Discogenic Pain

A diagnostic challenge

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To you my beloved parents,
for always believing in me and for your endless support

"If we knew what it was we were doing, it would not be called research, would it?"

Albert Einstein

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Study II   **In vivo discography in degenerated porcine spines revealed pressure transfer to adjacent discs.**
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Study III   **Pressure increase in adjacent discs during clinical discography questions the methods validity.**
Hebelka H, Nilsson A and Hansson T
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Study IV   **HIZ's relation to axial load and low back pain: investigated with axial loaded MRI and pressure controlled discography.**
Hebelka H, Hansson T
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Study V   **Comparison between pain at discography and morphological disc changes at axial loaded MRI in patients with low back pain.**
Hebelka H, Brisby H and Hansson T
Submitted

Thesis at a glance

Study	Hypothesis	Methods	Material	Answer
I	Discography induce pressure increase in adjacent discs	Experimental in vivo study	9 healthy porcine spines, 33 discs	Yes
II	Discography induce pressure increase in adjacent discs in degenerated spines	Experimental in vivo study	10 degenerated porcine spines, 28 discs	Yes
III	Discography induce pressure increase in adjacent discs in a clinical population	Prospective clinical study	9 patients, 22 discs	Yes
IV	Detection of HIZ alters when adding alMRI HIZ is a reliable predictor of discogenic pain	Prospective clinical study	41 patients, 140 discs (MRI), 119 discs (discography)	No/No
V	Painful discograms reveal specific features under axial load (alMRI) as compared with non-painful discograms Discogenic pain is provoked by alMRI	Prospective clinical study	41 patients, 154 discs (MRI) 119 discs (discography)	No/Yes

Abstract

Low back pain (LBP) is a common health complaint with a lifetime prevalence up to 80%. Patients with discogenic pain constitute a minority of all with LBP but represent an important group with substantial personal consequences and high demands on health-care and social systems. In spite of debated validity discography remains frequently used in the diagnosis of discogenic pain. A concordant pain provocation at discography is an indication of a painful disc. Discography is questioned, especially due to inconclusiveness regarding the rate of false positive responses. The primary aim of this thesis was to investigate a potential validity issue; whether a pressure increase is induced in adjacent discs during discography. Further it aimed to investigate the relationship between discography-induced pain and morphological disc changes, occurring during axial loaded MRI (alMRI) and if such axial load increase the detection of High Intensity Zones (HIZ). These aims were investigated in experimental in vivo studies and in clinical discography patients.

Study I-III

Discography was performed in nine healthy porcine lumbar spines (33 discs), in ten degenerated porcine spines (28 discs) and in nine patients (22 discs) with discogenic pain. During contrast injection disc pressure was recorded simultaneously in the injected and in one adjacent disc. All 33 adjacent discs in the healthy porcine spines displayed increased pressure of a mean of 5 psi (range 1-14) above baseline pressure, corresponding to a mean increase of 16 %. In the degenerated porcine spines 16 (57%) of the discs adjacent to the discograms revealed a pressure increase averaging 3 psi (range 2-8), corresponding to a mean increase above baseline of 11%. When including pressure reactions until 15 minutes after injection increased pressure was recorded in 89% of the adjacent discs. In the clinical study 12 (55%) of the discs adjacent to the discograms displayed a pressure increase of a mean of 13 psi (range 3-42), corresponding to an increase of 62%. This induced pressure increase in adjacent discs (potentially inducing pain) constitutes a potential major source of false positive responses, questioning the validity of discography.

Study IV

41 patients referred for discography underwent pressure controlled discography (PCD), CT, MRI and alMRI within 24 hours. 35 patients completed all MRI sequences (140 discs) and PCD was performed in 119 of the discs examined at MRI. The detection of HIZ was compared between conventional MRI and alMRI without significant differences. No significant correlation between HIZ

and pain provoked at PCD was found. With PCD discogenic pain can neither be confirmed in discs with HIZ (PPV 39%) nor ruled out in discs without (NPV 76%). Quantification of HIZ at conventional and alMRI are needed to fully rule out any dynamic component of HIZ.

Study V

41 patients referred for discography underwent PCD (119 discs), MRI and alMRI within 24 hours. Provoked pain at both discography and at alMRI was classified as concordant or discordant with daily pain as reference. Relationships between concordant pain at discography and morphological disc measures (degeneration, height, bulge, angle, area, and circumference) at MRI/alMRI were investigated. 98% of the patients experienced concordant pain at discography compared with 78% at the alMRI. No significant, clinically useful, differences between concordant and discordant discograms in terms of morphological MRI characteristics at either conventional MRI, alMRI or changes between these two were found. Alternative or more sensitive diagnostic methods are needed to understand the load-induced discogenic pain.

Conclusions

The validity of discography must be questioned due to induced pressure increase (potentially inducing pain) in adjacent discs. The detection of HIZ is not influenced by axial load. HIZ cannot be used as a reliable predictor of painful discs. Loading of the spine, alMRI, revealed no specific clinically useful morphological characteristics in discs with concordant discograms.

Svensk sammanfattning
(Abstract in Swedish)

Ett av de vanligaste hälsoproblemen är ländryggsmärta med upp till 80% livstidsprevalens. Individer med diskogen smärta utgör en mindre, men viktig grupp av alla som drabbas av ländryggssmärta eftersom smärtan ofta leder till betydande fysiska och psykosociala konsekvenser. Även den socioekonomiska bördan relaterad till denna grupp är stor och motsvarar 1-2% av BNP. Diskografi, smärtprovokation genom kontrastinjektion i disken, används för att ta reda på om en disk med avvikande morfologi är smärtsam. Kontrast-injektionen ökar disktrycket vilket sannolikt stimulerar smärtreceptorer i disken. En konkordant smärtprovokation används som en indikation på att den provocerade disken är smärtsam. Diskografins validitet är omdebatterad och ifrågasatt men metoden används fortsatt ofta, t.ex. i USA.

Syftet med denna avhandling var att undersöka ett potentiellt validitetsproblem; om det ökade trycket i disken vid diskografi inducerar en tryckökning även i angränsande diskar. Vidare syften var att klarlägga om belastad MR inducerar specifika morfologiska förändringar i smärtsamma diskar samt om belastad MR ökar detekteringen av HIZ.

Studie I-III

Diskografi utfördes på nio friska grisryggar (33 diskar) in vivo, på tio degenererade grisryggar (28 diskar) in vivo samt på nio patienter med förmodad diskogen smärta (22 diskar). Disktrycket registrerades i en angränsande disk simultant med registrering av trycket i den injicerade disken (diskogram). Samtliga av de undersökta angränsande diskarna i friska grisryggar visade ett ökat disktryck med medel på 5 psi (spridning 1-14) över grundtrycket, vilket motsvarar en genomsnittlig tryckökning på 16%. I degenererade grisryggar registrerades en tryckökning i 16 (57%) angränsande diskar med medel på 3 psi (2-8), motsvarande en genomsnittlig tryckökning på 11% över grundtrycket. När tryckregistreringen omfattade 15 minuter efter injektion uppvisade 89% av de angränsande diskarna en tryckökning. Hos kliniska patienter visade 12 (55%) av de angränsande diskarna ett ökat tryck med ett medelvärde på 13 psi (3-42), motsvarande en ökning på 62% över grundtrycket.

Denna tryckökning är av klinisk relevant magnitud och var ibland lika hög i angränsande disk som i injicerad disk. Detta innebär att provocerad smärta vid diskinjektion kan härröra från en angränsande smärtsam disk. Inducerad tryckökning i angränsande diskar vid diskografi utgör således en potentiell

viktig orsak till låg specificitet vilket gör att diskografins validitet måste ifrågasättas.

Studie IV

På 41 konsekutiva diskografipatienter utfördes vid ett och samma tillfälle tryckkontrollerad diskografi (PCD), CT, MR och belastad MR. 35 patienter fullföljde samtliga MR sekvenser. Totalt undersöktes 140 diskar och PCD utfördes i 119 av dessa diskar. Detektionen av HIZ jämfördes mellan vanlig MR och belastad MR utan några signifikanta skillnader. Framprovocerad smärta vid PCD korrelerades med förekomsten av HIZ på MR utan signifikant samband. Diskogen smärta kan varken bekräftas i diskar med HIZ (PPV 39%) eller uteslutas i diskar utan (NPV 76%). Kvantifiering av HIZ vid såväl konventionell som belastad MR är nödvändingt för att helt utesluta en dynamisk komponent av HIZ.

Studie V

41 konsekutiva diskografipatienter genomgick inom 24 timmar PCD (totalt 119 diskar), MR och belastad MR. Framprovocerad smärta klassificerades vid både diskografi och vid belastad MR som antingen konkordant eller diskordant med patienternas dagliga smärta som referens. Smärtan vid diskografi korrelerades med diskparametrar (degeneration, höjd, buktning, vinkel, area och omkrets) både på konventionell och belastad MR. 98% av patienterna upplevde en konkordant smärta vid diskografin jämfört med 78% vid belastad MR med en signifikant korrelation mellan modaliteterna (p=0.01). Inga signifikanta, kliniskt användbara, skillnader mellan konkordanta och diskordanta diskogram hittades avseende morfologiska MRI parametrar, varken med konventionell MR, belastad MR eller skillnaden mellan dem. Alternativa eller känsligare diagnostiska metoder behövs för att förstå belastningsrelaterad diskogen smärta.

Slutsats

Diskografin validitet måste ifrågasättas p.g.a. inducerad tryckökning (förutsättning för inducerad smärta) i angränsande diskar. Detektering av HIZ påverkas inte av belastad MR. HIZ är inte en tillförlitlig prediktor för smärtsamma diskar. Belastad MR inducerar ej några specifika morfologiska förändringar i diskar smärtsamma vid diskografi.

Abbreviations

AF   annulus fibrosus

ALL   anterior longitudinal ligament

alMRI   axial loaded Magnet Resonance Imaging

a.o.p.   above opening pressure

CLBP   chronic low back pain

CSF   cerebrospinal fluid

CT   Computed Tomography

DDD   Dallas Discogram Description

DRG   dorsal root ganglion

EP   endplate

FAD   functional anesthetic discography

FJ   facet joints

FOPT   fiber-optic pressure transducer

GDP   Gross Domestic Product

HIZ   High Intensity Zone

IASP   the International Association for the Study of Pain

ICC   intra-class correlation coefficient

ISIS   International Spine Intervention Society

IVD   intervertebral disc

LBP   low back pain

MRI   Magnet Resonance Imaging

MRS   Magnet Resonance Spectroscopy

NGF   Nerve Growth Factor

NP   nucleus pulposus

NPV   negative predictive value

NRS   numerical rating scale

o.p.   opening pressure

PCD   pressure controlled discography

PG   proteoglycan

PLL   posterior longitudinal ligament

PPV   positive predictive value

psi   pounds per square inch

RCT   randomized controlled trial

SI   sacroiliac

Definitions

Discogenic pain: Pain believed to originate from the disc without
                      structural abnormalities other than disc degeneration
                      explaining the pain. The pain is mostly localized in the
                      midline in the lower lumbar region and sometimes
                      accompanied with radicular symptoms but without
                      radiological signs of neural compression.

Opening pressure: The pressure that is required to overcome the intrinsic
                      hydrostatic pressure within the disc, i.e. when contrast
                      first is seen within the disc at fluoroscopy.

Discogram: Intervertebral disc injected with radio-opaque contrast.

Introduction

As a resident physician, I had the privilege to be responsible for the discography procedures in the south-western region of Sweden. Discography was a challenging and interesting procedure to perform but hardly a pleasant procedure for the patient - being not only invasive, very painful but also extended in time. Patients with back pain, suffering from sometimes incapacitating pain with severe physical, psychosocial and economic consequences, were interesting to work with but also challenging since the source of pain often is unknown and existing diagnostics limited. In spite of frequent use, at least in the USA, discography is and has for long been a controversial diagnostic tool. I began to immerse myself in several arising issues. What is the source of pain in these patients? What is diagnosed with the test? Is the test valid?

60-85% of all people have back pain at some time in their life and low back pain (LBP) is the most or second most common reason for impairment among young and middle-aged people [1-5]. 90-95% of patients with LBP recover spontaneously or with sparse treatment within 3 months [1, 6], but in approximately 5-10% of the patients the LBP turns into a chronic condition; chronic low back pain (CLBP) [1]. Discogenic pain constitutes approximately 26-45% of the patients with CLBP [7-11]. Even though this category of patients appears small it is an important such since in addition to personal consequences, like reduced life quality, the demand on the health-care and social systems are high and costly, compromising around 1% of GDP (Gross Domestic Product) [12, 13].

Of all spine surgeries in Sweden about 10% are performed on patients with discogenic pain [14]. Around 60% of those will improve, some even deteriorate [15]. The disc, more specific, internal disc disruption, is believed to be the source of discogenic pain. Discography by its pain provocation is regarded as the only diagnostic tool with capacity to identify painful discs and is primarily used to identify the pain generating disc level(s) preoperatively. Discography has been extensively debated during the last 60 years with diverging opinions about its validity and clinical utility, a debate that will continue until settled.

Background

The Intervertebral Disc

Overview disc anatomy and function

The intervertebral disc (IVD) is a complex articulation linking the vertebral bodies together. It is designed to allow movements in the spinal column but also to act as a damper and absorber to withstand the daily sometimes heavy loads it is subjected to [16]. In the lumbar spine the IVD is approximately 7-10 mm thick and 4 cm in diameter [17], thus being the largest avascular structure in the body [18]. The IVD consists of three functional units; a central nucleus pulposus (NP), surrounded by the annulus fibrosus (AF) (Figure 1) and attached caudally and cranially by the cartilaginous endplates (EP) to the adjoining vertebral bodies [6, 8]. These three components are different in structure and mechanical function but act as a unit contributing to the mechanical function of the disc [19]. Posteriorly the disc is supported by the facet joint (FJ) which contributes to spinal stability by limiting movements in all directions [20]. A more detailed description of the disc´s functional units, vascularization and innervation follows.

Figure 1. Anatomy of the disc and surrounding structures
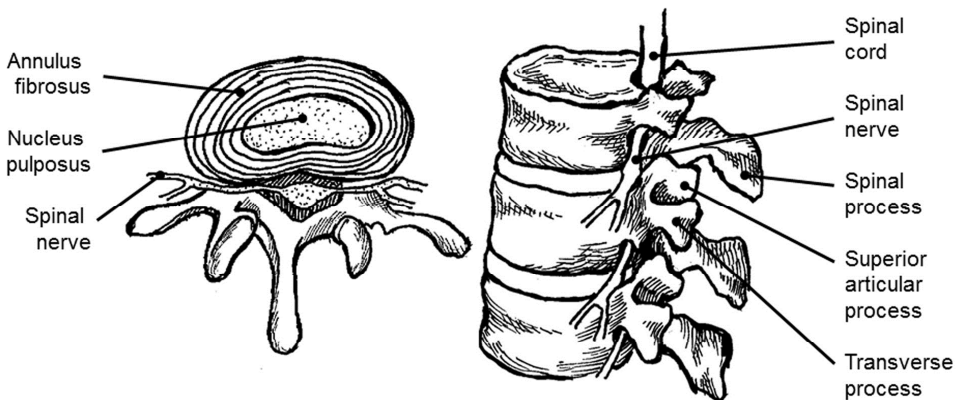
Figure design Emilie Hebelka

Nucleus Pulposus (NP)

NP is a gelatinous core of the IVD with critical function in the mechanical properties of the disc [21]. When axial load is applied to the spine the NP acts as a shock absorber and allows spinal movements in all directions like a semifluid ball. It is composed by approximately 80% water, 15% proteoglycans (PG) and 5% collagen [17]. The inner core of NP contains organized elastin and collagen fibers, surrounded by a PG rich gelatinous structure [17, 22]. This structure contributes to the viscoelastic properties of the disc and to its compressibility [17]. The negatively charged PG generates a high osmolality, which attracts and retain water molecules, this contributes to a high hydrostatic intradiscal pressure. The hydrostatic pressure is a prerequisite for the disc to disperse forces as a reaction to load. With increased load the NP bulges towards the EP and AF, spreading the load to a larger area and by that increase its capacity to withstand heavy loads [6, 23] (Figure 2).

Figure 2. Load distribution in the disc
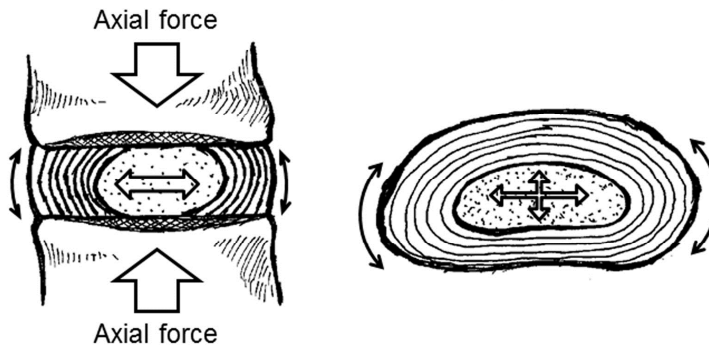
Figure design Emilie Hebelka

Annulus Fibrosus (AF)

The AF is composed of fibrocartilage and consists of up to 25 concentric highly organized lamellas, surrounding the NP (Figure 3 & 4) [17]. These lamellas create a three dimensional collagen network with lamella oriented between 30-150º to the transversal plane, running obliquely from vertebra to vertebra (Figure 3) where they attach to the EP by so called Sharpey´s fibers [24, 25]. In addition the lamellas run in 90º angle to each other and are linked to each other by elastin fibers. This specific organization provides the AF with both strength and tensile properties [17], distributing pressure evenly across the disc when axial load is applied (Figure 2) [6].

Figure 3. Schematic illustration of the structure of AF
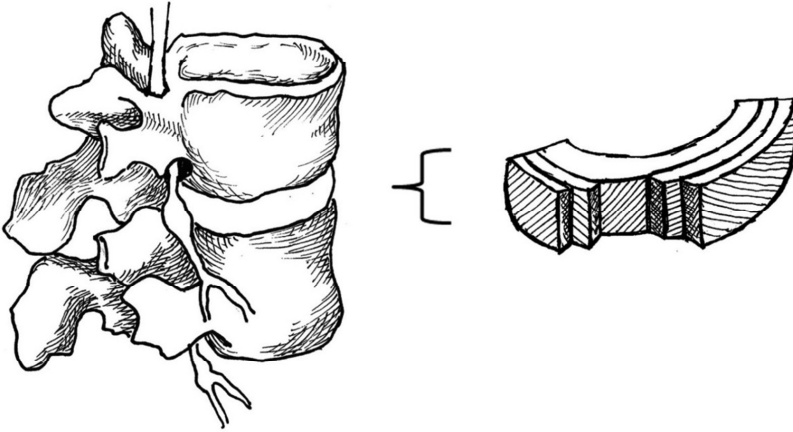
Figure design Emilie Hebelka

Vertebral Endplate (EP)

The EP covers the vertebral body both cranial and caudal interfacing the disc (Figure 4). The EP is constituted by <1 mm cartilage which is both of hyaline and fibrous type with increasing content of the latter with increasing age and corresponding decrease of the former [6, 17]. The EP serves both as a nutrient regulator of the disc as well as load absorber for mechanical loading of the spine [18]. The EP is usually the first structure to fail when vertebrae are tested in compression [26].

Figure 4. Composition of the EP, NP and AF

Nucleus pulposus
water 77%, proteoglycan 14%, collagen 4%

Annulus fibrosus
water 70%, proteoglycan 5%, collagen 15%

Endplate
water 55%, proteoglycan 8%, collagen 25%
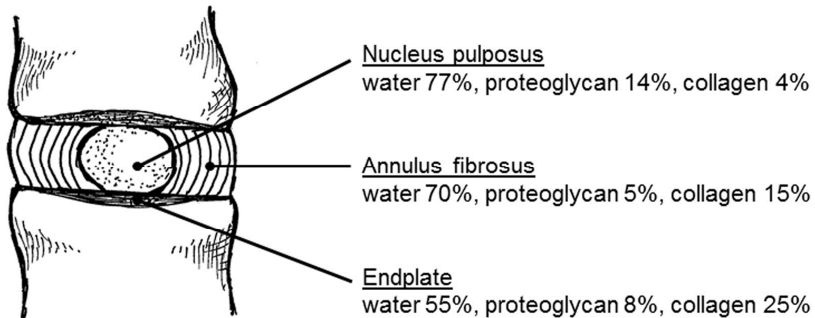
Figure design Emilie Hebelka

Vascularization/Nutrition

The healthy adult disc, including the cartilaginous EP, is as already noted avascular [27]. In the growing spine a network of microscopic blood vessels, emanating from the spinal artery [17] penetrates the EP before disappearing around the time of skeletal maturity [18]. In the adult disc the central NP may be as far as 8 mm from nearest capillary [18, 27] and therefore dependent solely on diffusion for nutrient supply [16, 28]. Like other structures the disc is dependent on oxygen and glucose, among others, to maintain an acceptable environment and pH level for the cells in the disc. Those nutrients are supplied through diffusion via capillary beds along the margins of the disc and metabolic waste products are removed by the reverse route [27]. These capillary beds are localized in the outer AF, in the subchondral bone adjacent to EP and in adjacent ligaments [8, 17, 27, 29, 30]. The subchondral vascular plexa is supplied by lumbar arteries and by branches from the spinal artery and supplies the AF and the ligaments. Drainage occurs mainly posteriorly to the anterior venous plexa in the spinal canal [27, 30, 31].

Innervation

The innervation of the disc is complex. Like the adult disc is avascular it is almost aneural with innervation only in the outer third of AF in healthy discs [32]. The EP is however well innervated [32]. The vertebral column is surrounded by interconnected nerve plexa anteriorly and posteriorly [33]. The anterior plexus is connected to the anterior longitudinal ligament (ALL) and receives branches from the sympathetic trunk, rami communicants' and from perivascular nerve plexa [17, 33]. The posterior plexus forms a net in the posterior longitudinal ligament (PLL) and the ventral dura and is innervated by nociceptive fibers from the sinuvertebral nerves [33, 34]. The latter comes from a somatic root of the ventral ramus (from the spinal nerve which exits at the dorsal root ganglion (DRG)) and from an autonomic root from gray rami communicants (from the sympathetic trunk) [17, 20]. The anterior and posterior nerve plexa are distributed in all directions forming a network around the disc (Figure 5) that is related to the autonomous nerve system. Groen et al.[33] however suggests that they may act as sensory nerves as well.

Figure 5. Innervation of the disc and adjacent structures

Supraspinous Ligament
Interspinous Ligament
Ligamentum Flavum
Zygapophysial Joint Capsule
Intertransverse Ligament
Dorsal Rami
Ventral Ramus
Posterior Ligament
Intervertebral Disc
Anterior Ligament
Grey Rami Communicantes
Sinuvertebral Nerve
Psoas Minor
Psoas major
Quadratus Lumborum
Intertransversarii
Longissimus Thoracis Iliocostalis Lumborum
Interspinales
Multifidus

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Biomechanical properties of the healthy disc

The disc´s viscoelastic behavior is a prerequisite for stabilizing the spine and to distribute loads evenly [16]. The major biochemically components contributing to these mechanical properties are water, PG, collagen and elastin fibers [17] (Figure 4). The major PG of the disc, the macromolecule aggregan, maintains disc hydration by osmotic pressure [17]. The high osmolality of the non-degenerated NP contributes to the disc´s hydrostatic behavior and helps NP to absorb applied mechanical stresses [17]. In a non-degenerated disc stress profilometry in vitro has shown uniform, isotropic high intra-nuclear pressure and a rapid drop of pressure in peripheral AF [35, 36]. As a consequence to the high NP pressure load is transferred to the surrounding AF [6, 36]. These forces are opposed by the tensile lamella in the annulus, transferring the applied load in caudal-cranial direction to the EP (Figure 2). Deflection of the latter has been shown as a response to increased intradiscal pressure [37]. Further response to spinal loading is that interstitial fluid is extracted from the disc, for example when the spinal column is under static load the disc pressure decreases with

15% after several hours [36, 38]. This also explains why at the end of the day people are shorter compared with in the morning after a night in prone position [39].

Intradiscal pressure

The intradiscal pressure is of both hydrostatic and osmotic character. Hydrostatic pressure is observed within all fluids and equals the pressure exerted by the fluid column above a certain point within the fluid. During axial load resistance is exerted mainly by hydrostatic forces [40]. Osmotic pressure on the other hand is exerted when two solutions with different concentrations, divided by a semi permeable membrane, interact. The solvent at the low concentration side tends to move towards the high concentration side, a vital mechanism in transferring water to the inside of the cells [40].

The internal disc pressure corresponds mostly to the pressure in NP and disc compression results in loss of water mainly in the NP rather than in the AF [41]. The intradiscal pressure will change depending on the posture and loading conditions of the vertebral column, and alter depending on state of degeneration [36, 42, 43]. In addition disc pressure is greatly affected by the recent load history [44], with the disc being less capable to withstand loads after exposure to heavy load [42, 45]. In healthy discs the pressure has been shown to increase linearly to increasing compressive load but paradoxically decreased when long lasting compressive creep load is applied [46-48].

In the pioneering studies of Nachemson internal disc pressure was shown to be highest in sitting position, lower in standing and lowest in prone position [49]. In upright position disc pressure was approximately 100 pound per square inch (psi), which increased to almost 300% of the total bodyweight if applying a small weight in standing. In subjects with non-degenerated discs intradiscal NP pressure is approximately 25 psi in prone unloaded position [50]. Under low loading conditions intradiscal pressures between 7-40 psi have been reported and as high as 300 psi under high external loads, such as lifting with flexed, rotated spine [38, 50, 51]. This exemplifies the enormous capacity of the disc to withstand pressure.

The intradiscal pressure also varies over the day with disc height, volume and pressure reduced after loading with individuals being 1% shorter at end of the day [39, 52-54]. Correspondingly the intranuclear pressure increases during night, likely due to osmosis and rehydration with a pressure increase of 240%, from approximately 15-35 psi [38]. These physiologic disc pressure variations affect matrix gene expression by stimulating cell synthesis. Conversely abnormal pressures inhibit this synthesis or act in a catabolic way [16, 55, 56].

The Porcine Disc

The porcine spine is considered a reasonable model for the human spine regarding experimental research [57, 58]. It resembles the human spine with comparable dimensions of the vertebral body, EP, pedicle size and the shape of the spinal canal [57]. Also the porcine disc resembles the human one, constituted by the same components; EP, AF and NP. However the porcine disc has notochordal cells even in adulthood as opposed to human ones where they are rare and in contrast to the human cartilaginous EP it is bony in the porcine [6, 59, 60].

The porcine lumbar spine consists of six lumbar vertebrae resembling the human vertebrae in anatomy but with relatively longer and broader transverse processes and different orientation of the FJ [6]. This as a result of the porcine spine being located horizontally instead of vertically as in the human spine, which also explains why porcine discs being smaller and the muscle mass larger compared with humans [6, 57, 58]. The relation between the disc and the vertebrae are equal between the species but the porcine disc is almost four times as small as the human one. In addition the human discs increase in size in caudal direction while the porcine disc is relatively constant in size [57, 58].

In spite of above discussed differences between the species [57, 60] the many similarities regarding anatomy and discs explain the frequent use of porcine as an animal model, especially in studies of biomechanical properties of the spine and the discs (Figure 6) [57, 58].

Figure 6. Comparison of sectioned degenerated porcine disc (left) and human degenerated disc (right)
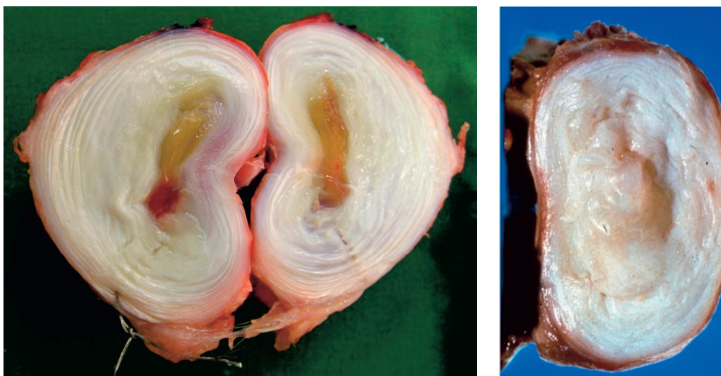
Experimentally induced degeneration

There are various models used for inducing disc degeneration in animals, either chemical or mechanical [61-63]. One mechanical model is a stab incision that induces both structural and biochemical changes such as; herniation of nuclear material, reduced water/PG content of the disc and fibrous transformation of NP [6, 61, 64, 65]. Holm et al. developed another model by drilling a hole obliquely through the vertebral body and the EP (Figure 7), intended to simulate micro fractures of the EP and underlying bone and to induce a degeneration more closely mimicking human degeneration [61, 66]. It was shown that three months postoperatively NP was discolored, had lost its gelatinous matrix and the annular layers were delaminated. NP pressure was also significantly lower in the degenerated discs. This model has been used frequently since, considered a representative model for experimentally induced disc degeneration [67].

Figure 7. Illustration of disc degeneration induced with drilling technique
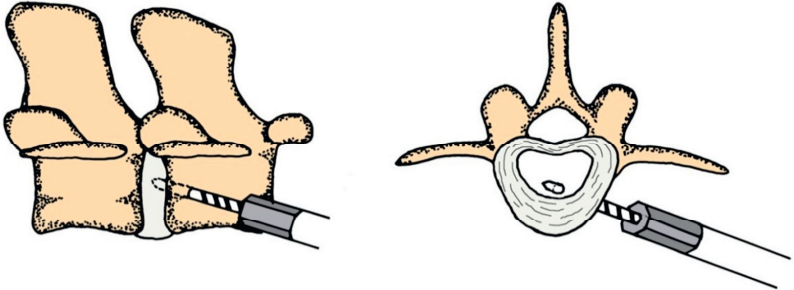
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Disc degeneration

Prevalence

The prevalence of morphologically abnormal discs in asymptomatic individuals is high [68-70], being most common in the lower lumbar spine [71]. As many as 85-95% of persons aged 50 have degenerative disc disease at autopsy [69]. Battie et al. performed an extensive review of disc pathology in asymptomatic individuals and found that 20-83% had reduced water signal at MRI, 6-56% displayed high-intensity zone (HIZ) (sign of annular disruption), 3-63% had disc protrusion and up to 81% showed disc bulging. L4/L5 and L5/S1 had the highest prevalence of disc pathology with the exception of Schmorl´s nodules, which were most common in upper lumbar spine [68].

Etiology

The disc conceptually changes from a fluid-filled substance to a solid state as a function of a more pronounced degeneration. The etiology of disc degeneration is multifactorial with both genetic and environmental factors such as smoking, work and physical activity influencing [16, 68, 72-75]. Genetic factors have been reported having the highest impact on disc degeneration [68, 76]. This is partly explained by different gene expressions considering for example PG and collagen. The finding of L4 to S1 being more degenerated compared with L1 to L4 discs, less affected by physical load, could indicate the importance of lifetime physical exposure [68, 71]. Age related changes of the disc can be seen already in the second decade [77] and appears to be initiated by diminished vascularization of the EP. Since the EP is a critical area for nutrient supply, diminished vascularization initiates catabolic disc reactions [27, 78]. This catabolic process results in degradation of disc matrix and cell death and by that increased degeneration [27, 79]. In addition work/lifestyle can result in minor insults/trauma to the disc. Such insults might be a single event of overload or repetitive low level stress, resulting in either micro-fracturing of the EP or ruptures in AF [20, 80, 81]. Which degenerative process that is due to natural aging or secondary to environmental/behavioral factors is presently not possible to distinguish. As Battie et al. concluded; "the genetically determined natural history of degeneration is modified by behavioral and environmental factors" [68].

Biomechanical/biochemical changes

With increasing age the biomechanical properties of the disc alters. The disc molecules change both quantitatively and qualitatively. There is for example a quantitative loss of PG content with remaining molecules impaired qualitatively. Such alterations result in reduced osmotic pressure which tends to dehydrate the disc [17, 31, 43, 82-86]. With dehydration the NP becomes less gelatinous and

the AF more fibrotic [17, 86]. Damage to the cartilage of the EP increases with age [87]. In addition to the above mentioned alterations the disc height is reduced which further degrades the biomechanical properties of the disc [31]. With compromised mechanical function the disc´s capacity to resist load is reduced, increasing the load exerted on AF and adjacent paravertebral structures like the FJ [17, 36, 88]. Such increased stress has been associated with discogenic pain and also has the potential to induce annular fissures, rim lesions and osteoarthritis of the joints and vertebrae [35, 42]. This shift of stress, concomitant with reduced stress on NP, impairs the PG production further, leading to a degenerative catabolic vicious circle [36].

Since the spine is a functional unit it is most likely that the biomechanical alterations accompanying disc degeneration affect most other tissues in or around the spine [17]. Interestingly all those alterations to the disc/spine and irrespective of degree of degeneration might or might not, at a given moment cause back problems.

Degeneration and intradiscal pressure

In degenerated discs the intradiscal pressure is reduced [17, 79, 89-91]. For example during discography (prone position) an opening pressure (o.p.) of 27 psi in healthy human discs has been reported compared with approximately 15 psi in degenerated ones [50, 92, 93].

Dependent on the state of degeneration the isotropic feature of the NP changes and becomes more anisotropic [35, 36, 45, 79]. Lee et al. showed that when injecting healthy discs the pressure in AF remained low despite high pressure in NP whereas in degenerated discs the NP pressure declined with corresponding increase in AF pressure, reaching almost as high pressures as in NP or even higher [45, 90, 94-96]. This anisotropic stress profilometry contributes to shear stresses in the tissue, which might be damaging as opposed to uniform isotropic load in the healthy gelatinous NP. AF is thinnest in its posterior portion providing an anatomical reason for the more frequent posterior tears as consequence to such shear stresses. Adams et al. for example showed that compressive peak stress in the posterior annulus increased with 160% during loading. They further theorized that complete annular disruptions may transfer the stress from the disc to the FJ, explaining pain relief in totally damaged discs [36].

The compliance of the disc is proportional to the grade of annular disruption [97]. The change in intradiscal pressure per injected contrast volume (elastance) is negatively correlated with grade of degeneration with for example elastance 43 psi/ml in disc s with degeneration grade 0 according to Dallas Discogram description (DDD) compared with 7 psi/ml in grade 5 [92].

In summary, the etiology of the degenerative process in the disc is multifactorial, influenced both by natural ageing and environmental/behavioral factors. This process results in various morphological changes such as: reduced disc height, reduction of PG, collagen and water, increased lamellar disorganization, depressurization, increased stiffness and reduced flexibility, EP damage, annular fissures and FJ damage. These changes are closely related to each other and results in altered biomechanical properties of the IVD.

Low back pain (LBP)

Prevalence/Definition

Pain is the leading reason for doctor visits with back pain being the most common complaint [5]. The lifetime prevalence of LBP is as high as 80% [2, 3, 98]. The majority (90-95%) of LBP is benign and resolves spontaneously or with only little treatment while a few patients continues to have pain with long lasting, disabling symptoms; chronic LBP (CLBP) [6]. In less than 20% of patients with LBP a specific morphological cause is identified i.e. spinal stenosis, disc herniation or spondylolisthesis [98]. These specific causes of LBP are not controversial as opposed to non-specific LBP, were the origin of pain is uncertain. Discogenic pain, belonging to non-specific LBP, is believed to stem from the disc and accounts for 26-45% of the patients with CLBP [9-11, 98, 99]. Additional terms of discogenic pain include internal annular tear, internal disc disruption, axial back pain and black disc disease [69]. Other pain generating sources to non-specific LBP are the FJ and sacroiliac (SI) joints, believed to account for 15-40% respectively 2-13% of the CLBP population [7, 8, 10, 100, 101].

Socioeconomic impact

Even though patients requiring investigation/treatment for their CLBP constitutes a minority of all patients with LBP they represent a heavy socioeconomic burden with a reported cost of 1-2% of GPD. In the USA the cost for LBP is estimated to 100-200 billion dollars/year including direct and indirect costs such as compensation costs, productivity loss and loss of salary [12]. In Sweden corresponding figure is 33 billion Skr/year [13]. In addition to enormous costs, the huge pain burden and its accompanying social impact result in reduced life quality with both physical and psychosocial consequences [12].

Characteristics of discogenic pain

Discogenic pain is frequently localized centrally in the lower lumbosacral region with a deep aching, dull character and aggravated by axial load such as sitting

and flexion [8, 102-104]. In addition discogenic pain can be accentuated with or without referred pseudo-radiculating pain to the buttocks, legs and groins. It is called pseudo-radiculating since there are no other signs of nerve root compression upon imaging or physical examination [8, 105, 106]. Consequently discogenic pain has a somatotropic pattern rather than dermatomal such.

Etiology

The true etiology of discogenic pain is not known despite extensive research. Based on studies on LBP patients, investigated with MRI, CT and discography, various patho-anatomic structures are believed to give rise to the pain. The disc is of course considered the primary source of discogenic pain [50, 73, 100, 101, 107-110]. Other possible sources of pain are the EP [83, 105, 111], SI joints [101, 102] or FJ [11, 112]. Psychosocial influences upon discogenic pain have also been highlighted [113-116]. In a prospective investigation Carragee et al. investigated a cohort with mild LBP and found that structural variables on MRI only weakly predicted future events of LBP while psychosocial variables predicted both short and long term back pain [115, 117]. In contrast Manchiakanti et al. concluded that discography in patients with or without somatization and/or depression did not differ [10]. It is not unlikely that discogenic pain has a multifactorial origin involving morphological changes as well as psychosocial variables.

Discogenic pain is believed to be activated by mechanical (direct pressure on nociceptive structures) or chemical stimulation (elicited by inflammatory mediators) or a combination of those, where sensitization might be the reason for that normal mechanical loading becomes painful [8, 20, 118]. Although the etiology of discogenic pain is far from fully understood several contributing factors have been revealed and will be discussed in following sections.

Annular tears/Degeneration

There is an association between discogenic pain and increased severity of degeneration [119, 120]. Degenerative signs are of limited use however since their sensitivity is poor and their prevalence do not differ between asymptomatic individuals and subjects with LBP [68, 69, 121]. The annular tear, especially when reaching the outer annulus, appears to be a fundamental factor in LBP [8, 108, 110, 118]. A recent study, using strict pressure controlled discography (PCD), reported that 95% of symptomatic discs had ≥ grade 3 annular tear according to Dallas Discogram Description (DDD) [110].

A non-degenerated disc is avascular with innervation only within the outermost lamella but as the disc degenerates the vascularization and innervation alters [122]. Annular fissures have been shown focally depleted of PG compared with adjacent intact AF. This depletion theoretically facilitates ingrowth of both

nerves and vasculature, which has been histologically confirmed showing nerves and vascularized granulation tissue extending from outer annulus into NP [107, 122-124]. Consequently conditions for mediating pain exist. Saifuddin et al. described contrast enhancement of epidural fat adjacent to annual tears, indicating an inflammatory response sometimes seemingly involving also the nerve root, i.e. chemical irritation of the same, a possible explanation for chemical radiculopathy [125].

Endplates

Several studies have described EP changes associated with increased incidence of LBP [83, 111, 115, 120]. Wang et al. performed discography in 109 subjects with history of LBP and investigated various EP lesions in the 443 discs [83]. They reported EP changes closely related with adjacent disc degeneration with a distinct dosage effect, illustrating the importance of the EP in maintaining disc integrity. In addition a strong association between EP lesions and LBP was found which remained after controlling for degeneration. A prospective study correlating EP abnormalities on MRI with discography findings in 116 discs reported 100% positive predictive value (PPV) if only moderate and severe EP abnormalities were included, further supporting the theory that EP lesions are associated with discogenic pain [111].

Innervation and discogenic pain

Pain pathways are not clearly established and still controversial. However, discogenic pain appears mediated not only by the usual pain pathway; nociceptive signals mediated to the adjacent nerve and then to the corresponding dorsal root ganglion (DRG) and further to the spinal cord. A favored hypothesis is that discogenic pain also is mediated via the sino-vertebral nerve and rami communicantes to the sympathetic trunk [33, 34] (Figure 5). In addition discogenic pain seems to be mediated also from lower disc levels to sympathetic nerves in the upper lumbar spine especially to the L2 level [17, 33, 34]. This pathway may explain dermatome symptoms of upper lumbar level even if pain is localized in lower lumbar spine, making the discogenic pain even more complex.

The DRG, serving as a stock for many peptides has been suggested having a pain modulating function in each spinal motion segment [107, 126, 127]. Umimura et al. recently reported that DRG neurons innervating one side of the multifidi muscles at the L5 level were all distributed from L1-L6 [128]. The authors hypothesized dichotomizing nerve fibers of sensory neurons as an explanation for referred pain. DRG neurons, containing such dichotomizing axons, were also shown to project to the lumbar multifidi, IVD, SI joints and FJ. This suggests that back pain may originate from posterior spinal structures, such

as FJ and SI joints, rather than from the disc itself, complicating the possible pain pathways of discogenic pain even more.

There are also other structures in close relation to the disc that possess neuroanatomical substrates for pain. Coppes et al. suggested that the profuse innervation of the PLL may contribute to pain [107]. Further they found mechanoreceptors in ALL and between the lamella of AF in degenerated discs. Such mechanoreceptors have been reported at an even higher grade in painful discs [129].

Inflammatory mediators

Degenerative lumbar discs contain a number of pro-inflammatory mediators such as; IL-6, IL-8, NO, PG-E2 [69, 107, 124, 130-132], some of these mediators are increased in painful discs. Histology of discs from patients undergoing fusion for discogenic LBP displayed, compared with patients operated for sciatica, increased concentration of TNF-α, IL-6 and IL-8 [133]. Freemont et al. compared positive and negative discograms and concluded that in painful discs micro-vessels and nerve fibers, expressing NGF, grew into the disc through the EP [124]. Micro- vasculature was detected also in negative discograms however NGF, required for nerve growth and maintenance, was not expressed.

Inflammatory pain cascade theory

Many hypotheses have been suggested as the cause or contribution to discogenic pain. One such theory is that pain is mediated by an inflammatory cascade, initiated either by age related changes or an acute incident, that sensitize nerves and elicit pain even after minimal mechanical stimulation [8, 118, 133, 134]. Such sensitization may explain why only some degenerated discs are painful. One should remember that these are only hypotheses.

Lumbar discography

Introduction

Discography, contrast injection into the disc, was introduced 1948 by Lindblom et al. replacing myelography, used for diagnosing herniated discs [135]. Back then herniated discs were thought to be the reason for both axial LBP as well as radiculating pain. Discography should not be a "first line" diagnostic study, rather a tool to use when other imaging modalities are insufficient in a patient with suspected discogenic pain, failing conservative therapies and in whom surgery might be an option [8, 103, 136, 137]. Today in many countries discography remains criterion standard to assess if a disc is painful. It consists of two parts; contrast injection to gain information about internal disc morphology and disc stimulation i.e. pain provocation [8, 137-139]. Since the resolution of CT and MRI successively has improved morphological abnormalities on discography has become less relevant to therapeutic decision making. Discography´s main purpose today is to provoke pain and thus confirm/refute a clinically suspected disc level [139].

MRI is excellent to gain imaging of the disc and adjacent structures, however limited due to lack of correlation between positive MRI findings and painful discs. The prevalence of degenerated disc features is similar in symptomatic and asymptomatic patient groups [68, 69, 121]. Currently the only available method to determine if a disc with morphological abnormalities is painful is by provocative discography. Disc stimulation is achieved by injecting contrast into NP, which increases the intra-nuclear pressure and provokes pain either mechanically by stretching nociceptive structures or indirectly by chemical stimulation [69, 94, 99, 133].

Discography is widely used despite controversy over its accuracy, utility and impact on surgical outcome [50, 103, 140-143]. The literature within the field is extensive but conflicting with controversies primarily related to discography's general validity and high rates of false positive responses. Many of the initial shortcomings have improved with refinements such as pressure registration which reduces false positive responses [8, 50, 91, 144, 145]. In spite of such refinements the method is still debated with opponents arguing over the methods validity, false positive rates, induction of degeneration and its clinical utility [2, 146-150]. Some recent systematic reviews conclude that there are strong evidence for a benefit of discography if used under controlled conditions with modern practice [151-154] while others state that lumbar discography continue to have inborn major shortcomings [11, 141, 142, 155]. Consequently the opinions regarding discography remain divergent.

Cervical and thoracic discography

Neither thoracic nor cervical discography is as common as lumbar discography [103]. Accordingly the research within those fields is not as extensive. The literature states that evidence for the use of cervical discography is moderate and for thoracic discography limited to poor [151]. Cervical and thoracic discographies are outside the scope of this thesis and will not be discussed further.

Discography and pain provocation

The exact mechanism of how discography elicits pain is not known, not the least since it has not been established clearly what structure(s) are responsible for the generation of pain. The contrast injected at discography increases the pressure in the NP, which is transferred to AF, with potential to stimulate nerve endings mechanically and probably also chemically [50, 132]. These reactions likely occur in the disc as well as in the adjacent surrounding tissues [126]. The increased intradiscal pressure causes also EP deflection which also might affect nerves in close relation to the EP or the vertebra [37]. A more extensive description about pain mechanisms can be found in section *Low back pain*.

Patient selection

Discography should only be considered in patients in whom surgical intervention might be an option [8, 139]. The patient selection is crucial and patients selected should have characteristic symptoms of discogenic pain (section *Low back pain*) with or without radiculating pain and duration of symptoms for an extended period i.e. at least 3-4 months [103, 137, 139, 156]. Further the patients should have failed conservative therapy and it is important to consider psychometrical testing before discography [103, 137, 157]. Some also advocate that it is crucial to rule out disease in FJ and SI joints before proceeding with discography [11, 137].

Psychometric factors have been reported to predict back pain and influence the outcome of discography [113-116, 158, 159]. Adversely Manchikanti et al. concluded that the discography is not affected by psychological factors when comparing discography results in groups with and without somatization, depression and anxiety disorder [160]. Despite the latter study, discography in psychologically unstable persons is considered a contraindication. Other contraindications, absolute or relative, are local or systemic infection, allergies to contrast agents or antibiotics, increased risk of hemorrhage, pregnancy and severe spinal stenosis at the site of disc injection [8, 103, 136, 137, 139].

Even though patient selection is carefully performed, discography results should be interpreted with caution especially in individuals with earlier back surgery, abnormal psychometric testing or other chronic pain conditions [157].

Current standards

In spite of discographic refinements there are neither any universal accepted criteria for how discography should be performed nor any definition for which criteria to accept for a positive discogram. This makes it difficult to conclude how discography should be best performed. In the literature it is often referred to "current standards" which all include pressure limits [110, 137, 139, 153, 161]. Pressure registration was already proposed in the nineties by Derby et al.[50] and is considered one of the most important primary criteria in current discography [145, 162]. Guidelines recommended and often used are those of International Spine Intervention Society (ISIS)/International Association for the Study of Pain (IASP) [104].

A positive discogram according to the ISIS/IASP guidelines requires;

1. Concordant pain provocation
2. Pain ≥7/10 on a numerical rating scale (NRS)
3. Pain provoked at ≤50 psi above opening pressure (a.o.p)
4. ≥ grade 3 annular tear
5. Negative control disc (pressurization to 80-100 psi a.o.p. in normal appearing discogram)
6. ≤ 3.5 ml injected contrast

O.p. is the pressure that is required to overcome the intrinsic hydrostatic pressure within the disc, i.e. when contrast first is seen within the disc [144]. Again those criteria are not widely accepted even if some have adopted them, partly or completely. For example there is a variation in how patients are asked to classify any provoked pain during discography ranging from two grades (i.e. concordant/discordant) [97, 110, 144, 145, 160, 163-165] to three or four grades (no pain/pressure, unfamiliar, similar and exact) [108, 111, 120, 139, 144, 146, 151, 166-171] and there is a diversity in how a concordant pain response is defined. For example instead of pain intensity ≥7/10 Manchicanti et al. define a positive discogram when at least 70% of highest estimated daily pain is provoked (if highest 7/10 = 70x7=5) [172] whereas ≥6/10 is used by others [93, 145]. Pressure is highly dependent on injection speed [91, 97, 144, 173] which is not included in discography "standards". Moreover injection speed is rarely mentioned in discography studies at all. Derby et al. as one of few used an injection speed (<0.05 ml/seconds) [93, 162]. In addition there are still surprisingly many studies where discography has been performed without any pressure registration or without controlled pressure registration (only estimating "thumb resistance") or reviews where pressure registration was not an inclusion criteria [10, 105, 107, 108, 111, 120, 122, 143, 151, 154, 163-165, 167-169, 174-183].

ISIS further recommends double needle technique and intravenous antibiotics. However antibiotics intravenously and double needle technique have not been shown superior to careful sterile conditions alone performed with styletted needle [184]. The inclusion of a negative control disc often results in puncture of "healthy discs", which is a concern since increased degeneration post puncture has been shown even with 25 gauge needles [147].

To summarize there are many guidelines how to perform discography, however no international accepted ones. This fact has had the consequence of huge differences in performance of discography with concomitant differences in the literature considering discography results and with accompanying difficulties to compare studies.

Subgroups of positive disc

Derby et al. categorized positive discs into subgroups, i.e. chemically versus mechanically sensitive with the former painful at ≤ 15 psi a.o.p. and the latter between 15-50 psi a.o.p. [50]. Both these groups were considered positive whereas discs painful between 50-90 psi indeterminate, with other pain sources possible [50]. Later O'Neill et al. suggested that discs concordant already at 0 psi were chemically sensitive while discs positive at ≥ 1 psi were pressure sensitive [144]. Neither of those sub-categories of positive discs constitutes criteria or guidelines, though used by some, but illustrate that discs respond at different pain thresholds when stimulated.

Why discography is debated

The rate of false positive responses in discography has been one of the most debated topics within the field. Adopting more strict criteria, with controlled injection pressure the rate of false positive discograms seem reduced to acceptable levels according to proponents [145, 153, 162, 172, 185, 186] while opponents still consider the rate of false positive discs being too high [144, 146, 148, 171, 187-189]. Another controversial issue is the fact that any true source of pain or structures provoked with discography has not yet been established [154, 172].

Discography is a diagnostic test and to evaluate its relevance it must be compared with a gold standard, i.e. how well does discography identify the disease compared with a gold standard? Such standard is missing emphasizing the challenge with research within the discography field.

Reliability issues within discography were summarized by Choi et al. [190];

- False positive rates
- The mechanism of pressurizing NP differ from normal axial load
- The lack of standardized discography technique
- Pain is subjective

Even if discography has the ability to provoke pain it is not synonymous with that the disc(s) is the source of pain since surrounding tissue has been suggested as sources of pain i.e. FJ, SI joint and muscles [83, 101, 102, 111, 112]. In addition there are several other competing potential reasons for a sensitive disc; somatization disorder, iliac crest donor site pain, chronic pain in general, mild benign LBP, history of post-discectomy [154, 187, 191, 192]. Despite these uncertainties of discogenic pain, discography is still considered the best available tool to determine if a disc is painful [99, 138, 139, 154].

In the following section a deeper penetration of confounding pain sources will be presented.

False positive discogram
The specificity of discography has been one of the major issues within the field with a reported rate of false positive responses ranging between 25-83% [146, 148, 155, 171, 187, 189, 193]. With some exceptions one institution is responsible for the studies reporting high false positive rates, criticized because their "asymptomatic" control groups are populations without discogenic back pain but with co-morbidities such as previous back surgery, abnormal psychometric testing, somatization disorder or other chronic pain processes. The highest reported false positive rate of 83% was reported in a group with somatization disorder [187]. It has been concluded that false positive rates can be heavily reduced with careful patient selection i.e. normal psychometric testing prior to discography and without other chronic pain syndromes [154, 187].

An inherent flaw when studying the rate of false positives in an asymptomatic population is that provoked pain is considered as a positive discogram. However for a disc to be considered positive it should be *concordant* with the daily pain (ISIS guidelines), which by definition is impossible in an asymptomatic population. Further the pain tolerance when undergoing discography has been shown higher in asymptomatic control subjects compared with patients [145, 194], which might influence outcome of such comparative studies. Another major limitation within many previous studies is once again lack of insufficient pressure registration [10, 105, 107, 108, 111, 120, 122, 143, 151, 154, 163-165, 167, 169, 174-183].

In 1999 Carragee et al. performed 24 discograms in eight patients with history of LBP, recruited from a cohort scheduled for iliac bone grafting. They reported that 50% responded with concordant pain provocation, thus being false positive [171]. However if adopting ISIS/IASP standards to the same study the rate of false positive responses were reduced to 12.5% per patient [153]. Later Carragee et al. re-analyzed their own previous publications using low pressure criteria and stated a false positive rate of 25% per patient in their 69 studied asymptomatic subjects [148]. However they defined low pressure as 22 psi compared with 15 psi using IASP standards. By using the latter cutoff the rate decreased to 10% per patient [172]. Several studies support this low rate, between 0-10%, if adopting low pressure criteria [145, 162, 185, 186]. Wolfer et al. concluded in an extensive meta-analysis of discographies on asymptomatic subjects that the rate of false positive responses was 6% per disc and 10% per patient [153].

Contradictory low specificity is reported in spite of low pressurization. O´Neill et al. highlighted that there is a risk when categorizing discs into only concordant or discordant and constructed a receiver operator curve [144]. By doing so they claimed that pressurizing disc $\geq$ 50 psi a.o.p. generated a 100% risk for false positive discograms! Keeping the pressure between 25-50 psi reduced this figure but only to 50%. Recently Derby et al. showed no differences in pain relief between cohorts receiving analgesics intradiscally in painful discograms compared with those without analgesics [188]. If analgesics did not result in subjective pain relief it might indicate that discs considered positive were in fact not. The authors assumed 36-40% false positive discs if a 50% pain relief was considered as significant such. They rather advocated 80% pain relief as significant, which increased assumed rate of false positive discograms to 80%. Those figures indicate either that other discs or structures are painful or that the analgesics do not reach the pain source sufficiently. There are other studies in which pain in positive discograms does not resolve when anesthetized, suggesting false positive responses from other spinal tissue in 20-46% [146, 189].

False negative discogram
Discography is a diagnostic instrument trying to simulate daily activity loadings. It differs however in many aspects from "true spine loading". One major difference is that fluid injection into NP particularly expands nucleus compared with compression during normal activities, which exerts a direct effect also on the annulus [6, 23]. Contrast injection into NP might not induce discogenic pain in a disc with intact inner annulus since the pressure remains low in AF if inner annulus is preserved, a potential source to false negative discograms [94]. Yu et al. selected 45 patients negative on discography but with clinical suspected discogenic axial back pain and treated them either with placebo or with dexamethasone intradiscally [195]. After 6 months follow up no statistical difference between the groups were noted in terms of pain but the steroid group

demanded reduced medication. The authors suggested that grade 5 annular disruptions were a likely source of false negative discograms, since negative discography significantly correlated with grade 5 DDD. They theorized that those discs are only mechanically sensitive thus not stimulated when a pressure gradient cannot be generated by contrast injection. Using surgical outcome as criterion standard, in itself questionable, provocative discography has been reported with a 10% false negative rate [196]. Putzier et al. reported discoblock (disc analgesia) being positive in 50% of 20 discograms with discordant pain or no pain induced upon discography, suggesting a false negative response at discography [177]. However the authors also suggested that painful inflammation of adjacent bone might be the reason to discordancy between the modalities.

Manometry versus automated injection technique
ISIS/IASP adopted a pressure limit of ≤ 50 psi a.o.p. in a disc with ≥ grade 3 annular disruptions. Such pressure limit may appear standardized but is not because the measured pressure is dependent on the method used [145, 190, 197], which will be discussed below.

A source of error to the debated discography accuracy is that manometric technique only registers post-syringeal static pressure and not actual dynamic pressure in NP, explaining why the real intradiscal pressure can be much higher [145, 197]. Further, with manual injection (manometer/conventional inflation syringes), it is difficult to inject below 0.01ml/seconds, recommended to reduce differences between external measured pressure and true pressures in NP [190]. Derby et al. compared manometry with automated discography and found neither significant differences in positive or negative discograms nor differences in rates of low pressure positive discograms with either method [93]. At initially evoked pain, contrast volumes were higher with automated technique compared with manometric such (mean 1.7 ml versus 0.8 ml). The pressures at onset of pain (12 versus 20 psi) and o.p. were lower (8 versus 14 psi) with automated technique compared with manometry. Assuming that increased volumes are innocuous the authors advocated automated injection because it is better controlled, reducing operator bias. Automated PCD is inherently overcoming several limitations that lies within the method, such as inconsistencies in injection speeds and dynamic pressure peaks, reducing the risk for both false positive and negative results [92, 97].

With conventional pressure recording techniques i.e. manometry, disc pressure is externally recorded. In such circumstances recorded pressure will depend on where the sensor element is located i.e. higher if the sensor is situated intra-syringeal compared with an externally localized sensor [190]. Extra-syringeal sensors are reported to improve the accuracy of intradiscal pressure measurements since the recorded pressure is reflecting a more "true" such.

However it should be highlighted that the best way to record intra-nuclear pressure evidently ought to be in the NP itself.

Injection speed
The injection speed used during discography also affects the recorded disc pressure. There are great differences between static and dynamic pressures when controlled low speed injection is not used. Seo et al. performed an in vitro study of 82 porcine cadavers with pressures measured both with a transducer in NP and a manometer outside the disc connected to the discography needle. At ≤ 0.08 ml/seconds injection speed pressure differences averaged only 4 psi whereas at ≥ 0.08 ml/seconds pressure differences were approximately 15 psi higher at manometer readout [197]. To minimize the differences between static and dynamic disc pressures recorded with manometry injection speed ≤ 0.07 ml/seconds for that reason was recommended. In their study static pressures were lower in NP compared with manometer read out. However when static pressures at manometer read out were compared with dynamic peaks in NP the latter were much higher.

Choi et al. confirmed that the difference in pressures between NP and externally post-syringeal recorded pressures decreased with reduced injection speed [190]. At 0.01 ml/seconds the difference was approximately 5 psi whereas at 0.1 ml/seconds as much as 38 psi with higher pressures recorded externally. However it cannot be generalized that pressures are higher with manometer compared with pressures measured directly in NP as mentioned above. Conventional manometers register static pressure with among others interconnecting tubes influencing the recorded pressure. Dynamic pressures are for example not always displayed at manometer read out why the real dynamic pressures in NP can be higher [145]. Contrast injection for example may give rise to unpredictable high pressure peaks in a torn posterior annulus, not visualized if using manometric static pressures [50].

To summarize; it is essential to register disc pressure during discography however despite doing so it is not synonymous with reflecting true pressures in the NP, since pressure recorded depend on injection speed and how the pressure is measured. When measuring disc pressure with a manometer "true" pressures in NP can be either higher or lower [50, 110, 190].

Pain
Discography relies on provoked pain, which is one of the method's greatest limitations since the pain is subjective and hard to standardize both qualitatively and quantitatively. In lack of a gold standard it is also impossible to confirm the source of pain. Moreover patients have different capacity to differentiate a painful stimulus from another and the ability to describe and convey provoked pain differs between patients. Provoked pain can for example be exactly

provoked concerning its character but localized slightly different compared with daily pain or being exactly localized but differ in character. Such variations can be hard to differentiate and describe for the patients and for the discographer to interpret.

Gold standard dilemma

As discussed there are many methodological uncertainties within discography including subjectivities concerning pain, observer's bias, selection bias and no international discography standards. One of the greatest challenges with discography is though the "gold standard dilemma". There is yet no method that with any certainty establishes the pain generating source, thus a gold standard to compare discography with does not exist. In spite of refined criteria for discography this methodological limitation cannot be overlooked and has been discussed in several extensive reviews [99, 141, 153, 154, 172]. Comparing a symptomatic population with an asymptomatic cohort is for example questionable because it's unethical to perform invasive discography in asymptomatic individuals but also due to the fact that they by definition ought to have no positive discs. To use treatment outcome as gold standard for diagnostic test is also questionable since the definition for diagnostic test is to detect disease.

Adverse effects

Complications associated with discography are estimated to less than 1% and are related to its invasiveness, radiation exposure and allergies. The most feared complication is discitis [136, 138, 139]. Infection of the disc may lead to osteomyelitis, disc destruction, meningitis and not least severe long lasting pain. The incidence of discitis has been reported to between 0.005%-0.15% per disc respectively between 0.17%-0.44% per patient [198-200]. The lower incidence with 0.005% per disc was revealed in an extensive retrospective analysis of 37.135 discs evaluated with single needle technique with intradiscal antibiotics which may favor the use of such [200].

The argument for intradiscal antibiotics, instead of intravenously administrated such, is better penetration to NP [201]. Conversely intravenously antibiotics have been advocated since intradiscal antibiotics have been reported toxic [202]. This controversy has resulted in different regional standards. Sharma et al. performed a review regarding prevention of infection post discography and found only seven reports of which none were an randomized controlled trial (RCT) [198]. They concluded that intravenous or intradiscal antibiotics have not been shown to reduce infection rate as compared with sterile conditions alone. The use of styletted needles, either with single or double needle technique, is superior to non-styletted techniques. A fourfold incidence of discitis with single technique compared with double have earlier been reported [203]. Sharma et al.

believe that this figure represented the use of stylettes rather than single or double technique.

One of the arguments against discography is its invasiveness. Carragee et al. compared two well- matched cohorts, performed with small gauge needles and controlled pressure at baseline and at follow up 10 years after discography [147]. Discography was performed in the study group with history of only mild LBP and compared with a matched cohort. The study group had significantly higher progression of degeneration compared with the control group in whom discography was not performed. 35% in the study group compared with 14% in the control group had progressed from normal to moderate degeneration (grade 3 degeneration) with significantly more herniation's, loss of disc height and nuclear signal. They found no significant difference between 22 and 25 gauge needles, why even small gauge needles seems to accelerate degeneration. Despite questioned by some [99] this article has been highly quoted and used as an argument against discographies. It has also been suggested that the injected contrast agent may be a cause to accelerated degeneration by inducing cell apoptosis [2].

Flaws within literature

There are several issues regarding discography within the literature that briefly will be discussed in addition to the already mentioned lack of gold standard. As Shah et al. concluded there is lack of RCT studies within discography and existing ones are difficult to compare because of great variations in design and technical performance [151]. For example disc stimulation varies from injection by hand with syringe to more controlled injections with various manometers and various automated injection techniques and injection speeds. Kim et al. performed a survey study among discography practitioners and found discography being performed by multiple specialties in order highest to lowest; anesthesiology, physical medicine and rehabilitation and radiology [204]. They found poor adherence to discography guidelines varying among those specialties, which likely affects the diagnostic value of the procedure. Despite that pressure registration during discography is considered mandatory only 44-80% used manometry, something the authors highlighted as essential to improve discography's value. In addition the majority of published papers did not mention the injection speed used.

Treatment discogenic pain

First line therapy for discogenic pain is conservative such including anti-inflammatory drugs, opioids, physical therapy, acupuncture etc. [205]. Second line therapy include invasive therapies ranging from major surgeries such as spinal fusion, disc replacement to minimal invasive treatment modalities; radiofrequency therapy intradiscal or at ramus communicants, intradiscal electrothermal annuloplasty (IDET), steroid injection, thermo-coagulation, and disc cell transplantation [17]. Many of these minimally invasive treatments are still at experimental stages.

Fusion has been and is still a major surgical treatment option for discogenic pain and is intended to stabilize assumed painful segment(s) [205, 206]. Despite outcomes similar to that of conservative treatment alone, or in combination with rehabilitation, spinal fusion remains a common treatment for chronic LBP [143, 205-209]. Willems et al. concluded in a recent review that currently used tests for patient selection, such as MRI, provocative discography, facet joint block etc. before spinal fusion could not identify which patient will benefit from surgery [143]. Resnick et al. [210] concluded in another review that fusion surgery based on discography alone was not recommended due to insufficient clinical response. However neither of those reviews had PCD as an inclusion criterion.

With disc replacement the assumed painful source is removed. There are however scarce evidence that disc replacement and fusion is more effective than conservative measures in treating discogenic pain [143, 155, 209, 211-215]. Minimal invasive treatments intend to more specifically treat the pain. Even after introduction of these newer minimally invasive therapies discogenic pain continues to be an entity difficult to treat with conflicting results in all areas with yet no treatment proven superior to another [179, 216].

It is beyond the scope of this thesis to in detail cover treatment therapies and surgery outcomes. To summarize there are no international consensus how to treat non-specific LBP and conflicting results almost within all therapy alternatives [140]. There is a lack of controlled studies evaluating surgical outcome based on pre-surgical discography and existing studies show variable results and great variability regarding adherence to discography guidelines. For example the majority of pre-surgical discographies are performed without controlled pressure injection. One of the few studies investigating surgery outcome (interbody fusion) after a pre-surgical discography performed with controlled pressure showed that chemically sensitive discs had more favorable outcome compared with discs painful at higher pressures [50].

Radiologic imaging

Introduction

Diagnostic imaging regarding LBP is needed only in a minority of patients i.e. those not responding adequately to conservative treatment during a longer period [137, 138]. Imaging should be used primarily to confirm the physicians suspected diagnose and/or rule out any serious underlying condition. Recent studies have shown rapidly increasing costs regarding LBP over the past two decades; with for example a 300% increase in MRI imaging [5]. This dramatically increased imaging rate is not accompanied by corresponding increase in patient improvement but with higher surgery rates. Systemic reviews and guidelines for non-specific LBP recommend against routine imaging i.e. if no neurologic deficits or no evidence of serious underlying condition exists [217]. It is essential to remember that the value of imaging is confounded by a high prevalence of morphologic findings also in asymptomatic [69].

Plain radiography

Plain radiography in LBP is used primary to assess anatomy and information about bony structures [138]. The height of both discs and vertebrae is revealed, with also other indirect signs of degeneration revealed such as osteophytes and FJ osteoarthritis. The strength of plain radiographs in LBP is that the spine can be imaged in axial weight bearing [218]. The alignment of the lumbar spine is revealed under axial load with the ability to reveal load dependent instability. Plain radiographs are in LBP primarily used to exclude structural abnormalities explaining the pain, such as compression fractures, olisthesis and congenital anomalies [138, 219].

Computed tomography (CT)

In diagnosis of LBP CT alone is of limited value beyond plain radiographs. Despite optimization regarding CT techniques such as reduced radiation the main disadvantage of CT compared with MRI is radiation exposure [220]. MRI has due to refinements during later years, with higher spatial resolution and increased field strengths, to a high extent replaced CT regarding spinal imaging. [20, 159, 165, 210, 221]. CT is however used post-discography to show internal disc morphology, with the combination CT-discography superior in displaying internal disc morphology compared with either technique alone [110, 118, 137, 222, 223] (Figure 8).

Figure 8. CT-discogram displaying internal disc architecture

In the discogram a broad dorsal annular fissure is displayed with contrast leaking circumferentially into the outer annulus.

Magnet resonance imaging (MRI)

MRI is the most used diagnostic imaging modality for degenerative disc disease, being important but not exclusive in imaging degenerative discs [109, 138, 139, 218, 224]. MRI is an excellent tool to assess spinal soft tissues such as disc appearance, neural structures, ligaments and the spinal canal. Also bony structures are well displayed although MRI has its limitations. The disc hydration is evaluated on MRI. On T2-weighted images a hydrated, healthy disc has high signal whereas with increased dehydration it loses signal, becoming very dark with loss of discrepancy between NP and annulus in the severely degenerated disc [69, 73, 138, 219, 225, 226]. Degenerated discs can be classified at MRI with Pfirrmann classification [226] (Figure 9). Despite being an excellent imaging tool regarding the disc it is not as sensitive as discography in imaging internal annular tears [138].

Figure 9. Pfirrmann Classification

| Grade I: Homogenous disc structure with bright, white hyperintense signal intensity and preserved disc height. | Grade II: Inhomogenous disc structure with hyperintense white signal Preserved distinction between annulus and nucleus. Normal disc height. With or without horizontal grey bands. | Grade III: Inhomogenous disc structure with intermediate grey signal intensity. Distinction between nucleus and annulus is unclear. Disc height normal or slightly decreased. | Grade IV: Inhomogeneous disc structure with dark grey signal intensity. Distinction between annulus and nucleus is lost. Disc height normal to moderately decreased. | Grade V: Inhomogeneous disc structure with hypointense dark signal intensity. Distinction between nucleus and annulus is lost. Collapsed disc space. |

Illustration by Hanna Hebelka according to Pfirrmann et al. [226]

High Intensity Zone (HIZ), a high signal within posterior annulus on T2-weighted images, as intense as the cerebrospinal fluid (CSF) and separated from NP, is suggested to indicate an annular rupture [109]. HIZ lesions in relation to LBP are covered in section *High Intensity Zone*.

One drawback with conventional, supine MRI is that the spinal alignment does not reflect true postural effects of body weight [38, 218, 227]. In addition MRI is not yet sufficient in detecting biochemical changes [124], at least there are not yet any quantitative MRI measures of disc degeneration used routinely. Various T2-mapping techniques appear promising as quantitatively measures of disc composition [141, 224, 228]. For example Borthakur et al. showed that T1rho (reveal early biochemical changes in cartilage) was significantly lower in painful discs compared with a control cohort as well as in non-painful discs in the same patients [85]. Such quantitative MR biomarkers are still within an experimental stadium and yet not used routinely in clinical context.

Axial loaded MRI (alMRI)

Dynamic imaging might add information regarding spinal morphology as it reflects the spine under loaded conditions [218, 227, 229, 230]. It is possible to simulate weight bearing by adding axial compression with axial loaded MRI (alMRI). The alMRI is performed with a non-magnetic compression device in a supine position with stretched legs, with an axial load of 50% of the total body weight applied to simulate an upright position. The compression device is composed of a patient harness attached to a footplate with the external load adjusted with side straps (Figure 10) [230].

Figure 10. Illustration of a non-magnetic compression device used for axial loaded MRI
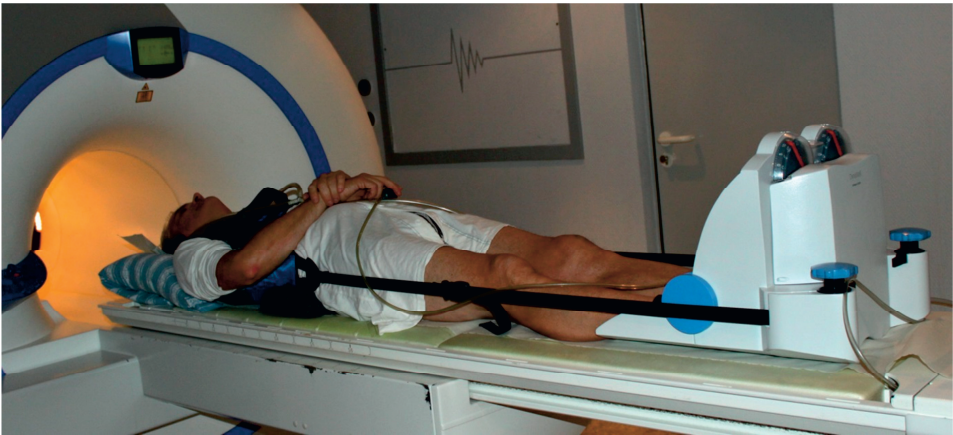
In addition there exists various MRI equipment's offering the possibility for the patient to maintain a standing position [218, 231]. Both alMRI and upright MRI have revealed alterations in spinal morphology, not displayed in supine position, or add valuable information as compared with conventional MRI [227, 229, 231-236]. During upright standing the axial load forces the lumbar spine into extension (increased lordosis), the tension in the ALL is increased which displace NP posteriorly [218, 236-238]. Further axial load has been shown to increase anterior disc height with concomitant posterior disc height reduction and increased posterior disc bulge [218, 232, 237, 239]. AlMRI, has been reported as a promising tool to increase diagnostic possibilities of conventional MRI since the effects on spinal loading where comparable between harness-induced load in supine position and physiologic loading in upright kneeling position [237].

High Intensity Zones (HIZ)

Definition
HIZ was first described by Aprill and Bogduk in 1992 and is defined as high signal within the posterior AF on T2-weighted images [109]. HIZ represents complete tears through the outer annulus, either radial or concentric [102, 103, 160, 167] and has been shown to be composed of vascularized granulation tissue [156]. It is accepted that HIZ represents annular tears reaching the outer AF. However not all annular ruptures display HIZ [156, 228] and its relation to pain is debated. This zone should be clearly separated from NP, hyper-intense in relation to the NP and as intense as CSF. HIZ lesions are highly indicative of annular grade 3- 4 disruptions with positive predictive value (PPV) for having such disruptions reported up to 90% [169].

Figure 11. Example of a HIZ in posterior annulus in a L5/S1 disc in sagittal and axial views
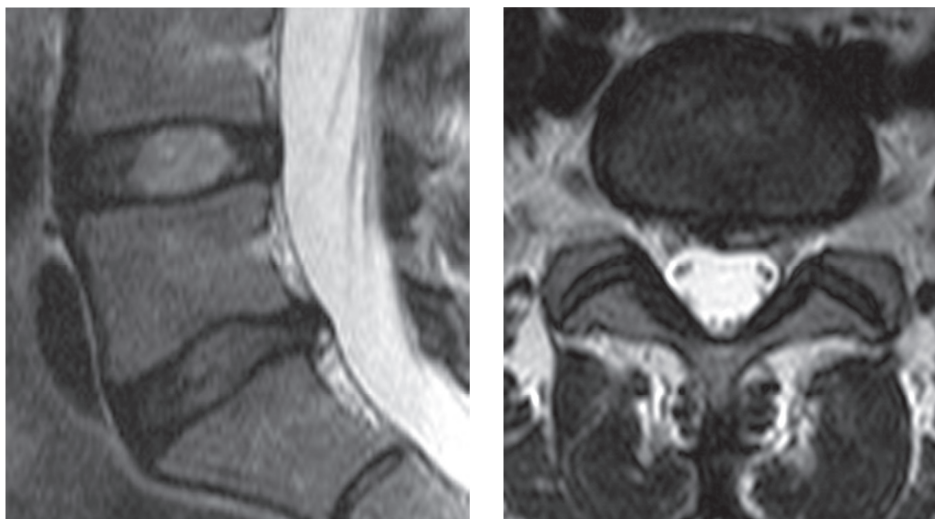
Relation between HIZ and painful discs
Aprill and Bogduk were first to claim HIZ being a reliable marker for painful discs with 89% PPV for HIZ being positive at discography. They further stated that positive discograms in 82% would display HIZ [109]. Their results have been supported by many with reported PPV between 85-89% [105, 108, 111, 169, 176]. Also the specificity for HIZ in detecting positive discs concerning LBP has been reported high, ranging between 70-100% [99, 120, 164, 165].

Several authors are however not unambiguously positive about HIZ as predictive sign for painful discs, mainly due to reported low sensitivity [99, 105, 111, 158, 164, 178]. Despite confirming a high PPV Saifuddin et al. for example noted as low sensitivity as 27%, meaning that a significant number of painful disc will not have HIZ [105]. Kang et al. found that HIZ in combination with disc protrusion correlated significantly with concordant pain (PPV 87% and specificity 98%) but HIZ alone was not helpful in identifying a painful disc [167]. In 2009 Chen et al. concluded in a review including ten articles that for painful discs the presence of HIZ has a limited predictive value. When absent the likelihood for painful discograms is small however [240].

There are many opponents for HIZ being a marker for LBP [105, 115, 117, 146, 158, 177, 178, 241]. Several independent investigators report a prevalence of between 15-70% of HIZ in an asymptomatic cohort compared with 50-70% in patients with discogenic pain confirmed by discography [158, 164, 178, 242]. The study reporting the highest prevalence in an asymptomatic cohort has however been criticized since the "asymptomatic" group were patients with previous back pain history but at the time for the study asymptomatic [158]. Even if these results are neglected the sensitivity has repeatedly been reported low, varying between 27-45%, demonstrating a poor utility of HIZ in detecting symptomatic annular tears [99, 105, 111, 120, 243].

To conclude, the evidence in the literature is conflicting whether or not HIZ is a reliable pain marker in LBP primarily due to inconsistent results regarding its sensitivity. HIZ predicts presence of annular tears, which have the capacity of being painful, but is not pathognomonic for symptomatic LBP [158, 159]. It needs to be highlighted that the majority of studies investigating correlation between HIZ and discogenic pain have not used PCD [105, 108, 109, 111, 120, 165, 167-169, 176-178, 244].

HIZ and alMRI
The relation between HIZ and axial loaded MRI (alMRI/upright MRI) has only been reported in two case reports and indicates that HIZ is a dynamic feature [229, 245]. Saifuddin et al. suggested that the reason for HIZ displayed only on alMRI in a patient with LBP could be changes in the intradiscal pressure forcing fluid into posterior annular tears [229]. This was an observation in one single subject urging a larger prospective study comparing appearance of HIZ between conventional MRI and alMRI at the same occasion. In another case report Alyas et al. demonstrated a possible dynamic component of HIZ in two LBP patients [245]. At upright MRI HIZ was not detected in neutral or in flexed position in one of the patients whereas in extended position the lordosis increased, discs bulged and two HIZ were revealed. In the second case the appearance of HIZ in an L3/L4 disc changed from horizontally oriented at sagittal view in neutral position to vertically oriented when the spine was loaded. The authors concluded

that HIZ may be unmasked by upright/alMRI, possibly increasing the sensitivity for the detection of HIZ.

Discography technique

Figure 12. Schematic illustration of discography
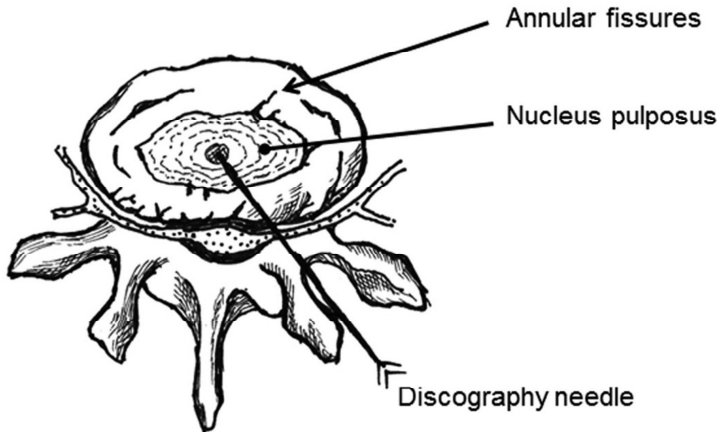
Figure design Emilie Hebelka

Preparations

Before initiating discography it is essential for the physician to obtain detailed information about the patient's symptomatology like character, distribution and intensity of the pain. This is required for interpretation of the patients' pain responses during the discography [137, 139]. The patients should carefully be informed about the procedure and how important it is to thoroughly describe any provoked pain. The use of a NRS is recommended to grade provoked pain from 0-10 [137, 139]. There is no consensus how provoked pain should be classified. Some classify pain into concordant or discordant [97, 110, 136, 144, 145, 160, 163-165] whereas others use three or four categories ranging from no pain/only pressure, unfamiliar pain, similar pain to exactly reproduced pain [108, 111, 120, 138, 139, 146, 151, 166-171, 177].

Sterile conditions are a prerequisite to limit the risk for spondylo-discitis [8, 137, 138]. The patient is positioned prone on the operation table, receiving antibiotics approximately 30 minutes before the procedure, either intravenously or

sometimes mixed with the contrast intradiscally (see section *current standard*s). Midazolam rectally or intravenously is sometimes administrated to lightly sedate the patients, who should still be able to respond adequately. Blood pressure and pulse should be monitored [8, 136-138, 156, 204].

Level determination

Determination of which levels to inject is based upon a combination of available information like; patient history, findings at physical examination, disc appearance at radiological examinations and inclusion of at least one negative control disc adjacent to the presumed symptomatic disc [8, 98, 137, 138]. The least suspected level/control disc should be punctured first to avoid provoked pain interfering with the subsequent discogram. The patient should be blinded to which levels are injected and carefully instructed prior to the exam to respond if the disc is painful and try to correlate any provoked pain with his/hers daily pain as reference standard [8, 110].

Fluoroscopy

Modern discography is often performed via a posterolateral extradural approach with the patient positioned in lateral decubitus [137, 138, 156]. Fluoroscopy in anterior and sagittal views is performed to confirm lumbar segmentation before initiating the procedure. Then a sagittal view over the disc to be injected is performed with the radiation beam exactly parallel with the EP to gain maximum disc height [8, 103, 137]. The image intensifier of the C-arm is then axially rotated until the superior articular process overlies the middle-posterior third of the disc (Figure 13).

Figure 13. The superior articular process overlies the middle-posterior third of the disc with the EP parallel
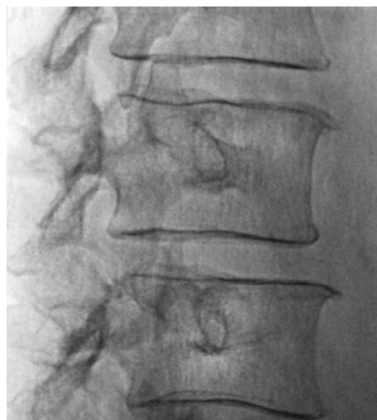
Figure 14. Needle positioning

Either single or double needle technique can be used [137]. To avoid irrelevant pain the skin and needle track are anesthetized under fluoroscopy guidance. Care should be taken not to advance the needle too deep to avoid anesthesia of the nerve roots. Then the discography needle, 22 gauge or smaller, is inserted parallel to the radiation beam approximately 1 mm anterior to the superior articular process (Figure 14). When puncturing the annulus a firm resistance is noticed. Patients often respond with a brief but intense pain incident when AF is penetrated. The objective is to insert the needle tip until positioned in the center of NP in both sagittal and anterior view (Figure 15 & 16) [110, 137, 156, 246].

Figure 15. Needle positioning central in NP, frontal view

Figure 16. Needle positioning central in NP, sagittal view
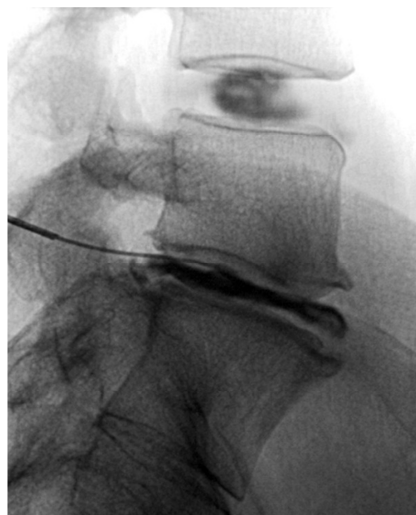
Even though double needle technique is advocated it is not always used and studies have shown that using either method does not influence the risk for discitis [198]. Due to its anatomic position it may however be an advantage to use double needle technique at the L5/S1 level. With a double needle, a "hooked" guide needle can be introduced to ease adequate positioning [137, 139, 156]. If the iliac crest obscures straight sagittal angle the image intensifier of the C-arm must be tilted ventro-cranially, sometimes up to 40 degrees, before introducing the needle [138, 139] (Figure 17).

Figure 17. Fluoroscopy view when injecting L5/S1 with obscuring iliac crest
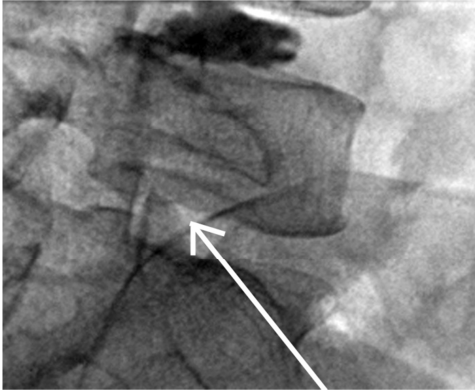
The arrow indicates where to insert the needle.

Contrast injection

Non-ionic contrast accepted for intrathecal use is mandatory since there is always a risk for epidural leakage [138, 139]. Initially contrast was injected by hand with a syringe relying on "thumb" resistance. This method is no longer recommended but still used. In the nineties pressure registration was introduced and since then current standards recommend controlled pressure injection of the contrast [50, 137, 139, 156]. Recently automated pressure controlled injection has been reported as superior to manometry giving better and more consistent control. Manometry is still frequently used however (see section *Manometry versus automated injection technique*). The injection rate should not exceed 0.05 ml/seconds to avoid dynamic pressure peaks that may result in false positive responses [97, 144, 197]. Parameters that should be monitored during injection are; o.p., contrast volume injected, pressure at initial onset of pain and peak pressure [8, 139]. Guidelines for discography vary (see section *Current standards*). Recommended is however that injection should continue until one of following endpoints; pain ≥7/10 on NRS, intradiscal pressure >50 psi a.o.p. in disc with ≥grade 3 annular tear or 80-100 in a normal appearing discogram or until maximum 3.5 ml contrast has been injected [137].

Pain registration

Verbal pain responses are noted during the examination but also face expressions etc. should be observed to retrieve a complete pain picture [136, 138, 139]. Pain intensity is graded according to NRS. A positive discogram is regarded as concordant pain provocation (see section *Current standards)*.

Post-procedure

After discography a CT is recommended however not mandatory to gain further information about internal disc morphology [137] (Figure 18). Sachs et al. developed a system describing the dye distribution in the disc after a discogram [222]. Their classification system categorized annular disruptions into grade 0-3; grade 0 intact AF, grade 1 disruption into inner annulus, grade 2 disruption into outer annulus and in grade 3 disruptions extends beyond the outer annulus. In 1992 Aprill and Bogduk added a fourth grade describing when contrast spread circumferentially through AF [109]. In addition this classification system was extended by Derby et al. to include also a grade 5 where contrast leaked epidurally [110]. This modified classification system of annular disruptions is called Dallas Discogram Description (DDD) (Figure 19).

The patient is carefully monitored during and after the exam with control of pain, blood pressure and pulse. Hospital discharge occurs after a couple of hours if no complications have been encountered. The patient should be carefully instructed to contact the hospital in case of any infection signs i.e. fever, worsening of pain and loss of neurological function [8, 137, 138].

Figure 18. Sagittal view of CT-discography
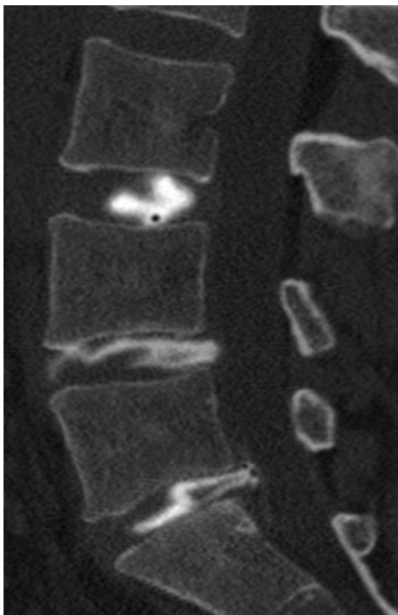
In the L3/L4 disc the NP is intact. L4/L5 and L5/S1 are degenerated with posterior annular disruptions and in addition a herniation with leakage epidurally at L5/S1.

Figure 19. Schematic illustration of annular disruptions according to the Dallas Discogram Description (DDD)

Dallas Discogram Description
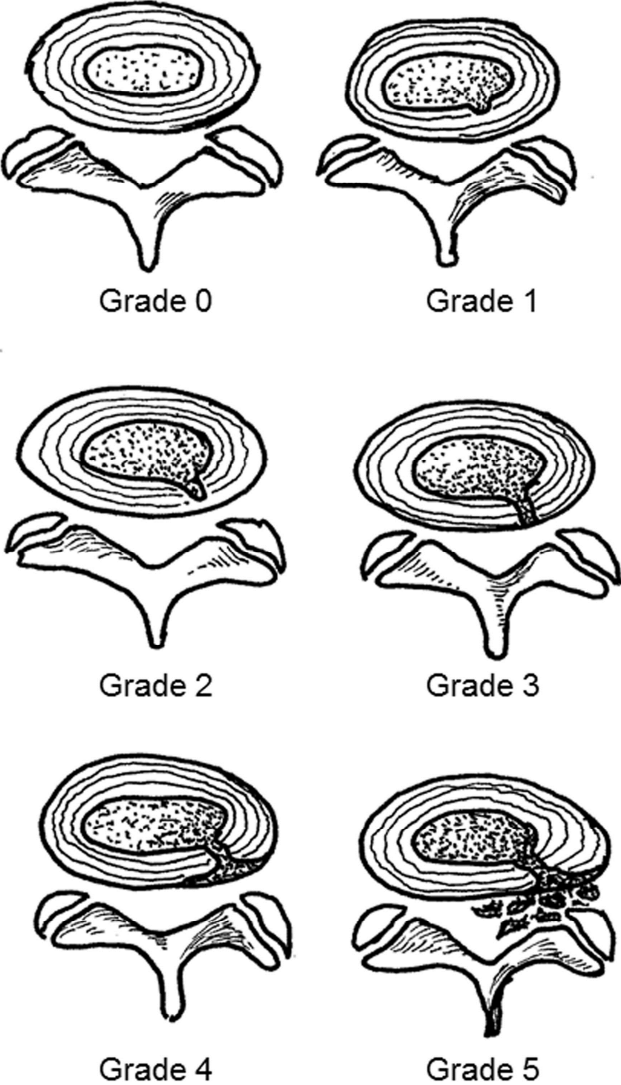
Figure design Emilie Hebelka according to a modified DDD by Derby et al. [110]

Aims of the thesis

The aims of the thesis were:

Study I
- To evaluate whether a pressure increase is induced in adjacent discs during in vivo discography in non-degenerated anesthetized pigs.
- To determine whether there are any difference in magnitude of induced pressure increase between previously injected (prefilled) adjacent discs and non-prefilled adjacent discs.

Study II
- To determine whether discography induces a pressure increase in adjacent discs in a degenerated pig disc model and evaluate the pressure reaction in adjacent discs during and after the injection.

Study III
- To investigate whether an increased pressure is induced in adjacent discs during clinical discography in subjects with morphologically abnormal discs and suspected discogenic pain.

Study IV
- To investigate whether the detection of HIZ is affected by axial load induced by alMRI.
- To study whether HIZ predicts discogenic pain when the discography is performed with controlled pressure injection.

Study V
- To investigate whether concordant discograms display any specific morphological characteristics under axial loading of the spine (alMRI).
- To investigate whether alMRI can induce discogenic pain and to what extent compared with discography.

Methods

Experimental studies (Study I & II)

Subjects

All experimental studies were approved by the Animal Research Ethics Committee of Gothenburg, Sweden (Reference number 207-2007).

Study I
Nine female healthy, domestic pigs, five months old and weighing 50-60 kg, were used in the study. Discography was performed at L2/L3 - L5/L6 in six of the animals and at L1/L2 - L4/L5 in three. The intradiscal pressure in adjacent discs was evaluated during discography.

Study II
Ten female domestic pigs, six months old and weighing 50-60 kg, were included. Disc degeneration was induced with a drill hole in one EP [61] (Figure 7). At testing after recuperation for three months, their weight was approximately 80-90 kg. In each animal discography was performed in three lumbar discs in which one was degenerated. Pressure during contrast injection was evaluated simultaneously in the injected disc and one adjacent disc as well as 15 minutes after injection.

General methods

Anesthesia
Each animal was first sedated and then anaesthetized, tracheotomized and placed on a respirator throughout the investigation. Details are given in paper I and II.

Specimen preparation
In study II the L3 vertebra (in two pigs L2) a drill-hole at mid-height of the L3 vertebra was used to induce disc degeneration (Figure 7). At the time of testing the animals were positioned in a left sided prone position at the operation table and a retroperitoneal approach exposed the L1/L6 motion segments. Details are given in paper I and II.

Pressure registration
Fiber-optic pressure transducers (FOPT) (Samba Sensors AB, Göteborg, Sweden), 0.36 mm in diameter, were used to measure the intradiscal pressure.

Two FOPT´s were used simultaneously and connected to two Samba 3200 control units. Details are given in paper I and II.

Discography set-up
The intradiscal pressure was measured simultaneously in two successive discs while performing discography in one, using automated contrast injection (Figure 20). Details are given in paper I and II.

Figure 20. Schematic illustration of the measuring set-up
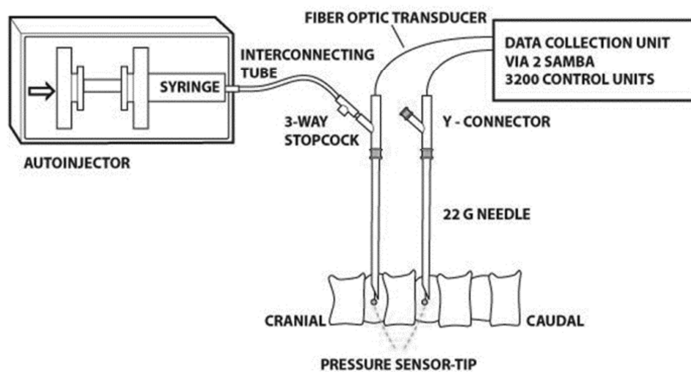
The intradiscal pressure was measured simultaneously in two adjacent discs while injecting contrast up to 8bar into NP in one of the discs. The pressure was measured with a FOPT (0.36mm diameter) located in NP.

Specific methods

Study I

Discography
Discography was performed in 36 discs while pressure simultaneously was recorded in the injected and one adjacent disc. Initially L2/L3 was injected (In three animals L1/L2) and pressure in the adjacent L3/L4 evaluated (Figure 20). Injection continued until the pressure in NP reached 8 bar (116 psi). Thereafter the autoinjector was connected to the L3/L4 disc which was injected while L4/L5 constituted the adjacent disc. The procedure was repeated to include even the L5/L6 level. To measure any pressure response in an already injected disc, the FOPT then remained in L4/L5 (prefilled with contrast) when injecting L5/L6.

Two different injection speeds were used. At the first injected disc "low-speed" injection (0.03 ml/seconds) was used followed by "high-speed" injection (0.07 ml/seconds) in the second level. The injection speed was then altered in every second disc level. Furthermore, the injection speed at the start of injection was altered between different pigs every other time.

In one pig three sensors were used to evaluate any pressure increase even more distant from the injected disc. After injecting the L2/L3 disc, the FOPT was left in the nucleus of L2/L3 and a discogram performed first in L4/L5 and then in L5/L6, thus evaluating how the pressure response in L2/L3 was affected when injecting those more distant discs. Details are given in paper I.

Imaging
Fluoroscopy after maximum injection confirmed needle placement and adequate dye injection (Figure 21).

Figure 21 Sagittal fluoroscopy view of porcine discograms

Definition of increased pressure
Any pressure increase above baseline pressure (steady baseline before start of injection) in the adjacent disc was considered as increased pressure. The baseline pressure as well as maximum pressure was collected at the peak of the respiratory oscillations superimposed on the pressure curve.

Study II

Discography
Discography was performed in 30 discs. The intradiscal pressure was measured at two successive disc levels simultaneously while performing discography in one of them. Initially L1/L2 was injected while pressure was registered in adjacent degenerated L2/L3 (Figure 22, step 1). Thereafter disc injection was performed in the degenerated L2/L3 while L3/L4 constituted the adjacent disc (Figure 22, step 2). In the last step L3/L4 was injected while pressure was recorded in the degenerated cranial L2/L3 that now also was prefilled from previous discogram (Figure 22, step 3). In the two animals with degenerated L1/L2 discs injection started at the Th12/L1 level thereafter following the same principal order as described above. By this procedure one disc in each animal was evaluated twice, once as adjacent disc before injected and once as prefilled with contrast. Contrast was injected at 0.03 ml/seconds and continued until approximately 8 bar. Pressure was recorded until 15 minutes after injection. Details are given in paper II.

Figure 22. Illustration of order of injection
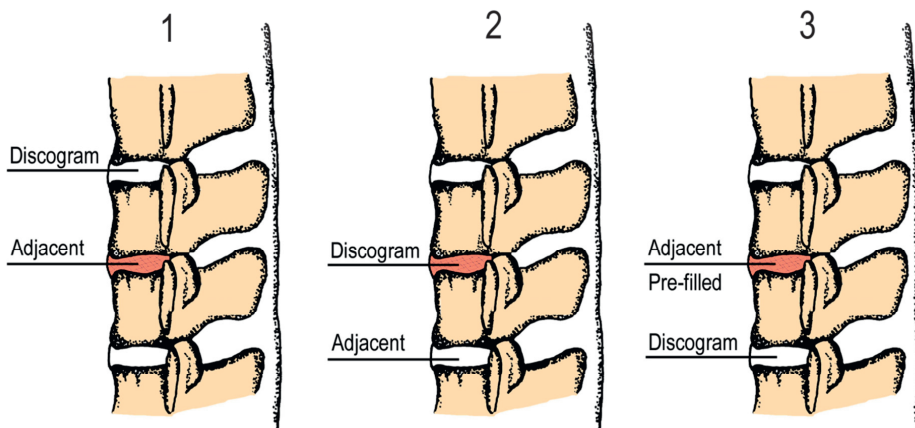
Imaging
After completed discography contrast location in NP was confirmed with fluoroscopy and in addition, within a couple of hours, by both a CT scan (Siemens 16 slice scanner) and a MRI (1.5 Tesla Siemens Magnetom Symphony Maestro Class, Erlangen, Germany). Due to ethical considerations these exams were only performed of the extracted spines after sacrifying the animals. T1 and T2-weighted 4 mm sagittal and axial images were obtained. CT images in all three dimensions were obtained from 0.75 mm axial images. Discs were classified according to Table 1.

Table 1. Classification of discs in the porcine spines

	Morphological appearance MR/CT
Non-degenerated (0)	Preserved disc signal with well-defined NP. Preserved disc height and no EP lesions
Degenerated (1)	Disc with reduced water signal, ill-defined NP and/or reduced disc height and/or EP lesions

The classification into non-degenerated or degenerated discs was made from a combined CT/MRI appearance, including both axial and sagittal images at MRI and at CT and in addition also coronary images.

Definition of increased pressure
A rise of intradiscal pressure ≥ 2 psi above baseline (the pressure before start of injection) was defined as increased pressure in the adjacent discs. This pressure cut-off was set with experience from pilot studies and from study I, aiming to avoid minor artifacts giving false positive results. The pressure was measured from one respiratory oscillation peak to another. The pressure reaction during injection as well as the pressure until 15 minutes after injection was recorded and evaluated.

Clinical studies (Study III-V)

Participants

All participants were recruited at the department of Radiology, Mölndals hospital, Sahlgrenska University Hospital. Patients referred for preoperative lumbar discography because of suspected discogenic pain were eligible. All referred patients had non-specific LBP for >6 months, resistant to conservative therapy. Allergies to contrast media or inability to undergo MRI (severe claustrophobia or metal implants) were exclusion criteria. It rested on the referring surgeon to carefully select discography patients why no further exclusion criteria were used except that eligible patients had to understand written and spoken Swedish. The studies were approved by the Ethics Committee (reference number: 366-07) and all participants received written information about the study a few weeks in advance of the examinations. All respondents approved to participate.

Study III
Nine consecutive discography patients (five male/four female) mean age 44 years, (range 35-55) were investigated by simultaneously measuring intradiscal pressure in the injected disc and in one adjacent disc. MRI, PCD and CT were in each patient performed within 8 hours.

Study IV & V
Forty-one consecutive discography patients (23 female/18 male; age 25-64 years), were included during a three year period. Each patient underwent MRI, alMRI, PCD and CT within 24 hours.

General Methods

Imaging

MRI
MRI was performed in study III-V with a 1.5 Tesla (Siemens Magnetom Symphony Maestro Class, Erlangen, Germany). T1 (TR 541 ms/TE 1 ms) and T2 (TR 4000 ms/TE 124 ms) weighted sagittal images (4 mm slices /FoV 300 mm) were obtained and 4 mm T2 (TR 5000-6970 ms/TE 114-116 ms) axial sections were generated.

alMRI
alMRI was added to the conventional discography protocol at our department since some patients referred for discography were shown to have intermediate spinal stenosis at the conventional MRI. alMRI was performed in study IV-V with the same MRI apparatus used for conventional sequences using a

compression device according to Figure 11 (DynaWell, Dynawell diagnostics AB, Las Vegas, Nevada USA). Corresponding parameters used at the conventional MRI were performed with axial load and in addition 4 mm T1-weighted axial images (TR 500ms/TE 15ms).

CT
As part of the clinical discography CT (Siemens Somatom Sensation 16 Slice) was performed within an hour after the discography to gain information about internal disc architecture. In study III and IV disc appearance was graded according to DDD (Figure 19) however only analyzed further in study IV. In study V the CT was not at all part of the study.

Fluoroscopy
Fluoroscopy was used in study III-V as part of the clinical discography for correct needle positioning, to monitor adequate injection and o.p. as well as to gain information of internal disc morphology. The imaging was not analyzed further in the studies.

Discography
Before initiating the examination a detailed interview regarding the character and localization of the patient's symptoms was performed. The patients were also carefully informed about the examinations and encouraged to report and describe any experienced pain during the procedure in detail and relate it to their daily LBP. The patients were asked to classify any provoked pain into one of four categories; no pain/pressure, unfamiliar pain, similar/familiar pain or exact pain with their daily pain as reference standard. In study III pain was only classified into three categories (as above but excluding unfamiliar pain). 30 minutes before the procedure intravenous antibiotics (cefuroxime 1.5gx1) and midazolam (10 mg rectally) were administrated. Discography was performed under aseptic conditions by one of two experienced radiologists (In study III only by one). After local anesthetics (carbocain 10 mg/ml), subcutaneous and intramuscular, the 22 gauge discography needle was inserted into NP with fluoroscopy guidance. In anatomic challenging discs, i.e. L5/S1 an 18 gauge introduction needle was used (Figure 23). Contrast (Omnipaque 180mg/ml, GE, Healthcare) was injected with a twist-manometer (Stryker Discmonitor**,** Kalamazoo Michigan, USA) until one of the following endpoints was reached; exactly reproduced pain with an intensity of $\geq 5/10$ on a NRS (0= no pain and10=worst experienced pain), pressure 100 psi (absolute pressure), contrast volume 3.5 ml or a steady state in the pressure/volume curve (i.e. further pressurization impossible due to high resistance or epidural leak). Approximately 0.2 ml was injected at each twist, resulting in an estimated injection speed below recommended 0.05 ml/seconds [97, 144, 197]. The patients were awake, alert and could respond adequately during the procedure. A

positive discogram was defined as; exactly or similar reproduced pain with an intensity >5/10, one negative control disc and pain reproduced at <50 psi a.o.p.

Figure 23 Double needle technique approaching L5/S1
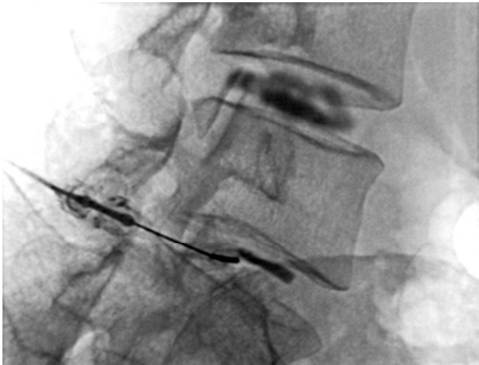
Specific methods

Study III

MRI
Disc degeneration was graded separately according to Pfirrmann (Figure 9) by an orthopedic surgeon and a radiologist, both blinded to the discography results. Their inter-observer variation was assessed. To test intra-observer variability the radiologist repeated the grading after two months.

Pressure registration
A 0.36 mm in diameter FOPT (Samba Sensors AB, Gothenburg), allowing introduction into NP through a 22 gauge needle, was used for pressure registrations. The sensor, which already is CE certified for in vivo purposes other than intradiscal pressure measurement, was approved and permitted for this purpose by the Ethics Committee according to the Medical Device Directive and Declaration of Conformity. Each FOPT was sterilized and calibrated before introduction into the NP. Based on experience from previous studies and pilot studies, pressure responses were categorized according to Table 2.

Table 2 Criteria for grading pressure reactions in discs adjacent to the discogram

Pressure increase	Pressure increase ≥ 2 psi above baseline (baseline = pressure 5 seconds before injection)
No pressure increase	Pressure increase < 2 psi above baseline

Excluded registrations	Technically inadequate pressure registrations (major artifacts and/or handling errors)
	Registrations with artifacts during only part of registration were not excluded

Discography

Twenty-five discograms were performed and intradiscal pressure recorded simultaneously in the discogram and in one adjacent disc (Figure 24).

Figure 24. Photography of the discography set-up

The y-connector, with a Tuohy-Borst valve and a Luer lock, is mounted on a 22 gauge needle inserted in each NP. A twist manometer is connected to the Luer lock at both the level of the injection and the adjacent disc level, although it was locked in the latter (not visualized in photo). At each level, a fiber-optic pressure transducer was inserted through the Tuohy-Borst valve and the seal was tightened. In the photo, the transducer at the most cranial level is already in position, while it has still not been introduced at the caudal level.

The discs that were going to be injected were selected according to the referring surgeon's request, the MRI disc appearance and the inclusion of one negative control disc. Discography needles were placed in NP under fluoroscopic guidance in the two most cranial discs, aimed to be provoked, and each needle connected to a y-connector with a Tuohy-Borst-Valve. The twist-manometer was connected to the y-connector´s side port while the FOPT was inserted

through the Tuohy-Borst-Valve according to Figure 20 & 24, extruding approximately 1 mm outside the needle tip. The most cranial disc was injected until above specified endpoints with the exception that maximum injection pressure was reduced to manometer readout ≤ 80 psi (absolute pressure). Due to the local hospital low-radiation policy, fluoroscopy was used sparsely. Consequently, the o.p. was registered but not rigorously monitored.

O.p. between 14-27 psi have been reported [91, 93] why maximum manometer pressure was set at approximately 50 psi above this i.e. at 80 psi. Pain response, pain intensity and pressure at initial onset of pain were registered during examination. Details of discogram order are given in paper III and in Figure 25.

Figure 25. Schematic illustration of discogram order

A positive discogram was defined as; pain with an intensity >5/10 on a NRS, one negative control disc and exactly reproduced pain at ≤ 50 psi a.o.p. In specific cases similar pain reproduction were taken into account if fulfilling the other criteria for a positive discogram.

Study IV

MRI
HIZ was evaluated at T2-weighted images at both conventional MRI and alMRI. The evaluation was performed, by an experienced radiologist blinded to the discography results, according to the criteria of Aprill and Bogduk [103]. To

assess intra-observer and inter-observer agreement the MRI examinations were evaluated both by a radiologist and by an experienced orthopedist with the radiologist repeating the evaluation after two months.

Discography
Discography was planned to be performed in 130 discs. Due to unfavorable anatomic positioning of six L5/S1 discs only 124 discs were injected in the 41 patients enrolled.

Pain classification
Pain is subjective and difficult to describe why four levels of provoked pain is advocated by some [103, 139, 151]. The four level scale was chosen when study IV and V were initiated in order to achieve a more differentiated pain spectrum; no pain/pressure sensation, unfamiliar pain, similar pain and exact pain reproduction. The patients graded provoked pain at discography according to this with their daily pain as reference. Their answers were registered by the discographer. Since classification into concordant/discordant also is common within discography context [110, 136, 145, 163, 164, 177] this classification was taken into account when analyzing the results by categorizing pain according to Table 3. Details are presented in paper IV.

Study V

MRI
Parameters measured at both conventional and at alMRI were; lumbar lordosis between superior EP of L1 and inferior EP of L5, disc angle, anterior and posterior disc height, anterior and posterior disc bulge, disc area and disc circumference (Figure 26). The MRI measurements were performed by one orthopedic spine surgeon and one radiologist, blinded to the results of the discography, and inter-reliability calculated. The differences between the parameters at the MRI examinations were calculated. Intra-observer variations have been presented in an earlier study and were not re-examined since these variations were minor [235].

Figure 26. MRI parameters evaluated

disc angel   disc height

anterior disc bulge   posterior disc bulge
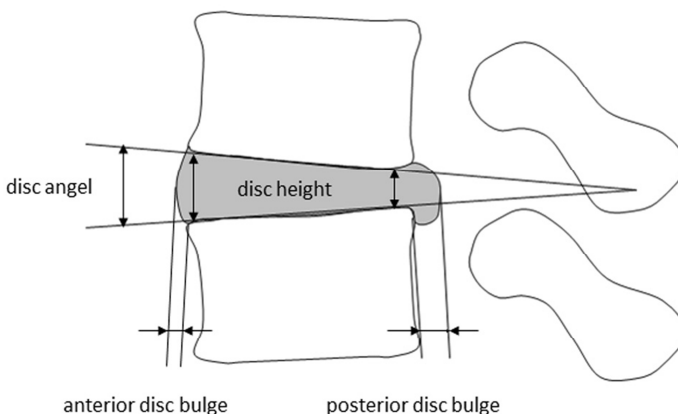
Discography
(See Study IV)

Pain classification
The patients graded their pain according to the 4-graded pain scale used in study IV at both alMRI and discography. Their answers were registered by the discographer at both the examinations and categorized into either concordant or discordant, a classification commonly used at discography [110, 136, 145, 160, 163, 164, 177], according to Table 3. This was done to ease comparison between the two modalities. Provoked pain at alMRI further required an intensity ≥5/10 to be regarded as concordant. Any provoked pain was registered immediately after the MRI examination, hence blinded to the results of the discography to come. To be able to compare up to four pain responses (one for each disc level) in the same patient at discography with just one pain response at alMRI each discography examination was summarized in terms of provoked pain in the following way. One concordant discogram was enough to consider the whole discography examination as a concordant such. In case of only discordant discs the examination was considered as discordant. Details are presented in paper V.

Table 3. Classification of reproduced pain

Provoked Pain	
none **unfamiliar**	discordant
similar **exact**	concordant

Provoked pain at both discography and alMRI was classified with daily pain as reference into one of four categories specified in the table and summarized into either discordant or concordant.

Statistical methods

Statistical Package for Social Sciences (SPSS) and SAS software were used for the statistical analysis. In all studies p-values ≤ 0.05 were regarded as statistically significant. In study I-III descriptive statistics were mainly performed and additional statistical methods used are described below. When using Cohen´s Kappa κ-values >0.80 represents excellent agreement beyond chance, 0.60-0.79 substantial agreement, 0.40-0.59 moderate agreement and <0.40 poor agreement [247].

Study I

Kruskal-Wallis was used to compare pressures (pressure increase/baseline pressure) between various disc levels and animals. Mann-Whitney U was used to investigate whether any difference between the two injection speeds and the magnitude of transmitted pressure could be demonstrated. Wilcoxon rank sum-test was used to compare pressure increase between prefilled and non-prefilled discs.

Study II

When comparing prefilled adjacent discs with those non-prefilled in terms of pressure increase Wilcoxon rank sum-test was used.

Study III

Cohen´s Kappa statistics were performed to determine inter-observer reliability of the raters´ Pfirrmann classification.

Study IV

Wilcoxon rank sum-test was used to compare HIZ before and after axial load. Chi^2 test, Fisher´s exact test and logistic regression analysis were used to analyze associations between HIZ and pain/annular disruptions. To correlate the grade of annular disruption with pain, contrast volumes and disc pressures, non-parametric Spearman test was used. The intra-and inter-observer agreement of HIZ was tested with Cohen´s Kappa-coefficient. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated considering discography as reference standard.

Study V

Wilcoxon rank sum test was used to compare pain responses at discography with pain at alMRI. Associations between pain and morphological MRI features were analyzed with Chi^2 test, Mann-Whitney U and logistic regression analysis. Non-parametric Spearman test and adjusted Spearman test were used to correlate Pfirrmann classification and morphological disc measures. Cross tabulations were used to calculate PPV considering discography reference standard. Inter-rater reliability was determined using intra-class correlation coefficient (ICC).

Results

Study I

Transmitted pressure was evaluated in 33 adjacent discs. Of those 24 were non-prefilled discs, distal to the discography level, and nine discs were prefilled with contrast and located cranial to the discogram. Injected disc and corresponding adjacent disc as well as pressure reactions are displayed in Table 4. During discography, there was a mean rise in intradiscal pressure in all adjacent discs of 5 psi (range 1-14) (Table 4, Figure 27).

Table 4. Baseline pressure and the intradiscal pressure increase above baseline in the 33 discs adjacent to the discography level

| porcine | injected disc | pressure in adjacent disc | | | | |
| | | baseline | | increase | | |
No	level	bar	psi	bar	psi	%
1	L2-L3	1.4	20	0.1	2	7
1	L4-L5	2.0	28	0.2	3	13
1	L5-L6	1.4	21	0.5	7	16
2	L2-L3	1.6	23	0.1	2	7
2	L3-L4	2.1	30	0.6	9	26
2	L4-L5	2.3	34	0.5	7	22
2	L5-L6	2.0	30	1.0	14	27
3	L2-L3	2.0	28	0.3	5	13
3	L3-L4	2.4	35	0.1	1	6
3	L4-L5	1.5	21	0.2	3	12
3	L5-L6	1.7	25	0.7	11	22
4	L2-L3	2.5	36	0.2	3	9
4	L3-L4	2.1	31	0.4	5	17
4	L4-L5	2.2	32	0.2	2	13
4	L5-L6	1.7	25	0.2	3	8
5	L1-L2	2.3	33	0.4	6	16
5	L3-L4	2.6	38	0.5	7	18
5	L4-L5	2.7	39	0.6	9	19
6	L1-L2	3.1	45	0.4	6	14
6	L2-L3	2.9	42	0.5	7	20
6	L3-L4	2.4	35	0.2	3	11
6	L4-L5	2.2	31	0.1	1	3
7	L2-L3	1.4	20	0.3	4	16
7	L3-L4	1.5	22	0.3	5	24
7	L4-L5	1.4	21	0.1	1	6
7	L5-L6	1.2	18	0.1	2	4
8	L1-L2	1.7	25	0.4	6	22
8	L2-L3	1.8	26	0.4	6	22
8	L3-L4	1.8	26	0.6	8	37
8	L4-L5	1.6	23	0.7	10	20
9	L2-L3	2.1	30	0.4	6	20
9	L4-L5	2.1	30	0.3	4	14
9	L5-L6	1.9	27	0.3	5	10

The disc levels are the discography levels and the pressure response in the table are that of the transmitted pressure in the adjacent discs. All adjacent discs are caudal to the discography level except for the last discography level in every animal in which transmitted pressure is measured in a prefilled disc cranial to the injection.

Figure 27. Pressure increase in percent above baseline in each of the 33 adjacent discs
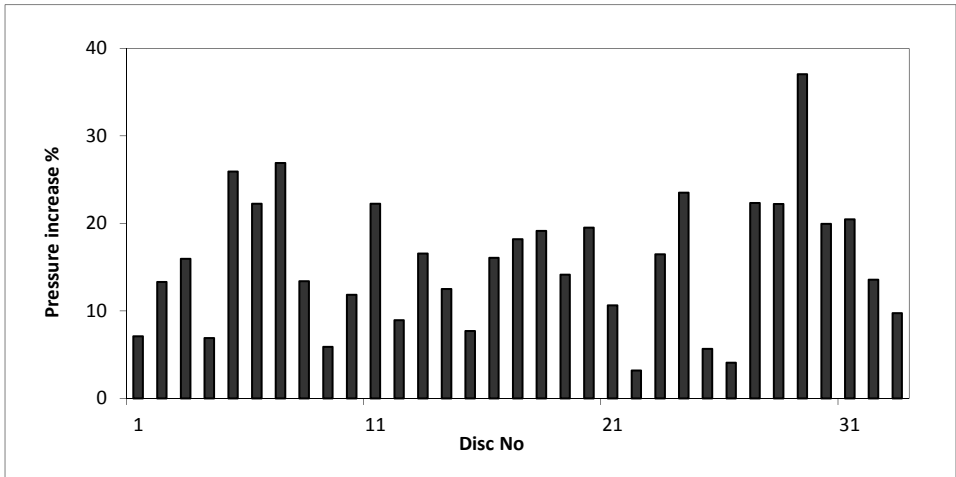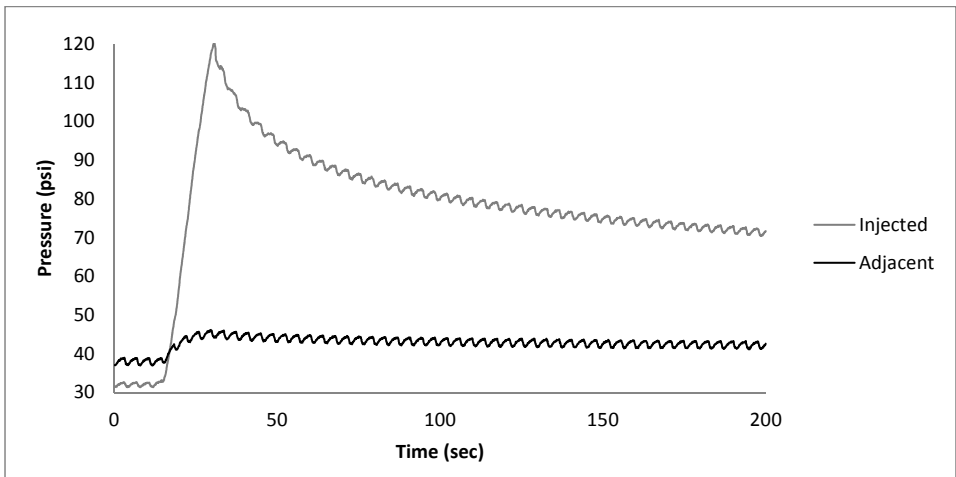

Figure 28. Example of pressure reaction in one injected and corresponding adjacent disc

The disc pressure reaction in a disc during discography in the injected disc (upper) and the corresponding pressure increase in the adjacent disc (lower). The variation in disc pressure due to breathing is superimposed on both curves.

Mean pressure increase was 16% (range 3-37) over baseline pressure. Example of the pressure reaction in both the discogram and the adjacent disc are shown in Figure 28.

As shown in Table 5 there was no significant difference in transferred pressure increase between non-prefilled and prefilled adjacent discs ($P <0.68$).

Table 5. Induced pressure increase in percent in prefilled and non-prefilled adjacent discs

	No.	min%	max%	average%	median%	SD
Prefilled	9	3.2	26.9	14.3	15.9	8.5
Non-prefilled	24	5.7	37.0	16.0	15.1	7.4

In vivo pressure increase in percent in the 33 lumbar porcine discs adjacent to discs injected with contrast up to 116 psi.

Figure 29. Pressure increase in adjacent discs at 4 bar (58 psi) in injected discs
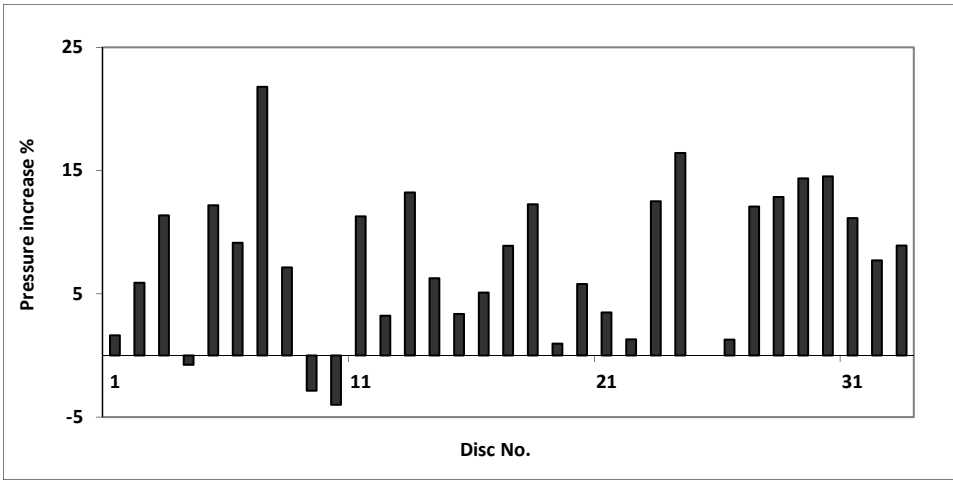
The pressure increase over baseline pressure in 33 discs adjacent to discs injected with contrast. The mean pressure increase at 4 bar (58 psi) was 8%. The baseline pressure was sampled at the peak of the respiratory oscillations superimposed on the pressure curve. The readout at exactly 4 bar could coincide with either a peak or a valley of those oscillations, hence some negative values.

Induced pressure increase in the adjacent disc could be recorded already at low pressures in the injected disc (Figure 29).

When evaluating pressure increase in discs further away from the injected, the pressure in L2/L3 rose to 4 psi when injecting the L4/L5 respectively 2 psi when injecting the L5/L6.

Mean baseline pressure was 29 psi (range 17-45). The baseline pressure was sampled in every disc before injection, hence the baseline pressure in the prefilled discs are not included. Reliable determinations of the amount of injected contrast in NP were impossible due to fluctuations secondary to the not perfectly rigid interconnecting tubes used during injection. Any difference between the two injection speeds and the magnitude of transmitted pressure could not be demonstrated. No correlations were detected between baseline pressure and lumbar disc level. The baseline pressure in the L5/L6 level was however generally lower compared to more proximal levels.

Study II

Twenty-eight discs were successfully injected and corresponding pressure reactions measured in 28 adjacent discs of which ten discs were prefilled from previous discogram (Figure 25). Injected disc level, corresponding adjacent disc and pressure reactions are displayed in Table 6.

*Table 6. Pressure parameters of the discograms and corresponding adjacent discs.*

DISCOGRAM							ADJACENT DISC								
Pig No	Disc Level	Degenerated = 1	Contrast (ml)	Baseline P	Max P	P↑	Disc Level	Degenerated = 1	Pre-Filled x	Baseline P	Max P	P↑	P↑ 15 min	P↑ %	P↑ % 15 min
1	L1-L2	0	0.7	20	115	95	L2-L3	1		17			**2**		9
1	L3-L4	0	1.5	38	128	90	L2-L3	1	x	29			**2**		7
2	L1-L2	0	0.8	19	125	107	L2-L3	1		19			**3**		18
2	L2-L3	1	2.0	22	125	104	L3-L4	0		27			**3**		11
2	L3-L4	0	0.8	31	125	95	L2-L3	1	x	23					
3	L1-L2	0	0.9	27	125	99	L2-L3	1		20	22	**2**	**2**	9	9
3	L2-L3	1	2.0	20	125	106	L3-L4	0		31	35	**4**	**3**	12	9
3	L3-L4	0	0.8	32	125	94	L2-L3	1	x	26	28	**2**	**5**	9	18
4	L1-L2	0	0.9	36	125	89	L2-L3	1		17			**3**		16
4	L2-L3	1	1.6	24	48	24	L3-L4	0		26	30	**4**	**6**	16	22
4	L3-L4	0	0.8	28	117	89	L2-L3	1	x	31	33	**2**	**2**	6	6
5	L1-L2	0	0.6	36	120	84	L2-L3	1		17					
5	L2-L3	1	1.9	24	48	24	L3-L4	0		19			**5**		25
5	L3-L4	0	0.9	28	117	89	L2-L3	1	x	28					
6	L1-L2	0	0.8	20	119	99	L2-L3	1		19	21	**2**	**2**	11	11
6	L2-L3	1	1.9	20	95	75	L3-L4	0		28	30	**2**	**4**	6	13
6	L3-L4	0	0.6	31	125	94	L2-L3	1	x	36	42	**6**	**6**	16	16
7	L1-L2	0	0.8	26	120	94	L2-L3	1		36	44	**8**	**8**	23	23
7	L2-L3	1	1.9	28	102	74	L3-L4	0		22			**2**		11
7	L3-L4	0	1.1	25	123	98	L2-L3	1	x	21	23	**2**	**2**	8	8
8	Th12-L1	0	0.5	24	126	103	L1-L2	1		23	25	**2**	**2**	9	9
8	L2-L3	0	0.6	27	125	99	L1-L2	1	x	40	44	**4**	**4**	9	9
9	Th12-L1	0	1.2	24	125	101	L1-L2	1		18			**6**		36
9	L1-L2	1	1.6	23	114	53	L2-L3	0		29	34	**5**	**7**	16	23
9	L2-L3	0	0.9	33	123	90	L1-L2	1	x	29	33	**4**	**4**	13	13
10	L1-L2	0	0.8	29	126	97	L2-L3	1		24	26	**2**	**2**	8	9
10	L2-L3	1	0.6	21	127	106	L3-L4	0		29			**3**		9
10	L3-L4	0	0.8	27	123	96	L2-L3	1	x	32	34	**2**	**5**	6	17

Table of parameters registered at the discogram level and in the corresponding adjacent disc. Pressures (P) in psi, contrast volume in ml and pressure increase displayed as (↑). Disc degeneration was classified according to Table 1.

A pressure increase during injection was detected in 16 of the 28 adjacent discs (57%) and mounted to mean 3 psi (range 2-8, SD 2). This pressure increase corresponded to a mean increase above baseline of 11% (range 6-23, SD 5). An example of the induced pressure increase is shown in Figure 30. Of those 16 adjacent discs with pressure increase four were non-degenerated and 12

degenerated of which 7 were prefilled. In adjacent discs with pressure increase the registrations displayed either a pressure peak simultaneous with the injection peak pressure (Figure 30) or a slow pressure increase with a delayed peak pressure in the adjacent disc (Figure 31).

Figure 30. Example of pressure reactions in one discogram and corresponding adjacent disc
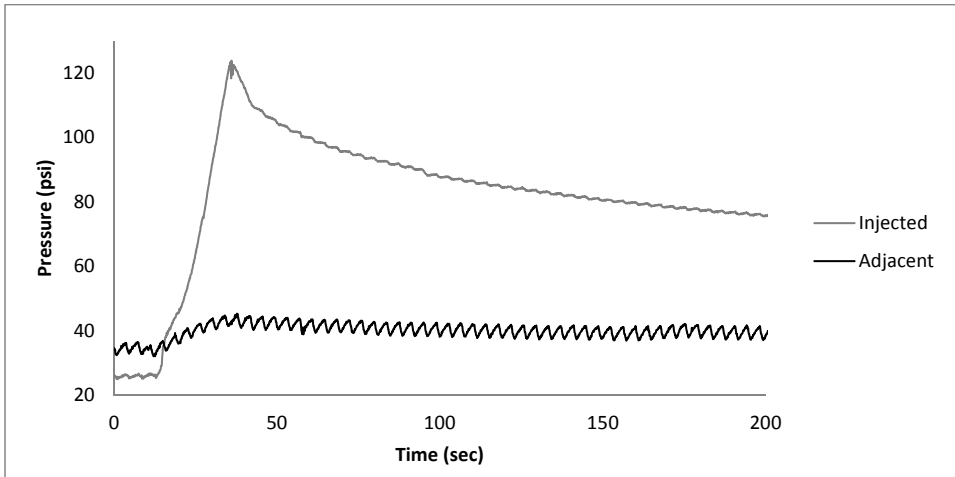
A pressure increase of 8 psi was induced in an adjacent degenerated L2/L3 when injecting a non-degenerated L1/L2 up to 100 psi above baseline. Note the respiratory oscillations superimposed on the pressure curve.

When the pressure increase from baseline until 15 minutes after injection was analyzed, 25 of the adjacent discs (89%) displayed a mean increase in pressure of 4 psi (1-8, SD 2) corresponding to a mean pressure increase of 14% above baseline. The reason for a pressure transfer in almost all adjacent discs during the extended observation could be a creep effect with rise in pressure after injection had ceased (Figure 31 & 32). In addition many adjacent discs responded with an initial decline in pressure simultaneous with the injection peak, followed by a subsequent increase in pressure (Figure 32).
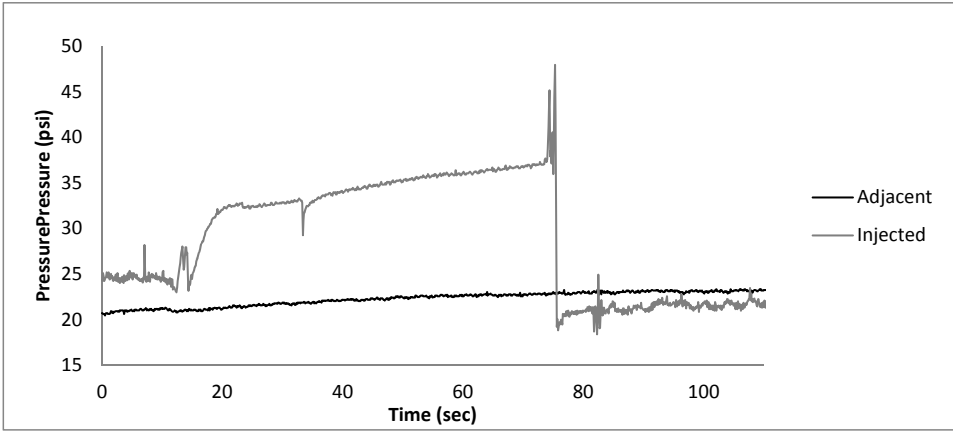
The degenerated L2/L3 was only pressurized to 24 psi above baseline still inducing a pressure increase in the adjacent disc. The pressure continued to rise even after the injection had stopped inducing an increase of 5 psi in the adjacent disc during the registration period.

Figure 32. Example of initial pressure decline in the adjacent disc when injecting a healthy disc
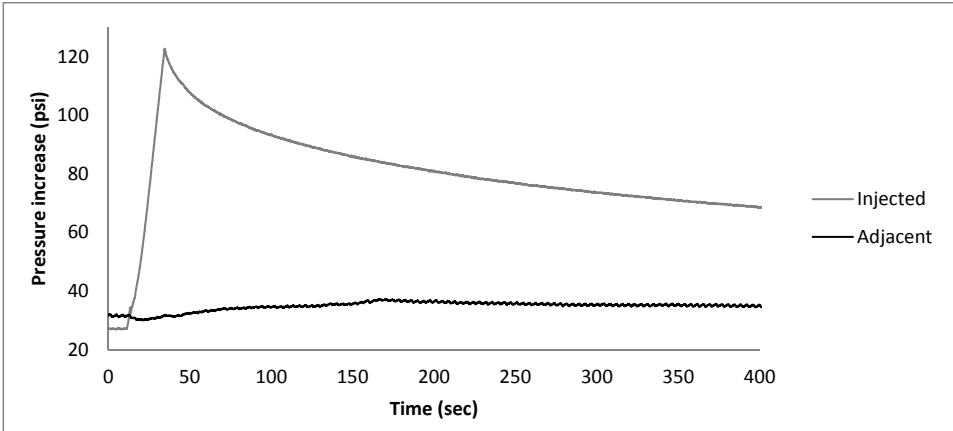

Injection in a non-degenerated L3/L4 induced an initial decline in pressure followed by a creep effect with peak pressure after injection in the adjacent prefilled degenerated L2/L3. The pressure increase during injection was only 2 psi but up to 5 psi after injection.

In the three (11 %) adjacent discs with no signs of a pressure increase only respiratory oscillations were noted on the pressure curve.

The mean contrast volume injected in the discs was 1.1 ml (0.5-2.0, SD 0.5).The mean contrast volume was greater in degenerated discs, 1.7 ml, than the mean 1.1 ml in discs without created degeneration. The mean pressure at baseline and mean maximum pressure in injected discs was 27 psi (19-38, SD 5) respectively 114 psi (48-127, SD 21). Corresponding figures in adjacent discs were 26 psi (17-40, SD 6) and 31 psi (21-45, SD 8) the latter though only measured in the 16 adjacent discs meeting our criteria for pressure increase during injection. Discs prefilled had higher pressure at baseline with a mean of 30 psi compared with 23 psi in those non-prefilled. Degenerated discs had lower baseline with a mean of 23 psi compared with 28 psi in non-degenerated ones. The differences in disc appearance between discs with induced degeneration and discs without are exemplified in Figures 33.

Figure 33. Illustration of the difference between a non-degenerated (left) and a degenerated (right) pig disc with the needle entrance marked with an arrow.
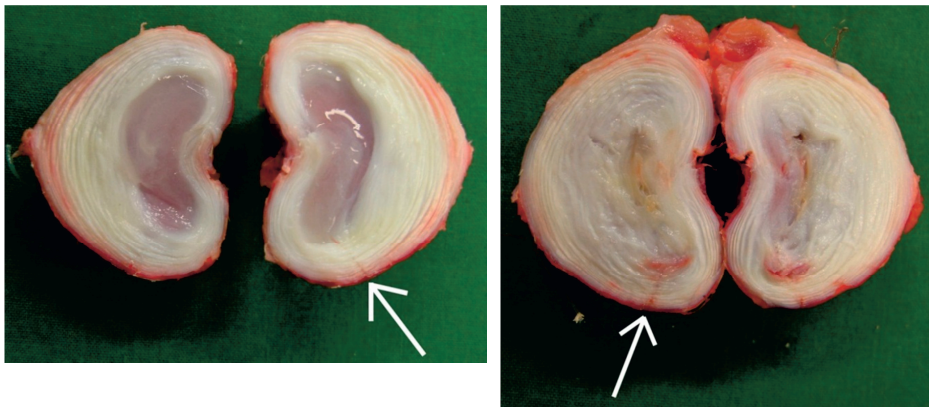
Study III

Of 25 discs injected 36% (9 discs) were positive discograms. Three adjacent discs were excluded due to artifacts. Intradiscal pressure was measured successfully in 22 adjacent discs in which seven were non-injected and 15 prefilled with contrast from the previous discogram (Figure 25). Pressure increase was registered in 55% (12) of the 22 adjacent discs (Table 7). In Figure 34 the pressure increase in each of these 12 discs is displayed. This pressure increase amounted to a mean of 13 psi (range 3-42, SD 11) above baseline.

Table 7. Parameters related to discography at both the discogram level and the corresponding adjacent disc

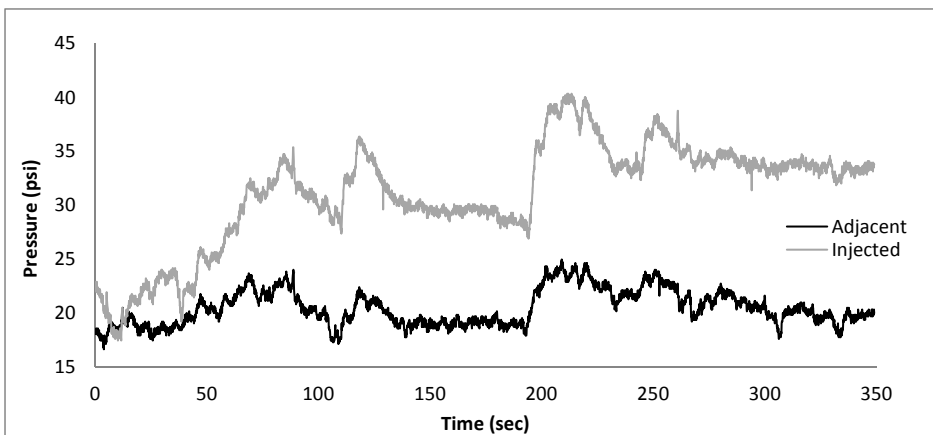| Injected Discs									Adjacent Discs					
Disc level	Pain	Pfirr-mann	o.p.	Max C	DDD	Max P a.o.p mano-meter	Max P NP	P increase NP	Pre-filled = X	Disc level	Pfirr-mann	Base-line P	Max P NP	P increase NP
L4-L5	similar	3	27	3.3	4	52			X	L3-L4	4			
L3-L4	none	4	33	2.0	1	28				L4-L5	3			
L4-L5	exact	4	28	2.6	4	28	22	7	X	L3-L4	4	50	60	**10**
L3-L4	similar	4	20	2.5	4	13			X	L4-L5	4			
L4-L5	similar	4	18	3.0	4	22	40	20	X	L3-L4	4	19	24	**5**
L5-S1	exact	5	13	2.0	5	43	56	41	X	L4-L5	4	13	31	**18**
L4-L5	none	2	24	2.5	2	44				L5-S1	4			
L5-S1	exact	4		2.7	4		45	26	X	L4-L5	2	52	57	**5**
L4-L5	similar	3	33	4.0	5	17			X	L3-L4	5			
L5-S1	exact	4	22	3.7	4	41	84	64	X	L4-L5	3	23	44	**21**
L3-L4	similar	3	27	4.0	4	10	43	23		L4-L5	4	7	20	**13**
L4-L5	exact	4		3.6	4				X	L3-L4	3			
L5-L6	exact	4		2.0	5		37	20	X	L4-L5	4	14	19	**5**
L3-L4	none	1	28	2.1	0	69				L4-L5	4			
L4-L5	exact	4	25	3.0	3	15	42	31	X	L3-L4	1	95	101	**6**
L5-S1	exact	4		3.0	3		47	40	X	L4-L5	4	11	22	**11**
L4-L5	none	1	34	2.5	0	66				L5-S1	3			
L5-S1	exact	3	31	2.0	5	29	56	48	X	L4-L5	1	78	120	**42**
L2-L3	none	3	30	3.0	4	33				L3-L4	4			
L3-L4	exact	4	25	3.5	4	47	61	51	X	L2-L3	3	27	30	**3**
L4-L5	exact	4	18	2.4	4	34	61	50	X	L3-L4	4	35	56	**21**
L5-S1	none	2	23	3.0	5	75			X	L4-L5	4			

Table of injected and adjacent discs with corresponding pressures (P) in psi, maximum injected contrast volume (Max C) in ml and degeneration grade displayed both with Dallas Discogram Description (DDD) and Pfirrmann classification. Pressures recorded simultaneously with manometer and fiber-optic pressure sensors in NP differ why both are displayed. Opening pressure = o.p., above opening pressure = a.o.p. Due to technical reasons registration of o.p. failed in four discs. Maximum pressures in NP are only displayed for adjacent discs with pressure increase and corresponding injected discs.

Figure 34. Pressure increase in psi in each of the 12 adjacent discs with induced pressure increase
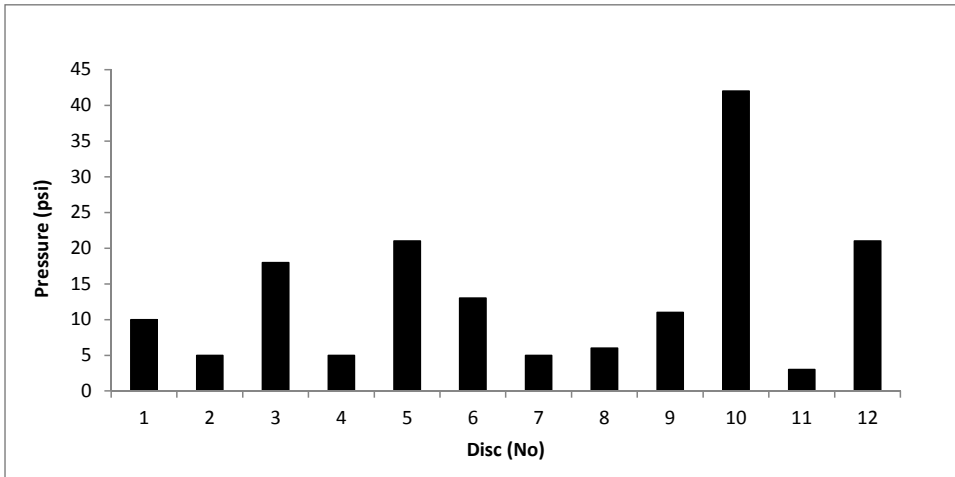
Of the 12 adjacent discs with pressure increase one was non-prefilled and 11 prefilled. Two types of pressure increase patterns were noted. One was a continuous pressure rise during disc injection while the other showed pressure peaks synchronous with the twist manometer-injections (Figure 35).

Figure 35. Synchronous pressure increase in one adjacent disc during disc injection in another

Pressurizing L4/L5 to approximately 40 psi (22 psi a.o.p. at manometer readout) induced an increase of 5 psi in the adjacent prefilled L3/L4.

Disc levels injected, grade of degeneration in each discogram and corresponding adjacent discs as well as corresponding pressure reactions in the latter are displayed in Table 7. Discograms inducing pressure increase in adjacent discs all had degeneration grade ≥ 3 while 75% of the adjacent discs with increased pressure had degeneration grade ≥ 3 (Pfirrmann classification). Pfirrmann classification showed moderate inter-observer agreement (k = 0.57) and substantial intra-observer agreement (k = 0.65).

The mean maximum manometer readout was 61 psi (33-100, SD 19) while the mean o.p. was 26 psi (13-34, SD 6). Hence mean maximum pressure a.o.p. was 35 psi (10-69, SD 16). The mean pressure at initial onset of pain was 8 psi a.o.p. (-15-37, SD 13) and the mean injected contrast volume 2.8 ml (2.0-4.0, SD 0.6). In four severely degenerated discs, with low manometer readout, more than 3.5 ml contrast was administrated. Mean maximum pressure measured with the FOPT was 48 psi (20-84, SD 18). In three discs the pressure rose quickly above 80 psi.

Among the ten adjacent discs without any signs of a pressure increase three categories were distinguished. The first included severely degenerated discograms in which assumingly no disc pressure was built up and consequently no pressure transferred to adjacent discs. Adjacent discs with a slowly declining pressure curve (prefilled discs with creep effect) but with small pressure peaks synchronous with injection belonged to a second category. The third category was adjacent discs with no signs of a pressure reaction despite pressure increase in the injected disc.

Study IV

Of 41 patients initially included 35 (19 men/16 women) completed all required MRI sequences. The mean age was 47 years (range 26-64). The reasons for incomplete examinations were in four cases handling errors with incomplete sequences and in two patients motion artifacts. In those 35 patients 140 discs were examined with both conventional and alMRI. 164 discs were examined with conventional MRI.

No significant difference in the detection of HIZ before and during axial load was found. 48 discs (34%) displayed HIZ at MRI and 49 (35%) at alMRI. However in three discs HIZ appeared at the loaded sequences (2 at L4/L5, 1 at L5/S1) whereas at four levels HIZ was detected before but not after axial load (2 at L3/L4, 2 at L5/S1). Kappa values for intra- and inter-observer agreement of the 164 discs (conventional MRI) were 0.87 and 0.84 respectively. Intra- and inter-observer agreement of HIZ at the 140 discs at the alMRI was 0.82 and 0.80 respectively.

Of the 164 discs examined with conventional MRI, PCD was performed in 124 discs. Due to anatomic unfavorable positioning of five L5/S1 discs only 119 discs were successfully injected. Maximum pressure, total contrast volume and both pressure and contrast volume at initial evoked pain are displayed in Table 8.

Table 8. Maximum pressure, total contrast volume and both pressure and contrast volume at initial evoked pain at discography

	Disc No.	Min	Max	Mean	SD
Total contrast volume	107	0.6	3.5	1.8	0.6
Volume at initial evoked pain	96	0.1	2.5	0.7	0.4
Maximum pressure	119	10	127	43	25
Pressure at initial evoked pain	94	3	72	24	16

Due to technical and human factors (questionable figures and when doubt existed if pain was evoked) all parameters were not registered in every disc. Volume is given in ml and pressure in psi. SD = Standard Deviation.

Absolute pressures were used in this study, why the o.p. was estimated to 14 psi, the mean o.p. Derby et al. found when using manometry [93]. The mean maximum pressure in the current study was 43 psi, subtracting the estimated o.p. results in a mean maximum pressure of 29 psi a.o.p. Low pressure positive discograms, positive at ≤ 15 psi a.o.p., were 14% if only exactly reproduced discs were included. If combining similar and exact pain provocation 23% were low pressure positive discograms. Seven patients experienced exactly reproduced pain at two or more discs. Provoked pain in relation to disc level is displayed in Table 9.

Table 9. Distribution of the disc levels and corresponding pain response in the 119 discs examined with pressure controlled discography

		Provoked pain at discography				
		none	unfamiliar	similar	exact	TOTAL
disc	L2/L3	6	4	2	1	13
	L3/L4	10	15	6	8	39
	L4/L5	3	5	18	14	40
	L5/S1	1	4	10	12	27
	TOTAL	20	28	36	35	119

The positive rate of discograms calculated per disc for exactly provoked pain was 29% (35/119) and 60% (71/119) when combining similar/exact pain. The pain provoked at discography was correlated with the patients' daily pain.

No significant associations were found between HIZ and discogenic pain (4 categories) (p=0.34), or between HIZ and similar/exact pain in combination (p=0.08). Of concordant discograms 44% displayed HIZ and 27% of the discordant ones. HIZ´s relation to provoked pain is displayed in Table 10.

Table 10. Relation between HIZ and provoked pain at discography

		Provoked pain at discography				
		none	unfamiliar	similar	exact	TOTAL
HIZ	absent	18	17	22	18	75
	present	2	11	14	17	44
	TOTAL	20	28	36	35	119

Discography was considered reference standard and a discogram positive when pain was either exactly provoked or similarly/exactly provoked. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of HIZ in revealing painful discograms were 49% (17/35), 69% (57/84), 39% (17/44) and 76% (57/75) for exactly reproduced pain. Corresponding figures for similar/exact pain were 44% (31/71), 73% (35/48), 70% (31/44) and 47% (35/75) respectively.

There was a significant association between HIZ and annular disruption according to DDD (p<0.01). Annular disruptions directly correlated with symptomatic discs when using PCD, both with the 4-graded pain scale (p<0.01, k=0.48) and when combining similar/exact pain reproduction (p<0.01). 82% of the discs with exact pain reproduction had grade 4 disruption according to DDD.

Injected contrast volume correlated neither with maximum pressure (p=0.08) nor with pain at discography (p=0.55). Significant correlation was however found between maximum pressure at discography and provoked pain at discography (p=0.01, k=-0.25). There was a strong correlation between annular disruption and maximum pressure (p<0.01, k= -0.41) and between annular disruption and contrast volume (p<0.01, k=0.42).

Study V

Of 124 discs injected 119 discograms were successful. Five discs, all at the L5/S1 level, could not be examined due to unfavorable anatomy or inadequate injection. The mean maximal pressure achieved during discography in the 119 discs was 43 psi (10-127) and the mean total contrast volume 1.8 ml (0.6-3.5). The first evoked pain occurred at a mean pressure of 24 psi (3-72) and a mean contrast volume at initially evoked pain of 0.7 ml (0.1-2.5). Details are presented in paper V.

At discography 98% of the patients experienced a concordant pain response (concordant pain from at least one disc) compared with 78% at the alMRI. Significant correlation was found between the pain provoked at alMRI and at discography (p=0.01). The PPV of a concordant discogram at discography when a concordant pain was evoked at alMRI was 97% (31/32) (Table 11).

Table 11. Distribution of provoked pain at both discography and at alMRI

		Pain at Discography		
		discordant	concordant	TOTAL
Pain at	discordant	0	9	9
alMRI	concordant	1	31	32
	TOTAL	1	40	41

Two patients were unable to complete the MRI due to claustrophobia, why 154 discs in 39 patients were evaluated regarding morphological disc characteristics. There was a high level of inter-observer agreement with ICC varying between 0,73-0,98 (Table 12). Compared with the conventional MRI, alMRI induced several morphologic disc alterations (Table 12). At conventional MRI lumbar lordosis averaged 44 degrees (SD 9) compared with 58 degrees (SD 9) at alMRI. Significant association between concordant discs and disc degeneration was found (p=0.02) however only at the L3/L4 level with for example concordant discs displaying Pfirrmann grade ≥4 in 27% compared with in 22% of the discordant discs.

Among all other morphological disc and spine features investigated (at MRI/alMRI/difference between MRI/alMRI) only anterior disc bulge at conventional MRI correlated significantly with painful discograms (p=0.02, odds ratio 1.8). The mean anterior bulge in concordant discs was 3.2 mm (SD 1.3) compared with mean 2.6 mm (SD 0.9) in discordant ones. Significant relation between anterior disc bulge and pain did not remain when axial load was added (p=0.09). For details regarding the relationships between concordant and discordant discograms and the change in morphological features when comparing MRI and alMRI see paper V.

Table 12. Descriptive statistics of morphological MRI measures

Disc feature		No	difference alMRI-MRI				MRI					alMRI				
							Examiner A		Examiner B			Examiner A		Examiner B		
			Min	Max	Mean	SD	Mean	SD	Mean	SD	ICC	Mean	SD	Mean	SD	ICC
Angle	degree	151	-8.7	12.2	2.2	3.3	6.4	4.7	6.8	4.2	0.86	8.6	4.8	8.1	3.5	0.87
Height anterior	mm	152	-7.9	9.8	0.8	1.6	9.1	2.3	8.8	2.5	0.85	9.9	2.5	9.5	2.4	0.91
Height posterior	mm	152	-3.9	2.4	-0.5	1.0	5.9	1.5	5.1	1.4	0.79	5.4	1.3	4.6	1.2	0.78
Bulge anterior	mm	151	-3.7	3.9	0.0	1.1	2.9	1.3	2.3	1.0	0.81	2.9	1.4	2.4	1.2	0.93
Bulge posterior	mm	152	-2.1	2.5	0.4	0.8	2.9	1.3	2.8	1.1	0.73	3.3	1.3	3.0	1.0	0.81
Circumference	mm	127	-16	47	0.7	6.6	158	26	161	12	0.97	158	25	163	12	0.96
Area	mm^2	126	-207	305	29.4	87	1752	395	1749	258	0.98	1778	395	1769	247	0.98

In one patient all sequences at the alMRI were not completed due to technical factors why the difference between conventional and alMRI only was calculated in 38 patients which also reduced the number of discs. Disc No. refers to number of discs in which the difference between alMRI-MRI was evaluated. In addition one L5/S1 was impossible to evaluate due to artifacts why there are discrepancies in the evaluated number of discs. Axial images were not performed on L1/L2 discs in every patient why area/circumference are measured in reduced disc numbers. The disc measures were determined by two examiners at both loaded and unloaded MRI examinations and are displayed as average, standard deviation (SD) and ICC (intra-class correlation coefficient).

Significant correlations were found between Pfirrmann classification and the majority of the morphological MRI parameters, both at conventional and at alMRI (Table 13).

Table 13. Disc degeneration (according to Pfirrmann) and correlations with morphological MRI features

Pfirrmann classification in relation to disc characteristics

		MRI		alMRI	
		r	p	r	p
Angle	**degree**	0.20	0.05	0.11	0.18
Height anterior	**mm**	-0.17	0.04	-0.13	0.10
Height posterior	**mm**	-0.40	<0.01	0.50	<0.01
Bulge anterior	**mm**	0.38	<0.01	0.55	<0.01
Bulge posterior	**mm**	0.49	<0.01	0.50	<0.01
Circumference	**mm**	0.34	<0.01	0.40	<0.01
Area	**mm^2**	0.35	<0.01	0.39	<0.01

Associations between Pfirrmann classification and MRI disc features are displayed with p-values (p) and correlation coefficients (r).

Discussion

Pressure transmission

Principal findings

The most important finding in this thesis is that discography induces a pressure increase in adjacent discs. This pressure transmission has potential to elicit pain also in other discs than the injected one and potentially constitute a major confounding factor, influencing the validity of discography. Transferred pressure was noted in degenerated and non-degenerated adjacent discs irrespective if the discs were non-injected or prefilled. The findings raise several questions. Is the induced pressure increase of a magnitude potentially influencing the discography results? Would it be enough to reduce pressure threshold in discography to avoid the phenomena or is pressure transfer a confounding factor in spite of low pressurization?

Several extensive reviews report strong evidence for discography as an accurate imaging tool with ability to provoke pain [151, 153, 154]. Even though PCD was not an inclusion criterion many of the reviewed articles used such. However despite strong evidence for discography as a pain provoking tool it is not synonymous with pain emanating from the injected disc as believed. This thesis shows induced pressure increase in adjacent discs, thereby a prerequisite exists for provoked pain to emanate from adjacent discs instead of the actually tested one during discography.

Is the pressure increase of clinical relevant magnitude? Discs provoked at ≤ 15 psi, are called chemically sensitive and those between 15-50 psi a.o.p., mechanically sensitive [50]. O'Neill et al. hypothesized that chemically sensitive discs can elicit pain already at 1 psi [144]. In study I-III the mean pressure increase in adjacent discs varied from 3 to 13 psi (range 1-42 psi) above baseline. Considering the above mentioned pressure limits even the lower pressure ranges would be sufficient to elicit false positive pain in an adjacent sensitive disc.

Would lower pressurization of the discogram eliminate the problem? The highest pressures induced in adjacent discs, in study I-II, were to a great extent noted during corresponding high pressurized discograms. However in Study III the three highest magnitudes of pressure increase in adjacent discs (42, 21 and 21 psi respectively) were induced by quite low pressurized discograms (Figure 36). This illustrates that in spite what is currently considered as low pressurization pressure induced increase in adjacent discs, with potential to elicit pain, cannot be excluded.
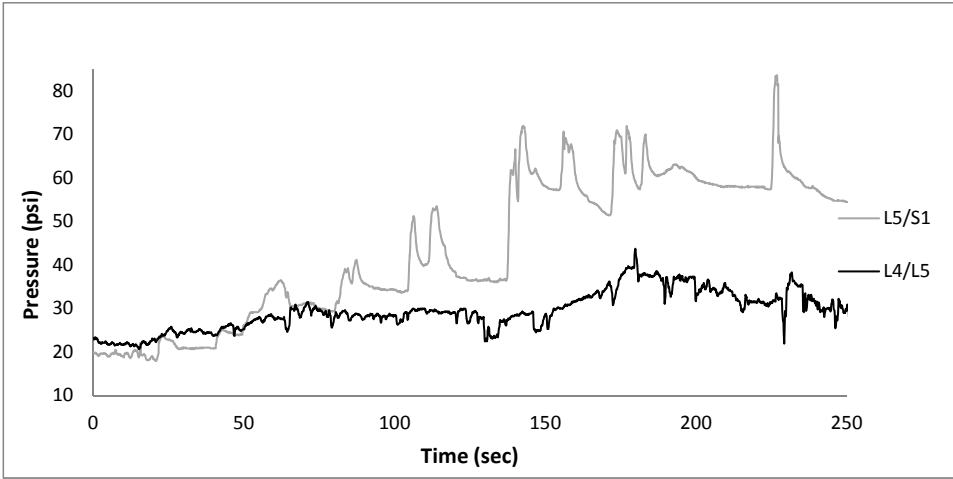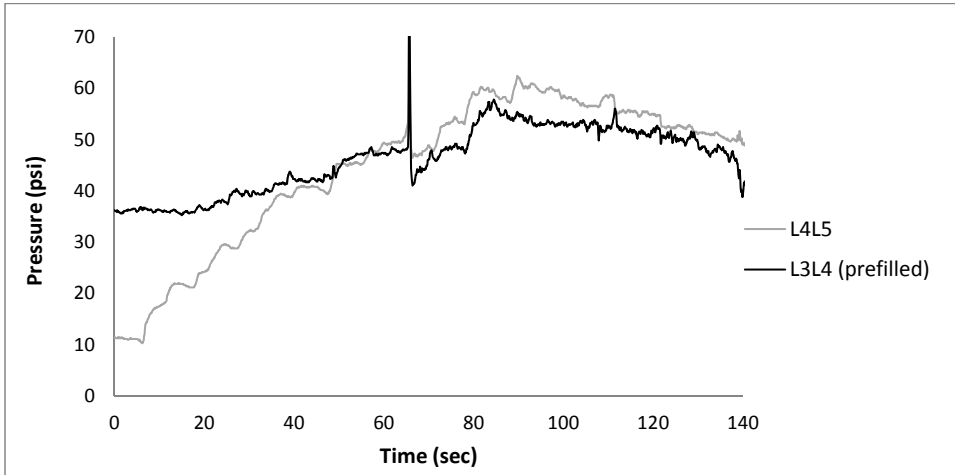
a) Injecting L5/S1 (DDD 4) induced a pressure increase of 21 psi in the adjacent L4/L5 (DDD 5) despite pressurization of only 42 psi a.o.p. at manometer readout (60 psi a.o.p. at sensor readout).
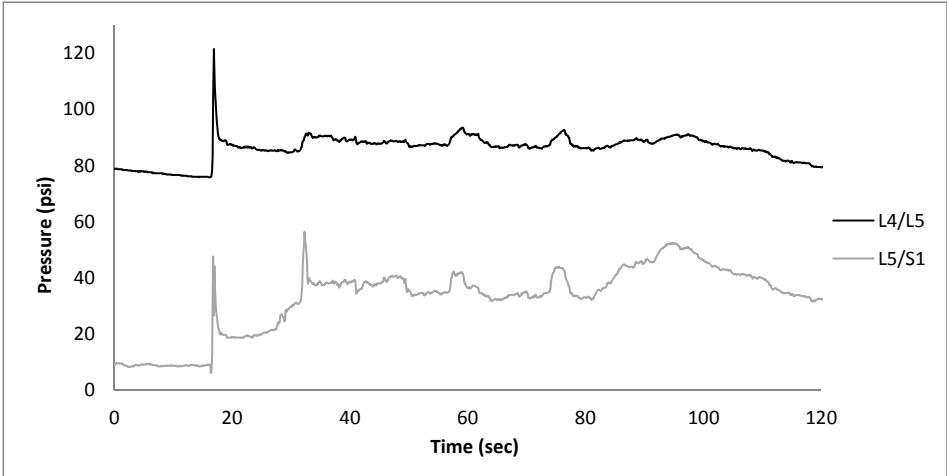
b) Pressurization of L5/S1 to 29 psi a.o.p at manometer readout (48 a.o.p. in NP) induced an increase of 42 psi in the adjacent prefilled non-degenerated L4/L5.

c) Pressurizing L4/L5 to 34 psi a.o.p (manometer readout,) respectively 50 a.o.p at sensor readout, induced an increase of 21 psi in the adjacent L3/L4. When L3/L4 was injected already 12 psi a.o.p. induced intense pain (8/10 NRS) why the induced pressure increase of 21 psi in L3/L4 when injecting L4/L5 must be assumed to induce pain. Consequently the concordant pain upon L4/L5 injection might emanate either from the disc itself, from the adjacent pain sensitive disc or from both.

Being able to reduce as many false positive responses as possible is crucial in optimizing the validity of discography and thereby also optimizing treatment decisions based upon it. O'Neill et al. performed discography on 838 discs in 253 patients [144]. Of the positive discograms 51 discs were painful already at 0 psi distention pressure, i.e. as soon as the contrast entered the disc. These discs were called contact-sensitive by the authors since elicited pain was assumed to be chemically rather than pressure induced. In 390 discs some pressure was needed to provoke pain; pressure sensitive discs. If analyzing the latter discs, a bimodal pattern was found with a peak pressure at 8 psi and an additional peak at 30 psi. The authors suggested that the reason for this bimodal pattern could be two separate disc populations with the group demanding higher thresholds to provoke pain being false positive. The authors' implied that at 50 psi a.o.p. all discs are false positive, at 25 psi approximately 50% and at less than 10 psi a.o.p. discs are either true concordant pressure sensitive or contact sensitive. Their data of false positive responses in quite many discograms are supported by several others [146, 189]. Pressure transfer might be a likely explanation for these findings. Applying O'Neill's data, a very low injection pressure i.e. maximum 10 psi a.o.p. would be one way to perform discography with minimal influence on adjacent discs.

It should be emphasized that even if the disc itself since long has been believed to be the primary pain source in CLBP [8, 223, 248, 249] adjacent structures like

the vertebral EP [83, 111] the adjacent spongy bone [81, 250], the FJ and the SI joints [11, 102, 112] have also been regarded as possible pain generators. The finding of pressure transmission has revealed that the disc cannot be evaluated as one separately evaluated unit when it comes to pressure-elicited discogenic pain. Rather disc injection seems to affect also adjacent discs and it is reasonable to assume that also surrounding EP, muscles and ligaments are affected. It has been shown for example that the pressure increase can activate afferent nociceptors [151]. Nociceptors in chronic pain patients might become sensitized and respond to low mechanical thresholds [8, 144, 194], thus respond with hyperalgesia already at low pressures [144, 194, 251]. This occurs in the primary stimulated area (painful area) but also further away [194] suggesting that pain induced by a discogram can originate from adjacent pain sensitive tissue. Such sensitization probably is aggravating the impact of pressure transmission.

Negative control discs

International standards advocate a negative control disc to address a disc as positive [137, 144], which often results injecting a non-suspected painful disc, i.e. only slightly degenerated or not at all. Even recently published studies with strict PCD criteria, use upper cutoff pressurization of 80-100 psi a.o.p. in such discs [93], why such high pressurization is within clinical context. Pressurization of a non-degenerated disc, inducing a pressure increase in adjacent degenerated disc is exemplified in Figure 37. One can speculate that pressure transmission when pressurizing such control disc might induce pain in an adjacent painful disc. Thereby the control disc might be falsely painful, and consequently true "positive" discs are overlooked due to lack of negative control discs. Thereby pressure transmission in addition to be a potential source of false positive responses also can act as a confounding factor by means of false negative responses.

Figure 37. Induced increase in a disc adjacent to non-degenerated discogram
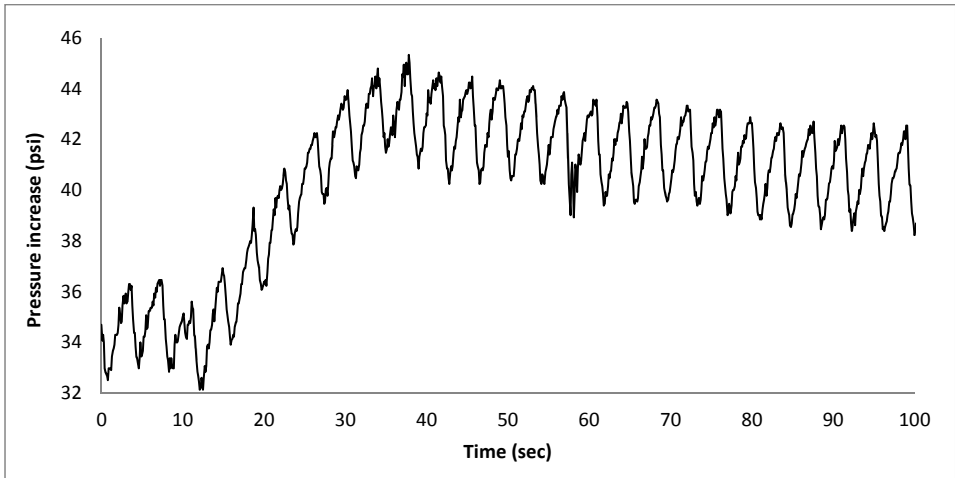
A pressure increase of 8 psi was induced in an adjacent degenerated L2/L3 when injecting a non-degenerated L1/L2 up to 100 psi above baseline. Only the pressure in the adjacent disc is displayed. Note the respiratory oscillations superimposed on the pressure curve.

Degenerated discograms

Discography is meant to be used mainly in discs with suspected discogenic pain. As shown in study IV majority of painful discs had ≥ grade 3 DDD, why it is of greatest interest if pressure transmits even when injecting degenerated discs. When a disc degenerate its biomechanical properties alter, reducing among others its capacity to withhold pressure [17, 89-91]. It was therefore hypothesized that if pressure transmits also in degenerated discs it would reasonably do so with a lower magnitude compared with non-degenerated discs. Our hypothesis seemed correct since pressure transmission was not detected in all adjacent discs in study II as opposed to the preceding study with a pressure increase averaging 11% above baseline compared with 16% in the non-degenerated spines. On the other hand in study III none of the discograms with Pfirrmann 2 or less induced an increase in adjacent discs. This finding was somewhat surprising since healthy discs have the capacity to withheld intradiscal pressure better than degenerated ones and you would for that reason expect those to transfer pressure better. Pressure transmission was mostly observed when injecting disc with Pfirrmann 4 (Table 14). Any obvious reason for this could not be detected. Accordingly pressure transmission exists also in degenerated discograms and cannot be excluded in spite of low pressurization (Figure 36a). In spite of slow twist injection with manometer, unintended dynamic peaks caused corresponding peaks in the adjacent disc (Figure 36a-c).

Table 14. Pfirrmann classification of discograms inducing pressure increase in an adjacent disc

		No. of discs inducing pressure increase
Pfirrmann classification	**3**	2
	4	9
	5	1
TOTAL		12

Prefilled versus non-prefilled discs

The majority of adjacent discs displaying pressure increase were pre-filled discs. One would assume that prefilled discs generate higher magnitude of pressure transmission since they are distended with a higher baseline pressure. Significant differences in the magnitude of pressure increase between prefilled and non-prefilled adjacent discs were not found.

"Pre-filling" discs might seem questionable, but it reflects the typical clinical scenario where the contrast is not aspirated but left within the NP to gain CT imaging of the internal disc morphology (Figure 8). During withdrawal of the needle, the injection canal is probably sealed by the annulus, preserving the high intradiscal pressure. In the light of the present findings, sealing of this kind might contribute to the transfer of pressure to adjacent discs. It should be emphasized that not all prefilled discs have a high intradiscal pressure, exemplified in Figure 38.

Figure 38. Last two twist injections of a discogram and an adjacent prefilled disc with low pressure
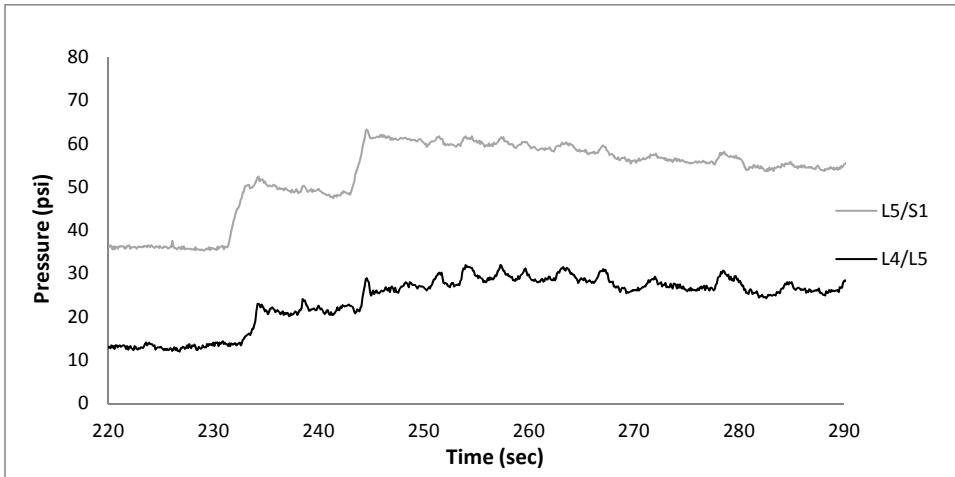

Injecting L5/S1 induced an increase of 21 psi in the adjacent prefilled L4/L5. Concordant pain was evoked upon injection in L5/S1 at 25 psi a.o.p. and when previously injecting L4/L5 concordant pain was induced already at o.p. Was the pressurization of L4/L5 sufficient to elicit pain in L5/S1 or did the concordant pain response in L5/S1 stem from the prefilled painful L4/L5?

Even if it was more common in study III that pressure transferred if the adjacent disc was prefilled also non-prefilled adjacent discs displayed significant pressure increase (Figure 39).

Figure 39. Example of the pressure reaction in a discogram and an adjacent non-prefilled disc (a) and the fluoroscopy image of the corresponding discogram (b)
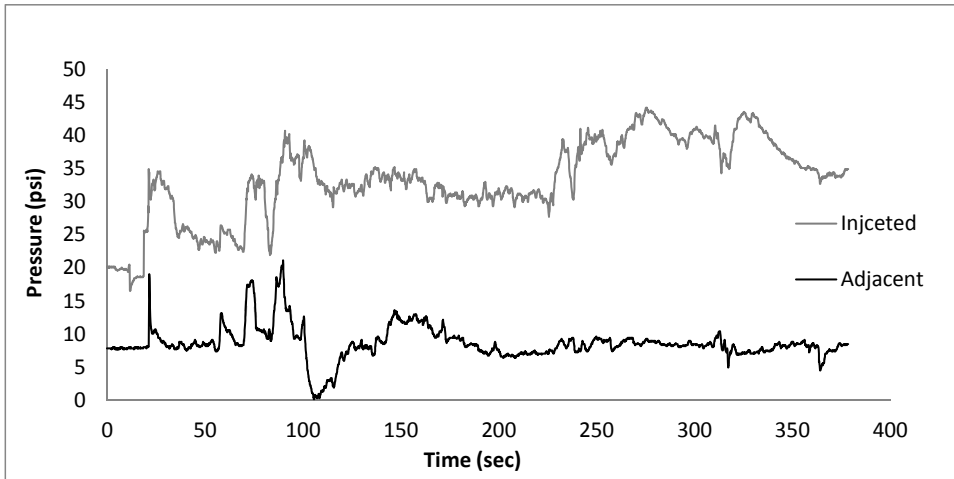

a) A low pressurization discogram induced an increase of 13 psi in the caudal degenerated adjacent disc.
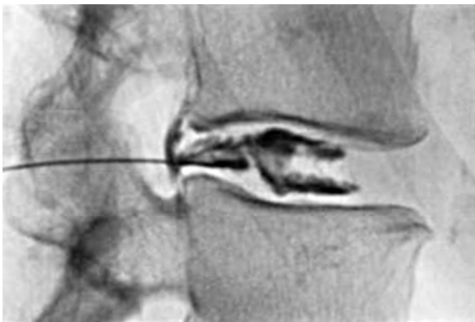
b) At fluoroscopy contrast was seen leaking out through a dorsal fissure in the L3/L4 disc, making the pressure drop both in the injected and the adjacent disc (at 100 sec).

Another example of induced pressure increase in an adjacent non-prefilled disc is shown in Figure 40. It should be noted that this was under best case scenario circumstances; i.e. injection by automated technique with slow injection avoiding dynamic peaks, no muscle tension, no pain etc.

Figure 40. Pressure registration in a degenerated porcine discogram inducing a pressure increase in an adjacent non-prefilled disc a), the latter registration is also displayed magnified (b)
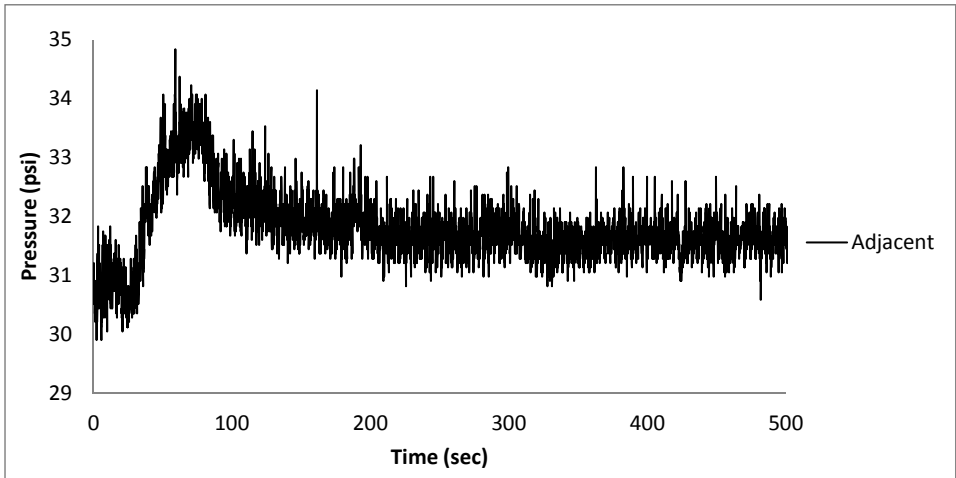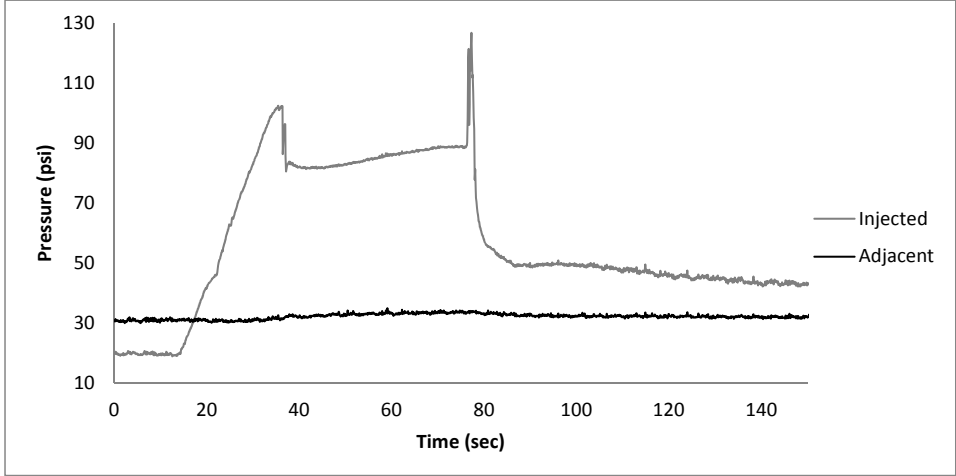
Apparently pressure transmission exist also in adjacent non-prefilled discs and induced pressure can occur independent if the adjacent discs are prefilled or not and seems to be of clinical relevant magnitude either way.

Impact on more distant disc levels

In this thesis the aim was to investigate the intradiscal pressure reaction in adjacent discs next to the discogram. In study I however, the potential transfer further away was investigated in one animal by measuring pressure in L2/L3 when injecting the discs two and three levels caudally. When injecting L4/L5 and L5/S1 the pressure in L2/L3 increased with 4 psi respectively 2 psi. Even if this pressure increase was relatively small it is important to emphasize that it was recorded up to three discs away from the injected one and in addition in an anesthetized sedated animal.

It is reasonable to assume that a similar phenomenon also exists in clinical discography in which the magnitude of pressure increase was higher, sometimes of a magnitude similar to that in the injected disc (Figure 36b). The highest magnitude of induced pressure increase in this thesis was 42 psi in an adjacent non-degenerated disc. Considering that pressure transmission seems to affect even discs further away this high magnitude probably influence discs and adjacent structures more distant in the lumbar spine, making the effect of pressure transfer even more widespread. The question that ought to be raised is what is tested with discography? The argument for discography is that it is the only diagnostic tool able to test separate discs for pain, which seems as a flaw considering the current results.

Reason for pressure transmission

The mechanisms behind the transfer of disc pressure from one level to an adjacent one, and seemingly also to more distant discs, are probably multifactorial. Factors contributing to pressure transmission could be;

- muscle contraction elicited by postural reflexes
- mechanical impact of the injected contrast
- pain-elicited muscle contraction

The findings of pressure transfer during discography in anesthetized pigs seemed to exclude any influence of pain elicited muscle contractions which could generate or add to the pressure transmission. This suggests that factors others than just pain, e.g. postural reflexes elicited from the annulus or adjacent ligaments and muscles could be involved in pressure transfer. The injection of contrast into the disc and subsequent changes in e.g. disc height could have elicited postural muscular reflexes affecting the disc pressure and the transfer of pressure, since no muscle relaxants were used. Such postural spinal reflexes have been assumed to explain the multilevel and bilateral muscular contractions found at experimental stimulation of the periphery of the pigs´ AF [252, 253]. The disc puncture at discography is likely to elicit similar muscular contraction stimuli.

Other hypothetical causes of pressure transfer could be the direct mechanical impact the injected contrast will cause. In a constrained structure like the spine a change of e.g. disc pressure directly would influence upon neighboring structures. An increase in one disc could induce an increase or decrease depending on the biomechanical properties of the disc, as shown in study II and exemplified in Figures 30 and 32.

In study I and III only the pressure reactions during injection were monitored. However when extending the observation to include also 15 minutes after injection as in study II, 89% of the adjacent discs displayed an increase. This gradual development of a pressure in some adjacent discs, sometimes with peak pressure after injection and sometimes with initial pressure decline simultaneously with the pressure peak in the discogram, could possibly be attributed to the time dependent characteristics of the intervertebral disc. Creep is load dependent and has two major time parts, one rapid (< 1 minute) where strain is relatively large and one more extended over time, where strain is less marked [254, 255].

Injecting a disc probably results in an expansion of the distance between the EP [37] and a corresponding diminish may occur in the adjacent disc. Consequently, a drop in pressure can be noted in the pressurized disc over time while in the adjacent the opposite occur (Figure 32). The rate at which these changes happen is dependent on segmental mechanical properties. Thus the slope for the corresponding pressure-time curve can differ between discs, particularly if a comparison is made between degenerated and non-degenerated discs. This slow pressure building might besides posing a threat against specificity also in an unknown way influence the result of a second discogram often performed directly after completion of the first one. These pressure reactions indicate if nothing else the complexity of intradiscal pressure and that the pressure in one disc probably cannot be evaluated independent of the other.

The recent finding of dichotomizing nerve fibers may at least theoretically transfer both postural and pain reflexes from a pressure distended annulus to the multifidi and other mono- and polysegmental erector spinae muscles [128]. Removal of paravertebral tissue as well as altered biomechanical properties in thawed discs is probably the explanation why Menkowitz et al. did not show pressure increase in adjacent discs despite pressurization up to 367 psi in 26 cadaver discs [256].

The magnitude of transferred pressure was greater in the clinical scenario compared with the experimental studies with a mean increase in adjacent discs of 62% above baseline compared with 11% in degenerated porcine spines. Speculatively, this might be a consequence of an additive effect of pain generation and subsequent muscle contractions and possibly also pain-induced patient body movements, circumstances eliminated in the animal studies. In

several cases pressure spikes with very high magnitudes were noted when the patients felt pain, both in the injected as well as in corresponding adjacent discs. When intense pain is generated it is impossible to be completely still. Even minor movements generate muscle contractions, likely contributing to those pressure spikes as illustrated by Figure 36c. In some cases a distinct pressure reaction was noted when contrast leaked out in a fissure (Figure 39) with a corresponding decline in pressure.

Reason for lack of pressure transmission

All of the discs in study I induced an increased pressure in the adjacent discs. The reasons for lack of such a reaction in some adjacent discs in the subsequent studies of degenerated spines are speculative. Significant number of discs in study II displayed a delayed increase, delays that not were recorded in study III for ethical reasons and therefore probably missed.

In order to eliminate artifacts, probably more likely to occur in degenerated discs with poorer hydrostatic environment, harsher criteria for pressure increase were set in both studies of degenerated spines, which might be another reason. Pressure reactions were detected during some part of the registration in some of the adjacent discs "without pressure increase" but, due to the "creep effect", this increase was masked, as it did not fulfill the criteria of ≥ 2 psi above baseline (Figure 41). The pressure increase was therefore probably underestimated especially in study III. However it cannot be excluded that some of the four discs in study I with pressure transmission < 2 psi were false positive regarding pressure increase.

Figure 41. An adjacent disc not fulfilling criteria for induced pressure
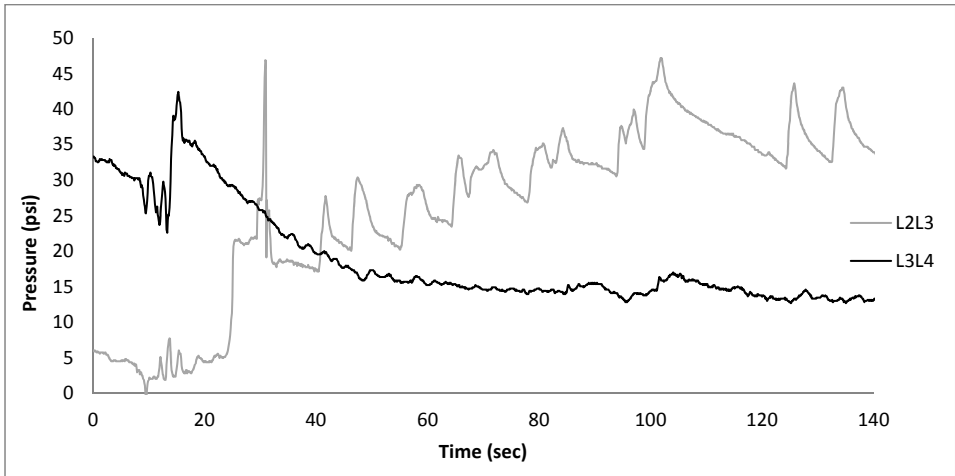
In the adjacent L3/L4 a pressure increase was induced (90 sec) but was masked due to the creep effect.

Another likely reason influencing the results, especially in study III, could be related to how pressure was measured. Ideally the perpendicularly sensing transducer needs to be placed in a hydrostatic environment, without mechanical influences from surrounding solid structures, which cannot be guaranteed in a severely degenerated disc. Some registrations were excluded probably due to such artifacts. Furthermore, pressure probably varies within NP itself, particularly in more degenerated discs with multiple annular fissures.

Pressure transmission in the literature

Induced pressure increase in adjacent discs during clinical discography has not previously been reported. There are some studies that indirectly point to its existence. Derincek et al. [163] reported that, when anesthetizing positive discograms with abnormal morphology, the pain in an adjacent previously painful disc with normal morphology resolved during a repeat discogram, implying false positive responses initially. In addition, more recent studies report that pain in positive discograms does not resolve when anesthetized, suggesting false positive responses. Derby et al. [189] reported that if greater than 80% pain relief upon anesthetics reflects a truly painful disc, then provocation discography has a false positive rate of 72-80%, since only 20-28% of patients receiving analgesics in painful discograms met the criteria for pain relief. The authors assumed that discography generates pain from other elements in the spine that are not anesthetized. Alamin et al. [146] reported discordancy

of 46% between functional anesthetic discography (FAD) (a catheter with anesthetics inserted into the disc followed by the patient trying to provoke pain by their ordinary behavior) and PCD, with FAD less likely being positive. They argued that since pain did not resolve when anesthetizing positive discograms such discs were false positive with pain induced likely originating from other sources. Schleissbach et al. [251] hypothesized that generalized hypersensitivity may be a cause to false positive responses not only at the level for disc injection but also further away.

Automated versus manual injection

Automated injection instead of manual injection is advocated to avoid operator biases like fast injection, dynamic pressure peaks etc. [92, 93, 197]. These afore mentioned cited studies recommend that if manometer injection is used it should only be done so by an experienced discographer and at low speed. The discographer in study III was experienced and used low injection speed; despite this dynamic peaks occurred (Figure 36 & 39). Such unintended dynamic pressure peaks was one reason for higher pressure magnitudes in study III compared with the automated scenario in the study I and II. This would strengthen arguments for usage of only automated discography although that will not completely eliminate pressure transmission to adjacent disc. Since automated injection was not used in the clinical study, it is unclear whether the increased magnitudes of the induced pressure in adjacent discs are due to injection technique, to aggravation secondary to pain and muscle reflexes or more likely, a combination of both.

As Derby et al. [93] pointed out with manual injection (manometer or conventional inflation syringes) it is impossible or very difficult to inject at a rate less than 0.01 ml/seconds, which is recommended to reduce differences between externally measured and intradiscally measured pressures [190]. Based on this they recommended automated injection assuming that increased volumes are innocuous, since automated injection in their study generated increased volumes compared with manometry. Considering the likely mechanical effect of pressure transfer increased volumes distends the discs more and thus cannot be considered innocuous in terms of pressure transmission.

Disc pressure recorded in NP versus externally

Another source of discography error is that modern manometric technique only registers post-syringeal static pressure and not the real dynamic pressure that induces pain [93]. Intradiscal pressures recorded externally differ from "true" pressures in NP, with manometer readouts either higher or lower compared with NP pressure [145, 190, 197].

Speed of injection, interconnecting tubes, needles etc. influence the pressure recorded [190, 197]. Differences between static and dynamic pressures has been reported as minor if the injection speed is below 0.07 ml/seconds while as low speed as 0.01 ml/seconds has been recommended to reduce differences between externally and intradiscally measured pressures [93, 197]. The differences in our study between NP and manometer pressure can be explained by variations in injection speed despite assumed constant twist injection. This illustrates the likely unconscious pressure errors in many discography studies using manometer.

Impact on literature

Even if there are no international discography standards, current recommendations include pressure registration with concordant pain provoked at less than 50 psi a.o.p. [99, 110, 153, 161]. In addition one negative control disc is recommended [91, 144, 153, 251] in which it is common to use a cut off value of 100 psi a.o.p. [50, 97, 110, 144, 145, 147, 148, 155, 166, 177, 188]. In spite of such recommendations there are still discography studies published with no pressure registration at all (i.e. just by thumb resistance).

It must be highlighted that even studies performed with a pressure limit of 100 psi a.o.p. must be re-evaluated in the light of pressure transmission. As shown in this thesis also lower pressurization induces an increase in adjacent discs why pressure transmission during discography likely constitutes a confounding factor even in clinical discographies with low pressurization. Thus old conclusion and "truths" about discography and discogenic pain must be questioned.

Diagnostic studies of accuracy attempt to assess the methods ability to detect the disease [257]. If disease is considered pain provoked in pressurized discs the accuracy of discography must be challenged after the findings of pressure transmission. As Shah et al.[151] pointed out: A diagnostic test with high sensitivity (low rate of false negative) is most useful as screening tool or ruling out the disease and conversely a diagnostic test with high specificity (low rate of false positives) is more useful in confirming the disease. The international recommendation is to use discography as a confirmatory test rather than a screening tool, i.e. demanding high specificity.

Discography as a diagnostic method provoking pain on a single disc level must be questioned, thereby challenging the validity of discography. This novel finding, in combination with the recent finding that even small gauge needles induce disc degeneration [147], strongly suggests that research must focus on finding alternative diagnostic methods regarding discogenic pain.

HIZ

Principal findings

The detection of HIZ was not influenced by axial loading. With PCD discogenic pain can neither be confirmed when having HIZ nor ruled out in discs without HIZ.

Impact of axial load

The hypothesis, that the increased pressure induced by alMRI could change the detection of HIZ, was not confirmed since no significant change between the appearances of HIZ was detected before or after axial loading. However in accordance with two case reports a small discrepancy in HIZ was discovered between axial loaded and conventional sequences, exemplified in Figure 42 [229, 245].

Figure 42. Example of HIZ appearance at conventional MRI (left) and at alMRI (right)

T2-weighted sagittal images of a patient in which HIZ was observed at L3/L4 and L5/S1 at conventional sequences (left) whereas when applying axial load HIZ was not shown at L5/S1 (right). Note the increased lordosis at the alMRI.

Reasons for the discrepancy exemplified in Figure 42 are speculative but we have categorized possible explanations into three main groups;

1) Different intensities of HIZ

The definition of HIZ is that the signal within posterior annulus must be as intense as the adjacent CSF [109]. However less bright zones, ranging from "low intensity zones" (LIZ) to "medium intense zones" (MIZ) have been described [109, 158]. Such less intense zones have been hypothesized to represented either less inflamed tears or non-activated tears that may become activated and more intense (HIZ) [109]. This displays that a spectrum of intensity variations within the posterior annulus exists [166, 258]. Quantitative digital signal analysis, relating HIZ to CSF signal, has been used to classify HIZ into sub-categories [158]. Recently a quantitative comparison of HIZ between patients with and without LBP was performed with significantly brighter intensity among LBP patients [242]. In the current study HIZ was only graded as existing or not but since the impression was that HIZ often varied in intensity/shape/size between the unloaded and loaded MRI the lack of quantifying HIZ is a limitation that possibly influenced the results.

2) Level dependent alterations of HIZ

The migration of NP in anterior or posterior direction varies with different positions and axial loading shown by different positions in MRI [239, 259]. The greatest differences in sagittal migration was found at L4/L5 and L5/S1 discs [259]. Such level dependent changes during axial loading might be another explanation to the discrepancy of HIZ appearance from one examination to another in the same patient. It is possible that vascularized granulation tissue is more or less affected by changes in intradiscal pressure. The level at which the HIZ is located decides the pressure during loading and also if the peak stress will appear at the anterior or posterior part of the disc. A HIZ situated at L1/L2 may be differently pressurized compared with a disc in for example L3/L4 level. At some discs the axial load might result in a disc pressure that also might exceed the intravascular pressure of the granulation tissue in HIZ, obstructing the vascular supply of the latter. Theoretically this could lead to a reduced signal in the posterior annulus.

3) Observers validation

Despite above discussed topics the most probable explanation to the discrepancy in HIZ between the MRI examinations are related to partial-volume effects and the observers' subjective validation of HIZ, deciding if zones are as bright as CSF or less. With a 1.5 Tesla the signal to noise ratio ought to be high enough for detecting HIZ. On the other hand HIZ might be undetected even in 3-4 mm sagittal images if the granulation tissue is too small or less vascularized [165].

The current study showed no significant change in HIZ between conventional and alMRI. Future research ought to include quantification possibilities to clarify if axial load affects HIZ in terms of intensity/size/shape.

HIZ and discogenic pain

Sensitivity and specificity
This PCD study in contrast to many previous studies showed HIZ to be a poor predictor of discogenic pain. The PPV of HIZ in terms of exactly reproduced pain was only 39% compared with between 83-95% in studies favoring HIZ as a reliable marker of discogenic pain [105, 108, 109, 169, 176]. A potential major reason for discrepancies between the current and previous studies is that controlled pressure registration was not used in the majority of numerous studies correlating HIZ and discogenic pain [105, 108, 109, 111, 164, 165, 167, 168, 176-178], with subsequent high risk for false positive responses [144, 162].

Among studies correlating HIZ and discogenic pain only O´Neill et al. and Carragee et al. used PCD [158, 166]. O´Neill et al. categorized HIZ into mild, moderate and hyper-intense with sensitivity as low as 15-44% although with higher specificity, 89-98%. Carragee et al. [158] concluded that HIZ was not a reliable marker of symptomatic discs since the prevalence was 25% in asymptomatic subjects compared with 59% in symptomatic. Approximately 70% of HIZ were painful at discography independent if the subjects had LBP or not. The sensitivity in the current study (44-49%) resembles the higher range in the study of O´Neill et al. but with lower figures regarding specificity (69-73%).

Discs with HIZ are sometimes positive at discography sometimes not why HIZ appears to be an unspecific morphologic sign. Can discs without this sign be excluded as discs without pain then? Chen et al. [120] concluded in a meta-analysis (without PCD as inclusion criteria) concerning the role of HIZ in discogenic pain that HIZ is limited as a sign of discogenic pain when positive but when negative pain can be excluded. The current study performed with PCD, showed however that discogenic pain neither can be confirmed when having HIZ nor ruled out in discs without with a NPV of 76%.

HIZ and pressure transmission
With the phenomena of pressure transmission in mind, with up to 42 psi increase in adjacent discs with controlled pressure injection, it is probable that the increase in adjacent discs is even higher when performing discography without such controlled conditions. Not using PCD was quite likely a strong confounding factor to many previous results regarding HIZ and discogenic pain. This fact makes previous results dubious, especially considering the high magnitude of pressure transmission revealed in this thesis.

Pressure transmission cannot be excluded in the current study but mean maximum pressure was low likely limiting false positive discograms. The few studies previously investigating HIZ and discogenic pain with PCD [158, 166] have not reported mean maximum pressure why the impact of pressure transmission in those studies is difficult to estimate.

HIZ and pain grade
The use of 4-graded pain scale instead of three or less may also have influenced discordant results between the current and previous studies. This is why also the combination of similar/exact pain reproduction (i.e. concordant) was taken into account when PPV became higher though still only 70% and NPV only 47%.

Time-Interval MRI and discography

Composed of granulation tissue HIZ can be assumed to change over time [165]. Mitra et al. [260] investigated the evolution of HIZ over time and found that at follow up MRI after 6-72 months 26% of the 64 initially identified HIZ had resolved. Fourteen percent had improved, 19% appeared worse and 41% unchanged. This study show the importance in performing MRI and discography in a close time-interval since a fair proportion of HIZ actually changes during an extended observation time. The time interval between MRI and discography in previous studies correlating HIZ and discography findings varied between 4 weeks [158] to 5 months [111], rendering the current study an edge with both examinations performed within 24 hours.

HIZ and disc disruption

Study IV confirmed previous results with a significant correlation between annular disruption and both HIZ and symptomatic discograms [70, 109, 169, 222]. Ninety-seven percent of the discs with exactly reproduced pain exhibited ≥grade 3 annular disruptions, indicating that annular tears are important in generating discogenic pain. Since HIZ was shown not necessarily painful, this morphologic feature should serve as an indicator of a disc with annular disruptions that might, or might not, be painful.

alMRI and discogenic pain

Principal findings

The primary finding was that no specific MRI parameters (MRI/alMRI/difference between those) predicted discogenic pain provoked at discography.

alMRI induced pain and morphological disc characteristics

Since the majority of patients spontaneously reported exactly provoked pain during the alMRI performed as clinical routine at our department the question was raised to what extent alMRI had the ability to provoke discogenic pain and if concordant discograms displayed any specific morphological features related to the applied load. Study V confirmed that alMRI to a high extent provoked concordant pain. In spite of the fact that discogenic pain is induced or aggravated by positions with increased load such as sitting and flexion [102, 103], recumbent unloaded MRI is traditionally used for imaging the painful spine. Numerous studies, without consensus however have tried to find morphological MRI parameters which can predict painful discs. Dynamic MRI has been shown to reveal spinal alterations not displayed at supine MRI [218, 227, 229, 233, 245]. In all of the patients in the present study morphological disc changes occurred in at least one of the discs at alMRI compared to unloaded MRI. With alMRI the loading conditions are different compared with physiologic upright loading. However in terms of influences on the discs alMRI have similar effects as physiologic loading of the spine in a kneeling position [237]. alMRI increased the lordosis with concomitant disc alterations in height, angel and bulge (Table 12) confirming previous findings during upright MRI and alMRI [218, 229-232, 236]. With 78% of the patients reporting a concordant pain reproduction when load was applied one might assume that some of these induced spinal alterations play a part in the generation of pain. The hypothesis that symptomatic discograms reacted significantly different compared with negative discograms in terms of morphological features when under axial load was not confirmed however.

The only morphological features significantly correlated with pain were the degree of disc degeneration (Pfirrmann classification) at L3/L4 and anterior disc bulge. The former association has been shown previously [183]. The rate of high grade degeneration was however frequent in both discordant and concordant discograms why Pfirrmann classification cannot be used as useful sign of painful discs. Pain at discography was significantly associated with anterior disc bulge at alMRI. The clinical use of the disc bulge to determine positive discs are not convincing since the difference in mean anterior bulge between concordant and discordant bulge was quite small (0.6 mm) and within the range of measurement errors.

That disc degeneration correlated significantly with the majority of the measured MRI features that changed between unloaded and loaded MRI was not surprising. It is known that in the disc molecules are reduced both quantitatively and qualitatively in degenerated discs, resulting in a disc with reduced capacity to resist load. The findings in this study do imply that provocation discography do not correlate well with biomechanically dysfunctional discs.

Without any specific pain-related load-induced morphological disc changes, which this study failed to reveal, discography remain a non-specific diagnostic method of discogenic pain. Proponents of discography might argue that failing in detecting morphological features predictive of painful discs also during alMRI further strengthens the use of discography and its capacity to provoke separate disc levels. Discography, as previously demonstrated in a number of studies and strengthened by this thesis, is a method with questioned validity as a tool provoking pain on a single disc level only. One reason for failing in detecting significant differences in load-induced morphological characteristics between concordant and discordant discograms, might be that a reasonable number of discograms were false positive. Simulating increased disc pressure by contrast injection in NP may selectively reach annular fissures thus producing pain more easily compared with exogenously applied load and cause pain in annular disruptions in otherwise asymptomatic patients [158, 159].

One limitation in the present study was that only traditional qualitative sequences in the MRI/alMRI were performed and that these may not be sensitive enough to detect subtle changes within the disc/paradiscal structures that are induced by increased loading. Quantitative MRI measures, although at an experimental level, appear promising as evaluating discs quantitatively. Borthakur et al.[85] used quantitative biomarkers of the disc; T1rho, and correlated it with discography results. Painful discs showed significantly lower T1rho (indicating loss of PG and water) compared with both controls as well as with non-painful discs in the same patients. Further magnetic resonance spectroscopy (MRS) has been reported to predict symptomatic discograms since the water/proteoglycan peak area ratio was significantly elevated in positive discograms compared with negative ones [261]. These results suggest that non-invasive techniques identifying painful discs can be developed.

Another limitation is that the morphological disc features were not evaluated in an asymptomatic control group.

Pressure transmission

The influence of pressure limits on the results has been discussed in study IV (section *pressure transmission)*.

Clinical application

In the great majority of patients with CLBP discography and alMRI provoked concordant pain. Loading of the spine, alMRI, revealed however no specific clinically useful morphological characteristics in the discs with concordant discograms suggesting that discography do not correlate well with biomechanically dysfunctional discs. The question that must be asked is if it is ethical to continue with discographies because of its questionable validity, its invasiveness potentially inducing disc degeneration and in addition without proven improved outcome in terms of surgical success [2, 103, 140, 144, 146, 147, 150, 189]. Alternative or more sensitive diagnostic methods are needed to understand the load-induced discogenic pain and further development of alMRI and other dynamic MRI instruments may be valuable tools in this research.

Conclusions

Study I

In vivo discography of porcine discs induces a pressure increase in adjacent discs. There was no significant difference in pressure increase between non-injected and prefilled adjacent discs. The pressure increase was of a magnitude enough to elicit pain in an adjacent sensitive disc during discography. If a similar pressure increase is induced in clinical discography it constitutes a potential specificity problem.

Study II

Increased pressure was induced in adjacent discs during in vivo discography in degenerated porcine spines. The pressure in adjacent discs continued to increase also after the injection. Despite "best case scenario discography" with slow automated injection and anesthetized (no motion, no pain) conditions, the pressure increase in adjacent discs was of a level sufficient to elicit pain in pressure sensitive discs. Consequently pressure transmission during discography is a confounding factor even in degenerated discs making the phenomenon a potential cause of false positive responses that needs to be investigated clinically.

Study III

Clinical discography induced a pressure increase in adjacent discs. The pressure increase was of clinically relevant magnitudes and was evident in spite of low absolute pressures in the injected discs. Pressure transmission occurred independent if the injected and the adjacent discs were degenerated or not, making pressure transmission a potential major source of false positive responses. Discography as a diagnostic method provoking pain on a single disc level must be questioned, thereby challenging the validity of discography.

Study IV

There was no significant change in the appearance of HIZ between conventional MRI and alMRI, indicating that the appearance of HIZ is not in any clinically useful way related to the loading of the spine. Quantification of HIZ with and without axial load is needed before any dynamic component completely can be ruled out. HIZ is a poor predictor of discogenic pain provoked by PCD. Discogenic pain can neither be confirmed in discs with HIZ nor ruled out in discs lacking the sign.

Study V

In the great majority of patients with CLBP discography as well as alMRI provoked concordant pain. Loading of the spine, alMRI, revealed however no specific clinically useful morphological characteristics in discs with concordant discograms, suggesting that discography do not correlate well with biomechanically dysfunctional discs. Alternative or more sensitive diagnostic methods are needed to understand the load-induced discogenic pain.

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