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SKIN CONDUCTANCE VARIABILITY AND STRESSFUL EXPOSURES IN CRITICAL CARE

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M.D.

Karolinska Institutet

Stockholm 2016

Published by Karolinska Institutet.

Printed by E-print AB

Cover illustration Stina Wirsén
ISBN 978-91-7676-235-6

Skin Conductance Variability and stressful exposures in Critical Care

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my family

”I dreamed of having a book of my own, of writing one that I could put on a shelf”

- Patti Smith

ABSTRACT

Numerous stressors affect the intensive care unit (ICU) patient. The ICU environment is busy and noisy, with monitoring and treatment around the clock. ICU patients may have problems in getting some sleep, due to lighting and noise. Many ICU survivors report having pain during their ICU stay. Stressful experiences from the ICU contribute to later development of posttraumatic stress symptoms. The comfort and well-being of ICU patients is today an important goal and methods and strategies to achieve this are developing.

In this thesis, two areas related to ICU patient exposures were evaluated: noise and pain. A method of monitoring skin conductance variability (SCV) was evaluated.

In Paper I, we compared sound pressure levels in three different ICU room types and three different shifts, as well as analysed the sources of disruptive sounds in the different room types. We found that sound pressure levels were similar in the different room types, with a trend towards lower night-time levels. Levels were well above international recommendations. Disruptive sounds were more frequent in three-bed rooms than in single-bed rooms. Main disruptive ICU sounds were from machine alarms and from noisy chatting.

In Paper II, we studied SCV as a measure of pain in 40 ICU patients. Increasing levels of stimulation was associated with elevation of SCV. In non-intubated patients, there was an interaction effect between pain and agitation on SCV.

In Paper III, we monitored 18 volunteers with SCV and exposed them to a standardised pain stimulus, to pictures with varying emotional content and to an ICU sound recording, in random combinations. SCV was significantly elevated by pain stimulation and to a lesser extent affected by emotion-inducing pictures or ICU sound.

In Paper IV, 30 recently discharged ICU patients were monitored with SCV and exposed to the same ICU sound recording as in study III. During SCV monitoring, patients were also asked questions regarding traumatic experiences from the ICU. SCV was significantly elevated in most patients in response to both ICU sounds and questions. There was, however no correlation with stress symptoms assessed with a specific questionnaire for ICU survivors.

In conclusion, the studies of this thesis show that a) sound levels preclude normal sleep and can potentially be modifying machine alarms and behaviour b) skin conductance variability may be difficult to interpret in awake patients but potentially has a room for monitoring pain in poorly communicable patients. Further studies in poorly communicable ICU patients during interventions may further elucidate the role of such monitoring.

“We don’t even ask happiness, just a little less pain.”

- Charles Bukowski

LIST OF SCIENTIFIC PAPERS

The thesis is based on the following papers, which will be referred to by their Roman numerals as indicated below:

I. **Levels and sources of sound in the Intensive Care Unit – an observational study of three room types**
Tegnestedt C, Günther A, Reichard A, Bjurström R, Alvarsson J, Martling C-R and Sackey P
Acta Anaesthesiol Scand 2013; 57: 1041-1050

II. **Palmar skin conductance variability and the relation to stimulation, pain and the motor activity assessment scale in intensive care unit patients**
Günther A, Bottai M, Schandl A, Storm H, Rossi P and Sackey P
Crit Care 2013, 17:R51

III. **Pain rather than induced emotions and ICU sound increases skin conductance variability in healthy volunteers**
Günther A, Schandl A, Bernhardsson J, Bjärtå A, Wållgren M, Sundin Ö, Alvarsson J, Bottai M, Martling C-R and Sackey P
Submitted

IV. **Skin conductance variability in response to reminders of intensive care**
Günther A, Schandl A, Sundin Ö, and Sackey P
Manuscript

CONTENTS

1 LIST OF ABBREVIATIONS

Ag/AgCl	Silver/Silver chloride
dB	Decibel
CRT	Cumulative
ECG	Electrocardiogram
EDA	Electrodermal activity
EEG	Electroencephalogram
fMRI	Functional Magnetic Resonance Imaging
IASP	International Association for the Study of Pain
IAPS	International Affective Picture System
ICU	Intensive Care Unit
L_{Cpeak}	C-frequency weighted peak sound pressure level
$L_{night, outside}$	A-weighted long-term average sound level as defined in ISO 1996-2: 1987, determined over all the night periods of a year; in which: the night is eight hours
L_{ASeq}	A-frequency Slow-time weighted equivalent continuous sound pressure level
L_{ASmax}	A-frequency Slow-time weighted maximum sound pressure level
MAAS	Motor Activity Assessment Scale
NSA	Nursing Station Alcove
NSCF	Numbers of Skin Conductance Fluctuations per second
NRS	Numeric Rating Scale
PTSS-10	Post-traumatic Stress Syndrome 10-question Inventory
PTSD	Post-traumatic Stress Disorder
SC	Skin Conductance
SCV	Skin Conductance Variability
VAS	Visual Analog Scale
VTS	Vårdtyngd Sverige (measure of nursing shift workload in ICU patients)

2 INTRODUCTION

2.1 BACKGROUND

Intensive care is primarily about treating and caring for a patient in a life-threatening situation, with support of vital functions such as for example the respiration, circulation and renal function.

In the last decades however, the perspective of critical care has broadened and now encompasses both short- and long-time survival and patient-reported outcomes after critical illness. A growing interest in and awareness of the benefits of assessing and treating the patient as a person in whole is evident in the literature.[1-4] Quality of life after intensive care unit (ICU) stay has become more important when validating outcome. While the primary focus of intensive care has been was on diagnosis and physiological parameters, today greater effort is made to address the needs and well-being of the human being in front of us. Being a patient in need of critical care is no longer only a matter of short-term survival.[1] Today ICUs are multi-professional with a wide range of medical specialties represented and engaged in patient care and well-being.[5,6] ICU treatment, tools, therapies and strategies are constantly developing and improving and the aims include giving the patients a good platform to rebuild their strength and life.

Critical illness, but also intensive care may have consequences for a long period of time beyond the time of discharge from ICU. One of the major late complications is the psychological effect of intensive care. The experience of being treated in the ICU has many implications on life afterwards.[7-10]The awareness of complications of intensive care treatment is growing. Today we can see the effects of this reasoning in follow-up clinics and more focus on questions to ICU survivors regarding patient experiences, comfort and outcomes relevant to the patient.[3,11,12]

2.2 STRESS

Just like environmental effects affect life on the planet, the ICU environment affects the critically ill patient. At a global perspective, climate warming is stressing organisms and plants. In the ICU, many patients suffer from internal and external stressors.

The response to stress

Many forms of stress affect the intensive care patient, the whole body struggles to survive with all its different methods.[13] The stress response is an evolutionary success, seen in all living creatures.[14] When the body answers to stressors a wide variety of reactions occur. The meaning of the stress reaction of an organism is to use its defences and preserve homeostasis.

This capacity is often referred to as resilience and involves both mental and physical defences.[15] One problem with the stress reaction is that in some extreme situations there is no brake; the stress response will be used to the extent that the effects may become counterproductive. This is the moment when the body needs help and when vital organs are affected, intensive care is crucial.

2.3 THE ICU ENVIRONMENT

The ICU environment has an impact on patients´ sleep, comfort and their outcome and is therefore an interesting potential area for improvement.[16-19] The conflict between the need of all sorts of interactions, monitoring and therapies and the stress these activities imply for the ICU patient is a challenge. Optimizing treatment and keeping the patient as comfortable as possible in parallel is demanding and relies on continuous research and improvement.

Intensive care implies support of, or close observation of vital functions. The activities required to achieve this homeostasis imply frequent assessments, diagnostics and interventions at the bedside day and night. Vigilance in the ICU is paramount, and one of the key factors in this ICU vigilance is early alerts when vital signs or support is out of optimal range. Currently, such alerts are mainly conveyed via sound alarms in various monitoring devices.[20,21] There are no formal regulations regarding upper limits for these alarms. From a marketing perspective, clients (i.e. clinicians) need to be convinced that a new device is safe, in that staff will be alerted that parameters are out of range. This has led to noisy alarms in life-supporting machines and monitors, such as ventilators and infusion pumps. Moreover, the design of many ICU´s, with shared rooms, is such that patients are exposed to the monitoring and treatment-related activities of other patients. Noise levels in ICUs have increased over the past decades.[22]

2.4 WORLD HEALTH ORGANISATION (WHO) SOUND RECOMMENDATIONS

The WHO recommends background sound levels to be less than 30 dB L_{ASeq} and peak levels 40 dB L_{ASmax}.[23] In WHOs night-noise guidelines for Europe 2009 there is much focus on the negative effects from noise on personal health.[24] The effects of outside noise are assessed using the measurement unit $L_{Anight,\ outside}$ which means the average A-weighted sound pressure level during night over a year. In the Guidelines it is concluded that L_{Anight} between 40 and 55 dB has detrimental effects for the exposed with health complications. When $L_{Anight,\ outside}$ is above 55 dB it is increasingly dangerous for public health and adverse health effects occur frequently. At $L_{Anight,\ outside}$ above 55 dB many people get annoyed and suffer sleep disturbances and the risk of cardiovascular disease is confirmed with evidence. Special precautions are advocated in vulnerable groups like children, sick and elderly. Documented effects and sound level thresholds based on evidence for both outdoors and indoor noise are presented in table 1 and 2.

Table 1. Documented threshold levels of outside noise for effects on sleep. Source WHO, Night noise guidelines for Europe.

Effect	Decibel threshold $L_{Anight\ (outside)}$
Increased motility during sleep	42
Self reported sleep disturbance	42
Using medicines for sleep	40
Environmental insomnia	42

Table 2. Documented threshold levels of inside noise for effects on sleep. Source WHO, Night noise guidelines for Europe.

Effect	Decibel threshold L_{Amax} (inside/indoors)
Awakenings on EEG	35
Onset of motility	32
Changes of sleep: **- Duration in different stages** **- sleep structure** **- Fragmentation of sleep**	35
Wake ups in night or too early	42

2.5 SLEEP

The effects of sleep have been investigated thoroughly and are shown to affect well-being and health in many ways. Adverse effects of sleep deprivation include impaired cognitive, endocrine and immune functions as well as augmented pain perception.[25-28]

Sleep is divided into different stages where stage III and REM sleep is of most importance to recuperation.[25] Since stage III and REM occurs at the end of the sleep-cycle repeated sleep interruption reduces these important stages.

Sleep among ICU patients is often insufficient and has been studied from many perspectives.[29-33] Noise is reported to be the most significant cause for lack of sleep in among ICU patients.[18]

2.6 PAIN

Definition of pain. From:

International Association for the Study of Pain (IASP)[34]

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

Note: The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Biologists recognize that those stimuli which cause pain are liable to damage tissue. Accordingly, pain is that experience we associate with actual or potential tissue damage. It is unquestionably a sensation in a part or parts of the body, but it is also always unpleasant and therefore also an emotional experience."

Wikipedia[35]

***"Pain** is a distressing feeling often caused by intense or damaging stimuli, such as stubbing a toe, burning a finger, putting alcohol on a cut, and bumping the "funny bone". Because it is a complex, subjective phenomenon, defining pain has been a challenge. In medical diagnosis, pain is a symptom.*

Pain motivates the individual to withdraw from damaging situations, to protect a damaged body part while it heals, and to avoid similar experiences in the future. Most pain resolves once the noxious stimulus is removed and the body has healed, but it may persist despite removal of the stimulus and apparent healing of the body. Sometimes pain arises in the absence of any detectable stimulus, damage or disease.

Pain is the most common reason for physician consultation in most developed countries. It is a major symptom in many medical conditions, and can interfere with a person's quality of life and general functioning. Psychological factors such as social support, hypnotic suggestion, excitement, or distraction can significantly affect pain's intensity or unpleasantness."

2.6.1 Pain in ICU patients

One of the main stressors that ICU patients report is pain.[36] Nearly all ICU patients report having experienced pain.[37-43] The reasons for pain are many, such as being intubated, mechanical ventilation, extubation, wound care and cannulation. But also normal patient care, like turning and mobilization after a period of immobility can be painful. Assessment of pain is a central issue in the care of critically ill patients. Frequent systematic pain assessment and following levelling of analgesia can reduce time with mechanical ventilation and hospital length of stay and is associated with better patient outcome[44]

Even though this is common knowledge among most clinicians pain still is under-treated.[45] Adverse effects of poor pain treatment are seen in both short and long perspective and has physiological as well as psychological cosequences.[46-48]

On the other hand, too much or to long administration of potent analgesics is not beneficial either. Overmedication with these drugs can lead to problems, including delirium and respiratory depression, gut immobility and dependence.[49-52] Pain is still a challenge, particularly in in those patients who cannot speak for themselves.

2.6.2 Pain assessment

Visual analogue Scale (VAS) and numerical rating scales are preferred and best validated in awake patients who can communicate their experience. Recently, behavioural assessment tools for non-communicative patients have been developed, including the Behavioural Pain Scale (BPS) and the Critical Care Pain Observation Tool (CPOT).[53-55] With these scoring instruments a number of clinical observations contribute to a summarized score. The items included are rated by an observer and can be for example muscle tension, breathing pattern/synchrony with ventilator, facial expression and sounds.

The use of physiological signs like heart rate, respiratory rate and blood pressure, are not usually recommended as single indicators of pain in critically ill patients, as these are often affected for other reasons than pain.[56,57]

2.7 SKIN CONDUCTANCE

Skin conductance (SC) is a measure of electrodermal activity (EDA) and a well known method in the field of psychophysiology. The scientific discipline of psychophysiology includes the study of anatomical features and physiological patterns in relation to psychological parameters including behavioural, social and psychological phenomena.

2.7.1 The history of skin conductance

Skin conductance as a method to assess reactions to psychological and physiological stimuli goes back to the nineteenth century. In the early1900s C G Jung used EDA measuring in his work when he studied emotional reactions to word associations.[58]During the 20th century EDA has been used in numerous studies in physiology as well as in psychology. A problem was that many different techniques and units were used, resulting in difficulties in standardising results and semi-scientific studies. At the beginning of the1970s, more rigorous and systematic measuring technique and units were proposed.[59,60]

EDA research has had important influence on the understanding of physiological reactions and on development of new techniques like electroencephalogram (EEG) and electrocardiogram (ECG). In recent years, the arsenal of psychophysiology has expanded and now includes neuroimaging with functional Magnetic Resonance Imaging (fMRI),

Typical examples of areas where EDA is used are studies of psychiatric diseases such as schizophrenia, depression and anti social behaviour.[61-63] In neuroscience, EDA is commonly used in settings studying emotions, attention and arousal.[64-66] Numerous studies on the autonomic response to pain have been performed using EDA. Various forms of sleep and effects of sleep deprivation have also been examined with EDA. One of the most well known applications of EDA is the polygraph, known as the lie detector but its reliability has been questioned. In the last 20-30 years, the use of EDA in neuroscience and neuropsychology has evolved even further. Today there are applications of EDA that can be connected to a mobile phone, giving the user biofeedback information, with the purpose of quantifying stress level and self-training in stress reduction.

The principles of skin conductance are based on the fact that electrical conductance in the hand varies with the sweating, as this affects the moisture of the skin. The sweating is a result of nerve signalling in the skin sympathetic branch of autonomic nervous system and can reflect emotional arousal.[67,68] By applying a constant small current between electrodes the conductance can be measured.[69] Increases in nerve activity lead to more sweat and results in higher skin conductance. The SI unit of skin conductance is microsiemens (μS).

2.7.2 Physiology of palmar sweating

Eccrine glands (sudomotor) produce and excrete sweat.[70] They are found all over the body but are most common in palms of hands and soles of feet.[71] There are approximately 400 sweat glands to be found within one square millimetre of the palm.[72] Eccrine sweating of the hand is a reaction to sympathetic nervous signalling. Muscarinic receptors on eccrine glands are activated by acetylcholine released from nerve endings that originate from the paravertebral chain of sympathetic ganglia. These ganglia receive input from up to six spinal levels via ipsilateral preganglionic neurons that have cell bodies in the intermediate zone of

the medulla of the spinal cord.[70] The origin of nerve signals leading to altering skin conductance is not fully understood, but the signals emanate from basal structures in the brainstem and limbic system. The mechanisms of EDA is still not fully understood despite its rather long history.[73] The complex contribution of both central and peripheral activation of EDA is one reason.[67] A number of higher brain functions are believed to play a part in activation of palmar sweating.[74] Since the receptors of the eccrine glands are muscarinic and the signaling is cholinergic, the glands are not affected by peripheral catecholaminergic actions.

The sympathetic response from emotional stress can be captured by measurement of the electrodermal activity. Pain is one of the stressors affecting emotional reactions and hence sympathetic activity.

2.7.3 The use of skin conductance peaks and troughs

Around year 2000, a derivative of classical skin conductance was developed, with the purpose of monitoring pain in the clinical setting. Since there is currently no objective method of identifying pain, and a proportion of hospitalized patients may have difficulties in conveying their pain level, an on-line monitor, detecting pain would be appealing. A problem with measurement of absolute skin conductance values in hospitalized patients is that varying body temperature and individual skin moisture affects basal skin conductance. These factors may vary significantly in patients. For these reasons, skin conductance variability (SCV) was investigated as a potential method to monitor the autonomous responses to pain. Palmar SCV is the consequence of the release and absorption of palmar sweat and has been demonstrated to specifically represent sympathetic nerve activity possible to measure per time unit. The algorithm was based on peaks and troughs of skin conductance, and with defined slope and amplitudes. Using earlier results of microneurographi studies NSCF was shown not to be influenced from environmental temperature.[75] The measure of number of skin conductance fluctuations (NSCF) was calibrated to correlate with ongoing sympathetic nerve activity to the sweat glands (figure 1).[68]

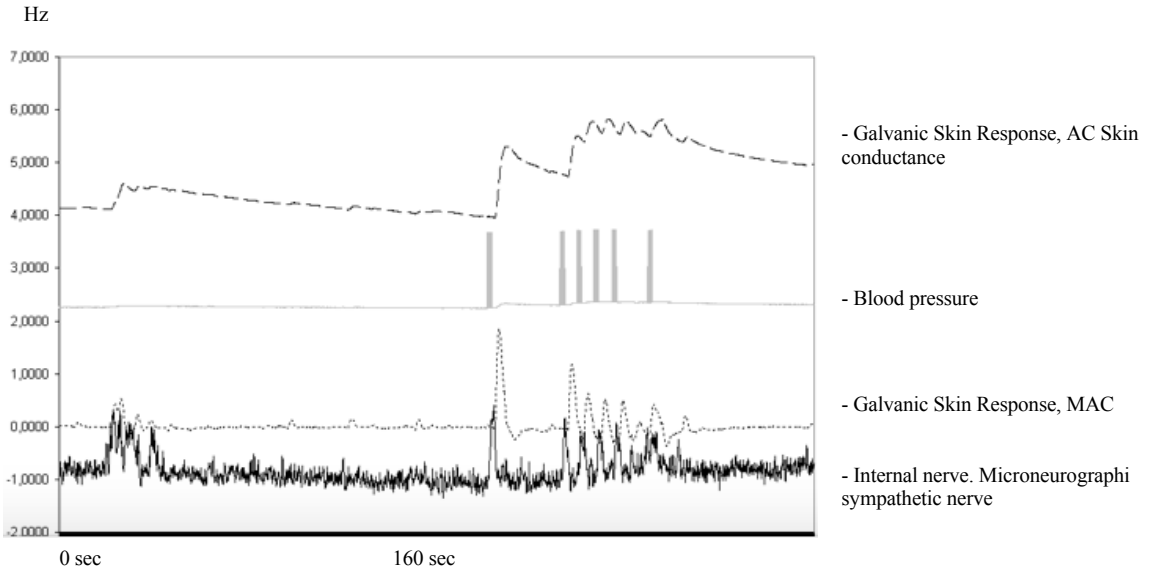

Fig 1. The four traces show changes in skin conductance (SC) (AC = alternating current), in blood pressure (BP), in converted skin resistance (GSR MAC=galvanic skin response mean amplitude converted), and in intra nerve activity (Int. Nerve) of the nervus medianus, by microneurographi of the skin sympathetic nerve (reference: Gjerstad AC, Storm H, Wallin G. Evaluation of the skin conductance method by using microneurographi, abstract, ISAP, Chicago 06)(With permission).

For every burst in the sympathetic nerve, there is one peak in the SC measurement. One SC peak is defined as an increase in SC of more than 0.02 microsiemens (μS), after one minimum point. Both peaks and minimum points are defined when the derivate of the SC curve is 0.

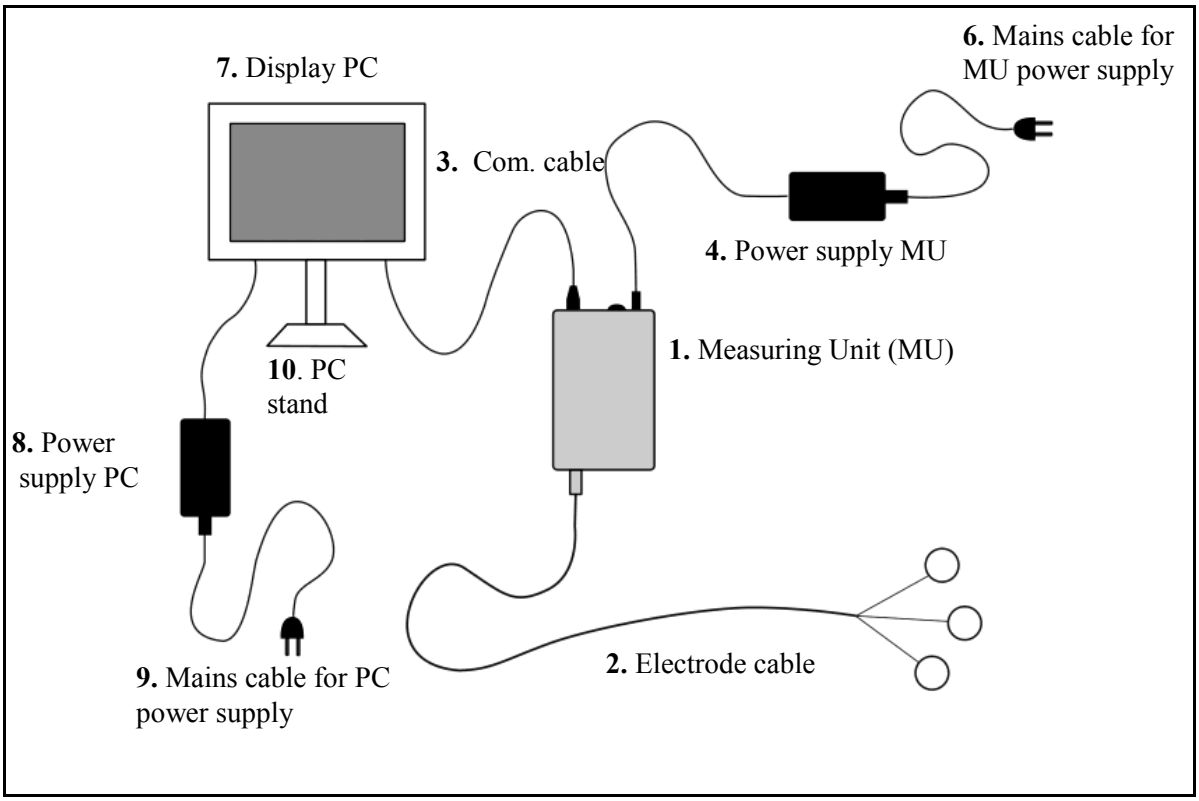

Figure 2. Schematic illustration of the skin conductance equipment tested in this thesis.

Figure 3. The monitor with an example of an on-line registration.

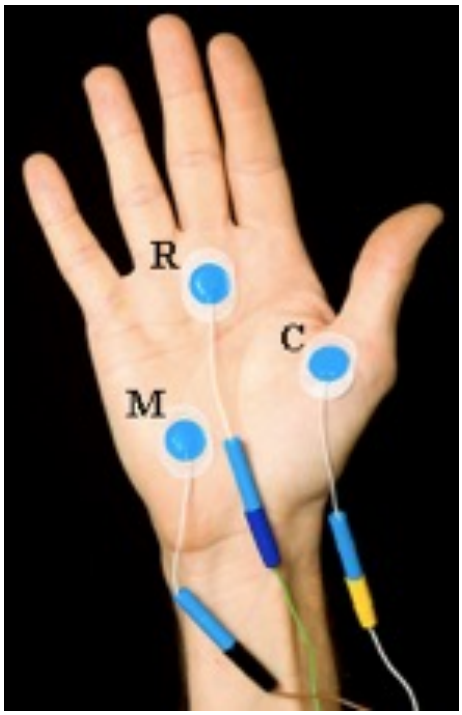

Figure 4. Placement of electrodes. R= reference, M=measure and C=current

A device was developed with software analysing the skin conductance changes and reporting NSCF, the "MEDSTORM Pain detector" (figures 2-4).[76,77] With the aid of this device, studies in hospitalized patients have been performed. In infants, a significant increase in NSCF when heel lancing is performed has been found but not during non-nociceptive care.[78,79] Two studies showed promising results in using the method to detect indications for stress during surgical stimuli.[80,81] Two studies in postoperative patients have demonstrated a correlation between self-reported pain levels and NSCF.[82,83]

Prior to the studies in this thesis, the new monitoring device and method had not been evaluated in the critical care setting. Given the lack of "objective" pain measures and the high proportion of patients unable to self-report, there was a rationale to investigate the monitor in this population. When we were introduced to the monitor the measure was named NSCF. Some other names are also used in the literature.

In this thesis Skin Conductance Variability (SCV) is used to describe the measure of the method and Number of Skin Conductance Fluctuations (NSCF) represents the unit of the measurements with the monitor. NSCF can be interpreted as peaks per second

.

3 AIMS

The overall aim was to investigate stressors affecting the intensive care patient and to evaluate skin conductance variability as a method for assessing pain and stress in the same category of patients.

Specific aims:

Paper I

To compare sound pressure levels and prerequisites for sleep in different room types and shifts in the ICU. To detect and quantify sources of disturbing sound in the ICU

Paper II

To examine a novel method of skin conductance variability for assessing pain in critically ill patients.

Paper III

To examine the impact of different stimuli (pain, emotional state and disturbing sound) on skin conductance variability in healthy volunteers.

Paper IV

To examine the effects of ICU reminders on skin conductance variability in ICU survivors, and the correlation between reminder-induced skin conductance variability and later symptoms of posttraumatic stress.

4 MATERIALS AND METHODS

4.1 ETHICS

All four studies were performed in compliance with the ethical principles of World Medical Association.[84] The fundamental principal is respect for the individual, patient or healthy volunteer, and their right to make informed consent to participate in a study. Study participants welfare was always prioritized before the interests of science. Ethical approval for study II-IV was obtained from the Regional Ethical Review Board. In study I, the board decided that the legalization concerning ethical review was not applicable since there was no patient involvement in the study

4.2 STUDY DESIGN AND OUTCOME MEASURES

Study design and outcome measures are summarized in table 3.

Table 3. Study design and outcome measures

Study	**I**	**II**	**III**	**IV**
Design	Single-center, observational study	Single-center, observational cohort study	Experimental cohort study	Single-center Experimental cohort study
Study population	-	ICU-patients	Healthy volunteers	Post ICU patients
Sample size	-	40	18	30
Intervention	-	-	Pain, sound and pictures	Sound and questions regarding ICU stay
Outcome measures	CRT dB (LASeq, LASmax, LCpeak) Disruptive sounds	NSCF MAAS VAS	NSCF VAS	NSCF PTSS-10

CRT=Cumulative Restorative Time, dB= Decibel, NSCF= Number of Skin Conductance Fluctuations, MAAS= Motor Activity Assessment Scale, VAS= Visual Analog Scale, PTSS-10= the modified Post-Traumatic Stress Syndrome 10-Questions Inventory

4.3 SETTING

Study I, II and IV were conducted at Karolinska University Hospital in Sweden. The hospital is a tertiary care hospital, serving the inhabitants in Stockholm County. The hospital is divided in two sites and has a capacity of treating approximately 1600 patients. The general intensive care unit in Solna is a 13 bed ICU treating around 1000 patients per year. Severely injured or critically ill patients are treated for traumatic injuries, infections, postoperative

complications or medical issues. Most patients are at least during some part of their ICU-stay sedated and are often not able to communicate in a proper way. Propofol is the most common used sedative often used in combination with morphine. Because of sedation and analgesia patient's perceptions of their environment and situation is many times altered. Study III was performed in a psychology laboratory at the Department of Psychology, Mid-Sweden University, Östersund, Sweden.

4.4 PAPER I

The study consists of two parts, one assessing sound pressure levels in the three room types and one quantifying intermittent disturbing sounds.

4.4.1 Study objects

At the time for study I, the general ICU had three room types (figure 5);

1) single-bed room with a nursing station alcove

2) single-bed room without a nursing station alcove and

3) three-bed room with a nursing station alcove.

Each room was eligible for assessment if all of the following criteria were met:

1. basic patient monitoring was used (continuous ECG, blood pressure, oxygen saturation monitoring, respiratory rate, body temperature, hourly diuresis control).

2. continuous or intermittent invasive or non-invasive ventilator treatment.

3. drug administration via syringe pumps.

4. vårdtyngd Sverige (VTS) exceeding 20 points (VTS is a Swedish national scoring system for the nursing workload. The score ranges from 11 to 33, higher number indicates a higher workload).

5. patient ICU length of stay more than 24 hours prior to inclusion. All three beds in the three-bed room had to be occupied and all patients had to be in the room at the time for assessment, otherwise data were excluded.

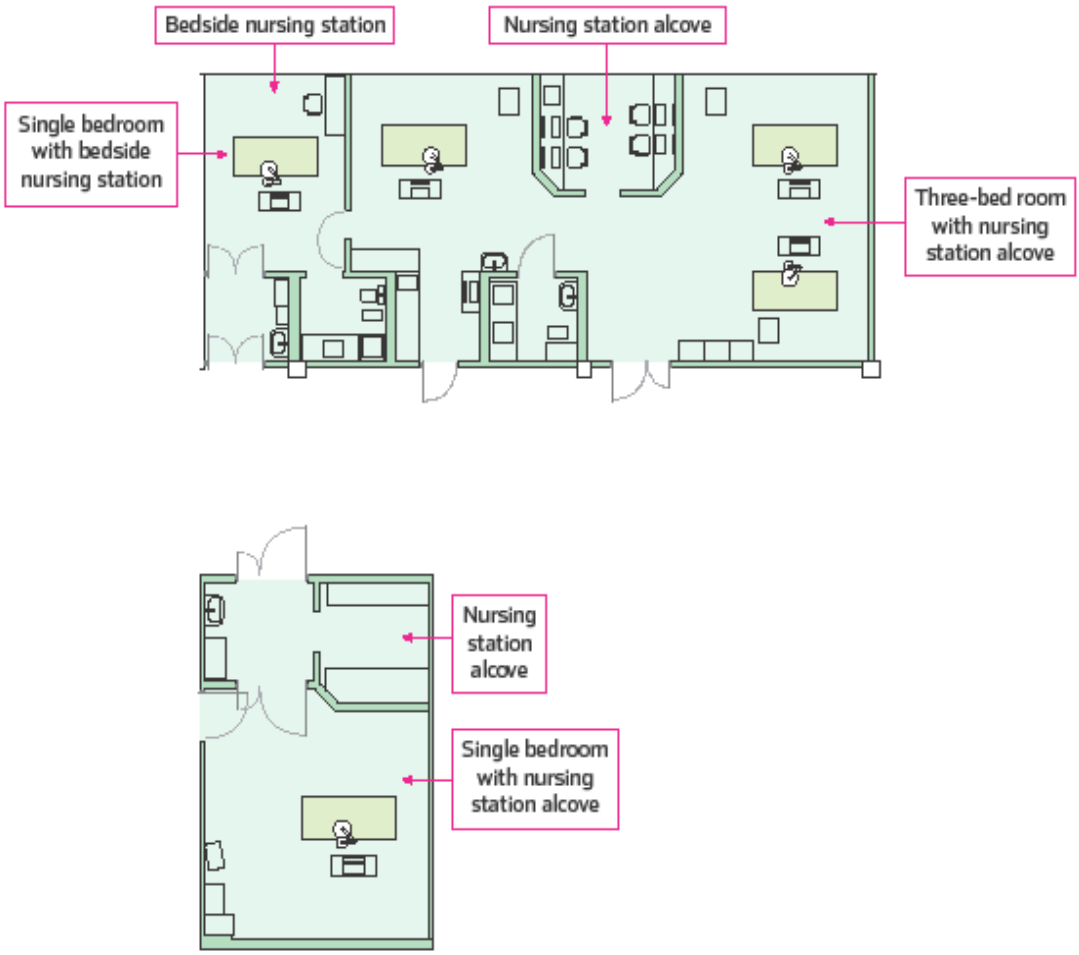

Figure 5. Architecture of the three different room types. The door between the single bedroom with bedside nursing station alcove and the adjacent three-bed room was closed during the study.

4.4.2 Data Collection

Five 24-hours sound level assessments were performed in each of the three room types. The 24 hours were divided in day shift (07-15), evening shift (15-23), and night shift (23-07).

In the observational part of the study a checklist with intermittent disturbing sounds was created, identifying sources of sound that were perceived high and disruptive (Table 4). During two day-shifts (07–15) in each setting the checklist was used to assess the frequency of disturbing sounds.

To assess sound pressure levels for comparison of room types and shifts a Spark 706 Larson Davis dosimeter (Larson Davis, Provo, UT, USA) was placed behind the headrest of the ICU bed, close to patient's head. This dosimeter was also used to measure sound pressure levels of staff conversation.

Two frequency-weighting filters were used to assess sound levels, A-weighting for low frequencies and C-weighting for high frequency. During all 24 hour sound monitoring three acoustic measures of sound pressure level in dB were used, namely A-frequency Slow-time weighted equivalent continuous sound level (L_{ASeq}), A-frequency Slow-time weighted maximum sound level (L_{ASmax}) and C-frequency weighted peak sound level (L_{Cpeak}).

The peak sound pressure levels from all machine- and monitor alarms were measured separately with a Brüel & Kjær 2225 sound level meter (Brüel &Kjær Sound & Vibration Measurement A/S, Nærum, Denmark). The same instrument was also used for measuring of background sound in an empty ICU room, with equipment in both stand-by mode and turned off.

Using a combination of two sound pressure level measures, L_{ASmax} and L_{Cpeak}, a criterion for restorative time was created. A restorative period was defined as a minimum of 5 min with L_{ASmax} below 55 dB combined with L_{Cpeak} below 75 dB. The sum of all restorative time was named Cumulative Restorative Time (CRT) and was one of the outcome variables.

Table 4.
Checklist for disruptive sounds used during the observational part of the study

1. Ventilator alarms
2. Patient monitoring alarms
3. Syringe pump alarms
4. Enteral feeding pump alarms
5. Dialysis machine alarms
6. Conversation unrelated to patient care
7. Telephone- and cell phone signals/Pager signals
8. Door sounds, open/close door
9. Patient bed alarms
10. Patient interventions
11. Pneumatic post system alarm/ Doorbell Front door
12. Other sources of sound

4.4.3 Statistical analysis

Repeated measures of analysis of variance were used to calculate sound levels and restorative periods between different room settings and working shifts. Student's t-test was used in pairwise comparisons between room types and shifts and chi-square test for frequency of sound sources and room type.

4.5 PAPER II

4.5.1 Participants

Forty adult critically ill patients treated in the general ICU were consecutively included in this study. Patients were excluded if they had a neuro- or myopathy diagnosis, if patients were receiving neuromuscular blocking agents, or were treated with atropine or glycopyrrolate the same day. Twenty intubated and 20 non-intubated patients were included.

4.5.2 Data collection

In all patients, skin conductance variability, pain/stimulation and arousal-agitation was monitored during one hour of routine daytime intensive care nursing and treatment, such as washing and turning of the patient, physiotherapy, or some invasive procedures. Skin conductance was monitored continuously. However, data was not blinded for the assessor. In parallel with this assessment, notes on everything that occurred around and with the patient were documented and synchronized with the on-line NSCF curve. In those patients able to communicate frequent pain ratings with Numeric Rating Scale 0-10 (NRS) was made and values were noted in correlation with the on-line curve. Also artefacts disturbing the NSCF registration were noted.

4.5.2.1 Skin conductance variability (SCV)

Skin conductance variability was monitored with Med-Storm Pain Monitoring System® (MED-STORM Innovation AS, Oslo, Norway). Three single use Ag/AgCl electrodes (MED-STORM Innovation AS, Oslo, Norway) were used for attachment to the patient's hand. The monitor measures skin conductance using alternating current at 66 Hz and an applied voltage of 50 mV. Skin conductance variability was measured as the number of skin conductance fluctuations per second (NSCF). The time frame for calculating NSCF was15 seconds (sampling time). The cut-off for identifying skin conductance fluctuations was set with skin conductance troughs and peaks of an amplitude > 0.02 micro Siemens (μS). The time a new measurement window was analysed (refreshing time), was one

second. Data was displayed continuously on a laptop connected to the monitor via a standard serial port and stored for analysis.

4.5.2.2 Assessment of stimulation/pain

During the procedure and monitoring, pain and stimulation was assessed and documented. In non-intubated patients that were able to answer, pain was rated with Numeric Rating Scale 0-10 (NRS). For non-communicative patients, pain or stimulation was categorized into four groups; a) No stimulation, b) Mild stimulation, c) Potentially painful stimulation and d) Painful stimulation according to a pre-set checklist (table 5 part C and D).

Table 5. Categories of stimulation/pain
A. No stimulation. The patient was lying undisturbed, without any observed or reported pain (see D).
B. Mild stimulation without observed or reported pain. The patient was being spoken to or procedures, such as gentle washing, were performed or the patient made slight movements without observed or reported pain.
C. Potentially painful stimulation without observed or reported pain. The patient did not report or show signs of pain but was exposed to any of the following procedures or conditions: 1. Needle stick. 2. Turning of the patient. 3. Suction of the mouth, hypopharynx or endotracheal tube. 4. Unsynchronized with the ventilator or abnormal breathing pattern. 5. Dressing of wound.
D. High pain rating or overt expression of pain in rest or during stimulation/procedure. The patient expressed pain verbally (NRS above 3). If the patient could not rate pain with the NRS the following signs were considered indicative of pain or discomfort: 1. Facial grimacing. 2. Moaning or groaning. 3. Localizing painful area, withdrawing from touch or resisting potentially painful movement or procedure.

4.5.2.3 Arousal/agitation assessment

Patient's arousal/agitation level was continuously assessed with the Motor Activity Assessment Scale (MAAS).[85] MAAS is originally a sedation scale used for measuring level of arousal and sedation. Responsiveness is graded from 0 (non responsive) to 6 (dangerously agitated, uncooperative). The scale is a reliable and valid instrument for use in mechanically ventilated patients.[85] At the time point for the study, the sedation scale was the current choice of sedation assessment scale in the general ICU.

4.5.3 Statistical analysis

The intubated and non-intubated patients were analyzed separately. Random-effects regression models were used to analyse NSCF over different pain and MAAS levels. In the regression models, stimulation and MAAS were introduced as numeric variables. Statistical significance level was set at $P < 0.01$. Analyses were performed with Stata version 12 (StataCorp, College Station, TX, USA).

4.6 PAPER III

4.6.1 Participants

Eighteen healthy volunteers (7 men and 11 women) were enrolled in this study. Median age was 25 (range 20-53). Reasons for exclusion were pregnancy, chronic pain, heart problems including pacemakers, or the use of psychotropic drugs. Participants were recruited by local advertisement in the Mid Sweden University and were mainly students. All participants received 2 movie vouchers. The study was performed in a laboratory environment.

4.6.2 The laboratory setting

The intention of the setting was to expose participants to stressors similar to those experienced by ICU-patients. Stimuli were; pain, disturbing sound and emotion inducing pictures.

E-prime (Psychology Software Tools Inc, Pennsylvania, USA) was used to program the experiment with triggers for electrical stimulation, pictures and sound playback, as well as data collection from on-line self-reports.

Each participant was exposed to twelve experimental conditions (sessions), each lasting 60 seconds. Between each session there was a one-minute resting period. The twelve sessions consisted of all possible combinations of two pain states (pain/no pain), three different

emotion-inducing picture batteries (positive, negative or neutral) and two sound states (sound/no sound) (table 6). After each session, a message on the screen instructed participants to rate pain with NRS and then relax until they heard a sound, indicating the start of the next session.

Table 6. Example of randomized exposures for an individual participant.

Negative emotion block				**Positive emotion block**				**Neutral emotion block**			
Pain	-	Pain	-	Pain	Pain	-	-	-	Pain	Pain	-
Sound	-	-	Sound	-	Sound	-	Sound	-	Sound	-	Sound

4.6.2.1 Emotion-inducing pictures

In order to induce three different emotions (positive, neutral or negative), a total of 36 emotionally charged pictures from the International Affective Picture System (IAPS) were used (12 for each emotion).[86] Positive pictures could be happy couples, smiling children or beautiful scenery. Neutral pictures were simple ordinary things like for example a spoon. The negative pictures were chosen to resemble horrifying descriptions from ICU patients and showed mutilated people, threatening situations and scary environments. The IAPS pictures are not allowed to be shown but are similar to the ones in figures 6 to 11 below. The pictures were presented on the computer screen in front of the participant. In each one-minute session, the twelve pictures from the same emotion category were shown twice (n=24), for 2.5 seconds each time. Each emotion-inducing picture battery was shown in four consecutive sessions (emotion block). The order of the three emotion blocks was randomized for each participant.

Figure 6.

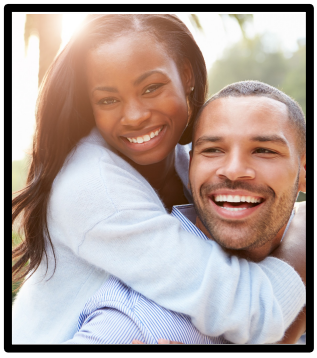

Figure 7.

IAPS-like pictures with the purpose to induce positive emotions. Example of positive emotion inducing pictures. These pictures were not used in the study.
Source: Pixabay.com (Free pictures)

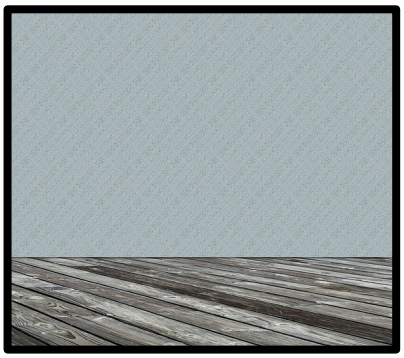

Figure 8.

Figure 9.

IAPS-like pictures with the purpose to induce neutral emotions. Example of neutral emotion inducing pictures. These pictures were not used in the study. Source: Pixabay.com (Free pictures)

Figure 10.

Figure 11.

IAPS-like images with the purpose of inducing negative emotion. Example of negative emotion inducing pictures. These pictures were not used in the study.
Source: Pixabay.com (Free pictures)

4.6.2.2 Pain

Pain was induced with the Coulbourn Transcutaneous Aversive Finger Stimulator (Coulbourn Instruments, Pennsylvania, USA), with remote triggering via Biopack Systems MP150 (BIOPACK Systems INC., California, USA). The electrical stimulus was delivered to the distal phalanges of the index and middle finger in 1 millisecond (ms) spikes set to 100 ms duration.

The electrical stimulus was individually titrated to VAS >4 and < 6 prior to the experimental exposures. This standardized pain stimulus was used throughout the experiment and participants received it during half of the twelve sessions. In the painful sessions electrical stimulation was given at random intervals, with a total of 24 electrical stimulations over the one minute (0.4/s). The order of the two pain sessions (pain/no pain) was randomized over the four sessions within each emotion block.

4.6.2.3 ICU sound

To simulate the background sound of an ICU environment, an authentic daytime sound recording from a fully occupied three-bed room at the General ICU, Karolinska University Hospital Solna, Sweden was used. The recording included background sounds (from ventilators and other machines), doctors and nurses talking and monitor alarms. The sound presentation lasted for 60 seconds, with volume peaks at 80 dB. The order of sound (sound/no sound) within each "emotion block" was randomized

4.6.3 Data collection

Skin conductance variability was monitored and recorded during the entire experiment. The same SCV-monitor as in paper II was used. Mean NSCF values over each minute of exposure were calculated. The individually experienced pain in each session was rated with NRS after each exposure. SCV and VAS were the outcome variables.

4.6.4 Statistical analysis

A within-subjects (2x3x2) analysis for dependent measures was used. NSCF and VAS were analyzed in two separate random-effect linear regression models. The participants' random effects were included to take into account the potential correlation between the repeated measures in each subject. Predictors of interest were type of pain stimulation (no pain/pain), emotion (positive, neutral or negative) and sound (no sound/sound). NSCF from the session with neutral pictures, no electrical stimulation, and no ICU sound was used as baseline for regression analysis. The same combination was also treated as the VAS 0 baseline condition

in the regression analysis of VAS. Based on the results of the regression models, NSCF and VAS reactivity were estimated for the different sessions. The intra-individual correlation was also estimated with Spearman´s rho. Statistical significance level was set at $P < 0.05$.

4.7 PAPER IV

4.7.1 Participants

Thirty adult patients (12 women and 18 men) with a median age of 65 years were enrolled. They were consecutively enrolled if they were Swedish speaking and had an ICU length of stay that exceeded 48 hours at the General ICU. Exclusion criteria were; documented neuromuscular dysfunction, brain injury, dementia, and treatment with alpha-2 agonists. Patients were approached within one week from ICU discharge at the hospital ward. If they rated pain or nausea more than 3 on a 0-10 numeric rating scale, they were temporarily excluded. The reason for excluding patients with pain or nausea was that it is likely to affect sympathetic activity and hence SCV. Such reactions would interfere with potentially reactions to ICU reminders.

4.7.2 Data collection

All patients were lying in their beds during the NSCF registrations. The same monitor and electrodes as in study II and III were used. Three one-minute registrations were made. The first was a baseline registration with no stimulation. The second registration was done while the patient listened to an authentic ICU sound recording (the same recording that was used in study III). The third one-minute registration of NSCF was made when the patient was asked four questions about memories from the ICU. The questions were part A in the modified Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10). These questions were read out load for the patient; “When I think back to the time of my severe illness and the time I spent in the ICU, I remember: nightmares (yes/no), severe anxiety or panic (yes/no), severe pain (yes/no), troubles to breath, feelings of suffocation (yes/no). After the registration was done, the patients filled out the remaining ten items in the PTSS-10. Three months later, the patients received the total PTSS-10 questionnaire, to evaluate potential symptoms of posttraumatic stress.

4.7.2.1 PTSS-10 questionnaire

To assess symptoms of posttraumatic stress both in an early phase and at three moths post ICU discharge PTSS-10 was used. PTSS-10 has been validated for use in ICU patients with a sensitivity of 77% and specificity of 97.5.[87] The reliability coefficient (Crohnbach's alpha) is 0.914 % in ICU patients. PTSS-10 has two sections, Part A and B. Part A consists of four

yes/no statements regarding traumatic memories from the ICU (nightmares, panic, pain, and suffocation). Part B holds 10 statements assessing symptoms of PTSD (sleep problems, nightmares, depression, jumpiness, avoiding others, irritability, labile mood, bad conscience/guilt, avoidance of activities reminding of the traumatizing event, and muscular tension). To answer the part B statements one needs to rate he intensity of feelings in the last few days from 1 (never) to 7 (always). A total score >35 in part B is associated with high probability of PTSD.

4.7.3 Statistical analysis

Baseline SCV and SCV during stimuli were compared with paired t-test. Spearman´s rank correlation test was used to analyse correlation between the different mean measures of NSCF and the degree of acute or posttraumatic stress symptoms (assessed with PTSS-10 part B in the ward and three months post-ICU) with. Five different NSCF variables were tested for correlation with signs of stress, namely 1) mean baseline NSCF, 2) mean NSCF during the minute of ICU sound exposure, 3) mean NSCF during the first 15 seconds of ICU sound exposure, 4) mean NSCF during the last 15 seconds of ICU sound exposure and 5) mean NSCF in response to the four questions regarding traumatic ICU memories. Data analysis was performed using GraphPad Prism version 6.00 for Mac OS X, GraphPad Software, La Jolla California USA, www.graphpad.com.

5 RESULTS

5.1 PAPER I

5.1.1 Rooms and shifts

The measurements of mean sound pressure levels (L_{ASeq}) in the three room types ranged between 52 and 58 dB, differences were not statistically significant. The mean cumulative restorative time in single-bed room with nursing station alcove (NSA) was longer but not statistically significant (p=0.074 when compared to tree-bed room with NSA).

In the overall comparison of shifts there was difference in mean sound pressure levels ($p< 0.001$), $\eta 2 = 0.49$. The night shifts had the lowest mean sound pressure level, when compared with level in the day ($p= 0.001$) and evening ($p= 0.01$) (figure 12).

For cumulative restorative time, there was also a difference between shifts ($p< 0.001$), $\eta 2 = 0.65$ with significantly more restorative time during the night than during the day ($p< 0.001$) and than during the evening ($p=0.003$). Also, there was significantly more restorative time during the evening than during the day ($p= 0.009$) (figure 12).

5.1.2 Bedside observations of disruptive sound sources

The observational part of the study revealed that disruptive sounds were 39.8% less frequent in the single-bed room with NSA than in the other two room types ($p< 0.001$) (figure 13). The observations also revealed that equipment alarms were significantly more frequent than any other disturbing sound source ($p< 0.001$). Aggregated over room types, alarms stood for 40.2% of the total number of disruptive sounds and conversations unrelated to patient care stood for 24.1% (figure 14).

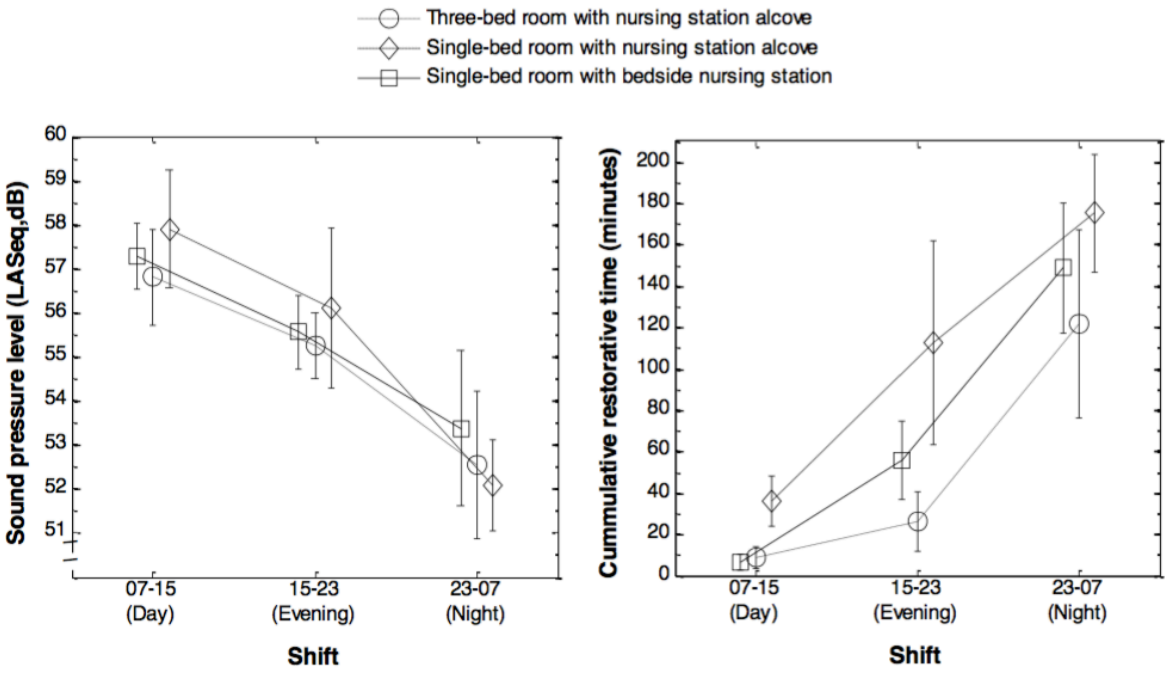

Figure 12. Mean sound pressure level and mean cumulative restorative time by room and shift. Sound pressure levels in A-frequency S-time weighted equivalent continuous sound (L_{ASeq}) (dBA) and cumulative restorative time in minutes per 8 h.

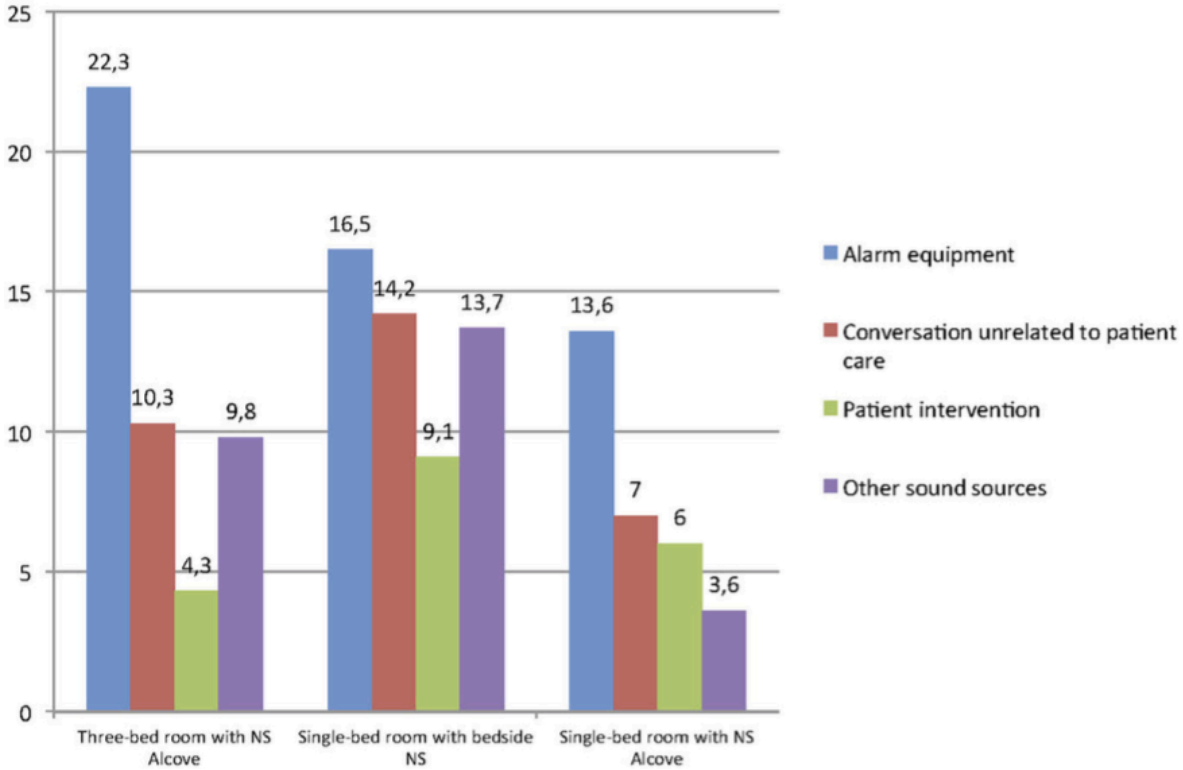

Figure 13. Frequency (numbers/h) of disruptive sound sources during bedside observation in the three different intensive care unit (ICU) room types.

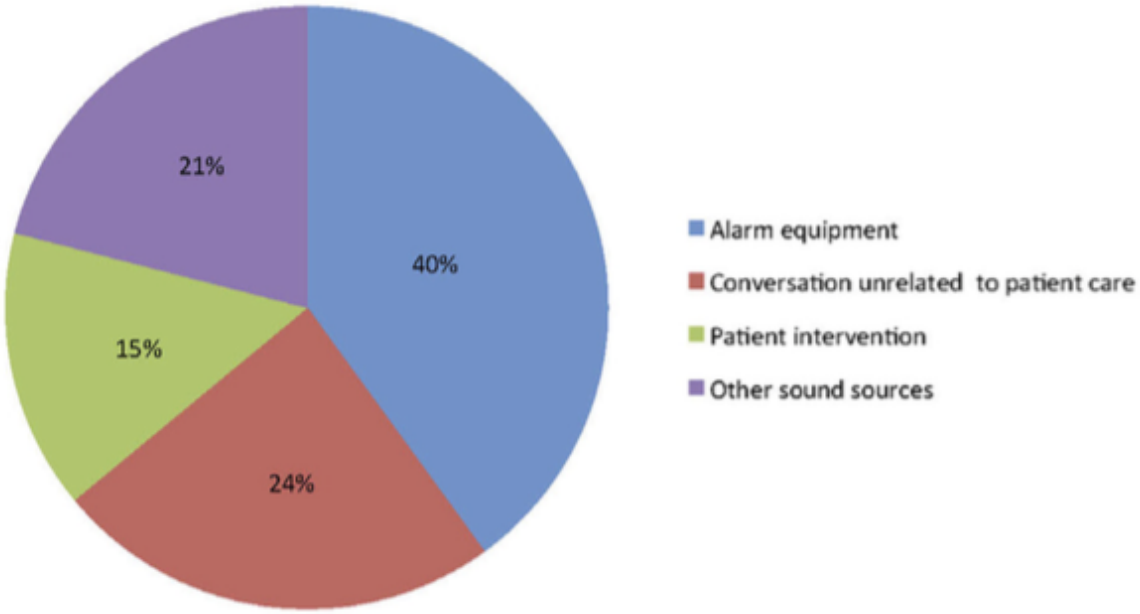

Figure 14. The overall distribution (percent) of disruptive sounds (n=840)

5.2 PAPER II

Patient demographics are presented in Table 7. In total, the non-intubated patients contributed 715 registrations and the intubated patients 735 registrations. Artefacts precluded adequate registration 206 times (28.8% of observations) in the non-intubated patients and 83 times (11.3% of observations) in the intubated patients.

Table 7. Patient demographics and characteristics

	Intubated	Non-intubated
Age; mean (SD)	60 (16)	55(18)
sex;		
Female	2	7
Male	18	13
ICU day*; median (range)	3 (1 to 13)	2 (1 to 19)
Diagnosis group (n);		
Medical	4	6
Surgical	4	4
Trauma	4	6
Sepsis	8	4

*Day of registration.

Sedative and analgesic drugs were more frequently used in intubated than in non-intubated patients. The MAAS score ranged between 2 and 5 for non- intubated patients and between 0 and 4 in the intubated patients. Fourteen of the 20 non-intubated patients rated their pain with the NRS.

5.2.1 Non-intubated patients

In non-intubated patients, there was a significant increase in NSCF with increasing stimulation/pain ($p = 0.002$) for all MAAS levels except MAAS 2 (figure 15, table 8). There was an interaction effect between stimulation and MAAS, with increased NSCF response to stimulation/pain with increasing MAAS ($p< 0.001$).

5.2.2 Intubated patients

In intubated patients, there was a significant increase in NSCF with increasing stimulation/pain ($p< 0.001$) at all MAAS levels (figure 16, table 9). No interaction effect was seen between stimulation and MAAS in this group ($p= 0.64$) (Figure 16).

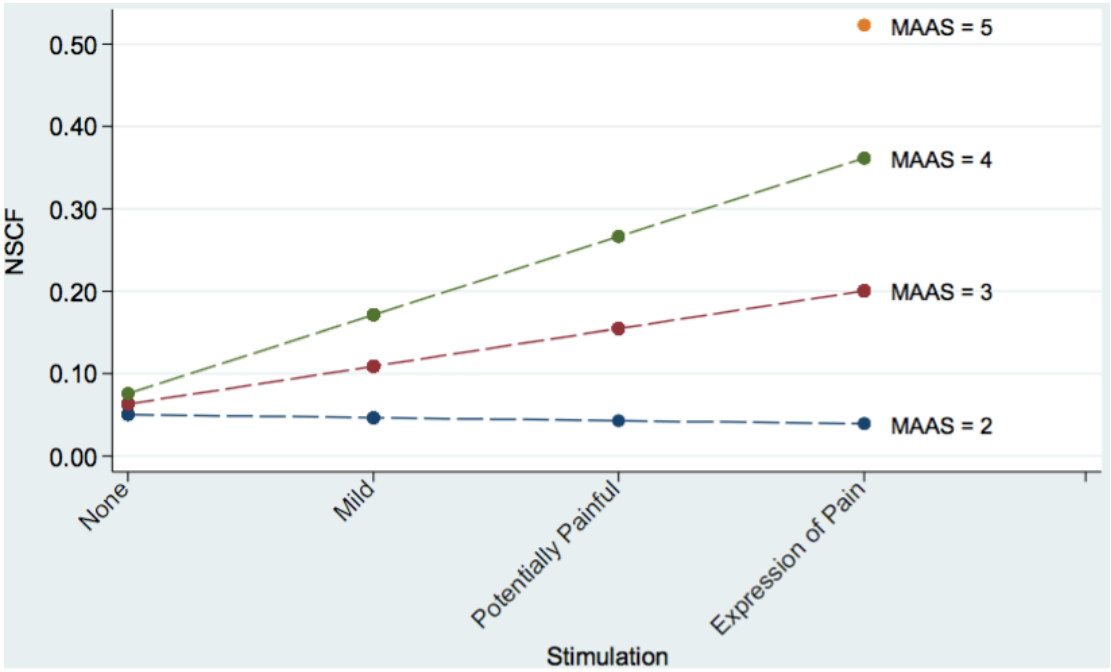

Figure 15. Skin conductance variability (NSCF), in relation to stimulation and Motor Activity Assessment Scale, **non-intubated** patients

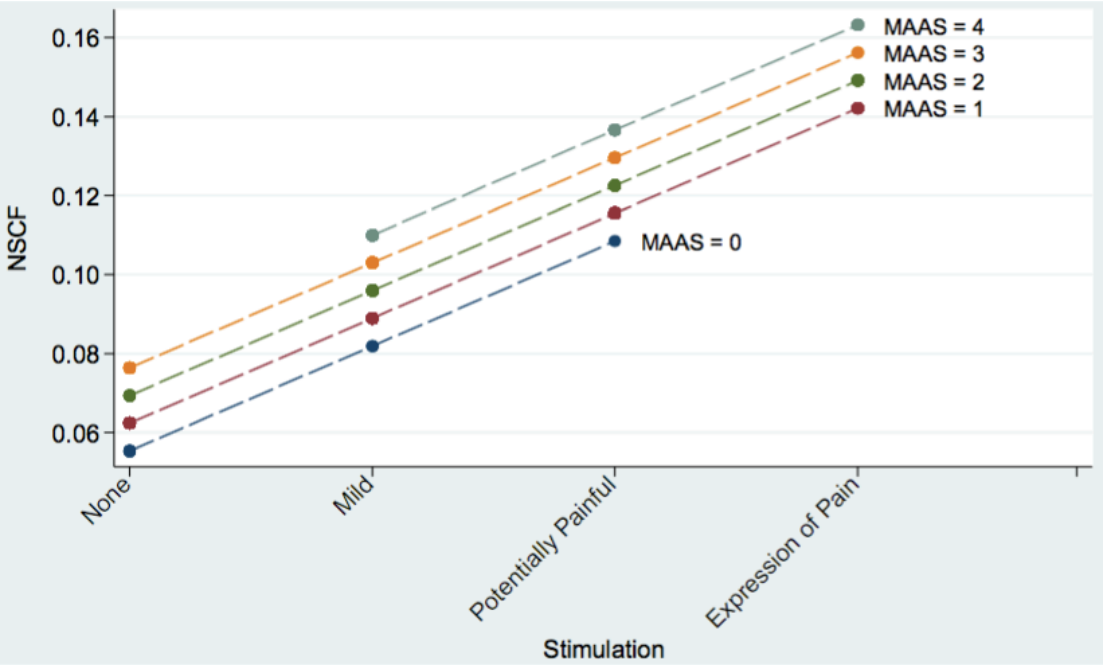

Fig. 16. Skin conductance variability (NSCF), in relation to stimulation and Motor Activity Assessment Scale, **intubated** patients

Table 8. NSCF in relation to MAAS and degree of stimulation in **non-intubated** patients

	MAAS 2 ***n* = 30**	**MAAS 3** ***n* = 589**	**MAAS 4** ***n* = 92**	**MAAS 5** ***n* = 4**
No stimulation ***n* = 77**	0,01 *n* = 14	0.07 *n* = 98	0,12 *n* = 5	No observation
Mild stimulation ***n* = 165**	0.08 *n* = 10	0.10 *n* = 256	0.18 *n* = 73	No observation
Potentially painful stimulation ***n* = 53**	0.30 *n* = 2	0.21 *n* = 66	0.46 *n* = 7	No observation
Expression of pain ***n* = 112**	0.03 *n* = 4	0.21 *n* = 169	0.50 *n* = 7	0.48 *n* = 4

Cross-tabulated mean (above) and count (below).

Table 9. NSCF in relation to MAAS and degree of stimulation in **intubated** patients

	MAAS 0 ***n* = 11**	**MAAS 1** ***n* = 339**	**MAAS 2** ***n* = 221**	**MAAS 3** ***n* = 96**	**MAAS 4** ***n* = 68**
No stimulation ***n* = 126**	0.04 *n* = 7	0.05 *n* = 85	0.08 *n* = 16	0.28 *n* = 18	No observation
Mild stimulation ***n* = 329**	0.09 *n* = 3	0.07 *n* = 110	0.06 *n* = 116	0.18 *n* = 64	0.24 *n* = 36
Potentially painful stimulation ***n* = 233**	0.07 *n* = 1	0.14 *n* = 129	0.10 *n* = 68	0.29 *n* = 12	0.26 *n* = 23
Expression of pain ***n* = 47**	No observation	0.14 *n* = 15	0.10 *n* = 21	0.23 *n* = 2	0.32 *n* = 9

Cross-tabulated mean (above) and count (below).

5.3 PAPER III

Pain stimulation, titrated to an individual visual analog scale (VAS) 5, resulted in increases in the number of skin conductance fluctuations (NSCF) in all but one participant (figure 17).

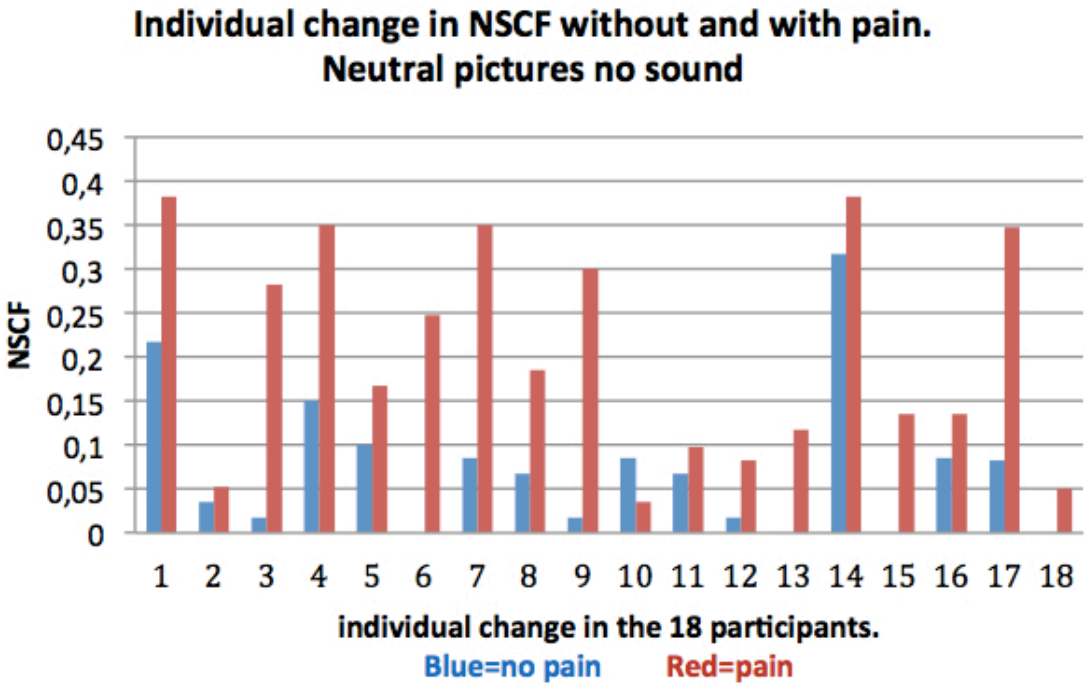

Figure 17. NSCF values for each participant in the neutral emotion block, no sound, without and with pain.

5.3.1 NSCF and VAS during pain stimulation

Median NSCF in the baseline session measurement (neutral pictures, no electrical stimulation and no sound) for the18 individuals was 0.067 peaks/second (range: p25 = 0.0175 and p75 = 0.085 peaks/second, respectively). Median NSCF in the 108 (18 times 6 sessions) measurements with pain stimulation was 0.225 peaks/second (range: p 25 = 0.146 and p75 = 0.3175 peaks/second), respectively. The median VAS during pain stimulation (all pain sessions) was 4, (range: p25=2 and p75=6, respectively).

5.3.2 NSCF in relation to pain stimulation, pictures and sound

There was a significant increase in NSCF (0.13 peaks/second) in the pain stimulation sessions compared to baseline, after adjusting for picture-induced emotion and ICU sound ($p < 0.001$)

(table 10, figure 18). NSCF also increased significantly, but to a lesser extent (0.03 peaks/second) in the negative emotion sessions compared to baseline after adjustment for the effect of ICU sound and pain ($p<0.05$). No significant effect was seen for positive emotion or ICU sound. Intra-individual correlation rho was 0.58 and indicates that 58% of the variability was due to inter-individual differences.

5.3.3 VAS in relation to electrical stimulation, pictures and sound

Rated pain increased, with VAS 3,95 during pain stimulation ($p<0.001$) (table 10, figure 19). Negative emotion also increased rated pain with VAS significantly but to a much lesser extent, by 0.36 units ($p<0.05$). No other stimuli affected VAS significantly. Intra-individual correlation rho 0.35 indicates that 35% of the variability was due to inter-individual differences.

The random-effect linear regression coefficients for NSCF as a VAS-dependent variable implied that a 1-unit increase in VAS was associated with a NSCF increase by 0.073 peaks/second ($p<0.001$). The intra-individual correlation rho 0.25 indicates that 25% of the variability was due to inter-individual differences.

Table 10. Changes in NSCF and pain rating induced by pain stimulation, emotion and sound, compared with baseline (neutral pictures, no sound, no pain), based on random-effects linear regression.

Variable	N	Change in NSCF peaks/sec	Change in Pain VAS
Pain stimulation	108	0.13***	3.95***
Positive emotion	72	0.02	-0.10
Negative emotion	72	0.03*	0.36*
ICU sound	108	0.01	0.21
Rho[a]		0.58	0.35

legend: * $p<0.05$; ** $p<0.01$; *** $p<0.001$

[a]intra-individual correlation

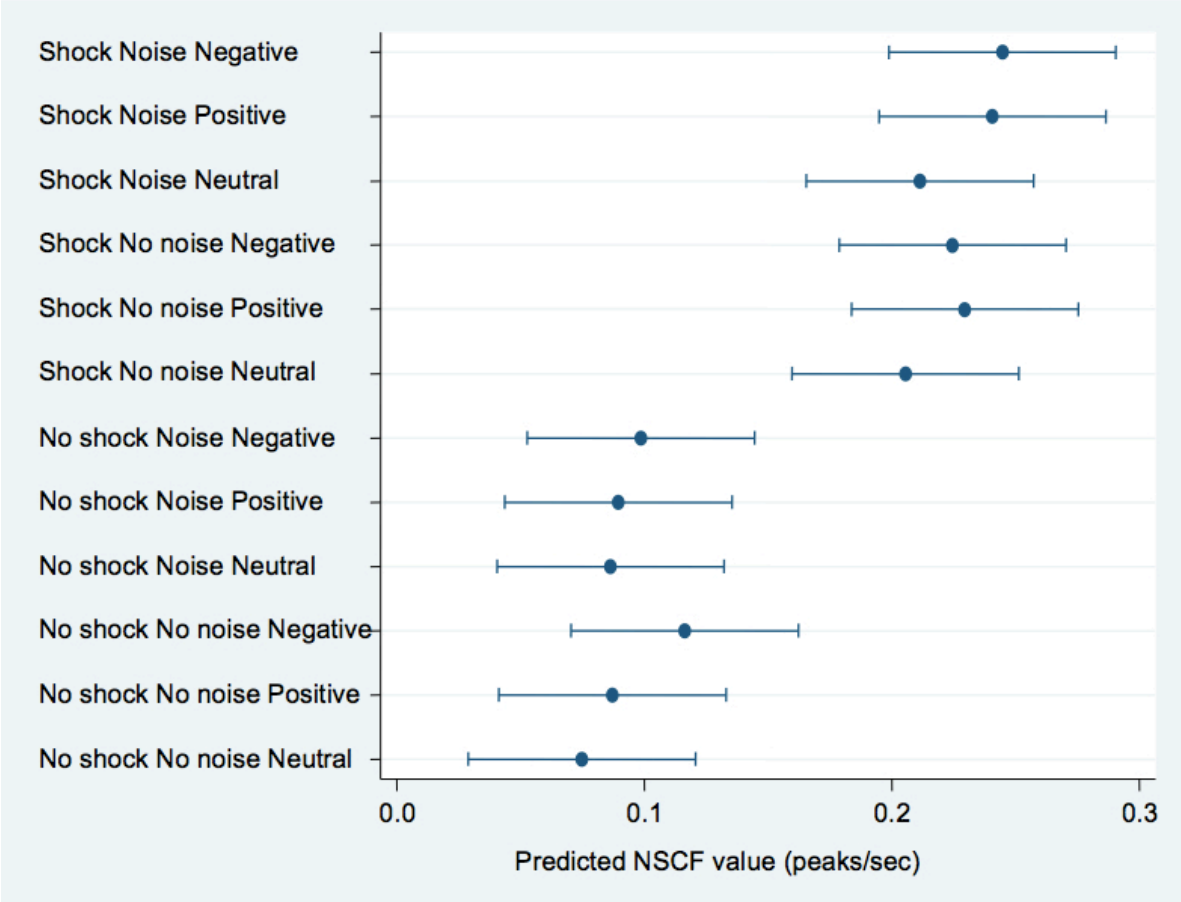

Figure 18. Mean NSCF values and 95% confidence intervals for the twelve sessions from the random-effects model.

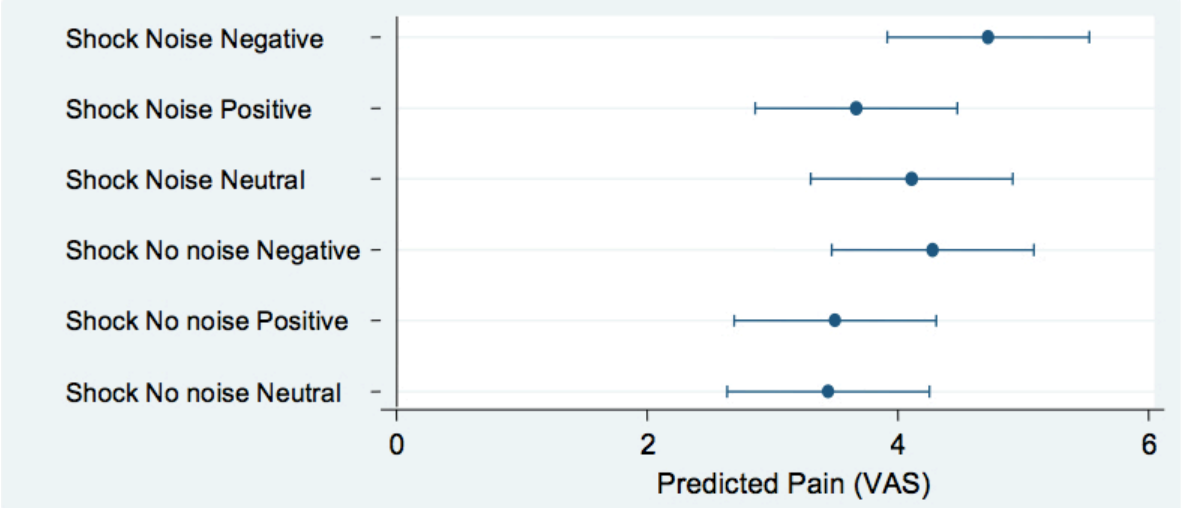

Figure 19. Mean VAS values and 95% confidence intervals for the 6 sessions with pain stimulation from the random-effects model.

5.4 PAPER IV

Patient demographics and characteristics are presented in table 11.

Table 11. Patient demographics and characteristics	
Age	
Median and range	**64,5 (26-87)**
Sex	
Female	**12**
Male	**18**
Time at the ICU (hours)	
Median and range	**83,5 (42-744)**
Diagnosis	
Medical	**16**
Surgical	**11**
Trauma	**3**
Medication	
Opioids	**8**
Betablockers	**8**
SSRI*	**1**
Benzodiazepine	**2**

5.4.1 NSCF changes to stimulation

Overall there was a significant increase when baseline SCV was compared with SCV registrations during reminders of ICU; sound 1 minute ($P=0.002$), the first 15 seconds of sound ($P< 0.0001$), the last 15 seconds of sound ($P < 0.0075$) and for registrations during exposure to traumatic ICU memories ($P < 0.0075$). Results shown in figure 20.

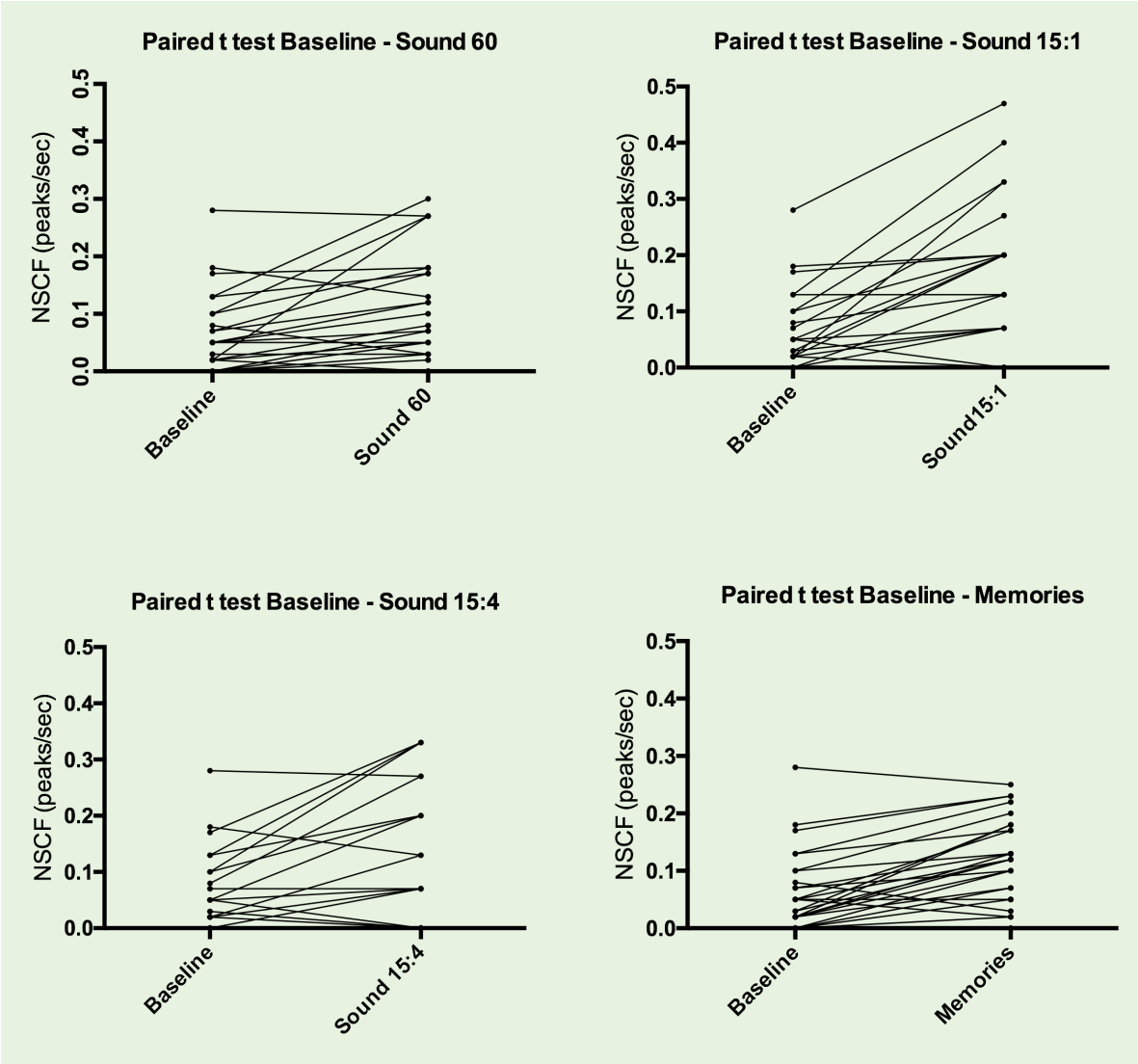

Figure 20. Individual change in NSCF between baseline and the four stressing exposures; ICU-sound one minute, the first 15 seconds of ICU-sound, the last 15 seconds of ICU-sound and during answering the four questions on traumatic ICU memories (PTSS-10, part A).

5.4.2 Correlation between NSCF and symptoms of acute or later stress

There was no correlation between NSCF in any of the tested variables and symptoms of acute stress or later signs of symptoms of PTSD as evaluated with PTSS-10 part B.

6 DISCUSSION

6.1 PAPER I

The main question in this study was: to what extent does room size/number of beds affect the sound pressure level and the frequency of disruptive sounds in a multidisciplinary ICU? We did not find any significant differences in mean sound pressure level between the studied room types. There was a trend towards longer restorative time in the single bed-room with nursing station alcove compared to the three bed-room. The frequency of disruptive sounds was significantly lower (40%) in the single bed-room with nursing station alcove compared to the other two room types. As expected the sound pressure levels were highest during the day-time shift 07 -15, likely due to the concentration of activities at the bedside in the day.

Given the threshold level of 48 dB for normal sleep and the findings in the study, changing room architecture is not sufficient to provide a sleep-promoting environment.[88] Even in the single room with a separate NSA, sound pressure levels were clearly above recommended hospital sound pressure thresholds.[23,89,90]

Two major changes in the ICU setting would likely contribute to an improved sound environment, namely reducing ICU alarms and loud chatting near the resting patient.

ICU alarm sound levels are regulated by manufacturer´s default settings, based on international standards, but can often be adjusted by the user.

According to international standard guidelines, alarm "signals need to be audible above the background noise level and different from other sounds" and "experience has shown that values between 45 dB and 85 dB can be reliably detected without being too intrusive in most situations."[91] With such recommendations, it is not surprising that all alarms in our study were set at above 80 dB.

Many alarms in the ICU environment leads to "alarm fatigue", which implies that staff can become inert to alarms if there are many "false" alarms, a behaviour which in itself implies a risk for the patient.[92-95] In a recent study, as few as 15 % of all alarms in an ICU were found to be of clinical importance.[96] Frequent assessment of alarm settings has been implemented in some settings and shown to be a means to effectively reduce unnecessary alarms.[97]

With little data regarding patient safety related to alarm volume reduction, or merely light signals, it is yet premature to state that sound alarms are unnecessary and can be replaced with light alarms only visible for staff.

Another means of reducing patients' exposure to the sometimes inevitable sounds of a modern ICU are earplugs. They are cheap and easy to apply. In an ICU simulation setting, the use of earplugs have been shown to be associated with improved cognitive function, most likely mediated via improved sleep and reduced stress.[98,99]

6.2 PAPERS II-IV

In our first study of skin conductance variability (study II), the monitor was new to us. At the time of planning study I, pain assessment in Swedish critically ill patients was very arbitrary

and tools for assessing pain in non-communicating patients were not widespread. There was a clear need for more objective pain assessments in these patients.

The correlation of NSCF with the observer´s assessment of potential or overt pain in study II was promising. The NSCF levels during clearly painful procedures in calm, cooperative patients (MAAS 3) are similar with levels of NSCF in postoperative patients, with VAS levels of 4-5. The fact that NSCF increased further in restless or agitated patients led to the question whether NSCF elevations were to be considered an indicator of pain or of general stress. For this reason, we performed study III, in healthy volunteers.

Exposures in study III were aimed to mimic exposures in the ICU situation. Many ICU patients report negative and delusional memories from the ICU.[100-104] Such experiences are likely to cause anxiety and distress. We used the IAPS pictures in order to induce emotions.[86] The authentic ICU sound recording was an attempt to further stress the subjects. Besides our ambition to understand what conditions could lead to elevated NSCF, we were interested to investigate possible interaction effects of exposures, as was noted in study II.

Study III revealed that NSCF responses to pain were similar to those in study II and what previous postoperative studies have shown.[82,83,105] We found only very mild NSCF effects of the picture series from the IAPS, despite clear differences in valence between the picture sets. The sound recording that the subjects were exposed to did not either elicit clinically important NSCF changes.

There are two possible explanations of these modest additional effects.

One is that the monitor in fact is specific for pain, in awake as well as sedated patients. For this to be true, the finding in study II of the highest NSCF elevations in response to pain stimulation were in patients with high MAAS, would have to be explained. Were high MAAS levels due to pain? Pain has been shown to sometimes be expressed as restlessness, agitation, or even delirium in hospitalized patient.[57,106,107]

The other possible explanation to the finding in study III, of pain as the sole significant condition leading to NSCF elevation would be the choice of subjects for the study. Many of these volunteers were young psychology students. It may have been that these subjects were resistant to the emotional or autonomous effects of awkward pictures from the IAPS, despite our attempts to compile representative picture sets, with well-separated valence between picture sets. Some individuals appear to be capable to voluntarily control their autonomous responses to unpleasant exposures.[108] If this was true, patients in study II, aware of their predicament might not have the same defences to intimidating exposures as young healthy psychology students.

Study IV was performed in ICU survivors recently discharged from the ICU. It aimed to further investigate if the findings in study III, of small effects of potentially distressing exposures were true also for patients. The same ICU sound recording as in study III led to significant NSCF elevation, in contrast to what was found in the volunteers in study III.

Questions of intimidating and fearful memories from the ICU also led to significant NSCF elevation, in some patients to levels equivalent of those seen in patients with moderate pain.

These findings demonstrate that NSCF elevation in awake patients does not necessarily represent pain alone. With these findings it is now clear that in vulnerable ICU survivors, there is a significant autonomous reaction to reminders of the ICU, even in the absence of pain.

We were not able to link these reactions to measures of acute stress or later posttraumatic stress symptoms. We did not explore patients' coping strategies or monitor how they managed potential distress in order not to develop posttraumatic stress, a condition relatively common in ICU survivors.[7,109-111] Thus, conclusions are difficult to draw regarding the potential clinical relevance of increased NSCF in this scenario. Studies III and IV together, however, inform us that in awake patients, NSCF is not always a sign of somatosensory pain and may vary, depending on the individual and situation.

Returning to the original question regarding the suggested potential benefit of NSCF monitoring in critical care – namely for patients unable to self-report - in study II, separate analyses were performed for intubated and non-intubated. The findings in the intubated patients were that there was less MAAS level dependence on the NSCF response to pain. This could indicate that these patients may be easier to monitor. The question arises whether patients, sedated beyond the conscious state may have a purer pain response. This is a potential next step to investigate in the clinical research of SCV.

6.3 METHODOLOGICAL CONSIDERATIONS

6.3.1 Paper I

There are a number of different methods to assess sound levels in working environments. We chose a continuous monitoring method, combined with a method measuring peak levels, in order to cover both aspects. Own experiences from the ICU setting are that background sound levels are high and combined with "sound bursts", which gives rationale to such a sound measuring approach. Further, we assessed the different sound sources by observation. This part may be subjective but is difficult to assess by other means. One possible option that might have been employed would have been to record the eight-hour shift. This recording could have been listened to by assessors and would have minimized potential bias or observer's fatigue. Identifying the different sound sources could then have been a problem.

6.3.2 Papers II-IV

In papers II-IV, skin conductance variability was measured with a specific monitor and algorithm.[76,77] The evaluation of this device was part of a project funded by the VINNOVA innovations Agency, Ministry of Enterprise, Energy and Communications. We chose to use and evaluate the main measure NSCF (or peaks per second) in the monitoring device.

Given the novelty of the device and algorithm, there are no norms of how long time frames that should be used in clinical practice or research. The most common used time frame and the one recommended by the developer is 15 seconds. The time frame influences the reported peaks/sec, depending on the number of peaks and if there is a variation in stimulation, since the measure is the average number of peaks in the measuring window. Another source of differing information may be the area of and type of electrodes used. [112] Evaluation of NSCF with different time frames were used in study II-IV, based on our clinical judgement and also both methods to evaluate our chosen time frames (study III and IV).

In the first study, the time frame was set to 15 seconds from the start of potential or overt pain stimulation. The device reports the number of skin conductance fluctuations per second and high levels are considered to be approximately 0,2 or more, three registered peaks over the 15 second window would be sufficient to lead to a number of 0,2. The 15-second time frame was based on the assumption that such a time frame should include the autonomic reaction to the stimulation, without too much time included after pain may have subsided.

In the second study of skin conductance variability, we assessed NSCF over one minute of exposure to the various combinations of stimulations. We explored NSCF changes over the entire minute of exposures, divided in four 15-second periods, without finding any major differences in NSCF levels over the minute of exposure. Thus NSCF appeared to be stable over the minute of exposure.

In study IV, we similarly measured NSCF over one minute and sought for possible "fade" or increase in NSCF over four 15-second windows. We found a small, non-significant reduction of NSCF in the end of the one-minute measurement during exposure to ICU sound.

In study III and IV, we used the same sound recording from our ICU. As stated above, the critically ill patient and a healthy volunteer likely differ in how they cope with a potential stressor. In hindsight, a sound recording from the ICU is likely to mean more to a patient who recently survived a threat to their life, than to a psychology student who might never have been in this environment. Having stated this limitation however, after performing study IV, the NSCF data in healthy volunteers provides a control group that gives meaning to the NSCF data in study IV.

6.3.3 Clinical Implications and future perspectives

Regarding the ICU environment, there is now data that indicate a need for rethinking the way we manage surveillance and alerts. Does the vulnerable patient need to experience the alarms that mostly are of no clinical significance? There is clear need for supporting the industry in the development of smart systems that detect true peril and inform us without contaminating the working and sickness environment.

Regarding skin conductance variability, there appears to be a potential for this method to be of use in critical care or anaesthesia, as an alert of pain or other distress. Further studies that could clarify its role would be both mechanistic studies, for example with functional MRI in parallel with SCV during various exposures, as well as clinical studies investigating how well skin conductance variability performs in the assessment of pain with validated measures, and the response to analgesia in the same population.

7 ACKNOWLEDGEMENTS

I wish I had more time to formulate my expression of gratitude to all you people who have, in one way or the other, helped me to finish this thesis.

Peter Sackey: First and most of all I wish to thank my supervisor and friend, who has guided me with an enormous patience and with fantastic engagement. I admire your never ending optimism and unreal capacity, your brilliant scientific knowledge and skills. It has been a great journey and I hope we will do some more trips together in the future.

Anna Schandl: my co-supervisor. You started off as co-writer in paper II, turned PhD and became co-supervisor and a major player in this project. Thank you for excellent support and tips, for fast answers to any question, for sharing your experience of thesis writing and for being a wise human being.

Örjan Sundin: co-supervisor and head of department of the psychology lab, Mid Sweden University, Östersund where study III was conducted. A master of experimental psychology and with fantastic knowledge you filled a huge gap and guided me through the marshes of psychophysiology.

Claes-Roland Martling: co-supervisor and former head of the ICU where study I, II and IV was conducted. As the experienced intensivist and researcher your important suggestions and ideas helped to form this project.

Anders Franco Cereceda and Jan van den Linden: Responsible for the research in the department of Cardiothoracic Surgery and Anesthesia, you lead a fantastic group. Thank you for your genuine belief in science and for giving us the possibility to do research and develop our skills. Anders, I am grateful for your generous and altruistic support giving me those weeks.

Lars I Eriksson: head of FOU, ANOPIVA. Thank you for always being enthusiastic and for impressive scientific work.

Eddie (or was it Freddie?) Weitzberg: Thanks for showing a nice approach to science, combining high-class research and a lust for life. And also for helping me with KI-formalities.

Lars Irestedt, Claes Frostell, David Konrad and Ulf Lockowant: Former and current Heads of department at ANOPIVA and at the Cardiothoracic department. Thank you for letting science be an important part of our work.

Åke Hellstöm and Lena Nilsson: fabulous bosses at the Anesthesia section in the Cardiothoracic department. Lena, thank you for giving me research time in the schedule.

Ulrik Sartipy: always helpful, thanks for reading manuscripts and knowing so much about computers, Endnote and statistics.

Matteo Bottai: co-writer and a magician when it comes to statistics. Thanks for your patience and kind answers to my simple questions.

More co-writers random order without ranking:

Jesper Alvarsson, Anna Reichard, Anna Bjärtå, Patrik Rossi, Jens Bernhardsson, Lotta Tegnestedt, Hanne Storm, Rasmus Bjurström and Max Wållgren. Thank you for your contribution and interesting discussions.

Fredrik Eidhagen: a steady clinician and good friend, Thank you for taking me to Thorax.

Andreas Gidlöf, Olof Brattström and Johan Nordström: good friends and fishers at ANOPIVA. This year I will not miss "Hemlijaure"

To All colleagues and friends at both Cardiothoracic and ANOPIVA, I am proud to be one of you.

Stina Wirsen: long-time friend and superb artist. Thank you for the picture on the front.

Stockholm Konstsim Herr (SKSH). No need for further comments.

All my non-work friends and family: You are too many to be named here but not less important. Thanks for all support, help and for waiting for me. I am coming back now. (OK, I need to mention some of you. For instance Olofs extra fathers when I couldn´t go: Lasse, Pelle, Jonas, Mattias, Pompe)

Ami & Christian Günther: my parents. Thank you for always believing in me and for all your loving. You taught me the most important thing in life, to be a good person.

Sara Günther: my sister. Kind of my best friend, you are always there and always care for me. You take care of the social activities so important for both of us and make me a part of it. Love you.

Olga, Nina & Olof: my children. You are my pride and represent the best part of me.

Helena: my wife and love. Actually the real researcher in our family. Looking forward to go with you to Kola Peninsula studying rock paintings or just building a gate at "Torpet".

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