From acute to chronic postsurgical pain: The Significance of the Acute Pain Response

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LIST OF PAPERS

This PhD thesis is based on the following four papers, which will be referred to by their roman numerals:

I. Early visceral pain predicts chronic pain after laparoscopic cholecystectomy Blichfeldt-Eckhardt MR, Ørding H, Andersen C, Licht PB, Toft P. PAIN.2014. Nov;155 (11):2400-7. doi: 10.1016/ j. pain. 2014.09.019. Epub 2014 Sep 22.

II. From Acute to Chronic Pain following Thoracic Surgery: The Influence of Different Components of the Acute Pain Response. Morten R. Blichfeldt-Eckhardt MD, Claus Andersen PhD, Helle Ørding DMSci, Peter B. Licht PhD, Palle Toft DMSci (submitted for publication)

III. Shoulder pain after thoracic surgery: Type and Time Course. Morten R. Blichfeldt-Eckhardt MD, Claus Andersen PhD, Helle Ørding DMSci, Peter B. Licht PhD, Palle Toft DMSci. J. Cardiothorac Vasc Anaesth 2016. May. DOI:10.1053/j.jvca.2016.04.032.

IV. Ultrasound-Guided Suprascapular Phrenic Nerve Block is Effective for Prevention of Ipsilateral Shoulder Pain after Thoracic Surgery. A Prospective, Randomized, Double Blind, Placebo-Controlled Trial. Morten R. Blichfeldt-Eckhardt M.D, Christian B. Laursen PhD, Henrik Berg M.D, Jimmy H. Holm MD, Lars N. Hansen MD, Helle Ørding DMSci, Claus Andersen PhD, Peter B. Licht PhD, Palle Toft DMSci. Anesthesia.2016.sept. DOI:10.1111/anae.13621

ABBREVIATIONS

PPP	Persistent Postsurgical Pain
RPA	Referred Pain Area
PTPS	Post-Thoracotomy Pain Syndrome
ISP	Ipsilateral Shoulder pain
HADS	Hospital Anxiety and Depression Scale
QST	Quantitative Sensory Testing
CDT	Cold Detection Threshold
WDT	Warm Detection Threshold
CPT	Cold Pain Threshold
HPT	Heat Pain Threshold
MDT	Mechanical Detection Threshold
MPT	Mechanical Pain Threshold
MPS	Mechanical Pain Sensitivity
WUR	Wind up Ratio
PPT	Pressure Pain Threshold
VT	Vibration Threshold
VAS	Visual Analogue Scale
NRS	Numerical Rating Scale
VATS	Video-Assisted Thoracic Surgery

DEFINITIONS

Definition of pain terms according to the International Association for the Study of Pain (IASP)1

Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Nociceptive pain:Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.

Neuropathic pain: Pain caused by a lesion or disease of the somatosensory nervous system.

Nociceptor: A high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli.

Central sensitization: Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input.

Noxious stimulus: A stimulus that is damaging or threatens damage to normal tissues.

Hyperalgesia: Increased pain from a stimulus that normally provokes pain.

Allodynia: Pain due to a stimulus that does not normally provoke pain.

Analgesia: Absence of pain in response to stimulation which would normally be painful.

Pain threshold: The minimum intensity of a stimulus that is perceived as painful

1. INTRODUCTION

Chronic pain is a major health problem in the western world with a prevalence of approximately 20 % in Denmark and the rest of Europe2,3. Persistent Postsurgical Pain (PPP) is an important and iatrogenic cause of chronic pain and has been reported in up to 6 % in the general Norwegian population and 40.4 % in patients more than 3 months after a wide range of surgeries4. In 10 pain clinics across Scotland, 22.5 % of patients related their chronic pain to surgery5. However, huge variance exists between different kinds of surgery6-8. Although PPP has received increasing attention during the last 20 years, the cause and pathology behind is still mainly uncovered8-10.

Several possible risk factors for PPP have been suggested including demographic factors (educational level, female sex, young age, genetics), psychological factors (catastrophizing, preoperative anxiety and depression, psychic vulnerability), intraoperative factors (open surgery, intraoperative nerve injury, duration of surgery, repeat surgery), and others (preoperative pain-related functional impairment, preoperative experimental pain response, preoperative pain, postoperative chemotherapy or radiation therapy, sleep disturbances). However, the importance of these factors differs substantially between operations and the reports from studies of risk factors are often equivocal11-19.

One of the strongest risk factors for PPP across many fields of surgery is intensity of the acute pain response12,20-27. The mechanism behind is, however, not yet uncovered and it is unclear whether acute pain in itself produce alterations that leads to chronic pain, or if acute and persistent postsurgical pain share a common pathology. Furthermore the acute pain response consists of several different components that may be differently associated to the development of chronic postsurgical pain.
This thesis explores the association between different types of the acute pain response and the developing of PPP in patients undergoing cholecystectomy and thoracotomy and the impact of acute pain control on PPP.

Acute postsurgical pain, mechanisms and components

Acute postsurgical pain is classically categorized as nociceptive, inflammatory or neuropathic8.

Nociceptive pain is the result of activation of high-threshold nociceptors (unmyelinated C-fibers or thinly myelinated Aδ-fibers),by direct intraoperative tissue injury (e.g. cutting of the skin by a scalpel blade) and normally subsides once the operation (and hence the noxious stimuli) is over.28 This is usually the driving force of peroperative pain.

Inflammatory pain is the result of the inflammatory response to tissue injury. This causes release of inflammatory mediators and cytokines producing the “inflammatory soup” that directly sensitize nociceptors, activate “sleeping” nociceptors and causes a cascade of intracellular changes in the primary neuron/nociceptor that both enhance peripheral sensitization29 and causes central sensitization.30 Clinically it is manifested by the four classical signs of inflammation: calor, dolor, rubor, tumor (heat, pain, redness, and swelling). Inflammatory pain outlasts tissue injury for hours to days and is believed to drive postoperative pain until wound healing. It is generally reversible, but will continue as long as a focus of inflammation exists.8

Neuropathic pain is the result of injury to neuronal structures e.g. peripheral nerves. It involves both peripheral mechanisms such as increased axonal sensitivity to mechanical, thermal, and chemical stimuli, possible ectopic pacemaker activity, and central mechanisms that lead to structural changes, neurodegeneration and central sensitization.31

In case of nerve injury, neuropathic pain is present in the immediate postoperative period and can continue as chronic pain. It is believed to be an important factor in the development of PPP and operation types which carry a high risk of PPP often involve frequent damage to peripheral nerves. Importantly, only a subset of patients who suffers intraoperative nerve damage will develop neuropathic pain. Thus neuropathic pain can be regarded as a maladaptive or dysfunctional type of pain as opposed to nociceptive and inflammatory pain, that mainly serve protective functions 8,32.

Visceral pain vs somatic pain

An often overlooked element when classifying the acute postoperative pain response is that it also consists of both a somatic and a visceral pain response after several types of surgery. While there are many similarities between somatic and visceral pain, there are also fundamental differences in peripheral33 and central34 pain processing that may affect the risk of central sensitization and hence the transition from acute to chronic postoperative pain.

Two fundamental differences are distinctive for visceral pain as opposed to somatic pain:

1. Neurophysiological mechanisms are different from those of somatic pain and knowledge from studies of somatic pain can not necessarily be extrapolated to visceral pain35.
   One example is that while visceral dorsal horn neurons show increased excitability upon prolonged noxious afferent stimulation, they do not present the same frequency dependent hyperexcitability as seen in somatic nociceptive neurons, termed “wind up”.34
   Another example is the nociceptor profile of visceral afferents which consists almost exclusively of thinly myelinated Aδ-fibers and unmyelinated C-fibres with polymodal receptors (reacts to a broad range of stimuli, e.g.

mechanical, thermal and chemical). This is opposed to somatic nerves which are usually more specialized and also include myelinated rapidly conducting Aβ-fibres33,36. Furthermore the biochemistry of nociceptors are different. Unmyelinated primary afferents can be classified as either peptidergic (express peptid neurotransmitters, such as substance P and calcitonin-gene-related peptide) or nonpeptidergic (do not express peptid neurotransmitters). Where somatic afferent fibres consists of both classes, visceral afferent fibres primarily consists of the peptidergic type35.

2. Psychophysics (the perception and psychological processing) of visceral pain is different from that of somatic pain35 (in the context of PPP this may be of specific relevance since several psychological factors are predictors for PPP).

This results in several clinical features that are unique to visceral pain:

1. Not all viscera produce pain (this is related to the functional properties of peripheral receptors. Many viscera are innervated by receptors that do not evoke conscious perception; examples are liver, kidney, and pancreas).35-37
2. Visceral pain is not necessarily related to injury (this is also related to functional properties of nerves that innervate certain viscera; examples are cutting of the intestine does not cause pain, but distension of hollow organs like the ureter and bladder produces pain. However, inflammation and ischemia will usually produce pain).35-37
3. Visceral pain is diffuse and poorly localized (explained by the central organization of visceral afferent fibers. The proportion of visceral afferent input to spinal cord neurons is sparse compared to the input of somatic nerves and have a more rostrocaudal spread on several spinal segments, that also receives convergence of input from several different viscera and somatic structures)35-37.
4. Visceral pain is accompanied by motor and autonomous reactions such as nausea, vomiting, sweating and changes in heart rate and blood pressure (this is explained by the proximity of visceral afferent fibres to autonomic ganglia enroute to the spinal cord with the exchange of collateral axons)33,35.
5. Visceral pain is referred to distant parts of the body35,36,38. Visceral pain can be referred to somatic structures (viscero-somatic convergence)39 or other viscera (viscero-visceral convergence)40.

The cause of referred pain is not fully elucidated, but several theories have been proposed: The convergent-projection theory suggest that afferent fibres from different structures (i.e. visceral and somatic) converges on the same dorsal horn neurons and that afferent input from one structure is misinterpreted as coming from another structure39,41,42. The convergence-facilitation theory originally suggested that an afferent input to dorsal horn neurons creates an irritable focus in the spinal cord that make input from other structures appear abnormal. This theory has later been related to the theory of central sensitization38,41. A further development of the convergence-facilitation theory, that has also been named the central-hyperexcitability theory41, suggest that latent connections between convergent afferents and dorsal horn neurons is activated due to noxious stimuli resulting in referred pain 39,41. The axon reflex theory suggests bifurcation of afferents from two different tissues as the cause of referred pain39,41. Alternatively it has been suggested that afferent noxious afferent input can create a reflex arch, whose afferent branch is represented by visceral afferent fibres and the efferent branch by somatic efferent fibres38. Finally, the thalamic-convergence theory suggests that referred pain is caused by summation of input from the injured area and the referred pain in the thalamus or other centers above the level of the spinal cord.

No theory has yet been able to fully explain all characteristics of referred pain, but extensive convergence on spinal neurons of afferent fibres from different somatic and visceral structures has been demonstrated by multiple studies. Neural plasticity is probably fundamental in the development of referred pain, and referred pain has been proposed as an indicator of chronic pain39,41. Thus we hypothesized that the presence of referred postoperative pain would be an early sign of the involvement of central neuroplastic mechanisms and a predictor of PPP.

Central sensitization and the transition from acute to chronic post-surgical pain

As previously stated, the intensity of the acute pain response is one of the strongest predictors of PPP across many fields of surgery. Whether this is a causal relationship or whether acute and chronic postsurgical pain share common pathologies are yet unclear. It has, however, been hypothesized that intense acute postoperative pain, if left untreated, in itself can cause or facilitate the development of PPP8-10.

The theoretical background for this theory is the concept of central sensitization which is defined by the IASP as: “Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input”1.

Central sensitization has been described in multiple animal experiments where intense, repeated or long lasting afferent noxious stimuli creates a state of hyperexcitability of dorsal horn neurons and probably higher levels of the central nervous system. This hyperexcitability can spread to other neurons in the proximity and outlasts the duration of the original stimulus. Sensitized neurons are characterized by increased membrane excitability, increased synaptic strength and decreased inhibition of affected neurons. The molecular mechanisms are complex, but two phases, each with specific mechanisms have been described. An early rapid-onset phase, characterized by rapid changes in the glutamate receptor an ion channel properties. And a later, more prolonged phase, which is dependent of transcription and synthesis of new proteins, which more substantially change the properties of the affected neurons. This later phase is central to neuropathic pain and is thought to be related to many other chronic pain conditions43

The consequence of central sensitization is that normally innocuous stimuli are perceived as pain, making the experience of pain relatively independent of the presence, intensity, and duration of a noxious stimulus. Clinically, presentations of central sensitization include allodynia (pain due to a stimulus that does not normally provoke pain), hyperalgesia (increased pain from a stimulus that normally provokes pain), spread of sensitivity to areas outside the stimulated/injured area (secondary hyperalgesia), aftersensations, and enhanced temporal summation of pain (increasing pain in response to repeated low-intensity stimuli)44.

Induction of prolonged pain hypersensitivity by afferent noxious stimuli has been demonstrated in multiple studies on human volunteers44 and central sensitization contributes to both inflammatory and neuropathic pain43. The importance of central sensitization in other clinical pain syndromes (e.g. fibromyalgia, osteoarthritis, irritable bowel syndrome, PPP etc.) is yet unclear. Especially concerning the spatial spread of hyperexcitable central neurons and to what extent widespread pain and widespread pain hypersensitivity can be explained by central sensitization 44-46.

Nevertheless the theory of central sensitization has led to several attempts to prevent PPP by improved perioperative analgesic treatment based on the concepts of pre-emptive analgesia47 (analgesia initiated before injury) and preventive analgesia48,49 (analgesia aimed at "blocking" any pain signals from injury until wound healing). The effect of these strategies remains to be finally clarified 50-53.

Acute and persistent pain following cholecystectomy

Persistent pain after laparoscopic cholecystectomy, post-cholecystectomy syndrome, is a common complication with an incidence ranging between 3-56 %6,7,54. The etiology is believed to be multifactorial and include sphincter of Oddi dysfunction, bile duct stone, and other diseases. In many cases, however, the cause remains unknown and visceral hyperalgesia and central sensitization have been suggested to be part of the pathophysiology55,56. Several risk factors have been identified including female gender, longstanding preoperative symptoms, and psychic vulnerability6,57,58. As in several other types of surgery, early postoperative pain has been shown to be a significant risk factor of persistent pain22, but little is known about this relation and it has been sparsely studied.

The acute pain response after cholecystectomy consists of a somatic, a visceral and a referred pain component59,60. In most subjects the somatic pain component is the worst followed by the visceral one, and the referred pain component is the least troublesome61. It is unknown which part of the acute pain response is associated with chronic pain, but the chronic postcholecystectomy pain is believed to be of visceral origin. Hyperalgesia in the referred pain area (RPA) has been discovered in subgroups of patients before62 and after55 cholecystectomy and has been suggested to be an indicator of central neuroplastic changes and central sensitization38,41.

Acute and persistent pain following thoracic surgery

Persistent pain after thoracotomy (post-thoracotomy pain syndrome, PTPS) affects 21-61% of patients8,63-65 and reduces activities of daily living in up to 60% of patients66,67, yet the cause of PTPS has not been established68,69. Though conflicting evidence exists, sex, age, and preoperative pain have been identified as possible predictive factors20,70-75. Again, acute postoperative pain is one of the strongest predictors of PTPS20,70-72. Intraoperative nerve damage has been suggested as a cause of both acute and chronic postoperative pain8,32,68,76-79, however several studies have indicated that nerve damage is only part of the cause for PTPS73,80-83. Central neuroplastic changes, caused by intense postoperative pain, leading to central sensitization have also been proposed as an important mechanism9,82,84,85.

The acute pain response after thoracic surgery primarily consists of chest pain and shoulder pain ipsilateral to the operation with chest pain usually being the dominating pain86. Nevertheless, ipsilateral shoulder pain is present in up to 88% of patients87-90 and usually described as moderate to severe89,91,92. The time course of ipsilateral shoulder pain (ISP) has not been well described (the pain is expected to last 3-4 days, but has also been reported in up to 23-59 % after 12 months as secondary findings)63,93-96.

Postoperative chest pain is believed to be partly somatic (injury to skin and costae) and partly neuropathic (injury to intercostal nerves), whereas the shoulder pain is believed to be partly somatic (injury to muscles and ligaments in the shoulder) and partly referred visceral pain from the mediastinal and diaphragmatic pleura86,88,93,97-100.

Where thoracic epidural analgesia or continuous paravertebral block is effective in relieving chest pain101, the treatment of ipsilateral shoulder pain has proven more difficult. Pharmacological treatment is only partly effective87,89,102. Treatment with interscalene91 and suprascapular103,104 nerve blocks are also only partly effective and additionally result in full motor block of shoulder muscles. Intraoperative phrenic nerve block95,96,105 with infiltration of the periphrenic fat pad near the diaphragm is also partly effective but only for a limited time period and since it requires surgical application it cannot be repeated. Moreover, many sensory fibers have already left the phrenic nerve at this level and a more cranial approach may theoretically be more effective.

Whether some components of the acute pain response after thoracic surgery are more important than others in predicting PTPS has not previously been reported.

2. AIMS OF THE THESIS

The aim of this thesis was to study the relation of the different components of the acute pain response to the development of persistent postoperative pain and to study whether improved control of the acute pain response would change the risk of developing persistent postoperative pain.

We chose two different types of surgery, cholecystectomy and thoracic surgery, with very different types of intraoperative tissue injury but with the common feature that the intensity of the acute pain response predicted persistent postsurgical pain.

More specifically the research questions were:

I) Which components of the acute pain response where associated post-cholecystectomy syndrome 12 months after cholecystectomy.
We hypothesized that visceral and referred pain would be dominating the acute pain response in patients with persistent postsurgical pain.

II) Is post-cholecystectomy syndrome related to hypersensitivity in the referred pain area before or 6 and 12 months after surgery.
We hypothesized that patients with post-cholecystectomy syndrome would have hyperalgesia in the referred pain area before and 6 and 12 months after surgery.

III) How many patients with ipsilateral shoulder pain after lobectomy suffer referred pain and how is this related to time course of pain, intensity of pain and surgical approach.
We hypothesized that most patients with ipsilateral shoulder pain after lobectomy would suffer referred pain and that this would be related to chronic pain, but not surgical approach.

IV) Which components of the acute pain response were associated to post-thoracotomy pain syndrome 12 months after lobectomy.
We hypothesized that chest pain and referred pain would be associated to persistent postsurgical pain.

V) Are there any signs of general hypersensitivity preoperatively or 12 months postoperatively in patients who develop post-thoracotomy pain syndrome after lobectomy.
We hypothesized, that patients with post-thoracotomy pain syndrome showed signs of general hypersensitivity to various sensory stimuli.

VI) Is ultrasound-guided, supraclavicular phrenic nerve block effective in relieving acute and chronic postoperative shoulder pain after major thoracic surgery.
We hypothesized that ultrasound-guided phrenic nerve block would be an effective treatment for ipsilateral shoulder pain after major thoracic surgery.

3. METHODS AND MATERIALS

3.1 DESIGN AND SETTINGS

To answer these research questions, three studies were performed:

- Study 1 was a prospective, observational, multicenter, cohort study of patients for elective cholecystectomy, with follow-up at 3, 6 and 12 months postoperatively. The study was conducted at Vejle, Kolding and Nyborg Hospitals.

- Study 2 was a prospective observational, cohort study of patients for elective lobectomy with follow-up at 12 months postoperatively, conducted at Odense University Hospital.

- Study 3 was a prospective, randomized, double blind, placebo-controlled trial using a parallel group superiority design with a 1:1 allocation ratio. Participants were patients for elective lobectomy or pneumonectomy at Odense University Hospital.

3.2 PATIENTS

All 3 studies only patients >18 years old, with Danish skills appropriate for perioperative questionnaires were included.

- Study 1 included patients scheduled for elective cholecystectomy. Exclusion criteria comprised previous abdominal surgery, diseases in the central nervous system or peripheral sensory disturbances.
- Study 2 included patients scheduled for lobectomy and excluded patients if they were re-operated during the first postoperative week, if they had undergone previous thoracic surgery, suffered preoperative pain in the chest or shoulders, suffered central nervous system disease or had sensory disturbances in the upper extremities.
- Study 3 included patients for elective lobectomy or pneumonectomy and excluded patients with known contralateral palsy of the phrenic nerve, preoperative history of ipsilateral shoulder pain, infection or eczema at the injection site, dementia or similar cerebral condition, pregnancy or acute porphyria.

3.3 PAIN ASSESSMENT

We used different pain assessment methods in all 3 studies. Pain intensity can be measured on several different scales, which are both valid and reliable106-110. Traditionally the 100 mm Visual Analogue Scale111 (VAS) (0=no pain, 100 mm=worst pain imaginable) has been most widely used in research. Thus, we chose the 100 mm VAS for our pain measuring tool in study 1. However, in our experience, some patients – especially among the elderly - found the scale difficult to use and needed extensive explanation of the scale. The same findings has been reported in the elsewhere112-115 and the 11-point numerical rating scale (NRS) (0=no pain, 10=worst pain imaginable) is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for this reason109. Thus, in study II and III we used the 11-point NRS.

Timing and frequency of assessment of acute and chronic pain is a core issue of pain research and the problem is still unsolved. Some studies show good correlation between several assessments of current pain and one retrospective measurement of pain, while other studies show less sensitivity of retrospective pain measurements116-121.With conflicting evidence on the method we chose to let practical matters and tradition in previous studies rule.

In study I, patients were expected to be discharged on the day of the operation and daily contacts with the patients were not possible. To ease compliance in fulfilling the questionnaire we chose 1 daily retrospective registration of maximum and average pain at 8 PM covering the preceding 24h for 7 days. Overall pain, incisional pain (somatic pain component), intraabdominal pain (visceral pain component), and shoulder pain (referred pain component) was registered. This was in accordance with previous studies on the area22,61.

Preoperative intensity during gall stone attacks was assessed as the worst experienced pain attack and the average pain intensity during pain attacks.

In study II, the situation was different. Patients were expected to be hospitalized for 3-4 days and were tended by a dedicated nursing staff, used to extensive pain assessments from previous studies on the department. Thus, we decided to let patients evaluate current pain 5 times per day for 4 days with help from the nursing staff. Overall pain, shoulder pain and chest pain during rest and activity was registered.

In study III, the situation was again slightly different. The primary outcome was presence of shoulder pain after the operation and through study II we learned that presence of shoulder pain was highly variable during the postoperative period. Repeated ratings of current pain carried a risk of missing periods of shoulder pain and we estimated that fewer pain assessments would result in fewer cases of missing data. Thus, we decided to measure pain retrospectively at 6 AM, 2 and 10 PM as the maximum, minimum and average NRS-score during the preceding 8 hours. Overall pain and shoulder pain was registered.

For all 3 studies, intensity of chronic pain was assessed retrospectively as the maximum, minimum and average for the preceding week.

3.4 Psychological evaluation

Patients were evaluated psychologically using the Hospital Anxiety and Depression Scale (HADS)122 preoperatively and at postoperative follow-up (six and twelve months in study 1, twelve months in study 2 and three months in study 3). In study 1 patients was also evaluated using the Psychic Vulnerability Scale123 preoperatively and after 6 and 12 months.

3.5 QUANTITATIVE SENSORY TESTING

Quantitative sensory testing (QST) was performed with the subject in a relaxed supine position at room temperature between 22 and 24 Co. The following parameters were tested according to the protocol described by the German Research Network on Neuropathic Pain (DFNS)124:

Cold detection threshold (CDT), warm detection threshold (WDT), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), wind-up ratio (WUR), and pressure pain threshold (PPT). Vibration threshold (VT) was determined as the mean of 3 series of ascending and descending stimulus intensities using a vibrameter IV (Somedic AB).

In study 1, additional tests were brush evoked allodynia and pinprick hyperalgesia as described by Nikolajsen et al 125. All tests were performed preoperatively and after 6 and 12 months. Test sites were the thenar on the dominant side, the referred pain area and the similar area on the contralateral side.

In study 2, mechanical pain sensitivity (MPS) was tested additionally according to the DFNS-protocol. Tests were performed preoperatively and after 12 months. Test sites were the kontralateral thenar and both shoulders. Additionally, the shoulder area was tested for allodynia and hyperalgesia at 8.00 am on the day after the operation using a brush (SenselabTM 0.5 Somedic AB), a thermroll 25 degrees (somedic AB) and a Von Frey Filament (169 g/mm2).

3.6 DEFINITION OF REFERRED SHOULDER PAIN

In study 2, all patients were examined by the same investigator at 8.00 am on POD 1, to characterize possible shoulder pain. The shoulder area and related muscles were palpated thoroughly to find signs of muscle tenderness. Shoulder pain was classified as referred if there were no muscle tenderness in the shoulder pain area, no shoulder pain could be reproduced by palpating tender muscles in other areas, and shoulder pain was not affected by movement of the shoulder.

3.7 FOLLOW-UP AND DIAGNOSIS OF CHRONIC PAIN

In study 1, patients reporting abdominal pain 3 months after surgery were seen in the office for an interview and further investigations. The following examinations were done until a diagnosis was reached: Physical examination (abdominal palpation, including port sites, evaluation of back pain due to facet joint syndrome), liver function tests, transabdominal ultrasound scanning, gastroscopy and magnetic resonance cholangiopancreatography (MRCP). If no diagnosis was reached, the pain was defined as unexplained pain.

In study 2, all patients were followed up with computed tomography (CT)-scans of the thorax 12 months after surgery. Patients reporting pain in the chest or shoulder 12 months postoperatively, with no other demonstrable pathology or relevant postoperative trauma, was defined as having chronic post-surgical pain.

3.8 PHRENIC NERVE BLOCK

From a pilot study on awake patients complaining of post thoracic surgery shoulder pain, we found that an effective ultrasound guided phrenic nerve block could be achieved both by using anatomical landmarks as well as visualizing the phrenic nerve itself.

Since the phrenic nerve is small and visualizing it sometimes requires superior ultrasound skills, we chose to let the block placement be guided primarily by anatomic landmarks. Patients were placed in the supine position. Under sterile conditions the phrenic nerve was located by ultrasound (1202 flex focus, BK Medical, Herlev, Denmark) using a 6-18 MHz linear array transducer. The brachial plexus was identified superficially and laterally to the subclavian artery and followed cephalad to identify the C5 ventral ramus. The phrenic nerve was identified as a small, hypoechoic structure as it separated from the brachial plexus and passed over the anterior scalene muscle. Supplementary Doppler mode was used to differentiate the nerve from vessels. The injection site was as medial to the brachial plexus as possible, always within 1 cm above the clavicle. If no blood was retracted during aspiration, 10 ml of study solution was injected around the nerve. If the phrenic nerve could not be located, the surrounding structures were used as surrogate markers and the study solution was injected in the space between the posterior border of the sternocleidomastoid muscle and the anterior scalene muscle, medial to the brachial plexus. Injection was considered successful when the space between the muscle fasciae was expanded, not involving the brachial plexus. After injection, a nerve catheter (ContiplexR 20G, B.Braun, Melsungen, Germany) was introduced through the needle (ContiplexR Tuohy 18G, 1.3x40 mm, B.Braun, Melsungen, Germany), the needle was withdrawn, and the catheter fixed with glue (HistoacrylR, B.Braun, Rubi, Spain) and patches. Postoperatively, 10 ml of study drug were given through the catheter as repeated boluses at 8 hour intervals (6 am, 2 and 10 pm) until removal of the chest tube or for a maximum of 3 days. This procedure was chosen because patients were discharged soon after removal of the chest tube and prolonged hospitalization for study purposes was not ethically acceptable.

3.9 PREDEFINED ENDPOINTS, PAPER 4

The primary endpoint was incidence of ISP within 6 hours of the operation postoperative day (POD) 0.

Secondary outcomes were incidence of ISP and pain intensity for ISP and overall pain for the first 3 postoperative days. Additional secondary outcomes were opioid consumption for the first 3 postoperative days, time spent in the Post Anesthesia Care Unit (PACU) (both extracted from patient records), and the incidence and intensity of ISP and thoracic pain, opioid consumption and shoulder function 3 months postoperatively. Shoulder function was assessed using the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire126. Patients completed the DASH-questionnaire on the day before surgery and 3 months after surgery. Data on opioid consumption after 3 months was planned to be extracted from the national prescription database.

3.10 SAFETY PARAMETERS AND ACCURACY OF THE PHRENIC NERVE BLOCK

To assess possible impact of the phrenic nerve block on respiratory function, spirometry127 was performed preoperatively and 2 hours after surgery (Schiller, Spirovit SP-2, Simonsen and Weel). Arterial blood gases were measured 2 hours after surgery. To test for motor blockade, shoulder strength was tested following the American Shoulder and Elbow Surgeons standardized shoulder assessment form128. Forward flexion, abduction, internal and external rotation each obtained a score from 0-5 (0=no contraction, 5=normal power). We defined 0-1 as paralysis, 2-3 as severe paresis and 4 as mild paresis using the

lowest obtained score. Finally, to test if paralysis of the diaphragm could affect postoperative lung expansion, time with chest tube and number of patients with postoperative pneumonia were registered.
To evaluate the accuracy of the phrenic nerve block, bilateral ultrasound of the diaphragm was performed 2 hours postoperatively using a 1202 flex focus (BK Medical, Herlev, Denmark) with a 2-6 MHz convex array transducer. The examination was performed by 1 of 4 different ultrasound operators who were blinded to randomization, allocation, block placement procedure, and any other aspect of patient treatment. Based on visual assessment in the B-mode during deep forceful inspiration, diaphragmatic movement was classified as paralytic (no movement or paradox movement), paretic (reduced movement) or normal (normal movement). In case of paretic or normal movement, maximum excursion of the diaphragmatic cupolas was measured in millimeters using the M-mode. See the appendix for the full ultrasound protocol.

3.11 RANDOMIZATION, ALLOCATION AND BLINDING
For study 3, the hospital pharmacy provided a computer generated randomization list, assigning each number to either ropivacaine or placebo, using block randomization with block sizes of 4. According to the list, a box with 12 doses of study solution was prepacked by the pharmacy with either ropivacaine or placebo (both colorless kept in similar 10 ml plastic vials) for each randomization number. Both vials and boxes were labeled with this number.

Patients were allocated in the operating room at the end of the operation, where each patient was assigned the next consecutive randomization number by the principal investigator. The study solution was thus blinded for all participants, healthcare providers and data collectors and the randomization list was not disclosed until after the 3 months follow-up for the last patient.

3.12 STATISTICAL ANALYSIS
Continuous parametric data are presented as means with standard deviations and compared with the student's t-test. Continuous non-parametric data are presented as medians with 25-75 interquartile ranges and compared using the Mann-Whitney U-test or Wilcoxon's signed rank test where relevant. Categorical data are presented as numbers and proportions and analyzed using the Chi2 or Fisher's exact test where relevant.

In paper 1 and 2, pain scores for each pain component was cumulated into 1 total pain score (TPS) for each pain component and a multivariate logistic regression model was used with backward stepwise selection of independent variables for final determination of risk factors.

In paper 3, the daily max NRS value was defined as the highest daily NRS score in activity or rest. A daily mean NRS score was calculated from all 5 NRS scores during the day for shoulder pain and thoracic pain.

In paper 4, NRS-scores over time were compared using a factorial repeated measures analysis of variance (ANOVA). A ΔDASH score was calculated as: preoperativeDASH - postoperativeDASH and compared using the T-test. ΔFEV1 and ΔFVC was calculated as %-difference from preoperative values: (postoperative value-preoperative value)/preoperative value *100. Based on M-mode measurements, paresis of the diaphragm was dichotomized into severe or mild paresis, defining > 70% reduction of diaphragmatic excursion on the operated side compared to the non-operated side as severe paresis.

A two-sided p-value < 0.05 was considered statistically significant.

4. SUMMARY OF RESULTS

4.1 PAPER I

Recruitment and study flow
One hundred patients were included, 4 patients were lost to follow up. 9 patients complained of chronic unexplained pain 12 months postoperatively

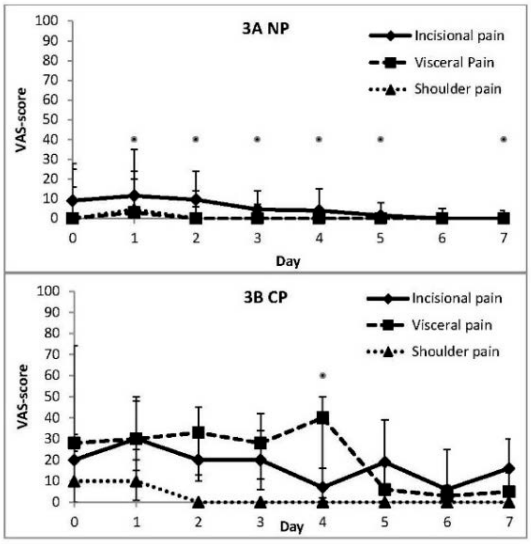
Acute pain response vs chronic pain
The relation between the different pain components in the acute pain response was different in patients with chronic unexplained pain 12 months postoperatively and patients with no pain 3, 6 and 12 months postoperatively (figure 1).
In pain free patients, incisional pain dominated significantly the whole week except day 6. In chronic pain patients, there visceral pain dominated on day 0-4 (only statistically significant on day 4). There were no differences in referred pain.

In a multivariate logistic regression analysis (table 1) only cumulated abdominal pain and number of preoperative biliary attacks per month where significantly and independently associated with chronic unexplained pain after 12 months.

Quantitative sensory testing
No significant differences in preoperative sensory thresholds were observed between patients who later developed chronic unexplained pain and those that did not. No clear pattern was observed 6 and 12 months postoperatively

Patients with chronic unexplained pain after 12 months were more sensitive to deep pressure before, 6, and 12 months after the operation. However, this difference was only statistically significant 6 months postoperatively. Chronic pain patients were also less sensitive to mechanical stimuli 12 months postoperatively but not at previous time points.

Figure 1 - Relation between the different pain components during the first postoperative week



* Statistically significant difference between incisional and visceral pain. Wilcoxon's signed rank test. 3A=No Pain (NP) patients. 2B= Chronic pain (CP) patients. Values are presented as medians with 25 and 75 percentiles

Table 1 – Multivariate analysis.

Variable	Univariate analysis		Multivariate analysis	
	OR	P-value	OR	P-value
No of BA-attacks	1.1	0.017	1.1	0.042
McGill-score for worst BA	1.1	0.03	NS	NS
TPS-incision	1.01	0.026	NS	NS
TPS-visceral	1.01	0.003	1.01	0.007
TPS-shoulder	1	0.815	NS	NS

Result of multiple logistic regression with backward stepwise selection of independent variables significantly associated with chronic pain.
OR=Odds Ratio. BA= Biliary attacks. NS=Not Significant. TPS-incision = cumulated incisional VAS-score for day 0-7. TPS-visceral = cumulated visceral VAS-score for day 0-7. TPS-shoulder = cumulated shoulder VAS-score for day 0-7. Thus the OR for TPS-scores, represents the odds for chronic unexplained pain after 12 months for each change of 1 mm on a 800 mm VAS-scale.

4.2 PAPER II

Recruitment and study flow
Sixty patients were included between January and December 2012. Fifty-two patients were followed up 12 months after surgery, sixteen patients developed PTPS. Twenty-seven patients were followed up with QST.

Acute pain response vs chronic pain
Patients with PTPS 12 months after surgery, suffered significantly more chest pain on POD 0-2, but there were no significant differences in shoulder pain (figure 1). Overall pain was significantly higher in PTPS-patients on POD 0-1.

TPS (analogue to the area under the curve) for shoulder pain, chest pain and overall pain are presented in table 1.

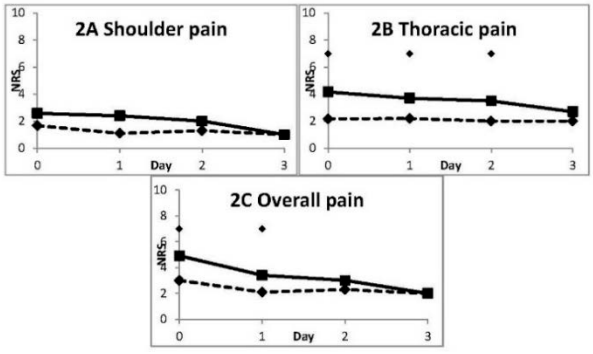


Figure 1 - Daily average NRS-scores from postoperative day 0-3
▬■▬ Post-thoracotomy pain syndrome; ▪▪♦▪▪ No post-thoracotomy pain syndrome; ♦ statistically significant difference (Mann-Whitney U-test). Data are presented as medians with 25 and 75 percentiles.

Table 1 - Total cumulated pain scores

	PTPS (n=16)	No PTPS (n=36)	P-value
TPS-shoulder pain	7.5	4.7	0.37
TPS-thoracic pain	13.6	8.8	0.03
TPS-overall pain	12.4	10.2	0.18

TPS=total pain score, calculated as the cumulated daily mean NRS-scores. Data are presented as medians with 25 and 75 percentiles. P-values were compared with the Mann-Whitney U-test.

In the multivariate logistic regression analysis (table 2) both chest pain and operation type was included in the final model, but only cumulated chest pain was significantly and independently associated to PTPS.

Table 2. Multivariate logistic regression analysis

	Univariate analysis			Multivariate analysis		
	OR	p-value	95% CI	OR	p-value	95% CI
Shoulder pain (TPS)	1.09	0.11	0.98-1.22	-	NS	
Referred pain	0.97	0.96	0.30-3.18	-	NS	
Thoracic pain (TPS)	1.12	0.02	1.02-1.24	1.12	0.02	1.02-1.24
Age	0.95	0.06	0.89-1.00	-	NS	
Preoperative pain	4.14	0.03	1.15-14.92	-	NS	
Surgical approach (VATS)	0.42	0.19	0.11-1.54	0.18	0.052	0.03-1.01

OR=Odds Ratio; CI=Confidence Interval;TPS=Total pain score, defined as the cumulated daily average pain scores (average of the 5 daily NRS-assessments). VATS=Video Assisted Thoracic Surgery.

Quantitative sensory testing
No signs of general hypersensitivity were seen in PTPS-patients but patients with PTPS had slightly, but significantly, lower preoperative warm detection thresholds.

PAPER III

Recruitment and study flow
The same cohort as reported in paper 2 was studied.

Table 1 - Time course and intensity of ISP

	ISP	Muscolos keletal vs Referred pain	ISP with max NRS > 3	ISP as the main pain problem
POD 0	45 (75 %)	20 vs 25	25 (42 %)	27 (45 %)
POD 1	37 (62 %)	20 vs 17	12 (20 %)	18 (30 %)
POD 2	38 (63 %)	18 vs 20	11 (18 %)	13 (22 %)
POD 3	27 (45 %)	14 vs 13	2 (3 %)	5 (8 %)
POD 4, morning	19 (32 %)	10 vs 9	4 (7 %)	3 (5 %)
12 months, n=53	4 (8 %)	2 vs 2	3 (6 %)	1 (2 %)

Data are given in numbers (%).
NRS = Numerical Rating Scale; ISP = Ipsilateral Shoulder Pain.

Time course of ipsilateral shoulder pain (table 1)

41 patients developed ipsilateral shoulder pain postoperatively. On day 5, 35% still suffered from ipsilateral shoulder pain, but only 9% suffered clinically relevant shoulder pain (NRS>3). Only 3 patients reported chronic shoulder pain 12 months after the operation

Type of pain and surgical approach

Ipsilateral shoulder pain was classified as either musculoskeletal or referred pain in the morning of POD1. Of the 47 patients who experienced shoulder pain, 26 patients (55%) was classified as having referred pain and 21 (45%) was classified as having musculoskeletal pain. Musculoskeletal shoulder pain was significantly more severe than shoulder pain of the referred type (figure 1). There was no difference in the course of the 2 types of shoulder pain, and no relation to surgical approach (figure 2). Patients for thoracotomy had significantly more intense shoulder pain on POD 0, but shoulder pain had no significant association to incidence or time course of shoulder pain (figure 3).

Figure 1 - Pain intensity of musculoskeletal versus referred type of shoulder pain

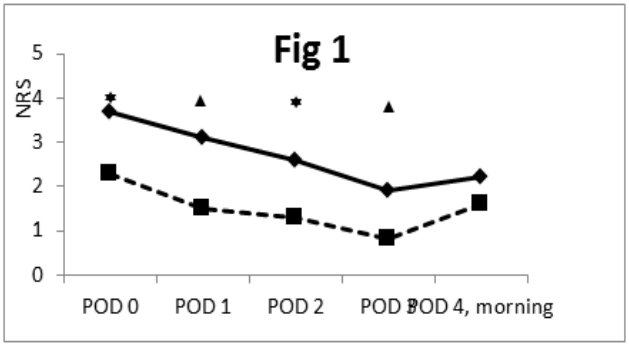
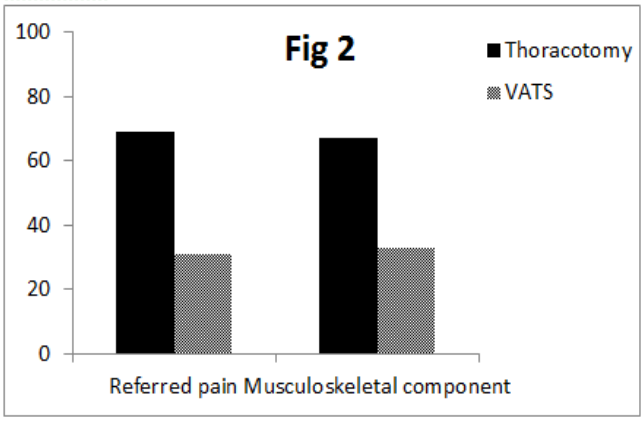


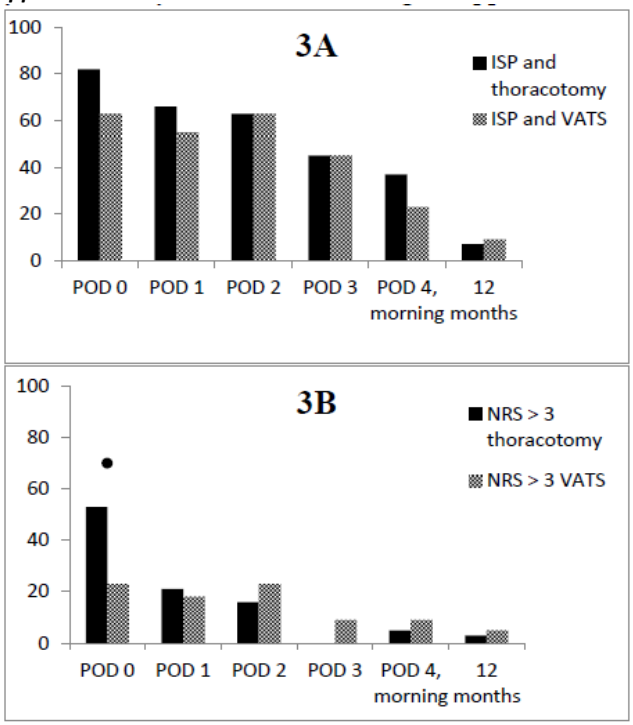
Figure 2 - Type of ISP related to surgical approach

Daily average NRS-scores during activity. —♦— Musculoskeletal shoulder pain; ▪▪■▪▪ Referred Shoulder Pain. *p< 0.05; ▲ p<0.01; NRS=Numerical Rating Scale; POD = Postoperative Day.



Frequency (percent) of patients for thoracotomy (black bars) and VATS (grey bars) with referred and musculoskeletal type of pain. VATS = Video Assisted Thoracic Surgery

Figure 3 - Frequency and intensity of ISP related to surgical approach



1A: Frequency (percent) of ISP in patients for thoracotomy (black bars) and VATS (grey bars). 1B: Frequency (percent) of ISP with clinically relevant pain (NRS-score > 3) in patients for thoracotomy (black bars) and VATS (grey bars). * p=0,031. ISP = Ipsilateral Shoulder Pain; VATS = Video Assisted Thoracic Surgery; NRS=Numerical Rating Scale

4.4 PAPER IV

Recruitment and study flow

Seventy-six patients were included from November 2012 to June 2014 and included in the intention to treat analysis of the primary endpoint. Most patients did not receive the study treatment during the full observation period (table 3). Either according to protocol due to early discharge or the nerve catheter was lost accidentally. Thus secondary endpoints for POD 1-3 was analyzed per protocol.

Table 3 - Patients receiving full study treatment postoperative day 1-4

	Ropivacaine Group n=38	Placebo Group n=38
POD 0	38 (100%)	38 (100%)
POD 1	11 (29%)	16 (42%)
POD 2	7 (18%)	9 (24%)
POD 3	2 (5%)	4 (11%)

Primary endpoint, incidence of shoulder pain POD 0

9 patients (24%) in the Ropivacainegroup and 26 patients (68 %) in the Placebogroup, experienced shoulder pain during the first 6 hours after surgery (p<0.0001, absolute and relative risk reductions were 44% (95% CI 22-67%) and 65% (95% CI 41-80%), respectively, number needed to treat was 2.2.

Pain intensity

Factorial repeated measures ANOVA of pain intensity demonstrated significantly lower shoulder pain scores in the treatment group compared to placebo during the first 36 hours following the operation, but not on POD 2 and 3 (figure 2, F=4.84; p=0.037).

There were no significant differences in overall pain scores (figure 3, F=1.20; p=0.278).

Additional secondary endpoints

There were no significant differences in time on PACU, opioid consumption, incidence of shoulder pain on POD 1-3 or on the 3 months endpoints (see appendix for specific data regarding additional secondary endpoints.

Figure 2 - Factorial repeated measures ANOVA demonstrate significantly lower shoulder pain scores in the treatment group compared with placebo during the first 36 hours following surgery

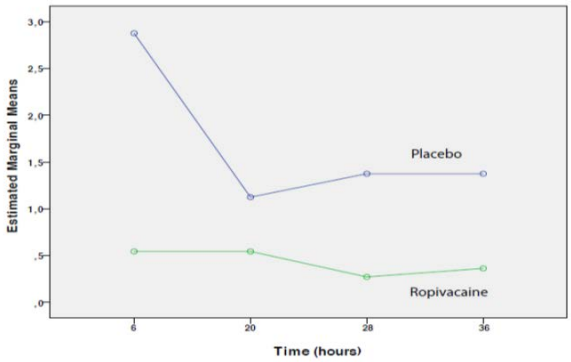
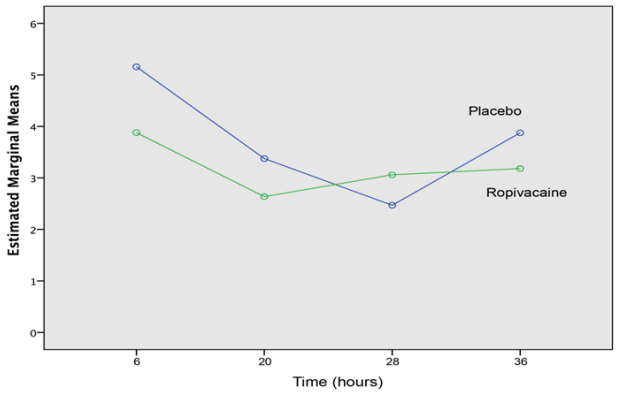


Figure 3 - Factorial repeated measures ANOVA demonstrate no significant difference in overall pain scores during the first 36 hours following surgery



Safety of the phrenic nerve block

No patients suffered subjective respiratory distress and there were no differences in postoperative respiratory function, arterial gasses, hours with chest tube or postoperative pneumonia. Six patients (17%) in the ropivacaine group experienced substantial motor block.

Accuracy of the phrenic nerve block

Evaluation of diaphragmatic movement was done in 60 patients (79%) (table 4). In the remaining patients, no blinded ultrasound operator was available within the predefined time frame (14 patients, 18 %) or image quality was too poor (2 patients, 3%) caused by air in the chest and abdomen. In the treatment group 93% of evaluated patients had paralysis or severe paresis of the ipsilateral diaphragm and 3,5% of evaluated patients had normal movement. In the placebo group, 23% of evaluated patients had paralysis or severe paresis of the ipsilateral diaphragm and 40% of evaluated patients had normal movement.

Table 4 - Diaphragmatic excursion

	Ropivacaine	Placebo
Diaphragmatic movement		
Evaluated patients	30 (79%)	30 (79%)
Normal Movement	1 (3.5%)	12 (40%)
Mild paresis	1 (3.5%)	11 (37%)
Severe paresis	7 (23%)	4 (13%)
Paralysis	21 (70%)	3 (10%)

5. DISCUSSION

This thesis describes the relation between different components of the acute pain response to the development of persistent postsurgical pain after cholecystectomy and lobectomy. Furthermore, we described the type and time course of ipsilateral shoulder pain after lobectomy and developed an effective treatment for acute ipsilateral shoulder pain after major thoracic surgery.

5.1 ACUTE TO CHRONIC PAIN

The relation between the acute pain response and the development of persistent postsurgical pain is well-known across many fields of surgery. Yet, the pathological background for this relation is uncovered and the importance of the individual

components of the acute pain response has not previously been reported.

In paper I we confirmed 22 that patients with persistent pain 12 months after cholecystectomy suffer significantly more intense pain during the first postoperative week, than patients with no persistent pain. Furthermore we found that the acute pain response is significantly different between patients with and without PPP. Where somatic pain has been found to generally dominate the acute pain response after cholecystectomy in both our study and others61, we found that visceral pain is dominating the acute pain response in patients who develop PPP after cholecystectomy.

Several possible explanations could be proposed

One is that preoperative visceral sensitization in some patients cause a more intense postoperative visceral pain response and increases the risk of persistent pain. This is supported by the finding that number of biliary pain attacks per months was the only other predictor for PPP after cholecystectomy. Thus a high frequency of biliary pain attacks could cause (or be caused by) visceral hypersensitivity in the gall bladder area.

However, we could not find any significant difference in preoperative hypersensitivity in the referred pain area between patients who developed persistent pain and those that did not. Neither did we find consistent significant differences in hypersensitivity in the referred pain area 6 or 12 months postoperatively. Our tests may have been insufficient to test for visceral hypersensitivity, since we only used percutaneous stimuli with the exception of deep pressure (pressure pain threshold). Hypersensitivity in the referred pain area to various stimuli has been demonstrated in several visceral pain conditions40,129-132 although results regarding gallbladder pathology have been conflicting55,62,133-136. Studies presenting hyperalgesia in the RPA in patients with gallbladder pathology have used more diffuse stimulation techniques such as deep pressure or electrical stimuli which may also affect deeper layers55,133 and hence represent deep hyperalgesia near the gall bladder, rather than the referred pain area. In our study, patients who developed persisting pain after cholecystectomy was more sensitive to deep pressure in the referred pain area preoperatively, and after 6 and 12 months, but it was only statistically significant at 6 months.

Another possible explanation is that intraoperative damage to visceral structures and nerves may carry a greater risk of central sensitization resulting in the development of chronic pain. The theoretical background for this hypothesis has been presented previously in this thesis (page 10-12), but does not explain the higher frequency of preoperative biliary attacks. Neither did we demonstrate any clear signs of visceral hyperalgesia, as discussed above.

For the same reasons, the hypothesis that high intensity of postoperative visceral pain in itself triggers central sensitization, leading to chronic pain could not be confirmed but neither rejected.

We found no other predictive preoperative factors that could explain a higher risk of both acute and chronic pain.

In paper II we also confirmed the association between acute and chronic postsurgical pain20,70. We also found that only thoracic pain, but not shoulder pain or referred pain was associated to PPP. Our results even indicated that acute thoracic pain is a better predictor for PPP than “overall pain”. We are not aware of other studies presenting associations between the different components of the acute pain response and post-thoracotomy pain syndrome.

We could not confirm any other predictive factors for PTPS; neither did we find any signs of general hypersensitivity in PTPS-patients before or after the operation.

This suggests that acute postoperative pain, per se, is not a direct causative factor in the development of PTPS. But rather that the relation between acute and chronic pain after thoracic surgery is tightly connected to intraoperative injury to local structures, i.e. nerves, causing both acute and persistent pain.

For the results presented in both paper I and II, it could be argued that the relation between acute and chronic pain is merely a result of report bias10: that some individuals simply report pain more frequently and as more serious than others. This is contradicted by the results in both paper I and II, since only some of the acute pain components were reported significantly more intense in PPP-patients. Furthermore we found no significant differences in preoperative pain in study 1. Neither in intensity of biliary pain attacks nor in incidence and intensity of other chronic pain conditions.

It has also been proposed that some individuals are generally more sensitive to pain and hence has a higher risk of developing acute and chronic pain. This could not be confirmed in either of the studies. On the contrary there were no differences in preoperative sensitivity to a broad range of experimental sensory stimuli. A recent systematic review13 concluded that 4-54% of the variance in acute postoperative pain can be predicted by various preoperative pain tests. The results for prediction of PPP in this review were more inconsistent and successful prediction of PPP by preoperative sensory tests was related to suprathreshold stimuli which were not part of our study protocol.

5.2 IPSILATERAL SHOULDER PAIN AFTER THORACIC SURGERY

In paper III, we confirmed that shoulder pain after lobectomy is a major pain problem93, with nearly half the patients reporting ipsilateral shoulder pain as their main pain problem on day 1. We also confirmed relatively new results that around 60% of patients suffered referred shoulder pain and around 40% of patients suffer musculoskeletal related pain97,103.

The findings regarding the time course of ipsilateral shoulder pain however, could not be confirmed. We are only aware of 2 studies95,96 following the incidence of ISP beyond the first 24 hours, which cannot readily be compared to our study. Nevertheless it has been generally anticipated that ISP lasts for 3-4 days after the operation93. We found that 32 % of patients still suffered ipsilateral shoulder pain on the morning on POD 4, but only few patients suffered clinically relevant pain (NRS > 3) beyond POD 2, which could explain previous anticipations.

More surprisingly, only 4(8%) patients suffered shoulder pain at 12 months. This is in contrast to the 23-59% reported in previous studies63,94 and cannot readily be explained. In the previous studies however, shoulder pain has not been the primary focus of the study and no corrections was made for comorbidity (shoulder pain from other causes) in this relatively old patient group.

Additionally, 2 important points regarding ISP was uncovered in this study: 1. ISP with a musculoskeletal component is a greater clinical problem than ISP of the referred type. 2. Incidence of musculoskeletal ISP was equally distributed between patients for thoracotomy and VATS. This suggests that positioning of the arm and shoulder are more important for eliciting postoperative shoulder pain than surgical trauma. Overall, surgical approach

was of relatively little importance for the development of ISP, as no difference was found in the incidence of shoulder pain between VATS and thoracotomy and the difference in pain intensity was confined to the day of the operation.

5.3 ULTRASOUND-GUIDED PHRENIC NERVE BLOCK

In paper IV, we found that ultrasound-guided supraclavicular phrenic nerve block was effective in preventing ipsilateral shoulder pain during the first 36 hours after surgery and more effective than reported in studies of the intrathoracic, supradiaphragmatic approach95,96,105. This is compatible with the theory that a more cranial approach would block more sensory fibers before they leave the nerve. Moreover, some affection of the brachial plexus would be expected in a subset of patients because of its proximity to the phrenic nerve. Even in patients without motor block, some degree of sensory brachial plexus block may be present, hence addressing both musculoskeletal and referred shoulder pain.

We found that the technique was safe, as there were no major complications to the treatment, including no incidences of respiratory compromise. The evaluation of the accuracy of the phrenic nerve block turned out to be difficult because many patients in the placebo group had reduced excursion of the diaphragm, probably due to the surgery itself. However, we estimate that the accuracy of the block placement was rather good since only 1 patient in the treatment group had normal diaphragmatic excursion and due to the large effect of the block on shoulder pain on POD 0.

That treatment with a phrenic nerve block did not have any effect on the 3 months endpoints is compatible with the findings in paper II where ipsilateral shoulder pain was not associated to the development of chronic pain.

6. CONCLUSION

The intensity of the cumulated visceral pain response during the first postoperative week after cholecystectomy is predictive for post-cholecystectomy syndrome 12 months postoperatively. No consistent, statistically significant signs of hyperalgesia could be demonstrated in the referred pain area before or 6 and 12 months after cholecystectomy in patients who developed post-cholecystectomy syndrome.

Only cumulated thoracic pain during the first 4 days after lobectomy was predictive for post-thoracotomy pain syndrome 12 months postoperatively.

No signs of generalized elevated sensory thresholds to various sensory stimuli could be demonstrated before or 12 months after lobectomy in patients who developed post-thoracotomy pain syndrome.

Ipsilateral shoulder pain is referred pain in 55 % and has a musculoskeletal component in 45% of patients after lobectomy. Musculoskeletal pain is more intense than referred pain but is not related to surgical approach. Ipsilateral shoulder pain is major clinical pain problem after lobectomy but usually declines in intensity after postoperative day 2 and only a small subset of patients experience chronic shoulder pain.

Ultrasound guided supraclavicular phrenic nerve block is a safe and effective treatment for ipsilateral shoulder pain after major thoracic surgery.

7. CRITICAL REMARKS

Study I and II was of exploratory nature and thus a formal pre-study power calculation could not be carried out. In both studies the proportion of patients with PPP was fairly small which carries the risk of type II errors. Thus, we may not have been able to uncover all predictive factors. On the other hand we may have been able detect the most important ones.

Quantitative sensory testing (QST) represents patient responses to strictly objectified stimuli. The patient response, however, is subjective and is influenced by several overall circumstances such as sleep, anxiety, depression, physical activity, socio-demographic factors, information, location, and inter observer variability137. Our protocol was thoroughly validated124,138 and previous studies have generally found good reproducibility in QST under experimental circumstances139,140. Furthermore inter observer variability was eliminated with only one person performing all QST's. In the clinical situation however, several factors may change during the course of the study which may impact QST and which are beyond control. These include anxiety regarding the operating procedure and the future prognosis and derived consequences such as sleep disturbance and possible reduced concentration. Especially, these circumstances may be different just before a major cancer operation (study 2) and 1 year after. Furthermore variability in normal sensory thresholds is known to be highly variable137,138 which possibly could make detection of pathological values more difficult.

Our QST's may have been insufficient to detect visceral hypersensitivity without referral of hypersensitivity to the referred pain area. This issue has been addressed previously.

In paper II and III further discrimination of thoracic pain into the somatic, neuropathic and possible visceral pain components would have been interesting but not practically possible.

In paper IV, most secondary endpoints where analyzed "per protocol" because most patients ended study treatment before the end of the study period. It is therefore possible that the effect of the phrenic nerve block on pain incidence and intensity on POD 1-3 is underestimated due to a statistical type II error because of the high drop-out rate to study treatment.

Finally, the distribution of surgical approach (thoracotomy vs. VATS) in paper IV was slightly different between the two groups. Results from other studies regarding whether the type of surgical approach has any influence on ISP are conflicting97,141. Results from paper III, which is based on the same population with few exceptions, showed no impact of surgical approach on incidence of ISP and a little impact on intensity of ISP on the day of the operation. Based on this, the small and statistically insignificant difference in surgical approach between the groups (13 percent points, p=0.118) compared to a relative risk reduction of 65%, and the post hoc analysis of risk factors, we consider the difference in surgical approach to have no impact on the primary endpoint and minimal impact on the secondary end point of pain intensity.

8. FUTURE ASPECTS

The cause for, and mechanism behind, most chronic pain conditions is still an unsolved issue. Even in well described conditions such as arthrosis and neuropathic pain, it is still not clarified why individuals with apparently similar lesions, experience very different degrees of pain and only about 5-10 % of patients with nerve lesions in general, develop neuropathic pain.

The theory that central sensitization plays a crucial role in persistent postsurgical pain and other pain conditions is appealing since it describes a situation where the experience of pain is relatively uncoupled to any noxious stimuli or tissue damage, but

rather reflects the state of the central nervous system. This could provide an explanation for many of the strange phenomena which is experienced in clinical practice when dealing with individuals suffering from a chronic pain condition – e.g. that pain predicts pain.

In the surgical setting, primary prevention of chronic pain can be difficult since many operations are necessary and different degrees of tissue injury are unavoidable. Tertiary prevention can likewise be difficult since chronic pain is difficult to treat once it has developed. Preventive analgesia offers a captivating opportunity for secondary prevention. – If, in fact, intense postoperative pain creates or facilitates the development of chronic pain.

The studies which this thesis is based upon do in no way finalize this discussion, but they reveal some interesting points. In paper I, the results could be interpreted in different directions, but the most likely would be that patients who developed chronic pain already suffered preoperative, local visceral hypersensitivity. This would explain the increased biliary pain attacks, increased postoperative visceral pain, and a higher risk of developing chronic pain. But it would lower the expectations to the effect of preventive analgesia. To test this hypothesis, sensitivity in the viscera should be tested, e.g. with electrical stimuli in a larger sample than the present.

In paper II, the results could be interpreted in the direction that only pain related to intraoperative injury and not pain per se was a predictor of chronic pain. This supports the theory that intraoperative nerve injury is the driving force behind most cases of post-thoracotomy pain syndrome and suggests that preventive analgesia may have limited effects, once the surgical damage is done. However, it is still not clear when nerve injury creates chronic pain as previously mentioned. Thus, it cannot be ruled out that intense postoperative pain may facilitate the transition from acute to chronic pain and large, possibly multicenter, trials of multimodal analgesic treatment is still warranted.

The overall conclusion to the study of early and late ipsilateral shoulder pain is that it may have been over reported as a clinical problem. Though the incidence was high, the incidence of patients with clinically relevant pain was considerably lower and relatively short lived. The low incidence of chronic shoulder pain was confirmed in paper IV. Nevertheless, a considerable proportion of patients experience intense musculoskeletal shoulder pain during the first postoperative days, and efforts should be on improve possible positional strain. While great efforts were done preoperatively to optimize positioning, intraoperative manipulation of the patients may have increased intraoperative positional strain on the shoulder and may be a future focus of improvement.

Ultrasound-guided supraclavicular phrenic nerve block offers a safe and effective treatment of ipsilateral shoulder pain. Subsequent treatment with a nerve catheter carries a risk of displacement as it was seen in our patients and repeated block placements should be considered in patients with prolonged shoulder pain.

9. SUMMARY

The thesis comprises an overview and four papers, all published or submitted for publication in international peer-reviewed scientific journals.

Background

Chronic pain after surgery is a common and debilitating complication after many types of surgery. The cause and pathology behind is still mainly uncovered, though several risk factors have been proposed. One of the strongest risk factors for persistent postsurgical pain is the intensity of the acute pain response though the mechanisms involved remains unsettled. The acute pain response consists of several different types of pain (ie. somatic pain, visceral pain, referred pain, neuropathic pain). Its uncovered whether some components of the acute pain response are closer correlated to chronic pain than others and whether treatment of acute pain can change the risk of developing chronic pain.

Aim

The aim of the thesis was to investigate which components of the acute pain response, was correlated to chronic postsurgical pain in patients for cholecystectomy and lobectomy.

Furthermore, to study the type and time course of ipsilateral shoulder pain after lobectomy and whether an ultrasound-guided supraclavicular phrenic nerve block was effective in preventing acute and chronic shoulder pain after major thoracic surgery.

Methods

Paper I is based on a prospective, observational, multicenter, cohort study, in which 100 patients for cholecystectomy was examined preoperatively, 1 week postoperatively and 3, 6, and 12 months postoperatively for pain, psychological factors and signs of hypersensitivity.

Paper II and III is based on a prospective, observational, cohort study, in which 60 patients for lobectomy was examined preoperatively, 4 days postoperatively and 12 months postoperatively for pain, psychological factors and signs of hypersensitivity.

Paper IV is based on a prospective, randomized, double-blind and placebo-controlled trial, where 76 patients were randomized to receive ultrasound guided supraclavicular phrenic nerve block with a blinded study solution (ropivacaine or saline). The primary endpoint was pain within the first 6 hours after surgery. Secondary endpoints included pain the following days and after 3 months.

Results

Paper I: Nine patients developed chronic unexplained pain 12 months postoperatively. In a multivariate analysis, cumulated visceral pain during the first week and number of preoperative biliary pain attacks were identified as independent risk factors for unexplained pain 12 months after surgery. There were no consistent signs of increased hypersensitivity in the referred pain area before or after the operation in patients with chronic pain.

Paper II: Sixteen patients developed chronic pain 12 months postoperatively. In a multivariate analysis thoracic pain during activity was the only significant predictor of chronic pain 12 months after surgery. Shoulder pain, referred pain and overall pain was not significant predictors. There were no signs of general hypersensitivity 12 months after surgery.

Paper III: Forty-seven (78 %) of patients experienced postoperative shoulder pain, but only 25 patients (42 %) experienced clinically relevant pain (NRS > 3). On postoperative day 4, 19 (32 %) of patients suffered shoulder pain, but only 4 (7 %) suffered clinically relevant pain. Only 4 patients (8%) suffered chronic shoulder pain. Ipsilateral shoulder pain of the

musculoskeletal type is more intense than referred ipsilateral shoulder pain, though referred shoulder pain is more common. Surgical approach was not related to incidence of shoulder pain or type of pain.

Paper IV: Shoulder pain within 6 hours of the operation was reported in 9 patients (24%) in the treatment group versus 26 (68%) in the placebo group ($p<0.0001$). Absolute and relative risk reductions were 44% (95% CI 22-67%) and 65% (95% CI 41-80%), respectively. No major complications, including respiratory compromise, were observed. Subsequent treatment with a nerve catheter was effective during the first 36 hours after surgery, but because of loss of nerve catheter or early submission of patients, data concerning pain the following days and after 3 months were inconclusive.

Conclusion

The intensity of the cumulated visceral pain response in the first postoperative week after cholecystectomy is predictive for post-cholecystectomy syndrome 12 months postoperatively. No consistent, statistically significant signs of hyperalgesia could be demonstrated in the referred pain area before or 6 and 12 months after cholecystectomy in patients who developed post-cholecystectomy syndrome.

Only cumulated chest pain during the first four days after lobectomy was predictive for post-thoracotomy pain syndrome 12 months after surgery.

Ipsilateral shoulder pain is major clinical pain problem after lobectomy but usually declines in intensity after day 3 and only a small subset of patients experience chronic shoulder pain. Shoulder pain of the musculoskeletal type is less common, but more intense than referred shoulder pain.

Ultrasound guided supraclavicular phrenic nerve block is a safe and effective treatment for ipsilateral shoulder pain after major thoracic surgery.

10. REFERENCES

1. Merskey H, Bogduk N: Classification of chronic pain, second edition. . Seattle: IASP Press 1994
2. Sjogren P, Ekholm O, Peuckmann V, Gronbaek M: Epidemiology of chronic pain in Denmark: an update. Eur J Pain 2009; 13: 287-92
3. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D: Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006; 10: 287-333
4. Johansen A, Romundstad L, Nielsen CS, Schirmer H, Stubhaug A: Persistent postsurgical pain in a general population: prevalence and predictors in the Tromso study. Pain 2012; 153: 1390-6
5. Crombie IK, Davies HT, Macrae WA: Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. Pain 1998; 76: 167-71
6. Perkins FM, Kehlet H: Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology 2000; 93: 1123-33
7. Macrae WA: Chronic pain after surgery. Br J Anaesth 2001; 87: 88-98
8. Kehlet H, Jensen TS, Woolf CJ: Persistent postsurgical pain: risk factors and prevention. Lancet 2006; 367: 1618-25
9. Macrae WA: Chronic post-surgical pain: 10 years on. Br J Anaesth 2008; 101: 77-86
10. Katz J, Seltzer Z: Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother 2009; 9: 723-44
11. Aasvang EK, Gmaehle E, Hansen JB, Gmaehle B, Forman JL, Schwarz J, Bittner R, Kehlet H: Predictive risk factors for persistent postherniotomy pain. Anesthesiology 2010; 112: 957-69
12. Althaus A, Arranz Becker O, Neugebauer E: Distinguishing between pain intensity and pain resolution: using acute post-surgical pain trajectories to predict chronic post-surgical pain. Eur J Pain 2014; 18: 513-21
13. Werner MU, Mjobo HN, Nielsen PR, Rudin A: Prediction of postoperative pain: a systematic review of predictive experimental pain studies. Anesthesiology 2010; 112: 1494-502
14. Werner MU, Bischoff JM: Persistent postsurgical pain: evidence from breast cancer surgery, groin hernia repair, and lung cancer surgery. Curr Top Behav Neurosci 2014; 20: 3-29
15. Cregg R, Anwar S, Farquhar-Smith P: Persistent postsurgical pain. Curr Opin Support Palliat Care 2013; 7: 144-52
16. Reddi D, Curran N: Chronic pain after surgery: pathophysiology, risk factors and prevention. Postgrad Med J 2014; 90: 222-7; quiz 226
17. Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA: Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. Clin J Pain 2012; 28: 819-41
18. Belfer I, Schreiber KL, Shaffer JR, Shnol H, Blaney K, Morando A, Englert D, Greco C, Brufsky A, Ahrendt G, Kehlet H, Edwards RR, Bovbjerg DH: Persistent postmastectomy pain in breast cancer survivors: analysis of clinical, demographic, and psychosocial factors. J Pain 2013; 14: 1185-95
19. Brandsborg B, Nikolajsen L, Hansen CT, Kehlet H, Jensen TS: Risk factors for chronic pain after hysterectomy: a nationwide questionnaire and database study. Anesthesiology 2007; 106: 1003-12
20. Katz J, Jackson M, Kavanagh BP, Sandler AN: Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 1996; 12: 50-5
21. Callesen T, Bech K, Kehlet H: Prospective study of chronic pain after groin hernia repair. Br J Surg 1999; 86: 1528-31
22. Bisgaard T, Rosenberg J, Kehlet H: From acute to chronic pain after laparoscopic cholecystectomy: a prospective follow-up analysis. Scand J Gastroenterol 2005; 40: 1358-64
23. Tasmuth T, Kataja M, Blomqvist C, von Smitten K, Kalso E: Treatment-related factors predisposing to chronic pain in patients with breast cancer--a multivariate approach. Acta Oncol 1997; 36: 625-30
24. Hickey OT, Burke SM, Hafeez P, Mudrakouski AL, Hayes ID, Shorten GD: Severity of acute pain after breast surgery is associated with the likelihood of subsequently developing persistent pain. Clin J Pain 2010; 26: 556-60
25. Gerbershagen HJ, Dagtekin O, Rothe T, Heidenreich A, Gerbershagen K, Sabatowski R, Petzke F, Ozgur E: Risk factors for acute and chronic postoperative pain in

patients with benign and malignant renal disease after nephrectomy. Eur J Pain 2009; 13: 853-60
26. Brandsborg B, Dueholm M, Nikolajsen L, Kehlet H, Jensen TS: A prospective study of risk factors for pain persisting 4 months after hysterectomy. Clin J Pain 2009; 25: 263-8
27. Peters ML, Sommer M, de Rijke JM, Kessels F, Heineman E, Patijn J, Marcus MA, Vlaeyen JW, van Kleef M: Somatic and psychologic predictors of long-term unfavorable outcome after surgical intervention. Ann Surg 2007; 245: 487-94
28. Julius D, Basbaum AI: Molecular mechanisms of nociception. Nature 2001; 413: 203-10
29. Woolf CJ, Ma Q: Nociceptors--noxious stimulus detectors. Neuron 2007; 55: 353-64
30. Abrahamsen B, Zhao J, Asante CO, Cendan CM, Marsh S, Martinez-Barbera JP, Nassar MA, Dickenson AH, Wood JN: The cell and molecular basis of mechanical, cold, and inflammatory pain. Science 2008; 321: 702-5
31. Costigan M, Scholz J, Woolf CJ: Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci 2009; 32: 1-32
32. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS: The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain 2013; 154: 95-102
33. Gebhart GF: Visceral pain-peripheral sensitisation. Gut 2000; 47 Suppl 4: iv54-5; discussion iv58
34. Cervero F: Visceral pain-central sensitisation. Gut 2000; 47 Suppl 4: iv56-7; discussion iv58
35. Cervero F, Laird JM: Visceral pain. Lancet 1999; 353: 2145-8
36. Joshi SK, Gebhart GF: Visceral pain. Curr Rev Pain 2000; 4: 499-506
37. Cervero F: Visceral versus somatic pain: similarities and differences. Dig Dis 2009; 27 Suppl 1: 3-10
38. Giamberardino MA: Recent and forgotten aspects of visceral pain. Eur J Pain 1999; 3: 77-92
39. Graven-Nielsen T: Fundamentals of muscle pain, referred pain, and deep tissue hyperalgesia. Scand J Rheumatol Suppl 2006; 122: 1-43
40. Giamberardino MA, Costantini R, Affaitati G, Fabrizio A, Lapenna D, Tafuri E, Mezzetti A: Viscero-visceral hyperalgesia: characterization in different clinical models. Pain 2010; 151: 307-22
41. Arendt-Nielsen L, Laursen RJ, Drewes AM: Referred pain as an indicator for neural plasticity. Prog Brain Res 2000; 129: 343-56
42. Giamberardino MA: Referred muscle pain/hyperalgesia and central sensitisation. J Rehabil Med 2003: 85-8
43. Latremoliere A, Woolf CJ: Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009; 10: 895-926
44. Woolf CJ: Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011; 152: S2-15
45. Hansson P: Translational aspects of central sensitization induced by primary afferent activity: what it is and what it is not. Pain 2014; 155: 1932-4
46. Woolf CJ: What to call the amplification of nociceptive signals in the central nervous system that contribute to widespread pain? Pain 2014; 155: 1911-1912
47. Wall PD: The prevention of postoperative pain. Pain 1988; 33: 289-90
48. Dahl JB, Kehlet H: Preventive analgesia. Curr Opin Anaesthesiol 2011; 24: 331-8
49. Gilron I, Kehlet H: Prevention of chronic pain after surgery: new insights for future research and patient care. Can J Anaesth 2014; 61: 101-11
50. Moiniche S, Kehlet H, Dahl JB: A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology 2002; 96: 725-41
51. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I: Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database Syst Rev 2013; 7: CD008307
52. Clarke H, Bonin RP, Orser BA, Englesakis M, Wijeysundera DN, Katz J: The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis. Anesth Analg 2012; 115: 428-42
53. Andreae MH, Andreae DA: Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. Br J Anaesth 2013; 111: 711-20
54. Lamberts MP, Lugtenberg M, Rovers MM, Roukema AJ, Drenth JP, Westert GP, van Laarhoven CJ: Persistent and de novo symptoms after cholecystectomy: a systematic review of cholecystectomy effectiveness. Surg Endosc 2013; 27: 709-18
55. Kurucsai G, Joo I, Fejes R, Szekely A, Szekely I, Tihanyi Z, Altorjay A, Funch-Jensen P, Varkonyi T, Madacsy L: Somatosensory hypersensitivity in the referred pain area in patients with chronic biliary pain and a sphincter of Oddi dysfunction: new aspects of an almost forgotten pathogenetic mechanism. Am J Gastroenterol 2008; 103: 2717-25
56. Kellow JE: Sphincter of Oddi dysfunction type III: another manifestation of visceral hyperalgesia? Gastroenterology 1999; 116: 996-1000
57. Bates T, Ebbs SR, Harrison M, A'Hern RP: Influence of cholecystectomy on symptoms. Br J Surg 1991; 78: 964-7
58. Jorgensen T, Teglbjerg JS, Wille-Jorgensen P, Bille T, Thorvaldsen P: Persisting pain after cholecystectomy. A prospective investigation. Scand J Gastroenterol 1991; 26: 124-8
59. Joris J, Thiry E, Paris P, Weerts J, Lamy M: Pain after laparoscopic cholecystectomy: characteristics and effect of intraperitoneal bupivacaine. Anesth Analg 1995; 81: 379-84
60. Ure BM, Troidl H, Spangenberger W, Dietrich A, Lefering R, Neugebauer E: Pain after laparoscopic cholecystectomy. Intensity and localization of pain and analysis of predictors in preoperative symptoms and intraoperative events. Surg Endosc 1994; 8: 90-6
61. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H: Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain 2001; 90: 261-9
62. Stawowy M, Funch-Jensen P, Arendt-Nielsen L, Drewes AM: Somatosensory changes in the referred pain area in patients with cholecystolithiasis. Eur J Gastroenterol Hepatol 2005; 17: 865-70
63. Dajczman E, Gordon A, Kreisman H, Wolkove N: Long-term postthoracotomy pain. Chest 1991; 99: 270-4

64. Perttunen K, Tasmuth T, Kalso E: Chronic pain after thoracic surgery: a follow-up study. Acta Anaesthesiol Scand 1999; 43: 563-7
65. Ochroch EA, Gottschalk A, Augostides J, Carson KA, Kent L, Malayaman N, Kaiser LR, Aukburg SJ: Long-term pain and activity during recovery from major thoracotomy using thoracic epidural analgesia. Anesthesiology 2002; 97: 1234-44
66. Kinney MA, Hooten WM, Cassivi SD, Allen MS, Passe MA, Hanson AC, Schroeder DR, Mantilla CB: Chronic postthoracotomy pain and health-related quality of life. Ann Thorac Surg 2012; 93: 1242-7
67. Wildgaard K, Ravn J, Nikolajsen L, Jakobsen E, Jensen TS, Kehlet H: Consequences of persistent pain after lung cancer surgery: a nationwide questionnaire study. Acta Anaesthesiol Scand 2011; 55: 60-8
68. Wildgaard K, Ravn J, Kehlet H: Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. Eur J Cardiothorac Surg 2009; 36: 170-80
69. Khelemsky Y, Noto CJ: Preventing post-thoracotomy pain syndrome. Mt Sinai J Med 2012; 79: 133-9
70. Kalso E, Perttunen K, Kaasinen S: Pain after thoracic surgery. Acta Anaesthesiol Scand 1992; 36: 96-100
71. Gotoda Y, Kambara N, Sakai T, Kishi Y, Kodama K, Koyama T: The morbidity, time course and predictive factors for persistent post-thoracotomy pain. Eur J Pain 2001; 5: 89-96
72. Pluijms WA, Steegers MA, Verhagen AF, Scheffer GJ, Wilder-Smith OH: Chronic post-thoracotomy pain: a retrospective study. Acta Anaesthesiol Scand 2006; 50: 804-8
73. Maguire MF, Latter JA, Mahajan R, Beggs FD, Duffy JP: A study exploring the role of intercostal nerve damage in chronic pain after thoracic surgery. Eur J Cardiothorac Surg 2006; 29: 873-9
74. Gottschalk A, Ochroch EA: Clinical and demographic characteristics of patients with chronic pain after major thoracotomy. Clin J Pain 2008; 24: 708-16
75. Hetmann F, Kongsgaard UE, Sandvik L, Schou-Bredal I: Prevalence and predictors of persistent post-surgical pain 12 months after thoracotomy. Acta Anaesthesiol Scand 2015
76. Benedetti F, Amanzio M, Casadio C, Filosso PL, Molinatti M, Oliaro A, Pischedda F, Maggi G: Postoperative pain and superficial abdominal reflexes after posterolateral thoracotomy. Ann Thorac Surg 1997; 64: 207-10
77. Benedetti F, Vighetti S, Ricco C, Amanzio M, Bergamasco L, Casadio C, Cianci R, Giobbe R, Oliaro A, Bergamasco B, Maggi G: Neurophysiologic assessment of nerve impairment in posterolateral and muscle-sparing thoracotomy. J Thorac Cardiovasc Surg 1998; 115: 841-7
78. Miyazaki T, Sakai T, Tsuchiya T, Yamasaki N, Tagawa T, Mine M, Shibata Y, Nagayasu T: Assessment and follow-up of intercostal nerve damage after video-assisted thoracic surgery. Eur J Cardiothorac Surg 2011; 39: 1033-9
79. Rogers ML, Henderson L, Mahajan RP, Duffy JP: Preliminary findings in the neurophysiological assessment of intercostal nerve injury during thoracotomy. Eur J Cardiothorac Surg 2002; 21: 298-301
80. Maguire MF, Ravenscroft A, Beggs D, Duffy JP: A questionnaire study investigating the prevalence of the neuropathic component of chronic pain after thoracic surgery. Eur J Cardiothorac Surg 2006; 29: 800-5
81. Steegers MA, Snik DM, Verhagen AF, van der Drift MA, Wilder-Smith OH: Only half of the chronic pain after thoracic surgery shows a neuropathic component. J Pain 2008; 9: 955-61
82. Wildgaard K, Ringsted TK, Hansen HJ, Petersen RH, Werner MU, Kehlet H: Quantitative sensory testing of persistent pain after video-assisted thoracic surgery lobectomy. Br J Anaesth 2012; 108: 126-33
83. Wildgaard K, Ringsted TK, Aasvang EK, Ravn J, Werner MU, Kehlet H: Neurophysiological characterization of persistent postthoracotomy pain. Clin J Pain 2012; 28: 136-42
84. Romero A, Garcia JE, Joshi GP: The state of the art in preventing postthoracotomy pain. Semin Thorac Cardiovasc Surg 2013; 25: 116-24
85. Wenk M, Schug SA: Perioperative pain management after thoracotomy. Curr Opin Anaesthesiol 2011; 24: 8-12
86. Gerner P: Postthoracotomy pain management problems. Anesthesiol Clin 2008; 26: 355-67, vii
87. Barak M, Ziser A, Katz Y: Thoracic epidural local anesthetics are ineffective in alleviating post-thoracotomy ipsilateral shoulder pain. J Cardiothorac Vasc Anesth 2004; 18: 458-60
88. Burgess FW, Anderson DM, Colonna D, Sborov MJ, Cavanaugh DG: Ipsilateral shoulder pain following thoracic surgery. Anesthesiology 1993; 78: 365-8
89. Mac TB, Girard F, Chouinard P, Boudreault D, Lafontaine ER, Ruel M, Ferraro P: Acetaminophen decreases early post-thoracotomy ipsilateral shoulder pain in patients with thoracic epidural analgesia: a double-blind placebo-controlled study. J Cardiothorac Vasc Anesth 2005; 19: 475-8
90. Pennefather SH, Akrofi ME, Kendall JB, Russell GN, Scawn ND: Double-blind comparison of intrapleural saline and 0.25% bupivacaine for ipsilateral shoulder pain after thoracotomy in patients receiving thoracic epidural analgesia. Br J Anaesth 2005; 94: 234-8
91. Barak M, Iaroshevski D, Poppa E, Ben-Nun A, Katz Y: Low-volume interscalene brachial plexus block for post-thoracotomy shoulder pain. J Cardiothorac Vasc Anesth 2007; 21: 554-7
92. Tan N, Agnew NM, Scawn ND, Pennefather SH, Chester M, Russell GN: Suprascapular nerve block for ipsilateral shoulder pain after thoracotomy with thoracic epidural analgesia: a double-blind comparison of 0.5% bupivacaine and 0.9% saline. Anesth Analg 2002; 94: 199-202, table of contents
93. MacDougall P: Postthoracotomy shoulder pain: diagnosis and management. Curr Opin Anaesthesiol 2008; 21: 12-5
94. Li WW, Lee TW, Lam SS, Ng CS, Sihoe AD, Wan IY, Yim AP: Quality of life following lung cancer resection: video-assisted thoracic surgery vs thoracotomy. Chest 2002; 122: 584-9
95. Danelli G, Berti M, Casati A, Bobbio A, Ghisi D, Mele R, Rossini E, Fanelli G: Ipsilateral shoulder pain after thoracotomy surgery: a prospective, randomized, double-blind, placebo-controlled evaluation of the efficacy of infiltrating the phrenic nerve with

0.2%wt/vol ropivacaine. Eur J Anaesthesiol 2007; 24: 596-601
96. Martinez-Barenys C, Busquets J, de Castro PE, Garcia-Guasch R, Perez J, Fernandez E, Mesa MA, Astudillo J: Randomized double-blind comparison of phrenic nerve infiltration and suprascapular nerve block for ipsilateral shoulder pain after thoracic surgery. Eur J Cardiothorac Surg 2011; 40: 106-12
97. Ohmori A, Iranami H, Fujii K, Yamazaki A, Doko Y: Myofascial involvement of supra- and infraspinatus muscles contributes to ipsilateral shoulder pain after muscle-sparing thoracotomy and video-assisted thoracic surgery. J Cardiothorac Vasc Anesth 2013; 27: 1310-4
98. Holt M: Ipsilateral shoulder pain following thoracic operations. Anesthesiology 1993; 79: 192; author reply 193
99. Mark JB, Brodsky JB: Ipsilateral shoulder pain following thoracic operations. Anesthesiology 1993; 79: 192; author reply 193
100. Koehler RP, Keenan RJ: Management of postthoracotomy pain: acute and chronic. Thorac Surg Clin 2006; 16: 287-97
101. Joshi GP, Bonnet F, Shah R, Wilkinson RC, Camu F, Fischer B, Neugebauer EA, Rawal N, Schug SA, Simanski C, Kehlet H: A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. Anesth Analg 2008; 107: 1026-40
102. Huot MP, Chouinard P, Girard F, Ruel M, Lafontaine ER, Ferraro P: Gabapentin does not reduce post-thoracotomy shoulder pain: a randomized, double-blind placebo-controlled study. Can J Anaesth 2008; 55: 337-43
103. Saha S, Brish EL, Lowry AM, Boddu K: In select patients, ipsilateral post-thoracotomy shoulder pain relieved by suprascapular nerve block. Am J Ther 2011; 18: 309-12
104. Ozyuvaci E, Akyol O, Sitilci T, Dubus T, Topac Og lu H, Leblebici H, Ac Ikgoz A: Preoperative ultrasound-guided suprascapular nerve block for postthoracotomy shoulder pain. Curr Ther Res Clin Exp 2013; 74: 44-8
105. Scawn ND, Pennefather SH, Soorae A, Wang JY, Russell GN: Ipsilateral shoulder pain after thoracotomy with epidural analgesia: the influence of phrenic nerve infiltration with lidocaine. Anesth Analg 2001; 93: 260-4, 1st contents page
106. Stambaugh JE, Jr., Sarajian C: Analgesic efficacy of zomepirac sodium in patients with pain due to cancer. J Clin Pharmacol 1981; 21: 501-7
107. Breivik EK, Bjornsson GA, Skovlund E: A comparison of pain rating scales by sampling from clinical trial data. Clin J Pain 2000; 16: 22-8
108. Jensen MP, Chen C, Brugger AM: Postsurgical pain outcome assessment. Pain 2002; 99: 101-9
109. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J, Immpact: Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005; 113: 9-19
110. Jensen MP, Karoly P, Braver S: The measurement of clinical pain intensity: a comparison of six methods. Pain 1986; 27: 117-26
111. Joyce CR, Zutshi DW, Hrubes V, Mason RM: Comparison of fixed interval and visual analogue scales for rating chronic pain. Eur J Clin Pharmacol 1975; 8: 415-20
112. Paice JA, Cohen FL: Validity of a verbally administered numeric rating scale to measure cancer pain intensity. Cancer Nurs 1997; 20: 88-93
113. Stahmer SA, Shofer FS, Marino A, Shepherd S, Abbuhl S: Do quantitative changes in pain intensity correlate with pain relief and satisfaction? Acad Emerg Med 1998; 5: 851-7
114. Kremer E, Atkinson JH, Ignelzi RJ: Measurement of pain: patient preference does not confound pain measurement. Pain 1981; 10: 241-8
115. Sze FK, Chung TK, Wong E, Lam KK, Lo R, Woo J: Pain in Chinese cancer patients under palliative care. Palliat Med 1998; 12: 271-7
116. Rigamonti G, Zanella E, Lampugnani R, Marrano D, Campione O, Bruni G, Mandelli V, Sacchetti G: Dose-response study with indoprofen i.v. as an analgesic in postoperative pain. Br J Anaesth 1983; 55: 513-9
117. Bolton JE: Accuracy of recall of usual pain intensity in back pain patients. Pain 1999; 83: 533-9
118. Salovey P, Smith AF, Turk DC, Jobe JB, Willis GB: The Accuracy of Memory for Pain - Not So Bad Most of the Time. Aps Journal 1993; 2: 184-191
119. Beese A, Morley S: Memory for acute pain experience is specifically inaccurate but generally reliable. Pain 1993; 53: 183-9
120. Heapy A, Dziura J, Buta E, Goulet J, Kulas JF, Kerns RD: Using multiple daily pain ratings to improve reliability and assay sensitivity: how many is enough? J Pain 2014; 15: 1360-5
121. Jamison RN, Sbrocco T, Parris WC: The influence of physical and psychosocial factors on accuracy of memory for pain in chronic pain patients. Pain 1989; 37: 289-94
122. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361-70
123. Andersen AB: Måling af psykisk sårbarhed. En analyse af visse egenskaber ved sårbarhestesten. English resume, University of Copenhagen, statistical institute, 1979
124. Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede RD: Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006; 10: 77-88
125. Nikolajsen L, Kristensen AD, Thillemann TM, Jurik AG, Rasmussen T, Kehlet H, Jensen TS: Pain and somatosensory findings in patients 3 years after total hip arthroplasty. Eur J Pain 2009; 13: 576-81
126. Hudak PL, Amadio PC, Bombardier C: Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med 1996; 29: 602-8
127. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET: Standardisation of spirometry. Eur Respir J 2005; 26: 319-38

128. Richards RR, An KN, Bigliani LU, Friedman RJ, Gartsman GM, Gristina AG, Iannotti JP, Mow VC, Sidles JA, Zuckerman JD: A standardized method for the assessment of shoulder function. J Shoulder Elbow Surg 1994; 3: 347-52
129. Pedersen KV, Olesen AE, Osther PJ, Arendt-Nielsen L, Drewes AM: Prediction of postoperative pain after percutaneous nephrolithotomy: can preoperative experimental pain assessment identify patients at risk? Urolithiasis 2013; 41: 169-77
130. Giamberardino MA, De Laurentis S, Affaitati G, Lerza R, Lapenna D, Vecchiet L: Modulation of pain and hyperalgesia from the urinary tract by algogenic conditions of the reproductive organs in women. Neurosci Lett 2001; 304: 61-4
131. Vecchiet L, Giamberardino MA, Dragani L, Albe-Fessard D: Pain from renal/ureteral calculosis: evaluation of sensory thresholds in the lumbar area. Pain 1989; 36: 289-95
132. Stawowy M, Rossel P, Bluhme C, Funch-Jensen P, Arendt-Nielsen L, Drewes AM: Somatosensory changes in the referred pain area following acute inflammation of the appendix. Eur J Gastroenterol Hepatol 2002; 14: 1079-84
133. Giamberardino MA, Affaitati G, Lerza R, Lapenna D, Costantini R, Vecchiet L: Relationship between pain symptoms and referred sensory and trophic changes in patients with gallbladder pathology. Pain 2005; 114: 239-49
134. Kjaer DW, Stawowy M, Arendt-Nielsen L, Drewes AM, Funch-Jensen P: Reversibility of central neuronal changes in patients recovering from gallbladder stones or acute cholecystitis. World J Gastroenterol 2006; 12: 7522-6
135. Stawowy M, Bluhme C, Arendt-Nielsen L, Drewes AM, Funch-Jensen P: Somatosensory changes in the referred pain area in patients with acute cholecystitis before and after treatment with laparoscopic or open cholecystectomy. Scand J Gastroenterol 2004; 39: 988-93
136. Stawowy M, Drewes AM, Arendt-Nielsen L, Funch-Jensen P: Somatosensory changes in the referred pain area before and after cholecystectomy in patients with uncomplicated gallstone disease. Scand J Gastroenterol 2006; 41: 833-7
137. Gierthmuhlen J, Enax-Krumova EK, Attal N, Bouhassira D, Cruccu G, Finnerup NB, Haanpaa M, Hansson P, Jensen TS, Freynhagen R, Kennedy JD, Mainka T, Rice A, Segerdahl M, Sindrup SH, Serra J, Tolle T, Treede RD, Baron R, Maier C: Who is healthy? Aspects to consider when including healthy volunteers in QST-based studies- a consensus statement by the EUROPAIN and NEUROPAIN consortia. Pain 2015
138. Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B: Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006; 123: 231-43
139. Arendt-Nielsen L, Yarnitsky D: Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J Pain 2009; 10: 556-72
140. Edwards RR, Sarlani E, Wesselmann U, Fillingim RB: Quantitative assessment of experimental pain perception: multiple domains of clinical relevance. Pain 2005; 114: 315-9
141. Bunchungmongkol N, Pipanmekaporn T, Paiboonworachat S, Saeteng S, Tantraworasin A: Incidence and risk factors associated with ipsilateral shoulder pain after thoracic surgery. J Cardiothorac Vasc Anesth 2014; 28: 991-4