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ORIGINAL ARTICLE

Long-term benefit of radon spa therapy in the rehabilitation of rheumatoid arthritis: a randomised, double-blinded trial

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Abstract This study investigates the effects of radon (plus CO_2) baths on RA in contrast to artificial CO_2 baths in RA rehabilitation using a double-blinded trial enrolling 134 randomised patients of an in-patient rehabilitative programme (further 73 consecutive non-randomised patients are not reported here). The outcomes were limitations in occupational context/daily living (main outcome), pain, medication and further quantities. These were measured before the start, after the end of treatment and quarterly in the year thereafter. Repeated-measures analysis of covariance (RM-ANCOVA) of the intent-to-treat population was performed with group main effects (GME) and group × course interactions (G × C) reported. Hierarchically ordered hypotheses ensured the adherence of the nominal significance level. The superiority of the radon treatment was found regarding the main outcome (RM-ANCOVA until 12 months: $p_{GME} = 0.15$, $p_{GxC} = 0.033$). Consumption of steroids ($p_{GME} = 0.064$, $p_{G \times C} = 0.025$) and NSAIDs ($p_{GME} = 0.035$, $p_{G \times C} = 0.008$) were significantly reduced. The results suggest beneficial long-term effects of radon baths as adjunct to a multimodal rehabilitative treatment of RA.

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Introduction

Recent treatment regimens of rheumatoid arthritis (RA) include disease-modulating and symptomatic drug therapy as well as multimodal rehabilitative programmes aiming at long-term disease management with pain relief, preservation of remaining functions and development of compensatory functions. Together with psychological care, specific exercises, physical and occupational therapy [1] spa applications represent an integral part of physical therapy for RA [2] in many European countries.

The chemically inert natural radioactive gas radon has been applied in rheumatology since the beginning of the 20th century with a few European health resorts as vanguard in its therapeutic use.

Evidence from several newer randomised controlled trials (RCT) [3–10], clinical observational studies [11–15] and empirical experience over decades are in keeping with sustained analgesic effects. Beyond pain relief, anti-inflammatory [16] and immune modulating effects [17] were reported from laboratory studies.

Within the last years, formerly restrictive health-care authorities and insurance companies became increasingly open-minded concerning radon therapy, not least because of the increasing evidence of beneficial mid/long-term effects, the very small radioactive doses [18] and the probably beneficial risk ratio.

The only RCT in RA patients [7, 9] reported superiority of radon spa therapy compared to reference

treatment regarding pain and health-related quality of life at the end of the 6 months' postintervention observation period. We designed a replication study aimed at comparing a series of baths of natural spring water containing radon plus carbon dioxide ($Rn + CO_2$) versus radon-free (CO_2) baths (control) within a complex rehabilitative programme, which is currently reimbursed by statutory health and pension insurance companies in Germany.

Methods

Study design

The study was a trial with two randomised parallel groups and patients, therapists, and investigator unaware of group allocation. It was performed in Bad Brambach, which is known for its natural springs containing both radon and carbon dioxide gas in therapeutically relevant concentrations. We hypothesised that the radon spa therapy is superior to the control treatment. Quarterly follow-ups had been performed until 1 year after the end of the intervention.

For the externally performed randomisation, a computer-generated random allocation sequence was provided by the responsible biometrician (AF). Randomisation was restricted to block lengths of four.

According to the list, a bar code card was prepared for each participant. An automated device activated by the patients' cards guaranteed correct tub fillings according to group assignment [16]. The de-blinding was performed not before the last follow-up unless in case of emergency. The ethics committee of the University of Dresden approved the protocol. Written informed consent was obtained from all patients.

Patients

Patients with RA according to the 1987 revised ACR criteria for RA [19] and with sufficient knowledge of the German language were eligible. Exclusion criteria were current exacerbations of the inflammatory process or other systemic inflammatory diseases, concomitant musculoskeletal diseases possibly interfering with outcome measurement, pregnancy, breast feeding, disorders of the central nervous system, a known tendency toward thrombosis, malignant hypertension, coronary heart disease, heart failure, arrhythmia, severe disorders of lungs, kidneys or liver, advanced malignancies, abuse of alcohol or drugs, major skin lesions, severe fever or infections.

Setting

The study participants were inpatients routinely referred to the rehabilitation hospital, Bad Brambach, from widespread regions of Germany. Because only three statutory health-care/pension bodies agreed to the randomisation procedure, patients were only invited to participate if they met the inclusion/exclusion criteria and were members of one of these three funds. As proposed by Fielding et al. [20], a third parallel group of non-randomised consecutive patients was formed including patients who did not consent to randomisation or who came from other financing bodies. These patients received the usual 3 weeks in-house rehabilitation programme including radon baths like the randomised index group. However, this group is not part of this report.

Interventions

The rehabilitative treatment consisted of daily specific exercises/ physiotherapy, occupational therapy and galvanic baths thrice a week each, and Swedish massage twice a week. In case of need/request, psychological care was provided. Furthermore, patients assigned to $Rn + CO_2$ took 15 baths in natural spring water (1.1 kBq per l Rn; 1.3 g per l CO_2), whereas the control group received 15 plain CO_2 baths (artificially produced, 1.6 g/l). The water temperature was 35°C.

Apart from Sundays, 20 min whole body baths were administered daily at the same time starting the fourth day after arrival. Additional offers (leisure time sport, relaxation therapy) were allowed in order to maximise the patients' compliance. Criteria for treatment discontinuation were adverse reactions, withdrawal of informed consent, current inflammatory episodes or need of steroid medication.

Outcomes

Primary outcome criteria were self-assessed limitations in everyday life and private activities as well as limitations in the occupational context both measured on 100 mm visual analogue scales (VAS) anchored at 'not at all' and 'dramatically restricted'. The mean of both scores was used as main outcome measure (MOM) for patients who were still on their jobs. The scale on everyday life restriction was used alone in pensioners/ unemployed persons. This pooled and rather global criterion met the interests of the cooperating health-care/pension bodies best. It was accompanied by pain intensity (PI), pain frequency (PF), morning stiffness (MS), functional capacity (FC) and drug consumption.

PI was measured on a VAS as well. All VAS were double measured at baseline and averaged to increase the reliability, although VAS are regarded as reliable, valid and sensitive to change [21, 22].

PF and MS were assessed on verbal scales. To compare the findings of the groups for both assessments, all changes were summed up over the course of time. This summarising measure was dichotomised to 'at least two levels improved' versus 'less two levels improved'.

FC was both patient-rated by the Hanover Functional Capacity Questionnaire for RA [23, 24] and investigator-rated by Keitel's functional test [25] (possible only before the start and after the end of treatment). Both proved to be valid and reliable [24, 26].

The drugs were categorised as (a) DMARD, (b) corticosteroids and (c) NSAIDs and/or analgesics. DMARD were assessed qualitatively, primarily to describe the groups. It was not expected to observe substantial changes in quantity or quality because of the rather short-termed study intervention (compared to the long-term duration of disease) and rehabilitative orientation of the treatment. For steroids, and NSAIDs and/or analgesics, we hypothesised a mid/long-term reduction after radon treatment. Therefore, all steroid intakes were transferred into prednisolone equivalents (in mg) according to guidelines [27, 28].

Operationalisation of NSAIDs and/or analgesics was more difficult because many patients used two or even three different drugs from a broad range of medications. We decided to use the percentage of recommended dose of every medication [29, 30] and summed up all intake percentages for further analyses. The ESR (Westergren method), and the serum concentration of CRP were measured before start of intervention to describe disease activity.

Data were gathered before the first and after the last treatment, as well as quarterly for 1 year thereafter by means of a postal questionnaire. Change scores built from start minus course differences were used for analyses.

Sample size

We assumed moderate between-group differences because of the intensive basic treatment in both groups. Given a two-sided type-I error probability of 5%, balanced groups and a test power of about 80%, 63 patients per treatment arm would be necessary to detect relevant between-group differences. Taking dropouts into account, about 140 patients should have to be included in the study. About 3 years' time was estimated for the patients' recruitment.

Statistical methods

Primary analysis was performed by intention-to-treat. All randomised patients were included. Missing values (MV) substitution was performed only for the MOM according to a predefined strategy. For MV at the end of intervention, the 'last observation carried forward' method was applied. Single missing follow-up (FU) values were handled by means of linear interpolation. For the few more MV, the mean change score of the respective group and time point [31, 32] was filled in. Repeated-measures analyses of covariance (RM-ANCOVA) were done using baseline scores as covariates. Hierarchically ordered hypotheses ensured the nominal significance level and allowed examining long-term effects [33, 34].

Based on previous evidence on treatment effects, until 6 months post intervention, the first RM-ANCOVA should be performed including data from the end of treatment, 3 and 6 months' FU. Only if this analysis resulted in significant group main effects (GME) *or* significant group × course-interactions (G × C), the data from 9 months' FU should be included into the respective second analysis. If the second analysis produced significant differences, a third analysis should be carried out including data from the 12 months' FU. No interim analysis was done. Neither statistical adjustments regarding multiple testing nor replacement strategies for MV were applied for secondary analyses. Inferential statistics on these outcomes were interpreted descriptively. RM-ANCOVA, Fisher's exact test and calculations of odds ratios with 95% CI for improvement rates were performed. Common descriptive statistics were presented in tables and figures.

Statistical analyses were done with SPSS Version 12 (SPSS Corp., Chicago, IL).

Results

Patient flow

The trial started in July 1998 and was completed (including the last patient's 12 months' FU) in May 2005. The recruitment period lasted that long because only three health-care/pension bodies agreed to the inclusion of their members, if they too consented. About 186 patients were screened of whom 35 did not fulfil the inclusion/exclusion criteria, and 14 refused randomisation because of possible exclusion from radon therapy. In total, 207 RA patients were enrolled of whom 134 were randomised ($n = 67$ per group) and

are reported here. Details of participants' flow are shown in Fig. 1.

Baseline characteristics

Table 1 summarises the characteristics of the enrolled sample. About two-thirds of the participants were women. Mean age was 56 years (SD 12 years) and mean duration of disease was reported as 11 years (SD 10 years).

For approximately two-thirds of the patients, marked erosions of joints, cysts, lesions or partial dislocations were found in X-rays. Nearly 90% were treated with DMARD, thereof 60% with MTX alone or in combinations. More than 60% were treated with corticosteroids and NSAIDs/analgesics. Disease activity according to the laboratory measures was low but showed a remarkable variation in both groups. All in all, baseline characteristics and outcome measures were quite well balanced between groups.

Protocol compliance

Neither violations of inclusion and/or exclusion criteria occurred nor were there erroneous allocations to the false treatment. The mean number of baths was 15.8

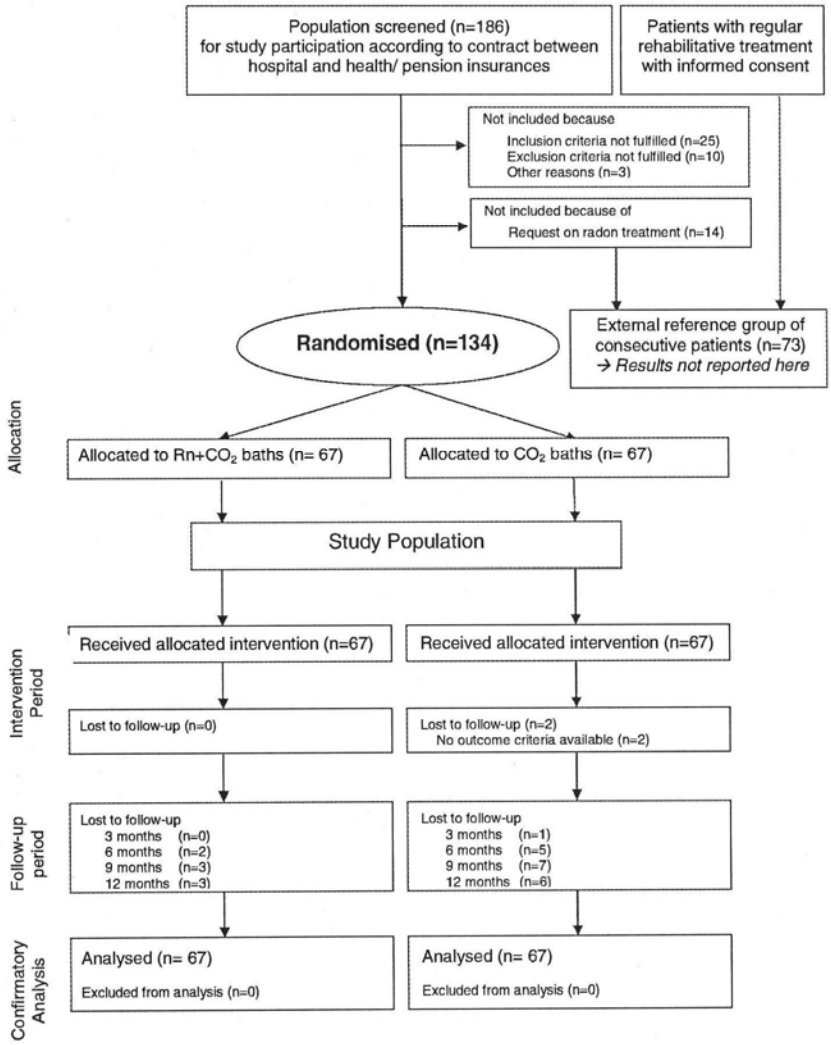

Fig. 1 Flow of participants through the study

Table 1 Patient characteristics of the study population

Characteristics	Rn + CO_2 baths ($n = 67$)[a]	CO_2 baths ($n = 67$)[a]	Total ($n = 134$)[a]
Female, No. (%)	46 (68)	47 (70)	93 (69)
Age, mean (SD), years	58.3 (11.3)	54.1 (11.5)	56.2 (11.6)
Body mass index, mean (SD), kg/m^2	26.7 (3.9)	27.4 (5.0)	27.0 (4.5)
Live in family context, No. (%)[a]	41 (69)	46 (82)	87 (76)
Employment status, No. (%)[a]			
Employed	7 (10)	13 (20)	20 (15)
Sick leave	10(15)	12(18)	22(16.5)
Unemployed	9 (13)	6 (9)	15 (11)
Retired	41 (61)	35 (53)	76 (57)
Application for pension/intention to apply for pension, No. (%)[a]	3/4 (27)	0/2 (7)	3/6 (18)
Duration of disease, mean (S.D.), years	12 (10)	10 (10)	11 (10)
X-ray classification[b], No. (%)			
Grade 0 + I[c]	11 (18)	15 (25)	26 (21)
Grade II + III[d]	43 (70)	36 (59)	79 (65)
Grade IV[e]	7 (12)	10 (16)	17 (14)
Medications, No. (%)			
DMARD, before start of treatment	57 (88)	56 (88)	113 (88)
Thereof[f]: MTX/SSZ/LEF/AZA	41/ 8/ 6/4	39/ 8/ 4/3	80/ 16/ 10/7
Thereof: two DMARDs	8	6	14
DMARD, at 12 months' FU	61 (91)	60 (90)	121 (90)
Thereof[f]: MTX/SSZ/LEF/AZA	41/ 6/ 7/3	41/ 9/ 7/2	82/ 15/ 14/5
Thereof: two DMARDs	10	12	22
Steroids, before start of treatments	41 (63)	42 (66)	83 (64)
NSAIDs/analgesics, before start of treatments	40 (62)	39 (61)	79 (61)
Erythrocyte sedimentation rate, mean (SD), mm first hour	14 (11)	31 (20)	17 (15)
C-reactive protein, mean (SD)[a], mg/l	10.6 (9.1)	17.4 (17.5)	14.1 (14.4)
Pain intensity, mean (SD), 100 mm VAS	58.9 (22.8)	57.0 (24.3)	57.9 (23.5)
Frequency of pain, No. (%)			
Permanently	19 (28)	22 (33)	41 (31)
Not permanently, but daily	36 (54)	33 (49)	69 (51
Not daily	12 (18)	12 (18)	24 (18)
Morning stiffness, No. (%)			
No	13 (19)	9 (13)	22 (16)
Up to 2 h	43 (64)	42 (63)	85 (64)
Up to noon or longer	11 (17)	16 (24)	27 (20)
Functional questionnaire Hanover FFbH-P, mean (SD)	73.6 (20.9)	74.4 (19.5)	74.0 (20.1)
Keitel functional test, mean (SD)	76.0 (16.6)	76.4 (14.7)	76.2 (15.6)
Limitations in everyday life/job, mean (SD), 100 mm VAS	56.8 (23.7)	58.2 (23.2)	57.5 (23.4)

No number, SD standard deviation, *MTX* methotrexate, *SSZ* sulfasalazine, *LEF* leflunomide and *AZA* azathioprine

[a] Due to missing data on various baseline characteristics, actual sample sizes may be somewhat smaller (range: 1–8%)

[b] d.p. view of both hands and feet

[c] No or insignificant erosion of joints; only slight decalcification

[d] Clear signs of erosion of joints; cysts, lesions, or partial dislocations

[e] Atrophy, destruction of joints

[f] Including combinations

(SD 2.6) in the radon group and 15.3 (SD 2.0) in the control group, with 65 and 68% of patients receiving 15 baths exactly. Less 14 baths were applied in 6/65 respectively 3/66 patients because of menorrhoea (4×) and long holiday periods (Easter/Christmas) or early discharge (4×). The remaining patient suffered from intercurrent illness so that the bath treatment had to be interrupted. No series was less than 11 baths. No relevant group discrepancies of treatment intensity were found (Table 2).

Guessing after end of treatment whether they believed having received radon therapy, 30/61 of the radon group and 37/60 of the control group were unsure. About 44% of the whole sample assumed their allocation correctly. Not less than 25% of the control group guessed as being treated with radon baths. De-

Table 2 Treatment programme within 21 days of rehabilitation

Number of specific treatment modality	Rn + CO_2 baths ($n = 67$)	CO_2 baths ($n = 67$)
Treatment period, mean (SD), days	21.3 (1.6)	21.2 (1.3)
Treatment under investigation		
Baths, mean (SD), either Rn + CO_2 or CO_2	15.8 (2.6)	15.3 (2.0)
Basic rehabilitation programme		
Physiotherapy	14.9 (4.9)	13.5 (3.9)
Occupational therapy	8.1 (1.8)	8.1 (2.4)
Hydrogalvanic baths	9.0 (1.5)	8.8 (1.2)
Swedish massage	6.4 (1.1)	6.2 (.9)
Additional offers, mean (SD)		
Medical training therapy/ leisure time sports	6.4 (1.7), $n = 8$	6.8 (2.1), $n = 11$
Psychological care, individual	2.7 (2.0), $n = 11$	3.1 (1.2), $n = 8$
Psychological care, in groups	4.7 (1.8), $n = 42$	5.3 (1.9), $n = 40$

blinding before the end of FU period happened in just one case after the 6 months' FU on patient's request.

Outcomes

Change scores of outcome measures and results of statistical analyses are shown in Table 3.

Primary analysis

Both groups showed comparable treatment effects at discharge (Fig. 2) but between-group differences increased with longer follow-up periods until 9 months post intervention. Therefore, RM-ANCOVAs in all hierarchically ordered analyses (until 6, 9 and 12 months' FU) resulted in significant G × C interactions. Regarding the GME, no statistical significance, although consistently low p values were observed (Table 3).

Despite a decreased extent of effects after the 6 months' FU, the radon group did better until at least 9 months' postintervention as compared to baseline, whereas the control group had returned to values below the baseline level already at the 6 months' FU (Fig. 2, Table 3).

Secondary analyses

Favourable longitudinal changes of pain relief were observed at least until the 9 months' FU in the radon group. Between-group differences were most pronounced 9 months' postintervention, resulting in RM-ANCOVA *P*-values for G × C until 9 and 12 months' FU of borderline significances (Table 3). These PI results were observed in spite of reduced drug intakes of corticosteroids and NSAIDs and/or analgesics in the radon group (Figs. 3, 4).

Regarding corticosteroids, an increasing dose reduction was found in the radon group during the entire FU period, whereas the dose remained essentially unchanged in the control group (Fig. 3). A borderline significant group main effect was found until the end of observation (Table 3).

For NSAIDs and/or analgesics, reduced intake was observed until the 9 months' FU (Fig. 4), and the 12 months' FU was still comparable to that of the pretreatment phase in the radon group. In contrast, in the control group an increased dose was observed 1 year postintervention. These differences proved to be significant (GME) for RM-ANCOVAs until the 9 and 12 months' assessments (Table 3).

No significant group differences were found regarding PF, MS or functional capacity. Consistently to the FFbH questionnaire, (Table 3) the Keitel test provided small and non-significant between-group differences at the end of treatment. For PF and MS, the dichotomised summary parameter resulted in 19/64 versus 17/60 (OR = 1.07 [49; 2.32]) and 17/61 versus 16/60 (OR = 1.06 [48; 2.37]) improvements respectively.

During the course of study neither intervention-related adverse reactions nor serious adverse events occurred. Two intercurrent illnesses were observed with causality to both baths and other interventions judged unlikely.

Discussion

Our study is the second RCT comparing radon spa therapy to radon-free treatment for RA and demonstrates that Rn + CO_2 baths are superior to plain CO_2 baths within a multimodal rehabilitation in the long run. Secondary analyses support the results of the primary analysis. Longer lasting improvements in pain intensity, as well as reduced doses of corticosteroids and NSAIDs and/or analgesics were observed in favour of the radon treatment. Protocol adherence and tolerability could be judged as excellent.

Furthermore, reduced drug consumption in the radon group might correspond with a lower risk of known side effects, especially, as the combination of steroids plus NSAIDs is known for an even higher risk rate than NSAID alone [35].

Various years ago, the mortality due to gastro-intestinal complications following NSAID consumption was estimated to be about 2.000 per year in Germany [36] and 16.500 per year in the USA [37]. Therefore, additional use of gastro-protective agents or consumption

Table 3 Change scores and ANCOVA results of outcome criteria

Characteristics	Rn + CO_2 baths	CO_2 baths	RM-ANCOVA p value of groups main effect (GME)	RM-ANCOVA p value of group × course interaction (G × C)
Confirmatory analyses (ITT)				
Limitations in everyday life/job, mean (SD)	$n = 67$	$n = 67$	Model using measures up to ...	
Baseline score	56.8 (23.7)	58.2 (23.2)		
Change score, end of treatment	3. 34 (12.50)	4.12 (15.83)		
Change score, 3 months' FU	3.41 (20.86)	1.97 (21.95)		
Change score, 6 months' FU	8.24 (23.30)	−0.09 (19.79)	$P = 0.151$[a]	$P = 0.016$*,[a]
Change score, 9 months' FU	2.21 (21.92)	−1.82 (18.44)	$P = 0.110$[a]	$P = 0.025$*,[a]
Change score, 12 months' FU	−1.86 (22.66)	−1.99 (19.78)	$P = 0.170$	$P = 0.033$*
Secondary analyses[b]				
Pain intensity, mean (SD)	$n = 63$–66[c]	$n = 60$–66[c]		
Baseline score	58.9 (22.8)	57.0 (24.3)		
Change score, end of treatment	13.06 (18.45)	16.36 (24.56)		
Change score, 3 months' FU	5.97 (28.62)	4.83 (29.09)		
Change score, 6 months' FU	6.43 (27.68)	−0.65 (30.32)	$P = 0.803$	$P = 0.249$
Change score, 9 months' FU	4.06 (30.76)	−4.77 (24.00)	$P = 0.479$	$P = 0.096$**
Change score, 12 months' FU	−2.46 (28.26)	−2.56 (25.45)	$P = 0.632$	$P = 0.091$**
Functional capacity FFbH-P, mean (SD)	$n = 64$–67[c]	$n = 59$–67[c]		
Baseline score	73.6 (20.9)	74.4 (19.5)		
Change score, end of treatment	−0.35 (9.04)	−1.15 (10.92)		
Change score, 3 months' FU	2.62 (11.58)	1.45 (11.90)		
Change score, 6 months' FU	3.31 (14.55)	3.22 (13.26)	$P = 0.551$	$P = 0.699$
Change score, 9 months' FU	3.79 (11.67)	3.58 (12.52)	$P = 0.491$	$P = 0.604$
Change score, 12 months' FU	4.89 (15.08)	6.53 (13.30)	$P = 0.782$	$P = 0.542$
Patients with corticosteroid intake				
Before start of treatment	41 (63%)	42 (66%)		
At 12 months' FU	38 (61%)	39 (64%)		
Corticosteroid intake, mean (SD)				
(mg Prednisolone equivalent)	n[d] = 44–46	n[d] = 42–45		
Baseline score	6.56 (5.34)	5.60 (3.91)		
Change score, end of treatment	0.24 (1.40)	0.20 (2.56)		
Change score, 3 months' FU	0.55 (3.11)	−0.68 (3.09)		
Change score, 6 months' FU	1.06 (4.55)	−0.44 (3.79)	$P = 0.159$	$P = 0.232$
Change score, 9 months' FU	1.02 (4.54)	−0.18 (2.93)	$P = 0.137$	$P = 0.363$
Change score, 12 months' FU	1.48 (4.54)	−0.33 (3.08)	$P = 0.064$**	$P = 0.254$
Patients with NSAIDs/ analgesics intake				
Before start of treatment	40 (62%)	39 (61%)		
At 12 months' FU	32 (51%)	38 (62%)		
NSAIDs/ analgesics intake, mean (SD)				
[sum of all reported drugs;	n[d] = 42–45	n[d] = 41–43		
Each in% of recommended daily dose]				
Baseline score	68.61 (44.15)	78.92 (67.11)		
Change score, end of treatment	3.98 (25.31)	3.44 (26.17)		
Change score, 3 months' FU	7.41 (44.44)	1.11 (35.42)		
Change score, 6 months' FU	12.22 (39.48)	−3.25 (35.17)	$P = 0.106$	$P = 0.124$
Change score, 9 months' FU	13.46 (43.94)	−2.34 (63.36)	$P = 0.015$*	$P = 0.138$
Change score, 12 months' FU	2.28 (51.35)	−10.52 (44.79)	$P = 0.035$*	$P = 0.215$

ITT intention to treat analysis of all randomised patients, *Change score* difference of baseline minus course score

*$P < 0.05$

**$P < 0.10$ (borderline significances)

[a] According to hierarchically ordered hypotheses significant main effects or interactions are necessary to add the next point in time to the model

[b] Significance levels should be interpreted 'descriptively'

[c] No replacement strategy for missing values; FU: follow-up

[d] Patients with medication on one time point at least

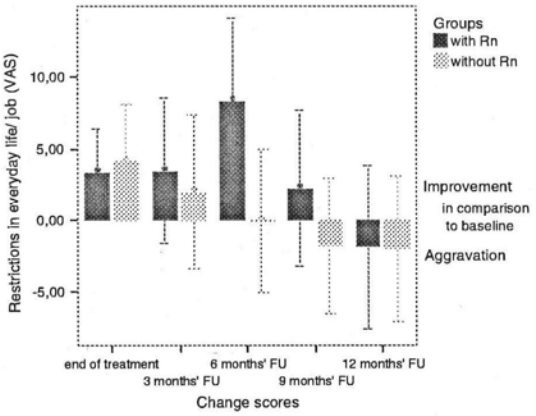

Fig. 2 Change scores of limitations in everyday life/job (mean and 95% CI) for the treatment groups (main outcome measure)

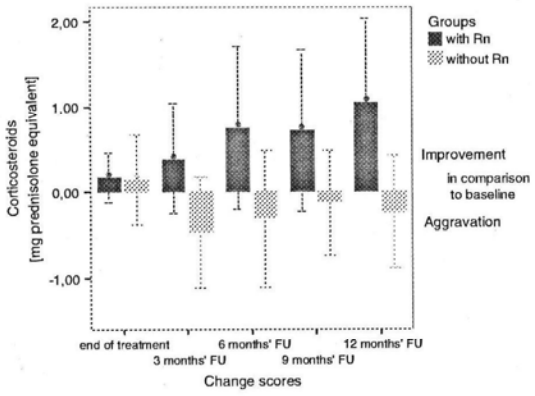

Fig. 3 Change scores of corticosteroids (mean and 95% CI) for the treatment groups

of COXIB was recommended. Nevertheless, in 2004, still 1/400 NSAID consumers suffered from and 1/8,000 died because of ulcer complications in Germany [38]. Whilst a remarkable decrease in gastro-intestinal event rates was associated with development and launching of COXIB [39, 40], the focus regarding adverse reactions changed to cardiovascular complications [41] for both NSAID and COXIB.

Taking into account the annual frequency of 11 million NSAID prescriptions in Germany [38], there is consensus that even small reductions in medication may positively affect the individual long-term career of RA patients [41–43].

Our results are, in general, in accordance with those of other trials in patients with inflammatory rheumatism ([9] in RA; [5, 10, 30] in AS). All trials showed more pronounced mid-term/long-term benefits in

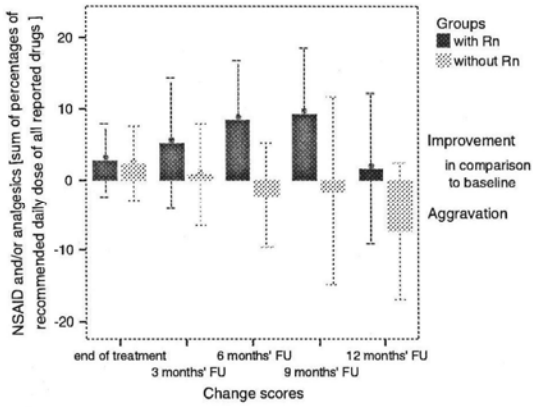

Fig. 4 Change scores of NSAIDs and/or analgesics (mean and 95% CI) for the treatment groups

favour of radon therapy over various months of FU than that suggested by between-group differences at the end of treatment. In the AS trial of van Tubergen et al. increased functional capacity could be demonstrated (using BASFI), which could not be shown in our RA trial. Sensitivity to change of the FFbH-P self-assessment questionnaire may be limited; its results, however, were consistent with the Keitel test after the end of treatment. Similar to our findings, a reduced NSAID consumption was also reported by Lind-Albrecht [30] in AS patients. The consistency in the current and former results strengthens the evidence of benefits of radon treatment.

Various lines of evidence indicate a potentially causal relationship between radon spa therapy and the inhibition of inflammation and pain relief. Radon (^{222}Rn) dissolved in bath water is incorporated via the skin and by inhalation, and is distributed via blood circulation all over the body. Retention time in the body is short, with 50% disappearing within 15–30 min [44], mainly through exhalation [45, 46] and also through excretion and diffusion through the skin after the bath. The decay rate is about 0.2% during the passage through the body [47], while small doses of high energetic alpha-particle radiation are being emitted. The short-living decay daughters of radon—^{218}Po, ^{214}Pb, ^{214}Bi and ^{214}Po—mainly deposited on the skin and in the lung [47], further fuel the applied dose of energy.

Due to its relatively high atomic mass, alpha radiation is absorbed immediately on contact with matter and is therefore only effective over very short distances [44]. The relatively large transfer of energy associated with this absorption causes a series of complicated reactions on the molecular and cellular level, resulting in cell apoptosis with high efficiency.

Evidence from physiological studies underpins the biological plausibility of radon as a therapeutically active substance. Alpha particles stimulate the release of anti-inflammatory cytokines (like TGF-β and IL-10) as a consequence of the phagocytosis of apoptotic cells by dendritic cells. These cytokines act as antagonists against the pro-inflammatory cytokines (like TNF-α, IL-12, IL-1β, etc.) and thus down-regulate the cellular response regarding the activity of macrophages and neutrocytes and limit the migration of leucocytes. This mode of action is already well known for UV-B and low-dose X-rays and is increasingly supported by experiments and physiological observations under low-dose alpha-particle irradiation. The intensified biological efficacy of low-dose alpha radiation compared to that of X-rays is explained by the enhanced linear energy transfer along the tracks of the alpha particles in tissue and by the so-called 'bystander' effect. It has been shown that not only those cells hit directly by alpha particles react in this manner but also the neighbouring ones [47, 48].

Furthermore, CO_2 also dissolved in the spring water may contribute to enhanced effects because it forwards the blood circulation and intensifies the radon transfer and the incorporated concentrations within the body [46].

Currently, no evidence on anti-rheumatic effects of CO_2 baths (exclusively) exists based on controlled clinical trials. The only available trial in musculoskeletal conditions was performed by Mucha [49] in stage-I patients with algodystrophy. Although it reported pain relief and functional improvement, the study suffered from various methodological flaws and was regarded insufficient to prove therapeutical effectiveness [50].

It could be assumed that the known CO_2 effect of hyperaemisation of peripheral vessels contributes to a quicker and/or better removal of analgetic substances. But, to date, this is not supported by data. There is no hint that CO_2 might be able to influence the pathogenesis of the rheumatic processes, although it possibly may have an impact on reactive concomitant symptoms.

Nevertheless, in applying CO_2 to both treatment groups, the effect differences observed could only be explained by radon, which was the sole systematic distinction in the treatment of both groups. Therefore, the benefits we found in our trial are assignable to radon spa therapy, in general.

Considering the meanwhile established reproducibility of positive long-term clinical outcomes with a series of radon baths, future studies should address aspects of its cost-effectiveness as done in AS [51] and the underlying immunological processes regarding the long-term reactions in inflammatory rheumatism. Also, dose-finding studies seem to be reasonable to combine best benefit and least risk for the patients. Additionally, the role of radon spa therapy in osteoarthritis and other degenerative musculoskeletal disorders should be further researched.

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References

1. Scott DL, Shipley M, Dawson A, Edwards S, Symmons DPM, Woolf AD (1998) The clinical management of RA and OA: strategies for improving clinical effectiveness. Br J Rheumatol 37:546–554
2. Verhagen AP, de Vet HCW, de Bie RA, Kessels AGH, Boers M, Knipschild PG (1997) Taking Baths: the efficacy of balneotherapy in patients with arthritis. A systematic review. J Rheumatol 24:1964–1971
3. Pratzel HG, Legler B, Aurand K, Baumann K, Franke T (1993) Wirksamkeitsnachweis von Radonbädern im Rahmen einer kurortmedizinischen Behandlung des zervikalen Schmerzsyndroms. Phys Rehab Kur Med 3:76–82
4. Lind-Albrecht G (1994) Einfluss der Radonstollentherapie auf Schmerzen und Verlauf bei Spondylitis ankylosans (M.Bechterew)—eine randomisierte prospektive Studie [Thesis]. Mainz, Johannes-Gutenberg-Universität
5. Lind-Albrecht G, Droste U (1996) Zusatzeffekt der Radonstollentherapie bei spondylitis ankylosans (M.Bechterew). Bad kreuznach: Karl-Aschoff-Klinik, Rheumazentrum Rheinland-Pfalz
6. Heisig S (1997) Zur analgetischen Wirksamkeit von Radonbädern bei patienten mit degenerativer erkrankung von wirbelsäule und gelenken [Thesis]. München, Ludwig-Maximilians-Universität
7. Reiner L (1998) Wirksamkeit und Verträglichkeit von Radonbädern bei Patienten mit RA [Thesis]. München, Ludwig-Maximilians-Universität
8. Skorepa P (1999) Wirkungsverstärkender Effekt von Radonbädern durch Kohlensäure? Ergebnisse einer prospektiven randomisierten Doppelblindstudie bei Patienten mit muskuloskelettalem Schmerzsyndrom bei degenerativen Erkrankungen von Wirbelsäule und Gelenken [Thesis]. München, Ludwig-Maximilians-Universität
9. Franke A, Reiner L, Pratzel HG, Franke T, Resch KL (2000) Long-term efficacy of radon spa therapy in rheumatoid arthritis: a randomised, sham-controlled study and follow-up. Rheumatol 39:894–902
10. van Tubergen A, Landewe R, van der Heijde D, Hidding A, Wolter N, Asscher M et al (2001) Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: a randomized controlled trial. Arthritis Rheum pp 430–438

11. Callies R (1989) Radonbädertherapie bei entzündlichen rheumatischen Ekrankungen. In: Jordan E (ed) Abhandlungen der Sächsischen Akademie der Wissenschaften, Mathematisch-Naturwissenschaftliche Klasse. Leipzig: Akademie-Verlag, Berlin, pp 133–134
12. Vulpe B, Zielke A, Häntzschel H, Tautenhahn B (1989) Klinische Langzeitbeobachtungen nach Kurorttherapie auf Radonbasis bei Rheumatoid Arthritis (RA) und Spondylitis ankylosans (SPA) In: Jordan E (ed) Abhandlungen der Sächsischen Akademie der Wissenschaften, Mathematisch-Naturwissenschaftliche Klasse. Leipzig, Akademie-Verlag, Berlin, pp 139–142
13. Zielke A, Vulpe B (1989) Was leistet eine Radon-CO2-Bäder-Monotherapie bei Rheumatoid Arthritis und Spondylitis ankylosans? In: Jordan E (ed) Abhandlungen der Sächsischen Akademie der Wissenschaften, Mathematisch-Naturwissenschaftliche Klasse. Leipzig, Akademie-Verlag, Berlin, pp 135–138
14. Griessmayer H, Tripathi R, Falkenbach A (1997) Development of RA during a radon thermal cure treatment. Br J Rheumatol 36(Suppl1):187
15. Bernatzky G, Graf AH, Saria A, Lettner H, Hofmann W, Adam H et al (1997) Schmerzhemmende Wirkung einer Kurbehandlung bei Patienten mit Spondylarthritis Ankylopoetica. In: Pratzel HG, Deetjen P (eds) Radon in der Kurortmedizin Zum Nutzen und vermeintlichen Risiko einer traditionellen medizinischen Anwendung, 1st edn. Geretsried: I.S.M.H. Verlag, Berlin, pp 144–157
16. Jöckel H (1997) Praktische Erfahrungen mit der Radontherapie. In: Pratzel HG, Deetjen P (eds) Radon in der Kurortmedizin. Geretsried: I.S.M.H., Berlin, pp 84–91
17. Soto J (1997) Effects of radon on the immune system. In: Pratzel HG, Deetjen P (eds) Radon in der Kurortmedizin Zum Nutzen und vermeintlichen Risiko einer traditionellen medizinischen Anwendung, 1st edn. Geretsriet: I.S.M.H., Berlin, pp 03–113
18. Hofmann W (1997) Radon doses compared to X-ray doses. In: Pratzel HG, Deetjen P (eds) Radon in der Kurortmedizin Zum Nutzen und vermeintlichen Risiko einer traditionellen medizinischen Anwendung, 1st edn. Geretsriet: I.S.M.H., Berlin, pp 57–67
19. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS et al (1988) The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31:315–323
20. Fielding PGR, Hittinger R (1999) Patients who are eligible but not randomised should be included as an additional arm in study. BMJ 318:874f
21. Price D, McGrawth P, Rafii A, Buckingham B (1983) The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 17:45–56
22. Jensen M, Karoly P, Braver S (1986) The measurement of clinical pain intensitiy: a comparison of six methods. Pain 27:117–126
23. Raspe HH, Hagedorn U, Kohlmann T, Mattusek S (1990) Der Funktionsfragebogen Hannover (FFbH): ein Instrument zur Funktionsdiagnostik polyartikulärer Gelenkerkrankungen. In: Siegrist J (ed) Wohnortnahe Betreuung Rheumakranker. Stuttgart, New York: Schattauer, Birlin, pp164–182
24. Kohlmann T, Raspe H (1994) Die patientennahe Diagnostik von Funktionseinschränkungen im Alltag. Psycho Med 6:21–27
25. Keitel W, Hoffmann H, Weber G, Krieger U (1971) Ermittlung der prozentualer Funktionsminderung der Gelenke durch einen Bewegungsfunktionstest in der Rheumatologie. DtGesundheitswesen. 26(27–52):1901–1903
26. Keitel W (1988) Das Messen in der Rheumatologie—Probleme der Standardisierung und Verläßlichkeit. Akt Rheumatol 13(2):43ff
27. Langer HE (1997–2006) Rheuma von A-Z: Prednisolon-Äquivalent; www.rheuma-online.de/a-z/ Langer,G
28. Kaiser H (1996) Praxis der Cortisontherapie. 4, neu bearb (ed) München–Wien–Baltimore: Urban Schwarzenberg 29. Constant F, Guillemin F, Herbeth B, Collin JF, Boulange M (1997) Measurement methods of drug consumption as a secondary judgment criterion for clinical trials in chronic rheumatic disaeases. Am J Epidemiol 145(9):826–833
29. Lind-Albrecht G (1999) Radoninhalation bei Morbus Bechterew. In: Deetjen P, Falkenbach A (eds) Radon und Gesundheit. Frankfurt/Main Berlin Bern Bruxelles New York Wien: Peter Lang Europäischer Verlag der Wissenschaften pp 131–138
30. Unnebrink K, Windeler J (2001) Intention-to-treat: methods for dealing with missing values in clinical trials of progressively deteriorating diseases. Stat Med 20(24):3931–3946
31. Unnebrink K (2002) Regulatory guidance for handling missing data in clinical trials: ICH Topic E9, CPMP points to consider on missing data, FDA recommendations for trials on dementia. Inf Biom Epi Med u Biol 33:1–10
32. Maurer W, Hothorn LA, Lehmacher W (1995) Multiple comparisons in drug clinical trials and preclinical assays: a-priori ordered hypotheses. In: Vollmar J (ed) Biometrie in der chemisch-pharmazeutischen Industrie. Stuttgart: G. Fischer; pp 3–18
33. Kieser M, Bauer P, Lehmacher W (1999) Inference on multiple endpoints in clinical trials with adaptive interim analyses. Biom J 41(3):261–277
34. Garcia Rodriguez LA, Hernandez-Diaz S (2001) The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. Arthritis Res 3(2):98–101
35. Bolten WW, Lang B, Wagner AV, Krobot JJ (1999) Konsequenzen und Kosten der NSA-Gastropathie in Deutschland. [Consequences and costs of NSAID-gastropathy in Germany.] Aktuell Rheumatol 24:127–134
36. Singh G (2000) Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. Arthritis, Rheumatism, and Aging Medical Information System. Am J Ther 7(2):115–121
37. Koelz HR, Michel B (2004) Nichtsteoridale Antirheumatika—Magenschutztherapie oder COX-2-Hemmer? Dt Ärztebl101 (45):A3041–A3046
38. Laine L, Bombardier C, Hawkey CJ, Davis B, Shapiro D, Brett C et al (2002) Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcomes study in patients with rheumatoid arthritis. Gastroenterol 123(4):1006–1012
39. Rahme E, Marentette MA, Kong SX, Lelorier J (2002) Use of NSAIDs, COX-2 inhibitors, and acetaminophen and associated coprescriptions of gastroprotective agents in an elderly population. Arthritis Rheum 47(6):595–602
40. Baigent C, Patrono C (2003) Selective cyclooxygenase 2 inhibitors, aspirin, and cardiovascular disease: a reappraisal. Arthritis Rheum 48(1):12–20
41. Hunt RH, Barkun AN, Baron D, Bombardier C, Bursey FR, Marshall JR et al (2002) Recommendations for the appropriate use of anti-inflammatory drugs in the era of the coxibs: defining the role of gastroprotective agents. Can J Gastroenterol 16(4):231–240
42. Bolten WW (2005) [Recommendations for treatment with nonsteroidal anti-inflammatory drugs]. MMW Fortschr Med 147(31–32):24–27

43. Deetjen P (1997) Epidemiology and biological effects of radon. In: Pratzel HG, Deetjen P (eds) Radon in der Kurortmedizin Zum Nutzen und vermeintlichen Risiko einer traditionellen medizinischen Anwendung, 1st edn. Geretsriet: I.S.M.H., Berlin, pp 33–39
44. Hofmann W, Lettner H, Winkler R, Foisner W (1999) Perkutaner Radon-Transfer und Strahlenexposition durch Radonzerfallsprodukte. In: Deetjen P, Falkenbach A (eds) Radon und Gesundheit. Frankfurt/M—Berlin—Bern—Bruxelles—New York—Wien: Peter Lang Europäischer Verlag der Wissenschaften, pp 83–92
45. Grunewald WA, Von Philipsborn H, Just G (1999) Radon-Transfer Haut-Blut-Exspirationsluft. In: Deetjen P, Falkenbach A (eds) Radon und Gesundheit. Frankfurt/M—Berlin—Bern—Bruxelles—New York—Wien: Peter Lang Europäischer Verlag der Wissenschaften, pp 93–102
46. Harder A (2005) Molekulare und zelluläre Wirkungsmechanismen. In: RADIZ e.V. Schlema (eds) Radon als Heilmittel, 1st edn. Hamburg,: Verlag, Dr.Kovac pp 23–56
47. Soto J (1999) Radon effects at cellular and molecular levels. In: Deetjen P, Falkenbach A (eds) Radon und Gesundheit. Frankfurt/M—Berlin—Bern—Bruxelles—New York—Wien: Peter Lang Europäischer Verlag der, Wissenschaften pp 63–66
48. Mucha C (1992) Einfluß von CO2-Bädern im frühfunktionellen Therapiekonzept der Algodystrophie. Phys Rehab Kur Med 2:173–178
49. Windeler J (2005) Gutachten zum Stand des Nachweises der Wirksamkeit von Kohlendioxidbädern aufgrund klinischer Studien. In: Bühring M, Kemper FH, editors. Naturheilverfahren und unkonventionelle medizinische Richtungen (Lose-Blatt-Sammlung). Heidelberg, 2005: Springer, Medizin Verlag, 1997 pp2.08;1–14
50. Van Tubergen A, Boonen A, Landewe R, Rutten-Van Molken M, Van Der Heijde D, Hidding A, et al (2002) Cost effectiveness of combined spa-exercise therapy in ankylosing spondylitis: a randomized controlled trial. Arthritis Rheum pp 459–67