

# Impact of systemic cryotherapy on the rheological properties of the blood in women with rheumatoid arthritis

## Wpływ krioterapii ogólnoustrojowej na wskaźniki reologiczne krwi u kobiet z reumatoidalnym zapaleniem stawów

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### Key words

systemic cryotherapy, blood rheology, blood morphology, rheumatoid arthritis

### Abstract

**Study aim:** The aim of this study was to assess the effects of systemic cryotherapy on the rheological properties of the blood in women with rheumatoid arthritis.

**Study group:** The study group consisted of 10 women with rheumatoid arthritis, aged  $57.2 \pm 9.4$ , who underwent systemic cryotherapy treatments (3 min treatment time,  $-120^\circ\text{C}$  chamber temperature, 10 treatment sessions – 5 times a week). Their average body height was  $165.5 \pm 4.6$  cm, weight  $68.5 \pm 4.9$  kg and BMI  $24.8 \pm 2.2$  kg/m<sup>2</sup>. In order to analyze morphological and rheological parameters of the blood, venous blood samples were drawn from the participants of the study twice. The first study was held on the day of beginning treatments and the second test was conducted after a series of 10 treatments.

**Methodology:** The morphological blood test – measurements were taken using the ABX MICROS 60 (USA) hematology analyser. Erythrocyte deformability and aggregation were tested using the LORCA analyser (Laser-assisted Optical Rotational Cell Analyser RR Mechatronics, The Netherlands). The results were obtained as the index of elongation and aggregation according to the Hardeman method (2001).

**Results:** Analysing the average values of morphological and rheological parameters of the blood in women with rheumatoid arthritis in the study group, the mean values of RBC, Hct and AI following the series of 10 treatments were significantly higher after cryotherapy in comparison to the measurements taken before treatments. Analysing the mean concentrations of  $T_{1/2}$ , there was statistically significant reduction after the series of 10 treatments.

**Conclusions:** Regular usage of cryotherapy treatments may affect the levels of morphological and rheological parameters of the blood in women with rheumatoid arthritis – RBC, Hct and AI (increase) and  $T_{1/2}$  (reduction) in the blood.

### Słowa kluczowe

krioterapia ogólnoustrojowa, właściwości reologiczne krwi, reumatoidalne zapalenie stawów

### Streszczenie

**Cel badań:** Celem pracy było zbadanie wpływu krioterapii ogólnoustrojowej na właściwości reologiczne krwi u kobiet z reumatoidalnym zapaleniem stawów.

**Materiał:** Grupę badaną stanowiło 10 kobiet z reumatoidalnym zapaleniem stawów w wieku  $57,2 \pm 9,4$  lat, które korzystały z zabiegów krioterapii ogólnoustrojowej (czas zabiegu 3 min, temperatura komory  $-120^\circ\text{C}$ , 10 zabiegów – 5 razy w tygodniu). Średnia wysokość ciała wynosiła  $165,5 \pm 4,6$  cm, waga  $68,5 \pm 4,9$  kg i BMI  $24,8 \pm 2,2$  kg/m<sup>2</sup>. W celu analizy parametrów reologicznych krwi uczestniczącym w badaniu pobrano dwukrotnie krew żylną. Pierwsze badanie odbyło się w dniu rozpoczęcia zabiegów, a drugie po serii 10 zabiegów.

The individual division of this paper was as follows: a – research work project; B – data collection; C – statistical analysis; D – data interpretation; E – manuscript compilation; F – publication search

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**Metodyka:** Pomiary wykonano przy użyciu analizatora hematologicznego ABX MICROS 60 (USA). Do badania agregacji i odkształcalności erytrocytów wykorzystano analizator LORRCA (Laser-assisted Optical Rotational Cell Analyser RR Mechatronics, Holandia). Wyniki otrzymano jako indeks elongacji i agregacji, według metody Hardeman (2001).

**Wyniki:** Analizując średnie wartości wskaźników morfologicznych i reologicznych krwi u kobiet z reumatoidalnym zapaleniem stawów w grupie badanej średnie wartości RBC i Hct i AI po serii 10 zabiegów były znacząco wyższe w porównaniu do pomiarów wykonanych przed zabiegami. Analizując średnie wartości  $T_{1/2}$  zaobserwowano statystycznie istotne zmniejszenie wartości po serii 10 zabiegów.

**Wnioski:** Regularne korzystanie z zabiegów krioterapii ogólnoustrojowej może wpływać na wskaźniki morfologiczne i reologiczne krwi u kobiet z reumatoidalnym zapaleniem stawów – RBC, Hct i AI (zwiększenie) oraz  $T_{1/2}$  (zmniejszenie).

## INTRODUCTION

Rheumatoid arthritis (RA) is a systemic, chronic, autoimmune connective tissue disease with multifactorial pathogenesis and unknown etiology. The disease has higher prevalence among women and elderly people. Rheumatoid arthritis is characterized by nonspecific inflammation of the synovial, symmetrical joints together with the occurrence of extra-articular changes and organ damage leading to disability, worsening of quality of life and life-span shortening<sup>1</sup>. This disease, despite treatment, has a chronic course with periods of exacerbation and remission. The inflammatory process begins in the synovium of the joints and progresses to joint destruction, deformation, disability and early death<sup>2</sup>.

In an arthritic joint, the temperature increases<sup>3,4</sup>. Local cryotherapy e.g. with cold packs, is widely used to alleviate pain in inflammatory diseases, injuries and overuse symptoms. In in-vitro studies, the increase of local temperature accelerated cartilage collagenolysis<sup>5</sup>. A temporary decrease in intra-articular temperature, lasting at least three hours, is achievable with local cold therapy<sup>6,7</sup>, and with intra-articular glucocorticoid injections<sup>3</sup>. Based on these findings, local cryotherapy has been recommended for patients with active arthritis.

Whole-body cryotherapy (WBC) is currently used to alleviate inflammation and pain in arthritis and osteoarthritis, and for pain relief in fibromyalgia. WBC has been found useful in neurological diseases in reducing spasticity, as a method of kinesiotherapy in rheumatic diseases and multiple sclerosis, and for its sedative effect in psoriasis and neurodermatitis<sup>8,9,10</sup>.

The usage of systemic cryotherapy is one of the ways to reduce pain

threshold or cause its abolition. Systemic use of extremely low temperatures results in increased exercise tolerance and immunity of the body, and has a positive effect on mental state, causing a decrease in fear, anxiety and hyperactivity; improving perception and concentration and creating better resistance of the central nervous system to fatigue<sup>11,12</sup>.

Morphological and biochemical research carried out after application of cryotherapy is indicative of an increase in levels of haemoglobin, leucocytes and blood platelets compared to baseline values. There is also an increase in serum concentrations of epinephrine, norepinephrine, acetylcholinesterase, cortisol, testosterone (in men), and a reduction of inflammatory parameters such as ESR (erythrocyte sedimentation rate), Waaler-Rose reaction and seromuroid<sup>13,14</sup>.

The aim of this study was to assess the effects of systemic cryotherapy on the rheological parameters of the blood in women with rheumatoid arthritis.

## STUDY DESIGN

The study group consisted of 10 women with rheumatoid arthritis (RA type II – classification criteria RA according to American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) – 2010) – patients of the Malopolska Cryotherapy Centre in Krakow (preliminary research - without calculation), aged  $57.2 \pm 9.4$ , who underwent systemic cryotherapy treatments (3 min treatment time,  $-120^{\circ}\text{C}$  chamber temperature, 10 treatment sessions, 5 times a week). Their average body height was  $165.5 \pm 4.6$  cm, weight  $68.5 \pm 4.9$  kg and BMI  $24.8 \pm 2.2$  kg/m<sup>2</sup>. Illness duration was  $18.6 \pm 12.9$  years. In order

to analyse the morphological and rheological parameters of the blood, venous blood samples were drawn from the study participants twice. The first study was held on the day of beginning treatments and the second test was conducted after a series of 10 treatments. Methodology was the same as in previous studies<sup>15,16</sup>.

The parameters obtained in the cryo-chamber:

- aerial temperature:  $-60^{\circ}\text{C}$
- chamber temperature:  $-120^{\circ}\text{C}$

The time of a single treatment for the group of males was 1.5 min (1<sup>st</sup> treatment), 3 min (2<sup>nd</sup>-10<sup>th</sup> treatment). 3 ml of blood were drawn from the vein inside the elbow from the participants on an empty stomach in the morning, into EDTA tubes. Blood samples were drawn by a qualified nurse under medical supervision, in accordance with applicable standards of the Pathology of Locomotion Laboratory at the University School of Physical Education in Krakow, where rheological and morphological parameters of the blood were determined. The study was approved by the Bioethics Committee at the Regional Medical Chamber in Krakow.

## Morphological blood test

Measurements were taken using the ABX MICROS 60 (USA) haematology analyser.

Determined parameters:

1. Red blood cell count – RBC [ $10^{12}/\text{L}$ ];
2. Hematocrit – Hct [ $\text{L}/\text{L}$ ];
3. Haemoglobin – Hgb [ $\text{g}/\text{L}$ ];
4. Mean corpuscular hemoglobin index – MCH [ $\text{fmol}$ ];
5. Mean corpuscular volume index – MCV [ $\text{fL}$ ];
6. Mean corpuscular hemoglobin concentration – MCHC [ $\text{mmol}/\text{L}$ ];
7. White blood cell count – WBC [ $10^9/\text{L}$ ];
8. Platelet count: PLT [ $10^9/\text{L}$ ].

## Determination of elongation index

Erythrocyte deformability was tested using the LORCA analyser (Laser-assisted Optical Rotational Cell Analyser RR Mechatronics, The Netherlands). The results were obtained as the index of elongation and aggregation according to the Hardeman method<sup>17,18</sup>. Tests using the above apparatus were conducted within 30 minutes after blood collection, at 37°C and according to standard protocol.

The results of the elongation index (EI) were given in the range of 0.30 to 59.97 of the shear stress measured in Pascals. The elongation index is a measure of the amount of deformation of red blood cells during their movement in the measuring chamber<sup>17,18</sup>.

## Determination of aggregation index

Before the actual test, the blood sample was subjected to oxygenation by incubation and mixing with carbon dioxide within 15 minutes of collection. Blood in the amount of 1.5 ml was put into the measuring chamber of the LORCA analyser. The result of computer analysis is the curve presenting the relationship of the scattered light intensity with time (for a given shear rate), i.e. selectogram<sup>19,20</sup>.

The following parameters determining erythrocyte aggregation kinetics were assessed:

- AI [%] – aggregation index.
- Also analysed were:
- AMP [au] – total extent of aggregation;
- $T_{1/2}$  [s] – half time kinetics of aggregation.

## Statistical analysis

Continuous variables are presented as mean  $\pm$  standard deviation (SD) or median and interquartile range, depending on the normality of distribution. The normality of distribution was tested using the Shapiro-Wilk test. To assess changes between the beginning and after cryotherapy, we used the t-test for dependent samples or the Wilcoxon signed-rank test.  $SS_{1/2}$

and  $EI_{max}$  were calculated by fitting SS versus EI to equation, representing 4 – parameter Streekstra-Bronkhorst model, using a non-linear curve-fitting algorithm available in a commercial statistical package (Prism 7.02, GraphPad Software Inc., La Jolla, CA). The methodology was described in detail by Baskurt et al.<sup>21,22,23</sup>. Calculations were performed using the Statistica 12 (StatSoft®, USA) software. All *p*-values were two-tailed, statistical significance was defined as  $p \leq 0.05$ .

## RESULTS

Analysing the average values of morphological and rheological parameters of the blood in women with rheumatoid arthritis in the study group, the mean values of RBC (3.54%), HCT (3.94%) and AI (13.10%) following the series of 10 treatments were significantly higher after cryotherapy in comparison to the measurements taken before treatments. Analysing the mean concentrations of  $T_{1/2}$  (35.76%), statistically significant reduction after the series of 10 treatments was noted. Other parameters did not change (Tab. 1-3).

## DISCUSSION

The research presented in this paper is intended to show changes in the rheological properties of blood in women with rheumatoid arthritis who underwent a series of 10 systemic cryotherapy treatments at -120°C. A review of literature indicates a lack of detailed data on the effects of systemic cryotherapy on rheological properties of the blood in patients with RA.

In our research, we have noted an increase in RBC, Hct, AI and a reduction in  $T_{1/2}$  in the women undergoing cryotherapy treatments in relation to the measurements made on the day of beginning the cryotherapy treatment. However, there were no changes in the average values of Elongation Index or other morphological indicators (Hgb, MCH, MCV, MCHC, WBC, PLT).

The results of the research carried out so far (very little) are difficult to interpret or compare because of differences in their research protocols. Lubkowska and Szyguła<sup>24</sup> showed that the number of cryotherapy sessions (3 min at -130°C) has significant impact on changes in morphological indices<sup>24</sup>.

After a few days of stimulation by cryogenic temperatures, an increase in the level of haemoglobin, platelet count and creatinine concentration as well as severity of glycaemia was observed<sup>28,29</sup>. Some reports indicate a decrease in erythrocytes<sup>2,25,26,27,28</sup> and an increase in leukocyte number<sup>21,31</sup>, while others declare no changes in the number of erythrocytes and/or white blood cells, most likely due to the low number of sessions<sup>2,19,26,27,29</sup>. A decrease in leukocytes and erythrocytes in healthy individuals after a series of treatments was observed by Blatteis<sup>30</sup>. However, Banfi, et al.<sup>2</sup> showed a decrease in haemoglobin concentration with a simultaneous increase in the average mass of the haemoglobin molecule and the mean haemoglobin concentration in the erythrocyte after completion of treatments (30 seconds at -60°C and 2 min at -110°C)<sup>2</sup>.

Franzini et al.<sup>32</sup> and Marchewka et al.<sup>33</sup> linked the decrease in red blood cell deformability with age. They found that these changes were the result of elevated levels of cholesterol in the walls of blood vessels and in the cell membrane<sup>31,32,33</sup>. They also noticed that the increase in total cholesterol can affect the deformability of red blood cells<sup>32,33</sup>. In our studies, we have observed no changes in the deformability of erythrocytes.

Kępińska et al.<sup>34</sup> described assessment of the impact of a single systemic cryotherapy treatment on morphological and rheological properties of the blood in 5 healthy males (aged 20-25). To analyse the morphological (RBC, Hb, Ht, MCHC) and rheological (EI, AI) properties of the blood, blood was drawn immediately before treatment, approx. 20-30 minutes and 24 hours after completion. The authors indicated that a single systemic cryotherapy treatment does not result in any statistically significant

**Table 1**

Mean values ± standard deviations of the selected morphological parameters at the beginning of the study and after 10 whole-body cryotherapy sessions in rheumatoid arthritis patients. N = 10 subjects				
	Baseline	After cryotherapy	p	change %
WBC (10 <sup>9</sup> /L)	6.10 ± 1.45	6.12 ± 1.39	0.94	0.33
RBC (10 <sup>12</sup> /L)	3.96 ± 0.35	4.10 ± 0.36	<b>0.019</b>	<b>3.54</b>
Hgb (g/L)	12.21 ± 0.93	12.44 ± 1.27	0.25	1.88
Hct (%)	33.29 ± 3.41	34.60 ± 3.37	<b>0.024</b>	<b>3.94</b>
MCV (fL)	84.10 ± 4.41	84.60 ± 4.09	0.14	0.59
MCH (fmol)	30.88 ± 1.85	30.38 ± 1.36	0.37	1.62
MCHC (mmol/L)	35.55 (35.3-39.6)	35.98 (35.9-36.6)	0.27	1.21
PLT (10 <sup>9</sup> /L)	212.70 ± 69.08	233.50 ± 48.45	0.27	9.78

WBC [10<sup>9</sup>/L] – white blood cell count; RBC [10<sup>12</sup>/L] – red blood cell count; Hgb [g/L] – haemoglobin; Hct [L/L] – hematocrit; MCV [fL] – mean corpuscular volume index; MCH [fmol] – mean corpuscular hemoglobin index; MCHC [mmol/L] – mean corpuscular hemoglobin concentration; PLT [10<sup>9</sup>/L] – platelet count

**Table 2**

Mean values ± standard deviations of the total extent of aggregation (AMP), half time of total aggregation (T <sub>1/2</sub> ) and aggregation index (AI) at the beginning of the study and after 10 whole-body cryotherapy sessions in rheumatoid arthritis patients. N = 10 subjects				
	Baseline	After cryotherapy	p	change %
AMP (au)	16.86 ± 2.83	15.22 ± 2.36	0.18	9.73
T <sub>1/2</sub> (s)	2.32 ± 1.26	1.49 ± 1.08	<b>0.030</b>	<b>35.76</b>
AI (%)	63.35 ± 10.72	71.63 ± 11.21	<b>0.020</b>	<b>13.10</b>

AMP [au] – total extent of aggregation; T<sub>1/2</sub> [s] – half time kinetics of aggregation; AI [%] – aggregation index

**Table 3**

Mean values ± standard deviations of SS <sub>1/2</sub> , EI <sub>max</sub> and SS <sub>1/2</sub> /EI <sub>max</sub> ratio at the beginning of the study and after 10 whole-body cryotherapy sessions in rheumatoid arthritis patients. N = 10 subjects				
	Baseline	After cryotherapy	p	change %
SS <sub>1/2</sub>	2.91 ± 0.51	2.93 ± 0.49	0.65	0.69
EI <sub>max</sub>	0.59 ± 0.03	0.59 ± 0.03	0.65	0.00
SS <sub>1/2</sub> /EI <sub>max</sub>	4.93 ± 1.01	4.99 ± 1.01	0.72	1.22

SS<sub>1/2</sub> – half-maximal shear stress; EI<sub>max</sub> – maximum elongation index

cant changes in the morphological or rheological properties of the blood in healthy individuals<sup>34</sup>.

The aim of a different study by Kepinska et al.<sup>35</sup> was to evaluate the effect of a series of cryotherapy treatments on the morphological and rheological properties of the blood in 10 healthy males. 24 cryotherapy treatments were performed (3 times a week, every other day). There was a statistically significant decrease in mean corpuscular haemoglobin concentration and an increase in the average size of the platelet count. Again,

however, there were no statistically significant changes in the rheological properties of the blood<sup>35</sup>.

According to Maeda et al.<sup>36</sup> the normal deformability of red blood cells constitutes a leading role in the flow of blood within the vascular system. Nonetheless, the correct shape of the red blood cells, intracellular viscosity and stiffness of the walls of their cell membrane depend on the level of hemoglobin, which has significant impact on their deformities. As it is known, red blood cell deformability is very important because it allows

them to pass through the capillaries. The smaller capacity for deformability, the greater the viscosity and poorer flow of the blood microcirculation. It was found that aggregation is the most important factor responsible for increased viscosity<sup>36,37,38</sup>. In our studies, women with rheumatoid arthritis were marked by an increase in the index of aggregation as high as 13.10%.

Yalcin et al.<sup>39</sup> studied the effects of rheological properties after hard anaerobic exercise in untrained male human subjects. In their studies, exercise resulted in decreased erythrocyte ag-

gregation 30 minutes after exercise<sup>39</sup>. In contrast – Kayatekin et al.<sup>40</sup> found the increase in erythrocyte aggregation immediately after swimming in water at the temperature of 26-27°C. In our studies, although stimulus in the form of cold, we observed the same relationship (increased AI). Chmiel et al.<sup>41</sup> conducted a study on rats, which remained in cold water for 5 hours. This resulted in a reduction of red blood cell deformability, probably under the influence of reactive oxygen species<sup>41</sup>.

Among the patients with Rheumatoid Arthritis, the progress of disease and impact of treatment on pain is usually the subject of evaluation. The study conducted by Istrati et al.<sup>42</sup> showed the effect of cryotherapy on changes in fibrinolytic activity of patients with rheumatoid arthritis. After applying ten cryotherapy treatments, they noticed that the t-PA (tissue plasminogen activator) parameter decreased, and PAP complexes (plasmin- $\alpha$ 2-antiplasmin) were increased in the serum. All patients experienced an improvement in mood and a decrease in pain intensity<sup>42</sup>.

The aim of the study, which was conducted by Krekora et al.<sup>43</sup>, was to show the influence of cryotherapy on the change in pain intensity in patients with rheumatoid arthritis (26 patients, 10 treatments). After treatments, noted a downward trend in the intensity of the sensation of pain by patients, by reducing the intensity of pain, the downward trend has the duration of morning stiffness and lowered the threshold limit physical activity<sup>43</sup>.

The research carried out by Braun et al.<sup>44</sup> involved 48 patients with RA. They used cryotherapy treatments twice a day. The researchers observed a reduction in pain after the application of treatments<sup>44</sup>.

Książopolska et al.<sup>45</sup> compared the effects of two rehabilitation programmes for patients with RA. The physiotherapy programme lasted three weeks. The first group used kinesiotherapy, the second cryotherapy additionally. The authors found that comprehensive rehabilitation in RA has a positive effect on the clinical condition of the patient. The rehabilitation programme including cryotherapy

gives a more long-lasting effect. Rehabilitation using cryotherapy is more effective in improving motor function compared to traditional rehabilitation. Rehabilitation using cryotherapy significantly reduces the intensity of pain experienced by patients with RA, and the positive effect lasts for 3 months after rehabilitation<sup>45</sup>.

Cryotherapy used as an adjuvant therapy and applied using standardized and optimized protocols could help to spare corticosteroid and NSAID (nonsteroidal anti-inflammatory drugs) doses in these patients, and subsequently, decrease cardiovascular, infectious or gastrointestinal morbidity and mortality. This treatment option may be of special interest in an increasing number of patients with NSAID and/or corticosteroid contraindications (cardiovascular diseases, diabetes, kidney deficiency, and so on)<sup>46</sup>.

In summary, these studies have reported that exposure to cold in the form of systemic cryotherapy can modulate the morphological and rheological properties of the blood in women with rheumatoid arthritis. It is believed that these results are important in determining the safety of WBC in the field of clinical trials.

However, these studies require expansion to become acquainted with the body's response under these conditions. Despite many studies on hemorheological changes in a variety of disorders, this study, as we know, is the first to have been conducted in patients with rheumatoid arthritis.

## CONCLUSIONS

Regular usage of cryotherapy treatments may affect the levels of morphological and rheological parameters of the blood in women with rheumatoid arthritis – RBC, Hct and AI (increase) and T<sub>1/2</sub> (reduction) in the blood.

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