Cobb angle is the angle formed between these two lines (**Figure 5**).

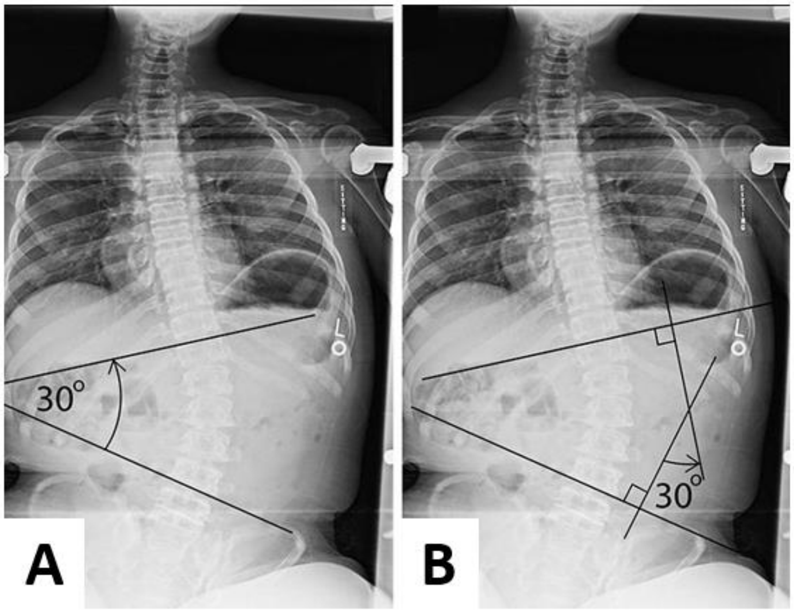


Figure 5. Scoliosis x-ray and demonstration of Cobb angle: **A**) The patient is a 17-year-old boy with Duchenne muscular dystrophy. The x-ray shows a levoconvex scoliotic curvature of the lumbar spine with the apex of the curve at L2. Lines are drawn for calculation of the Cobb angle. The upper line is drawn parallel to the superior vertebral end plate of T12, and the lower line is drawn parallel to the inferior vertebral endplate of L4. The Cobb angle (30°) is the angle formed by the intersection of these two lines. **B**) An alternative method for calculating the Cobb angle also begins by drawing primary lines parallel to the superior and inferior vertebral endplates above and below the curve. Secondary lines are then drawn perpendicular to the primary lines. The Cobb angle is the angle formed by the intersection of these secondary lines. The measured Cobb angles are equivalent with the techniques in A and B.

Formal diagnostic criteria for scoliosis is lateral curvature of the spine with a Cobb angle greater than 10°.[1] Curves less than 10° are considered a normal variant, and these patients should not be diagnosed with scoliosis. Thoracic hyperkyphosis is generally defined by a Cobb angle greater than 50°, although this is a subject of debate.[7-12]

For patients with a known etiology for their scoliosis, the evaluation focuses on identifying any underlying conditions. High-quality radiographic images from the cervicothoracic junction to the pelvis should be obtained for all patients suspected of having scoliosis and scrutinized for any evidence of underlying abnormalities, such as endosteal scalloping, interpedicular widening, rib penciling (small rib diameter), enlarged intravertebral foramina, and soft tissue masses. When any type of spinal cord pathology is suspected, MRI is indicated. MRI is indicated for a history or examination suggestive of underlying neurologic problems, congenital deformity, onset less than 10 years of age, kyphosis across the apex, and atypical curve patterns.[42]

1.7 Traditional Early-onset Spinal Deformity Treatment Options

Prior to the early 2000's, anterior and posterior spinal fusion (PSF) and spinal instrumentation were the standard of care for children with progressive early-onset spinal deformity. This approach could effectively correct spinal deformity. However, this surgery interrupted spinal growth along the fused segments. When performed in young children the result was a straight but short spine, eventually leading to a disproportionate body habitus, reduced pulmonary development, and ultimately respiratory failure.[6] In the past two decades, modern treatment has shifted to a more holistic approach that emphasizes not only correction of the deformity, but also preservation of spinal growth and thoracic cavity volume that sufficiently supports adequate pulmonary development.[15]

A variety of growth-sparing treatments exist for early-onset spinal deformity, and the indications for each type of treatment depend on the severity and rate of curve progression. In curves with lateral curvature of <60°, bracing or derotational casting methods are often first attempted to control the spinal deformity.[43] Bracing is usually ineffective at correcting the deformity and, at best, slows or halts deformity progression.[44] Derotational casting can effectively correct mild curves.[45,46] Patients with progressing curves or curves of magnitude >60°, in which bracing or casting methods have failed or were contraindicated, are candidates for surgical intervention. There are many surgical methods that are used. The two most common methods are: 1) growing rods, and 2) VEPTR (Vertical Expandable Prosthetic Titanium Rib) (**Figure 6**). Both of these methods are distraction-based surgical techniques and will be discussed in more detail below. While these techniques have demonstrated positive results in their ability to correct curves, their complication rates are high.[47]

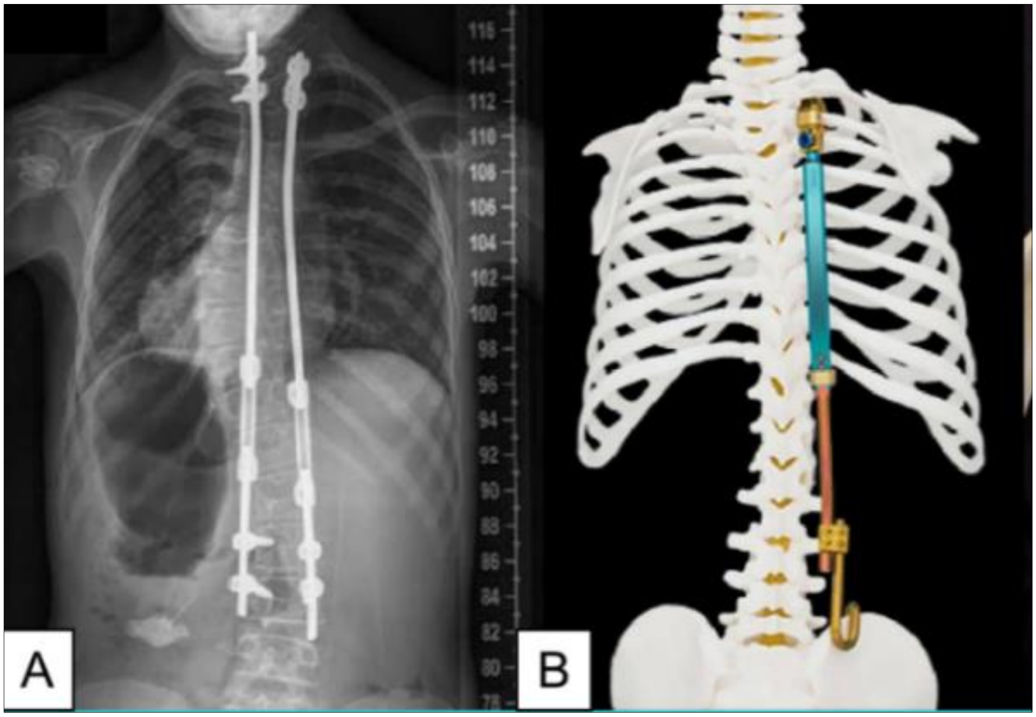


Figure 6. A) Growing-rods are a distraction-based construct that straightens the spine, while allowing for spinal growth with serial lengthening procedures. Growing rods are anchored using pedicle screws proximally to the spine and distally to the spine or pelvis with limited fusion at the spinal foundation sites. **B**) VEPTR, like growing-rods, is a distraction-based system that can correct a scoliotic spinal deformity, while preserving growth. The spine is stabilized by the insertion of a unilateral or bilateral rib-to-spine or rib-to-pelvis VEPTR, and another rib-to-rib VEPTR may provide additional support. With VEPTR, proximal fixation is achieved with a single cradle on the second or third rib. Images adopted from SpineUniverse.com.

Bracing

Indications

Bracing is indicated as an early form of treatment for early-onset spinal deformity with mild to moderate progressive curves.[48] Some curves are inherently more flexible or stiff than others, depending on the anatomical features of the deformity and the morphology of the vertebrae. Better results tend to be observed when curves are flexible.

Clinical Outcomes

Bracing usually does not successfully correct curves. Instead, at best, bracing slows the progression of the curves. Bracing's effectiveness at slowing curve progression is highly variable.[48]

Derotational Casting

Indications

Derotational casting is indicated for curves that have progressed >25° but <60° in the coronal plane or have documented progression of 10°-20° in a 6-month period.[49] Candidates for derotational casting should not have undergone previous surgery for scoliosis.

Mechanism

Unlike bracing methods, serial casting can effectively correct spinal curvature. The child is anesthetized and placed on a specially designed table that exposes the trunk. Proximal and distal traction is applied to rotate the ribs, using a posteriorly directed force on one side and an opposite anteriorly directed force to the other side. The casts are replaced in EOSD patients every two to four months. Treatment is continued either until the curve becomes <10°-20°, or the treatment fails due to curve progression beyond an acceptable magnitude. Even if the curve is not completely corrected or continues to progress, derotational casting offers the advantage of preserving spinal growth while delaying the need for growth-sparing surgery. Growth-sparing surgical lengthening procedures have been associated with diminishing returns in spinal growth. With each lengthening procedure, the magnitude of spinal growth tends to decrease.[50] Derotational casting provides a means of delaying the need for growth-sparing surgery, thus minimizing these diminishing returns.

Clinical Outcomes

Casting tends to be most effective in patients who have coronal curve magnitudes <60°, begin treatment at a young age, and have idiopathic etiologies.[50] In a study conducted by Mehta, 136 children with a mean coronal curve of 32° and a mean age of 1.6 years had scoliosis resolve at the age of four years. In contrast, patients with a mean coronal curvature of 52°, that began treatment at a mean age of 2.5 years, all had progression of their scoliosis.[51] Thus, derotational casting of mild curve magnitudes at a younger age tends to be more effective than casting of larger curve magnitudes at an older age. The effectiveness of casting methods in patients with hyperkyphosis has not been widely studied. In our experience, substantial hyperkyphosis complicates attempts to create a properly fitting cast and often fails to control progressive deformities.

Distraction-based growth-sparing surgery

Indications

Distraction-based surgery for EOSD is indicated when conservative treatment methods have failed or were contraindicated, and the patient has considerable growth remaining. In general, the coronal plane curves for these patients are >40°-60°.

Growing Rods

Mechanism

Growing rods are a distraction-based construct that provide a means for the surgeon to straighten the spine, while allowing for spinal growth with serial lengthening procedures.[51-54] Traditionally, growing rods are anchored using pedicle screws proximally to the spine, and distally to the spine or pelvis with limited fusion at the spinal foundation sites. The construct can be lengthened by sliding the rod through a connector in a series of lengthening procedures. These serial lengthening procedures are typically performed once every 6-12 months as the child grows. Single or dual growing rod constructs may be used. At the end of the serial lengthening process, growing rods can be replaced with standard dual rod instrumentation for definitive fusion.

Clinical Outcomes

Evidence suggests that dual growing rods provide improved stability and curve correction, compared to single growing rods.[52] In a study by Akbarnia et al. (2005), dual growing rods improved the coronal curvature from a mean of 82° preoperatively to 36° at the final follow-up and allowed an average of 1.2cm per year of spinal growth between T1 and S1.[53] Another more recent growing rod study demonstrated even better curve correction, from a mean of 92° preoperatively to 26° at the final follow-up.[54] However, complication rates are extremely high, and growing rods with pedicle screw fixation can be ineffective in certain patient populations. This will be discussed in more detail in **Chapter 1.8**.

VEPTR

Mechanism

VEPTR (vertical expandable prosthetic titanium rib), like growing rods, is a distraction-based system that allows for correction of the scoliotic spinal deformity, while preserving growth.[54-57] VEPTR effectively corrects curves and is widely used, especially for the treatment of thoracogenic early-onset spinal deformity. The spine is stabilized by the insertion of a unilateral or bilateral rib-to-spine or rib-to-pelvis VEPTR, and another rib-to-rib VEPTR may provide additional support. The construct is lengthened as the child grows. It is preferable to continue this until skeletal maturity, at which time a final fusion is performed.

Clinical Outcomes

VEPTR provides reasonable correction in patients without hyperkyphosis. In a series by Campbell et al., 29 children with a mean coronal curvature of 74° were treated with VEPTR. Curvature was reduced to 49° at final follow up, with 7.1 mm per year of spinal growth.[55] In another study, the mean curve was 59° preoperatively and 35° at final follow up.[56] However, in patients with hyperkyphosis or kyphoscoliosis, results are not as positive. Unlike growing rods, a primary problem with the use of VEPTR is that VEPTR can be pro-kyphotic, especially in the presence of hyperkyphosis. In a study comprised of 14 patients with early-onset spinal deformity and hyperkyphosis, initial thoracic kyphosis averaged 68.1° prior to treatment with VEPTR, and 90.7° at final follow up.[57] This demonstrated a substantial 22° *increase* in thoracic hyperkyphosis. At a minimum, this indicates that VEPTR fails to adequately control hyperkyphosis progression, and likely worsens progression of the hyperkyphosis. Reinker et al. described several strategies to minimize the pro-kyphotic effect of VEPTR in hyperkyphotic patients.[57] One strategy is to place the upper cradle of the construct during initial surgery no lower than the third rib. Lower placement appears to be associated with greater increases in kyphosis. Some earlier versions of VEPTR required lower rib placement in certain patients. However, recent versions allow better proximal fixation above the kyphosis. In addition, more distal placement of the distal anchor appears to provide better control over the hyperkyphosis. While best results seem to occur when the distal anchor is extended down to the pelvis, the presence of hypolordosis may make pelvic fixation less than ideal.

In addition to being pro-kyphotic, VEPTR does not fit well on some patients with hyperkyphosis. The construct is designed to fit flush to the spine or ribs. The upper and lower components can be bent and fitted for a patient. However, the extendable middle section has a fixed radius and cannot be bent while maintaining its extendibility. Thus, VEPTR does not fit some patients with hyperkyphosis.

Emerging Treatments

Several other growth-sparing treatments for early-onset spinal deformity exist but are not as commonly used. Anterior shape-memory alloy (SMA) staples and spinal tethering are compression-based techniques that can inhibit growth on the convex side of the deformity while the concave side continues to grow. As a result, the spine may straighten over time. However, these techniques are indicated only for curves of moderate magnitude (<45°).[58]

The MAGEC system is a distraction-based implant, similar to standard growing rods. However, this system is extendible via an external magnetic remote-control system. Thus, the need for repeated lengthening surgeries is eliminated. This technique is called "magnetic growing rods" (MGR), as opposed to the traditional growing rods (TGR) described above. This technology has begun to gain traction in the United States, and preliminary studies have demonstrated favorable outcomes.[59] However, as with VEPTR, these systems have issues with implant fit in hyperkyphotic patients, since the remotely controlled extendible portion cannot be contoured and remain functional. They are also prone to similar implant related complications as growing rods and some studies have documented uses with metallosis.[60]

1.8 Challenges with Traditional Treatments

The goal of treatment for early-onset spinal deformity is to correct the deformity while maximizing spinal growth and pulmonary function.[51-59] Currently, most surgical early-onset spinal deformity is managed with dual growing rods (GR), which generally employ intraspinal pedicle screw fixation to the spine.[61] The growing rods are distractible and periodically lengthened to align the spine until skeletal maturity.[62]

Unfortunately, treatment with growing rods with pedicle screw fixation is often unsatisfactory. The stiff nature of growing rods fixed to the spine with pedicle screws causes auto-fusion of the vertebrae in >80% of patients, resulting in diminishing returns with each lengthening procedure, stunted spinal growth, and compromised pulmonary function.[63] In addition, instrumentation-related mechanical complications are common, especially in high risk patients with non-idiopathic etiologies and/or osteoporosis.[64-68] In fusionless growing-rod surgery, implants bear mechanical loading during the entire treatment period, increasing the risk of implant failure, compared to spinal fusion, in adolescent cases.

Proximal fixation failure with pedicle screw pull-out is one of the most common instrumentation mechanical failures in early-onset spinal deformity patients, especially with hyperkyphosis and osteoporosis (**Figure 7**). This complication occurs in >33% of these high risk patients.[64,65] This is due to high stress on the pedicle screws, thus causing them to pull out of the bone. Rod fracture is also a common problem with growing rods.[63,64] This is likely due to the stiff nature of pedicle screw fixation, resulting in high stress in the rods. Growing rods with pedicle screws can also produce a localized kyphosis just superior to the proximal fixation, called proximal junctional kyphosis (PJK) in >28% of patients.[66] Finally, neurological injury from operating in close proximity to the spinal canal is a potentially catastrophic complication.[67,68] Implantation of pedicle screws into the small thoracic vertebrae of a child imparts a steep learning curve to the orthopedic surgical

Figure 7. Growing rod pedicle screw pull-out in a hyperkyphotic patient.

novice, and many early-onset spinal deformity patients have pedicles with abnormal morphology, making placement of pedicle screws in these patients challenging and dangerous. Post-operatively, pedicle screws implanted into the vertebrae carry a risk of displacement into the spinal canal, and paraplegia has resulted. Due to high complication rates with growing rods with pedicle screw fixation, early fusion of the spine is often necessary. The VEPTR (Vertical Expandable Prosthetic Titanium Rib) is an alternative device, but it cannot be contoured in the sagittal plane and cannot be used for hyperkyphosis and kyphoscoliosis.[69-71] Therefore, there is a critical need to develop a new approach for treating EOSD that achieves spinal correction and preserves spinal growth while minimizing surgical complications.

1.9 Purpose of This Study and Specific Aims

We have developed a hybrid technique to treat early-onset spinal deformity called the “rib construct.” Instead of anchoring corrective instrumentation to the spine with pedicle screws, the rib construct moves proximal fixation to the ribs, using a series of hooks with expandable rods and conventional pedicle screw distal fixation. This represents a conceptual shift from pedicle screw fixation in that the thorax is the primary structure of manipulation to secondarily reposition the spine. There are numerous advantages of the rib construct compared to traditional growing rods with pedicle screw fixation. Rib fixation with the rib construct can be achieved with either: 1) off-label laminar hooks, which are already commercially available for spinal fixation to the lamina but can also be used on the ribs, or 2) rib hooks as part of our novel R-FIX (Rib-FIXation System). The objectives of this research are twofold: 1) to obtain basic science and clinical data that proves the overall concept of rib fixation with the rib construct using off-label laminar hooks (**Aims 1-**

3), and 2) to develop the R-FIX System with rib hooks specifically designed for rib fixation (**Aim 4**).

Aim 1: Evaluate the biomechanics of the rib construct (Chapter 3).

Ex vivo bending and torsional biomechanical testing were performed with a mechanical testing system using porcine spines (with rib cages) instrumented with either pedicle screws or a rib construct with laminar hooks.

Aim 2: **Assess the ability of the rib construct to correct hyperkyphosis in a pediatric porcine animal model (Chapter 4).**

A pediatric hyperkyphotic porcine animal model was created to mimic hyperkyphosis observed in childhood spinal deformity, and subsequently corrected with the rib construct.

Aim 3. Assess the safety and effectiveness of the rib construct in a clinical study (Chapter 5).

A retrospective study was conducted on 24 human patients that were treated using the rib construct with laminar hooks for severe non-idiopathic spinal deformity at The Medical University of South Carolina (MUSC) between 2007 and 2015.

Aim 4: Develop R-FIX (Rib-FIXation) Surgical System for the rib construct technique (Chapter 6).

Aims 1-3 focus on testing the rib construct with off-label laminar hooks, which are already commercially available for spinal fixation to the lamina but can also be used on the ribs. While rib fixation with laminar hooks has advantages compared to pedicle screws, they are used entirely off-label and there is no commercially available surgical system designed specifically for this technique. The R-FIX System was design to optimize the rib construct surgical technique.

We hypothesized that the rib construct would be a safe and effective treatment for early-onset spinal deformity. It is possible that the rib construct and specifically the R-FIX System will replace growing rods with pedicle screw fixation and VEPTR as the standard of care for early-onset spinal deformity, or at least provide an attractive alternative.

Chapter 2. Rib Construct: An Emerging Treatment for Early-onset Spinal Deformity

2.1 Rib Construct and Theoretical Advantages over Traditional Treatments

The rib construct is a new hybrid technique for correcting early-onset spinal deformity that is designed to improve patient outcomes. Instead of anchoring corrective rods to the spine with pedicle screws, the rib construct moves proximal fixation to the ribs using a series of laminar hooks. Down-going hooks are placed bilaterally on the superior surfaces of ribs 2 and 3, and up-going hooks are placed on the inferior surfaces of ribs 4 and 5. The hooks are then anchored to expandable rods and mated with distal fixation (**Figure 8**).[72] The rib construct allows the surgeon to manipulate the thorax in any combination of sagittal, coronal, and axial planes, allowing much more versatility. This approach represents a conceptual shift, in that more attention is devoted to correcting the position of the rib cage and entire thorax as a unit, rather than just the spine. The surgeon, in effect, is a sculptor of the spine and thorax, having the freedom to consider all 3 planes of motion to achieve spinal balance.

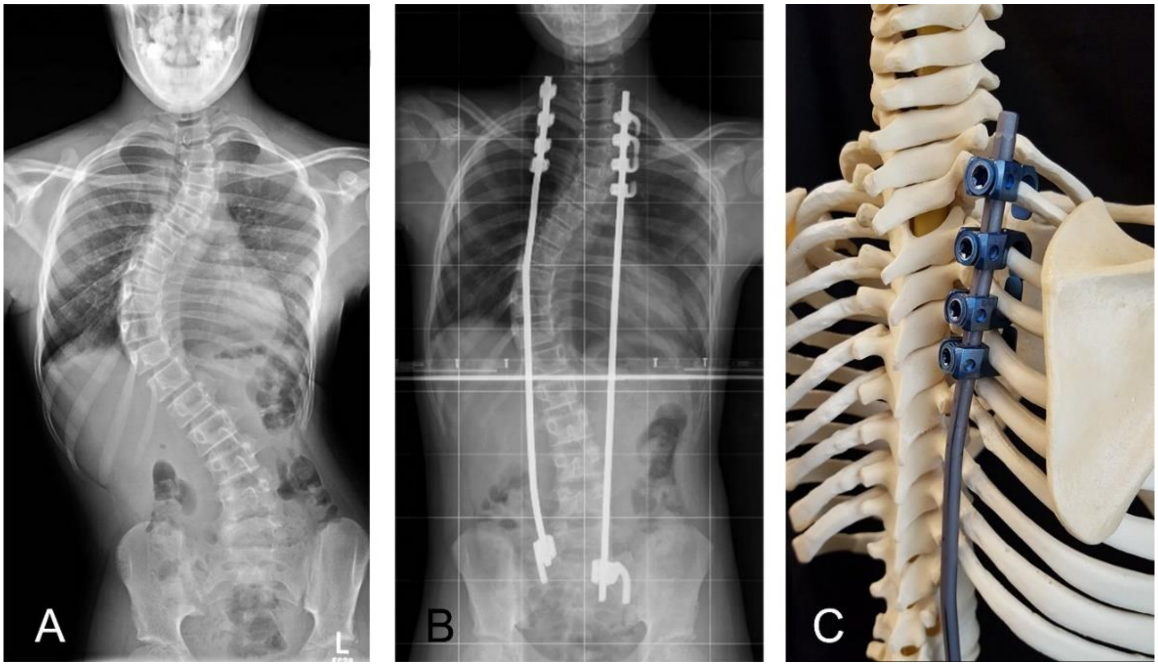


Figure 8. **A**) pre-op, **B**) post-op rib construct with laminar hooks, **C**) rib construct with laminar hooks on spinal model (only unilateral shown).

Because the rib construct directly manipulates the thoracic cavity, it can improve the alignment of the rib cage and pulmonary function. Because the rib construct uses extra-spinal fixation to the ribs, it avoids spinal fusion of fixation sites and auto-fusion of other levels, thus maximizing natural spinal growth. Mechanical complication rates may also be greatly improved with the rib construct. Compared to growing rods with pedicle screw fixation, the rib construct has more bone-implant interface with strong cortical bone, while pedicle screws have limited interface with weaker cancellous bone. As a result, much higher corrective forces can be safely applied by the surgeon using the rib construct, especially in the sagittal plane, without the potentially disastrous effects of pedicle screw failure. With the rib construct, motion at the costovertebral joints makes the rib construct less stiff than growing rods, reducing the risk of rod fracture.

The risk of proximal junctional kyphosis is also reduced with the rib construct. By manipulating the thorax instead of the spine, the important posterior midline spinal ligaments remain intact and act as a tether. This, combined with the less ridged nature of rib fixation compared to pedicle screw fixation, reduces the risk of developing proximal junctional kyphosis (**Figure 9**). Finally, since the rib construct does not require manipulation of structures close to the thoracic spinal cord, the risk of neurological injury is reduced.

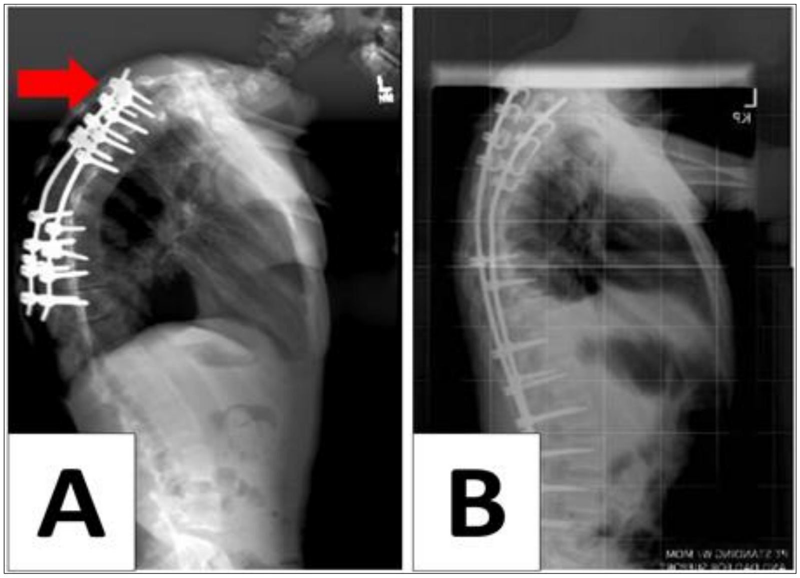


Figure 9. **A**) An 8-year-old boy with severe hyperkyphosis and osteoporosis. PJK, pedicle screws pulling out, and poor deformity correction. **B**) Rib construct with off-label laminar hooks secured fixation and deformity correction is improved.

Brief History of the Rib Construct

The rib construct concept was conceived in 2007 when Dr. Richard Gross was faced with managing a child with VATER syndrome and a rapidly progressive kyphoscoliotic deformity and concurrent osteoporosis. For this patient, the combination of severe kyphoscoliosis and osteoporosis portended failure of spinal fixation with pedicle screws.

At the time, rib fixation with the VEPTR device had been introduced with the initial goal of managing thoracic insufficiency syndrome and subsequently expanded to treating early-onset spinal deformity. However, the fixed radius of the VEPTR instrumentation renders it ineffective for hyperkyphotic deformity. Nevertheless, work with VEPTR had demonstrated that the ribs can provide multiple strong anchor points without the need for direct spinal instrumentation. This inspired Dr. Gross (a pediatric orthopaedic surgeon at MUSC) and Dr. Yao (a bioengineer in the Clemson-MUSC Bioengineering Program) to devise a rib construct utilizing this favorable feature and adapting it for hyperkyphotic and kyphoscoliotic deformities. The patient was treated with a growth-sparing rib construct with laminar hooks, which completely corrected his hyperkyphosis, greatly improved his scoliosis, and leveled his shoulders and pelvis. The case report was published in the Journal of Pediatric Orthopaedics in 2012.[72] Since then, Dr. Gross, Dr. Yao, and Daniel Bonthius (the author of this dissertation) have been refining the rib construct concept through clinical, biomechanical, and animal studies.

2.2 Rib Construct Operative Technique

Full weightbearing anteroposterior and lateral view radiographs are obtained prior to surgery. Surgeries are performed under general anesthesia with the patient in the prone position on a Jackson table. Sensory and motor neuromonitoring are used in all cases. A straight midline incision is made from T2-T5. For the initial cases, a subperiosteal dissection was performed from the laminae to the proximal second to fifth ribs, leaving the midline structures intact. This was modified to performing a subcutaneous dissection laterally to the region of the proximal second to fifth proximal ribs, at which point an incision is made through the paraspinal muscles, followed by a subperiosteal exposure 1 cm lateral to the costo-transverse junction on ribs 2-5. A tract is created with a laminar finder over the superior surfaces of ribs 2 and 3, and the inferior surfaces of ribs 4 and 5. Down-going lumbar laminar hooks are placed on the superior surfaces of ribs 2 and 3 and up-going hooks on the inferior surfaces of ribs 4 and 5. After bilateral proximal rib anchor placement, traditional distal lumbar and/or pelvic anchor fixation is placed.

Appropriate length titanium 4.5 mm or 5.5 mm rods are contoured. The rods are provisionally loaded superiorly, and the hooks gently compressed. Rods are then mated to distal fixation. Deformity correction in the sagittal plane is achieved by contouring the rods *in situ* with L-benders, and in the coronal plane by a combination of distraction and contouring the rods.

Instrument lengthening procedures are performed with a frequency that depends on growth rate. For definitive fusion procedures in skeletally mature patients, the rib construct can either be left in place and crushed cancellous bone graft placed along the transverse processes, or the rib construct can be removed and replaced with traditional instrumentation for fusion. Deformity correction is evaluated with clinical follow-up and radiographs.

Chapter 3. Superior *Ex Vivo* Biomechanical Performance of Rib Construct Compared to Pedicle Screws

3.1 Introduction

This chapter describes the biomechanical performance of the rib construct. *Ex vivo* bending and torsional biomechanical testing was performed with a mechanical testing system using porcine spines (with rib cages) instrumented with either pedicle screws or a rib construct with laminar hooks. The maximum force/torque and deflection/torsion angle applied to the instrumented spine before mechanical failure of instrumentation was recorded. It was discovered that spines instrumented with laminar hooks tolerated greater maximum force/torque and deflection/torsion angles without fixation failure or bone fracture compared to pedicle screws. The biomechanics of the rib construct was further explored using a Finite Element (FE) computer model. This testing was critical because it showed the biomechanical advantages of the rib construct compared to current standard treatment and explains why the rib construct reduces implant-related complication rates.

3.2 Methods

Porcine cadaver spines were used to evaluate the biomechanical performance of the rib construct with laminar hooks, compared to pedicle screws, when subjected to bending and torsional tests. A mechanical testing system applied a bending or torsional force to instrumented spines. The maximum force and deflection angle, as well as torque and torsion angle, applied to the instrumented spine before mechanical failure of instrumentation were recorded for bending and torsional testing, respectively. These experiments were performed in Dr. Yao's lab within the Clemson-MUSC (Medical University of South Carolina) Joint Bioengineering Program on the MUSC campus.

Specimen Preparation

Twenty pig spines from C5 to L6 with intact rib cages (ten for the rib construct group, ten for the pedicle screw group) were harvested from 8-week-old Yorkshire domestic male pigs. Pigs of this age were used because the size and weight of their spines and rib cages (length 53.6±4.1cm, weight 21.3±1.3kg) are similar to those of the pediatric human patient population. Specimens were cleaned of paravertebral soft tissues, with care taken to preserve ligamentous structures. Titanium rods (5.5mm×500mm) were instrumented bilaterally in both groups. The pig has 15 ribs, so based on the contour of the superior ribs, laminar hooks were placed on the ribs in a claw formation, with two down-going hooks on ribs 3 and 4 and two up-going hooks on ribs 5 and 6. In the pedicle screw group, pedicle screws (5.0mm×20mm) were placed in T3 and T4 bilaterally in accordance with standard technique. Proximal fixation was affixed to bilaterally contoured rods (**Figure 10**). After the spines were instrumented, the specimens were potted (Bondo Filler, 3M, Maplewood, MN) proximally and distally in custom potting fixtures. The proximal ends of the specimens were potted to T1, while the distal ends were potted to L4.

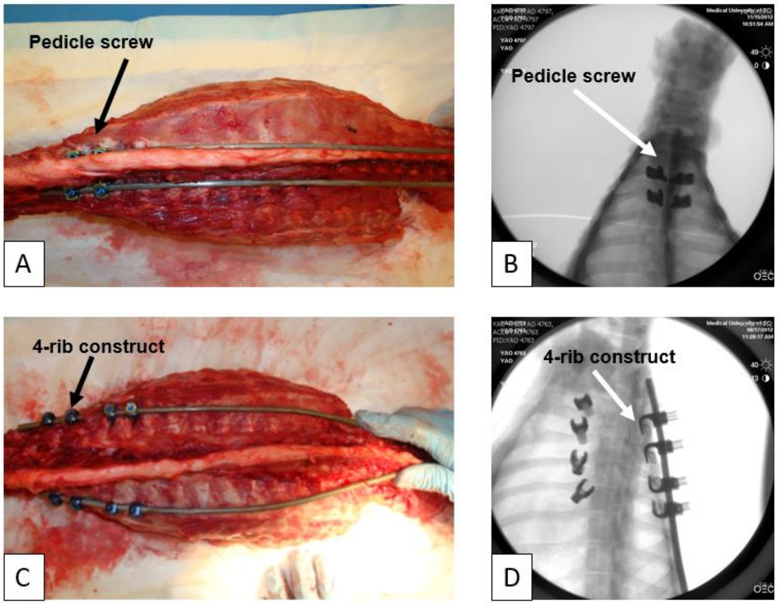


Figure 10. A) Growing-rod pedicle screw fixation on T3 and T4. **B**) Radiographic image of T3 and T4 growing-rod pedicle screw fixation. **C**) Rib construct fixation on ribs 3-6. **D**) Radiographic image of rib-hook construct. fixation (**5D**).

Mechanical Testing

The distal potted ends of the spines were anchored with custom mounts to the base of the mechanical testing system (858 Mini Bionix II, MTS, Minneapolis, MN). Two types of mechanical tests were performed: 1) bending testing, simulating pull-out forces on proximal instrumentation (N=6), and 2) tortional testing, simulating twisting forces on instrumentation (N=4). For the bending test, a pure bending force was applied by the mechanical testing system to the proximal end (**Figure 11**).[73] For torsional testing, a rotational force was applied to the proximal end (**Figure 12**). The force (F) and deflection angle (θ) were measured by a load cell and optical tracking system, respectively, and were time synchronized. Bending testing quantified the force and deflection angle, and torsional testing quantified the torque and torsional angle applied to the spine that induced mechanical failure of the instrumentation.

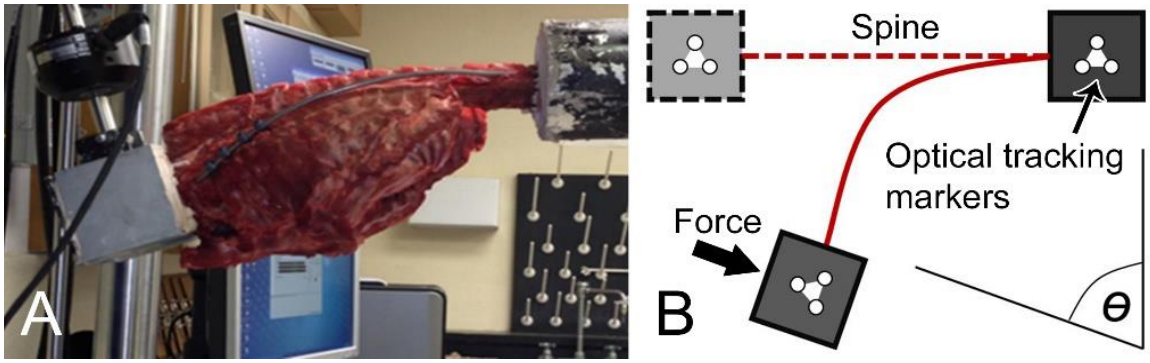


Figure 11. A) Test configuration for bending using an MTS system. Inline load cell with actuator measured bending force at potted proximal end of specimen. **B**) Schematic of bending test. The bending force (*F*) and deflection angle (θ) were measured by the load cell and tracking markers, respectively.

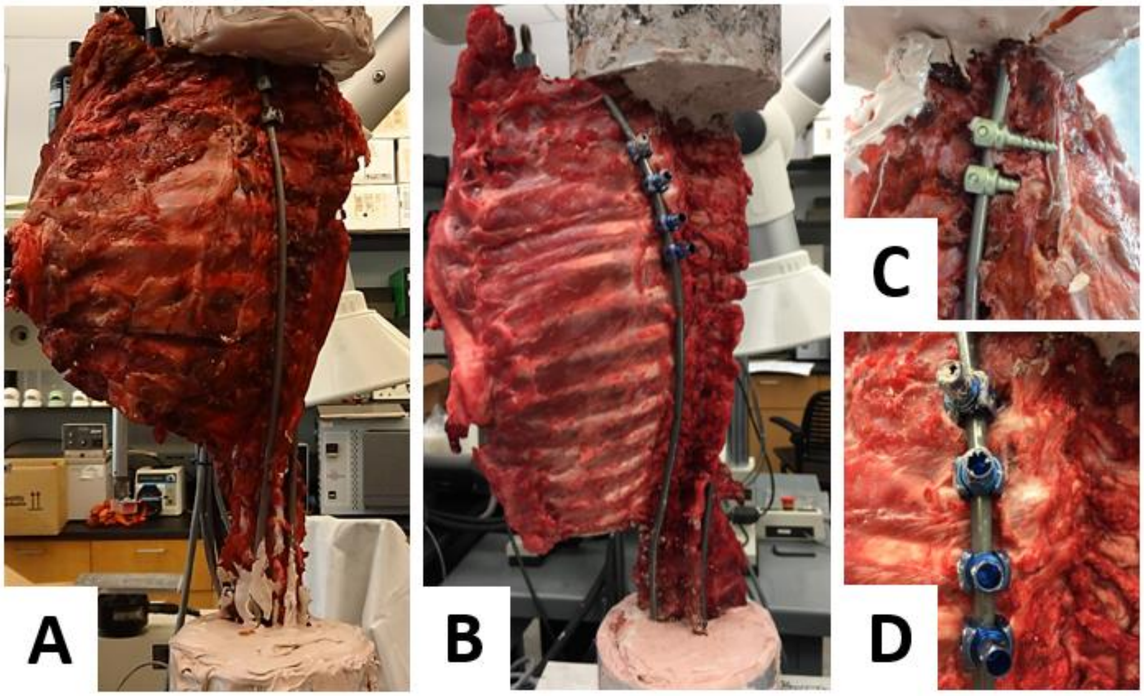


Figure 12. A,B) Test configuration for torsion with pedicle screws and rib hooks respectively, using an MTS system. Load cell measured torque at potted proximal end of specimen. The torque (*T*) and deflection angle (θ) were measured by the load cell and tracking markers. **C**) Failure of pedicle screws (plowing through vertebrae). **D**) Failure of rib hooks (hook migration).

Finite Element Model

To determine how the mechanical stress of the rib construct is distributed to the spine, the rib construct was integrated into a Finite Element model for a human spine. CT scans of the thoracic and lumbar spine and rib cage in DICOM format were segmented in Amira Software (Thermo Fisher Scientific) to obtain the 3D geometry of the bones. SolidWorks (Dassault Software) was used to assemble the instrumentation and intervertebral discs. Abaqus (Abaqus Inc) was used for FE modeling. A fixed boundary condition was applied to the inferior surface of Vertebrae L5 and a 200N anterior dragging force was applied to T1 as the loading condition to simulate hyperkyphotic bending forces on the spine. The instrumentation was bound to the bone using tie connection. The displacement and stress distribution in the bone and implants were analyzed. Specifically, the stresses at instrumented vertebrae were calculated to determine whether loss of fixation, bone fracture, or PJK is likely to occur.

3.3 Results

For bending testing with the pedicle screw group, fixation failure occurred for all tested spines (**Figure 13A**). All spines experienced pedicle screw pull-out as the failure mode (**Figure 13B**). In contrast, the rib construct group had no failures despite each bending test reaching the maximum spine deflection allowed by the testing system (**Figure 13C-D**).

Table 1 compares the biomechanical outcomes of the pedicle screw and rib construct groups for bending testing and demonstrates the superior performance of the rib construct.

The pedicle screw group withstood 64.6 ± 7.3° of bending and 118.6 ± 25.7 N of maximal force, at which point all proximal fixations failed. This was significantly less than the rib construct group, which withstood 97.9 ± 10.0° of bending ($p<0.001$) and 119.7 ± 13.9 N of maximal force with no proximal fixation failure. The average construct stiffness for the pedicle screw group was 3.58 ± 0.78 N/degree, which was significantly greater than the 2.75 ± 0.34 N/degree observed in the rib construct group ($p<0.05$). The rib construct approach was also technically successful, as the pleura was not violated, and there were no rib fractures in any of the six specimens.

For torsional testing, fixation failure occurred in 3/4 spines tested for both the pedicle screw and rib construct groups. Pedicle screw pull-out was the failure mode for the pedicle screw group, while hook migration on the ribs was the failure mode for the rib construct group. Even though both groups failed at the same rate, the rib construct group withstood significantly greater torque/torsion angles than the pedicle screw group prior to failure (**Figure 13 E-F, Table 2**).

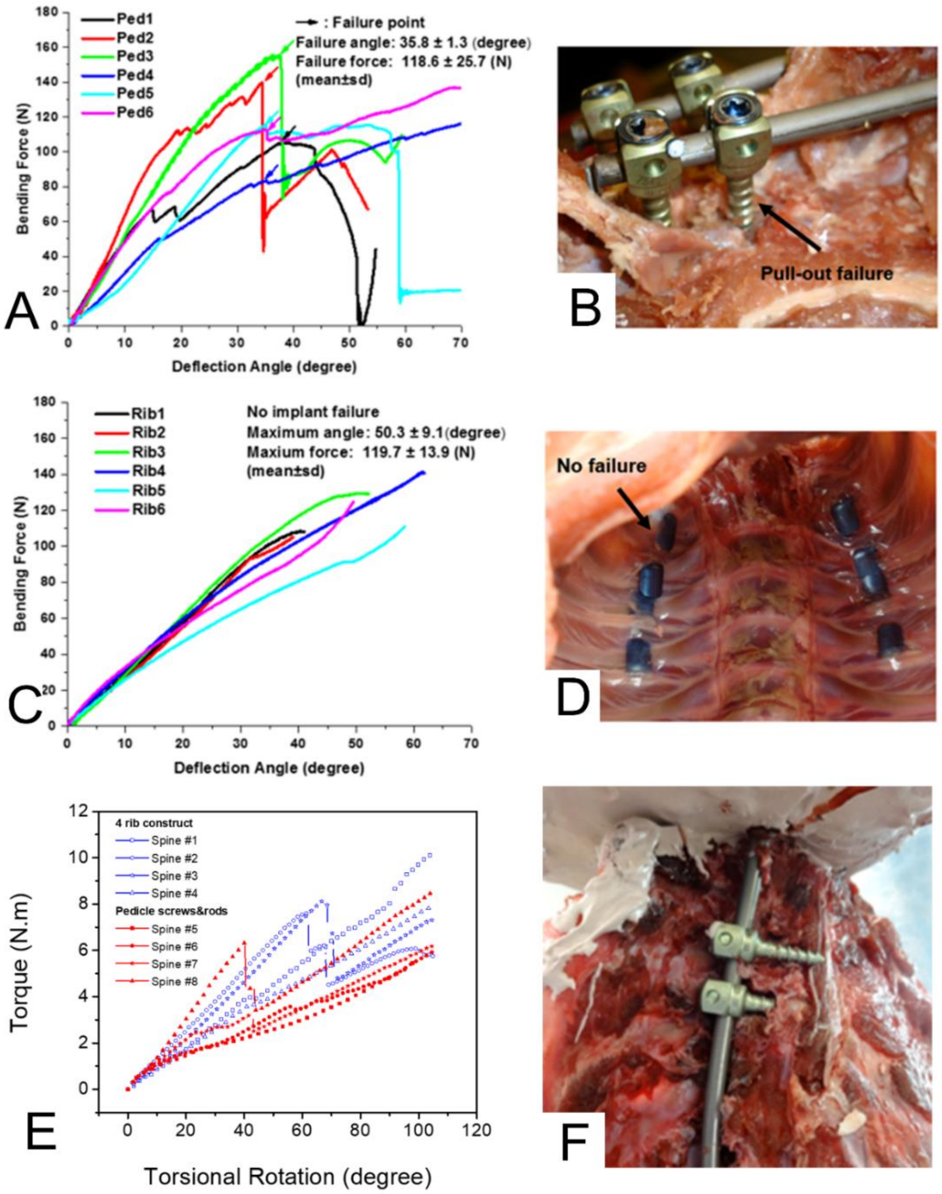


Figure 13. A) Bending force vs. deflection angle for each specimen in the growing rod group. **B**) Proximal fixation failure was recorded for all six spines tested for bending testing, with the failure mode being pedicle screw pull out (arrow). **C**) Bending force vs. deflection angle for each specimen in the rib construct group. **D**) No proximal fixation failure was observed for any of the six spines tested, with each bending test reaching the maximum spine deflection allowed by the test system. **E**) Torque vs tortional rotation for each specimen tested in the pedicle screw group (red lines) and rib construct group (blue lines). Proximal fixation failure occurred in 3/4 specimens tested for both groups, with **F**) pedicle screw plowing and hook migration being the respective failure mechanisms.

Table 1. Bending Test Performance of Pedicle Screws vs. Rib Construct

	Pedicle Screws	**Rib Construct**
Proximal fixation failure	Yes (6/6)	No (0/6) *
Deflection angle	64.6 ± 7.3°	97.9 ± 10.0° *
Maximal force	118.6 ± 25.7N	119.7 ± 13.9N
Construct stiffness	3.58 ± 0.78 N/degree	2.75 ± 0.34 N/degree *

Table 2. Torsional Test Performance of Pedicle Screws vs. Rib Construct

	Pedicle Screws	**Rib Construct**
Proximal fixation failure	Yes (3/4)	Yes (3/4) *
Deflection angle	46.9 ± 9.2°	57.9 ± 13.3° *
Maximal Torque	3.7 ± 0.7N.m	6.0 ± 2.0N.m*

Finite Element model results are shown in **Figure 14**. FE analysis revealed stress distribution over the bone, hooks at each vertebral level, and the rods. The ribs,

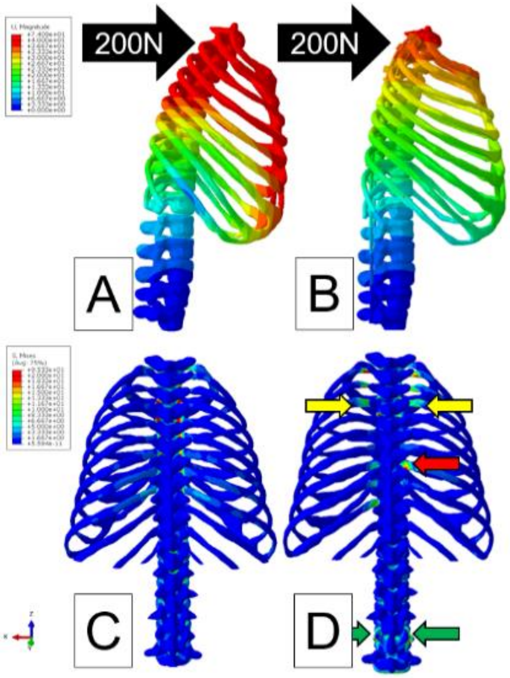


Figure 14. FE model of human spine subject to 200N anterior dragging force. **A)** Displacement without rib construct, **B)** Displacement with rib construct. **C)** Stress distribution without rib construct. **D)** Stress distribution with rib construct (implant not shown). Elevated stress at ribs 2,3, & 4 with hook fixation (yellow arrow), contact of rods on ribs (red arrow), and pedicle screw distal fixation (green arrow). Minimal stress at upper instrumented vertebrae (PJK not likely to occur). Stress elevated on ribs as expected but low enough that fracture is unlikely.

costovertebral joint, and posterior vertebral bodies absorbed most of the stress, and no points of stress exceeded the yield point of the hooks, rods, or bone.

3.4 Discussion

Since the spine is not fused in patients undergoing growth sparing treatment for early-onset spinal deformity, implants are under mechanical loading for the entire duration of treatment, and mechanical failure rates are high. Proximal fixation failure with pedicle screw pull-out is one of the most common types of instrumentation mechanical failures, especially with hyperkyphosis and osteoporosis.[64,65] This is due to high stress on the pedicle screws causing them to pull out of the bone. Patients with neuromuscular and syndromic etiologies are especially prone to osteoporosis.[64-68] In these patients with low bone quality and complicated three-dimensional deformities, proximal fixation failure can be a recurrent problem that makes treatment difficult and in some cases impossible. Compared to growing rods with pedicle screw fixation, the rib construct has greater surface area contact with strong cortical bone on the outer surface of the ribs, while pedicle screws have less surface area contact with weaker cancellous bone on the inside of the pedicles and vertebral bodies. Thus, the rib construct is able to distribute stress from the corrective forces of the instrumentation over a larger surface area of stronger bone. As a result, much higher corrective forces can be safely applied by the surgeon using the rib construct, especially in the sagittal plane, without the potentially disastrous effects of pedicle screw failure. *Ex vivo* biomechanical results documented that the rib construct provides stronger proximal fixation that is less prone to failure when loaded with bending and torsional forces.

Ex vivo biomechanical results also documented that the rib construct was less stiff than pedicle screw fixation. When subjected to bending and torsional forces, spines instrumented with the rib construct were able to reach greater deflection angles with less force applied by the mechanical testing system. In the rib construct, motion at the highly mobile costovertebral joints and micro-motion at the rib-hook interface, allows for more movement compared to pedicle screws and renders the construct less stiff. In contrast, pedicle screws have no motion at their interface with the vertebrae, and the construct is very stiff. This has both mechanical and biological implications.

From a mechanical perspective, the less stiff nature of the rib construct likely reduces the risk of rod fracture and proximal junctional kyphosis. Rod fracture and proximal junctional kyphosis are common problems with growing rods.[61,62] Some studies show that rod fracture and proximal junctional kyphosis are even more common than proximal fixation failure. This is likely due to the stiff nature of pedicle screw fixation, resulting in high stress in the rods, especially in sections of the rods immediately adjacent to pedicle screws and also at the upper instrumented vertebrae. As a result, fatigue stress in the growing rods can cause the rods to fracture, and high stress concentration at the upper instrumented vertebrae can cause proximal junctional kyphosis. In the rib construct, since the construct is less stiff compared to growing rods with pedicle screws, this high stress concentration is less likely to occur, reducing the risk of rod fracture and proximal junctional kyphosis. Preservation of spinal ligaments with the rib construct even further reduces the risk of proximal junctional kyphosis. This is consistent with clinical results in human studies, discussed in **Chapter 5**.

From a biological perspective, the less stiff nature of the rib construct also has benefits. The stiff nature of growing rods fixed to the spine with pedicle screws causes auto-fusion of the vertebrae in >80% of patients, resulting in diminishing returns with each lengthening procedure, stunted spinal growth, and compromised pulmonary function.[63] In contrast, since the rib construct is less stiff, motion is preserved between the vertebrae and auto-fusion is less likely. Auto-fusion of the vertebrae was not observed in any patient in the clinical study (**Chapter 5**). Furthermore, since the rib construct is less stiff compared to pedicle screws, fewer lengthening procedures are required to facilitate spinal growth (also discussed in more detail in **Chapter 5**).

None of the biomechanical studies comparing the rib construct with pedicle screws have examined distal fixation failure yet. Complications with distal fixation are not as common as proximal fixation. Thus, the rib construct and traditional growing rods both use pedicle screws or other conventional methods (ie: sacral hooks, iliac screws) for distal fixation and this appears to be effective.

Chapter 4. The Rib Construct is a Safe and Effective Technique in an *In Vivo* Hyperkyphotic Porcine Animal Model

4.1 Introduction

In early-onset spinal deformity patients with hyperkyphosis, implant-related complications are frequent and results are often unsatisfactory.[74-76] These ongoing problems warrant creation of modeling systems as venues for validating surgical techniques and instrumentation for children with thoracic hyperkyphosis. While *ex vivo* biomechanical testing with cadaveric spines and computer modeling for spinal instrumentation can be useful, the present study focuses on developing an *in vivo* animal model and using this model to test the rib construct. Results showed that the rib construct is a safe and effective technique for the correction of hyperkyphotic spinal deformity in an immature porcine model.

Additional Background on Spinal Deformity Animal Models

To date, there have been almost a hundred publications on *in vivo* scoliotic animal models in pigs, goats, sheep, chickens, and mice.[77-78] The most common method involves placement of a tether on lateral vertebral bodies, then relying on subsequent asymmetric growth to produce a scoliotic deformity.[79] There are a few reports describing animal models of hyperkyphotic deformity in the cervical and lumbar spines.[80-84] However, no animal models have yet been created that simulate childhood thoracic hyperkyphosis in an immature spine.

The objective of the present study was to create a porcine thoracic hyperkyphotic deformity to evaluate the effect of the rib construct and other therapies on the immature spine. Yorkshire pigs were selected for this study due to their similar size and shape to the human spine.[85] In addition, pigs normally undergo large spinal growth in their first 6 months of life, making them ideal for a spinal deformity animal model. The model outlined in this paper established a thoracic hyperkyphotic deformity at the time the weight of the pigs was 20-25 kg, comparable to the weight of a 7 year old child, the average age of initial surgery in recent studies on early onset spinal deformity.[86,87] Furthermore, the kyphotic deformity was created at a developmental stage at which the pigs still had considerable future spinal growth remaining, thus allowing for accurate validation of the effect of surgical instrumentation on an immature spine.

4.2 Methods

Husbandry

All procedures were approved by the Institutional Animal Care and Use Committee at the Medical University of South Carolina (MUSC). Domestic Yorkshire farm pigs (male, 5-week old, 10-11 kg; n=6) were acquired one week before surgery from a class A USDA-registered swine vendor (Valley Brook Research, Madison, GA). The size of the pigs was selected to ensure that they were sufficiently mature to survive a thoracotomy, while still small enough that the created deformity would be well-established by the time they weighed 25 kg, a weight that would provide a reasonable counterpart to the size of many children undergoing surgery for early onset scoliosis.

Upon arrival in the animal care unit, all pigs received a broad-spectrum antibiotic (Excede; 5 mg/kg, IM) for prevention of post-shipping respiratory disease. Pigs received ad lib reverse osmosis water, twice daily measured commercial diet, rotated environmental enrichment devices and an automated 12:12 light:dark cycle. A liquid diet

(Ensure®, Abbott Laboratories, Abbott Park, IL) was provided the day before surgery to reduce the amount of ingesta in the gastrointestinal tract compressing the diaphragm cranially toward the surgical site. The pigs were bathed 1-3 days before surgery using chlorhexidine soap, ensuring contact time was at least 10 minutes before rinsing. The pigs were then fasted overnight with constant access to water.

Anesthesia

The pigs were pre-medicated subcutaneously with atropine (0.04 mg/kg), acepromazine (1.1 mg/kg) and ketamine (22 mg/kg). Anesthesia was then induced with isoflurane in oxygen administered by face mask, and the pigs were intubated with a cuffed endotracheal tube (5.0 mm internal diameter) for maintenance. Combination preemptive analgesia was administered subcutaneously (sustained release buprenorphine; 0.24 mg/kg) and intramuscularly (carprofen; 2 mg/kg). A 1-inch, 22-gauge intravenous (IV) catheter was placed in a marginal ear vein and secured for administering sterile crystalloid fluids (10 mg/kg/hr) using a fluid line warmer (Hotline® 37184, Smiths Medical PM Inc., Waukesha, WI) and volumetric infusion pump (Vet/IV 2.2™, Heska Corp., Loveland, CO) throughout surgery. Whole blood was collected for measurement of baseline packed cell volume and total solids. Cefazolin (62.5 mg/kg; IV) was administered prophylactically, since orthopedic screws and wires were chronically implanted.

Intraoperative monitoring included continuous electrocardiogram, heart rate, esophageal temperature, and pulse oximetry for oxygen saturation (SurgiVet Advisor, Smiths Medical PM Inc., Waukesha, WI). The pigs were mechanically ventilated (Model 2000, Hallowell EMC, Pittsfield, MA) using a calculated tidal volume of 10 ml/kg, and end tidal CO_2 was maintained between 30 and 40 mmHg by adjusting airway pressure (15-25 cm H_2O) and respiratory rate (12-20 breaths/min). Pigs were kept warm with a circulating warm water heating blanket and a convection warmer.

Lateral Thoracotomy

A left lateral thoracotomy was performed at the 10th-11th intercostal spaces (**Figure 15A**), and the anterior vertebral bodies were exposed. Procedures were performed on T9-11, where the least retraction on the immature porcine lung was necessary. Anteroposterior screws were placed in the anterior surface of T9 and T11 vertebral bodies, as far removed as possible from T10 to preserve a strong anterior cortex for secure purchase. Through a separate dorsal incision, an open release of the supraspinous and interspinous ligaments was performed from T9-11. Then, a partial vertebrectomy of the anterosuperior and anteroinferior sections of T10 was performed. A wire loop was placed around the screws and tightened, compressing the anterior T9-11 vertebral bodies (**Figure 15B**). Fluoroscopic images were acquired using a c-arm (OEC® 9800 Plus, GE Healthcare, Chicago, IL) intraoperatively and postoperatively (**Figure 15C-E**). Immediate hyperkyphosis after surgery was ~29° between T6-T14 (~30° T9-T11) with the apex at T10. The hyperkyphosis increased to ~35° between T6-T14 (~40° T9-T11) at 4 weeks post-op, prior to corrective surgery.

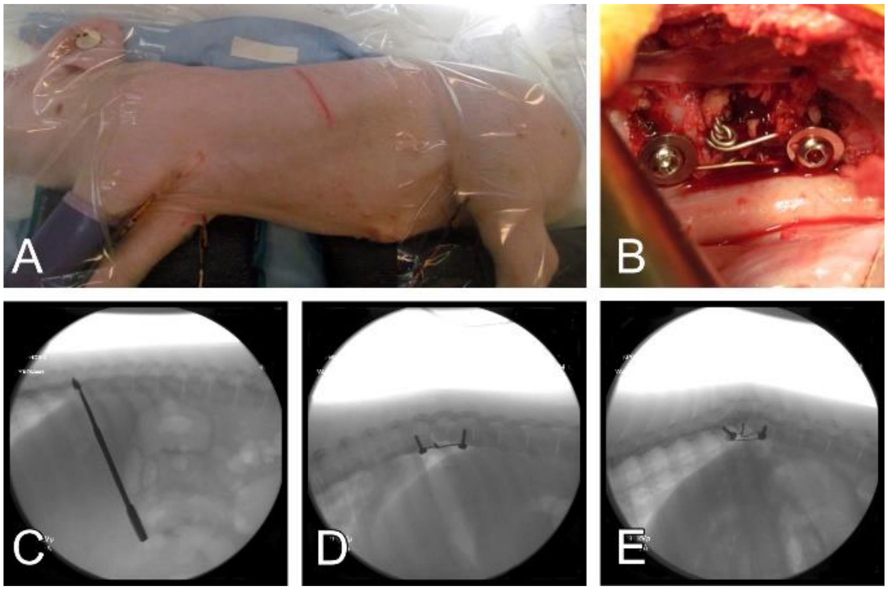


Figure 15. **A**) Site of thoracotomy between ribs T10-T11. Exposure of the spine, placement of screws and partial resection of T10 vertebral body. **B**) Wire loop placed around screws and tightened. Radiographic imaging. **C**) Approximately 8° T9-T11 Cobb angle pre-op, **D**) 30° post-op, and **E**) 41° at follow-up prior to corrective surgery.

Postoperative care

Analgesia was provided using a fentanyl patch, 5 µg/kg applied to the distal forelimb and a single dose of buprenorphine, 5 µg/kg. Pigs received intra-operative IV fluid support at a rate of 10 ml/kg/hour and were ventilated at a rate of 10-12 ml/kg using end-tidal CO_2 measurements to make ventilator adjustments. After surgery, the pigs were maintained in the animal research facility at MUSC and allowed to grow for four weeks prior to corrective surgery with the rib construct.

Hyperkyphosis correction with rib construct

Initially, distal fixation for corrective instrumentation was placed in the lumbar spine, but immediate junctional failure uniformly occurred because the lumbar spine is hypermobile relative to the thorax.[88] Thus, a totally thoracic extraspinal construct was developed. With the hyperkyphotic deformity at T9-11, a superior claw was placed on ribs 6-8, and an inferior claw at ribs 12-14. The rods were placed without contouring, thus placing an extension moment on the deformity (**Figure 16**).

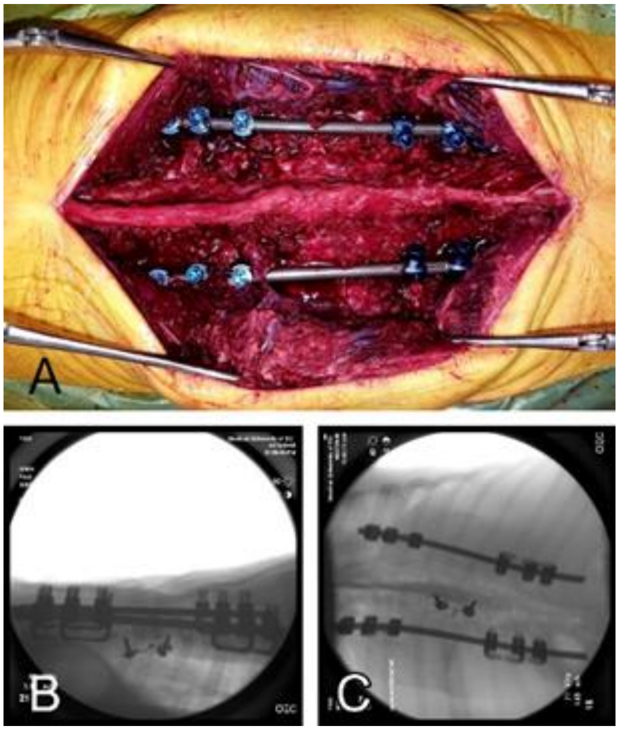


Figure 16. A) Proximal fixation with rib construct T6-T8, hyperkyphosis apex T9-T11, distal fixation with rib construct T12-T14. **B-C**) post-op radiographs.

Radiographic evaluation

Sagittal fluoroscopic images of the thoracic spine were acquired using a c-arm (OEC® 9800 Plus, GE Healthcare, Chicago, IL) pre-op, immediately post-op, and at regular intervals until final follow-up 8 weeks after corrective surgery. With each radiograph, thoracic kyphosis was measured between T6-T14. Pigs were euthanized 8 weeks post-op. At necropsy, computed tomography (CT) scans were obtained, and three-dimensional reconstructions were generated. CT was used to measure wedging of vertebral bodies (in degrees).

Histologic evaluation

Instrumentation was removed, and spinal segments from T4-L1 were immersion fixed in Cal-Ex II (Fisher Scientific) for fixation and decalcification. Spines were hemi-sected longitudinally. A 3.0 mm thick slab section was then removed from the cut face and subsequently bisected to allow placement into tissue cassettes. Tissues were paraffin embedded, with 5 um thick sections placed on negatively charged glass slides and stained with hematoxylin and eosin (H&E). Sections were examined, and digitally reconstructed sub-gross images were captured. Growth plates were examined qualitatively for chondrocyte cellularity and column length in the anterior and posterior growth plates of instrumented spinal segments adjacent to T9-T11.

Statistical Analysis

Statistical analysis included one-way ANOVA and Tukey’s post hoc tests to determine differences in pre-op, post-op, and final follow-up radiographic measurements and biomechanical outcomes.

4.3 Results

Hyperkyphosis creation and subsequent correction with the rib construct was successfully performed without complications in three consecutive pigs. Hyperkyphosis creation with no correction was successfully performed in an additional three pigs.

Radiographic Data

Sagittal fluoroscopic images were obtained pre-op, immediately post-op, and at regular intervals until necropsy 8 weeks after corrective surgery. The pre-op T6-T14 thoracic kyphosis was 16.7 ± 2.9°. The T6-T14 thoracic hyperkyphosis created at the time of initial hyperkyphosis creation surgery was 29.0 ± 1.7, and increased to 35.3 ± 4.5° prior to corrective surgery. In response to corrective surgery with the rib construct, T6-T14 thoracic hyperkyphosis decreased immediately post-op to 15.8 ± 3.9° and continued to decrease to 10.6 ± 3.5° at final follow-up 8 weeks post-op (p<0.001) (**Figure 17**).

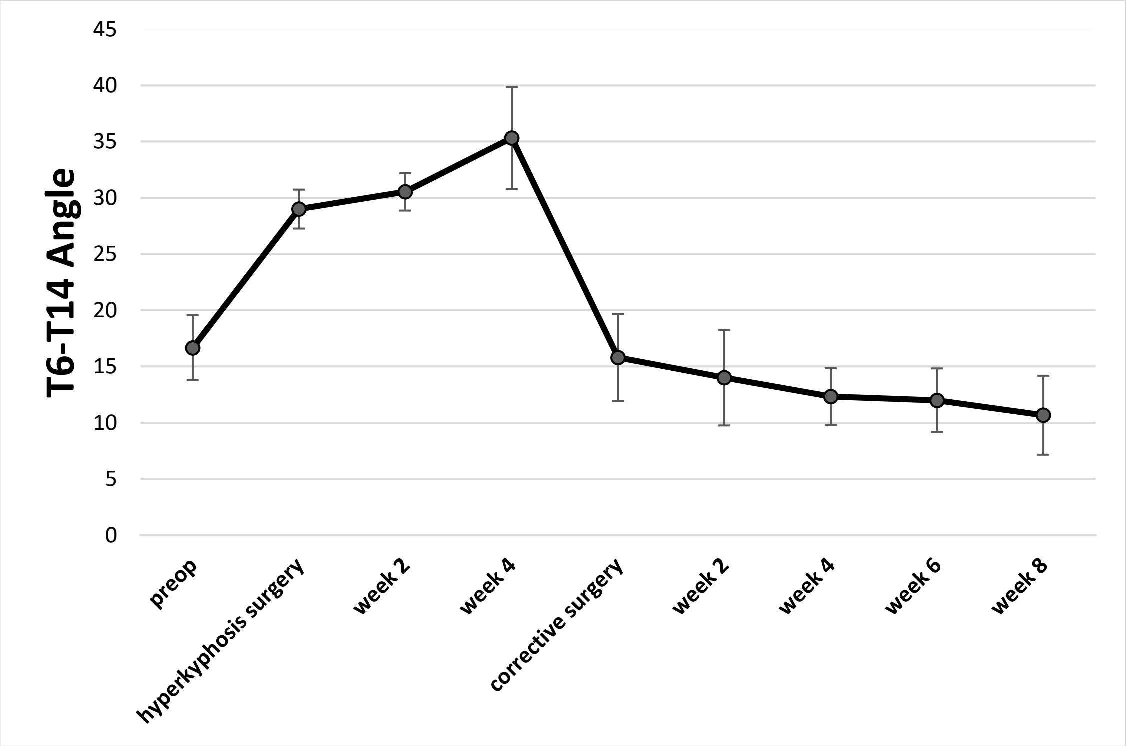


Figure 17. The average pre-op T6-T14 thoracic kyphosis was 16.7 ± 2.9°. The T6-T14 thoracic hyperkyphosis created at the time of initial hyperkyphosis creation surgery was 29.0 ± 1.7° and increased to 35.3 ± 4.5° prior to corrective surgery. In response to corrective surgery with the rib-hook construct, T6-T14 thoracic hyperkyphosis decreased immediately post-op to 15.8 ± 3.9° and continued to decrease to 10.6 ± 3.5° at final follow-up 8 weeks post-op.

CT images at necropsy showed wedging, thus indicating that growth modulation was occurring in the pigs with corrective surgery. Wedging averaged 4.7 ± 4.1°, 10.6 ± 4.3°, and 1.6 ± 2.8° in vertebral bodies T7, T8, and T12 respectively, adjacent to T9-T11 in corrected spines. In contrast, control spines showed no wedging (**Figure 18**). Three dimensional reconstructions of a hyperkyphotic and a corrected spine are shown (**Figure 19**).

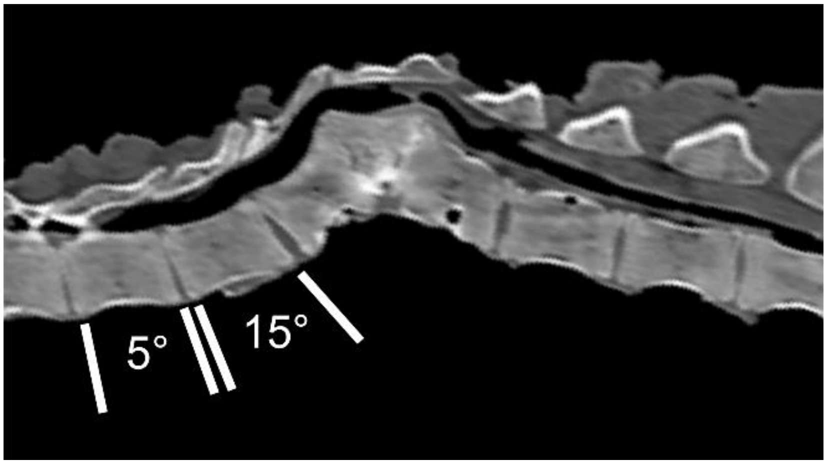


Figure 18. Wedging of vertebral bodies indicative of growth modulation in response to rib construct surgery. In this specimen there was approximately 5° wedging of T7 and 15° wedging of T8.

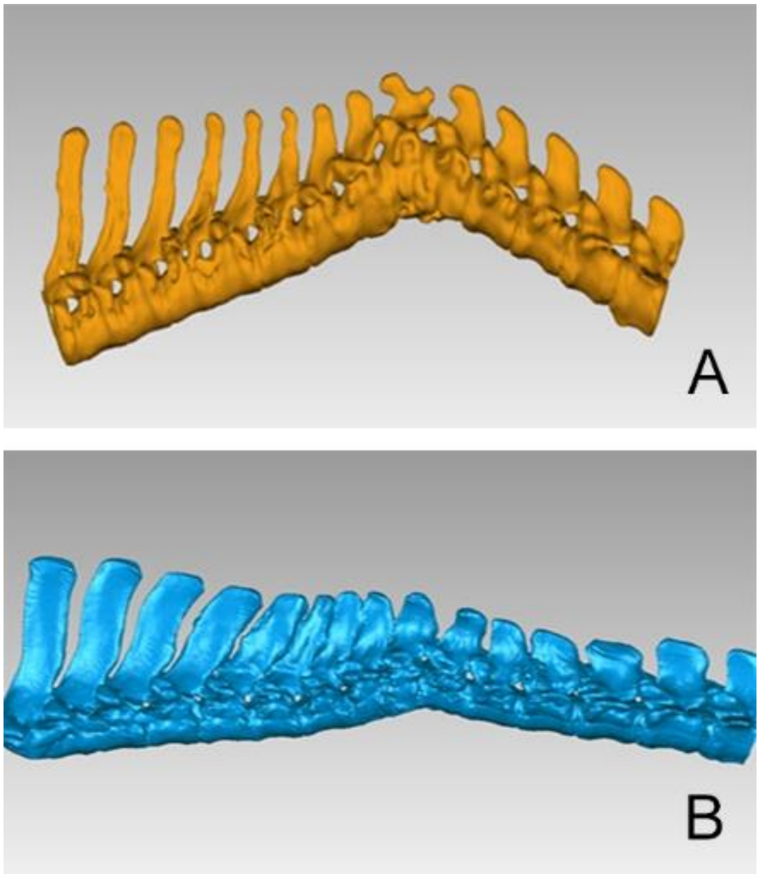


Figure 19. 3-D reconstructed CT images of porcine spine. Top panel was taken immediately after the deformity was created. Bottom panel was taken eight weeks after the deformity was corrected using the rib construct.

Histologic evaluation

Histologic evaluation of spinal segments T4-L1 revealed fusion and stunted growth of the anterior growth plates between T9-T10 and T10-T11, as expected from hyperkyphotic deformity creation surgery (**Figure 20**). The posterior growth plates in these segments remained intact and continued to grow relatively uninhibited. It is for this reason that the deformity progressed prior to corrective surgery. Growth plates and intervertebral discs in segments adjacent to T9 and T11 remained intact.

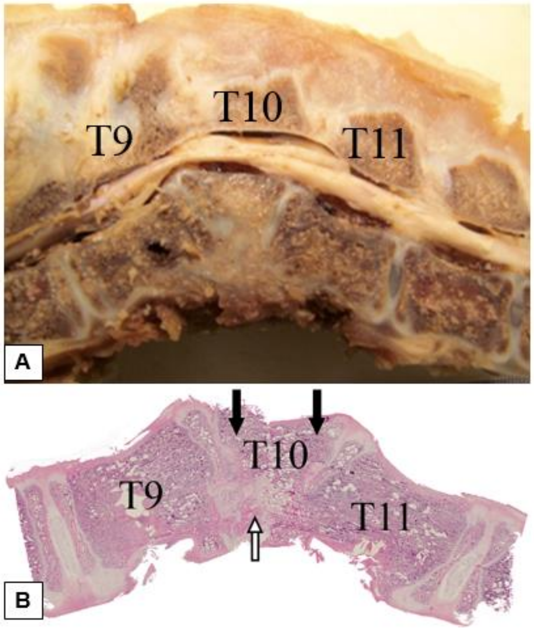


Figure 20. A) Slab section of uncorrected deformity at necropsy. **B**) Histology of hyperkyphotic deformity. The anterior portion of the T9-T11 growth plates was disturbed by the vertebrectomy and are partially fused (white arrow). The posterior portion of the growth plates remain active after intial surgery (black arrows). Growth plates and intervertebral discs in adjacent segments remain healthy.

In response to correction with the rib construct, analysis of spinal segments adjacent to T9-T11 revealed realigned orientation with a concavity on the posterior side and convexity on anterior side. This resulted in a straighter, more anatomically aligned, spine. The nucleus pulposus between instrumented segments was extruded anteriorly with compression of the posterior disc space. Cellular changes indicative of growth modulation were observed in the growth plates of instrumented spinal segments. Macroscopically, growth plates in corrected spines were bowed inwards (**Figure 21**). In contrast, control spines showed straight symmetrical growth plates. Qualitatively, there appeared to be greater cellularity and column length in hypertrophic and proliferative zones of the anterior (distracted) section of growth plates, compared to the posterior (compressed) section

(**Figure 22**). Control spines showed no such differences. This was not explored quantitatively, be could be in future studies.

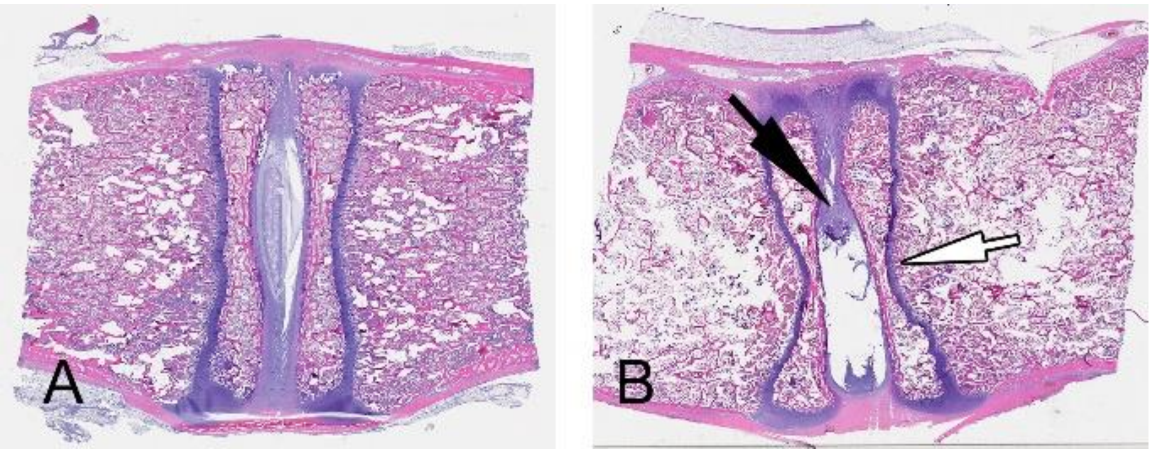


Figure 21. A) HE staining at T8-T9 of normal spine with straight symmetrical growth plates and centrally located nucleus pulposus. **B**) T8-T9 of hyperkyphotic spine corrected with the rib-hook construct. Growth plates bowed inwards (white arrow), compression of posterior discs and anterior extrusion of nucleus pulposus (black arrow) in instrumented disc spaces of corrected spine.

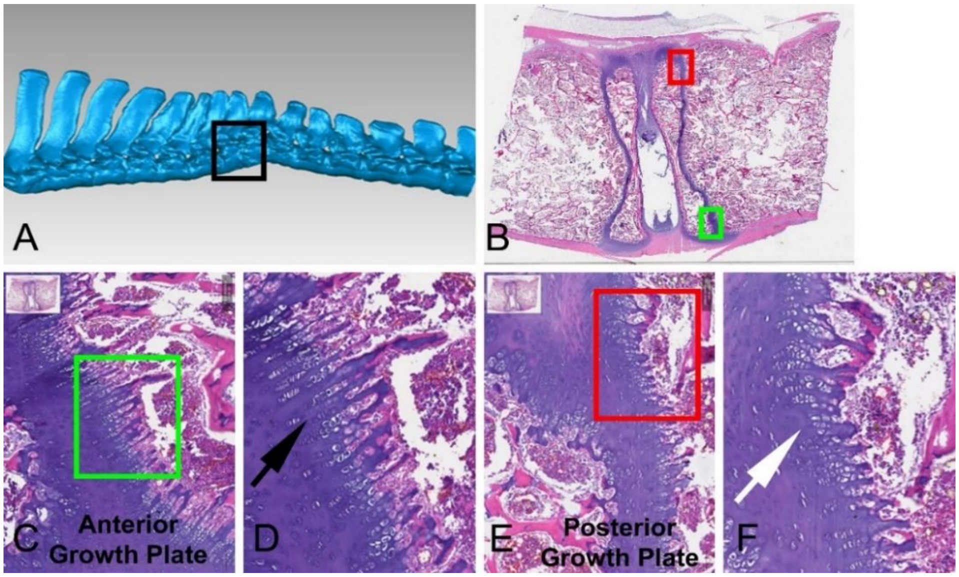


Figure 22. A-B) Black box shows location of histology images on three-dimensional reconstructed corrected spine at T8-T9. **C-D**) Section of anterior proximal T9 growth plate that was distracted with rib construct. **D-F**) Section of posterior proximal T9 growth plate that was compressed with rib construct. Greater cellularity, larger chondrocyte columns in anterior (distracted) portion of growth plate, compared to posterior (compressed) portion of growth plate.

Rib observations

There were no rib fractures or violations of the pleura in any of the pigs treated with the rib construct. However, ossification was observed on the implant surface. This ossification was unique to the pig model and did not occur in the clinical study. Potential reasons for this are covered in the discussion.

4.4 Growth Modulation: Longitudinal Bone Growth Mechanisms and Basic Science

Instrumentation for early-onset spinal deformity is designed to provide some immediate deformity correction by realigning vertebral bodies. However, it is hypothesized that the technique also straightens the spine gradually by growth modulation. Indeed, in the growing spine, compression or distraction of vertebral bodies changes the rate of growth of the growth plates. Instrumentation can be strategically applied to take advantage of this process to straighten a deformed spine. The principle behind this is referred to as the "Hueter-Volkmann Law," which states that tensile forces stimulate longitudinal bone growth and that compressive forces inhibit growth.[86,87] This section will describe the basic science of growth modulation and relate the findings from our animal model.

Longitudinal Bone Growth

Longitudinal bone growth occurs via synthesis of cartilaginous tissue that is subsequently transformed into bone by endochondral ossification. This process occurs at the growth plate, which is an avascular, aneural section of chondrocytes embedded within extracellular matrix. The growth plate is located between the epiphysis and metaphysis of the bone. The growth plate can be divided into four zones: 1) reserve zone, 2) proliferative zone, 3) hypertrophic zone, and 4) ossification zone. Each zone contains chondrocytes with unique activity and morphology (**Figure 23**).

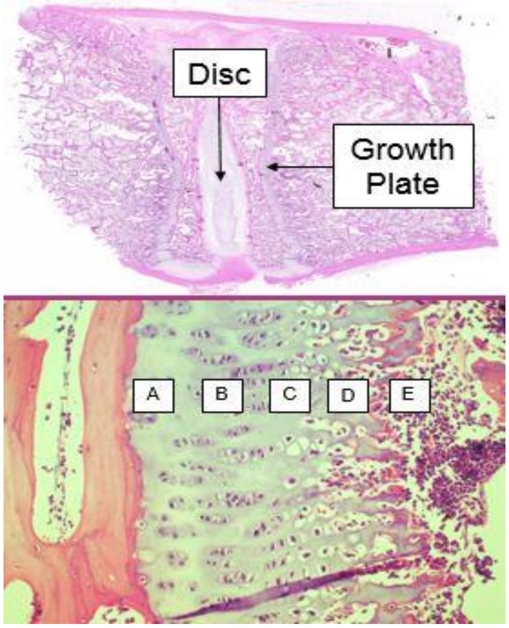


Figure 23. H&E staining of vertebral body growth plate from a pig that underwent corrective surgery with the rib construct. **A)** Reserve Zone, **B)** Proliferative Zone, **C)** hypertrophic Zone, **D)** Ossification Zone, and **E)** Trabecular Bone.

Longitudinal bone growth at the growth plate results from a complicated interplay of chondrocyte proliferation, hypertrophy, and synthesis of extracellular matrix. Beginning in a pool of chondrocytes within the reserve zone, chondrocytes undergo proliferation in the proliferative zone and hypertrophy in the hypertrophic zone. Extracellular matrix synthesis and degradation occur in both the proliferative and hypertrophic zones. Type II collagen and aggrecan are the most common matrix components. Type X collagen is also prevalent, but only in the hypertrophic zone. While matrix is synthesized, it is concomitantly partially degraded by several enzymes, including Collagenase 3 (MMP-3) and aggrecanases (ADAMTS-4 and-5). Chondrocytes in the proliferative and hypertrophic zones eventually undergo apoptosis. This is followed by blood vessel invasion into the tissue and calcification in the zone of provisional calcification.

The rate of longitudinal bone growth is governed by the rate at which the chondrocytes proliferate, hypertrophy, and synthesize extracellular matrix. The overall height of the growth plate, as well as the heights of its separate components, the proliferative and hypertrophy zones, positively correlate with the growth rate.[91] The number of proliferative chondrocytes and the size of hypertrophic chondrocytes are both correlated with the growth rate, with larger values associated with faster growth rate.[91,92]

The regulation of longitudinal bone growth is complex and poorly understood. It is likely multi-factorial, involving genetics, hormone levels, local growth factors/cytokines, cell nutritional status, blood supply, solute transport, autocrine/paracrine signaling, and mechanical loading.

The Effects of Mechanical Loading on Longitudinal Growth

The Hueter-Volkmann law states that longitudinal bone growth is slowed by compression and enhanced by distraction of the growth plate. There is evidence that this effect occurs by both sustained static loading and dynamic loading. The mechanism behind the Hueter-Volkmann law is not known, but likely involves the transduction of loading forces to chondrocytes and subsequent signaling to the nuclei, where gene expression is altered.

While the mechanism is not known, the effects of mechanical loading on growth plate size and morphology have been well-described. Compressive loading reduces overall growth plate thickness, especially in the proliferative and hypertrophic zones. Compressive loading reduces chondrocyte number in the proliferative zone, reduces chondrocyte number and size (height and volume) in the hypertrophic zone, and alters chondrocyte column structure. Distraction of the growth plate has the opposite effects. The results from our hyperkyphotic animal model study seem to verify this. Posterior sections of vertebral growth plates, which were compressed by the rib construct, qualitatively showed fewer chondrocytes and had shorter, more disorganized chondrocyte columns. Anterior sections of vertebral plates, which were distracted by the rib construct, seemed to show more chondrocytes and had larger chondrocyte columns. Future studies can use stereology and cell counting techniques to objectively quantify this effect.

Several studies have documented the effects of mechanical loading on growth plate gene expression. Mechanical loading has reduced mRNA expression and immunostaining for type II and type X collagen within the proliferative and hypertrophic zones. In addition, some studies have shown that mechanical loading upregulates MMP-3, which, as described above, degrades bone matrix. Proteins involved in cartilage ossification (alkaline phosphatase, osteopontin, and osteonectin) are upregulated in compressed growth plates, suggesting that compression accelerates ossification of the growth plate.

4.5 Discussion

Porcine model results validated the safety and effectiveness of the rib construct in an animal model. There are limitations to this animal model that should be acknowledged. The weight bearing forces on the quadrupedal pig place a tensile force on the anterior spine, which is not the case for the spine in bipedal humans. While it is true that bipedal primates likely provide the most accurate simulation of forces on the vertical spine, the ethical and financial considerations involved in such a model are prohibitive. Quadrupedal animal models are standard in spinal deformity research, especially porcine models which closely resemble the human anatomically.[93] Furthermore, the vast majority of loading in both human and porcine spines is due to compressive loading from paraspinal musculature and ligamentous tension, not due to gravity.[94] Thus, the mechanical environments in bipedal human versus quadrupedal porcine spines are quite similar.

An additional limitation is that the technique disrupts spinal anatomy in a way that does not mimic all etiologies of kyphosis. Initial attempts were made to create kyphosis with a less invasive method by using a simple tether between T9-T11, with no vertebrectomy or posterior ligament release. However, this technique failed to create substantial kyphosis prior to the pigs reaching maturity. The technique described in this proposal is almost identical to the type of deformity in congenital kyphosis (**Figure 24**). Congenital kyphosis is commonly angular and arises from failure of anterior vertebral body formation, failure of anterior vertebral body segmentation, or a combination of both.

Figure 24. Congenital kyphosis in a human patient, similar to our porcine model.

One final limitation to this study is that there were not time matched controls (ie: pigs that received hyperkyphosis creation surgery but no corrective surgery, allowed to live for the same duration as pigs that received corrective surgery). During the initial stages of development of this animal model, a pig was allowed to live for 6 weeks with no corrective surgery. Without corrective surgery, the deformity continued to increase to dangerous levels and caused paralysis. This happened when the pig reached >45° of kyphosis. The pig had to be euthanized. For this reason, all of the pigs received corrective surgery, and there were no time matched controls for pigs that received hyperkyphosis creation surgery but no treatment. It would be unethical to not correct the deformity in a control group, knowing that the deformity would continue to increase and put the pig at risk for paralysis and substantial pain, similar to what occurs in untreated humans.

Young immature pigs were selected for this study because they are age and size appropriate for the types of patients undergoing surgery for EOSD.[95,96] Additionally, porcine bone mineral content is lowest in their first 5 weeks of life (comparable to that of a child with osteoporosis) and increases linearly as the pig gains weight, so it is beneficial to use young pigs to simulate poor bone quality in humans.[97,98] Thus, this porcine animal model is highly suitable.

While this was a highly effective model, this model was technically difficult and had a steep learning curve. Numerous techniques were attempted to create and correct deformity before the final technique was established. During creation of the hyperkyphotic spinal deformity, an anterior approach was used to access the spine through the rib cage. The parietal pleura surrounding the lungs of an immature pig is very fragile, so extreme caution must be taken to avoid damaging the pleura and lungs. Also, the anterior approach with partial vertebrectomy requires mobilization of the aorta and cauterization of the segmental vessels, which can be small, delicate, and difficult to locate in the pig.

Initially, attempts were made to create hyperkyphosis by placing an anterior tether consisting of screws and a wire loop between vertebra T9-T11 with no vertebrectomy. The idea was that this would create an initial angular deformity that would compress the anterior growth plates, and the deformity would increase as the pig grew in subsequent weeks. However, this failed to create adequate deformity, so we paired the tether with a partial vertebrectomy at T10 and posterior interspinous ligament release in future attempts. The partial vertebrectomy removed a wedge-shaped section of vertebrae (including the growth plate) from the anterior portion of T10. This increased the angular hyperkyphotic deformity created at the time of surgery, and also completely removed the anterior growth plates in T10, while the posterior growth plates continued to grow after surgery. The posterior interspinous ligament release increased the flexibility of the spine, allowing for greater deformity creation. The result was substantial angular hyperkyphotic deformity at the time of surgery, which continued to increase in subsequent week post-op until corrective surgery.

Initial attempts to correct the deformity used rib fixation with the rib construct, paired with traditional distal fixation, as is performed in human patients. However, we found that since the porcine lumbar spine is highly mobile, this resulted in distal junctional kyphosis. This could be an effective model to study junctional kyphosis in future studies, but was not a desired outcome in the present study, that aimed to study rib fixation. Therefore, we attempted a thoracic-only rib construct that used rib fixation for both proximal and distal fixation. This allowed us to correct the deformity while avoiding the hypermobile porcine lumbar spine.

This model elucidated the mechanobiological mechanism by which the rib construct and other growth-sparing techniques, correct early-onset spinal deformity. The rib construct provides some immediate deformity correction by realigning vertebral bodies. Additional correction is gradually achieved over time by growth modulation. Indeed, in the growing spine, compression or distraction of vertebral bodies changes the rate of growth of the growth plates. Instrumentation can be strategically applied to take advantage of this process to straighten a deformed spine. The principle behind this is referred to as the “Hueter Volkmann Law,” which states that tensile forces stimulate longitudinal bone growth and that compressive forces inhibit growth. The present study found wedging of vertebral bodies in response to instrumentation with the rib construct. Histology showed macroscopic bowing of growth plates and qualitatively greater cellularity and chondrocyte column length in the anterior distracted sections of growth plates compared to posterior compressed sections. This was the first study to create and subsequently correct hyperkyphotic spinal deformity in a skeletally immature animal model and examine the outcomes at the sub-gross and cellular level. Future studies may assess the biological outcomes of the rib construct on the vertebral growth plate in more detail. Possible future studies are discussed in **Chapter 7**.

An interesting outcome from this porcine animal study was the observation of excessive scar tissue and calcified/ossified material on the implant surface. The implant surface appeared to be encapsulated by scar tissue with an inner calcified/ossified layer surrounding the implants. This was unique to the pig model and did not occur in the clinical study. There are several possible reasons for this. One likely explanation is that since the rate of growth in immature pigs is much greater than humans, the pigs may form bone and/or scar tissue at a faster rate. Another possible explanation is that compared to humans, the pigs have less bending and axial rotation of their thoracic spine during their daily lives. This relative lack of motion in the thoracic spine compared to humans, may promote ossification around the implant surfaces.

Chapter 5. The Rib Construct is a Safe and Effective Technique for Correction of Early-onset Spinal Deformity in a Human Clinical Study

5.1 Introduction

A retrospective study was conducted on 24 human patients that were treated using the rib construct for severe non-idiopathic spinal deformity at The Medical University of South Carolina (MUSC). The rib construct provided similar coronal plane correction and superior sagittal plane correction, compared to what can be achieved with growing rods with pedicle screws and VEPTR.

5.2 Methods

Study design and patients

A retrospective study was conducted on 24 human patients that were treated with the rib construct (RC) for severe non-idiopathic spinal deformity at The Medical University of South Carolina (MUSC) between 2007 and 2015. There were 14 patients that received the rib construct as a growth-sparing treatment for early-onset spinal deformity (EOSD), meaning it was lengthened as the patients grew. An additional 10 patients received definitive fusion only with the rib construct, and no growth-sparing treatment. This study was approved by the MUSC Institutional Review Board (IRB).

Follow-up and data collection

Data collected included diagnosis, age at index surgery, length of follow-up, T-score bone density, complication rates, procedure time, operative blood loss, and radiographic outcomes. Specific radiographic data included pre-op, post-op, and final follow-up sagittal and coronal Cobb angles, sagittal vertical axis (SVA), coronal vertical axis (CVA), pelvic tilt (PT), pelvic incidence (PI), sacral slope (SS), C2-C7 angle, C2-C7 sagittal vertical axis (SVA), lumbar lordosis (LL), spinal height (T1-S1), thoracic height (T1-T12), apical vertebral translation (AVT), T1 tilt, clavicle angle (CA), and total lung capacity (TLC). TLC was estimated using antero-posterior radiographs according to the established technique described by Schlesinger et al.[99] The longitudinal distance (cm) from the apex of the right lung to the right costophrenic angle was designated "L," while the transverse width from the right to the left costophrenic angles was designated "W". The numeric relationship among TLC (in liters), L (in cm), and W (in cm) is provided in equation 1

$TLC = (0.163*L)+(0.189*W)-4.928$ (**Equation 1**)

5.3 Results

Patient Population and Surgery Information

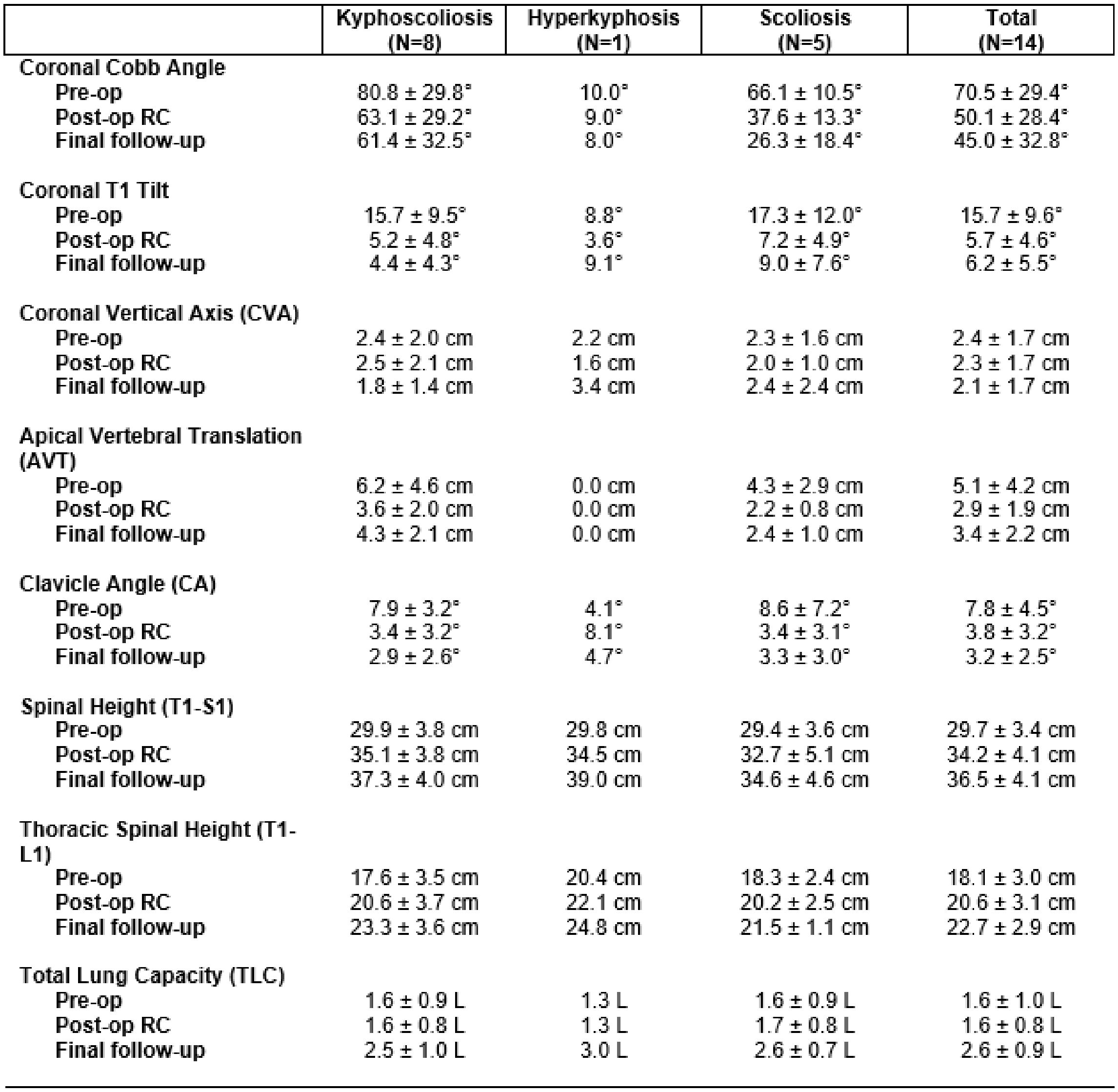
A total of 24 patients that received the rib construct (RC) were studied. There were 14 patients that received the rib construct as a growth-sparing treatment for early-onset spinal deformity (EOSD), and 10 patients received definitive fusion only with the rib construct. Of the 14 EOSD patients that received growth-sparing treatment, 13 of them underwent definitive fusion procedures upon reaching skeletal maturity (9 with the rib construct and 4 with pedicle screws). There were 17 patients that had kyphoscoliosis, 1 with isolated hyperkyphosis, and 6 with scoliosis. Etiology was syndromic (11), neuromuscular (10), congenital (2), and Scheuermann's (1). 19 of the 24 patients had bone density studies, all documenting osteoporosis. Bone density was T -3.9 ± 0.9. Age at rib construct index surgery was 11.1 ± 1.7 years for early-onset spinal deformity (EOSD) patients receiving growth-sparing treatment, and 16.0 ± 2.9 years for fusion patients. Procedure time was 5:00 ± 1:30 hours for rib construct index surgery for early-onset spinal deformity and 6:00

± 1:15 for fusion. Blood loss was 277 ± 159 mL for index surgery for early-onset spinal deformity and 1006 ± 532 mL for fusion. Number of lengthening procedures was 2.7 ± 1.6.

Radiographic Data

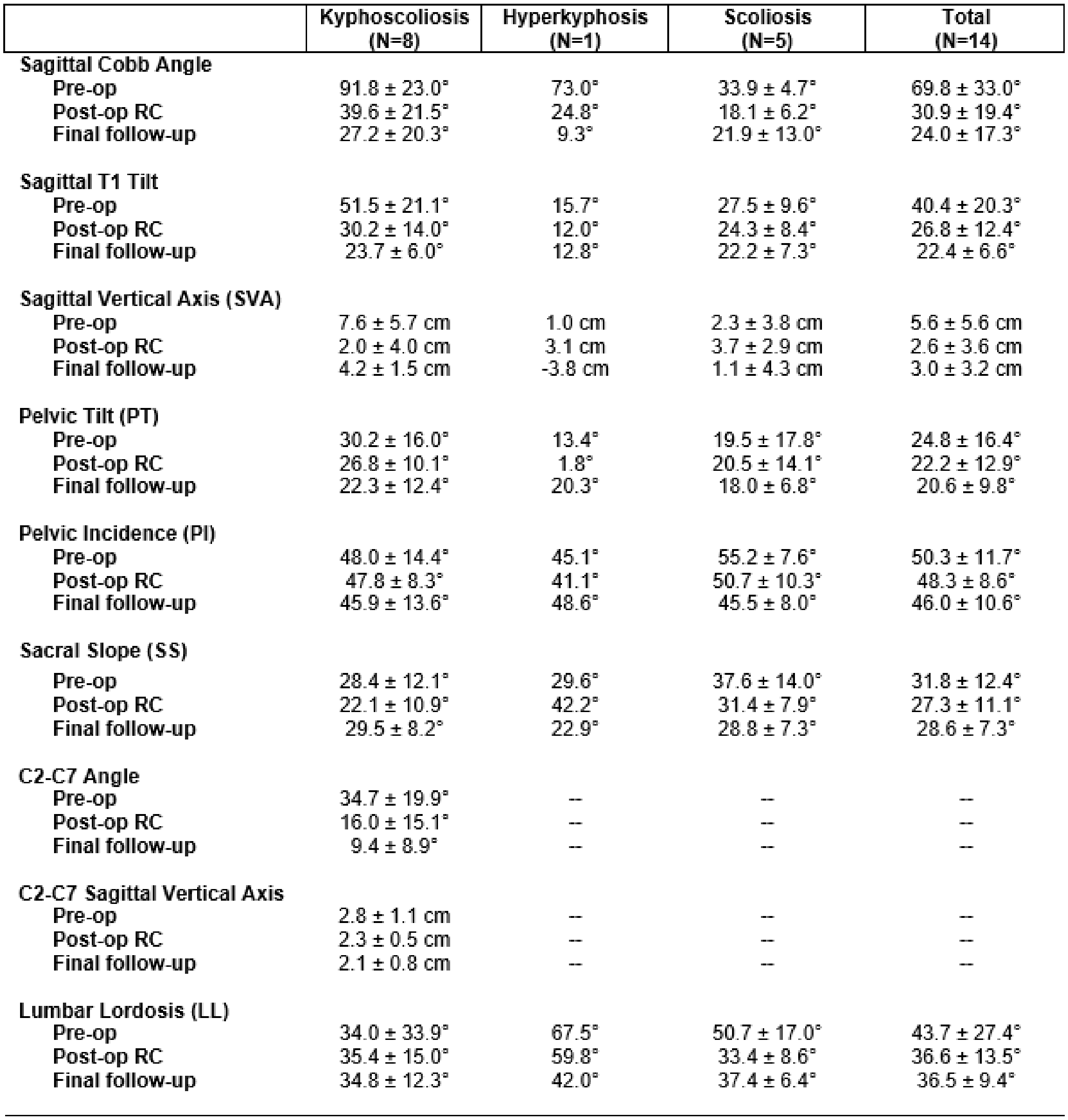
For patients that received growth-sparing treatment, kyphoscoliosis coronal Cobb angle was 80.8 ± 29.8° pre-op, 63.1 ± 29.2° post-op, and 61.4 ± 32.5° after definitive fusion procedure or at final follow-up; a 24% correction ($p<0.001$) (**Table 3**). Scoliosis coronal Cobb angle was 66.1 ± 10.5° pre-op, 37.6 ± 13.3° post-op, and 26.3 ± 18.4° at final follow-up; a 60% correction ($p<0.001$). Kyphoscoliosis sagittal Cobb angle was 91.8 ± 23.0° pre-op, 39.6 ± 21.5° post-op, and 27.2 ± 20.3° at final follow-up; a 100% correction ($p<0.001$) (**Table 4**). Hyperkyphosis sagittal Cobb angle was 73.0° pre-op, 24.8° post-op, and 9.3° at final follow-up. These parameters improved significantly in fusion-only patients as well. Spinal height (T1-S1) and total lung capacity (TLC) increased in all groups. There was improved alignment of the shoulders, neck, head and thorax, supported by improvements in coronal and sagittal T1 tilt, clavicle angle (CA), sagittal vertical axis (SVA), C2-C7 angle, and C2-C7 sagittal vertical axis (SVA). A comprehensive summary of all radiographic outcomes for that received growth-sparing treatment can be found in **Table 3 and 4**. Patients that received definitive fusion only are reported in **Table 5 and 6**.

Table 3. Growth-Sparing RC Treatment Coronal Plane Radiographic Outcomes



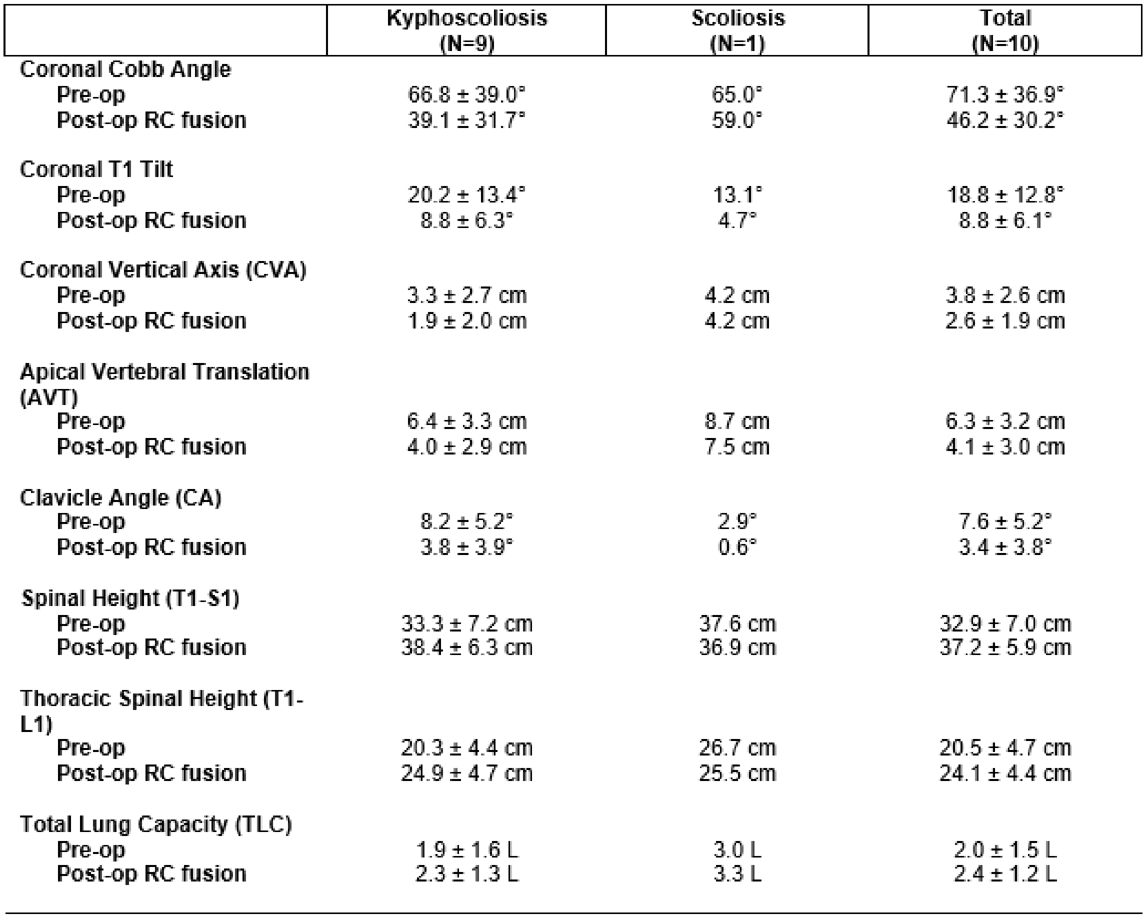
	Kyphoscoliosis (N=8)	Hyperkyphosis (N=1)	Scoliosis (N=5)	Total (N=14)
Coronal Cobb Angle				
Pre-op	80.8 ± 29.8°	10.0°	66.1 ± 10.5°	70.5 ± 29.4°
Post-op RC	63.1 ± 29.2°	9.0°	37.6 ± 13.3°	50.1 ± 28.4°
Final follow-up	61.4 ± 32.5°	8.0°	26.3 ± 18.4°	45.0 ± 32.8°
Coronal T1 Tilt				
Pre-op	15.7 ± 9.5°	8.8°	17.3 ± 12.0°	15.7 ± 9.6°
Post-op RC	5.2 ± 4.8°	3.6°	7.2 ± 4.9°	5.7 ± 4.6°
Final follow-up	4.4 ± 4.3°	9.1°	9.0 ± 7.6°	6.2 ± 5.5°
Coronal Vertical Axis (CVA)				
Pre-op	2.4 ± 2.0 cm	2.2 cm	2.3 ± 1.6 cm	2.4 ± 1.7 cm
Post-op RC	2.5 ± 2.1 cm	1.6 cm	2.0 ± 1.0 cm	2.3 ± 1.7 cm
Final follow-up	1.8 ± 1.4 cm	3.4 cm	2.4 ± 2.4 cm	2.1 ± 1.7 cm
Apical Vertebral Translation (AVT)				
Pre-op	6.2 ± 4.6 cm	0.0 cm	4.3 ± 2.9 cm	5.1 ± 4.2 cm
Post-op RC	3.6 ± 2.0 cm	0.0 cm	2.2 ± 0.8 cm	2.9 ± 1.9 cm
Final follow-up	4.3 ± 2.1 cm	0.0 cm	2.4 ± 1.0 cm	3.4 ± 2.2 cm
Clavicle Angle (CA)				
Pre-op	7.9 ± 3.2°	4.1°	8.6 ± 7.2°	7.8 ± 4.5°
Post-op RC	3.4 ± 3.2°	8.1°	3.4 ± 3.1°	3.8 ± 3.2°
Final follow-up	2.9 ± 2.6°	4.7°	3.3 ± 3.0°	3.2 ± 2.5°
Spinal Height (T1-S1)				
Pre-op	29.9 ± 3.8 cm	29.8 cm	29.4 ± 3.6 cm	29.7 ± 3.4 cm
Post-op RC	35.1 ± 3.8 cm	34.5 cm	32.7 ± 5.1 cm	34.2 ± 4.1 cm
Final follow-up	37.3 ± 4.0 cm	39.0 cm	34.6 ± 4.6 cm	36.5 ± 4.1 cm
Thoracic Spinal Height (T1-L1)				
Pre-op	17.6 ± 3.5 cm	20.4 cm	18.3 ± 2.4 cm	18.1 ± 3.0 cm
Post-op RC	20.6 ± 3.7 cm	22.1 cm	20.2 ± 2.5 cm	20.6 ± 3.1 cm
Final follow-up	23.3 ± 3.6 cm	24.8 cm	21.5 ± 1.1 cm	22.7 ± 2.9 cm
Total Lung Capacity (TLC)				
Pre-op	1.6 ± 0.9 L	1.3 L	1.6 ± 0.9 L	1.6 ± 1.0 L
Post-op RC	1.6 ± 0.8 L	1.3 L	1.7 ± 0.8 L	1.6 ± 0.8 L
Final follow-up	2.5 ± 1.0 L	3.0 L	2.6 ± 0.7 L	2.6 ± 0.9 L

Table 4. Growth-Sparing RC Treatment Sagittal Plane Radiographic Outcomes



	Kyphoscoliosis (N=8)	Hyperkyphosis (N=1)	Scoliosis (N=5)	Total (N=14)
Sagittal Cobb Angle				
Pre-op	91.8 ± 23.0°	73.0°	33.9 ± 4.7°	69.8 ± 33.0°
Post-op RC	39.6 ± 21.5°	24.8°	18.1 ± 6.2°	30.9 ± 19.4°
Final follow-up	27.2 ± 20.3°	9.3°	21.9 ± 13.0°	24.0 ± 17.3°
Sagittal T1 Tilt				
Pre-op	51.5 ± 21.1°	15.7°	27.5 ± 9.6°	40.4 ± 20.3°
Post-op RC	30.2 ± 14.0°	12.0°	24.3 ± 8.4°	26.8 ± 12.4°
Final follow-up	23.7 ± 6.0°	12.8°	22.2 ± 7.3°	22.4 ± 6.6°
Sagittal Vertical Axis (SVA)				
Pre-op	7.6 ± 5.7 cm	1.0 cm	2.3 ± 3.8 cm	5.6 ± 5.6 cm
Post-op RC	2.0 ± 4.0 cm	3.1 cm	3.7 ± 2.9 cm	2.6 ± 3.6 cm
Final follow-up	4.2 ± 1.5 cm	-3.8 cm	1.1 ± 4.3 cm	3.0 ± 3.2 cm
Pelvic Tilt (PT)				
Pre-op	30.2 ± 16.0°	13.4°	19.5 ± 17.8°	24.8 ± 16.4°
Post-op RC	26.8 ± 10.1°	1.8°	20.5 ± 14.1°	22.2 ± 12.9°
Final follow-up	22.3 ± 12.4°	20.3°	18.0 ± 6.8°	20.6 ± 9.8°
Pelvic Incidence (PI)				
Pre-op	48.0 ± 14.4°	45.1°	55.2 ± 7.6°	50.3 ± 11.7°
Post-op RC	47.8 ± 8.3°	41.1°	50.7 ± 10.3°	48.3 ± 8.6°
Final follow-up	45.9 ± 13.6°	48.6°	45.5 ± 8.0°	46.0 ± 10.6°
Sacral Slope (SS)				
Pre-op	28.4 ± 12.1°	29.6°	37.6 ± 14.0°	31.8 ± 12.4°
Post-op RC	22.1 ± 10.9°	42.2°	31.4 ± 7.9°	27.3 ± 11.1°
Final follow-up	29.5 ± 8.2°	22.9°	28.8 ± 7.3°	28.6 ± 7.3°
C2-C7 Angle				
Pre-op	34.7 ± 19.9°	--	--	--
Post-op RC	16.0 ± 15.1°	--	--	--
Final follow-up	9.4 ± 8.9°	--	--	--
C2-C7 Sagittal Vertical Axis				
Pre-op	2.8 ± 1.1 cm	--	--	--
Post-op RC	2.3 ± 0.5 cm	--	--	--
Final follow-up	2.1 ± 0.8 cm	--	--	--
Lumbar Lordosis (LL)				
Pre-op	34.0 ± 33.9°	67.5°	50.7 ± 17.0°	43.7 ± 27.4°
Post-op RC	35.4 ± 15.0°	59.8°	33.4 ± 8.6°	36.6 ± 13.5°
Final follow-up	34.8 ± 12.3°	42.0°	37.4 ± 6.4°	36.5 ± 9.4°

Table 5. Fusion-Only RC Treatment Coronal Plane Radiographic Outcomes



	Kyphoscoliosis (N=9)	Scoliosis (N=1)	Total (N=10)
Coronal Cobb Angle			
Pre-op	66.8 ± 39.0°	65.0°	71.3 ± 36.9°
Post-op RC fusion	39.1 ± 31.7°	59.0°	46.2 ± 30.2°
Coronal T1 Tilt			
Pre-op	20.2 ± 13.4°	13.1°	18.8 ± 12.8°
Post-op RC fusion	8.8 ± 6.3°	4.7°	8.8 ± 6.1°
Coronal Vertical Axis (CVA)			
Pre-op	3.3 ± 2.7 cm	4.2 cm	3.8 ± 2.6 cm
Post-op RC fusion	1.9 ± 2.0 cm	4.2 cm	2.6 ± 1.9 cm
Apical Vertebral Translation (AVT)			
Pre-op	6.4 ± 3.3 cm	8.7 cm	6.3 ± 3.2 cm
Post-op RC fusion	4.0 ± 2.9 cm	7.5 cm	4.1 ± 3.0 cm
Clavicle Angle (CA)			
Pre-op	8.2 ± 5.2°	2.9°	7.6 ± 5.2°
Post-op RC fusion	3.8 ± 3.9°	0.6°	3.4 ± 3.8°
Spinal Height (T1-S1)			
Pre-op	33.3 ± 7.2 cm	37.6 cm	32.9 ± 7.0 cm
Post-op RC fusion	38.4 ± 6.3 cm	36.9 cm	37.2 ± 5.9 cm
Thoracic Spinal Height (T1-L1)			
Pre-op	20.3 ± 4.4 cm	26.7 cm	20.5 ± 4.7 cm
Post-op RC fusion	24.9 ± 4.7 cm	25.5 cm	24.1 ± 4.4 cm
Total Lung Capacity (TLC)			
Pre-op	1.9 ± 1.6 L	3.0 L	2.0 ± 1.5 L
Post-op RC fusion	2.3 ± 1.3 L	3.3 L	2.4 ± 1.2 L

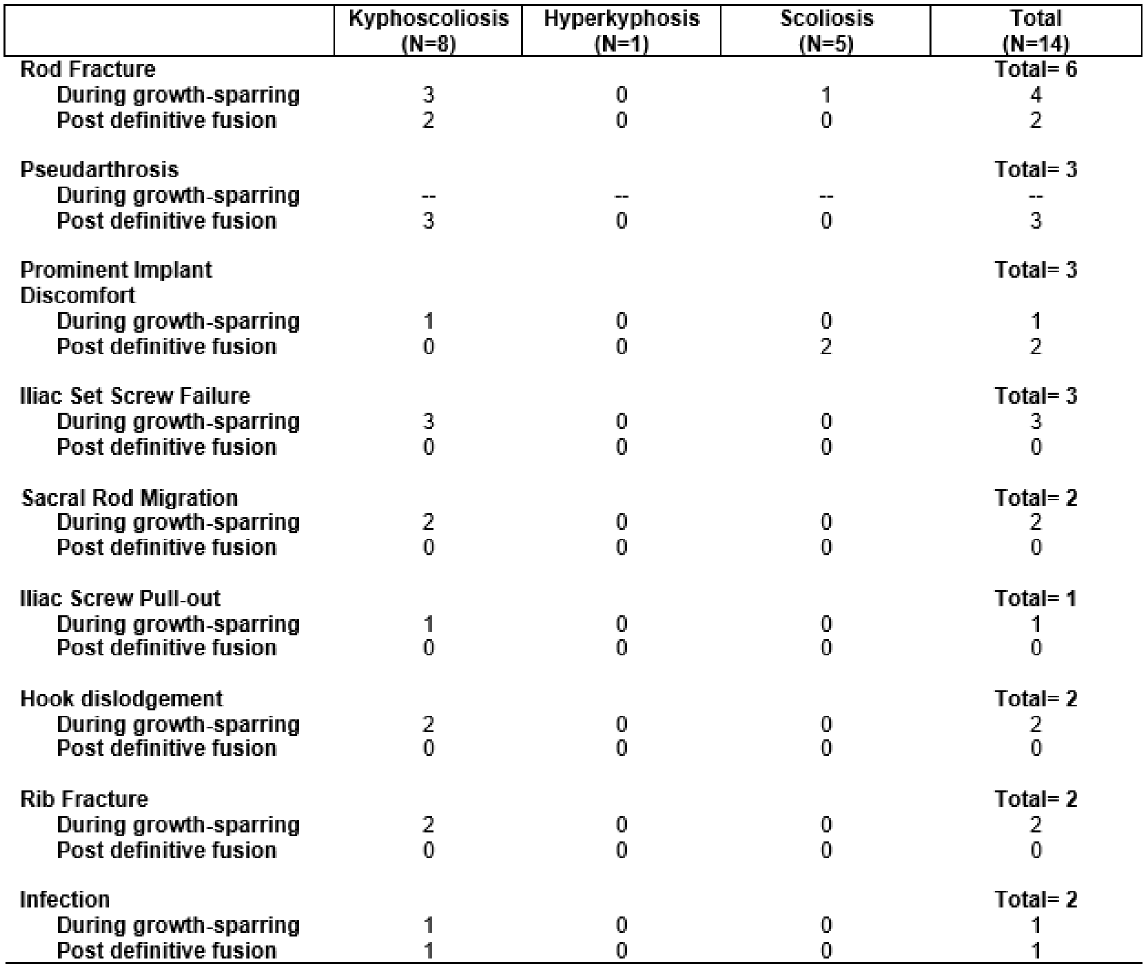
Table 6. Fusion-Only RC Treatment Sagittal Plane Radiographic Outcomes

	Kyphoscoliosis (N=9)	Scoliosis (N=1)	Total (N=10)
Sagittal Cobb Angle			
Pre-op	104.9 ± 30.0°	26.4°	99.0 ± 38.1°
Post-op RC fusion	54.9 ± 29.7°	16.3°	54.6 ± 31.0°
Sagittal T1 Tilt			
Pre-op	57.9 ± 19.5°	21.8°	55.2 ± 21.8°
Post-op RC fusion	41.4 ± 13.2°	12.7°	39.3 ± 15.6°
Sagittal Vertical Axis (SVA)			
Pre-op	4.2 ± 4.7 cm	8.0 cm	4.6 ± 4.5 cm
Post-op RC fusion	0.7 ± 3.5 cm	9.6 cm	1.5 ± 4.4 cm
Pelvic Tilt (PT)			
Pre-op	20.8 ± 12.4°	29.9°	20.1 ± 12.2°
Post-op RC fusion	19.2 ± 12.7°	23.3°	18.9 ± 12.0°
Pelvic Incidence (PI)			
Pre-op	45.8 ± 13.1°	56.3°	47.9 ± 12.7°
Post-op RC fusion	47.3 ± 8.4°	52.7°	46.4 ± 8.2°
Sacral Slope (SS)			
Pre-op	27.5 ± 19.7°	27.7°	31.4 ± 18.5°
Post-op RC fusion	29.4 ± 13.9°	23.6°	31.0 ± 13.3°
C2-C7 Angle			
Pre-op	21.4 ± 17.6°	9.6°	19.0 ± 16.8°
Post-op RC fusion	14.3 ± 15.4°	6.5°	12.4 ± 14.5°
C2-C7 Sagittal Vertical Axis			
Pre-op	4.5 ± 2.2 cm	4.0 cm	4.8 ± 2.1 cm
Post-op RC fusion	3.4 ± 2.2 cm	2.7 cm	3.7 ± 2.1 cm
Lumbar Lordosis (LL)			
Pre-op	60.0 ± 21.7°	34.3°	60.5 ± 22.5°
Post-op RC fusion	48.5 ± 17.3°	24.5°	49.9 ± 18.8°

Complications

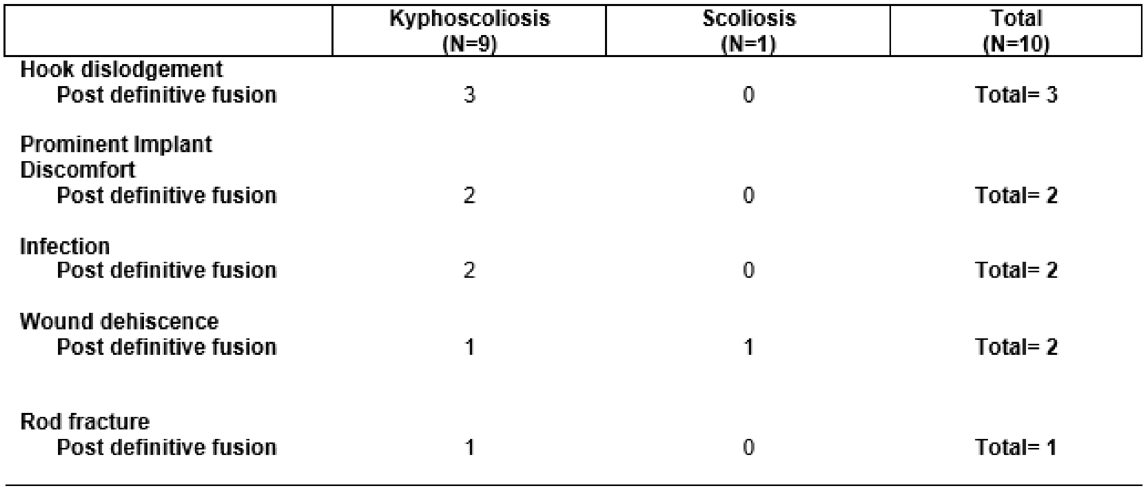
The group as a whole was medically fragile, with severe spinal deformity, osteoporosis, and many other medical comorbidities. There were a total of 34 complications. There were 16 complications during growth-sparing treatment with the rib construct, with a complication rate of 1.75, 0.0 and 0.4 complications per patient in the kyphoscoliosis, hyperkyphosis, and scoliosis groups respectively. There were 18 complications post-definitive fusion in the entire study, with a complication rate of 0.94, 0.0, and 0.33 complications per patient in the kyphoscoliosis, hyperkyphosis, and scoliosis groups respectively. The most common complications were rod fracture (7), hook dislodgement (5), and prominent implant discomfort (5). Four rod fractures occurred during growth-sparing treatment with the rib construct, at a rate of 0.38, 0.0, and 0.2 per patient in the kyphoscoliosis, hyperkyphosis, and scoliosis groups respectively. The next most common complications were infection (4), pseudarthrosis (3), and iliac set screw failure (3). One pseudarthrosis followed a repeat insertion of a rib construct placed one year after removal for a delayed deep wound infection. A second occurred under a synovial cyst overlying the thoracic spine, which blocked any posterior vasculature of the fusion mass. There was no proximal junctional kyphosis, no changes in intra-operative neuromonitoring, no complications that induced neurological deficits, and no intercostal neurovascular injury. A comprehensive list of complications can be found in **Table 7 and 8**.

Table 7. Growth-Sparing RC Treatment Complications



	Kyphoscoliosis (N=8)	Hyperkyphosis (N=1)	Scoliosis (N=5)	Total (N=14)
Rod Fracture				Total= 6
During growth-sparring	3	0	1	4
Post definitive fusion	2	0	0	2
Pseudarthrosis				Total= 3
During growth-sparring	--	--	--	--
Post definitive fusion	3	0	0	3
Prominent Implant Discomfort				Total= 3
During growth-sparring	1	0	0	1
Post definitive fusion	0	0	2	2
Iliac Set Screw Failure				Total= 3
During growth-sparring	3	0	0	3
Post definitive fusion	0	0	0	0
Sacral Rod Migration				Total= 2
During growth-sparring	2	0	0	2
Post definitive fusion	0	0	0	0
Iliac Screw Pull-out				Total= 1
During growth-sparring	1	0	0	1
Post definitive fusion	0	0	0	0
Hook dislodgement				Total= 2
During growth-sparring	2	0	0	2
Post definitive fusion	0	0	0	0
Rib Fracture				Total= 2
During growth-sparring	2	0	0	2
Post definitive fusion	0	0	0	0
Infection				Total= 2
During growth-sparring	1	0	0	1
Post definitive fusion	1	0	0	1

Table 8. Fusion-Only RC Treatment Complications



	Kyphoscoliosis (N=9)	Scoliosis (N=1)	Total (N=10)
Hook dislodgement			
Post definitive fusion	3	0	Total= 3
Prominent Implant Discomfort			
Post definitive fusion	2	0	Total= 2
Infection			
Post definitive fusion	2	0	Total= 2
Wound dehiscence			
Post definitive fusion	1	1	Total= 2
Rod fracture			
Post definitive fusion	1	0	Total= 1

Case reports

Case 1: A 12-year-old boy with VATER Syndrome, had a 70° thoracic curve at age 5, had rapid deterioration at age 12 with severe rigid kyphoscoliosis. His pre-operative radiographic measurements were 73° thoracic scoliosis, 72° thoracolumbar scoliosis, and 102° thoracic hyperkyphosis. He had progressive osteoporosis with a T score -3.9. Conventional instrumentation failed and was not tolerated by the patient (**Figure 25, top panel**). He was treated with a growth-sparing rib construct, which completely corrected his hyperkyphosis, greatly improved his scoliosis, and leveled his shoulders and pelvis (**Figure 25, middle panel**). Once skeletal maturity was reached, definitive fusion was performed, leaving the rib construct in place on the concave side. His rib construct was prominent on the convex side, so it was replaced with pedicle screws (**Figure 25, bottom panel**).

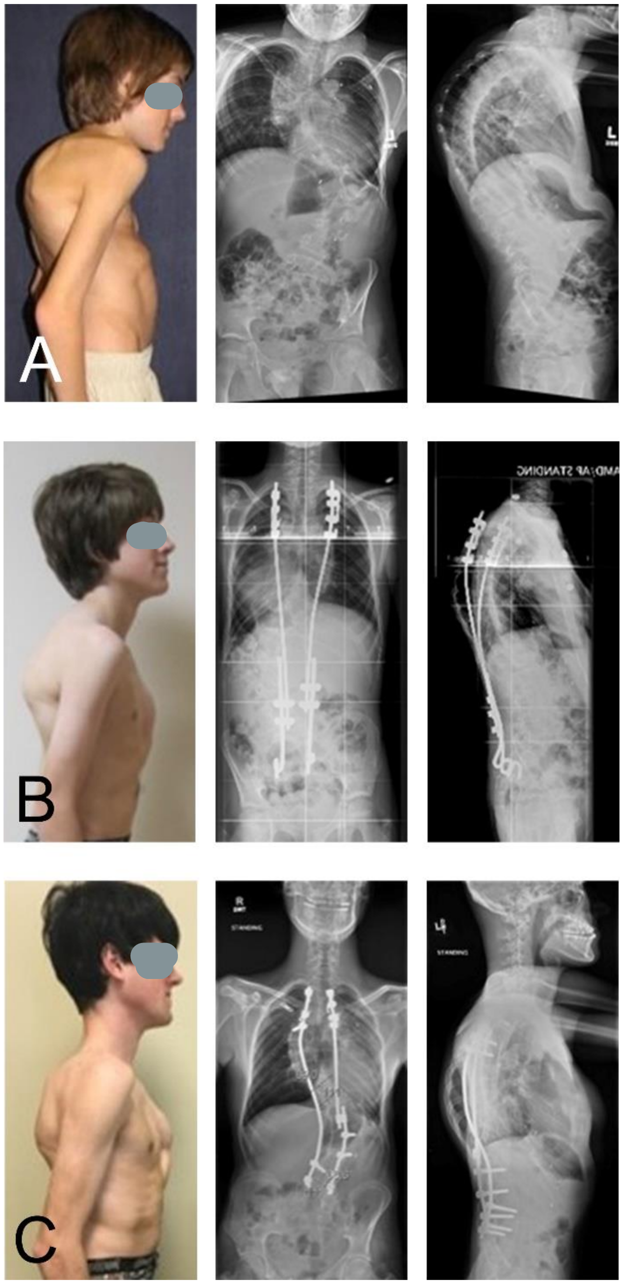


Figure 25. Rib construct treatment for kyphoscoliosis. **A**) Pre-op, **B**) post-op, **C**) final follow-up.

Case 2: An 11-year-old boy with spastic quadriparesis had severe hyperkyphosis of 130° with his head positioned towards his groin area (**Figure 26 A,C**). He was severely osteoporotic with a T score -4.6. A rib construct was placed (**Figure 26 B,D**). His hyperkyphosis was completely corrected and he was able to sit up in his chair.

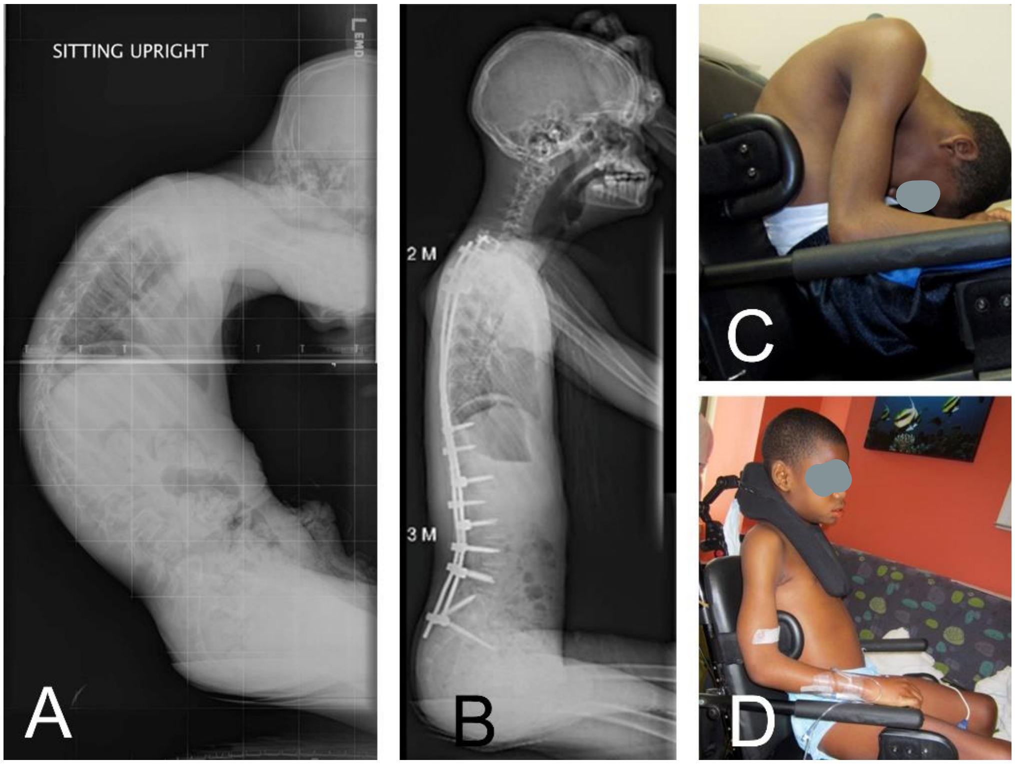


Figure 26. Rib construct treatment for hyperkyphosis. **A and C**) Pre-op, **B and D**) post-op.

5.4 Discussion

The rib construct effectively corrects spinal deformity

Radiographic results indicate that growth-sparing treatment with the rib construct provides similar coronal plane Cobb angle scoliosis correction and superior sagittal plane hyperkyphosis correction compared to growing rods with pedicle screws and VEPTR. In addition to improvements in coronal and sagittal Cobb angles, other parameters of trunk, shoulder, neck and head alignment improved as well. Since the rib construct allows the surgeon to manipulate the whole thorax as a unit, rather than just the spine, the rib construct is highly effective at correcting trunk, shoulder, neck and head malalignment. This was supported by notable improvements in coronal and sagittal T1 tilt, clavicle angle (CA), sagittal vertical axis (SVA), C2-C7 angle, and C2-C7 sagittal vertical axis (SVA). Critically, by manipulating the thorax instead of the spine, the important posterior midline spinal ligaments remain intact and act as a tether. When hyperkyphosis is corrected, these preserved ligaments pull the head and neck into a more upright position, resulting in substantially improved forward gaze of the head.

The rib construct supports spinal growth and pulmonary development

By directly manipulating the rib cage and extending the thorax, the rib construct appears to provide more lung space. This study documented improvements in total lung capacity in hyperkyphotic patients, measured by radiographs, after treatment with the rib construct. This is especially important for patients who have compromised respiratory function due to generalized muscle weakness. Furthermore, because the rib construct uses extra-spinal fixation to the ribs, it avoids spinal fusion of fixation sites and auto-fusion of other levels, thus maximizing natural spinal growth and pulmonary development. Excellent improvement in spinal height (T1-S1) and thoracic spinal height (T1-L1) were observed. No auto-fusion was observed in any patient. These findings indicate that manipulation of the trunk with the rib construct creates more space available for the lungs and preserves spinal growth. Finally, because the rib construct is less rigid compared to growing rods with pedicle screw fixation, fewer lengthening surgeries are needed to preserve spinal growth. Motion at the costo-vertebral joint and micromotion at the rib-hook interface allows for more growth of the spinal in between lengthening procedures. In contrast, pedicle screws are very rigid and attach directly to the spine, thus more lengthening procedures are needed. With pedicle screws, lengthening surgeries are needed approximately every 6-8 months. With the rib construct, lengthening surgeries with performed every 8-12 months.

The incidence of the most troublesome complications associated with treatment of EOSD are dramatically reduced with the rib construct

The clinical study group was medically fragile, with etiologies and severity of deformity associated with high complication rates.[100] Therefore, although this series is small, it represents the most challenging portion of the spectrum of severity for early-onset spinal deformity. The complication rate was comparable with other studies, but notable in the lack of proximal junctional kyphosis (PJK). In fact, the chin brow angle was improved in 3 patients with pre-exising proximal junctional kyphosis following failed prior fusions. We submit that the less rigid nature of rib fixation as well as the maintenance of the posterior spinal ligaments was responsible for the lack of proximal junctional kyphosis. The reported incidence of proximal junctional kyphosis resulting from treatment is generally around 25-28% with both growing rods and VEPTR.[101,102] All of these studies report thoracic hyperkyphosis as a risk factor. Thus, the absence of proximal junctional kyphosis in this series is particularly notable. In this series, there was also a notable lack of neurological injuries or neuromonitoring changes. This avoidance of neurological complications was likely due to the fact that the rib construct does not require manipulation of structures close to the thoracic spinal cord.

The rib construct may reduce the need for halo gravity traction (HGT) and osteotomy techniques such as vertebral column resection (VCR)

The higher corrective forces that can be safely applied with the rib construct reduce the need for halogravity traction (HGT) and osteotomies in definitive fusion cases. HGT is a technique that can be used pre-operatively where traction is applied to the spine through a metal ring (halo) that is attached to the patient's head. This is typically used for patients with large rigid curves, with the goal of stretching out the spine slowly over a period of weeks prior to surgery. Osteotomies of the posterior spinal structures are currently being performed with increasing frequency for all types of pediatric deformity.[103-105] Although generally safe in experienced and skilled hands, they are associated with increased blood loss, neuromonitoring changes, and possible neurological injury.[106] Vertebral column resection (VCR) is a particularly invasive osteotomy technique that is widely utilized as a corrective measure for spinal deformity. We show that the use of the rib construct may lessen the need for HGT, VCR, and other types of osteotomies. HGT was used for no patients in this series, and the only patients in this series for whom osteotomies were performed were those with a prior fusion, indicating substantial correction is possible without their use.

The rib construct is easier to implant compared to growing rods with pedicle screw fixation to the thoracic spine, and this may have a global impact

Implantation of the rib construct was convenient, less technically demanding, and required reduced need for intra-operative fluoroscopic imaging and intra-operative neuromonitoring compared to growing rods with pedicle screws. There was also no need for osteotomies during fusion procedures. This makes the rib construct a particularly attractive option in developing nations around the globe, where access to physicians with adequate training in pedicle screw placement, expensive imagining and neuromonitoring equipment, and complicated osteotomy techniques may not be readily available. Thus, millions of children around the world currently going untreated could have a viable treatment option with the rib construct.

Potential problems with the rib construct and insights from this study

In comparison to spinal fixation, does rib fixation require a larger surgical area and increase post-op recovery time?

Rib fixation did require dissection further laterally (approximately 1cm further) from the midline. However, this is actually a benefit because it allows the surgeon to avoid disturbing the paraspinal muscles and ligaments directly along the thoracic spine. Instead, a subcutaneous dissection can be performed laterally until the appropriate area is reached over the ribs, and then the dissection is taken deeper down to the ribs. Our clinical data indicates that this preservation of paraspinal muscles and ligaments actually speeds up recovery time and decreases risk of proximal junctional failure. In our series of 24 patients, operative time was 5:00 ± 1:30 hours and blood loss only 277 ± 159 mL, which are impressive results for EOSD surgery. No patients had prolonged recovery time after surgery.

Does the rib construct lack the rigidity needed for spinal fusion?

Biomechanical testing results confirmed that the rib construct is less stiff compared to pedicle screw fixation. This has numerous advantages during growth sparing treatment for early-onset spinal deformity, including reducing the risk of spinal auto-fusion, rod fracture, proximal junctional kyphosis, as well as decreasing the number of lengthening surgeries needed and increasing the amount of time between each surgery. However, contrary to growth sparing surgery, for spinal fusion surgery when a patient reaches skeletal maturity, it is beneficial for the construct to be more stiff to promote formation of the bony fusion mass with bone graft. Movement of the spine disrupts this process. Since the rib construct is less stiff than pedicle screw fixation, it was unclear whether rib fixation would be appropriate for this process. Most of the patients in this study underwent fusion at the end of their treatment with the rib construct. There were 3 patients that developed pseudarthrosis (failure of spinal fusion). There were also 3 cases of hook dislodgement after fusion, and 3 rod fractures. These results suggest that although the rib construct is an attractive option for growth sparing treatment, it may be better to use traditional pedicle screws as the primary form of fixation for spinal fusion surgery. However, rib hooks could also supplement pedicle screw fixation in fusion surgery to prevent proximal junctional kyphosis (discussed in **Chapter 6**).

Does the rib construct cause implant prominence?

There is slightly less soft tissue coverage over the ribs compared to the spine. Thus, there is the possibility of implant prominence with the rib construct, where the impants can be felt through the skin and cause discomfort. This occurs sometimes with VEPTR as well. Implant prominence did occur in 5 patients in this study. These patients tended to be especially thin with minimal fat and muscle coverage over their implants. This complication could be reduced by lowering the profile of the implants in future designs, and also avoiding use of the rib construct in extremely thin patients.

Does the rib hook-tissue interface have long term stability in comparison to pedicle screws?

While there are many advantages to rib fixation, there are some potential disadvantages as well. One unknown prior to this study was whether rib hooks would have long term stability compared to pedicle screws, or if the hooks would be prone to dislodgement, migration, rib fracture, etc. The patients in this study had long term stability of their instrumentation. Furthermore, after we published the initial case study for this technique, it has been used in over 200 additional patients worldwide with promising results. Thus, this technique has been tested in humans with long term follow-up, and the device-tissue interface does have long term stability. In our study, we did experience 5 cases of hook dislodgement, which occurred at a lower rate than pedicle screw failure in previous studies on similar patient populations. When hook dislodgment occurred, it was corrected with revision surgeries to place the hook back in the proper location. There were also 2 cases of rib fracture in severely osteoporotic patients. It is likely that the incidence of hook dislodgment and rib fracture could be reduced by improved implant design (**Chapter 6**).

One limitation of this study is small sample size for the clinical study. However, because this is a novel technique, small sample size is appropriate for preliminary data to support safety and efficacy. Another limitation is the fact that this was not a case control clinical trial. There was no control group with pedicle screws for growing rods or fusion. Most of the patients treated with the rib construct were challenging cases, and four had previously been unsuccessfully treated with growing rods and pedicle screws. It would have been difficult to justify continued treatment of these patients with growing rods, knowing that they would likely fail. Despite these limitations, this paper clearly demonstrates that the rib construct is safe and effective. The rib construct may be a substantial advancement in the treatment of children with spinal deformity around the globe, especially in cases that involve EOSD and kyphoscoliosis.

Chapter 6. Creation of R-FIX (Rib-FIXation) System for Rib Construct Technique

6.1 Introduction

Rib fixation with the rib construct can be achieved with either: 1) off-label laminar hooks, which are already commercially available for spinal fixation to the lamina but can also be used on the ribs, or 2) rib hooks as part of our novel R-FIX (Rib-FIXation System). We published the first case report using off-label laminar hooks for the rib construct, and since then over 200 patients have been successfully treated by other surgeons at various institutions. While laminar hooks have performed favorably compared to pedicle screws, these have been used entirely off-label for the rib construct and there is no commercially available surgical system designed for this technique. Thus, access to this technique by surgeons is limited. Furthermore, our preliminary clinical and biomechanical data have found that although off-label laminar hooks performed favorable compared to pedicle screws, they were not without problems. Laminar hooks are designed for spinal fixation to the lamina, not the ribs. The most superiorly placed laminar hooks are prone to slipping off the rib which caused 5 incidences of proximal fixation failure in our series of 24 patients. The narrow design of laminar hooks also causes relatively

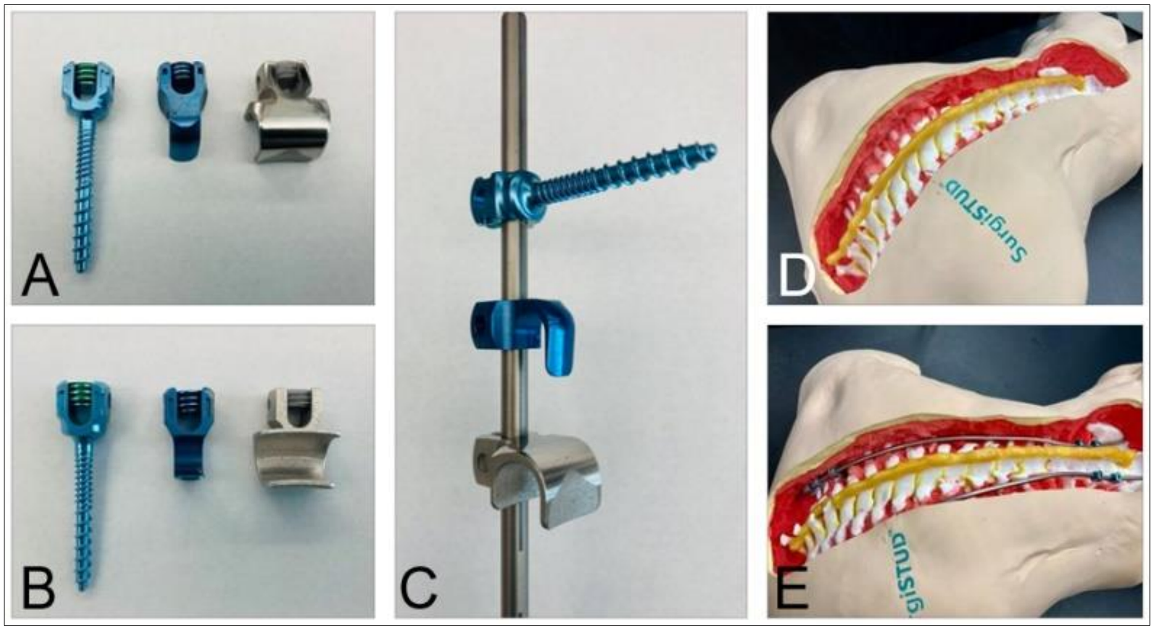


Figure 27. **A-C**) pedicle screw (left), laminar hook (middle), R-FIX rib hook (right). Compared to the laminar hook, the R-FIX rib hook has a wider blade to distribute stress more evenly across the rib, curvature/dimensions to match the anatomy and geometry of the rib, and is lower profile to avoid implant prominence through the skin. **D**) SpineSTUD surgical training model with hyperkyphosis. **E**) SpineSTUD model with hyperkyphosis corrected with R-FIX System. R-FIX rib hooks used for proximal fixation, and pedicle screws used for distal fixation. Spinal alignment is now normal.

high stress at the rib-implant interface, and 2 rib fractures were observed in patients that were severely osteoporotic. Lastly, the current laminar hooks have a higher profile than what would be ideal and can sometimes result in minor or moderate implant prominence through the skin, which occurred in 3 patients. The R-FIX System by Apex Orthopedic Technologies is designed to resolve these issues. Our surgical system includes rib hooks, rods, and all necessary equipment to perform this surgical technique with a user-friendly interface (**Figure 27**). Our rib hooks have a curved blade that is wider than laminar hooks and matches the unique anatomy and geometry of the ribs, thus minimizing risk of loss of fixation, rib fracture, and other mechanical failures. The rib hooks are also lower profile to avoid implant prominence. **Development of this surgical system is absolutely critical for widespread dissemination of the rib construct technique, as well as important**

for maximizing safety and efficacy. In October 2019 Clemson University obtained a utility patent for hooks designed specifically for rib fixation (**United States Patent 10,441,321**). This patent also includes a connector device that pairs rib fixation with spinal fixation.

6.2 Company Overview

Apex Orthopedic Technologies is a start-up orthopedic device company that produces a new surgical device called the R-FIX (Rib-FIXation) System, which utilizes rib fixation for the treatment of early onset spinal deformity and certain types of adult deformity. The rib construct concept was conceived when Dr. Gross (member of our research team) was faced with managing a child with VATER syndrome and a rapidly progressive kyphoscoliotic deformity and concurrent osteoporosis. For this patient, the combination of severe kyphoscoliosis and osteoporosis portended failure of spinal fixation with pedicle screws. At the time, rib fixation with the VEPTR device had been introduced with the initial goal of managing thoracic insufficiency syndrome and subsequently expanded to treating EOSD. However, the fixed radius of the VEPTR instrumentation renders it ineffective for hyperkyphotic deformity. Nevertheless, work with VEPTR had demonstrated that the ribs can provide multiple strong anchor points without the need for direct spinal instrumentation. This inspired Dr. Gross (a pediatric orthopaedic surgeon at MUSC) and Dr. Yao (a bioengineer in the Clemson-MUSC Bioengineering Program) to devise a rib construct utilizing this favorable feature and adapting it for hyperkyphotic and kyphoscoliotic deformities. The patient was treated with a growth-sparing rib construct with laminar hooks, which completely corrected his hyperkyphosis, greatly improved his scoliosis, and leveled his shoulders and pelvis. The case report was published in the Journal of Pediatric Orthopaedics in 2012. Since then, we have been refining the rib construct concept through clinical, biomechanical, and animal studies, resulting the R-FIX (Rib-FIXation) System which was patented in 2019 through the Clemson University Research Foundation (CURF). We founded a company named Apex Orthopedic Technologies with a goal to translate the R-FIX into a mature technology that is ready to be manufactured, marketed, and distributed. Our multi-disciplinary team is ideally suited to conduct this work. Dr. Yao is the PI of our Clemson-MUSC bioengineering lab, which specializes in engineering design, 3D-printing of orthopaedic implants, and biomechanics. The lab is located on the Medical University of South Carolina campus. Dr. Yao is also the director for the SC COBRE for Translational Research Improving Musculoskeletal Health (SC-TRIMH, P20GM130451). Dr. Gross is the chief technology officer at Apex Orthopedic Technologies and is a professor emeritus of pediatric orthopedic surgery at MUSC. Dr. Kalhorn is an attending neurosurgeon and professor at MUSC, and serves as a consultant for Apex Orthopaedic Technologies. Daniel Bonthius, co-mentored by Drs. Yao and Gross, is an MD-PhD student with a strong interest and background in pediatric orthopedics and is chief operating officer. He received the Spine Section Podium Award with this project at the 2020 ORS meeting and 2nd place in the Business Innovation Competition at the 2022 ORS meeting. Our group has access to a Clemson machine shop fabrication lab, multiple mechanical testing systems, and a fully equipped anatomy lab, animal care facility, and OR at MUSC.

6.3 Preliminary Market Analysis

Market segments

There are four main types of spinal deformity. 1) Hyperkyphosis is exaggerated anterior curvature of the spine in the sagittal plane. 2) Scoliosis is curvature of the spine in the coronal plane. 3) Lordosis is exaggerated posterior curvature of the spine in the sagittal plane. 4) Rotational deformity is torsion of the spine in the axial plane. Spinal deformity frequently occurs in three dimensions, involving a combination of the above. Spinal deformity can be further divided based on age of onset including adult and childhood spinal deformity. Childhood spinal deformity can be further divided into infantile (0-3 years old), juvenile (4-9 years old), and adolescent (10-16 years old). Infantile and juvenile spinal deformities collectively are called early-onset spinal deformity (EOSD). Finally, these categories can be further subdivided based on etiology including idiopathic, congenital, neuromuscular, infectious, syndromic, traumatic, degenerative, or postural. The R-FIX system can be used to treat any type of thoracic deformity mentioned above. However**, it is particularly useful for EOSD and also adult deformity at risk of developing PJK.**

Customer profile

The proposed R-FIX system can be used to treat any type of patient population mentioned above. However, the R-FIX system is particularly useful for EOSD, and adult deformity at risk of developing PJK, such as patients with substantial residual kyphosis or T9/T10-pelvis fusion patients. These groups experience unacceptably high complication rates with surgery. The R-FIX directly addresses the need to develop a new way to manage these deformities in a way that reduces instrumentation-related complication rates and enhances deformity correction. We have already gained some traction in getting several surgeons outside of our research group to embrace the R-FIX pilot technique with off-label laminar hooks, and this will be accelerated by converting the pilot technique into a mature technology that is designed specifically for the ribs. The actual costumer will be outpatient surgery centers and hospitals, with the product delivered in metal instrument cases, autoclaved prior to surgery, as is typical with pedicle screw systems.

Market trends

Adult scoliosis has a prevalence of 8%, which increases to 68% in adults over the age of 60.[98] Infantile, juvenile, and adolescent scoliosis has a prevalence of 0.03%, 0.6%, and 3% respectively. Adult hyperkyphosis has a prevalence between 20-40% with populations over the age of 60 showing the highest prevalence.[32] Childhood hyperkyphosis has a prevalence of 1-8%.

There are nearly 20,000 adults that undergo spinal fusion for adult spinal deformity including both scoliosis and hyperkyphosis in the United States alone, with average hospital charges of $188,727 per patient.[107] Market size is $3.7B for adult spinal deformity surgery. Nearly 30,000 adolescents undergo surgery for spinal deformity every year costing $92,000 per patient.[108,109] Market size is $2.8B for adolescent spinal deformity. Epidemiological data on the number of early-onset spinal deformity surgeries performed every year for infantile and juvenile spinal deformity is not available. However, early-onset spinal deformity is more likely to require surgery than adult or adolescent cases and the average cost of treatment is $149,234. Thus, the market size is substantial.

Over 100,000 children are diagnosed with spinal deformity each year, and the consensus among scoliosis surgeons is that children with severe scoliosis >45-50° and hyperkyphosis >70° will need surgery to lessen the curve and prevent it from getting worse. Posterior fusion with instrumentation is the most common surgical approach (75%). Pedicle screw instrumentation has thus far been the standard of care in management of pediatric spinal deformity.

However, there is a rise in distraction-based techniques. The R-FIX can serve as either a distraction-based device or posterior fusion. The distraction-based “growth friendly” strategy is where the field appears to be trending in early-onset spinal deformity patients, as adjustments to the device can be made to mimic normal growth.

The growth of the spine deformity treatment market is mainly driven by high prevalence of the disease, and advancement of technology to meet demand for non-invasive therapies. The Americas are projected to dominate the market during the forecast period, due to the increasing per capita healthcare expenditure and the high adoption of new technology in the region. Rising cases of spinal deformity in the US and Canada are also expected to drive the market.

The global spine surgery devices market is forecasted to exceed $17 billion by 2021 and grow at 5.3% annually. Major companies in the spine devices market include Medtronic, Depuy Synthes (Johnson & Johnson), NuVasive, Stryker, Globus Medical, Zimmer Biomet, Aesculap, Alphatec Spine, Seaspine and Orthofix. These companies account for 90% of the spine market, with the remaining 10% market share distributed among approximately 400 other companies. Market size is $2.8B for adolescent spinal deformity. Epidemiological data on the number of early-onset spinal deformity surgeries performed every year for infantile and juvenile spinal deformity is not available. However, early-onset spinal deformity is more likely to require surgery than adult or adolescent cases and the average cost of treatment is $149,234. Thus, the market size is substantial. An emerging treatment for EOSD is the MAGEC X System launched by NuVasive in 2018. MAGEC X is a growing rod system similar to standard growing rods. However, this system is extendible via an external remote-control system. Thus, the need for repeated lengthening procedures is eliminated. We intend to make the R-FIX rib hooks compatible with the MAGEC system so they can be used together. This could be a potential strategic collaboration between our group and NuVasive, and NuVasive representatives have already expressed interest in collaboration with us at the 2019 and 2020 Orthopaedic Research Society annual meetings. MAGEC has an addressable market of 690,000 annual procedures, worth up to $570 million in global annual revenue. Additionally, while the focus of our efforts have been for treatment of early-onset spinal deformity, we believe R-FIX can also be applied to more common adult procedures as well. Several of our clinical collaborators have expressed interest in using rib fixation with R-FIX to supplement pedicle screw fixation in T9-pelvis fusions for adult deformity, in order to prevent proximal junctional kyphosis.

Competitive analysis

***Growth sparing surgery*:** Growth sparing surgery is used to correct spinal deformity in skeletally immature early-onset spinal deformity patients while preserving spinal growth.

Growing rods with pedicle screw fixation: Growing rods are a distraction-based construct that provide a means for the surgeon to straighten the spine, while allowing for spinal growth with serial lengthening procedures. Growing rods are anchored using pedicle screws or claw hooks proximally to the spine, and distally to the spine or pelvis. The construct can be lengthened by sliding the rod through a connector in a series of lengthening procedures. These serial lengthening procedures are typically performed once every 6-8 months as the child grows. Single or dual growing rod constructs may be used. At the end of the serial lengthening process, growing rods can be replaced with standard dual rod instrumentation for definitive fusion. Complication rates for distraction-based treatments are high. Studies have reported variable results when quantifying complication rates, but generally range from 0.38-2.06 complications per patient, with the most common complications being rod breakage, proximal fixation site loosening, migration, or dislodgement, infection, and prominent implant.

VEPTR: VEPTR (vertical expandable prosthetic titanium rib), like growing rods, is a distraction-based system that allows for correction of the scoliotic spinal deformity, while preserving growth. The VETPR is produced by DePuy Synthes, which is part of the Johnson & Johnson family of companies. VEPTR is only FDA cleared for the treatment of spinal deformity originating from thoracic insufficiency syndrome (TIS), which is a small subcategory of early-onset spinal deformity cases. However, it is used off-label to treat a larger number of patients. The spine is stabilized by the insertion of a unilateral or bilateral rib-to-spine or rib-to-pelvis VEPTR, and another rib-to-rib VEPTR may provide additional support. The construct is lengthened every 4-6 months as the child grows. It is preferable to continue this until skeletal maturity, upon which a final fusion is performed. VEPTR is effective for scoliosis but it is pro-kyphotic and difficult to contour in the sagittal plane, and actually makes hyperkyphosis worse.

Emerging technologies: Several other growth-sparing treatments for early-onset spinal deformity exist, but are not commonly used. Anterior shape-memory alloy (SMA) staples and anterolateral spinal tethering can inhibit growth on the convex side of the deformity while the concave side continues to grow. As a result, the spine may straighten over time. However, these techniques are indicated only for curves of moderate magnitude (<45°).

The MAGEC system produced by NuVasive is a distraction-based implant, similar to standard growing rods. However, this system is extendible via an external remote-control system. Thus, the need for repeated lengthening surgeries is eliminated. This technology has just begun to gain some traction in the United States in the last several years, and preliminary studies have demonstrated favorable outcomes. However, there have been some reported issues with metallosis from the implant. MAGEC also has issues with implant fit in hyperkyphotic patients, since the remotely controlled extendible portion cannot be contoured and remain functional. MAGEC is also prone to similar implant related complications as growing rods. We intend to make the R-FIX rib-hooks compatible with the MAGEC system so that they can be used together. This could be a potential strategic collaboration between our group and NuVasive, and NuVasive representatives have already expressed interest in collaboration with us.

Non-growth sparing surgery (definitive spinal fusion): This type of surgery is used to correct spinal deformity in skeletally mature patients. Rods are anchored using pedicle screws or claw hooks to the spine. The rods are contoured to realign the spine and bone graft is placed to fuse the corrected segments of the realigned spine. Initial cost is similar to growing rod surgery, but lengthening procedures are not needed. Overall this treatment works well but it cannot be used to treat patients with early-onset spinal deformity because doing so would result in premature stunted growth, disproportionate body habitus, and inhibited cardiopulmonary development.

Larger Market Opportunity: Rib construct R-FIX (Rib-FIXation System) for adult deformity

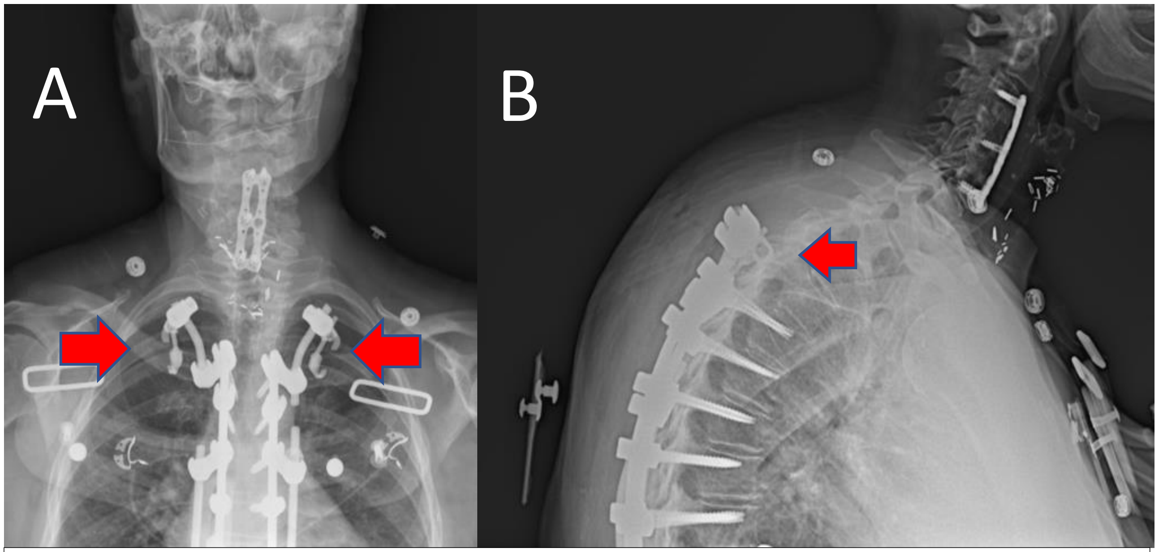


Figure 28. (**A**) AP view of post-operative films demonstrating use of hooks on the ribs in a hyperkyphotic patient that would otherwise be prone to developing PJK if only pedicle screw fixation was used. (**B**) Lateral view of post-operative films demonstrating use of hooks on the ribs.

For adult deformity, we recommend using traditional pedicle screw-based constructs for primary fixation, since rigid spinal fixation is preferable to achieve reliable spinal fusion. However, in patients that are at high risk of developing proximal junctional kyphosis such as patients with substantial residual sagittal plane deformity and patients undergoing T9/T10-pelvis fusions, the pedicle screw fixation can be supplemented with rib fixation at the proximal end of the construct. This is achieved by pairing the proximal rods to hooks on the ribs with a connector (**Figure 28**). This rib fixation at the proximal end of the construct reduces the stiffness at the upper instrumented vertebrae compared to traditional pedicle-screw only constructs, and also decreased disruption of the posterior ligamentous and muscular support. The result is a decreased risk of developing proximal junctional kyphosis.

6.4 Intellectual Property

The Clemson University Research Foundation (CURF) and the Medical University of South Carolina – Foundation for Research Development (MUSC-FRD), jointly own the subject technology embodied in Confidential Invention Disclosure Form 2016-007 titled "Rib Apparatus and Associated Methods for Upper Thoracic Spine Instrumentation." **US Patent No. 10,441,321 titled "Rib Hook Devices, Systems, and Methods of Use"** issued on October 15, 2019 serves as the foundational IP covering the actual rib hook device and associated components of the complete system along with an independent claim covering a method of use. This utility patent has broad scope for the use of rib-hook fixation to correct spinal deformities. The following researchers/clinicians are named inventors on the patent: Dr. Hai Yao (Clemson), Gregory Wright (Clemson), and Dr. Richard Gross (MUSC). An Inter-Institutional Agreement is in place between CURF and MUSC-FRD with CURF serving as the marketing and licensing lead. Apex Orthopedic Technologies has a two-year option agreement with CURF to exclusively develop the R-FIX system. After this two-year option period, Apex will pursue a permanent exclusive license to the technology.

Additional design patents covering specific tools needed to surgically implant the rib hook device are expected soon along with copyrightable protection for accompanying surgical training aids (audio, visual, and print) that are currently under development.

6.5 Financial Plan

Grant funding and investment

We have already secured approximately $300,000 in funding to support this project, including grants from the Scoliosis Research Society, the Southeast Xlerator Group, the South Carolina Research Authority, South Carolina Clinical and Translational Research Institute, the MUSC TL1 program, and an F31 grant from the NIH. This has funded preliminary fabrication of R-FIX designs, biomechanical studies, animal model studies, and a retrospective clinical study. We hope to obtain additional $300,000 funding from an SBIR Phase I grant this year, and $1,000,000+ from a Phase II grant in 2023.

We have submitted an NIH SBIR Phase I grant application in the September 5th, 2021 cycle and scored well. We received an impact score of 28, which is a fundable score, and we are currently awaiting funding when it becomes available in the NIAMS budget. We were also recently awarded grants from SCRA and SCTR totaling $50K. In total, this funding combined with pending SBIR funding will likely be sufficient to get R-FIX through 510(k) clearance with the FDA. We will continue to pursue corporate investment from large medical device companies and foundation grant funding. We will seek to use synergies between R-FIX and the portfolios at existing companies, particularly NuVasive. Since R-FIX will be compatible with MAGEC from NuVasive, this will be a potentially mutually beneficial relationship. This will also allow us to leverage access to established manufacturing, sales and distribution channels, will enhance our company’s credibility, and will provide us with a built-in exit strategy. Ultimately, we may decide to either remain in a strategic partnership with a larger corporation or be acquired outright. Based on our preliminary manufacturing cost, operating expenses, and salary cost projections we anticipate that $1-3M investment is needed to get this technology to this exit point.

6.6 Regulatory Path and Reimbursement Strategy

In 2014, the FDA Center for Devices and Radiological Health CDRH cleared the VEPTR-VEPTRII device, which was reclassified as a Class II device and was considered substantially equivalent to other similar predicate devices through the 510(k)-approval process. Pedicle screws are also classified as a Class II device subject to 510(k) approval. The R-FIX regulatory approval documents will cite VEPTR and pedicle screws as primary predicate devices and pursue the same 510(k) regulatory pathways. The indications for this novel device are likely as follows: Treatment of patients with severe, progressive thoracic spinal deformities. The preparation for regulatory clearance of R-FIX will involve mechanical testing and development of labeling and sterilization protocol. Our already completed animal and human studies using the R-FIX pilot technique will also be used to supplement the 510(k) application. New animal and human studies will not be required. For reimbursement, CPT codes are already in place that will and have previously covered spine deformity surgery with the rib construct.

Based off the codes used for VEPTR, the CPT codes are as follows:

- For INITIAL surgery (first implanting the VEPTR device)

A) Rib-to-rib or Rib-to-pelvis: CPT 22189 unlisted thoracic (price based on 22840)

$800.07 national payment amount based on Medicare & Medicaid

B) Rib-to-spine: CPT 22899 Unlisted Spinal (price based on 22840)

$804.39 national payment amount based on Medicare & Medicaid

- For EXPANSION surgery: CPT 21899 unlisted procedure thorax (price based on 22849)

$1,359.76 national payment amount based on Medicare & Medicaid

- For EXCHANGE surgery: CPT 22899 (price based on 22849)

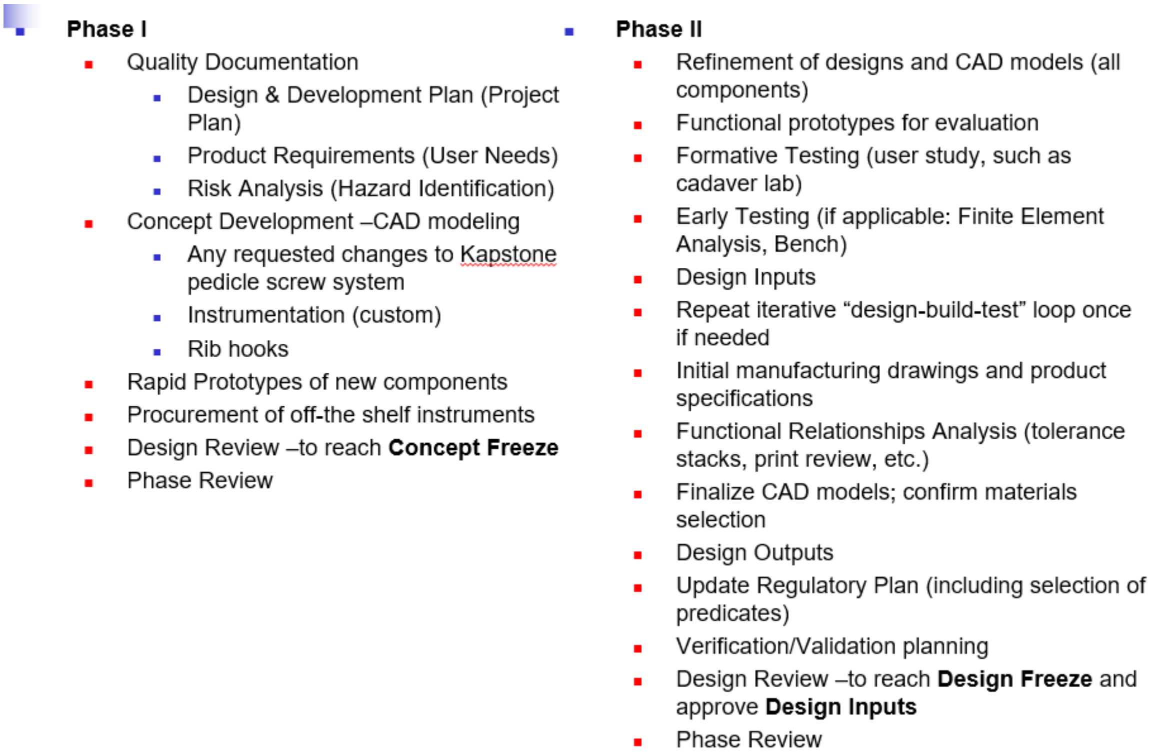
See above pricing ^

6.7 Production and Marketing Plan

Computer-aided design (CAD) files have been developed using SolidWorks (Dassault Software) for R-FIX rib hooks and set screws. Our initial prototypes have been machined using metal 3D printing with titanium in the Clemson Machining and Technical Services (MTS) center. The remainder of the R-FIX System instrumentation kit, including tools necessary for surgery, has been machined at Eaven Medical. Initial R-FIX prototypes have been tested in cadavers and artificial spine models and function appropriately (**Figure 27, 29)**.

Figure 29. Spinal surgery tool kit and spine deformity models for surgical simulation.

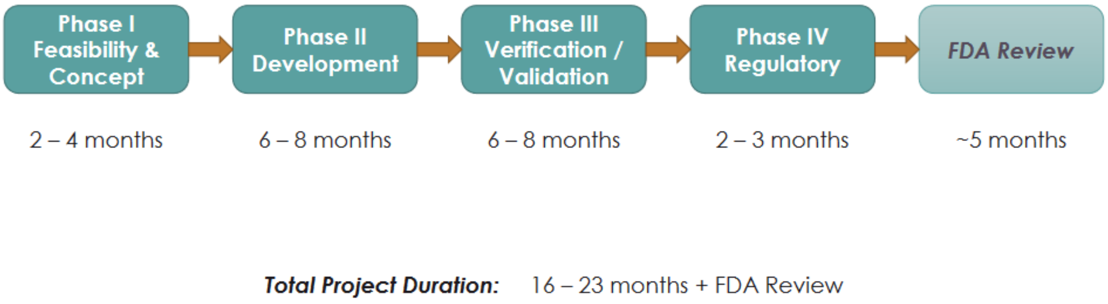
The design and development process will include a complete kit of implants and instruments specifically designed for the R-FIX spinal deformity correction system. Final components will be manufactured and undergo biomechanical and animal model testing with our already established animal model. A 510(k) application will be prepared for FDA clearance. Kapstone Medical, based in Charlotte, NC, is our consulting, manufacturing, and marketing firm. Kapstone will work in collaboration with our team at Apex to spearhead this project. The proposed timeline is as follows: Phase 1 Feasibility & Concept, Phase 2 Development, Phase 3 Verification & Validation, Phase 4 Regulatory, Phase 5 FDA Review. Total estimated required investment is $545k-$660k.



- **Phase I**
    - Quality Documentation
        - Design & Development Plan (Project Plan)
        - Product Requirements (User Needs)
        - Risk Analysis (Hazard Identification)
    - Concept Development –CAD modeling
        - Any requested changes to Kapstone pedicle screw system
        - Instrumentation (custom)
        - Rib hooks
    - Rapid Prototypes of new components
    - Procurement of off-the shelf instruments
    - Design Review –to reach **Concept Freeze**
    - Phase Review
- **Phase II**
    - Refinement of designs and CAD models (all components)
    - Functional prototypes for evaluation
    - Formative Testing (user study, such as cadaver lab)
    - Early Testing (if applicable: Finite Element Analysis, Bench)
    - Design Inputs
    - Repeat iterative “design-build-test” loop once if needed
    - Initial manufacturing drawings and product specifications
    - Functional Relationships Analysis (tolerance stacks, print review, etc.)
    - Finalize CAD models; confirm materials selection
    - Design Outputs
    - Update Regulatory Plan (including selection of predicates)
    - Verification/Validation planning
    - Design Review –to reach **Design Freeze** and approve **Design Inputs**
    - Phase Review

- **Phase III**
  - Finalize manufacturing specifications – drawings, quality plans
  - Pilot Production build for testing and validations
  - Surgicalcase/trydesignandbuild
  - Create IFU, STG, and product labels
  - Continue compiling regulatory documents
  - Summative testing (user study, such as cadaver lab)
  - Final bench testing (mechanical, biocompatibility, etc.)
  - Other verifications/validations (cleaning, sterilization, packaging, shelf-life, etc.)
  - Final risk analysis
  - Design Review –to approve **Design Outputs**and **Risk Analysis**
  - Phase Review
- **Phase IV**
  - Regulatory submission compilation
  - Regulatory submission
- **Phase V**
  - Finalize marketing materials
  - Manufacturing validations
  - Final Design History File (DHF) documentation
  - Design Transfer

Figure 30. Phase 1 Feasibility & Concept, Phase 2 Development, Phase 3 Verification & Validation, Phase 4 Regulatory, Phase 5 FDA Review.



6.8 Risks to Commercialization

Some general risks in the spine deformity surgery market include a burdensome regulatory environment and falling reimbursement rates for spine procedures. We are mitigating the first risk by pursuing the 510(k)-clearance process for our Class II device, rather than a more difficult, expensive, and time-consuming premarket approval (PMA).

VEPTR and pedicle screws are Class II devices subject to 510(k) clearance, and these clearly qualify as predicate devices for R-FIX. The risk of declining reimbursement rates is more than rectified by the increasing demand and volume of spine procedures. A third risk is that surgeons will be slow to adapt the new technology or will not believe that R-FIX benefits are strong enough to warrant embracing the new technology. This risk is being mitigated by obtaining a wide variety of input from many different surgeons early on in this process, and by obtaining strong biomechanical testing, animal model, and human data to clearly and objectively demonstrate the advantages of R-FIX.

6.9 Revenue Stream

In addition to grant funding, in the short-term Apex Orthopedic Technologies will obtain revenue via fee-for-service biomechanical testing services. Dr. Yao's Tissue Biomechanics Laboratory (rooms BE221 and BE223, ~1,600 square ft.) is located on the second floor of the Bioengineering Building at the Medical University of South Carolina (MUSC). The laboratory is supported and funded by the Clemson-MUSC Bioengineering Program, NSF grants (EPS-0903795, MRI-0923311), and NIH grants (P20RR016461, R03DE018741, R03AR055775, R01DE021134). The laboratory has facilities for joint dissection, tissue/cell culture, biomechanical and bio-transport testing, micro-CT imaging, and computer simulation. Ultimately, the majority of Apex Orthopedic Technologies revenue will come from the sale of our flagship product, the R-FIX (Rib-FIXation) System.

Chapter 7. Summary Discussion

Pediatric spinal deformity is a substantial global public health problem. There is a lack of consensus among spine surgeons regarding management. Early-onset spinal deformity is a subset of pediatric deformity that is particularly difficult to treat. Current published treatment strategies are directed toward preserving as much spinal growth as feasible, at the same time attempting to minimize existing deformity. The methods generally used are growing rods placed with pedicle screws as a temporizing measure spanning the deformed portion of the spine, or the Vertical Expandable Prosthetic Titanium Rib (VEPTR) which was originally designed to distract the portion of the thorax affected by thoracic insufficiency, and subsequently the indications expanded to control early onset spinal deformity during the growing years. For more rigid deformity, complex vertebral resection procedures requiring considerable technical expertise are indicated, sometimes combined with halo gravity traction where the “halo” is connected by screw fixation to the cranium, allowing body weight to distract the spine with gravity over a period of weeks to months to slowly correct the deformity. The treatment is arduous over a period of years.

We propose a redirection of emphasis from spinal correction to thoracic realignment using rib fixation. The goal is to manage the deformity while promoting a well-developed thoracic cavity, improved lung volume, and improved pulmonary function with minimal complications. We submit that of all current treatment methods, rib construct technique most closely fulfills those goals. Our proposed method involves a “paradigm shift”, using rib fixation instead of spinal linkage, but varying from the VEPTR which is a rigid device, in that the rib construct can be tailored to the individual deformity and contoured in the sagittal plane. This was the first body of work to comprehensively investigate the biomechanics, mechanobiological mechanism, and clinical outcomes of the rib construct. Results from this study support the value of the rib construct as a safe and effective method for correcting pediatric spinal deformity, especially in the setting of EOSD and hyperkyphosis or kyphoscoliosis. We demonstrate that ribs offer a stronger purchase point than the spine, and allow the surgeon to more safely correct deformity, including those with hyperkyphosis. The basic science data documents the superior biomechanical performance of rib construct compared to spinal fixation (**Aim 1**) and the ability of rib fixation to facilitate remodeling of deformity in the growing spine (**Aim 2**). The clinical data documents exceptional deformity correction in the sagittal plane and the diminished rate of serious and/or troublesome complications.(**Aim 3**).

This technique provides a viable alternative to growing rods with pedicle screws or VEPTR. The main advantages and disadvantages of the rib construct are summarized below, based on the comprehensive outcomes of all stages of this research.

Advantages Supported by our Studies

The rib construct has biomechanical advantages compared to growing rods with pedicle screw fixation, thus lowering rates of the most common mechanical complications.

Since the spine is not fused in patients undergoing growth sparing treatment for early-onset spinal deformity, implants are under mechanical loading for the entire duration of treatment, and mechanical failure rates are high. Proximal fixation failure with pedicle screw pull-out is one of the most common types of instrumentation mechanical failures in early-onset spinal deformity patients, especially with hyperkyphosis and osteoporosis.[64,65]

This complication occurs in >33% of these high risk patients.[64,65] Compared to growing rods with pedicle screw fixation, the rib construct has greater surface area contact with strong cortical bone on the outer surface of the ribs, while pedicle screws have less surface area contact with weaker cancellous bone on the inside of the pedicles and vertebral bodies. Thus, the rib construct is able to distribute stress from the corrective forces of the instrumentation over a larger surface area of stronger bone. *Ex vivo* biomechanical results documented that the rib construct provides stronger proximal fixation that is less prone to failure when loaded with bending and torsional forces. This was further supported by the porcine animal model and clinical study. No fixation failure occurred with the rib construct in the animal study. In the clinical study, there were 5 incidences of proximal fixation failure with the rib construct (20.8%), with hook dislodgement being the failure mechanism. This fixation failure occurred at a lower rate compared to previous studies on patients with early-onset spinal deformity and osteoporosis, and was easily corrected with revision surgeries.[64,65]

Rod fracture is another common complication with growing rod surgery. Previous studies have shown that this can occur in >40% of patients.[111] Rods anchored with pedicle screws are rigid and thus are subject to high levels of fatigue stress. The rods are prone to fracturing, especially in areas where stress is highest, such as near proximal or distal fixation sites. *Ex vivo* biomechanical results documented that the rib construct was less stiff than pedicle screw fixation. When subjected to bending and torsional forces, spines instrumented with the rib construct were able to reach greater deflection angles with less force applied by the mechanical testing system. In the rib construct, motion at the highly mobile costovertebral joints and micro-motion at the rib-hook interface, allows for more movement compared to pedicle screws and renders the construct less stiff. In contrast, pedicle screws have no motion at their interface with the vertebrae, and the construct is very stiff. This likely reduces the risk of rod fracture. There were no cases of rod fracture with the porcine animal model, and 7 cases (29%) with the clinical study, which is relatively low compared to other studies on similar patient populations.[111]

The rib construct reduces the rate of proximal junctional kyphosis.

Proximal junctional kyphosis (PJK) is a common complication. This is not a mechanical failure of the implant, but rather localized kyphotic deformity that develops just superior to the proximal fixation. This can occur in >28% of patients.[66] The rigid nature of pedicle screw fixation creates elevated stress at the upper instrumented vertebrae (UIV), and can result degeneration of the disc and spinal ligaments surrounding the vertebrae, resulting in kyphotic deformity. Furthermore, these ligaments can be damaged during the implantation of the instrumentation, thus also putting the patient at risk of developing proximal junctional kyphosis. The rib construct is less rigid than pedicle screw fixation and lowers the stress concentration at the upper instrumented vertebrae by moving fixation to the ribs. The spinal ligaments and paraspinal musculature can also be avoided by moving fixation to the ribs. Both of these factors together greatly reduce the risk of proximal junctional kyphosis. None of the pigs in the animal study or the patients in the clinical study developed proximal junctional kyphosis. Rib fixation can also be used to supplement pedicle screw fixation with a hybrid construct in adolescent/adult fusion cases to proactively prevent proximal junctional kyphosis in patients that are at risk.

The rib construct reduces the rate of neurologic injury.

With pedicle screws, neurological injury from operating in close proximity to the spinal canal is a potentially catastrophic complication.[67,68] Implantation of pedicle screws into the small thoracic vertebrae of a child imparts a steep learning curve to the orthopedic surgical novice, and many early-onset spinal deformity patients have pedicles with abnormal morphology, making placement of pedicle screws in these patients challenging and dangerous. Post-operatively, pedicle screws implanted into the vertebrae carry a risk of displacement into the spinal canal, and paraplegia has resulted. By moving proximal fixation to the ribs, the rib construct avoids this potential complication in the thoracic spine. There were no neurological injuries and no neuromonitoring changes observed with the rib construct in the animal and clinical studies.

The rib construct optimizes spinal growth

Preserving spinal growth and pulmonary development is an important goal of growth sparing surgery. Unfortunately, the stiff nature of growing rods fixed to the spine with pedicle screws causes auto-fusion of the vertebrae in >80% of patients, resulting in diminishing returns with each lengthening procedure, stunted spinal growth, and compromised pulmonary function.[63] Because the rib construct is less rigid compared to growing rods with pedicle screws, auto-fusion of the spine is less likely, thus maximizing natural spinal growth. Patients in our clinical study had well-preserved spinal growth and no detectable auto-fusion of their spines.

The rib construct requires fewer lengthening surgeries and allows more time in between lengthening surgeries.

In patients that receive growing rods with pedicle screw fixation, lengthening surgeries are generally performed every 6-9 months. With the rib construct, fewer lengthening surgeries are required. Motion at the costo-vertebral joint and micromotion at the rib-hook interface allows for more growth of the spinal in between lengthening procedures. In contrast, pedicle screws are very rigid and attach directly to the spine, thus more lengthening procedures are needed. In our clinical study, lengthening surgeries were performed every 8-12 months. In the animal study, deformity correction and remodeling of the spine was achieved with no lengthening procedures.

The rib construct allows for excellent sagittal plane correction of hyperkyphosis, and good coronal plane correction of scolioisis.

Since the rib construct provides stronger proximal fixation than pedicle screws that is more resistant to pull-out failure, greater corrective forces can be applied, especially in the sagittal plane. This is especially valuable in patients with hyperkyphosis and osteoporosis. In both the animal study and clinical study, the rib construct achieved excellent sagittal plane corrections of hyperkyphosis. The rib construct also achieved good coronal plane correction in patients with scoliosis.

The rib construct is easier to implant compared to pedicle screws.

Implantation of the rib construct was convenient, less technically demanding, and required reduced need for intra-operative fluoroscopic imaging and intra-operative neuromonitoring compared to growing rods with pedicle screws. There was also no need for osteotomies during fusion procedures. I was able to perform these surgeries in spine models, cadavers, and the *in vivo* animal model as an MD/PhD student. *In vivo* animal study surgeries were also performed with Dr. Richard Gross.

Theoretical Advantages Not Yet Explored by Our Studies

The rib construct may realign the pulmonary ribs and optimize pulmonary development.

It is possible that because the rib construct directly manipulates the thoracic cavity, it can improve the alignment of the rib cage and pulmonary function. Patients with hyperkyphotic or kyphoscoliotic deformity also generally have deformity of the rib cage, and this impedes pulmonary development and function. In hyperkyphotic patients, the rib construct can “pull” the ribs back and create more space available at the apex of the lungs, in a way that is difficult to achieve with traditional pedicle screw fixation to the spine. None or our studies directly measured pulmonary function. We did, however, estimate lung volume radiographically and found substantially improved lung volume post-op in hyperkyphotic patients.

Disadvantages Supported by our Studies

The rib construct may not be as effective as pedicle screws for definitive spinal fusion.

While the less rigid nature of the rib construct is an advantage for growth sparing treatment in early-onset spinal deformity patients, it is likely a disadvantage for definitive fusion. Fusion constructs should be rigid to promote ossification. The additional movement allowed by the rib construct interferes with this process. There were 3 cases of pseudarthrosis in the clinical study. Also, the rib hooks can still slip off the ribs after fusion which happened in 3 patients, and this loss of fixation generally does not occur with pedicle screws after fusion.

The rib construct can cause rib fracture.

There were 2 cases of rib fracture in the clinical study. There were no rib fractures in the biomechanical or animal model studies. The cases of rib fracture likely occurred because the patients were severely osteoporotic. Pedicle screws likely would have failed in these patients as well. Nevertheless, this is a complication that surgeons should be aware of.

The rib construct can cause implant prominence.

There were 5 cases of implant prominence in the clinical study. There is less soft tissue covering the ribs compared to the spine. This implant prominence occurred in patients that were particularly thin. Very thin stature with little soft tissue coverage could be a relative contraindication for use of the rib construct.

Theoretical Disadvantages Not Yet Explored or not Supported by Our Studies

The rib construct may cause intercostal neurovascular injury or pleural violation.

There were no cases of this in the animal or clinical studies. However, these are potential complications that are unique to rib fixation that surgeons should be aware of.

The rib construct may cause decrease in pulmonary compliance.

Movement of the ribs and chest wall is necessary for normal breathing. Since the rib construct is attached to the ribs, it is possible that it could inhibit normal expansion and contraction of the chest wall during breathing. We did not have any pulmonary complications in the animal or clinical study. However, we did not specifically measure pulmonary function. The kinetics or chest wall movement and pulmonary function could be examined in future studies.

Up to this point, the rib construct technique has mostly been investigated using off-label laminar hook. The R-FIX (Rib-FIXation) System has been designed with rib hooks specifically for rib fixation (**Aim 4**). Future work will further develop this surgical system. It is possible that the rib construct and specifically the R-FIX System will replace growing rods with pedicle screw fixation and VEPTR as the standard of care for EOSD, or at least provide an attractive alternative.

Proposed Future Studies

Aim1: Evaluate the biomechanical performance of R-FIX rib hooks compared to pedicle screws and laminar hooks. *Ex vivo* bending and torsional biomechanical testing can be performed with a mechanical testing system using porcine spines (with rib cages) instrumented with either rib hooks, pedicle screws, or laminar hooks (N=6) (Milestone 1). The maximum force/torque and deflection/torsion angle applied to the instrumented spine before mechanical failure of instrumentation could be recorded. It is anticipated that spines instrumented with rib hooks will tolerate greater maximum force/torque and deflection/torsion angles without fixation failure or bone fracture compared to pedicle screws and laminar hooks.

Aim 2: Assess the safety and efficacy of R-FIX rib hooks compared to pedicle screws and laminar hooks in a pediatric hyperkyphosis porcine animal model. Our lab has already created a pediatric porcine animal model to test spinal implants (described in this dissertation). Immature 9-week-old hyperkyphotic pigs could be instrumented with either R-FIX rib hooks, pedicle screws, or laminar hooks for a period of 8 weeks (N=6). Fluoroscopic radiographs could be obtained weekly to observe correction of the deformity, spinal growth, and mechanical failure if it occurs.

Aim 3: Evaluate the biological mechanism of spinal growth modulation with the rib construct at the tissue and cellular level. The rib construct provides immediate spinal deformity correction by realigning vertebral bodies. Additional correction is likely achieved over time via spinal growth modulation. Indeed, in the growing spine, compression or distraction of vertebral bodies changes the rate of growth of the growth plates. Instrumentation can be strategically applied to take advantage of this process to straighten a deformed spine. The principle behind this is referred to as the "Hueter Volkmann Law," which states that tensile forces stimulate longitudinal bone growth and that compressive forces inhibit growth. However, the mechanism of this process is poorly understood. In general, the rate of longitudinal bone growth is governed by the rate at which chondrocytes in the growth plate proliferate, hypertrophy, and synthesize extracellular matrix. Our lab could explore the mechanism by which the rib construct corrects early-onset spinal deformity by studying the spines of pigs sacrificed from Aim 2 at the tissue and cellular level. We have already previously examined the growth plates of pigs that underwent surgery with the rib construct (described in this dissertation). We observed wedging of the vertebrae and what qualitatively appeared to be larger more organized chondrocyte columns on the anterior (distracted) sections of growth plates compared to posterior (compressed) sections. However, this did not include any quantitative measurements of cell size, number, etc. Future studies could conduct a histologic analysis using H&E and Safranin O staining of vertebral body cross sections and quantify chondrocyte density, total chondrocyte number, and chondrocyte cell volume on the anterior and posterior sections of growth plates T5-T15 in the hypertrophic and proliferative zones. We could also measure overall growth plate thickness and qualitatively assess chondrocyte column structure in these regions in response to the instrumentation. In addition, we could explore the changes in marker genes and proteins related to chondrogenesis and osteogenesis. We could immunostain for Type II, Type X collagen, and aggrecan in growth plates to assess the expression of these important matrix proteins. We could use RT-PCR to assess the mRNA expression of matrix metalloproteinases (MMP's), and aggrecanases ADAMTS-4 and -5, which are enzymes that degrade matrix structural proteins and may be upregulated in the compressed posterior portions of growth plates. Expression of proteins involved in cartilage ossification, including alkaline phosphatase, osteopontin, and osteonectin could be assessed. It is possible that increased expression of these proteins will be found in the compressed posterior portions of growth plates suggesting that compression accelerates ossification of the growth plate. To explore a specific mechanistic pathway that may be involved in growth modulation, we could use RT-PCR to asses FGF receptor 3 (FGFR3) expression in the growth plate reserve zone. FGFR3 is involved in a negative feedback signaling pathway that reduces chondrocyte proliferation in the growth plate. Mutations in FGFR3, which is expressed in the reserve zone, cause the most common form of dwarfism. FGFR may be upregulated in posterior compressed growth plates and may play a critical mechanistic role in spinal growth modulation. The data generated could be critical for identifying the mechanism responsible for growth modulation of the spine and would be the first study to comprehensively assess these parameters in an immature hyperkyphotic porcine model.

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