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Infrared-Mediated Hyperthermia Is Effective in the Treatment of Scleroderma-Associated Raynaud's Phenomenon

To the Editor:

Scleroderma is a systemic autoimmune disease featuring variable organ involvement as well as Raynaud's phenomenon (RP). To date, no studies exist on the effect of systemic body temperature elevation on the severity of RP. Water-filtered near-infrared (infrared A (IRA)) irradiation is particularly effective in transdermal heat delivery (Meffert and Sonnichsen, 1974; Meffert *et al*, 1989; Meffert and Meffert, 2000). Prompted by preliminary findings (Meffert *et al*, 1990), we here examined the effect of IRA treatment on RP. We employed fingertip rewarming in response to cold challenge (Wise *et al*, 2004; Foerster *et al*, in press) as well as a clinical activity score (Merkel *et al*, 2002) as outcome variables. In addition, we explored the effect of IRA treatment on skin thickness and scleroderma-associated joint pain. Methods, a study flow chart, as well as immediate effects of IRA treatment are detailed in the online supplement. Because of the specified inclusion criteria (see Tables S1–S3), patients were in stable-disease phase.

Response to Cold Challenge

Fingertip rewarming after a defined cold challenge was determined using a recently described device (Foerster *et al*, in press). The variable τ denotes the time elapsed until 63% of pre-cooling fingertip temperature has been regained. Figure 1 shows that the median cold response, though varying between individuals, is significantly improved after only one IRA treatment and continues to improve until the tenth treatment. After the end of treatment, this effect is steadily reversed but still detectable 6 wk after the last treatment. Importantly, there was no correlation between the τ-values obtained and ambient temperature (not shown). Table I summarizes the corresponding mean τ-values for the entire cohort as well as the subgroup presenting with digital ulcers. The latter subgroup exhibited slight, but not statistically significant increased mean τ-values. Thus, IRA-mediated hyperthermia has a significant effect on fingertip rewarming after cold challenge. Moreover, we also found that the improvement to be expected from a series of IRA treatments for a given individual can be predicted based on a single treatment (Figs S1 and S2).

RP Severity

We assessed patient self-assessment of RP severity by a previously validated visual analog scale (VAS) (details in the online supplement). A statistically significant reduction of subjectively felt RP severity is observed after five IRA treatments (Table II). The maximum VAS reduction is observed at the end of treatment, remaining detectable 6 wk after the last treatment, thus closely paralleling the cold challenge response. The magnitude of VAS reduction (29.1% in the unstratified cohort; 44% in patients with ulcers), as well as the reversal noted in the observational phase suggest that the observed VAS changes are unlikely because of placebo effect alone.

Effect of IRA on Skin Thickness

Modified Rodnan skin scores (MRSS) were obtained in order to detect changes in skin thickness. The mean MRSS decreased by 25.4% of pre-treatment values at the end of IRA treatment and remained at this level throughout the observational phase (Table III). In patients with diffuse scleroderma a maximum mean MRSS reduction of 28% was observed at 3 wk post-treatment. As expected, MRSS scores were significantly lower in patients with limited scleroderma. Nevertheless, a similar magnitude of MRSS reduction upon IRA treatment was found in this subgroup as well. Of note, MRSS scores did not decrease further during the observational phase, suggesting that the score changes did not represent spontaneous improvements in the trial setting. Thus, these data indicate that IRA-mediated hyperthermia may exert a transient beneficial effect on skin thickness.

Effect of IRA on Joint Pain

We quantified joint complaints in scleroderma patients using the DAS28 score (see online Methods). DAS28 scores decreased slightly, but statistically significant after five treatments (Table IV). As the unstratified patient cohort contains patients with no or minimal joint complaints at baseline we also analyzed the subgroup positive for rheumatoid factor. The reduction in arthralgia score is even more pronounced in this subgroup, exhibiting a reversal beginning 3 wk post-treatment. The observed reduction of arthralgia severity was not because of an effect on systemic inflammatory status, as the erythrocyte sedimentation rate, which is included in the DAS28, did not change during IRA treatment (not shown). The magnitude of DAS28 reduction seen in the present cohort by far exceeds changes attributable to placebo effects based on several placebo-controlled studies (e.g., (Gerlag *et al*, 2004; McCarey *et al*, 2004; Choy *et al*, 2005), especially given the 11-wk study

Abbreviations: CI, confidence interval; IRA, infrared A; MRSS, modified Rodnan skin scores; RP, Raynaud's phenomenon; SD, standard deviation; VAS, visual analog scale

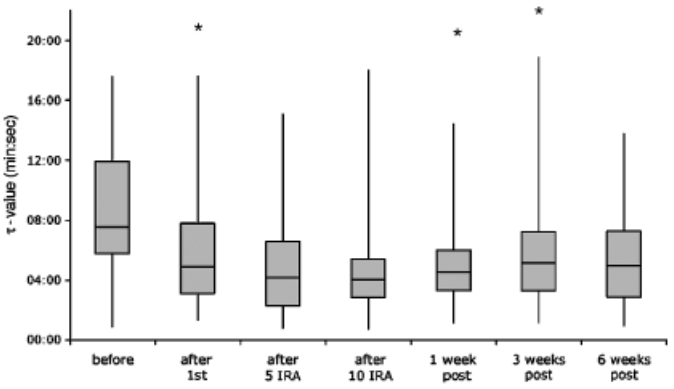

Figure 1
Effect of near-infrared (IRA) hyperthermia treatment on fingertip cold response in scleroderma patients. Fingertip rewarming in response to cold challenge was measured as described in Methods before, during, and after a series of IRA treatments at the time points indicated. The τ-values shown on the y-axis represent the time elapsed until 63% of pre-cooling temperature has been regained (see Methods). Data shown represent median (*horizontal bars*), first and third quantiles (*boxes*), and range (*vertical lines*) of n = 58 patients. Asterisk (*) denotes τ-values >20:00. Individual outliers ⩾25:00 are not graphed and were observed as follows: 26:24 (before); 28:00 (after first); 25:30 (after 5 ×); 28:24 (after 10 ×).

period. Thus, IRA-mediated hyperthermia transiently improves arthralgia in scleroderma patients harboring joint complaints.

General Disease Activity and Other Response Parameters

Changes in the health assessment questionnaire paralleled the results described above (see online supplement). Furthermore, we did not observe IRA-mediated hyperthermia on systemic inflammatory status. Unexpectedly, however, lung diffusion capacity improved in those patients presenting with ⩽75% of predicted baseline DLCO. The mean % DLCO in this subgroup increased from 61.3 ± 11.3 to 66 ± 15.9 (p = 0.005; two-sided paired *t* test) at 6-wk post-treatment.

This study demonstrates that IRA-mediated hyperthermia reduces the severity of RP. Two independent outcome variables (fingertip cold response and VAS-RP) confirm this conclusion. Remarkably, the effect is detectable at least 6 wk after the end of IRA treatment, suggesting

Table I. Response to cold challenge[a]

	Before IRA	At first IRA	After 5 × IRA	After 10 × IRA	1 wk post	3 wk post	6 wk post
All patients (n = 58)							
Mean ± SD	8.39 ± 4.54	6.00 ± 3.45	5.07 ± 4.12	4.53 ± 4.18	5.21 ± 3.34	5.58 ± 4.13	5.36 ± 3.15
95% CI	7.24–9.54	5.01–6.55	4.01–6.13	3.44–6.01	4.25–6.18	4.52–7.05	4.44–6.27
p-value[b]		0.001	<0.001	<0.001	<0.001	0.003	<0.001
Patients with digital ulcers (n = 15)							
Mean ± SD	9.01 ± 4.07	6.35 ± 3.08	5.41 ± 3.23	5.31 ± 2.31	5.53 ± 2.24	5.23 ± 2.27	6.03 ± 3.08
95% CI	6.56–11.06	5.00–8.10	3.58–7.24	4.12–6.50	4.37–7.08	4.06–6.41	4.24–7.41
p-value[b]		0.079	0.022	0.011	0.019	0.008	0.038

[a]Fingertip rewarming after cold challenge was determined as detailed in Methods. The τ-value represents the time elapsed before approximately 63% of pre-cooling temperature is regained. Data shown represents n = 56 individuals.
[b]One-sided paired Student's *t* test.
IRA, infrared A; CI, confidence interval; SD, standard deviation.

Table II. Visual analogue scale (VAS)—Raynaud's phenomenon[a]

	At first treatment	After 5 × IRA	After 10 × IRA	1 wk post	3 wk post	6 wk post
All patients (n = 58)						
Mean ± SD	1.17 ± 0.71	0.94 ± 0.68	0.83 ± 0.58	0.94 ± 0.72	0.90 ± 0.71	0.94 ± 0.62
95% CI	0.98–1.35	0.76–1.12	0.68–0.99	0.75–1.13	0.71–1.08	0.77–1.10
% reduction		19.7	29.1	19.7	23.1	19.7
p-value[b]		0.002	<0.001	0.004	0.003	0.005
Patients with digital ulcers (n = 15)						
Mean ± SD	1.28 ± 0.66	0.88 ± 0.68	0.71 ± 0.59	0.76 ± 0.7	0.79 ± 0.66	0.73 ± 0.55
95% CI	0.95–1.62	0.53–1.22	0.4–1.02	0.39–1.13	0.45–1.14	0.44–1.01
% reduction		31.3	44.5	40.6	38.3	43.0
p-value[b]		0.002	0.001	0.011	0.011	0.001

[a]The VAS was administered as detailed in Methods at the time points indicated in the table. Data shown represent mean ± SD for n = 58 patients.
[b]Compared with pre-treatment value in a one-sided paired Student's *t* test.
IRA, infrared A; CI, confidence interval; SD, standard deviation.

Table III. Skin thickness before and after IRA treatment[a]

	Before	After 5 × IRA	After 10 × IRA	1 wk post	3 wk post	6 wk post
All patients (n = 58)						
Mean ± SD	12.9 ± 9.3	11.3 ± 8.4	9.6 ± 7.5	9.7 ± 7.9	9.3 ± 6.8	9.8 ± 7.3
95% CI	10.5–15.3	9.1–13.4	7.6–11.6	7.6–11.8	7.5–11.1	7.9–11.8
% reduction		12.4	25.6	24.8	27.9	24.0
p-value[b]		<0.001	<0.001	<0.001	<0.001	<0.001
Limited SSc (n = 31)						
Mean ± SD	7.7 ± 5.4	6.5 ± 4.6	5.8 ± 4.4	5.7 ± 4.5	5.7 ± 4.4	6.1 ± 4.7
95% CI	5.8–9.6	4.8–8.1	4.3–7.4	4.1–7.3	4.2–7.3	4.5–7.8
% reduction		15.6	24.7	26.0	26.0	20.8
p-value[b]		0.001	<0.001	<0.001	<0.001	<0.001
Diffuse SSc (n = 27)						
Mean ± SD	18.7 ± 9.4	16.6 ± 8.4	14.2 ± 8.1	14.5 ± 8.5	13.6 ± 6.6	14.3 ± 7.3
95% CI	15.2–22.3	13.4–19.8	11–17.3	11.1–17.8	11.1–16.2	11.4–17.2
% reduction		11.2	24.1	22.5	27.3	23.5
p-value[b]		<0.001	<0.001	<0.001	<0.001	0.003

[a]The modified Rodnan skin thickness score was obtained as detailed in Methods.
[b]As compared with pre-treatment value by a paired two-sided Student's *t* test.
IRA, infrared A; CI, confidence interval; SD, standard deviation.

that this treatment may be of considerable practical value, especially in light of its favorable safety profile.

Regarding the effect of IRA on skin sclerosis, documented levels of intra- and inter-observer variability (see online Methods) rule out artifacts. In a recent trial of relaxin, patients with a baseline MRSS $\geqslant$ 20 exhibited a mean MRSS reduction from 27.5 to 20.0 within 12 wk (placebo: from 26.7 to 24.4; Seibold *et al*, 2000). When analyzing this particular subgroup (baseline MRSS $\geqslant$ 20) in the present cohort, a mean MRSS reduction from 28.6 to 21.8 is found in this 11-wk study period, suggesting that mild hyperthermia may harbor a comparable therapeutic potential. As the MRSS score has been proposed as a marker for natural disease progression (Steen and Medsger, 2001), our data also raise the question as to whether long-term IRA-mediated hyperthermia may be able to modify natural disease progression.

Although joint complaints are frequent in scleroderma patients (La Montagna *et al*, 2005), appropriate scores have not been validated. Therefore, we employed the DAS28 index, which has been proposed as outcome for joint involvement in scleroderma (Akesson *et al*, 2003). The rheumatoid-factor-positive subgroup that we analyzed may in fact include a significant subgroup of patients fulfilling diagnostical criteria for RA (Misra *et al*, 1995). The effect of IRA treatment on scleroderma-associated arthralgia was highly significant, especially considering the 11-wk study period. Therefore, IRA-mediated hyperthermia should be evaluated for use in RA.

In conclusion, IRA-mediated mild hyperthermia is effective for the treatment of scleroderma-associated RP and may be therapeutically effective for other disease manifestations. Based on these data, further randomized-

Table IV. Joint involvement before and after IRA treatment[a]

	Before	After	After 5 × IRA	After 10 × IRA	1 wk post	3 wk post	6 wk post
All patients (n = 58)							
Mean ± SD	4.2 ± 1.5	4.1 ± 1.5	3.8 ± 1.4	3.8 ± 1.3	3.9 ± 1.3	3.8 ± 1.3	3.9 ± 1.5
95% CI	3.8–4.6	3.7–4.5	3.4–4.2	3.5–4.1	3.5–4.2	3.5–4.2	3.5–4.3
p-value[b]		NS	0.019	0.021	0.026	0.008	0.021
Rheumatoid factor-positive patients (n = 21)							
Mean ± SD	4.8 ± 1.3	4.9 ± 1.3	4.5 ± 1.2	4.2 ± 1.0	4.2 ± 0.9	4.5 ± 1.0	4.5 ± 1.2
95% CI	4.3–5.4	4.3–5.4	3.9–5.0	3.8–4.7	3.8–4.6	4.0–4.9	4.0–5.0
p-value[b]		NS	0.017	0.003	0.005	0.060	0.019

[a]The arthralgia score DAS28 was employed to quantify joint complaints (see Methods).
[b]As compared with pre-treatment value by a paired two-sided Student's *t* test.
IRA, infrared A; CI, confidence interval; SD, standard deviation.

controlled studies are warranted to establish whether a long-term maintenance treatment may be able to sustain treatment responses. If so, mild hyperthermia may offer a valuable complementary treatment when drug side effects are limiting.

All data obtained from human subjects in this study were subject to prior approval by the Charité institutional review board and were carried out in accordance to the Helsinki declaration. All patients gave written informed consent prior to enrolling in the study.

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Supplementary Material

The following material is available online for this article.
Figure S1. Effect of near-infrared (IRA) hyperthermia on fingertip cold-challenge.
Figure S2. Time course of scleroderma-associated variables improved by IRA-mediated hyperthermia.
Table S1. Study flow chart
Table S2. Patient cohort
Table S3. General scleroderma activity before and after IRA treatment.
Supplemental text Detailed Methods section, description of immediate effects of IRA treatment, data on the prediction of therapy response, as well as additional references.

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