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Nina Zaproudina

Methodological Aspects of Use of Infrared Thermography in Healthy Individuals and Patients with Non-specific Musculoskeletal Disorders

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ABSTRACT:

Changes in the skin temperature (Tsk) are known to be connected with diseases and subsequently infrared thermography (IRT) has been proposed to be a diagnostic aid, e.g. in musculoskeletal disorders (MSD). However, mostly due to conflicting results of previous studies, IRT lost credibility. Now interest in IRT is growing again but valid methodological studies are needed in order to avoid new disillusions due to an underestimation of the limitations of the IRT. The purposes of present study were to examine the methodological properties of the IRT, including the analysis of inter- and intra-examiner reproducibility of measured results and cold-induced reflex Tsk changes in healthy individuals, and Tsk findings in patients with non-specific MSD such as chronic low back and neck pain, with a special focus on the general problems associates with Tsk measurements.

The results indicated good inter-examiner reproducibility of the IRT results. However, the stability of Tsk findings varied from good in the core parts to poor in the distal areas of the subject. During cold provocation, Tsk changes varied extensively between individuals and measured areas; however, a good intra-individual correlation of responses was found. In MSD, differences in Tsk findings between the patients and control subjects were related to pain intensity, this being only in distal extremities. Moreover, IRT findings were strongly related to the actual Tsk and dependent on several other confounding factors.

The results suggest that IRT has the potential to be an objective indicator of dysfunction of small nerve fibers through the changes in cutaneous microcirculation and thus, in the Tsk values. However, the signs of impaired Tsk regulation may vary over time which limits the usefulness of single measurements. Dynamic IRT with different provocation tests offers better possibilities to investigate the cutaneous circulation. Nevertheless, in applications such as non-specific LBP and NP, interpretation of Tsk findings is not straightfoward due to their heterogeneous origin and extensive variability, and IRT seems to be suitable for screening and observation purposes rather than for providing quantitative values.

Overall, the complex regulation of skin blood flow, which is closely related to the function of the autonomic nervous system with a strong impact of individual reactivity, and variable physiological characteristics of the skin in different areas may lead to considerable variations in the Tsk values. In addition, numerous confounding factors exist. In summary, while IRT is a promising method for investigation of cutaneous circulation, certain precautions and considerations of the characteristics of skin blood flow are needed in the interpretation of the recorded Tsk values.

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TIIVISTELMÄ:

Ihon pinnan lämpötilamuutokset on yleisesti yhdistetty sairauksiin ja siten lämpökuvausta on yritetty hyödyntää diagnostisena menetelmänä, mm. tuki- ja liikuntaelinvaivojen (TULE) yhteydessä. Valtaosassa aikaisemmista tutkimuksista tulokset ovat olleet ristiriitaisia, mikä vaikutti lämpökuvauksen uskottavuuteen. Viime vuosina kiinnostus menetelmää kohtaan on ollut kuitenkin uudelleen kasvussa ja on tarvetta metodologisille tutkimuksille, joiden avulla voidaan selvittää lämpökuvausmenetelmän mahdollisuudet ja käyttörajoitukset ja välttyä virhetulkinnoilta tulevaisuudessa. Tämän tutkimuksen tavoitteina oli tarkastella lämpökuvausmenetelmän käyttömahdollisuuksia metodologisesta näkökulmasta mm. selvittämällä lämpökuvaustuloksien toistettavuutta ja kylmäaltistuksen aiheuttamia lämpötilamuutoksia ihon eri alueilta sarjamittauksissa terveillä koehenkilöillä, kiinnittäen huomiota mittaustulosten vaihtelevuuteen ja tuloksiin vaikuttaviin tekijöihin. Lämpökuvauksen käyttökelpoisuutta TULE-vaivojen tutkimuksessa tarkasteltiin vertaamalla alaselkä- ja niskakipupotilaiden ihon lämpötilalöydöksiä kontrollihenkilöiden vastaaviin tuloksiin.

Kahden tutkijan välinen mittaustulosten toistettavuus oli suhteellisen hyvä mutta vaihteli kahden päivän vertailussa, toistettavuuden ollessa hyvä vartalon alueella mutta heikkoa raajoissa. Kylmä-altistuksessa ihon lämpötilavasteet vaihtelivat laajasti mittausalueiden ja eri henkilöiden välillä mutta saman henkilön mittaustulokset korreloivat hyvin keskenään. TULE-vaivoissa, ihon lämpötilan puolierot olivat merkittävästi suurempia potilailla ja korreloivat selkä- tai niskakivun voimakkuuteen raajojen ääreisalueilla. Kaikkiaan, useampi tekijä ja mm. erityisesti ihon alkulämpötila näyttivät vaikuttavan löydöksiin.

Tulokset viittaavat siihen että lämpökuvaus voi paljastaa hermotushäiriöihin liittyvät ihon mikroverenkierron muutokset ja antaa tietoa ohuiden hermosäikeiden toiminnasta mm. TULE-vaivoissa. Mittaustulokset voivat kuitenkin vaihdella ajan myötä mikä laskee kertamittausten merkitystä. Toisaalta, dynaaminen lämpökuvaus provokaatioon yhdistettynä antaa paremmat käyttömahdollisuudet ihon verenkierron tutkimiselle. TULE-vaivojen yhteydessä, lämpötilalöydösten tulkinta saattaa olla ongelmallista niiden epäselvän syntyperän ja merkittävän vaihtelevuuden vuoksi mikä tekee menetelmästä pikemmin kuvaavaan tai seulontamenetelmän kuin kvantitatiivisen. Kaiken kaikkiaan, lämpökuvaus on lupaava ihon verenkierron tutkimusmenetelmä, mutta mm. ihon fysiologiset ominaisuudet ja sen lämpötilan monimutkainen säätely, tutkittavan yksilöllinen reaktiivisuus sekä useamman muun sekoittavan tekijän vaikutukset voivat heijastua lämpökuvauslöydöksiin. Näin ollen, varovaisuus ja ihon verenkierron fysiologisten ominaisuuksien huomioon ottaminen ovat tarpeen lämpökuvien tulkinnassa.

Yleinen Suomalainen asiasanasto: lämpökuvaus; iho - lämpötila; iho - verenkierto; tuki- ja liikuntaelinten taudit; autonominen hermosto

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List of the original publications

This dissertation is based on the following original publications:

I Zaproudina N, Varmavuo V, Airaksinen O and Närhi M. Reproducibility of infrared thermography measurements in healthy individuals. *Physiological Measurement 29: 515-524, 2008*.

II Zaproudina N, Ming Z and Hanninen O. Plantar infrared thermography measurements and low back pain intensity. *Journal of Manipulative and Physiological Therapeutics 29: 219-223, 2006*.

III Zaproudina N, Airaksinen O and Närhi M. Are the infrared thermography findings skin temperature-dependent? A study on neck pain patients. *Skin Research and Technology* (accepted).

IV Zaproudina N, Lipponen J, Eskelinen P, Tarvainen M, Karjalainen P, Närhi M. Measurements of skin temperature responses to cold exposure of foot and face in healthy individuals: variability and influencing factors. *Clinical Physiology and Functional Imaging 31: 307-314, 2011.*

Contents

Abbreviations

AVA	Arteriovenous anastomoses
BF	Blood flow
CE	Cold exposure
CHC	Cold hands controls
CHNPP	Cold hands neck pain patients
CRPS	Complex regional pain syndrome
DBP	Diastolic blood pressure
ENMG	Electroneuromyography
HR	Heart rate
ICC	Intraclass correlation coefficient
IRT	Infrared thermography
LBP	Low back pain
LDF	Laser Doppler flowmetry
MRI	Magnetic resonance imaging
MSD	Musculoskeletal disorders
NP	Neck pain
SARS	Severe acute respiratory syndrome
SBP	Systolic blood pressure
SSR	Sympathetic skin response
SSNA	Skin sympathetic nerve activity
Tsk	Skin temperature
VAS	Visual analog scale
WHC	Warm hands controls
WHNPP	Warm hands neck pain patients
δT	side-to-side temperature difference

1 Introduction

Skin is the largest organ of the human body with a fluctuating blood flow (BF). The relationship between disease and skin temperature (Tsk) changes has been known since the time of Hippocrates: he described a method of measuring how quickly wet mud smeared on the skin dried as a way of indicating the site of underlying pathology (Otsuka and Togawa 1997). One of the methods for investigation of the skin microcirculation is a measurement of the Tsk, and infrared thermography (IRT) has been used for this purpose since the 1960s. Since there has been a major need for objective techniques in studies of nerve function and skin BF, IRT has been evaluated as a diagnostic aid in a wide variety of clinical conditions including neuromuscular disorders. However, the use of the IRT as a diagnostic tool has given rise to vigourous debate among researchers. Due to conflicting results, the IRT method went through the typical history for a new technique: from initial enthusiastic interest to almost complete obscurity. However, the interest in IRT is on the increase again which may be partly explained by the developments in IRT technology offering new sensitive and user-friendly devices for the recording of skin surface temperature with a wide variety of possibilities for image analysis, also the possibility to use this technique in follow-up examinations since it is applicable for tests involving different types of challenges.

However, analysis of the background reasons for the conflicting IRT findings in earlier reports may help to avoid new disappointments. Most of the previous studies were descriptive and focused on the differences between patients and healthy subjects at the group level despite the fact that great inter-individual variability was depicted (Hart and Owens 2004, van Ooijen et al. 2001). One-time registered Tsk findings have been usually reported, although the results of Tsk measurements are known to change with time (Sherman et al. 1994). The influences of factors related to the measurement protocol, environment, and technique have been reported (Pusnik and Drnovsek 2005, Ring et al. 2002, Ring et al. 2004). However, the process of the "living" Tsk of the human body has been less extensively studied as well as creating a normal database of Tsk recordings in healthy individuals has been the topic of only a few studies (Feldman and Nickoloff 1984, Uematsu 1985, Uematsu et al. 1988a, Niu et al. 2001). Moreover, changes in skin BF, leading to Tsk changes, are known to be poorly predictable due to the interplay of different regulating mechanisms including psychophysiological characteristics related to the personality of the individual (LeBlanc et al. 2003, Wallin and Charkoudian 2007) and test-related stress reactions (Fagius and Traversa 1994). Those mechanisms are rarely understood and thus, Tsk responses are impossible to standardize. In addition, different baseline states of the activity of autonomic nervous system, and as a consequence, Tsk have been not always analysed and taken into account in IRT studies even though the influence of baseline characteristics on the vascular reactions is recognized (Oberle et al. 1988, Isii et al. 2007, Ley et al. 2011). In addition, the borderline between health, usually meaning symptom-free, and disease is not always completely clear because, according to some reports, changes in skin BF are claimed to be the earliest symptoms of certain diseases e.g. hypertension (Boutcher et al. 2009) and some probably genetic discordances of vascular reactivity (Wu et al. 2010) and peripheral vascular tone (Nagashima et al. 2002) are known also among the symptom-free individuals.

On the other hand, skin BF reflects the microcirculatory function and offers wide investigation possibilities in studies examining disorders of the nerve function involving the autonomic nervous system and thus, peripheral BF. In musculoskeletal disorders (MSD), diagnostics are based mostly on the standard techniques (X-rays, magnetic resonance imaging (MRI) or computerized tomography) which image the morphological structures. However, as

Tsk changes are a functional phenomenon related to vasomotor activity regulated by the small nerve fibers, IRT is poorly comparable with other study methods (Gold et al. 2009). Disturbances in the nerve function can be measured also with electroneuromyography (ENMG), which can reveal the function of the large myelinated nerve fibers. However, some of the symptoms encountered in MSD complaints to a great extent may be related to the function of the small sensory and sympathetic fibers but techniques for evaluating their function have been less extensively used in clinical practice and the small-fiber neuropathy has been claimed to be underdiagnosed (Fink and Oaklander 2006; Tavee and Zhou 2009). Since there is a need for objective indicators of autonomic disorders, IRT has been widely applied also in MSD and claimed to be able to distinguish areas with impaired innervation (Campero et al. 1993). According to Berz and Sauer (2007), due to its high specificity, IRT can therefore identify the first abnormalities in vascular function. Thus, IRT may be potentially helpful in early diagnostics and screening of neuropathy, but further studies are needed to explain the mechanisms behind those findings. However, the interpretation of the signs of impaired Tsk regulation is difficult without a more complete understanding of the complicated physiological characteristics of skin BF.

Therefore, the intent of the present studies was to examine the methodological properties of IRT in medical applications, particularly in patients with non-specific MSD, with the objective to help to avoid future errors in the interpretation of Tsk findings. The present study defines the Tsk changes as a multifactorial whole body process with the complex regulation of cutaneous circulation, being attributable, firstly, to internal factors such as the physiological variability and the lability of skin BF for a variety of reasons, including also individual stress reactivity and, secondly, to technical and other external factors such as the accuracy characteristics of the IRT equipment, measurement environment and technique with the first set of factors being more significant, less studied and difficult to control.

The study includes the following consecutive steps:

1) investigation of the intra- and inter-examiner reproducibility of IRT with special attention on factors influencing the results.

2) analysis of Tsk findings in single measurements in LBP and NP patients, in the latter group with special attention to the relationship with the actual Tsk.

3) study of the cold-induced reflex Tsk changes with the analysis of the inter-regional and inter-indivudual differences in the responses to different types of cold exposure in healthy men and the usefulness of IRT for the monitoring of cold-induced Tsk changes.

2 Literature Review

2.1 INFRARED THERMOGRAPHY

IRT is a method which can be used to measure the temperature of the object by the sum of infrared radiation emitted at the surface. The IRT method has the several technical, industrial or building applications e.g. as a "night vision" device. In medicine, it was first integrated into diagnostic systems in the 1960s.

The skin surface radiates infrared rays in a wavelength range of 900–14,000 nanometers of the electromagnetic spectrum. The thermographic camera has sensors for detecting this infrared radiation and producing a visible two-dimensional image of the distribution of the skin surface temperatures of the human body. The earliest infrared cameras had poor characteristics such as a weak resolution, instability and a lack of computer software (Berz and Sauer 2007). More recently, the developments in the digital IRT technology have created the possibility to record, analyse and save various body surface temperature images for follow-up examinations.

The medical applications of IRT are connected with the Tsk changes typically encountered in some clinical conditions e.g. inflammation which evokes an increase in the Tsk of the affected body areas. On the other hand, due to nerve entrapment or in cases of vascular pathologies, the blood circulation may decrease, and the affected tissue will be colder than its surroundings. As a diagnostic device, IRT is a non-invasive, non-contact, safe tool which allows visualization of the distribution of the skin surface temperatures. The most widely studied fields are mammology (for examination of breast cancer), neurology, MSD, vascular diseases and vasospastic syndromes. The peak of the medical applications of IRT occurred in the period 1970-1980. Afterwards, the clinical use of the method declined, partly due to conflicting results of various IRT studies and attempts to replace some other diagnostic methods with IRT. However, IRT has been often utilised for research purposes due to its safety, simplicity of use and the possibility to screen large skin areas simultaneously and to obtain a Tsk distribution for a defined body region.

Previously, IRT has been found to be comparable with the contact thermometry as the method for the measurement of Tsk (Livingston et al. 1987, van den Heuvel et al. 2003). Moreover, in the study of Livingston et al. (1987) it was reported that measuring of Tsk with only a single termistor was insufficient because of the large variations in temperatures in different locations in the body. In addition, the superficial veins may have an impact on local Tsk, and the temperature values are unreliable, if measured only from single small-sized sites (Vainer 2005; Werdehausen et al. 2007).

In the measurement of skin BF, methods such as laser Doppler flowmetry (LDF) and plethysmography have been mostly used (Charkoudian 2003). However, IRT did not always provide results which would be comparable with those BF measurements. A correlation was found between the Tsk levels in fingertips and LDF results (Akata et al. 2004, Merla et al. 2007) and, according to the results of the latter report, IRT provides better and faster imaging of cutaneous perfusion. It was claimed to assess the total skin BF, including both superficial flow and flow through deep arteriovenous anastomoses (AVA:s; Häbler et al. 1997). Werdehausen et al. (2007) stated the changes in Tsk measured by IRT represented heat-exchange vessels located deeper i.e. LDF can only detect the BF in superficial vessels to a depth of 1 to 2 mm. Moreover, IRT is claimed to assess the larger skin areas simultaneously and does not depend on the separate blood vessel function whereas LDF records the BF in only a small focal area (Wilder-Smith et al. 2005).

According to Clark et al. (2003), there was a poor correlation between the results of the above two methods e.g. in Raynaud's phenomenon, although LDF has been regarded as being more sensitive to small changes in skin BF (Stikbakke and Mercer 2008). In direct foot cold immersion, the relationship between changes in skin BF and Tsk was reported to be ambiguous; it was linear in the dorsal foot but not in the toe region (Bornmyr et al. 1997). However, when vasoconstrictive responses have been studied with both LDF and Tsk measurements, Tsk responses appear within a short time delay after the changes detected by LDF (Allen et al. 2002, Kistler et al. 1998). The recorded Tsk changes were claimed to be a good indicator of the sympathetic responses mediated via central nervous system (Kistler et al. 1998). The results correlated closely in terms of the response to cigarette smoking although the Tsk changes appeared somewhat later than LDF (Bornmyr and Svensson 1991). Monitoring of the Tsk has been discussed e.g. for evaluation of peripheral perfusion during surgical operations (Akata et al. 2004) or for following the effectiveness of spinal anaesthesia (van Haren et al. 2010).

According to some authors, IRT is able to evaluate the small-fiber disorders and to indicate the area of the affected innervation (Campero et al. 1993), which is difficult to detect by current conventional methods. In MSD, IRT findings have been previously compared with the results of other methods such as MRI or computerized tomography as ways of illustrating the morphological changes. An overview of the different medical imaging aids within the electromagnetic spectrum has been presented in the study of Hildebrandt et al. (2010). However, the comparability of the results of structural imaging (X-ray, MRI) and methods describing the functional changes of skin BF such as IRT recordings, has been criticized earlier as being poor (Berz and Sauer 2007). According to Gold et al. (2009), IRT is poorly comparable also with ENMG which is able to record the function of the thick myelinated nerve fibres. Quantitative sensory testing is a known way to assess the function of the small sensory nerve fibers in the peripheral nerve lesions (Verdugo and Ochoa 1993) but this technique is not widely used in routine clinical work.

For investigation of peripheral autonomic fibers, a method known as the sympathetic skin response (SSR, also known as galvanic skin response) has been widely used (Vetrugno et al. 2003). SSR assesses the sympathetic acetylcholine-mediated sudomotor function through the activation of the sweat glands as well as also the quantitative sudomotor axon reflex test, thermoregulatory sweat test and measurement of the skin evaporation. Park et al. (1994) claimed IRT to be a more sensitive test than SSR in assessing sympathetic dysfunction in peripheral neuropathy, apart from these cases in which there are symmetrical changes. They concluded that combined SSR and IRT tests would be better in the evaluation of the sympathetic function in peripheral neuropathy (Park et al. 1994). For investigation of peripheral sympathetic function, measurements of skin sympathetic nerve activity (SSNA) with microneurography have been reported to provide more exact information about the function of the autonomic nervous system. However, it is difficult to interpret the irregular SSNA bursts and differentiate the changes related to different types of sympathetic fibers (Wallin and Charkoudian 2007, Young et al. 2009). Moreover, its use in clinical routine is limited.

2.2 REGULATION OF THE SKIN BLOOD FLOW

The infrared irradiation from the skin surface and in that way also Tsk values are dependent on the skin microcirculation. There is a complex relationship between skin, inner tissue and local blood vessel function which is regulated by the autonomic nervous system in order to maintain homeostasis (Merla and Romani 2006).

The skin BF plays an important role in thermoregulation which is the primary function of the cutaneous circulation (Berne and Levy 1996). The core temperature is controlled by the thermoregulation centre located in the preoptic area of anterior hypothalamus and maintained constant via the heat producing and conserving reactions of the body. The sympathetic nervous system is the most important component in controlling of the body temperature because it regulates the circulation and thus the conduction of the heat to skin. An increase in internal temperature and Tsk results in increased heat dissipation via cutaneous vasodilation and sweating. A decrease of Tsk or internal temperature evokes reflex decreases in heat dissipation via cutaneous vasoconstriction and increased heat generation by shivering (Charkoudian 2003). The skin is an effectively controlled "heat radiator" system, and 60% of the total heat loss of the naked human being occurs as infrared radiation (Guyton and Hall 2006). The BF to the skin is about 5% of the cardiac output under normothermic conditions but it may vary from nearly zero during periods of maximal vasoconstriction to as much as 60% in times of maximal vasodilation when the body temperature is elevated (Kellogg 2006).

The skin BF is dependent mostly on the SSNA. The autonomic outflow regulating the blood vessels originates from the intermediolateral cell column of the spinal cord. This area receives signals from different systemic and central receptors and other brain regions e.g. hypothalamus. The preganglionic neurons of the sympathetic division of autonomic nervous system leave from the thoracolumbar region in spinal segments T1 - L2 and pass through the ventral roots before synapsing with the postganglionic neurons in the paravertebral ganglia. Subsequently, the postganglionic sympathetic fibers extend to the target organs, also to the blood vessels and the sweat glands with the peripheral nerves or blood vessels.

There are four types of sympathetic nerve fibres: adrenergic vasoconstrictive, cholinergic vasodilative releasing acetylcholine, sudomotor and pilomotor fibres (Wallin and Charkoudian 2007). Most of the skin vessels are innervated by sympathetic adrenergic nerves releasing mostly norepinephrine. These nerves induce vasoconstriction, which leads to an increase in the vascular resistance and arterial blood pressure and a decrease of distal BF. In addition, circulating catecholamines can influence the cutaneous vessels and also other co-transmitters may participate in the vasoconstriction (e.g. neuropeptide Y). Sensory fibers and nitric oxide also play a role in local regulation (Charkoudian 2003) and the small afferents have been stated to influence the skin vascular tone through the release of neuropeptides such as substance P (Yonehara et al. 1992).

Skin BF changes dynamically due to the continuous interplay between the vasoconstricting and vasodilating mechanisms influencing skin BF (Wallin 1990). Sympathetic vasoconstictive fibres at rest are always tonically active in normal ambient temperatures (Wallin and Charkoudian 2007). However, the vasodilative fibers are activated only when the core temperature increases significantly and are then responsible for 80–90% of the BF increase, including the contribution of nitric oxide, with the remaining 10-20 % coming from the cessation of the vasoconstrictor tone (Charkoudian 2003). Sympathetic innervation differs in hairy and glabrous skin (lips, palms, soles) where only constrictors exist and activation leads exclusively to vasoconstriction (Charkoudian 2003, Kellogg 2006). The parasympathetic branch of the autonomic nervous system does not commonly innervate the blood vessels, apart from certain cranial arteries and the area of genitalia (Berne and Levy 1996). In the facial area, e.g. parasympathetic vasomotor fibers also innervate the facial skin via the facial and glossopharyngeal nerves (Drummond 1994).

The cutaneous microvasculature consists of arterioles, capillaries and postcapillary venules, with the precapillary sphincters and AVA:s. It includes two horizontal plexuses with the several interconnections between the blood vessels. The superficial plexus lies under the skin surface in the papillary dermis. From this plexus, arterial branches give rise to capillary loops. This venous plexus represents the thermal radiator of the skin (Braverman 1997). The lower cutaneous plexus is situated in the dermal-subcutaneous junction. Those horizontal structures are extremely important in the physiology of the skin microcirculation (Braverman 1997).

In the regulation of skin BF, AVA:s play a significant role through the connections between the skin arteries and veins (Berne and Levy 1996, Bergensen 1993, Lossius et al. 1993). The number of AVA:s varies in different skin areas being maximal in glabrous skin in the most exposed skin areas such as the inside of the hand and foot, the nail bed, lips, cheeks, ears and the nose, which are regarded as the thermoregulatory windows of the body (Berne and Levy 1996, Guyton and Hall 2006, Lossius et al. 1993). Those highly muscular structures are richly supplied by sympathetic vasoconstrictive nerve fibers. Skin arterioles are under basal sympathetic tone but this is not the case for AVA:s and these are opened in warm and virtually closed in the cold due to the influence of the sympathetic nervous system which leads to rapid fluctuations in skin BF in distal areas. However, precapillary sphincters are not innervated instead having a myogenic tone and they are sensitive to the local changes in tissue metabolism. In addition to AVA:s, the thermoregulatory capability of the skin may be determined by an abundance of subcutaneous skin vessels (Werdehausen et al. 2007). In addition, differences in the innervation of the glabrous skin containing sympathetic vasoconstrictor nerve fibres and hairy skin containing, in addition, cholinergic vasodilator fibers, are important in this respect (Charkoudian 2003). The activation of the sudomotor cholinergic fibers may also result in vasodilation of the skin resistance vessels. In summary, in the regulation of skin BF, neural control is more important than local factors (Berne and Levy 1996).

2.3 FACTORS INFLUENCING SKIN BLOOD FLOW AND THE SKIN TEMPERATURE

Tsk levels may vary extensively, especially in distal extremities. However, also in trunk skin, Tsk has been shown to be rather variable (van Haren et al. 2010) this being related to the anatomical characteristics of skin, the nature of the cutaneous innervation and the circulation. In addition, many factors are known to affect the vasoregulation of the skin.

The main function of the skin BF is the participation in the maintaining of the constant body temperature, even when the ambient temperature is different and thus, body temperature is an important factor influencing SSNA (Wallin and Charkoudian 2007). Roddie et al. (2003) described a high level of sympathetic tone in the extremities, ears, nose and lips which was reduced when there was an increase in body temperature. When core temperature increases, it activates also the vasodilator nerves which, as mentioned before, are responsible for the large increase in skin BF seen in hyperthermia (Charkoudian 2003). The changes of ambient temperature lead to an increase of SSNA in cold exposure (Sawasaki et al. 2001) and a decrease when the ambient temperature increases (Iwase et al. 2002). Thus, the environmental factors such as low ambient temperature may provoke a significant decrease in the Tsk in peripheral areas. Higher variations of Tsk values in cold have been described (Livingston et al. 1987, Frim et al. 1990). For example, in the study of Nardin et al. (2010), Tsk of feet was found to be strongly associated with the ambient temperature, being very variable ranging from 15.9 °C in winter up to 37.5 °C in summer. In addition, the mental stress-induced vascular responses were found to vary in the different ambient temperatures (Hayashi et al. 2008) and thermal responses were found to be affected by room temperature and seasonal conditions (Harada et al. 1998, Mäkinen et al. 2004). In finger Tsk, significant seasonal differences have been also reported despite an identical room temperature (Gardner-Medwin et al. 2001).

In turn, the actual Tsk may influence the vascular reactions: Oberle et al. (1988) have found that the same stimuli can evoke cutaneous vasodilation in cooled subjects and vasoconstriction in those warmed, and also in cold skin (Tsk less than 28° C for hands) vasoconstrictive responses due to noxious stimuli are transformed into vasodilation (Krogstad et al. 1995). In line with those findings, an inverse relationship between vascular adrenergic responsiveness and the tonic SNA has been demonstrated (Charkoudian et al. 2006). Moreover, among young women, about 20% have usually cold extremities without any vasospastic disease or any other symptoms, this being probably due to their higher sensitivity to the sympathetic input or the differences in vascular tone (Gasser et al. 1992, Nagashima et al. 2002). They also display conflicting responses in a cold test (Isii et al. 2007), pain conditioning and mental stress (Oberle et al. 1988) and in tests with arterial occlusion (Ley et al. 2011).

Age is one of the factors impairing the skin microcirculation. This can lead to problems in thermoregulation in older subjects. Ferreira et al. (2008) reported a lower resting temperature and slower heat dissipation in elderly subjects. In addition, reflex vasoconstriction was found to be diminished in older men during whole body cooling due to impairment of the thermoregulatory control of SSNA (Kenney and Armstrong 1996, Grassi et al. 2003). The mechanisms involved in the age-related impairment of vasoconstriction and vasodilation have been shown to be complex, including a decline in the sympathetic outflow and vascular responsiveness, and impairments in neurotransmitter synthesis and signaling (Holowatz and Kenney 2010). In children, lower variations of Tsk values as compared to adults have been reported (Kolosovas-Machuka and Gonsales 2011).

Gender may influence the Tsk findings. According to Chamberlain et al. (1995), the tympanic temperature in women is higher than that of men. Higher Tsk of the back area (Hashiguchi et al. 2010) and higher intestinal, rectal and m. pectoralis temperatures but lower hand temperatures (van Ooijen et al. 2001) were found in females as compared to males. The vasoconstriction in response to a change of the ambient temperature (van Ooijen et al. 2001) and local cooling (Cankar and Finderle 2003) also differed, pointing to a gender difference in thermoregulation. Isii et al. (2007) found a lower Tsk in the fingertips of young females compared to males. These findings indicate that the thermoregulatory responses in skin BF may be gender-dependent. However, no difference in vascular or autonomic nervous system reactivity related to the different phases of the menstrual cycle was found (Cankar and Finderle 2003) but after menopause, the thermoregulatory control of the skin BF may be impaired (Charkoudian 2003).

Body composition has been found to influence the thermographic results (Livingston et al. 1987), greater calculation errors were encountered in fat subjects, especially in colder environments. The Tsk of the hand has been found to be elevated in obese adults (Savastano et al. 2009).

Changes of Tsk may be related to pain which can induce a vasoconstrictive response in the cutaneous vessels (Blessing and Nalivaiko 2000). During cold exposure, more intense cold-induced reactions were demonstrated when the intervention was painful (Kregel et al. 1992, Takahashi et al. 2003) and the pain intensity correlated with the degree of vasoconstriction in the fingers (Kreh et al. 1984). Skin vasomotor reflexes can appear even under anaesthesia and they correlated with the intensity of the noxious stimuli (Shimoda et al. 1998).

In addition, factors such as arousal and mental stress can activate skin vasoconstrictors (Krogstad et al. 1995). Mental stressors have been applied in psychophysiological studies which have utilized IRT to study Tsk (Kistler et al. 1998). On the other hand, mental stress can be a confounding factor e.g. the stress and experienced pain may interfere, leading to inhibition of pain perception (Fechir et al. 2009). In simulated diving, stress-induced changes in SBP were found before the intervention (Fagius and Traversa 1994). Cold pressor test-induced cortisol elevations were found to differ in two sessions when males were watched by a female or videotaped or not observed at all (Schwabe et al. 2008).

Wallin and Charkoudian (2007) highlighted also other important modifiers of SSNA such as posture and blood pressure, and reflex vasoconstriction in the skin due to the activation of orthostatic and baroreflexes also play a role. In addition, deep breathing may change the cutaneous vasoconstrictor activity (Wallin 1990). Smoking is also known to evoke vasoconstriction (Bornmyr and Svensson 1991).

In addition to those general factors listed above, changes in skin BF, leading to the Tsk changes, are variable at the individual level and poorly predictable. Previously, it was noted that some subjects demonstrated greater variations in Tsk values than others (Hart and Owens 2004). Individual-based characteristics of body temperature and the resting metabolic rate have been demonstrated (van Ooijen et al. 2001). In studies of vascular responses, an inexplicably high variability exists among healthy individuals. According to previous studies (Mohan and Marshall 1994, Mourot et al. 2009), some healthy individuals exhibit contrary reactions to cold than others. This individual variability in the vascular reactivity has been less extensively studied and may be determined genetically (Wu et al. 2010) and ethnically (Lambert et al. 2008). The importance of inter-individual differences in personality has been also emphasized (LeBlanc et al. 2003, Wallin and Charkoudian 2007). Thus, the nature of the cutaneous vasoregulation is complex and multifactorial due to the presence of numerous regulatory and partially conflicting effects.

2.4 IRT RESULTS AND REPRODUCIBILITY

Previously, IRT has been mostly utilized in different clinical complaints. However, before the use of IRT in diagnostic examinations, the reliability and reproducibility of the measured results need to be investigated. In previous reports, only a few studies of the whole body Tsk findings of healthy individuals have been published, mostly measured with older technology (Feldman and Nickoloff 1984, Uematsu 1985, Uematsu et al. 1988a, Niu et al. 2001). A database of normal Tsk distribution in healthy persons is under construction (Ring et al. 2004, http://www.comp.glam.ac.uk/pages/staff/pplassma/MedImaging/Projects/IR/Atlas/index.html). In previous studies, the Tsk of the various parts of the human body, including the face, has been claimed to be symmetrical in healthy persons (Uematsu 1985, Uematsu et al. 1988a, Niu et al. 2001, Gratt and Sickles 1995, Weinstein et al. 1991). Asymmetrical images were claimed to be connected to pathological changes of vascular, inflammatory or neurologic origin (Porgel et al. 1996). The inter-examiner reliability of IRT has been investigated e.g in patients with knee pain. Ten raters evaluated thermal findings in the knee area and the intraclass correlation coefficients were good, ranging from 0.82 to 0.97 (Selfe et al. 2006). Similar results were found in patients with arthritis in the hands (Varju et al. 2004; Spalding et al. 2008).

On the contrary, the stability of side-to-side temperature differences (δT values) with time has been described as being low e.g. in patients with CRPS (complex regional pain syndrome; Sherman et al. 1994). With regards to the applicability of IRT, the problem of its unclear reliability has been discussed earlier (Herrick and Hutchinson 2004). The reproducibility of Tsk measurements with time has only been investigated in certain skin areas e.g. this has been found to be poor in breast (Mustacchi et al. 1990) but good in hand (Oerlemans et al. 1999). In patients with osteoarthritis, the reproducibility of IRT images of the hands was also high between two scans (Varju et al. 2004). In the back area, high reproducibility (Owens et al. 2004, Roy et al. 2006) and stability (Hart and Owens 2004) of IRT results have been reported, but some subjects demonstrated higher variations than others (Hart and Owens 2004). In CRPS, while IRT has been shown to be capable of distinguishing patients from healthy controls, the reliability and repeatability of the observer assessment of thermographic findings were claimed to be low (Niehof et al. 2007).

2.5 MUSCULOSKELETAL DISORDERS

Musculoskeletal disorders (MSD) are a major health problem in the western countries and are responsible for discomfort for the patient and a financial burden for national economies. Chronic low back pain (LBP) and neck pain (NP) are the most common MSD complaints in industrialised countries, with the highest incidence in the working population and a lifetime prevalence up to 84 % in LBP and more than 70 % in NP (Deyo et al. 1992; van Tulder et al. 2002; Mäkelä et al. 1991; Mäkelä et al. 1993; Ferrari and Russell 2003, Gues et al. 2002). In Finland, these kinds of disorders, especially low back and neck problems, are one of the main reasons for sick leaves (Pohjolainen and Ylinen 2003).

2.5.1 Chronic low back pain

LBP is defined as pain and discomfort, localized below the costal margin and above the inferior gluteal folds, with or without referred leg pain and it is classified as chronic if the pain has lasted for more than 12 weeks. In only one tenth of the LBP cases can a specific cause of the pain be found (Deyo et al. 1992). The most common type of back pain is non-specific chronic LBP, which is not connected with the presence of any recognisable specific pathology such as infection, a tumour, osteoporosis, fracture, structural deformity, inflammatory disorders, radicular syndrome or cauda equine syndrome (European Guidelines for the Management of Chronic Non-specific Low Back Pain, 2004). The most common of the specific lumbar disorders is radicular pain or sciatica where symptoms are related with the compression or irritation of sciatic nerve root due to herniated intervertebral disk or the mechanical compression of the neural structures in the spinal stenosis (Frymojer 1988). In radiculopathy, in addition to the usually encountered unilateral irradiating pain, the muscular weakness and sensory disorders such as numbness may also exist.

Thus, most back pain cases are usually classified as non-specific LBP. Compared to the radicular pain associated with nerve root compression and which is radiated below the knee, pseudoradicular symptoms may also exist in LBP patients. Those symptoms above the knee are not related to the nerve roots (Freyhagen et al. 2008).

2.5.2 Chronic neck pain

NP is pain or discomfort localized in the cervical region. In NP or cervicalgia, the underlying reasons of the problem may be connected with several structures such as intervertebral discs, ligaments, muscles, facet joints, dura and nerve roots (Bogduk 1988) but in most of cases, no specific cause for the complaint can be identified. Accordingly, the condition is defined as being non-specific with a predominantly mechanical and degenerative background, with or without irradiating arm pain (Borghouts et al. 1998).

Mechanical NP may be related to poor working posture and daily use of a computer may increase the risk of neck pain also in adolescents (Hakala et al. 2006). Similarly as in LBP, the specific type of NP is cervical radiculopathy when the compression of the cervical nerve root due to herniated disc or cervical degeneration or spondylosis produces pain, weakness and sensory disorders in arm.

2.5.3 Clinical findings in non-specific NP and LBP

The etiology of those non-specific conditions is not still completely understood because of the wide variety of potential causes of pain. The diagnosis is usually based on the history of disease and clinical examination with the purpose of excluding possible specific underlying reasons for the pain. In these cases additional investigations should be performed. Neurophysiological examinations may help to exclude the peripheral nerve lesions. The disc herniation or degeneration may be detected by MRI. In non-specific pain, however, the radiological examinations are not necessary because of their poor correlation with the clinical findings (Maus 2010) and the presence of abnormal MRI findings also in healthy subjects (Jensen et al. 1994).

In the clinical examination, spinal mobility is usually lowered and local tenderness may exist in paravertebral areas. As a way of manifesting the presence of radiculopathy in LBP, the straight leg raising test is used and the spinal mobility can be evaluated with flexibility tests such as modified Schober' test and finger-floor distance. Combined examination including testing of flexion, extension, lateral flexion, bilateral passive and active straight leg raising, sit-up test and the presence of spinal tenderness have been proposed as providing an index of impairment in LBP (Waddell et al. 1992). In NP, different clinical tests are also useful as ways to diagnose cervical radiculopathy (Viikari-Juntura et al. 1989). The severity of condition may be indicated with parameters such as the intensity of pain (visual analogue scale, VAS, Scott and

Huskinsson 1976) and level of pain-induced disability in LBP (Oswestry Disability Questionnaire, Fairbank et al. 1980) and in NP (Neck Disability Index, Vernon and Mior, 1991).

2.6 USE OF IRT IN MEDICINE AND PARTICULARLY IN MUSCULOSKELETAL DISORDERS

The IRT method was first used in medicine in 1956 when R. Lawson reported a higher Tsk over a breast tumor (Lawson 1956). During the following 50 years, a large number of applications for IRT have been proposed in mammology, rheumatology, orthopedics, neurology, vascular imaging, occupational medicine (e.g. in the examination of vibration related vasospastic syndrome), surgery, and different kinds of other screenings or physiological response examinations (Jones 1998, Ring 2004, Berz and Sauer 2007). The most recent areas where this screening method has been claimed to be helpful are the epidemic diseases as well as SARS (severe acute respiratory syndrome)(Ring et al. 2009).

The use of medical IRT is growing in investigations of pain, metabolism and malignancies e.g. breast cancer. In addition to single measurements, different kinds of stress response examinations (Niehof et al. 2006, Jankovic et al. 2008) have been used. Vainer (2005) has stated that IRT is applicable for the studies of thermoregulatory processes, perspiration and stimulated vascular responses. The method has diagnostic value as a non-invasive measurement of physiological functions because of objective visualisation of Tsk which can vary for several reasons e.g. due to pain and disorders of innervation for example in peripheral nerve injuries. IRT has been applied also in studies of knee injuries in sports medicine (Hildebrandt et al. 2010) and of sympathetic responses in psychophysiology (Kistler et al. 1998). The monitoring of the fingertip Tsk changes after arm cuff occlusion is one very promising way for evaluating the vascular reactivity and detection of endothelial dysfunction (van der Wall et al. 2010).

The diagnostic significance of the IRT has been based mainly on the side-to-side temperature differences (δT-values) as since there are believed to be the most important pathological signs (Uematsu et al. 1988a). This is justifiable in cases of unilateral complaints such as inflammatory processes or malignancies leading to hyperthermia, and nerve entrapments, degeneration or obliterating artery disease causing hypothermia. The asymptomatic side usually serves as the control. Patients with bilateral involvements have been studied usually in comparison with healthy subjects.

Since there is a need for objective indicators for the evaluation of autonomic dysfunction, IRT has been widely used also in neuromuscular disorders. The IRT technique has been reported to be useful in studies of CRPS (Wasner et al. 2002) and in painful neuropathies (Novak et al. 2001) and its use in a computerized assessment of pain-associated thermal disorders has been proposed (Herry and Frize 2004).

The examination of spinal nerve root pathology is another of the potential uses of IRT. In LBP and sciatica, after the first study describing Tsk measurements in this field (Albert et al. 1964), several reports related to this topic have been published. However, the results of the studies have been controversial. Some have reported Tsk abnormalities associated with spinal radiculopathy with a high sensitivity of IRT and good correlations between the thermographic results, severity of the complaints and the other findings such as those obtained with computerized tomography, myelography and MRI (Gillström 1985, Uematsu et al. 1988b, LaBorde 1989, Thomas et al. 1990, Takahashi et al. 1994). The degree of coldness of the sciatic leg was found to correlate with the probability of spinal nerve root compression (Hakelius et al. 1969, Lindholm et al. 1981). Sherman et al. (1987) described a good relationship between pain intensity and asymmetry in Tsk values. However, the ability to differentiate between painful and healthy conditions has varied e.g. being high in knee pain (98% of the cases) but lower in leg and back pain (56% of the cases, Sherman et al. 1987).

However, some other authors have reported that IRT has low diagnostic and localizing capabilities, poor stability and that obtained findings were non-specific and variable. The affected side could be either cold or warm as compared to its healthy counterpart. Accordingly, the use of IRT was recommended only for research purposes (Ash et al. 1986, So et al. 1989, Hoffman et al. 1991, McCulloch et al. 1993, Leclaire et al. 1996).

In neck problems, IRT has been less extensively studied. In some published reports (Zhang et al. 1999, Ben-Eliyahu 1989), the thermographic findings have differed between healthy subjects and patients with cervical radiculopathy. A high asymmetry of Tsk in the neck area has been found in patients suffering from pain associated with instability of the cervical segment of the spine (Jasiak-Tyrkalska and Frańczuk 1998) and thermographic hot spots have been proposed as a marker of the trigger points in myofascial pain syndrome (Kruse and Christiansen 1992). However, So et al. (1990) in a comparison of IRT and electromyography found Tsk abnormalities in distal parts of the upper extremities only and concluded that Tsk measurements did not give any additional diagnostic information compared to ENMG. In addition to cervical radiculopathy, the presence of vasomotor changes has been demonstrated also in patients with non-specific conditions e.g. forearm pain (Sharma et al. 1997). Sluiter et al. (2000) reported that coldness of forearms, wrists and hands was a frequent symptom in patients with upper limb MSD. Gold et al. (2009) described the relationship between the severity of upper extremity MSD and reduced Tsk in hands.

Nonetheless, the discordance of study findings led to loss of credibility of the IRT method. On the basis of the research results, American Academy of Neurology, Therapeutics and Technology Assesment Subcommittee has not recommended the use of IRT in the diagnostics of radiculopathies or musculoskeletal pain (1990).

However, the interest in Tsk changes in paraspinal tissues has traditionally been high among chiropractioners. The American Chiropractic Association has proposed the use of infrared imaging in several areas e.g. in the evaluation of patients for early diagnosis and monitoring of reflex sympathetic dystrophy syndromes, evaluation of spinal nerve root irritation and distal peripheral nerve fiber pathology (detection of sensory/autonomic dysfunction), evaluation and monitoring of soft tissue injuries, including segmental dysfunction/subluxation, and strains and myofascial pain syndromes not responding to clinical treatment (Council on Chiropractic Practice, 1998). Some authors have recommended IRT also in cases with sympathetically maintained pain, in patients with chronic, unexplained pain following trauma, but who lack the physical findings and criteria for the diagnosis of reflex sympathetic dystrophy (Friedman 1994). Ellis et al. (1989) found more Tsk abnormalities in LBP patients without any clinical findings. In the last decade, a strong correlation between the severity of the condition and Tsk findings was also reported in patients with osteoarthritis (Varju et al. 2004; Spalding et al. 2008). However, the mechanisms behind the Tsk changes in different clinical conditions vary and these mechanisms are not completely understood.

3 *Aims of the Study*

The purposes of this study were to investigate the methodological properties of the IRT for use in studies of the human body, in healthy individuals and patients with chronic non-specific MSD, with the special attention to methodological problems in the interpretation of Tsk findings.

The aims consist of the following consecutive steps:

3.1 to examine the reproducibility and stability of the whole body skin IRT measurements in different skin areas in healthy individuals with the intention of revealing how the area of measurement could influence the IRT results

3.2 to compare the Tsk findings in patients with chronic non-specific LBP and NP and reference individuals and to evaluate the relationship between the temperature abnormalities and pain intensity or other clinical signs of these conditions

3.3 to study the occurrence of δT values as the main pathological thermographic findings in patients with chronic non-specific NP and LBP in relation with the actual Tsk in measured areas

3.4 to investigate the regional intra- and interindivudual differences in Tsk responses to the different types of cold exposure in healthy men in relation to changes in central autonomic activity, and to examine factors influencing those responses

3.5 to clarify the advantages and limitations of the IRT method and thus, to examine the applicability of Tsk measurements as a diagnostic aid, particularly, in non-specific painful musculoskeletal conditions such as chronic LBP and NP

4. Subjects and Methods

4.1 SUBJECTS

A total of 156 patients and 81 healthy persons participated in the four studies (Table 1). All subjects completed a standard questionnaire and provided written consent. The study was approved by the Kuopio University Hospital Research Ethics Committee and it was performed according to the Helsinki Declaration. The subjects did not have any prior injuries, nor had they undergone surgery or suffered severe structural deformities. Other exclusion criteria were neurologic, metabolic or cardiovascular diseases and use of any vasoactive drugs. Local vascular diseases as varicose veins, skin inflammation were also among the exclusion criteria.

Table 1. Characteristics of the study subjects; mean (SD)

	Healthy subjects				**LBP patients**	**NP patients**
Study	I	II	III	IV	II	III
Number of subjects	16	20	30	15	65	91
Age (years)	21.9 (3.2)	40.3 (5.9)	42.2(5.9)	24.2 (2.7)	41.4 (5.8)	41.3(5.9)
Gender M/F	16/0	7/13	12/18	15/0	29/36	33/58
Height (cm)	181.1 (7.4)	169.9 (9.3)	170.6(7.7)	181.3 (5.7)	171.3 (8.6)	169.1(8.2)
Weight (kg)	77.5 (6.7)	75.4 (16.4)	69.8(10.2)	79.1 (7.2)	73.3 (12.8)	71.9 (13.7)
BMI	23.7 (1.8)	25.9 (3.6)	23.9 (2.7)	24.1(2.3)	24.9 (4)	23.0 (4.0)
Pain intensity (VAS 0-100):						
Low back pain					43.5 (20.3)	
Lower limb pain					26.8 (19.7)	
Neck pain						46.4 (20.4)
Upper limb pain						32.1 (26.2)
Disability score (0-100)					20.6 (9.3)	22.7 (4.7)
Depression score (0-21)		3.2 (2.6)	1.8 (2.3)*		3.7 (3.2)	3.7 (3.1)*

* p < 0.001 between patients and controls

4.1.1 Healthy subjects

Thirty-one symptom-free young men participated in study I (n=16) and study IV (n=15). They did not report any pain or disability or problems in daily activities and they were not consuming any medications during the two weeks previous to the measurements.

Two reference groups consisted of persons comparable with the LBP (study II) and NP (study III) patients with regards to the age, gender and BMI. The controls did not suffer from LBP (study II) and NP or upper limb MSD (study III) during the study period or in the preceding six months before the study. In study III, healthy controls were in addition divided into the two subgroups, 11 persons with cold hands (CHC, with Tsk in fingertips less than 25 °C) and 19 persons with warm hands (WHC, with Tsk in fingertips more than 30 °C).

4.1.2 Low back pain patients

The study group consisted of 65 patients suffering from chronic unilateral LBP with (n=41) or without (n=24) referred non-radicular leg pain. Patients with current nerve root entrapment or spinal cord compression, previous back surgery or acute disk herniation (occurring less than one year before the study) were excluded. The average duration of their low back problems was 10.6 years.

4.1.3 Neck pain patients

There were 91 patients in the study group with non-specific uni- or bilateral chronic NP with (n=60) or without (n=31) irradiating arm symptoms. The symptoms were unilateral in 46 and bilateral in 45 of the subjects. Patients with signs of upper limb radiculopathy or carpal tunnel syndrome or previous neck surgery were excluded. The two subgroups, 21 persons with cold hands (CHNPP, with Tsk in fingertips less than 25 °C) and 56 persons with warm hands (WHNPP, with Tsk in fingertips more than 30 °C) were chosen from the patients for further analysis.

4.2 METHODS

4.2.1 Skin temperature recording

The subjects were asked to avoid the use of medications and cosmetics before the study, and to avoid from taking intense physical exercise and alcohol consumption also on the previous day. Smoking, eating and drinking were not allowed two hours prior to the start of studies. In studies I and IV, the measurements were done at the same time of the day in summer time. In studies II and III, season and time of investigation were not controlled. Before the measurements, the subjects were undressed and thermo-equilibrated in the laboratory space for 20 minutes. The room temperature was 22-24 °C, the air conditioning was switched off and there was no direct sunlight. In study IV, the subjects were dressed in t-shirts and shorts and were sitting in a resting position with their feet on the soft plate so that the subjects' feet were covered with a thermoblanket at 40 °C temperature for 15 min before the measurements.

Tsk measurements were performed using a digital infrared camera IRTIS-2000 (IRTIS Ltd, Moscow, Russia) with the single element InSb detector, cooled by liquid nitrogen and the Minimum Detectable Temperature Difference of 0.05 °C. The camera was calibrated against a blackbody at 1 m distance with the 1.00 emissivity setting.

The thermographic images of the whole body surface were taken in standard views (anterior, lateral and posterior) at the set distance for each view and an angle of measurement of 90° when standing. The images of the dorsal and plantar surfaces of feet were taken when the subjects were sitting and the feet were placed in a horizontal position (study II) or on the soft plate on the floor (study IV).

In studies II and III, whole body IRT measurements were performed once, but in study III, the examinations were repeated in 20 of CHNPP. In study I, IRT measurements were performed four times (on two consecutive days by the two investigators in a random order with a short time interval). In study IV, changes of Tsk of dorsal surface of the left foot were followed with IRT during facial and contralateral foot CE test with a few days' interval between tests. Tsk values were recorded 5 minutes before CE and during the 15 minute follow-up period at 10 second intervals. The Tsk of the palmar side of left middle finger was recorded simultaneously with a thermal sensor (TSK100C/MP150, BIOPAC Systems Inc).

4.2.2 Other measurements

Studies II and III: The intensity of low back and neck pain was assessed by using a 100 mm Visual Analogue Scale (VAS, Scott and Huskinsson 1976) and mood by Rimon's brief depression scale questionnaire (Keltikangas – Järvinen and Rimon 1987). Patients indicated their pain localization through pain drawings. Functional disability was recorded with the aid of the Oswestry Disability Index (0-100, Fairbanks 1980) and Neck Disability Index (0-100, Vernon and Mior, 1991). Spinal mobility tests as modified by Schober, straight leg raising test, finger-floor distance and side-bending (study II) were also recorded.

Study IV: Blood pressure was measured continuously from the finger using the volume clamp method and Portapress device (Finapress Medical Systems, Amsterdam, The Netherlands). ECG was recorded using modified chest lead 5 (V5) and HR was calculated using a QRS-detector. Changes in SBP, DBP and HR were analysed using the mean values at 30 second intervals with the mean values at the baseline period as reference values. Cold-induced pain and unpleasantness were self-reported using a scale of 0-10.

4.2.3 Interventions

In study IV, a foot (3 minutes) and facial (1 minute) CE with ice water was performed to investigate reflex cold-induced Tsk changes in contralateral finger, toe and dorsal foot areas in relation to central circulatory changes reflecting the general responses of the autonomic nervous system. Measurements were performed during the 5 minutes before CE, during CE and the 15 minutes after the challenge, at the same time of the day with a 2-6-day interval between the sessions. The foot CE was done first, by placing the right foot up to the level of the malleoli into ice water (0°C) for three minutes. In face CE, a soft flexible plastic bag with ice water was placed on the face so that the cold affected predominantly the forehead and cheek areas.

4.2.4 Data analysis

Paired (right and left) areas of skin surface were examined using the prearranged scheme of identification of regions of interest related to the anatomical structures. Mean Tsk values for each area were calculated by summation of temperature in every pixel of the defined area and then dividing the result by the amount of summated pixels with IRTIS-thermography software. The results were corrected using a skin emissivity factor of 0.97 (Togawa 1989).

The regional δT values were calculated for each area by subtracting the mean Tsk of the left side from that of the right side in healthy individuals and the Tsk of the affected side from that of the healthy side in patients. Tsk gradients for the anterior and posterior surfaces were calculated as the difference between Tsk of the higher third part of thigh and the lower part of calf in study II. In study IV, cold-induced Tsk changes of the left foot dorsal surface, the nail area of the big toe and the ring fingertip during follow-up time were analysed with the definition of the initial decrease (dTmin), the amplitude of Tsk change (Tampl) and the maximal Tsk level (Tmax) compared to the baseline level. The modified foot Tsk gradient was calculated as Tsk of dorsum minus toe.

4.2.5 Statistical methods

All analyses were conducted using the SPSS Statistical Software for Windows, versions 11.5 and 14.0. The normality of the distributions was assessed with the Kolmogorov-Smirnov test.

In study I, the results of the Tsk recordings were compared between the two examiners and between the two recording days for each observer using the intra-class correlations analyses (2-way mixed model, consistency agreement). The same analyses were conducted for the δT values. ICC was classified as poor (0-0.39), moderate (0.4-0.59), good (0.6-0.79) and excellent (0.8-1.0). Coefficients of variation were calculated by the formula
Cv=(Standard Deviation/Mean) x 100.

In study II, Mann-Whitney-U test was applied to evaluate the differences between patient and control groups, the relationship between the LBP level and δT values was assessed with the Spearman's correlation analysis, and the linear regression analysis was used for evaluation of relations between Tsk disorders and other clinical signs as self-reported disability, spinal mobility tests and mood statement.

In study III, the Tsk changes and factors influencing them were investigated in patients with non-specific chronic NP using mixed model analysis. Thereafter, the Tsk levels and δT values were compared between two subgroups of patients and two subgroups of controls in relation to the Tsk level in the hands using the Kruskal-Wallis test with a post-hoc Mann-Whitney U-test and the Bonferroni correction. The stability of IRT findings in CHNPP in repeated measurements was studied with the Wilcoxon test when the results were compared between the two measurements sessions in 14 patients (with cold and warm hands) and in the six patients with cold hands during both measurement sessions. Correlations of δT values with the actual Tsk and neck pain level were checked with Spearman's correlation analysis.

In study IV, cold-induced Tsk changes were compared between the three areas (dorsal foot, toe and fingertip) and between the two sessions (foot and facial CE) in relation to simultaneous changes of blood pressure, HR and the foot Tsk gradient values with mixed model analysis. The influence of different factors on the findings was also examined. The Wilcoxon test and Paired Samples t-test were used for the comparison of the intensity and onset time of responses with the level of significance set at $p<0.05$.

5 Results

5.1 RESULTS OF THE IRT MEASUREMENTS

The evaluation of IRT results, firstly, included an analysis of Tsk values in different areas and, secondly, an assessment of δT values in those areas as signs of potential pathology.

5.1.1 Skin temperature

The measured Tsk values varied extensively in all four studies. The variability was high in distal parts of the body e.g. hands and feet but low in the "core" areas. However, despite the high variability, the coefficients of variation were abnormal only in the hands and feet of healthy young men (Study I). Values of Tsk in different skin areas of sixteen healthy individuals are presented in Figure 1.

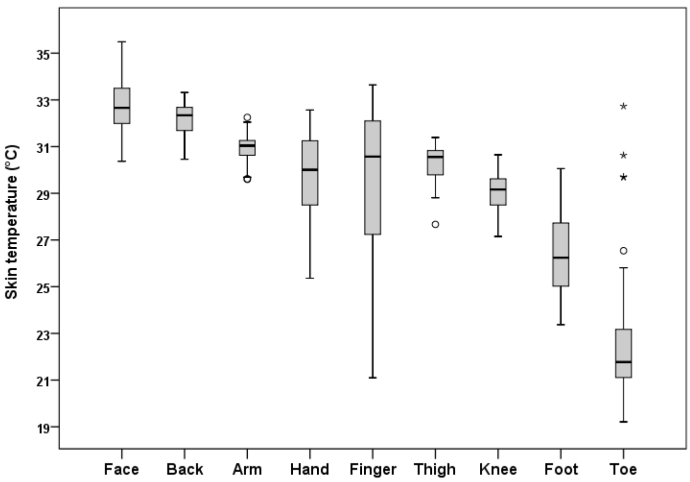

Figure 1. Boxplots of the regional skin temperature levels in different skin areas of healthy young men (°C). The box of the plot is a rectangle which encloses the middle half of the sample, with an end at each quartile. Extreme values which are more than three times of the box length are marked by asterisks. Values which are between one and a half and three times greater than the box length are marked with the open circles.

In addition, in study II, Tsk levels in lower extremities varied significantly in both subgroups e.g. in plantar foot from 20.71 °C to 30.92 °C. In NP patients (Study III), Tsk values were found to be strongly dependent on the area of measurement ($p<0.001$, Mixed model analysis). Tsk was also found to be related to gender, BMI, and weight ($p<0.05$) but only in the "core" parts of the body.

In the four subgroups (Study III), Tsk levels were significantly lower in the distal parts of the upper extremities in CHNPP and CHC than in WHNPP and WHC ($p<0.05$ in hands, $p<0.000$ in fingertips, Kruskal-Wallis test, post-hoc Mann-Whitney U-test). In CHC, the fingertips were also colder than in CHNPP ($p<0.05$). There were no Tsk differences between the WHNPP and WHC groups (Figure 2).

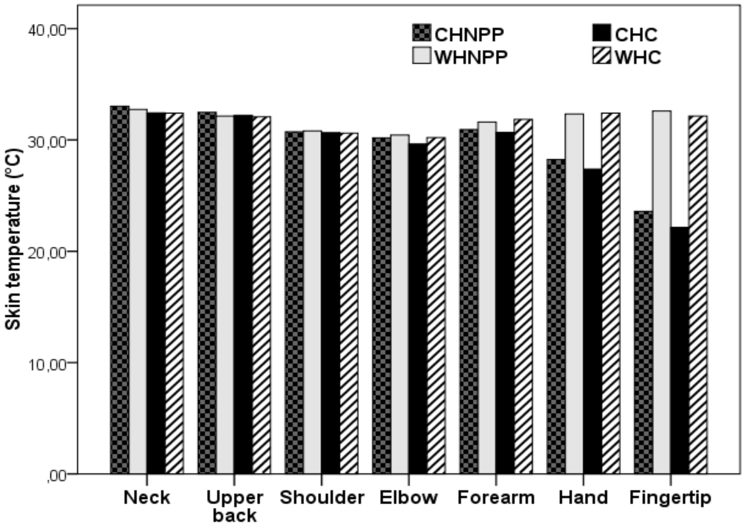

Figure 2. The mean values of regional temperatures (°C) in grouped skin areas of NP patients with cold (CHNPP) and warm hands (WHNPP) and controls with cold (CHC) and warm hands (WHC) calculated as the average of Tsk values of the right and left sides and for the upper extremity, the average values between dorsal and palmar surfaces of both sides.

In study IV, highly variable levels of baseline Tsk were registered in the dorsal foot (25.6 °C-33.9 °C), in the toe (22.8 °C-32.6 °C) and in the fingertip (22.6 °C-34.4 °C), in spite of the preceding thermoequilibration of the feet. Baseline Tsk values were related to the level of the foot Tsk gradient depicting peripheral vasoconstriction.

5.1.2 Regional side-to-side temperature differences (δT values)

Mean levels of the absolute regional δT values measured in studies I-III are presented in Table 2.

Table 2. The mean values of regional δT (°C) with the standard deviations in grouped different skin areas of the study subjects

	Healthy subjects			**LBP patients**	**NP patients**
Study	I	II	III	II	III
Number of subjects	16	20	30	65	91
Area					
Head	0.18 (0.16)				
Neck	0.15 (0.11)		0.17 (0.13)		0.20 (0.15)
Trunk	0.12 (0.11)	0.18 (0.11)	0.15 (0.09)	0.22 (0.18)	0.13 (0.12)
Upper extremities:					
Arm	0.25 (0.17)		0.27 (0.21)		0.29 (0.25)
Elbow	0.3 (0.26)		0.3 (0.22)		0.29 (0.22)
Hand	0.22 (0.25) #		0.49 (0.43) #		0.37 (0.36) #
Fingertips	0.5 (0.43) *		0.41 (0.22) *		0.78 (0.86) *
Lower extremities:					
Thigh	0.16 (0.14)	0.19 (0.1)		0.25 (0.25)	
Knee	0.28 (0.28)	0.28 (0.3)		0.32 (0.26)	
Plantar foot	0.39 (0.49) *	0.2 (0.17) *		0.32 (0.21) *	
Toes	0.42 (0.39)				

* p< 0.05 between subgroups

# p< 0.001 between subgroups

In study I, mean levels of absolute regional δT values were only more than 0.3 °C mostly in the distal parts of extremities (Table 2). However, healthy individuals without any pain or other clinical signs or symptoms demonstrated significant temperature variations and δT values were greater in some skin areas such as fingertips and feet.

In study II, significant regional Tsk alterations (at least one regional δT value more than 0.3 °C) were found in the lower extremity in the majority of the cases in both LBP patients (92.7 %) and control persons (87.8 %). δT values were significantly higher in LBP patients compared to controls in the plantar surface of the feet only (p<0.05, Figure 3). In addition, the side-to-side difference in the Tsk gradient calculated as the difference between proximal and distal parts of the lower extremities was higher in the patients with referred leg pain compared to the controls (p<0.05).

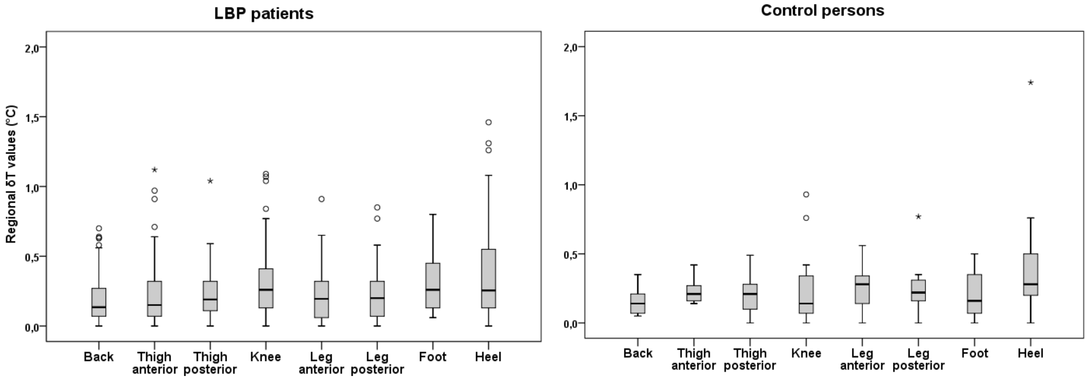

Figure 3. Boxplots of the mean values and distribution of absolute regional δT (°C) in different skin areas of LBP patients and control subjects (Study II). The box of the plot is a rectangle which encloses the middle half of the sample, with an end at each quartile. Extreme values which are more than three times of the box length are labeled by the asterisks. Values which are between one and a half and three times greater than the box length are marked with the open circles.

In NP patients (Study III), mean δT values did not differ between patients and healthy controls. However, when the thermographic findings in NP patients were divided into subgroups according to the actual Tsk in the hands, higher δT values in the distal parts of the upper extremities were demonstrated in CHNPP compared with WHNPP ($p<0.000$ in the fingertips and $p<0.005$ in the hand), with WHC ($p<0.005$ in the fingertips), and with CHC ($p<0.05$ in the fingertips, Mann-Whitney test). In WHNPP and WHC, the results did not differ in this respect.

In patients, the Tsk abnormalities were variable: the affected side was either colder or warmer than the healthy counterpart. In study II, in the plantar surface of feet, the affected side was colder in half of the patient group (50.8 %) and in the other half (49.2 %) it was warmer compared to the healthy side. The LBP levels (VAS 0-100) varied in the subgroups with the different types of Tsk changes: the affected side was colder when pain was more severe. In addition, δT values differed between patients with local LBP and those with referred leg pain e.g. in heel area (Mann-Whitney-test, $p<0.05$) and tended to differ in the whole plantar surface ($p=0.052$). In patients with unilateral NP (study III, n=46) the affected side was either warmer or colder than the healthy one, but in cases with irradiating arm pain, the affected side was warmer while in those without such pain it showed a tendency to be colder (e.g. in palmar hand, $p<0.01$, Mann-Whitney test).

5.2 REPRODUCIBILITY OF IRT RESULTS

In study I, the inter-examiner reproducibility of the IRT measurements was found to be high, with the mean ICC of 0.88 (0.73 - 0.99). The mean ICC values were highest in the abdomen and heel and lowest in the face. The day-to-day stability of the recorded results varied depending on the measured area: it was good in the core and poor in the distal areas with a mean ICC of 0.47 (0.08-0.78, SD 0.21).

The reproducibility of the δT values was moderately good between the two observers (mean ICC 0.68; range 0.42-0.98) being high in the anterior trunk, knee and heel areas. The lowest values were found in the upper parts of the back and the dorsal forearm, as well as in the lateral surfaces of thigh and shoulder. The reproducibility of the δT values was lower and variable in day-to-day measurements, especially in the extremities with a mean ICC of 0.4 (range -0.01-0.83). However, in some areas such as knee, posterior calf and heel those values were moderately stable. The reproducibility of the Tsk measurement results in different areas is presented in Table 3.

Table 3. The mean ICC values for the reproducibility of the regional temperature (Tsk) and δT values in the different body areas of the studied subjects (n=16)

Skin area	Inter-examiner reproducibility of regional Tsk (2 researchers)	Intra-examiner reproducibility of regional Tsk (2 consecutive days)	Reproducibility of δT values (2 researchers)	Reproducibility of δT values (2 days)
Face	0.76	0.47	0.66	0.54
Trunk anterior	0.94	0.72	0.83	0.76
Arm	0.85	0.67	0.64	0.38
Forearm	0.85	0.31	0.59	0.33
Hand	0.92	0.39	0.59	0.18
Fingertips	0.90	0.16	0.69	0.22
Neck	0.81	0.52	0.51	0.38
Back	0.85	0.71	0.61	0.32
Thigh	0.90	0.63	0.64	0.42
Knee	0.93	0.52	0.96	0.76
Calf	0.84	0.66	0.74	0.52
Plantar foot	0.96	0.61	0.82	0.63
Heel	0.99	0.65	0.98	0.71
Toes	0.83	0.40	0.63	0.52

In study III, the IRT examinations were repeated in 20 CHNPP and in 14 of them Tsk in the fingertips had reverted to normal. The high δT values registered when the hands were cold had vanished (Figure 4).

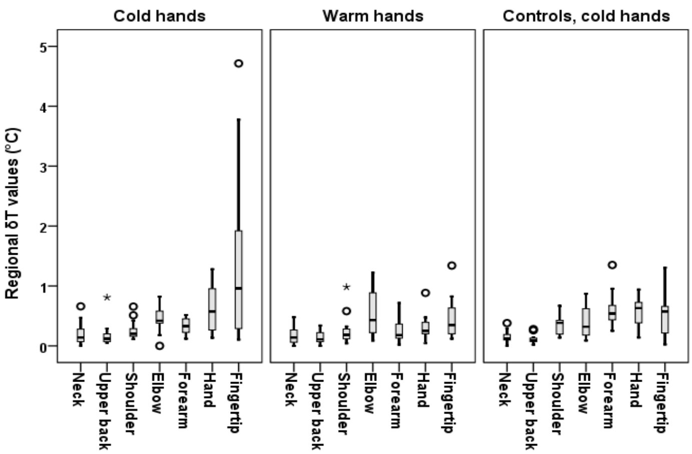

Figure 4. The boxplots for regional δT values (°C) in the different skin areas of NP patients (n=14), when measurements were repeated with cold and warm hands, compared with those of CHC (n=15). The box of the plot is a rectangle which encloses the middle half of the sample, with an end at each quartile. Values which are between one and a half and three times greater than the box length are marked with the open circles.

5.3. REFLEX SKIN TEMPERATURE CHANGES IN RESPONSE TO COLD EXPOSURE

In study IV, both of facial and foot CE induced changes in blood pressure and HR which were seen in some subjects before the actual CE. Those changes were greater in response to the foot compared to those occurring in the facial CE (p<0.005, Paired Samples t-test, Table 4).

Table 4. SBP, DBP and HR changes (an initial increase and amplitude of changes, mean (min; max)) in the study subjects (n=15) during foot and facial CE

		Increase/prevalence	Amplitude of changes
Foot CE	SBP (mmHg)	24.9 (10.7; 47.6)/ 15	31.3 (19.4; 56.1)
	DBP (mmHg)	14.8 (4.5; 28.5)/ 15	18.2 (8.4; 31.6)
	HR (beats/min)	16.1 (6.6:29.3)/15	22.9 (13.4:36.5)
Facial CE	SBP (mmHg)	10.6 (0.2; 24.7)/ 14	16.7 (3.6; 31.5)
	DBP (mmHg)	4.5 (1.2; 8.8)/ 13	6.7 (2.9; 11.6)
	HR (beats/min)	4.9 (0.8; 11.9)/ 13	12.3 (3.6; 21.2)

Tsk changes followed the changes in blood pressure and HR. The Tsk reaction was seen in almost all measured areas typically as an initial decrease of Tsk followed by a fluctuating increase. The Tsk responses varied in different areas being the most prevalent and prominent in the fingertip: mean 1.38 °C (range, 0.1-2.44°C) in foot CE and 0.7 °C (0.17-1.26°C) in facial CE, smaller in the toe: mean 0.61 °C (range, 0-2.37°C) in foot CE and 0.54 °C (0-1.2°C) in facial CE, and weak or absent in dorsal foot: mean 0.39 °C (range, 0-0.88°C) in foot CE and 0.34 °C (0; 1.12°C) in facial CE, respectively. The amplitude of Tsk changes varied widely, reaching 4.46 °C in finger and 3.6 °C in the toe, being greater in foot compared to facial CE. The difference in the Tsk changes between the foot and facial CE was significant in all studied areas ($p<0.001$), the mean differences being 0.51 (CI: 0.21-0.81) in the dorsum, 0.78 (CI: 0.37-1.19) in the toe and 1.29 (CI: 0.70- 1.88) in the fingertip. The changes were more prominent in the response detected in the foot compared to facial CE. The distribution of the Tsk changes during foot and facial CE is presented in Figure 5.

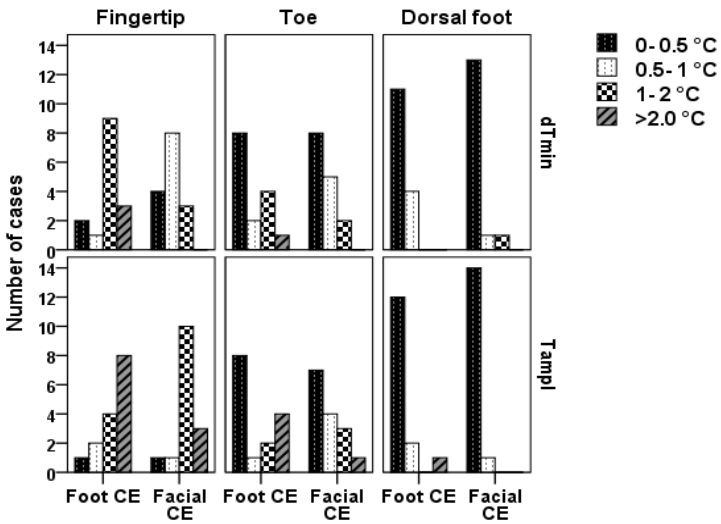

Figure 5. Distribution of the levels of the initial temperature decrease (dTmin, °C) and amplitude of changes (Tampl, °C) in three different skin areas among the subjects (n=15) in response to foot and facial CE.

5.4 RELATIONSHIP BETWEEN δT VALUES AND ACTUAL SKIN TEMPERATURE

In all four studies, the δT values were found to vary depending on the actual Tsk. In healthy subjects (Study I), δT values and the actual Tsk values correlated negatively in the fingertips ($p<0.001$, $r=-0.421$, Spearman correlation analysis). In study IV, the baseline levels of Tsk and foot Tsk gradient were found to clearly influence the CE-induced Tsk changes in all measured areas ($p<0.001$, Mixed model analysis) and subjects with cold extremities showed aberrant responses. In study II, a linear relationship between Tsk and δT values in the plantar area and heel area existed ($p<0.05$) the mean Tsk being 26.3 (SD 1.7).

In study III, in NP patients a similar relationship was seen. The level of Tsk was found to influence the δT values mostly in distal parts such as in palmar hand, fingertips but also in upper back ($p<0.001$), in the dorsal hand and palmar side of forearm ($p<0.05$, Mixed model analysis).

The relationship between Tsk and δT values in fingertips was negative in warm skin (WHNPP, $p<0.000$, $r=-0.615$, middle finger, Spearman's correlation analyses), but positive in cold skin (CHNPP, $p<0.000$, $r=0.574$) when the subgroups with cold and warm hands were analysed separately, and non-linear in the whole study group with the turning point at 27 °C ($p<0.000$, $r=-0.682$). The distribution of all measured δT values in the fingertips in relation with the actual skin temperature (°C) is presented in Figure 6.

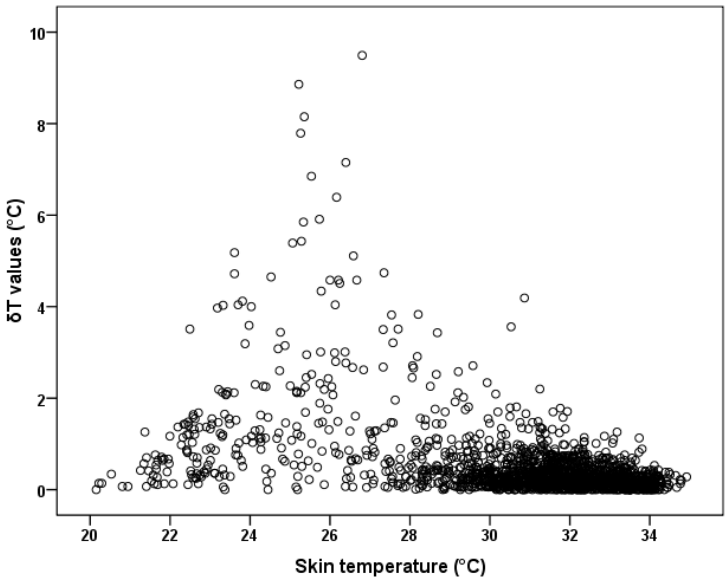

Figure 6. The distribution of the δT values in relation to the actual skin temperature (°C) in the fingertips of NP patients (n 91, p=0.000, r=-0.452, Spearman's correlation analyses).

5.5 SKIN TEMPERATURE CHANGES IN RELATION WITH PAIN INTENSITY IN LOW BACK AND NECK PAIN PATIENTS

In patient groups, Tsk and self-reported pain intensity (VAS) were found to be related. In study II, δT values in the plantar area of the foot and the heel correlated with LBP intensity ($p<0.005$, $r=0.506$). In study III, a similar relationship between the δT values in the neck area ($p<0.05$), and fingertips ($p<0.000$) and NP intensity was also found in CHNPP but not in WHNPP (Figure 7). Tsk levels in the fingertips of CHNPP were also related to the intensity of the neck pain (e.g. in ring finger, $p<0.05$, Spearman's correlation analyses).

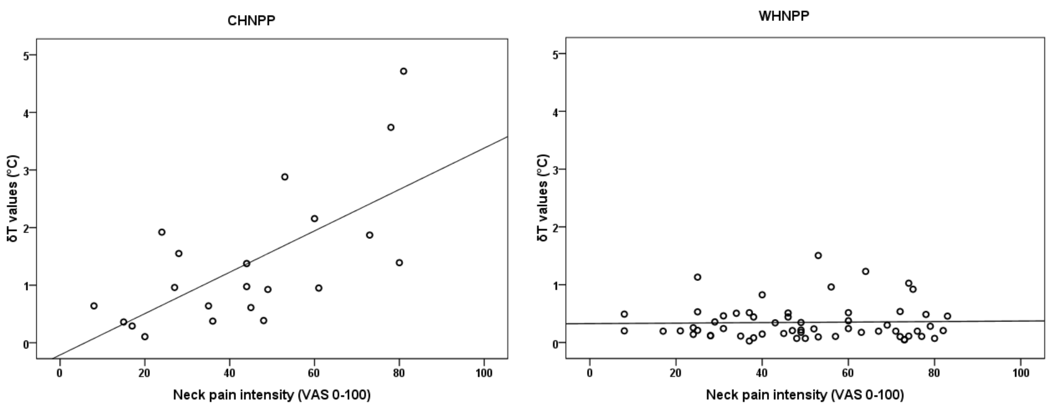

Figure 7. The relationship between the side-to-side temperature differences (δT values, y-axis) and pain intensity (VAS 0-100, x-axis) in middle finger of CHNPP (left) and WHNPP (right, study III).

In the repeated examination of CHNPP (n=20), in six of them, their hands were still cold. The NP levels were lower in second than in the first session (VAS 13.3 vs 40.8, $p<0.05$, Wilcoxon test). The results of IRT recordings of these six patients were compared between the two measurements. Both Tsk in the hand and fingertips and δT values in fingertips were higher in those experiencing pain compared to those in a painless state ($p<0.05$, Wilcoxon test).

5.6 FACTORS RELATED TO THE IRT RESULTS

In study IV, factors influencing the CE-induced Tsk changes were studied using a mixed model analysis. Those Tsk changes were found to be related to CE type and duration, baseline levels of SBP, DBP and HR and their CE-induced changes, baseline levels of Tsk, CE-induced pain and unpleasantness, environmental factors, e.g. room temperature and humidity ($p<0.001$). The baseline level of the foot Tsk gradient was also found to influence those responses ($p<0.001$).

The relationship between IRT findings and results of other measurements was also evaluated. In studies II and III, the functional disability of LBP and NP patients measured with the Ostwestry disability index and Neck Disability Index correlated with the thermal disorders, e.g. in LBP patients, the level of disability correlated with the δT values of both anterior and posterior surfaces of the legs and the Tsk gradient of anterior surface of the lower extremity (linear regression analyses, $p <0.05$ and $p<0.005$, respectively, study II). In NP patients (study III), the values of Tsk in central parts of the body were found to be related to disability, gender, BMI and weight ($p<0.05$, Mixed model analysis).

In study II, δT values of the low back area correlated with the results of spinal mobility tests, i.e. straight leg raise ($p<0.005$) and mean lateral bending ($p<0.05$, linear regression analyses). Mood, age, gender or the presence of other autonomic disorders of patients did not influence the Tsk findings. In healthy subjects, the Tsk values were not related to the handedness of the subjects (study I).

5.7 REGIONAL INTRA- AND INTER-INDIVIDUAL DIFFERENCES IN RESPONSES TO DIFFERENT TYPES OF COLG EXPOSURE

In all four studies, results of Tsk recordings varied extensively between individuals, both in healthy subjects and patients. In addition, in dynamic IRT measurements, Tsk curves varied highly between the individuals and one half of the study group demonstrated significantly stronger reactions than the others (Figure 8).

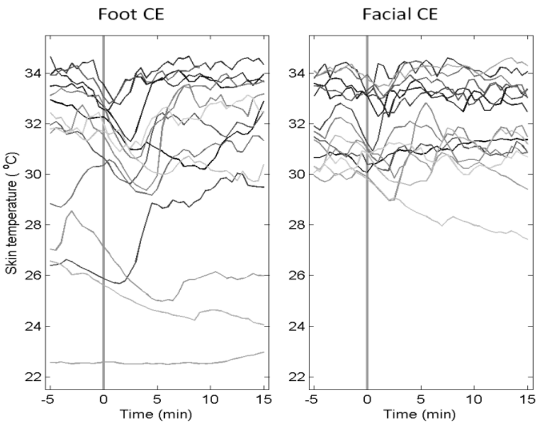

Figure 8. The individual fingertip skin temperature curves (°C) five minutes before and 15 minutes after foot and facial cold exposure in healthy men (n 15).

However, irrespective of the different cold stimuli and technique of temperature recording, Tsk changes in all measured areas correlated well within individuals when adjusted for CE type, skin area and time (r=0.57; Mixed model analysis). A similar correlation was found for SBP (0.56), for DBP (0.57) and for HR (0.79). In addition, the foot Tsk gradient was high at baseline in the same persons in both sessions and the curves of foot Tsk gradient changes were rather similar in both sessions in the same subjects (Figure 9).

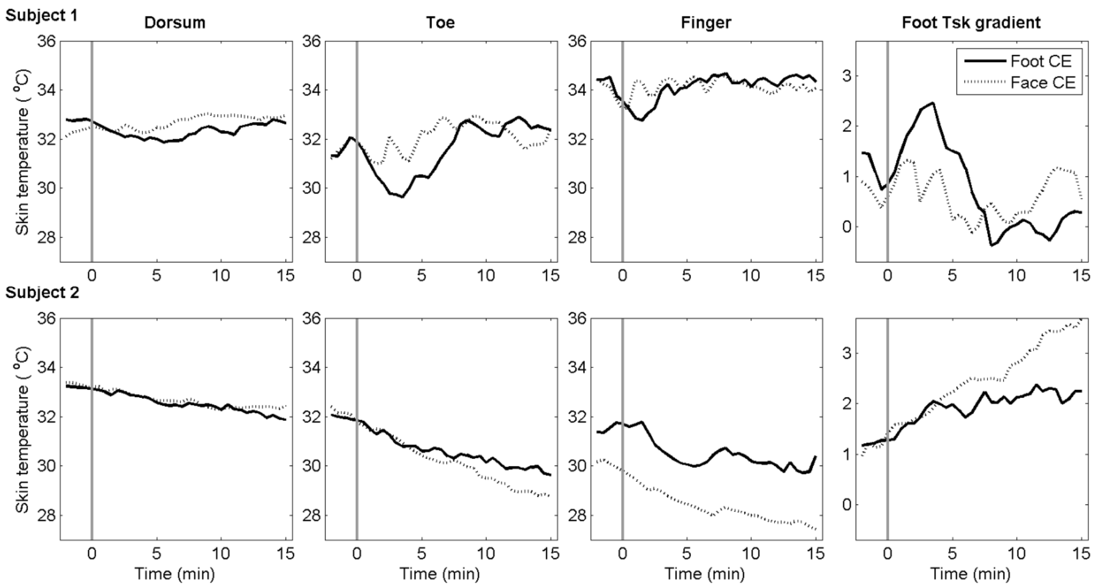

Figure 9. Tsk changes in three different skin areas and foot Tsk gradient calculated as Tsk difference between dorsal surface of the foot and the toe (°C) two minutes before and 15 minutes after foot and facial CE in two study subjects.

6. *Discussion*

6.1 MAIN STUDY FINDINGS

This study aimed to investigate the methodological properties of the IRT method for use in evaluating of human Tsk distribution and variation, and particularly its applicability as a diagnostic aid for examining MSD patients. To this end, the reproducibility of the recording of the regional Tsk patterns in healthy individuals was studied first. Subsequently, IRT findings of a few groups of patients with such MSD as non-specific LBP and NP were analyzed with special attention paid to the factors which may influence the Tsk findings. In addition, in study IV, IRT was used for the monitoring of cold-induced Tsk reactions in healthy young men. In the present series of studies, the goal was to proceed from basic IRT measurements designed to test the reproducibility of the method to more complex experiments including provocation tests to reveal the possibilities to reveal the dynamic autonomic regulation of the circulation and, consequently the Tsk. The main attention was focused on possible reasons for the methodological artefacts in IRT measurements. This knowledge may help to avoid the errors due to an excessively mechanistic interpretation of IRT data obtained from living subjects. Compared to measurements of other objects, e.g. in technical applications of IRT, human skin is a considerably more complicated dynamic system due to the complex physiological mechanisms involved in the regulation of skin BF and its high inter-individual variability.

6.1.1 Influence of the area of measurement on IRT results

The variability and stability of IRT scan were found to be dependent on the area where Tsk was being measured. IRT findings were clearly different in core and distal regions, also the findings in NP and LBP patients and Tsk responses to cold varied depending on the measurement area. It may be related to the differences between "core" and "periphery" or also between glabrous and hairy skin due to differences in blood circulation in areas containing various number of subcutaneous blood vessels and AVA:s, the nature of the sympathetic innervation and other characteristics of the particular skin area. The heterogeneity of reflex vascular responses to different provocations has been also demonstrated in upper and lower extremities (Rusch et al. 1981, Oberle et al. 1988) supporting a spatial organization of the neural control of the skin BF. These variations may partly explain the conflicting results e.g. when findings of the measurements done in different surfaces of the hand were compared (Birklein et al. 1998). The sympathetically mediated vascular responses have been described also in the hairy skin (Mayrovitz and Groseclose 2002; Krogstad et al. 1995), possibly due to reaction of resistance vessels or also occasional AVA:s. However, areas of glabrous skin in distal extremities seem to be more applicable for studies of vascular responses due to the higher reactivity of skin BF in response to various external and internal effects. Another area of interest is the face e.g. the Tsk of the nose area has been considered as the most sensitive indicator of internal vascular and thermoregulatory processes (Vainer 2005). In the face, in the analysis of the baseline Tsk values, nasal and periorbital regions were found to be more labile (Nhan and Chau 2009), most probably due to the complicated character of innervation of the facial skin, with several mechanisms influencing the skin BF (Drummond 1994).

6.1.2 Stability of IRT findings

The use of regional δT values in single measurements as a diagnostic aid faces the problem of the poor stability of IRT findings, especially in acral parts. In those areas, Tsk values vary with time as well as δT values. In study I, the best inter-examiner reproducibility of Tsk values was found in the plantar surface of feet, when the subject did not move between the measurements performed by the two examiners with a short interval. In CRPS studies, Sherman et al. (1994) also remarked on the poor reproducibility of Tsk findings in single measurements due to dynamic changes in the Tsk asymmetries. This limits the applicability of single Tsk measurements, in line with an earlier report when IRT without tests, challenging the autonomic function, has been claimed to be poorly applicable in studies of neuromuscular disorders (Wasner 2010).

Although, in some distal areas, such as knee and heel, the δT values were found to be well reproducible which support the use of IRT for the screening purposes as has been described e.g. in traumatic knee injuries (Hildebrandt et al. 2010) but it seems that the underlying reasons of Tsk abnormalities in such conditions are probably different from those in non-specific MSD. Moreover, the stability of Tsk findings in patients may differ from that in healthy individuals.

Thus, due to the high lability of skin BF, especially in the distal extremities, an IRT scan provides the data at the moment of measurement and in the current environment only, and one will not necessarily obtain the same result on a subsequent occasion. This makes the method suitable for screening and observation purposes rather than for the quantitative measurements. On the other hand, measurements of acral Tsk are well applicable for studies of microvascular reactivity with dynamic IRT. In those tests, the analysis of the whole Tsk curve is preferred instead of at certain time points because of the fluctuating nature of Tsk. Moreover, sufficient time is needed between the repeated interventions to avoid an overlap of the responses.

6.1.3 Relationship between the δT values and actual Tsk in the measured area

In measurements of Tsk in acral areas another problem emerges. In all of the present series of experiments, the δT values were related to the actual Tsk which may vary greatly, especially in the distal extremities. This phenomenon has been described also earlier as higher Tsk variations in colder skin (Livingston et al. 1987) and as different types of the vascular reactions depending on the actual Tsk (Oberle et al. 1988; Krogstad et al. 1995; Ley et al. 2011). This leads to errors in interpretation of IRT results and could partly explain their high discordance in previous studies. Furthermore, the “normal” resting Tsk level varies individually as does the thermal sensitivity, with some subjects displaying more or less continuously low Tsk in distal parts. Those individuals are known to react differently to the same stimuli and are suspected to exhibit some dissimilarities in their vascular regulation compared to those with warm hands (Nagashima et al. 2002, Gasser et al. 1992). In study IV, subjects with different baseline Tsk and high gradient levels showed diverging Tsk responses to CE. Vascular reactions of “cold-handers” have been less studied and represent an interesting topic for future research.

In the EMG-studies, the changes detected have been more pronounced at lower temperatures. Accordingly, coldness may probably help to expose disorders in nervous function in measurements of Tsk. Thus, the signs of impaired innervation may become more discernible due to diverging responses of normal and impaired nerves. In the present study, a non-linear relationship was demonstrated between those parameters, similar to the relationship between the temperature and the distal sensory nerve conduction latency (Todnem et al. 1989). In study III, “pathological” non-symmetrical Tsk values were only found in those NP patients with cold hands. In Fig. 6, δT values of fingertips of NP patients, presented in relation to the actual Tsk, are distributed as the arrow tended to zero when Tsk increased and dilated capillary loops had probably a masking effect. However, in control persons with cold hands, the Tsk values were more symmetrical. Thus, the differences in δT values between patients and controls appeared mostly in some exceptional conditions e.g. in cases of low Tsk or also probably only in persons who have some dissimilarities in regulation of skin BF or sensitivity. Those findings emphasize the need for caution in use of IRT data if one intends to distinguish between abnormal and normal conditions. They also indicate that to achieve more reliable data, there is a need to use provocation tests which would give better comparable conditions for all study subjects. In fact, this was proposed already in the earliest IRT studies (Pulst and Haller 1981).

In some previous studies, subjects with cold extremities were excluded as being abnormal (Wilder-Smith et al. 2005) or studies of the vasoconstrictive responses were recommended to be performed only in the vasodilated state (Allen et al. 2002, Kistler et al. 1998). Another way to overcome this problem is to attain artificially the same Tsk level in all study subjects, but this will not be a true physiological condition for all of them. In study IV, pre-test warming of the feet did not help to avoid those differences and Tsk had changed significantly ten minutes later. In the practical terms, evaluation of Tsk gradients such as previously reported (Rubinstein and Sessler 1990) seems to be helpful for the depiction of the degree of peripheral vasoconstriction in the distal extremity and abnormally high levels need to be taken into account. However, in non-acral areas, it is less confusing and in some areas with rich BF, an initial temperature is near to constant e.g. in oral cavity.

6.1.4 Pain intensity and skin temperature abnormalities in patients with chronic non-specific musculoskeletal disorders

Tsk findings in patients with the painful non-specific MSD were found to be related to pain intensity. In LBP patients, δT values in plantar foot were greater when the subjects experienced more intense pain. In CHNPP, δT values in the distal parts of cold hands were higher in those experiencing pain than in the painless state, indicating that pain can have an impact on Tsk changes. Pain is known to induce a vasomotor response in the skin vessels (Kreh et al. 1984, Shimoda et al. 1998, Blessing and Nalivaiko 2000). According to Burton et al. (2009), both cutaneous and muscle pain can induce an increase of SSNA and sweating. As has been described earlier, Tsk disorders are known to be variable: the affected area can be either colder or warmer than the healthy side. Previously, in painful feet due to idiopathic peripheral neuropathy, Tsk asymmetry has been described also as being more prominent in distal parts and pain accompanied vasoconstriction as well as vasodilation (Novak et al. 2001). In CRPS, patients with different type of Tsk disorders (with higher or lower Tsk) had also different risks e.g. of chronic pain and nociceptive and other sensory disturbances (Eberle et al. 2009). In sciatica, Tsk in the proximal parts, such as the lumbo-sacral and gluteal regions, was found to be higher in the affected side (Pappalardo et al. 1992). In our study, the difference in Tsk between the patients with LBP and control subjects was seen in distal foot only and the type of temperature asymmetry in LBP patients was connected with the severity of unilateral symptoms: the lower Tsk and greater δT values were related to more severe pain. In the proximal parts, no difference in δT values was found between the patients and control subjects, probably due to the presence of bilateral symptoms in some patients. In addition, the search for the thermographic markers of the trigger points in myofascial pain was not performed.

It has been claimed that Tsk is symmetrical in healthy subjects (Uematsu et al. 1988a) and so, any temperature differences may be reflecting the disorders in innervation or circulation. However, the mechanisms behind the pain-provoked Tsk changes are not completely clear; unfortunately, Tsk changes have been not studied widely in MSD. One of the exceptions is entrapment neuropathy, where Tsk changes in most of cases are connected with the peripheral nerve injury and the affected area can be defined. In peripheral nerve injuries or entrapment neuropathies, a typical variation of Tsk changes with time has been described: firstly, the vasoconstriction occurs due to irritation of the sympathetic fibers. Therefore, a sympathetic nerve injury and denervation may result in hyper- or hypothermia: at first vasodilation may be seen due to loss of vasoconstrictor tone, and then the affected side becomes colder because of vasoconstriction due to the post-denervation hypersensitivity of the blood vessels to circulating catecholamines (Pulst and Haller 1981).

The mechanisms of the Tsk disorders in non-specific neck and back problems are less well studied and Tsk changes have been usually associated with chronic lumbar (Hakelius et al. 1969; Uematsu et al. 1988b; Thomas et al. 1990; Takahashi et al. 1994) or cervical radiculopathy (Zhang et al. 1999, Ben-Eliyahu 1989) due to herniated intervertebral disk. In patients after failed back surgery, the dysfunction of the sympathetic innervation, as reflected by SSR, was found to be related to the intensity and chronicity of pain (Sahin et al. 2009). However, in the study of Maigne et al. (1996), vascular abnormalities in the lower extremity were found in LBP patients with sciatica and those without the latter condition when comparing the affected side with the contralateral one and with values from healthy subjects. A reduced local BF in the painful side was described by Larsson et al. (1999) in cervico-brachial syndrome and by Pritchard et al. (1999) in repetitive strain injury. In the present study, skin thermal abnormalities were also found in non-specific painful conditions such as LBP and NP, but their mechanisms may differ. Compared to radicular pain, non-specific complaints appear to have a more heterogeneous origin probably including also cases with slight nerve root irritation or compression and those with functional neural irritation as neurovascular symptoms of the thoracic outlet syndrome in NP (Lindgren et al. 1995). Moreover, according to Freynhagen et al. (2008), the boundary between radicular and pseudoradicular LBP is not always clear because the subclinical sensory loss was found also in the latter case, pointing to the presence of a neuropathic component in this condition.

In LBP, Tsk abnormalities in the back area were first claimed to be caused by muscle spasms (Raskin et al. 1976). Thermal findings such as hot spots have been described in the myofascial pain (Kruse and Christiansen 1992). Subsequently, the connections between the sensory dermatome and thermal disorders have been discussed (Uematsu 1985). Accordingly, the temperature abnormalities in certain skin areas would be related with irritations to certain nerve roots. For this reason, changes in Tsk values may have different origins, e.g. a sympathetic vasoconstrictive reflex caused by irritation of the nerve roots (Uematsu et al. 1988b; Takahashi et al. 1994). However, in the opinion of other authors, the dermatomal theory is not valid (Ash et al. 1984; de Weerdt et al. 1987). In the study of So et al. (1990), the location of the Tsk abnormalities did not correspond to the dermatome of the involved cervical root and, in the other study, some patients with known lesions of the peripheral nerve did not reveal any signs of sympathetic denervation and thermoasymmetry (Pulst and Haller 1981). The sympathetic fibres are not always located within the nerve trunks e.g. this has been demonstrated in upper extremity (Campero et al. 1993). In addition, the preganglionic sympathetic fibers may ascend or descend within the sympathetic trunk which probably accounts for an extension of the sympathetic responses into the segments above or below the involved root level shown in back problems (Uematsu et al. 1988b; Thomas et al. 1990). According to de Weerdt et al. (1987), the anastomoses between the sympathetic chain and lumbar nerves through the rami communicantes and also the links between the sympathetic chain and capsules of intervertebral disks may play a role in the above findings.

IRT has been claimed to describe primarily the responses induced by the efferent sympathetic output and, thus, the function of the small unmyelinated postganglionic sympathetic fibers (Konen 2000). However, also the primary afferents, mostly the thin A-delta and C-fibers play a significant role in the regulation of skin BF (Wasner 2010, Yonehara et al. 1992). Activation and sensitization of nociceptive C-fibers results in edema, redness and flare due to the influence of substances such as calcitonin gene-related peptide and substance P, causing cutaneous vasodilation and an increase in capillary permeability. In addition, in peripheral nerve lesions, the reorganization of peripheral neurons may lead to chemical coupling of the afferent sensory and sympathetic neurons which may result in activation of the primary afferents by the sympathetic nerves (Baron 1998).

Regional disturbances of the peripheral circulation, reflected in Tsk, may also be due to more central activation of the sympathetic nervous system. The relation of the pain intensity to the Tsk may indicate that central mechanisms could play a role in these changes. The role of neurotransmitters in Tsk findings has been discussed previously (Lindholm et al. 1981). In neuropathy, Fink and Oaklander (2006) claimed that the causes of small-fiber dysfunction were multifactorial and attributable to focal nerve ischemia, cytokine-mediated inflammatory processes and disturbances of the oxidative metabolism in the distal axon. In CRPS, Wasner proposed that those mechanisms may include dysfunction of the sympathetic efferents and nociceptive afferents as well as altered sensitivity of alpha-adrenoreceptors and, also non-neural mechanisms such as endothelial dysfunction and centrally located thermoregulatory dysfunction with, additionally, a high level of inter-individual variation (2010).

Thus, while the relationship between the Tsk abnormalities and pain has been demonstrated, the mechanisms of Tsk changes in MSD, such as non-specific LBP and NP, are unclear and probably highly variable between individuals. Moreover, the affected side cannot be identified without additional information and δT values are small if there is bilateral involvement. The variety of Tsk changes is a challenge for interpretation of the recorded IRT data.

6.1.5 Variability of IRT findings and factors influencing them

In all studies, a high variability was found in the Tsk recordings also among the healthy individuals. The problem of wide intra- and inter-individual variations of Tsk values has been noted already in the earliest studies (Pulst and Haller 1981). To diminish this variation, the necessity of standardization of the experimental conditions and methodology has been previously underlined (Thermography Guidelines, IACT, 2002). Factors related to the measurement accuracy due to the technical characteristics of the IRT scanning systems, measurement environment, equipment, and protocol (Pusnik and Drnovsek 2005, Ring et al. 2004) have been widely investigated. In the present studies, it was found that the influence of the environmental temperature on δT values may be significant and a short equilibration time at room temperature was not always sufficient after exposure e.g. to cold outdoor temperatures. Moreover, the ambient temperature (22-24° C), usually recommended for thermoequilibration, is not completely comfortable for semi-naked subjects. In addition, it may vary between the seasons (Gardner-Medwin et al. 2001). Thus, in countries with a cold climate it is recommended that the measurements should not to be performed in winter-time or at least to request the study subjects to avoid a cold environment for a few hours prior to the measurements. The reasons leading to the interpretation artifacts or reading errors have been also analysed previously (Ring et al. 2002).

However, control of technical and environmental factors can help to eliminate only part of the confounding factors because the skin BF changes continuously also due to the influence and interaction of a number of internal factors. Previously, in paraspinal IRT measurements, it was concluded that changes in repeated scans were most likely due to physiological changes rather than to technical errors (Owens et al. 2004). In study IV, it was found that after local warming, Tsk in feet still varied widely ten minutes later, emphasizing the important effect of internal regulatory factors. The physiological variability and lability of skin BF, especially in distal areas, has been less extensively studied and are more difficult to control. It has been previously emphasized that SSNA can be easily activated by different stimuli and variables including the psychopysiological state of the study subject (Wallin and Charkoudian 2007). Accordingly, Young et al. (2009) highlighted that caution was needed in between-group comparisons in SSNA measurements. In human studies, it is difficult to create a similar initial state and to obtain comparable results due to the simultaneous interplay of the multiple mechanisms involving neural, endothelial and smooth muscle contributions to the complex interactions in vascular responses (Holowatz et al. 2008). To achieve, as far as possible, similar conditions in the study subjects, complete relaxation in thermo-neutral environment with full elimination of all confounding stimuli should be a prerequisite, but this would be difficult to achieve in clinical work. Most of the previous studies were done in a normal laboratory environment and thus, possible confounding effects need to be taken into account in the interpretation of the results.

In addition, many other factors may lead to interpretation errors. For example, an emotional pre-test stress in studies of the sympathetic responses has been described (Bini et al. 1980, Fagius and Traversa 1994), and this may be very variable between subjects. This leads to the question of the impact of stress in tests utilizing some kind of unpleasant challenge. The magnitude of peripheral thermal responses to facial CE in the fingertip were found to be only one-fifth compared to the awake state and less in non-REM-sleep (Jennings et al. 1993). In study IV, some subjects demonstrated an increase of blood pressure and HR and signs of peripheral vasoconstriction before being exposed to the provocation, most probably due to pre-test stress. Grassi et al. (1999) described a significant increase of SSNA as the white-coat effect during a doctor's visit, and emotional sweating may occur in palmar and plantar areas (Vetrugno et al. 2003). The nature of stress reactions is individual, e.g. some unpredictable factor in the study room may be stressful for certain study subjects (Schwabe et al. 2008).

The provocation-induced stress may inhibit the perception of pain which is one modifier of Tsk changes (Fechir et al. 2009). On the other hand, pain is also a subjective sensation and, in study IV, the evaluation of the same stimuli varied widely and Tsk changes correlated with the experienced unpleasantness rather than with pain. The specific character of stress reactivity may be related to the subjects' personalities (Wallin and Chacoudian 2007) and may be changed e.g. due to anxiety disorders (Fisher et al. 2010). The confounding effect of psychophysiological state should be taken into account and personality testing may well be helpful when interpreting the IRT results.

In provocation tests, the comparisons have been often conducted between groups of patients and healthy controls. However, the wide variability in the IRT results in healthy persons at rest and in provocation-induced responses means that it is also necessary to take into account the individual nature of the skin BF and Tsk regulation. In study IV, the individual reaction type was almost the same with both different tests and registered responses correlated within individuals as previously described (Nyarko-Adomfeh 1992). Those results highlight the important role of individual reactivity of the autonomic nervous system in studies examining the microcirculation.

6.2 LIMITATIONS

6.2.1 Limitations of IRT

IRT suffers from some limitations connected to the general factors influencing the skin BF. According to Konen (2000), problems related to equipment and standardization in IRT studies hinder its feasibility e.g. for the measurement of nerve dysfunction. Some of those factors e.g. environmental sources may be eliminated by ensuring a constant ambient temperature and humidity. The role of thermoequlibration before the recordings is important. However, the thermoregulatory state of the subject is highly individual, i.e. what is considered as a comfortable ambient temperature may also vary between individuals. Moreover, internal regulatory factors may still pose a problem. The role of the baseline characteristics of activity of the autonomic nervous system and stress have been discussed before. In addition, certain confounding factors e.g. preceding physical loading on the previous day, may be observed in thermograms (unpublished data). The use of vasoactive drugs also needs to be excluded but this is not always possible.

In the interpretation of the IRT findings, despite the definition of the regions of interest in relation to anatomic structures, some areas have no clear demarcation lines and evaluation can be difficult in cases with structural side-to-side asymmetry (Herry and Frize 2004). This can lead to errors e.g. in persons with an asymmetrical face or due to a rotated pelvis in patient with sciatica. Some confounding effects may be related to pathological conditions such as an inflammation, varicose veins or malignancies which can locally increase the Tsk or obstructive artery disease can unilaterally or bilaterally decrease Tsk values.

6.2.2 Limitations of present studies

In the present studies, the use of vasoactive drugs or factors which could provoke local Tsk changes were excluded but there were some factors, such as physical loading on the previous day or air humidity which were not controlled. However, the environmental conditions in the study room were virtually the same between the measurements. In studies I-III, measurements were performed after the recommended thermo-equilibration at a room temperature of 22-25 °C which may well be too low for a partly undressed subject. In addition, in studies with the monitoring of Tsk after CE with 25 minutes of follow-up time (study IV) this may probably have evoked an additional vasoconstrictive effect.

In all studies, apart from the last one, Tsk was measured with IRT alone. In study IV, however, also a contact thermal sensor was used for the measurement of Tsk in the fingertip. This method may possibly be subject to some differences in the measured values, but previously Tsk responses were found to appear when vasoconstriction lasted for five seconds which points to the usefulness of IRT in such studies (Kistler et al. 1998). Morever, in inter-individual comparisons, this may not have a very significant impact.

The subjects participating in studies I and IV, were healthy young men with normal BMI without any health problems nor taking any medications for two weeks before the measurements. Only men were included in studies I and IV to avoid gender-related differences. Although they did not report any health problems they may still have had some trauma or local inflammatory disease in the past and some of them were practicing different sports. However, the significant disorders and the use of drugs were excluded but questioning about their genetic background or personality testing was not performed. In addition, the relationship between IRT results and smoking history was not analysed.

The patients participating in studies II and III, suffered from chronic non-specific LBP and NP but they were in employment and had relatively low pain and disability scores. The patients had suffered from chronic non-specific complaints with or without referred non-radicular extremity pain, probably with significant heterogeneity in the underlying reasons for their pain symptoms. It is possible that some of them had a slight radiculopathy. In cases with bilateral symptoms, false-negative IRT results may be observed. In NP patients, also a latent carpal tunnel syndrome or TOS-symptoms cannot be completely excluded. The studies were performed in an ordinary laboratory and the screening of the subjects was performed by a general practitioner and based on clinical evaluation only without any additional examinations. However, the patients were also examined by a neurologist, if necessary.

The control groups consisted of persons without LBP (study II) or NP (study III) during the study period and the preceding six months. While study groups included more women than men, the gender distribution was similar in the subgroups and therefore comparable. Moreover, no significant gender-related differences in δT values were found. Some of the controls in study III had cold hands, however, without any specific disorders, e.g. symptoms of Raynaud's phenomenon. Most of the CHNPP had warm fingers in the second examination indicating recovery of the Tsk back to normal, but in six of them, their fingers were still cold, probably due to some more persistent vasospastic abnormality. However, the subjects did not complain of any other symptoms indicating that any serious pathological condition would have existed. Moreover, in addition to the patients, similar acral coldness was present also in the control subgroup and the reason for this coldness remained unknown. However, the focus of the present study was rather on the relationships between δT values and actual Tsk, mostly from the methodological point of view.

6.3 CLINICAL SIGNIFICANCE OF THE PRESENT STUDIES AND THE NEED FOR FURTHER INVESTIGATIONS

In general, the study of skin BF through the cutaneous temperature represents a useful tool for examination of the microcirculatory function (Holowatz et al. 2008). In several clinical conditions, differences in skin BF and Tsk between the patients and healthy subjects have been demonstrated. However, the signs of abnormal Tsk regulation may occur at an earlier phase of the disease e.g. due to changes in peripheral vascular resistance during an early phase of hypertension (Boutcher et al. 2009) or due to endothelial dysfunction in cardiovascular pathology (van der Wall et al. 2010). Another study field is diabetic neuropathy where early diagnostics may be vitally important for the patient. The rapidly changing skin BF in the acral areas could well be detected by Tsk measurements with IRT for the studies of sympathetically mediated responses during different interventions (Akata et al. 2004; Jankovic et al. 2008) e.g. in psychophysiology (Kistler et al. 1998). However, those and other promising areas of the use of IRT e.g. in diagnostics of malignancies such as breast cancer or inflammatory diseases were not evaluated in the present study. Nevertheless, in those diseases as well as possibly many other applications, IRT may provide information which is difficult to obtain by any other means.

In MSD, IRT has been widely applied in the search for a method capable of providing objective signs of pathology. This is because, especially in non-specific neuromuscular disorders, other pathological findings may be scarce although the presence of vasomotor and sensory disorders has been shown to occur (Reading et al. 2003; Greening et al. 2003; Sluiter et al. 2000; Sharma et al. 1997). Sympathetic and sensory disorders are associated with neuropathies. The necessity of the early detection of signs of neuropathy would be of immense value since this would provide the hope of better prognosis and possible reversibility of the condition due to earlier treatment and, also, to the possibility of follow-up evaluation of the treatment outcome (Konen 2000, Fink and Oaklander 2006).

However, in LBP patients, vascular disorders were found both with and without sciatica (Maigne et al. 1996). In that study, it was postulated that those disorders may possibly result from alterations in the regulation of sympathetic vascular tone and could be more important than previously believed. In studies of nerve function, only severe nerve damage connected with the function of the large myelinated fibres can be detected in electrodiagnostic studies whereas dysfunction of the small nerve fibers may occur at an earlier stage during the development of the condition (Gold et al. 2009). Moreover, in unilateral sciatica, C-fibers were found to be more severely impaired than the myelinated Aδ-fibers (Zwart et al. 1998) and the preoperative damage of C-fibers was related to poorer prognosis in lumbar surgery (Nygaard et al. 1998). However, the objective documentation of the disturbances in the function of the small fibers e.g. in pathology of peripheral nerves, is confronted by many diagnostic problems. The techniques for the evaluation of these kinds of disorders are not widely available in clinical practice. The development of feasible methods is an area of future research and Tsk measurements may be potentially helpful in the investigation and screening of the thin nerve fibres disorders including those linked with the sympathetic nerve dysfunction.

In addition, in patients with non-specific LBP and NP, an incidence and localization of thermographic hot spots in comparison with pain drawings may represent an interesting topic of future research.

Tsk changes are straightforward to interpret in cases with unilateral abnormalities. In sciatica, the non-intact extremity has been commonly used as a control i.e. the so-called healthy side. However, according to some study reports, there are changes in BF also in the control "healthy" side, these being mediated possibly through central pathways (Kurvers et al. 1996; Sahin et al. 2009) and in unilateral sciatica, skin sensory disorders may also be present on the asymptomatic side (Nygaard et al. 1998). Freynhagen et al. (2008) claimed that in sciatica these contralateral sensory changes result from the effects of inflammatory mediators released from the damaged disk. Clarifying the mechanisms behind these contralateral changes will represent a challenge for the future studies.

The extensive inter-individual variability in Tsk findings e.g. in individuals with cold extremities, still requires a mechanistic explanation and it also represents an interesting direction for future studies. In fact, future IRT studies need to concentrate more on the factors influencing Tsk changes with the analysis of each individual case; the exceptional cases may provide evidence for very early signs of peripheral microvascular dysfunction. In addition to studies into the function of the autonomic nervous system, the investigation of personality may well partly explain those divergent findings. For those purposes, the combined use of IRT and SSR may provide more information about the simultaneous interplay of the vasoconstrictive and sudomotor neural activity. The comparison of results of SSR and IRT determinations during CE is one topic worthy of future research (unpublished data, study IV).

In summary, Tsk measurements have many potential applications but further studies are needed to better understand the pathophysiological mechanisms behind the Tsk changes and the central nervous control of skin microcirculation both in clinical conditions and in healthy individuals.

7. *Conclusions*

In general, IRT is a promising method, at least for investigative purposes. However, in its history there are periods when it lost credibility e.g. due to under-estimation of its limitations. Now interest in IRT is on the increase again and, hopefully, new methodological studies can help to avoid a new loss of credibility. As has been emphasized earlier, the temperature of human skin cannot be studied as a stable property because it is impossible to standardize the continuously changing physiological responses. The regulation of the skin BF is complex and multifactorial, and closely related to the function of the autonomic nervous system and with the significant impact of psychophysiological factors. Thus, according to the present results, one needs to bear in mind some methodological aspects.

The high variability of Tsk findings, demonstrated in healthy persons both in resting conditions and cold challenges, has multifactorial origins, being related to both external factors related to the accuracy of IRT equipment, measurement environment and technique, which can possibly be controlled, and internal factors such as the physiological variability and lability of the skin BF. The latter factors are poorly controllable and the individual reactivity of the autonomic nervous system has probably the main role in the determining Tsk changes. An analysis of this variability may help in understanding the central nervous control of skin BF. However, more studies are needed to clarify the influence of different factors in Tsk regulation.

When the skin area for the Tsk measurement is being chosen and the IRT findings interpreted, it is important to recognize the differences between “core” and “periphery” and also between glabrous and hairy skin due to their distinct innervations and the different blood circulation in the different skin areas. Moreover, because of the poor stability of Tsk e.g. in distal areas, the definition of the “normal” values may be problematic and a single IRT scan is valid only at the moment when it is measured.

In non-specific MSD, a relationship between the Tsk changes and pain intensity was found but the mechanisms behind this relationship are not completely clear and probably highly heterogeneous as well as being individual-based. Moreover, according to the study findings, signs of possible impairment of the function of sympathetic nerves, shown as acral Tsk disorders, are not stable and are more easily detectable in cold skin of the distal extremities both in non-specific LBP and NP patients. This confirms the clear relationship between the actual Tsk and IRT findings and supports the necessity of challenges for the autonomic nervous system in IRT studies.

The reproducibility of δT values as a main diagnostic finding in thermography was found to vary over time both in healthy and in patients with MSD which also limits the usefulness of single measurementst as a diagnostic tool. Thus, IRT combined with various challenges to the sympathetic nervous system seems to be more useful for these kinds of investigations and may help to provide more comparable results in Tsk assessments. However, the different Tsk at baseline may lead to divergent vascular responses and problems in interpretation. Moreover, coldness in acral regions per se may indicate some dissimilarity in microvascular regulation, also in healthy individuals.

Sympathetic and sensory disorders are uncomfortable for patients with neuropathy and these are connected with the poorer prognosis. The methods for the quantification of the autonomic disturbances are, however, not widely used in clinical routine. The results of the present study show that despite the variability and variable stability of IRT findings, measurements of Tsk may provide important information about the disorders of innervation related to the small nerve fibers, particularly, in MSD. This opens the possibilities for using this method for investigation and diagnostic screening of neuropathies. Thus, the IRT-technique has the potential to be an objective indicator of impaired sympathetic nerve function through the cutaneous circulation. However, in applications such as non-specific LBP and NP, interpretation of Tsk findings is not simple due to their unclear origin. This means that the method is more applicable for screening and observation uses rather than for quantitative purposes.

In general, when compared to other methods, IRT has some advantages but also several limitations. The benefits include its safety, non-invasiveness, ease of use and the possibility for the follow-up of the particular condition and this informative method may well gather wide applications in human studies. However, certain caution and a consideration of the physiological characteristics of the skin BF are needed in the interpretation of the recorded Tsk patterns and the many confounding factors and limitations need to be taken into account.

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Methodological Aspects of Use of Infrared Thermography in Healthy Individuals and Patients with Non-specific Musculoskeletal Disorders

Infrared thermography is a promising method for investigation of cutaneous microcirculation. However, in non-specific musculoskeletal disorders, interpretation of findings is not simple due to their heterogeneous origin and extensive variability, and IRT seems to be suitable for screening and observation rather than for quantitative purposes. Thus, certain caution is needed in the interpretation of the recorded results and the complex regulation of skin blood flow with an impact of individual reactivity and numerous confounding factors need to be taken into account.

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