Autonomic Reactivity in Muscle Pain
-
Clinical and Experimental Assessment

av

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Akademisk avhandling

som med vederbörligt tillstånd av rektorsämbetet vid Umeå universitet för
avläggande av filosofie doktorsexamen framläggs till offentligt förvar i Stora
föreläsningssalen, Arbetslivsinstitutet, torsdagen den 30 november 2006,
kl.10.00.
Avhandlingen kommer att förvaras på engelska.

Fakultetsopponent: Prof. Stein Knardahl, Statens arbeidsmiljöinstitutt, Oslo,
Norge

Institutionen för kirurgisk och perioperativ vetenskap, Idrottsmedicinska enheten,
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Abstract

There are numerous indications of possible involvement of the autonomic nervous system in the genesis of chronic pain. The possibility exists that sympathetic activation is related to motor dysfunction and changes in sensory processing, which have otherwise been implicated in musculoskeletal disorders.

The primary aim has been to investigate autonomic regulation at rest and in response to laboratory tests of autonomic function in subjects suffering from chronic pain in the lower back (LBP n=93), neck-shoulder (WAD n=40, non traumatic - NT n=40) and neck-jaw (WAD, n=21) regions, and its relation to proprioceptive acuity and clinical data. Secondary aim has been to assess autonomic regulation in fit, pain-free subjects in response to experimentally induced pain and in occupationally relevant settings.

Each chronic pain group was subjected to a battery of functional tests combining cognitive, physical, sensory and motor tasks as well as the activation of reflex pathways, and compared to an age- and gender balanced control group. Autonomic regulation was also assessed in exposure to experimentally induced acute muscle pain in healthy subjects (n=24). Further assessment was carried out during monotonous repetitive work and dynamic work in healthy subjects (n=10) and in a three-day monitoring of ambulance personnel (n=26) in occupational settings.

Autonomic regulation was evaluated using cardiovascular (heart rate and heart rate variability - HRV, blood pressure and local blood flow), respiratory (breathing rate) electrodermal (skin conductance), muscular (trapezius and masseter EMG) and biochemical (insulin, cortisol, catecholamines) variables. Proprioceptive acuity was assessed using active-active repositioning tests. Pain levels were assessed using Visual-analogue or Numerical Rating scales. Short-Form SF-36 Health Related Quality of Life, Self-Efficacy Score, Oswestry Low Back Pain, Pain Disability and Neck Disability Index questionnaires were used for clinical description in addition to the McKenzie evaluation and primary healthcare diagnoses. Self-reports of pain, stress and exertion were acquired prior to, during and post-testing.

Chronic pain subjects were characterised by increased sympathetic and decreased parasympathetic activity as reflected in heart rate (LBP, WAD), heart rate variability (LBP, WAD), blood pressure (WAD) and electrodermal activity (LBP). In general, WAD showed more pain and dysfunction than NT, with lower self-efficacy and health-related quality of life. Increased responsiveness to sensory stimuli (HRV, electrodermal activity), and motor tasks (heart rate) and decreased response to cognitive challenge (HRV, electrodermal activity) was seen in WAD. A significant part of WAD subjects with neck-jaw symptoms showed sensorimotor impairment and low endurance in chewing tests, concomitant with a cardiovascular response that correlated with pain levels. Proprioceptive acuity was not impaired in chronic pain, and there were no indications of significant individual response specificity. Response to experimentally induced muscle pain was characterised by a prominent cardiovascular component. Autonomic activation and transient insulin resistance were detected in healthy subjects following monotonous repetitive work, with no such effects following dynamic exercise. Modest deviations in circadian HRV patterns during work were detected in ambulance personnel with musculoskeletal symptoms.

Autonomic balance observed in chronic pain subjects was characterised by a trend towards increased sympathetic activity in comparison with pain-free controls. Moderate signs of affected reactivity to autonomic function tests were observed in patients with WAD, however no specific reaction patterns have been observed in any chronic pain group. Correspondence between the intensity of pain and autonomic activity was observed in acute pain and in chronic pain groups characterised by higher pain levels. As indicated by autonomic and neurohormonal changes in the recovery from real and simulated work, further studies with physiological monitoring of the effects of work-related stress are warranted for better understanding of the mechanism of musculoskeletal disorders.

Key words: autonomic reactivity, stress, chronic pain, experimental pain, back, shoulder, neck

Language: English ISBN: 91-7264-144-4 Number of pages: 62 + 6 papers

Signature: Date: 30 October 2006
Autonomic Reactivity in Muscle Pain
- Clinical and Experimental Assessment

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From the Department of Surgical and Perioperative Science,
Sports Medicine Unit, Umeå University
and
The Centre for Musculoskeletal Research, University of Gävle
To Irena and Ivana

Ирени и Ивани

“...and now remains
That we find out the cause of this effect
Or rather say, the cause of this defect,
For this effect defective comes by cause”

William Shakespeare, Hamlet
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### Abbreviations

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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
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<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>BRE</td>
<td>Breathing</td>
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<tr>
<td>CE</td>
<td>Constant error</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>CRPS</td>
<td>Chronic regional pain syndrome</td>
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<td>ECG</td>
<td>Electrocardiogram</td>
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<td>EDA</td>
<td>Electrodermal activity</td>
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<td>EMG</td>
<td>Electromyogram</td>
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<td>FM</td>
<td>Fibromyalgia</td>
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<td>HF</td>
<td>High frequency spectral power</td>
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<tr>
<td>HPA</td>
<td>Hypothalamic-pituitary-adrenal</td>
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<td>HR</td>
<td>Heart rate</td>
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<td>HRV</td>
<td>Heart rate variability</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<td>IRS</td>
<td>Individual response specificity</td>
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<td>LBP</td>
<td>Low back pain</td>
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<tr>
<td>LF</td>
<td>Low frequency spectral power</td>
</tr>
<tr>
<td>MANOVA</td>
<td>Multivariate analysis of variance</td>
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<td>MSD</td>
<td>Musculoskeletal disorders</td>
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<td>MSSD</td>
<td>Mean square of successive differences</td>
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<tr>
<td>NDI</td>
<td>Neck disability index</td>
</tr>
<tr>
<td>NN50</td>
<td>Number of normal to normal intervals &gt; 50 ms</td>
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<tr>
<td>NT</td>
<td>Non-traumatic</td>
</tr>
<tr>
<td>PPG</td>
<td>Photoplethysmogram</td>
</tr>
<tr>
<td>RMSSD</td>
<td>Root mean square of successive differences</td>
</tr>
<tr>
<td>SDNN</td>
<td>Standard deviation of normal to normal intervals</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form 36 general health survey</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumour necrosis factor</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>VE</td>
<td>Variable error</td>
</tr>
<tr>
<td>WAD</td>
<td>Whiplash-associated disorder</td>
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This thesis is based on the following original articles, referred to by their Roman numerals in the text:


## Thesis overview

<table>
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<tr>
<th>Study</th>
<th>Aims</th>
<th>Subjects</th>
<th>Methods</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study I</strong></td>
<td>To investigate autonomic activity at rest and in functional tests in chronic LBP, as well as its relations to pain, disability, diagnoses and general health.</td>
<td>LBP (n=93) Con. (n=52) f:m~1:1</td>
<td>Stroop, Orthostatic, Handgrip, Paced breathing; HRV, PPG, BRC, EDA, VAS pain, SF-36, Oswestry, Mc Kenzie Lumbar proprioception* Cross sectional, controlled</td>
<td>Differences in resting HRV, EDA. No differences in reactivity. No diff. in proprioception* No sign. patterns No correlation ANS activity - pain, disability.</td>
<td>Indications of increased sympathetic tonus in chronic LBP at rest, regardless of pain levels, functional disability and status indices and without indications of differences in physiological reactivity or response patterns.</td>
</tr>
<tr>
<td><strong>Study II</strong></td>
<td>To investigate autonomic activity at rest and in functional tests, as well as shoulder proprioception in subjects with WAD and non-traumatic neck-shoulder pain, in relation to symptoms, functioning and disability.</td>
<td>WAD (n=40) NT (n=40) Con. (n=40) f:m~2:1</td>
<td>Stroop, Handgrip, Paced breathing, Unpleasant sound HRV, BP, PPG, BRC, EDA, trapezius EMG VAS pain, SES, SF-36, NDI, PDI Shoulder proprioception Cross sectional, controlled</td>
<td>Differences in resting HRV (WAD) Higher HR, EDA reactivity to sound, lower HR react. to Stroop (WAD) No diff. in proprioception No sign. patterns Correlation between HR reactivity and pain</td>
<td>Moderate signs of autonomic involvement, as seen in resting levels and reactivity differences in response to sensory and cognitive tasks, were present in WAD but not in NT neck pain, without sensorimotor dysfunction in either group. More intense symptoms in WAD impede from attributing this involvement to etiological factors.</td>
</tr>
<tr>
<td><strong>Study III</strong></td>
<td>To assess autonomic reactivity, masseter reactivity and muscle倦 के विकास</td>
<td>WAD (n=21) Con. (n=21) f:m~3:1</td>
<td>Chewing test HRV, BP, mass. EMG; NSR of pain Cross-sectional, controlled</td>
<td>Difference in resting HR, BP; Difference in HR reactivity; Correlation between BP and pain level</td>
<td>Signs of significant autonomic involvement in minor motor tasks such as chewing in both pain-free and WAD subjects. Consistent signs of increased autonomic activity in WAD reflect low endurance, caused by tiredness rather than local muscle fatigue.</td>
</tr>
<tr>
<td><strong>Study IV</strong></td>
<td>To evaluate effects of a magnetic field on the intensity of experimental muscle pain and to evaluate pain-related changes in the ANS activity in exposure to experimentally induced muscle pain</td>
<td>n=24 f:m~1:1</td>
<td>HRV, BP, NSR pain; Hypertonic saline injection in m. erector spinae. Cross-over</td>
<td>Pain related elevation of BP Pain higher in males</td>
<td>Link between blood pressure response to experimental pain and subjective pain ratings, in both genders</td>
</tr>
<tr>
<td><strong>Study V</strong></td>
<td>To investigate whether insulin resistance is promoted by monotonous, repetitive arm work common in working life, as compared to dynamic exercise and rest.</td>
<td>n=10 males</td>
<td>Monotonous work, ergometer cycling, rest HRV, BP; cortisol, catecholamines, insulin, glucose, FFA, leptin, adiponectin, TNF-alpha, IL-6 Cross-over</td>
<td>Increase in catecholamines but not cortisol, and presence of HRV changes during monotonous work Transient insulin resistance post-work.</td>
<td>Repetitive monotonous work might acutely promote insulin resistance in healthy subjects, as opposed to dynamic work, most probably due to the effects of catecholamines and sympathetic activation</td>
</tr>
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<td><strong>Study VI</strong></td>
<td>To assess physiological and subjective stress markers during a 24-h ambulance work shift and in work-free days, and relate those parameters to self-reported health complaints</td>
<td>n= 26 f:m~1:12</td>
<td>Mental arithmetic, orthostatic, handgrip; HRV, BP SEQ, Nordic SQ, diary; Cross-sectional;</td>
<td>Higher BP reactivity to mental arithmetic and morning cortisol in subjects with many complaints. Slight circadian HRV deviations between work and work-free days in symptomatic subjects.</td>
<td>Stress-related health complaints (musculoskeletal symptoms) were associated with moderate differences in cortisol reactivity, modest deviations in circadian HRV during work and increased reactivity to mental stress</td>
</tr>
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</table>

* - data reported in Åsell et al. (2006)
Introduction

Social aspects and prevalence of musculoskeletal disorders

Musculoskeletal disorders (MSD) present a significant burden for the individual in the form of deteriorating health and increased suffering, and for the society due to associated costs and loss of productivity.

Pain is the third leading reason for absence from work in the United States (US). One in five adults suffers from it and the bulk of all non-malignant pain conditions represent musculoskeletal pain (Katz 2002). Some estimates put MSD-related expenditures at about 1% of the US Gross National Product (GNP) (Yelin 2003). Indirect costs such as lost earnings and profit, and litigation expenses in case of accidents or work-related pain are of course even higher.

Almost exactly the same figure of about 1% of the GNP is being spent in Sweden on the treatment and associated costs of problems in the back and neck (Hansson 2005). Direct MSD-related costs that a suffering individual in the European Union is faced with are estimated at ca. 7800 € per year for fibromyalgia, and as much as 8500 € for chronic low back pain (Boonen et al. 2005).

In Sweden the most common causes of sick leave and early retirement in the general population are low back pain and neck and shoulder pain. About 40% of persons suffering from either low back pain or neck and shoulder pain are reported to have been sick-listed sometime during a five-year period (1995-2001). As many as 59% of those experiencing pain in both low back and neck areas went on sick-leave (Nyman et al. 2006).

In a screening of population in Norway, apart from a prevalence of neck pain at 38% and back pain at 21% during a one-month period, significant attribution of pain to the working conditions was reported (Mehlum et al. 2006). A cross-sectional study of Dutch working population showed that the prevalence of low back pain was about 27% and neck and shoulder pain about 21%. Approximately one third of those suffering from pain reported pain-related limitations in daily life and about 30-40% of pain sufferers were seeking medical help (Picavet and Schouten 2003).

In a 24-year follow-up study of general population in Sweden, 24% of subjects developed low back pain over the years (Thorbjornsson et al. 2000). Incidence in a three-year follow up of Dutch working population was 32% for the neck and shoulder and 15% for the lower arm (van den Heuvel et al. 2005).
Risk factors for MSD

Monotonous repetitive work, high repetitiveness or high force are significant risk factors for MSD. Frequent repetition of shoulder movements is related to subsequent musculoskeletal complaints, and notably also high job demands and distress are predictive of future musculoskeletal symptoms (Andersen et al. 2003). Heavy lifting and bending, insufficient social support and psychosocial stress were shown to be predictive of future neck-shoulder symptoms (Feveile et al. 2002).

Associations between monotonous work, high perceived workload, time pressure and musculoskeletal complaints were indicated previously (Bongers et al. 1993). Physical and psychosocial exposure during work has been linked to subsequent care seeking for musculoskeletal disorders, with significant gender and time effects reported, and for women an interaction between job and family factors has been found (Fredriksson et al. 2002). Both prevalence and incidence of MSD are higher in women (Cassou et al. 2002), and it is reported that highly repetitive work is more of a risk factor for women than for men with respect to neck and shoulder pain (McGeary et al. 2003), and that psychosocial stress affects more women than men (Kaiser et al. 2001).

Job demands have been identified as a risk factor for both neck-shoulder and elbow/wrist/hand symptoms in the working population (van den Heuvel et al. 2005). High job demands seem to be related to neck and shoulder pain, and the tendency to become overworked together with low social support from colleagues have been found to be related to low back pain (Skov et al. 1996). Job strain (high demands and low decision latitude) is also reported to be a significant risk factor for the development of neck and shoulder pain in females (Ostergren et al. 2005).

Definitions of MSD

The International Association for the Study of Pain defines pain as “an unpleasant sensory, and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. Comparable definitions of work-related MSD, of which chronic pain is a primary component, have been much harder to come by.

Repetitive Strain Injury is a term used to describe work-related MSD that affect the back, neck and upper limbs, and are characterised by local diffuse pain, allodynia and hyperalgesia (Cohen et al. 1992). The term implies connection to monotonous work, and besides musculoskeletal symptoms does not exclude for example local nerve entrapment (Yassi 1997). Cumulative Trauma Disorder is a frequently used term describing non-specific upper extremity pain and also implying the connection with repeated occupational exposure (Melhorn 1998).
Work-Related Upper Limb Disorder is yet another common term used in the literature to describe MSD (e.g. in the UK Chen et al. 2006), and there are others such as Non-Specific Arm Pain (Greening et al. 2003), Work-Related Myalgia or Cervicobrachial Syndrome (Blair et al. 2003). Autonomic involvement in MSD, as seen in symptoms such as swelling and local vasomotor changes, is reflected in the use of the term Reflex Sympathetic Dystrophy in the description of non-specific myalgia (Gibbons and Wilson 1992). Application of sympathetic blockade in the treatment of some MSD, based on clinical features shown by the patients, supports the concept of Sympathetically Maintained Pain which implicates autonomic involvement in the genesis and maintenance of pain (Baron et al. 1999).

Recently an attempt was made to classify MSD, with or without autonomic manifestations, under the term Complex Regional Pain Syndrome (Merskey and Bogduk 1994). Complex Regional Pain Syndrome (CRPS) type I is thus characterised by an initiating noxious event, subsequent pain, swelling, vasomotor instability, skin changes and motor function impairment (Blair 2003). In an evaluation of the validity of these diagnostic criteria, it was seen that pain appears as an independent diagnostic factor, vasomotor and sudomotor changes also appear independently, whereas changes in the range of motion together with motor dysfunction form a separate factor, proposed as an additional diagnostic criterion (Harden et al. 1999).

Diagnostic criteria for MSD have so far been based essentially on reports of pain in resisted motion regarding muscle and tendon damage, and on pain and range of motion in conditions involving problems in joints. Accordingly, a significant part of the diagnostic work is based on self-reports of pain, discomfort and dysfunction. Much of the diagnostic work is dependent upon the examiner, with inconsequent inter- and intra-tester and inter-subject reliability (Punnett and Gold 2003). The problem of valid and specific diagnostic criteria in different forms of MSD is emphasized by the fact that there seems to be a lot of commonality in diagnostic criteria and symptoms across different MSD (Marinus and Van Hilten 2006).

Pathophysiological models of MSD

Lack of reliable diagnostic criteria, huge social impact of MSD, lack of effective treatment and the link between psychosocial stress and MSD led to the development of a number of pathophysiological models in an effort to explain the origin and development of MSD.

Feedback loops at spinal and supraspinal levels and in particular the link between chemosensitive afferent fibres and muscle spindles have been proposed as a possible mechanism of muscle pain in an integrated model of chronic work-related myalgia (Johansson et al. 2003). Prolonged muscular activity or
inflammation causes the release of metabolites and inflammatory substances into the interstitium, and thus activates chemosensitive fibres, which in their turn may excite gamma-motoneurons on both sides of the spinal cord and modulate muscle spindle function. Muscle spindle afferents themselves affect both motoneurons (affected also directly by chemosensitive fibres, and inhibited via Renshaw cells) and interneurons, and thus create a possible mechanism for the maintenance of pain through sensorimotor derangement. Additionally, chemosensitive afferents might excite sympathetic preganglionic neurons, and may thus affect muscle contraction and blood supply. The latter link might account for a number of autonomic symptoms observed in chronic pain. Finally, supraspinal projections of nociceptive fibres might account for a number of cognitive and autonomic symptoms seen in some forms of chronic muscle pain.

Different phenomena observed at the peripheral level have been implicated in the origin of MSD. A notion that low-threshold motor units might be overloaded or excessively activated in low level contractions, as present in some occupational settings, led to the postulation of the Cinderella hypothesis, where structural changes in these fibres are quoted as the initiating factor in pain genesis (Hägg 1991). Some electrophysiological and histological findings seem to confirm prolonged activation and morphological changes of these fibres (Kadi et al. 1998; Kadefors et al. 1999). In contrast with low-threshold fibre overuse is the evidence of motor unit rotation even in low level contractions (Fallentin et al. 1993). Moderate metabolic disturbance in the muscle, as seen in some occupational settings, is presumably not alleviated by pressor reflexes since the contraction level is too low. This disturbance could lead to insufficient inhibition of low-threshold motor unit activity via group III and IV afferents combined with the lack of perceived fatigue, and as a consequence to the existence of Cinderella fibres (Fallentin 2003).

Other mechanisms which do not support the role of muscle hyperactivity in the development of chronic pain have been proposed. According to the pain adaptation model, pain-induced decrease in agonist muscle activity and increase in antagonist activity represent an adaptive change, and account for the reduction in force and range of movement seen in patients, as well as for the changes in coordination (Lund et al. 1991). In muscle pain in general the level of resting activity of the muscle does not seem to be changed, but the endurance in submaximal contractions and maximal voluntary contraction are reduced (Graven-Nielsen et al. 2003). Central sensitization, on the other hand, has been proposed as the mechanism through which chronic pain is maintained. Both allodynia (painful reaction to non-painful stimuli) and hyperalgesia (excessive painful reaction to painful stimuli) are present in chronic muscle pain (Arendt-Nielsen and Graven-Nielsen 2003). Potentially irreversible changes at different levels of the central nervous system (CNS), triggered by an initial event or a process, might maintain the pain past its acute stage. Psychological stress could
be a contributing factor in the development of hypersensitivity due to possible imbalance between supraspinal and descending modulatory mechanisms (Curatolo et al. 2004).

The role of blood vessels and nociceptors in their vicinity could be crucial in the genesis of muscle pain. In skeletal muscles nociceptors seem to be placed adjacent to vessel walls of arteries and arterioles, with free nerve endings in contact with outer vessel walls. Possible mechanisms through which pain might be generated include mechanical activation of nerve endings in vasomotion, vascular production and release of algogenic substances such as bradykinin, prostaglandins, serotonin and nitric oxide, and inflammation-induced increase in vessel permeability and cell leakage. The absence of direct involvement of muscle in the proposed model would also account for the lack of strong relationships between muscle activity and pain in experimental studies (Knardahl 2002).

It is worth noting that most models of chronic pain pay attention to the significant role of autonomic involvement in the pathogenesis of chronic pain. Summarizing possible mechanism of ANS (and primarily sympathetic activation) on the development of muscle pain, four important effects are noticeable. These include the effects of an increase in sympathetic outflow on vasoconstriction, contractile properties of the muscles, proprioceptive information as transmitted by muscle spindles and finally on the sensitisation of peripheral nociceptive pathways (Passatore and Roatta 2006). These theoretical constructs have certain support in clinical studies on patients with chronic muscle pain. Clinical findings also seem to reiterate the pathophysiological models postulating significant autonomic involvement in chronic pain.

**Autonomic activity in MSD**

Theoretical models and experimental findings seem to be in agreement with a number of clinical observations in patients with MSD.

Autonomic imbalance may be detected through differences between the affected and the control group in resting values or in recovery from stressors. Increased resting levels of heart rate were observed in neck and shoulder pain (Gockel et al. 1995) and increased baseline electrodermal activity in LBP (Peters and Schmidt 1991). Men suffering from fibromyalgia (FM) exhibit consistent sympathetic hyperactivity and parasympathetic withdrawal, as seen in heart rate variability (HRV, Cohen et al. 2001). Reduced circadian HRV and reduced parasympathetic activity are also seen in FM (Martinez-Lavin et al. 1998).

Increased or decreased reactivity in response to stimuli has been implicated in the genesis of muscle pain and stress-related disorders. In LBP, paraspinal muscle reactivity but not cardiovascular reactivity was shown to correlate with pain severity in subjects with high depression scores (Burns et al. 1997).
Hyporeactivity of the hypothalamic-pituitary-adrenal (HPA) axis characterised by a reduction in morning cortisol response is observed in WAD (Gaab et al. 2005). Lower sympatho-adrenal reactivity to stress is also indicated in FM (Okifuji and Turk 2002). In healthy subjects, higher cardiovascular reactivity to mental stress was shown to reduce pain thresholds following a cold pressor tests (Caceres and Burns 1997).

Existence of specific response patterns has been associated with the genesis of pathological conditions since it was supposed that hyperactivity of a particular effector line would in time lead to pathological process, damages in the places of least resistance and thus to the creation of pathological response patterns (McEwen 1998; McEwen 2000). Patterns would thus refer to amplitude-ranked orders of physiological responses in exposure to a set of different conditions. In response to a battery of tests including mental arithmetic, cold pressor, imaging, Valsalva manoeuvre and sensory stimulation, individual response specificity (IRS) in healthy subjects seems to be rather low (Berman and Johnson 1985). IRS is estimated to be present in about 15% of subjects in cognitive and in up to 30% of subjects in emotional stress, as assessed using cardiovascular, sudomotor and vasomotor activity (Marwitz and Stemmler 1998).

There is still conflicting evidence as to the relative contributions of the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) in autonomic regulatory imbalance associated with MSD. Stimulus specificity in response to many of the functional tests remains to be elucidated, as well as the interplay of hyperactivity along certain effector lines and related hypoactivity in compensatory effector systems.

**Stress and allostasis**

The use of the term stress and the understanding of what is meant by the term have evolved over the years. Stress was initially defined by Hans Selye as the internal reaction to external challenges, as opposed to the original meaning of the word which implies external loads. General Adaptation Syndrome was his term for what he presumed to be a non-specific reaction to external threats, characterised by three phases - alarm, resistance and exhaustion. A distinction was made by Selye between positive, neutral and negative stress, indicating awareness of the subjective appraisal of stress (Thibodeau and Patton 1999). It was proposed later that stressors as the external agents interact in a complex manner with individual make-up of a person (taken as a very wide term embracing everything from physiological to social aspects) and only then produce a stress response (Morse 1995).

Job strain at work is the result of an interaction between job demands and job decision latitude (Karasek 1979). Job dissatisfaction is associated with high demands and low decision latitude, and is followed by higher frequency of
depression, exhaustion and life dissatisfaction. Job strain is also a significant risk factor for cardiovascular disease (Karasek et al. 1981). The demand - decision latitude model was evaluated earlier in terms of musculoskeletal symptoms, physiological states and absenteeism (Theorell et al. 1991).

Imbalance in the form of high effort and low reward at work is also often associated with higher prevalence of risk factors for cardiovascular disease, both in women and men (Peter et al. 1998). Discrepancy between effort and reward was shown to lead to reduced physiological reactivity as seen in heart rate, cortisol and adrenaline response to the Stroop test, following long-term exposure to unfavourable conditions at work (Siegrist et al. 1997). This implies exhaustion in cardiovascular and hormonal regulatory systems, indicating the presence of allostatic loads.

It was shown that healthy employees who regularly use computers and find themselves in the high job strain quadrant experience higher incidence of musculoskeletal problems in the neck and shoulder than comparable subjects in the low strain quadrant (Hannan et al. 2005). In a study of recently employed subjects, incidence of pain was associated with psychosocial stress, and those who experienced most stress were also most likely to develop neck and back pain (Nahit et al. 2001). Psychophysiological factors may be decisive in the process which turns an acute painful event into chronic pain (Knardahl 2005). Many muscle pain conditions are associated with a stressful and traumatic trigger event and a disturbed stress-response system characterised by impaired sympathetic reactivity could be a contributing factor in the origin of pain. However, there is also evidence of antinociceptive effects of increased autonomic activity, through beta-endorphins and increased blood pressure. The areas that process nociceptive information also interface with the baroreflex system and the inhibition of pain processing is thus possible. (Okifuji and Turk 2002).

Initially the concept of stress as a threat to homeostasis embraced the role of the ANS as a regulatory mechanism which maintains homeostasis as a set of equilibrium points, both physically and psychologically, and is supported by the activity of the HPA axis. Later, the dynamics of the adaptation were emphasised through the use of the term allostatic - achieving stability through change. The term allostatic load was introduced to describe the disruption of normal regulatory mechanisms as a consequence of repeated activation, loss of habituation, or insufficient recovery (McEwen 2000). Importantly, allostatic load on one regulatory system might elicit an increased load on another system, which in normal circumstances compensates the actions of the former (McEwen 1998). Regulatory imbalance thus created might be manifested in the activity of both the HPA and ANS axes.

In conditions of work-related stress, regulatory imbalance might result in the existence of typical reaction patterns - individual response specificity. Allostatic
loads might be manifested in autonomic and hormonal activation and in metabolic and immune functions. The interplay of the ANS with neuro-hormonal, metabolic and immune systems in conditions of work-related stress has not been sufficiently investigated.

Autonomic regulation of cardiac and vascular function is very frequently assessed. Sympathetic and parasympathetic fibres innervate the atria, ventricles and coronary arteries, as well as peripheral vessels, and their activity is modulated through baroreflexes. Monitoring of cardiac and vascular regulation is therefore important, and is made possible through beat-to-beat analysis of heart rate, blood pressure and heart rate variability. Usual clinical manipulations embrace respiratory (Valsalva manoeuvre, paced breathing) or posture-induced (tilt-tests, orthostatic challenge) changes in the levels of autonomic activity (Ravits 1997; Freeman 2006). Test outcome variables for clinical use are based on heart rate changes, for which there are clinically accepted limits of normal function, whereas heart rate variability in time and frequency domains and beat-to-beat blood pressure measures reflect the dynamics of individual responses. Local blood flow is also indicative of sympathetic influence on vascular regulation. Handgrip and cold pressor tests have also been found useful as manipulations in the experimental assessment of autonomic function (Hilz and Dutsch 2006).

Sudomotor activity is indicative of general sympathetic activity, and whereas in clinical settings quantitative sudomotor axon reflex tests are frequent, in physiological studies sympathetic skin response and electrodermal activity are of greater importance as measures of the response to experimental manipulation (Ravits 1997; Hilz and Dutsch 2006). Recordings of respiration rate, apart from being informative per se, are also useful as a complement to heart rate variability analyses (Grossman et al. 1990). Many of the measures used in the assessment of autonomic function are also age-dependent (Ziegler et al. 1992)

The use of more direct measurements of autonomic activity such as microneurography or pharmacological manipulations as exemplified by the administration of sympathomimetics or adrenergic agonists is technically rather demanding and therefore difficult to implement when large samples in dynamic test situations are involved (Freeman 2006).

**Pain and proprioception**

Proprioception can be defined as the sense of limb position or movement. Its sensory input originates in mechanoreceptors, and it is characterised by two modalities - position and movement sense. Proprioception tests assessing these two modalities most often take the form of position sense tests using active or passive movements, movement detection tests and velocity detection tests. Outcome measures in position sense tests are most often absolute, constant and
variable errors, where the latter two represent sensory bias and acuity, respectively (Domkin 2005).

A number of symptoms such as postural instability and dizziness seen in chronic pain might be attributed at least partly to proprioceptive deficit. Possible link between sympathetic activation and changes in proprioceptive acuity as a consequence of altered muscle spindle information has been hypothesized (Passatore and Roatta 2006).

In chronic low back pain (LBP) patients which exhibit lumbar segment instability, lumbar positioning error is larger than in asymptomatic controls (O'Sullivan et al. 2003). Differences between LBP and asymptomatic subjects were also found in back repositioning test in different postures (Gill and Callaghan 1998), and in rotation tests (Koumantakis et al. 2002). There are however studies where no effect is observed in lumbar repositioning tests (Newcomer et al. 2000).

In arm position-matching tests whiplash associated disorder (WAD) subjects showed lower shoulder proprioceptive acuity than controls. Proprioceptive acuity in shoulder movements in WAD subjects was found to be associated with low self-rated physical functioning, but not with self-rated pain (Sandlund et al. 2006). In cervical pain the ability to relocate the head on the trunk following an active movement is significantly poorer in patients than in controls (Revel et al. 1991). In neck repositioning tests WAD subjects show worse results than control subjects (Loudon et al. 1997; Treleaven et al. 2005). There are also indications that WAD subjects perform worse than non-traumatic (NT) pain sufferers in head repositioning tests (Kristjansson et al. 2003).

Velocity discrimination in shoulder movements is significantly affected by hard work, the effect being stronger in female subjects (Pedersen et al. 1999). Similarly, an increase in absolute error in shoulder repositioning tests was observed in healthy subjects following low intensity monotonous repetitive work which simulates occupational settings (Bjorklund et al. 2000). However, stressful computer work involving time-limited and accuracy based mouse operation failed to show effects on wrist proprioceptive acuity in spite of the physiological activation and an increase in subjective ratings of stress (Heiden et al. 2005). Anticipatory stress through the threat of electrical shocks has no effect on lumbar proprioception, in spite of a clear cardiovascular response to stress (Hjortskov et al. 2005a). Similarly, in response to stressors such as oral glucose ingestion and cold pressor there is no reduction in ankle movement detection thresholds, in spite of an increase in plasma noradrenaline and mean arterial pressure (Matre and Knardahl 2003).
Muscle activity in MSD

In some conditions characterised by muscle pain, such as FM, reduced muscle activity at rest is seen (Thieme and Turk 2005). Lower electromyographic (EMG) levels in sub-maximal isometric contractions in the trapezius were associated with more pronounced musculoskeletal complaints in an assessment of musculoskeletal and psychological complaints in a sample of working population (Steingrimsdottir et al. 2004).

In muscles not involved in task performance, there is evidence of increased muscle activity associated with psychological (but not musculoskeletal) complaints (Steingrimsdottir et al. 2005). In pain-free subjects exposed to mental stress, there is some evidence of task-irrelevant increase in the trapezius muscle activity (Bansevicius et al. 1997). However, there are also relatively numerous evidence of an increase in muscle activity in occupational settings in employees showing musculoskeletal symptoms (Lundberg et al. 1999) and in chronic pain subjects during the movement embracing the affected area (Sterling et al. 2004). It may be summarised that in chronic muscle pain muscle activity at rest is generally not affected, there is a decrease of activity in static contractions and in dynamic contractions there is an inhibition on the side of the agonist, and a disinhibition on the side of the antagonist (Graven-Nielsen et al. 2003).

Hypotheses

Based on these premises, we hypothesised that:

- Chronic muscle pain is characterised by signs of autonomic imbalance, detectable in resting conditions as well as in changes in the amplitude and pattern of responses to functional tests

- Occupational stress associated with musculoskeletal symptoms is characterised by signs of autonomic imbalance similar to those in subjects with chronic muscle pain.

- Chronic muscle pain is associated with changes in sensorimotor functions as reflected in proprioception and muscle activity.
Aims

Principal aims of the thesis were:

1. To investigate autonomic regulation in subjects with different forms of documented MSD and to explore relations between perceptive and autonomic components of muscle pain in chronic conditions. Additionally we wanted to investigate characteristics of autonomic regulation in relation to sensory-motor functioning.

2. To evaluate the characteristics of autonomic response in subjects with stress-related health complaints including musculoskeletal symptoms.

3. To investigate autonomic and neuro-hormonal regulation in real working conditions and in experimental low-level monotonous work.
Materials and methods

Subjects

In Study I there were 93 subjects suffering from low back pain (LBP). They were compared to an age- and gender-matched pain-free control group consisting of 32 subjects. Both genders were equally represented in the sample and a single subject was excluded in each group due to technical difficulties in the recording. Age range was 20-50 years (Study I, Table I). Chronic pain subjects were diagnosed with one of the following conditions while in primary healthcare: lumbago, lumbago sciatica, slipping discs and spondylolisthesis.

Exclusion criteria in Study I were back surgery less than three months prior to the testing for the LBP group, and presence of back pain and musculoskeletal symptoms in the back in the control group, as assessed by the Standardized Nordic Questionnaire. However, presence of secondary pain in the thoracic and cervical spine was not an exclusion criterion for LBP.

In Study II, there were three groups equal in size, consisting of subjects suffering from WAD and those suffering from work-related non-traumatic pain in the neck and shoulder area (NT), both of which were compared mutually and to a pain-free control group. Each group had 40 subjects, the groups were age- and gender matched and there was a predominance of female subjects which accounted for slightly less than two-thirds of the sample. WAD subjects were classified into WAD groups II and III according to the Quebec Task Force Classification (Spitzer et al. 1995). Exclusion criteria for the chronic pain groups were fibromyalgia, fractured or dislocated discs and in NT the presence of earlier trauma to the trunk or upper spine. Since the study involved unilateral tests of shoulder proprioception, care was taken that all the subjects were right-handed and not affected by recent arm, shoulder or neck surgery.

In Study III, 21 subjects suffering from concurrent WAD and temporomandibular dysfunction were compared to a control group consisting of as many age- and gender-matched subjects. All WAD subjects were referred to the hospital for the assessment and treatment of WAD-related pain and dysfunction in the jaw-face-neck area. Initial WAD trauma had resulted in WAD grade II or III injury in these patients, with an additional development of symptoms in the jaw, face and neck. Slightly less than three quarters of the subjects were female.

Common exclusion criteria for all groups in Studies I-III were rheumatic disease, diabetes, asthma, neurological conditions, psychiatric disorders and regular use of beta-blockers.

In Study IV 24 healthy subjects participated, equally divided between genders. Presence of pain, infectious diseases or medication at the time of testing were exclusion criteria, as were possible chronic conditions.
In Study V, ten lean physically active and healthy males participated. Exclusion criteria were musculoskeletal symptoms and regular medication. Regular use of bicycle for transportation was an inclusion criterion due to the use of a relatively long ergometer cycling task.

Finally, in Study VI 24 male and two female ambulance personnel participated. The subjects were generally free from medication and none had diagnosed medical conditions or hypertension. The age- and gender composition of the participating subjects reflected well the general composition of the staff at the station.

In all studies relevant ethical approval was obtained from the Ethics Committee of Umeå University. There were no voluntary drop-outs during the studies.

**Functional tests**

In Studies I and II a battery of four functional tests was used, which in both cases included a modified version of the Stroop Colour-Word conflict test as a cognitive test, paced breathing as a test of autonomic regulation, handgrip as a test of autonomic reactivity in physical effort and finally in Study I (LBP) we employed the orthostatic test whereas in Study II (WAD) sensory stimulation was used. A single functional test was used in the WAD group in Study III with respect to the clinical application of the test. In Study IV we used hypertonic saline-induced pain for 20 minutes as a model of chronic pain in pain-free subjects in order to evaluate the autonomic response and its relation to pain levels. In Study V, we used a repetitive monotonous task which mimicked assembly line work, in addition to experimental sessions involving strenuous exercise and rest for a comparison. In Study VI autonomic function tests included mental arithmetic task as the cognitive challenge, handgrip as the test involving physical activity and finally the orthostatic test for the assessment of reflex loops and autonomic regulation.

The Stroop test was used as the mental stress test involving sensory rejection. A series of words depicting colours (in our case red, blue, yellow and green) are presented to the subjects, written in a particular colour that may (congruent task) or may not (incongruent task) correspond to the meaning of the word. The goal is to recognize and report the ink colour and ignore the semantic content of the written word. In our studies we added another dimension by playing pre-recorded words denoting different colours. The test was written in Matlab (MathWorks Inc, USA) and presented, as all other functional tests in Studies I and II through a computerised slide presentation, which eliminated the need for excessive direct communication between the subject and the experimenter.

In Study VI we used the mental arithmetic test as the means of imposing cognitive stress. The subjects were asked to solve a series of additions and
subtractions presented to them, as many as possible within the given time frame for the test.

Paced breathing is a test of autonomic function widely used in clinical practice. Through a computer presentation with pre-recorded verbal and written commands (inhale, exhale) we imposed a rhythm of about 5-6 breaths per minute. The ratio of the maximal to minimal heart rate was used as the measure of autonomic function.

Handgrip test was used as the functional test involving physical activation. The subjects were asked to produce and keep maximal voluntary contraction grasping the handle for about 15 seconds, and were then instructed to reduce the contraction to about 30% of the maximum and maintain that level of force for another minute and a half. Hand-held dynamometer and verbal feedback from the experimenter were used to control the force level. In case the subjects terminated the test early due to muscle fatigue, endurance time was noted.

Orthostatic test was performed by asking the subjects who were seated to stand up, and maintain the upright position for one minute, and then allowing them to sit down again. In response to the postural change and associated change in blood pressure and blood distribution, a compensatory cardiovascular response is initiated and evaluated through the 30:15 ratio, comparing the maximal and minimal inter-beat intervals in the cardiac baroreflex response.

In Study III the chewing test was conducted twice, once on the preferred side and once on the opposite. The subjects were given three pieces of ordinary chewing gum which they broke down and fused into a homogenous bolus after about a minute and entered into a rhythmical pattern of chewing with respect to the electromyographical activity. In those cases where the subjects could not tolerate the test, it was ended and total endurance time noted.

**Experimental procedure**

In Studies I, II, III and VI a battery consisting of two to four functional tests was used. Typically, after a resting period of about five minutes, a succession of functional tests in a counterbalanced (Studies I, II) or fixed (Studies III, VI) order would follow, with recovery periods following each test. An exception to the counterbalanced order was made in Study II in case of paced breathing which always came last in order to avoid possible carry-over effects. Typical length of the functional tests was two minutes (five in the case of Study III), whereas the length of the recovery periods was mostly two minutes, three minutes being allowed following paced breathing. In Study III the tests and the recovery periods took five minutes, since the selectivity of the functional tests demanded that exhaustion be reached in some subjects. In Study VI we allowed 10 minutes of relaxation following the orthostatic test, 5 minutes following the mental arithmetic and had 15 minutes of recordings in resting conditions.
An overview of experimental procedures is given in Table I

<table>
<thead>
<tr>
<th>Cognitive</th>
<th>Physical</th>
<th>Sensory</th>
<th>Autonomic</th>
<th>Order of tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>Stroop</td>
<td>Handgrip</td>
<td>Paced breathing, Orthostatic</td>
<td>counter-balanced</td>
</tr>
<tr>
<td>Study II</td>
<td>Stroop</td>
<td>Handgrip</td>
<td>Sound</td>
<td>Paced breathing, counter-balanced</td>
</tr>
<tr>
<td>Study III</td>
<td>Chewing</td>
<td></td>
<td></td>
<td>sequential</td>
</tr>
<tr>
<td>Study VI</td>
<td>Mental arithmetic</td>
<td>Handgrip</td>
<td>Orthostatic</td>
<td>sequential</td>
</tr>
</tbody>
</table>

**Measurements**

**Heart Rate Variability**

In Studies I-V bipolar electrocardiogram (ECG) was continuously recorded throughout the experiment using Biopac© (BIOPAC Systems, Inc, Goleta, US; Study I) or LabLineV® (Coulburn Instruments, Allentown, US; Studies II-IV) equipment which was also used for other recordings, with the exception of Study IV where heart rate data was obtained indirectly via blood pressure measurements due to external disturbances. In Study VI, in addition to the wrist cardiac monitor used in the field recordings of autonomic reactivity to functional tests, 24-hour ECG was recorded using the Holter cardiac monitor for three consecutive days.

Mean values of heart rate in particular stages of the experiments were calculated and reported.

Following screening of the original ECG record and the removal of artefacts and ectopic beats, series of inter-beat intervals expressed as instantaneous heart rate was plotted vs. time as a regularly sampled time-series. Non parametric (Fast Fourier) spectral decomposition methods were used following interpolation of the instantaneous heart rate curve. Spectral powers in low (LF, 0.04-0.15 Hz) and high (HF, 0.15-0.4 Hz) spectral bands were calculated. Usual length of the moving window used for the calculation of HRV parameters was 2 minutes, and the window moved throughout the recording at a step of 10-15 seconds. Time-domain HRV parameters, based on inter-beat intervals and successive differences of inter-beat intervals were also calculated (Task Force 1996).

Mean values of time- and frequency-domain HRV parameters were then calculated.
**Blood pressure**

Remotely controlled automatic brachial cuff measurements were applied in Study II, at discrete time points during the experiment, so that they coincided with the beginning and the end of recordings in resting conditions, with each functional test and with subsequent recovery period. Non-invasive beat-to-beat blood pressure measurements and hemodynamic monitoring using finger cuffs were applied in Studies III and IV, using the oscillometric method (Portapres®, Finapres Medical Systems, Amsterdam, The Netherlands). Manual brachial cuff measurements were used in Study V and in Study VI an Omron wrist cardiac monitor was used.

**Local blood flow**

Fingertip plethysmogram was recorded in Studies I and II. We measured the envelope of the plethysmographic signal and used the inverse of the integral of rectified plethysmogram as the index of local vasoconstriction. Mean value of the sympathetic vasoconstriction index, which was calculated each 15 seconds, was derived for each experimental stage.

**Respiration**

In Study I the respiration rate was recorded using a tension strip placed across the chest at approximately the lower end of the sternum. In Study II the respiration rate was recorded using a bellows pressure transducer placed at approximately the same location. By means of a Matlab script which detected the pivotal point of each inspirium, instantaneous breathing rate was calculated on a breath-to-breath basis and plotted against time, and means per stage calculated.

**Electrodermal activity**

In Studies I and II electrodermal activity was assessed through the measurement of skin conduction using a commercially available transducer-amplifier. Measurements were conducted in AC-coupled mode so that only phasic activity (electrodermal responses and spontaneous activity) rather than tonic changes were recorded. Following scrutinization for artefacts the records were fed into a Matlab script that calculated the number of electrodermal responses and their intensity measured as the area under the rectified curve at 15 second steps. Experimental stage means were then calculated.

**Muscle activity**

In Study II trapezius EMG was recorded using a pair of electrodes placed on the descending fibres of the right trapezius, by means of a differential amplifier. In Study III similar electrodes were placed on the masseter, paralleling the direction of the fibres. In both studies root mean square of the EMG signal was calculated and used as the measure of electromyographical amplitude, whereas mean power frequency was used in order to detect possible signs of fatigue. In
Study III wavelet-based algorithms were employed. In the latter case an attempt was made to describe the electromyographical pattern of mastication by looking at the peak amplitude in each bite, and by calculating bite-to-bite intervals.

In Study I the use of paraspinal EMG was deliberately avoided, in order not to introduce a source of discomfort for the seated subject, and since there are relatively numerous earlier indications of paraspinal muscle behaviour in chronic pain (Collins et al. 1982; Cohen et al. 1986; De Good et al. 1994; Burns et al. 1997; Crossman et al. 2004).

Proprioceptive tests

Lumbar proprioception

The data on lumbar proprioception were not included in Study I, but became available at the time of writing. The tests were carried out in seated subjects who were led to a target position and then asked to reproduce it. Through sensors at three spinal levels angular positioning error was measured and variable and constant errors calculated. Detailed procedure and the results are described in Åsell et al (2006).

Shoulder proprioception

In Study II active-active ipsilateral arm repositioning tests were used for the assessment of shoulder position sense. A motorized rig connected to a recording system was used (for a detailed description see Bjorklund et al. 2000; Sandlund et al. 2006). A series of 24 movements towards two target positions, corresponding to 18.5 degrees from the sagittal plane ("long" movement) and 31.5 ("short") were initiated from the starting position of 50 degrees measured from the sagittal plane, in a counterbalanced sequence between targets. Familiarization trials were allowed in the beginning. Audio indication of the target position area was given to the subjects, who were otherwise blindfolded and an attempt was made to exclude all other sensory cues such as cutaneous and mechanical. Variable and constant errors were calculated for each target position separately.

Biochemical tests

In Study V a number of biochemical measures were used with the aim of assessing possible neurohormonal, humoral and metabolic changes which might explain hypothesized changes in glucose metabolism and insulin sensitivity. Furthermore, some of these measurements were also important in the description of the autonomic response to the model of monotonous fatiguing work which has earlier been shown to have effects on proprioception (Bjorklund et al. 2000).

Euglycemic hyper-insulinemic clamp is a procedure assessing whole-body glucose turnover. It starts with a priming dose of insulin injected i.v. for about
10 min in order to activate as many insulin receptors as possible, followed by a steady infusion of insulin for another 110 minutes which aims to achieve steady hyperinsulinemia. Glucose injection is initiated during clamp, and blood glucose measured at five-minute intervals. The rate of glucose injection is adjusted so that approximately constant level of blood glucose is maintained in repeated sampling. Glucose infusion rate is then taken as the measure of insulin sensitivity, adjusted per body mass.

Commercially available analytical kits and procedures were used for the measurement of blood glucose, serum insulin and cortisol, and plasma free fatty acids, lactate, noradrenaline, adrenaline, leptin, adiponectin, TNF-alpha, IL-6 and C-peptide.

In Study VI salivary cortisol was measured. Five daily measurements were performed and the analysis was relegated to a third party, following the collection and deep freezing of samples, using commercially available tubes.

An overview of measured parameters in each study is given in Table II.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Physiological</th>
<th>Biochemical</th>
<th>Proprioceptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>HRV, PPG, BRE, EDA</td>
<td></td>
<td>lumbar CE VE *</td>
</tr>
<tr>
<td>Study II</td>
<td>HRV, BP, PPG, BRE, EDA, tr. EMG</td>
<td></td>
<td>shoulder CE VE</td>
</tr>
<tr>
<td>Study III</td>
<td>HRV, BP, PPG, masseter EMG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study IV</td>
<td>HRV, BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study V</td>
<td>HRV, BP</td>
<td>serum cortisol, catecholamines, glucose, insulin, leptin, IL-6, TNF-alpha</td>
<td></td>
</tr>
<tr>
<td>Study VI</td>
<td>HRV, BP</td>
<td>salivary cortisol</td>
<td></td>
</tr>
</tbody>
</table>

* - Data presented in Åsell et al, 2006.

**Questionnaires**

In Studies I, II, III and VI a number of questionnaires assessing pain-related disability, perceived stress, self-efficacy and musculoskeletal symptoms were applied. An overview of the questionnaires is given in Table III.
Table III - Assessment of pain, disability, general health and functioning in individual studies

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pain / Symptoms</th>
<th>Disability</th>
<th>General health</th>
<th>Stress / Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>VAS pain</td>
<td>Oswestry Disability Questionnaire</td>
<td>SF-36</td>
<td>Self-efficacy Scale</td>
</tr>
<tr>
<td>Study II</td>
<td>VAS pain</td>
<td>Neck Disability Index</td>
<td>SF-36</td>
<td>Self-efficacy Scale</td>
</tr>
<tr>
<td>Study III</td>
<td>pain ratings, symptom description</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study VI</td>
<td>Standardized Nordic Questionnaire</td>
<td></td>
<td>Stress-energy questionnaire</td>
<td></td>
</tr>
</tbody>
</table>

Pain estimates

In Studies I and II 100-mm Visual Analogue Scales (VAS) were used for pain assessment. In Study III an 11-point (0-10) Numerical Rating Scale (NRS) was used, drawn on a 100-mm line. In Study IV an ordinary 11-point (0-10) Numerical Rating Scale was used. The scale was presented to the subjects at all times, within their sight, and frequent successive estimates obtained from them verbally.

Data analysis

Normalisation

In psychophysiology the Law of Initial Values is used to denote the concept that the starting level of a particular physiological variable determines the increase of that variable in subsequent activation. Regulation span of physiological variables is not indefinite, due to exhaustion or saturation of the effectors systems, and pre-activation levels ought to be taken into account when comparing the absolute increases in response to functional tests (e.g. Fahrenberg et al. 1995).

Normalised differences were used for the assessment of autonomic reactivity in Studies I-IV. The differences were calculated by subtracting the value of a particular parameter during the rest period preceding a functional test from the value of the same parameter during the functional tests. The differences were then divided by the value of the parameters preceding the test. The formula was:

\[ X_{\text{norm}} = \frac{(X_{\text{test}} - X_{\text{relax}})}{X_{\text{relax}}} \]

Additional transformations in the form of logarithms were used in electrodermal reactivity scores. In Study VI, absolute increases were compared in the assessment of reactivity. The design of the study allowed this since the
measurements were repeated within subjects, and there were no major a priori differences in resting levels between the subgroups.

**Statistical procedures**

**Comparison of main effects**

Type of distribution of physiological and clinical variables was assessed using the Kolmogorov-Smirnoff test and checking for the normal distribution.

In Studies I-III, normally distributed data were examined using univariate or multivariate analysis of variance (ANOVA, MANOVA) with group as the between-subject factor and in cases where the existence of confounding factors was confirmed by using (multivariate) analysis of covariance with group as the between-subject factor and age and gender as covariates. Bonferroni’s correction for multiple comparisons was used when necessary. In some studies (V, VI), Student’s t-test was used for group comparisons.

In Study II, proprioceptive data was analysed using mixed-model ANOVA with group as the between-subject factor and target as the within-subject factor.

Non-normally distributed data were analyzed for group effects using the Kruskal-Wallis and Mann-Whitney non-parametric tests.

In comparisons of pre- and post effects in a single experimental session, or when the independence of measurements could not have been assured, repeated measures ANOVA was used. If the sphericity assumption had not been met, Huyn-Feldt correction was used. In Study VI paired Student’s t-test was also used for pre-post comparisons (Study VI). For non-normally distributed data Wilcoxon’s signed-ranks test was used.

Relationships between the observed variables were detected using Spearman’s or Pearson’s correlations, depending upon the type of distribution of variables.

**Patterning**

Individual response specificity is defined as the tendency of a person to show similar patterns of physiological response across a set of diverse conditions during a single tests session. We described the response patterns using two independent ways of pattern description, on the ordinal and interval scale levels (Marwitz and Stemmler 1998). On the ordinal scale, Kendall’s coefficient of concordance (Kendall’s W) was calculated on the basis of rank-ordered, scaled (z-transformed) physiological responses. Chi-squared based comparisons of the similarity of response patterns are used to evaluate significance of patterns. Correlation statistics were used on the interval scale and correlations coefficients calculated for all variables and experimental conditions, giving a single average correlation coefficient per subject. Average correlation coefficient across all subjects, variables and conditions was then calculated and subtracted from
individual correlation coefficients to obtain a measure of individual response specificity.
Overview of individual studies

Study I

The aim of the study has been to investigate autonomic activity at rest and in response to functional laboratory tests in patients with chronic LBP, and to study its relationships with the clinical picture as seen in pain, activity limitations and general health.

We detected significant differences between groups in resting values of heart rate (gender x group interaction p<0.001), low (p=0.001) and high (p=0.001) frequency spectral powers and in electrodermal activity (p=0.048). Significantly higher resting heart rate was detected in female LBP subjects, whereas in males both the control group and the LBP group showed higher values of heart rate. In all LBP subjects we detected an increase in spontaneous electrodermal activity at rest, an increase in LF spectral power and a decrease in HF spectral power as compared to the control group, as shown in Figure 1.

Figure 1 - Resting values in LBP and in control subjects (mean ± SE), asterisks indicate significant differences at p<0.05.
We failed to detect any differences between the groups with respect to the reactivity scores in response to the functional tests. Repeated measures ANOVA revealed that each functional test succeeded in changing the level of activation in comparison with the preceding relaxation period, but group differences in the responses were absent.

An attempt to characterise the pattern of responses to each functional test amongst the two groups did not reveal the presence of significant patterns.

In tests of autonomic function such as the orthostatic test and the paced breathing tests we detected that subjects performed within clinically accepted limits of normal function.

Clinical characterisation of the LBP subjects was made, using the initial diagnoses from the primary healthcare, the McKenzie evaluation, Oswestry Disability Questionnaire and VAS pain levels in the lumbar region. The criteria for sub-grouping were, for each specific parameter:

- Diagnoses - specific (lumbago sciatica, slipping discs, spondylolisthesis, n=49) and non-specific (lumbago, n=39), contrasted to controls (n=31).
- McKenzie diagnoses: derangement (n=36), dysfunction (n=27), contrasted to controls (n=31)
- VAS pain - low pain (0-60 mm, n=46), high pain (60-100 mm, n=41), contrasted to controls (n=31)
- SF-36 bodily pain index - range 0-35 (n=43, including the controls), 36-70 (n=45), 71-100 (n=29)
- Oswestry Disability Questionnaire score: disability level minimal or moderate (0-40 points, n=69), high disability (41-60 points, n=19), contrasted to controls.

No differences in autonomic regulation between any of the subgroups were detected. There were no significant correlations between pain ratings, disability scores and autonomic reactivity.

Integral parts of the project were also proprioception tests. As reported in Åsell et al (2006), no differences in lumbar proprioception between the groups were detectable. Åsell et al also found rather weak correlations between disability and proprioception (VE and the Oswestry score for walking, and CE and the Oswestry score for personal care).

On the basis of above presented data, we concluded that there are indications of increased sympathetic and decreased parasympathetic tonus in CLBP at rest, regardless of pain levels, functional disability and status indices and without indications of differences in physiological reactivity or response patterns.
### Study II

The aim has been to investigate autonomic activity at rest and in response to autonomic function tests, as well as the acuity of shoulder proprioception in subjects with WAD and non-traumatic neck-shoulder pain, in relation to subjective symptoms and self-rated functioning and disability.

Recordings during resting revealed higher heart rate (\(p=0.005\)) and lower heart rate variability in time-domain in the WAD group (SDNN, \(p=0.004\); MSSD, \(p=0.007\); NN50 \(p=0.012\)), as compared to the control group. In comparison with the controls, NT pain group showed only significantly lower amplitude of local blood flow as recorded by plethysmography (\(p=0.050\)), Figure 2.

![Figure 2](image)

**Figure 2** - Physiological variables during resting (mean ± SE) in WAD and NT groups and controls, asterisks indicate significant differences at \(p<0.05\).

When exposed to sensory stimulation in the form of unpleasant sound, the WAD group showed increased reactivity as measured by relative increases in heart rate (\(p=0.002\)) and electrodermal responses (\(p=0.047\)), with concurrent trends towards heart rate variability increase (SDNN, \(p=0.093\)) and an increase in diastolic blood pressure (\(p=0.096\)), as compared with the control group. In exposure to the same type of stimulus the NT group showed only a trend towards increased electrodermal reactivity (\(p=0.061\)).
However, in response to the cognitive challenge in the form of Stroop Colour-Word test, opposite result were noted in WAD - namely a decrease in reactivity, as seen in trends towards a smaller increase in heart rate (p=0.070) and a smaller decrease in heart rate variability (MSSD, p=0.063), and in significantly lower electrodermal reactivity (p=0.002) as compared to the control group. No changes in reactivity were noted in the NT group compared to controls, Figure 3.

In response to the paced breathing test there were no differences between the groups with respect to respiratory sinus arrhythmia and autonomic reactivity. Similarly, there were no differences between the groups with respect to autonomic reactivity during the performance of the handgrip test.

It is worth noting that WAD subjects performed significantly worse in the Stroop Colour-word test than the other two groups (number of correct responses, WAD-NT p=0.001, WAD-Control p=0.001).

In shoulder proprioception tests no differences between the groups were detected. Similarly, there were no differences in the amplitude and frequency content of trapezius EMG between the groups during functional tests or recovery periods.
WAD was in general characterised by more pain (p<0.001), both in the week prior to the testing, immediately before the testing and after it (Figure 4). WAD pain scores also increased significantly following the experiment. In addition to pain scores, WAD had consistently higher scores of mental stress and exertion compared to the NT and control subjects immediately before, during and after the testing (see Study II, Table V for details). Both chronic pain groups also showed a reduction in pain scores from the week prior to the testing up until the commencement of the experiment.

With respect to the clinical and functional data, a comparison between WAD and NT groups revealed that WAD was characterised by lower self-efficacy scores (p<0.001), higher disability (NDI p<0.001, PDI, p=0.002) and lower health-related quality of life (Figure 5).

WAD reported worse SF-36 scores for pain (p=0.002), physical (p<0.001) and social (p<0.001) functioning, role limitation due to physical factors (p=0.002) and less energy and vitality (p=0.001, Figure 6).

**Figure 4** - VAS-scale ratings of pain (mean ± SE). Asterisks indicate significant differences at p<0.05

**Figure 5** - Self Efficacy Scale, Pain disability Index and Neck Disability Index total scores, (mean ± SE). Asterisks denote significant differences at p<0.05.

**Figure 6** - SF-36 subscale scores (mean ± SE). PF-physical functioning; RP-role limitation due to physical factors; RE - role limitation due to emotional factors; SF - social functioning; MH - mental health; EV - energy and vitality; BP - bodily pain; HP - health perception; Asterisks denote significant differences at p<0.05.
Heart rate reactivity during the Stroop test was found to negatively correlate with NDI scores in the WAD group (r=-0.502, p<0.001). No other relationships between autonomic reactivity parameters and pain and disability indices were found.

Higher pain and disability levels in WAD than in NT prompted the comparative analysis of similar levels of disability in the two chronic pain groups. None of the NT subjects were classified as having severe or moderate disability according to the Neck Disability Index (i.e. NDI score > 30). Most of the NT subjects (n=25) and slightly more than a half of the WAD subjects (n=23) fell into the groups showing mild disability and were directly compared with respect to pain levels disability, function and autonomic reactivity. Only the health perception according to the SF-36 questionnaire differed, with worse physical and social functioning detected in WAD.

We concluded that moderate signs of autonomic involvement, as seen in differences at rest (HRV) and in differences in reactivity (HRV, EDA) in response to sensory and cognitive tasks, were present in WAD but not in NT neck pain, without signs of sensorimotor dysfunction in either group. More intense symptoms in WAD than in NT impede from attributing this involvement to etiological factors.

**Study III**

The aim of the study has been to assess autonomic regulation, masseter EMG, pain and exertion in individuals suffering from WAD in response to a functional chewing test.

A significant component of the chewing tests was the evaluation of endurance, which was previously shown to be much shorter in WAD (Haggman-Henrikson et al. 2004). All healthy subjects completed the test without signs of pain or distress. Twelve out of 21 subjects failed to complete one or both tests (on the preferred and opposite side, presented in that order in the experiment). Early termination of the tests was paralleled in the appearance of a number of autonomic symptoms ranging from dizziness (n=8), vertigo (n=6), sweating (n=5) and tachycardia (n=5) to nausea (n=2). Tiredness and exhaustion were indicated by 14 out of 21 subjects.

In Study III pain levels were not significantly different between the preferred and opposite side. There was a clear increase in pain from resting to the chewing tests (p<0.001), and a partial recovery after the chewing tests (p=0.053), but recovery levels were still significantly higher than rest (p<0.001, Figure 7)
Consistently increased heart rate, systolic and diastolic blood pressure were noted in the WAD group, in comparison with the control group (p<0.001 for all variables). This difference was present in resting, during the chewing tests and in recovery periods. Similar difference between the groups was noted in HRV parameters, with significantly higher LF spectral power (p=0.044), a trend towards lower HF spectral power (p=0.070) and significantly lower time-domain measures of HRV (SDNN, NN50 p<0.001). Data are presented on Figure 9 on the opposite page.

Cardiac reactivity was consistently higher in the WAD group than among the controls, as reflected in increased heart rate reactivity scores (p=0.039 for the preferred side chewing test, p=0.049 for the opposite side).

There was however no difference between those WAD patients that completed the tests and those who failed to complete them with respect to autonomic reactivity and pain levels (see Study III for details).

**Figure 7 - Pain levels in WAD during the experiment (mean ± SE)**

**Figure 8 - Cardiac reactivity in response to the chewing tests on the preferred and opposite side (mean ± SE). Asterisks indicate significant differences at p<0.05.**
Pain levels during tests were significantly positively correlated with systolic and diastolic blood pressure (0.001<p<0.038, Study III, Table 2), and the group showing above-median pain levels also had significantly higher systolic and diastolic blood pressure during preferred-side chewing, with trends toward significance for the opposite side.
There were no differences between the groups in masseter peak amplitude in bite, root mean square amplitude, mean power frequency and the rhythm of chewing (see Study III, Figure 2). Electromyographic findings thus indicate absence of differences in muscle activity between the WAD group and controls.

On the ground of findings in Study III we concluded that there are signs of significant autonomic involvement in minor motor tasks such as chewing in both pain-free and WAD subjects. Consistent signs of increased autonomic activity seen in WAD reflect low endurance in tests, which seems to be caused by tiredness rather than local muscle fatigue.

**Study IV**

The aims of the study have been to investigate possible effects of a particular magnetic field on the intensity of experimental muscle pain as well as to evaluate pain-related changes in the ANS activity in exposure to experimentally induced muscle pain. The latter aim was naturally connected to the aim of the thesis dealing with relations between perceptive and autonomic components of muscle pain.

Infusion of hypertonic saline for 20 minutes into the erector spinae muscle simulated perceptive characteristics of chronic muscle pain in the low back region. Autonomic reaction to acutely appearing constant back pain was characterised by a significant increase in systolic (p=0.037) and diastolic (p=0.033) blood pressure. The response to pain as seen in cardiovascular variables was not gender specific, and did not involve an increase in heart rate.

![Figure 10 - Pain levels and physiological reaction to experimentally induced pain](image-url)
Systolic blood pressure response was positively correlated to averaged pain ratings (p=0.017), with a somewhat weaker correlation being noted for the diastolic blood pressure (trend towards significance at p=0.076).

Relevant conclusion in Study IV with respect to the aims of the thesis concerns the rather clear correlation between blood pressure reaction and the intensity of low back pain induced by the infusion of hypertonic saline.

**Study V**

The aim of the study has been to investigate whether insulin resistance is promoted by monotonous, repetitive arm work with a significant static component, as related to the aim of the thesis regarding autonomic and neurohormonal regulation in experimental low-level monotonous work.

In response to repetitive work, a significant increase in heart rate (p<0.001), low frequency spectral power (p=0.038) and a reduction in high frequency spectral power (p=0.032) were noted (Figure 11).

![Figure 11 - HRV parameters during the monotonous work task (mean ± SE)](image)

Simultaneously there was an increase in systolic blood pressure during repetitive work, whereas the diastolic blood pressure remained fairly constant. In comparison with dynamic exercise this increase in systolic blood pressure was significantly smaller, and in dynamic exercise there was a significant reduction in diastolic blood pressure as compared to the repetitive work (interaction condition x time, p=0.020 for systolic, p=0.044 for diastolic, Figure 12). Recovery from dynamic exercise took longer, with higher levels of heart rate (p=0.001) and LF spectral power (p=0.005), and lower HF spectral power (p=0.004) during the post-exercise period, see Study V, Table 2.
An increase in catecholamine levels in both active tasks was detected, with significant differences from the resting condition. There were also differences between the active tasks, where repetitive work was characterised by lower catecholamine levels than cycling (Figures 13, 14). Cortisol levels, however, were unaffected by the different conditions. Plasma lactate levels increased in both active tasks, in cycling and repetitive work, and there were no differences between the tasks with respect to lactate levels. Detailed data and significance levels are presented in Study V (Tables 3, 4).

Leptin and adiponectin levels were similar for all groups, as was TNF-alpha. A slight tendency towards increased IL-6 levels in cycling was found, as well as an increase in plasma free fatty acids towards the end of the cycling task.

The most important finding is the detection of transient insulin resistance during the steady state period of the hyperinsulinemic clamp as seen both in M-values (glucose utilisation rate) and when calculated as the insulin sensitivity index, at
80 (p=0.040) and 100 minutes (p=0.010) post-work, Figure 15. There was a complete restitution of free fatty acid levels and cytokines towards the end of the clamp, as well as no difference in cortisol levels.

![Graph showing insulin sensitivity index during a steady-state hyperinsulinemic clamp.](image)

**Figure 15** - *Insulin sensitivity post-task, during the steady-state hyperinsulinemic clamp (mean ± SE). Asterisks denote p<0.05.*

We concluded that repetitive monotonous work might have subtle effects in acutely promoting insulin resistance in healthy subjects, as opposed to dynamic work, most probably due to the effects of catecholamines and sympathetic activation on metabolic function.

**Study VI**

The specific aim of the study has been to assess physiological and subjective stress markers during a 24-h ambulance work shift and in work-free days, and relate those parameters to self-reported health complaints. The aim of the study is related to the general aim of the thesis to investigate the characteristics of autonomic regulation in subjects with stress-related health complaints including musculoskeletal symptoms.

In Study VI assessment of autonomic reactivity at the start and the end of the working shift revealed no significant differences between the first and the second session. However, when comparing personnel with many health complaints to those with few complaints, we detected higher heart rate at rest (p=0.043) and higher systolic blood pressure reactivity in response to the mental arithmetic test, both in the first and the second session (Figures 16, 17). In subjects with many health complaints an increase in morning cortisol levels during the working day was also detected (p=0.038, Study VI, Table 2).
Figure 16 - Difference in resting heart rate (mean ± SE). Significant differences between the groups are marked with an asterisk.

Figure 17 - Blood pressure reactivity in mental arithmetic tasks (mean ± SE). Significant differences between the groups are marked with an asterisk.

Circadian variation of HRV was on the general more pronounced in the group having few health complaints. The group with few complaints was also younger than the one with many complaints (p=0.002). Among subjects with many health complaints we noted a difference in circadian HRV, with a tendency towards higher sympathetic activity (as seen in LF spectral power) and lower parasympathetic activity (HF spectral power) late in the night and in early morning hours of the workday (LF: p=0.022; HF p=0.025, compared to the first work-free day, Figure 31). These differences were not observed on the work-free days in the complaining group and no differences in circadian HRV were detected between the days in the group with few health complaints.

Figure 18 - Circadian HRV as measured by low frequency spectral power (mean values) during the work shift and in work-free days, in subjects with many (left panel) and few (right) musculoskeletal complaints. Asterisk in the left panel indicates significant differences at p<0.05.

On the basis of the results in Study VI, we concluded that there were no strong physiological indications of occupational stress although in workers with many stress-related health complaints higher morning cortisol and modest deviations in circadian HRV during work and increased reactivity to mental stress were detected.
Discussion

**Autonomic regulation and balance**

The ANS maintains its regulatory function through the activity of its two branches, the sympathetic and the parasympathetic. A number of autonomic reflexes are involved in the regulatory role, whereby sensory afferent input evokes autonomic efferent activity. Among the most important autonomic reflexes is the baroreceptor reflex, where specialised mechanoreceptors in the aortic arch and carotid sinus respond to the changes in arterial blood pressure. Their activation results in the inhibition of the vasomotor centre in the medulla, and consequent reduction in sympathetic arterial tone, and at the same time through the stimulation of cardiovagal neurons to a reduction in heart rate. Modulation of heart rate through breathing is also accomplished through autonomic reflexes and cardiovagal efferentation. Baroreflexes are central to a number of autonomic function tests such as the Valsalva maneuver, whereas exercise reflexes are involved in tests such as the orthostatic and the handgrip test (Levine and Luders 2000). In general, normal response to tests of autonomic function usually involves orchestrated action of both autonomic branches in a number of reflex loops such as exercise- and baroreflexes in the orthostatic test or handgrip (Ravits 1997).

Activation patterns of the two branches of the ANS are not necessarily reciprocal. The two branches may be activated in a reciprocal manner, but also concurrently or unilaterally. Increased cardiac output, for example, may be achieved through sympathetic activation, but slight bradycardia induced by concurrent parasympathetic activation might allow for a greater diastolic filling of the heart. Unilateral changes in vascular regulation (sympathetic activation), or in response to mental stress (parasympathetic withdrawal) have also been described. Discrete and specialised functional pathways exists in autonomic regulation for example in vascular control where baroreflex activation mostly affects muscular but not cutaneous vascular tone (Sharkey and Pittman 1996). By using tests of autonomic function which involve a timed sequence of changes in the sympathetic and parasympathetic activation it is possible to assess relative contributions of each of these systems in normal autonomic reflexes (Freeman 2006).

It has been proposed that certain cortical and sub-cortical circuits (central autonomic network and the anterior executive region) play a mutually competitive role in regulating autonomic and behavioural features, thus linking both structurally and functionally physiological and psychological processes. When the prefrontal cortex reduces its inhibitory role in such a dynamic situation, reduction in parasympathetic activity follows and autonomic imbalance in the form of sympathetic dominance is established. This is reflected...
in lower HRV, immune dysfunction etc., and is claimed to be potentially pathogenic (Thayer and Brosschot 2005). It has also been argued that the imbalance between mineralocorticoid receptors (responsible for activation thresholds) and glucocorticoid receptors (responsible for recovery) and the activity in the limbic system affects the HPA axis. Imbalance between the activity of these two types of receptors, either due to genetic factors or chronic stress is thought to contribute significantly to stress-related disorders (De Kloet 2003). Chronic imbalance of the ANS is thought to be a prevalent risk factor for cardiovascular disease (CVD), for example, and events stimulating the parasympathetic tone are to be encouraged from the clinical point of view (Curtis and O'Keefe 2002).

With this in mind it has been hypothesized that signs of autonomic imbalance would be present in chronic pain, and possibly also in pre-clinical working population.

A consistent finding in our studies on chronic pain patients was the presence of differences in resting levels between patients and control subjects.

Cardiovascular differences in resting values were rather consistent in our sample, and were observed in three out of four chronic pain groups (LBP, WAD in Study II and WAD in Study III) in HRV values, and in one group in blood pressure. HRV differences were almost equally represented among time- and frequency-domain measures.

Differences in autonomic regulation at rest have been indicated in a number of chronic pain conditions. In case of fibromyalgia, there are indications of both circadian changes in autonomic activity levels (Martinez-Lavin et al. 1998) and pre-test levels of autonomic activity, as seen in heart rate variability and muscle sympathetic nerve activity (Furlan et al. 2005). In our studies the increase in resting values was most consistent for cardiovascular variables. It has been argued previously that changes in heart rate might reflect more of a central command aspect, whereas vascular changes are subject to more local influences (Hjortskov et al. 2004). Such an explanation is certainly plausible in our sample as well. Additionally, as argued in Study VI, the anticipatory arousal cannot be excluded as a possible cause, especially in the group of pain-free subjects in normal occupational settings.

In one group of chronic pain subjects (LBP) we detected significant increase in resting levels of electrodermal activity (EDA). Higher resting EDA was indicated previously in chronic low back pain (Peters and Schmidt 1991), and is thought to reflect predominantly affective and emotional components of arousal (Kohlisch and Schaefer 1996; Bradley and Lang 2000). Our findings fully corroborate earlier findings in LBP (Peters and Schmidt 1991) and indicate sympathetic arousal at rest in that group. In our study EDA was used as a good indicator of general arousal rather than a clinical parameter.
Changes in peripheral blood flow at rest were observed only in the NT group, which had a more prominent sympathetic vasoconstriction in comparison with the control group. This finding might be explained by the so-called paradoxical vasoconstriction. At low levels of sympathetic activity the antidromic vasodilatatory mechanism usually prevails over the sympathetic vasoconstriction (Habler et al. 1997; Vissing 1997). However, opposite might also be true, as evidenced by a relatively frequent occurrence of a paradoxical temperature increase in response to cognitive challenge in some chronic pain patients. Such a reaction pattern is interpreted as a reflection of psychophysiological dissociation, since no differences between subjects with and without such paradoxical vasoconstriction were found in electrodermal activity (Wickramasekera et al. 1998).

We did not detect any differences between the groups with respect to resting respiration rate. Some earlier studies have found signs of changes in baseline breathing rate, in painful conditions such as temporomandibular disorder (Curran et al. 1996), while others fail to detect any, e.g. in chronic low back pain (Peters and Schmidt 1991). Our findings seem to corroborate those of the latter study.

Taken together, our findings regarding cardiovascular differences at rest appear to indicate rather high sensitivity of such measurements, and in particular heart-rate derived parameters. Local (NT) and systemic (WAD) vascular changes could potentially also be a good marker of muscle pain. The only group that does not show signs of consistent cardiovascular imbalance is the NT group, which is otherwise characterised by least pain and disability and best functioning.

**Autonomic reactivity**

Psychophysiological reactivity has been implicated in the origin of cardiovascular disease for a long time. It has been postulated for example that increased reactivity might originate at three distinct levels - the cortico-limbic, subcortical (brainstem) and finally the peripheral level. The first of these is characterised by cognitive and emotional sources of activation, whereas the second reflects mostly hypothalamic activity. Finally, changes at the peripheral level are usually characterised by underlying pathophysiological processes. It is argued that changes in each of these different origins of altered reactivity might cause, or contribute to, the development of cardiovascular disease (Lovallo and Gerin 2003). High reactivity as seen in cardiac sympathetic activity and catecholamines has been linked to a reduction in the cellular immunological response (Cacioppo et al. 1998), and high blood pressure reactivity to cognitive challenge is also thought to be a precursor of hypertension (Sherwood et al. 1995). There are opinions that the major significance of the findings of increased reactivity to acute laboratory stressors is in the role of stressors as
triggering events in personally relevant situations rather than causes of cardiovascular disease (Pickering 1990).

We hypothesised that changes in reactivity might be characteristic for chronic pain, and might be observed in pre-clinical populations.

There are essentially two divergent types of response in our sample, both of which occur in the WAD group. One is characterized by an increase in reactivity to sensory stimulation in comparison with the control group, as seen in cardiovasacular and sudomotor parameters. The other is seen in HRV and sudomotor parameters, in the same subject group in response to cognitive activation, and is characterized by a reduction in reactivity as compared to the control group. Thus there seems to be signs of sensory hyperreactivity and cognitive hyporeactivity in WAD.

Sensory hypersensitivity has been implicated in WAD with respect to mechanical and thermal stimuli (Sterling et al. 2003). Painful sensations originating from diverse sites and not only from the site of initial trauma in WAD are probably a consequence of altered central processing of nociceptive and other sensory input, which is possibly further aggravated by psychosocial stress (Curatolo et al. 2001). Increased reactivity in WAD in our study might be a reflection of sensory hypersensitivity.

We also notice diminished reactivity to cognitive challenge in WAD. There are reports of diminished sympathetic reactivity (vasoconstrictor response) in WAD which are correlated to higher indices of disability (Sterling et al. 2003; Sterling et al. 2005). In healthy subjects higher cardiovascular reactivity to mental arithmetic was associated with lower pain thresholds in subsequent cold pressor tests (Caceres and Burns 1997), which might indicate a normal response, whereas reduced reactivity might be characteristic for chronic pain.

The other traumatic neck pain group, WAD in Study III, showed only increased cardiac reactivity in response to what is in essence a physical task, but with a presumably strong sensory component (see the Discussion section, Study III). We saw no indications of increased reactivity in LBP, and noticed only signs of sudomotor reactivity in NT.

Reactivity to sensory and cognitive challenge distinguishes between WAD and NT groups in our study. There are earlier reports of a difference in the type of hypersensitivity between WAD and NT - in WAD sensory hypersensitivity is widespread whereas in NT it is localised over the cervical spine. WAD is also reported to have higher disability than the NT group (assessed through NDI) at comparable levels of pain (Scott et al. 2005). One confounding factor in our study has been the inequality of pain and disability ratings between the WAD (showing higher values of both) and NT, but still the difference in autonomic reactivity patterns between WAD and NT in response to sensory stimulation
seems to reflect the difference in central sensory processing between these two groups.

In FM at least, there are indications of blunted sympathetic reactivity as seen in blood flow in response to the cold pressor test (Qiao et al. 1991), in response to isometric contractions as seen in MSNA (Elam et al. 1992) and in response to auditory stimulation (Vaeroy et al. 1989). However, there are opposite findings in response to static contractions until exhaustion, where FM patients do not show signs of attenuated cardiovascular response (Kadetoff and Kosek 2007). The relationship between autonomic reactivity and chronic pain seems to be inverse (Okifuji and Turk 2002). In irritable bowel syndrome, for example, reduced cardiac reactivity to cold pain was noticed in patients as compared to controls, with a parasympathetic dominance in HRV measures (Tousignant-Laflamme et al. 2006). However, in our WAD group we noticed decreased reactivity in cognitive and not physical or sensory challenge. It seems possible that this reduction in reactivity in our sample could also be dependent upon the cognitive impairment earlier reported in WAD (Antepohl et al. 2003) or might depend upon some form of strategy used by subjects to reduce cognitive effort.

It has also been proposed that the appearance of specific reaction patterns might be characteristic for certain stress-related diseases. For example, in FM, in response to a series of acute stressor and relaxation tasks, four patterns of responses were identified, on the basis of sudomotor, vasomotor and muscular response (Thieme and Turk 2005). In asthma there are reports of two types of responses, where one is characterised by defensiveness, parasympathetic hyperarousal and sympathetic hypoarousal in response to stress, as seen in sudomotor and respiratory changes, whereas the other showed no defensiveness and also better spirometry results after stress (Feldman et al. 2002). Whether such observations are of any importance for the aetiology of these conditions is unclear. Subjects in our sample display no differences in the pattern of responses (individual response specificity) when compared to their respective control groups.

Pain and autonomic imbalance

Pain is a multidimensional experience, whose components reflect different aspects of nociceptive processing. Muscle pain, due to its nature, can be characterised by rather special representation of sensory-discriminative, affective and cognitive-evaluative components (Melzack and Casey 1967). Not enough is known about its autonomic component. Data from relevant experimental studies are predominantly concentrated on perceptive components of muscle nociceptive stimulation (Graven-Nielsen et al. 1998). Results concerning the reaction to experimentally induced muscle pain in Study IV confirmed our expectations that the perceived pain would be clearly correlated to increased blood pressure. Such relations, typical for other pain conditions,
were recently discussed in the context of common central mechanisms of pain perception and blood pressure regulation (France 1999).

Observed autonomic imbalance in subjects with MSD, characterized by increased sympathetic activity and decreased parasympathetic efferentation, could contribute to several mechanisms through which elevated levels of catecholamines increase the sensitivity to nociceptive signals from the muscles. These mechanisms include the sensitisation of peripheral receptors and the modulation of nociceptive afferent activity on segmental and suprasegmental levels (Passatore and Roatta 2006) and might also apply to the facilitation of perception of non-nociceptive signals including mechanical and thermal stimuli and to other sensory modalities. These findings thus lend physiological support to the phenomenon of general hypersensitivity observed in some forms of MSD. It is also worth noting that the perception of interoceptive signals is influenced by enhanced arousal, whereby amplification and misinterpretation of physiological signals might play a role in development of somatic pain (Barsky and Borus 1999).

In view of autonomic regulation on the basis of our data it may be concluded that three out of four chronic pain groups (LBP, WAD in Study II and III) exhibited clear signs of increased cardiovascular and sudomotor activity in resting conditions. Chronic pain groups characterised by generally higher levels of pain (WAD) were also characterised by increased cardiovascular reactivity to sensory and physical challenge and decreased reactivity to cognitive effort (Figures 3, 9).

We would also have to emphasise that there are numerous limitations in the adequate assessment of the intensity and other characteristics of pain experience. In our study we assumed that the preceding week’s pain ratings are valid for the characterisation of chronic pain groups for two reasons. Firstly, it has been shown that such measurements reliably represent general pain levels in patient groups (Jamison et al. 2006) and secondly they are less affected by expectations or anticipatory arousal than pain ratings in connection with testing, which might explain the reduction in pain ratings in our study from the preceding week to the day of testing. Increase in pain ratings following the testing was observed in some chronic pain groups, whereas among others and in controls it was absent. This seems to indicate that the tests themselves do not induce pain, but that the slight increase in pain ratings after testing is a consequence of patients’ generally increased sensitivity.

**Disability, self-efficacy and general health**

The LBP group in our sample was not characterised by differential reactivity and did not show highest pain levels, but still it shows high disability. The
reason for this could be that low back pain is perceived as more debilitating than neck pain given comparable pain levels.

One important difference between the WAD and NT groups in our studies with respect to the disability levels is the absence of NDI disability levels moderate/severe (NDI > 30) from the NT sample. NDI has been used as a predictor for the development of chronic musculoskeletal and psychosocial complaints as well as motor derangement in WAD (Sterling et al. 2003). Consequently, no “equal-symptom” comparisons with possible repercussions for the aetiology could have been possible between these two groups in our sample.

All of our chronic pain groups seem to be similar to the comparable chronic pain groups in previously published studies with respect to the SF-36 scores (Laursen et al. 2005; Zanoli et al. 2006). One should of course bear in mind that our groups and those listed for comparison do not always embrace similar diagnoses, and that there could be considerable differences in sample size.

**Proprioception**

The data about possible changes in proprioception in patients with MSD remain controversial. In the context of this work we were especially interested in relations between autonomic imbalance and possible worsening of proprioception. Direct effects of sympathetic activation on muscle spindle afferentation were mainly observed in animal studies (Grassi et al. 1993; Hellstrom et al. 2005).

In human experimental studies the effects of sympathetic activation on proprioception seem to be less clear. Hjortskov et al (2005b) investigated the effects of sympathetic outflow on the stretch reflex and found that the sympathetic nervous system can exert a direct influence on human muscle spindles. However, shoulder proprioception is not affected if a short-lasting high-intensity experimental protocol is used (Sterner et al. 1998). Matre & Knardahl (2003) did not observe any impairment of ankle proprioception following exposure to acute stressors in the form of cold pressor and glucose tolerance tests, the latter even reducing movement detection thresholds in flexion. Likewise, Macefield et al (2003) were not able to detect any modulation of muscle spindle activity during sympathetic bursts caused by inspiratory capacity apnoeas.

Experimental data on humans indicate that muscle fatigue due to monotonous low-level muscle load might cause an impairment of position sense. Björklund et al (2000) found diminished position sense acuity in the shoulder following ten minutes of repetitive load designed to imitate a working episode typical for assembly line work. A decrease in shoulder position- as well as movement sense is also found following fatiguing exercise (Voight et al. 1996; Carpenter et al. 1998). There are also indications of impaired shoulder proprioception in neck
and shoulder pain (Revel et al. 1991), and WAD in particular (Kristjansson et al. 2003; Sandlund et al. 2006).

In spite of indications of impaired lumbar proprioception in LBP (O'Sullivan et al. 2003) no such differences were detected in our sample (Asell et al. 2006). Absence of proprioceptive changes in LBP (Newcomer et al. 2000; Koumantakis et al. 2002) has been explained by the inability of repositioning tests to adequately assess altered sensorimotor processing as seen in for example lumbar instability and impaired coordination, both of which are often reported in LBP (Asell et al. 2006).

In WAD it is possible that the intensity of autonomic imbalance as observed in our studies is not sufficient to evoke effects on proprioception. Methodological differences could also be behind the discrepancy in findings in WAD shoulder proprioception, since the tests used in Study II and in the study by Sandlund et al. (2006) differed in the presentation of the target position (see Study II, Discussion section).

**Occupational stress**

An essential role of the autonomic imbalance is assumed in the genesis of MSD. Therefore one might expect that occupational risk factors such as psychosocial stress and monotonous work would promote, even if only transiently, changes in autonomic regulation similar in character to those seen in MSD.

As the results of Study V show, a reduction in insulin sensitivity has been detected following a bout of monotonous repetitive work. An important aspect of autonomic activity is its influence on metabolic processes as part of a normal stress response. Impaired insulin function is closely related to hypertension and excessive vascular reactivity (Nazzaro et al. 2000). Even short-lasting laboratory stressors are able to significantly affect metabolic regulation. Physical stress (cold pressor) and its associated autonomic reaction were shown to be able to affect insulin function (Lindmark et al. 2003). We assessed the association between autonomic activity and insulin resistance in monotonous work. Changes in autonomic balance during the work were accompanied by an increase in catecholamine levels but not cortisol. All other possible causes of impaired insulin sensitivity, such as adipokines and cytokines did not show significant change during task performance. Our data therefore seem to corroborate the reports indicating autonomic imbalance as a factor in the genesis of insulin resistance. One possible systemic indicator of insulin resistance is blood pressure, which in our case increased in task, and there are earlier reports that increased vascular resistance is negatively correlated with insulin sensitivity (Baron et al. 1993). On the basis of our data it may be concluded that autonomic imbalance associated with certain types of occupational exposure might
transiently adversely affect metabolic function as seen in insulin-mediated glucose uptake.

Study VI was conceived as an evaluation of subjective and physiological stress in a working population initially assumed to be under sizeable psychological stress. Post-traumatic stress syndrome has been indicated among ambulance personnel in earlier studies (Clohessy and Ehlers 1999; Jonsson et al. 2003). We evaluated the relation between stress at work, self-reported health and physiological reactivity. When dichotomising the subjects with respect to subjective health complaints, a pattern emerged where the subjects with many complaints exhibited more worry about working conditions, slight difference in resting heart rate and morning cortisol, increased blood pressure reactivity to the mental arithmetic test and a slight alteration of the circadian HRV pattern during the work shift as compared to work-free days (Study VI, Figure 4, Tables 2, 3). One possible explanation for the observed differences in heart rate at the beginning of the shift and morning cortisol values at work might lie in the effects of anticipatory stress and related worry about work conditions, whereas increased blood pressure reactivity and circadian HRV could simply reflect age-related changes. As our data show (Study VI, Figure 3), stress and energy scores were rather close to the neutral line, indicating that in the studied group stress usually takes the form of relatively seldom appearing high-impact events rather than consistent exposure to series of stressful events. This is also confirmed by the long hours of presence at the station between call-outs and generally satisfactory amount of sleep during the night on duty.

**Methodological considerations and directions for further research**

The choice of methods in our studies has been based on the need to process a substantial number of subjects in clinical settings. In practice this limited us to the use of non-invasive physiological recordings where every effort has been made to cover as many relevant effector systems as possible. More demanding techniques that also provide information on sympathetic activation, such as direct measurements of sympathetic efferent activity using microneurography, or the measurements of blood flow using the Doppler laser, although desirable, were thus effectively excluded.

Tests of autonomic function were grouped in a test battery and presented in succession. Adequate time for familiarisation with laboratory surrounding, sufficient time for the avoidance of anticipatory arousal, and sufficient time for recovery have been taken into account in test design. However, the addition of long-term monitoring of autonomic regulation would be beneficial. It would add potentially important information from the standpoint of circadian regulation in both chronic pain and occupational exposure.
Cross-sectional design of the studies does not permit one to establish the causality of the observed effects. However, efforts have been made to stratify the subjects as well as possible with respect to pain, function and diagnoses. In chronic pain conditions it is rather difficult to determine the exact time of the onset of symptoms. Any retrograde analysis is dependent upon subjects’ recollection and possible attribution of symptoms which are significant sources of variability in the data.

The model of repetitive work used in Study V is becoming increasingly less represented in current occupational settings. In spite of its use in studies on autonomic and metabolic regulation and proprioception, a more relevant model of work might be desirable.

In spite of frequent use of ambulance personnel as the model of occupational stress, relatively low levels of psychosocial stress were detected in Study VI. Irrespective of what the reasons for these relatively low stress levels might be, further studies of autonomic regulation in dynamic occupational settings would be appropriate.

Proprioceptive tests in current literature vary with respect to the testing procedure and outcome measures. There still does not seem to be a general consensus on which type of measurement would be preferable, and as to which proprioceptive modality is being measured by a particular test, although there are good indications on the basis of previous research (Lönn 2001; Domkin 2005). Therefore, it is possible that some relatively moderate effects on position sense go unnoticed in our current tests.

In the presented projects we were able to investigate autonomic involvement at a given time, through a sample that is representative of the general patient population with respect to age and gender. Possible lines of research that might stem from these projects could include follow-up studies of autonomic activity in selected patient groups, studies where gender issues would be principally addressed, or studies where clinical applicability of some of these findings would be evaluated.
Conclusions

Autonomic imbalance observed in chronic pain subjects was characterised by a trend towards increased sympathetic and decreased parasympathetic activity in comparison with pain-free controls, as seen in changes in cardiovascular and sudomotor activity at rest and in recovery.

Moderate changes in the reactivity to autonomic function tests were seen in the patient group showing high pain and disability levels (WAD). Differential cardiovascular and sudomotor reactivity to sensory and cognitive tests, as well as signs of impaired endurance in chewing tests were observed.

Correspondence between autonomic activity and the intensity of pain was observed in acute pain and in the chronic pain group characterised by higher pain levels (WAD).

No specific reaction patterns were observed in any chronic pain group when compared to respective control groups.

Proprioceptive deficit was not detected in chronic pain subjects, and proprioceptive function did not correspond to the levels of autonomic activity.

As indicated by autonomic and neurohormonal changes in the recovery from real and simulated work, further studies with physiological monitoring of the effects of work-related stress are warranted for better understanding of the mechanism of musculoskeletal disorders. Taken together our data would seem to corroborate the notion of autonomic imbalance as an important symptom of chronic muscle pain.
Summary in Swedish

Det finns åtskilliga tecken på det autonoma nervsystemets inblandning i uppkomsten av kronisk smärta. Sympatisk aktivering är sannolikt relaterad till motorisk dysfunktion och förändringar i bearbetning av sensoriskt inflöde, som båda i sin tur anses vara involverade i musculoskeletala besvär.

Avhandlingens huvudsyfte har varit att undersöka autonom reglering i vila samt vid exponering för en rad laboratoriska tester av autonom funktion, främst hos patienter som lider av kronisk smärta i olika områden (ländrygg, Nacke - skuldra, Nacke - käke) samt att studera förhållanden mellan autonom reglering, proprioceptiv förmåga och kliniska data. Ett ytterligare syfte har varit att undersöka autonom reglering hos friska, smärtfria personer vid utsättning för experimentell framkallad smärta samt i arbetslivsrelevanta situationer.

Sammanfattningvis har 194 personer med kronisk smärta deltagit i studier (ländryggsbesvär - LBP n=93; icke-traumatisk nacksmärta - NT n=40; pisksnärtskador - Whiplash-associated disorder, WAD n=40; samt WAD patienter med symptom i käken - temporomandibulär dysfunktion - n=21). Varje grupp av patienter med kronisk smärta hade genomgått ett stresstestbatteri bestående av kognitiva (Stroop färg - ord test), fysiska (handgrepp) sensoriska (obehagligt ljud) och motoriska (tuggtest) uppgifter, samt tester av autonom funktion (reglerad andning samt orthostatisk test) och jämförts med likadana kontrollgrupper med avseende på ålder och kön. Autonom reglering har också undersömts vid utsättning av friske individer för experimentell framkallad smärta (n=24) för att kunna beskriva akut smärtreaktion. Vidare undersökning har genomförts vid monotont repetitivt arbete och dynamisk träning hos friska individer (n=10) såsom i en tredagars uppföljning av ambulanspersonal (n=26) på arbetsplatser samt under fritid.

Autonom reglering har undersökts genom kardiovaskulära (hjärtfrekvens, hjärtfrekvensvariabilitet, lokalt blodflöde samt blodtryck), respiratoriska (andningsfrekvens) elektrodermala (hudkonduktans), muskulära (trapezius och masseter EMG) samt biokemiska (insulin, kortisol, katecholaminer) mått. Proprioceptiv förmåga har undersöks genom repositioningstester. Smärtnivåer mätttes med hjälp av VAS eller numeriska skalar. Bedömning av allmän hälsa har skett genom frågeromulären Short-Form SF-36 Health Related Quality of Life och Self-Efficacy Score medan funktionalitet blev utvärderad genom Oswestry Low Back Pain, Pain Disability och Neck Disability Index, samt McKenzie diagnoser och genom diagnoser från kliniska undersökningar. Självrapporterad smärta, stress samt ansträngning registrerades innan, under och efter försöken.

Individer med kronisk smärta kännetecknades av förhöjd sympatisk aktivitet samt minskad parasympatisk aktivitet, vilket kunde upptäckas genom

Autonom obalans som sågs hos individer som lider av kronisk smärta kännetecknades av en trend mot en ökning av den sympatiska aktiviteten jämfört med smärftfria kontrollpersoner. Moderata tecken på förändrad reaktivitet vid exponering för tester av autonom aktivitet sågs endast i WAD gruppen, men inga specifika reaktionsmönster upptäcktes i någon av grupperna med kronisk smärta. Associationer mellan smärtnivåer och autonom aktivitet noterades vid akut smärta samt hos de smärtindividualgrupper som karakteriserades av högre smärtnivåer. De påvisade autonoma och neurohormonella förändringarna under återhämtningen efter verkligt eller simulerat arbete tydliggör behovet av vidare forskning omfattande fysiologisk registrering av effekterna av arbetsrelaterad stress för att få en bättre förståelse av mekanismerna bakom muskuloskeletala besvär.

Nyckelord: autonom reaktivitet, stress, kronisk smärta, experimentell smärta, rygg, skuldra, nacke
Acknowledgements

Dr Eugene Lyskov was my supervisor during the work on this thesis. I would like to express my sincere gratitude to him for many hours of fruitful discussions, for inspiring me to view the scientific problems in all their complexity and for teaching me how to formulate and systematically approach any research question. He also taught me how to write with "more matter and less art" - not the easiest of tasks, I’d be the first to admit.

I would also like to thank my co-supervisors, Dr. Margareta Barnekow-Bergkvist and Prof. Håkan Alfredson for valuable discussions and skilful guidance in the preparation of individual studies and of the thesis itself.

Over the years as a PhD student working at the Centre for Musculoskeletal Research I have had the chance to take part in some of the projects led by Drs. Mats Djupsjöbacka and Albert Crenshaw, and Profs. Svend Erik Mathiassen and Per-Olof Eriksson. I learned a lot from them, and I truly appreciate it. I also owe a lot of gratitude to Dr. Crenshaw for valuable advice regarding scientific writing, and to other researchers whom I cooperated with - Drs. Mona Bergfors, Yuka Noborisaka, Martin Björklund, Minori Nakata and Fredrik Hellström, as well as all the others who have helped at one time or another.

Most of my fellow peers, Ph.D. students at the Centre for Musculoskeletal Research, have already defended their theses or are about to do so. We’ve had quite a few laughs and a few frowns along the way and I enjoyed your company very much - so thanks Marina, Maria, Ulrika, Eva, Dmitry (all Ph.D.s by now), Malin, Gerd, Jonas, Ulrik, Jenny and Per L.

In numerous projects we have enjoyed the help of our laboratory and teaching assistants - Maggan, Kerstin and Majken. Always in a good mood and always at hand, they made us all - subjects, students and researchers alike - feel relaxed and welcome, and they saw to it that things ran smoothly during the experiments.

Work at the Centre would have been very difficult indeed without the skilful help of our engineering department. Theodore von Karman allegedly once said that “scientists study the world as it is; engineers create the world that never has been” and I guess he was not too far off. Thank you Göran A., Göran S. and Per for your help and advice on many occasions.

None of the work at the Centre would have been possible without our administrative staff - Alice, Vivi-Anne, Chicki, Christina and Kalle, and without the help of Gunilla at the Sports Medicine Unit. There is no substitute for your experience and knowledge of how things work at the Centre and at the University. Never have I left your rooms with a question unanswered, and you really keep the daily hassles on your shoulders so that the rest of us could work interrupted.
It has been almost three years since Prof. Håkan Johansson passed away. He was a true erudite and a great judge of character, and he could see beyond the hill when all I could see were steep slopes. I regret that he did not live to see this work finished for he inspired and supported it, and helped us a lot in many ways. He will always be fondly remembered.

Wherever life throws you, and whatever life throws at you is much more endurable if you know you have a family to turn to. I’ve been blessed by having two wonderful girls at home, our daughter Irena who always surpasses all my expectations and manages to surprise me when I least expect it, and my wife Ivana, with whom I’ve shared most of my adult life. Without their endless love and understanding none of this would have ever been possible. We have already been through a lot together, and I know we’ll stick together come hell or high water.

Throughout the years I was lucky to have had all the love, support and encouragement from my parents Slobodanka and Mirko, as well as from my aunts Ivanka and Mira, uncles Zoran and Nikola and in recent years my mother-in-law Ilona. Both my brother Zoran and my cousin Ivan (a true brother in everything but the name) have been great to grow up with and have now their own families. With their wives Maja and Sanja and their children Dositej, Ognjen and Mateja I’m sure we will have as much fun in the years to come as we did when we were kids.
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