

WORKSHOP

New Biological and Biomechanical Approaches to Orthopedic Management of Pediatric Neuromuscular Disorders

(In Collaboration with Pediatric Orthopaedic Society of
North America)

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NEUROMUSCULAR SPINAL DEFORMITY IN CHILDREN: HOW CAN BIOLOGY AND ENGINEERING HELP ALLEVIATE THE BURDEN OF DISEASE

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According to the National Scoliosis Foundation, the incidence of scoliosis ranges between 2-3% amongst the general population [1]. A subset of these patients (1-2 per 10,000 births) present at an age at which the majority of musculoskeletal growth has yet to occur [1]. Early onset (EOS) represents a group of congenital and acquired conditions that affect the growth and development of the spine and thorax in children. Besides affecting the height, posture, and functional mobility of affected children, the resultant spinal deformity has a significant impact on their overall health by limiting the volume of the thorax and the subsequent ability for lung growth [2-4]. Scoliosis is not just a spine deformity; it represents a three-dimensional skeletal malformation that directly affects the volume, symmetry, and function of the thorax and indirectly affects lung growth and function [7-9] by limiting excursion of the diaphragm and restricting inspiratory expansion of the rib cage [5, 13]. In an effort to develop a unifying principle that emphasizes how structural deformities of the spine and rib cage can degrade respiratory function and lung development, Campbell introduced the concept of thoracic insufficiency syndrome (TIS), which is defined as the inability of the thorax to support normal respiration or lung growth [2, 3]. TIS represents a novel form of postnatal pulmonary hypoplasia and restrictive respiratory disease that occurs in patients with congenital, infantile, or neuromuscular scoliosis and congenital or acquired anomalies of the ribs and chest wall that induce prolonged mechanical inhibition of respiration and/or pulmonary growth. Several studies have demonstrated poor outcomes in patients who underwent early fusion of the spine due to the development of TIS [6, 9, 14].

Over the past two decades, the treatment of scoliosis in young children has evolved. The previous paradigm of making a "crooked" spine "straight" by instrumenting and fusing the spine early has been replaced by implanting a fusionless device that improves the three-dimensional thoracic deformity while preserving pulmonary function and increasing trunk height. Several of these devices are now approved for use in growing children, with a few more in the midst of clinical trials, subject to critical evaluation. These devices must maintain correction of the thoracic deformity, modulate growth of the spine and rib cage, and preserve pulmonary function without failing mechanically for an indeterminate number of years. With the myriad of options available, there are no established performance criteria for non-fusion spinal instrumentation systems nor are there protocols for optimizing the growth of the spine and thorax while simultaneously ameliorating the associated deformity. There are endless, unique considerations in children that complicate successful application of these devices. While it is possible to safely engineer devices that meet the progressive mechanical demands of growing children, the pathophysiologic processes that contribute to spine and thoracic deformity and the mechanobiologic principles that govern growth of the spine and thorax in health and disease have yet to be elucidated.

Beyond developing implant systems that incrementally straighten the spine and/or rib cage, basic and applied research is required to better understand how to predictably modulate growth of the spine and thorax in children using these devices. Several retrospective clinical studies revealed apparent over or under correction of scoliosis, thereby highlighting our *imprecision* in optimizing patient outcomes with minimal morbidity. Before these devices can be implemented reliably for the treatment of early onset scoliosis, it will be necessary to: 1) characterize normal vs. abnormal spine and thoracic growth; 2) define what metrics we should be measuring to predict the remaining growth of the spine and thorax; 3) develop analytic models of spine growth that accurately predict progression of the deformity and specific interventions (e.g. inhibition of growth by applying compression along the convexity of a scoliosis versus stimulation of growth by applying distraction across the concavity of a scoliosis) over how many vertebral segments and for what time duration to achieve the desired clinical outcome. This will require collaboration among clinicians

caring for these patients, scientists investigating the biologic processes that contribute to spinal deformity and the mechanobiologist researching the mechanisms of mechanotransduction to optimize instrumentation systems and treatment protocols to predictably regulate growth of the spine and rib cage in order to correct thoracic deformity and preserve pulmonary function.

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Duchenne Muscular Dystrophy (DMD)

Duchenne Muscular Dystrophy (DMD) is a recessive X-linked disorder resulting from mutations in the gene encoding for dystrophin. Dystrophin is an intra-cytoplasmic protein that functions as a component of a large glycoprotein complex whose function is to stabilize the sarcolemma. When dystrophin is non-functional the glycoprotein complex is compromised and the resulting membrane instability and increased mechanical stress results in myofiber necrosis which triggers a state of muscle inflammation in the DMD patient. A chronic state of mononuclear cell infiltration precedes the onset of weakness in the DMD muscle, and this inflammatory state has effects on the skeleton and spine.

DMD is the most prevalent form of muscular dystrophy in children, affecting approximately 1 in 4700 males. While there is variability in the phenotype of boys with DMD, the clinical manifestations in untreated children follows a predictable course. This progressive disorder is characterized by muscle fiber degeneration causing gradual worsening of muscle weakness. The onset of weakness usually occurs between 2-3 years of age, and is subtle at first. Weakness begins in the proximal musculature, and the Gower's sign, in which children use their arms to "climb up their body" when standing from the floor, can be used to suggest this diagnosis in young children. The weakness is progressive, and walking ability slowly declines. This decline in ambulatory capability is associated with hypertrophy of the musculature and the development of contractures. An infiltration of fatty-fibrous tissue into the muscles causes hypertrophy and contributes to contracture development. By the teen years, patients become full time wheel chair users. The progressive muscle weakness effects respiratory function, and eventually cardiac function. There is a roughly 2% per year decline in predicted pulmonary function tests. Ultimately, patients succumb to the disease in their third decade of life from respiratory embarrassment and or cardiomyopathy.

Over the past decade, glucocorticoids such as prednisone and deflazacort, have come into widespread use in DMD. These agents were initially utilized for short time periods in boys transitioning to full time wheelchair use. They were found to slow the decline in strength, but concerns about side effects, and the finding that once the agents were stopped, strength returned to the same level as in boys who did not use the drugs limited their use. However, starting in the late 1990, long-term glucocorticoid treatment was attempted in patients to determine if the benefits would outweigh possible side effects. The initial cohort of boys treated with long-term deflazacort, now has been followed for

twenty years. Treatment with deflazacort results in a significant slowing of the progressive decline in muscle strength and function, pulmonary function, and cardiac function. This results in continuation of mobility, a decreased incidence of skeletal deformity, and improved survival. Side effects of therapy, however, do exist, such as cataracts, and osteoporosis, resulting in long bone and vertebral compression fractures. These side effects can be managed with appropriate ophthalmologic and medical management. Interestingly, however, a recent population study found that steroid use did not increase fracture incidence; raising the possibility that long-term suppression of the inflammation associated with the disease by glucocorticoids may also improve bone health. While there have been discussions about the relative efficacy of different glucocorticoids, there is no comparative data showing the superiority of one drug over another.

Several ongoing studies are examining alternative therapeutic approaches

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Spinomuscular atrophy (SMA)

The disorder is caused by a genetic defect in the SMN1 gene, which encodes SMN, a protein necessary for survival of motor neurons. Lower levels of the protein results in loss of function of neuronal cells in the anterior horn of the spinal cord and subsequent system-wide atrophy of skeletal muscles.

Current therapeutic approaches for SMA can be grouped into four concepts: Providing a functional gene via a viral vector (e.g. Avexis); Increase SMN protein from SMN2 gene by modifying SMN2 mRNA splicing to increase amount of functional SMN protein (e.g. SPINRAZA, RG7916, branaplam); Prevent motor neuron death by maintaining mitochondria integrity in neurons. (e.g. olesoxime); and Increase muscle strength and endurance by utilizing fast skeletal muscle troponin activator to amplifies muscle response to nerve impulses (e.g. Cytokinetics)

The following are some of the drugs in the pipeline:

AVXS - 101 (AveXis). Results from a Phase 1 study in SMA Type I patients demonstrate that AVXS - 101 appears to be well - tolerated, with a favorable safety profile. Intrathecal delivery is being tested, and intravenous contemplated. Preexisting antibodies for the AAV9 virus need to be considered.

SPINRAZA (Biogen) . This drug is in clinical use. It demonstrated a favorable safety profile in trials. Approved for all SMA Type patients in U.S., E.U., Japan and Canada following a sham- controlled trial.

RG7916 (Roche) Phase I studies demonstrated that this agents was safe and well tolerated

branaplam (Novartis) A Phase 2 study in SMA patients is underway

olesoxime (Roche). In a Phase 2 clinical trial olesoxime was found to be safe.

CK2127107 (Cytokinetics). Phase 1 studies did not identify any safety concerns in healthy volunteers. Currently being tested in Phase 2 trial.

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POSNA/ORS Workshop: New Biological and Biomechanical Approaches to Orthopedic Management of Pediatric Neuromuscular Disorders

Shifting the paradigm of neuromuscular contractures: Lessons from brachial plexus birth injury

Roger Cornwall, MD
(No Relevant Financial Disclosures)

Background

1. Brachial Plexus Birth Injury (BPBI)
 - a. Traction on the nerves of the brachial plexus during birthing process
 - b. Occurs in 1-3 per 1,000 live births
 - i. The most common birth injury
 - ii. Most common cause of upper limb paralysis in children
 - c. Most nerve injuries affect the C5-C7 nerve roots
 - i. Incomplete shoulder/elbow paralysis
 - d. 20-40% have permanent nerve injuries
2. Clinical effects of BPBI
 - a. Residual paralysis of denervated muscles
 - b. Contractures of muscles around the shoulder and elbow
 - c. Deformity/dislocation of the glenohumeral joint
3. Treatment of BPBI
 - a. Occupational/Physical Therapy
 - i. Stretch tight muscles
 - ii. Encourage motor learning in the developing child
 - b. Nonsurgical modalities
 - i. Splinting/casting/botox
 - ii. Aimed at assisting with muscle stretch, joint positioning, function
 - c. Surgery
 - i. Nerve reconstruction via nerve grafting/transfers (10-20%)
 - ii. Secondary surgery (80-90%)
 1. Muscle releases
 2. Muscle transfers
 3. Glenohumeral joint reduction
 4. Osteotomies
4. Outcomes of treatment of BPBI
 - a. Motor function cannot be restored to normal
 - b. Joint range of motion cannot be returned to normal
 - c. Physical function (measured by various scales) at most 80% of normal
 - d. We are far from a cure!

An opportunity for game-changing strategies

1. Muscle/Joint contractures cause the vast majority of physical disability and need for surgery
 - a. How can we prevent contractures?
 - b. Need to know why contractures occur
2. Mechanical (muscle imbalance) theory
 - a. Functioning muscles overpower weak muscles leading to static joint posturing and ultimately contractures
 - i. Cannot explain elbow flexion contracture, where elbow flexors are weaker than elbow extensors
 - ii. Cannot explain abduction and external rotation contractures of the shoulder, when the abductor and external rotator muscles are denervated
 - iii. Most current surgery, which does not solve the problem, is based on this theory
3. Impaired muscle growth theory
 - a. Neonatal denervation impairs postnatal longitudinal muscle growth, leading to relative muscle shortening and ultimately contractures
 - i. Anatomically consistent with distribution of nerve injury and clinical phenotype of contractures
 - ii. Tested in an animal model
 - iii. Confirmed with computer simulation of human shoulder movement
 - b. Mechanisms of impaired muscle growth following neonatal denervation
 - i. Challenge of not knowing mechanisms of normal longitudinal muscle growth
 - ii. Satellite cell (muscle stem cell) pool is altered, but not responsible – myonuclear accretion is unaffected
 - iii. Protein balance is disrupted, with increased protein degradation
 - iv. Role of afferent, sympathetic innervation
4. Moving forward
 - a. “Stem cell” therapies unlikely to be fruitful
 - b. Addressing the underlying perturbations:
 - i. On the nerve side – recapitulating afferent/sympathetic input
 - ii. On the muscle side – restoring muscle protein balance/sarcomerogenesis
 - c. Implications for cerebral palsy, other neuromuscular contractures
 - i. Potential final common pathway of impaired muscle growth by perturbation of innervation during critical neonatal period
 - ii. No animal model of CP-induced contractures, so all muscle contracture research in human spastic muscles is observational, and after contractures have already formed: cannot distinguish cause from effect

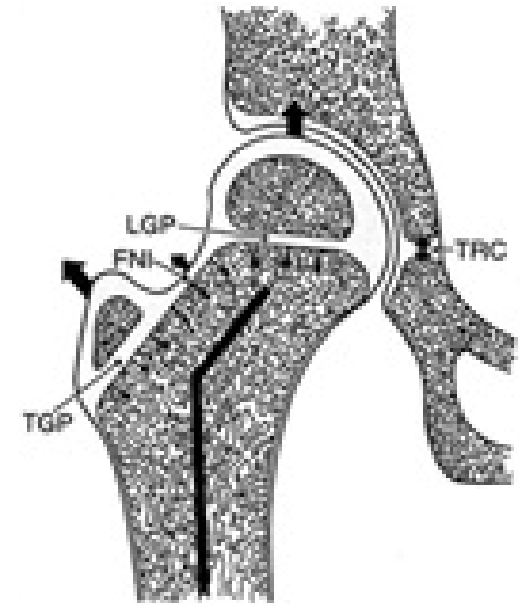
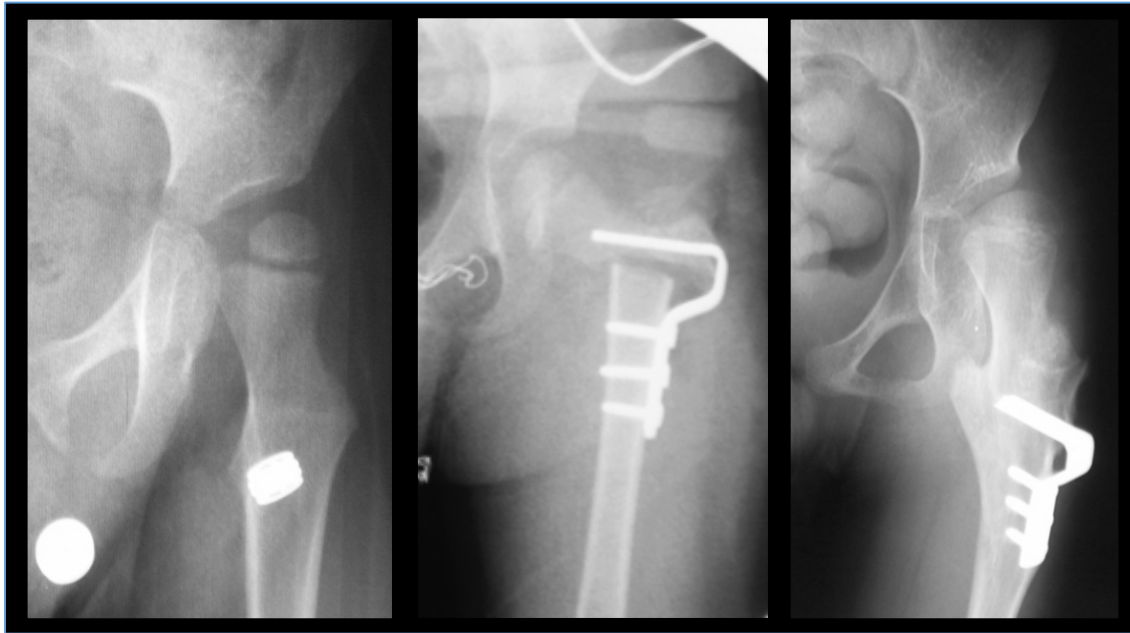
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From Osteotomies to Guided growth of the hip: basic science, indications in the human

James McCarthy, MD, MHCM

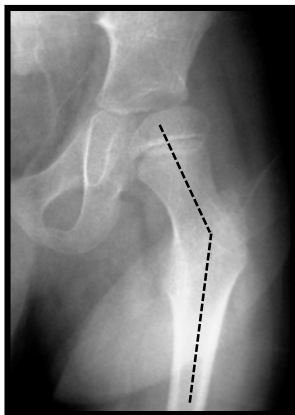
- Guided growth
 - Used in lower extremities of children
 - Limited research focused on use to correct hip deformity
 - Excessive valgus in CP or varus in LCP



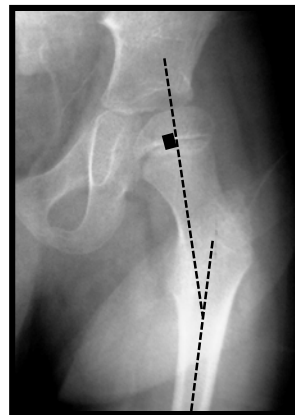
Hip Dysplasia in CP

10-degree difference in HSA results in a 1.6-times higher risk of hip displacement

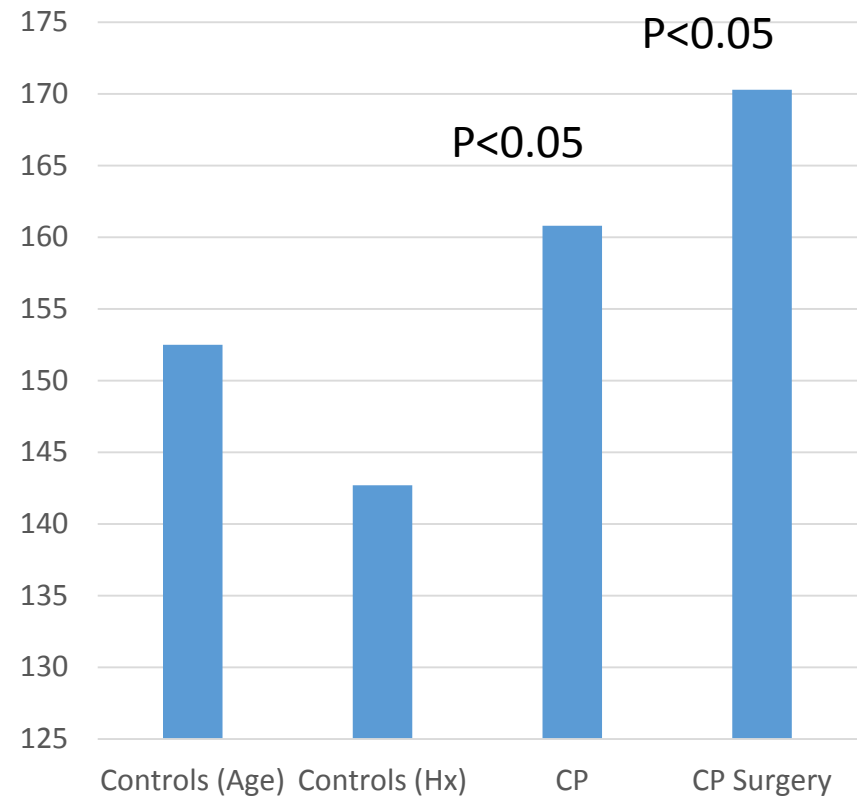
NSA = 140°



HSA = 158°



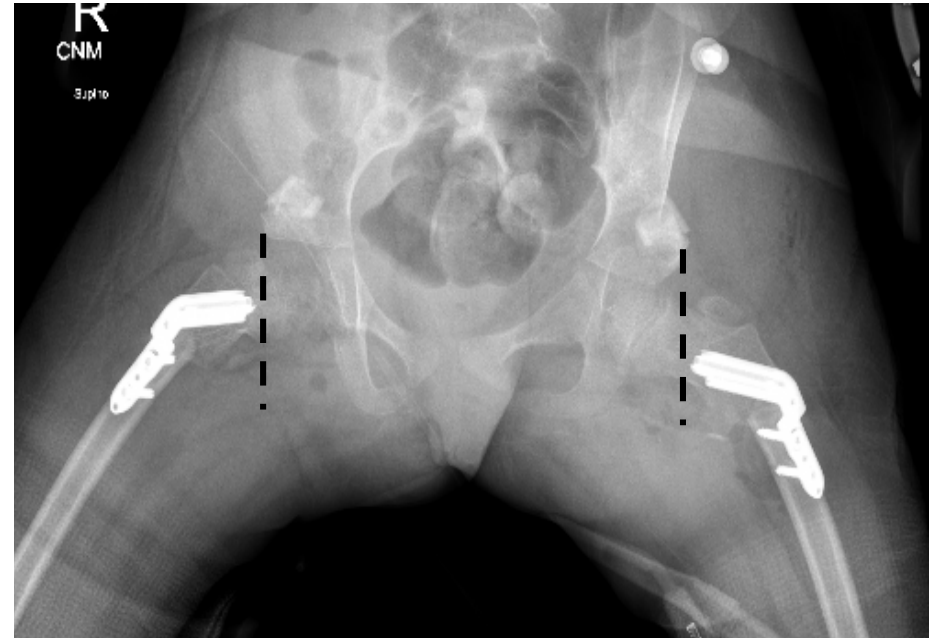
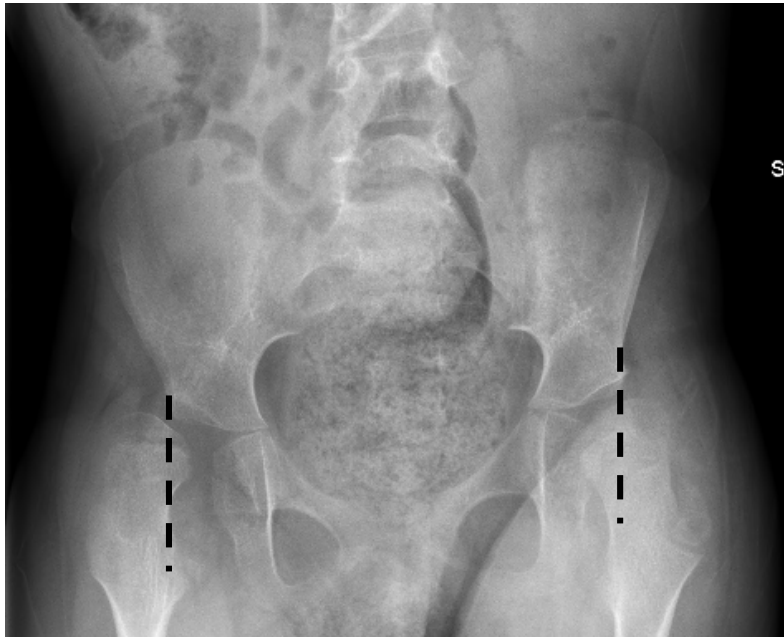
Head Shaft Angle



Foroohar A, McCarthy JJ, Yucha D, Clarke S, Brey J. [Head-shaft angle measurement in children with cerebral palsy](#). J Pediatr Orthop. 2009 Apr-May;29(3):248-50
[Acta Orthop](#). 2015 Apr;86(2):229-32. doi: 10.3109/17453674.2014.991628. Epub 2014 Nov 27.
Head-shaft angle is a risk factor for hip displacement in children with cerebral palsy.
[Hermanson M](#)¹, [Hägglund G](#), [Riad J](#), [Wagner P](#).

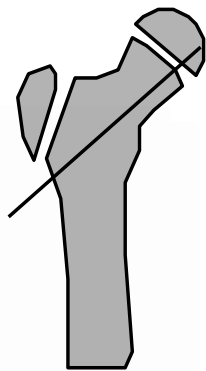
Hip Dysplasia in CP

4 year old with Progressive hip subluxation-over reduction

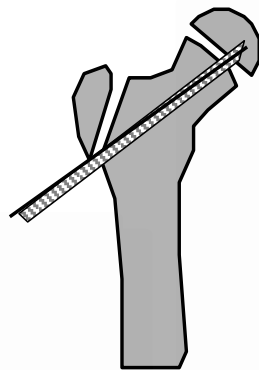


Guided growth of the Hip

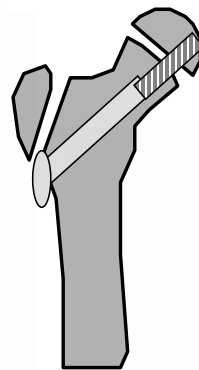
(McCarthy et al JPO 2010, Change et al JPO-B 2006)



Guide pin

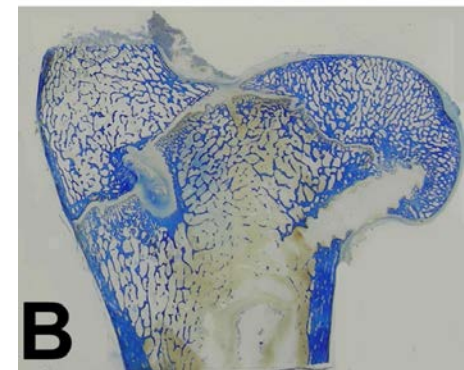
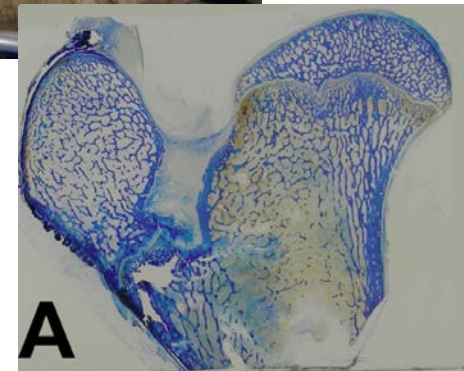


Drill



Screw

NSA decreased by 10 degrees



McCarthy JJ, Noonan KJ, Nemke B, Markel M. [Guided growth of the proximal femur: a pilot study in the lamb model.](#) J Pediatr Orthop. 2010 Oct-Nov;30(7):690-4.

Journal of Pediatric Orthopaedics B: [July 2006 - Volume 15 - Issue 4 - pp 302-306](#)

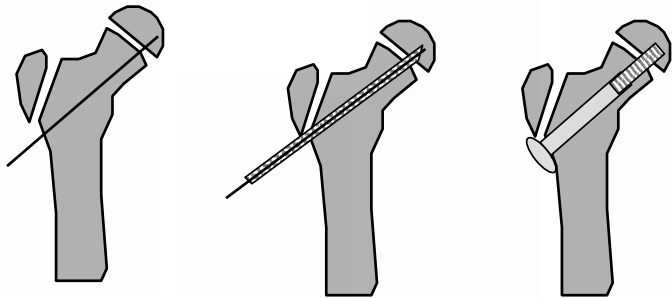
Progressive coxa vara by eccentric growth tethering in immature pigs

Chang, Chia-Hsieh^a; Chi, Chau-Hwa^b; Lee, Zhon-Liau^a

Methods: Surgical

Screw

Technique for hemiepiphyseal **screw** placement in proximal femur



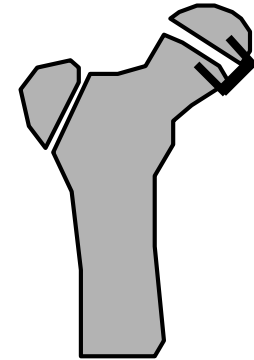
1. Guide pin

2. Drill

3. Screw

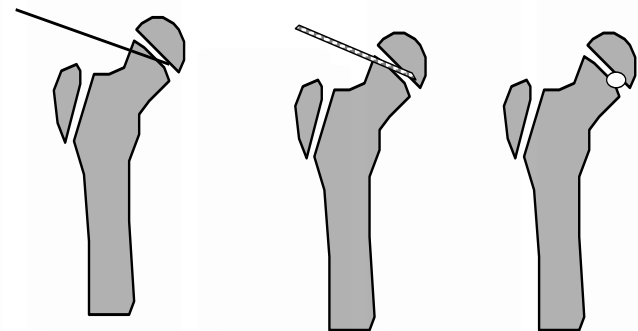
Plate

Technique for hemiepiphyseal **plate** on proximal femur



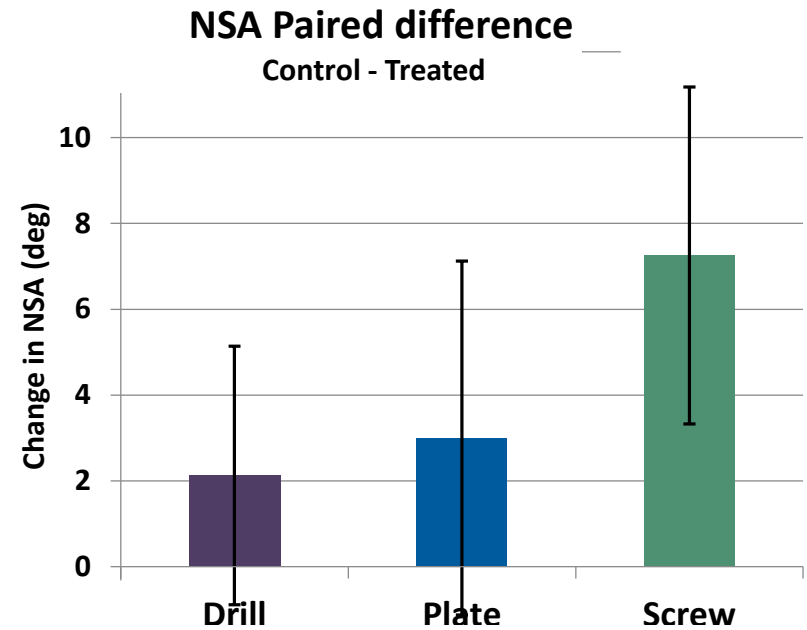
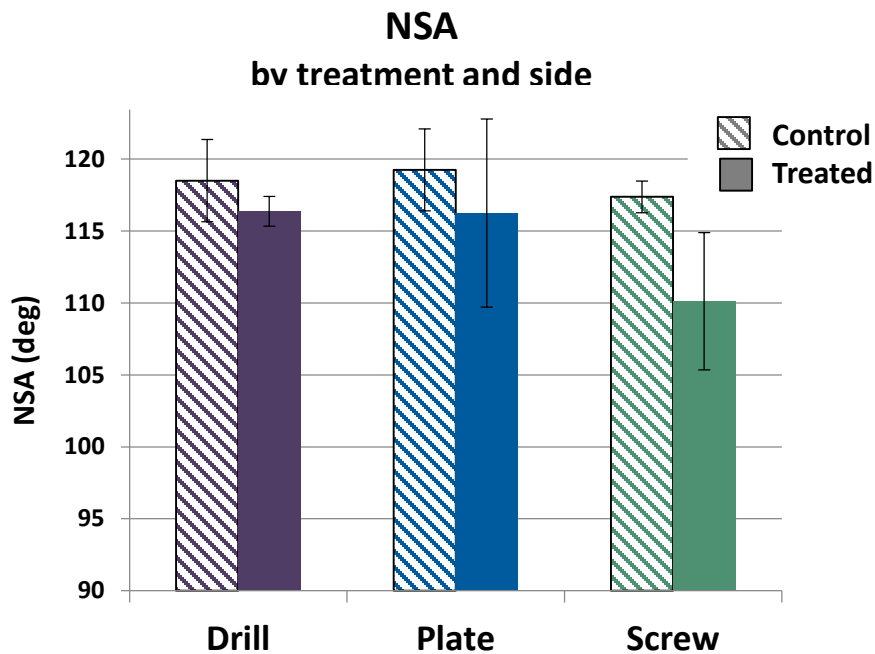
Drill

Technique for hemiepiphyseal **drilling** of proximal femur



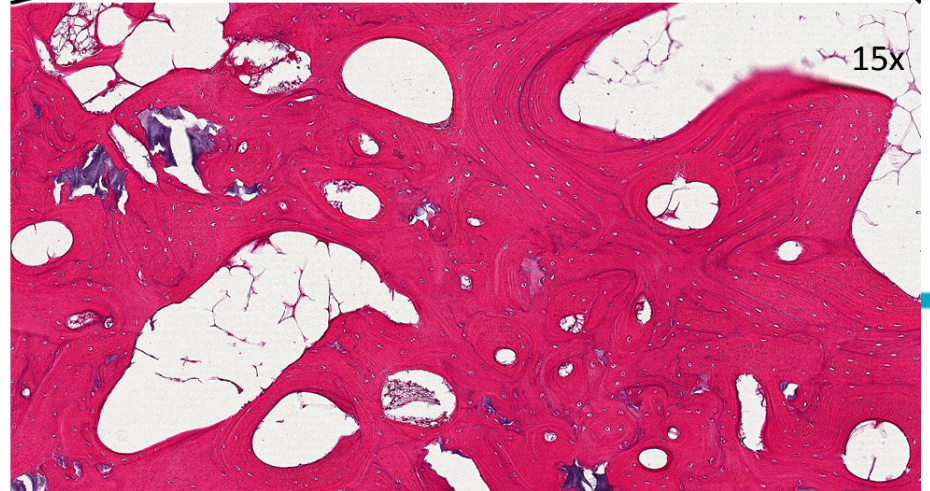
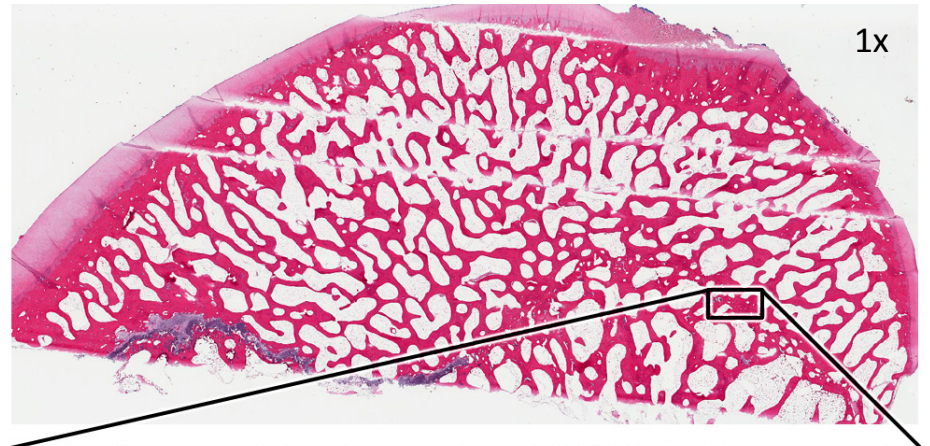
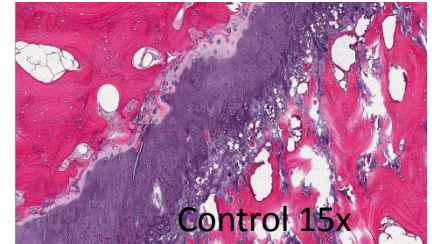
Results: Radiographic

- **NSA** mean paired differences: **Drill** < **Plate** < **Screw**
 - Maximum change in NSA, respectively: **6°**, **7.5°**, and **12.5°**
- **ATD**: No differences



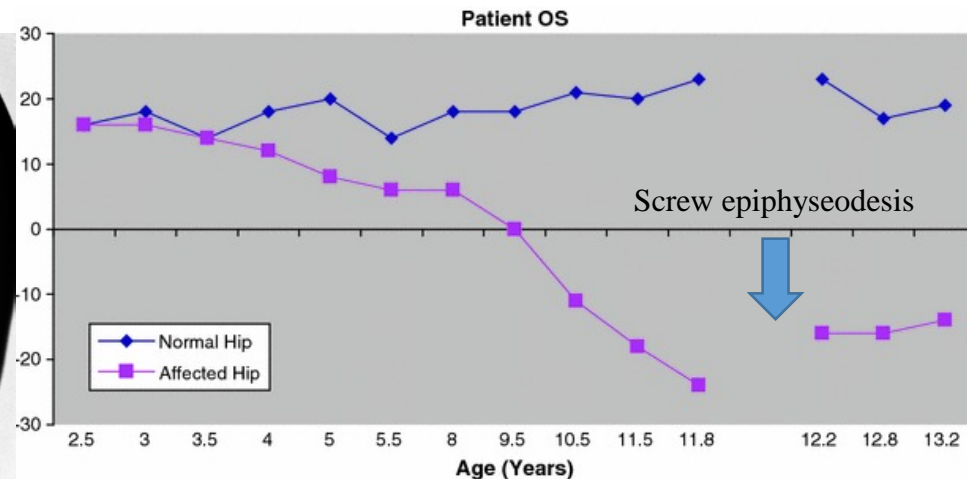
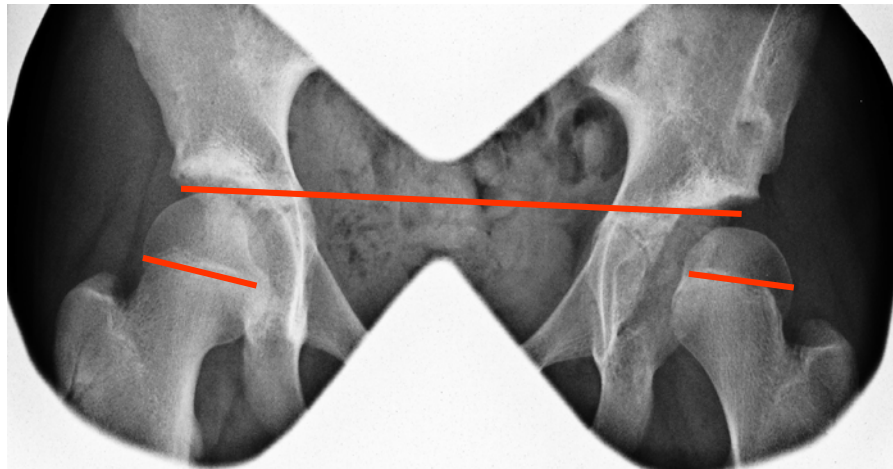
Results: Histologic

- **Physeal changes** on operative side of operative limb
- **Screw** exhibited most extensive changes
 - Growth plate closure over half section



McGillion and Clarke JCO 2011

- Present tilt angle-lat growth arrest-not CP
- Assess the radiological outcomes of medial screw hemiepiphysodesis
- Average age **12 years**
- 11 patients with lateral growth arrest
- 10 had screw hemiepiphysodesis
- 6 demonstrated improved tilt angles post screw at final follow up/4 unchanged



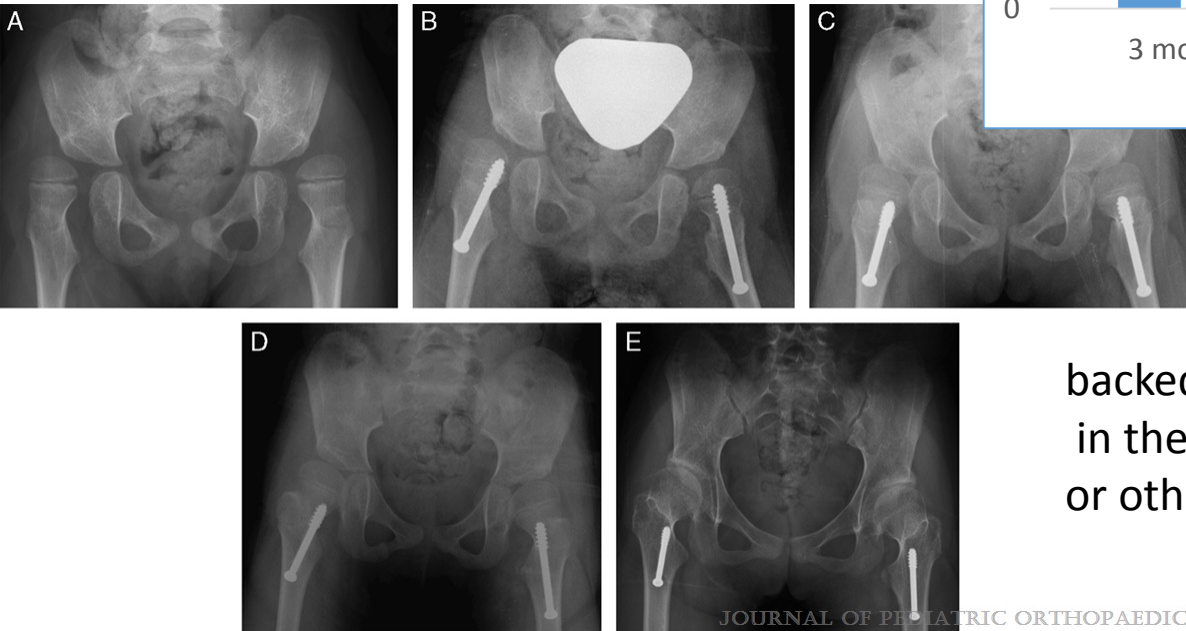
[S. McGillion](#) and [N. M. P. Clarke](#) *J Child Orthop*. 2011 Jun; 5(3): 201–207. **Lateral growth arrest of the proximal femoral physis: a new technique for serial radiological observation**

Lee et al JPO 2016

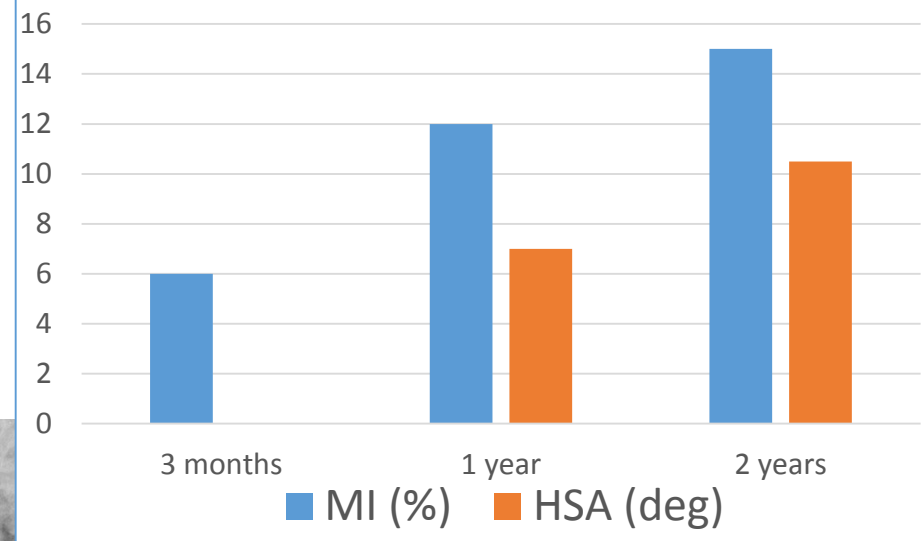
9 children, 13 spastic displaced hips

Mean age 6.2 years

followed up for a mean of 45.6 months



Improvement in MI and HSA



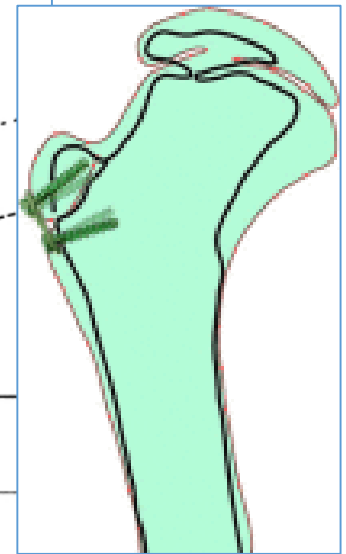
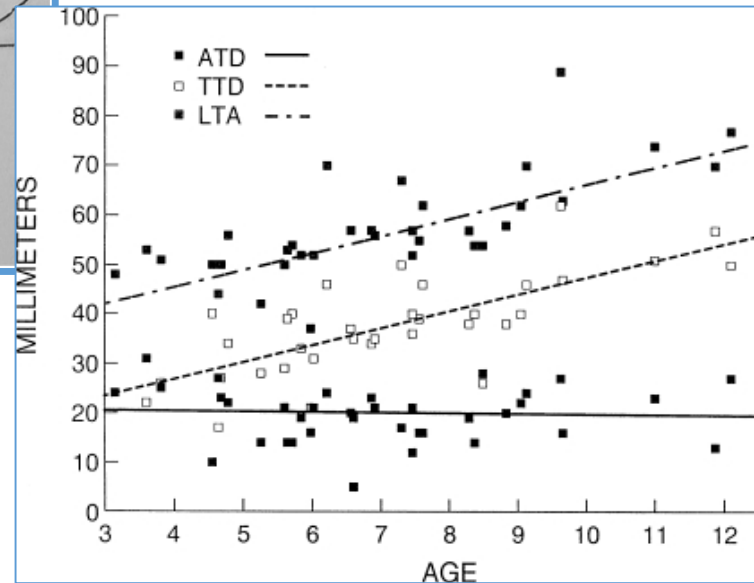
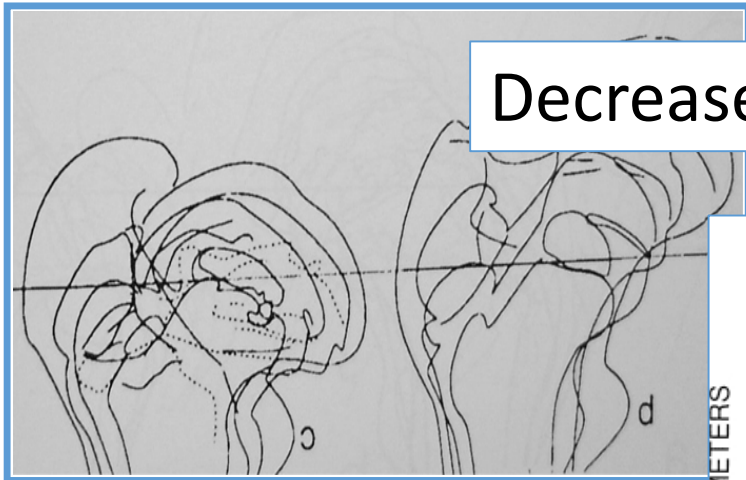
backed out from the femoral epiphysis in the 2nd year, no radiologic bony bar or other surgical complications occurred.

JOURNAL OF PEDIATRIC ORTHOPAEDICS

Guided Growth of the Proximal Femur for Hip Displacement in Children With Cerebral Palsy Lee, Wei-Chun; Kao, Hsuan-Kai; Yang, Wen-E.; Ho, Pei-Chi; Chang, Chia-Hsieh *Journal of Pediatric Orthopaedics*. 36(5):511-515, July/August 2016.

Guided growth laterally

Decrease GT growth about 1 mm/year



- [Int Orthop](#). 2008 Aug; 32(4): 531–534. Greater trochanteric epiphysiodesis James J. McCarthy¹ and Dennis S. Weiner²
- [Strategies Trauma Limb Reconstr](#). 2014 Apr;9(1):37-43 Guided growth of the trochanteric apophysis combined with soft tissue release for Legg-Calve-Perthes disease. Stevens PM¹, Anderson LA, Gililand JM, Novais E.
- [J Pediatr Orthop](#). 2012 Sep;32(6):626-30. Multilevel guided growth for hip and knee varus secondary to chondrodysplasia. Stevens PM¹, Novais EN.

Putting it all together

- Children with CP have valgus hips
- Increased HSA is a/w subluxation
- Guided growth techniques appear to be effective
- Growth is limited so affects are small than the knee
- Clinical studies are limited and indications are not established
 - Prevent recurrence if removing hardware
 - Mild subluxation if undergoing surgery and no rotational issues

Thank You

