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## **Impact of regular cold exposure on electrical skin resistance in patients with joint degenerative diseases**

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## **Abstract**

**Objective.** Common features in chronic inflammatory disease patients (CIDP) are inflammation, mental stress (MS), and autonomic nervous system imbalance. Whole-body cryotherapy (WBC) exposure and regular physical exercise are known to regulate these features. In this study, we assessed the impact of regular physical exercise and the use of WBC exposure in CIDP on the level of electrical skin resistance (SR) in order to estimate the sympathetic nervous activity and MS levels. **Methods.** SR was evaluated before and after a 10-day-period of daily physical exercise preceded or not by WBC (*3 min at -110°C*) in two groups of 134 CIDP (*WBC vs non-WBC groups*). **Results.** At baseline, the number of severe MS patients was similar in both groups. However, after the training period, the number of severe MS patients significantly decreased in the WBC group, only. An increase in SR (a decrease in stress level) was noted in the WBC group only, and such increase was higher in men than in women and in patients younger than 60 vs patients older than 60 years old. **Conclusion.** The use of daily WBC combined with physical exercise induced physiological adaptations, lowered the sympathetic nervous activity and reduced stress level in CIDP. *These adaptations seem to depend on gender and age.*

**Key words:** Cryotherapy, chronic inflammatory diseases, physical exercise, skin resistance.

## **1.Introduction:**

Chronic inflammatory diseases (CID) are often diagnosed in 80-90% of older people and are considered to be age-related diseases (Tran et al. 2021). CID cover systemic inflammatory diseases including joint degenerative diseases notably Rheumatoid Arthritis, Osteoarthritis, Infectious Arthritis, Ankylosing Spondylitis (Heap and van Heel 2009). Such illnesses represent the main cause of disability and handicap worldwide due to the associated joint degeneration, chronic pain and stiffness that make daily tasks difficult (Brady and Sniezek 2003). CID do not only affect joints and immune system, but also have a deleterious effect on autonomic nervous system (ANS) (Aydemir et al. 2010). However, little is known about the role of ANS in CID. ANS could be involved in joint homeostasis and the pathophysiology of joint degenerative diseases (Courties et al. 2017). The sympathetic nervous system (SNS) may influence inflammation via a direct influence of neurotransmitters on immune cells or an indirect effect via regulating blood and lymphatic flows (Pongratz and Straub 2014). Parasympathetic nervous system (PNS) could also be involved in local control of inflammation in rheumatic diseases through the vagus nerve activity and the properties of acetylcholine (Borovikova et al. 2000). Furthermore, it has been reported (Maule et al. 2003) that patients with inflammatory diseases have an impaired autonomic nervous function. The physiological mechanism of this dysfunction could be explained by the presence of circulating anti-neuronal autoantibodies directed against sympathetic and parasympathetic nervous structures (Maule et al. 2003).

Cryotherapy is widely used in rheumatology for analgesic, anti-inflammatory and pain relief (Guillot et al. 2017). Experimental evidence indicates that cold-induced vasoconstriction is

mainly mediated by activation of sympathetic system activation (Durand et al. 2004). The sympathetic activation that occurs during cold stress is likely influenced by the amount of thermal and/or pain receptors in the skin that are stimulated. Biological indicators such as heart rate variability, respiration, and electrodermal activity have been used as indicators of human response to stress 3/27/2024 3:22:00 PM and physiological signals can be used to measure the adaptations to cold stress. Galvanic skin response (GSR), electrical skin resistance (SR), or electrodermal activity (EDA) are biomarkers of sympathetic nervous activation (SNA). These markers are linked to the changes in skin electrical conductance which is controlled by the SNS. The human organism response to cooling is strictly connected with skin sympathetic nerve activity and SR responses. There are several studies, which propose different methods of detecting changes in SNA by measuring SR (Lee et al., 2005; Rosebrock et al., 2017). SR responses actually represent one of the most widely used psychophysiological measures of ANS activity. Whole-body cryotherapy/cryostimulation (WBC) exposure is a cold stress, which has an impact on SNA and emotional status (Bouzigon et al. 2021) . Therefore, in this study, we are using SR to estimate the level of skin sympathetic nerve activity (SSNA) before and after regular WBC and physical exercise in CID patients. Moreover, we examine if differences exist in reaction to cryogenic temperatures in terms of age and gender.

## **2. Methods.**

The research was carried out at the Centre of the Medical University of Lodz - OPiR Creator Sp. z o.o., Vitamed Rehabilitation Clinic in Kowal and Remedium Rehabilitation Clinic in Głowno in 2014-2016. The research was approved by the Research Ethics Committee of the Institute of the "Polish Mother's Health Center"(75/2014).

### **2.1. Population characteristics:**

268 patients (140 women and 128 men) were included (Table 1), all of them with diagnosed joint degeneration disease (pathologies distribution in patients was as follow: 16 % with gonarthrosis, 21% with coxarthrosis, and 63% with spondyloarthritis). Participants were randomly assigned to one of the two groups (WBC and non-WBC groups). In both groups, the majority of patients were over 60 years old, overweight, or obese (53 vs 63%, 56 vs 57%, and 22 vs 21%, in the WBC and in the control group; respectively). Twenty-two percent of patients had a health-related BMI in both groups. All of patients were moderately physically active, and no outdoor workers or patients who used WBC in the previous 6 months were included. Patients were asked to maintain their physical activity habits during the study. No subjects had symptoms or signs of skin problems, central or peripheral nervous system diseases, or were on medication affecting autonomic function system.

### **2.3. Skin resistance measurements:**

BioKat MV ® apparatus (BioKat Systeme GbmH, Lahr, Germany) was used to measure electrical skin resistance. The test method is based on measurements of skin resistance at biologically active points (BAP) at patients' feet and hands levels (SP 1 zone for the feet and L 11 zone for the hands) (Prokhorov et al. 2000). An increase in SR indicates a decrease in the sympathetic nervous system activity. Low level of SR (e.g. < 21 kΩ) indicates high level of mental stress and a strong activity of the sympathetic nervous system, whereas a high level of SR (e.g. > 92 kΩ) indicates a very low activity of the sympathetic nervous system and are considered to be hypoergic and are characteristic of prostration (Iacono 1983). SR was measured in WBC group: 1) before cold exposure as basal value; 2) immediately after WBC; 3) after a 30-min of physical exercise. The SR was also measured in the control group before (twice) and after the 30 min of exercise program mimicking the procedure used for the WBC group. All the measurement collection was organized twice in the two groups: before and after a 10-day period of daily training preceded or not by WBC (Figure1).

## **2.4. Statistics:**

All data were stored in an electronic database and analysed using specialized statistical software (Statistica 7.0, StatSoft, Tulsa, OK, USA). The Gaussian distribution was tested for each variable using the Shapiro–Wilk test. The results were expressed as the means with the standard deviation (SD). Two-Way Repeated-Measures analysis of variance (ANOVA) was applied to compare changes in skin resistance between groups with different interaction with age [ANOVA: condition (WBC/Non-WBC) x Age] and sex [ANOVA: condition (WBC/Non-WBC) x sex]. Multiples comparisons were made and the Tukey analysis was used as post-hoc test. Differences were considered significant when the significance was 0.05.

## **3. Results:**

At baseline, no differences (age, BMI, body surface) between the WBC and non-WBC groups were observed.

### **3.1. Impact of WBC and physical training on stress level:**

At baseline, the number of severe stress patients was similar in both groups (10.0 vs 11.2 % in the WBC and the control groups, respectively). After the 10-day period, the number of severe stressed patients significantly decreased in the WBC group and stayed stable in the control group (3.2 vs 11.5 % in the WBC and the control groups, respectively,  $p < 0.05$ ).

### **3.2. Impact of WBC and physical training on skin resistance:**

At baseline, the regular regimen of WBC + exercise was able to induce a significant increase in the skin resistance between the 1<sup>st</sup> and the 10<sup>th</sup> day both in men and women ( $p < 0.05$ ). This increase was noted on both feet and hands. Moreover, the increase was higher in men than in women ( $p < 0.05$ ) excepted at the right-hand level where the difference did not reach the statistical threshold. The data are presented in Table 2.

We have also compared the direct effect of the first and the last session of cryostimulation on SR (Table 3). SR significantly increased after WBC on the 1st and 10th day, with a much higher increase after the 10th day than after the 1<sup>st</sup> day ( $p < 0.01$ ). Regarding the control group, the exercise program did not induce any significant changes in SR between the 1st and 10th day of exercising. Men presented a higher level of SR than women at the right hand and at the two feet levels ( $p < 0.01$ ) after the training regimen. For the left hand, we noted an interaction condition  $\times$  time F ( $p < 0.01$ ) and a post-hoc analysis revealed a significantly higher SR in WBC group compared to the control condition ( $p < 0.01$ ) at the 1st and 10th day with no significant differences between men and women.

To compare the effects of WBC + exercise program (WBC group) vs the effect of exercise program (non-WBC group) on SR, we have compared the delta SR values in both groups: (1) Before and after first exercise session (SR after 1st exercise session minus SR at Baseline) and (2) Before and after the last exercise session (SR after 10th exercise session minus SR at baseline on 10th day). The results are shown in Fig 2. No significant difference was observed at feet levels in experimental and control groups on 1st day and 10th day. However, the ANOVA revealed a time  $\times$  condition  $\times$  sex interaction ( $p < 0.05$ ) at the left-hand level. The delta values of SR after training are significantly higher in the experimental group than in the control group in men and women on the 1st and 10th day (at  $p < 0.05$ ). In addition, the ANOVA revealed a condition  $\times$  time interaction ( $p < 0.05$ ) at the right-hand level. Subsequently, a post-hoc analysis showed a significant increase in the delta SR values after exercising for the experimental group compared to the control group on the 1st and 10th day (at  $p < 0.05$ ).

Changes in skin resistance was also assessed in the experimental group (WBC + exercising) and the control group (training program) according to the median age of our subjects (60 years old). Results are shown in Fig 3. An increased level of skin resistance ( $p < 0.05$ ) in the experimental group (following WBC + exercising) compared to the control group (following



the exercising program) at feet and left-hand level. We also observed that SR was significantly higher in the experimental group compared to the control group ( $p < 0.05$ ) in subjects whose age is less than 60 years old.

#### **4. Discussion:**

In the present study, we used the measurement of SR to estimate the skin sympathetic nervous activity and mental stress (MS) level in a large number of CID patients. Our study explored the SR changes before and after a 10-day period of daily exercising preceded or not by WBC. To the best of our knowledge, this is the first work studying the impact of regular exposure to WBC on SR response in patients with joint degeneration diseases. Our main results show that regular exposure to cold induces a significant increase in SR. Such increase is related to a decrease in the activity of the skin sympathetic nervous system and may have a global impact of the level of stress in our CID patients. Indeed, it has been reported that low level of SR indicates a strong activity of the sympathetic nervous system and a high level of mental stress (Abdullah and Hassan 2012, Fernandes et al. 2014). We observed that after the studied period, the number of severe-stressed patients significantly decreased in the WBC group and remained stable in the control group. We also observed that the increase in SR in the WBC group was superior in men as compared to women and superior in patients aged less than 60 years old as compared to older patients.

The ANS adaptation to WBC that we observed has been demonstrated in previous studies (Louis et al. 2015, 2020) through other predictors of ANS activity such as heart rate variability and blood catecholamine concentrations. It has recently been reported (Louis et al. 2020) that daily WBC exposures during five days induced an autonomic nervous habituation to WBC and a better modulation of ANS, suggesting thereby a better balance between sympathetic and parasympathetic activity. The adaptative response that we observed could be also explained by

human organism adaptability to changing environmental conditions, which is conditioned by interrelated regulatory processes that occurred at the molecular, cellular, tissue, organ and systemic levels (Charkoudian, 2003, 2010). In response to thermal stress, humans invoke several critical thermoregulatory reflexes including shivering, sweating, and profound changes in cutaneous blood flow. These mechanisms are controlled by higher brain centers, primarily at the preoptic/anterior hypothalamus, which is considered as a main integration and control center of thermoregulation (Nakamura 2011). Humans are much more sensitive to low temperature because there are ten times more cold receptors than heat receptors in the dermis (Adair 1999). Our results also indicate an increased sympathetic activation after acute and chronic exposure to cold in older subjects which is less pronounced than in younger patients. The early phase of vasoconstriction after cooling is mainly dependent on neural regulation and the later phase relies more on non-neural mechanisms including the cardiovascular system which is sensitive to critical adjustments in autonomic activity to maintain blood pressure and organ perfusion in response to a thermal stress (Charkoudian, 2010; Greaney et al., 2016). Such adaptations seem less effective in aged subjects. SR has been used to evaluate emotional status, MS and pain perception in healthy subjects and in CID patients (Turner et al. 2013, Posada-Quintero et al. 2020, Greco et al. 2021). In this line, Turner et al (Turner et al. 2013) assessed SR at biologically active points to explore whether SR varies with pain intensity and whether it differentiates rheumatoid arthritis patients from healthy patients. The authors have observed differences between healthy subjects and CID patients. It has previously been reported that people with anxiety and inflammatory disorders present a dysfunction in autonomic control (Maule et al. 2003) and an altered SR level can be observed (Perry et al., 1989; Rosebrock et al., 2017). Our results show that regular exposure to cold associated with exercising decreases severe stress and induces an adaptive autonomic action. These observations could be beneficial for patients suffering from inflammatory disorders since stress may aggravate disease activity.

It has been suggested that minor stress (lasting from minutes to a few days with small intensity) may lead to a short rise of neurotransmitters and could increase the inflammatory response and the disease activity in CID patients (Straub et al. 2005). Nevertheless, WBC has previously been shown to be effective in lowering inflammatory responses and improving quality of life and alleviating mental health problems in athletes and also in CID patients (Vitenet et al. 2018, Doets et al. 2021). The observations of Rymaszewska et al (Rymaszewska et al. 2008) are also in accordance with our results, as they observed that a regular cryotherapy (a cycle of 15 WBC sessions) improves the mental state, the resolution of some psychopathological symptoms, life satisfaction, mood, desire for physical activity and it further relieves perceived pain and fatigue (Rymaszewska et al. 2003, 2008). In addition, a recent meta-analysis (Doets et al. 2021) reports preliminary evidence proposing WBC as an efficacious add-on intervention for mental health problems.

Consistent with age differences in cardiovascular and thermoregulatory responses (Wagner and Horvath 1985, Matthews and Stoney 1988), our results show that the increase in SR was inversely related with age confirming adaptation difficulties as patients grow older. However, influences of age on human thermoregulatory responses to cold exposures is not fully understood and new studies are warranted to investigate central and peripheral autonomic adaptation to cold stimulus in older subjects.

## **5. Conclusion:**

Daily WBC exposures combined with physical exercise induced physiological adaptations and increased the levels of SR and reduced the level of mental stress in CID patients. These adaptations seem to depend on gender and age. The regular use of WBC combined with physical exercise could therefore be advisable in such patients in general and especially in young male patients.

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## **Conflicts of interest statement:**

Authors declare no conflicts of interest

## **NOMENCLATURE**

CIDP	Chronic Inflammatory Disease Patients
WBC	Whole-Body Cryotherapy
SR	Skin Resistance
SNA	Sympathetic Nervous Activation
MS	Mental Stress
ANS	Autonomic Nervous System
SNS	Sympathetic nervous System
PNS	Parasympathetic Nervous System
GSR	Galvanic skin response
EDA	Electrodermal Activity
SCR	Skin Conductance Response
SSNA	Skin Sympathetic Nerve Activity
BMI	Body Mass Index
BAP	Biologically Active Points

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### **Figures legends.**

**Figure 1.** Experimental design. SR: skin resistance; WBC: Whole body cryostimulation.

**Figure 2.** Changes in skin resistance (SR, in  $k\Omega$ ) measured on both feet and hands in experimental (data obtained after WBC + exercise minus data obtained at baseline) and control (data obtained after exercise minus data obtained at baseline) groups. Results are expressed as means and standard deviation. Abbreviations: \*: Significant difference between WBC + exercise and exercise alone.

**Figure 3.** Differences in the changes in skin resistance (SR, in  $k\Omega$ ) measured on both feet and hands in experimental and control groups obtained at Day 10 minus the changes obtained at Day 1 in CID patients younger and older than 60 years old. Results are expressed as means and standard deviation. Abbreviations: \*: Significant difference between experimental and control group; †: Significant difference between subjects aged <60-years-old and subjects aged >60-years-old.



**Table 1.** Subject characteristics.

Groups	Sex	Age (years)	Weight (kg)	Height (cm)	BMI (kg.m <sup>2</sup> )	Body surface (m <sup>2</sup> )
WBC	Women	59.2 ± 7.5	70.3 ± 10.0	162.1 ± 3.6	26.7 ± 3.8	1.8 ± 0.1
	Men	59.7 ± 7.5	88.7 ± 10.0	176.7 ± 5.4	28.4 ± 3.0	2.1 ± 0.1
Control	Women	59.0 ± 7.8	70.1 ± 9.7	162.4 ± 4.0	26.6 ± 3.8	1.8 ± 0.1
	Men	64.4 ± 7.5	89.4 ± 7.1	177.2 ± 5.2	28.5 ± 2.2	2.1 ± 0.1

**Table 2.** Baseline values of skin resistance (SR) in k $\Omega$  measured on both feet and hands at the 1<sup>st</sup> day and 10<sup>th</sup> day in WBC and control groups. Results are expressed as means and standard deviation. Abbreviations: †: Significant difference between WBC and Non-WBC; \*: Significant difference between women and men; <sup>±</sup>: significant difference between 1<sup>st</sup> day and 10<sup>th</sup> day. WBC: Whole-body cryostimulation.

Segment	Groups	Sex	SR (k $\Omega$ )	
			1 <sup>st</sup> day (Baseline values)	10 <sup>th</sup> day (Baseline Values)
Left foot	WBC	Men	40.3 ± 16.5	54.1 ± 18.3 <sup>*±†</sup>
		Women	38.0 ± 19.7	47.4 ± 20.8 <sup>*±†</sup>
	Non-WBC	Men	38.4 ± 14.9	37.4 ± 15.4
		Women	40.2 ± 16.4	37.1 ± 14.6
Right foot	WBC	Men	40.8 ± 18.2	55.2 ± 17.7 <sup>*±†</sup>
		Women	39.4 ± 21.8	49.5 ± 20.1 <sup>±†</sup>
	Non-WBC	Men	42.2 ± 17.3	41.2 ± 15.6
		Women	43.5 ± 18.8	39.6 ± 15.2
Left hand	WBC	Men	46.1 ± 22.7	55.8 ± 16.5 <sup>±†</sup>
		Women	41.1 ± 19.9	53.5 ± 17.6 <sup>±†</sup>
	Non-WBC	Men	41.3 ± 17.4	41.3 ± 16.7
		Women	39.9 ± 12.9	38.1 ± 11.8
Right hand	WBC	Men	42.1 ± 15.7	58.1 ± 16.9 <sup>±*†</sup>
		Women	40.0 ± 17.8	52.0 ± 18.5 <sup>±†</sup>
	Non-WBC	Men	43.5 ± 14.1	43.2 ± 14.2
		Women	44.0 ± 14.2	40.9 ± 12.1

**Table 3.** Skin resistance (SR) in k $\Omega$  measured on both feet and hands after the 1st session of WBC (before 1st exercise session) and after the 10th session of WBC (before the 10th exercise session). Results are expressed as means and standard deviation. †: Significant difference between WBC and Non-WBC; \*: Significant difference between women and men; ‡: significant difference between the 1st and the 10th day.

Segments	Groups	Sex	SR (k $\Omega$ )	
			1 <sup>st</sup> day (before 1 <sup>st</sup> exercise)	10 <sup>th</sup> day (before 10 <sup>th</sup> exercise)
Left foot	WBC	Men	59.0 ± 22.9	80.6 ± 31.1 <sup>**†</sup>
		Women	56.9 ± 25.9	69.7 ± 29.1 <sup>†</sup>
	Non-WBC	Men	38.4 ± 14.9	37.5 ± 15.4
		Women	40.2 ± 16.4	37.1 ± 15.8
Right foot	WBC	Men	66.4 ± 29.9	82.3 ± 29.6 <sup>**†</sup>
		Women	61.9 ± 25.4	75.5 ± 28.6 <sup>†</sup>
	Non-WBC	Men	41.3 ± 17.4	41.3 ± 16.6
		Women	43.5 ± 18.8	38.1 ± 11.8
Left hand	WBC	Men	59.1 ± 22.3	84.6 ± 29.5 <sup>†</sup>
		Women	59.1 ± 27.3	73.5 ± 28.6 <sup>†</sup>
	Non-WBC	Men	41.3 ± 17.4	41.2 ± 15.5
		Women	39.9 ± 12.9	39.6 ± 15.5
Right hand	WBC	Men	61.8 ± 19.9	82.7 ± 28.7 <sup>**†</sup>
		Women	56.1 ± 22.3	70.5 ± 28.4 <sup>†</sup>
	Non-WBC	Men	43.5 ± 14.2	43.2 ± 14.2
		Women	44.0 ± 14.2	40.9 ± 12.3

