Repetitive strain injury:
a novel focus on an ancient problem

m. extensor carpi radialis longus

m. extensor carpi radialis brevis

brachial artery endothelium dependent vasodilation was examined using the non invasive method of flow mediated dilatation.

brachial artery diameter and velocity were examined using color doppler

pneumatic cuff was placed proximally around forearm to provoke an ischemic stimulus by inflating the cuff

to 220 mmHg for 5 minutes

brachial artery

Jaap Brunnekreef
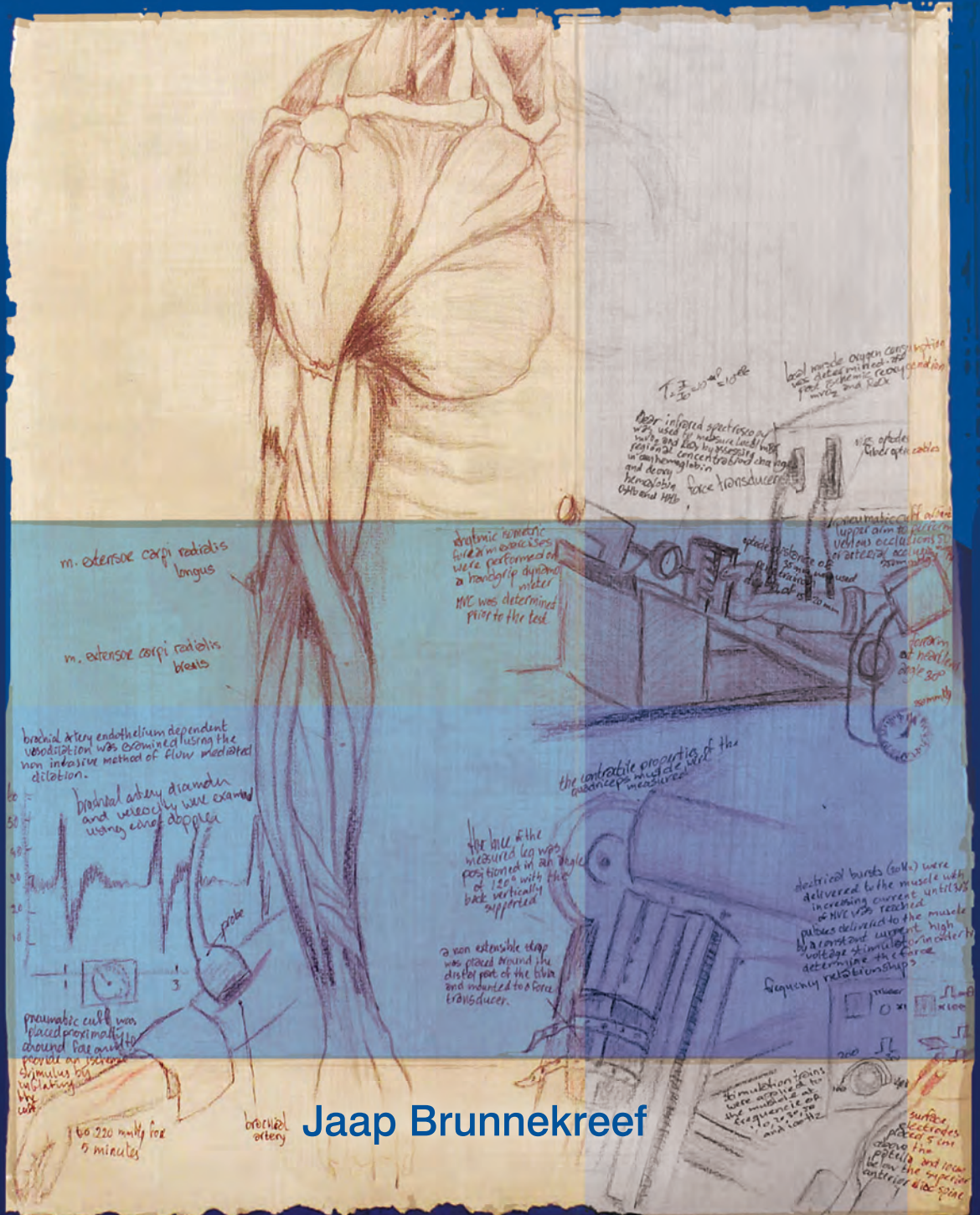
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Jaap J.J. Brunnekreef

RSI: a novel focus on an ancient problem

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Proefschrift

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Contents

Chapter 1

General introduction
and outline of the thesis

Repetitive Strain Injury

Repetitive Strain Injury (RSI) is used to describe a chronic musculoskeletal pain-related, over-use syndrome that involves the upper extremity, shoulder, and neck. These complaints may also be referred to as cumulative trauma disorders of the upper extremity (in North America), work-related upper-extremity musculoskeletal disorders (in USA), cervicobrachial syndrome (in Japan), or RSI in Canada and Europe. In the Netherlands, RSI has been recently renamed into complains of the arm, neck and/or shoulder (CANS) [1]. For convenience and comparability with international literature, we will use the term RSI in this thesis (for case description, see Box 1, for definition, see Box 2).

> **Box 1** Casus description RSI
>
> Marie is a 32 year old female with complaints that relate to her upper arm, elbow, and hand region. During repetitive computer activities, Marie experiences a diffuse pain in her forearm muscles that gradually worsens with the duration and intensity of repetitive movement tasks. Pain sometimes irradiates towards the shoulder and neck region. The level of her complaints has been fluctuating through the years. For these problems, Marie has visited her general practitioner several times. Her physician could not detect a specific anatomical or pathophysiological abnormality and referred Marie to physical therapy. Although some pain relieve occurred during treatment, the constant pain in her forearm, shoulder and neck remained present after finishing physical therapy. Marie has been working fulltime for a law company. Due to her complaints, she is unfortunately only able to work for two days a week.

RSI in a historical perspective

Although RSI is closely related to computer-work activities, the existence of RSI symptoms is not a new phenomenon. Bernardino Ramazzini described the RSI syndrome already in 1713. He described the occurrence of intense fatigue of the hand and the whole arm by office workers ("clerks"). These problems of the upper extremity were assumed to be caused by long periods of standing and sitting postures, repetitive motions, and mental stress [2]. He referred to this problem as writer's cramp.

The first epidemic of writer's cramp was reported among clerks of the British Civil Service in the 1830s, where it was attributed to the new steel dip pen, for which the user had to recharge the ink from an ink bowl in order to continue writing [3].

Box 2 Definition of Repetitive Strain Injury

RSI is a medical syndrome affecting the neck, upper back, shoulders, upper and lower arm, elbow, wrist or hand, or a combination of these areas. Its effects are restrictive or lead to participation problems. The syndrome is characterized by a disturbance in the balance between load and physical capacity, preceded by activities that involve repeated movements or prolonged periods spent with one or more of the relevant body parts in a fixed position. RSI is always caused by a combination of factors [15, 16].

In 1864, the British surgeon Samuel Solly introduced the term scrivener's palsy, from the Latin *scribere*: which means 'to write'. In a clinical lecture, he informed his colleagues of a severe and persistent arm pain syndrome that could affect men whose occupation demanded that they wrote incessantly. The symptoms of scrivener's palsy included a burning or aching pain that spreads through the arm, numbness in the fingers, a feeling of fatigue, and a cold feeling in the arm [4].

The seminal research which led to better understanding of these disorders was performed by the English physician George Vivian Poore. In 1878, he published a paper, in which he described 75 patients whose principal symptom was writer's cramp and impaired writing power [5]. The condition was subdivided into six categories; paralytic, spasmodic, degenerative, neuritic or neuralgic, 'true' writer's cramp, and an anomalous group. The first group included patients with definite peripheral nerve lesions, the second group involved extensive spasm that caused the writer's cramp, and a third group demonstrated a tremor of degenerative neurological origin which was suggested to interfere with writing. In the category of the 'true writer's cramp', patients suffered from pain after any attempt to use the arm, inability to find a comfortable position for the arm at night, numbness, and a feeling of cramping of the hand. Finally, in his 1878 paper, Poore refers to a new invention that '*entails no prolonged strain upon any of the muscles; this is the American type-writer machine, a machine which is worked by keys like a piano. This machine can be safely recommended by those who can afford to buy it; its only drawback is its noisy action"*[5].

Around the same time as Poore, German physicians published a paper in the 1880s in which they referred to writer's cramp as 'occupational neuroses' that was importantly caused by psychosocial factors. This view was further promoted by the English neurologist William Gowers in 1892. He found it remarkable how many patients, at time of onset of the disease were enduring anxiety from family trouble,

business worry, or weighty responsibilities. He suggested the presence of an under-lying dysfunction of the central nervous system as the cause of the neuroses [6].

In the early 20th century, telegraphists in Post Offices in the United Kingdom began experiencing 'telegraphist's cramp', this condition was first described by Thompson and Sinclair in 1912 [7]. Telegraphist's cramp was suggested to be caused by the rapid repetitive movements that are required to send Morse codes, and possibly induced by various psychosocial stressors. The psychological origin of telegraphist's cramp was further advocated by the English psychiatrist Culpin, who suggested a predisposition to psychoneurotic symptoms (like anxiety, obsessions or hysteria) to play a greater part in the development of occupational cramps than occupational factors did [8]. This view that promotes a central role for psychosocial factors in the etiology of the condition was given a prominent place in the occupational health literature up until the 1970s.

A revived interest in upper arm pain problems occurred during the early 1980s, the start of the era of personal computer technology. Ferguson was the first to report an epidemic of RSI in Australia in 1984 [9]. In 1971, Ferguson already focused attention on repetition injuries in electrical process operators, where problems did not follow the definite clinical pattern of tendosynovitis [10]. Although he named the condition occupational myalgia, this condition became later known as RSI. The name RSI, was introduced by John Matthews, a non-medical graduate and member of the Australian Council of Labor Unions in 1981. Surprisingly, without checking their source, the National Health and Medical Research Council of Australia adapted the term RSI in their occupational health guide of 1982 [11]. Two years later, the first epidemic of RSI occurred [9]. RSI was assumed to be a soft tissue disorder caused by the overloading of muscles from repetitive use or maintenance of constrained postures [12]. A few years after the introduction of the term RSI, the Royal Australian College of Physicians in 1986 strongly discouraged the use of this terminology. They argued that the condition had a primarily biomechanical cause without paying attention to the role of psychological factors. In addition, they argued that the term RSI was invented by labor-unions and RSI was attributed to all aspects of the workplace that unions wanted to improve. More skeptical commentators argued that, encouraged by fears of job loss and unwelcome changes in the organization due to the personal computer, RSI was an epidemic form of conversion hysteria, in which a psychological conflict between worker and employee was converted into physical symptoms of arm pain [13]. In an attempt to put the RSI epidemic to a rest, Ferguson wrote an editorial note to the Medical Journal of Australia in 1987 [14]. Although the nomenclature of arm pain in the occupational setting has been vigorously debated for nearly 300 years, the existence of people

with upper limb pain in and outside the occupational settings is still a problem for modern societies.

Incidence of RSI

RSI still is a silent epidemic in the workplace, with a reported prevalence that varies between 15% to 64% among computer workers [17-20]. In the European community, the prevalence of RSI is high with 25% of the working population reporting work-related neck/shoulder pain, and 15% reporting work-related arm pain [21]. In the Netherlands, the occurrence of RSI has been estimated to be between 20% to 40% among the working population [16]. Each year, eight percent of the Dutch working population report being sick due to RSI symptoms [22]. Therefore, RSI represents a substantial proportion of work-related illnesses and is associated with high medical costs and loss of work production [23, 24], making RSI a significant socioeconomic problem.

Prognosis of RSI

The prognosis of RSI has occasionally been subject for study in the literature. In a retrospective study, the cource of RSI was studied among 104 patients with RSI by van Eijsden-Besseling *et al.* (2010) [25]. After a mean follow-up period of 4.4 years, 14% of the patients developed a chronic benign pain syndrome, 9% recovered, and in the remaining 77% RSI worsened slightly throughout the years [25]. The course of RSI was studied among computer-screen workers. RSI among sewing machine operators shows a comparable prognosis, in which only 8% of the patients recovered from RSI symptoms after 2 years [26]. A large survey among 18,600 French workers revealed a better prognosis [27]. Re-examination of RSI patients after a 5 year follow-up period indicated a recovery in 65% and 53% of cases for male and female workers. Nonetheless, this indicates that > 40% of the patients with RSI still suffered from this disease 5 years later. A study conducted by Descartha *et al.* (2009) re-examined a cohort of 464 workers that were exposed to repetitive packaging work after a period of 3 year [28]. They found a high recovery for elbow symptoms (48%), a moderate recovery for neck or shoulder and hand or wrist symptoms (23% and 18%), and a low recovery for RSI in multiple locations (12%). Interestingly, this research group also studied the recovery of medial epicondylitis and found a far better prognosis for this condition. In 81% of cases, a full recovery was observed after the 3 years follow-up period [29]. Although the interpretation of these studies should be done with caution because of the large heterogeneity among studies regarding the location of RSI symptoms, different follow-up times, outcome measures, and research methods, the number of patients with RSI who still experience problems after 4 years follow-up is remarkably high and much higher compared to 'similar' disease states. The low rate of recovery of

RSI symptoms also clearly demonstrates that an effective treatment strategy for treating RSI symptoms is currently lacking. The lack of an effective therapy is possibly related to the fact that knowledge regarding the underlying mechanisms that contribute to the development of this condition is largely unknown.

Pathophysiology of RSI

To better understand the detrimental consequences of RSI and the long time-course of RSI symptoms, it is important to understand the pathophysiological mechanisms that contribute to the development of RSI symptoms. As RSI is regarded as a multi-factorial disease that influences various tissues, we have summarized potential mechanisms that may relate to the development of RSI.

Muscular changes

A central thought in the explanation of RSI symptoms during the last 300 years relates to the performance or repetitive movements and continuous activation of small muscle groups. Muscular damage during the development of RSI symptoms is believed to be caused via the 'Cinderella hypothesis' [30]. In short, this hypothesis assumes that, according to the 'size principle' of Hennemans [31], small type I fibers are continuously activated during prolonged muscle activity. The continuous activity of these motor-units is hypothesized to be causing damage to individual motor-units. Indeed, the study of Lexell provides evidence in support of this hypothesis, as they found that muscle fibers subjected to continuous stimulation are at increased risk for degeneration [32].

Mitochondrial changes

Biopsy studies of trapezius muscles of patients with RSI have revealed muscle fibers with an absence of cytochrome c oxidase [33-36]. The enzyme cytochrome c oxidase is the last enzyme of the respiratory electron transport chain in mitochondria. An absence of this ATP generating enzyme is suggestive for mitochondrial damage. Although these mitochondrial changes have been consistently observed at the affected side, the non-affected muscles in RSI, as well as those in healthy controls, have occasionally indicated signs of mitochondrial damage also [33, 37]. These observations of damage to the mitochondrion in RSI patients may therefore be non-specific and not related to RSI itself.

Intra-muscular pressure

Several studies have suggested that RSI symptoms could be provoked by a lack of blood supply owing to an increase in intra-muscular pressure during contraction

[38-40]. This phenomenon that is related to muscle fatigue was already studied by Barcroft in 1939 [41]. Also more recent studies, such as performed by Murthy *et al.* (1997), found that the forearm muscle oxygen consumption was attenuated at muscle pressures associated with muscle activation of only 10% of the maximal voluntary contraction [42]. Interestingly, patients with RSI were found to use higher pressure of their pen while writing and therefore presumably use higher muscle forces [43]. A study conducted by Pritchard *et al.* (2005) revealed that decompressive surgery of the extensor muscle compartment in patients with RSI reliefs RSI symptoms [44]. In summary, it seems plausible that (a too high) intra-muscular compartment pressure plays a role in the development or continuation of RSI symptoms.

Muscle fiber type distribution

Previous studies have found that the trapezius muscle of patients with RSI contains more type I fibers than trapezius muscles of healthy control participants [34, 36]. The low-twitch type I fiber has a high oxidative capacity and is known to sustain fatigue better than the fast-twitch type II fiber. Interestingly, biopsies of forearm muscles of patients with RSI revealed higher percentage of type II fibers in the extensor [45] and trapezius muscles [33]. This observation suggests that forearm muscles of patients with RSI consist of fibers that are poorly equipped to sustain long-term repetitive movement tasks. During these repetitive movement tasks, muscles are likely to rely more on type II-driven anaerobic glycolysis, which produces more lactic acid to maintain the required energy demand of the muscle and may consequently lead to earlier fatigue during this type of exercise. Indeed, a study conducted by Rosendal *et al.* (2004) found significantly higher levels of lactate during repetitive low-force exercise in patients with RSI [46]. This interesting finding supports the idea of a larger dependency on anaerobic metabolism in muscles of patients with RSI when performing repetitive muscle movement at low-force intensities. The increased production of anaerobic metabolites may contribute to the development of pain by stimulation of nocireceptors. Interestingly, Rosendal provides evidence for this hypothesis, as the level of anaerobic metabolites in RSI were found to be correlating with pain intensity that was observed by the patient [46].

Muscle relaxation

Some studies have indicated an impaired ability to relax muscles in patients with RSI [47-49]. A study that was conducted by Veiersted *et al.* (1993) found that healthy women with lower rates of brief unconscious interruptions in muscle activity, monitored with electromyography, were prone to develop RSI symptoms over time. The finding suggests that (uncontrolled) continuous muscle activation during muscle tasks is a predisposing factor for the development of RSI symptoms.

Presumably, when patients with RSI do not fully relax their muscles between repetitive activity, this leads to an increased intra-muscular pressure, partially blocking the arterial inflow (see above). Muscle circulation was found to be obstructed at relatively low exercise level of 10% of the maximal voluntary contraction [42]. Therefore, continuous muscle tensions may impair muscle blood flow and thereby causing a decrease in oxygen consumption [50].

Other metabolic changes that are hypothesized to play a role in the development of muscle injury in RSI is the accumulation of Ca^{2+}-ions into the muscle cell [51]. Calcium is stored inside muscle cells in the mitochondria or the endoplasmic reticulum. An influx of Ca^{2+}-ions into the cell plasma works as a second messenger and provokes a muscle contraction. However, excessive entry of calcium induced by prolonged muscle activity leads to the accumulation of Ca^{2+}-ions and subsequently causes damage to the muscle cells or even cause cells to undergo apoptosis [52]. Interestingly, prolonged electrical stimulation at low frequencies initiated accumulation of Ca^{2+} in muscles that are mainly composed of fast-twitch type II fibers, but not in the slow-twitch type I fibers [51]. These observations fit in the hypothesis that a larger content of type II fibers may place individuals at higher risk to develop the typical symptoms associated with RSI. The reason for the difference between the two types of muscle fibers is not yet understood.

Vascular changes
Blood flow
The vast majority of studies that examined potential mechanisms that play a role in the development of RSI focused on muscle function, with only a few studies that investigated the role of the vasculature in RSI. A study conducted by Larsson *et al.* (1999) found a lower local blood flow in the most painful trapezius muscle compared with the contralateral side in female patients with chronic trapezius myalgia [53]. A biopsy study by Larsson *et al.* (1990), who measured local muscle blood flow before a muscle biopsy was taken, also found a lower blood flow in the upper painful part of the trapezius muscle [36]. The reduction in blood flow was found to be correlated with muscle pain and the presence of mitochondrial changes in RSI.

A lower capillary to fiber area ratio was found in the trapezius muscle of patients with RSI [34, 35]. Moreover, Kadi *et al.* (1998) revealed that RSI patients who experienced higher pain intensity levels had a lower capillarisation of their muscle fibers. The observed lower capillarisation in muscles of RSI patients might partly explain the development of muscular fatigue and pain, since lower capillarisation may lead to an impaired oxygen delivery and removal of metabolites in the working muscles.

Although most studies support the presence of a lower blood flow in RSI, conflicting results have also been reported in the scientific literature. Research conducted by al-Nahhas *et al.* (1995, 1997) found an increase in blood flow to the affected limbs of patients with RSI using bone scintigraphy [54, 55]. However, the study by Amorim *et al.* (2006) did not confirm these findings in a larger group of patients when using the same technique [56]. Presumably, some of the patients included in the study by al-Nahhas *et al.* (1997) demonstrated an inflammatory process that results in a higher blood flow to the affected arm. Some other evidence for an increased blood flow in RSI has been provided by Cooke *et al.* (1993) [57]. They observed a higher blood flow at the affected hand in patients with RSI at baseline, but also after contralateral cold exposure, which normally would lead to a decrease in blood flow owing to activation of the sympathetic nerve system [57]. Patients with RSI had a lower reaction on this stimuli.

Conduit artery blood flow and endothelial function

Vascular changes at the level of conduit and resistance arteries have only been studied occasionally in patients with RSI. Pritchard *et al.* (1999) revealed lower blood flow in the radial artery during exercise and a lower change in artery diameter during exercise and after ischemic stimuli in patients with RSI [58]. The authors concluded that the radial artery of the forearm was relatively constricted and failed to vasodilate with exercise, which they explained by an endothelial dysfunction. Interestingly, elevated levels of inflammatory markers and C-reactive protein have been found in blood samples of patients with RSI [59]. These elevated levels of inflammatory markers were found to be correlated with the severity of the RSI complaints. Since previous studies found that cytokines can impair endothelial function (Landmesser et al., 2004), elevated levels of inflammatory markers in RSI could provoke a lower endothelial function. A lower endothelial function in RSI may contribute to lower blood supply during exercise and accordingly may play a role in the pathophysiology of RSI.

Skin temperature

Indirect evidence for lower supply of blood to the affected RSI arm has been provided by research that was conducted by Sharma *et al.* (1997) and Gold *et al.* (2004, 2009). They independently investigated skin temperature and found that the temperature at the affected side increased more in controls than in patients during typing activities [60-62].

In summary, the limited data above supports the presence of an impaired blood supply to the affected muscles in patients with RSI, and may be related to the presence of a lower endothelial function, especially under demanding conditions

such as exercise or during a sympathetic stimulus. However, much is still unknown about the impact of RSI on the vasculature.

Neural changes

A study that was performed by Byl *et al.* (1997) has indicated that prolonged repetitive hand-squeezing tasks lead to a central shrinking of the motor and sensory representation of the hand on the cerebral cortex of monkeys [63]. RSI therefore is suggested to be associated with alterations in motor- and sensor cortex representations. However, these results have not been confirmed in humans and future studies are necessary to elucidate the potential role for neural changes in the development of RSI in humans.

Psychological changes

Previous studies have identified female gender, Caucasian race, an increasing age, lower education, low self-reported physical fitness, psycho-neuroticism and neurotic perfectionism [64], as well as the level of job (dis)satisfaction with support from colleagues or supervisor [65] as factors that are associated with the development of RSI. These personal and environmental factors are suggested to have an effect on the relationship between work-related repetitive exposure and the development of RSI symptoms [66]. Although it is recognized by several authors that psychological aspects contribute to the development of RSI, the exact mechanism and importance of psychological factors is currently not well understood.

In summary, there is a significant evidence that RSI is associated with muscular adaptations that may play a role in the development of symptoms, whilst also a role for neural and psychological factors have been suggested. Although there is evidence that the vasculature is compromised in RSI, relatively little is known about the exact mechanisms, whether adaptations are present in vessels of different size and the local or systemic nature of vascular adaptations. Therefore, more research is needed to gain better inside into the pathophysiological mechanism of RSI, especially regarding the role of the vasculature.

Outline of the thesis

Aim of the present studies

RSI is increasingly recognized as a serious health problem affecting computer-workers around the world. Various treatment strategies have been adopted to diminish RSI complaints, including physical therapy. However, the effectivity of these various treatment strategies is disappointing [67]. One potential explanation for this is that the pathophysiological mechanism of RSI is poorly understood, hampering the development of a specific treatment strategy aimed at the underlying pathophysiological changes. Improving insight into these pathophysiological mechanisms of RSI is of paramount importance to ultimately improve treatment strategies, prevention, diagnosis and rehabilitation programs for patients with RSI. Therefore, the general aim of this thesis is to gain a better understanding of the pathophysiology of RSI, specially focusing on potential alterations in the vasculature.

RSI may be related to a lower blood flow to the forearm muscles during handgrip exercise, consequently contributing to the development of RSI. However, relatively little is known about the impact of RSI on forearm muscle blood flow and oxygen consumption. Therefore, in *Chapter 2,* we investigated local muscle blood flow and oxygen consumption at rest and immediately after exercise in forearm muscles that are affected by RSI. We included a group of RSI patients and a group of healthy control participants and measured local blood flow, oxygen consumption and post-ischemic reoxygenation in both forearms of all participants. We hypothesized that local forearm hemodynamic responses to exercise are lower in RSI.

Patients with RSI typically demonstrate unilateral complaints, whilst there is some evidence that systemic changes may be present. This allows for a within subject comparison of local forearm blood flow and oxygen consumption between the affected and the non-affected side in unilateral RSI. Such a comparison may reveal whether changes in local muscle blood flow and oxygen consumption are related to localized or systemic processes. In *Chapter 3* forearm muscle blood flow and oxygen consumption at the affected and non-affected forearm in patients with unilateral RSI were examined. We hypothesized that hemodynamic responses to exercise are lower at the affected, but normal at the non-affected forearm in patients with unilateral RSI.

The complex regional pain syndrome (CRPS-1) shows conspicuous similarities with RSI and has therefore been suggested to evolve through a common pathway [68]. In a study conducted by Marinus and van Hilten (2006), CRPS-1, Fibromyalgia, and RSI were systematically evaluated and compared towards each other. Similarities

were found for age distribution, male-female ratio, pain characteristics, and sensory signs and symptoms. In addition, the disease onset was frequently associated with traumatic origin, local symptoms that gradually spread to other body regions, and more frequent reports of anxiety and depression in patients than controls [68]. Moreover, previous studies suggested that CRPS-1 is related to lower blood flow and tissue oxygenation [69]. Therefore, in *Chapter 4* we investigated the hypothesis that patients with chronic CRPS-1 demonstrate a lower blood flow and tissue oxygenation in the affected forearm, similar to patients with RSI. We measured local blood flow, oxygen consumption and post-ischemic reoxygenation in both forearms of patients with unilateral CRPS-1 and controls.

Besides local changes in the vasculature, RSI has also been associated with systemic morphological abnormalities and higher percentages of the fast glycolytic (type II) muscle fiber. To further examine these interesting observations, we investigate the presence of systemic pathophysiological abnormalities in muscle function and vasculature in patients with RSI. For this purpose, in *Chapter 5* we measured lower limb contractile properties in the quadriceps muscle and upper limb oxygen consumption at rest and immediately after handgrip exercise in patients with RSI and controls. Assuming the presence of systemic abnormalities in muscle and vascular function, we expect to find differences in muscle function and vasculature between patients with RSI and their healthy controls.

Regulation of local blood flow is tightly regulated by the endothelial layer in blood vessels. An impaired blood flow at rest, but especially under more demanding conditions such as during exercise, may relate to endothelial dysfunction. Therefore, in *Chapter 6* we examined brachial artery endothelial function and exercise-induced brachial artery blood flow in RSI patients and age- and gender-matched controls. We hypothesize that patients with RSI demonstrate a lower endothelial function as well as an impaired exercise-induced blood flow during handgrip exercise.

Finally, the current knowledge on the pathophysiology of RSI is discussed in *Chapter 7*, with a specific focus on the role of the vasculature.

Methods applied in this thesis

Muscle blood flow

The local muscle blood flow was measured continuously using the non-invasive near-infrared spectroscopy (OXYMON®, Artinis Medical Systems, The Netherlands). Based on the relative transparency of tissue for light in the near-infrared region,

near-infrared spectroscopy (NIRS) can distinguish between oxygenated and deoxygenated changes of hemoglobin. Hemoglobin is the main component of the erythrocytes and the oxygen carrier of the blood. By using a modified Lambert-Beer Law described in detail by Livera *et al.* (1991) [70], the absorption changes measured directly by the NIRS instrument were converted into concentration changes of oxy- and deoxy hemoglobin. The near-infrared light, that generates light at 901, 848, and 770 nm, was transmitted from the source to the tissue and back to the detector by flexible fiber optic bundles called optodes. The NIRS optodes were positioned above the extensor carpi radialis brevis muscles of the forearm. The muscle blood flow was measured by inflating a blood-pressure cuff to 50 mmHg that was placed around the upper-arm. This results in a blockade of the venous outflow, without affecting the arterial inflow. Muscle blood flow was calculated from the NIRS data by evaluating the linear increase in total hemoglobin, being the sum of the oxy- and deoxy hemoglobin, within the first seconds of the venous occlusion [71, 72]. Concentration changes of total hemoglobin were expressed in micro molars per second and were converted to milliliters blood per 100 milliliters tissue per minute by using the individual hemoglobin-concentration that was obtained from a finger tip blood samples. The local muscle blood flow was determined at the start and the end of the exercise protocol.

Muscle oxygen consumption

The local muscle oxygen consumption was measured with the same near-infrared spectroscopy (NIRS) device. The NIRS optodes were positioning above the extensor carpi radialis brevis muscles of the forearm. The oxygen consumption was measured by inflating the blood-pressure cuff to 250 mmHg. The blood-pressure cuff was placed around the upper arm. The inflation of the cuff to 250 mmHg blocks the arterial inflow, whereby the forearm fully depends on the available oxygen. The decrease of the oxygen concentration signal over time represents the local muscle oxygen consumption (in $mLO_2/min/100g$) [72-74]. The muscle oxygen consumption was determined at rest and immediately after repetitive forearm exercises at 10%, 20%, and 40% of the individual maximal voluntary contraction (MVC).

Reoxygenation rate

The post-ischemic reoxygenation rate was measured by determining the recovery of oxygenated hemoglobin during the initial 3 seconds after releasing the cuff of an arterial occlusion (250 mmHg). During the sequential post-occlusive hyperemic response, blood volume rapidly increased, resulting in a fresh pool of oxygenated hemoglobin and a quick washout of deoxygenated hemoglobin. Reoxygenation represented the initial inflow of oxygenated hemoglobin and is therefore related to micro-vascular function (in $\mu MO_2Hb/s$) [74]. The muscle reoxygenation rate was

Figure 1a Experimental setup of the near-infrared spectroscopy measurements of the forearm

determined at baseline and after cuff releases that followed exercises at 10%, 20%, and 40% of the MVC.

The coefficient of variation for measuring forearm blood flow and oxygen consumption were found to be 22.4% and 16.2%, respectively [75]. Therefore, this procedure is considered a reliable and reproducible method for determining blood flow and oxygen consumption at rest as well as after a broad range of exercise intensities [72, 74].

Contractile properties of muscles

The contractile properties of the quadriceps muscle were measured by applying electrical stimulation trains of 1-second duration to the muscle at frequencies of 1, 10, 20, 50, and 100 Hz with a rest period of 2 minutes between each train. The quadriceps muscle was electrically stimulated using two surface electrodes (8 x 13 cm; Schwa-Medico Nederland BV, Woudenberg, The Netherlands). The electrodes were placed 5 cm above the patella (at 2/3 medial from the line between the patellar and superior anterior iliac spine) and 10 cm below the superior anterior iliac spine

Figure 1b Near-infrared spectroscopy signal that is presented real-time on screen during the measurements
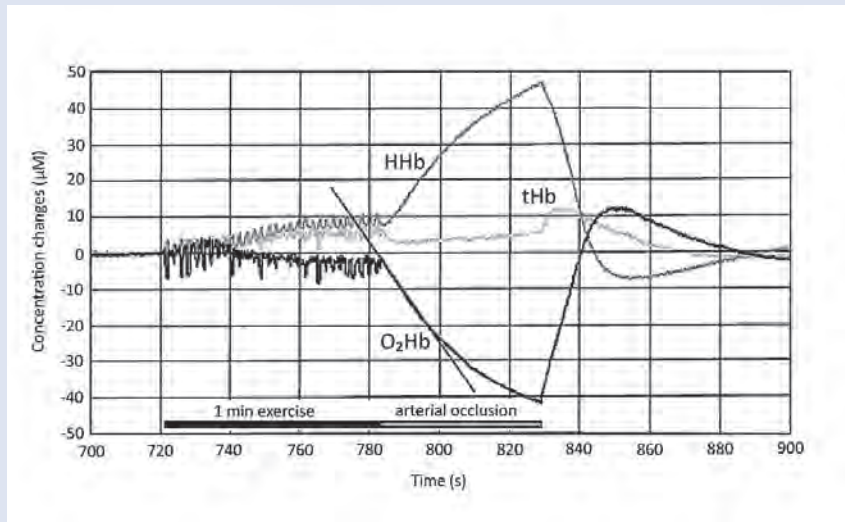
(at 2/3 lateral from the line between the patellar and superior anterior iliac spine). A personal computer running a custom-made software program controlled the frequency and number of square-wave pulses delivered to the muscle by a con-stant-current high-voltage stimulator (model DS7A; Digitimer Ltd, Welwyn Garden City, U.K.). To ensure that at representative part of the muscle was activated, electrical bursts (20 Hz) of 1-s duration were delivered to the muscle with increasing current until 30% of maximal voluntary contraction was reached. To determine the MVC, participants were asked to produce 3 maximal voluntary knee extensions of 3 seconds, separated by a 1-minute resting period. The highest of the three measurements was taken as the MVC. During the measurements participants were seated on an adjustable chair with a non-extensible strap placed around the distal past of the tibia and mounted to a force transducer (Peekel Instruments, Rotterdam, The Netherlands). The force signal was digitized with 1000-Hz sample frequency, and analyzed by custom developed software (MatLab, MathWorks, MA, USA). During off-line analysis, contraction and relaxation rates of isometric tetanic contractions were calculated as indications of muscle speed. Early-relaxation time was defined as the time taken of muscle contraction to decline from 100% to 50% of the peak force. The half-relaxation time was defined as the time taken for muscle contraction to decline from 50% to 25% of the peak force. Normalized maximal rate

of force rise was expressed as a percentage of peak force, using the method described by Buller and Lewis [76]. Finally, the force-frequency relationship was obtained from muscle stimulations at frequencies ranging from 1 to 100 Hz.

Figure 2a Near-infrared spectroscopy signal that is presented real-time on screen during the measurements
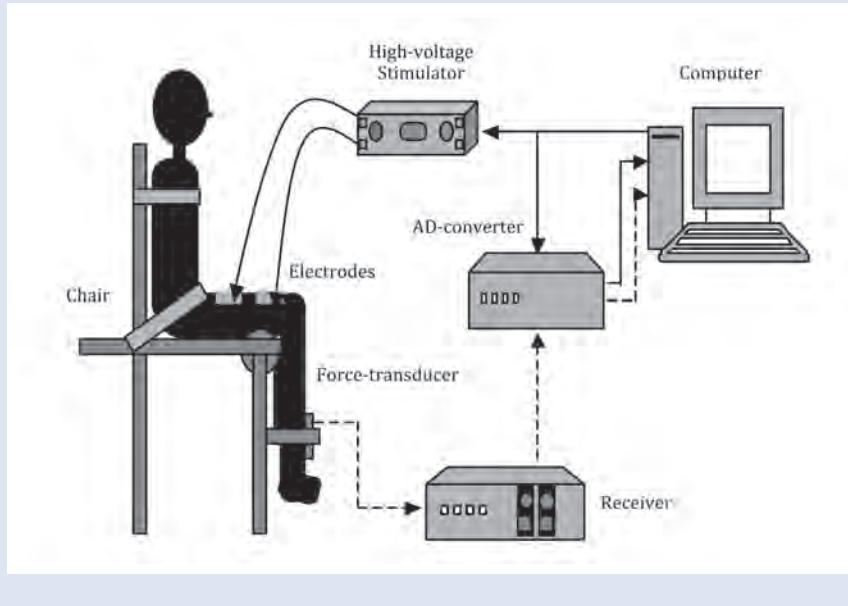
Arterial blood flow

Brachial artery blood flow was measured using a non-invasive duplex ultrasound (Terason t3000, Burlington, Massachusetts, USA). The probe of the duplex ultrasound was placed in the distal third of the upper arm, with an insonation angle of < 60-degrees [77, 78]. During the experiment, participants were positioned in the supine position with the dominant arm extended in an 80-degree position from the torso, so that they could grasp the hand dynamometer. The brachial artery blood flow was measured at rest and during repetitive forearm exercises at 15%, 30%, and 45% of the MVC. Participants performed handgrip exercise for 3 minutes at 30 contractions per minute, separated by a 5 minutes resting period. Handgrip exercise was performed on a hand dynamometer with visual feedback to maintain a constant workload during exercise. Blood flow measurements were continuously measured during exercise and for 1 minute after exercise.

Figure 2b Representative signal of a muscle contraction
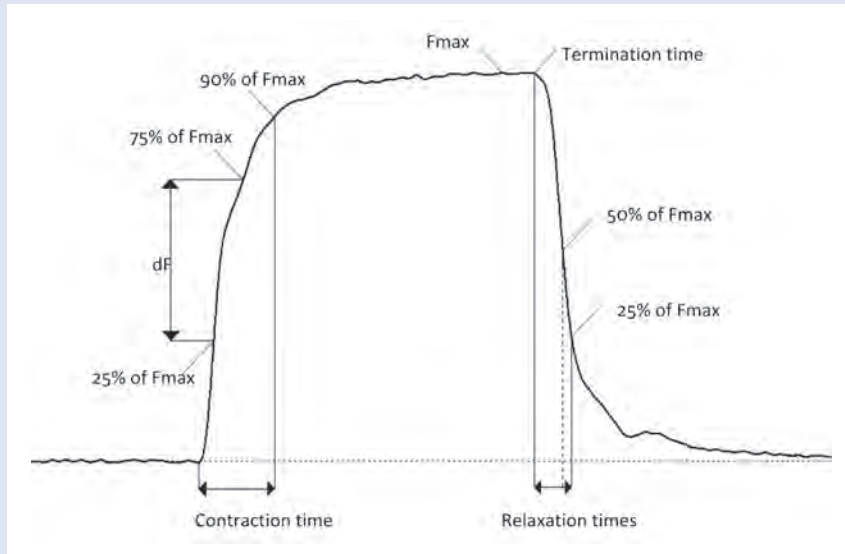
Maximal Force Rise = Slope of contraction of 25% to 75% of Fmax. Early relaxation = time of muscle relaxation from 100% to 50% MVC, Late relaxation = time of muscle relaxation from 50% to 25% MVC.

Endothelial function

The endothelial function of the brachial artery was determined with the same duplex ultrasound as the artery blood flow with the position of the probe on the same location. The endothelial function was determined using the non-invasive method of flow-mediated dilation (FMD). During the experiment, participants rested in the supine position and a rapid inflation/deflation pneumatic cuff (Howkanson Inc., Bellevue, WA, USA) was placed proximally around the forearm to provide an ischemic stimulus. The pneumatic cuff was inflated to 220 mmHg for 5 minutes. The brachial artery endothelium-dependent vasodilatation is based on the characteristic that vessels dilate in response to shear stress (increase in blood flow), which is largely mediated by nitric oxide. Brachial artery diameter and velocity were examined, proximal to the cuff, using echo-Doppler. Baseline scans for resting vessel diameter and blood velocity were recorded over 1 minute. Diameter and flow recordings resumed 30 seconds prior to cuff deflation and continued for 3 minutes thereafter. The FMD was examined in the dominant arm of controls and the affected and contralateral arm of patients with RSI. We have adopted recent guidelines to

Figure 3a Experimental set-up for measuring arterial blood flow and
endothelial function of the brachial artery

examine the FMD [79]. The FMD is a valid and frequently used technique to examine
the endothelial function which reflects largely nitric oxide (NO)-mediated, endothe-
lium-dependent dilation [80].

Figure 3b Arterial ultrasound image and Doppler signal that is presented
real-time on screen during the measurements
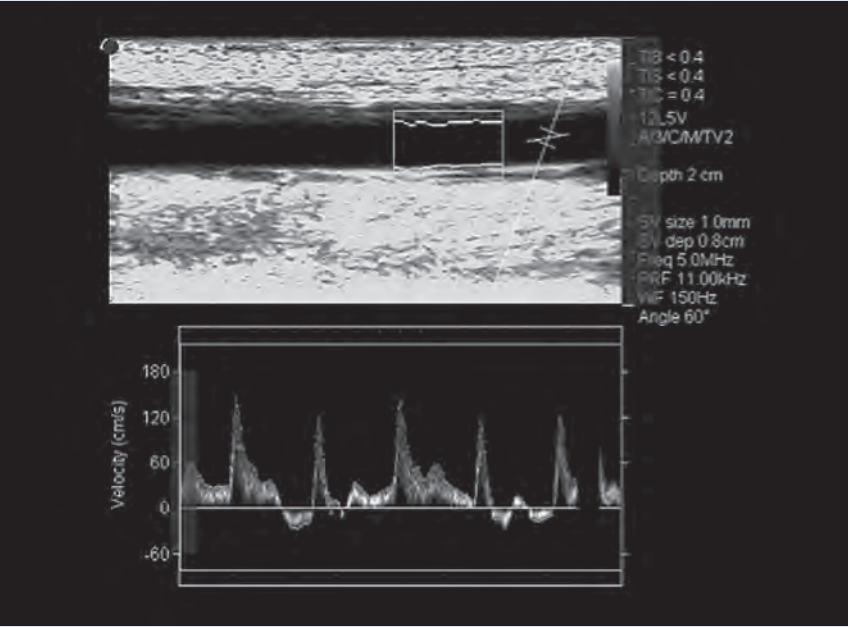
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Chapter 2

Forearm blood flow and oxygen consumption in patients with bilateral repetitive strain injury measured by near-infrared spectroscopy

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Abstract

Objectives: The main objective of this study was to assess the local muscle oxygen consumption (mVO_2) and blood flow (mBF) of the forearm in individuals with repetitive strain injury (RSI) during isometric contractions of the forearm. **Background:** Despite the social impact of RSI, little is known about its pathophysiological mechanism. Insight into this mechanism is a prerequisite for the theoretical basis to understand the risk factors, prevention, and treatment of RSI. **Methods:** We employed the non-invasive optical technique Near-Infrared Spectroscopy (NIRS) to assess forearm mVO_2 and mBF. These variables were assessed at 10, 20, and 40% of their individual maximal voluntary strength. Twenty-two patients with RSI symptoms in both arms (bilateral RSI) and 30 healthy age-matched controls participated in this cross-sectional study. **Results:** The results showed lower mVO_2 during exercise and a reduced mBF after exercise (all $p < 0.05$). **Conclusions:** The results suggest that mVO_2 and mBF are lower in the forearms of individuals with RSI compared with their controls at similar working intensities. This finding indicates that the underlying vasculature may be impaired. Although these findings contribute to the understanding of RSI, future research is necessary to further unravel the mechanisms of this area.

Introduction

The term Repetitive Strain Injury (RSI), also known as cumulative trauma disorder or work-related upper limb disorders, describes a variety of musculoskeletal disorders concerning the neck, upper back, shoulder, arm, elbow, hand, wrist, and fingers. People performing repetitive motions, forceful exertions, vibration, or sustained and awkward postures on a regular basis are at risk of developing RSI [1]. With an expected increase of computerizing jobs in the near future, RSI is likely to become an even larger problem for Western societies. Work-related neck and upper limb musculoskeletal disorders are a significant problem within the European Union with respect to ill health, productivity and associated costs [2]. Despite the social impact of RSI, little is known about its pathophysiological mechanism. Insight into this mechanism is a prerequisite for the theoretical basis to understand the risk factors, prevention, and treatment of RSI [3]. Several authors have stressed the important role of blood flow (BF) in RSI-related symptoms. The physiological impairments they discussed include a dysfunction in vascular endothelium [4], reduced sympathetic reflex vasoconstriction [5], or the continuous recruitment of low-threshold motor units, referred to as the Cinderella hypothesis [6]. In addition, it has been suggested that RSI symptoms are provoked by a decrease in intra-muscular BF during contraction [7]. However, studies on blood circulation in RSI show contradictory results; some report decreased, [4] and others report increased BF [8, 9]. Consequently, it is still to debate in which way the BF in RSI is disturbed. In the normal situation, the local effect on muscle activity is characterized by an increase in local muscle blood flow (mBF) to fulfill an increase in metabolic demand and aerobic production of ATP. A complex series of local vasodilator and central vaso-constrictor events mediate this rise in BF [10]. It is hypothesized that an insufficient rise in BF will lead to the accumulation of metabolic waste products. Subsequently, this may lead to stimulation of nocioreceptors, resulting in pain and eventually ceasing activity level. An impaired peripheral circulation could be an important factor in the development of RSI. Therefore, we hypothesize that local forearm hemodynamic responses to exercise are lower in RSI. To test this hypothesis, forearm BF, muscle oxygen consumption (mVO_2), and reoxygenation responses of individuals with RSI and healthy controls during isometric contractions of the forearm were assessed using the non-invasive near-infrared spectroscopy (NIRS).

2

Methods

Participants

Twenty-two patients with bilateral RSI symptoms (female = 14) and 30 healthy control participants (female = 14) participated in this study. The Hospital's occupational health physician, the Dutch RSI patients organization, and local physical therapy practices recruited patients. Control participants were recruited among employees of the Radboud University Medical Centre. Patients were included if they were diagnosed with bilateral RSI, defined as pain in the elbow region expressed in both arms, diagnosed by a physician, and performed computer work for at least 2 hours a day. The control participants were also computer workers, but they had no signs of RSI during measurements or within the previous 12 months. Participants were excluded if they suffered from systemic illness or used any medication known to interfere with the vascular system. The participants had a comparable age, daily amount of computer use, smoking history, level of education, forearm circumference, and adipose tissue thickness (ATT) (Table 1). The average pain level in the RSI group was 38.9 mm on the visual analog scale (VAS) [11] with a mean duration of RSI symptoms of 40.7 months. The Ethics Committee of our institute approved the study and written informed consent was obtained from all participants.

Demographics

Participants characteristics were registered to ascertain suitability for inclusion, comparability of groups, and to identify confounding variables. Participants were questioned about localization, extent, and duration of their RSI symptoms. Pain intensity was measured daily at the same time for 1 week, using a 10-cm VAS. In addition, age, hand dominance, hours of work per week, daily computer use, smoking history, and the level of education were recorded. The circumference of the forearm and the ATT were measured at the same location NIRS-optodes were positioned. ATT was measured using a skinfold calliper (Holtain Ltd., Crymmych, UK). The hemoglobin (Hb)-concentration was determined from a fingertip blood sample (HemoCue AB, Sweden). The maximal voluntary contraction (MVC) was measured (JAMAR, hand-held dynamometer, Lafayette Instruments Co, IN) during 3 seconds and repeated 3 times with 1-minute intervals, using the highest score as the MVC.

Procedure

All participants were seated in a comfortable chair. A pneumatic cuff was placed distally around the upper arm. The hand rested on a handgrip dynamometer with the forearm at heart level at an upward angle of 30-degree on an inclined platform. The participants' MVC of the forearm muscles was determined prior to the test.

2

Table 1 Participants characteristics

	RSI group (n=22)			p-value*	Control group (n=30)			p-value*	p-value
	most painful	least-painful			dominant	non-dominant			
Age (years)	34.7 ± 8.6				33.1 ± 11.9				.57
Gender (n)									
Female/male	14/8				14/16				.23
Hb-concentration (mmol/L)	8.6 ± 0.9				8.5 ± 0.9				.73
Dominant side (n)									
Right/left	19/3				24/6				.55
Most painful side (n)									
Dominant	10								
Non-dominant	5								
Both	7								
Pain level (VAS) (0-10 cm)	3.9 ± 2.1								
Duration of RSI symptoms (months)	40.7 ± 38.2								
Daily computer use (hours)	6.1 ± 2.5				4.3 ± 2.1				.31
Smoking history (n)	2				3				
Level of education (n)									
High	16 (73%)				20 (67%)				
Middle	6 (27%)				9 (30%)				
Low	-				1 (3%)				
Circumference forearm (cm)	26.0 ± 2.2	25.8 ± 2.2		.13	25.4 ± 1.9	24.9 ± 2.0		<.001†	
Adipose tissue thickness (mm)	8.6 ± 4.6	9.4 ± 4.3		.37	5.0 ± 2.3	5.5 ± 3.1		.12	
Maximal voluntary contraction (kg)	33.9 ± 14.8	32.5 ± 14.5		.16	39.2 ± 12.0	36.7 ± 12.5		.002†	

Values are represented as mean ± SD. RSI indicates repetitive strain injury; Hb, hemoglobin; VAS, visual analog scale. *p-value refers to within-group comparisons. †Significant differences between arms (p<0.05).

After a 5-minutes rest period (Figure 1), five venous occlusions (50 mmHg), each lasting 15 seconds with a 45-seconds resting intervals were used, to obtain the average local mBF at rest. The experiment continued with an arterial occlusion (250 mmHg) for 60 seconds, in order to determine local mVO_2 and post-ischemic reoxygenation rate (ReOx) at rest. After a rest period between 120 and 240 seconds, participants performed rhythmic isometric forearm exercises on a handgrip dynamometer (1-second contraction, 1-second relaxation) assisted by a metronome for 1 minute at 10%, 20%, and 40% MVC, respectively. For feedback to the participants, the level of exercise was clearly marked on a display. Immediately after each exercise period, an arterial occlusion was applied for 30 seconds to assess mVO_2 and ReOx. Rest periods of 120 to 240 seconds between the exercise bouts at 10 and 20% MVC allowed BF to return to baseline value. The protocol was completed by one venous occlusion for 15 seconds to determine the mBF after exercise. This venous occlusion was given 75 seconds after the last exercise at 40% MVC (Figure 1).

Figure 1 Timetable of the near-infrared spectroscopy protocol, stages of the protocol, and time periods (seconds)

Procedure	Rest-period	VO		VO		VO		VO		VO		AO	Rest	→
Time	5-min	15	45	15	45	15	45	15	45	15	45	60	120 - 240	

10% MVC	AO	Rest	20% MVC	AO	Rest	40% MVC	AO		VO	Stop
60	30	120 - 240	60	30	120 - 240	60	30	45	15	-

VO, venous occlusion; AO, arterial occlusion; MVC, maximal voluntary contraction

NIRS

Near-infrared spectroscopy (NIRS) was used to measure local mBF, mVO_2, and ReOx by assessing regional concentration changes in oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb), using a continuous-wave near-infrared spectrophotometer (OXYMON, Artinis Medical Systems, Zetten, the Netherlands). This technique is described in detail elsewhere [12, 13]. Briefly, this technique is based on the relative transparency of tissue for light in the near-infrared region and on the oxygen dependent absorption changes of hemoglobin and myoglobin. As one cannot

distinguish between myoglobin and hemoglobin, the combined effect of these two substances are studied. For convenience, we will refer to hemoglobin only. The absorption changes measured directly by the NIRS instrument are converted into estimates of concentration changes of O_2Hb and HHb by using a modified Lambert-Beer law described by in detail by Livera *et al.* (1991) [14]. To correct for the light scattering inside the tissue a differential path length factor of 4.0 was used. The sum of O_2Hb and HHb reflects changes in blood volume, represented by the total hemoglobin signal (tHb). NIRS measurements in the forearm were obtained by positioning the optodes on the extensor carpi radialis brevis muscles of the forearm. The depth of the measuring signal is determined by the distance between light emmiting and light-receiving fiber-optic cable (the inter-optode distance), and is approximately half the distance of this inter-optode distance. In this study, an inter-optode distance of 35 mm was used, resulting in a pentration depth of about 15 to 20 mm.

Main outcomes

The local muscle blood flow (mBF) was determined at baseline and after repeated muscle contractions. By inflating a blood-pressure cuff to 50 mmHg, a blockage of the venous outflow, without affecting the arterial inflow, was achieved. The BF was then measured by analyzing the increase of the slope of the total hemoglobin signal, which is the sum of the oxy- and deoxy hemoglobin (in mL/min/100mL) [12, 15].

The local muscle oxygen consumption (mVO_2) was determined at baseline and at 10%, 20%, and 40% of MVC. It was measured by inflating the blood-pressure cuff to 250 mmHg. This blocked the arterial inflow, whereby the forearm fully depends on the available oxygen. The initial 8-seconds decrease over time of the O_2Hb-concentration signal represented the local mVO_2 (in mLO_2/min/100g) [12, 15].

The post-ischemic reoxygenation rate (ReOx) was determined at baseline, at 10%, 20%, and 40% of MVC. ReOx was measured by determining the recovery of O_2Hb during the initial 3 seconds after releasing the cuff of an arterial occlusion (in μMO_2Hb/s). During the sequential post-occlusive hyperemic response, blood volume rapidly increased, resulting in a fresh pool of O_2Hb and a quick washout of HHb. ReOx represented the initial inflow of O_2Hb and is therefore related to microvascular function [16, 17].

Statistics

Univariate analyses were performed to determine differences between the most painful and least painful arm in RSI and between the dominant and non-dominant arm of the control participants. If both arms in RSI were equally painful, then the

dominant site was considered the most painful. A Pearson two-tailed correlation analysis was used to identify confounding variables. When present (p<0.05), these variables were included in the analysis as covariates. A general linear model with repeated measure procedure was used to examine changes in mBF, mVO_2, and ReOx, with 'group' (RSI or control group) as between-subjects factor and the different exercise intensities (rest, 10%, 20%, and 40% of MVC) as within-subjects factor. The level of significance was set at 0.05.

Results

Identification of confounding variables
ATT and grip strength were significantly correlated with the outcome measures mVO_2 and ReOx at all intensities (p<0.05). Other variables were not significantly related to mBF, mVO_2, or ReOx.

Table 2 Comparison of hemodynamic variables between the most painful and the less painful forearm of patients with bilateral repetitive strain injury. Values are represented as mean (95% CI)

| | RSI | | |
| | *Most painful* | *Least painful* | |
	Mean (95% CI)	Mean (95% CI)	p-value
Muscle Blood Flow (mL/min/100mL)			
Rest	1.12 (0.86 – 1.38)	1.13 (0.85 – 1.40)	.96
After exercise	1.65 (1.08 – 2.23)	1.57 (0.98 – 2.17)	.75
Muscle oxygen consumption (mLO_2/min/100g)*†			
mVO_2 rest	0.07 (0.05 – 0.08)	0.06 (0.05 – 0.08)	.63
mVO_2 10%	0.23 (0.14 – 0.33)	0.20 (0.10 – 0.30)	.59
mVO_2 20%	0.36 (0.22 – 0.49)	0.24 (0.10 – 0.39)	.25
mVO_2 40%	0.42 (0.24 – 0.61)	0.43 (0.23 – 0.62)	.97
Reoxygenation rate (μMO_2Hb/s)*†			
ReOx rest	2.55 (2.12 – 2.98)	2.69 (2.23 – 3.15)	.65
ReOx 10%	2.94 (2.42 – 3.46)	3.37 (2.83 – 3.92)	.26
ReOx 20%	3.37 (2.70 – 4.03)	3.63 (2.94 – 4.33)	.58
ReOx 40%	3.82 (3.15 – 4.49)	4.04 (3.33 – 4.74)	.65

Values are represented as mean (95% CI). CI indicates confidence interval; RSI, repetitive strain injury; mBF, muscle blood flow; mVO_2, muscle oxygen consumption; ReOx, post-ischemic reoxygenation rate;. *Adjusted for adipose tissue thickness. †Adjusted for maximal voluntary contraction.

Intra-subject arm differences

There were no differences found between the hemodynamic variables of the painful and least painful forearm in patients with bilateral RSI (Table 2) and between the dominant and non-dominant forearm of the control participants (Table 3). Therefore, both the most and least painful forearms of patients with RSI were compared to both forearms of the control participants.

Table 3 Comparison of hemodynamic variables between the dominant and non-dominant forearm of the control participants

	Control		
	Dominant arm	*Non-dominant arm*	
	Mean (95% CI)	Mean (95% CI)	p-value
Muscle Blood Flow (mL/min/100mL)			
Rest	1.20 (0.98 – 1.42)	1.09 (0.87 – 1.32)	.55
After exercise	2.59 (2.11 – 3.08)	2.38 (1.89 – 2.87)	.60
Muscle oxygen consumption (mLO$_2$/min/100g)*†			
mVO$_2$rest	0.16 (0.12 – 0.21)	0.10 (0.06 – 0.15)	.08
mVO$_2$10%	0.66 (0.51 – 0.81)	0.59 (0.43 – 0.74)	.51
mVO$_2$ 20%	0.84 (0.64 – 1.03)	0.81 (0.61 – 1.02)	.87
mVO$_2$ 40%	1.33 (1.03 – 1.64)	1.15 (0.84 – 1.47)	.41
Reoxygenation rate (μMO$_2$Hb/s)*†			
ReOx rest	3.95 (3.34 – 4.57)	3.57 (2.93 – 4.21)	39
ReOx 10%	5.67 (4.67 – 6.65)	5.59 (4.58 – 6.61)	.92
ReOx 20%	6.72 (5.57 – 7.86)	6.12 (4.93 – 7.31)	.47
ReOx 40%	7.64 (6.36 – 8.93)	6.90 (5.57 – 8.23)	.43

Values are represented as mean (95% CI). CI indicates confidence interval; RSI, repetitive strain injury; mBF, muscle blood flow; mVO$_2$, muscle oxygen consumption; ReOx, post-ischemic reoxygenation rate.
*Adjusted for adipose tissue thickness. †Adjusted for maximal voluntary contraction.

Local muscle blood flow

At rest, no differences were found in mBF between patients with bilateral RSI and controls (p=0.85). After completing the exercise protocol at 40% MVC, mBF was found to be significantly lower in patients with bilateral RSI than controls (p=0.001) (Table 4).

Table 4 Comparison of hemodynamic variables between RSI and control participants

	(n)	RSI Mean (95% CI)	(n)	Control Mean (95% CI)	p-value
Muscle Blood Flow (mL/min/100mL)					
Rest	42	1.12 (0.94 – 1.27)	60	1.15 (0.99 – 1.30)	.85
After exercise	42	1.62 (1.21 – 2.03)	60	2.49 (2.14 – 2.83)	.001‡
Muscle oxygen consumption (mLO$_2$/min/100g)*†					
mVO$_2$rest	40	0.08 (0.05 – 0.12)	58	0.12 (0.10 – 0.15)	.06
mVO$_2$10%	40	0.31 (0.20 – 0.43)	58	0.57 (0.47 – 0.66)	.002‡
mVO$_2$ 20%	40	0.46 (0.28 – 0.59)	58	0.75 (0.62 – 0.87)	.003‡
mVO$_2$ 40%	40	0.62 (0.38 – 0.85)	58	1.13 (0.93 – 1.32)	.002‡
Reoxygenation rate (μMO$_2$Hb/s)*†					
ReOx rest	41	3.25 (2.77 – 3.73)	58	3.32 (2.92 – 3.71)	.85
ReOx 10%	40	4.01 (3.38 – 4.81)	58	4.95 (4.35 – 5.55)	.09
ReOx 20%	40	4.65 (3.79 – 5.51)	58	5.59 (4.88 – 6.30)	.12
ReOx 40%	40	5.19 (4.24 – 6.13)	58	6.37 (5.58 – 7.16)	.07

Values are represented as mean (95% CI). CI indicates confidence interval; RSI, repetitive strain injury; mBF, muscle blood flow; mVO$_2$, muscle oxygen consumption; ReOx, post-ischemic reoxygenation rate. * Adjusted for adipose tissue thickness. †Adjusted for maximal voluntary contraction. ‡Significant differences from controls (p<0.05).

Local muscle oxygen consumption

At rest, mVO$_2$ tended to be lower in RSI patients, however, not significant (p=0.06). During exercise, mVO$_2$ was found to be significantly lower in RSI patients during all 3 intensities, p=0.002, 0.003, and 0.002, respectively (Figure 2). Repeated measures ANOVA showed that the response in mVO$_2$ that occurs with increasing handgrip exercise intensity was lower in RSI, compared with controls (F (df 1.66) = 6.42; p=0.004).

Reoxygenation rate

No statistical differences in ReOx were found between patients with RSI and control participants at rest and during all 3 intensities (p=0.85, 0.09, 0.12, and 0.07, respectively) (Figure 3). Repeated measure ANOVA showed that the response in ReOx that occurs with increasing handgrip exercise intensity was not different between RSI and the control group (F (df 2.02) = 2.98; p=0.052).

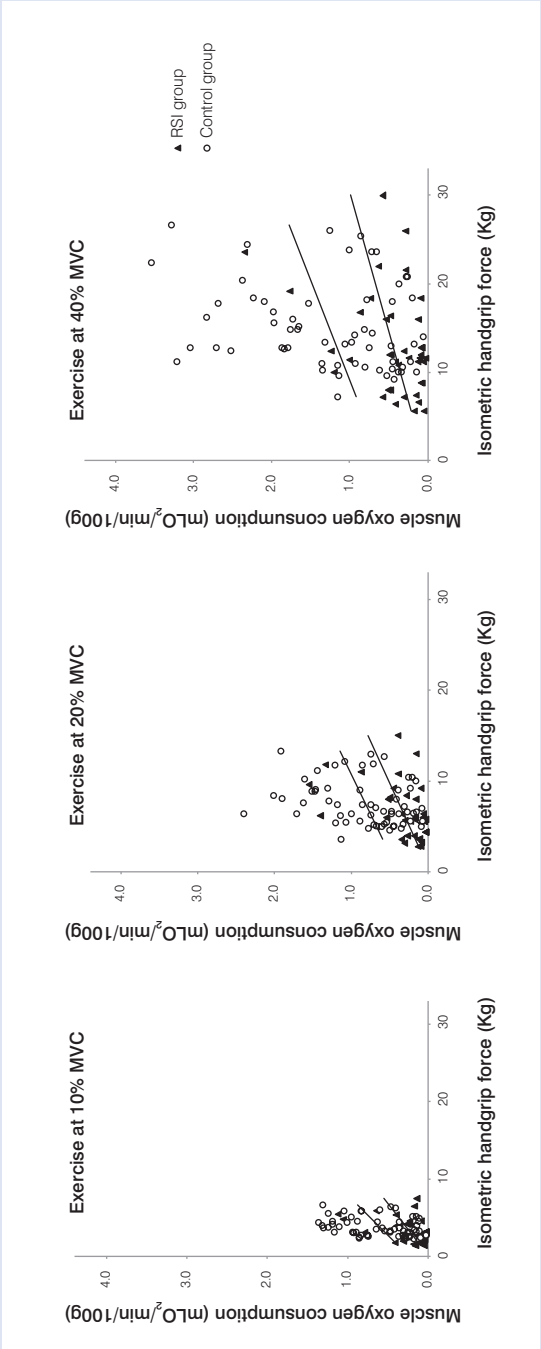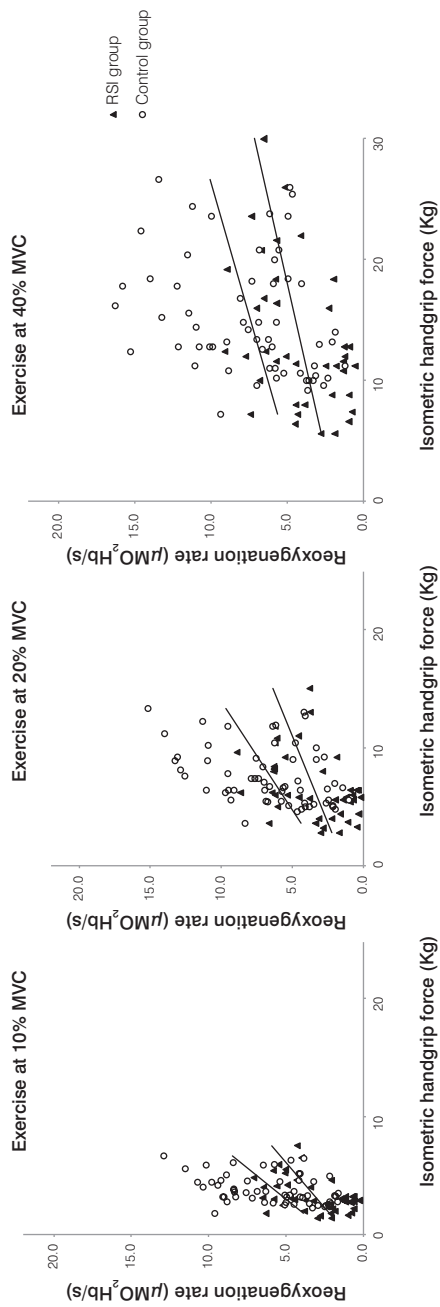**Figure 2** Local muscle oxygen consumption at 10, 20, and 40% MVC

Figure 3 Reoxygenation rate at 10, 20, and 40% MVC

Discussion

The results of this study show that patients with bilateral RSI have a reduced local mVO_2 in both forearms during repetitive hand exercise. In addition, after rhythmic exercise, local mBF remained lower compared with healthy controls. No differences were found between the ReOx in patients with RSI and controls. Although the control participants had a tendency towards a higher ReOx for all intensities, these differences were not statistically significant.

In contrast to other studies on RSI-related symptoms [4, 9], which focused on the circulation of the whole forearm, our study focused on a specific part of the forearm. Using NIRS enabled us to more specifically assess hemodynamic characteristics of the affected tissue; the extensor muscles of the elbow and wrist. To the best of our knowledge, this is the first study that has used NIRS to study local mVO_2 and mBF responses in patients with RSI.

Previous research indicated that the work intensity is associated with local mVO_2 [13]. As the RSI group tended to have a lower maximal voluntary contraction (p=0.07), one might argue that differences in absolute workload between RSI and controls influences our results. Therefore, workload was used as a covariate in the statistical analysis. Using workload as a covariate altered the outcomes, yet the mVO_2 stayed significantly different between both groups.

The results of our study suggest that the mVO_2 and mBF are impaired in the forearms of individuals with RSI. Compared to other literature on vascular function in RSI, these findings are similar to those of Cooke *et al.* (1993) [9]. They investigated the vascular response to contralateral cooling in RSI, reflex sympathetic dystrophy, and control participants, using plethysmography. RSI was defined as chronic upper limb pain occurring in otherwise fit patients performing repetitive tasks, and in whom a specific lesion of joints, tendons or muscle had been confidently excluded. They found the response to contralateral cold challenge in RSI either to follow the normal pattern or to remain unchanged, with a vasodilatation and a reduced vasomotion to be characteristic in this condition. Another study on the vascular function in RSI was conducted by Pritchard *et al.* (1999) [4]. They found a reduced blood flow in the forearm in patients with diffuse forearm pain, assessed by echo-Doppler. However, Pritchard did not include a control group without complaints but instead compared patients with diffuse forearm pain to those with specific complaints. Our finding of a decreased mVO_2 during exercise is in concordance with Pritchard *et al.* (1999), who found the radial artery relatively constricted and failing to dilate with exercise in patients with diffuse forearm pain.

A possible mechanism for a reduced mBF in RSI has been postulated by Valencia [7]. Suggesting that a local static muscle contraction could be a precursor for RSI, in which the mBF is obstructed during muscle tensions higher than 20% of the MVC [18]. However, the level of the contraction at which this obstruction occurs seems to vary among different studies, with different techniques and muscle groups being studied [7].

The Cinderella hypothesis also suggests the vasculature in RSI to be decreased. An overload of low-threshold motor units during long-time occupational static work is assumed [6]. This may lead to a degenerative process, which results in metabolically overloaded and damaged muscle fibers [19]. Rationale for this hypothesis is the finding of chronically affected muscles fibers with mitochondrial changes in patients with RSI [6]. In addition, a reduced mBF was recorded in the exposed muscle before a biopsy was taken [20] and fiber necrosis, signs of muscle regeneration, and higher percentages of the fast-twitch oxidative (type II) fibers in their forearm muscle [21] were found in RSI. These changes may directly or indirectly decrease the vascular function in patients with RSI.

Furthermore, it is known that stress in the workplace and outside work affects the RSI rates [22], and psychological distress seems to be an important predictor of the onset of forearm pain [22, 23]. Stress conditions are strongly related to activity of the sympathetic nervous system and therefore influence the vascular function [6, 10]. The ability of exercising muscles to withdraw sympathetic innervation, commonly referred as functional sympatholysis [24], may be impaired in RSI [5]. Greening *et al.* (2003) reported that patients with non-specific arm pain demonstrate a smaller vasoconstriction compared with controls during sympathetic stimulation. This finding suggests an increased baseline sympathetic activity in these patients. This may partly cause to the lower mVO_2 and mBF found in our study, in which the arterioles of the forearm muscle in individuals with RSI were not sufficiently capable to vasodilate during exercise.

We are well aware that other factors than RSI may contribute to differences in hemodynamic variables between the control group and the group of patients with RSI. Therefore, we checked our data on possible confounders. When identified, factors such as ATT and MVC these were included in the analyses as covariates to adjust for their influence on the outcomes. Some other factors, which have not been assessed, may also alter the data. However, we think that the important known confounders have been accounted for in this study.

Future research is warranted to investigate the relation between RSI symptoms and the vasculature, in order to develop an adequate therapy. Since many rehabilitation therapies concentrate treatments on physical symptoms, such as pain and mobility, the finding of a decreased mVO_2 may have important clinical relevance. In conclusion, patients with bilateral RSI were found to have reduced mVO_2 during exercise and reduced mBF after exercise, indicating a possible underlying impairment in the vasculature.

2

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2

Chapter 3

Bilateral changes in forearm oxygen consumption at rest and after exercise in patients with unilateral repetitive strain injury: a case control study

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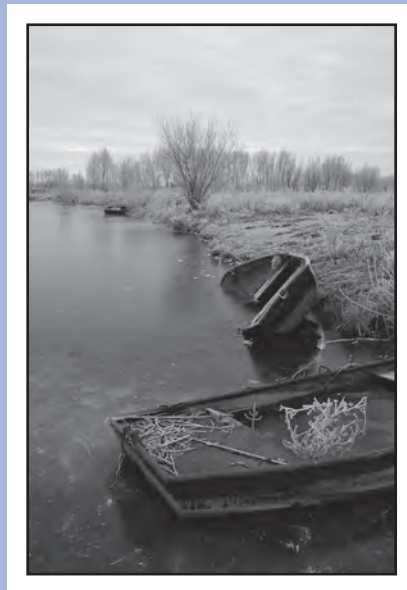
Abstract

Objectives: To investigate whether oxygen consumption and blood flow at rest and after exercise are lower in the affected arm of patients with repetitive strain injury (RSI) compared to controls, and lower in the healthy non-affected forearm within patients with unilateral RSI. **Background:** RSI is considered an upper extremity overuse injury. Despite the local presentation of complaints, RSI may be represented by systemic adaptations. Insight into the pathophysiology of RSI is important to better understand the development of RSI complaints and to develop effective treatment and prevention strategies. **Methods:** Twenty patients with unilateral RSI and 20 gender-matched control subjects participated in this study. Forearm muscle blood flow (mBF) and oxygen consumption (mVO_2) were measured using near-infrared spectroscopy at baseline and immediately after isometric handgrip exercises at 10%, 20%, and 40% of the individual maximal voluntary contraction. **Results:** Unilateral RSI resulted in a lower mVO_2 and mBF in the affected forearm at baseline and lower mVO_2 after incremental handgrip exercises compared to controls ($p<0.05$). In addition, exercise-induced mBF and mVO_2 in the non-affected forearm in patients with RSI was similarly reduced. **Conclusion:** mBF and mVO_2 after exercise are similarly attenuated in the affected and non-affected arm of patients with unilateral RSI. Our findings suggest that, despite the unilateral character in clinical symptoms, RSI demonstrates systemic adaptations in forearm mBF and mVO_2 at rest and after exercise.

Introduction

Repetitive strain injury (RSI) is considered a non-specific neck, shoulder, elbow, forearm, wrist, and/or hand-related overuse pain syndrome caused by sustained low-level static and/or repetitive muscle activity. This type of prolonged, low-intensity, and repetitive muscle activities induces local changes in skeletal muscle morphology and circulation, such as changes in the amount and distribution of muscle type I and IIA fibers [1-5], mitochondrial alterations [2-7], reduced capillarization [1, 4, 8], lower local blood flow [9, 10], inhibited local vascular responses [11], and an increase in anaerobic metabolism [12]. These local changes have been found in muscles affected by RSI and are believed to contribute to the clinical presentation of RSI complaints. Interestingly, RSI is also related to systemic problems such as reduced function of small and large sensory and sympathetic fibers [13]. Moreover, a lower skin temperature was found in both arms of patients with unilateral RSI, which may be related to an underlying systemic change in the regulation of skin blood flow [14-16]. Nonetheless, previous studies have typically examined muscular or vascular adaptations of the affected side only. Recently, we found lower muscle oxygen consumption in forearm muscles affected by RSI [9]. Whether changes in oxygen consumption are also present in the non-affected arm of patients with unilateral RSI has not been investigated and may have important clinical implications. To date, treatment of RSI has often focused on local complaints only; however, if systemic changes are present in patients with RSI, optimal treatment may require a more systemic approach. For example, whole-body exercise training has well-established beneficial and systemic effects on the vasculature [17, 18]. Therefore, the aim of the study was to examine the hypothesis that oxygen consumption and blood flow at rest and immediately after exercise would be lower in the affected arm of patients with RSI compared to controls and lower compared to the healthy non-affected forearm in patients with unilateral RSI. RSI symptoms primarily occur on the dominant side. The comparison of the affected forearm versus the non-affected forearm in patients with RSI may therefore be confounded by dominancy of the forearm. To control for this, we have examined whether there is a systemic difference between the dominant and non-dominant forearm in healthy controls.

Methods

Participants

A total of 20 patients with unilateral, computer work-related pain in at least their elbow/forearm region for at least 6 months were included. All patients were diagnosed with RSI by their family physician. The recruitment of patients with RSI was performed

through physicians or physical therapists treating patients with RSI. In addition, patients with RSI were recruited by advertisement through the Dutch RSI patients' organization. All patients reported unilateral pain symptoms in their elbow/forearm region, which were aggravated by computer-related work. Moreover, all patients reported having pain when performing computer-related activities on the day of testing. Participants performed computer work for at least 2 hours a day. Individuals with RSI were excluded if there was any evidence of vasospastic disease, occlusive atherosclerosis, diabetes mellitus, peripheral neuropathies, history of complex regional pain syndrome type-1, a diagnosed muscular disease other than RSI, or use of medications known to interfere with the vascular system. We also included a gender-matched control group of 20 healthy computer workers without a history of RSI symptoms. The control group was recruited among employees of the Radboud University Nijmegen Medical Centre. The study was approved by the Dutch Central Committee on Research Involving Human Subjects, in accordance with the Declaration of Helsinki (2000) of the World Medical Association. Prior to the study and after a detailed explanation of the study, all participants gave their informed consent.

Experimental procedures

After reporting to our laboratory, particpants completed a standard questionnaire to gain insight into localization, extent, and duration of the RSI symptoms. The affected RSI locations were recorded on a body diagram. All participants in our study reported unilateral RSI symptoms that were at least present around the elbow region. Therefore, location of RSI symptoms matched with the location of the near-infrared spectroscopy (NIRS) assessment of blood flow and oxygen uptake. The daily level of pain was measured on a 10-cm visual analog scale (0 to 10 scale, with 0 as no pain and 10 as maximum pain) and was scored by the patient after an experienced researcher provided verbal information. In addition, age, hours of work per week, and daily computer use were recorded. Forearm circumference and adipose tissue thickness were measured at the same location as placement of the NIRS-optodes. Adipose tissue thickness was measured using a skinfold caliper (Holtain Ltd., Crymmych, UK). Hemoglobin-concentration was determined from a capillary blood sample from the fingertip (HemoCue AB, Ängelholm, Sweden). Maximal voluntary muscle contraction (MVC) was measured using a handgrip dynamometer (JAMAR, hand-held dynamometer, Lafayette Instruments Co, IN). Participants were requested to perform a maximal contraction for 3 seconds, repeated 3 times, with a 1-minute interval between each, using the highest score as MVC. Participants refrained from smoking or drinking coffee for at least 5 hours prior to the experiment to avoid possible influence of caffeine or nicotine on the local vascular bed. For testing, all participants were seated in a comfortable chair.

A pneumatic cuff was placed distally around the upper arm. The hand rested on a handgrip dynamometer, with the upper arm at the level of the heart, and the forearm at an upward angle of 30-degrees on an inclined platform. Our protocol is described in detail elsewhere [9]. Briefly, we started with a 5-minutes rest, followed by 5 venous occlusions (15 seconds, 50 mmHg), separated by a 45-seconds rest to obtain the average local muscle blood flow at rest. Subsequently, arterial occlusion (60 seconds, 250 mmHg) was applied to determine baseline local muscle oxygen consumption. After a rest period of 120 to 240 seconds, participants performed 60 seconds of rhythmic handgrip exercises on a dynamometer (1-second contraction, 1-second relaxation), assisted by a metronome in a consecutive order of 10%, 20%, and 40% of MVC. For visual feedback, the level of workload was indicated on a computer. Immediately after each exercise period, an arterial occlusion was applied (30 seconds, 250 mmHg) to assess the muscle oxygen consumption after exercise. Between exercise sessions, rest periods (120 to 240 seconds) were used to allow blood flow to return to baseline. Finally, 45 seconds after the test at 40% MVC, a venous occlusion was applied (15 seconds, 50 mmHg) to determine post-exercise muscle blood flow.

Measuring hemoglobin oxygenation

NIRS was used to assess regional concentration changes in oxyhemoglobin and deoxyhemoglobin, using a continuous wave near-infrared spectrophotometer (OXYMON; Artinis Medical Systems, Zetten, The Netherlands). This technique is described in detail elsewhere [19-21]. Briefly, this technique is based on the relative transparency of tissue for light in the near-infrared region and on the oxygen-dependent absorption changes of hemoglobin and myoglobin. As one cannot distinguish between myoglobin and hemoglobin, the combined effect of these 2 substances is studied. For convenience, we refer in this article only to hemoglobin. These changes are converted into concentration changes of oxyhemoglobin and deoxyhemoglobin. NIRS measurements in the forearm were obtained by positioning the NIRS optodes over the extensor carpi radialis brevis muscles, 50-mm distal to the lateral epicondyle. This area corresponded with localization of the RSI symptoms in all participants. The distance between the 2 optodes was fixed at 35-mm to allow sufficient penetration of the near-infrared light and to assess the underlying muscle tissue.

Outcomes

The local muscle blood flow was determined at baseline and at the end of the protocol, 45 seconds after release of an arterial cuff that followed the exercise at 40% MVC. The blood flow was measured by inflating a blood-pressure cuff to 50 mmHg. This results in a blockage of the venous outflow, without affecting the

arterial inflow. The muscle blood flow is then measured by analyzing the slope of the total hemoglobin signal, being the sum of the oxyhemoglobin and deoxyhemo-globin (in mL/min/100mL) [20, 21].

The local muscle oxygen consumption was determined at baseline and at 10%, 20%, and 40% of MVC. It was measured by inflating the blood-pressure cuff to 250 mmHg. This blocks the arterial inflow, whereby the forearm fully depends on the available oxygen. The decrease over time of the oxygen concentration signal represents the local muscle oxygen consumption (in mLO_2/min/100g) [20, 21].

The coefficient of variation for measuring forearm blood flow and oxygen consumption are 22.4% and 16.2%, respectively [19]. Therefore, this procedure is considered a reliable and reproducible method for determining blood flow and oxygen consumption at rest, as well as after a broad range of exercise intensities [19-21].

Statistics

Statistical analyses were performed using SPSS Version 16.0 (SPSS Inc, Chicago, IL). All data are reported as mean $\pm$ SD and statistical significance was set at $p \leq 0.05$. On the basis of our previous study that found differences of 0.26 mLO_2/min/100g between individuals with RSI and controls in muscle oxygen consumption at 10% MVC, with a standard deviation of 0.30 mLO_2/min/100g, we included 18 participants per group, based on an alpha of 0.05 and a power of 80%. Repeated-measures 2-way analyses of variance (ANOVA) were used to detect changes in forearm muscle blood flow and oxygen consumption across the various exercise intensities (baseline, 10%, 20%, and 40% MVC) within groups (affected versus non-affected and dominant versus non-dominant arm). Another 2-way mixed-model ANOVA was used to detect changes between groups (affected versus dominant control and non-affected versus non-dominant arm). Because the dominant arm was most often the affected arm in patients with RSI, the comparisons between controls and RSI were performed between the dominant and affected forearm, as well as the non-dominant and non-affected forearm, respectively. In addition, this comparison was done to correct for the potential influence of arm dominancy. A Pearson 2-tailed correlation analysis identified adipose tissue thickness as a potential confounding variable. Therefore, we included adipose tissue thickness as a covariate in the re-peated-measures ANOVA. Because both smoking and age have an impact upon vascular function, these variables were also added as covariates in the analyses. Student *t*-tests were used to calculate differences in adipose tissue thickness, maximal voluntary contraction, and forearm circumference between both arms (paired) or between groups (unpaired).

Results

No differences were found between the patients with unilateral RSI and their gender-matched controls for daily computer use, hemoglobin concentration, and working hours per week. Comparison between the dominant and non-dominant arm of controls showed a higher MVC on the dominant side (p=0.002). Comparison within subjects showed a larger circumference of the forearm for both the dominant control and affected RSI arm (p=0.002 and p=0.001, respectively). Comparison between participants showed no differences in forearm circumference, adipose tissue thickness, or MVC (p>0.05). The average duration of the RSI symptoms was 2 years and 5 months. The mean $\pm$ SD pain level in the RSI group was 3.6 $\pm$ 1.7 cm on the visual analog scale (Table 1).

Local muscle oxygen consumption

At baseline, muscle oxygen consumption in the affected arm of the individuals with RSI was significantly lower compared to the dominant arm of controls (p<0.01). We found a significant exercise-by-group interaction effect (p<0.001) for increase in oxygen consumption during the 3 stages of incremental handgrip, indicating a lower increase in oxygen consumption after exercise in patients with RSI compared to their gender-matched controls (Figure 1). No difference in baseline oxygen consumption was observed between the affected and non-affected arm of patients with unilateral RSI (Table 2). We found no significant exercise-by-arm interaction effect (p=0.68) for oxygen consumption after incremental exercise between the affected and non-affected forearm in patients with unilateral RSI. There was also no main effect for arm (p=0.99), indicating a similar increase in oxygen consumption after exercise in both arms. Similarly, for the healthy controls, no differences in oxygen consumption were found at baseline and during the incremental exercise protocol between forearms (ANOVA, exercise by arm, p=0.44 and arm main effect: p=0.80).

Local muscle blood flow

At baseline, muscle blood flow in the affected arm of the individuals with RSI was significantly lower compared to that in the dominant arm of the individuals in the control group (p=0.03). A significant time-by-group interaction (p=0.04) revealed that the increase in blood flow after the 3 levels of incremental exercise was significantly lower in patients with RSI compared to controls (Figure 2). No differences in baseline blood flow were observed between the affected and non-affected arm of patients with unilateral RSI (Table 2). No significant time-by-arm interaction (p=0.47) was found for the increase in blood flow after exercise between the affected and non-affected forearm in patients with unilateral RSI.

Table 1 Participant characteristics

	RSI group (n = 20)			Control group (n = 20)		
						p-value
Age (years)	40.5 ± 11.0			35.5 ± 13.2		.20
Gender (male/female) (n)	6/14			6/14		
Affected side (dominant/non-dominant) (n)	19/1					
Pain level (VAS) (0-10 cm)	3.6 ± 1.7					
Duration of RSI symptoms (months)	28.9 ± 35.1					
Daily computer use (hours)	5.4 ± 2.1			4.8 ± 1.5		.24
Work per week (hours)	30.7 ± 8.2			35.7 ± 8.6		.35
Smoking history (n)	7			3		
Hemoglobin concentration (mmol/L)	8.4 ± 0.9			8.1 ± 0.7		.85
	affected	non-affected	p-value*	dominant	non-dominant	p-value*
Forearm circumference (cm)	25.2± 2.2	24.9 ± 2.1	.001†	24.9 ± 1.8	24.5 ± 1.8	.002†
Adipose tissue thickness (mm)	6.5 ± 3.0	6.6 ± 3.1	.51	5.7 ± 2.5	6.4 ± 3.2	.08
Maximal voluntary muscle contraction (kg)	34.2 ± 12.3	34.4 ± 12.4	.84	35.4 ± 11.4	32.1 ± 11.0	.002†

Values are represented as mean ± SD. RSI indicates repetitive strain injury; VAS, visual analog scale. *p-value refers to within-group comparisons. †Significant differences from controls (p<0.05). We found no differences between groups for forearm circumference, adipose tissue thickness, and maximal voluntary muscle contraction for the affected/dominant (p=0.71, 0.38, and 0.77, respectively) and non-affected/non-dominant side (p=0.59, 0.86, and 0.53, respectively).

Table 2 Muscle blood flow and oxygen consumption for the affected and non-affected forearm of patients with unilateral RSI. Values are represented as mean (SD)

	RSI affected mean ± SD	RSI non-affected mean ± SD	Control dominant mean ± SD	Control non-dominant mean ± SD
Muscle blood flow (mL/min/100mL)				
Rest	0.83 ± 0.39	0.96 ± 0.53	1.38 ± 0.89*	1.22 ± 0.63
After exercise	1.64 ± 0.80	1.62 ± 0.80	3.04 ± 2.24*	2.58 ± 1.27††
Muscle oxygen consumption (mLO$_2$/min/100g)				
Rest	0.08 ± 0.04	0.08 ± 0.03	0.15 ± 0.07**	0.09 ± 0.04
After exercise at 10% MVC	0.27 ± 0.22	0.31 ± 0.20	0.60 ± 0.37**	0.59 ± 0.46†
After exercise at 20% MVC	0.37 ± 0.27	0.37 ± 0.27	0.74 ± 0.52**	0.81 ± 0.53††
After exercise at 40% MVC	0.55 ± 0.28	0.50 ± 0.38	1.34 ± 0.91**	1.11 ± 0.93††

Values are represented as mean ± SD. RSI indicates repetitive strain injury; MVC, maximal voluntary contraction. *$p<0.05$ and **$p<0.01$ for comparisons between the side affected by RSI and the dominant side of control participants. †$p<0.05$ and ††$p<0.01$ for comparisons between the side not affected by RSI and the non-dominant arm of control participants. No differences in oxygen consumption and blood flow were found between the affected and non-affected arms of the RSI group and between the dominant and non-dominant arm of the control group.

There was also no significant main effect for arm (p=0.82). Also, in healthy controls, there was no significant time-by-arm interaction (p=0.59) between the dominant and non-dominant forearm in controls for the increase in blood flow after exercise. There was also no significant main effect for arm (p=0.44).

Figure 1 Forearm muscle oxygen consumption at rest and after incremental handgrip exercise at 10, 20, and 40% of maximal voluntary contraction for patients with RSI (black line) and age matched controls (gray line). Error bars represent SE
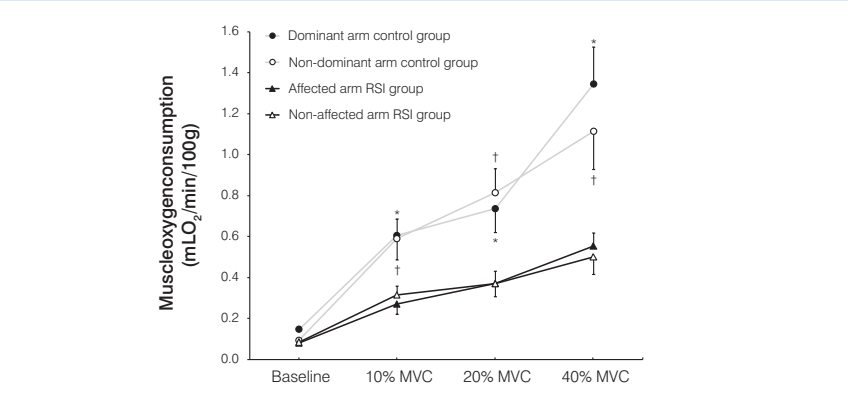
Post hoc significantly different between the affected RSI arm and dominant arm in controls (* at p<0.01) and between the non-affected RSI arm and non-dominant arm in controls († at p<0.01).

Figure 2 Forearm muscle blood flow at rest and after incremental handgrip exercise in patients with unilateral RSI (black line) and controls (gray line). Error bars represent SE
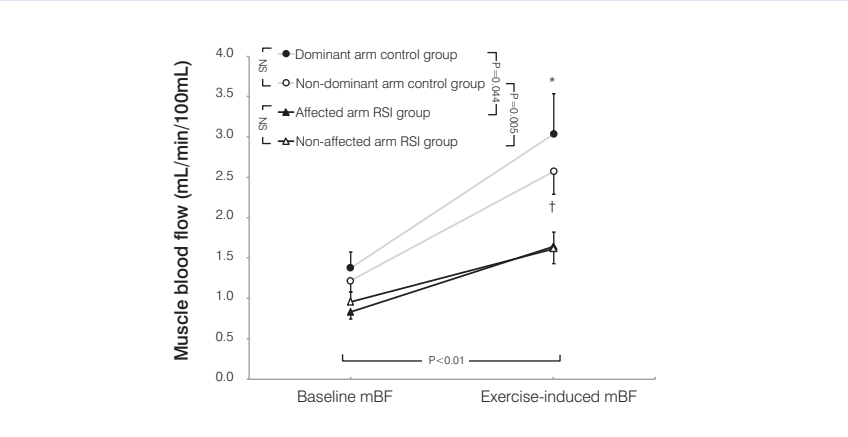
Post hoc significantly different between the affected RSI arm and dominant arm in controls (* at p<0.01) and between the non-affected RSI arm and non-dominant arm in controls († at p<0.01).

Discussion

The results of our study indicate that patients with unilateral RSI demonstrate a lower oxygen consumption and blood flow at baseline, as well as after incremental handgrip exercise in the affected forearm, compared to healthy controls. The most innovative finding of this study, however, is that the non-affected forearm, where no symptoms of RSI were experienced, showed a similarly decreased oxygen consumption and blood flow after exercise compared with the affected forearm of patients with unilateral RSI. This latter finding suggests that the impaired muscle oxygenation and blood flow in patients with RSI is not limited to the affected forearm in unilateral RSI but are present in both forearms. Whether this predisposes individuals to the development of RSI or bilateral RSI, or it is a consequence of unilateral RSI, remains to be determined.

A main finding of this study is that local oxygen consumption is attenuated in both arms after incremental levels of handgrip exercise in patients with unilateral RSI. Also, baseline and post-exercise blood flow in the affected forearm are significantly lower than that of healthy gender-matched controls. Our finding of a significant interaction effect indicates that the exercise-associated increase in oxygen consumption and blood flow is attenuated in patients with RSI. This indicates that, when patients with RSI and controls perform handgrip exercise at the same relative intensity, lower blood flow and oxygen consumption are present in patients with RSI. The finding of lower oxygen consumption and blood flow levels reinforces previous of localized adaptations in musculature and vasculature in the affected forearm of patients with RSI [1-6, 10-12], including lower oxygen consumption after exercise [9]. Oxygen consumption and blood flow levels were studied in the extensor muscles of the forearm because this area is commonly affected in patients with computer work-related RSI complaints. It is hypothesized that the sustained low-intensity activities of the forearm extensor muscles during computer work cause muscle cell damage and contribute to the development of RSI complaints [22]. Our findings suggest that impaired blood flow and oxygen consumption may contribute to the development of RSI symptoms in the elbow region in these individuals.

A potential explanation for the lower oxygen consumption in the affected forearm at baseline and after exercise may be related to the presence of an impaired exercise-induced increase in blood flow in the forearm of patients with RSI. Such impaired exercise-induced forearm blood flow and decreased levels of oxygen uptake have been reported in other clinical populations [23-26]. Another explanation for lower oxygen consumption at baseline and after exercise may be related to the presence of muscle damage. Muscle biopsy studies revealed the occurrence of "moth-eaten"

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fibers, a marker for muscle damage [1, 4, 8] in forearm muscles in patients with chronic epicondylitis [5] and in the trapezius muscle of individuals with trapezius myalgia [1-4, 7]. Future studies should further examine the underlying mechanisms for the lower baseline and exercise-induced forearm oxygen consumption in patients with RSI.

Muscle oxygen consumption is directly related to the amount of work performed by the forearm musculature [20, 21, 27]. Therefore, a potential explanation for the lower oxygen consumption and blood flow in patients with RSI may be related to the lower workload in patients with RSI. However, no differences were found for MVC between the affected forearm in patients with RSI and the dominant forearm in controls (p=0.77) nor between both forearms within patients with RSI (p=0.53). Therefore, our results cannot be explained by differences in muscle force between arms or between groups.

Our study adds the important novel finding that oxygen consumption and blood flow after incremental handgrip exercise is similarly impaired in both arms in patients with unilateral RSI. This suggests that impaired oxygen consumption and blood flow after exercise are relate to systemic changes rather than localized adaptations in the affected region alone. This finding of systemic changes in RSI raises an important question related to the mechanism of RSI. Studies have reported impaired vascular responses after typing in the affected arm of patients with RSI (evidenced by a lower hand temperature) [14, 16] and after a brief application of an ice pack to the C7 area of the cervical spine [13]. Although no direct evidence was provided, these changes were hypothesized to relate to inappropriate reflex vasodilatation, possibly via the sympathetic nervous system.

Another hypothesis is related to an impaired ability to relax muscles in patients with RSI [28-30]. Veiersted *et al.* (1993) found that healthy women with lower rates of brief unconscious interruptions in muscle activity, monitored with electromyography, were prone to develop RSI symptoms over time [30]. The finding suggests that continuous muscle activation during muscle tasks is a predisposing factor for the development of RSI symptoms. Accordingly, patients with RSI in our study might not have fully relaxed the forearm muscles between repetitive handgrip exercises, leading to vascular blockade. Muscle circulation is obstructed at a relatively low exercise level of 10% MVC [31]. Therefore, continuous muscle tensions may impair muscle blood flow and thereby cause a decrease in oxygen consumption [32]. However, whether poor muscle relaxation in RSI explains such high differences in oxygen consumption found in our study remains disputable.

Clinical relevance

Our novel findings suggest the presence of systemic changes in the vasculature in patients with unilateral RSI. Whether these changes are indicative of a predisposing factor for RSI or represent a direct consequence of RSI cannot be answered by the results of our study. The fact that unilateral RSI is accompanied by bilateral changes in oxygen consumption and blood flow suggests a progression to a bilateral condition, and systemic changes could be an indication that a person with unilateral symptoms may progress to bilateral symptoms in the future. These findings suggest that the management of RSI symptoms should not focus on the affected region only. For example, treatment strategies, such as whole-body exercise training, represent a well-established and potent stimulus to induce systemic improvements in the vasculature [17, 18]. Exercise training may therefore be recommended in addition to current treatment guidelines to improve the vascular impairments found in patients with RSI.

Limitations

Our study benefits from inclusion of a large group of patients, well-controlled experiments using a within-subject design (allowing for comparison between the affected and non-affected forearm) and measurements performed at baseline as well as after physical activity. A potential limitation is that RSI is a nonspecific diagnosis. We tried to include a homogenous group of patients by focusing on RSI symptoms related to computer-work only. Other pathologies often associated with RSI, like lateral epicondylitis, were not included in our study. Therefore, our results apply to patients with nonspecific RSI-related arm pain occurring or sustained by computer-work activities only. Other factors, such as high perceived work stress, non-work-related work stress and high job demands [33], and personal characteristics such as psycho-neuroticism and neurotic perfectionism [34], are also suggested to play a role in the development or continuation of RSI symptoms. However, these psychological factors were not taken into account in our study.

Conclusion

Patients with RSI demonstrate impaired oxygen consumption and blood flow in the affected forearm at rest and after incremental levels of handgrip exercise. These pathophysiological impairments are present to a similar extend in the symptom-free, non-affected forearm. This finding suggests that, despite the unilateral character in clinical symptoms, patients with unilateral RSI demonstrate a similar impairment in forearm oxygen consumption and blood flow in both forearms. Because changes in muscle circulation in RSI are not exclusively limited to forearm muscles affected

by RSI, the implications for clinical management of RSI are that it should not be exclusively targeted to the local structures.

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Chapter 4

No impaired hemoglobin oxygenation in forearm muscles of patients with chronic CRPS-1

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Abstract

Objectives: The aim of the present study was to investigate whether muscle loading in chronic complex regional pain syndrome type-1 (CRPS-1) patients is associated with impairments in muscle circulation of the forearm of the affected limb. **Background:** Physiotherapy is considered an important treatment option in patients with upper limb CRPS-1. In case of chronic CRPS-1, exercise therapy of the affected limb forms an important part of the physiotherapeutic program. **Methods:** Thirty patients with chronic CRPS-1 unilaterally affecting their upper limbs, and 30 age-and gender-matched control participants were included in this study. Local muscle blood flow and hemoglobin oxygenation were measured by near infrared spectroscopy within the muscles of the forearm at rest, after 1-minute isometric handgrip exercises, and after arterial occlusion. Main outcome parameters were: local muscle blood flow (mBF), oxygen consumption (mVO_2), and post-ischemic reoxygenation (ReOx). **Results:** We found no differences in baseline mBF, mVO_2, and ReOx between the affected CRPS-1, unaffected CRPS-1, and control arms. After exercise, mVO_2 of the affected CRPS-1 arms was not different from the clinically unaffected CRPS-1 arms. Furthermore, in comparison with the control arms, unaffected CRPS-1 arms showed no difference in mVO_2 or ReOx (all $p > 0.05$). **Conclusion:** Muscle loading does not seems to be related to impairments in muscle oxygen uptake in forearm muscles of upper limbs affected by chronic CRPS-1. Our results suggest that exercise therapy can be safely used in physio-therapeutic training programs for chronic CRPS-1 of the upper limb.

Introduction

Complex regional pain syndrome type 1 (CRPS-1) forms a typical clinical picture of impairments in sensory, motor, and autonomic functions after a trauma without obvious nerve damage [1]. Physiotherapeutic treatment is considered an important element in the treatment of patients with upper-limb CRPS-1 [2-4]. In case of chronic CRPS-1, most CRPS-1 patients will report pain during physiotherapy. Although this is accepted as a limiting factor in acute CRPS-1, in chronic CRPS-1 there is an increasing tendency to ignore the occurrence of pain as a barrier for exercising the affected limb [5, 6]. It is likely that increased pain during muscle loading in chronic CRPS-1 patients is a result of functional changes in central nervous system [7, 8], and not a sign of metabolic impairment (eg, reduced blood flow or hypoxia) in the muscles concerned. Therefore, we investigated whether muscle loading in chronic CRPS-1 patients is associated with signs of muscle hypoxia. To demonstrate possible impairments in muscle circulation, we measured forearm oxygen consumption and blood flow by near-infrared spectroscopy (NIRS). NIRS has shown to be a sensitive tool to detect differences in absorption spectra for oxygenated and deoxygenated forms of hemoglobin (Hb) in muscles at rest and during exercise [9-11]. Abnormal oxygenation owing to insufficient oxygen uptake into muscle cells has been demonstrated using NIRS in patients with mitochondrial myopathies [12-14] and by our research group in patients with repetitive strain injury [15]. To date, studies of blood circulation in CRPS-1 have focused mainly on skin blood flow [16-21] or muscle energy phosphate metabolism [22]. Interestingly, Koban *et al*., (2003) found tissue hypoxia in the skin of patients with CRPS-1 [18]. Whether this is the case for muscle tissue has not been investigated to date. Therefore, the aim of our study was to investigate whether signs of muscle hypoxia are present in muscles of limbs affected by CRPS-1 using NIRS. To this end, we investigated whether Hb oxygenation is disturbed in forearm muscles of patients with chronic CRPS-1 at rest, after exercise, and after arterial occlusion.

Methods

Participants
The study was approved by the Dutch Central Committee on Research Involving Human Subjects, in accordance with the Declaration of Helsinki (2000) of the World Medical Association. All participants signed an informed consent form after full explanation of the purpose, nature and risk of all procedures.

Participants were recruited by advertisement in the Newsletter of the Dutch CRPS-1 patients organization. In addition, CRPS-1 members living near our University Hospital Centre were sent an information folder attached to the Newsletter. The information folder described the purpose of the research, and readers were asked to participate in the study. Patients willing to participate were questioned by telephone on their CRPS-1 symptoms, on the initiating event, and whether the CRPS-1 diagnosis was confirmed by a physician. Inclusion criteria were: CRPS-1 symptoms for longer than 6 months, meeting the Bruehl criteria for CRPS-1 [23], CRPS-1 symptoms located unilaterally in their upper arm or wrist or hand, and minimal age of 18 years. Patients were excluded if there was any evidence of vasospastic disease, occlusive athero-sclerosis, diabetes mellitus, peripheral neuropathies, or a history of work-related upper limb disease. Patients were also asked to invite a friend or family member of similar gender and comparable age ($\pm$ 5 years) to serve as a control participant. When the patient was not accompanied by a control participant, or the control participant did not meet the inclusion criteria, the researcher recruited a suitable control participant among employees of the University Medical Centre. Finally, all participants had to refrain from smoking or drinking coffee for at least 5 hours prior to the experiment, to avoid possible influence of caffeine or nicotine on the local vascular bed.

CRPS-1 measures
Hyperalgesia or allodynia were objectified by using light touch of a paint brush. Skin temperature asymmetry (> 0.5-degree C) was measured by an infrared temperature scanner on dorsal and palmar sites of the hand, and compared with a measurement at the forehead (between both eyes) (DermaTemp, Infrared surface skin scanner, Exergen corporation, MA). Pain intensity was measured daily at the same time for 1 week on a 10-cm Visual Analog Scale (0 cm = no pain; 10 cm = extreme pain). Presence of oedema, sweating, trophic changes (hair, nail, and skin), and motor dysfunction (tremor and dystonia) were assessed clinically. Presence of a decreased range of motion was also assessed clinically, whereas presence of hand muscle weakness (> 10% side difference in maximal voluntary muscle contraction) was tested with a hand-held dynamometer (JAMAR, hand-held dynamometer, Lafayette Instruments Co, IN).

Activity and participation
The Radboud Skills Questionnaire (RASQ) measures limitations in self-care, domestic life, and participation restriction in community, social and civic life, work and employment, using a numeric score (1 = normal, 5 = not able to do). The RASQ has been validated for patients with CRPS [24]. To measure the health-related quality of life, the Dutch version of the SF-36 was used [25].

Physical characteristics

Maximal voluntary muscle contraction (MVC) was determined by the person's highest value of 3 exercises with 1-minute intervals on the hand-held dynamometer. Hemoglobin (Hb)-concentration was measured from a fingertip blood sample using a spectrophotometer (HemoCue B-Hemoglobin, HemoCue AB, Ängelholm, Sweden). The circumference of the forearm and the adipose tissue thickness (ATT) were measured at the NIRS-optode location (location at which the 2-infrared light cables are attached to the forearm) and positioned on top of the extensor carpi radialis brevis muscle. ATT was measured using a skin fold caliper (Harpenden skin fold caliper, model: HSK-BI, Holtain Ltd., Crymych, UK).

Near-infrared spectroscopy

Near Infrared Spectroscopy (NIRS) is a noninvasive, continuous, and direct method based on the relative tissue transparency for light in the near-infrared region and on the oxygen-dependent absorption changes of hemoglobin (Hb) and myoglobin (Mb). The use of a continuous-wave near-infrared spectrophotometer (Oxymon, Artinis Medical Systems, Zetten, the Netherlands), generating light at 901, 848 and 770 nm, permits differentiation between oxyhemoglobin/Mb and deoxyhemoglobin/Mb (O_2Hb/O_2Mb and HHb/HMb, respectively). Because of identical spectral characteristics, it is not possible to distinguish between Hb and Mb. NIRS has shown to be a sensitive tool to quantify differences in oxygen consumption and forearm blood flow at rest as well as during exercise [9-11]. The NIRS measurements were performed on top of the extensor carpi radialis brevis muscles of the forearm with an inter-optode distance of 35 mm. The near-infrared light was transmitted from the source to the tissue and back to the detector by flexible fiber optic bundles called optodes. The absorption changes at the discrete wavelengths were converted into concentration changes of O_2Hb and HHb by using a modified Lambert-Beer law, in which a differential path-length factor of 4.0 was used to correct for scattering of photons in the tissue. In this way, quantitative values for oxygen consumption and blood flow were calculated. The sum of O_2Hb and HHb concentrations was used to calculate the total amount of hemoglobin (tHb) in the tissue. The change in tHb during a venous occlusion was used to calculate the muscle blood flow (mBF), the decrease in O_2Hb during arterial occlusion was used to calculate the oxygen consumption, and the rate of increase in O_2Hb after arterial cuff release was used to calculate the post-ischemic reoxygenation rate (ReOx).

Main outcome measures

The local muscle blood flow (mBF) was determined during the last 8 seconds of a 15-seconds venous occlusion (50 mmHg), in which the venous outflow was blocked and the increase in tHb is directly related to arterial inflow [9, 14]. Concentration

changes of tHb were expressed in mL/min/100mL, using the individual Hb-concentration (Hb in mmol/L). The local muscle oxygen consumption (mVO_2) was determined during the first 8 seconds of an arterial occlusion (230 mmHg), in which the arterial inflow was blocked and the muscle fully depended on the available oxygen [9, 14, 26]. Concentration changes of mVO_2 were expressed in mLO_2/min/100g. The post-ischemic reoxygenation rate (ReOx) was determined during the initial 3 seconds immediately after releasing the cuff of an arterial occlusion, in which the blood volume rapidly increased, resulting in a fresh pool of O_2Hb and a quick washout of HHb [26, 27]. Concentration changes of ReOx were expressed in $\mu MO_2Hb/s$.

NIRS procedure

The participants were seated in a comfortable office chair. The participant's hand rested on a handgrip dynamometer with the forearm on a 30-degree inclining platform at heart level, to avoid venous pooling of the blood. The participant's MVC was determined before the test and a pneumatic cuff was placed distally around the upper arm. After a 5-minute rest period, the experiment started with 5 venous occlusions (50 mmHg) to obtain the average baseline local mBF. Each venous occlusion lasted for 15 seconds with 45-seconds recovery intervals. The experiment continued with an arterial occlusion for 60 seconds to obtain the baseline local mVO_2. Immediately after deflating the pneumatic cuff, the ReOx was obtained. After a rest period of 3 to 5 minutes, the blood flow returned to the previous baseline value, and participants performed rhythmic isometric handgrip exercises on a handgrip dynamometer (1-second contraction, 1-second relaxation) at 40% of the MVC for 1 minute. For feedback to the participants, the squeezing exercise was assisted by a metronome and the level of the muscle contraction was visible on a display. Immediately after this 1-minute exercise, an arterial occlusion was given for 30 seconds, to obtain the mVO_2 after exercise. Directly after deflating the pneumatic cuff, the ReOx after exercise was obtained.

Exercise loads

Exercise levels of 40% MVC were chosen to imitate workloads of normal daily use. Both the affected CRPS-1 and unaffected CRPS-1 arm performed exercises at 40% MVC of the affected arm to compare both arms. To compare the unaffected CRPS-1 with the control arm, both arms performed loading exercises at 40% of the participant's own MVC. To prevent differences related to arm dominance, the arm dominance of the patient was matched with the control arm. For example, when the affected CRPS-1 arm concerned the dominant arm, the dominant arm of the matched control participant was tested likewise.

Statistics

A Shapiro-Wilk test was used to test demographic variables for normality (p<0.05). The non-parametric Mann-Whitney *U* test was used if demographic variables failed the normality test. Otherwise, the Student independent *t*-test was used. A general linear mixed model was used to examine differences in mBF, mVO$_2$, and ReOx between the affected CRPS-1, unaffected CRPS-1, and control arm. Spearman correlations were used to identify confounding variables. When present (p<0.05), these variables were included in the analysis as covariates. The level of statistical significance was set at p<0.05.

Results

Participants

All patients who underwent the NIRS measurement fulfilled the Bruehl criteria for CRPS-1 [23]. Evidence for Bruehl criteria are displayed in table 2. Thirty patients with CRPS-1 (24 females and 6 males) with a mean age of 52.0 years (range: 25 to 67 years) participated in the study. The average mean Visual Analog Scale pain score was 5.4 (range: 0.5 to 9.5 cm) and median symptom duration 73.5 months (range: 7 to 240 months). The control group consisted of 30 healthy control participants (24 females and 6 males) with a mean age of 50.4 years (range: 25 to 67 years). In 23 cases, the control participant was selected by the patient, and accompanied the patient during their hospital visit. In the other 7 cases, the control participant was selected by the researcher (Figure 1). Comparison between groups showed no significant differences for age, Hb concentration, adipose tissue thickness, forearm circumference, and skin temperature at the forehead and NIRS location (Table 1).

Activity and participation

Our group of patients scored statistically significantly lower on all six dimensions of the RASQ. In addition, the general health-related quality of life (SF-36 questionnaire) was scored statistically significantly lower at the physical and the mental health-related questions (Table 1).

Identification of confounding variables

Spearman correlation showed ATT and MVC to be correlated with the outcome measures mVO$_2$, ReOx, or mBF (p<0.05). Therefore, ATT and MVC were entered as covariates into the analyses. Other variables were not statistically significantly correlated to mBF, mVO$_2$, or ReOx.

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Figure 1 Trail flow chart

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│ Patients recruited among members│   │ Patients recruited by additional │
│ of Dutch CRPS-1 patients         │   │ information folder attached to   │
│ Organization (n = 4000)          │   │ newsletter (n = 270)             │
└─────────────────────────────────┘   └─────────────────────────────────┘
          Response = 1.4 %                     Response = 5.2 %

              ┌──────────────────────────────────────────┐
              │ Patients willing to participate in study  │
              │ (n = 70)                                  │
              └──────────────────────────────────────────┘

┌──────────────────────────────────┐
│ Exclusion after telephone         │
│ interview:                        │
│ - Not meeting Bruehl criteria     │
│   (n = 4)                         │
│ - Wrong age or CRPS-1             │
│   localization (n = 31)           │
└──────────────────────────────────┘

        ┌───────────────────────────────┐      ┌──────────────────────────┐
        │ Patients included in study     │ ←──→ │ Controls included in      │
        │ (n = 35)                       │      │ study (n = 30)            │
        └───────────────────────────────┘      │ Selected by patient       │
                                               │ (n = 23)                  │
┌──────────────────────────────────┐           │ Selected by researcher    │
│ Exclusion during hospital visit:  │           │ (n = 7)                   │
│ - Sympathectomy (n = 1)           │           └──────────────────────────┘
│ - Not meeting Bruehl criteria     │
│   (n = 3)                         │
│ - Technical problem with NIRS     │
│   (n = 1)                         │
└──────────────────────────────────┘

        ┌──────────────────────┐              ┌──────────────────────┐
        │ Data analyzed (n = 30)│              │ Data analyzed (n = 30)│
        └──────────────────────┘              └──────────────────────┘
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Baseline muscle blood flow, oxygen consumption and post-ischemic reoxygenation

Table 3 describes the baseline mBF, mVO_2 and ReOx of patients with CRPS-1 and controls. The general linear mixed model showed no statistically significant differences in baseline mBF, mVO_2, and ReOx between the affected CRPS-1, unaffected CRPS-1, and control arms.

Oxygen consumption and ReOx in CRPS-1

In table 4, the Hb oxygenation measured after loading exercises and cuff release are presented for the affected and unaffected CRPS-1. Both CRPS-1 forearms performed loading exercises at 40% MVC of the affected arm. After exercise, no statistically significant differences were found in local mVO_2 and ReOx between the affected and unaffected CRPS-1 arms. In addition, the mVO_2 of the affected forearm increased with approximately 300% from baseline to loading exercises. The increase was comparable to the increase in oxygen consumption of the clinically unaffected side.

Table 1 Participant characteristics

		CRPS-1 group (n = 30)			Control group (n = 30)	
		Affected	Unaffected	p-value*	Control arm	p-value†
Age (years)		52.0 ± 10.7			50.4 ± 10.9	.46
Gender (n)	Male	6			6	
	Female	24			24	
Pain intensity (VAS) (0-10 cm)		5.4 ± 2.6			-	-
Duration of symptoms (months)		73.5 ± 58.2			-	-
Hemoglobine (Hb) concentration		8.3 ± 0.8			8.2 ± 0.8	.68
Skin temperature forehead (°C)		33.5 ± 0.9			33.9 ± 0.7	.09
Skin temperature palmar hand (°C)		31.8 ± 2.1	32.0 ± 1.8	.77	32.9 ± 1.3	.04‡
Skin temperature dorsal hand (°C)		30.9 ± 2.2	31.0 ± 2.1	.49	32.3 ± 1.5	.02‡
Skin temperature NIRS location (°C)		32.0 ± 1.1	32.3 ± 1.0	.19	32.1 ± 1.1	.49
Adipose tissue thickness (mm)		9.8 ± 4.3	10.1 ± 4.5	.85	10.2 ± 3.9	.83
Circumference forearm (cm)		26.6 ± 2.4	26.7 ± 2.3	.37	26.9 ± 2.4	.79
Maximal voluntary contraction (Kg)		15.4 ± 11.4	32.3 ± 8.9	<.001‡	35.7 ± 9.7	.14
Level of disability (Radboud Skills Questionnaire) *Numeric score (1, normal; 5, not able to do)*						
Personal care		2.1 ± 0.8			1.0 ± 0.0	<.001‡
Housekeeping		3.0 ± 1.0			1.0 ± 0.0	<.001‡

4

Table 1 Continued

	CRPS-1 group (n = 30)		p-value*	Control group (n = 30)	p-value†
	Affected	Unaffected		Control arm	
Recreational activities		3.1 ± 1.1		1.1 ± 0.2	<.001‡
Social activities		2.0 ± 1.1		1.0 ± 0.1	<.001‡
Work		3.1 ± 1.5		1.0 ± 0.0	<.001‡
Other activities		2.6 ± 0.9		1.0 ± 0.1	<.001‡
Health-related quality of life (SF-36)					
Physical component summary (0% - 100% quality of life)					
Physical functioning		53.5 ± 27.2		92.6 ± 10.9	<.001‡
Role Physical		33.9 ± 37.9		94.0 ± 20.8	<.001‡
Bodily pain		49.8 ± 28.9		95.2 ± 9.0	<.001‡
General Health		56.5 ± 20.3		77.2 ± 16.6	<.001‡
Mental component summary (0% - 100% quality of life)					
Vitality		57.9 ± 18.4		77.8 ± 15.7	<.001‡
Social functioning		67.7 ± 23.0		94.0 ± 9.2	<.001‡
Role emotional		75.3 ± 37.5		96.6 ± 18.6	.001‡
Mental health		75.9 ± 17.0		84.1 ± 13.7	.04‡

Values are represented as mean ± SD. CRPS-1 indicates complex regional pain syndrome type-1; NIRS, near-infrared spectroscopy; VAS, Visual Analog Scale. *p-value of analysis between affected and unaffected CRPS-1 arm. †p-value of analysis between unaffected CRPS-1 and control arm. ‡Statistical significant (p<0.05).

Table 2 Evidence for Bruehl criteria

Category		Tested	Outcome
1a) Presence of an initiating noxious event or a cause of immobilization		History	30/30
1b) Continuing spontaneous pain		History	30/30
2) Sensory	Hyperalgesia or allodynia	Paint brush	27/30
3) Vasomotor	Temperature asymmetry*	Infrared scanner	21/30
	Skin colour changes	Clinically	14/30
	Skin colour asymmetry	Clinically	10/30
4) Sudomotor/ oedema	Oedema	Clinically	6/30
	Sweating chances	Clinically	12/30
	Sweating asymmetry	Clinically	13/30
5) Motor/ trophic	Decreased range of motion	Clinically	27/30
	Motor dysfunction (weakness)†	Dynamometer	28/30
	Motor dysfunction (tremor)	Clinically	10/30
	Motor dysfunction (dystonia)	Clinically	0/30
	Trophic changes (hair)	Clinically	4/30
	Trophic changes (nail)	Clinically	14/30
	Trophic changes (skin)	Clinically	1/30

*Defined as more than 0.5-degree C in dorsal hand temperature difference, measured with infrared temperature scanner (DermaTemp, Exergen Corp, MA). †Defined as more than 10% difference in maximal voluntary muscle contraction in the hand, measured with the hand-held dynamometer (JAMAR, hand-held dynamometer, Lafayette Instruments Co, IN).

Oxygen consumption and ReOx in CRPS-1 and controls

Table 5 describes the Hb oxygenation measured after loading exercises and cuff release for the unaffected CRPS-1 and control arm. The unaffected CRPS-1 and control arm performed loading exercises at 40% of their MVC. After exercise, no statistically significant differences were found in local mVO_2 and ReOx between the unaffected CRPS-1 and control arm. Furthermore, the increase in mVO_2 and ReOx from baseline to loading exercises was also not different for both arms.

Table 3 Baseline local muscle blood flow (mBF), oxygen consumption (mVO$_2$), and post-ischemic reoxygenation (ReOx) of the affected CRPS-1, unaffected CRPS-1, and matched control arm

	CRPS-1 Affected	CRPS-1 Unaffected	Control Matched arm	
	(n = 30)	(n = 30)	(n = 30)	
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	p-value
mBF (mL/min/100mL)*	2.05 (1.36 – 2.74)	1.56 (0.87 – 2.25)	1.43 (0.74 – 2.12)	.74
mVO$_2$ (mLO$_2$/min/100g)*†	0.16 (0.10 – 0.22)	0.14 (0.08 – 0.19)	0.13 (0.07 – 0.19)	.56
ReOx (μMO$_2$Hb/s)*†	4.66 (2.80 – 6.52)	3.28 (1.42 – 5.13)	3.17 (1.31 – 5.03)	.33

Values are represented as mean (95% CI). CI indicates confidence interval; CRPS-1, complex regional pain syndrome type-1; mBF, muscle blood flow; mVO$_2$, muscle oxygen consumption; ReOx, post-ischemic reoxygenation rate. *Adjusted for adipose tissue thickness. †Adjusted for maximal voluntary muscle contraction.

Table 4 Comparison of the local muscle oxygen consumption (mVO$_2$) and post-ischemic reoxygenation (ReOx) between the affected CRPS-1 and unaffected CRPS-1 arm

	CRPS-1 Affected	CRPS-1 Unaffected	
	(n = 30)	(n = 30)	
	Mean (95% CI)	Mean (95% CI)	p-value
mVO$_2$ (mLO$_2$/min/100g)*	0.55 (0.35 – 0.76)	0.50 (0.29 – 0.71)	.84
ReOx (μMO$_2$Hb/s)*	5.32 (2.59 – 8.05)	4.33 (1.60 – 7.06)	.67
Change in oxygen consumption (%)	301 (178 – 424)	408 (283 – 533)	.24
Change in reoxygenation rate (%)	25 (13 – 92)	53 (14 – 93)	.75

Values are represented as mean (95% CI). CI indicates confidence interval; CRPS-1, complex regional pain syndrome type-1; mBF, muscle blood flow; mVO$_2$, muscle oxygen consumption; ReOx, post-ischemic reoxygenation rate. Both arms performed exercise at 40% of the maximal voluntary muscle contraction of the affected CRPS-1 arm. *Adjusted for adipose tissue thickness.

Table 5 Comparison of the local muscle oxygen consumption (mVO$_2$) and post-ischemic reoxygenation (ReOx) between the unaffected CRPS-1 arm and matched control arm

	CRPS-1 Unaffected	Control Matched arm	
	(n = 30)	(n = 30)	
	Mean (95% CI)	Mean (95% CI)	p-value
mVO$_2$ (mLO$_2$/min/100g)*†	0.72 (0.47 – 0.97)	0.86 (0.60 – 1.11)	.68
ReOx (μMO$_2$Hb/s)*†	5.03 (3.61 – 6.45)	5.58 (4.16 – 6.99)	.94
Change in oxygen consumption (%)	580 (396 – 764)	694 (513 – 874)	.38
Change in reoxygenation rate (%)	74 (28 – 119)	108 (62 – 154)	.29

Values are represented as mean (95% CI). CI indicates confidence interval; CRPS-1, complex regional pain syndrome type-1; mBF, muscle blood flow; mVO$_2$, muscle oxygen consumption; ReOx, post-ischemic reoxygenation rate. *Adjusted for adipose tissue thickness. †Adjusted for maximal voluntary muscle contraction.

4

Discussion

We found no differences in baseline local mBF, mVO$_2$, and ReOx between the affected and unaffected arms of patients with CRPS-1 and the arm of the control group. After loading exercises, oxygen consumption within the affected CRPS-1 forearm was not different from the clinically unaffected arm or control arm. These results suggest that there is no tissue hypoxia within muscles of limbs affected by chronic CRPS-1 at rest, after exercise, or arterial cuff release.

Other research on blood flow in CRPS-1 has indicated lower blood flow and signs of hypoxia within the skin of the affected CRPS-1 limb [16-21]. These findings were, however, not confirmed by our results for the muscles of the affected CRPS-1 limb. Previous research on muscle energy metabolism in CRPS-1 has shown signs of intracellular muscle hypoxia [22]. This research was performed using nuclear magnetic resonance spectroscopy, and showed an average increase in tissue pH inside the muscle cells of the calf by 11 patients with reflex sympathetic dystrophy.

In the present study, we investigated extracellular muscle oxygenation (microcirculation outside the muscle cells) by means of near infrared spectroscopy. Although we found no signs of hypoxia in the muscles of the forearm, our results do not, however, exclude that intracellular muscle energy metabolism or blood flow of the skin was normal in our group of patients.

No impaired circulation at rest or after sympathetic-related vasoconstriction stimuli was found in our study. Arterial cuff release and isometric stimuli are known to cause peripheral vasoconstriction. Other research on skin blood flow in CRPS-1 has shown increased levels of peripheral vasoconstriction after sympathetic provocational maneuvers in CRPS-1 [16, 20, 28-30]. These findings we not confirmed in muscles of limbs affected by CRPS-1 by our results. After arterial cuff release and exercise, no impairments in hemodynamic functions were recorded, indicating a normal muscle vascular reaction to sympathetic occlusive stimuli in our group of chronic CRPS-1 patients.

The forearm exercises at the affected CRPS-1 arm were performed at an average intensity of 6.2 kg, which corresponded with approximately 20% of the maximal voluntary contraction of the unaffected CRPS-1 arm. Therefore, it could be questioned whether exercises at such a low intensity are clinically relevant. However, in many physiotherapeutic treatment programs the hand and arm movements of patients are trained in a functional manner at relatively low exercise intensity. In addition, most of the home-related activities require only light intensity levels [31].

An important finding was the normal increase in oxygen consumption from baseline to exercise within the forearm muscles of the CRPS-1 affected arm (Table 4). This finding implies that the tissue oxygenation of the affected forearm in patients with chronic stage CRPS-1 is able to respond normally to submaximal forearm loading exercises. Normal extracellular muscle oxygenation during exercise may have important implications for physiotherapeutic training programs, since the affected extremity is subjected to exercise in many CRPS-1 rehabilitation programs. Our results suggest there is no need for particular caution for applying muscle loading exercise therapy in chronic CRPS-1 patients. However, the response of CRPS-1 affected arms to higher exercise loads clearly needs further study.

Our results show a decreased motor function in the affected arm of chronic CRPS-1 patients, demonstrated by lower maximal voluntary muscle contraction of the affected side, in our group of patients. In addition, relatively high levels of physical and social activity limitation owing to the CRPS-1 problems were found. On the basis of the results of our study, these disabilities are unlikely to be related to

disturbed muscle oxygenation or blood flow. Therefore, other mechanisms such as peripheral or central sensitization of pain processing are likely to play the more eminent role in maintaining pain and restrictions of hand movement in daily life in CRPS-1 patients. In support of the latter, research on pain processing in CRPS-1 has shown shrinkage of the extension of the cortical area representing the hand at the CRPS-1 affected side [8], and different brain activation patterns during pin pricking of the hyperalgesic CRPS-1 side [7].

Conclusion

This study does not confirm an impaired Hb oxygenation in muscles of limbs affected by chronic CRPS-1 at rest, during loading exercises, or after an arterial occlusion in patients with chronic stage CRPS-1. Nevertheless, these patients do express severe limitations in activities of daily living and restrictions in social life. The increase of pain during muscle loading does not seems to be related to impairments in muscle oxygen uptake in forearm muscles of upper limbs affected by chronic CRPS-1. Our results suggest that muscle-loading exercise can be safely used in physiotherapeutic training programs for chronic CRPS-1 of the upper limb.

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4

Chapter 5

Muscle contractile properties in patients with repetitive strain injury

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Abstract

Objectives: The purpose of the present study was to examine muscular function in the lower limb of patients with upper limb repetitive strain injury (RSI). **Background:** RSI is a multi-factorial overuse syndrome that has been associated with local vascular and muscular impairments. Recently, we found vascular changes also in the non-affected site, which is suggestive for systemic changes in RSI. Whether RSI is associated with systemic changes in muscle function is unknown. **Methods:** Ten patients with RSI (including complaints in the forearm) and 10 healthy control participants participated in the study. Local muscle oxygen consumption (mVO_2) of the forearm muscles was examined at baseline and after exercise using near-infrared spectroscopy. Quadriceps muscle contractile properties were examined using isometric contractions and electrical stimulations. **Results:** Patients with RSI demonstrated a mVO_2 in the forearm muscles after exercise (p=0.05), indicative for localized muscular changes, and a leftward shifted force frequency relationship (ANOVA, group-effect: p=0.02) in the quadriceps muscle. These contractile properties point in the direction of a larger amount of type II fibers in the quadriceps muscle of patients with RSI. **Conclusions:** These findings suggest that the unaffected quadriceps muscles of patients with upper limb RSI demonstrate probably a predominance for type II fibers. Whether this reflects a systemic predisposition for individuals to be prone to develop RSI has to be elucidated.

Introduction

Repetitive strain injury (RSI), also known as cumulative trauma disorder or work-related upper limb disorder, is a multi-factorial overuse syndrome that affects the neck, shoulder region, hand/wrist or elbow/lower arm, or a combination of these areas, leading to impairment and participation problems in the occupational situation as well as in leisure time [1-3]. RSI has a high prevalence among computer workers of 15% to 64% [4-7] and high associated socioeconomic costs [8-10]. Nonetheless, relatively little is known regarding the pathophysiological mechanism of RSI. Previous studies have demonstrated local changes in vascular and muscular function in muscles of patients with RSI. Vascular abnormalities that were found include lower blood flow [11-13], lower oxygen consumption [11, 13] and reduced capillarisation [14, 15]. Muscular changes that were found relate to higher percentages of the fast glycolytic muscle (type II) fiber in the forearm [16] and trapezius muscles [14], muscle fiber damage [14-19], and changes in mitochondrial function [14, 15, 18-21]. Interestingly, in a recent study we found that the lower oxygen consumption and blood flow is also present in the contralateral, non-affected forearm muscles of patients with unilateral RSI [13]. Previous studies reported mitochondrial and fiber disturbances in the non-affected muscles in RSI [14, 17]. These observations suggest the presence of systemic changes in RSI. However, no previous study examined muscle function in the non-affected muscles in RSI. Therefore, the primary aim of this study is to examine lower limb contractile properties in the quadriceps muscle in RSI patients with complaints in their upper limb. On the basis of results of previous findings of systemic changes [13], we expect to find differences in contractile properties of the (non-affected) lower limb quadriceps muscle between patients with RSI and controls.

Methods

Participants
Ten patients with RSI (38 ± 11 years; 7 female and 3 male) and 10 control participants (31 ± 11 years; 6 female and 4 male) participated in this study. RSI patients were recruited by advertisement on the website of our University Hospital and on the website of the Dutch RSI patients' organization. Control participants consisted of computer workers (4.7 ± 1.6 hour/day) who did not have a history of RSI-related complaints. RSI-related complaints were defined as experience of pain in the arm, neck, or shoulder that worsened by performing computer-work activities. The RSI-related pain had to exist for at least 6 months. Participants had to perform computer-work for at least 2 hours a day. Individuals with RSI were excluded if

there was any evidence of occlusive atherosclerosis, diabetes mellitus, peripheral neuropathies, history of complex regional pain syndrome type-1, a diagnosed muscular disease other than RSI, a history of smoking, or use of medication known to interfere with the vascular system (Table 1). All participants gave written informed consent after a careful explanation of the methodology and testing procedures. The study was approved by the Medical Ethical Committee of the Radboud University of Nijmegen.

Table 1 Participant characteristics

	RSI (n = 10)	Control (n = 10)	p-value
Age (years)	38.4 ± 10.9	31.1 ± 11.0	.15
Gender (n)			
Female	7	6	
Male	3	4	
Pain level of RSI symptoms (VAS-score)	3.1 ± 1.8	-	
Duration of RSI symptoms (months)	82.8 ± 15.5	-	
Daily computer use (hours)	4.7 ± 1.6	4.5 ± 1.6	.79
Circumference forearm (cm)	26.2 ± 2.6	25.3 ± 2.0	.38
Adipose tissue thickness (mm)	8.7 ± 3.7	5.4 ± 2.2	.04*
Forearm mVO2 at rest (mLO$_2$/min/100g)	0.10 ± 0.08	0.16 ± 0.13	.10
Forearm mVO2 after exercise (mLO$_2$/min/100g)	0.27 ± 0.24	0.45 ± 0.27	.05*
Maximal voluntary contraction (Kg)			
Forearm	36.8 ± 15.8	43.5 ± 14.3	.34
Leg	56.7 ± 20.3	77.1 ± 22.1	.05*

Values are represented as mean ± SD. RSI indicates, repetitive strain injury; mVO$_2$, muscle oxygen consumption; VAS, visual analog scale. *Significant differences from controls (p≤0.05).

Study design

All participants reported to the laboratory once, where arm muscle oxygen consumption was measured at rest. These measurements were performed to establish the presence of changes in the vasculature of the affected forearm. After a resting period of at least 30 minutes, quadriceps muscle characteristics were tested during electrical stimulation of the quadriceps muscle.

Measurements

After reporting to our laboratory, participants filled in a standardized questionnaire to gain insight into localization, extent and duration of the RSI symptoms. Prior to the study, pain intensity was measured using a 10-cm visual analog scale (VAS) (0 cm = no pain, 10 cm = extreme pain). In addition, age, hours of work per week, daily computer use were recorded, forearm circumference, and adipose tissue thickness of the forearm were measured (Holtain Ltd., Crymmych, UK).

Electrical stimulation procedure

The contractile properties of the quadriceps muscle were measured with the participant seated on an adjustable chair. The knee of the measured leg was positioned in an angle of 120-degrees (complete knee extension was defined as 180-degrees) with the back vertically supported. To minimize movements of the leg during the measurements, straps were used to securely fixate the pelvis, upper thigh, and upper body. A non-extensible strap was placed around the distal past of the tibia and mounted to a force transducer (Peekel Instruments, Rotterdam, The Netherlands). The force signal was digitized with 1000-Hz sample frequency and analyzed by custom developed software (MatLab, MathWorks, MA, USA). To ensure that a representative part of the muscle was activated, electrical bursts (20 Hz) of 1-second duration were delivered to the muscle with increasing current until 30% of maximal voluntary contraction (MVC) was reached. To determine the MVC, participants were asked to produce three maximal voluntary knee extensions of 3 seconds, separated by a 1-minute resting period. The highest of the three measurements was taken as the MVC. The quadriceps muscle was electrically stimulated using two surface electrodes (8 x 13 cm; Schwa-Medico Nederland BV, Woudenberg, The Netherlands). The electrodes were placed 5 cm above the patella (at 2/3 medial from the line between the patellar and superior anterior iliac spine) and 10 cm below the superior anterior iliac spine (at 2/3 lateral from the line between the patellar and superior anterior iliac spine). A personal computer running a custom-made software program controlled the frequency and number of square-wave pulses (0.20 ms duration) delivered to the muscle by a constant-current high-voltage stimulator (model DS7A; Digitimer Ltd, Welwyn Garden City, U.K.). In order to determine the force-frequency relationships, which can distinguish fast-twitch from slow-twitch muscles [22, 23], stimulation trains of 1-s duration were applied to the muscle at frequencies of 1, 10, 20, 30, 50 and 100 Hz with a rest period of 2 minutes between each train.

Forearm muscle oxygen consumption

Local oxygen consumption (mVO_2) was measured with the non-invasive, optical method near-infrared spectroscopy (NIRS), which provides continuous, real-time

5

monitoring of local hemodynamic and tissue oxygenation (PortaMon, Artinis Medical Systems, Zetten, the Netherlands). The NIRS optodes were positioned on the extensor carpi radialis brevis muscle, at the same position where the adipose tissue thickness and the circumference of the forearm were measured. The participants were seated on the same adjustable chair as used for measuring contractile properties. The forearm was placed at heart level at an upward angle of 30-degree to avoid venous pooling of the blood, and a pneumatic cuff was placed around the upper arm. During a 1-minute arterial occlusion of 250 mmHg, the mVO_2 was determined at rest. After a rest period of 120 to 240 seconds, participants performed 60 seconds of rhythmic handgrip exercises on a dynamometer (1-second contraction, 1-second relaxation) assisted by a metronome at 10% of the MVC of the forearm. For visual feedback, the level of workload was indicated on a computer. Immediately after this exercise, an arterial occlusion was applied (30 seconds, 250 mmHg) to assess the muscle oxygen consumption after exercise. The main principle upon which the NIRS device relies is the difference in absorption spectrum of the reflected light of oxy- and deoxyhemoglobin. The oxygen consumption was calculated from the steepness of the slope of oxyhemoglobin during the first 8 seconds immediately after inflating the pneumatic cuff. This protocol has been used before in various papers to examine baseline and post-exercise levels of local mVO_2 [11, 13, 24-28], and is considered a reliable and reproducible method [27-29].

Data analysis

During off-line analysis, data of the quadriceps contractile characteristics were analyzed with custom-made software program (Matlab, MathWorks, MA, USA). The isometric tetani contractions at 100-Hz were used to calculate contraction and relaxation rates. The time of muscles to contract from 0 to 90% and from 25 to 75% of the peak force were determined. The normalized maximal rate of increase in force (maximal force rise; MFR) was calculated from the slope of contraction from 25% to 75% of the peak force [30]. Early-relaxation time was defined as the time taken by muscles to decline from 100% to 50% of the peak force. The half-relaxation time was defined as the time taken to decline from 50% to 25% of the peak force. Finally, the force-frequency relationships was obtained from peak forces that were achieved during stimulations at frequencies ranging from 1 to 100 Hz. Reproducibility of this technique has been proven good using the set-up and technology used in this paper [31].

Statistical analysis

Statistical analyses were performed using SPSS Version 16.0 (SPSS Inc, Chicago, IL). All data are reported as mean $\pm$ SD and statistical significance was assumed

at p≤0.05. A 2-way analyses of variance (ANOVA) was used to detect changes in the quadriceps force frequency relationship across the six stimulation frequencies (1, 10, 20, 30, 50 and 100Hz) between groups (RSI *versus* controls; time x group). Student independent *t*-tests were used to detect differences in participant characteristics and to detect differences in contractile properties of the quadriceps muscle between groups. When data did not follow a normal distribution, a non-parametric Mann-Whitney *U* test was performed.

Results

The average duration of the RSI symptoms was 82.8 ± 15.5 months. The mean pain level in the RSI group was 3.1 ± 1.8 cm on a 10-cm Visual Analogue Scale. No differences were found for daily computer work, forearm circumference, forearm maximal voluntary contraction, and local muscle oxygen consumption at rest between RSI patients and healthy controls. Local oxygen consumption of the forearm after exercise, the maximal voluntary contraction of the leg, and the adipose tissue thickness were lower in patients with RSI than in controls (Table 1).

5

Contractile properties of the quadriceps muscle
No statistical differences were found between both groups for the contraction time, maximal rate of force rise, relaxation time, and the intensity of electrical stimulation during the 100 Hz stimulation at 30% of the MVC (Table 2). The force-frequency
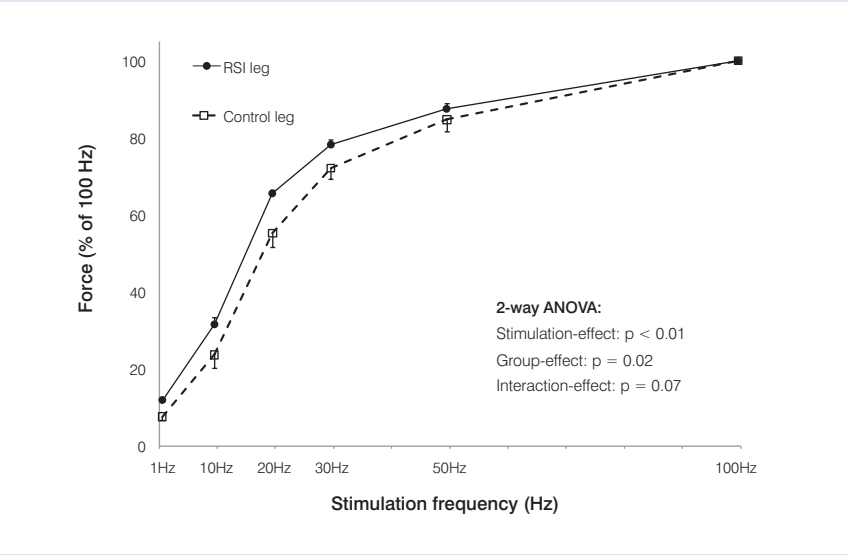
Table 2 Muscle properties of the quadriceps muscle of patients with RSI and controls

Muscle properties	RSI (n = 10)	Control (n = 10)	p-value
Electrical stimulation (mA)	79.3 ± 22.6	71.0 ± 7.7	.29
Contraction time 0 – 90 % Fmax (s)	0.29 ± 0.08	0.34 ± 0.12	.27
Contraction time 25 – 75 % Fmax (s)	0.09 ± 0.03	0.12 ± 0.05	.12
Maximal Force Rise (%/s)	612 ± 204	507 ± 288	.37
Early relaxation time (s)	0.13 ± 0.01	0.12 ± 0.01	.06
Late relaxation time (s)	0.04 ± 0.03	0.03 ± 0.01	.28

Values are represented as mean ± SD. RSI indicates repetitive strain injury. Electrical stimulation = amount of current (mA) needed to produce 30% of the MVC of the quadriceps. Maximal Force Rise = Slope of contraction of 25% to 75% of Fmax. Early relaxation = time of muscle relaxation from 100% to 50% MVC, Late relaxation = time of muscle relaxation from 50% to 25% MVC.

curve of the quadriceps muscle of the RSI group was significantly shifted leftwards compared to the force-frequency curve of the control group (ANOVA, group-effect: p=0.02) (Figure 1).

Figure 1 Force responses of quadriceps muscles of patients with RSI (black circles) and controls (open squares) at frequencies of 1, 10, 20, 30, 50 and 100 Hz. Error bars represent SE

Discussion

The purpose of this study was to examine muscle contractile properties in non-affected muscles in patients with RSI. Measurements of the contractile properties of the quadriceps muscle showed that patients with RSI have a leftward shifted force frequency relationship compared to controls. This difference in contractile properties correspond with a larger amount of type II fibers in the quadriceps muscle of RSI patients compared to their healthy controls. Interestingly, this observation is in line with previous studies that reported a larger amount of type II fibers in the affected muscles of RSI patients [16]. These findings suggest that differences in muscular characteristics between RSI and controls are not exclusive for the affected arm, but may also be present in non-affected regions, possibly reflecting a systemic predisposition for individuals to be prone to develop RSI.

A shift to the left of the normalized force-frequency curve suggests a difference in muscle fiber composition, with a change towards a higher amount of the fast glycolytic (type II) muscle fiber in RSI patients [23]. These fast-twitch fibers have higher glycolytic and lower oxidative capacity and are known to fatigue more readily than the slow-twitch (type I) fibers. Interestingly, a previous study conducted by Ljung *et al.* (1999), found a significantly higher proportion of type II fibers in the extensor carpi radialis brevis muscles of patients with epicondylitis [16]. We add the novel knowledge that patients with RSI also demonstrated a higher content of type II fibers in non-affected muscles. The higher amount of type II fibers is related to a lower oxidative capacity and lower energy production. Possibly, the higher content of fibers with a lower oxidative capacity in RSI patients may lead to a lower dependence on oxygen for muscle contractions and explain the lower oxygen uptake after exercise that we found in the forearm muscles of patients with RSI compared to controls. Moreover, the predominance of type II fibers, makes these muscles more susceptible for fatigue and/or ischemia during repetitive movement tasks. We support future studies to examine whether a higher amount of type II fibers in RSI could contribute to the occurrence or aggravation of RSI symptoms.

The altered contractile and circulatory properties in muscles in patients with RSI raises an important question whether these observed changes are a predisposing factor in the development of RSI or are simple a consequence of RSI. Our observations may partly be explained by a systemic deconditioning effect induced by RSI that attenuates daily life activity and/or participation in sports (e.g. racquet sports, rowing, upper limb dominant sport activities). Indeed, previous studies have demonstrated that physical inactivity leads to a shift of the force-frequency curve to the left [23], a larger content of type II fibers [32] and a lower oxygen consumption [33]. This idea of relative deconditioning after RSI is supported by the lower maximal force of the leg in patients with RSI. Taken together, whether our novel findings of a systemic difference in muscle function between RSI and controls relates to the development or consequence of RSI, remains to be studied in future research.

Clinical relevance

Our findings may have important clinical implications. Based on the biochemical processes that take place in the muscle fiber, oxidative type I fiber is best equipped to perform long-term repetitive movement tasks; i.e., movements that have been related to the development of RSI complaints. As RSI patients demonstrate type II dominant muscles, it may be beneficial to alter fiber composition to a predominant type I fiber type. Previous studies suggested that prolonged and intense endurance training is required for such changes in fiber type [34]. Whether for example physical therapeutic training programs are effective in triggering a fiber type transformation

5

and/or increase in oxygen consumption at the affected arm of patients with RSI, and whether such changes contribute to the change in complaints, has not been studied to date.

Study limitations

A potential limitation of the study is that we did not examine the muscle function and muscle type distribution in the contra-lateral, non-affected forearm muscles of unilateral RSI patients. This procedure, however, is associated with important ethical issues as this would involve muscle biopsies since non-invasive assessment of muscle function and constructing a force frequency curve of forearm muscle is not possible. Nonetheless, we believe that our approach is robust and provides important and novel insight into the pathophysiology of RSI.

Conclusion

We found that individuals with RSI demonstrate lower oxygen consumption in the affected forearm muscles, compared with healthy normal controls, and a longer relaxation time and a shift in the force-frequency curve, suggestive for a higher amount of type II muscle fiber, in the non-affected quadriceps muscle. Our findings suggest that RSI patients demonstrate a systemic difference in muscular function compared to their healthy peers, rather than local changes in the affected arm only.

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Chapter 6

Impaired endothelial function and blood flow in repetitive strain injury

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Abstract

Objectives: In this study we investigated whether repetitive strain injury (RSI) is associated with endothelial dysfunction and impaired exercise-induced blood flow in the affected forearm. **Background:** RSI is an disabling upper extremity overuse injury that may be associated with pathophysiological changes in the vasculature. **Methods:** Ten patients with RSI and 10 gender- and age-matched control participants participated in this study. Brachial artery blood flow was measured at rest and during 3-minute periods of isometric handgrip exercise at 15%, 30%, and 45% of the individual maximal voluntary contraction. Brachial artery endothelial function was assessed as the flow mediated dilation (FMD), by measuring brachial artery diameter and velocity before and after a 5 minute ischemic occlusion. **Results:** We found a lower exercise-induced brachial artery blood flow in patients with RSI than in controls (p=0.04). Brachial artery FMD was significantly lower in patients with RSI than in controls (p<0.01), whilst a lower FMD was also found within patients with unilateral RSI when comparing the affected arm with the non-affected arm (p=0.04). **Conclusions:** Our results suggest that patients with RSI have an attenuated exercise-induced blood flow and an impaired endothelial function in the affected arm. These findings importantly improve our understanding of the pathophysiological mechanism of RSI.

Introduction

Repetitive strain injury (RSI) represents a common pain syndrome that relates to a variety of musculoskeletal complaints of the upper extremity ranging from the neck to the hand and fingers [1, 2]. The onset and progression of RSI is associated with the performance of repetitive and/or forceful tasks and with psychosocial risk factors [3, 4]. Although the prevalence of RSI is 15% to 64% among computer workers [5-8] and is associated with high socio-economic costs [9-12], the patho-physiological mechanisms underlying the development of RSI are still not fully understood. Previous studies have reported local abnormalities in the vasculature, such as a reduced capillarisation [13, 14] and lower resting blood flow, in patients with RSI [15, 16]. The endothelium represents the inner layer of cells in blood vessels and plays an important role in regulating blood flow [17]. Therefore, an impaired blood flow and vascularisation in RSI might be related to the presence of endothelial dysfunction. This endothelial dysfunction may contribute to an attenuated blood flow supply to the exercising muscles, and thereby contributing to the exaggeration of RSI complaints. Interestingly, we recently found impaired oxygen consumption in the affected forearm muscles of patients with RSI after incremental handgrip exercise [15, 18]. In addition, a previous study found an impaired radial artery dilatation in response to exercise in RSI patients [19]. However, no previous study examined brachial endothelial function in RSI, and whether RSI alters the exercise-induced blood flow in the affected forearm. Therefore, the aim of this study was to examine brachial artery endothelial function and the exercise-induced brachial artery blood flow in the affected forearm of RSI patients compared to gender- and age-matched controls. We hypothesized that patients with RSI demonstrate an impaired endothelial function as well as an attenuated exercise-induced blood flow during handgrip exercise.

6

Methods

Participants

Ten patients with RSI (40.2 ± 10.3 years; 8 female and 2 male) and 10 gender- and age-matched control participants (38.0 ± 12.4 years; 8 female and 2 male) participated in this study. Patients with RSI were recruited by advertisements on websites of the Radboud University Nijmegen Medical Centre and the Dutch RSI patients' organization. All patients were diagnosed with RSI by a physician and were under treatment for these complaints. We included patients with RSI when they presented with pain in their elbow/forearm region, which was exaggerated by computer-related work activities and was present for at least 3 months. Control participants

were all computer workers without (a history of) RSI symptoms that performed computer-related activities and/or repetitive movement tasks for at least 10 hours per week. We excluded participants that were diagnosed with diabetes mellitus type I or type II, history of complex regional pain syndrome type-1, hypertension (>140 or >90 mmHg for systolic and diastolic pressure), or cardiovascular disease as this interferes with our primary outcome parameters. Participants who were obese (BMI > 30), smokers or those who used supplementation that interferes with the cardiovascular system were also excluded [20, 21]. The study was approved by the Radboud Ethical Committee, in accordance with the Declaration of Helsinki (2000) and with the ethical standards of this journal [22]. Prior to the study, all participants gave their informed consent after detailed explanation of the study.

Study design
Participants reported on one occasion to our laboratory. After obtaining participant characteristics, the maximal voluntary contraction (MVC) was determined by 3 consecutive maximal handgrip contractions. After a resting period of 20 minutes in the supine position, exercise-induced blood flow was examined during 3-minute cycles of dynamic handgrip exercise at 15%, 30%, and 45% of the MVC, separated by a 5 minute break. After another 30-minute resting period, brachial artery endothelial function (using the flow-mediated dilation) was examined in the dominant or affected arm in controls and RSI, respectively. In the RSI patients who demonstrated unilateral complaints (n=6), the brachial artery endothelial function was also investigated in the contralateral (non-affected) forearm.

Measurements
All measurements were performed in a quiet and temperature-controlled room (19-22°C). Participants were instructed not to take coffee, tea, alcohol, anti-inflammatory medication, chocolate, and vitamin C 18 hours prior to the measurement to prevent (sub)acute effects of these substances on endothelial function (see recent guidelines: [23]). All participants were tested in a fasted state (fasted > 6 hours), and participants refrained from exercise in the 24 hours prior to the test. Measurements in pre-menopausal woman were performed during the early follicular phase, to minimize variation owing to the menstrual cycle [24].

Participant characteristics
Participants completed questionnaires to quantify information regarding work, relevant (musculoskeletal) medical history and the use of medication. Height and weight were measured. Blood pressure and heart rate were measured using a sphygmomanometer after a resting period in the sitting position. Forearm circumference was measured 2.5 cm distally from the lateral epicondyl for both

arms. Furthermore, pain intensity during the last 2 weeks was registered on a 10-cm visual analog scale (VAS) in all participants. The VAS ranged from 0 to 10 cm, with 0 reflected 'no pain' and 10 reflected 'maximal pain'. Participants scored pain intensity for; 1) maximal pain, 2) minimal pain, 3) average pain, 4) pain during computer-work activities, and 5) pain during daily life activities. In addition, all participants filled in the Disability of the Arm, Shoulder and Hand (DASH) questionnaire [25], which represents a valid questionnaire to assess the degree of difficulty in performing different physical activities because of RSI complains.

Table 1 Participant characteristics

	RSI (n=10)	Control (n=10)	p-value
Age (years)	39.8 ± 10.3	37.5 ± 12.3	.66
Gender (female:male)	8:2	8:2	1.00
Height (m)	1.74 ± 0.1	1.75 ± 0.1	.83
Weight (Kg)	72.3 ± 0.9	69.2 ± 6.5	.42
BMI (Kg/m^2)	23.8 ± 3.3	22.7 ± 3.4	.46
Systolic blood pressure (mmHg)	120.4 ± 12.2	117 ± 12.7	.56
Diastolic blood pressure (mmHg)	78.6 ± 5.1	77.8 ± 10.4	.85
Heart rate (beats/min)	62 ± 7	66 ± 14	.39
Duration of RSI symptoms (months)	82.7 ± 54.1	-	-
DASH (range 0-100)			
Disability/symptoms scale	24.6 ± 12.3	0.5 ± 0.9	<.001*
Work disability scale	35.4 ± 26.1	0.0	.004*
Sport/music disability scale	20.8 ± 20.0	2.1 ± 6.2	.02*
Pain level (0-10cm)			
Maximal	6.2 ± 2.9	0.1 ± 0.3	<.001*
Minimal	1.7 ± 1.7	0.1 ± 0.3	.013*
Average	4.0 ± 2.0	0.1 ± 0.3	<.001*
During computer-work	6.2 ± 2.5	0.6 ± 1.3	<.001*
During daily life activities	4.0 ± 2.6	0.1 ± 0.3	<.001*
Computer use (hours/week)	13.3 ± 7.3	22.0 ± 11.9	.06
Sport activities (hours/week)	2.9 ± 1.8	2.4 ± 1.2	.44
Maximal voluntary contraction (N)	42.8 ± 9.3	49.6 ± 8.7	.11
Circumference of the forearm (cm)	25.3 ± 1.9	25.2 ± 1.4	.90

Values are represented as mean ± SD. RSI indicates repetitive strain injury; BMI, body mass index; DASH, disease arm, shoulder and hand questionnaire. *Significant differences from controls (p<0.05).

6

Brachial artery blood flow measurement

Brachial artery blood flow was measured using non-invasive duplex ultrasound. We used a 10-mHz linear array probe attached to a high-resolution ultrasound machine (Terason t3000, Burlington, Massachusetts, USA). The probe of the duplex ultrasound was placed in the distal third of the upper arm, with an insonation angle of < 60-degrees [26, 27]. Before the exercise protocol, ultrasound parameters were set to optimize longitudinal B-mode images of the lumen/arterial wall interface [26].

Participants were positioned in the supine position with the dominant arm extended in an 80-degree position from the torso, so that they could grasp the hand dynamometer. First, the maximal voluntary contraction (MVC) of the forearm was determined by 3 consecutive maximal handgrip contractions, where participants were instructed to maintain a constant maximal grip for 3 seconds under verbal support of the examiner. These maximal handgrip contractions were separated by a 1-minute resting period. The highest value was used as the MVC and was used to calculate workload that matched with 15%, 30%, and 45% of the MVC.

Blood flow measurements were performed in the dominant arm in control participants and in the (most) affected arm in RSI patients. After a 1-minute baseline measurement of brachial artery blood flow, participants performed 3 incremental stages of 3-minute dynamic handgrip exercise using a hand dynamometer, separated by a 5 minute resting period. Participants performed handgrip exercise at 15%, 30%, and 45% MVC at 30 contractions per minute. Handgrip exercise was performed with visual feedback to maintain a constant workload during exercise. We continuously measured brachial artery blood flow during exercise, whilst the last minute of exercise was used for analysis as a plateau in blood flow is reached after 2 minutes of this type of handgrip exercise [28]. All tests were performed by a well-experienced sonographer.

Flow mediated dilation

After a 30-minute resting period in the supine position, brachial artery endothelium-dependent vasodilatation was examined using the non-invasive method of flow-mediated dilation (FMD) in the dominant (i.e., in controls) or affected arm (i.e., in RSI patients). This technique is based on the characteristic that vessels dilate in response to shear stress (frictional force of the blood flow on the endothelium), which is largely mediated by nitric oxide [29, 30]. The FMD is a valid and frequently used technique to examine the endothelial function. In 6 RSI patients that presented with unilateral complaints only, we also examined FMD in the contralateral (non-affected) forearm.

To examine brachial artery FMD, a rapid inflation/deflation pneumatic cuff (Hokanson Inc., Bellevue, WA, USA) was placed proximally around the forearm to provide an ischemic stimulus by inflating the cuff to 220 mmHg for 5 minutes. Brachial artery diameter and velocity were examined, proximal to the cuff, using echo-Doppler. Baseline scans for resting vessel diameter and blood velocity were recorded during 1 minute before cuff inflation. Diameter and flow recordings resumed 30 seconds prior to cuff deflation and continued for 3 minutes thereafter [31].

Data analysis

For blood flow analysis, edge-detection and wall-tracking of high resolution B-mode arterial ultrasound images combined with synchronized Doppler waveform envelope analysis was performed (using custom designed software). This technique is extensively described in previous studies [26, 31]. In brief, the video signal was taken from the ultrasound machine and stored as an AVI-file on the PC. The diameter of the brachial artery was stored and displayed with synchronized Doppler velocity signals. The analysis used custom-designed edge-detection and wall-tracking software and was performed at 30 Hz. Blood flow was calculated continuously from the synchronized diameter and velocity data. This technique possesses an excellent reproducibility for resting brachial artery diameter and flow-mediated dilation [32]. Furthermore, this method of blood flow assessment was closely correlated with actual flow through a phantom artery [33].

Flow mediated dilation analysis was performed using the same software previously described for the blood flow analysis. Baseline diameter, flow and shear stress were calculated as the mean of the data acquired across the 1-minute preceding the cuff inflation period. After cuff deflation, the peak diameter was automatically detected using an algorithm. FMD was calculated as the percentage of this peak diameter to the preceding baseline diameter. The time to peak diameter was calculated from the point of cuff deflation to the maximum post-deflation diameter. Calculation of FMD and time to peak were therefore observer-independent and based on standardized algorithms applied to data, which had undergone automated edge-detection and wall-tracking [31, 32].

Statistical analysis

Statistical analysis was performed using SPSS Version 16.0 (SPSS Inc, Chicago, IL, USA). Group differences in baseline characteristics were compared using unpaired *t*-tests, whilst differences between both limbs in RSI patients were compared using paired *t*-tests. When data did not follow a normal distribution, the non-parametric Mann-Whitney *U* test was used. The exercise-induced blood flow between patients with RSI and controls were analyzed using a 2-way repeated-measures analyses of

variance (ANOVA) with a between subject factor ('group': controls *versus* RSI) and a within subject factor ('exercise intensity': 15%, 30%, and 45% MVC). When a significant effect was observed, we used LSD post-hoc tests to identify differences. We also calculated the blood flow area-under-the curve during the exercise protocol using the data derived at baseline and during exercise at 15-30-45% MVC. We considered a statistically significant effect at a two-sided p-value of <0.05.

Results

Participants characteristics
We found no significant differences between groups in age, BMI, blood pressure, heart rate, arm circumference, maximal voluntary contraction, hours spent on computer-work related activities and hours spent on sport activities (Table 1). The average duration of the RSI symptoms was 82.7 months (SD 54.1, range 5-144 months). Patients with RSI reported pain during computer-work and daily life activities, and also experienced significant disabilities (Table 1).

Exercise-induced brachial artery blood flow
Brachial artery blood flow increased significantly in both groups during incremental handgrip exercise (ANOVA, p<0.001). We found a significant difference in brachial artery blood flow between groups during exercise (ANOVA, *group-effect;* p=0.039), indicating that blood flow during exercise in RSI patients was lower than in controls. Post-hoc analysis revealed differences in exercise-induced blood flow between groups at exercise intensities of 30% and 45% MVC (p=0.03 and p=0.04, respectively). A trend was observed for a smaller exercise-induced increase in brachial artery blood flow in RSI compared to controls (ANOVA, *time*group;* p=0.078) (Figure 1). The brachial artery blood flow area-under-the-curve was significantly lower in RSI compared to controls (RSI patients 478 ± 136 ml/min, controls 658 ± 216 ml/min, p=0.04).

Brachial artery flow mediated dilation
Due to technical problems, we excluded the data of 2 participants from the analysis (1 control participant and 1 RSI patient). We found no difference in baseline brachial artery diameter between RSI patients and controls (p=0.75). Brachial artery FMD was significantly lower in RSI patients compared to their healthy peers (p<0.01). We found no significant differences between groups in time to peak diameter and the shear rate area-under-the-curve (Table 2).

Figure 1 Brachial artery blood flow at baseline and during incremental handgrip exercise at different intensities (15, 30, and 45% of maximal voluntary contraction) in patients with RSI (black triangles) and gender- and age-matched controls (open circles)
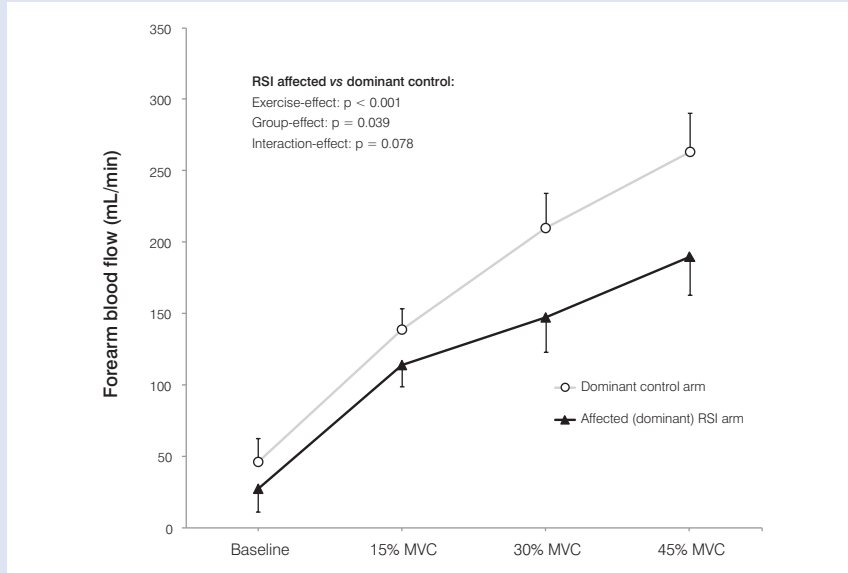
P-values for the 2-way ANOVA are presented. Error bars represent SE. *Post-hoc significantly different between groups at $p<0.05$.

6

Table 2 Brachial artery flow-mediated dilation in the affected arm of RSI (n=9) and dominant arm of control participants (n=9). Due to technical problems, we excluded 2 participants from the analysis (1 control participant and 1 RSI patient)

|	RSI	Controls	p-value
Baseline diameter (cm)	0.34 ± 0.03	0.33 ± 0.04	.75
Peak diameter (cm)	0.36 ± 0.03	0.37 ± 0.04	.56
FMD (%)	4.6 ± 2.0	9.4 ± 2.6	.001*
Time to peak diameter (s)	60 ± 22	54 ± 26	.63
Shear rate area-under-the-curve (s)	23515 ± 14357	26724 ± 5142	.54

Values are represented as mean $\pm$ SD. RSI indicates repetitive strain injury; FMD, flow mediated dilatation. *Significant differences from controls ($p<0.05$).

Table 3 Brachial artery flow-mediated dilation in the affected and non-affected arm of patients with unilateral RSI (n=6). Due technical problems, we excluded one RSI patient from the analysis

	RSI affected	RSI non-affected	p-value
Baseline diameter (cm)	0.33 ± 0.03	0.31 ± 0.05	.08
Peak diameter (cm)	0.35 ± 0.04	0.33 ± 0.06	.14
FMD (%)	4.1 ± 1.7	6.1 ± 3.3	.04*
Time to peak diameter (sec)	59 ± 21	60 ± 35	.89
Shear rate area-under-the-curve (per sec)	20221 ± 8546	29830 ± 14841	.50

Values are represented as mean ± SD. RSI indicates repetitive strain injury; FMD, flow mediated dilatation. *Significant differences from controls (p<0.05).

Figure 2 Brachial artery flow mediated dilatation in the affected arm of patients with RSI (black triangle, n=9), the non-affected arm in patients with unilateral RSI (open triangle, n=5) and the dominant arm of control participants (open circles, n=9)
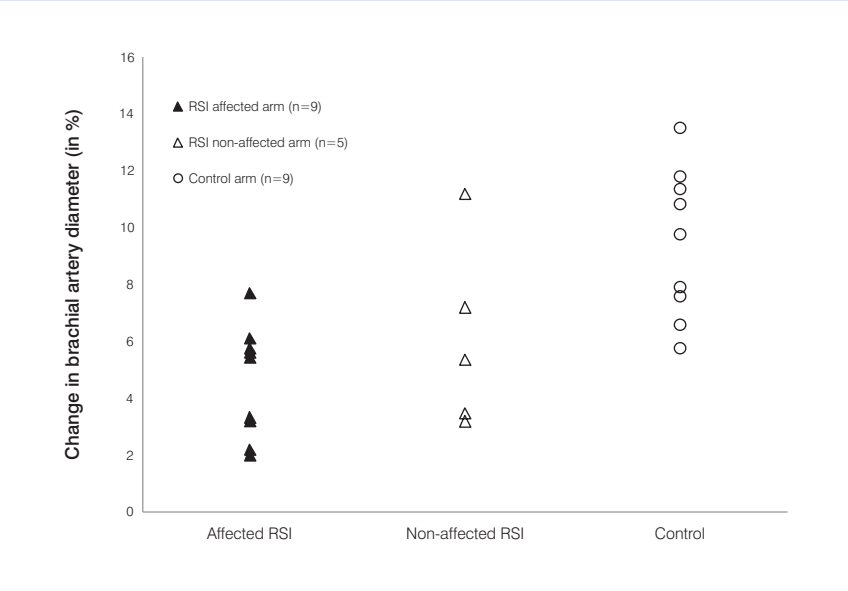
In a subgroup of patients with unilateral RSI (n=6), we compared the brachial artery FMD of the affected forearm and the contralateral, non-affected forearm. Brachial artery FMD was lower in the affected compared to the non-affected arm within patients with unilateral RSI (p=0.04). A trend was observed for a lower brachial artery FMD of the non-affected forearm compared to controls (p=0.06). No differences in baseline diameter, peak diameter, time to peak diameter, and shear rate area-under-the-curve were found between arms (Table 3 and Figure 2).

Correlation between flow mediated dilatation and blood flow

We found no significant correlation between the brachial artery FMD and the exercise-induced brachial artery blood flow area-under-the-curve (*r*=0.41, p=0.09). However, within groups, we found a significant correlation between these measurements in the RSI group (r=0.71, p=0.03), but not in the gender- and age-matched controls (r=-0.07, p=0.86) (Figure 3).

Figure 3 Correlation between the brachial artery flow-mediated dilation and the brachial artery blood flow area-under-the-curve in the affected RSI arm (black triangles, n=9) and the dominant arm of controls (open circles, n=9)

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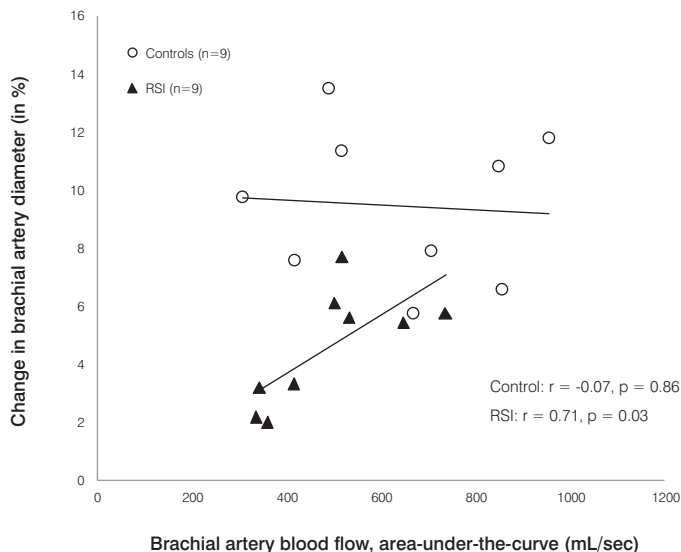
Discussion

The main findings of our study are that the brachial artery endothelium-dependent vasodilatation is impaired in the affected arm of patients with RSI compared to controls, whilst also a lower endothelial function is found in the affected forearm compared to the non-affected arm within RSI patients. Moreover, we found an attenuated exercise-induced blood flow in the brachial artery during incremental handgrip exercise in patients with RSI compared to healthy gender- and age-matched controls. Interestingly, the impaired endothelial function in RSI significantly relates to the attenuated exercise-induced blood flow. This study provides evidence for detrimental changes in the forearm vasculature of RSI patients, potentially contributing to the development of RSI.

A novel finding in our study is that patients with RSI demonstrate a lower flow mediated dilation in the affected arm compared to controls, which indicates the presence of an impaired endothelial function. This is supported by the observation that the shear rate area-under-the-curve, i.e., the eliciting stimulus for dilatation, was similar in both groups. Moreover, a within subject analysis of patients with unilateral RSI complaints revealed that endothelial function in the affected arm is lower compared to the non-affected arm, which indicates the involvement of a local impairment of endothelial function in RSI patients. Our results confirm the findings of a previous study, which found an impaired dilatation of the radial artery during exercise and after ischemic stimuli [19]. However, this study did not include a control group, whilst methodological concerns can be raised regarding the analysis and data collection.

One potential explanation for the impairment in endothelial function in RSI patients may relate to pro-inflammatory cytokines, since previous studies found that cytokines can impair endothelial function [17]. Pro-inflammatory cytokines indicate the presence of trauma, infection and cellular/tissue repair, clinical signs that have been reported in relation to RSI (22, 26). Interestingly, previous studies have found elevated levels of inflammatory markers and C-reactive protein in RSI [34]. These elevated levels of inflammatory markers were found to correlate with the severity of the RSI complaints. Therefore, an underlying low-grade inflammatory process owing to tissue damage in the affected arm of patients with RSI may relate to the local endothelial dysfunction in patients with RSI. Alternatively, the impaired endothelial function may be related to the sympathetic nerve activity, given the strong inverse relation between sympathetic nerve activity and endothelial function [35, 36]. In our study, sympathetic nerve activity was not specifically tested. Despite local character of the endothelial dysfunction, endothelial function of the

non-affected forearm in patients with unilateral RSI tended to be lower than healthy controls. Although non-RSI-related factors may explain this finding, we cannot exclude the possibility that systemic factors, such as the sympathetic nervous system or systemic inflammatory responses, may partially contribute to this finding.

Another factor that has a well-established and marked effect on endothelial function relates to physical inactivity. We and others have found that local and systemic physical inactivity is known to induce marked changes in the vascular function, for example after prolonged bed rest [37] or lower limb deconditioning [38]. Our RSI patients, however, did not differ from healthy peers in sport activities, whilst RSI patients also reported a normal use of the affected arm during daily life. Although it is difficult to measure the exact workload of the affected arm during daily activities, we do not believe that differences in (local) physical activity level explain our results. The presence of endothelial dysfunction in patients with RSI may contribute to an attenuated dilatation, and therefore a lower supply of blood, under various conditions. Indeed, we found that RSI patients demonstrated an attenuated exercise-induced blood flow in the affected forearm. Moreover, the level of endothelial dysfunction was significantly related to the exercise-induced blood flow in RSI patients; indicating that a low endothelial function is related to a low exercise-induced blood flow. The attenuated blood flow response to exercise in RSI patients is in agreement with a recent study [15, 18]. Brunnekreef *et al.* (2006) found that forearm oxygen consumption, which is assumed to be closely related to blood flow, was attenuated in the affected forearm after handgrip exercise [15]. The observation of an attenuated exercise-induced blood flow may have clinical consequences. The attenuated blood flow and diminished removal of waste products of the metabolic processes during exercise may contribute to an early nociceptor stimulation and early fatigue. The impaired blood flow responses may therefore contribute to the typical RSI symptoms that are evoked during repetitive movement tasks. Although suggestive at this stage, the impaired endothelial function may play an important role in the pathophysiology of RSI.

Our observation of endothelial dysfunction and lower blood flow in patients with RSI raises an important question whether these changes are a predisposing factor in the development of RSI or are simply a consequence of RSI. Previous studies have identified female gender, Caucasian race, an increasing age, lower education, low self-reported physical fitness, psycho-neuroticism and perfectionism [39], the level of job dissatisfaction without support from colleagues or supervisor [40], and problematic muscle relaxation [41] as risk factors for the development or maintenance of RSI symptoms. Whether a physiological impaired endothelial dysfunction also plays a role in the development or continuation of RSI symptoms

6

should be addressed in future research, for example by examining RSI symptoms after improvement of FMD or by examining whether an *a priori* impaired FMD predicts future development of RSI symptoms.

Clinical implications

Our observation of endothelial dysfunction and attenuated exercise-induced blood flow in RSI provides a potential target for future interventions in RSI patients. Previous studies have examined the potential of (handgrip) exercise training to improve brachial artery endothelial function. Assuming the presence of endothelial dysfunction before training, such as found in patients with cardiovascular disease, (handgrip) exercise training leads to significant improvement in conduit and resistance artery endothelial function [42]. Exercise training may therefore be a potentially beneficial intervention in RSI patients. Whether exercise training in RSI improves brachial artery endothelial function and/or alleviates RSI-specific symptoms remains to be elucidated. An alternative therapeutic approach to improve endothelial function relates to the administration of vasoactive drugs, which may improve exercise-induced peripheral blood flow in RSI. In addition, on the basis of the predictive capacity of the brachial artery FMD for future cardiovascular events [43], the lower FMD may be interpreted as an increased risk for cardiovascular disease. However, to the best of our knowledge, there is no longitudinal or cross-sectional data that supports the presence of an increased cardiovascular risk in patients with RSI. Moreover, endothelial function is lower in the affected forearm compared to the non-affected forearm in unilateral RSI, making it unlikely that endothelial function of the affected forearm reflects endothelial function of coronary arteries.

A possible limitation of our study was that the comparison between the affected and non-affected arm within patients with RSI was performed in a small population (n=6). However, this analysis relates to a within subject comparison, whilst limited variation in FMD was present. This may have contributed to the observation of a statistically significant difference between both arms in this relatively small group of patients. Therefore, including a larger cohort of unilateral RSI patients unlikely alters the primary findings of this study. Another limitation of the study was that we cannot rule out the possibility that the impaired endothelial function in RSI relates to changes in the endothelium-independent dilation. Nonetheless, this does not invalidate our principle finding of an impaired brachial artery response to a 5 minutes ischemia (i.e. FMD) or blood flow response to handgrip exercise in RSI patients. Future research is warranted to further investigate whether a change in smooth muscle cell sensitivity underlies our novel findings.

Conclusion

In conclusion, our study is the first to reveal that patients with RSI demonstrate an impaired endothelial function and an attenuated exercise-induced brachial artery blood flow in the affected forearm. Moreover, we found that the degree of endothelial dysfunction relates to the attenuated exercise-induced blood flow in patients with RSI. These findings may importantly contribute to understand the pathophysiology of RSI, and support a detrimental role for endothelial dysfunction in RSI.

6

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6

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6

Chapter 7

General discussion

Despite the high incidence and related socio-economic consequences of RSI, relatively little is known about its pathophysiological background. The general aim of this thesis is to gain better insight into the pathophysiology of RSI, especially focusing on potential alterations in the local muscle vasculature. In this final chapter, findings of our study are summarized and discussed with current literature, and future perspectives are indicated.
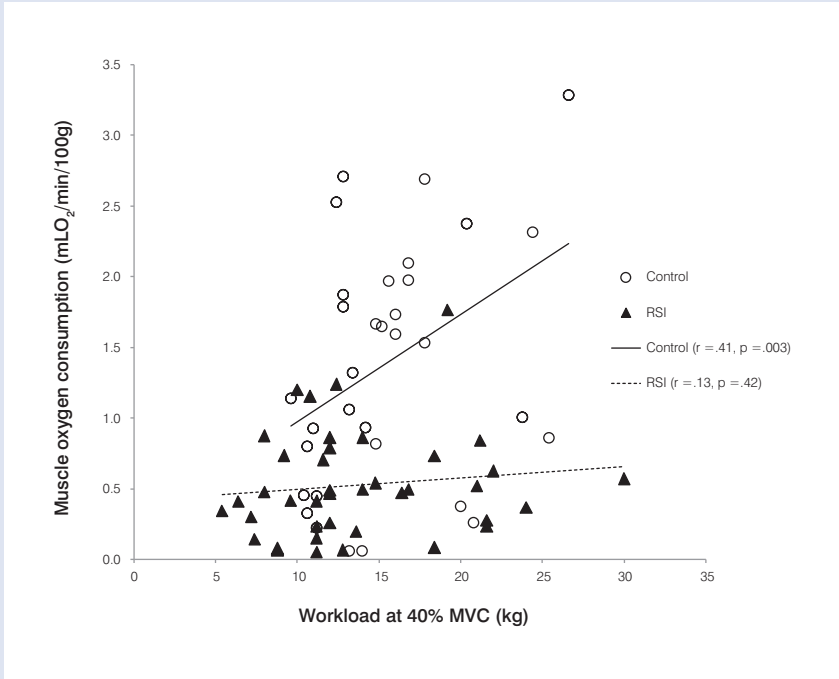
RSI is as old as the industry itself

RSI is not a new phenomenon. In *chapter 1*, we report that RSI was already observed in office clerks as far back as 1713 [1]. The nomenclature has been debated for almost 300 years, and resulted in names like; writer's cramp [2], scrivener's palsy [3], occupational neuroses [4], telegraphist's cramp [5], and, more recently, complaints of the arm, neck, and shoulder (CANS) [6]. In 1982, at the start of the era of personal computer technology, the combination of symptoms was referred to as RSI. The term RSI was introduced probably as a reference to the repetitive and small movements of the hand that frequently induce serious complaints in the upper limbs of computer workers [7]. Inventing new names for the same condition has not served RSI well, especially for the recognition of patients who suffer from this disease. The various names for RSI also demonstrate that the etiology has been topic of debate for many decades, as some refer RSI to neurological signs ('neuroses') and others to muscular signs ('cramps' or 'palsy'). On the basis of the evidence that is presented in this thesis, we hypothesize that RSI complaints can also be attributed to physiological changes of the local blood flow and vasculature. Although these findings may provide a rationale to re-name RSI around a vascular angle, I would not support renaming RSI.

Oxygen consumption and blood flow

In *chapter 2 and 3*, we assessed local muscle oxygen consumption and blood flow in forearm muscles of patients with bilateral RSI and in patients with unilateral RSI. At baseline, differences in oxygen consumption and blood flow were observed between the affected forearm muscles of patients with RSI and the dominant arm of control participants. During exercise, patients with unilateral RSI and patients with bilateral RSI both demonstrated a lower oxygen consumption and a lower blood flow post-exercise in the affected muscle of the forearm. Although this subject has only been studied occasionally in the literature, these findings are complimentary with other studies that indicates signs of a lower blood flow [8-10] and a lower vasodilator function [11] in patients with RSI. When we look more closely to the relationship between the oxygen consumption and exercise intensity, by combining the results of *chapter 2 and 3*, we see that oxygen consumption is significantly correlated with the workload of the forearm in healthy control participants.

7

Interestingly, no such correlation is found in patients with RSI (Figure 1).

Figure 1 Relation between muscle oxygen consumption and workload of the forearm

This finding demonstrates that in patients with RSI, there is a disturbed relation between increases in workload and increments in oxygen consumption. Possibly, the arteries in the affected arm of patients with RSI vasodilate less with exercise or, alternatively, oxygen demand, and therefore the demand for blood flow, in the affected arm of RSI is simply lower than in healthy control participants. In *chapter 6,* we found evidence that supports the presence of a lower oxygen supply, since we found a hampered blood flow during exercise. In addition to this, the endothelial function of the brachial artery was also lower in patients with RSI. When arteries have a lower ability to vasodilate during exercise, this likely results in a lower or insufficient nutrient flow (i.e. supply of oxygen) to the working muscle. On the other hand, redundancy in oxygen delivery is large, the muscle does not consume all oxygen that is available to him. A lower endothelial function, therefore, may partly explain the impaired relation between workload and oxygen consumption as well

as the lower oxygen supply to the exercising muscles in patients with RSI. In *chapter 5,* we found evidence that patients with RSI have a larger amount of fast twitch type II fibers. The fast twitch type II fiber is less dependent on oxygen that is availability to him during exercise. Also other studies found some evidence for changes in muscle fiber type and/or muscle fiber content, such as a lower amount and/or quality of mitochondria in patients with RSI [10, 12-14]. An impaired mitochondrial function supports the observation of a lower oxygen consumption during exercise in patients with RSI. Finally, the lower local muscle oxygen consumption might also indicate more anaerobic metabolism in muscles of patients with RSI. A higher anaerobic metabolism in RSI has also been suggested by one study [15], and leads to an increased production of lactic acid and therefore a more rapid fatigue during exercise. This rapid fatiguing in response to repetitive exercise and early development of pain during such exercise is one of the most important and characteristic complaints of patients with RSI. Taken together, although patients with RSI deliver a similar force with their arm, their local muscle oxygen consumption is lower compared to healthy controls. Whether this is caused by a lower supply or demand for oxygen is currently unknown. This thesis provides evidence that support the importance of both factors.

Unilateral RSI complaint and bilateral vascular changes?

Since many patients with RSI experience RSI complaints at the other arm as well, the pathophysiological background of RSI may be more complex than the presence of a local vascular disturbance alone. Indeed, research that investigated muscular function in RSI occasionally observed muscular changes at the non-affected muscles of patients with RSI [14, 16]. These observations suggest the presence of systemic changes in RSI, rather than local changes alone. In *chapter 3 and 6*, we found evidence to support systemic differences in the vasculature between patients with RSI and their healthy peers. In *chapter 3,* we discovered that at the non-affected forearm, where no symptoms of RSI were experienced, a similarly decreased oxygen consumption and blood flow was found after exercise compared with the affected forearm of patients with unilateral RSI. This finding is new and was not observed by others before. In *chapter 6*, we found a lower endothelial function at the affected arm, but also a trend for a lower endothelial function at the non-affected arm in unilateral RSI patients. This implicates that systemic differences in local muscle oxygen consumption and possibly also in endothelial function are present in patients with RSI. As a consequence, when systemic differences are involved, one might argue that also the non-affected arm of patients with unilateral RSI might be at risk to develop problems over time. Whether the patients that we included in our bilateral RSI study started as unilateral RSI patients, we do not know. Only the

7

duration of RSI symptoms was remarkably longer in patients with bilateral RSI (40.7 months) than in patients with unilateral RSI (28.9 months). This might reflect that RSI starts out as unilateral RSI and gradually evolves in bilateral complaints. However, more research is needed on this topic, and should examine whether patients with unilateral RSI who present systemic vascular changes are prone to develop RSI symptoms in the non-affected arm.

Systemic changes: a predisposing factor for the development of RSI?

The finding of systemic changes in RSI raises another highly important question; 'are these changes a cause or a consequence of RSI?' The current research design of our studies (cross-sectional studies), unfortunately, does not allow to answer this specific question. However, when a lower oxygen consumption and blood flow are related to inactivity that is caused by RSI, one might expect that oxygen consumption would be related to the severity of complains or the duration of RSI symptoms. To examine this hypothesis, we combined the results of *chapter 2 and 3*, and found no significant relation between the duration of RSI, pain intensity, and the forearm oxygen consumption ($p=0.69$ and $p=0.39$, respectively) (Figure 2a and 2b). The fact that there is no relation supports the idea that the lower blood flow and oxygen consumption are part of the pathophysiology of the disease, rather than the result of disuse. It also suggests that the lower vasculature might have already been present and that the onset of RSI symptoms has no effect on it. However, a within-subject comparison will be necessary to truly study this topic. Whether healthy individuals with a lower oxygen consumption, blood flow, or endothelial function are at risk to develop RSI is currently unknown and should be subject for future studies.

RSI: a member of the CRPS-1 family?

In *chapter 4*, we examined oxygen consumption and blood flow in the forearm of patients with chronic complex regional pain syndrome type-1 (CRPS-1). This chronic disabling pain syndrome is known for its alterations in vasculature owing to over-activity of the sympathetic nervous system. The results of our study did not indicate a lower oxygen consumption in the forearm muscles at the affected site, nor at the non-affected site, when compared to healthy control participants. In the other chapters of this thesis, that includes patients with RSI, we consistently found a lower oxygen consumption in forearm muscles that are affected with RSI. This finding was not present in patients with chronic CRPS-1. We found that the affected muscles in patients with CRPS-1 were able to increase their oxygen consumption level with 300% from baseline to exercise. This finding suggests that there is no particular problem in the oxygen supply or demand in forearm muscles of patients with chronic CRPS-1. However, patients experienced pain and had an impaired function of their CRPS-1 hand. An exercise training program to improve the hand

Figure 2 Relation between the muscle oxygen consumption and duration
of RSI (**A**) and pain intensity (**B**)
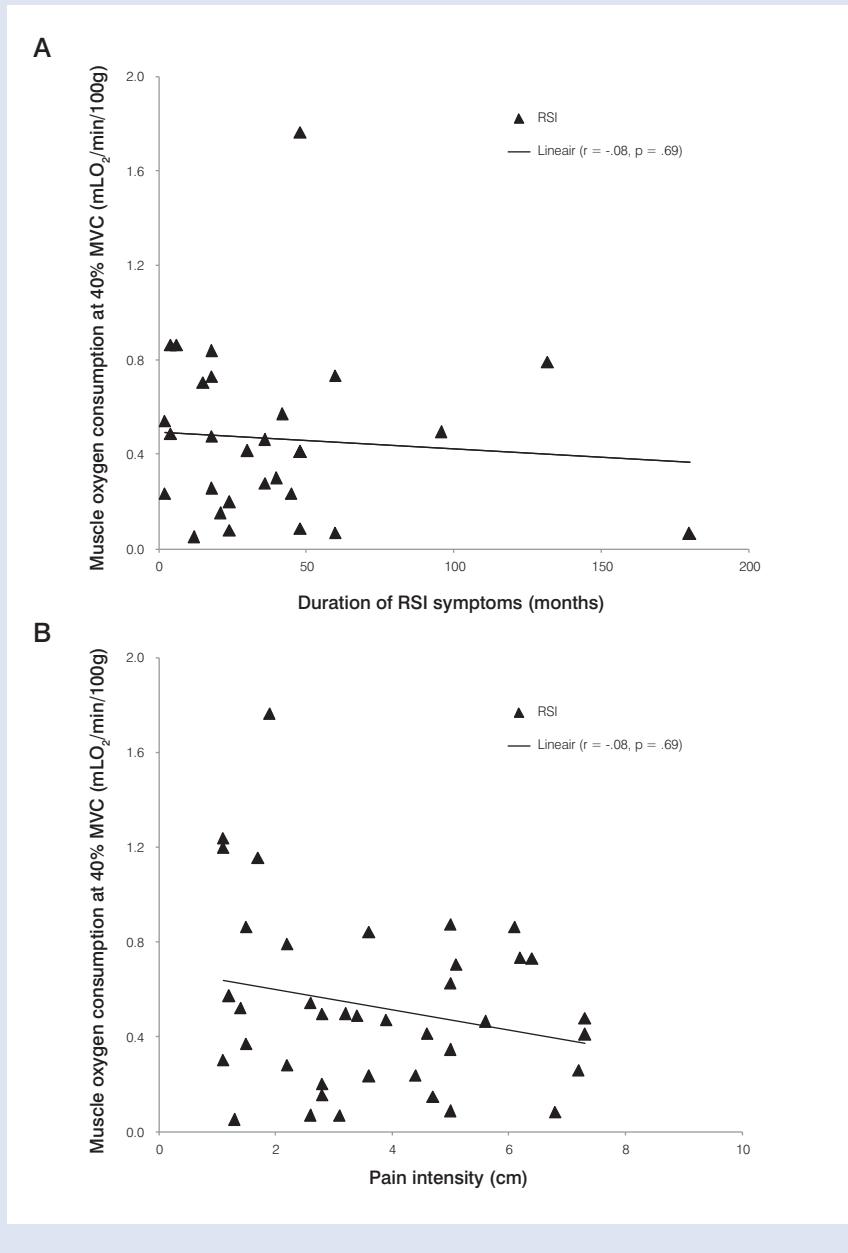
function could be effective. Treatment should also focus on sometimes false assumptions or thoughts that patients with CRPS-1 might have about the origin or prognosis of their pain syndrome. A limitation of this study is that we only studied patients with chronic CRPS-1. Whether this finding also appeals to patients with more acute forms of CRPS-1 is currently unknown. On the other hand, if we do not see changes in muscle metabolism in the severe patients, you may expect that less severe patients show no differences as well. Taken together, the vascular pathophysiology of chronic CRPS-1 is different than the pathophysiology of RSI. Therefore, based on these grounds, we have to consider RSI as being no member of the CRPS-1 family.

Psychosocial factors

Already in 1892, the English neurologist William Gowers observed that many patients with RSI could be characterized by certain psychosocial factors or personal characteristics [17]. He found that many patients were anxious which could be related to family troubles, business worries, or weighty responsibilities. Current studies indeed identified some personal (e.g. age [18], Caucasian race [19], female gender, lower education, low self-reported physical fitness [20]) and work-related psychosocial factors (e.g. psycho-neuroticism, perfectionism [21], or the level of job dissatisfaction without support from colleagues or supervisor [22]). On the other hand, almost every patient that is seen by a doctor or physical therapist has personal or social factors that affects their condition. Interestingly, if we look more closely to the prognosis of RSI, we see that only 9% of the patients fully recover after a period of 4.4 years [20]. This is a devastating prognosis. Note the contrast with presumably related musculoskeletal disorders, such as medial epicondylitis, in which 81% of the patients have a full recovery after a 3 years follow-up period [23]. This again emphasizes the complexity of RSI as a pain syndrome, but also implies that there might be important perpetuating or predisposing factors involved that put patients at risk of developing RSI and maintaining of RSI complaints. Whether these factors have a psychological or physiological origin cannot be answered in this thesis. However, on the basis of the current finding that patients with RSI have physiological changes in blood flow and vasculature, a predisposing or perpetuating factor might very well be of a physiological origin.

Therapeutic consequences

Although some evidence was provided for the effectiveness of exercise therapy in the treatment of RSI [24], many other treatment strategies or combinations, such as massage, behavior treatment, ergonomic adjustments, and manual therapy, are often disappointing [25]. It is therefore important to gain a better understanding of the RSI condition and its underlying pathophysiology. In *chapter 3* we found

evidence that oxygen consumption and blood flow is systemically affected in patients with RSI. This finding implies that the treatment of patients with RSI should not focus on the affected region only, optimal treatment may require a more systemic approach. For example, whole body exercise training has well established beneficial local and systemic effects [26, 27]. Exercise training may, therefore, be an effective strategy for patients with RSI. The presence of systemic changes also suggests that the clinical management of RSI should include proactive assessment of every part functionally involved in the task, even in the absence of symptoms. In addition to exercise training, treatment of RSI might also focus on other established disorders and impairments that are associated with RSI. For example, psychological and social factors that influence the course of RSI. A self-management program, in which patients learn to identify situations that provoke muscular overload, or learn adequate strategies to deal with personal or social influences that facilitate the onset of complaints, may be effective.

The mechanism of RSI

An important aim of the thesis was to provide a better understanding of the patho-physiology of RSI. In this last part, based on the novel findings in this thesis, a new model is introduced that explains important elements that are involved in the pathogenesis of RSI. Since many studies have pointed out a strong relationship between physical exposure and the occurrence of RSI [19, 28-34], repetitive muscle movement was chosen as the starting point of the model (Figure 3).

To meet a higher demand for energy (ATP), and to maintain a stable homeostasis, repetitive muscle movement results in an increase in local muscle blood flow under normal physiological conditions. In a steady-state situations, and with the presence of sufficient oxygen and blood supply available, aerobic oxidation of glucose (and production of ATP) is achieved, without the production and the accumulation of lactic acid. Muscle fibers that are best equipped to perform this type of long-term repetitive movements, at low-forces, are the type I fiber. This fiber contains high amounts of mitochondria and has a high capillary density. When oxygen supply is too low, or the metabolic demand too high, ATP production will shift from aerobic glycolysis towards the anaerobic breakdown of glucose. This results in an increase in the production of metabolites (e.g. lactic acid), which stimulates nociceptors and leads to the experience of pain. Consequently, the stimulation of nociceptors will lead to a change in behavior, most likely resulting in cessation of the movement or lowering the intensity of the repetitive movement. The process above is believed to occur under normal physiological situations in healthy individuals and is reflected in the model with thick solid lines.

7

Figure 3 Model of the pathophysiology of RSI
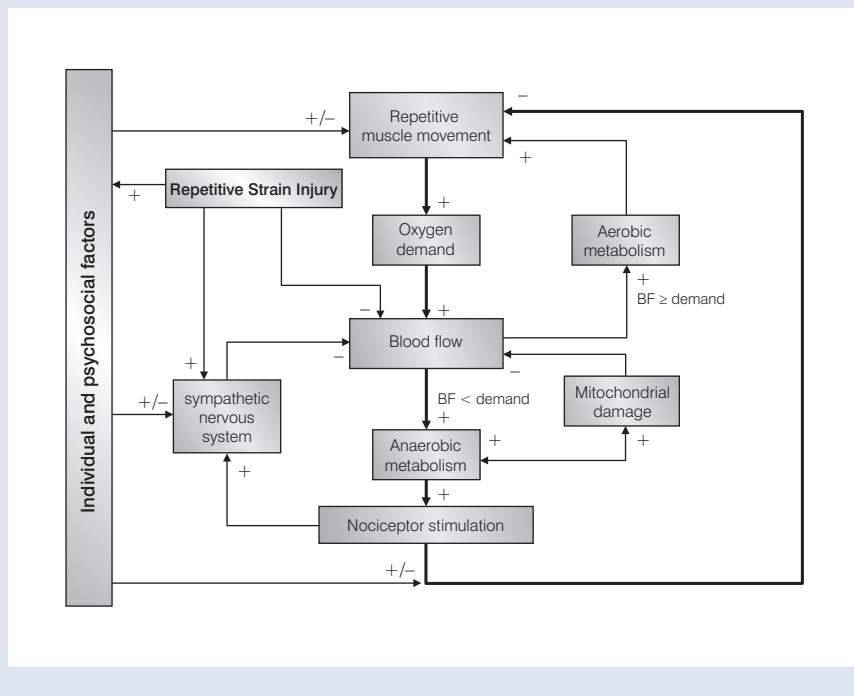
In patients with RSI, a similar process takes place. However, a number of findings in this thesis suggest an interference with this process. First, in c*hapters 2, 3, and 6,* we provide evidence for an impaired blood flow during exercise, an impaired oxygen consumption after exercise, and a lower endothelial function. These processes may interfere with the increase in blood flow that is necessary to meet the increase in metabolic demand. If this process fails, as the results in our thesis suggest, this may lead to a more rapid dependency on the anaerobic glycolysis and more rapid accumulation of metabolic waste products. Consequently, this leads to nociceptor stimulation and cessation of the repetitive movement.

In *chapter 5*, we found a larger amount of type II fibers. These fast-twitch fibers are sub-optimally equipped for repetitive movements that are sustained for a long period of time. Presumably these fibers sooner shift towards an anaerobic metabolism when performing long-term repetitive movements. In addition to morphological changes, psychological factors are also suggested to play a role in the etiology of RSI. Their influence on muscle blood flow runs through the sympathetic nervous system.

In a pathological situation, where a person experiences higher levels of stress, e.g. due to a combination of extreme job demands, perfectionism, and other job related stressors, the activity of the sympathetic nervous system increases. The increase in sympathetic activity leads to a decrease in local muscle blood flow, and lower washout of waste products from the exercising muscle [35]. This facilitates the occurrence of anearobic metabolism. In addition, personal and psychosocial factors also have a strong influence on the performance of the repetitive muscle movement itself. They determine whether a person stops or ignores the nociceptor stimulation, and continues working.

Another factor in the model that has an important effect on local muscle blood flow is the occurrence of tissue damage. Prolonged repetitive muscle activity is known to cause tissue damage [36]. Especially, mitochondrial damage has an important influence on the ATP production. A lower production of ATP will lead to a sooner shift from aerobic towards an anaerobic metabolism. The production of lacid acid stimulates nociceptors. Pain is a powerful stressor, since pain increases the secretion of stress hormones via adrenal glands of the kidney and the sympathetic nervous system. These stress hormones (e.g. noradrenaline) stimulate the sympathetic nervous system and decreases the local muscle blood flow. By stimulation of metabolite accumulation, more nociceptor stimulation occurs. This process has a vicious circular character. Interestingly, long-term exposure to pain can also cause reduction in pain threshold by central sensitization for pain. The clinical manifestation of this is that patients do not only experience local pain, but experience referred pain in their whole upper extremity region. Whether some individuals experience RSI symptoms sooner than others, depends on the persons capacity and the variability of the involving factors. For example, some individuals are able to keep a stable muscle homeostasis much longer under difficult circumstances than others. In addition, some individuals are more sensitive to stress, feel more obligated to ignore pain, or have a different individual pain tolerance than others. These variability's in personal and social factors give variation in the outcome of the model. However, we believe that the model, in its essence, applies to any individual or situation. Future preventative and therapeutic efforts could be designed on the basis of the elements that are described in this model.

7

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7

Chapter 8

Summary

The introduction of the personal computer in the 1980s coincided with a revived interest in chronic arm pain, namely a musculoskeletal pain-related, over-use syndrome that involves the upper extremity, shoulder, and neck and that was previously referred to as writer's cramp or occupational neuroses. This time, the condition was renamed repetitive strain injury (RSI). Three decades later, however, an effective treatment strategy has still not been developed. One potential explanation for this is that the pathophysiological mechanism of RSI is poorly understood. Therefore, the main focus of this thesis was to gain a better understanding of the pathophysiology of RSI, with a specific focus on the role of the vasculature.

In **chapter 1** the term RSI was reviewed from a historical perspective. Current knowledge about potential muscular, vascular, neural, and psychological mechanisms that may relate to the development of RSI were also presented. When current knowledge regarding potential underlying mechanisms for the development of RSI was combined, a 'gap' emerged in the field of the vasculature. The final part of **chapter 1** dealt with the purpose and hypotheses of the studies presented in this thesis and the applied research methods.

In **chapter 2** local muscle blood flow, oxygen consumption, and post-ischemic reoxygenation were examined with near-infrared spectroscopy in the forearm muscles of patients with RSI symptoms in both arms (bilateral RSI) and control participants at rest and immediately after handgrip exercise. The results suggested that muscle oxygenation and blood flow immediately after exercise are lower in the forearms of individuals with bilateral RSI compared with healthy controls. This finding indicates the presence of an impaired oxygen consumption and blood flow response to exercise in patients with RSI.

In **chapter 3** forearm muscle blood flow and oxygen consumption at the affected and non-affected forearm in patients with unilateral RSI were examined. We hypothesized that hemodynamic responses to exercise are lower at the affected, but normal at the non-affected forearm in patients with unilateral RSI. Hemodynamic variables were measured using near-infrared spectroscopy at rest and after incremental stages of handgrip exercise. Blood flow and oxygen consumption after exercise were lower at the affected site, but we also found a similarly impaired blood flow and oxygen consumption in the non-affected forearm. This finding suggests that systemic changes in the vasculature of both forearms are present in patients with unilateral RSI, despite the unilateral character in clinical symptoms.

8

The scientific literature indicates some conspicuous similarities between RSI and other chronic pain syndromes, like the complex regional pain syndrome type-1 (CRPS-1). These observations suggest that both syndromes may follow a common pathway. Therefore, in **chapter 4** local muscle blood flow, oxygen consumption and post-ischemic reoxygenation were measured with near-infrared spectroscopy in forearm muscles of patients with chronic CRPS-1 and controls at rest and immediately after handgrip exercise. Our hypothesis that patients with CRPS-1 demonstrate lower blood flow and oxygen consumption in the affected muscles could not be confirmed. Our results indicate that chronic CRPS-1 is not associated with lower blood flow or oxygen consumption in the affected muscles. CRPS-1 therefore seems to be a different entity from RSI, whilst the vascular impairments may be specific for RSI patients.

Previous studies have demonstrated that muscle function is altered in the impaired upper limb in RSI patients, with type II fibers predominating. In **chapter 5**, we investigated whether such differences in muscle function and fiber type are also present in the lower limbs of upper limb RSI patients so as to establish the potential systemic nature of these findings. Local muscle oxygen consumption was measured with near-infrared spectroscopy in forearm muscles of patients with RSI and control participants at rest and immediately after handgrip exercise. With this we confirmed our previous observations of lower oxygen consumption in RSI patients in the upper limb. In addition to this, quadriceps muscle contractile properties were examined using isometric contractions and electrical stimulations. Patients with RSI demonstrated a leftward shift in the force frequency relationship, which corresponds to a presence of a larger amount of type II fibers in the quadriceps muscle of patients with RSI. These findings suggest that the quadriceps muscles of patients with upper limb RSI demonstrate predominance for type II fibers. On the basis of previous findings from other studies, this observation may reflect a systemic dominance for type II fibers, which could predispose individuals to develop RSI.

The regulation of local blood flow and oxygen consumption is tightly regulated by the endothelial layer in blood vessels. An impaired blood flow under demanding conditions such as exercise, may therefore be related to endothelial dysfunction. In **chapter 6** we examined brachial artery endothelial function and exercise-induced blood flow with duplex ultrasound in patients with RSI and control participants at rest, during handgrip exercises, and after a 5 minutes ischemic occlusion. Our hypothesis that patients with RSI demonstrate a lower endothelial function as well as an impaired exercise-induced blood flow during handgrip exercise was confirmed. Moreover, our results indicated that the degree of endothelial dysfunction was related to the attenuated exercise-induced blood flow. The endothelial

dysfunction might therefore underlie the impaired vasculature in muscles of patients with RSI.

In **chapter 7** the current knowledge on the pathophysiology of RSI was discussed on the basis of previous studies and with the data available from this thesis. We speculated whether the lower local oxygen consumption in RSI was related to a lower oxygen demand or supply of oxygen to the exercising muscle. By combining data from previous chapters, we aimed to gain a better understanding of whether the impaired vasculature might be a predisposing factor in the development of RSI. We also discussed the therapeutic consequences of our findings for patients with RSI and for patients with CRPS-1. Finally, based on the findings of this thesis, a new model was introduced that explains the development of RSI symptoms and how the vasculature contributes to the development of RSI.

8

Chapter 9

Samenvatting

Repetitive Strain Injury (RSI) is een verzamelnaam voor klachten die zich manifesteren aan de nek, schouders, arm en/of hand en ontstaan als gevolg van langdurige, repeterende bewegingen of statische houdingen. Waar deze aandoening voorheen bekend stond als "writers cramp" en "occupational neuroses", werd de aandoening in het begin van het computertijdperk in de jaren ´80 omgedoopt tot RSI. Nu, drie decennia later, is er helaas nog geen effectieve behandeling gevonden voor RSI. Een mogelijk verklaring hiervoor is dat het pathofysiologische mechanisme dat ten grondslag ligt aan deze aandoening nog grotendeels onbekend is. Het doel van dit proefschrift is om meer inzicht te verkrijgen in de pathofysiologie van RSI, door met name de rol van de vasculatuur te belichten.

In **hoofdstuk 1** wordt de aandoening RSI beschreven vanuit een historisch perspectief. Kennis over potentiële musculaire, vasculaire, neurale en psychologische mechanismen die mogelijk ten grondslag liggen aan RSI worden besproken. Het overzicht van de huidige kennis rondom deze mechanismen laat zien dat kennis over de circulatie van het aangedane spierweefsel nog onderbelicht is in de wetenschappelijke literatuur. In het laatste deel van dit hoofdstuk worden de doelen en hypothesen van de verschillende studies van dit proefschrift beschreven en worden de verschillende onderzoeksmethodes toegelicht.

In **hoofdstuk 2** onderzoeken we de lokale doorbloeding en zuurstofopname van de spieren in de onderarm bij patiënten met RSI-klachten aan beide armen (bilaterale RSI) en vrijwilligers zonder klachten. De zuurstofopname en doorbloeding van het spierweefsel werd hierbij gemeten in rust en direct na afloop van een serie hand knijpoefeningen. De niet-invasieve methode Near-Infrared Spectroscopy, ofwel nabij-infrarood spectroscopie (NIRS), werd gebruikt om deze waarden te meten. De resultaten van dit onderzoek laten zien dat patiënten met RSI in de spieren van de onderarm een lagere zuurstofopname hebben tijdens inspanning en een lagere doorbloeding na afloop van inspanning in vergelijking met vrijwilligers zonder RSI. Deze resultaten wijzen op de aanwezigheid van een verstoorde zuurstofopname en doorbloeding tijdens inspanning in de spieren van de onderarm bij patiënten met RSI.

In **hoofdstuk 3** wordt de lokale doorbloeding en zuurstofopname van het spierweefsel gemeten in de aangedane en niet-aangedane arm van patiënten met RSI, waarbij de RSI klachten zich manifesteerden aan één van de armen (unilaterale RSI). De verwachting voorafgaande aan dit onderzoek was dat de aangedane arm een lagere zuurstofopname heeft na hand knijpoefeningen in vergelijking met de niet-aangedane arm alsmede in vergelijking met vrijwilligers zonder RSI. De lokale doorbloeding en zuurstofopname in de spieren werd gemeten met behulp van

9

NIRS in rust en direct na afloop van hand knijpoefeningen met een toenemende intensiteit. De resultaten van dit onderzoek laten zien dat de spieren aan de aangedane zijde een lagere doorbloeding hebben en een lagere zuurstofopname na afloop van de knijpoefeningen in vergelijking met vrijwilligers zonder RSI. Echter, de doorbloeding en zuurstofopname is ook lager in het spierweefsel aan de niet-aangedane zijde. Deze bevinding suggereert dat, ondanks de RSI klachten zich aan één arm manifesteren, er gegeneraliseerde veranderingen in de weefsel-circulatie aantoonbaar zijn in beide armen bij patiënten met RSI.

De wetenschappelijke literatuur laat enkele opvallende overeenkomsten zien tussen RSI en andere chronische pijn syndromen, zoals het complex regionaal pijn syndroom type-1 (CRPS-1). Deze observatie suggereert dat beide syndromen mogelijk ontstaan vanuit eenzelfde oorsprong. In **hoofdstuk 4** onderzoeken we de weefselcirculatie in de spieren van de onderarm bij patiënten met chronische CRPS-1. De doorbloeding en zuurstofopname werden gemeten met behulp van NIRS in rust en direct na afloop van hand knijpoefeningen. De verwachting voorafgaande aan dit onderzoek was dat patiënten met CRPS-1, net zoals aangetoond bij RSI patiënten in hoofdstukken 2 en 3, een lagere doorbloeding en zuurstofopname zouden hebben in de spieren van de aangedane arm. Deze hypothese werd niet bevestigd door ons onderzoek. De resultaten laten zien dat CRPS-1, in een chronisch stadium, niet leidt tot een lagere doorbloeding en zuurstofopname van het spierweefsel aan de aangedane zijde. Deze bevinding suggereert tevens dat CRPS-1 een andere aandoening is dan RSI, waarbij de verlaagde weefselcirculatie meer specifiek lijkt te zijn voor RSI.

Studies die de functie van de spieren van patiënten met RSI hebben onderzocht laten veranderingen zien in de spierfunctie, waarbij meer type II spiervezels werden aangetoond in de spieren van de nek en de spieren van de onderarm. In **hoofdstuk 5** onderzoeken we of dergelijke veranderingen in spiervezel typering ook aanwezig zijn in de benen van patiënten met RSI klachten in de arm. Dit onderzoek is uitgevoerd om de potentiële gegeneraliseerde veranderingen in de weefselcircula-tie, zoals aangetoond in hoofdstuk 3, beter te kunnen begrijpen. De lokale zuurstofopname in de spieren van de onderarm werd hierbij gemeten met behulp van NIRS in rust en direct na afloop van hand knijpoefeningen. Met deze meting bevestigden we onze voorgaande bevinding dat de spieren in de onderarm een lagere zuurstofopname hebben tijdens inspanning. De contractiele eigenschappen van de spieren werden in het bovenbeen onderzocht door middel van isometrische aanspanningen en elektrische stimulaties. Patiënten met RSI laten een verschuiving zien van de kracht-frequentie relatie-curve naar links, hetgeen aangeeft dat er mogelijk meer spierweefsel type II aanwezig is in de spieren van het bovenbeen bij

patiënten met RSI. Op basis van deze bevinding, en bevindingen uit andere studies, kan gesuggereerd worden dat patiënten met RSI een gegeneraliseerde dominantie hebben voor het type II spierweefsel, hetgeen mensen zou kunnen predisponeren om in de toekomst RSI te ontwikkelen.

De regulatie van de lokale doorbloeding en zuurstofopname van het spierweefsel wordt gereguleerd door de binnenbekleding van de bloedvaten, ook wel het vasculaire endotheel genoemd. Een verminderde doorbloeding van spierweefsel tijdens inspanning kan daarom worden veroorzaakt door een verminderde functie van het endotheel. In **hoofdstuk 6** onderzoeken we met behulp van echo Doppler metingen de bloeddoorstroming tijdens hand knijpoefeningen en de functie van het endotheel van de bloedvaten in de arm bij patiënten met RSI en vrijwilligers zonder RSI. De bloedstroomsterkte werd hierbij gemeten in rust, tijdens hand knijpoefeningen met een toenemende intensiteit en na afloop van een 5 minuten durende afsluiting van de bloedvaten. De verwachting voorafgaande aan dit onderzoek was dat patiënten met RSI een lagere endotheel functie en een lagere bloeddoorstroming zouden hebben in de bloedvaten van de aangedane arm. Deze vooronderstelling werd door ons onderzoek bevestigd. Daarbij hebben we tevens aangetoond dat de mate van vermindering van de endotheel functie is gerelateerd aan de afname van de bloedstroomsterkte tijdens inspanning. Een verminderde endotheel functie kan hierdoor een mogelijke oorzaak zijn van de lagere doorbloeding van het spierweefsel bij patiënten met RSI.

Hoofdstuk 7 bevat een algemene discussie over de resultaten uit dit proefschrift en hun relatie tot de resultaten uit eerdere studies. We bespreken of de lagere zuurstofopname in de spieren het gevolg is van een lagere zuurstofvraag of het gevolg is van een lager aanbod van zuurstof naar het spierweefsel. Door de resultaten uit de verschillende hoofdstukken te combineren wordt onderzocht of de lagere doorbloeding van het spierweefsel een voorspellende factor is in de ontwikkeling van RSI klachten. Ook wordt besproken wat de therapeutische consequenties zijn van onze bevindingen voor patiënten met RSI en voor patiënten met CRPS-1. Uiteindelijk wordt op basis van de resultaten uit dit proefschrift een model geïntroduceerd waarmee de ontwikkeling van RSI klachten, en met name de rol die de fysiologie hierin speelt, wordt besproken.

9

Chapter 10

Dankwoord
List of publications
Curriculum vitae

Dankwoord

En dan is het nu, na vele jaren aan dit onderzoek gewerkt te hebben, tijd voor een andere hobby. Ik heb me de afgelopen jaren met veel plezier bezig gehouden met dit onderzoek, maar ben toch blij dat het doel bereikt is en er weer tijd komt voor andere uitdagingen. Promoveren is als een lange reis, waar je naast kennis over onderzoek, ook veel leert over jezelf. Het afleggen van zo'n reis doe je gelukkig niet alleen. In de loop van de tijd zijn er veel mensen geweest die op de een of andere manier een stukje hebben meegelopen en daarmee een bijdrage hebben geleverd aan het tot stand komen van dit proefschrift. Wellicht dat ik niet iedereen hier noem, maar mijn dank is er niet minder om.

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Curriculum Vitae

Jaap Brunnekreef werd op 6 februari 1977 geboren in de stad Groningen. Op 5 jarige leeftijd verhuisde het gezin naar Almelo, alwaar hij het voortgezet onderwijs (HAVO) volgde aan de christelijke scholengemeenschap het Noordik. Na het behalen van zijn eindexamen begon hij in 1994 met de studie Fysiotherapie aan de Saxion Hogeschool in Enschede. Na de studie Fysiotherapie te hebben afgerond was hij enige tijd werkzaam als fysiotherapeut in de eerste lijn. In 1999 startte hij met de studie Biomedische Gezondheidswetenschappen, met als afstudeerrichting Bewegingswetenschappen aan de Radboud Universiteit Nijmegen. Deze opleiding werd in 2002 afgerond. Vervolgens werkte hij gedurende 6 jaar als fysiotherapeut op de afdeling Fysiotherapie Centraal van het UMC St Radboud. In deze periode werd de basis gelegd voor dit proefschrift. Van 2006 tot 2008 was hij naast zijn werkzaamheden als fysiotherapeut, als onderzoeker verbonden aan het Pijn Kennis Centrum van de afdeling Anesthesiologie. In deze periode werd o.a. het onderzoek naar spierdoorbloeding bij CRPS-1 patiënten uitgevoerd. Sinds 2007 is hij parttime werkzaam als onderzoeker op de afdeling Orthopedie van het UMC St Radboud. Alwaar hij zich bezighoudt met de coördinatie van het klinisch na- onderzoek van patiënten waarbij een totale heupprothese is geplaatst. Daarnaast is hij sinds 2007 werkzaam als docent op de opleiding Fysiotherapie van de Hogeschool van Arnhem en Nijmegen. Sinds 2011 is hij naast zijn werkzaamheden als docent, ook lid van de kenniskring van het lectoraat Arbeid en Gezondheid. In 2009 begon hij aan een promotieonderzoek op de afdeling Fysiologie van het UMC St Radboud. Onder begeleiding van Prof. Dr. Maria Hopman en Dr. Dick Thijssen werden de resterende onderzoeken uit dit proefschrift uitgevoerd. Jaap is getrouwd, heeft twee kinderen en woont in Nijmegen.