Effectiveness of different cryotherapies on pain and disease activity in active rheumatoid arthritis. A randomised single blinded controlled trial

H.E. Hirvonen[1], M.K. Mikkelsson[1], H. Kautiainen[1], T.H. Pohjolainen[2], M. Leirisalo-Repo[3]

[1]Rheumatism Foundation Hospital, Heinola, Finland; [2]Orton, the Rehabilitation Unit of the Invalid Foundation, Helsinki; [3]Helsinki University Central Hospital, Helsinki, Finland.

Abstract

Objective

Local cryotherapy is used to relieve pain and inflammation in injuries and inflammatory conditions. Whole-body cryotherapy is an extreme method administered at -110 ºC for 2 to 3 minutes. The aim of the study was to compare the effect of cryotherapies on pain and inflammation in patients with rheumatoid arthritis (RA).

Methods

Sixty patients with active seropositive RA were recruited in a randomised controlled single-blinded study to receive whole-body cryotherapy at -110°C, whole-body cryotherapy at -60ºC, application of local cold air at -30ºC and the use of cold packs locally. In the final analysis, the last 2 groups were pooled. The patients had 2-3 cryotherapy sessions daily for one week plus conventional physiotherapy. Clinical and laboratory variables and patient's and physician's global assessments were used to assess the outcome. Disease activity was calculated by DAS.

Results

Pain decreased in all treatment groups, most markedly in the whole-body cryotherapy (-110°C) group. DAS decreased slightly with no statistically significant differences between the groups. No serious or permanent adverse effects were detected. Six of 40 patients (15%) discontinued the whole-body cryotherapy.

Conclusion

Pain seemed to decrease more in patients in the whole-body cryotherapy at -110°C than during other cryotherapies, but there were no significant differences in the disease activity between the groups. However, cryotherapy at -110ºC is expensive and available only in special centres and may have minor adverse effects. Based on our results, whole-body cryotherapy at -110ºC is not superior to local cryotherapy commonly used in RA patients for pain relief and as an adjunct to physiotherapy.

Key words

Rheumatoid arthritis, pain, cryotherapy, rehabilitation.

Hanna E Hirvonen, MD; Marja K Mikkelsson, MD, Associate Professor; Hannu Kautiainen, BA, biostatistician; Timo H Pohjolainen, MD, PhD, Associate Professor; Marjatta Leirisalo-Repo, MD, PhD, Professor.

This study was supported by the Social Insurance Institution and the Ministry of Social Affairs and Health, Finland, PATU Development Project of the Rheumatism Foundation Hospital, and the European Social Fund of the European Commission and the Provincial State Office of Southern Finland.

Please address correspondence and reprint requests to: Hanna Hirvonen, MD, Reumasäätiön sairaala, Pikijärventie 1 , FI-18120 Heinola, Finland.
E-mail: hanna.hirvonen@pp4.inet.fi

Received on October 24, 2005; accepted in revised form on February 24, 2006.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory and destructive joint disease. Decreased mobility due to chronic pain and morning stiffness suppress the quality of life of the patients and cause functional disability. Previous studies have shown that physical activity is beneficial in RA, even in patients with active disease (1-3). An effective non-pharmacological method to relieve pain and inflammation would decrease the need for non-steroidal anti-inflammatory drugs (NSAID) which often cause adverse gastrointestinal effects, and would also improve the patients' ability to exercise.

In an arthritic joint the temperature increases (4, 5). Local cryotherapy e.g. with cold packs is widely used to alleviate pain in inflammatory diseases, injuries and overuse symptoms. In *in vitro* studies the increase of local temperature accelerated cartilage collagenolysis (6). A temporary decrease in intra-articular temperature, lasting at least for three hours, is achievable with local cold therapy (5, 7, 8), and with intra-articular glucocorticoid injections (9). Based on these findings, local cryotherapy has been recommended for patients with active arthritis. In the north, winter swimming in cold water is a traditional modification of cold therapy approved by a proportion of rheumatic patients to relieve pain and inflammation and to increase a feeling of general well-being.

Whole-body cryotherapy in a room with a temperature of -110ºC is an extreme form of cryotherapy, introduced and modelled for therapeutic purposes by Yamauchi in 1970s (10). In Europe the treatment was adopted in Germany in 1984-1985 (11). The trials of whole-body cryotherapy have included small numbers of patients, demographic data of patients has been limited and the studies have not been properly randomised. Most studies have been published only as abstracts or congress reports and details of the experiments are not available.

Studies on physiological effects of cold air and cold water and whole-body cryotherapy on healthy young subjects have shown that skin temperature decreases abruptly, but a moderate cold impulse of short duration does not have any significant effect on core temperature (12-16). Taghawinejad and coworkers noticed a mean change of -0.38°C in sublingual temperature in 229 persons during -100°C whole-body cryotherapy in 90 seconds (17). Simultaneously the metabolic rate increases and a rise in blood pressure can be detected (13-15, 18). There are inter-individual differences in the capacity to resist cold (19). A painless period up to two hours has been observed following one visit to the whole-body cryotherapy room at -110ºC (20-22). Decreased duration of morning stiffness, a feeling of better general health, a decrease in disease activity and an increased pain threshold have been reported in rheumatic patients (22-25). The therapeutic target is not hypothermia. It is believed that whole-body cryotherapy acts via neuroendocrinological, humoral and immunomodulative mechanisms and induces body hardening (26-29).

Although evidence of its effectiveness was limited, whole-body cryotherapy was started in Finland at the Rheumatism Foundation Hospital in August 2000. As little is known about the effects of various cryotherapies on pain and disease activity in patients with RA, we carried out a study to compare the effects of whole-body cryotherapy (-110°C) with whole-body cryotherapy (-60°C) and local cryotherapy as an adjunct to physiotherapy in patients with active RA.

Patients and methods

Study population

The study was carried out during the period from September 2000 to May 2003. RA patients from all over Finland who were referred by the treating physician and accepted by the Social Insurance Institution for a treatment period for 8 days - 3 weeks at the Rheumatism Foundation Hospital because of active or seriously disabling arthritis were informed about the study beforehand and asked to participate.

The patients were examined at entry to the hospital. Patients who had active seropositive RA were eligible for the study if they fulfilled the following

inclusion criteria: 5 or more swollen and 5 or more tender joints, erythrocyte sedimentation rate (ESR) 20 mm/h or greater at inclusion and/or C-reactive protein (CRP) concentration in serum greater than 20 mg/l, and a duration of morning stiffness of 30 minutes or more. The medication had to be stable for at least one month before the study and no intra-articular glucocorticoid injections carried out during the previous month. The exclusion criteria included uncontrolled hypertension (diastolic blood pressure over 100 mmHg), a history of cardiac arrhythmia, symptomatic cardiovascular or lung disease, severe Raynaud's phenomenon, cold allergy or cold induced bronchospasm. During the study period there were 1098 possible patients with seropositive RA for the cryotherapy trial. Of these, 928 were not eligible, 796 because they did not meet the inclusion criteria, 170 were eligible for the study, but 110 refused. (Fig. 1) Thus, the final number of patients included is 60.

Study design

At the beginning, the target was 160 patients, randomised in 4 groups (local cold packs, local cold air -30°C, whole-body cryotherapy at -60ºC or whole-body cryotherapy at -110ºC). However, the recruitment rate was very slow due to the strict inclusion criteria. At the time when the study had been ongoing for two and a half years, we lowered the target to 60 patients, and combined the two local cold groups. Thus, 60 patients who fulfilled the criteria were included in the study, 20 in each group. On arrival the patients were randomised to use traditional local cryotherapy (cold packs or cold air -30ºC), whole-body cryotherapy at -60ºC or whole-body cryotherapy at -110ºC for the next 7 days 3 times daily (twice on Sunday). Local cryotherapy was applied on five swollen joints at a time, cold packs for 10-30 minutes and cold air for 1-5 minutes. To maintain and improve the range of motion of joints, the patient also had individual physiotherapy or low impact group exercise for arthritis not more than twice a day. The medication was stable and no glucocorticoid injections were given during the trial.

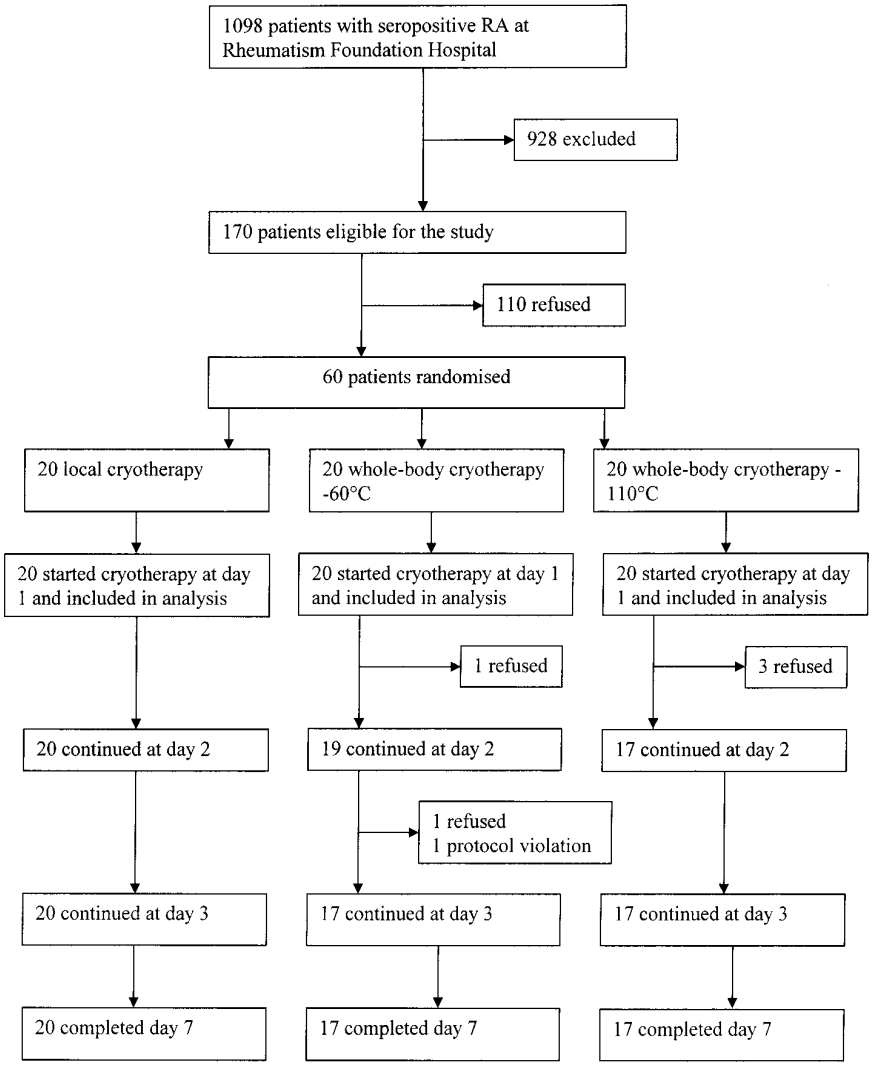

Fig. 1. Trial profile.

A rheumatologist (HEH) blinded for the treatment arm examined the patients on day 0 before any therapies and on day 7 after the last cryotherapy. She recorded the number of swollen and tender joints and the duration of morning stiffness. Blood samples were taken before the first cryotherapy and after the last cryotherapy for evaluation of sensitive CRP by an immunoturbidometric method (Orion Diagnostica Cat.No.68025 Espoo, Finland) with the lowest sensitivity level of 0.3 mg/l. In addition, ESR by Westergren was examined.

At baseline and at the end of the study pain was measured by visual analogue scale (VAS, 0-100mm) and general well being (VAS, 0-100mm) assessed by both the patients and the blinded rheumatologist (global assessment). In addition, disease activity was expressed by DAS (30). A blinded physiotherapist measured hand grip strength of the patient on days 0, 2, 4, 6 and at the end of the study at the same time of the day. Hand grip strength was measured in kilograms (kg) using a hand dynamometer (Digitest Force, Finland). The subject was seated with his/her elbow angle adjusted at 90º. The grip of the dynamometer was adjusted to the size of the hand. The subject performed three tries with both hands, and the mean value of the best results of each hand was calculated. Radiographs of hands and feet were obtained if the latest radiographs were older than 6 months. The x-rays were read by an experienced radiologist and

Table I. Baseline demographic, clinical and radiographic characteristics of patients.

Characteristics	Treatment Group		
	Local cold (N = 20)	Cryotherapy -60ºC (N = 20)	Cryotherapy -110ºC (N = 20)
Demographic:			
Sex (Female/Male)	16/4	18/2	17/3
Age (years), mean (range)	58 (50 – 73)	52 (37 – 65)	50 (21 – 61)
Duration of disease (years), median (range)	16 (<1 – 35)	17 (<1 – 44)	12 (<1 – 32)
Body Mass Index (Kg/m2) mean (SD)	25.7 (4)	24.6 (3.6)	28.3 (5.9)
Clinical:			
Duration of morning stiffness (min), median (IQR)	120 (60 , 240)	60 (60 , 120)	90 (45 , 150)
Health Assessment Questionnaire (HAQ), median (IQR)	1.62 (0.87 , 2.22)	1.00 (0.75 , 1.11)	1.12 (0.75 , 1.72)
Radiographic:			
Number of x-ray pictures available	20	20	19
Larsen score (0-100), median (IQR)	40 (12 , 90)	38 (10 , 75)	23 (4 , 67)

scored by the Larsen method (31), by the modification of Kaarela and Kautiainen (32).

All the patients gave their written informed consent. The study protocol was approved by the ethical committee of Päijät-Häme Hospital district.

Statistical analysis

The outcome was analyzed using the last observation carried forward (LOCF) principle. The results were expressed as means, standard deviations (SD) and 95 per cent confidence intervals (CI), medians and interquartile ranges (IQR). The statistical significance was evaluated by analysis of covariance (ANCOVA) with the baseline value as covariable or Kruskal-Wallis test and chi-square test. Post hoc testing of several univariate comparisons were made with Sidak's test. The normality of variables was evaluated by the Shapiro-Wilk test. The α level was set at 0.05 for all tests.

Results

Clinical and radiographic characteristics of patients at baseline are shown in Table I. There were differences between the groups in age ($p = 0.004$) and disease activity measured by the original DAS ($p = 0.016$), BMI ($p = 0.044$), HAQ ($p = 0.047$) and physician's global assessment of general well being ($p = 0.040$). The local cryotherapy group had the highest mean age, disease activity and HAQ whereas BMI was highest in the whole-body cryotherapy (-110ºC) group. Medication of the patients is shown in Table II. Regular and occasional use of NSAIDs have not been differentiated. The patients were asked to take NSAIDs and other pain killing drugs in the same way as they were used to.

All 20 patients in the local cryotherapy group completed the study. Three (15%) discontinued the whole-body cryotherapy (-60°C) and three (15%) the whole-body cryotherapy (-110°C), all in the early phases of the intervention. Of the planned cryotherapy sessions 98% were carried out in the local cryotherapy group and 83% and 80% in the whole-body cryotherapy -60°C and -110°C groups respectively, including the drop out patients.

The main clinical results are presented in Table III. During all modalities of cryotherapy, the DAS showed a slight but statistically significant reduction in all groups without significant difference between the groups. Pain decreased significantly in the local and whole-body cryotherapy (-110°C) groups during the seven day intervention period. The decrease was statistically significantly greater in the group of whole-body cryotherapy at -110°C than in the whole-body cryotherapy at -60°C or in the local cryotherapy group. No statistically significant changes were observed in the ESR or CRP levels. Physician's global assessment improved in all groups.

Local cryotherapy was well tolerated. Of the 20 patients, 19 felt local cryotherapy acceptable or at least tolerable and one patient did not answer this question. Four cases of minor adverse effects were recorded in this group: one grade I frostbite, two cases of respiratory infection and one patient found that joint pain became worse.

Two patients in the whole-body cryotherapy at -110°C group discontinued because they found the therapy very uncomfortable although they did not mention any adverse effects, and one

Table II. Numbers of patients on DMARDs and other medications at baseline.

	Local cold (N = 20)	Cryotherapy -60°C (N = 20)	Cryotherapy -110°C (N = 20)
DMARD	10	9	9
Cytostatics	11	14	12
Prednisolone	10	14	9
Median dose, mg (range)	5.0 (5.0-10.0)	5.0 (2.5 – 15.0)	5.0 (2.5 - 7.5)
NSAID	16	17	18
Thyroid hormone	2	3	1

NSAID: non-steroidal anti-inflammatory drugs (includes both regular and occasional use).
DMARD: disease modifying anti-rheumatic drugs (excluding cytostatics).

Table III. Results in individual outcome measures from baseline to 7 days.

Variables	Baseline			Change from baseline to day 7			P value between groups †
	Local coldn Mean (SD)	Cryotherapy -60ºC Mean (SD)	Cryotherapy -110ºC Mean (SD)	Local cold Mean (95% CI)	Cryotherapy -60ºC Mean (95% CI)	Cryotherapy -110ºC Mean (95% CI)	
DAS	5.14 (1.10)	4.24 (0.94)	4.56 (0.87)	-0.39 (-0.65 to -0.14)	-0.54 (-0.78 to -0.29)	-0.65 (-0.99 to -0.31)	0.29
Swollen joint count	19 (8)	15 (6)	14 (7)	-1 (-3 to 0)	-1 (-3 to 0)	-3 (-5 to -1)	0.057
Tender joint count	22 (12)	14 (8)	19 (9)	-4 (-7 to -1)	-4 (-6 to -2)	-5 (-8 to -2)	0.67
Global assessment:							
Patient's (VAS)	48 (28)	38 (24)	43 (22)	-11 (-20 to -2)	-15 (-24 to -6)	-15 (-25 to -6)	0.35
Physician's (VAS)	46 (20)	32 (14)	39 (18)	-18 (-23 to -12)	-11 (-18 to -3)	-21 (-28 to -14)	0.17
Pain (VAS)	43 (26)	29 (25)	43 (23)	-11 (-19 to -4)	-3 (-11 to 5)	-24 (-35 to -14)	0.006‡
ESR (mm/h)	42 (16)	32 (18)	39 (17)	5 (1 to 8)	3 (-1 to 6)	4 (-1 to 8)	0.96
CRP (mg/L)	23 (22)	28 (21)	20 (17)	0 (-6 to 5)	-1 (-7 to 4)	-2 (-10 to 6)	0.85
Hand grip (Kg)	11.6 (8.9)	13.2 (6.0)	12.5 (6.0)	1.1 (-0.2 to 2.4)	1.3 (-0.1 to2.6)	1.7 (0.4 to 3.0)	0.80

† Analysis of covariance (ANCOVA). Baseline value as covariable.
‡Multiple comparison: Local/-110°C p = 0.024, -60°C/-110°C p = 0.012.

patient in this group dropped out because of malaise. There were three discontinuations also in the whole-body cryotherapy at -60°C group; one due to headache, another due to malaise and another due to a stable neutropenia already present before cryotherapy, considered to be a risk for infective complications.

Altogether 15 patients mentioned adverse effects: 4 patients in the local cryotherapy group, 6 patients in the whole-body cryotherapy -60°C group and 5 patients in the whole-body cryotherapy -110°C group (Table IV). No serious or permanent adverse effects occurred. Sixteen out of 17 completing patients in the whole-body cryotherapy -110°C group and all 17 completing patients in the whole-body cryotherapy -60C group felt the therapy acceptable or tolerable.

Discussion

This is the first randomised controlled trial of whole-body cryotherapy for patients with RA. The results showed that during the seven day treatment period of patients with active RA, both the patient's and the physician's global assessments showed an amelioration during the treatment period. In addition, there was a decrease of pain in patients in both the local cryotherapy and whole-body cryotherapy at -110°C groups but there was no change in the activity of the disease. Of the several variables, change in the patients' report of pain was the only one in favour in whole-body cryotherapy at -110C.

Unfortunately, our randomised study groups were not identical. There were differences both in demographic and clinical data. The study sample was smaller than expected at the time we planned the study. It was not easy to find voluntary patients who fulfilled the strict activity and stability inclusion criteria even at the Rheumatism Foundation Hospital, which traditionally focuses on rehabilitation of rheumatic patients with severe rheumatic disease. The main reasons for refusal were that the patient felt uncomfortable with the idea of cryotherapy, she/he could not stay in hospital long enough for personal reasons, or the patient required local glucocorticoid injections at entry.

In most studies cryotherapy has been combined with physical exercise as in the present study. The content of the reference therapies has varied greatly. Several studies have used local heat therapy as a control therapy (21, 24) or traditional physical exercise without cryotherapy (23). Richter *et al* mention in an abstract that they had whole-body cryotherapy -60°C as control therapy (29). We did not have a control group

Table IV. Number of adverse effects during the trial. [1]

Adverse effect	Local cold (N = 20)	Cryotherapy -60°C (N = 20)	Cryotherapy -110°C (N = 20)
Respiratory infection	2	0	1
Frost bite	1	0	0
Headache	0	1	0
Hypertension	0	1	1
Dizziness	0	1	0
Urticaria	0	0	1
Long lasting freezing	0	0	2
Malaise	0	2	1
Joint or muscle pain	1	1	0
Nervousness	0	1	0

[1] 15 patients with 17 adverse effects.

with only physiotherapy twice a day, an evident weakness of this study. Instead we used physiotherapy in all patients with the goal of maintaining the range of movement of joints; other physical pain treatment methods were not allowed. Therefore, it is unlikely that physiotherapy would have caused bias in the study.

The result of pain relief is in accordance with previous studies (20, 25). Pain intensity reduced clearly during the whole period of seven days. Global assessments of general well being improved, as in a previous report of whole-body cryotherapy (22), but differences between the local and whole-body cryotherapy groups were not found. Birwe and coworkers have reported better joint function after whole-body cryotherapy (22), but we did not use any tests to measure joint mobility. Laboratory variables measuring inflammation (ESR or CRP) did not change significantly, as also reported by Birwe and coworkers (33).

Adverse effects were frequently reported; five patients (25%) mentioned that whole-body cryotherapy at -110C caused side effects, most of which were mild. The main adverse effect was a feeling of discomfort and two patients discontinued the trial because of it. The profile of side effects fits well with our clinical experience and previous reports of whole-body cryotherapy (17, 20). Using pre-screening and excluding patients with uncontrolled hypertension, cardiac or lung problems, cold allergy or circulatory problems, we have used whole-body cryotherapy at our institution for about five years without any health-threatening effects.

According to this study all modalities of cryotherapy reduced pain during the seven day period. The reduction of pain was greater in the whole-body cryotherapy (-110ºC) group than in the other treatment groups. No significant differences were observed in inflammatory variables between the treatment groups.

We conclude that whole-body cryotherapy (-110ºC) seems to relieve pain more effectively than other cryotherapies. However, it is expensive and available only in special centres, and may have minor adverse effects. There was no other statistically significant difference between the treatment groups with respect to disease activity measured by DAS, or laboratory tests indicating inflammation. Although local cryotherapy is widely used to alleviate joint inflammation, the lack of a control group with no cold treatment added in the physiotherapy in the present study does not allow us to make the conclusions on the usefulness of any kind of cryotherapy for RA patients as a self-care for pain relief and as an adjunct to physiotherapy.

Acknowledgements

We thank Dr. Irma Soini, PhD, for reading the radiographs, Tarja Westerlund, MSc, physiotherapist, for measuring grip strengths, and Riitta Lahti for assisting the study.

References

1. HÄKKINEN A, SOKKA T, KOTANIEMI A, HANNONEN P: A randomized two-year study of the effects of dynamic strength training on muscle strength, disease activity, functional capacity and bone mineral density in early rheumatoid arthritis. *Arthr Rheum* 2001; 44: 515-22.
2. VAN DEN ENDE CH, BREEDVELD FC, LE SESSIE S, DIJKMANS BA, DE MUG AW, HAZES JM: Effects of intensive exercise on patients with active rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis* 2000; 59: 615-21.
3. STENSTRÖM CH, MINOR MA: Evidence for the benefit of aerobic and strengthening exercise in rheumatoid arthritis. *Arthr Rheum* 2003; 49: 428-34.
4. HOLLANDER JL, HORVARTH SM: The influence of physical therapy procedures on intra-articular temperature of normal and arthritis subjects. *Am J Med Sci* 1949; 218: 543-8.
5. OOSTERWELD FGJ, RASKER JJ: Effects of local heat and cold treatment on surface and articular temperature of arthritic knees. *Arthr Rheum* 1994; 37: 1578-82.
6. HARRIS ED JR, MCCROSKERY PA: The influence of temperature and fibril stability on degradation of cartilage collagen by rheumatoid synovial collagenase. *N Engl J Med* 1974; 290: 1-6.
7. KERN H, FESSL L, TRNAVSKY G, HERTZ H: Kryotherapie – Das Verhalten der Gelenkstemperatur Unter Eisapplikation – Grundlage für die Praktische Anwendung. *Wien Klin Wochensch* 1984; 96: 832-7.
8. OOSTERWELD FGJ, RASKER JJ, JACOBS JWG, OVERMARS HJA: The effect of local heat and cold therapy on the intra-articular and skin surface temperature of the knee. *Arthr Rheum* 1992; 35: 146-51.
9. HOLLANDER JL, BROWN EM JR, JESSAR RA, BROWN CY: Hydrocortisone and cortisone injected into arthritic joints; comparative effects of and use of hydrocortisone as a local antiarthritic agent. *JAMA* 1951; 147: 1629-35.
10. YAMAUCHI T, KIM S, NOGAMI S, ABE D, KAWANO Y: Extreme cold treatment (-150°C) on the whole body in rheumatoid arthritis. Ilar XVth international Congress of Rheumatology, Paris June 21-27, 1981. (Abstract) *Rev Rhum* 1981;48 (Suppl.): P1054.
11. FRICKE R: Ganzkörperkältetherapie in einer Kältekammer mit Temperaturen um -110°C. *Z Phys Med Baln Med Klim* 1989; 18: 1-10.
12. HAYWARD JS, ECKERSON JD, COLLIS ML: Thermoregulatory heat production in man: prediction equation based on skin and core temperatures. *J Appl Physiol* 1977; 42: 377-84.
13. LAMKE L-O,LENNQUIST S, LILJENDAHL S-O, WEDIN B: The Influence of Cold Stress on Catecholamin Excretion and Oxygen Uptake of Normal Persons. *Scand J Clin Lab Invest* 1972; 30: 57-62.
14. LEPPÄLUOTO J, KORHONEN I, HUTTUNEN P, HASSI J: Serum levels of thyroid and adrenal hormones, testosterone, TSH, LH, GH and prolactin in men after a 2-h stay in a cold room. *Acta Physiol Scand* 1988; 132: 543-8.
15. KAUPPINEN K: Sauna and winter swimming. Academic dissertation. University of Helsinki, 1989.
16. WESTERLUND T, OKSA J, SMOLANDER J, MIKKELSSON M: Thermal responses during and after whole-body cryotherapy (-110°C). *J Therm Biol* 2003; 28: 601-8.
17. TAGHAWINEJAD M, BIRWE G, FRICKE R, HARTMANN R: Ganzkörperkältetherapie – Beeinflussung von Kreislauf- und Stoffwechselparametern. *Z Phys Med Baln Med Klim* 1989; 18: 23-30.
18. WESTERLUND T, SMOLANDER J, UUSITALO-KOSKINEN A, MIKKELSSON M: The blood pressure responses to an acute and long-term whole-body cryotherapy (-110°) in men and women. *J Therm Biol* 2004; 29: 285-90.
19. WENNMALM Å: Catecholaminergic Defence against Hypothermia during Brief Cold Exposure. *Scand J Clin Lab Invest* 1973; 32: 305-8.
20. METZGER D, ZWINGMANN C, PROTZ W, JÄCKEL WH: Die Bedeutung der Ganzkörperkältetherapie im Rahmen der Rehabilitation bei Patienten mit rheumatischen Erkrankungen. *Rehabilitation* 2000; 39: 93-100.
21. SAMBORSKI W, STRATZ T, SOBIESKA M, MENNET P, MÜLLER W, SCHULTE-MÖNTING J: Intraindividueller Vergleich einer Ganzkörperkältetherapie und einer Wärmebehandlung mit Fangopackungen bei der generalisierten Tendomyopathie (GTM). *Z Rheumatol* 1992; 51: 25-31.
22. BIRWE G, FRICKE R, HARTMANN R: Ganzkörperkältetherapie (GKKT). Beeinflussung der subjektiven Beschwerdelinderungen und der Gelenkfunktion.*Z Phys Med Baln Med Klim* 1989; 18: 11-5.
23. KSIEZOPOLSKA-PIETRZAK K, MILLER H, WOJTECKA-LUKASIK E *et al*.: The Influence of Cryotherapy on Patients with Rheumatoid Arthritis (RA). EULAR 2000. Annual Euro-

pean Congress of Rheumatology, Nice June 21-24, 2000. (Abstract) *Ann Rheum Dis* 2000; 59 (Suppl.): POS-375.
24. WICHMANN J, FRICKE R: Ganzkörperkältetherapie von -110°C bei Ankylosierender Spondylitis. *Phys Rehab Kur Med* 1997; 7: 210.
25. FAKHARI B, HOLLENSTEINER B, FRICKE R: Analgetische Wirkung einer Ganzkörperkältetherapie von -110°C, 3 min im Vergleich zu einer Moortherapie. (Abstract) II Internationales Kryotherapie Symposium, Vlotho 5. Februar 2000.
26. DUGUÉ B, LEPPÄNEN E: Adaptation related to cytokines in man: effects of regular swimming in ice cold water. *Clin Physiol* 2000; 20: 114-21.
27. SIEMS W, BRENKE R: Changes in the glutathione system of erythrocytes due to enhanced formation of oxygen free radicals during short-term whole body cold stimulus. *Arct Med Res* 1992; 51: 3-9.
28. SIEMS WG, VAN KUIJK FJGM, MAASS R, BRENKE R: Uric acid and glutathione levels during short-term whole body cold exposure. *Free Radic Biol Med* 1994; 16: 299-305.
29. RICHTER C, POHLEN-FRICKE B, FRYE K, LINNEMAN E, FRICKE R: Cytokin- und CD4-Zellsupprimierung im zirkulierenden Blut durch Kältekammare – Therapie von -110°C bei chronischer Polyarthritis und ankylosierender Spondylitis.(Abstract) *Z Rheumatol* 1997; 56 (Suppl. 1): 34.
30. VAN DER HEIJDE DMFM, VAN'T HOF MA, VAN RIEL PLCM *et al*.: Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990; 49: 916-20.
31. LARSEN A, DALE K, EEK M: Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta *Radiol Diagn* (*Stockh*.) 1977; 18: 481-91.
32. KAARELA K, KAUTIAINEN H: Continuous progression of radiological destruction in seropositive rheumatoid arthritis. *J Rheumatol* 1997; 24: 1285-7.
33. BIRWE G, TAGHAWINEJAD M, FRICKE R, HARTMANN R: Ganzkörperkältetherapie (GKKT) Beeinflussung hämatologischer und entzündlicher Laborparameter. *Z Phys Med Baln Med Klim* 1989; 18: 16-22.