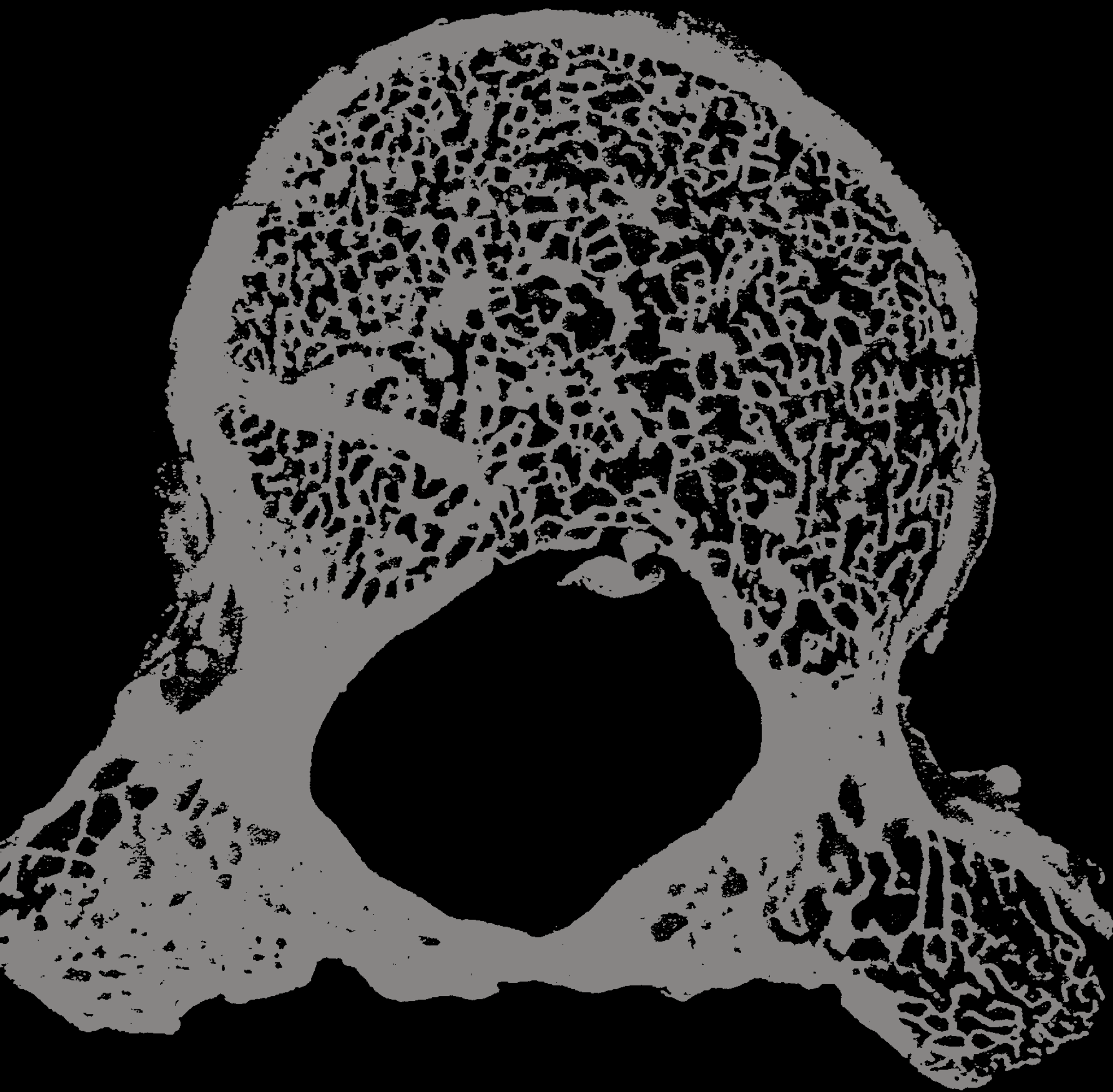
The Role of Intrinsic Spinal Mechanisms in the Pathogenesis of Adolescent Idiopathic Scoliosis



J.W.M. Kouwenhoven

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ISBN 978-90-393-4518-4
Cover: Multimedia, UMC Utrecht
Design & Layout: Frank Boesveld, Multimedia, UMC Utrecht
Press: Gildeprint Drukkerijen

Financial support for the reproduction of this thesis was generously funded by the following institutions/companies

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The Role of Intrinsic Spinal Mechanisms in the Pathogenesis of Adolescent Idiopathic Scoliosis

De Rol van Intrinsieke Spinale Mechanismen in de Pathogenese van Adolescente Idiopathische Scoliose

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht,
op gezag van rector magnificus, prof.dr. W.H. Gispen,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op donderdag 21 juni 2007 des ochtends te 10.30 uur.

door

Johannes Wilhelmus Maria Kouwenhoven
geboren 5 juni 1978 te Helmond

Promotoren: Prof.dr. R.M. Castelein
Prof.dr.ir. M.A. Viergever

Co-promotoren: Dr.ir. K.L. Vincken
Dr.ir. Th.H. Smit

This thesis is based upon the following publications

1. Kouwenhoven JWM, Castelein RM. The Pathogenesis of Adolescent Idiopathic Scoliosis – A Systematic Review of the Literature. Submitted to *Spine* 2007.

2. Kouwenhoven JWM, Smit ThH, Van der Veen AJ, Kingma I, Van Dieën JH, Castelein RM. Effects of Dorsal Versus Ventral Shear Loads on the Rotational Stability of the Thoracic Spine - A Biomechanical Porcine and Human Cadaveric Study. In press *Spine* 2007.

3. Kouwenhoven JWM, Vincken KL, Bartels LW, Castelein RM. Analysis of Preexistent Vertebral Rotation in the Normal Spine. *Spine* 2006;31(13):1467-72.

4. Kouwenhoven JWM, Van Ommeren PM, Pruijs JE, Castelein RM. Spinal Decompensation in Neuromuscular Disease. *Spine* 2006;31(7):E188-91.

5. Kouwenhoven JWM, Vincken KL, Bartels LW, Meij BP, Öner FC, Castelein RM. Analysis of Preexistent Vertebral Rotation in the Normal Quadruped Spine. *Spine* 2006;31(20): E754-58.

6. Kouwenhoven JWM, Bartels LW, Vincken KL, Viergever MA, Verbout AJ, Delhaas T, Castelein RM. The Relation Between Organ Anatomy and Preexistent Vertebral Rotation in the Normal Spine – Magnetic Resonance Imaging Study in Humans With Situs Inversus Totalis. *Spine* 2007;32(10):1123-28.

Contents

Introduction

1

Despite numerous years of dedicated research into the origin of idiopathic scoliosis, the pathogenesis of this classic orthopaedic disorder has so far remained elusive.[1-16] Scoliosis is a complicated three-dimensional deformity of the spine that is characterized by deformation in the sagittal, frontal, and transverse plane. Although there are many forms of scoliosis – such as congenital, neuromuscular and degenerative scoliosis – most cases of scoliosis actually have no known cause, it is thus called *idiopathic* scoliosis.
Over the years, practically every structure of the body has been incriminated in the pathogenesis of idiopathic scoliosis, from the collagen-type of the back muscles to the deep centers of the central nervous system. Despite all this effort, no single cause of this intriguing disorder has been defined. What we do know about idiopathic scoliosis is that it is a three-dimensional rotational deformity of the spine that occurs in otherwise healthy children, predominantly adolescent girls with a genetic predisposition, and typically progresses during the adolescent growth spurt. Furthermore, idiopathic scoliosis has never been observed in animals, it is a condition related exclusively to humans.[2;17]
Since the aetiology of idiopathic scoliosis has still not been revealed, it has not been possible to introduce an adequate causal treatment. Therefore, primary treatment or prevention of idiopathic scoliosis is not possible, and until now treatment is focussed on secondary prevention in order to overcome curve progression.

Anatomy and Morphology of Scoliosis

Scoliosis is defined as a lateral curvature of the spine with rotation of the vertebrae within the curve. Although the definition of scoliosis emphasises the abnormal lateral curvature of the spine, the disorder actually involves changes in the frontal (lateral curvature), sagittal (thoracic lordosis), and transverse (axial rotation) planes of the spinal column, and should therefore be considered as a complex three-dimensional deformation of the spine.
Accurate three-dimensional descriptions of the anatomy of scoliosis were given by several anatomists in the late 19th century.[1;13;18;19] This culminated in the work of Nicoladoni (1904), who, in his book "Anatomie und Mechanismus der Skoliose", gave a careful description of early morphological changes in scoliosis, using transverse, frontal, and sagittal anatomical slices of scoliotic vertebrae *(Figure 1)*.[13] His findings in the transverse plane showed that the pedicle on the concave side was longer and thinner than on the convexity of the curve, which is an important finding for modern day scoliosis surgeons who use pedicle screws. The cancellous bone showed denser architecture on the concavity and the transverse process was more massive on this side. The neurocentral cartilage had remained open on the concavity, and was found to be closed on the convexity of the curve *(Figure 1a)*. The whole

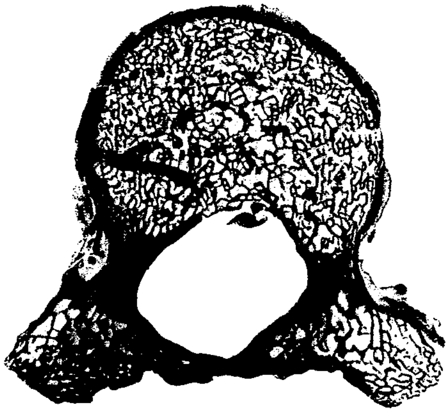
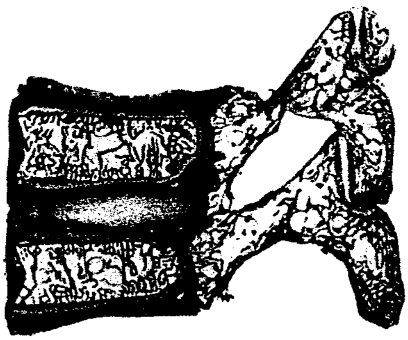
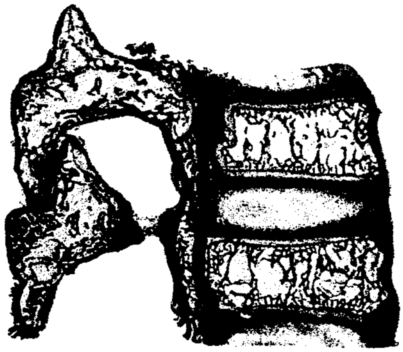


Figure 1a. Transverse section of T9 vertebra from a 6.5-year-old female cadaver spine specimen with a right convex thoracic curve showing an open neurocentral cartilage on the concavity and closed neurocentral cartilage on the convexity of the curve.

Figure 1b. Frontal section of T4-T5 segment from a 7-year-old male cadaver spine specimen with a right convex thoracic curve showing that the nucleus pulposis has shifted to the convex side of the curve, and the fibres of the annulus fibrosis are extended on the convex side and compressed on the concave side.



Concave



Convex

Figure 1c. Sagittal section of T6-T7 segment from a 6-year-old female cadaver spine specimen with a left convex thoracic curve showing the intervertebral disc to be expanded on the convex side and compressed on the concave side. Furthermore, the superior intervertebral joint of the lowermost vertebra has developed an extra, horizontally placed facet, as an expression of the fact that it has become partially weight bearing.
Data compiled from Nicoladoni.[13]

architecture of the vertebral body and the nucleus pulposus of the intervertebral disc appeared to be shifted to the convex side *(Figure 1b and c)*. In the sagittal and frontal planes, wedging of the vertebrae was found in such a manner that the posterior elements on the concavity of the curve were found to have the highest bone density, corresponding to the fact that this part of the vertebra apparently bears most of the weight.

Regarding the three-dimensional shape of the scoliotic spine as a whole, Nicoladoni and several other authors have emphasized that a thoracic hypokyphosis, or lordosis, is an essential element of scoliosis.[1;5-7;13;15;16;19-22] Another typical feature of scoliosis is the coupling mechanism between transverse plane vertebral rotation and the development of lateral curvature. In scoliosis, rotation of the vertebral bodies is always directed into the convexity of the curve.[23] Since the anterior structures of the vertebral column are rotated farther from the midline than the posterior elements, overall, the spine has to be in lordosis – or, as Von Meyer already in 1866 stated: "Die normale Kyphose der Brustwirbelsäule ist mit dem Bestehen einer Skoliose unverträglich".[19]

With the introduction of roentgenography in the beginning of the 20th century, the appreciation of scoliosis as a complex three-dimensional deformity gradually diminished, and scoliosis was eventually reduced to a projection in one plane. More recently, a number of authors (Dickson, Perdriolle, Vidal) have re-emphasized the three-dimensional nature of the disorder,[5;6;22] which has led to the development of three-dimensional methods of assessment.[24-27]

Adolescent Idiopathic Scoliosis

Classification

Idiopathic scoliosis can be categorized into three age groups: 0-3 years old (infantile), 3-9 years old (juvenile), and 10-18 years old (adolescent).[8] Wynne-Davies simplified matters by distinguishing *early onset* scoliosis (under eight years) versus *late onset* scoliosis (eight years and over), based on a hereditary predisposition.[28] Adolescent idiopathic scoliosis (AIS) obviously develops in adolescents, predominantly girls, and typically progresses during the adolescent growth spurt. AIS accounts for approximately 80 percent of all cases of idiopathic scoliosis.

The most prevalent curve type of AIS is characterized by a primary thoracic curve to the right and a compensatory lumbar curve to the left side.[1;8;13;29-32] In 1983, King and Moe introduced a radiographic classification system for adolescent idiopathic scoliosis.[33] This system describes 5 specific types of thoracic curves based upon coronal radiographs, and recommends specific fusion levels depending upon the curve type *(Figure 2)*. The King-Moe system was originally designed for the Harrington

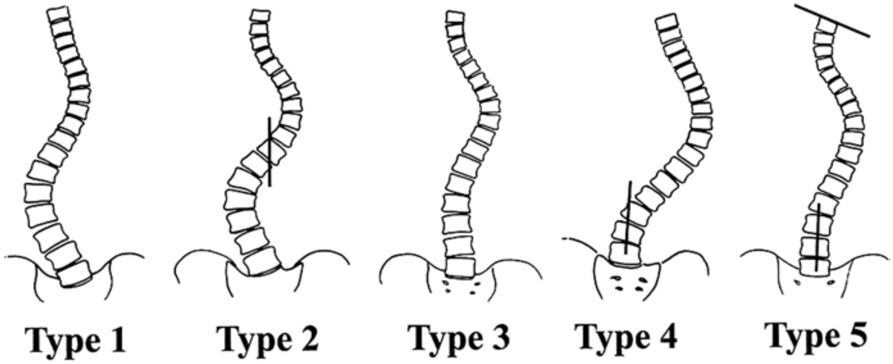


Figure 2. The five curve types according to the King-Moe classification.
Data compiled from Richards *et al*.[36]

rod instrumentation that corrects spinal curvature in the coronal plane. Since the introduction of segmental spinal fixation systems that provide 3D correction of the spine, the King-Moe system became less useful. Recently, Lenke *et al* introduced a new classification system that provides more parameters for classification of additional curve types, such as thoracolumbar, lumbar, double-major, or triple-major curves, and classification of sagittal alignment of the spine *(Figure 3)*.[34-36]

Prevalence

The frequency by which adolescent idiopathic scoliosis occurs in the community depends on an exact definition of what constitutes the disease, and what should be considered as normal variants of a not perfectly straight spine. It is a well-known fact that the normal spine is never straight or symmetrical. As recognized by many anatomists, the postnatal development of the spine becomes asymmetric around the age of 6 years, resulting in a slight scoliotic curvature in the majority of people, a phenomenon known as " physiological scoliosis".[37;38]
Adolescent idiopathic scoliosis occurs relatively frequently, with a wide range of prevalence reported by numerous studies in the literature.[32;39-44] A classical report on the prevalence of AIS was given by Shands and Eisberg, who analyzed 50,000 chest X-rays taken for tuberculosis screening, they found scoliotic curves of at least 10° to exist in 3.1% of subjects between 15 and 19 years of age.[32] Other studies reported idiopathic scoliosis to occur with a prevalence varying between 2 and 10% in healthy in schoolchildren.[40-43] As pointed out by Vercauteren, the differences in

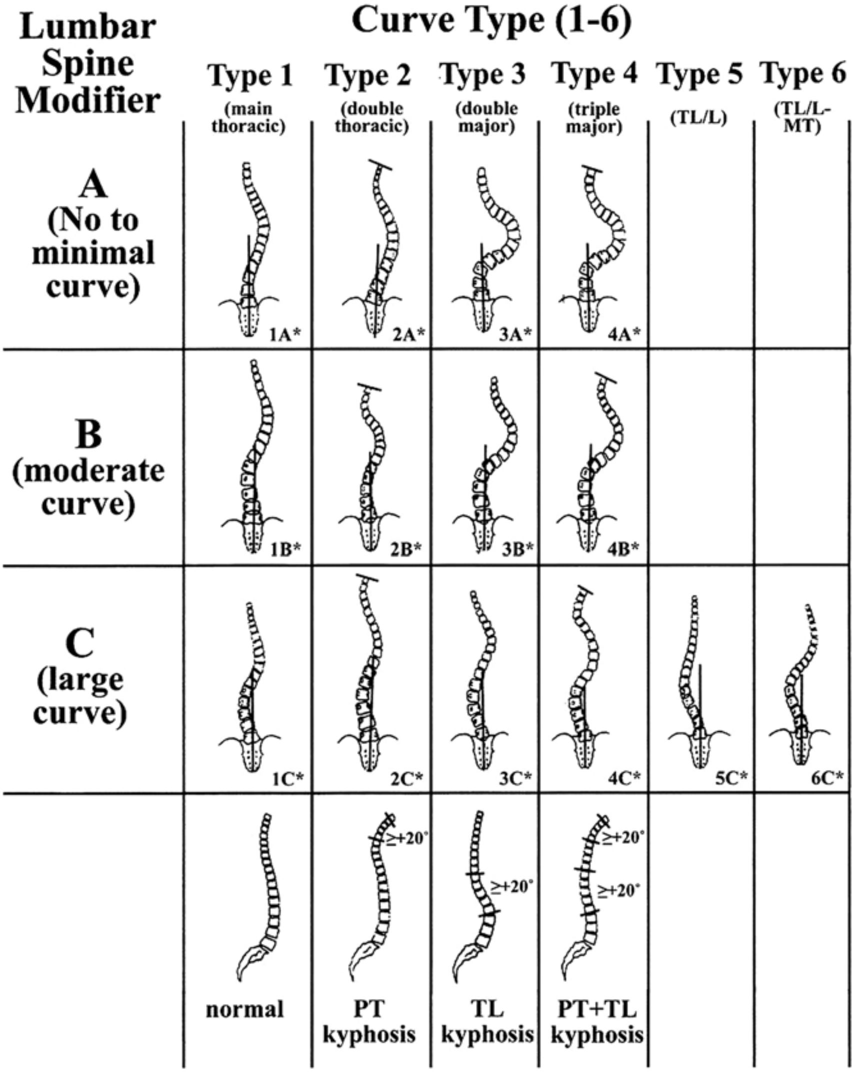


Figure 3. Curve types, potential lumbar modifiers, and sagittal structural criteria according to the Lenke classification. Data compiled from Lenke *et al*.[34]

these reports can to a large extent be accounted for by lack of uniformly accepted criteria for what actually constitutes an idiopathic scoliotic curvature, as distinct from physiological curvatures of the spine in the frontal plane, and postural curves.[45] According to the Scoliosis Research Society (SRS), scoliosis is defined as a lateral deviation of the normal vertical line of the spine, which is greater than 10 degrees measured by X-ray. Using 10 degrees as the cutting point for the diagnosis, in most populations, the adolescent idiopathic scoliosis population consists of approximately 2.5% in the at-risk age category of 10-16 years.[46-48]

Natural history of untreated AIS

Idiopathic scoliosis is known to increase during periods of rapid growth.[8] The rate of progression of scoliosis was found to depend primarily upon curve pattern, initial Cobb angle, apical vertebral rotation, age of the patient at the time of onset, the Risser sign, and in girls the menarchal status.[49-53] Lonstein et al reported that immature patients (Risser grades 0 and 1) with curves measuring 5 to 19 degrees had a 22% probability of progression.[49] Immature patients with a spinal curvature measuring 20 to 29 degrees were found to have a 68% probability of progression of 6 degrees or more during remaining growth. Patients closer to maturity (Risser grades 2 to 4) and with the same degree of scoliosis had a 23% probability of progression. Generally, curves less than 30 degrees will not progress after the child is skeletally mature, however, progression of moderate scoliotic curvature has also been reported after skeletal maturity diagnosed by Risser's method.[52-54] It has been suggested that chronologic age is a better predictor of scoliosis progression than is the Risser sign.[55] Curves greater than 30 degrees tend to progress at about 1 degree per year in adults.

Approximately 4 per 1000 children will develop a progressive form of scoliosis and need intensive medical (conservative or operative) treatment by a specialist. Girls are eight times more likely to need treatment for scoliosis than boys, because (for so far unknown reasons) they tend to have curves that are much more likely to progress. If scoliosis is neglected, curves may progress dramatically, creating a significant spinal deformity and significant alterations of the thoracic cage, resulting in cardiopulmonary compromise.[56-59] Furthermore, regarding the health and well being of persons with AIS, Goldberg *et al* found that subjects with AIS have a poorer perception of body image, have more difficulty with physical activities, and experience significantly more episodes of back pain than controls.[60;61]

Treatment of AIS

The present treatment is either conservative or operative. The treatment options of AIS depend upon several parameters, among which age and maturation of the patient, curve progression, and severity of the curve are the most important.

Conservative treatment

It is recommended to treat patients with moderate curves from 25 to approximately 40° conservatively, which primarily consists of brace treatment.[46;50;62] Brace treatment is also indicated for children and adolescents in whom a rapid increase in the curve is predicted. The treatment purpose of bracing is to prevent moderate curves from becoming severe, bracing ultimately does not lead to improvement of already present curvature. According to a multi-centre study conducted by Nachemson *et al*, bracing was found to be effective in altering the natural history of idiopathic scoliosis favourably.[62] They reported that treatment with a brace was found to be 20-40% more effective than observation alone; the latter showed a risk of curve progression of 6° or more until maturity was reached.
Bracing, however, is not an easy treatment for a teenager. Especially during the stressful period of puberty, wearing a brace that is hot, hard, and uncomfortable has an adverse psychological impact on a child.[63] This can result in a low compliance, which may contribute to a bad result.[64] Other disadvantages of brace treatment are high costs, reduction of spinal mobility,[65] possible disc degeneration, and back pain.[66;67] Although non-operatively treated patients may do very well in the long run,[68] they may still experience a significant cosmetic burden with asymmetrical shoulder line and rib hump resulting in negative psychological effects. [69-71]
The effectiveness of brace treatment to actually arrest curve progression has been questioned, since 20 to 50% of moderate curves showed progression in spite of bracing.[50;62;64;66;72-78] To be effective, a brace should be worn 20-23 hours a day, however, even a brace worn properly does not guarantee that the curve will not continue to increase.[79] Debate continues about the effectiveness of conservative treatment of scoliosis.[73;78] The best result that can be obtained with brace therapy seems to be a halt of progression with persistent deformity.

Operative treatment

When there is curve progression in spite of bracing, surgical treatment is indicated. Other indications for surgical treatment are curves over 50°, curves over 40° in a skeletal immature patient, or when the deformity is unacceptable to the patient. The goals of surgical treatment are correction of spinal deformity, improving cosmesis, preservation or improvement of pulmonary function, arresting progression of degenerative changes of the vertebral column, minimization of morbidity and pain, and patient return to full function.[80] The gold standard for surgical treatment of AIS is spinal correction and bony fusion (arthrodesis) with instrumentation systems for stabilization. Correction of scoliotic deformation can be performed by means of posterior or anterior instrumentation.

Posterior instrumentation

In the early 1960's, the introduction of the Harrington rod provided the first internal fixation system for posterior correction and fusion of idiopathic scoliosis.[81] This system provided a method of intraoperative correction through concave distraction of the curve, predominantly in the coronal plane. Disadvantages of this system were limited ability to provide control in the sagittal plane (flatback syndrome), virtually no derotation of the spine, and the necessity of postoperative external immobilization.[82]

In the early 1970's, Luque introduced the first instrumentation system that provided segmental multi-plane correction and fixation by means of rods and sublaminar wires.[83] This system was found to be an effective method of rigid internal fixation of the spine leading to a rapid efficient arthrodesis without the need of postoperative external support. The normal sagittal contour could be maintained better with Luque rods, and resulted in less loss of correction compared with the Harrington system. However, neither method could achieve significant derotation of the scoliotic curvature.[84]

In the following years, new techniques were developed to achieve better correction in all 3 planes of the spine. In 1984, Cotrel and Dubousset introduced a double rod rotational corrective technique, which consisted of bilateral posterior fixation with multiple hooks on the same rod to apply forces in different directions.[85] The Isola instrumentation system (1985) consisted of a hybrid construct using hooks, sublaminar wires, and pedicle screw anchors to correct spinal deformity by means of segmental vertebral translation to a predetermined contoured rod (a translational corrective technique). The major advantages of these systems were stable fixation without postoperative immobilization, and preservation of segmental lumbar lordosis.[86-88] The degree of axial plane spinal derotation, however, still remained limited.[88-93]

Today, pedicle screw instrumentation in scoliosis surgery has gained popularity because of its higher rigidity and strength than conventional hook systems.[94;95] Pedicle screw constructs have shown better correction of frontal, sagittal and rotational deformity, shorter fusion length, less blood loss, and less loss of correction *(Figure 4)*.[96-99]

Anterior instrumentation

In 1969, anterior instrumentation for correction and fusion of scoliosis was first developed by Dwyer.[100] Instead of distraction of the concave side, as in the Harrington method, the Dwyer system applied compressive forces to the convex side via an anterior approach using screws and a cable. In 1978, this system was first modified by Zielke *et al* who replaced the cable with a threaded rod, in an attempt to prevent post-operative hyperkyphosis.[101] Later on this system was further modified by Slot, and was also used for anterior instrumentation of the spine in burst fractures.[102] Al-

Figure 4. Spinal full-length radiograph of a 14-year-old girl with AIS showing a typical right thoracic curve pattern before (a) and after (b) surgical correction with pedicle screw instrumentation.

though the anterior approach was initially only used to correct thoracolumbar and lumbar curves, more recently, anterior instrumentation for selected thoracic curves also gained some popularity.[103-105]
Anterior spinal fusion has historically offered the advantages of better curve correction, more derotation, and shorter fusion length compared with posterior instrumentation.[106-108] Disadvantages of anterior techniques, however, are increased postoperative kyphosis, pseudoarthrosis, implant failure, loss of correction, and the potential of reduced pulmonary function.[106;109] The use of rigid, dual rod instead of single rod instrumentation has provided better outcomes of anterior scoliosis correction, with higher screw pullout resistance and less loss of correction.[103;104;108;110]
Anterior approaches performed by means of open thoracotomy have the disadvantages of a large scar, the possibility of marked post-operative pain, and persistent reduced pulmonary function.[111] More recently, video-assisted thoracoscopic surgery (VATS) with spinal instrumentation has become available. Compared to the anterior open thoracotomy approach, the VATS technique is less invasive; associated with smaller incisions, less intraoperative blood loss, less postoperative pain, and less impact on pulmonary function.[112;113] However, this technique has the same disadvantages as other anterior approaches, such as the risk of pseudoarthrosis, implant failure, and loss of correction.[114;115] Furthermore, it is most applicable to moderately severe and flexible curves, it has a steep learning curve and often postoperative bracing is necessary.[116]

Treatment Today and Tomorrow

At present, there is no strong data to suggest that one technique is better than others – each technique has its pros and cons. Posterior spinal fusion with segmental instrumentation is most commonly used, followed by open and endoscopic anterior instrumentation.
Until now, operative treatment takes place in a relatively late stage, which makes extensive operations necessary to correct large and stiff curves with angles of 40 to 50 degrees or more. Full correction is difficult and poses certain well appreciated risks, and therefore the vertebral column is fused in a more or less acceptable position, often not fully correcting the 3D deformity Long trajectories have to be permanently arthrodesed disabling further motion of the spine, possibly overloading adjacent segments resulting in disc degeneration.[66;117;118] Furthermore, continued postoperative deformation during subsequent growth cannot be ruled out.[119] These operations have a risk of serious complications, e.g. pseudoarthrosis, failure of instrumentation, infection, and neurological deficit.[120-125]
The latest trend in scoliosis surgery is an attempt at fusionless curve correction, using minimal invasive approaches to the anterior or posterior spine. In theory, mini-

mal invasive fusionless scoliosis correction has several advantages over fusion surgery, such as preservation of growth, motion, and function of the spine, and to prevent overloading of adjacent spinal segments. In 1951, Nachlas and Borden already showed that experimentally induced scoliosis in immature dogs could be corrected by placing staples across the convex side of the curves.[126] Attempts to treat idiopathic scoliosis in humans by similar operations so far have shown little success, because of hardware failure and curve progression.[127-129] Therefore this kind of scoliosis correction did not have a breakthrough at that moment. Recently, Betz *et al* demonstrated that vertebral body stapling can be successful when used in children with curves of less than 50°.[130] This finding is supported by studies of Braun *et al*, who showed halting of progression of experimentally induced scoliosis in immature goats by using an anterior shape memory alloy staple.[131] Although preliminary outcomes of these new fusionless techniques are promising,[132] complete correction of spinal curvature is still not possible, and indications and outcome are somewhat similar to brace treatment.[131;133]

In conclusion, both conservative and operative treatment modalities have their specific indications, results, complications, and drawbacks. The efficacy of conservative treatment, which primarily consists of brace therapy, is debatable – the best result that can be obtained is persistent deformity. More correction can be obtained by surgical treatment, however, since surgery often takes place in a late phase of scoliosis, extensive operations are necessary to obtain curve correction. An earlier and more reliable identification of children at risk for unacceptable curve progression, in combination with a better understanding of the pathogenesis of the disorder, could lead to an earlier, less severe and optimized treatment regime.

Questions to be addressed in this thesis

Idiopathic scoliosis is a condition restricted exclusively to humans.[2;17] An important difference between humans and other vertebrates is the fact that humans ambulate in a fully erect position. In previous work by Castelein *et al*, it has been demonstrated that certain parts of the human spine, more specifically the *dorsally* inclined segments, are subject to dorsally directed shear loads.[134]

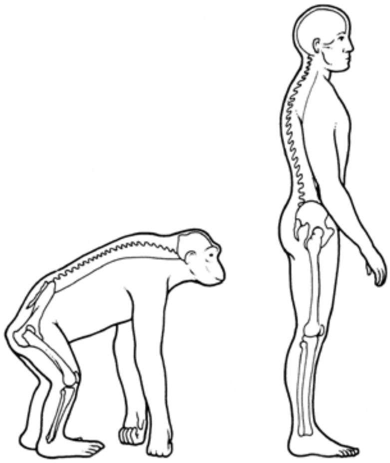


Figure 5. All vertebrates except man have a flexed position of the hips and a centre of gravity that is in front of the pelvis. The spine is subject to physiologic ventral and axial forces. In man also unphysiologic backward forces act upon certain regions of the spine. Data compiled from Castelein *et al*.[134]

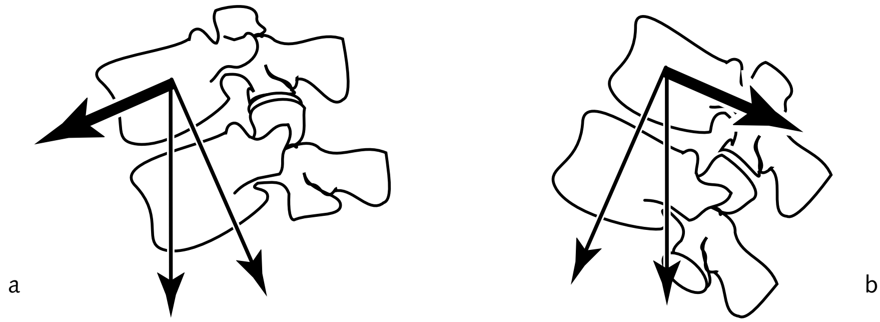


Figure 6. Depending on their orientation, vertebrae in the human spine may be subject to ventral (a) or dorsal (b) shear forces. Data compiled from Castelein *et al*.[134]

It was hypothesized that these dorsal shear loads, which seem unique to the upright human posture, reduce the rotational stability of the spine. In combination with Hueter Volkmann's law, this rotational instability could, in certain circumstances, lead to the irreversible cascade of progressive idiopathic scoliosis. The first question in this thesis therefore was:

1 What are the effects of dorsal and ventral shear loads on the rotational stability of the spine?

An important component of idiopathic scoliosis is transverse plane vertebral rotation. The reason why thoracic curves rotating to the right side predominate in AIS is not clear.[1;8;13;29-32] Rotation in the normal spine is relevant to the curve patterns seen in AIS. Data available on axial rotation measurements in the normal spine, however, are scant and limited to only a few vertebrae. If a preexistent pattern of vertebral rotation exists in the normal spine, it could offer an explanation for the specific curve patterns seen in idiopathic scoliosis. The second question to be answered therefore was:

2 Does a preexistent pattern of vertebral rotation exist in the normal, nonscoliotic human spine?

Neuromuscular insufficiency has long been recognized as a possible etiological factor in the development and progression of idiopathic scoliosis. If we assume that the direction of the spinal curvature is directly determined by the strength or weakness of the involved muscles, a random distribution of muscle paralysis would logically imply an unpredictable and random curve pattern, without any side dominance in neuromuscular scoliosis. If, on the other hand, we assume that muscular weakness is merely one of the many possible non-specific triggers that may cause the spine to deform in a predetermined manner, curve patterns in neuromuscular scoliosis may be more predictable, and show similarities with idiopathic scoliosis. However, the literature about this subject is contradictory. Therefore, the third question was:

3 Are curve patterns in neuromuscular scoliosis randomly distributed, or does a predominant curve pattern exist comparable to what is seen in AIS?

Idiopathic scoliosis does not occur naturally in quadrupeds. In humans, we suggest that the normal, *nonscoliotic* spine shows a preexistent pattern of vertebral rotation that plays a role in determining the direction of scoliotic curvature in AIS. This prompted us to pose the next question in this thesis:

4 Does a preexistent pattern of rotation exist in the normal, nonscoliotic spine of quadrupeds?

A number of factors have been held responsible for the predominance of right sided thoracic curves in idiopathic scoliosis, most notably the asymmetry of the thoracic organs, with the descending thoracic aorta closely related to the left side of the vertebral column, and the predominance of right handedness in the general population. No data are available on vertebral rotation in the normal spine of humans with a complete mirror image reversal of the internal body organs, called situs inversus totalis (SIT). Therefore, the last question in this thesis was:

5 Does a preexistent pattern of vertebral rotation exist in the normal, nonscoliotic spine of humans with a situs inversus totalis, and if so, to what side are the vertebrae rotated? Furthermore, what is the relation between rotational pattern and handedness in this population?

Contents of this thesis

The overall aim of this project is to investigate the role of dorsal shear loads and preexistent vertebral rotation in the development of adolescent idiopathic scoliosis.
In **Chapter 2**, a systematic review of the literature is presented in which the different pathogenetic theories that have evolved in the literature are discussed. In previous work, Castelein *et al* hypothesized that intrinsic spinal mechanisms may play an important role in the initiation and progression of idiopathic scoliosis. They postulated that dorsal shear loads, which uniquely act on the growing human spine, play a role in the pathogenesis of idiopathic scoliosis by rendering the spine rotationally less stable . The effects of these dorsal shear loads on axial vertebral rotation are investigated in **Chapter 3**, which represents a biomechanical *in vitro* study on porcine and human spinal segments.
The reason why thoracic curves rotating to the right side predominate in AIS is not clear. We hypothesized rotation in the normal spine to play a role in this predominant rotational pattern. **Chapter 4** reports on a newly developed CT measurement method that was used to investigate transverse plane vertebral rotation from T2 to L5 in the normal, *nonscoliotic* spine of humans. In **Chapter 5**, a retrospective radiography study on curve shape and direction in 198 patients with neuromuscular scoliosis is presented. **Chapter 6** addresses a CT study on vertebral rotation in the transverse plane of the normal, *nonscoliotic* canine spine using the previously mentioned computer-based measurement method. **Chapter 7**, reports on a cross-sectional MRI study in which vertebral rotation was measured in the transverse plane of the normal, *nonscoliotic* spine of persons with a complete mirror image reversal of the internal body organs – called situs inversus totalis (SIT). Furthermore, the relation between rotational pattern and handedness in this population was assessed.
Finally, in **Chapter 8**, we discuss the results and conclusions of the previous chapters, and propose our perspectives on future research.

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The pathogenesis of adolescent idiopathic scoliosis

A systematic review of the literature

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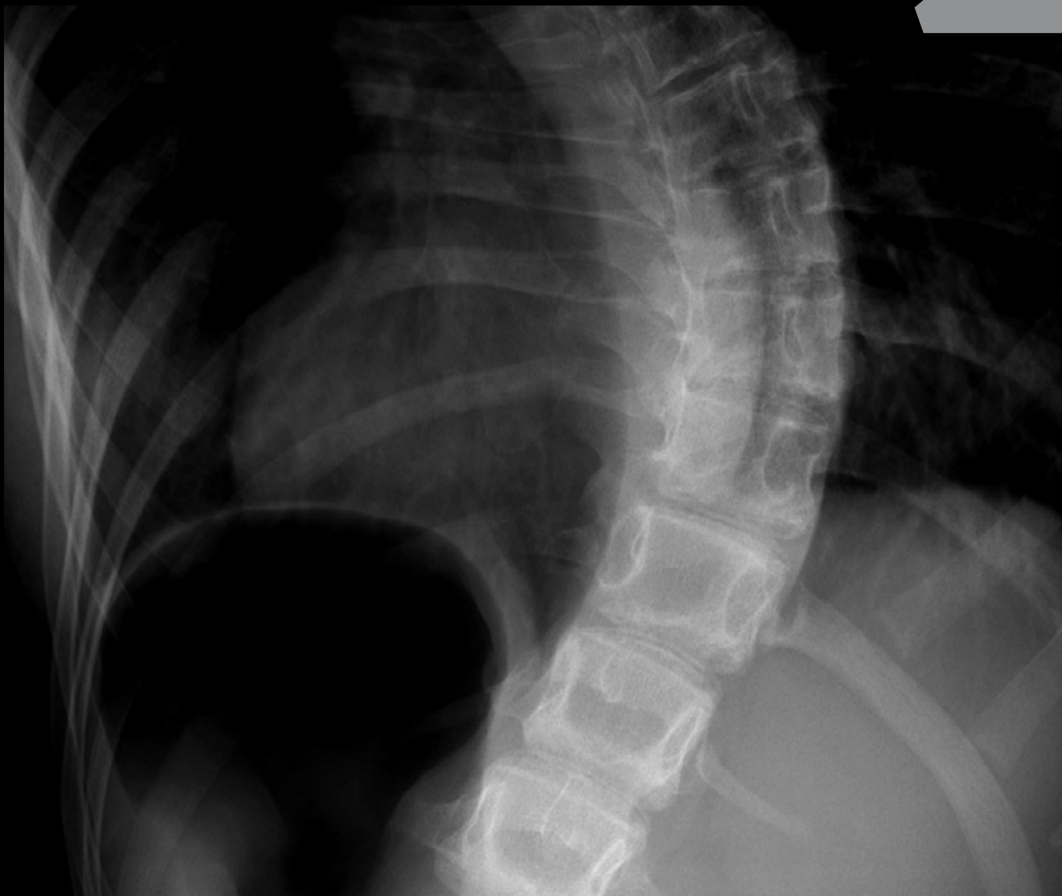

Kouwenhoven JWM
Castelein RM

Adapted from: The pathogenesis of adolescent idiopathic scoliosis –
A systematic review of the literature. Submitted *Spine* 2007

Introduction

Adolescent idiopathic scoliosis (AIS) is a classic orthopaedic problem. Despite many years extensive research into the field of AIS, the cause of this sometimes crippling disorder in previously healthy children has still not been resolved. Practically every structure of the body has been incriminated in the pathogenesis of AIS. In an attempt to reproduce this deformity, a variety of animal models has been created, nonetheless, no single cause has been identified, and the condition is thus termed multi-factorial.

The amount of literature that has appeared on this subject is overwhelming. This is a systematic review of the different pathogenetic theories that have evolved in the literature. The first part deals with the possibility of a primary disturbance in the development of the different parts of the vertebral column, e.g. the vertebrae, discs, and spinal ligaments – the second part deals with the possible causative factors outside the vertebral column.

Intrinsic factors

Vertebral body

The vertebral body grows in height and in diameter, analogous to the bones of the extremities. Vertical growth is accounted for by enchondral ossification at the two epiphysial growth plates at the upper and lower surfaces of the vertebral body.[1;2] These areas where growth takes place should not be confused with the ring apophysis, which is a traction apophysis for insertion of the fibres of the longitudinal ligaments and the annulus fibrosus.[3;4] Growth in diameter occurs by bone apposition from the periosteum on the outer layer of the vertebral body. According to Knutsson this appositional growth is not equally distributed, occurring only at the anterior and lateral sides of the vertebral body.[5] Growth of the vertebral body takes place during childhood and adolescence until approximately 18-20 years of age.

A primary unilateral growth disturbance of one or several of the epiphysial plates could lead to wedging of vertebrae, which is always found in the more pronounced forms of idiopathic scoliosis. Haas could induce scoliosis in young dogs by unilateral operative injury to the epiphyseal cartilage.[6] Arkin and Simon produced experimental scoliosis in rabbits by asymmetric radiation on the epiphyseal plates.[7] Nicoladoni described this wedging even in early scoliosis; however, he found no evidence of a primary growth disturbance.[8]

Vertical growth of vertebrae depends on mechanical loading of the spine according to the law of Hueter and Volkmann, which states that increased compressive forces at the epiphyseal plates reduce growth, and increased distractive forces result in ac-

celerated growth.[9;10] According to this law, asymmetric loading of the epiphysial plates results in asymmetric growth and wedging of the vertebrae, resulting in a progressive scoliotic deformation of the spine.[11;12] Nachlas and Borden developed mild scoliosis in immature dogs by placing staples across consecutive vertebral bodies.[13] After removal of the staples, the deformity continued to progress in a matter similar to idiopathic scoliosis in humans. They were also able to obtain correction by placing staples across the convex side of the curves.[14] In previous studies by Stokes *et al*, it has been demonstrated that asymmetric loading of growing vertebrae resulted in AIS-like deformities in animals, and could explain the development and progression of the deformity in humans.[15-18]
Attempts to treat idiopathic scoliosis in humans by unilateral growth arrest were performed by Roaf, who reported success in preventing deterioration, and in a number of cases correction through continuing growth at the unoperated side.[2;19] Although these findings are in agreement with recent stapling procedures in small curves by Betz *et al*,[20;21] other authors reported very little success with similar operations.[22-24] It has been suggested that some curves are too severe for this type of operation.[25]

Posterior elements

Growth of the vertebral arch is analogous to the cranium. The arch, consisting of 2 halves, closes between 1 and 2 years of age.[5] Increase of the vertebral canal after this age occurs by growth at the bilaterally situated neurocentral cartilage, a structure that will be discussed in the next section. In addition to the wedging of the vertebral bodies, the morphometry of the posterior elements of scoliotic vertebrae also differs significantly from that in normal vertebrae. Concerning the pedicles, it has been demonstrated that at the concave side of the scoliotic vertebra the pedicle is significantly longer and thinner compared to the convex side.[8;26-30] Furthermore, it has been shown that the facets at the concave side of the curve, which are subject to compression, have a significantly thicker cortex than the convex facets, which are subject to distraction.[31]
In 1882, Adams stated that lordosis plus rotation equals lateral flexion. In 1952, Somerville also suggested that the affected segment of the spine was in lordosis before rotation and lateral deviation of the spine became evident. He was able to produce experimental scoliosis in young rabbits by cauterisation of the laminae on each side of the spinous processes, and wiring them together to prevent further growth of the neural arch. He concluded that a localised failure of growth of the posterior elements of the vertebrae could initiate the development of idiopathic scoliosis.[32] Later on, other authors also observed that a lordosis was always present in the scoliotic spine.[8;33-38] Roaf suggested that a relative overgrowth of the anterior elements was responsible for this structural lordosis.[38] Dickson *et al* were successful in producing

experimental scoliosis by posterior tethering and lateral release.[39] They believed that hypokyphotic or lordotic human spines would predispose for the development of idiopathic scoliosis, and stated that thoracic lordosis in combination with asymmetry in the transverse or frontal plane (biplanar spinal asymmetry) was the essential lesion of idiopathic scoliosis.[33-37;40] To determine whether asymmetrical growth of the posterior elements could induce idiopathic scoliosis, Enneking and Harrington examined the articular processes of normal children and patients with idiopathic scoliosis.[41] The observed changes were not related to the severity of the deformity, and there was no evidence of an altered metabolic state in the investigated material. These findings suggested that the observed changes were secondary adaptations to the deformity. Recently, however, Cheng *et al* demonstrated that the anterior column of AIS patients was more active in terms of the zonal area and height, proliferative chondrocytes, and apoptotic chondrocytes than the posterior column.[42] It was hypothesized that relative anterior spinal overgrowth might be due to a loss of coupling between endochondral growth of the vertebral bodies and the appositional membranous growth of the posterior elements.[43]

Neurocentral cartilage

The vertebral body is linked to the vertebral arch by means of the neurocentral cartilage. In contrast to the epiphysial plates in long bones, the neurocentral cartilage has growth columns at both sides; thereby providing growth of both the vertebral body and the vertebral arch.[44] The conditions required for normal development of the vertebral column are that growth at the neurocentral junctions occurs at the same rate on both sides.[5] Asymmetrical growth of the neurocentral cartilage has been implicated in the development of idiopathic scoliosis.[1;5;45;46]

Nicoladoni observed premature closure of the growth plate on the convexity of the scoliotic curve in human infant autopsy material.[8] Although he first believed this unequal growth rate to be a causative factor in the initiation of idiopathic scoliosis, he concluded that these changes were probably of passive nature, caused by unequal pressure on growing vertebrae. Ottander created a slight lumbar curve in an immature pig by unilateral injury of the neurocentral cartilage of L2, using a rotating drill.[47] Beguiristain *et al* used compression screws to effectively compress the neurocentral cartilage on 4 to 5 vertebrae of the mid and lower thoracic spine of growing pigs. In all 8 animals, this procedure resulted in significant scoliotic curves with the vertebral bodies rotated to the side of operation into the convexity of the curve.[48] The animals had no scoliosis directly after the procedure, suggesting that the deformity was attributed to further growth of the undamaged neurocentral cartilage, and not to the procedure itself.

In humans, the role of the neurocentral cartilage in the development of AIS is controversial, because data in literature on the age of closure of the neurocentral cartilage are contradictory. Taylor reported interesting observations on asymmetrical fusion of the neurocentral cartilages in human infant and juvenile skeletons.[45;46] The neurocentral cartilage is believed to be most active at the age of 5 years,[49] and according to most anatomic studies, the neurocentral cartilage closes before the age of 10 years, after which it becomes a bilateral dense plate of bone.[1;4;44] More recently, however, several MRI studies showed that the neurocentral cartilage is still open in the adolescent period, and closes between the age of 11 to 16 years.[50-52] If the neurocentral cartilage still has significant growth activity after 10 years of age, which is unknown, these findings suggest that it could play a role in the development and progression of AIS.

Intervertebral disc

The role of the intervertebral disc in the development of idiopathic scoliosis is not clear. In 1909, Nicoladoni noticed that intervertebral discs become wedge-shaped at an earlier phase in the development of scoliosis than the vertebrae.[8] Wedging of the vertebrae and discs is greatest at the apex of the curve.[53] Bick *et al* described the histology of the disc in 2 very early cases of structural scoliosis without vertebral anomalies and found the nucleus pulposus to be shifted to the convexity of the curve, thus suggesting a developmental asymmetrie of the disc.[54] Michelsson demonstrated that, in experimentally induced scoliosis in rabbits, the nucleus pulposis had shifted to the convex side and the fibres of the annulus fibrosis were extended on the convex side and compressed on the concave side.[55] To determine whether the observed changes were of primary or secondary nature, Ponseti and Pedrini performed histological and biochemical studies of the intervertebral disc. They found a decrease in the glycosaminoglycan and an increase of the collagen content of the nucleus pulposis, correlating with the severity of the curve.[56] Zaleske showed that the activity of degradative enzymes in the scoliotic disc is increased in both idiopathic and neuromuscular scolisis, and suggested that these changes are secondary to the development of scoliosis.[57] Recent CT and MRI studies showed that migration of the nucleus pulposus in the disc and migration of the mechanical properties within the vertebrae both occur early in the development of idiopathic scoliosis.[58-60] However, it is not clear which phenomenon occurs first.

Spinal ligaments

The stability of the vertebral column is mainly determined by the spinal ligaments and muscles. In animals, Langenskiöld and Michelsson showed that the smallest procedure on the ligaments that would reliably cause scoliosis in rabbits was unilateral sectioning of the costotransverse ligaments.[55;61] Although scoliosis is frequently seen in patients with diseases affecting the tensile qualities of collagenous structures, patients with idiopathic scoliosis do not seem to have a generalized connective tissue disorder.[62] Several authors compared the interspinous and intraspinous ligaments of patients with idiopathic scoliosis with normal controls, and no significant differences were found in mechanical properties, morphology, and biochemistry between the scoliosis patients and the controls.[63;64]

Extrinsic factors

Genetics

With growing interest in the early detection of mild cases of idiopathic scoliosis, awareness of its mode of inheritance grew as well. The role of certain genetic factors has been established by a number of authors.

Wynne-Davies screened first, second, and third degree relatives of 114 patients with idiopathic scoliosis. Her findings indicated a dominant or multiple gene inheritance pattern.[65] Robin *et al* evaluated the pedigree of five generations of one family, father to son transmission occurred more than once, suggesting autosomal or multiple gene inheritance.[66] De George and Fisher concluded that there was insufficient evidence that idiopathic scoliosis was inherited; however, they did not examine X-rays of all family members of the scoliotic patients.[67] Cowell *et al* emphasized the need to obtain X-rays of all individuals examined, since moderate curves may occur in family members without their awareness. These authors concluded that idiopathic scoliosis was inherited in a sex-linked dominant mode with variable expressivity and incomplete penetrance.[68] Evidence for sex-linked dominant inheritance of familial idiopathic scoliosis was also found by other authors.[69]

In recent studies, Miller *et al* performed a genomic screen and statistical linkage analysis of 202 families with at least two individuals with idiopathic scoliosis. Linkage analyses have identified several candidate regions for familial idiopathic scoliosis. Candidate regions on chromosomes 6, 9, 16, and 17 were considered to have the strongest evidence for linkage.[70] These authors also showed candidate regions on chromosome 19, which is in agreement with earlier reports of Chan *et al*.[71;72] No evidence was found for disorders in the structural genes encoding for extracellular matrix components of elastin and type-I collagen.[73] Data in literature on the association between familial idiopathic scoliosis and the aggrecan gene, which has been linked to multiple skeletal disorders, are contradictory and inconclusive.[74;75]

The role of genetic factors in the development of AIS has been well described; however, the specific mode of genetic inheritance has still not been resolved. Although most authors agree that genetics play a role in the development of idiopathic scoliosis, all agree that other factors play a role as well.

Left-right asymmetry

It is a well-known fact that a symmetric human body does not exist. In 1909, the normal asymmetries of the human body were extensively described by Gaupp.[76] In addition to the asymmetrically positioned internal body organs (e.g. the heart, lungs, aorta, liver, stomach and spleen), Gaupp also reported asymmetries of the thorax, pelvis, arms, legs, and the spine.

The normal spine is never straight or symmetrical. The 5th to 8th thoracic vertebrae in the normal spine are asymmetrical in the transverse plane, their bodies being flattened at the left side. This phenomenon has been ascribed to the constant pressure of the thoracic aorta, which descends at the left side of the mid and lower thoracic spine.[8;26;35;36;40;76;77] According to Farcas, some degree of scoliosis is always present in everyone, a fact that was also recognized by many anatomists.[78]

Like in normal children, extra-spinal left-right skeletal length asymmetries have also been demonstrated in children with idiopathic scoliosis.[79;80] In most cases of AIS, it has been observed that the upper limb is longer at the side of the convexity of the scoliotic curve. Upper arm length asymmetry in thoracic scoliosis was found to be significantly related to apical vertebral rotation in school screening referrals.[81] The reason for this association and its relation with AIS is unknown. Sacral tilt has also been mentioned as possible causative factor in AIS. Sacral tilt can be caused by leg length discrepancies, pelvic asymmetry, or a combination of the two. According to Dickson, almost 40% of the curves detected by school screening of 5303 children in England were caused by sacral tilt.[82;83] However, contrary to idiopathic scoliosis, this type of scoliosis is characterized by a predominance of small curves (< 15 degrees), an equal boy girl ratio, a primary lumbar curve, and an equal distribution of right and left sided curves. Furthermore, in most patients with progressive idiopathic scoliotic curves no sacral tilt can be detected, and no relation could be demonstrated with spinal curvature.[84]

Another typical example of normal human body asymmetry is the existence of right and left-handedness.[76] In the general population almost 90% of the people is right-handed. Goldberg *et al* found an association between handedness and the predominance of right sided thoracic curves in AIS.[85] However, this association could not be confirmed in left-handed children, since the direction of spinal curvature in this group was found to be randomly distributed.[86] Handedness is a very complex characteristic, and data in literature on this subject are contradictory and inconclusive.[77;84-88]

Growth and development of sagittal spinal profile

It is generally recognized that the development and progression of idiopathic scoliosis are growth related. Many studies analyzed body length in normal and scoliotic

children. Although some studies found no significant difference in length between children with idiopathic scoliosis and normal controls,[89;90] most of the anthropometric studies showed that children with AIS are taller and more slender compared to their peers. Willner and Nordwall found this tendency to start at birth, and to become more pronounced in the years preceding the diagnosis.[91] Nissinen *et al* showed body height, sitting height, and growth of sitting height to be greater in prescoliotic children, but were found to be insignificant risk factors in the development of idiopathic scoliosis.[79] Cheung *et al* compared the height of normal and scoliotic girls corrected for skeletal maturity. They demonstrated that scoliotic girls were significantly taller and had longer limbs than the normal controls after the onset of puberty.[92] Since the proportion of leg length to trunk length in scoliotic children was found to be the same as in the normal population, there seems to be a generalized growth disturbance in AIS rather than one confined to the spine.[93]
To compare growth of normal healthy individuals with scoliotics, Zorab measured the total urinary hydroxyl proline (THP) excretion in normal and scoliotic children. THP excretion is increased by high turn-over of bone collagen and corresponds with growth and repair of bone. The results of his study showed that the (THP) excretion in children with idiopathic scoliosis was significantly higher than in normal controls, indicating either an increased growth, or an increased bone remodelling in AIS.[94] Clark *et al*, however, performed the same measurements and showed that the levels in scoliotics were within the range of normal.[95]
Growth hormone has also been mentioned as a possible causative factor in the development of AIS. Willner *et al* compared growth hormone and somatomedin-A levels between girls with AIS and non-scoliotic controls.[96] The basal growth hormone level as well as the somatomedin-A concentration were found to be significantly higher in the scoliotic children. These differences were thought to point to an altered sensitivity of the growth hormone release mechanism in girls with idiopathic scoliosis. Other authors, however, performed the same measurements and showed that the levels of serum growth hormone and somatomedin-A in children with AIS were within the range of normal.[97;98]
The development of the sagittal spinal profile during pubertal growth has been described in many studies. The normal thoracic kyphosis and lumbar lordosis have been reported as ranging from 30-45 degrees and 30-60 degrees, respectively, with various parameters of measurement.[79;99-112] During the adolescent growth spurt the thoracic kyphosis flattens slightly, where after it turns back to normal in most instances.[100;105;112] This flattening was found to occur in boys and girls at the same age, independent of maturity. It has been demonstrated that patients with idiopathic scoliosis have a flatter thoracic kyphosis than normal children.[111;113-116] It was hypothesized that in patients with AIS the equilibrium between anterior and posterior column growth is disturbed, resulting in hypokyphosis or lordosis of the thoracic spine by relative anterior spinal overgrowth.[33-38;40;43;117] According to Dickson *et al*,

thoracic lordosis is a rotationally unstable configuration initiating the development of idiopathic scoliosis.[36;37] The reason for AIS to occur more in girls than in boys was explained by the fact that girls mature earlier in life than boys, and go through peak adolescent growth velocity when the thoracic kyphosis is at its minimum, suggesting a higher risk of developing thoracic lordosis.[36]

In several anthropometric studies, the three-dimensional character of the deformity was not taken into account, as Archer and Dickson pointed out.[118] They suggested that children with idiopathic scoliosis are not growing faster than their peers, but seem to be taller because of the flattening of the thoracic kyphosis. This affect is even increased in some studies by attempting to correct for lost height due to frontal curvature by the method of Bjure, which does not take sagittal plane morphology into consideration.[119]

Idiopathic scoliosis is known to increase during periods of rapid growth.[120;121] Calvo noticed that scoliotic curves do not increase when the growth rate of the T8-T12 segment is less than 0.30 mm per month.[122] Contrary to the findings of Risser and Ferguson,[121] complete ossification of the iliac apophysis did not always correlate with the cessation of vertebral growth. Several authors reported progression of scoliotic curves after skeletal maturity, diagnosed by Risser's method.[123-125] It was recognized that the rate of progression of scoliosis depended primarily upon curve pattern, apical vertebral rotation, and initial Cobb angle.

Much of the presented evidence is conflicting, and difficult to interpret. The fact that most of the anthropometric studies showed that children with AIS are taller and more slender than normal controls, could indicate a faster growth pattern in children with AIS, or that spines that happen to be longer and slimmer, are more susceptible to the development of scoliosis. Although it is generally accepted that growth is related to scoliosis development and progression, there is no evidence that growth itself is a causative factor.

Paravertebral muscles

The stability of the spine depends upon the interaction between intrinsic factors (bone, facet joints and ligaments) and extrinsic factors (e.g. gravity, muscular force).[126] The ligamentous spine is held upright by the paravertebral muscles. In the absence of muscle forces, the ligamentous spine cannot support vertical compressive forces and buckles at an axial load of only 20 N.[127] Many diseases that affect muscles or their function are associated with the development of secondary scoliosis.[128-134] Muscle imbalance has also long been recognized as a possible etiological factor in idiopathic scoliosis.[135-137]

In the 19th century the development and progression of different types of scoliosis were supposed to depend primarily and essentially upon neuromuscular insufficiency. Adams (1882) was the first to question this opinion. In his post-mortem investigations he found muscle hypertrophy at the convex side and atrophy at the concave side of the scoliotic curve, suggesting muscle force to play an active role in prevention of spinal deviation rather than inducing it.[26] Riddle and Roaf used surface electrodes to assess the role of muscle imbalance and showed an increased muscle activity at the convex side of the curve. They concluded that this overactivity indicated stronger activity of the deep rotator and transverse muscle on the convexity of the curve, as an initiating factor in the development of AIS.[137] Histochemical studies of Fidler and Jowett demonstrated a greater proportion of slow twitch fibers compared to fast twitch fibers in multifidus muscle at the convexity of the curve in idiopathic scoliosis.[136] They also suggested that increased tonic activity of the deep medial paraspinal muscles at the convex side of the spine could play an important role in the development of AIS. Over the years, several other authors – and most recently Cheung *et al* – also found that the most active muscles in AIS are located on the convex side of the curve, and supported Adam's theory that the increased muscle activity at the convexity of the curve is a compensatory mechanism to prevent further deformation of the spine, rather than initiating it.[138-142] Whether the observed differences are primary or secondary remains a matter of debate.

Ribs

The ribs are attached to the spine by the superior and lateral costotransverse ligaments. The ribs are involved in the transmission of muscle forces from the sternum to the vertebral column through the transverse processes, and the costotransverse articulations and ligaments. In 1962, Langenskiöld and Michelsson reported that unilateral resection of the heads and necks of six adjacent ribs produced progressive scoliosis in young animals.[55;61] Several other authors also showed that unilateral resection of the posterior rib ends induced scoliotic deformation in animals.[143-145] It has been hypothesized that the stability of the thoracic spine is maintained by equal support through the ribs from both sides, resulting in unequal growth of the vertebrae if this balance is disturbed.[146]

Nervous system

Scoliosis is seen in various neurological disorders at different levels of the nervous system, from peripheral nerves up to the central nervous system.[131;147;148] In many neuromuscular disorders, such as poliomyelitis, cerebral palsy, spinal muscular atrophy, spina bifida, and many others, the impairment of the efferent nervous system results in the development of secondary scoliosis.[128-134;149] Petersen and Sahlstrand reported EEG deviations from normal in a high percentage of scoliotic patients compared to normal controls. These changes could indicate a lesion or dysfunction of cerebelar structures at the level of the brainstem.[150] In 1978, Sahlstrand *et al* quantified postural equilibrium by stabilometry in patients with AIS compared with healthy controls. The area of sway was greater for subjects with AIS than for the controls.[151] They also investigated the role of the vestibular function in the development of idiopathic scoliosis by analyzing spontaneous nystagmus, positional nystagmus, and caloric respons in 47 patients with idiopathic scoliosis and 30 normal controls, using electronystagmography. Twenty-four of 47 subjects with scoliosis had spontaneous and positional nystagmus compared to 1 subject in the control group.[152;153] Pincott reported scoliosis to occur in monkeys after intraspinal injection of poliomyelitis vaccine for routine virulence testing. Significantly more damage was observed in the sensory areas than in the motor areas of the spinal cord, suggesting that a decreased sensory (proprioceptive) input could play a role in the development of AIS.[154] This is in agreement with studies in which scoliosis has been induced experimentally in animals by posterior rhizotomy.[25;155-158] More recently, Cheng *et al* showed an abnormal somatosensory function in patients with AIS.[159;160] Discrete dysfunction of different levels of the central nervous system, and, more specifically, of areas involved in maintaining the upright posture, may play a role in the development of idiopathic scoliosis. However, whether these observations are of etiological importance, or whether they are secondary to the deformity is not clear.

Spinal cord

In 1966, Roth suggested that idiopathic scoliosis is caused by a short spinal cord. He explained the pathomechanism of idiopathic scoliosis with a spring-string model, and believed that disturbed nerve tension symmetry causes lateral flexion of the spine towards the side of increased tension.[161] More recently, Porter analyzed the axial lengths of the vertebral column and the vertebral canal in persons with normal spines compared with to persons with idiopathic scoliosis. He found no significant difference between the lengths of the vertebral column and the spinal canal in the normal spine. In the scoliotic spine, however, the spinal canal was found to be significantly shorter.[162] He hypothesized that a short spinal canal could tether the posterior elements, and with continuing growth of the vertebral bodies resulting in buckling and rotation of the spine around the axis of the spinal cord – his so called theory of uncoupled neuro-osseous growth.[163;164] Recently, Cheng *et al* demonstrated a relative overgrowth of the spinal column in AIS without a corresponding increase in the length of the spinal cord.[165] They postulated that the fixed spinal cord could act as a functional tether, which is in agreement with Porter's hypothesis of uncoupled neuro-osseous growth. The role of the spinal cord in the development of AIS, however, remains controversial.[166]

Osteoporosis

Osteoporosis is a disease of bone in which the bone mineral density (BMD) is reduced, bone microarchitecture is disrupted, and the amount and variety of non-collagenous proteins in bone is altered as a result of a mismatch between osteoclast and osteoblast activity. Osteoporosis is defined by the World Health Organiztion (WHO) as a bone mineral density 2.5 standard deviations below peak bone mass (20-year-old sex-matched healthy person average) as measured by bone densitometry (DEXA). Although osteoporosis is more common in the elderly than in adolescents, several studies reported low bone density in adolescent patients with idiopathic scoliosis.[167-170]

Cheng *et al* performed a cross-sectional study to assess the lumbar spinal and proximal femoral bone mineral density in 81 girls aged 12, 13, or 14 years with AIS, and compared them with bone mineral densities of an age-matched control group (220 girls). The results of this study showed a lower bone mineral density in patients with AIS than in normal controls.[171] The prevalence of osteoporosis in AIS was found to be 20%. Cheng *et al* also investigated the relation between osteoporosis and curve severity in idiopathic scoliosis. Patients with progressive scoliosis were found to be younger at the time of diagnosis, had a later onset of menarche, and had a lower bone mineral density than patients with moderate curves.[172;173] Therefore, the authors concluded that osteopenia might be an important risk factor of curve progression in AIS. In comparison with normal controls, AIS patients seem to have a higher bone turnover and a relative low calcium intake.[174-176] Cheng *et al* hypothesized that low bone mineral density in AIS could be the result of abnormal bone mineralisation in combination with increased bone growth during puberty. The majority of AIS patients with a low bone mineral density were shown to have persistent osteopenia at the time of skeletal maturity, resulting in increased risk of osteoporotic fractures at older age.[177;178]

Platelet abnormalities

Several studies have reported abnormal morphology and function of platelets in patients with idiopathic scoliosis.[179-182] An electron microscopic X-ray microanalysis and X-ray fluorescence spectrometry done on platelets from patients with idiopathic scoliosis by Yarom *et al* showed a significant increase in intracellular calcium and phosphorus concentrations.[182] Studies on platelet aggregation and biochemical analysis of platelets in idiopathic scoliosis, performed by the same authors, showed a depressed aggregation with epinephrine and ADP, and a decreased ATPase activity of the cytoplasmic myosin compared with normal platelets.[181;183] These findings were thought to be caused by a mild calcium transport defect related to membrane and/or contractile protein metabolism. Yarom *et al* also noted that platelets of patients with AIS have an increased number of intracellular dense bodies, and an increased surface negative charge.[184;185] Impairment of platelet aggregation and dysfunction of myosin in patients with idiopathic scoliosis were also reported by several other authors,[180;186;187] and platelet aggregation was found to be more impaired in patients with progressive curves than in patients with stable curves.[180] Since it has been demonstrated that platelets share similar contractile proteins as muscles (actin and myosin),[188;189] it was suggested that a muscle disorder may play an important causative role in the development of idiopathic scoliosis. This theory, however, is not supported by previous studies of Suk and Kahmann, in which no significant difference could be demonstrated between platelet morphology and function in AIS patients compared with normal controls.[190;191]

More recently, platelet calmodulin, a calcium-binding receptor protein, has been mentioned as a possible predictor of curve progression in AIS. Kindsfater *et al* showed that the level of platelet calmodulin in patients with a progressive curve was significantly higher than in patients with stable curvature.[192] Lowe *et al* noted that treatment of AIS by means of bracing or spinal fusion resulted in a decrease of the platelet calmodulin levels in the majority of patients with AIS.[193] The cause of this decrease in platelet calmodulin is not clear. The authors of this study suggest that the changes in platelet calmodulin could be ascribed to paravertebral muscle activity, and hypothesize that calmodulin could serve as a systemic mediator of tissues having a contractile system. This theory, however, is controversial.[194]

In conclusion, platelet abnormalities are suggested to play a role in the development of idiopathic scoliosis; however, its mode of action remains unclear and more research is necessary to further investigate this possible relationship.

Melatonin

In 1959, Thillard was the first to report that resection of the pineal gland in chickens induced severe scoliotic deformation of the spine.[195] This finding was confirmed in a study of Dubousset *et al* in 1983.[196] Based on these results, the pineal gland was believed to play a role in the development of idiopathic scoliosis. In 1993, Dubousset and Machida performed pinealectomy in chickens, and noticed that scoliosis developed in 100% of the animals within 2 weeks after the operation. When the resected pineal gland was grafted in the intramuscular tissue of the trunk, or when the chickens were treated with melatonin after pinealectomy, scoliosis was found to develop in respectively 10 and 20% of the chickens.[197;198] The authors hypothesized that a defect in melatonin synthesis after pinealectomy induced a disturbance in the postural equilibrium, resulting in the development of idiopathic scoliosis.[199] Machida *et al* also investigated the effect of pinealectomy in rats. They performed pinealectomy in a group of quadrupedal rats, and in a group of rats that were made bipedal by resection of the forarms and tails. It was found that scoliosis developed in all of the bipedal rats, but in none of the quadrupedal rats.[200;201] Based upon these results, the authors postulated that the bipedal condition, as well as melatonin metabolism, plays an important role in the development of idiopathic scoliosis.

The role of melatonin in the development of idiopathic scoliosis has also been investigated by other authors. Using the same technique, pinealectomy in chickens did result in the development of scoliosis, however, the percentages in which scoliosis developed were found to be much smaller (50-80%).[202-204] It has been suggested that it is not the deprivation of melatonin but the operation itself playing a role in the development of experimentally induced scoliosis,[205] however, bipedal C57BL/6J mice – with reduced plasma and pineal melatonin levels – developed scoliosis without resection of the pineal gland.[206;207] Recently, Chung *et al* investigated the effects of pinealectomy in monkeys, which are much closer to human beings. They demonstrated that melatonin deficiency in nonhuman primates did not induce scoliosis.[208] These findings suggest that the factors producing scoliosis in lower animals, as chickens and rats, are different from the etiological factors in nonhuman and human primates.

Data in literature on the role of melatonin in the pathogenesis of AIS in humans are not conclusive. Machida *et al* reported that the melatonin concentration throughout a 24-hour period was significantly lower in patients with progressive scoliosis than in patients with stable curves and normal controls.[209;210] Several other studies did not find reduced melatonin levels in patients with AIS.[211-213] Changes in melatonin receptor binding have also been mentioned as a possible factor in the development of idiopathic scoliosis.[214] However, recent studies in humans have shown that there is no evidence of mutations in the melatonin receptor genes in patients with AIS.[215;216] Asymmetric expression of melatonin receptor mRNA in bilateral paravertebral muscles, and melatonin signalling dysfunction in osteoblasts have been demonstrated in AIS, but it is not clear whether these findings are causative or secondary changes.[217;218]

Overview

The pathogenesis of idiopathic scoliosis has been the subject of numerous studies, however, a single cause for this complex spinal deformity has still not been revealed. A typical feature of idiopathic scoliosis is the fact that it is related exclusively to humans.[219;220] All forms of scoliosis reported in other vertebrates are either congenital, neuromuscular, or experimentally induced.[47;48;55;197;200;201;220-222]

The fully erect posture, which is unique to humans, seems to be a prerequisite for the development of idiopathic scoliosis. This has been confirmed by the experimental rat studies of Machida *et al*, in which they demonstrated that pinealectomy only resulted in scoliosis when rats were made bipedal and had to walk upright.[200;201] Although melatonin can play a role in the development of idiopathic scoliosis, we agree with earlier reports by Lowe *et al*,[223] that the deprivation of melatonin in general is not very likely to be the cause of such a localized deformation of the spine as seen in AIS.

Dysfunction of the nervous system and imbalance of the paraspinal muscles both play an important role in the development of neuromuscular scoliosis, however, in idiopathic scoliosis these findings probably are secondary to the spinal deformation rather than a primary cause. Functional tethering by a relative short spinal cord has also been mentioned as a causative factor in the development of AIS, however, neurological dysfunction after scoliosis correction by distraction of the spinal curvature is fortunately an exception rather than the rule in daily practice. Other factors as growth and osteoporosis are definitely related to the development of AIS, but there is no evidence that they are causative factors.

Although any or all of the mentioned factors may play a role in the initiation and progression of idiopathic scoliosis at a certain stage, the presented material suggests that the observed deformation is primarily related to the mechanics of the upright human spine, and is the result of asymmetric loading of growing vertebrae. This is in agreement with recent work of the authors, which demonstrated the possible role of intrinsic spinal mechanisms in the pathogenesis of idiopathic scoliosis.[224-229]

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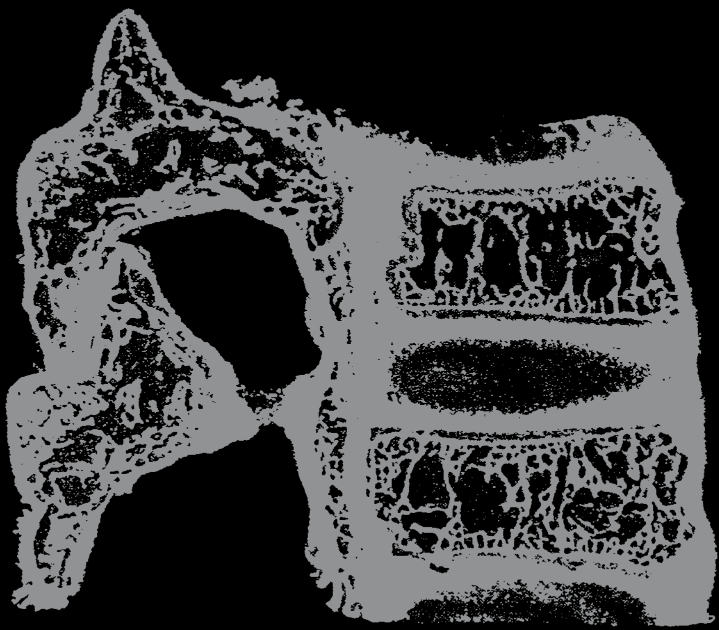
Effects of dorsal versus ventral shear loads on the rotational stability of the thoracic spine

3

A biomechanical porcine and human cadaveric study



Kouwenhoven JWM
Smit TH
Van der Veen AJ
Kingma I
Van Dieën JH
Castelein RM

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Introduction

Despite years of extensive research, the aetiology of idiopathic scoliosis still has not been resolved. Scoliosis is characterized by a deformation in the frontal (lateral curvature), sagittal (thoracic lordosis), and transverse plane (axial rotation).[1-8] Although the basic anatomy of the spine shows many similarities in all vertebrates,[9-11] idiopathic scoliosis has never been observed in vertebrates other than humans.[12;13]
An important difference between humans and other vertebrates is the fact that humans ambulate in a fully erect position, with the upper body's center of mass positioned directly above the pelvis. All other vertebrates – quadrupeds and bipeds – ambulate with flexed hips and knees and therefore have a more horizontally positioned spine, thus putting the upper body's center of mass in front of the pelvis.[14] In a previous study, the authors demonstrated that the fully upright posture, which is unique to humans, significantly alters spinal loading conditions.[15] This is in agreement with the studies of Machida *et al* that showed that pinealectomy in rats only resulted in scoliosis when rats were made bipedal and had to walk upright.[16;17]
The forces working on the spine can be decomposed into an axial compression component and anterior-posterior and lateral shear components. In all vertebrates, including humans, the spine is predominantly loaded by axial compression, which is mainly carried by the anterior column (intervertebral discs, endplates and vertebral bodies).[10] Shear loads, however, were found to be different between humans and other vertebrates. In the more horizontally positioned animal spine, shear loads are mainly ventrally directed and are counteracted by the facet joints and the posterior pull of muscles and spinal ligaments.[18] In humans, unlike other vertebrates, it was shown that certain parts of the spine, more specifically the dorsally inclined lower thoracic and high lumbar parts, are subject to *dorsally* directed shear loads.[15] While several studies have addressed the mechanical properties of the spine under ventral[19-22] and dorsal shear loads,[23;24] to the authors' knowledge, the effects of shear loads on vertebral rotation have thus far not been considered.
The facet joints not only counteract ventral shear loads, but also play an important role in providing rotational stability to the spine.[18;25-31] The anatomy of the facet joints and the central location of the major spinal ligaments suggest that vertebrae are not well designed to resist dorsally directed shear loads.
In the present study, it was hypothesized that dorsal shear loads render the facet joints less operative in their rotational control. To test our hypothesis, axial vertebral rotation was measured under dorsal and ventral shear loads, applied inside as well as outside the midsagittal plane of the thoracic spine. Human specimens could be obtained from adults; immature porcine specimens served as a model for the immature human spine. The aim of this study was to investigate if a significant difference exists between axial rotation occurring under dorsal and ventral shear loads.

Materials and Methods

Specimens and Specimen Preparation

A total of 7 fresh-frozen porcine cadaveric spines and 7 fresh-frozen human cadaveric spines were obtained for this study. The porcine specimens were harvested from immature female Landrace pigs (mean weight 58.1 kg, range 56-61 kg), which were obtained from the Animal Care Facility of the Utrecht University, The Netherlands. The human specimens were harvested from 1 female and 6 male human cadavers (mean age 66 years, range 51-85 years), which were obtained from the Department of Anatomy of the Utrecht University, The Netherlands.
Prior to dissection, computed tomography was performed of all specimens for documentation of vertebral abnormalities. Scans were made using a Brilliance Power 64 Slice CT scanner (Philips CT Secura, Philips Medical Systems, Eindhoven, The Netherlands). Volume scans were made with a slice thickness of 0.6 mm and a reconstruction index of 0.6 mm. Examination of the CT scans showed a normal thoracic spine without signs of congenital or acquired deformities in all porcine specimens. The human specimens showed a normal, mildly degenerated thoracic spine without radiological evidence of scoliosis or other spinal pathology.
Each specimen (porcine and human) was sectioned to obtain 2 thoracic functional spinal units (FSUs). A functional spinal unit consists of two vertebrae and the connecting soft tissue.[32] We obtained 1 FSU from the mid thoracic spine and 1 FSU from the lower thoracic spine. Porcine FSUs were obtained at the levels T7-T8 (7 samples) and T9-T10 (7 samples). Human FSUs were obtained at levels T6-T7 (7 samples), T8-T9 (3 samples), T9-T10 (1 sample), and T10-T11 (3 samples). The residual muscular tissue was carefully resected, leaving all ligaments and joint capsules intact. At both sides of each FSU 2 cm of the ribs were preserved, including the costotransverse and the costovertebral articulations. All specimens were wrapped in plastic bags and stored in a freezer at -20°C. Prior to biomechanical testing, the samples were left to thaw for 12-17 hours at 4°C. Testing was performed at room temperature (20°C). During preparation and testing, the specimens were wrapped in gauzes to keep them moist.

Experimental Procedure

The upper and lower vertebrae were both embedded in aluminum cups using a low melting temperature alloy (Cerrolow-147). To optimise the connection between the FSU and the Cerrolow, three wood screws were screwed through the top endplate of the upper vertebra and the bottom endplate of the lower vertebra to a maximum depth of 5 mm. All articulating parts were kept free. In larger specimens, spinous processes had to be partly removed to allow embedding in the moulds. A plastic marker containing 3 LEDs was rigidly fixed to the anterior surface of each vertebral body *(Figure 1)*.

The test rig consisted of two sliding tables – a horizontally positioned table that could slide in the axial direction of the spine (= Y-direction) and a vertically positioned table that could slide in the shear direction (= Z-direction).[33] The aluminum cups were connected to the sliding tables in such a way that the mid-disc plane of the FSU was vertical and formed the XZ plane of an anatomic three-dimensional coordinate system. A shear load (Fs, *Figure 1*) was applied to the upper vertebra of the FSU in dorsal or in ventral direction. These shear loads were applied directly to the sliding table of the upper vertebra by a hydraulic material testing machine (model 8872; Instron & IST, Canada). The load direction could be changed from dorsal to ventral by rotating the specimen 180 degrees around the Y-axis. While the lower vertebra was rigidly fixed to the horizontal table, two bearings allowed low-friction axial rotation and lateral translation of the upper vertebra. These boundary conditions allowed the upper vertebra to rotate along the anatomic spinal Y-axis. In both dorsal and ventral directions, shear loads were applied to the upper vertebra at 3 positions: (1) in the midsagittal plane (centrally); (2) at 1 cm to the right; and (3) at 1 cm to the left of the midsagittal plane (eccentrically) *(Figure 2)*. The applied loads were 50, 100, and 150N, resulting in additional torsion moments of 0.5, 1.0, and 1.5 Nm, respectively for the eccentric loading conditions. The torsion moments for the central position obviously were zero for all load cases. Tests were performed in random order. After each load increment, the load was maintained 30 seconds to allow for visco-elastic creep. The FSU was preloaded in the Y-direction with a compression force of 500 N (Fc, *Figure 1*), using a dead weight connected to the horizontal table with a pulley system.

Motion of the markers was recorded at 100 Hz by an automated optoelectronic 3D movement registration system with 1 array of 3 cameras (Optotrak©). The 3D resolution of this system at 2.25 m distance is equal to 0.01 mm. Before testing, the axes of the Optotrak system were aligned with the anatomical axes of the FSU. Based upon the trajectories of the markers attached to the vertebrae, a computer program written in Matlab (Mathworks inc, version 7.0.4 R14 SP2) was used to calculate rotation of the upper vertebra relative to the lower vertebra in the transverse plane of the FSU.

Statistics

The statistical analyses were performed using SPSS statistical software, version 14.0 (SPSS, Inc., Chicago, IL). For each combination of load magnitude and point of application, the effects of dorsally directed shear loads were compared with the effects of ventrally directed shear loads using a paired t-test. A P-value of less than 0.01 was considered to be statistically significant.

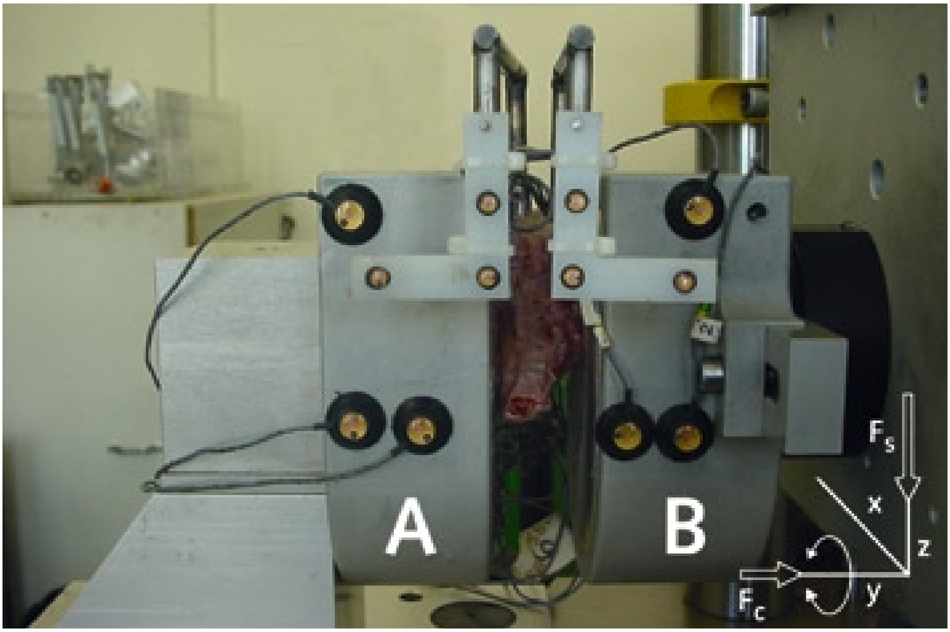

Figure 1. Spine tester with a human T8-T9 spinal segment mounted. The lower vertebra (T9) is embedded in the fixated cup (A), and the upper vertebra (T8) in the cup that could rotate friction-free along the anatomic spinal Y-axis by using two bearings (B). A plastic marker (in white) containing 3 LEDs was rigidly fixed to the anterior surface of each vertebral body.

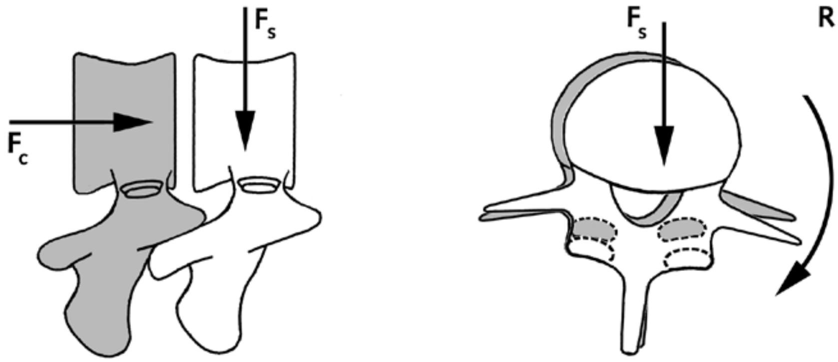

Figure 2. Example of a dorsally directed shear load (F_s) applied to the upper vertebra (in white) at the right side of the midsagittal plane, resulting in rotation of the vertebral body to the right side of the subject (from a cranial view, clockwise rotation of the upper vertebra). F_c = compression preload.

Results

Porcine FSU specimens

Shear loads applied in the midsagittal plane resulted in marginal rotation of the upper vertebra *(Figure 3)*. In the midsagittal plane, a dorsally directed shear load of 50N resulted in a mean rotation of 0.06° at the mid thoracic levels, and of 0.15° at the lower thoracic levels. A ventrally directed shear load of 50N resulted in an average of 0.10° and 0.05° rotation at respectively the mid and lower thoracic levels. Increment of the shear loads to a maximum of 150N resulted in only a marginal increase of vertebral rotation, and no statistically significant difference could be demonstrated between the effects of dorsally and ventrally directed shear loads.
By applying shear loads eccentrically, an additional rotary moment was introduced to the FSU. Loads were applied to the right and to the left side of the midsagittal plane to a maximum load of 150N (1.5 Nm). As shown in *Figure 3*, this resulted in an incremental rotation of the upper vertebra. The ranges of motion for axial rotation to the left plus right (means and SEM) at the mid and lower thoracic levels are listed in *Table 1*. In the mid thoracic spine, dorsally directed shear loads resulted in significantly more rotation than ventrally directed shear loads at all force levels ($P <$ 0.005). In the lower thoracic spine, no significant difference could be demonstrated

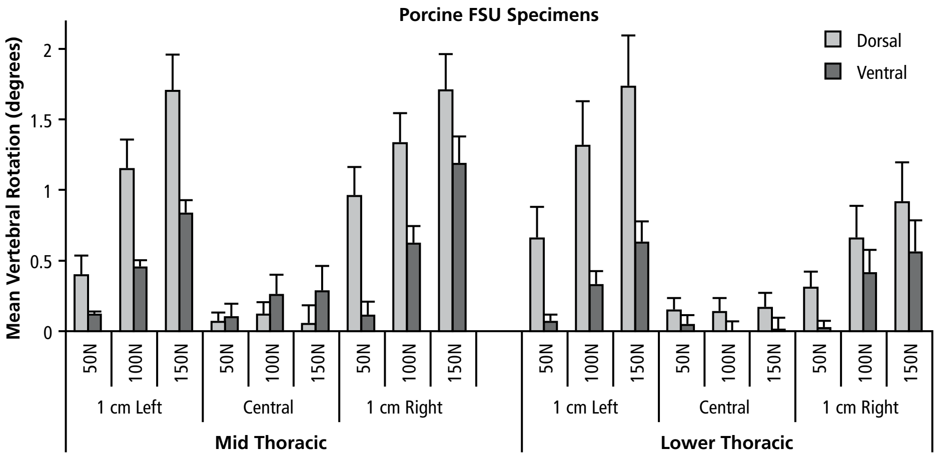

Figure 3. Mean values of axial vertebral rotation (± SEM) of the mid and lower thoracic FSU's of the porcine spines (for convenience the absolute values are presented). In both dorsal and ventral directions, shear loads were applied to the upper vertebra in the midsagittal plane (centrally), and at 1 cm to the right and to the left at incremental loads of 50, 100, and 150N. This resulted in incremental torsion moments of 0.5, 1.0, and 1.5 Nm.

at 50N. At 100 and 150 N, significantly more rotation was observed under dorsal shear loads, by 168% at 100N and 124% at 150N ($P < 0.005$).

Table 1. Porcine FSU specimens. Eccentrically applied shear loads.

Level	Shear Force (N)	Vertebral Rotation (°)		*P*
		Dorsal Direction	Ventral Direction	
Mid-thoracic	50	0.68 ± 0.14*	0.11 ± 0.05*	0.002
	100	1.24 ± 0.19*	0.54 ± 0.06*	0.003
	150	1.70 ± 0.23*	1.01 ± 0.10*	0.003
Lower thoracic	50	0.48 ± 0.15	0.04 ± 0.04	0.011
	100	0.99 ± 0.24*	0.37 ± 0.11*	0.003
	150	1.32 ± 0.28*	0.59 ± 0.16*	0.003

Ranges of motion for axial rotation to the left plus right (mean and SEM) of the mid and lower thoracic porcine FSU's at torsion moments of 0.5, 1.0, and 1.5 Nm, for the *eccentric* dorsal and ventral loading conditions. * Mean rotation angle under dorsal shear loads is significantly larger compared with ventral shear loads ($P<0.01$).

Human FSU specimens

Shear loads applied in the midsagittal plane resulted in minimal vertebral rotation *(Figure 4)*. A dorsally directed shear load of 50N resulted in a mean rotation of 0.01° at the mid thoracic levels, and 0.03° at the lower thoracic levels. Ventral shear loads resulted in respectively 0.003° and 0.02° rotation. Increment of the shear load up to a maximum of 150N resulted in marginal increase of vertebral rotation, and also no statistically significant difference could be demonstrated between the effects of dorsal and ventral shear loads.
As in the porcine FSU's, eccentrically applied shear loads to the human segments resulted in rotation of the upper vertebra relative to the lower vertebra *(Figure 4)*. The ranges of motion for axial rotation to the left plus right (means and SEM) at the mid and lower thoracic levels are listed in *Table 2*. At the mid-thoracic levels, dorsal shear loads resulted in significantly more rotation than ventral shear loads, by 244% at 100N and 131% at 150N ($P < 0.005$). At the lower thoracic levels the effects of dorsal shear loads were also significantly larger ($P < 0.01$), except at 150N.

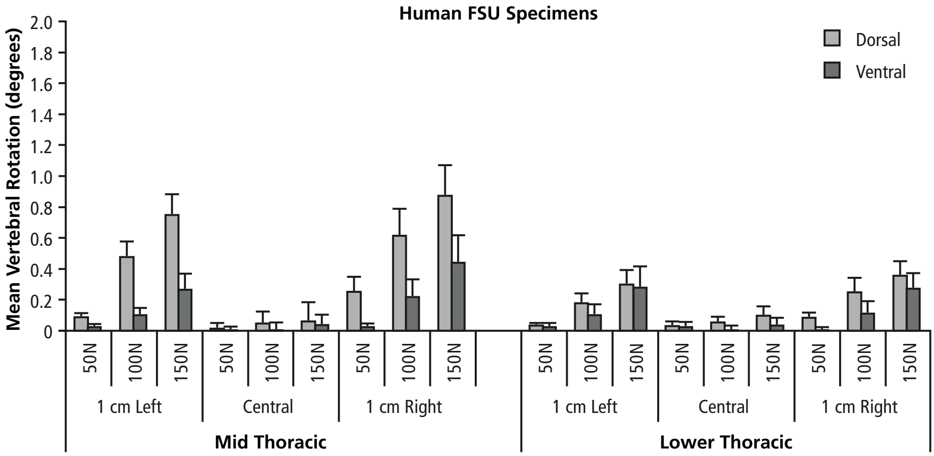

Figure 4. Mean values of axial vertebral rotation (± SEM) of the mid and lower thoracic FSU's of the human spines under the same loading conditions as the porcine segments (for convenience the absolute values are presented).

Table 2. Human FSU specimens. Eccentrically applied shear loads.

Level	Shear Force (N)	Vertebral Rotation (˚)		*P*
		Dorsal Direction	Ventral Direction	
Mid-thoracic	50	0.17 ± 0.04	0.02 ± 0.01	0.011
	100	0.55 ± 0.10*	0.16 ± 0.07*	0.002
	150	0.81 ± 0.12*	0.35 ± 0.13*	0.002
Lower thoracic	50	0.06 ± 0.01*	0.01 ± 0.01*	0.006
	100	0.21 ± 0.06*	0.11 ± 0.07*	0.007
	150	0.33 ± 0.06	0.28 ± 0.11	0.505

Ranges of motion for axial rotation to the left plus right (mean and SEM) of the mid and lower thoracic human FSU's at torsion moments of 0.5, 1.0, and 1.5 Nm, for the eccentric dorsal and ventral loading conditions. * Mean rotation angle under dorsal shear loads is significantly larger compared with ventral shear loads ($P<0.01$).

Discussion

The basic anatomy of the spine shows many similarities between vertebrates.[9-11] Broad vertebral endplates and discs are well suited to resist axial loads, and strong posterior muscles and ligaments can counteract ventral shear loads.[18] The intervertebral facet joints also counteract ventral shear loads, and play an important role in providing rotational stability to the spine.[25-31] Despite these similarities in spinal anatomy, idiopathic scoliosis has never been observed in quadrupeds, it is a condition restricted exclusively to humans.[12;13]

In a previous study, model simulations predicted that a fully upright posture significantly alters spinal loading conditions, possibly facilitating rotational instability.[15] As in other vertebrates, the human spine is mainly loaded in axial direction, however, in the dorsally inclined segments of the human spine shear loads were found to be *dorsally* directed. We postulated that the spinal column is not well designed to resist these dorsally directed shear loads, because of the anatomy of the facet joints and the posterior location of the major spinal muscles and ligaments. Other support for the upright position as a prerequisite for idiopathic scoliosis is provided by Machida *et al* in their studies on pinealectomized rats. Scoliosis developed only and consistently in fully erect bipedal rats, but not in otherwise similarly treated quadrupedal rats.[16;17]

In the present study, the effects of dorsally and ventrally directed shear loads on the rotational stability of the thoracic spine were investigated in human and porcine specimens. As in most *in vitro* studies, human specimens had to be obtained from adults, because immature human specimens are scarce. To obtain information about the effects on the immature spine, we used immature porcine vertebrae because they closely resemble human vertebrae in terms of vertebral dimensions, facet orientation, and contour.[34-36] Mid and lower thoracic spinal segments were used for biomechanical testing, because the most prevalent types of adolescent idiopathic scoliosis (AIS) show a primary thoracic curve rotated to the right side with the apex located between T6-T11.[37-42] Since research on the position of the rotational axis of the spine showed contradicting results,[25;28;43-45] an experimental setup was developed in which the FSU was allowed to seek its own anatomical axis of rotation.

The results of this study showed that in porcine as well as in human specimens, dorsally and ventrally directed shear loads applied in the midsagittal plane of the spine did not induce relevant vertebral rotation. However, when dorsal shear loads were applied eccentrically, significant rotation was shown of the mid and lower thoracic vertebrae. Furthermore, at both thoracic levels, significantly more vertebral rotation occurred under *dorsal* shear loads than under *ventral* shear loads, in human as well as in porcine specimens. In the human spine, overall, less rotation occurred in the lower thoracic segments than in the mid thoracic segments. This is in agreement with other studies, which showed increasing torsional stiffness towards the thoracolumbar junction of the human spine.[18;46] Under the same loading conditions, more rotation was observed in the porcine segments than in the human segments. This finding can probably be explained by the fact that the human specimens were obtained from older subjects and showed mild degeneration of the vertebrae and soft tissues, resulting in increased stiffness of the spinal segments. We postulate that in the immature human spine dorsal shear loads result in even more vertebral rotation, because the physiological range of motion in the pediatric spine is greater than that of the adult,[47;48] and the intervertebral disc space in humans is higher than in quadrupeds, resulting in more flexibility.[11;34;49]

The exact sequence in which scoliotic deformation takes place is not yet revealed. However, it has been recognized that vertebral rotation takes place in the early development of scoliosis.[50] Previously, the authors demonstrated the existence of a preexistent pattern of vertebral rotation in the normal, *nonscoliotic* spine.[51-53] In humans, as well as in quadrupeds, the mid and lower thoracic vertebrae showed a predominant rotation to right side. This rotational pattern is similar to what is seen in the most prevalent types of AIS.[37-42] If dorsal shear loads act upon an already slightly rotated spinal segment, this may lead to an increase in rotation in the already predetermined direction.

The findings of the present study suggest that the more or less horizontally positioned animal spine, which is subject to axial compression and ventral shear loads, is a very stable construct. In the human spine, however, the dorsally inclined spinal segments are subject to dorsally directed shear loads.[15] During the adolescent growth spurt the thoracic kyphosis flattens slightly, where after it turns back to normal in most instances.[3;54] In children with a more dorsally inclined thoracic spine, dorsal shear loads are larger, which based upon the results of the present study, is likely to result in a rotationally less stable spinal segment. This is in agreement with earlier research in which it has been demonstrated that backward inclination of vertebrae in the sagittal plane has prognostic significance in the progression of AIS.[55]

We assume that dorsal shear loads working on the dorsally inclined segments of the growing immature human spine can, if they exceed a certain threshold, render the facet joints less operative in their rotational control and may induce rotation of the spinal segment. If progressive, these dorsal shear loads not only reduce rotational stability, but also can enhance a slight pre-existent vertebral rotation, as is the case in the normal spine.[51] According to the law of Hueter-Volkmann,[56-58] asymmetric loading of the vertebrae then would lead to asymmetric growth in all three planes of the vertebrae, resulting in a progressive scoliotic deformation of the spine.[59-61] Asymmetric loading of growing vertebrae has been shown to result in AIS-like deformities in animals,[62-66] and could explain the development and progression of the deformity in humans.

Conclusions

The effects of dorsal and ventral shear loads on vertebral rotation in the mid and lower thoracic spine were analyzed in human and porcine spinal segments. In both species, eccentrically applied dorsal shear loads induced more vertebral rotation than ventral shear loads. *In vivo*, dorsal shear loads occur only in the erect human spine. This *in vitro* study demonstrated that dorsal and ventral shear loads have a similar effect on the porcine as on the human spine, and therefore, rotational stability seems to be more related to the way the spine is loaded, than to specific anatomical differences between human and quadruped spines.

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Analysis of preexistent vertebral rotation in the normal spine

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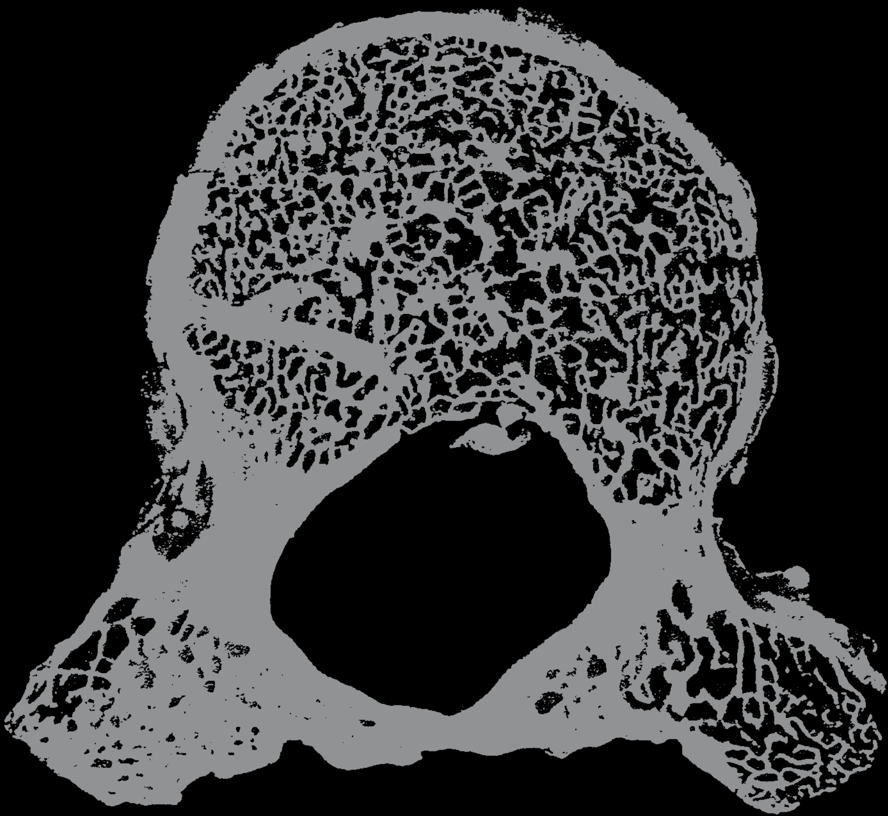

Kouwenhoven JWM
Vincken KL
Bartels LW
Castelein RM

Spine 2006;31(13):1467-72

Introduction

Vertebral rotation is an essential component of adolescent idiopathic scoliosis (AIS). Although the typical curves and their associated rotation in AIS have been well described,[1-15] little is known of possible patterns of rotation in the normal, *nonscoliotic* spine. Few studies have dealt with this question, often using relatively inaccurate measurement techniques, one of the problems being reproducible landmark definition.[16-18] Rotation in the normal spine is relevant to the curve patterns seen in AIS.
We developed a CT-based computerized and semi-automatic, reproducible measurement method to determine vertebral rotation in the transverse plane from T2 to L5 in *nonscoliotic* spines. The purpose of this study was to determine if there is a preexistent pattern of rotation in the normal *nonscoliotic* spine.

Subjects and Methods

Twenty-five males and 25 females with a mean age of 33.3 years (range, 7-74 years), without clinical or radiological evidence of scoliosis or other spinal pathology had undergone CT examination of the thorax and abdomen for reasons such as pulmonary disease or Hodgkin lymphoma. Scans were made using the Philips Tomoscan AVE and MX 8000 CT scans. The slice thickness was 5 mm. None of the patients had a history of spinal deformity according to the charts; furthermore, the alignment of the spine in the frontal plane was evaluated from the overview scan in all 50 patients. Any deviation from a straight vertebral column led to exclusion of the patient. Vertebral rotation was measured in the transverse plane at all levels from T2 down to level L5, using the method as described below.

CT Measurement Method

We developed a new semi-automated procedure using an interactive application to calculate the rotation angle of the vertebrae. Vertebral rotation was defined as the angle between the longitudinal axis of each vertebra and the midsagittal axis of the trunk (= reference line). The reference line was defined as zero degrees rotation. Rotation to the right was defined as a positive angle, to the left as a negative angle.
For each vertebra, a single slice of the CT volume was selected at the center of the vertebral body such that the pedicles were clearly visible.[19] The reference line was defined at level T5 as the line between the center of the spinal canal and the center of the sternum; the longitudinal axis of each vertebra was defined as the line through the middle of the vertebral body and the center of the spinal canal. To be able to calculate the rotation angle of each vertebra fully automatically, we needed to segment the vertebrae and the spinal canal in every selected slice. Furthermore, we also

segmented the sternum at level T5. The spinal canal and the sternum were uniquely defined by a simple region growing step. We also used a region growing step for the segmentation of the vertebrae; in case of a small contrast between the vertebrae and the surrounding tissues, the surplus of segmented tissue was manually erased. Next we calculated the center of mass (COM) of the spinal canal (point A), of the sternum at level T5 (point B), and of the segmented vertebra (point C), because they accurately represent the center of these objects *(Figure 1)*. The reference line is the line through points A and B, the longitudinal axis is the line through points A and C. In practice, it could occur that A and C are close together, which may lead to an unstable definition of the longitudinal axis. An elegant and robust way to circumvent this is to calculate the COM only of the anterior half of the segmented vertebral body (point C'). To define this region of interest, two lines perpendicular to the initial longitudinal axis AC were implemented fully automatically *(Figure 2)*.
To evaluate the reliability of this method we performed an interobserver and intraobserver analysis. Three different observers manually segmented the slices of T2-T6 in the same four randomly chosen subjects independently. For the intraobserver analysis, Observer 1 manually segmented these slices three times at separate sittings. The vertebral rotation angles were calculated automatically and the obtained results were used to calculate the intraclass correlation coefficient as a measure for interobserver and intraobserver reliability.

Statistics

Statistical analysis was performed by means of SPSS statistical software (SPSS, Inc., Chicago, IL). The observed frequencies of right and left vertebral rotation were used to test the null hypothesis of equal probability with the binomial test. To determine if the mean vertebral rotation angles were statistically significant we used the one-sample T test. To calculate the 95% confidence interval, we used a t-value of $t^{49} = 2.01$. A P value of less than 0.05 was considered to be statistically significant.

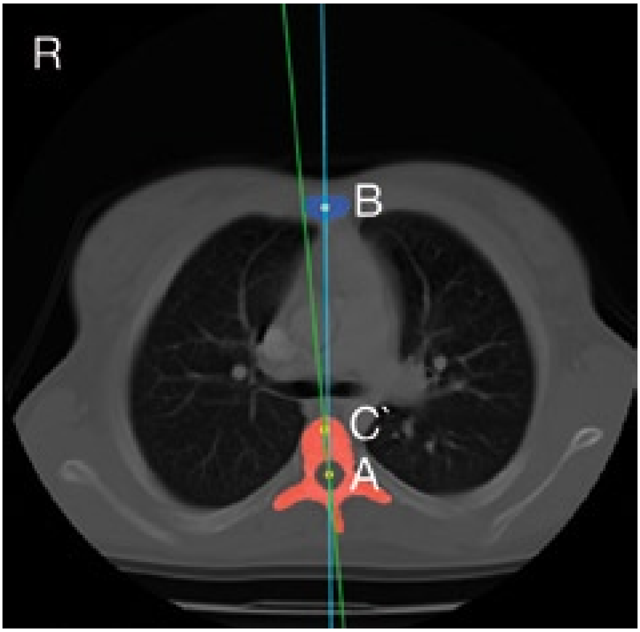

Figure 1. Longitudinal axis of vertebra T5 (red) represented by the line (green) through the COM (A) of the vertebral canal and the COM (C′) of the anterior half of the vertebral body. Reference line (light blue) drawn through the COM (point A) of the vertebral canal and the COM (point B) of the sternum (dark blue).

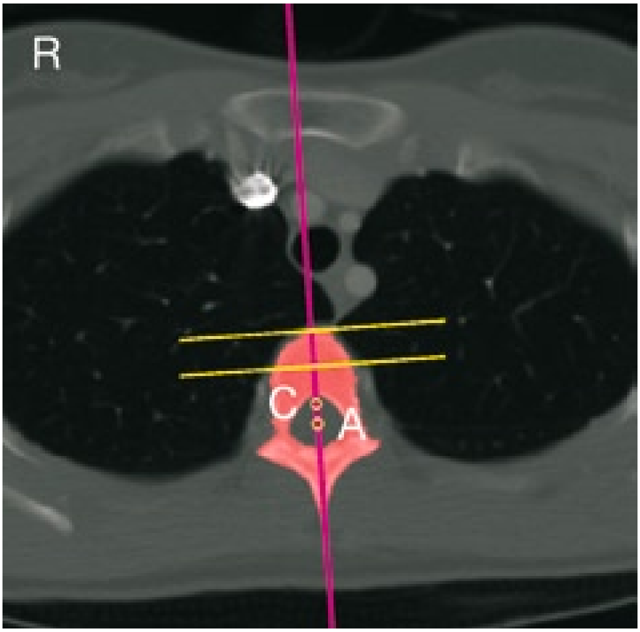

Figure 2. Initial longitudinal axis of vertebra T3 (red) represented by the line (purple) through the COM (A) of the vertebral canal and the COM (C) of the vertebra.
The two yellow parallel lines are perpendicular to the initial longitudinal axis defining the anterior half of the vertebral body.

Results

Vertebral rotation in the transverse plane was determined from level T2 down to L5 in all 50 persons. The intraclass correlation coefficient calculated for interobserver and intraobserver reliability of our method were, respectively 0.96 ± 0.06 and 0.99 ± 0.01 (mean ± SD). *Table 1* demonstrates the observed frequencies of right and left vertebral rotation. In the high thoracic spine (T2-T4), vertebrae showed a predominant rotation to the left. At levels T3 and T4, this proportion differed significantly from an equal right-left distribution (P<0.05). In the mid and lower part of the thoracic spine and the lumbar spine (T5-L5), vertebrae showed a predominant rotation to the right, which was significant at levels T6-T10 (P<0.001) and T11 (P<0.02).

Table 1. Right-left distribution of vertebral rotation (T2-L5).

Vertebra	Direction of rotation		*P*
	Right	Left	
T2	26 (52%)	24 (48%)	0.888
T3	17 (34%)*	33 (66%)*	0.033
T4	16 (32%)*	34 (68%)*	0.015
T5	30 (60%)	20 (40%)	0.203
T6	42 (84%)*	8 (16%)*	<0.001
T7	41 (82%)*	9 (18%)*	<0.001
T8	42 (84%)*	8 (16%)*	<0.001
T9	41 (82%)*	9 (18%)*	<0.001
T10	38 (76%)*	12 (24%)*	<0.001
T11	34 (68%)*	16 (32%)*	0.015
T12	31 (62%)	19 (38%)	0.119
L1	31 (62%)	19 (38%)	0.119
L2	32 (64%)	18 (36%)	0.065
L3	31 (62%)	19 (38%)	0.119
L4	26 (52%)	24 (48%)	0.888
L5	24 (48%)	26 (52%)	0.888

Right-left distribution of vertebral rotation at T2-L5 in 50 persons with normal, non-scoliotic spines. The observed frequencies of right and left vertebral rotation at each level are given along with the significance level. *statistically significant (P < 0.05).

Measurement of the vertebral rotation angle for the whole group showed a mean rotation angle to the left in the high thoracic spine of which T3 and T4 were statistically significant ($P < 0.01$). Vertebrae T5 to L5 had a mean rotation angle to the right, that was significant at level T6 (2.5°) to T11 (1.4°) with a maximum rotation of 2.6° at T7 ($P < 0.001$) *(Table 2; Figure 3)*.

Table 2. Mean vertebral rotation angle (T2-L5).

Vertebra	Mean rotation angle (°)	95 % confidence interval		*P*
		Lower bound (°)	Upper bound (°)	
T2	-0.1664	-0.9974	0.6646	0.689
T3	-1.0138*	-1.7210	-0.3066	0.006
T4	-1.0176*	-1.7299	-0.3053	0.006
T5	0.6142	-0.2045	1.4329	0.138
T6	2.4886*	1.7472	3.2300	<0.001
T7	2.6118*	1.7585	3.4651	<0.001
T8	2.365*	1.4841	3.2459	<0.001
T9	1.9902*	1.2488	2.7316	<0.001
T10	1.6962*	0.8799	2.5125	<0.001
T11	1.4454*	0.5854	2.3054	0.001
T12	0.8008	-0.2212	1.8228	0.122
L1	0.5156	-0.3637	1.3949	0.244
L2	0.6086	0.2046	1.4218	0.139
L3	0.5612	-0.3446	1.4670	0.219
L4	0.0718	-0.8360	0.9796	0.874
L5	-0.0160	-1.0679	1.0359	0.976

Mean vertebral rotation angles (in degrees) with 95% confidence interval of T2-L5 in 50 persons with normal, *nonscoliotic* spines. *statistically significant ($P < 0.05$).

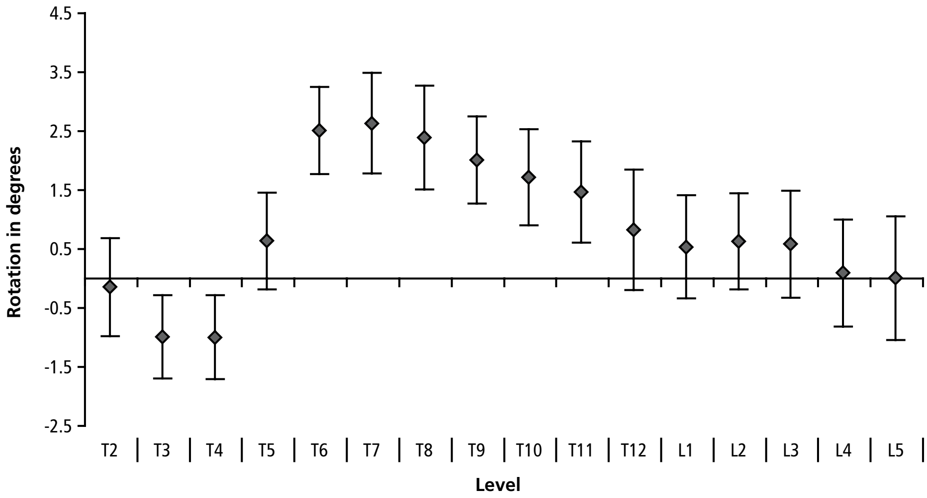

Figure 3. Mean vertebral rotation angles (in degrees, with 95% confidence interval) in the transverse plane at level T2-L5 in 50 persons with a normal, *nonscoliotic* spine.

When this group was separated into males and females, the mid and low thoracic spine (T6-T11) still demonstrated a significant rotation to the right. In females, rotation of the high thoracic vertebrae was also significant to the left, as in the group as a whole. In males, however, rotation in this region became insignificant *(Figure 4)*.

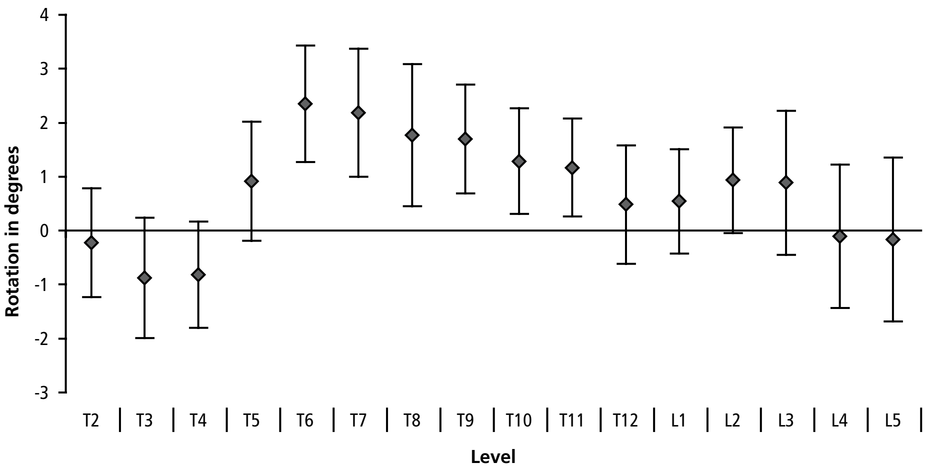

Figure 4a. Mean vertebral rotation angles (in degrees, with 95% confidence interval) in the transverse plane at level T2-L5 in 25 males with a normal, *nonscoliotic* spine.

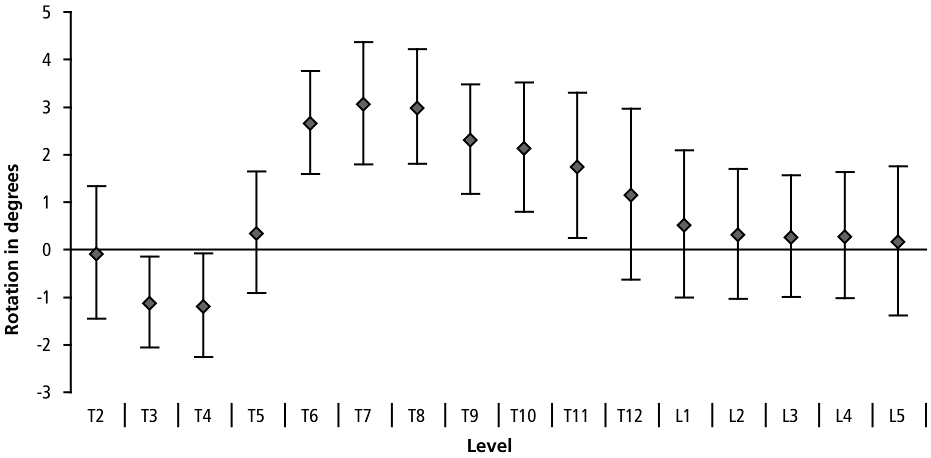

Figure 4b. Mean vertebral rotation angles (in degrees, with 95% confidence interval) in the transverse plane at level T2-L5 in 25 females with a normal, *nonscoliotic* spine.

Discussion

Our study in the normal, *nonscoliotic* spine showed a predominant rotation to the left of the high thoracic vertebrae, and to the right of the mid and lower thoracic vertebrae, which differed significantly from an equal right-left distribution. When males and females were analyzed separately, rotation remained significant to the right in the mid and lower thoracic region, in the high thoracic region however, rotation to the left was only significant in the female group. Around the thoracolumbar junction, this rotation was shown to decrease back towards the midline; however, we did not demonstrate a reversal of its direction to the left in the lumbar spine.

Rotation and lateral flexion of the spine are coupled phenomena[20]. Vertebral rotation into the convexity of the curve is known to be an essential component of AIS.[21] The majority of cases shows a structural midthoracic right convex curve with compensatory curves to the left above and below.[1-15] *(Figure 5)*.

Several methods have been developed to measure rotation of vertebrae on plain radiographs, based either on the projection of the spinous process[22;23] or on the projection of the pedicles.[18;24-26] In idiopathic scoliosis, it is easy to determine the direction of rotation and to get an impression of its magnitude on plain radiographs. However, it is impossible to measure the exact angle of vertebral rotation. Although CT measurements have been shown to be far superior in this respect, problems of finding reliable landmarks, as well as a neutral reference line, remained.[1;16;19;27-31] In only two studies, vertebral rotation has been measured in the normal, *nonscoliotic*

spine.[16;18] Furthermore, no other study before has systematically analysed rotation throughout the entire thoracic and lumbar spine.
Because of difficulties and inaccuracies in finding reliable reference points in the methods mentioned previously, we developed a new semi-automatic computerized CT measurement method. Vertebral rotation was defined as the angle between the longitudinal axis of each vertebra and the midsagittal axis of the trunk (= reference line).

Figure 5. A typical example of an idiopathic thoracic curve pattern, with a mid thoracic curve convex to the right and compensatory high thoracic and lumbar curves convex to the left. (Note that the vertebral bodies are rotated away from the midline more than the spinous processes).

Although we considered using the reference line as defined by Aaro *et al*,[1;27;28] which is a good representation of the anatomic midline of the trunk, we could not use their reference points, because of their proven inaccuracy.[31] To define our reference line we used the COM of the vertebral canal and the COM of the sternum as reference points, because they accurately represent the center of these objects. Practice revealed that the longitudinal axis of the vertebrae was most accurately defined when the COM was calculated of the anterior half of the vertebral body. The other reference point we used was the COM of the spinal canal, which forms the axis of rotation in idiopathic scoliosis.[8;32] Interobserver and intraobserver analysis demonstrated high reliability and reproducibility of our method.

The fact that rotation in the *nonscoliotic* spine is not neutral or randomly distributed is an important finding, because it may explain to a large extent the most prevalent patterns of rotation in AIS. Apparently, once the spine starts to decompensate due to a still unknown cause, it logically follows this already built-in rotational tendency.

The cause of this preexistent rotation is not clear. In the 19th century, anatomists described the fifth to eighth thoracic vertebrae in the normal spine to be asymmetric in the transverse plane, the left sides of their body being flattened by the pressure of the aorta.[2;7;10;11;33-36] Our CT analysis showed the descending aorta to approximate the vertebral column on the left from T5 down to the thoracolumbar junction. The left anterolateral position of the aorta offers the possibility to exert an asymmetric rotational force to the right.[34;35] This is in agreement with the results of our study, which demonstrated a rotation to the right of the mid and lower thoracic vertebrae starting at level T5. Furthermore, we observed a rotation to the left of the high thoracic vertebrae, which was more significant in the female group. Although we have no explanation for this opposite rotation, it could possibly be a compensatory mechanism similar to what is seen in AIS *(Figure 5)*. In an effort to explain the most prevalent patterns of AIS with its predominance of right sided thoracic curves, predominance of right-handedness as well as the position of the heart and the aorta[34;35] have been implicated in causing the rotation of the vertebrae. However, data on the direction of rotation in scoliosis in left handed patients[37;38] and patients with situs inversus are scarce and inconclusive. We are presently organizing a similar study in patients with situs inversus.

Our study, by no means, offers an answer to questions concerning the pathogenesis of idiopathic scoliosis. It does show, however, that there are factors built into the normal, *nonscoliotic* spine that may govern the direction of rotation once scoliosis starts to develop.

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Spinal decompensation in neuromuscular disease

5

Kouwenhoven JWM
Van Ommeren PM
Pruijs JEH
Castelein RM

Spine 2006;31(7):E188-91

Introduction

Scoliosis secondary to neuromuscular disease is probably one of the oldest forms of spinal deformity[1-25]. Duchenne's muscular dystrophy, cerebral palsy, spinal muscular atrophy, and spina bifida all lead to random and unpredictable patterns of paralysis, not favoring any muscle group on either side of the body's midline.[13;17]
The purpose of this retrospective study was to determine if in different types of neuromuscular scoliosis, despite their differences in etiology, a predominant curve shape and direction can be found, and if similarities with idiopathic scoliosis exist.

Subjects & Methods

A retrospective radiographic review was performed on patients with scoliosis secondary to neuromuscular disease treated at the University Medical Center Utrecht, Utrecht, The Netherlands. Clinical charts and spinal full-length radiographs of 198 patients, including 105 males and 93 females, with a mean age of 12 years and 2 months (range, 3-32 years), were obtained and reviewed. An orthopedic surgeon, a neurologist and a physical therapist had examined all patients, and no asymmetric muscle weakness was reported. All curves greater than 10°, measured according to Cobb, were included. Patients with radiologic evidence of congenital deformities of the vertebral bodies were excluded.
Curves were classified according to their apical vertebra or apical disc space as thoracic (T2-T11), thoracolumbar (T12, T12-L1 disc space, or L1), or lumbar (apex at or below L1-L2 disc space), as defined by the Scoliosis Research Society. C-type curves that extended along the total length of the spine in 1 direction were assumed to represent the most typical neuromuscular curve pattern[26]. Although these involve the whole length of the spine, their apex varied, and they could also be classified as thoracic, thoracolumbar, or lumbar[12;24], as well as the single and double structural curves in this group. Double curves were classified based on the apical level or apical disc space of their major curve.[21] Patients were divided into four groups according to the kind of their neuromuscular disease. There were 40 patients with Duchenne muscular dystrophy, 25 with spinal muscular atrophy (9 males, 16 females), 68 with cerebral palsy (25 males, 43 females), and 65 with spina bifida (31 males, 34 females).

Statistics

Statistical analysis was performed by means of SPSS statistical software (SPSS, Inc., Chicago, IL). After cross tabulation, the observed frequencies of right and left curve distribution were used to test the null hypothesis of equal probability with the binomial test.

Results

In the total group of 198 patients, 131 had a single curve and 67 had a double curve pattern. Only 27 patients (14%) had a C-shaped curve that extended all along the spine *(Figure 1)*. Although in this group all apices were located around the thoracolumbar junction, its exact level varied, with apparent consequences for curve con-

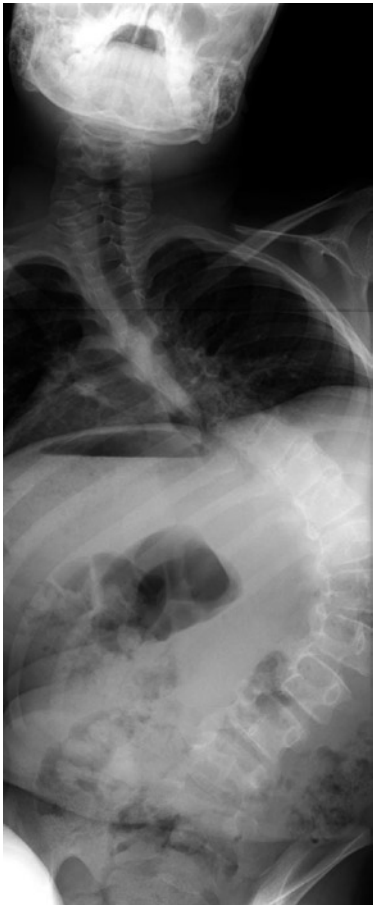

Figure 1. An example of a right convex C-shaped curve in a 14 years old child with cerebral palsy. This curve was classified as thoracolumbar according to the apex at L1.

vexity. Twelve had a somewhat higher mean apex at T11 (10.75 ± 0.62) and were classified as thoracic; 67% of these were found to have their convexity to the right. Fourteen had a mean apex at T12 (12.14 ± 0.36) and were classified as thoracolumbar, and one was classified as lumbar (apex at L2); all these curves had their convexity to the left *(Table 1)*.

Table 1. Right-left distribution of C-shaped curves.

C-type curve	N	Direction		*P*
		Right	Left	
Thoracic	12	8 (66.7%)	4 (33.3%)	0.388
Thoracolumbar	14	0 (0%)*	14 (100%)*	<0.001
Lumbar	1	0 (0%)	1 (100%)	-

Right-left distribution of C-shaped curves in 27 patients with neuromuscular scoliosis.
The observed frequencies of right and left curve distribution are given along with the significance level.
*statistically significant ($P < 0.05$).

A total of 171 patients had a single, non-C-shaped curve of which 52 were classified as thoracic, 51 as thoracolumbar, and 68 as lumbar. Concerning the thoracic curves, 40 or 77% of 52 patients had a right convex scoliosis, which differed significantly from a random distribution ($P < 0.001$) *(Table 2)*. Mean apex in this group was at T8 (7.98 ± 2.17). In the group of thoracolumbar curves, 42 or 82% of 51 patients also had a right convex scoliosis ($P < 0.001$), with a mean apex at the T12-L1 disc (12.51 ± 0.51), and in the group of lumbar curves, 45 or 66% of 68 patients had a left convex scoliosis ($P = 0.01$), with a mean apex at L2 (2.18 ± 0.52).
When the direction of the convexity of the different curve types was analysed per diagnosis, we got the following results *(Table 3)*. Thoracic and thoracolumbar curves overall showed a convexity to the right and lumbar curves to the left, except in the spina bifida group, but diagnostic subgroups were too small to differ significantly from a random distribution. Only lumbar curves in the Duchenne and the cerebral palsy groups and the thoracic curves in the spina bifida group were statistically significant.

Table 2. Right-left distribution of non-C-shaped curves.

Curve type	N	Direction		P
		Right	Left	
Thoracic	52	40 (76.9%)*	12 (23.1%)*	<0.001
Thoracolumbar	51	42 (82.4%)*	9 (17.6%)*	<0.001
Lumbar	68	23 (33.8%)*	45 (66.2%)*	0.010

Right-left distribution of non-C-shaped curves in 171 patients with neuromuscular scoliosis.
The observed frequencies of right and left curve distribution are given along with the significance level.
*statistically significant ($P < 0.05$).

Table 3. Right-left distribution of curves per diagnostic subgroup.

Diagnosis	Curve type	N	Direction		P
			Right	Left	
Duchenne	Thoracic	8	5 (62.5%)	3 (37.5%)	0.727
	Thoracolumbar	17	11 (64.7%)	6 (35.3%)	0.332
	Lumbar	15	2 (13.3%)*	13 (86.7%)*	0.007
Spinal muscular atrophy	Thoracic	10	7 (70.0%)	3 (30.0%)	0.344
	Thoracolumbar	9	5 (55.6%)	4 (44.4%)	1.000
	Lumbar	6	4 (33.3%)	2 (66.7%)	0.688
Cerebral palsy	Thoracic	21	13 (61.9%)	8 (38.1%)	0.383
	Thoracolumbar	25	15 (60.0%)	10 (40.0%)	0.424
	Lumbar	22	5 (22.7%)*	17 (77.3%)*	0.017
Spina bifida	Thoracic	25	23 (92.0%)*	2 (08.0%)*	<0.001
	Thoracolumbar	14	11 (78.6%)	3 (21.4%)	0.057
	Lumbar	26	14 (53.8%)	12 (46.2%)	0.845

Right-left distribution of curves in 198 patients with neuromuscular scoliosis. The observed frequencies of right and left curve distribution are given per diagnostic subgroup along with the significance level.
*statistically significant ($P < 0.05$).

Discussion

This study was performed to determine if in different types of neuromuscular scoliosis a predominant curve pattern can be found and if similarities with idiopathic scoliosis exist.

Stability of the spine obviously depends upon the interaction between intrinsic factors (bone, facet joints and ligaments) and extrinsic factors (e.g. gravity, muscular force)[27]; impairment of the normal equilibrium as the result of muscular weakness during growth triggers a decompensation, which results in a scoliotic deformity. However, which parameter determines the direction of the scoliotic curve is still unknown. In previous studies no significant correlation has been found between muscle asymmetry and the scoliotic curve pattern in different types of neuromuscular disorders.[5;9;15;17] The controversy about the role of muscles in the origin of scoliosis has been debated extensively.[4;5;9;13;17;28-31]

Although C-type curves are reported to predominate in neuromuscular scoliosis, we demonstrated that they occur only in a minority of cases (14%). In the group of non-C-shaped curves, our study shows a significant predominance of right sided thoracic ($P < 0.001$) and thoracolumbar curves ($P < 0.001$), and left sided lumbar curves ($P = 0.01$) *(Table 2)*. Although most diagnostic subgroups in this study were small, analysis of these subgroups shows a right-left distribution that is comparable to what is seen in the total group of non-C-shaped curves. The only exception was the group of patients with spina bifida in which lumbar curve convexity was slightly predominant to the right instead of the left side *(Table 3)*. A possible explanation for the slight right sided predominance in the lumbar curves of patients with spina bifida is the fact that most of these children had surgical correction of myelomeningocele during childhood, and scar tissue and muscle transpositions may influence curve convexity.

The results of this study demonstrate a predominance of right sided thoracic and thoracolumbar curves, and of left sided lumbar curves, which differed significantly from an equal right-left distribution. These curve patterns and their apical levels are similar to what is seen in the most prevalent types of adolescent idiopathic scoliosis[5;28;32-43] *(Figure 2)*.

Although a multitude of factors theoretically may determine curve direction, none has ever been considered conclusive. Side of dislocated hip or asymmetric muscle weakness for instance, have been shown not to bear a direct relationship to curve convexity.[9;14;44] Furthermore, it has been shown that a scoliotic curve leads to secondary, adaptive phenomena in trunk muscles.[28;29]

Recently we showed that there is a preexistent vertebral rotation in the normal, *non-scoliotic* spine that corresponds to what is seen to a larger extent in the most prevalent types of thoracic idiopathic scoliosis.[45] If we assume that muscular weakness is 1 of the many possible nonspecific triggers of spinal decompensation, this built-in, preexistent rotational pattern could also guide the curve direction in cases of neuromuscular scoliosis.

Figure 2. An example of a double curve pattern in a 15 years old child with cerebral palsy. The major curve (46°) is thoracic and convex to the right, the minor curve (43°) is lumbar and convex to the left. This double curve is comparable to the most prevalent curve pattern seen in adolescent idiopathic scoliosis.

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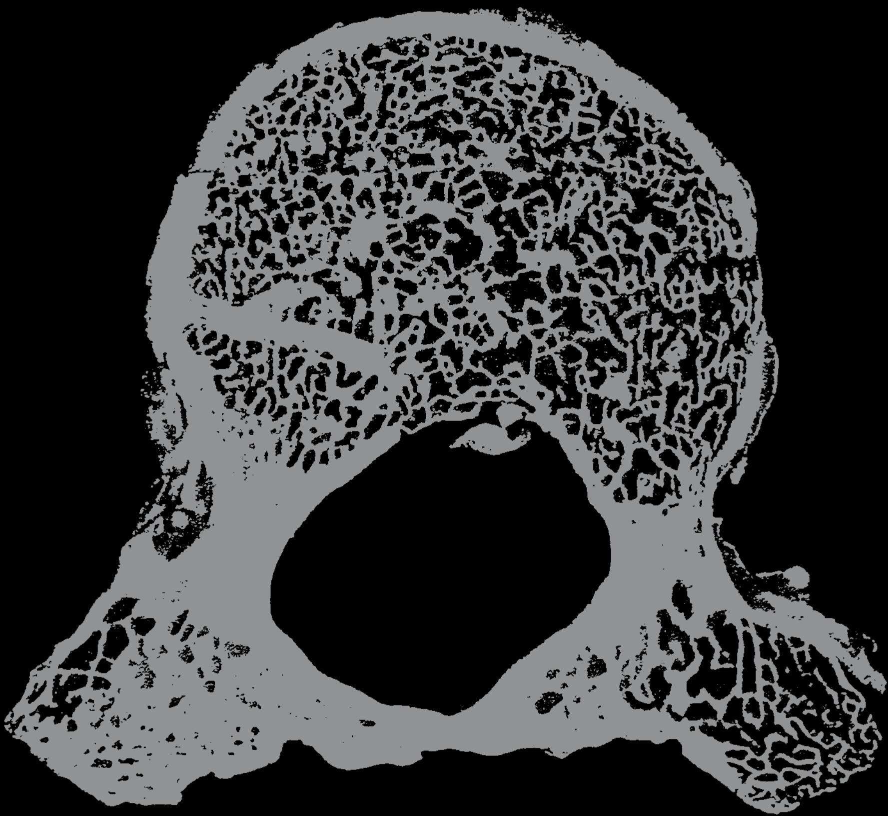
Analysis of preexistent vertebral rotation in the normal quadruped spine

6



Kouwenhoven JWM
Vincken KL
Bartels LW
Meij BP
Öner FC
Castelein RM

Spine 2006;31(20):E754-8

Introduction

Idiopathic scoliosis has never been observed in quadrupeds, it is a condition restricted exclusively to humans.[1;2] All forms of scoliosis reported in animals are either congenital, neuromuscular or experimentally induced.[2-10] Many theories exist about the pathogenesis of idiopathic scoliosis, however, the cause of this complex spinal deformity still has to be resolved.

An essential component of scoliosis is transverse plane vertebral rotation.[1;11-26] Recently, the authors demonstrated the existence of a consistent pattern of rotation in the normal, *nonscoliotic* human spine, which is similar to what is seen in the most prevalent types of idiopathic scoliosis.[27] Since vertebral rotation and the development of lateral curvature are coupled phenomena,[26] it is likely that this preexistent rotational pattern plays an important role in determining the direction of curvature once scoliosis starts to develop. If this rotational pattern is unique to humans, it could be considered as a first step in the pathogenesis of idiopathic scoliosis.

Therefore, the aim of this study was to analyse vertebral rotation in the normal, *nonscoliotic* quadruped spine to determine if a pattern of rotation exists, similar to what was found in the normal human spine.

Subjects and Methods

Animals and Computed Tomography

This CT study was performed in dogs admitted to the Department of Clinical Sciences and Companion Animals, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands. The dogs had undergone plain radiograph and CT examination of the thorax for reasons unrelated to the spine, such as evaluation of pulmonary disease. According to the medical records none of these dogs had a history of spinal trauma or spinal deformity. Assessment of the AP and lateral radiographs showed a normal thoracic spine without signs of congenital or acquired deformities in all dogs; further CT examination did not show any abnormalities in the vertebrae or discs. Forty-two dogs (26 males and 16 females), without clinical or radiological evidence of scoliosis or other spinal pathology were included in this study. The breed distribution consisted of several different breeds and cross breeds. Among the breeds there were 7 Labrador Retrievers. The mean age of the dogs was 7.1 years (range, 1-13 years) and the mean body weight was 28.9 kg (range, 6 - 87 kg).

Computed tomography was performed with the dogs in prone position under general inhalation anaesthesia and controlled ventilation. Scans were made using a single slice spiral CT scanner (Philips CT Secura, Philips Medical Systems, Eindhoven, The Netherlands). Volume scans with slice thickness of 3 mm and reconstruction index of 2 mm were made with a scan time of 0.7 sec at 120 KV and 160 mA. Consecutive series of 6 scans were made during 4.2 sec scanning time during which ventilation was interrupted to minimize movement artefacts.

CT Measurement Method

Vertebral rotation was measured in the transverse plane from T1 to T13 using the same CT measurement method as used in our previous study in humans.[27] This method consisted of a semi-automated procedure using an in-house created, interactive application to calculate the rotation angles of the vertebrae in a robust and reproducible way. Vertebral rotation was defined as the angle between the longitudinal axis of each vertebra and the midsagittal axis of the trunk (= reference line). The reference line was defined as zero degrees rotation. Rotation to the right was defined as a positive angle, rotation to the left as a negative angle. The reference line was defined at level T5 as the line between the center of mass (COM) of the spinal canal and the COM of the sternum; the longitudinal axis of each vertebra was defined as the line through the COM of the spinal canal and the COM of the anterior half of the vertebral body. After segmentation by means of a simple region growing step *(Figure 1)*, these points and next the rotation angles of the vertebrae were calculated fully automatically (for details see Kouwenhoven et al 2006).[27]
The intraclass correlation coefficients calculated for interobserver and intraobserver reliability of this method were respectively 0.96 ± 0.06 and 0.99 ± 0.01 (mean ± SD).

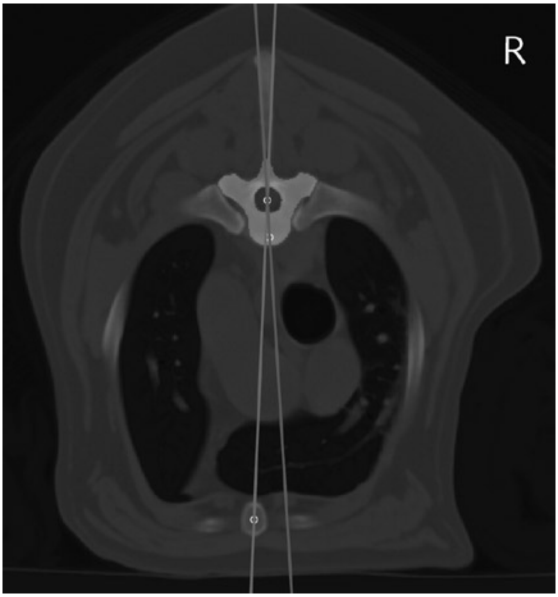


Figure 1. Transverse CT scan of the canine thorax. Longitudinal axis of vertebra T5 (red) represented by the line (green) through the COM of the vertebral canal and the COM of the anterior half of the vertebral body. Reference line (light blue) drawn through the COM of the vertebral canal and the COM of the sternum (dark blue).

Statistics

Statistical analysis was performed by means of SPSS statistical software (SPSS, Inc., Chicago, IL). The observed frequencies of right and left vertebral rotation were used to test the null hypothesis of equal probability with the binomial test. To determine if the mean vertebral rotation angles were statistically significant we used the one-sample T test. A *P* value of less than 0.05 was considered to be statistically significant.

Table 1. Right-left distribution of vertebral rotation (T1-T13).

Vertebra	Direction of rotation		*P*
	Right	Left	
T1	28 (67%)*	14 (33%)*	0.044
T2	29 (69%)*	13 (31%)*	0.020
T3	26 (62%)	16 (38%)	0.164
T4	27 (64%)	15 (36%)	0.088
T5	31 (74%)*	11 (26%)*	0.003
T6	28 (67%)*	14 (33%)*	0.044
T7	25 (60%)	17 (40%)	0.280
T8	25 (60%)	17 (40%)	0.280
T9	24 (57%)	18 (43%)	0.441
T10	26 (62%)	16 (38%)	0.164
T11	27 (64%)	15 (36%)	0.088
T12	30 (71%)*	12 (29%)*	0.008
T13	25 (68%)*	12 (32%)*	0.047

Right-left distribution of vertebral rotation at T1-T13 in 42 dogs with normal, non-scoliotic spines. The observed frequencies of right and left vertebral rotation at each level are given along with the significance level. *statistically significant ($P<0.05$).

Results

Analysis of the data demonstrated a predominant rotation to the right at all thoracic levels of the canine spine. At levels T1, T2, T5, T6, T12, and T13, the observed frequencies of right and left vertebral rotation differed significantly from an equal right-left distribution *(Table 1)*. Transverse CT scans of vertebra T13 were not available in 5 dogs.

Measurement of the angles of vertebral rotation demonstrated that the mean vertebral rotation angle was to the right at all thoracic levels. In the upper thoracic spine these values differed significantly from zero degrees rotation at level T1 and T4 ($P < 0.05$), and in the midthoracic spine at level T5-T7 with a maximum rotation of 1.8° at level T6 ($P < 0.005$). In the lower thoracic spine the mean vertebral rotation angles were significant from level T11-T13 with a maximum rotation of 2.9° at level T13 ($P < 0.005$) *(Table 2; Figure 2)*.

Table 2. Mean vertebral rotation angle (T1-T13).

Vertebra	Mean rotation angle (°)	95% confidence interval		*P*
		Lower bound (°)	Upper bound (°)	
T1	1.457*	0.153	2.762	0.029
T2	0.815	-0.284	1.913	0.142
T3	0.665	-0.566	1.896	0.282
T4	1.185*	0.061	2.309	0.039
T5	1.435*	0.337	2.534	0.012
T6	1.848*	0.641	3.055	0.004
T7	1.304*	0.043	2.565	0.043
T8	0.986	-0.288	2.261	0.126
T9	0.802	-0.563	2.168	0.242
T10	1.289	-0.228	2.806	0.094
T11	2.050*	0.470	3.630	0.012
T12	2.613*	0.948	4.278	0.003
T13	2.905*	0.981	4.829	0.004

Mean vertebral rotation angles (in degrees) with 95% confidence interval of T1-T13 in 42 dogs with normal, non-scoliotic spines. *statistically significant (P<0.05).

Analysis of vertebral rotation in the subgroup of 7 Labrador Retrievers also showed a predominant rotation to the right at all thoracic levels. Mean vertebral rotation angles differed significantly from zero degrees rotation in the upper thoracic spine at level T1 ($P < 0.05$), in the mid-thoracic spine at level T5-T8 with a maximum ro-

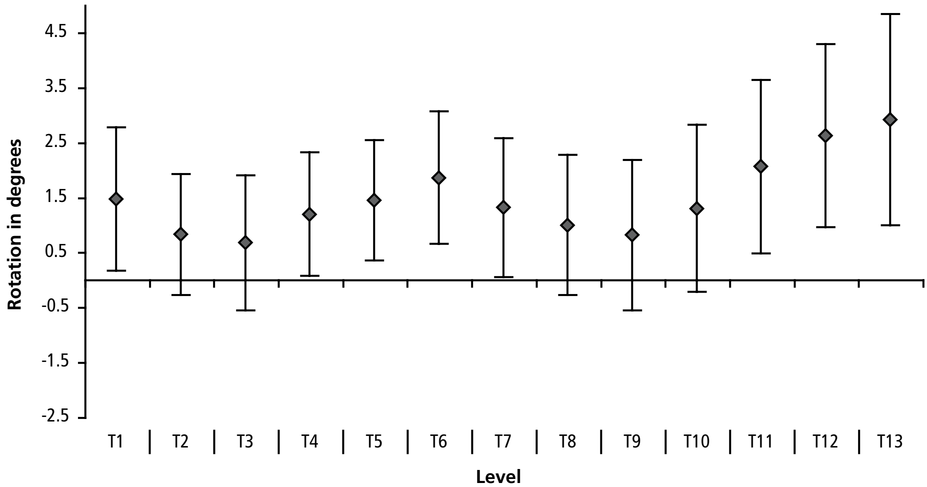


Figure 2. Mean vertebral rotation angles (in degrees, with 95% confidence interval) in the horizontal plane at level T1-T13 in 42 dogs with a normal, non-scoliotic spine.

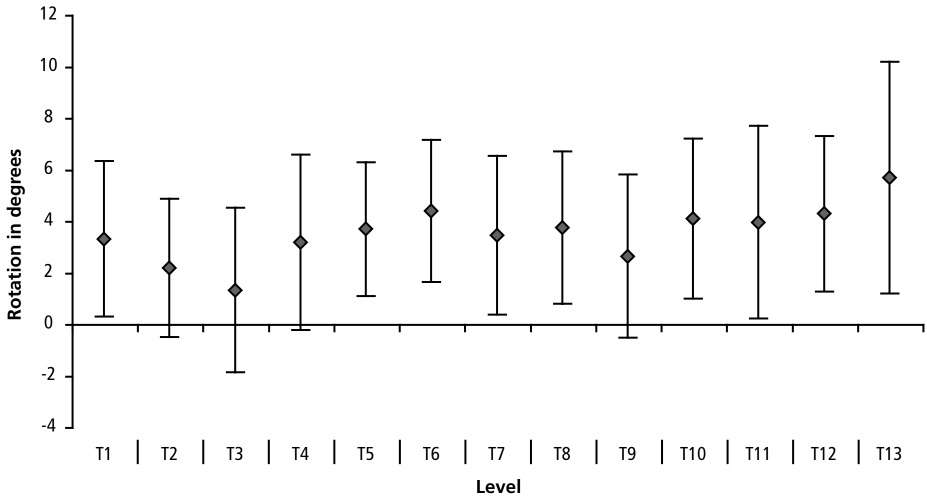


Figure 3. Mean vertebral rotation angles (in degrees, with 95% confidence interval) in the horizontal plane at level T1-T13 in 7 Labrador Retrievers with a normal, non-scoliotic spine.

tation of 4.4° at level T6 ($P < 0.01$), and in the lower thoracic spine at level T10-T13 with a maximum rotation of 5.7° at level T13 ($P < 0.05$) *(Figure 3)*.

Discussion

Idiopathic scoliosis is a three-dimensional deformity of the spine with an unknown etiology and pathogenesis. A typical feature of scoliosis is the coupling mechanism between transverse plane vertebral rotation and the development of lateral curvature – rotation of the vertebral bodies always being directed into the convexity of the curve.[26] The most prevalent curve types in adolescent idiopathic scoliosis (AIS) show a thoracic curve to the right.[11;12;22;28-31] Although many theories have been suggested about the cause of this predominant pattern, there is no consensus on this matter.

In a previous study, the authors demonstrated that a consistent pattern of vertebral rotation exists in the normal, *nonscoliotic* human spine.[27] The results of that study showed that the majority of people with a normal spine have a significant rotation to the right of the mid and lower thoracic vertebrae, a pattern that is similar to what is found in the most prevalent types of AIS, and even in neuromuscular scoliosis.[32] Although the cause of this preexistent rotation remains to be resolved, it is likely that it governs the direction of curvature once scoliosis starts to develop.

Since this rotational pattern had only been demonstrated in humans, we could not be sure whether it is part of the pathogenesis of scoliosis or that it is a physiological process in normal spinal development. To determine if this preexistent rotational pattern exists in the spine of quadrupedal vertebrates as well, in the current study, vertebral rotation was analysed in the normal, *nonscoliotic* canine spine. Measurements were performed by using the same measurement method as in our previous study in humans.[27] Interobserver and intraobserver analysis showed that this method was highly reliable in terms of robustness and reproducibility.

The results of this study demonstrated a preexistent rotational pattern in the thoracic canine spine with a preferred direction to the right at all thoracic levels (T1-T13). Measurement of the degree of rotation showed mean rotation angles to the right of the upper, mid, and lower thoracic vertebrae with significant values at level T1, T4-T7, and T11-T13. Vertebral rotation was also analyzed in the group of 7 Labrador Retrievers, which showed a similar pattern of rotation as for the group as a whole.

The cause of this preexistent rotational pattern is not clear. In humans, the anatomy of the descending thoracic aorta, closely related to the left side of the vertebral column, has been implicated in causing rotation to the right by exerting an asymmetric rotational force on the growing mid and lower thoracic vertebrae.[33;34] In quadrupedal vertebrates the descending thoracic aorta is also situated in the left side of the thorax.[35] Analysis of our data revealed that the aorta is situated at the left side of the vertebral column from level T5 to T13, at the same position as in humans.[36] The results of our previous study in humans demonstrated a rotation to the right of the mid and lower thoracic vertebrae starting at level T5,[27] which is comparable to the results of this study.

Despite these similarities in spinal development, idiopathic scoliosis has never been observed in dogs or in any other vertebrate than humans. Man is the only vertebrate that ambulates in a fully erect position with the body center of mass positioned directly above the pelvis. All other vertebrates ambulate with flexed hips and knees and therefore have a more horizontally positioned spine.[37] It has been demonstrated that a fully upright posture significantly alters spinal loading conditions, possibly facilitating rotatory instability.[38] This is in agreement with the studies of Machida *et al* that demonstrated that pinealectomy in rats only resulted in scoliosis when rats were made bipedal and had to walk upright.[7;8] Since idiopathic scoliosis occurs only in humans, the unique fully upright posture may play an important role in the development of this spinal deformity.

Conclusions

The normal spine of quadrupeds shows rotation of the thoracic vertebrae with a preferred direction to the right, similar to what we demonstrated previously in humans. In humans, the predominance of right-rotating thoracic curves in idiopathic scoliosis can be explained by this preexistent rotation. However, since vertebral rotation also occurs in species that do not develop scoliosis naturally, this anatomical feature can be considered as a physiological process in the normal development of the spine, independent of the pathogenesis of scoliosis. Although the cause of this preexistent rotational pattern still has to be resolved, we assume that the asymmetric anatomy of the thoracic organs is an important causative factor.

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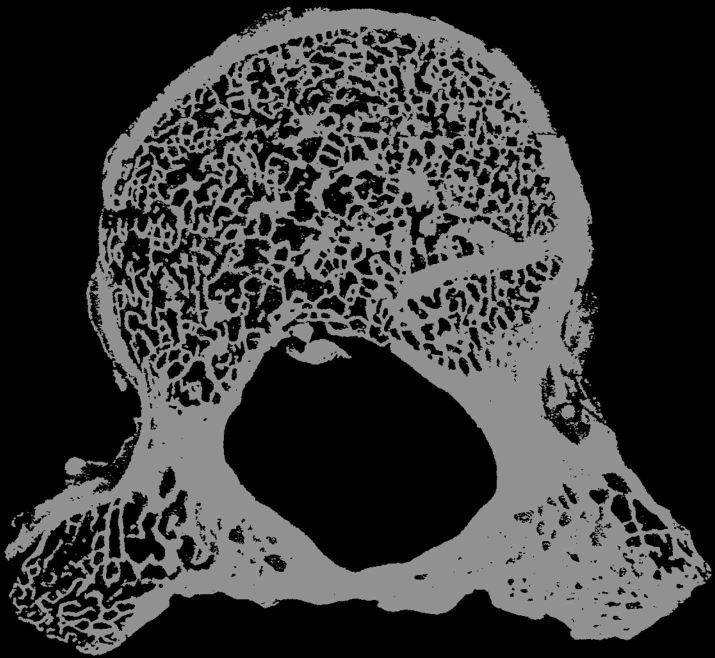
The relation between organ anatomy and preexistent vertebral rotation in the normal spine

7

Magnetic resonance imaging study in humans with situs inversus totalis



Kouwenhoven JWM
Bartels LW
Vincken KL
Viergever MA
Verbout AJ
Delhaas T
Castelein RM

Spine 2007;32(10):1123-28

Introduction

Adolescent idiopathic scoliosis (AIS) has been the subject of many studies, however, the pathogenesis of this complex rotational deformity remains little understood.[1-12] Scoliosis is a three-dimensional deformity of the spine characterized by deformation in the sagittal (thoracic lordosis), frontal (lateral curvature) and transverse plane (vertebral rotation). A typical feature of scoliosis is the fact that vertebral rotation and the development of lateral curvature are coupled phenomena (*i.e.*, rotation of the vertebral bodies is always directed into the convexity of the lateral curve).[13] In AIS, the most prevalent curve types show a primary thoracic curve that is rotated to the right side.[1;10;14-18] Although several explanations have been suggested,[4;5;8;9;19-25] of which handedness and the anatomy of the thoracic aorta most frequently, the cause of this preferred direction still has to be resolved and remains one of the classical enigmas in orthopaedic surgery.

In humans, as well as in quadrupeds, the authors recently demonstrated a pattern of vertebral rotation in the normal, *nonscoliotic* spine (*i.e.*, the mid and lower thoracic vertebrae showed a predominant rotation to the right side).[26;27] This pattern is similar to the most prevalent patterns of rotation in AIS. Apparently, humans and quadrupedal vertebrates share a common factor that causes this rotation. In both species, the thoracic organs (heart, lungs and aorta) are asymmetrically situated and in close contact with the vertebral column.[22;28] We postulate that this asymmetry may play an important role in the development of this preexistent rotational tendency.

Occasionally, individuals have a complete mirror image reversal of the internal body organs, called situs inversus totalis. Situs inversus totalis is a rare anatomic variant with an estimated incidence of only 1 per 20,000 in the general population.[29;30]

The aim of this study was to analyze vertebral rotation in the normal, *nonscoliotic* spine of humans with situs inversus totalis to investigate if a pattern of rotation exists opposite of what was found in humans with normal organ anatomy. Furthermore, we wanted to establish the role of handedness in this particular population.

Subjects and Methods

Subjects and Magnetic Resonance Imaging (MRI)

This cross-sectional MRI study was performed in 39 persons with a presumed diagnosis of situs inversus totalis. None of these persons had a history of scoliosis or other spinal pathology. Exclusion criteria were: (1) incomplete situs inversus, (2) congenital or acquired deformation of the spine, (3) history of spinal trauma, and (4) history of spinal surgery or chest surgery. The institutional ethics committee approved this study, and all persons gave written informed consent for participating in the study.

As part of the protocol, all persons were screened for handedness by asking them whether they were right or left handed, and asking them to write down their names. After physical examination, which did not show any signs for scoliosis or other spinal deformity, MRI scans of the thorax and abdomen were made in supine position using a 1.5-Tesla MR scanner (Achieva, Philips Medical Systems, The Netherlands). After standard multi-stack survey scans, T2-weighted Turbo Spin Echo (TSE) images were acquired in the sagittal and coronal plane of the spine. These images were used to assess spinal alignment and for planning transverse T2-weighted TSE scans that were used for the actual measurement of vertebral rotation. For each vertebra (T2 to L5), a stack of 6 slices was acquired in the transverse plane of the vertebra. The most important scan parameters were: TR/TE = 1500 ms/100 ms, field of view (FOV) = 188×250 mm^2, slice thickness = 3 mm (no gap), acquired matrix = 144×256, reconstructed matrix = 192×256, number of signal averages (NSA) = 8, turbo factor = 45. A spine coil was used as a receive coil. For planning of these stacks, both the coronal and the sagittal T2-weighted TSE scans were used.

MRI Measurement Method

Vertebral rotation was measured in the transverse plane from T2 to L5 using the same measurement method as used in our previous study in humans and dogs.[26;27] This method consisted of a semi-automated procedure using an in-house created, interactive computer program to calculate the rotation angle of the vertebrae in a robust and reproducible way. For each vertebra, a single slice of the MRI volume was selected at the center of the vertebral body such that the pedicles were clearly visible.[31] The axis of rotation was defined through the Center Of Mass (COM) of the spinal canal. Vertebral rotation was defined as the angle between the longitudinal axis of each vertebra and the mid-sagittal axis of the trunk (= reference line). The reference line was defined at level T5 as the line between the COM of the spinal canal and the COM of the sternum; the longitudinal axis of each vertebra was defined as the line through the COM of the spinal canal and the COM of the anterior half of the vertebral body. After manual segmentation *(Figure 1)*, these points and, subsequently, the rotation angles of the vertebrae were calculated fully automatically. The reference line was defined as zero degrees rotation. From a caudal view, counter-clockwise rotation of the vertebrae (rotation of the vertebral body to the right side of the subject) was defined as a positive angle *(Figure 1)*, rotation to the left side (clockwise) as a negative angle (for details see Kouwenhoven *et al* 2006).[26]

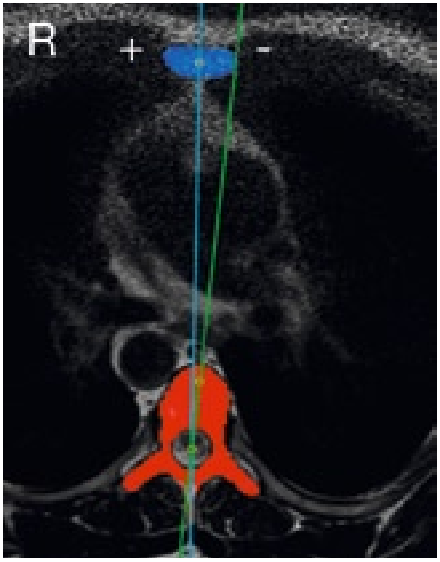


Figure 1. Transverse MRI scan at level T5. Longitudinal axis of vertebra T5 (red) represented by the line (green) through the COM of the vertebral canal and the COM of the anterior half of the vertebral body. Reference line (light blue) drawn through the COM of the vertebral canal and the COM of the sternum (dark blue).

Because of the radiation dose and its associated health risks, computed tomography (CT) could not be used in this cross-sectional study. For this reason, we used MRI, which does not involve ionizing radiation. The switch from CT to MRI demanded a re-evaluation of the reliability of our method. Therefore, three different observers manually segmented the slices of T2-T6 in the same four randomly chosen subjects independently. For the intraobserver analysis, Observer 1 manually segmented these slices three times at separate sittings.

Statistics

Statistical analysis was performed by means of SPSS statistical software, version 12.0.1 (SPSS, Inc., Chicago, IL). The observed frequencies of right and left vertebral rotation were used to test the null hypothesis of equal probability with the binomial test. To determine if the mean vertebral rotation angles were statistically significant, we used the one-sample T test. A *P*-value of less than 0.05 was considered to be statistically significant.

Results

Evaluation of the MRI images showed that all persons had a normal spinal alignment in the frontal and sagittal plane, without congenital or acquired spinal deformities. It, however, also revealed that 2 persons where found to have an incomplete situs inversus and, therefore, had to be excluded from this study.

Table 1. Right-left distribution of vertebral rotation (T2-L5).

Vertebra	Direction of rotation		P
	Right	Left	
T2	27 (73%)*	10 (27%)*	0.008
T3	27 (73%)*	10 (27%)*	0.008
T4	21 (57%)	16 (43%)	0.511
T5	11 (30%)*	26 (70%)*	0.020
T6	6 (16%)*	31 (84%)*	<0.001
T7	6 (16%)*	31 (84%)*	<0.001
T8	9 (24%)*	28 (76%)*	0.003
T9	11 (30%)*	26 (70%)*	0.020
T10	13 (35%)	24 (65%)	0.099
T11	12 (32%)*	25 (68%)*	0.047
T12	17 (46%)	20 (54%)	0.743
L1	19 (51%)	18 (49%)	1.000
L2	20 (54%)	17 (46%)	0.743
L3	22 (59%)	15 (41%)	0.324
L4	23 (62%)	14 (38%)	0.188
L5	23 (62%)	14 (38%)	0.188

Right-left distribution of vertebral rotation at T2-L5 in the normal, *nonscoliotic* spine of 37 persons with SIT. The observed frequencies of right and left vertebral rotation at each level are given along with the significance level. * The observed frequencies differ significantly from an equal right-left distribution (P<0.05).

Vertebral rotation was analyzed in the group of 37 persons who had a complete situs inversus. This group consisted of 20 males and 17 females, with a mean age of 32.1 years (range 7-74 years). Thirty-two persons were right handed (86%), and 5 were left handed (14%). There were no persons who were ambidextrous.

Analysis of the data showed a predominant rotation to the left side of the mid and lower thoracic vertebrae (T5-T12). The observed frequencies of right and left vertebral rotation differed significantly from an equal right-left distribution at levels T5-T9 and at level T11 ($P<0.05$). The upper thoracic (T2-T4) and lumbar vertebrae (L1-L5) showed a predominant rotation to right side, with significant values at levels T2 and T3 ($P<0.01$) *(Table 1)*.

Measurement of the angles of vertebral rotation showed a mean rotation angle to the left side of the mid and lower thoracic vertebrae. These values differed significantly from zero degrees rotation at level T5-T11, with a maximum rotation of 2.7° at level T7 ($P<0.001$). In the upper thoracic and lumbar part of the spine, the vertebrae had a mean rotation angle to the right side that was significant at level T2 ($P<0.05$) *(Table 2, Figure 2)*.

The intraclass correlation coefficient calculated for intraobserver and interobserver reliability of our method were, respectively, 0.91 ± 0.03 and 0.87 ± 0.10 (mean ± standard deviation).

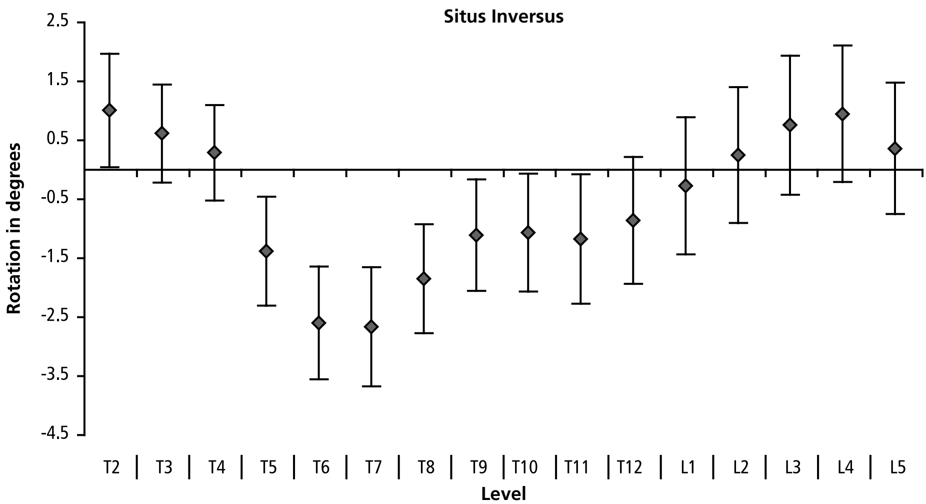


Figure 2. Mean vertebral rotation angles (in degrees, with 95% confidence interval) in the horizontal plane at level T2-L5 in the normal, *nonscoliotic* spine of 37 persons with SIT.

Table 2. Mean vertebral rotation angle (T2-L5).

Vertebra	Mean rotation angle (°)	95% confidence interval		*P*
		Lower bound (°)	Upper bound (°)	
T2	0.984*	0.019	1.950	0.046
T3	0.593	-0.240	1.426	0.158
T4	0.271	-0.539	1.081	0.502
T5	-1.403*	-2.329	-0.477	0.004
T6	-2.619*	-3.577	-1.661	<0.001
T7	-2.685*	-3.694	-1.676	<0.001
T8	-1.872*	-2.798	-0.946	<0.001
T9	-1.132*	-2.078	-0.186	0.020
T10	-1.090*	-2.092	-0.087	0.034
T11	-1.196*	-2.291	-0.101	0.033
T12	-0.880	-1.957	0.196	0.106
L1	-0.296	-1.457	0.865	0.609
L2	0.229	-0.919	1.378	0.688
L3	0.737	-0.452	1.926	0.217
L4	0.928	-0.233	2.088	0.114
L5	0.338	-0.777	1.453	0.542

Mean vertebral rotation angles (in degrees) with 95% confidence interval at T2-L5 in the normal, *nonscoliotic* spine of 37 persons with SIT. * Mean rotation angle differs significantly from zero degrees rotation ($P<0.05$).

Discussion

Despite extensive research, the pathogenesis of idiopathic scoliosis, which accounts for 80% of all cases of scoliosis, remains elusive.[1-12] An important component of scoliosis is vertebral rotation. In AIS, the most prevalent curve types show a thoracic curve that is rotated to the right side.[1;10;14-18] Although several explanations for this rotational pattern have been proposed, the cause of this preferred direction is still not clear.

In a previous study, the authors systematically analyzed rotation of the thoracic and lumbar vertebrae in the normal, *nonscoliotic* human spine. The results of that study showed the existence of a consistent pattern of rotation in the thoracic part of the spine (*i.e.*, the upper thoracic vertebrae were predominantly rotated to the left, and the mid and lower thoracic vertebrae to the right side) *(Figure 3)*.[26] This preexistent rotational pattern is comparable to what is seen in the most prevalent types of AIS, which show a primary thoracic curve rotated to the right side with compensatory curves to the left above and below *(Figure 4)*. We assume that once the spine starts to decompensate, for reasons that still have to be clarified, this built-in rotational tendency determines the direction of spinal curvature.

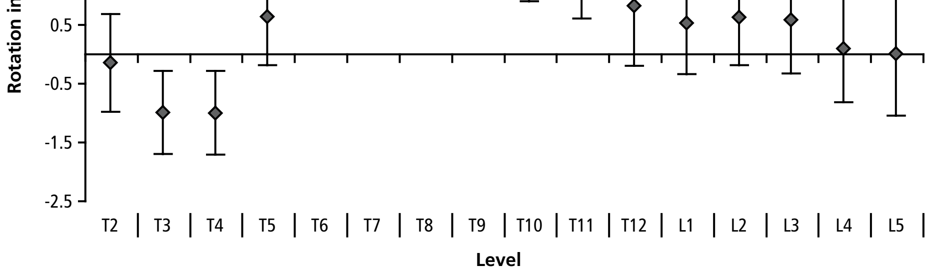


Figure 3. Mean vertebral rotation angles (in degrees, with 95% confidence interval) in the horizontal plane at level T2-L5 in the normal, *nonscoliotic* spine of 50 persons with normal organ anatomy. Reprinted with permission from *Spine*.[26]

Recently, the authors demonstrated that in the normal, straight spine of quadrupeds, the thoracic vertebrae also have a predominant rotation to the right side.[27] Since idiopathic scoliosis does not occur in quadrupeds,[2;32] this preexistent rotational pattern must be a normal anatomic feature, unrelated to the pathogenesis of AIS. The cause of this vertebral rotation probably must be sought in a factor that humans and quadrupedal vertebrates have in common, and is working on the developing spine continuously.

Figure 4. A typical example of an idiopathic thoracic curve pattern, with a mid thoracic curve convex to the right and compensatory high thoracic and lumbar curves convex to the left. Note that the vertebral bodies are rotated away from the midline more than the spinous processes.

In both species, the descending thoracic aorta is situated on the left side of the mid and lower thoracic spine.[22;26-28] In humans, it has been suggested that the pulsatile force of the thoracic aorta causes asymmetrical growth of the mid and lower thoracic vertebrae,[4;5;8;9;33] resulting in rotation of the vertebral bodies to the right.[34;35] It is tempting to speculate about one single factor that is responsible for this rotation, however, not only the aorta, but also the heart and the lungs are asymmetrically positioned in the thorax and could play an important role.[19;22;28]

To investigate the relation between asymmetrical organ anatomy and preexistent vertebral rotation, in the current study, vertebral rotation was analyzed in the normal, *nonscoliotic* spine of persons with a complete mirror image position of their internal body organs, called situs inversus totalis.

The results of this study showed a preexistent pattern of vertebral rotation opposite to what we found in persons with normal organ anatomy (*i.e.*, the mid and lower thoracic vertebrae were predominantly rotated to the left, the upper thoracic and lumbar vertebrae to the right side). Measurement of the degree of vertebral rotation showed mean rotation angles of the mid and lower thoracic vertebrae to the left side with significant values at level T5-T11. Although in opposite direction, the distribution and magnitude of these rotational patterns were found to be similar; both in the normal population as well as in situs inversus totalis, the mid and lower thoracic vertebrae showed a significant rotation with a maximum at level T7 *(Figures 2 and 3)*. These findings suggest that the position of the thoracic organs is likely to play an important role in the development of this preexistent rotation. However, since this rotational pattern could not be demonstrated in all subjects, besides organ anatomy, there also have to be other factors that are involved in this preexistent rotation.

A factor that also could play a role in the development of this rotational tendency is handedness. The existence of right and left handedness is a typical example of normal human body asymmetry.[36] In the general population almost 90% of the people are right handed. Right handedness has been related to the predominance of right-rotating thoracic curves in AIS.[20;21] However, handedness is a very complex characteristic; data in literature on this subject are contradictory and inconclusive.[20-23;25;37]

To investigate the relation between handedness and vertebral rotation in the normal, *nonscoliotic* spine, we determined the distribution of right and left handedness in our research group. Analysis of our data showed that only 14% of the subjects were left handed, which is similar to what is seen in the general population.[38] Since we showed that in situs inversus rotation of the thoracic vertebrae was predominantly to the left side, these data seem to suggest that handedness is not involved in the direction of vertebral rotation.

Conclusions

The normal, *nonscoliotic* spine of humans with a situs inversus totalis shows a preexistent pattern of vertebral rotation opposite of what is seen in humans with normal organ anatomy. This study shows a relation between preexistent vertebral rotation and the asymmetrical position of the thoracic organs. No relation with handedness could be demonstrated. Based upon these findings, we assume that the asymmetrical anatomy of the thoracic organs is an important causative factor in the development of this built-in rotational tendency. Since this relation could not be demonstrated in all subjects, other factors should not be ruled out.

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Summary and General Discussion

8

In this chapter, the results of the studies that were performed for this thesis are summarized by addressing the five questions that were formulated in **Chapter 1** (Introduction and aims).

Question 1: What are the effects of dorsal and ventral shear loads on the rotational stability of the spine?

In **Chapter 3**, a biomechanical *in vitro* study on porcine and human spinal segments is presented. The aim of this study was to investigate axial rotational stability of the thoracic spine under dorsal and ventral shear loads. A total of 7 fresh-frozen porcine cadaveric spines and 7 fresh-frozen human cadaveric spines were obtained for this study. Each specimen was sectioned to obtain 2 thoracic functional spinal units (FSUs), 1 from the mid thoracic and 1 from the lower thoracic spine, with intact costotransverse and costovertebral articulations. In both dorsal and ventral directions, shear loads were applied to the upper vertebra of the FSU in the midsagittal plane (centrally), and at 1 cm to the right and to the left (eccentrically), resulting in a rotary moment. Vertebral rotation was measured at three incremental loads by an automated optoelectronic 3D movement registration system. The results of this study showed that eccentrically applied shear loads induce vertebral rotation in mature human as well as in immature porcine spinal segments. At the mid and lower thoracic levels, significantly more vertebral rotation occurred under *dorsal* shear loads than under *ventral* shear loads. From these data we concluded that in humans and in quadrupeds, the thoracic spine is less rotationally stable under dorsal shear loads than under ventral shear loads. We assume that dorsal shear loads working on the dorsally inclined segments of the growing immature human spine can, if they exceed a certain threshold, render the facet joints less operative in their rotational control and may induce rotation of the declive spinal segment. It was postulated that these dorsal shear loads not only reduce rotational stability, but also can enhance a slight preexistent vertebral rotation, which could contribute to the initiation and progression of AIS in humans.

Question 2: Does a preexistent pattern of vertebral rotation exist in the normal, nonscoliotic human spine similar to what is seen in the most prevalent curve patterns of AIS?

The typical and rather predictable curve patterns and their associated rotation in AIS have been well described; however, the cause for this predictability is unknown. We hypothesized that, in the development of scoliosis, the spine might follow an already built-in, preexistent rotational pattern. Little is known of possible patterns of rotation in the normal, *nonscoliotic* spine. Systematic analysis of the thoracic and lumbar vertebrae of the normal spine, based on computed tomography, has not been performed previously. In **Chapter 4**, we report on a newly developed CT measurement method that was used to investigate transverse plane vertebral rotation from T2 to L5 in the normal spine of 50 persons without clinical or radiological evidence of scoliosis. Vertebral rotation was defined as the angle between the longitudinal axis of each vertebra and the midsagittal axis of the trunk (= reference line). The results of the present study showed a predominant rotation to the left of the high thoracic vertebrae, and to the right of the mid and lower thoracic vertebrae in the normal, non-scoliotic spine, which differed significantly from an equal right-left distribution. The mean vertebral rotation angles differed significantly from zero degrees rotation at level T6 to T11 with a maximum rotation of 2.6° at T7 ($P<0.001$). This rotational pattern was found to be present in both males and females. It is concluded from this study that the normal, *nonscoliotic* human spine demonstrates a preexistent pattern of vertebral rotation that corresponds to what is seen in the most prevalent types of thoracic idiopathic scoliosis. Although the cause of this preexistent rotation remains to be resolved, it is likely that it governs the direction of curvature once scoliosis starts to develop.

Question 3: Are curve patterns in neuromuscular scoliosis randomly distributed, or does a predominant curve pattern exist comparable to what is seen in AIS?

One possible explanation for the direction of curvature (and thus rotation) in scoliosis could be muscle imbalance. If the direction of curvature is governed by muscle imbalance, disorders with a more or less random distribution of muscle weakness would exhibit random distribution of curve patterns. In **Chapter 5**, we report on a retrospective radiography study on curve shape and direction in 198 patients with neuromuscular scoliosis. Patients were divided into four groups consisting of Duchenne muscular dystrophy, cerebral palsy, spinal muscular atrophy and spina bifida. The results of this study demonstrated a predominance of right-sided thoracic and thoracolumbar curves, and left-sided lumbar curves, which differed significantly from an equal right-left distribution. Apical levels were respectively at T8, T12/L1 disc and L2. In conclusion, we found that in neuromuscular scoliosis, curve direction and apical levels are similar to what is seen in the most prevalent types of adolescent idiopathic scoliosis. Based upon these results, we postulate that the built-in, preexistent rotational pattern that we demonstrated to exist in the normal, *nonscoliotic* spine plays a more important role than muscle imbalance in guiding the direction of rotation (and thus curvature) in cases of neuromuscular scoliosis, as it does in idiopathic scoliosis.

Question 4: Does a preexistent pattern of rotation exist in the normal, nonscoliotic spine of quadrupeds?

If preexistent rotation were a unique finding in humans, it could be related to the pathogenesis of idiopathic scoliosis. If however, it also occurs in other vertebrates, who are known not to develop idiopathic scoliosis, it must be a factor that *in itself* is unrelated to the pathogenesis.
In **Chapter 6**, we present a CT study, in which vertebral rotation was analyzed in the transverse plane of the normal, *nonscoliotic* quadruped spine to determine if a rotational pattern exists similar to what was found in our previous study in humans (**Chapter 4**). CT scans of the thorax of 42 dogs without clinical or radiological evidence of scoliosis were used to measure axial vertebral rotation from T1 to T13 (dogs have 13 thoracic vertebrae) with a previously developed computer-based CT measurement method. The results of this study demonstrated a predominant rotation to the right of the upper, mid and lower thoracic vertebrae of the normal canine spine. The mean vertebral rotation angles differed significantly from zero degrees rotation at level T1, from level T4 to T7, and from T11 to T13. It was found that the normal spine of quadrupeds shows rotation of the thoracic vertebrae with a preferred direction to the right, which is similar to what is seen in the normal human spine. Since idiopathic scoliosis does not exist in quadrupeds, these results suggest that this preexistent rotation seems to be a physiological process in normal spinal development, independent of the pathogenesis of idiopathic scoliosis.

Question 5: Does a preexistent pattern of vertebral rotation exist in the normal, nonscoliotic spine of humans with a situs inversus totalis, and if so, to what side are the vertebrae rotated? Furthermore, what is the relation between rotational pattern and handedness in this population?

Having demonstrated the existence of a preexistent rotational pattern in humans and certain types of quadrupeds (**Chapter 4 and 6**), it became relevant to investigate a possible cause for this rotational asymmetry. In **Chapter 7**, a cross-sectional MRI study is presented in which vertebral rotation was measured in the transverse plane of the normal, *nonscoliotic* spine of persons with a complete mirror image reversal of the internal body organs – called situs inversus totalis (SIT). Handedness in this population was determined as well. MRI scans of the thorax and abdomen of 37 persons with SIT and a normal, *nonscoliotic* spine were acquired to measure axial vertebral rotation from T2 to L5 with a previously developed computer-based measurement method. The results of this study showed a predominant rotation to the left side of the mid and lower thoracic vertebrae, and to the right side of the upper thoracic and lumbar vertebrae. The mean vertebral rotation angles differed significantly from zero degrees rotation at the mid and lower thoracic levels, with a maximum rotation of 2.7° at level T7 ($P<0.001$). Handedness in this specific population was distributed in a manner similar to the normal population, 86% was right-handed. In conclusion, the normal spine of humans with a situs inversus totalis shows a preexistent pattern of vertebral rotation opposite to what is seen in humans with normal organ anatomy. Furthermore, no relation with handedness could be demonstrated. Based upon the results of the studies described above, it was postulated that the asymmetrical anatomy of the thoracic organs is likely to play an important role in the development of this preexistent rotational tendency.

General Discussion

Idiopathic scoliosis is an intriguing and classic orthopaedic disorder. Although many theories concerning its pathogenesis have evolved over more than a century of research, involving structures related directly to the spine,[1-6] as well as more general concepts such as growth disturbances,[7-10] neuromuscular disregulation,[11-17] osteoporosis,[18;19] and melatonin metabolism,[20;21] so far no single cause has been identified, and the pathogenesis of idiopathic scoliosis is therefore termed multifactorial.
A striking feature of idiopathic scoliosis is the fact that it does not occur in vertebrates other than humans, despite many similarities in the basic architecture of the vertebral column across the species.[22;23] The spinal column is very well capable to withstand axial compressive loads as well as ventral shear due to its broad endplates and discs, and the posterior location of the facets and most muscle groups and ligaments. In this respect, the quadruped spine is similar to a suspension bridge, which is a very stable construct under normal loading conditions (*Figure 1*). Intuitively, this structure would become very unstable if it were tilted 90° into the upright position. The human spine differs from this basic concept, in the sense that humans are the only vertebrates that consistently ambulate in a fully erect position with the body's center of mass directly above the pelvis. The human pelvis developed an extension curvature between the ischium and ilium, the lumbar lordosis was introduced, and the usual flexion contracure of the hips and knees disappeared during the evolution of bipedal gait (*Figure 2*). Even man's closest relative, the Bonobo, always keeps the body's center of mass in front of the pelvis, and ambulates with a flexion contracture of the hips and knees.[24] The fact that an upright posture is a prerequisite for scoliosis to develop is in agreement with studies of Machida *et al*, in which they showed that rats that were surgically made bipedal, and had to walk erect, developed scoliosis after pinealectomy, whereas similarly pinealectomized quadrupedal rats did not.[25;26] Apparently, certain ill-defined factors in bipedalism contribute to the pathogenesis of idiopathic scoliosis. Therefore, in this thesis, we focussed on possible intrinsic mechanisms that could be related to the pathogenesis of idiopathic scoliosis.

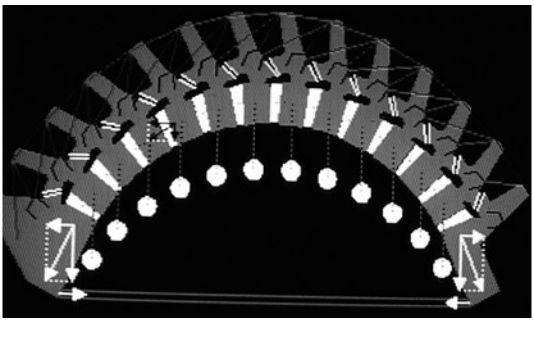

Figure 1. The quadruped spine shows similarities to a "suspension bridge".
Data compiled from B. Kummer. Development of human bipedalism. Köln.

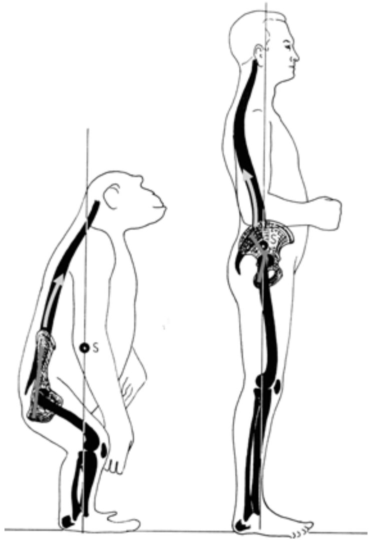

Figure 2. The ischio-iliac axis (red) is straight in the quadrupedal apes. In humans, the bent ischio-iliac axis (red) and lumbar lordosis (green) allow full extension in the leg joints. Data compiled from B. Kummer. Development of human bipedalism. Köln.

From recent work by Castelein *et al*, it was demonstrated that the fully erect posture, which is unique to humans, significantly alters spinal loading conditions.[27] Although the vertebral column in humans is still predominantly loaded in an axial direction, in a mathematical model of the spine it was shown that certain segments of the human spine, more specifically the backward inclined or 'declive' segments, are subject to *dorsal shear loads* as well. These dorsal shear loads are an important distinction between the human spine and the spine of all other vertebrates. Evidence for the existence of a resultant *dorsal* shear load on certain areas of the human spine can be found in the fact that in disc and facet joint degeneration certain vertebrae may exhibit degenerative antelisthesis, but others can also show retrolisthesis depending on their initial position in space. Obviously, any force can become greater than the body's coping mechanisms. It is interesting to note that in the growing spine, the equivalent of a long lasting excess of axial compression on the vertebral bodies is a well-known clinical entity, which is called Scheuermann's disease or osteochondrosis. This spinal disorder is characterized by irregularities of the vertebral endplate that develop during growth. Furthermore, a chronic excess of anterior shear during growth contributes to the development of spondylolysis and spondylolisthesis.[28-30] However, no clinical equivalent of excessive dorsal shear on the spine during growth has so far been described, a fact also noted by Vercauteren.[31]
In this thesis, it was postulated that excessive dorsal shear loads (as related to the body's compensating mechanisms), during the period of rapid growth, could lead to rotational instability of certain segments of the spine. To test our hypothesis, we developed a biomechanical *in vitro* model in which the effects of dorsal shear loads on

the rotational stability of the spine were compared with ventrally directed shear loads. The results of this experiment showed that more intervertebral rotation occurred under a dorsally directed shear load as compared to an identical ventrally directed load (**Chapter 3**). From this study, it was concluded that the spine is less rotationally stable under dorsal shear loads than under ventral shear loads. This points out that the human spine, on which these dorsal shear loads uniquely act, is a less stable construct, as far as rotation is concerned, compared to the spine of other vertebrates (including bipedal animals). We believe that these dorsally directed shear loads can, under critical circumstances during growth, act as an enhancer of slight preexisting rotation, whereas ventrally directed loads counteract rotation. This rotation-enhancing force in a growing spine, can result in a progressive deformation of individual vertebrae due to Hueter-Volkmann's law, and ultimately lead to progressive scoliosis due to a combination of mechanical and growth related factors. The magnitude of this dorsal shear load seems to depend on the number of vertebrae that show a backward inclination, and their individual inclination angle. A greater number of 'declive' vertebrae with less backward tilt could thus lead to a long and gradual rotational deformity (*Figure 3*), whereas less 'declive' vertebrae with a steeper backward tilt would lead to a shorter deformity (*Figure 4*). It is a well known fact that girls experience their pubertal growth spurt at a younger age than boys, when the thoracic kyphosis is still less developed,[32] thus leading to more declive vertebrae at the critical age of growth acceleration, possibly making their spines less rotationally stable. Boys, on the other hand, go through their growth spurt at a later age, already having more kyphosis. It is well appreciated by clinicians that they may develop short, non progressive rotated curves below the area of their increased kyphosis (*Figure 4*). Obviously, the basic question remains what the critical thresholds are that determine why most spines remain stable in their development, and some do not.

Another important question in scoliosis research concerns the direction of curvature. The most prevalent types of AIS are characterized by a primary thoracic curve rotated and deviated to the right side, usually exhibiting a high thoracic curve of smaller magnitude and a compensatory lumbar curve, both rotating in the opposite direction.[1;5;33-37] Although several theories have been suggested to explain why thoracic curves are convex to the right in the majority of children with AIS, such as right-handedness,[38;39] muscle imbalance,[13;16;40] or the asymmetrically situated descending thoracic aorta,[41;42] the cause of this preferred direction has so far not been resolved.

An important component of idiopathic scoliosis is transverse plane vertebral rotation. We hypothesised that a preexistent pattern of rotation might already exist in the normal, *nonscoliotic* spine. If the spine would then start to decompensate into scoliosis, it would seem logical that this built-in rotational pattern would be followed. To analyze vertebral rotation in the normal spine, we developed a new semi-automatic measurement method. Our study in 50 persons with a normal, *nonscoliotic*

Figure 3. Lateral and AP X-ray of a typical idiopathic scoliosis. A long, backwardly declined segment of the spine in the sagittal plane (a) is subject to dorsal shear forces. This segment corresponds with the rotated segment in the frontal plane (b). Data compiled from Castelein *et al*.[27]

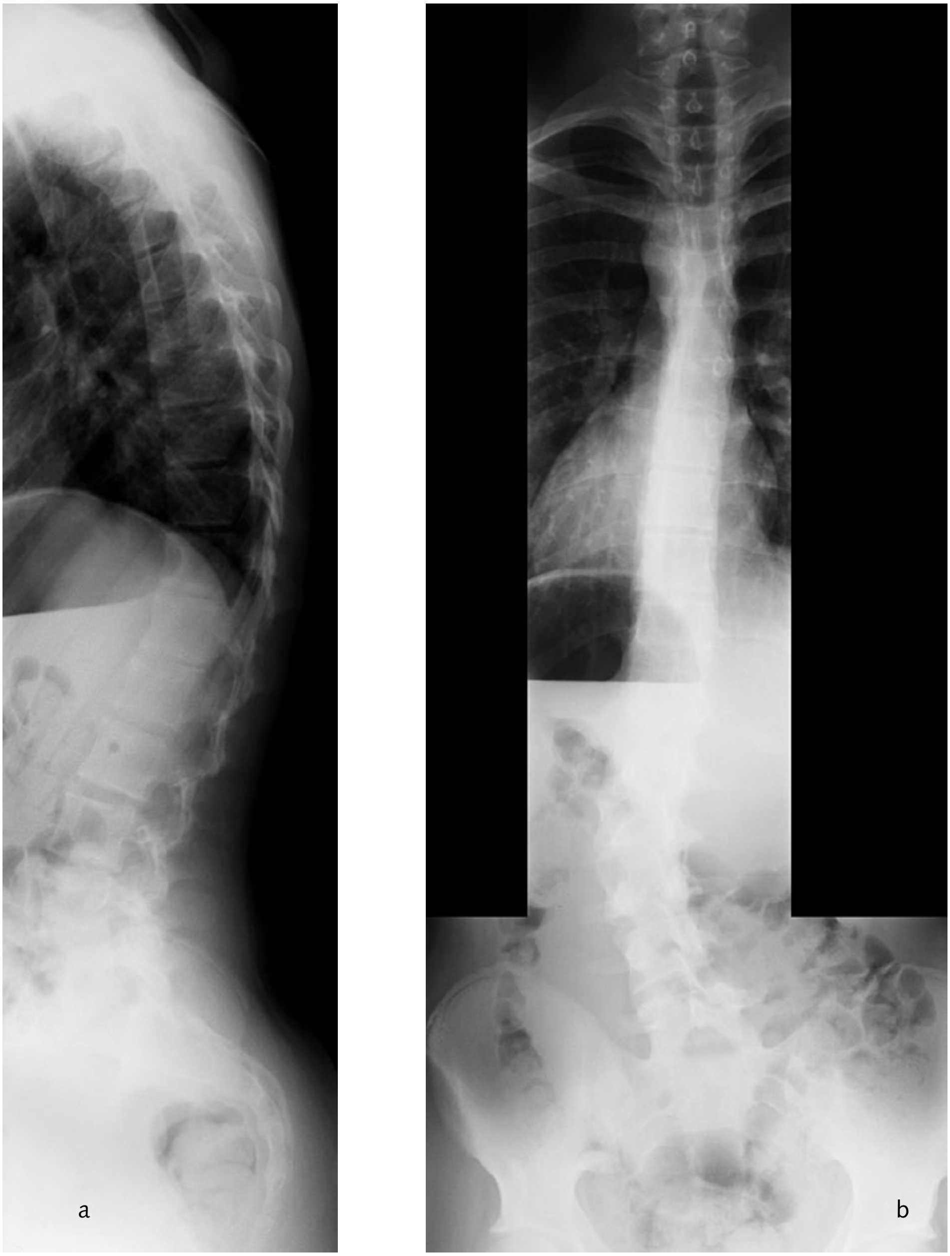

Figure 4. Lateral and AP X-ray of a Scheuermann's kyphosis. A shorter, but more backwardly declined segment of the spine (a) is subject to a greater dorsal shear force over fewer vertebrae. This corresponds to the rotated segment in the frontal plane (b). Data compiled from Castelein *et al*.[27]

spine showed the existence of a consistent pattern of rotation that is identical in direction, although not in magnitude, to what is seen in the most common types of thoracic idiopathic scoliosis (**Chapter 4**). High thoracic vertebrae tend to rotate to the left, lower and mid thoracic vertebrae rotate to the right, whereas towards the thoraco-lumbar junction this rotation reverts back to the midline.

Having found this preexistent rotation in the normal spine, the question became relevant what the role of muscle force in determining the direction of curvature and rotation would be. We hypothesised that, if muscle imbalance plays an important role in governing the direction of rotation and curvature, patients with different types of neuromuscular disease and scoliosis would exhibit rather random patterns of rotation and curvature. On the other hand, if muscle imbalance was merely one of the many possible triggers that can cause the spine to decompensate into scoliosis, curve patterns could be determined by the demonstrated preexistent rotation as well, thus showing similarities with idiopathic scoliosis. Controversy exists in the literature concerning this subject and no unequivocal data could be found. For this purpose, we analysed curve patterns in a large group of patients with scoliosis secondary to neuromuscular disease (**Chapter 5**). The results of this study showed that despite the difference in origin, curve patterns in neuromuscular disease show many similarities with those in idiopathic scoliosis, such as a strong prevalence of right convex thoracic curves. Based upon these results, we concluded that preexistent rotation, rather than muscle imbalance, also plays an important role in directing subsequent rotation in neuromuscular disease, as it does in idiopathic scoliosis.

Next, we wondered if this preexistent rotation was unique to humans, or if other vertebrates would exhibit a similar phenomenon. If it would be restricted to the human spine, it could be related to the pathogenesis of idiopathic scoliosis itself. If, on the other hand, similar patterns could be demonstrated in species that do not develop idiopathic scoliosis, it would rather be a factor related to the general development of the spine. No data on this subject could be found in the literature. For this purpose, we studied preexistent vertebral rotation in dogs with normal straight spines (**Chapter 6**). Strikingly, this study showed a predominant rotation of the canine thoracic vertebrae to the right; similar to what was found in humans. From this study, it was concluded that preexistent rotation can be considered as a physiological process in the normal development of the spine, independent of the pathogenesis of idiopathic scoliosis.

We postulated that the cause of this built-in rotational tendency must be sought in a factor that humans and quadrupedal vertebrates have in common, and is working asymmetrically on the immature growing spine. In the literature, concerning curve pattern in scoliosis, organ asymmetry and handedness have been implicated, however, no conclusive data on this subject could be found. Therefore, we designed a cross-sectional MRI study in which vertebral rotation was measured in the transverse plane of the normal, *nonscoliotic* spine of persons with a complete mirror image reversal of the internal body organs – called situs inversus totalis (SIT) (**Chapter 7**). Although this is a rare disorder with an estimated incidence of only 1 per 20,000 in the general population, we were fortunate to be able to locate a large group of people with SIT that were willing to cooperate in this study. In addition to vertebral rotation, handedness in this population was determined as well. The results of this study showed that handedness was distributed in this population identical to the normal population, in which 90% is right-handed. Nevertheless, this group demonstrated a rotational pattern exactly opposite to what was found in the normal population. Based upon these findings, it was concluded that the asymmetrical anatomy of the thoracic organs, perhaps most notably the eccentric position of the thoracic aorta in close relationship to the vertebral column, is likely to play an important role in the development of this preexistent rotational tendency, and handedness does not.

In this thesis, the role of dorsal shear loads and preexistent vertebral rotation in the development of idiopathic scoliosis were investigated. This knowledge should result in a better understanding of the onset and progression of AIS, thereby giving us new clues for an early prevention and/or treatment of AIS. The existing and future knowledge will be used for the development of a new screening technique for early detection of spinal misalignment in pubertal children, and a new minimal invasive surgical treatment aimed at a reversal of the pathogenetic mechanism of idiopathic scoliosis.

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Samenvatting en Discussie

In dit hoofdstuk worden de resultaten van de eerder beschreven hoofdstukken van dit proefschrift samengevat door de vragen te beantwoorden die werden gesteld in **Hoofdstuk 1** (Introductie en doelstellingen).

Vraag 1: Wat is het effect van dorsale en ventrale schuifkrachten op de rotatiestabiliteit van de wervelkolom?

In **Hoofdstuk 3** wordt een biomechanische *in vitro* studie op varkens en humane wervelsegmenten beschreven. Het doel van deze studie was om de axiale rotatiestabiliteit van de thoracale wervelkolom onder dorsale en ventrale schuifkrachten te onderzoeken. Voor dit onderzoek werden 7 kadaver wervelkolommen van varkens en 7 humane kadaver wervelkolommen gebruikt. Uit elke wervelkolom werden 2 thoracale wervelsegmenten geprepareerd, 1 van midthoracaal en 1 van laagthoracaal niveau, met intacte costotransversale en costovertebrale gewrichten. In beide richtingen (dorsaal en ventraal) werden de schuifkrachten op 3 posities aangebracht op de bovenste wervel van het segment: centraal (in het sagittale vlak), en 1 cm rechts en 1 cm links van het midden (excentrisch) wat resulteerde in een torsiemoment. Rotatie van de wervels werd gemeten op 3 krachtniveaus met een automatisch 3D bewegingsregistratiesysteem. De resultaten van deze studie toonden aan dat excentrische schuifkrachten rotatie veroorzaken in varkens als wel humane wervelsegmenten. Op mid- en laagthoracaal niveau werd significant meer rotatie waargenomen onder invloed van *dorsale* dan onder invloed van *ventrale* schuifkrachten. Hieruit werd geconcludeerd dat de thoracale wervelkolom bij mensen en bij viervoeters minder rotatiestabiel is onder invloed van *dorsale* dan onder invloed van *ventrale* schuifkrachten. Op basis van deze gegevens veronderstellen wij dat als deze dorsale schuifkrachten, die aangrijpen in het dorsaal geïnclineerde segment van de humane wervelkolom, een bepaalde grens overschrijden de functie van de facetgewrichten met betrekking tot de rotatiestabiliteit van de wervelkolom zal verminderen, hetgeen in de immature wervelkolom van het kind rotatie van het declieve (= achterover hellende) segment tot gevolg zou kunnen hebben. Wij vermoeden dat deze dorsale schuifkrachten, als gevolg van het verminderen van de rotatiestabiliteit, tevens een pre-existente rotatie in de wervelkolom zouden kunnen doen toenemen, hetgeen een rol zou kunnen spelen in het ontstaan en de progressie van AIS.

Vraag 2: Bestaat er een pre-existent rotatiepatroon in de normale, niet-scoliotische humane wervelkolom dat overeenkomt met het curvepatroon in de meest voorkomende vormen van AIS?

De kenmerkende en enigszins voorspelbare curvepatronen en rotatie in AIS zijn uitvoerig beschreven, echter de oorzaak voor deze typische patronen is niet bekend. Wij veronderstelden dat de karakteristieke rechts-thoracale bocht in AIS mogelijk bepaald wordt door een reeds pre-existent aanwezig rotatiepatroon in de normale, niet-scoliotische wervelkolom. Voor zover bekend is rotatie van de thoracale en lumbale wervels in de normale wervelkolom nog niet eerder systematisch geanalyseerd. In **Hoofdstuk 4** wordt in een retrospectieve studie een voor dit doel ontworpen en goed gevalideerde CT meetmethode beschreven, die is gebruikt om wervelrotatie te meten in het transversale vlak van T2 tot L5 in de normale wervelkolom van 50 personen zonder klinische of radiologische verschijnselen van scoliose. Rotatie was gedefinieerd als de hoek tussen de longitudinale as van een wervel en de midsagittale as van de borstkas (= referentielijn). De resultaten van deze studie toonden aan dat er overwegend een rotatie naar links bestaat van de hoogthoracale wervels en naar rechts van de mid- en laagthoracale wervels in de normale, niet-scoliotische wervelkolom, hetgeen significant verschilde van een ‘at random’ rechtslinks verdeling. Op niveau T6 tot T11 verschilden de gemiddelde rotatiehoeken significant van nul graden rotatie met een maximale rotatiehoek van 2,6° op niveau T7 (P<0,001). Dit rotatiepatroon bleek zowel bij mannen als bij vrouwen te bestaan. Er werd geconcludeerd dat de normale, niet-scoliotische wervelkolom een pre-existent rotatiepatroon vertoont wat qua richting overeenkomt met de meest voorkomende vormen van thoracale idiopathische scoliose. Hoewel de oorzaak van dit pre-existente rotatiepatroon nog moet worden achterhaald, is het aannemelijk dat dit patroon een belangrijke rol speelt in het bepalen van de richting van de bocht tijdens de ontwikkeling van een scoliose.

Vraag 3: Zijn curvepatronen in neuromusculaire scoliose gelijk verdeeld, of is er een overheersend curvepatroon overeenkomstig met AIS?

Eén van de mogelijke verklaringen die in de literatuur wordt gegeven voor de richting (en dus de rotatie) van de scoliotische bocht is een discrete verstoring van de spierbalans tussen de linker en rechter zijde van het lichaam. Als de richting van de bocht bepaald zou worden door spierimbalans, dan zouden aandoeningen met een min of meer ‘at random’ verdeling van spierzwakte een ‘at random’ verdeling moeten laten zien van curvedistributie. In de literatuur werden hieromtrent tegenstrijdige berichten gevonden. **Hoofstuk 5** is een retrospectieve studie waarin bij 198 patiënten met diverse vormen van neuromusculaire scoliose de vorm en richting van de curvatuur werden beschreven. Patiënten werden onderverdeeld in vier groepen, bestaande uit Duchenne’s spierdystrofie, infantiele encephalopathie, spinale musculaire atrofie en spina bifida. De resultaten van deze studie toonden een overheersing van rechtszijdige thoracale en thoracolumbale bochten en linkszijdige lumbale bochten aan, hetgeen significant verschilde van een willekeurige rechtslinks verdeling. De apex van de bochten bevond zich respectievelijk op niveau T8, T12/L1 en L2. Hieruit werd geconcludeerd dat de richting van de bocht (en dus rotatie) en het niveau van de apex in neuromusculaire scoliose vergelijkbaar zijn met de meest voorkomende vormen van adolescente idiopathische scoliose. Op basis van deze resultaten veronderstellen wij dat ook in neuromusculaire scoliose het pre-existente rotatiepatroon, dat werd aangetoond in de normale, niet-scoliotische, humane wervelkolom, een belangrijkere rol zou kunnen spelen in het bepalen van de richting van rotatie (en dus van curvatuur) dan spierimbalans.

Vraag 4: Bestaat er een pre-existent rotatiepatroon in de normale, niet-scoliotische wervelkolom van viervoeters?

Als pre-existente rotatie uniek is voor de humane wervelkolom zou het een relatie kunnen hebben met de pathogenese van idiopathische scoliose, echter niet als pre-existente rotatie ook voorkomt bij andere gewervelden, waarvan bekend is dat ze geen idiopathische scoliose ontwikkelen. In **Hoofdstuk 6** wordt een CT studie beschreven waarin wervelrotatie in het transversale vlak werd geanalyseerd in de normale, niet-scoliotische wervelkolom van viervoeters met als doel te bepalen of er een pre-existent rotatiepatroon bestaat overeenkomstig met het patroon dat wij aantoonden in de normale humane wervelkolom (**Hoofdstuk 4**). CT scans van de thorax van 42 honden die geen klinische of radiologische verschijnselen van scoliose hadden, werden gebruikt om wervel rotatie te meten van T1 tot T13 (honden hebben 13 thoracale wervels) met de eerder beschreven gevalideerde CT meetmethode. De resultaten van deze studie toonden aan dat de hoog-, mid- en laagthoracale wervels van de normale wervelkolom van honden overwegend naar rechts geroteerd zijn. Op niveau T1, T4 tot T7 en T11 tot T13 verschilden de gemiddelde rotatiehoeken significant van nul graden rotatie. Deze studie toonde aan dat de thoracale wervels in de normale wervelkolom van viervoeters een voorkeursrotatie naar rechts hebben, hetgeen overeenkomt met wat eerder werd aangetoond in de normale humane wervelkolom. Aangezien idiopathische scoliose niet voorkomt bij viervoeters suggereren deze bevindingen dat pre-existente rotatie een fysiologisch fenomeen is in de normale ontwikkeling van de wervelkolom wat los staat van de pathogenese van idiopathische scoliose.

Vraag 5: Bestaat er een pre-existent rotatiepatroon in de normale, niet-scoliotische wervelkolom van personen met situs inversus totalis, en zo ja, naar welke richting zijn de wervels geroteerd? Wat is de relatie tussen pre-existente rotatie en rechts/linkshandigheid in deze populatie?

Na aangetoond te hebben dat er een pre-existent rotatiepatroon bestaat in de wervelkolom van mensen en viervoeters (**Hoofdstuk 4 en 6**), rees de vraag wat de mogelijke oorzaak is van deze rotatie. In **Hoofdstuk 7** wordt een cross-sectioneel MRI onderzoek beschreven waarin wervelrotatie in het transversale vlak werd geanalyseerd in de normale, niet-scoliotische wervelkolom van personen met een volledige spiegelligging van de inwendige organen, hetgeen situs inversus totalis wordt genoemd (SIT). Verder werd er ook onderzocht hoe de verdeling rechts/linkshandigheid in deze groep is. Er werden MRI scans van de thorax en het abdomen gemaakt bij 37 personen met SIT en een normale, niet-scoliotische, wervelkolom met als doel wervelrotatie te meten in het transversale vlak van T2 tot L5 met de eerder beschreven meetmethode, die werd geadapteerd voor MRI scans. Deze meetmethode werd separaat gevalideerd. De resultaten van deze studie toonden aan dat de mid- en laagthoracale wervels overwegend naar *links* en de hoogthoracale en lumbale wervels naar *rechts* geroteerd waren. Op de mid- en laagthoracale niveaus verschilden de gemiddelde rotatiehoeken significant van nul graden rotatie, met een maximale rotatiehoek van 2,7° op niveau T7 (P<0,001). De verdeling van rechts/linkshandigheid in deze unieke populatie bleek in overeenstemming te zijn met de normale populatie, waarin ongeveer 90% rechtshandig is. Hieruit werd geconcludeerd dat de normale wervelkolom in personen met een situs inversus totalis een pre-existent rotatiepatroon vertoont dat gespiegeld is aan het patroon in de normale wervelkolom van personen met een normale orgaanligging. Er werd geen verband aangetoond met rechts/linkshandigheid. Gebaseerd op de resultaten van bovenstaande studies werd aangenomen dat de asymmetrische ligging van de thoracale organen een belangrijke rol zou kunnen spelen in de ontwikkeling van dit pre-existente rotatiepatroon.

Discussie

Idiopathische scoliose is een klassieke en intrigerende orthopaedische aandoening. Hoewel er gedurende ruim een eeuw gericht onderzoek meerdere theorieën over de pathogenese van deze aandoening zijn gepubliceerd, zowel met betrekking tot structuren direct gerelateerd aan de wervelkolom,[1-6] als wel betreffende meer algemene factoren zoals groeistoornissen,[7-10] neuromusculaire disregulatie,[11-17] osteoporose[18;19] en bijvoorbeeld het metabolisme van melatonine,[20;21] is er tot nu toe nog geen

eenduidige oorzaak aangetoond en wordt de pathogenese van idiopathsiche scoliose dan ook als multifactorieel beschouwd.
Een typisch kenmerk van idiopathische scoliose is het feit dat deze aandoening, ondanks de gelijkenissen in bouw van de wervelkolom tussen alle gewervelden, uitsluitend voorkomt bij de mens en niet bij andere gewervelden.[22;23]
De algemene architectuur van de wervelkolom, met zijn brede sluitplaten en dikke disci, en de posterieure ligging van de facetgewrichten, spieren en ligamenten, maakt dat de wervelkolom mechanisch gezien goed bestand is tegen *axiale* belasting en *ventrale* schuifkrachten. In dit opzicht is de wervelkolom van de viervoeter een zeer stabiele constructie, vergelijkbaar met een hangbrug (*Figuur 1*). Het is voorstelbaar dat deze constructie rotatoir instabiel wordt als hij 90° rechtop wordt gekanteld. In dat opzicht wijkt de humane wervelkolom af van dit algemene concept, in de zin dat de mens de enige gewervelde is die continu rechtop loopt met het zwaartepunt van het lichaam precies boven het bekken. Gedurende de totstandkoming van het rechtoplopen van de mens ontwikkelde zich een extensie curvatuur tussen het os ischium en het os ilium van het humane bekken, tevens ontwikkelde zich een lumbale lordose, en de (bij andere gewervelden) gebruikelijke flexie contractuur van het heup- en kniegewricht verdween (*Figuur 2*). Zelfs bij de Bonobo, die van alle gewervelden het meest verwant is aan de mens, bevindt zich het zwaartepunt van het lichaam altijd vóór het bekken en vertonen de heupen en knieën een flexie contractuur tijdens het lopen.[24] Het feit dat een rechtopgaande houding een voorwaarde is voor het ontstaan van scoliose is in overeenstemming met de experimenten van Machida e.a., waarin werd aangetoond dat ratten waarbij de epifyse (= pijnappelklier) chirurgisch werd verwijderd alleen scoliose ontwikkelden als ze door amputatie van de voorpoten en de staart bipedaal waren gemaakt en niet in als ze gewoon op 4 poten konden lopen.[25;26] Blijkbaar spelen dus bepaalde, vooralsnog slecht gedefinieerde, kenmerken van het "humane tweevoeterschap" een rol in de ontwikkeling van idiopathische scoliose. Om die reden hebben we ons in dit proefschrift specifiek gericht op de intrinsieke mechanismen van de wervelkolom, die mogelijk een rol zouden kunnen spelen in de pathogenese van idiopathische scoliose.
Recent onderzoek van Castelein e.a. heeft aangetoond dat de belasting van de wervelkolom significant verandert als gevolg van deze, voor de mens unieke, volledig rechtopgaande houding.[27] Hoewel ook de humane wervelkolom voornamelijk in *axiale* richting wordt belast, werd middels een rekenkundig model van de wervelkolom aangetoond dat bepaalde segmenten van de humane wervelkolom, en meer specifiek de dorsaal geïnclineerde of "declieve" segmenten, naast de axiale belasting, tevens onderhevig zijn aan *dorsale schuifkrachten*. Deze dorsale schuifkrachten vormen een belangrijk verschil tussen de humane wervelkolom en de wervelkolom van andere gewervelden. Bewijs voor het bestaan van deze dorsale schuifkrachten, werkzaam op bepaalde delen van de humane wervelkolom, wordt ook geleverd door het feit dat bij discus- en facetdegeneratie niet alleen een degeneratieve antelisthesis kan

worden gezien, maar dat bepaalde wervels ook een *retrolisthesis* kunnen vertonen, afhankelijk van de oorspronkelijke positie van de wervels.
Vanzelfsprekend kan iedere op het lichaam inwerkende kracht groter worden dan de compensatie mechanismen waarover het lichaam beschikt. Veelal leidt dat vervolgens tot herkenbare klinische entiteiten. Een interessant voorbeeld hiervan is het feit dat tijdens de groei langdurige axiale overbelasting van wervels kan leiden tot het ontstaan van een irregulaire ontwikkeling van de eindplaat, hetgeen in de kliniek bekend is als de ziekte van Scheuermann (= osteochondrose). Een voorbeeld van chronische overbelasting gedurende de groei in *ventrale* richting is de ontwikkeling van een spondylolyse of spondylolisthesis.[28-30] Gegeven het feit dat het nu dus aannemelijk is dat op de groeiende wervelkolom ook *dorsale* schuifkrachten inwerken, is het intrigerend dat voor een overmaat aan belasting in deze richting geen klinisch equivalent lijkt te bestaan. Tot nu toe is er geen aandoening beschreven die het gevolg kan zijn van overbelasting van de wervelkolom door *dorsale* schuifkrachten, hetgeen ook reeds werd geconstateerd door Vercauteren.[31]
In dit proefschrift werd verondersteld dat extreme dorsale schuifkrachten (in relatie tot de compensatiemechanismen van het lichaam) tijdens de groeispurt zouden kunnen leiden tot rotatie-instabiliteit van bepaalde segmenten van de wervelkolom. Om deze hypothese te testen werd een biomechanisch *in vitro* model ontworpen waarin het effect van dorsale schuifkrachten werd vergeleken met het effect van ventrale schuifkrachten op de rotatiestabiliteit van de wervelkolom. De resultaten van dit experiment toonden aan dat er meer rotatie optreedt onder invloed van dorsale schuifkrachten dan onder invloed van ventrale schuifkrachten (**Hoofdstuk 3**). Uit deze studie werd geconcludeerd dat de wervelkolom onder dorsale schuifkrachten minder rotatiestabiel is dan onder ventrale schuifkrachten. Dit geeft aan dat de humane wervelkolom, waarop deze dorsale schuifkrachten, anders dan bij andere gewervelden, werkzaam zijn, wat betreft rotatie, een minder stabiele constructie is vergeleken met de wervelkolom van andere gewervelden (inclusief tweevoeters). Wij vermoeden dat deze dorsale schuifkrachten, onder bepaalde omstandigheden tijdens de groei, een lichte pre-existente rotatie van de wervelkolom kunnen verergeren, terwijl ventrale schuifkrachten deze rotatie juist tegengaan. Deze dorsale schuifkrachten zouden aanleiding kunnen geven tot een progressieve deformatie van de wervels volgens het principe van Hueter-Volkmann, hetgeen uiteindelijk, als gevolg van mechanische en groeigerelateerde factoren, kan resulteren in de vicieuze cascade van een progressieve scoliose. De grootte van deze dorsale schuifkrachten hangt vermoedelijk af van het aantal wervels dat naar dorsaal is geïnclineerd en van de inclinatiehoek van de wervels afzonderlijk. Een groot aantal 'declieve' wervels met relatief weinig dorsale inclinatie zou per definitie dus kunnen leiden tot een deformiteit van de wervelkolom over een lang traject (*Figuur 3*), terwijl een kleiner aantal 'declieve' wervels met relatief veel dorsale inclinatie tot een deformatie over een kort traject zou kunnen leiden (*Figuur 4*). Het is een bekend gegeven dat meisjes op jon-

gere leeftijd in de puberteit geraken dan jongens, op een moment dat de thoracale kyphose nog nauwelijks is ontwikkeld.[32] Dit heeft tot gevolg dat er tijdens de groeispurt bij meisjes meer wervels naar dorsaal geïnclineerd staan dan bij jongens, wat er toe zou kunnen leiden dat de wervelkolom bij hen in deze fase daardoor minder rotatiestabiel is, waardoor idiopathische scoliose bij meisjes frequenter voor kan komen. Jongens maken hun groeispurt door op een moment dat er al meer thoracale kyphose is. De vertebrale deformiteit die bij jongens in deze kwetsbare fase van versnelde groei frequenter optreedt is de versterkte thoracale kyfose, of de M. Scheuermann. Het is overigens een bekend verschijnsel dat er onder het niveau van deze versterkte kyphose vaak een korte, niet progressieve, verkromming optreedt met een rotatie die beperkt blijft tot het versterkt achteroverhellende, of declieve segment (*Figuur 4*). Voor de hand liggend blijft natuurlijk de vraag wat nu precies bepaalt waarom de groeiende wervelkolom in de meeste gevallen rotatoir stabiel blijft en slechts in sommige gevallen niet.

Een andere belangrijke vraag in het onderzoek naar scoliose betreft de richting van de bocht. De meest voorkomende vormen van AIS worden gekenmerkt door een primaire thoracale bocht die naar rechts is geroteerd, meestal in combinatie met een kleine hoogthoracale bocht en een compensatoire lumbale bocht die beiden naar links zijn geroteerd.[1;5;33-37] Hoewel er meerdere theorieën bestaan over deze voorkeursrichting, zoals het overheersen in de bevolking van rechtshandigheid,[38;39] discrete en subklinische spierimbalans,[13;16;40] of de asymmetrische ligging van de descenderende thoracale aorta,[41;42] ontbreekt tot op heden in de literatuur een eenduidige verklaring voor deze voorkeursrichting.

Een belangrijk onderdeel van idiopathische scoliose is rotatie van de wervels in het transversale vlak. Wij veronderstelden dat er in de normale, niet-scoliotische, wervelkolom reeds een pre-existente rotatie aanwezig is, die zal worden gevolgd als de wervelkolom (om wat voor reden ook) in een scoliose decompenseert. Om rotatie in de normale wervelkolom te analyseren, werd een nieuwe semi-automatische, gecomputeriseerde methode ontwikkeld. Onze studie in 50 personen met een normale, niet-scoliotische, wervelkolom toonde aan dat er een consistent rotatiepatroon bestaat dat wat betreft rotatierichting (niet wat betreft grootte), identiek is aan wat wordt gezien in de meest voorkomende vormen van thoracale idiopathische scoliose (**Hoofdstuk 4**). Hoogthoracale wervels vertoonden voornamelijk een rotatie naar links, mid- en laagthoracale wervels naar rechts en rond de thoracolumbale overgang werd een rotatie terug naar de middenlijn gezien.

Nadat we aangetoond hadden dat er een pre-existent rotatiepatroon in de normale wervelkolom bestaat, vroegen we ons af wat de rol van spierkracht zou kunnen zijn in het bepalen van de richting van de laterale bocht en de daaraan gekoppelde rotatie. Wij veronderstelden dat, als spierimbalans hier een belangrijke rol in zou spelen, het curve- en rotatiepatroon bij patiënten met scoliose secundair aan een neuromusculaire aandoening 'at random' zou moeten zijn verdeeld. Anderzijds, als spierimba-

lans en zwakte alleen een trigger zijn voor het ontstaan van een scoliotische deformatie van de wervelkolom, dan zou bij neuromusculaire scoliose de richting van de curvatuur wellicht eveneens bepaald kunnen worden door pre-existente rotatie met als gevolg curvepatronen vergelijkbaar aan AIS. Aangezien er in de literatuur geen eenduidigheid bestaat over dit onderwerp, hebben wij in een grote groep patiënten met neuromusculaire scoliose de patronen van de scoliotische verkromming en bijbehorende rotatie geanalyseerd (**Hoofdstuk 5**). De resultaten van deze studie toonden aan dat, ondanks de verschillende oorzaken, de meest voorkomende curvepatronen bij neuromusculaire scoliose veel overeenkomsten vertonen met idiopatische scoliose, qua richting van de bocht en de rotatie, evenals de locatie van de apex. Gebaseerd op deze resultaten concludeerden wij dat pre-existente rotatie, net als bij idiopathische scoliose, ook bij neuromusculaire scoliose vermoedelijk een belangrijkere rol speelt bij het bepalen van de richting van de bocht en de rotatie dan asymmetrische spierkracht.
Vervolgens vroegen we ons af of dit pre-existente rotatiepatroon uniek is voor de mens of dat een vergelijkbaar fenomeen ook bij andere gewervelden voorkomt. Indien dit alleen voor zou komen in de humane wervelkolom, zou het gerelateerd kunnen zijn aan de pathogenese van idiopathische scoliose. Als het echter ook voor zou komen bij andere diersoorten, waarbij idiopathische scoliose niet voorkomt, zou dat kunnen betekenen dat het een fenomeen is dat tot de normale ontwikkeling van de wervelkolom behoort. Er werden geen data over dit onderwerp in de literatuur gevonden. Om deze vraag te kunnen beantwoorden, hebben we onderzocht of pre-existente rotatie voorkomt in de normale, rechte wervelkolom van honden (**Hoofdstuk 6**). Deze studie liet zien dat de thoracale wervels bij deze viervoeter voornamelijk naar rechts geroteerd waren wat opmerkelijk genoeg overeenkomt met het patroon dat werd aangetoond bij de mens. Uit deze studie werd geconcludeerd dat pre-existente rotatie beschouwd kan worden als een fysiologisch proces in de normale ontwikkeling van de wervelkolom, onafhankelijk van de pathogenese van idiopathische scoliose.
Wij veronderstelden dat de oorzaak van deze pre-existente rotatie vermoedelijk ten grondslag ligt aan een factor die mensen en viervoeters gemeen hebben en continu asymmetrisch inwerkt op de zich ontwikkelende immature wervelkolom. Als mogelijke oorzaak van de kenmerkende curvepatronen van AIS zijn in de literatuur onder andere asymmetrische orgaanligging en rechtshandigheid aangeduid, echter er bestaan geen conclusieve data omtrent dit onderwerp. Om deze vraag nader te analyseren hebben we een cross-sectioneel MRI onderzoek opgezet, waarin wervelrotatie werd gemeten in het transversale vlak van de normale, niet-scoliotische, wervelkolom van mensen met een volledige spiegelligging van de inwendige organen, hetgeen bekend is als situs inversus totalis (SIT) (**Hoofdstuk 7**). Hoewel dit een zeldzame aandoening is met een geschatte incidentie van 1 per 20.000 in de normale populatie, gelukte het om een relatief grote groep mensen met SIT te achterhalen

die bereid waren om te participeren in dit onderzoek. In deze studie werd er behalve naar wervelrotatie ook gekeken naar de verdeling van rechts/linkshandigheid in deze groep. De resultaten van dit onderzoek toonden aan dat de verdeling van rechts/linkshandigheid bij mensen met SIT identiek was aan de normale populatie, waarin 90% rechtshandig is. Daarentegen werd er in deze onderzoeksgroep een pre-existent rotatiepatroon gezien dat omgekeerd is aan het patroon dat we aantoonden bij mensen met een normale orgaanligging. Gebaseerd op deze resultaten werd er geconcludeerd dat de asymmetrische ligging van de thoracale organen, en wellicht voornamelijk de excentrisch gelegen thoracale aorta die dicht tegen de wervelkolom ligt, waarschijnlijk een belangrijke rol speelt in de ontwikkeling van dit pre-existente rotatiepatroon. Rechts/linkshandigheid leek in deze populatie geen rol te spelen.

In dit proefschrift werden dorsale schuifkrachten en pre-existente rotatie van de wervelkolom onderzocht in relatie tot de ontwikkeling van idiopathische scoliose. De kennis voortgekomen uit dit proefschrift moet leiden tot een beter inzicht in het ontstaan en de progressie van AIS met als doel de totstandkoming van vroegtijdige preventie en/of behandeling. De bestaande en nog te verkrijgen kennis zal moeten worden gebruikt voor de ontwikkeling van een nieuwe screeningsmethode voor vroegtijdige constatering van een afwijkende vorm van de wervelkolom bij kinderen in de puberteit, en voor de ontwikkeling van een nieuwe, minder invasieve chirurgische techniek gericht op het omkeren van het mechanisme achter de pathogenese van idiopathische scoliose.

Acknowledgements

This thesis could not have been written without the help and support of many people. I would like to express my deep gratitude for their help in this project. Especially the following people have contributed, directly or indirectly, to great extent to the manuscript.

Professor René Castelein
Koen Vincken
Theo Smit
Wouter Dhert
Wilbert Bartels
Professor Max Viergever
Idsart Kingma
Albert van der Veen
Professor Jaap van Dieën
Cumhur Öner
Brendan Bakker
Peter van Ommeren
Micha Paalman and colleagues
Willem van Wolferen
Simon Plomp
Tammo Delhaas
Tiny Visser
Björn Meij
Professor Paul Barthez
Professor Mark Jorissen
Hans Pruijs
Ria Matthijssen
Professor Ab Verbout
Cees Verlaan and all of the GDL personnel
Ger Vink and all of the KDL personnel
Karin Thijn
Cees Haaring
Roy Sanders
Gert Faber
Ronald Bleys
Frank Boesveld
Paul Westers
My fellow research-residents
Stichting Anna Fonds
Biomet Nederland
Fondation Yves Cotrel

All the participating volunteers

Timo Kouwenhoven
Olaf Kuijpers

My parents, Wim and Henriëtte
My sister-in-law Claire

Mariëlle

Curriculum Vitae

The author of this thesis was born on June 5th 1978 in Helmond, The Netherlands. In 1996 he graduated from high school (VWO, Dr. Knippenberg College, Helmond) and started to study medicine the same year at the University of Utrecht. After receiving his medical degree in 2002, he worked for two years as a non-training orthopaedic resident at the Vrije Universiteit Medical Center (head: Prof. dr. P.I.J.M. Wuisman) and the University Medical Center Utrecht (head: Prof. dr. R.M. Castelein). In January 2005 he started working as a fulltime research-resident on a PhD project on the pathogenesis of adolescent idiopathic scoliosis (AIS) under supervision of Prof. dr. R.M. Castelein. The present work has resulted in several publications, a number of presentations at international conferences, and this thesis. Since September 2006 the author is working as a general surgery resident at the Meander Medical Center in Amersfoort (head: Dr. G.H.M. Verberne), which is part of his training in orthopaedic surgery.