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Efficiency of a Whole-Body Cryotherapy protocol at -110 °C for hand rheumatoid arthritis: a controlled trial

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Abstract

While the recent literature on Whole-Body Cryotherapy pointed to its beneficial systemic effects on inflammatory markers in rheumatoid arthritis, it was not clear whether it could also have more localized effects, with the attainment of analgesic thresholds on hands that are usually protected during protocols. Twenty-five young, healthy subjects (12 males aged 25.1 ± 3.5 years and 13 females aged 23.5 ± 2.6 years) agreed to participate in this study. Two study groups were defined: (1) a control group with a hand fully gloved and (2) an experimental group with a partially ungloved hand during the WBC session. In both groups, the achievement of analgesic thresholds of skin temperature was established through thermal imaging, focused on the measurement of temperatures at the different joint locations. Using a new protocol with direct exposure of the hands during the last 40 s of a standard WBC session of 3 min at −110 °C made it possible to respect this risk/benefit balance. Infrared thermography analyses revealed that for all regions of interest (except MCP and IP, CMP for thumb), there was a clinically meaningful reduction of skin temperature in participants from the experimental group. The thermal analysis suggests that a protocol of Whole-Body Cryotherapy at −110 °C where hands must be ungloved during 40 s could be a useful tool for the management of hand rheumatoid arthritis by achieving local antalgic thresholds.

Keywords Whole-Body Cryotherapy · Protocol · Hand rheumatoid · Arthritis · Antalgic threshold

Abbreviations

RA	Rheumatoid arthritis
WBC	Whole-Body Cryotherapy
ROI	Region of interest
CMC	Carpometacarpal
MCP	Metacarpophalangeal
PIP	Proximal interphalangeal
IP	Interphalangeal
DIP	Distal interphalangeal

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that is the most common form of chronic inflammatory rheumatism characterized by inflammation of the synovial membrane lining the joints, joint swelling, joint tenderness, and destruction of synovial joints leading to severe disability and premature morbidity [1, 2]. The occurrence of RA is relatively constant with a prevalence between 0.5 and 1.0%, a frequency that has been reported in several European and North American populations [3]. During the development of RA, the joint becomes the site of an imbalance between pro- and anti-inflammatory regulators, resulting in the repression of anti-inflammatory factors and induction of pro-inflammatory factors. Analysis of the synovial fluid shows a high production of pro-inflammatory cytokines such as interleukins IL-1, IL-6, IL-17, IL-23, and tumor necrosis factor alpha (TNF-α) [4, 5]. These cytokines will maintain the inflammation and gradually lead to the destruction of cartilage, affecting primarily bones and tendons in the hands and feet. As a result, thermal properties in biological tissues from RA patients significantly differ from healthy individuals

[6]. Both joint-related skin and intra-articular temperatures of patients with RA have been shown to be increased by a margin of more than 3 °C compared to damage-free joints [7]. RA is a chronically progressive disease that is not yet curable despite all progress made in the associated therapeutic approach to reduce its intensity and time course. In order to decrease the pain threshold, it is well established that the application of cold modalities to rheumatoid joints may be used during the acute phase of RA to decrease inflammation and pain [8] and may inhibit collagenase activity induced by pro-inflammatory cytokines in the synovium due to a decrease in joint temperature [9].

In this regard, Whole-Body Cryotherapy (WBC) may appear as an efficient treatment modality since it combines both a systemic focus and a more local one by targeting the achievement of antalgic thresholds [10, 11]. Despite numerous studies in the literature, scientific evidence confirming the effectiveness of systemic cryotherapy remains still insufficient and available findings are contradictory. One of the reasons for these controversies is certainly related to the implementation of different WBC protocols from one study to another. It appears that two types of effects can be distinguished in the literature; the response to systemic inflammation (serum concentrations of cytokines) has been found to be related to the number of cryotherapy sessions, while the measurement of pain intensity and disease activity has not, and seems to be independent of the number of sessions with an immediate positive effect. In the context of RA, WBC can be understood as an adjuvant physical therapy that can assist in achieving a therapeutic effect by targeting inflammatory biomarkers. In healthy males, findings from Lubkowska et al. [12] showed that in response to whole-body cryostimulation, the levels of anti-inflammatory cytokines IL-6 and IL-10 increased, while IL-1α cytokine level decreased. In healthy endurance-trained males who performed a high-intensity running protocol, Krueger et al. [13] found that WBC did not attenuate exercise-induced changes in several biomarkers (i.e., IL-6, IL-10, myoglobin, cortisol, testosterone) compared to a control group without WBC. However, important limitations for this study included the lack of measures for TNF-alpha, IL-8, and IL-15 levels, the limited duration of the study (24 h), and a small sample size ($n = 11$). A significant reduction in IL-6 and TNF-α was shown in patients with RA after WBC treatment [14, 15] and also in interleukin IL-1 [16]. In addition to decreased pro-inflammatory cytokines in the blood, prior research revealed that WBC can induce an improvement in pain and fatigue [14, 17–19].

It should also be noted that WBC has also been used in the treatment of other rheumatoid inflammatory diseases, such as ankylosing spondylitis [20–24].

Exploring the efficacy of WBC in patients with hand rheumatoid arthritis involves that hands must be protected against extreme cold during the WBC session, in accordance with the safety guidelines edited by the French Society of Whole-Boby Cryotherapy (SFCCE). Does wearing gloves help achieve skin analgesic temperature thresholds during WBC sessions? Is a specific protocol in which hands would be ungloved for a given amount of time feasible?

The objective of the present study is to answer these questions by setting up an experimental protocol in which, for a given time, the participants have one hand gloved, while the other hand is not. By doing so, and based on the previously documented thermal symmetry of the upper and lower extremities in healthy subjects [25], two study groups were defined: (1) a control group with one hand fully gloved and (2) an experimental group with a partially ungloved hand during the WBC session. In both groups, the achievement of analgesic thresholds of skin temperature was established through thermal imaging, focused on the measurement of temperatures at the different joint locations. Since thermoregulatory responses to cold have been suggested to be gender dependent, sex influence was also analyzed. In addition, healthy subjects were also included for reference data purposes.

Materials and methods

Participants

A prospective power analysis has been conducted before the study for the estimation of the sample size. Anticipating a large effect of WBC on body temperature, it has been estimated that a sample size of twenty-four participants was needed to achieve a power of 80% (level of statistical significance alpha = 0.05, two-tailed test). Twenty-five young, healthy subjects (12 males aged 25.1 ± 3.5 years and 13 females aged 23.5 ± 2.6 years) agreed to participate in this study. These subjects were recruited among the students of our medical faculty. A summary of the participants' anthropometric and body composition characteristics is presented in Table 1. None of the participants presented low skeletal muscle mass (ALMI index beyond gender-specific cut points for sarcopenia in younger people [26]) which may be a prognostic marker in early RA. Prior to the study, they were examined by a physician who confirmed that they had no medical contraindications to the practice of WBC among those listed by the French Society of Whole-Body Cryotherapy (SFCCE, Paris, France). None of the participants had experienced WBC before the study. Of the female participants, five were in the follicular phase of their menstrual cycle, six in their luteal one, while the other two had no menstrual periods.

Table 1 Anthropometric and body composition data of participants (Mean ± SD); BMI (body mass index); BF (body fat); AF (Arm Fat); ALMI (appendicular lean mass index)

	Males		Females		*P*-value
	Mean	SD	Mean	SD	
Age/years	25.1	3.5	23.5	2.6	0.2186
Height/CM	178.9	7.8	163.8	4.5	$^{\beta}$0.0000
Mass/KG	71.5	8.9	56.8	7.0	$^{\beta}$0.0001
BMI/KG.M^{-2}	22.1	1.7	22.3	1.7	0.1086
BF/%	21.2	2.2	31.5	1.8	$^{\beta}$0.0000
AF/%	21.4	2.9	33.7	5.3	$^{\beta}$0.0002
ALMI/KG.M^{-2}	8.0	0.8	6.1	0.4	$^{\beta}$0.0010

$^{\beta}$indicates a significant difference between sexes ($P \leq 0.01$)

Materials

The whole-body cryochamber used for the study (Mecotec Cryoair, Pforzheim, Germany) is divided into two compartments of different temperatures in which the subject is entirely exposed to the cold treatment. This type of device is widespread in the literature [27–32]. Cryochamber consists of a pre-chamber with a temperature of -60 °C, where subjects adapt to low temperature during 30 s, and the main chamber with a temperature of -110 °C in which subjects are exposed to extreme cold during 3 min. The ambient temperature in the laboratory (adjacent to the cryochamber) where thermal imaging cameras were installed was set to 21 °C in accordance with usual recommendations [33]. Because thermal imaging is an accurate and reliable method of collecting skin temperature data following cryotherapy [34–37], hand skin temperatures were recorded in orthostatic position using a Variocam HD thermal imaging camera 1024 × 768 px (Jenoptik, Germany) in respect with the standard protocol for infrared imaging in medicine [38]. An emissivity factor of 0.98 for the human skin has been used to get appropriate skin thermographs. The analysis of the thermal images was made possible with the use of post-processing software IRBIS 3.1 (InfraTec, Germany). To access the body composition of the participants, especially adipose and lean indices, dual-energy X-ray absorptiometry technology has been used (Horizon DXA system, Hologic, Marlborough, USA). Body mass index (BMI), total body % fat (BF), arm % fat (AF), and appendage lean mass index (ALMI), defined as the ratio of lean mass of limbs to the height squared, are summarized in Table 1. To protect hands against extreme cold, participants were equipped with gloves (Mittens 400 Woolpower, Ostersund, Sweden) with double layers of terry knit fabric for optimal insulation and 70% sheep wool with a coefficient of thermal conductivity between 0.035 and 0.042 W m^{-1} K^{-1} and specific heat in the range 1720–1750 J kg^{-1} K^{-1}.

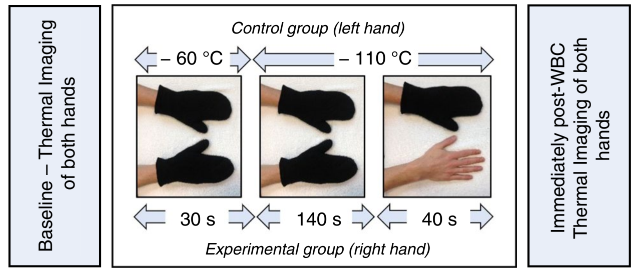

Fig. 1 Timeline of the WBC protocol

Study design

Participants were asked to refrain from consuming alcohol, caffeine, or food for 3 h before the cryosession and from vigorous activities. During cryosessions, participants wore minimal clothes, gloves, socks, shoes, woolen caps to protect ears, and surgical masks to avoid any risk of cold burns of the skin and/or respiratory tract. Before cold treatment, subjects had to rest for at least 30 min in the adjacent laboratory room to acclimatize to ambient temperature in order to avoid any bias in the examination of the reference temperature. The protocol required participants to first enter the pre-chamber at −60 °C for 30 s, and then they entered the main chamber (−110 °C) for three minutes. Based on discussions with qualified professionals (French Society of Whole Body Cryotherapy) having significant expertise in WBC, an exposure time of 40 s might be the upper limit that patients can tolerate at such temperatures without feeling discomfort. So, during the last 40 s of the protocol, participants were asked to remove their right glove as shown in Fig. 1.

Methodology

Prior to the cold exposure (baseline) and immediately after the WBC sessions (post-WBC), infrared thermal imaging of both hands was performed (Fig. 2a). The study focused exclusively on the dorsal side of the hand, which is the side most exposed to cold, particularly in patients with severe rheumatoid arthritis inducing ulnar drift in the hand with fingers curling inwards toward the palm. Because finger joints are the most common site of RA in hands, skin temperature measurements concentrated on MCP (metacarpophalangeal), PIP (proximal interphalangeal), and DIP (distal interphalangeal) joints for the 2nd to 5th finger and on MCP and IP (interphalangeal) joints for the thumb (Fig. 2b). At these 14 regions of interest (ROIs) specific to phalanges, a measurement of the CMC (carpometacarpal) joint was also made for the thumb, in order to better show how thermal gradient evolves along the thumb, although this joint is less

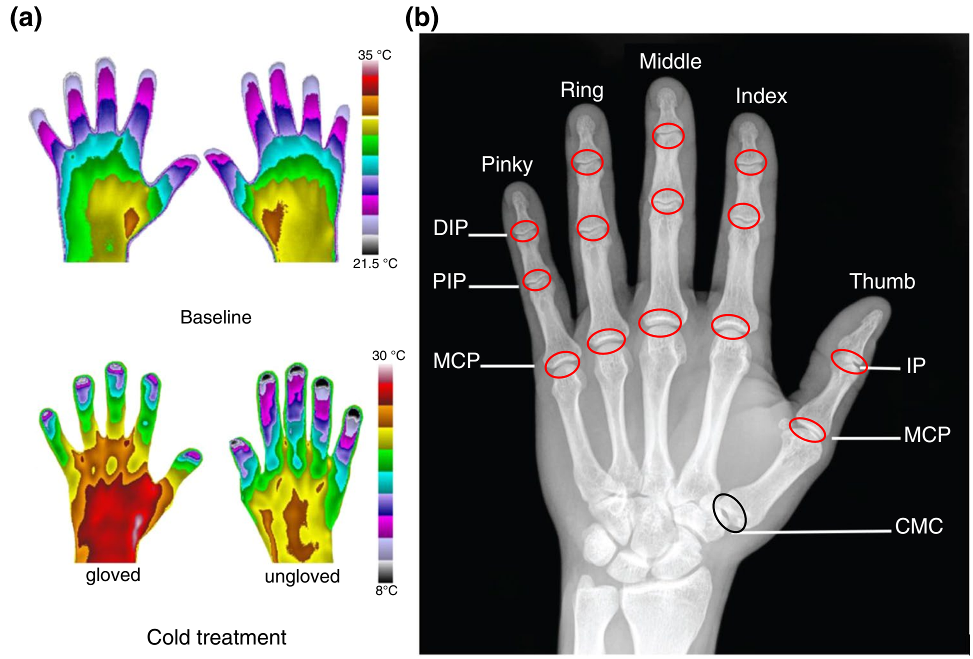

Fig. 2 **a** Thermal imaging of hands pre- (symmetrical thermal response) and post-treatment **a, b** target joints and selected ROIs (red and black outlines)

concerned by RA. Corresponding elliptic selected areas for the fifteen ROIs located on the hand dorsum are presented in Fig. 2b.

Results

Table 2 summarizes all skin temperature measures. All data are expressed as means and standard deviations. Associations between sex and changes in skin temperature were analyzed using classical T test (bilateral distribution, equal variance). Statistical significance was set at $p < 0.05$.

Table 2 Average skin temperatures and SD (*) gloved hand (control group), (**) partially ungloved hand (experimental group)

		Females ($n = 13$)				Males ($n = 12$)			
		Baseline		Cryosession		Baseline		Cryosession	
		Left hand	Right hand	Left hand (*)	Right hand (**)	Left hand	Right hand	Left hand (*)	Right hand (**)
Thumb	CMC	30.01 (1.92)	30.48 (1.45)	26.64 (2.02)	21.37 (2.02)	30.33 (1.21)	30.21 (1.18)	27.09 (1.04)	22.59 (1.66)
	MCP	27.77 (2.07)	27.40 (1.98)	23.04 (2.12)	17.17 (2.37)	26.96 (1.85)	26.96 (1.79)	22.93 (1.84)	16.42 (2.51)
	IP	25.58 (2.46)	25.35 (2.42)	19.60 (2.50)	12.72 (2.80)	25.40 (2.06)	25.45 (1.99)	19.98 (2.01)	13.40 (2.36)
Index	MCP	26.92 (2.53)	27.00 (2.44)	21.50 (2.19)	18.08 (3.35)	25.84 (1.95)	26.10 (1.57)	20.82 (1.88)	16.46 (1.88)
	PIP	25.08 (2.43)	25.04 (2.32)	17.36 (3.00)	11.79 (3.02)	24.55 (2.22)	24.29 (2.16)	17.28 (2.34)	11.94 (3.07)
	DIP	24.36 (2.48)	24.20 (2.27)	16.82 (2.63)	10.53 (2.53)	24.28 (2.08)	24.05 (2.07)	17.51 (2.26)	11.57 (2.34)
Middle	MCP	26.93 (2.53)	26.82 (2.46)	21.00 (2.02)	16.57 (2.68)	26.26 (1.51)	26.08 (1.59)	20.51 (1.57)	15.25 (2.20)
	PIP	24.97 (2.50)	25.03 (2.50)	18.89 (2.50)	12.45 (2.37)	24.25 (2.04)	24.34 (2.46)	18.08 (2.48)	12.42 (2.79)
	DIP	27.17 (2.50)	24.10 (2.43)	17.53 (2.68)	11.02 (2.09)	24.02 (1.96)	23.92 (2.26)	17.62 (2.00)	11.68 (2.23)
Ring	MCP	27.06 (2.72)	27.03 (2.64)	22.27 (2.08)	17.83 (2.24)	26.28 (1.69)	26.29 (1.72)	21.87 (1.77)	16.72 (2.06)
	PIP	24.79 (2.58)	24.76 (2.60)	18.86 (2.75)	11.70 (2.15)	24.02 (1.95)	24.20 (2.31)	18.25 (2.22)	11.90 (2.90)
	DIP	23.82 (2.46)	23.66 (2.44)	16.83 (2.83)	9.84 (1.99)	23.71 (1.85)	23.81 (2.27)	17.85 (1.52)	11.06 (2.52)
Pinky	MCP	26.76 (2.72)	26.57 (2.47)	21.50 (2.13)	17.05 (1.99)	26.20 (1.67)	26.18 (1.86)	21.05 (1.80)	15.74 (2.29)
	PIP	24.49 (2.58)	24.46 (2.43)	17.76 (2.32)	9.88 (2.82)	24.10 (2.00)	24.07 (2.14)	17.21 (2.24)	9.94 (2.73)
	DIP	23.41 (2.47)	23.22 (2.44)	16.24 (2.46)	8.31 (2.07)	23.44 (1.83)	23.44 (2.02)	16.69 (1.80)	9.26 (2.27)

Baseline skin temperature

First, since this study involved young adult females only, the link between their menstrual cycle phase and recorded hand skin temperature data at rest was explored. Since menstrual cycles are likely to alter core temperature [39], substantial evidence suggesting that increased progesterone levels during the luteal phase would lead to increased skin temperatures seems less established. Bartelink et al. [40] showed a skin temperature dependence on hormonal variations, while White et al. [41] demonstrated that the menstrual cycle changes do not appear to be followed by parallel changes in skin temperature. Although examination of the skin temperatures of the females in this study does not provide any statistical information on the role of the luteal phase (only six participants) and the follicular phase (only five participants), it revealed a trend for the influence of the menstrual phase. The baseline measure was defined as the average of the measures for all 15 joints. In both hands, skin temperature was 24.95 ± 2.63 °C for females in the follicular phase, while it reached 26.56 ± 3.21 °C for those in the luteal phase of the menstrual cycle. The direct consequence of these differences, although not statistically significant ($0.230 < p$-values < 0.758, joint by joint analysis), may explain the higher variability in skin temperatures in females than in males.

Studying the influence of removing a single glove on the rate of skin cooling is based on the assumption of thermal symmetry of both ungloved hands at rest. This assumption is considered established if thermal symmetry does not deviate by more than 0.5ºC, with a standard deviation of no more than 0.3 ºC for one individual [20]. In the present study, the average skin temperature deviation between both hands at baseline was found to be 0.15 ± 0.13 °C for females and 0.11 ± 0.09 °C for males, which confirmed the symmetrical thermal nature for contralateral hands prior to cold treatment. No significant gender differences in joint skin temperature were observed for baseline measurements, with p-values ranging from $p = 0.247$ (MCP Index) to 0.973 (DIP Pinky). This is consistent with findings by Chudecka and Lubkowska [42].

Skin temperature post-WBC

No cold-related pain was reported among participants during the protocol. The lowest skin temperature recorded was 4.75 °C in one of the female participants at Pinky DIP joint. This value is well above the estimated freezing point of human finger skin of −0.55 °C which can induce cold injuries [43]. The overall analysis of data using all thermal measurements (including also the measurement above the CMC of the thumb) made it possible to evaluate the impact of fully and partially gloved hands on skin temperature during WBC. Based on data from both hands (including 15 ROIs), the mean pre-treatment hand temperature was found to be 25.71 ± 2.93 °C for females and 25.30 ± 2.53 °C for males, respectively. Immediately following WBC, the skin temperature for participants with fully gloved hands (control group) was of 19.73 ± 3.66 °C for females and 19.65 ± 3.32 °C for males, corresponding to a drop of about 6 °C. There was no significant difference between males and females ($p = 0.837$). One possible reason for this absence of gender-based difference might be that hands do not contain much adipose tissue in subjects of normal mass. When looking at the results of the experimental group with ungloved hands, the overall skin temperature reached 13.75 ± 4.46 °C and 13.75 ± 4.07 °C for females and males, respectively, with an average temperature drop of about 12 °C compared to baseline. Similarly, no modulating effect of gender was found ($p = 0.998$).

Fingers, as distal parts of the body, are extremely vulnerable to heat dissipation in cold environments and consequently particularly sensitive to extreme cooling due to a high heat exchange surface with the environment when compared to their volume. Due to hand anatomy, joints located at the furthest distance from the center of the hand (DIP and IP for thumb) are the most exposed to cold. Indeed, skin temperatures recorded at these joints were found to be particularly low, with values of 9.26 ± 2.27 °C and 8.31 ± 2.07 °C for pinky in males and females respectively. Skin temperatures at the joint level decrease along the longitudinal axis of the fingers, yielding an axial temperature gradient. These same little fingers have the largest heat loss gradient along their axis, reaching about 6.5 °C for males and 8.7 °C for females between MCP and DIP for the experimental group, while it was limited to about 4.4 °C for males and 5.3 °C for females in the control group.

Discussion

The cooling ratio appears to be an interesting parameter in evaluating the impact of WBC on skin cooling. Several definitions exist in the literature [37]. In the present study, it is defined as the thermal gradient between pre- and post-treatment measurements. It is presented in Fig. 3 for each measurement position, separately for males and females in the control and experimental groups. The existing literature on skin cooling is quite limited and provides a very wide range of cooling efficiency, varying from −5 °C to −15 °C [44]. Figure 3 clearly shows that regardless of protocol modality, group, and gender, our findings support the validity of this cooling ratio window of effectiveness. In particular, for the control group, the gradients of skin temperature cooling are in the upper margin of this range. It is therefore conceivable that WBC in its usual form may still have a beneficial effect in the treatment of RA of the hands, even when the

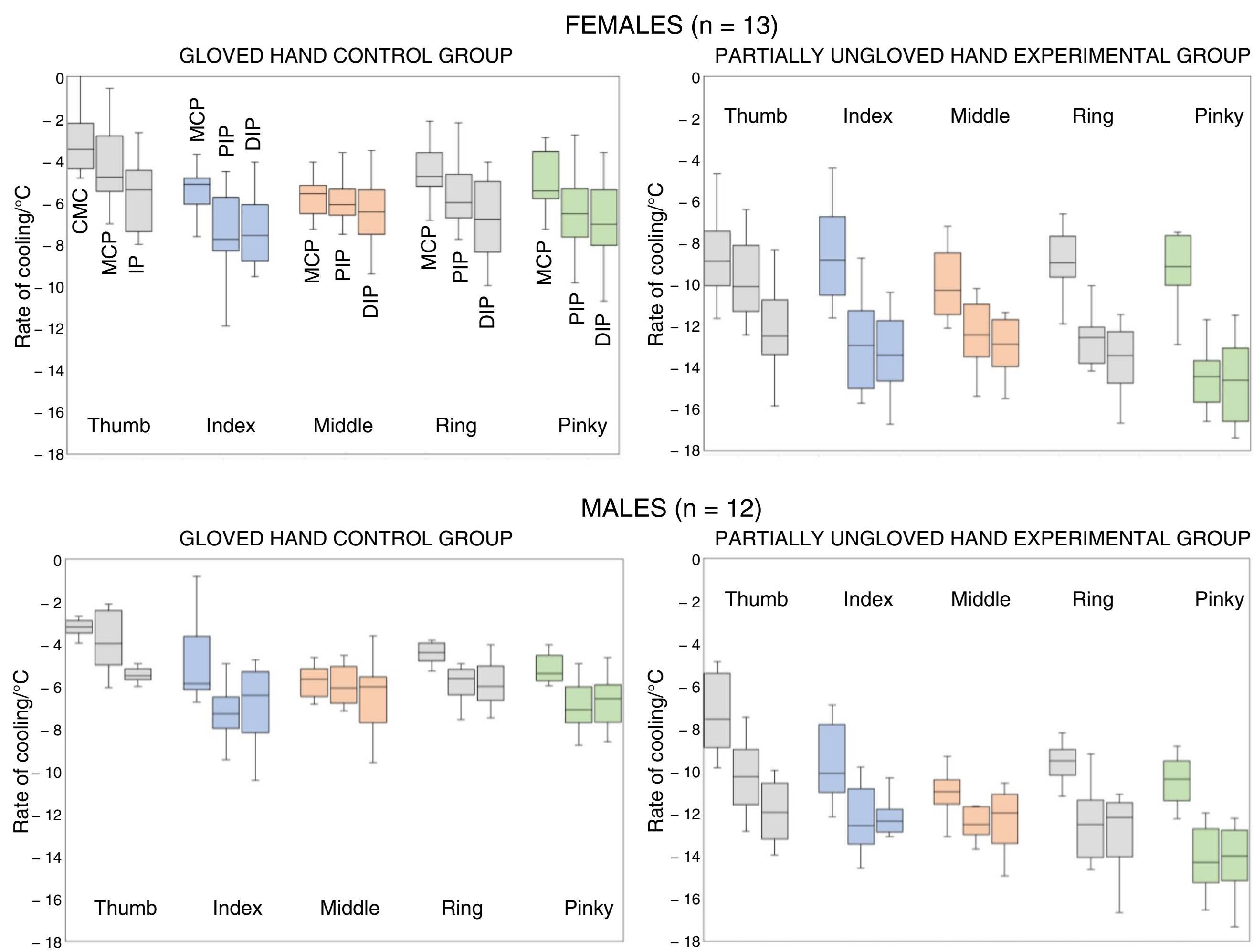

Fig. 3 Box plot graphics representing the rate of cooling (°C) in males and females for the two control and experimental groups (median, maximum and minimum values)

hands are protected, especially since these local effects are combined with systemic effects. The experimental group, on the other hand, integrates the low end of this range. One can legitimately assume that the beneficial effects will therefore be enhanced.

One of the main concepts that characterize the effectiveness of a skin cooling process is the local achievement of analgesic thresholds. Recent guidelines updated in 2010 by the Association of Chartered Physiotherapists in Sports and Exercise Medicine (ACPSM) and endorsed by the Chartered Society of Physiotherapists (London) stated that the currently accepted threshold for inducing effective local analgesia was when absolute skin temperature is reduced to less than 13 °C. This threshold value is very close to that of Bugaj [45], which was previously the gold standard, set at 13.6 °C. Although skin thermoregulatory responses may be gender dependent [36, 37] when considering body areas directly exposed and held for 3 min in extreme cold (popular WBC dosage), the present study revealed that thermal effects of WBC on hands did not vary between genders, suggesting that thresholds allowing to reduce skin temperature at the level that produces an optimal effect are not gender dependent.

Figure 4 exhibits the different skin temperatures at all joints, under a radar graphic design allowing direct reading of the measured values in relation to the analgesic threshold (set at 13 °C). Since females and males had very similar results, only skin temperatures for males are shown.

It clearly appears that the analgesic thresholds are never reached for participants in the control group (fully gloved hands). In contrast, for the experimental group, 9 of 15 joints are sites where skin temperatures reach these analgesic thresholds. In particular, for fingers 2–5, the temperatures of the DIP and PIP joints reach the optimal target level, while only the IP joint of the thumb meets this threshold. This analysis shows that the modality of the implemented protocol, consisting in taking off gloves

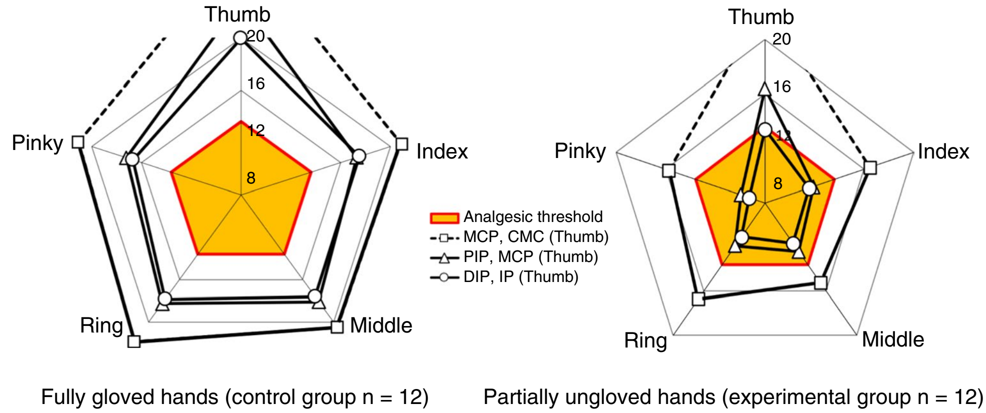

Fig. 4 Radar graphic design for raw skin temperature at all joints in males. Yellow regular pentagons correspond to the thermal range of analgesic thresholds

during the last 40 s of the cryosession, seems to be globally suitable to efficiently cool skin temperature over the joints.

The present study has some limitations that need to be addressed in the future. First, in the same way that when one hand is immersed in a cold environment, the other hand, which is not immersed, partially cools down by a contralateral reflex reaction [38, 39], one may legitimately wonder whether the measurements recorded when the left hand is gloved would have been the same if both hands had been gloved. Moreover, it remains unclear whether the antalgic threshold values measured in the present protocol can be directly unbiased if applied to patients with RA, because the vasomotor responses of RA patients with sluggish vasoconstriction in response to cold [50] may differ from those of healthy subjects. Pauk et al. [51] found that baseline temperature of fingers in RA did not significantly differ from healthy participants ($p > 0.05$) and was not influenced by RA severity. However, the same authors [52] observed diverging patterns of responses in fingers cooling (water at 0 °C for 5 s) between patients with varying RA severity. After water immersion, fingers' skin temperature dropped by a larger amount in patients with moderate disease activity ($3.2 < \text{DAS28} < 5.1$) compared to patients with high RA activity ($\text{DAS28} > 5.1$). This raises the question of whether WBC duration should be individualized according to RA severity. This issue is in urgent need of further attention in the next future. Another limitation concerns the selected sample and more specifically their BMIs. For males and females, the average BMI was 22.3 ± 1.7 kg m^{-2} and 22.1 ± 1.7 kg m^{-2} respectively, which corresponds to normal-mass individuals ($18.5 < \text{BMI} < 25$). Since obesity is highly prevalent in RA patients [53], and BMI strongly influences the body response to cold because heat dissipation is associated with adiposity, future research should consider BMI as a target for an investigation to improve WBC protocols for hand health in RA patients.

Conclusions

While the recent literature on WBC pointed to its beneficial effects on inflammatory markers in rheumatoid arthritis, it was not clear whether it could also have more localized effects, with the attainment of analgesic thresholds on body extremities—hands in the present study—that are usually protected during protocols. By partially removing the gloves and exposing the hands directly to the extreme cold, the duration of this exposure must be governed by a balance between benefits and risks. The benefits are the achievement of a low skin temperature corresponding to the analgesic threshold, while the risks correspond to discomfort or even cold burns. Using a new protocol with direct exposure of the hands during the last 40 s of a standard WBC session of 3 min at −110 °C made it possible to respect this risk/benefit balance. Infrared thermography analyses revealed that for all regions of interest (except MCP and IP, CMP for thumb) there was a clinically meaningful reduction of skin temperature in participants from the experimental group. This beneficial effect was less pronounced in control participants.

This study included healthy subjects, but findings can be transposed to patients with hand rheumatoid arthritis. However, particular attention should be paid to RA severity since it has been suggested to be associated with skin temperature response to cold exposure. Further studies need to be conducted to confirm our findings in clinical samples and understand the influence of RA severity.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethical statement No permission from the local ethics committee was obtained since only biomedical/clinical studies require this approval according to French law. However, the research participants provided written informed consent and the study was conducted in line with the principles of the Helsinki Declaration and its following amendments.

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