

No adverse physiological responses to infrared whole body hyperthermia in patients with rheumatoid arthritis and ankylosing spondylitis compared to healthy subjects.

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Abstract: - **PURPOSE:** Since about ten years a new modality for whole body hyperthermia, a compact and user-friendly infrared (IR) 'sauna' has become available. Patients with musculoskeletal disorders report positive effects. **RELEVANCE:** Until now hardly any research was done in this field. Therefore in this study the short-term physiological and clinical effects in healthy subjects and patients with Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) were investigated. **SUBJECTS:** 17 RA patients (3 male, 14 female), 19 AS patients (12 male, 7 female) and 21 healthy subjects (11 male, 10 female) with a mean age (sd) of 47 (13), 45 (10) and 45 (7) years respectively were included in the study. **METHODS AND MATERIALS:** Patients with RA or AS and healthy subjects were treated with whole-body hyperthermia by means of a 30 minutes stay in a IR sauna cabin at an adjusted temperature of 55°C. Before and directly after the sauna treatment in both RA and AS patient groups pain and stiffness and were measured on a 10 centimetres Visual Analogue Scale. Besides that in all groups body weight was measured before and after treatment. Additionally during the treatment heart rate, systolic and diastolic blood pressure, skin surface and core temperature were continuously monitored. Also general well-being during and after treatment was investigated. **RESULTS:** Pain and stiffness improved significantly during treatment; mean between 40% and 60%. The mean weight loss during treatment due to transpiration was significant ($p < 0.001$) in all groups, but it was significantly higher ($p < 0.001$) in healthy subjects (-0.5 kg) than in patients (both RA and AS -0.3 kg). During treatment mean heart rate, skin and core temperature increased significantly ($p < 0.001$) in all groups, while blood pressures showed small but significant declines. No significant differences between groups were observed. On average all subjects felt comfortable during and especially after treatment. **CONCLUSION:** Infra red whole body hyperthermia has statistically significant positive direct effects upon pain and stiffness in RA as well as in AS patients. Looking at the physiological effects, RA and AS patients do not respond differently from age and gender matched healthy controls.

Key-Words: physiology, physiotherapy, infrared hyperthermia, rheumatoid arthritis, ankylosing spondylitis, healthy subjects

1 Introduction

Heat treatment in patients with rheumatic disorders is a well-accepted form of physiotherapy treatment. Through the ages it has been widely used. Initially the basis for local application of heat was largely empirical. In the last few decades more evidence for its beneficial effects has been obtained from clinical

research [1,2]. Pain and stiffness diminish and grip strength and joint function (range of motion) improve after local heat therapy [3]. Although beneficial effects of total body hyperthermia have been reported [4], the methodological quality of the studies is poor [5] and the use of this therapy is not widely spread over Western Europe. Results from studies

concerning Finnish saunas showed good clinical effects for rheumatic and musculoskeletal disorders [6-8]. For a few years a compact and user friendly infrared 'sauna' has become available in the Netherlands. Patients reports and clinical experience appeared to be promising and a recent study showed short-term improvement of pain and stiffness, including a trend towards long-term beneficial effects in Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) [9]. The infrared sauna has the heating effect of a high ambient temperature, like a traditional Finnish sauna, but also due to the physical properties of infrared, some radiant heat penetrates, depending on the wave length, maximally up to 4 mm. into the superficial skin. This may result in different physiological responses compared to the Finnish sauna. For that reason we previously investigated the physiological effects of infrared whole body hyperthermia in young healthy subjects [10]. Fifteen healthy subjects were exposed to heat treatment in an infrared cabin at three different intensities (40°C, 55°C and 70°C). Mean skin surface temperature, core temperature and heart rate increased significantly. Significant loss of bodyweight after treatment was also found. In general a small decrease of systolic and diastolic blood pressure was shown. According to the majority of the subjects the treatment at 70°C was too intense and considered as uncomfortable towards the end of the 30 minutes session. The 55°C mode was well tolerated, but the treatment intensity at 40°C was unsatisfactory. So from that moment the intensity for clinical treatment of rheumatic diseases was chosen at 55°C. Despite the fact that no physiological problems in young healthy subject were encountered, the issue still is how rheumatic patients physically cope with such an intense heat stress. Nevertheless they are dealing with a chronic and systemic inflammatory disease that may be negatively influenced by IR heat. Therefore the purpose of this study is to investigate the influence of whole body IR hyperthermia upon superficial skin temperature, core temperature, heart rate, blood pressure, body weight, wellbeing, perceived pain and stiffness.

2 Patients, subjects and methods

Patients were recruited consecutively from the rheumatology out-patients clinic (JJR) in the general district hospital Medisch Spectrum Twente in Enschede, the Netherlands. All healthy volunteers

were employees from the same hospital.

2.1 Inclusion criteria

People with Rheumatoid Arthritis (RA) according to the revised ARA [11] or with Ankylosing Spondylitis (AS) according to the New York [12] criteria and between 18 and 70 years of age were included. Only patients with chronic disease that had been stable during at least 3 months without change of medications were allowed to participate.

2.2 Exclusion criteria

Patients with signs of acute inflammatory activity as judged by the consulting rheumatologist were excluded; if morning stiffness lasted longer than 1 hour or when more than three joints were actively inflamed. Patients with inflammation activity were not included because heat treatment may aggravate clinical signs in an acute phase of the disease. Patients were excluded who were permanently wheelchair bound or bed ridden. Those with the following co-morbidities were also excluded: heart disease, skin disease, malignancy, asthmatic bronchitis or psychiatric disorders. Healthy subjects who had a history of systemic disease and had been treated by a general practitioner or a hospital consultant for any gastro-intestinal, cardio-vascular or respiratory symptoms during the previous year were excluded.

2.3 Approval

All subjects and patients had previous experiences with traditional Finnish sauna, but not with infrared sauna. After oral and written information about the study and the possible clinical effects and side effects of IR whole body hyperthermia, patients were invited to participate. Informed consent was obtained from all patients and subjects, according to the Declaration of Helsinki. The hospital's ethics committee approved the study design.

2.4 Treatment

The subjects were treated in the Health Company Infrared Cabin (The Health Company, PO Box 321, 2400 AH Alphen a/d Rijn, the Netherlands), which was 130 cm x 90 cm x 190 cm in size. The temperature in the cabin can be adjusted from normal ambient room temperature up to 90°C. The subjects were seated in the infrared cabin, which has 6 heating sources; 3 at the back, 2 in front besides the entrance

and 1 under the bench behind the lower legs of the subjects. The infrared used in this study had an ultra long wavelength between 5.000 nm and 1.000.000 nm. All treatments were given between 1 and 6 pm. During one single session, the subjects were treated in the infrared cabin for 30 minutes at an adjusted temperature of 55°C. According to the manufacturers recommendation a pre-heating time of 15 minutes was used. Before the session, the subjects sat in bathrobe next to the cabin to relax for 15 minutes. Their left knee was not covered with the bathrobe but was exposed to the environment (mean ambient temperature outside the cabin during the study was 22°C). This was done to create comparable baseline values because during treatment, skin temperature was recorded over the knee joint. During the 30 minutes of infrared treatment the subject sat naked on the bench in the middle of the infrared cabin and no drinks were provided during that time. Leaning against the wall of the cabin was not allowed.

2.5 Measurements

Before, during and after this single treatment session, several measurements were taken to monitor the subject's physiological condition.

2.5.1 Skin and core temperature

The skin surface temperature was measured on the left knee using a flexible Exacon S-01 (Polystan Benelux, De Steiger 172, Almere-Haven, The Netherlands) probe. The tip of the probe was placed over the joint line between the medial femoral condyle and the medial aspect of the tibial plateau. The measuring tip of the probe was protected from direct influence of the infrared radiation by a 0.3 cm-thick felt layer and fixed to the skin with tape. The possibility of temperature conduction through the probe to the measuring tip was investigated. Heat application to the wire of the probe did not change the temperature as measured at the tip, indicating good isolation of the probe [13].

A flexible Ellab rectal probe (Lameris Medical Equipment, Groenekanseweg 10 3737 AG Groenekan, the Netherlands), covered with a plastic coating, was used to measure core temperature. The subjects were instructed to insert the probe by themselves.

Both probes were introduced into the infrared cabin through a small hole (diameter 2 cm.) in the window and connected to an Exacon MC 9200 medical

thermometer with a measuring range of -80°C to 120°C and an accuracy of $\pm 0.1^\circ\text{C}$. The Exacon thermometer was connected to an Exacon RC-2120 recorder for continuous recording of the skin surface and core temperature for at least 30 minutes of treatment.

2.5.2 Blood pressure and heart rate

A Dynamap CCU (Portanje, Kabelweg 44, 1014 BB Amsterdam, the Netherlands) was used to measure systolic and diastolic blood pressure and for measuring heart rate. The cuff of the Dynamap was wrapped around the left upper arm of the subjects and measurements were taken every 5 minutes directly before, during and up to end of treatment.

2.5.3 Body weight

Before and after infrared treatment every subject was weighed naked on a SECA 711 Mechanical Column Scale (SECA gmbh & Co, Hammer Steindamm 9-25, 22089 Hamburg, Germany)

2.5.4 Wellbeing

The subjects scored their well being on a 5-point ordinal Likert scale (1 = very uncomfortable, 2 = uncomfortable, 3 = neutral, 4 = comfortable, 5 = very comfortable). This measurement was taken 15 and 30 minutes after the start of the treatment, when they were still in the infrared cabin and 30 minutes afterwards.

2.5.5 Pain and stiffness perception

Besides these physiological measurements the AS and RA patients were asked to score their perceptions of pain[14] and stiffness[15] just before and after treatment on a 100 millimeters Visual Analogue Scale.

2.6 Statistical analysis.

Normally distributed continues data were expressed as means with standard deviations or 95% confidence intervals. This was done with the descriptive statistics explore command in SPSS 17.0 [16] by making histograms, scatter graphs, normality plots, normal curves and carrying out normality tests (Kolmogorov–Smirnov and Shapiro–Wilk). The median was additionally used for presenting central tendency in not normally distributed data. Nominal and ordinal data are presented in frequency tables. Differences within and between groups were

Table 1: Patients' characteristics			
	RA patients	AS patients	Healthy subjects
Gender	3 male, 14 female	12 male, 7 female	11 male, 10 female
Age	47 sd 13 (26-70)	45 sd 10 (23-58)	45 sd 7 (39-55)
Disease duration	13 sd 10 (3 – 29)	21 sd 10 (4 – 40)	
Mean in years; Standard Deviation (Minimum – Maximum); RA rheumatoid arthritis, AS ankylosing spondylitis.			

Table 2: Summary of effects on physiological variables			
	RA patients	AS patients	Healthy subjects
Heart rate (beats/min)			
Treatment begin	87 (79 – 95)	82 (75 – 89)	82 (75 – 89)
Treatment end	115 (106 – 124)	112 (104 – 120)	110 (102 – 118)
difference	28 (20 – 35) **	30 (24 – 36) **	28 (21 – 35) **
Skin temperature (°C)			
Treatment begin	32.1 (31.4 – 32.8)	32.6 (31.9 – 33.3)	33.0 (32.4 – 33.7)
Treatment end	38.1 (37.7 – 38.4)	37.9 (37.5 – 38.2)	38.6 (38.2 – 38.9)
difference	6.0 (5.2 – 6.8) **	5.3 (4.7 – 5.9) **	5.5 (5.1 – 6.0) **
Core temperature (°C)			
Treatment begin	37.4 (37.2 -37.7)	37.1 (36.9 – 37.4)	37.0 (36.8 – 37.2)
Treatment end	37.8 (37.6 – 38.0)	37.6 (37.4 – 37.8)	37.8 (37.6 – 37.9)
difference	0.4 (0.3 – 0.5) **	0.4 (0.3 – 0.5) **	0.7 (0.5 – 0.9) **
Systolic Blood pressure (mmHg)			
Treatment begin	131 (124 – 139)	134 (127 -141)	130 (124 – 137)
Treatment end	119 (111 – 127)	119 (112 – 127)	125 (118 – 132)
difference	-12 (-22 - -1) *	-14 (-21 - -8) **	-5 (-12 – 5)
Diastolic Blood pressure (mmHg)			
Treatment begin	78 (72 – 85)	81 (74 – 87)	80 (75 – 86)
Treatment end	67 (62 – 73)	66 (60 – 71)	72 (66 -77)
difference	-11 (-21 – 0) *	-15 (-22 - -7) **	-9 (-14 - -4) **
Body weight (kg)			
Treatment begin	76.6 (68.5 – 84.7)	76.6 (72.0 – 81.2)	72.6 (68.8 – 76.8)
Treatment end	76.3 (68.2 – 84.4)	76.4 (71.7 – 80.9)	72.1 (68.1 – 76.1)
difference	-0.3 (-0.4 - -0.2) **	-0.3 (-0.3 – 0.2) **	- 0.5 (-0.6 - -0.5) **
Mean (95% CI); RA rheumatoid arthritis, AS ankylosing spondylitis.			
* p<0.05, ** p<0.001.			

respectively analysed by means of repeated measures analysis with Bonferroni correction. For non-parametric data (Wellbeing on an ordinal Likert scale) within groups Wilcoxon Signed Rank Test for related samples was applied. For comparison between groups the Kruskal Wallis test was applied. Level of significance (α) was chosen at 0.05. All Statistical calculations were done using SPSS 17.0 for Windows.

3 Results

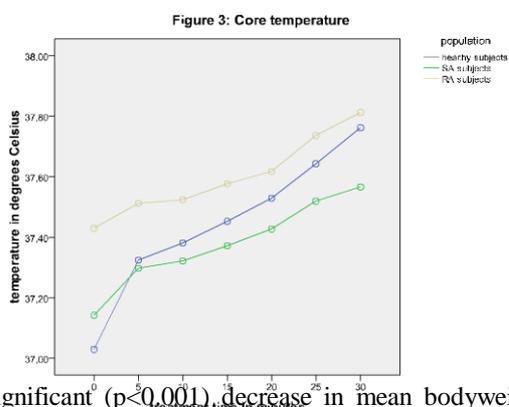
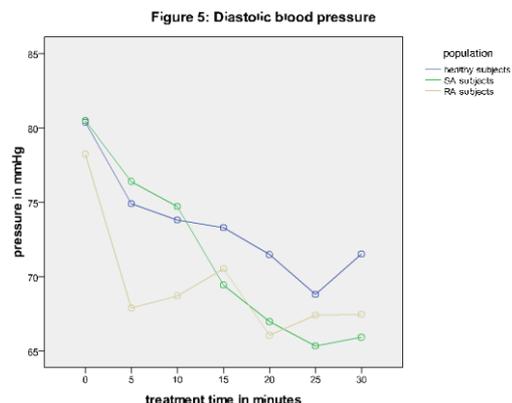
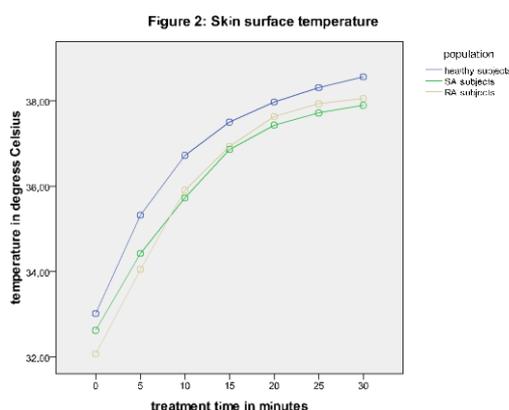
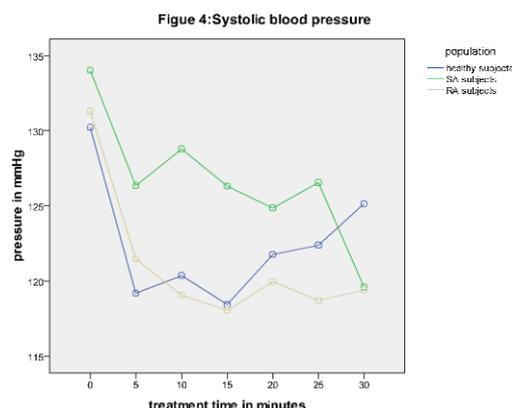
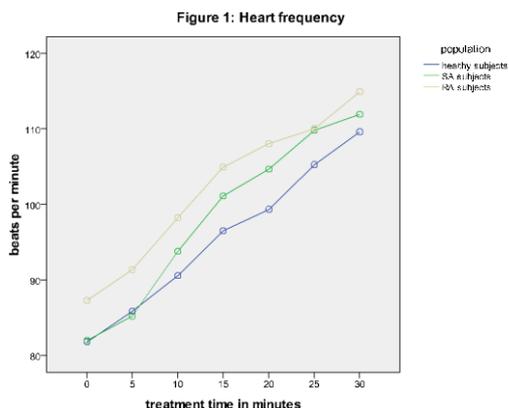
All invited patients agreed to cooperate in the study, only one AS patient could not participate due to non medical reasons.

In total 57 subjects took part in the study; 17 RA patients, 19 AS patients and 21 healthy volunteers. Subject's characteristics age, gender and disease

duration are summarized in table 1. No statistically significant differences were found between subgroups.

Table 2 shows the changes in heart frequency, skin surface and core temperature, and blood pressure. Comparing the start to the end of the treatment, mean heart rate and skin and core temperature increased statistically significant ($p<0.001$) within groups. Both mean systolic and diastolic blood pressure decreased statistically significant ($p<0.05$ or $p<0.001$) within all groups. Only the decrease in systolic blood pressure in the healthy subjects group was not statistically significant ($p=0.12$). Between groups no statistically significant differences were found (Table 2). The similarities between groups is illustrated in figures 1-5.

All three groups demonstrated a small but statistically



significant ($p < 0.001$) decrease in mean bodyweight following treatment (Table 2). The healthy subject lost statistically significant ($p < 0.001$) more weight than RA and AS patients.

All subjects felt comfortable during and after the treatment session. Especially after treatment, 84.2% to 88.5% in each group felt comfortable or even very comfortable (Table 3). There was no statistically significant difference in wellbeing as measured between the two first instances (during treatment), although the AS patients felt less comfortable towards the end of treatment, but a half an hour after they almost all felt (very) comfortable (Table 3). The perceived wellbeing 30 minutes

after treatment in all groups showed better statistically significance compared to the other two measurement points ($p < 0.01$). Between groups no statistically significant differences were detected.

The improvement of pain and stiffness in RA and AS patients during an infrared session was clinically relevant and also statistically significant (Table 4).

4 Conclusion

Patients with non-acute Ankylosing Spondylitis and Rheumatoid Arthritis respond to IR whole body hyperthermia in the same way as healthy subjects with comparable age. Despite their stable inflammatory disease, physiological reactions to heat stress do not differ from healthy persons. From that point of view there are no contraindications for IR whole body hyperthermia. Besides that, clear clinically beneficial direct effects upon pain and stiffness were observed. So immediate symptomatic relief, without aggravation of inflammatory disease activity seems to be feasible.

5 Discussion

Large increases in skin surface temperature were found during treatment (mean changes from 5.3°C to

Table 3: Wellbeing during and after IR sauna						
RA patients	After 15 minutes		After 30 minutes		30 minutes after treatment	
	n*	%	n*	%	n*	%
1	0	0	2	11.8	0	0
2	2	11.8	2	11.8	0	0
3	3	17.6	2	11.8	2	11.8
4	10	58.8	9	52.9	10	58.8
5	2	11.8	2	11.8	5	29.4
AS patients						
1	0	0	3	15.8	0	0
2	4	21.1	4	21.1	1	5.3
3	3	15.8	4	21.1	2	10.5
4	10	52.6	2	10.5	10	52.6
5	2	10.5	6	31.6	6	31.6
Healthy Subjects						
1	0	0	0	0	0	0
2	0	0	3	14.3	0	0
3	6	28.6	7	33.3	3	14.3
4	12	57.1	7	33.3	9	42.9
5	3	14.3	4	19.0	9	42.9

* Number of patients; 1 = very uncomfortable, 2 = uncomfortable, 3 = neutral, 4 = comfortable, 5 = very comfortable, RA rheumatoid arthritis, AS ankylosing spondylitis

Table 4: Immediate clinical effects				
	Pain		Stiffness	
	Before	After	Before	After
RA patients	25 (13 - 36) 20	15 (6 - 25) 10*	25 (15 - 36) 31	12 (6 - 18) 12*
AS patients	26 (18 - 34) 28	14 (6 - 22) 7*	41 (29 - 53) 38	17 (8 - 26) 6**

VAS, 0-100 mm; Mean (95%CI) and Median; * p < 0.01; ** p < 0.001, RA rheumatoid arthritis, AS ankylosing spondylitis.

6.0°C). However the mean core temperature increased only slightly (0.3°C tot 0.5°C) but significantly. To our knowledge no previous studies concerning infrared whole body hyperthermia treatment were performed. Although not quite comparable, studies in healthy subjects investigating the effect of Finnish dry heat sauna showed mean core temperature increases of 0.8°C to 2.9°C [17-20]. The differences between these results and those from our study can be explained by the relatively lower cabin temperature during infrared treatment. In most of these studies the core temperature was not measured rectally, but the sublingual or oral temperature was chosen as an estimate for the core temperature, which may have influenced results. It appears that the human physiological temperature-regulation system in healthy subjects as well as in rheumatic patients is capable of maintaining the core

temperature at values between 37°C and 38°C, despite moderate to severe ambient temperature increases and radiant heat from the infrared devices. In order to achieve this homeostasis, physiological mechanisms such as increased perspiration and vasodilatation of superficial skin vessels occur. These phenomena were also found in our study. Subjects lost between 0.3 and 0.5 kg of bodyweight during treatment, probably due to the increased perspiration. In a previous study we found significant correlations of -0.51 (p=0.05), -0.58 (p=0.04) and -0.91 (p=0.01) respectively at increasing cabin temperature intensities, between the loss of bodyweight on one hand and the increase of relative humidity during treatment on the other hand [10]. Due to the vasodilatation of superficial vessels, a decrease in blood pressure can be expected. To compensate for these lower values predominantly the

heart rate and the cardiac output are increased. As mentioned in our study only small and irregular decreases of blood pressure were found and the heart rate increased clearly (Table 2, Fig. 1, 4 and 5). In previous studies dealing with the effects of Finnish sauna [18-20] there have been similar findings of an average increase in heart rate and a slight decrease in diastolic blood pressure. From the literature [18-20] hardly any changes in systolic blood pressure were found during sauna treatment, however our subjects showed a decrease in systolic blood pressure. A reasonable explanation for this discrepancy is not available at this moment.

As far as we know from literature searches in Medline, Embase, Cinahl, EBSCOhost, Cochrane library, in the database of the documentation centre from the Dutch National Institute for Allied Health Care and from an extensive hand search, our study is the first to investigate the physiological effects of infrared whole body hyperthermia in patients and comparable healthy controls. Although people with rheumatic diseases or disorders of the musculoskeletal system have reported infrared whole body hyperthermia treatment to be beneficial and some immediate effects are relatively proven, further research is necessary. Especially controlled longitudinal studies investigating the long term outcome and possible side effects are warranted.

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References:

- [1] Robinson VA, Brosseau L, Casimiro L, Judd MG, Shea BJ, Tugwell P, Wells G. Thermotherapy for treating rheumatoid arthritis. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: D002826. DOI:10.1002/14651858.CD002826.
- [2] French SD, Cameron M, Walker BF, Reggars JW, Esterman AJ. Superficial heat or cold for low back pain. Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004750. DOI: 10.1002/14651858.CD004750.pub2.
- [3] Oosterveld FGJ, Rasker JJ. Treating Arthritis With Locally Applied Heat or Cold. *Semin Arthritis Rheum* 1994;24:82-90.

Rheum 1994;24:82-90.

- [4] Sukenik S, Abu-Shakra M, Flusser D. Balneotherapy in autoimmune disease. *Isr J Med Sci* 1997;33:258-61.
- [5] Verhagen AP, Bierma-Zeinstra SMA, Cardoso JR, de Bie RA, Boers M, de Vet HCW. Balneotherapy for rheumatoid arthritis Cochrane Database of Systematic Reviews 2004 Issue 1. Art. No.:CD000518.DOI:10.1002/14651858.CD000518.
- [6] Isomäki H. The sauna and rheumatic diseases. *Ann Clin Res* 1988;20:271-275.
- [7] Nurmikko T, Hietaharju A. Effect of exposure to sauna heat on neuropathic and rheumatoid pain. *Pain* 1992;49:43-51.
- [8] Kukkonen-Harjula K, Kauppinen K. Health effects and risks of sauna bathing. *Int J Circumpolar Health*. 2006;65(3):195-205.
- [9] Oosterveld FGJ, Rasker JJ, Floors M, Landkroon R, van Rennes R, Zwijnenberg J, van de Laar MAFJ, Koel GJ. Infrared sauna in patients with rheumatoid arthritis and ankylosing spondylitis. *Clin Rheum*. 2009;28:29-34.
- [10] Oosterveld FGJ, Westhuis B, Koel GJ, Rasker JJ. Infrared Sauna and Healthy Subjects; the Physiological effects of Hyperthermia. *Herb Compl Med*. 2002;3(2):40-52.
- [11] Arnet FC, Edworthy SM, Bloch AD et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
- [12] Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for Ankylosing Spondylitis: a proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:315-24.
- [13] Oosterveld FGJ, Rasker JJ, Jacobs JWG, Overmars HJA. The effect of local heat and cold therapy on the intraarticular and skin surface temperature of the knee. *Arthritis Rheum* 1992;35:146-151.
- [14] Melzack R and Katz J. Pain measurement in persons in pain. In: Wall PD and Melzack R, ed. *Textbook of pain*. Ed. 3. Edinburgh: Churchill Livingstone, 1994: 337-51.
- [15] Oosterhof J. The reliability of Visual Analogue Scale measurements for stiffness in patients with rheumatoid arthritis. Amersfoort, NPI, 1992.
- [16] SPSS Inc. *SPSS Base 17.0 User's Guide*. Upper Saddle River, NJ, Prentice Hall, 2009.
- [17] Jezova D, Kvetnansky R, Vigas M. Sex differences in endocrine response to hyperthermia in sauna. *Acta Physiol Scand* 1994;150:293-298.

[18] Kukkonen-Harjula K, Oja P, Laustiola K, Vuori I, Jolkkonen J, Siitonen S, Vapaatalo H. Haemodynamic and hormonal responses to heat exposure in a Finnish sauna bath. *Eur J Appl Physiol* 1989;58:543-550.

[19] Kukkonen-Harjula K., Oja P, Vuori I, Pasanen M, Lange K, Siitonen S, Metsa-Ketela T, Vapaatalo H. Cardiovascular effects of atenolol, scopolamine and their combination on healthy men in Finnish sauna baths. *Eur J Appl Physiol* 1994;69:10-15.

[20] Vescovi PP, DiGennaro C, Coiro V. Hormonal (ACTH, cortisol, B-endorphin and met-enkephalin) and cardiovascular responses to hyperthermic stress in chronic alcoholics. *Alcohol Clin Exp Res* 1997;21:1195-1198.