

Cryotherapy

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Cryotherapy

*Theoretical bases, biological effects,
clinical applications*

Edited by:

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and Agata Stanek

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The authors made all efforts to base the information included in this book, particularly therapeutic parameters of local and whole-body cryotherapy and cryoablation used for individual treatment, on available data and the results of own research. However, the final therapeutic decision is the responsibility of a doctor supervising cryotherapy. Hence, both Authors and Publisher cannot bear any legal responsibility for consequences resulting from improper treatment application or misinterpretation of information in the publication.

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Foreword

The development of treatment methods exploiting various physical factors and implementation of modern electromedical equipment, including native products, resulted in increased demand for handbook, which explains in a clear, transparent and practical way the possibilities of applying various medical technologies and scientific achievements in every day basis. Undoubtedly, the handbook entitled „Cryotherapy”, written under the guidance of Professor Aleksander Sieroń, Associate Professor Grzegorz Cieślak and Doctor Agata Stanek, matches this demand.

In order to understand the significance of cryotherapy procedures, first of all the impact of whole-body cryogenic temperatures on human organism has to be presented, which was clearly described by the Authors of this handbook.

Whole-body cryotherapy procedures are most efficient if are used for treatment of pathologic changes in the locomotor system. They are based on 2-3 minute stay in cryogenic chamber where in temperature -150°C or lower. They cause a number of clinical, hormonal and biochemical effects, including particularly beneficial effect on mood in patients who suffer from depressive syndrome. It also results in regression of tiredness, putting in good mood, willingness to physical activity and taking exercise as well as readiness to co-operate with a doctor and physiotherapist. After cryotherapeutic procedure, sleeping disorders retreat, and in the patients with fibromyalgia subjective painlessness related not only to joint pains, but also to body surface area and internal pains are recorded. Moreover relaxation of muscles taut in response to pain or damaging CNS (central nervous system), as well as sensorimotor conductivity deceleration in nerves, including also central spasticity, appears. Therefore, cold temperature is effective if it is applied prior to any other treatment that requires muscle tension and trials involving increase in movement range in joints restricted by surrounding muscles' contractions or spasticity.

Cryogenic temperatures affect inflammation symptoms and neutralize algogenic and flogogenic substances. They also result in abundant blood flow through skin capillaries causing flare and hot sensation. One of visible and most important qualities of cryotherapy is its antioedematous effect, resulting in increased capillary blood flow several hours after treatment, as well as increased pressure in lymph circulation in reaction to extreme cold. It improves drainage of intercellular space of tumid areas. It considerably increases efficiency of movement of treated joints. The most evident effect is visible on third day of a cycle of cryotherapy and kinesitherapy procedures.

The cold prevents from secondary injuries caused by excess swelling that occurs in an injury-affected area. Cryotherapy may be chosen for treating serious burns and abrasion of the first and second degree, as this prevents or decelerates inflammatory

reaction after injury that may destroy even greater number of tissues than the first injury. Cooling therapy is also useful for treating local infections because of its antiinflammatory effect.

Hitherto existing clinical trials proved therapeutic efficiency of cryotherapy. Cryotherapeutic methods seem to be expensive from the investor point of view, however, cryogenic equipment offers wide range of treatment possibilities: it may be used both in hospitals and domestic environment carrying out up to several hundred treatments a day in ambulatory conditions, and in sanatorium treatment several procedures a day in a few-weeks series, helping to reduce considerably individual treatment costs.

This handbook, as one of the very few, is intended for everyone who professionally practises physiotherapy, especially cryotherapy, so both physicians, physiotherapists and students of medical and non-medical universities. It is a valuable, superbly written elaboration introducing theoretical and practical knowledge in this field. I hope, this handbook will be particularly useful for the individuals involved in cryotherapy and I would like to strongly recommend it as essential textbook for realization of didactic hours in all types of schools educating physiotherapists and physicians.

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Preface

The cryogenic temperatures have been used in medicine for dozens of years. Until now, they have been most commonly applied in surgery and dermatology, where therapeutic effect of cold includes intracellular water crystallization and secondary destruction of subcellular structures and, as a consequence, entire cells.

Surgical cryotherapy is used for treating precancerous and cancerous lesions and some inflammatory ones. In recent years, there have been trials to use of interstitial cold effect to treat cancers in various internal organs (eg. kidney cancer).

The second trend in therapeutic application of low temperatures below -100°C is so called cryostimulation. In this case, local cold application on pathologically changed tissues is used. It includes mainly degenerative and inflammatory lesions of joints and some posttraumatic syndromes. Well known analgesic effect, along with immunostimulating and regenerative ones, of cryogenic temperatures are used. Application of local cryotherapy is used especially in treatment of rheumatoid arthritis.

Since the end of the 70-ties, some countries such as: Japan, Russia, Germany and Poland as well, put whole-body cryotherapy into clinical practice. In Poland, whole-body cryotherapy became very common and virtually every sanatorium, rehabilitation or physiotherapy centre is equipped with various cryochambers. The essence of whole-body cryotherapy is cryogenic temperature effect on the whole organism.

The reduction of cryochamber building costs as well as popularization of academic literature regarding the subject enables development of whole-body cryotherapy also in countries others than above-mentioned.

The author of the preface, along with his team, has many years' professional experience in application of cryotherapy for treatment of various diseases and hopes that this book devoted to application of cold in medicine will contribute to develop this medical discipline.

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The history of cryotherapy

The history of using low temperatures in medicine goes back to the ancient times. Cryotherapy – a contemporary definition used for modern therapeutic methods of utilizing low temperatures – comes from Greek (Greek cryos means frost).

The first evidence of using the cold as an independent method of treatment comes from Egypt from 2500 B.C. It was when the cold was associated with anti-inflammatory and pain relieving effect to injured area. Few hundred years later, in the 5th century B.C., Hippocrates used the cold in order to decrease edemas, bleedings and pain [7,8].

These observations were a starting point for medical use of low temperatures by doctors in our millennium. And during Napoleon's Russian campaign, French surgeon D.J. Larrey observed that the cold could reduce bleeding and pain during amputations of injured limbs. Hence forth he made a conclusion that beneficial effects of the cold derived from its influence on nervous system and reduced sensation. Slightly later in 1845 J. Arnott initiated analgesia through local cooling in treatment of neuralgia, rheumatism and also in relieving pain in patients with a terminal form of neoplasm. Two years later P. Flarens discovered analgetic effects of ethyl chloride used superficially. However it was used in patients only in 1866 in the form of aerosol. Analgesic effects of ethyl chloride are connected with the fact that its vaporization from skin surface lowers skin temperature to $-15\text{--}20^{\circ}\text{C}$. Moreover this liquid is still used in sport medicine to relieve traumatic pain [1-3,5,9].

The development of modern cryotherapy started at the decline of the 19th century when physicist discovered how to condensate gases. The huge contribution to this was made by Karol Olszewski and Zygmunt Wróblewski (among other scientists), who in 1883 condensed oxygen nitrogen. In 1907 Whitehouse constructed the first device which allowed releasing vapours of liquid, and was used to treat superficially located neoplasm and to treat some dermatological diseases [5,9].

Since that time industrial scale production became possible, and moreover gas storing and practical use, for example in medicine.

The beginnings of whole-body cryotherapy goes back to 1978 when T. Yamauchi used for the first time a cryochamber to treat patients with rheumatoid arthritis [10]. Four years later in Germany R. Fricke introduced whole-body cryotherapy for curing pathologically changed joints and he formulated first standards of using cryotherapy in medicine [4,5,7,9].

The start of the Polish cryotherapy dates back to 1983 and its „cradle” was the Department of Physiotherapy of the University School of Physical Education in Wrocław managed by the professor Zdzisław Zagrobelny.

In Poland the first cryochamber was constructed in 1989 and was installed at Rheumatologic Department of the Janusz Korczak Specialist Hospital of Disorders of

Movement System in Kamienna Gora. This cryochamber was second in Europe and third in the world and its constructor and also a creator of all generation of cryogenic devices is M.Sc. Engineer Zbigniew Raczkowski from Low Temperatures and Structural Researches Institute of the Polish Academy of Sciences in Wrocław managed by the professor Tadeusz Stręk, Ph.D. Eng. [1,2,5,6,9].

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Theoretical bases of cryotherapy

The low temperatures' influence on living organisms can be explained on the basis of fundamental laws ruling thermodynamics processes [3-5,7,8,11-13].

The laws of thermodynamics

The zero law of thermodynamics

When two systems A and B are separated with adiabatic (insulation) wall, but each of them is connected with the third system C through a diathermic wall (allowing one system to influence another), after some time two first systems achieve a thermal equilibrium with the third system. After replacing adiabatic wall separating systems A and B with diathermic wall no changes will be observed.

On the other hand in situation when instead of simultaneous reaching equilibrium between systems A and B with the system C, first the equilibrium between systems A and C will be achieved and then between system B and C, finally after contact between the system A and the system B through a diathermic wall, it will turn out that they are in a thermal equilibrium.

On the basis of the experimental facts described in the preceding section it may be concluded that two systems are in thermal equilibrium with the third system are in a thermal equilibrium with each other.

Heat and the first law of thermodynamics

Heat is a form of energy that transfers from one body to another as a result of temperature differences between them.

It was Joule who proved in his experiments that, when we change mechanical work into heat, the same amount of energy is generated. At the same time he formulated the rule of heat and mechanical work equivalence as two different forms of energy.

Helmholtz proved that all forms of energy are equivalent to each other and no amount of energy will „disappear“ without a simultaneous „appearing“ of the same amount of energy in a different form.

The heat unit Q is defined by definite temperature changes that occur during specific thermal processes. For example, when during heating the temperature of one kilo-

gram of water rises from 14.5°C to 15.5°C, one kilocalorie [kcal] is delivered to a system. A calorie equalling 10⁻³ kcal is also used as a heat unit.

The ratio to energy delivered to a body in a form of heat (ΔQ) to corresponding to this energy temperature gain (ΔT), is called body heat capacity (C):

$$C = \frac{\Delta Q}{\Delta T} \quad (1)$$

To put it in another way, heat capacity can be defined also as an amount of energy that should be delivered in form of heat to increase its temperature by one degree.

Heat capacity at body mass unit, referred to as specific heat (c) is a characteristic feature of a substance, of which this body is built:

$$c = \frac{\Delta Q}{m\Delta T} \quad (2)$$

where: m – mass

Heat capacity and specific heat of material are not stable but they depend on the temperature to which this material is exposed to at the moment.

Heat that should be delivered to body is characterised by mass (m) and specific heat (c), to increase its temperature from T_i (temperature at beginning) to T_f (final temperature) at assumption that $\Delta T \ll T_f - T_i$, after going to differential temperature increases, may be expressed using a following formula:

$$Q = m \int_{T_i}^{T_f} c dT \quad (3)$$

Heat transferring caused by differences in temperature between neighbouring body parts is called heat conduction.

For a flat material of area (A) and thickness (Δx), which surfaces are kept at different temperatures, heat transfer (ΔQ) in time (Δt) is defined by a relation:

$$\frac{\Delta Q}{\Delta t} \sim - A \frac{\Delta T}{\Delta x} \quad (4)$$

The ratio presented above shows that speed of heat transfer through surface (heat flux) depends on temperature gradient ($\Delta T/\Delta x$). Heat flows in a direction of decreasing temperature T , and that is why in the equation (4) there is a minus sign.

Heat transfer between a system and its surrounding occurs only when there is temperature difference at both sides of boundary surface. When there is no difference between temperatures, energy transfer is connected with work.

Work (W) may be defined as:

$$\mathbf{W} = \int d\mathbf{W} = \int_{V_i}^{V_f} p dV \quad (5)$$

where: p – pressure,
 V – volume.

As it has already been mentioned, heat and work are different forms of energy, however they are strictly related to each other and this relation can be presented in a form of mechanical heat equivalent.

The quantities Q and W do not characterize system equilibrium, but they are connected with thermodynamic processes, which as a result of system interaction with surrounding take system from one equilibrium status to another. During these processes energy in a form of heat and (or only) work may be introduced to a system or may be taken out of it.

The work executed by a system depends not only on a status at the beginning and at the end but also on intermediate statuses i.e. on a process way. Also amount of heat lost or gained by system depends on: volume at the beginning (i), volume at the end (f) and intermediate statuses, so on a way of process.

There are functions of thermodynamic coordinates that depend exclusively on starting and final coordinates and do not depend on a way at which transfer between these terminal points takes place. The example of such function is internal energy of system U. The internal energy has a specific value $\Delta U = U_f - U_i$, independent from the transfer mode from a state (i) to a state (f).

The change of internal energy is connected with energy delivered in the form of heat Q and energy released from the system in the form of work (W) in the following way:

$$\Delta U = Q - W \quad (6a)$$

or in a differential form:

$$dU = \delta Q - \delta W \quad (6b)$$

This dependence is called the first law of thermodynamics.

This rule admits existence of only such thermodynamic processes, in which a total amount of energy is maintained. It has to be remembered that not all thermodynamic processes of the first rule of thermodynamics take place in nature. For instance air which occurs in a specific room never „spontaneously” concentrates in one point of such room. What is more it is not possible that after coming into contact between two macroscopic bodies of different temperatures, the one that is cooler, „spontaneously” transfers part of its internal energy to a warmer one what would result in decrease in a cooler body’s temperature and increase in a warmer one’s.

Entropy and the second law of thermodynamics

The process during which effects, such as acceleration, wave motion, turbulences, friction etc. do not take place and a system and its surrounding behave in a perfect way is called a reversible process. It only exists when we observe the uniformity between all features characterizing the system such as: pressure, temperature, magnetization etc. which means that a value of these parameters must be identical at each point of the system, which must be very close to equilibrium all the time. Although a reversible process is a purely theoretical issue and practically it cannot exist in reality. However, it is possible to achieve similar process, provided it will happen very slowly.

On the other hand irreversible process is a process in which a system goes through many states that cannot be described by a small number of macroscopic uniform features and in time when effects connected with energy dissipation take place (friction, electrical resistance, inelasticity etc.).

Executing series of thermodynamic processes which result in system's coming back to its original equilibrium, a process known as a circle process or a cycle is observed. If all subsequent cycle's processes are reversible processes, it is a reversible cycle. The example of such cycle is the Carnot's cycle.

An important thermodynamic function of the state is entropy (S). The change of a system's entropy during a specific process is connected with heat exchange irrespective of the fact whether any work was or was not executed simultaneously. The only condition is the fact that a process must be reversible.

For small reversible changes of a system a product of temperature (T) and entropy's increase (dS) is equal to amount of supplied heat (Q):

$$T dS = dQ \quad (7)$$

This relation constitutes basis for the second rule of thermodynamics that may be formulated in the following way: Spontaneous processes that start in one equilibrium and finish in another may take place only in such direction that is connected with increase of sums of entropies of a system and a surrounding.

If the process is reversible and also adiabatic ($dS = 0$ and $S = \text{const.}$), by joining the first and the second law of thermodynamics, we get:

$$dU = T dS - dW \quad (8)$$

and in the case when work is not executed:

$$T = \frac{dU}{dS} \quad (9)$$

Reversible processes, for which internal energy increase is connected only with heat supply, relation between temperature, entropy increase and heat is defined by equality: $T dS = dQ$.

On the other hand for all irreversible processes inequality: $T dS > dQ$ is satisfied. If all changes and relations connected with irreversible process close within considered

system, then between this isolated system and its surrounding there is no heat exchange, which means $dQ=0$ and then $dS > 0$.

This proves that if in an isolated system approaching equilibrium irreversible process takes place, then its entropy increases. Equilibrium is then a state of increased entropy.

The entropy is connected with disorder by the following relation:

$$S = k \ln w \quad (10)$$

where: k – Boltzmann's constant,

S – system's entropy,

w – disorder parameter (probability that a system is in a specific state with reference to all other states available for it).

In classic thermodynamics existence of other functions characterizing a system's state is observed, which lack in a reversible process is equal to maximum usable work what results from equation:

$$\delta W_{\max} = TdS - dU - pdV \quad (11)$$

where: $\delta W_{\max} = \partial W + pdV$.

The following are included in these functions, referred to as thermodynamic potentials:

- Internal energy (U), stable parameters: S,V;
- Enthalpy (H): $H=U+pV$, at stable parameters S, p;
- Free energy (F): $F=U-TS$, at parameters T, V;
- Free enthalpy (G): $G=F+pV$, at constants T, p.

Using partial derivatives of thermodynamic potentials we can present thermodynamic characteristics of a system. For thermodynamic potentials F and G we receive:

$$\left(\frac{\partial F}{\partial T} \right)_V = -S, \quad \left(\frac{\partial F}{\partial V} \right)_p = -p \quad (12a)$$

$$\left(\frac{\partial G}{\partial T} \right)_p = -S, \quad \left(\frac{\partial G}{\partial p} \right)_T = V. \quad (12b)$$

As one can see, a free energy (F) decreases with increase of volume and temperature and a free enthalpy (G) decreases with increase of temperature but it increases at increase of pressure.

The second law of thermodynamics by introducing a definition of an irreversible process indicates which of processes admitted by the first law of thermodynamics may exist in reality. This law also defines a direction (tendency) of processes occurring in

a nature, for instance a direction of mass flux of specific component from its higher to its lower concentration (the Fick's diffusion) or of energy from a body of higher temperature to a body of lower temperature (the Fourier's heat conductivity).

The third law of thermodynamics

All theoretical and experimental evidence lead to a conclusion that there is no finite number of thermodynamic processes that are able to cause achieving absolute zero temperature and at the same time in real conditions the following equal formulas of the third law of thermodynamics are binding:

- It is not possible to take a system to an absolute zero temperature at finite number of operations in any, even mostly idealized process. Such statement is known as a rule of inaccessibility of an absolute zero or (according to Fowler or Guggenheim) formulating the third law of thermodynamics through failure to achieve an absolute zero.
- The change of condensed system's entropy accompanying isothermal (without a temperature's change) reversible process approaches zero at a temperature approaching a zero. This definition, known as the Nerst-Simon formula of the third law of thermodynamics, is expressed by a following equation:

$$\lim_{T \rightarrow 0} S = 0 \quad (13)$$

Ways of heat exchange

Heat exchange for each body located in the air and of temperature higher than temperature of its surrounding may take place in three ways: through conduction, convection and radiation.

Heat conduction takes place in solid bodies, as well as liquids and gases. In solid bodies it is an effect of vibrations of crystalline system and (in bodies conducting electric current) of dislocating free electrons. Contrary to convection, conduction is not connected with dislocation of particles of increased energy to greater distances but with heat transfer of surrounding particles.

Heat conduction is also described by the Fourier's equation:

$$\Phi = -k \cdot \frac{\partial T}{\partial x} \quad (14)$$

where: Φ – heat flux [W/m^2] conducted by unit surface,
 k – heat conductivity of material [W/mK],

$\frac{\partial T}{\partial x}$ – temperature gradient in direction of heat transfer [K/m].

This relation shows that in the case of uniform centre heat transfer decreases together with distance in compliance with equation:

$$\Phi = -k \cdot \frac{T_2 - T_1}{l} = \frac{P}{A} \quad (15)$$

where: P – thermal power flowing through a specific surface [W],
 A – surface normal to heat transfer direction [m²],
 $T_2 - T_1$ – temperature difference [K],
 l – distance [m].

A „minus“ sign shows that a heat flow in this case is directed from an area of higher temperature to an area of lower temperature.

Heat convection is a process, in which energy is transferred as a result of liquid or gas flow. It is a substantial factor of heat exchange between solid bodies and moving liquids and gases.

There are two types of convections: forced and natural. If a centre flow results from using external sources, such as ventilators or pumps, we refer to a forced convection. In the case when this flow takes place as a result of local changes of a centre's density caused by a temperature's gradient we refer to a natural convection.

There are four mutually connected phenomena that co-participate in convection:

- Heat conduction from a solid body surface to directly adhering liquid or gas molecules,
- Absorption and maintaining of such transferred heat by these molecules result in increase of their internal energy,
- Migration of increased heat molecules to areas of lower temperature cause exchange of part of this energy,
- Transport of energy through a centre flow.

To simplify an analysis, operation of particular components is unified, describing a convection phenomenon based on the Newton's law:

$$\Psi = -h \cdot (T_s - T_\infty) \quad (16)$$

where: Ψ – density of power given up per a surface unit (heat flow) [W/m²]
 h – convection coefficient [W/m²·K],
 T_s – a solid body temperature [K],
 T_∞ – a liquid (gas) temperature outside a close zone [K].

Radiation is a process of heat exchange in a form of electromagnetic waves between objects that are far from each other of different temperatures. In this process a phenomenon of solid bodies emission and absorption are significantly important.

Emission and absorption properties of solid bodies

All solid bodies in a temperature higher than zero absolute emit electromagnetic radiation which is called a heat or thermal radiation. A substantial parameter is a total energy emission of radiation marked as E [W/m^2], showing a speed of a total energy emission through a surface unit of a specific body. A total emission of radiation (E) may be calculated after integrating spectral emissive power (E_λ) (a speed of energy emission equalling waves length included in a range λ and $\lambda + d\lambda$) on all wavelengths ($d\lambda$) in compliance with equation:

$$E = \int_0^{\infty} E_\lambda d\lambda \quad (17)$$

An ideal radiation emitter is a black body, which also has absorption characteristics, which means that it fully absorbs electromagnetic radiating to it.

Radiation of a black body is defined by the Planck's law:

$$E_\lambda = \frac{c_1}{\lambda^5} \left[\exp \frac{c_2}{\lambda T} - 1 \right]^{-1} \quad (18)$$

where: λ – wavelength of emitted radiation,
 c_1, c_2 – constants,
 T – absolute temperature [K].

At formulating his theory in 1900 Planck assumed that electromagnetic oscillators might absorb or loose energy only with equal portions:

$$E = h\nu \quad (19)$$

where: ν – oscillator's density,
 h – the Planck's constant.

Constant $h=6.626 \cdot 10^{-34}$ [Js] existing in a formula turned out to be a fundamental nature constant.

Other relations, which can be derived from the Planck's law serve as a description of a black body. They are: the Wien's displacement law and the Stefan-Boltzmann's law.

The Wien's displacement law is defined by a relation:

$$\lambda_{\max} \cdot T = \text{const.} \quad (20)$$

In compliance with this equation, together with a body temperature increase, maximum of spectral emission of radiation moves in direction of shorter waves.

The Stefan-Boltzmann's law specified relation of a total radiation emission of a black body in a function of temperature:

$$E = \sigma T^4 \quad (21)$$

where: σ – the Stefan-Boltzmann's constant = $5.67 \cdot 10^{-8}$ [Wm⁻²K⁻⁴],
 T – temperature [K].

The Stefan-Boltzmann's law is also performed for biological systems. The total power of radiation of such system, in which a body has a temperature higher from surrounding is expressed in a following way:

$$E_{\text{tot}} = S\sigma(T_0^4 - T_s^4) \quad (22)$$

where: T_0 – temperature of object,
 T_s – temperature of surrounding.

All mentioned laws of thermodynamics are in force also in biological systems, including also a human body [3,4,7,11,12].

The laws of thermodynamics in biological processes

The first law of thermodynamics

Each living organism needs energy to maintain life processes. This energy is released in oxidizing processes of food products, which usually take place at steady temperature and at steady pressure. In relation to this, a free enthalpy (G) or enthalpy (H) may be defined as a measure of internal energy in heterotrophs.

The first law of thermodynamics as a rule of keeping energy in biological processes may be defined in the following way:

$$\Delta H = W + Q \quad (23)$$

where: W – external work,
 Q – metabolism heat.

External work of biological objects is understood as a work executed with muscular exercise. In organism there is also an internal work connected with chemical changes, transport against concentration gradients, blood circulation, breathing and digesting. During these processes different resistances are overcome what leads to formation of heat, which is called a metabolism heat.

If organism does not execute external work ($W = 0$), then the whole collected energy (ΔH) is equal to heat produced in organism ($\Delta H = Q$). A human being is a homoiothermal organism and that is why to avoid overheating, he has to give heat away.

The second law of thermodynamics

As it is known, a highly organized living organism is an open system and may exchange entropy with surrounding.

If one accepts that a human organism together with a surrounding is an isolated system, then – in compliance with the second law of thermodynamics – entropy (S) in such system could only increase in compliance with relation:

$$\Delta s_{\text{organism}} + \Delta S_{\text{surrounding}} = \Delta S_{\text{nature}} > 0 \quad (24)$$

This means that life process, such as any other physical process, increases entropy of the nature.

Generally entropy gained in a moment of birth decreases during a lifetime, achieving specific plateau, to increase again in a moment of death.

Maintaining organism alive is connected with entropy changes. It is accepted that entropy of a living organism consists of two factors in compliance with the following relation:

$$\frac{dS_{\text{org}}}{dt} = \frac{dS_e}{dt} + \frac{dS_i}{dt} \quad (25)$$

where: S_e – external entropy,
 S_i – internal entropy.

Internal entropy is connected with irreversible process that takes place in organism. If a living organism were a closed system ($\frac{dS_e}{dt} = 0$), its entropy $\frac{dS_{\text{org}}}{dt} = \frac{dS_i}{dt} > 0$ would increase until its death $\frac{dS_i}{dt} \rightarrow 0$. However an organism, being an open system, changes entropy dS_e with surrounding. It takes entropy with food products and gives back – together with degraded products of metabolism and degraded energy (in a form of heat). But the resultant exchange of entropy with surrounding is negative causing that entropy of an organism in a predominating life period shows a specific stability. This means that a grown organism is in a stationary state, in which a speed of entropy creation is equal to a speed of its emitting:

$$\frac{dS_i}{dt} = \left| \frac{dS_e}{dt} \right| \text{ and,} \quad (26)$$

that organism's entropy does not change in time:

$$\frac{dS_{\text{org}}}{dt} = 0, S_{\text{org}} = \text{const.} \quad (27)$$

Kinetics of biological processes

Biological processes have to a great extent a character of chemical reactions and speed of their course depends on temperature. The speed of biological processes, similarly as chemical processes, may be defined using Arrhenius's law, according to which:

$$k = A e^{-N_A E_a / RT} \quad (28)$$

where: k – speed of reaction,
 A – proportionality coefficient,
 E_a – activation energy,
 R – gas constant,
 N_A – Avogadro number.

Activation energy E_a supplies information on a biological process mechanism. A precise defining of activation energy for biological systems is however difficult. Influence of temperature on a speed of biological reactions is usually specified using the Vant Hoff's coefficient called as coefficient (Q_{10}):

$$Q_{10} = \frac{v_{T+10}}{v_T} \quad (29)$$

This coefficient specified a relation of process speed in temperature ($T+10K$) to its speed in temperature (T). Based on the Arrhenius's law, coefficient (Q_{10}) may be in approximation defined as:

$$Q_{10} \cong e^{\left\{ \frac{10 N_A E_a}{RT^2} \right\}} \quad (30)$$

Knowing coefficient (Q_{10}), one may conclude on activation energy (E) referred to 1 mole of substance in compliance with the following formula:

$$E = N_A E_a \cong \left\{ 1,91 T^2 \lg Q_{10} \right\} \frac{J}{mol} \quad (31)$$

For processes which take place in living organisms a value (Q_{10}) is within 1÷4. For processes of physical character it is approximately 1.03÷1.3, for processes of chemical character – it is usually 2÷3, and for enzymatic processes – it does not exceed 2.

The preceding deliberations show that there is a specific optimum range of temperatures, in which biological processes take place in a correct way. In the case of temperatures that are too low or too high there is usually a clear disturbance of these processes.

Temperature and methods of its measurement

The substantial issue connected with verification of cryotherapy effects is evaluation of temperature of body's surrounding subject to cryotherapy and temperature of the whole organism.

Temperature describes an energy state of examined body and is a measure of average kinetic energy of thermal motion, which is proportional to a square of average speed of molecule motion. In normal conditions (a surrounding's temperature approximately 20°C, atmospheric pressure 1013 hPa) a state of thermodynamic equilibrium and a definition of temperature is properly defined for such state.

If two systems A and B, previously isolated from each other, will be brought together through a diathermic wall (i.e. a wall, which allows one system to interact on other system), then it will turn out that they be in thermal equilibrium. This state will be specified through a system's characteristics called as a temperature. When two or more systems are in a thermal equilibrium, then we say that they have the same temperature.

The temperature of all systems that are in thermal equilibrium may be expressed by numbers. To specify the scale of temperatures, some rules were accepted assigning temperatures adequate numbers.

The basic scale of a temperature, to which obtained results of its measurement should be referred to, is a thermodynamic scale. One uses as well, so-called current thermodynamic temperature's scale, specified by a definition equation:

$$\frac{T_1}{T_2} = -\frac{Q_1}{Q_2} \quad (32)$$

where: T_1 – thermodynamic temperature of a tank giving away a heat,
 T_2 – thermodynamic temperature of a tank absorbing energy,
 Q_1 – heat given away,
 Q_2 – absorbed heat.

The basic point of a temperature scale is a water triple point, which equals to temperature 273.16 K or 0°C.

Since October 1968, the binding one is International Practical Scale of Temperatures which has names, symbols and units common with the thermodynamic scale. The said scale allows using the Celsius's scale, in which temperature t [°C] is defined with the following formula:

$$t = T - T_0 \quad (33)$$

where: $T_0 = 273.16$ K,
 T – a temperature of examined body in a thermodynamic scale.

It was assumed that 1°C = 1 K.

Methods of temperature measurements

Contact methods of temperature measurement

To specify temperature of a specific number of systems, in the simplest way is to choose one of them as an indicator of thermal equilibrium between a chosen system and other systems. Such a chosen system is called a thermometer.

The zero law of thermodynamics shows that the value indicated on a thermometer is a temperature of each system that is in equilibrium with it.

The most common temperature measurement device is a liquid thermometer, in which a thermometer vessel is filled with liquid (mercury, alcohol, toluene etc.) Changes of its volume under influence of temperature changes allow estimation of a specified temperature.

Another type of thermometer which enables sensitive and precise measurement of temperature is a gas thermometer. In this device, filled with a steady gas volume, a gas pressure depends on its temperature and increases proportionally to its increase. Gas thermometers are usually used in laboratories, because they are uncomfortable in use and slowly achieve thermal equilibrium.

The next type of thermometer is a resistance thermometer, which is made of a fine wire (usually platinum) coiled on a mica frame and placed in a shield of thin-walled silvery tube. The thermometer element is connected through copper ducts with a system measuring electric resistance (for instance Wheatstone's bridge). Because electric resistance, which is proportional to temperature, may be measured with a high accuracy, the resistance temperature is one of the most precise devices for measuring temperature. In measurement in extremely low temperatures a carbon pin or germanium crystal is used instead of a coil made of a platinum wire. Currently for temperature measurements the following modern temperature sensors are used, such as: thermoresistors, thermistors, semiconductor joint sensor and thermocouple.

The most popular among mentioned sensors are thermocouples, which are based on discovered by the Seebeck thermoelectric effect. This effect consists in fact that if both connections of closed circuit made of different metals are located in different temperatures, then in this circuit there is an electric current. It means that through a measurement of voltage in such circuit, one may measure a temperature difference between joints. If one joint is maintained in a steady temperature (a so-called cold joint placed in water with ice of temperature 0°C), then – by measuring the voltage in a circuit – one can specify a temperature of a measurement joint (a so-called hot joint). The voltages appearing in a system are usually very low and usually a change of temperature with causes a voltage change at a level of microvolts.

Examples of thermometers and temperature's sensors and ranges of temperatures measured by them are presented in the Table No.1.

Table 1. Example thermometers and temperature's sensors together with ranges of temperature's measurement.

<i>Type of thermometer of sensor</i>	<i>Range of measured temperatures</i>
Gas thermometer	~ -240°C to ~1000°C
Liquid thermometer	mercury: -39°C to 300°C alcohol: from -100°C pentan: from -190°C
Resistance thermometer (platinum)	0°C to 660°C
Thermocouple	-184°C to 2300°C
Thermoresistor	-200°C to 850°C
Thermistor	-20°C to 100°C
Semiconductor joint sensor	-55°C to 150°C

Another way of measurement of temperature is a liquid-crystalline thermography, it is not such a popular method as those mentioned above. Liquid crystals join both mechanical properties of liquid (for instance liquidity) and structural characteristics of solid bodies. It is a specific spatial order of molecules that allows using liquid crystal in temperature measurement. Dislocation of liquid crystal molecules in its layers is partially put in order, so one can specify an average resultant direction of putting in order a long axis of molecules, so-called director. Directors in particular layers of liquid crystals are twisted against one another, which causes existence of a screw structure. This structure is characterized by a factor called a jump (p) of screw structure equalling a distance between the closest layers of molecules' order of the same direction, what takes place at a director's turn with 180°. When a white light falls on a liquid crystal, it goes through it nearly without any energy losses with the exception of some wavelength (λ_s) defined by the following formula:

$$\lambda_s = n \cdot p \quad (34)$$

where: n – average co-efficient of liquid-crystal layer light's refraction,
 p – jump of a screw structure.

A wave of length (λ_s) after coming through a liquid crystal structure is subject to reflection in the first half and in the second half – it goes through it. When a crystal is laid on a black base (i.e. skin which is similar to black body), a part of light coming through a layer of a liquid crystal is absorbed, the only observed part of light is the one that is subject to reflection with a wavelength equalling (λ_s). A specific light colour corresponds with a specific wavelength, that is why a colour of a liquid crystal placed on a black base will correspond with a wavelength of a light reflected from it. Because a liquid crystal structure and value (p) are subject to changes due to temperature increase, specific changes of liquid crystal colouring give a possibility to measure temperature.

Contactless methods of temperature measurement

Contactless methods of temperature measurement are based on detection of electromagnetic radiation emitted by an examined body. The most known devices made on the basis of this phenomenon are pyrometers and optical thermographs.

Both types use the same rule of radiation detection, yet they have different ways of displaying obtained data.

A pyrometer is used for point measurements of temperature in a way of detection of radiation emitted by examined object and thermograph has additional ability to display a bigger image including a defined number of measurement points, which exist as image pixels. Each pixel is assigned a temperature value, which may be presented in a form of grey scale or colour (pseudocolor) scale. In the case of digital devices of a choosing a specific pixel enables reading a temperature in a numeric form.

Currently thermovision cameras have the biggest possibilities of using detection of electromagnetic radiation emitted by an examined body to measure a temperature.

Thermovision is a relatively recent and rapidly developing method used more commonly in a medicine including also evaluation of cryotherapy efficiency [1,2,6,14]. In thermographic evaluation of temperature measurement of a human body a similarity of its characteristics and characteristics of a perfectly black body is applied. The coefficient of a human body emission is approximately 0.98 – this is a very good emitter as well as absorber of infrared (IR) radiation.

At using in thermography of a human body adequate detectors operating only in a specific range of emitted radiation one can avoid possible influence of a skin colour on measurement results. Pigmentation plays an important role in absorbing and reflecting of a visible light, however because its influence becomes totally insignificant for wavelengths exceeding 2.5 mm, practically it does not influence emission of infrared radiation. Thanks to it, in classic thermography of a human body skin colour does not play important role.

It is extremely important to provide adequate measurement conditions during thermographic examinations. It was stated that a body of undressed man located in a room temperature, cools quickly within the first 15 minutes, through the next 45 minutes it cools slower and then it gets to thermal equilibrium with surrounding with a secondary stabilization of body's temperature. That is how conclusions concerning preparation of patient for examinations are formulated [1,2,6,14]. To minimize changes of body's temperature, influence of external factors should be reduced. That is why a surrounding's temperature should be, if possible, steady (18-22°C). Conditions of heat exchange depend significantly on air humidity, so this parameter should also be strictly controlled. It is recommended to maintain air humidity at the level of 45÷55%. A patient subjected to thermographic examination should not use any stimulants or drugs nor make any physical exercise. Directly before examination the patient should stay in rest for at least 30 minutes, but earlier waiting in an examination room, enables shortening acclimation period, due to which in practice vary from 5 to 30 minutes. Within this period a body's surroundings, which are subject to thermographic examination should not be covered to make heat exchange conditions fully stabilized.

Obtaining low temperatures

A significantly important issue from the point of view of cryotherapy efficiency is obtaining extremely low temperatures, so-called cryogenic temperatures.

Technique dealing with producing and maintaining very low temperatures is called cryogenics.

Below we present the most important dates in the history of cryogenics:

- 1860, Kirk (Scotland) obtained a temperature below Hg solidification point (234 K),
- 1877, Cailletet (France) received a liquid oxygen due to using choking process from pressure vessel (90.2 K),
- 1884, Wróblewski and Olszewski (Poland) used thermal features of liquid nitrogen and oxygen (77.3 K),
- 1898, Dewar (England) used Joule-Thomson's effect and a counter current heat exchange to receive liquid hydrogen (20.4 K),
- 1908, Kammerlingh-Onnes (Holland), using the same method, received a liquid helium (4.2 K),
- 1927, Simon (Germany, England) used adiabatic expansion from a pressure vessel with preliminary cooling using a liquid hydrogen (4.2 K),
- 1933, Giaouque and McDougall (USA) used adiabatic demagnetization method (0.25 K),
- 1934, Kapica (England, Soviet Union) condensed helium without using a liquid hydrogen (4.2 K),
- 1946, Collins (USA) used expanding aggregate and counter current heat exchangers (2.0 K),
- 1956, Simon and Kurti (England) used adiabatic demagnetization in nuclear stage of paramagnetic salts (10^{-5} K),
- 1960, Kurti (England) using a method of nuclear cooling he received a temperature of 10^{-6} K.

Currently used methods of producing low temperatures are mostly based on applying: gases expansion effect in a so-called expansive machine, Joule-Thompson effect (often with preliminary cooling, for instance a liquid nitrogen) and magnetocaloric effect (allowing for obtaining the lowest temperatures of a range 10^{-6} K) [9,10].

Gas expansion effect in an expansive machine

The easiest way of temperature lowering is adiabatic expansion of a specific gas volume located in a cylinder with a moving piston. During such process the temperature lowers as a result of work operation with expending internal energy of gas. However, application of this method is obstructed by some problems of technical nature. Those problems are connected with necessity of securing adequate greasing of moving piston and eliminating mechanical disturbances, which occur during a piston's movement, of air located inside a cylinder. The significant problem which limits a possibility of using this technique is a fact of gradual lowering of temperature proportionally to a pressure decrease appearing as gas cools down.

The Joule-Thomson's effect

The problems described in the preceding section, receiving lower and lower temperatures, caused elaboration of other, more efficient method of lowering a temperature, based on Joule-Thomson's effect.

Gas internal energy, as energy of particles' motion, may be increased through gas heating or compression within a closed area and it may be decreased through gas cooling or expansion. The change of internal energy value is a function of pressure, volume and temperature, that is $U = f(P, V, T)$. In equilibrium state, when a free energy $F(P, V, T) = 0$, internal energy may be defined as a function of two random parameters:

$$U = f_1(P, V) = f_2(P, T) = f_3(V, T) \quad (35)$$

Because internal energy of perfect gases depends exclusively on their temperature, that is $U = f(T)$ and that is why:

$$\left(\frac{\partial U}{\partial P} \right)_t = \left(\frac{\partial U}{\partial V} \right)_t = 0 \quad (36)$$

This equation presents the Joule-Thomson's law.

Its consequence is a thermodynamic phenomenon, known as throttling process, used in practice for obtaining liquid gases and low temperatures. It consists in fact, that a liquid or a gas that is under a high pressure filters adiabatically and in an irreversible way through a small opening or a row of small openings to an area of a lower pressure. During such throttling a significant lowering of temperature takes place. To achieve a gas condensation effect Joule-Thomson's effect should be repeated several times, what is executed in liquid gases condensing units (for instance hydrogen or helium).

Magnetocaloric effect

Thermodynamic equilibrium state may be defined using such variables as: magnetic field (H), magnetization (M) and temperature (T).

Deriving from the first law of thermodynamics $dU = dQ + HdM$ one may demonstrate that for adiabatic processes a change of magnetic field intensity leads to a change of temperature in compliance with the following equation:

$$\Delta T = -T / C_H \left(\frac{\partial M}{\partial T} \right)_H \Delta H \quad (37)$$

where: C_H – a specific heat at constant intensity of magnetic field.

Because for a normal paramagnetic salt $\left(\frac{\partial M}{\partial T}\right)_H$ it is negative, then increase of magnetic field intensity (H) leads to heating and vice versa – decrease of magnetic field intensity causes an increase of a salt temperature. This phenomenon is called magnetocaloric effect.

The magnetocaloric effect is used to obtain temperatures below 1 K. In practice it consist in isothermal magnetization of paramagnetic salt, during which lowering of its entropy takes place. In the second stage of adiabatic magnetization, at maintaining entropy lowering of a salt's temperature takes place. In this way temperatures of 10^{-2} K can be achieved.

Further lowering of a temperature to a value of 10^{-6} K is possible through a nuclear demagnetization. In compliance with the third rule of thermodynamics, it is not possible to obtain temperature of zero absolute.

Very low temperature causes significant changes in physical properties of a substance. It was proved that in extremely low temperatures electric resistance of pure metals decrease to very low values. Some metals below a specific temperature have a zero resistance, what is an essence of superconductivity phenomenon. Moreover many substances in extremely low temperatures become very brittle. In reference to biological tissues this feature enables cutting many elastic tissues (for instance blood vessels) and is one of bases of therapeutic use of the cold in cryosurgery.

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Biological effects of the cold

Biological effects of the cold influence on living organisms depend mainly on a range of used temperatures, speed of tissues cooling and exposure time. Depending on the afore-mentioned parameters, cold may both destroy pathologically changed tissues and stimulate physiological processes.

The first mentioned effect is used in cryosurgery where temperatures of -190°C are used to remove tissues by freezing (cryoablation or cryopexion) and the later effect is the basis of cryotherapy using temperatures of higher values (of -110°C) both in a form of a whole-body action and local applications [172].

The factors responsible for effects of low temperatures influence on organisms are as follows: a way of applying low temperatures (on a whole body or on its limited area), a way of heat loss (for instance through conductivity, radiation or convection), a humidity level of cold air, personal adaptation capabilities to the cold, age, co-existing chronic diseases, taken medicines or physical activity and used condiments.

Thermoregulation mechanisms in conditions of low temperatures influence

Maintenance of relatively constant internal temperature is indispensable condition of efficient action of homoiothermal organism. However it is obvious that constancy of temperature concerns mainly internal factors, while a temperature of surface layers mostly depends on external factors [172]. A cooling process concerns mainly surface tissues even during applying cryogenic temperatures (up to -160°C), and therefore a body's integument and limbs have poikilothermal features.

The biggest heat losses have these parts of a body, which are relatively big in relation to its volume (mainly limbs and particularly fingers and toes). Value of heat loss in fingers and toes is nearly ten times higher than in a trunk [3,17]. During a whole-body exposure to the cold in a decrease in trunk temperature is about 3°C and a decrease in limbs temperature is as low as 12°C . It results from different thermoregulation mechanisms of these parts and from difference of temperatures that are in a cryogenic chamber on a level of a trunk and feet, which is approximately 10°C .

Despite of a change of body surface structures temperature, a temperature of organs in chest and abdominal cavity, of skull inside and of blood is steady due to mi-

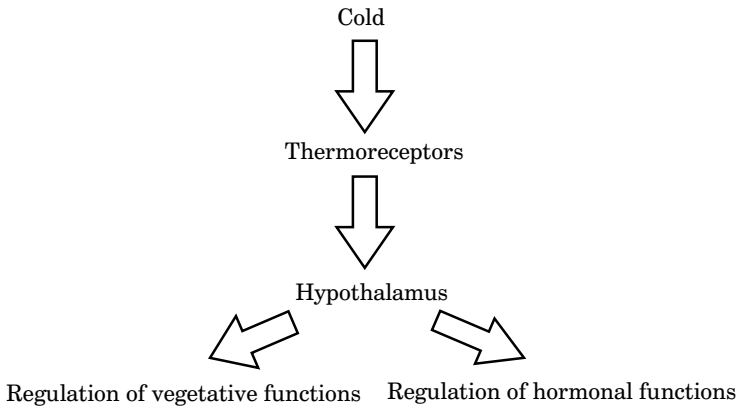


Fig. 1. Mechanism of response to action of the cold being an element of maintaining heat homeostasis of a human body.

circulation and changes of intensity of metabolic cell processes leading to heat generation. In conditions of increased physical activity or exposure to the cold action, increased amounts of heat are generated. In cold surrounding, this is integument (skin and subdermic fatty tissue) that performs a function of thermoinsulator and in surrounding of hot temperature it is main way of removing heat from organs and tissues which are located deeper. The protection function of integument in adaptation processes to changing thermal conditions is connected with changes of blood flow [21,159].

Thermoregulation system of an organism consists of three basic elements:

- thermoreceptors and thermodetectors,
- thermoregulation centre,
- effectors of thermoregulation system.

Thermoreceptors – depending on their location – are divided into two groups: thermoexteroceptors and thermoenteroceptors. The first one, as external receptors, are located on body surface and they receive heat stimuli from environment. The second one control a temperature inside of organism. Part of thermoexteroceptors functioning in a skin reacts to the cold, others to warm and others to heat. The most important task of thermoexteroceptors is transfer of nervous impulses through centripetal ways to hypothalamus being a centre controlling of all vegetative functions of a human body (and also a majority of hormonal functions) [98,126].

All thermoregulation phenomena in organism are subject to a superior control of hypothalamus performing a function of „biological thermostat“ (Fig. 1) [13,172].

Thermoregulation processes are divided into biophysical and biochemical processes. The main effectors of physical thermoregulation are: circulatory system and sweat glands, while effectors of chemical thermoregulation are mostly skeletal muscles, liver and fatty tissue (particularly brown one).

As a result of a continuous or repeated actions of cold on organism, beneficial physiological changes may be caused including three basic forms of adaptation to the cold:

- hypothermal,
- insulating,
- metabolic.

Hypothermal adaptation consists in adaptation lowering of heat generation and decrease of internal temperature without feeling uncomfortable (for instance at Laplanders who live in cold climate). Insulating adaptation is a result of increase in subdermic fatty tissue thickness and development of peripheral vessels abilities to contraction (for instance at swimmers swimming long distances in a cold water). The metabolic adaptation to the cold is connected with a longer time of maintaining or repeated occurrence of a brown fatty tissue.

The change of a functional state of effectors leads to increase or decrease in heat loss through organism (effectors of physical thermoregulation) or to decrease or increase in speed metabolic heat generation in organism (effectors of chemical thermoregulation) [153].

Effectors of physical thermoregulation

Physiological effectors mechanisms securing organism against cooling, being part of physical thermoregulation, include constriction of peripheral blood vessels. Taking into account variable blood supply of body circumference in a process of thermal regulation, there is a poikilothermal „integument” and homoiothermal „nucleus”. Constriction of integument vessels and its cooling is aimed at protection of thermal nucleus against heat loss. In the course of this phenomenon, thermoregulation narrowing of blood vessels is accompanied by blood transfer to volume blood vessels that are located deeper, what leads to volume increase of a so-called central blood. Blood transfer from superficial veins to deep veins, which are in neighbourhood of arteries and have relatively high temperature, causes passing of heat to a cold vein blood. It allows to maintain heat inside organism. The similar function is also served by contrary behaviour of metabolism processes in both afore-mentioned structures. In „integument” inhibition of metabolism processes speed takes place and in „thermal nucleus” processes connected with heat generation intensify. Decrease in heat loss is also caused by decrease in a body surface by taking an adequate position (bending) which is connected with increase in muscles tension leading to intense of muscle work and secondary heat generation. Taking into account conditions that are in cryochambers, important defensive factor against excessive cold action is active motion causing increase in heat generation. In other (non medical) situations adequate changes of activity and behaviour counteract cooling [84].

Effectors of chemical thermoregulation

Increase in muscles tension and muscular shiver observed in organisms, which are subject to influence of low temperatures lead to heat generation. Muscular spasms

are very efficient method of heat generation and they are the basis of shivering thermogenesis. Intensification of this expensive, from energetic point of view, process depends on temperature of a surrounding and on a time of organism exposure to the cold. The energy source of a muscular shiver is decomposition of ATP to ADP and non-organic phosphate. Fast generated ADP accelerates oxidizing of substrates in mitochondria. The basic energetic substrates for muscles work are definitely carbohydrates, however in conditions of low temperatures action, an important role of energy source for muscular shiver may also be played by lipids.

In low temperature of environment an activity of adrenergic system increases and many hormones are released: catecholamine, glucagon and triiodothyronine. These hormones, acting on tissues and organs of an organism (mainly brown fatty tissue and liver), may cause acceleration of their metabolism speed and increase of heat generation on a non-shivering way [98].

The characteristic feature of brown fatty tissue is a great number of mitochondria and rich sympathetic innervations. Noradrenaline released from nervous endings acts on adrenergic receptors of adipocyte of brown fatty tissues, triggering a chain of metabolic reactions. In this tissue, peptide called thermogenine (UCP1) has been discovered, which, decreasing a speed of oxidative phosphorylation, significantly intensifies heat generation. Non-shivering thermogenesis connected with heat generation as a result of processes taking place in brown fatty tissue occurs only in a presence of thermogenine. Researches [22,80] conducted on mice exposed to the cold, which were deprived of the protein UCP1, prove with that lack of this protein it is impossible to generate non-shivering thermogenesis.

Adaptation mechanisms to stressful cold action are more complex than in the case of heat influence. To maintain homeostasis in response to low temperature, bigger synchronisation of systems is required, mainly circulatory and endocrine systems and also metabolic processes. In these conditions stimulation of both somatic and autonomous nervous system takes place. Increase in activity of sympathetic and adrenal parts of autonomous nervous system leads to increase in secretion of catecholamines and stimulation of β -adrenergic receptors. The final consequence of this phenomenon is intensification of the following processes: lipolysis, β -oxidation with secondary mobilization of substrates to oxidative phosphorylation, ATP hydrolysis, glycogenesis and catabolism of proteins and also inhibition of insulin activity and increase in membrane transport activity in muscles [3,51].

An important effect observed during cryotherapy procedures is reduction of metabolism with approximately 50% leading to decrease of energy requirement of tissues and connected thereto requirement for oxygen. Contrary metabolic reactions occur after completion of procedure. Blood supply of internal organs increases which allows a better metabolism and also elimination of collected harmful metabolic products [14,92].

In homoiothermal organisms maintenance of a steady body's temperature determines optimum course of reactions and intermediate transformations of cells, which activity depends on a narrow range on cells' temperature. Within a cell, operation of enzymes is mutually dependant and chemical reactions take place in chains cataly-

zed through series of enzymes, which are coupled with many different transformation chains [30]. Phenomena connected with cryotherapy are subject to thermodynamics laws. Their mathematic exponents are previously mentioned laws of Arrhenius and Van't Hoff. They prove that logarithm of chemical reactions intensity is proportional to temperature changes. In practice, coefficient (Q_{10}) is used specifying a scope of metabolism change at a temperature change with 10°C . It was shown that during a heart operation at infants with applying of a surface cooling, the values of coefficient (Q_{10}) were between 1.9 and 4.2. These big personal changes may be explained by a different sensibility of organism to cooling which depends on genes expression [103].

Influence of low temperatures on a course of thermodynamic processes in skin – biophysical mechanism of thermoregulation

Since recently – in relation to increase of interest in cryotherapy and due to technical possibilities – one has started to examine and describe phenomena taking place during whole-body and local cold therapy.

In a research [35], in which in 16 healthy men and women a temperature of skin and muscles at a depth of 1, 2 and 3 cm below a skin surface before, during and 20 minutes after a completion of local applying of cold compresses was monitored, it was proved that penetration of cold to tissues cooled with using of a cold compress was relatively low: it referred only to a skin and subdermic tissues to a depth of approximately 2.0 cm. The significant decrease in temperature in skin and at depth of 1 cm was observed in examined patients starting from the 8th minute of compresses application, while at different depths (2 and 3 cm) significant changes in temperature values were not observed. After a completion of 20-minute cooling, changes in temperature of deeper tissues occurred – they were subjected to cooling with giving back heat to surface tissues. As an effect, 40 minutes after a completion of cooling surprising temperature inversion occurred – surface tissues became warmer than deep tissues (the difference was approximately 1°C). Heat given back to surface tissues by deep tissues allows for temperature restoring of previously cooled surface tissues with lowering of temperature in deeper layers in a way of intensive thermodynamic exchange.

Despite the fact that short-term exposure to the cold does not lead to big temperature changes inside particular body cavities and temperature changes take place almost exclusively in external integuments of body (depending on a type of used method, this decrease may come even to 12°C), cooling has significant influence on a course of metabolic processes and functioning of many organs and systems.

All physical and chemical processes which take place in a living organism, to a bigger and smaller level, depend on a temperature. Temperature influences metabolic processes, transport, value of bioelectrical potentials, speed of chemical reactions and sustainability of biochemical compounds that come into existence in organism. The hi-

ghest organized organisms, including a human beings, are homoiothermal, because it secures operation (among others) of specialized nervous system.

A human body inside – due to heat generated in metabolic processes in such organs as liver, heart, kidneys, brain and muscles is characterized by constant temperature. Blood is mainly responsible for transfer of metabolism heat using a convection method in a whole organism including as well external integument. It is accepted that the external integument, which protects body inside against variable temperature conditions of a surrounding, may have a different thickness and temperature. The thickness of this integument may come to 2.5 cm, what is 20-30% of a body's mass and at firm cooling – even up to 50%. The significant role in a heat transport in external integument of a body is performed by heat conductivity of particular skin layers and subdermic tissues, which value depends on blood supply resulting out of extension of blood supply vessels. Heat conductivity together with other heat parameters of chosen biological tissues *in vitro* are presented in Table 2.

Table 2. Average values of particular heat parameters of biological tissues *in vitro*.

<i>Tissue</i>	<i>Density</i> <i>p</i> [kg/m ³]	<i>Conductivity</i> <i>k</i> [W/(m·K)]	<i>Specific heat</i> <i>c_w</i> [J/(kg·K)]	<i>Volumetric heat</i> <i>p·c_w</i> [J/(m ³ ·K)]
Soft tissues				
Cardiac muscle	1060	0.49-0.56	3720	3.94·10 ⁶
Skeletal muscle	1045	0.45-0.55	3750	3.92·10 ⁶
Brain	1035	0.50-0.58	3650	3.78·10 ⁶
Kidney	1050	0.51	3700	3.89·10 ⁶
Liver	1060	0.53	3500	3.71·10 ⁶
Lung	1050	0.30-0.55	3100	3.26·10 ⁶
Eye – vitreous body	1020	0.59	4200	4.28·10 ⁶
Skin	1150	0.27	3600	4.14·10 ⁶
Subdermic fat	920	0.22	2600	2.39·10 ⁶
Bone marrow	1000	0.22	2700	2.70·10 ⁶
Hard tissues				
Tooth – enamel	3000	0.9	720	2.16·10 ⁶
Tooth - dentine	2200	0.45	1300	2.86·10 ⁶
Cortical bone	1990	0.4	1330	2.65·10 ⁶
Trabecular bone	1920	0.3	2100	4.03·10 ⁶
Whole-body fluids				
Blood (HCT=44%)	1060	0.49	3600	3.82·10 ⁶
Plasma	1027	0.58	3900	4.01·10 ⁶

The indicator which is easy to measure of external integument of body is a temperature of skin's surface, which thermodynamic state is a result of mutual relation of internal environment of an organism and surrounding, in which an organism is placed. It is accepted that a body temperature inside is approximately 37°C and external temperature on skin's surface depends on measurement location and may differ wi-

thin specified limits according to on external conditions. For instance a temperature of feet varies within $25^{\circ}\text{C}\div 34^{\circ}\text{C}$, of hands $-29^{\circ}\text{C}\div 35^{\circ}\text{C}$ and of a head $34^{\circ}\text{C}\div 35.5^{\circ}\text{C}$.

The average external temperature on a skin's surface (T_s) may be specified temperature measurements executed in different places in compliance with the following empiric formula according to Pilawski [111]:

$$T_s = 0.07T_{\text{feet}} + 0.32T_{\text{shins}} + 0.17T_{\text{back}} + 0.18T_{\text{breast}} + 0.14T_{\text{arm}} + 0.05T_{\text{hands}} + 0.07T_{\text{head}} \quad (38)$$

In compliance with this formula, shins, breasts, back and arms play the most important role on creating an average temperature of skin's surface.

In our own researches [25,26] we examined an influence of whole-body cryotherapy on a temperature of body parts surfaces, which have the biggest role in creating an average temperature of a body surface, i.e. back, breasts and legs. In compliance with accepted thermographic researches standards [11,12,106], just before entering a cryogenic chamber patients were for $15\div 20$ minutes in a room of a temperature of approximately 18°C with open thermographic areas, not showing any physical activities. A temperature distribution on surface of patients' body was examined using a thermovision camera Agema 470 manufactured in Germany. Images received from a camera were analyzed by a computer based on software IRVIN 5.3.1.

Thermographic image of particular areas of patients' bodies prior to commencement of cryotherapy procedure are presented in Figures 2, 3 and 4.

The thermographic image of back was relatively uniform (Fig. 2). The dominant part of back showed temperature within $31^{\circ}\text{C}\div 33^{\circ}\text{C}$. Only along spine a distinct strip of higher temperature of approximately 34°C was observed and in the area of waist (mainly on left hand side) small areas of lowered temperature of 29°C were observed.

Thermographic image of a front part of a chest was definitely much more diversified. (Fig. 3). Although a temperature scope, similarly as in the case of back, was within the range of $31\div 33^{\circ}\text{C}$, however areas of breasts of a lower temperature within

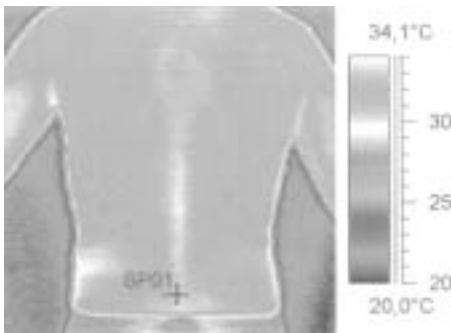


Fig. 2. Thermographic image of a patient's back prior to commencement of cryotherapy procedure. (See also: illustrated Appendix).

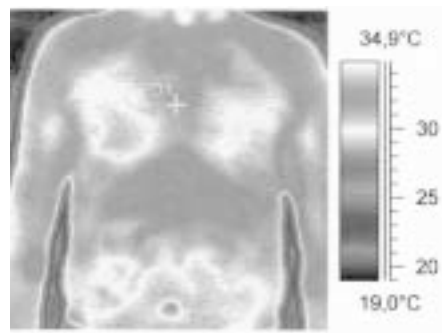


Fig. 3. Thermographic image of a front part of a patient's breast chest prior to commencement of cryotherapy procedure. (See also: illustrated Appendix).

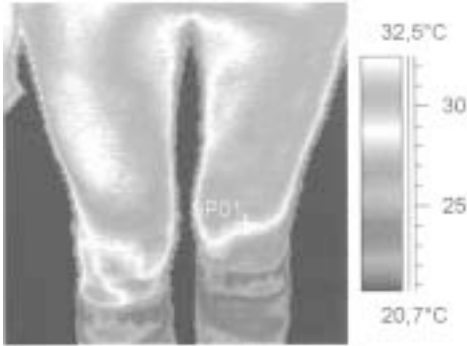


Fig. 4. Thermographic image of patient's thighs prior to commencement of cryotherapy procedure. (See also: illustrated Appendix).

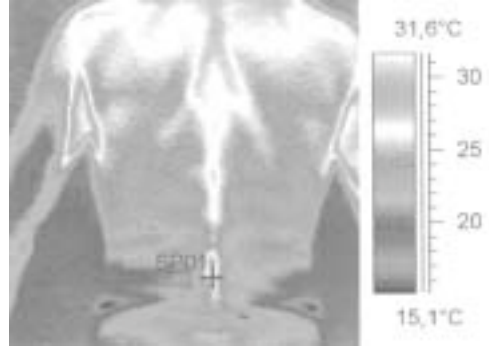


Fig. 5. Thermographic image of patient's back directly after cryotherapy procedure. (See also: illustrated Appendix).

28÷30°C significantly distinguished from the background and the areas of the left breast were colder than the areas of a right breast.

Thermogram of lower extremities presented in Figure 4 does not include shins because during cryotherapy procedures patients had to wear heavy woollen knee socks which enabled thermographic evaluation. The surface temperature of thighs was within 28°C÷32°C, however there were also warmer area of a temperature above 32°C (particularly on a right thigh) and the areas of perineum showed a temperature below 28°C.

Thermographic image of the same areas directly after patient is leaving a cryotherapy chamber was presented in Figures 5, 6 and 7.

Thermographic image of back after cryotherapy procedure showed significantly higher than previously uniformity (Fig. 5). Generally, a temperature of back's surface

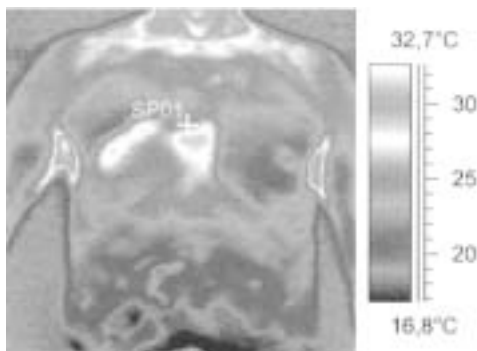


Fig. 6. Thermographic image of a front part of a patient's breast chest directly after cryotherapy procedure. (See also: illustrated Appendix).

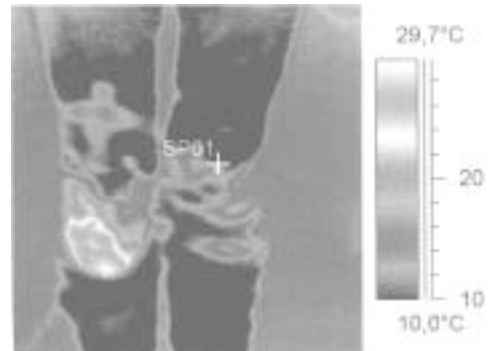


Fig. 7. Thermographic image of patient's thighs directly after cryotherapy procedure. (See also: illustrated Appendix).

declined within $26^{\circ}\text{C}\div 28^{\circ}\text{C}$. The significant change in a temperature along spine was observed ($26^{\circ}\text{C}\div 28^{\circ}\text{C}$), and small areas near a waist showed even lower temperature coming to 20°C .

The thermographic image of front chest was also subject to significant change (Fig. 6). The temperature of predominant part of a chest was within $20^{\circ}\text{C}\div 28^{\circ}\text{C}$, with dominating areas of lower temperatures – $21^{\circ}\text{C}\div 24^{\circ}\text{C}$. There were also areas of increased temperature near sternum and at its right side.

The most significant changes however were observed in a thermogram of thighs (Fig. 7). The drastic lowering of temperature of predominant part of thighs was noticed to the values within $10^{\circ}\text{C}\div 13^{\circ}\text{C}$. Due to existence within this area of minimum temperature, in conventionally accepted scale this effect could be labeled as „thermal amputation“.

The presented results prove the statement that a whole-body cryotherapy causes a significant decrease in a skin's surface temperature, which obviously depends on a measurement location. Comparison of thermograms executed just before and after staying in a cryogenic chamber shows that ranges of temperatures observed in the case of a chest and back were changing respectively from $33\div 29^{\circ}\text{C}$ to $28\div 20^{\circ}\text{C}$ and from $34\div 29^{\circ}\text{C}$ to $28\div 20^{\circ}\text{C}$. In the case of legs temperature changed in the range from $32\div 28^{\circ}\text{C}$ to $10\div 13^{\circ}\text{C}$. The average temperature decrease on a trunk surface was $5\div 9^{\circ}\text{C}$ and in the case of legs it was even 20°C .

The similar results were obtained during a research [131], in which thermograms of chosen 29 body fragments of 48 healthy patients were compared – before and after a procedure of whole-body cryotherapy at temperature from -110°C to -140°C lasting 1-3 minutes. Prior to procedure the highest temperatures were observed in the areas of shoulder strip from the front and from the back and the lowest temperatures were observed in the area of knee joints. Directly after a cryotherapy procedure temperatures of particular areas of a body (particularly lower extremities) were subject to lowering and then in the majority of areas they got back to initial values or they even exceeded them. There were no substantial differences of temperature changes appearing under influence of cryostimulation between symmetrical parts of a body.

Such differences in decrease in temperature of a skin surface between a trunk and thighs obtained by cooling may be explained by basic differences in anatomical structure of these parts of a body. In trunk there are basic, main organs responsible for a course of metabolic processes: heart, kidneys, liver and muscles producing majority of heat in an organism and generated heat is transferred through, big arterial vessels. In the case of legs we deal with practically one source of metabolic heat, which are muscles and heat is distributed mainly through small capillary vessels.

The substantial influence on maintenance of a temperature of cooled extremity has simultaneous making physical exercise. In a research [161] a local cryotherapy was conducted in 32 patients in majority with degenerative and traumatic changes of a knee joint, who were divided into two groups. In the first group directly after a completion of cryotherapy procedure the exercises of lower extremities were conducted and in the second group physiotherapeutic programme included exercises executed 30 mi-

minutes after a completion of the procedure. Cryotherapy procedure in both groups of patients lead to cooling of a knee joint area with approximately 10°C. Temperature measurements executed 15 minutes after a completion of cryotherapy procedure showed significantly higher values in the first group, and it proves that kinesitherapy conducted directly after local cryotherapy procedure causes faster warming of tissues in the area subjected to this form of cooling.

The conducted researches show that cooling of a human body intensifies differences in temperature distribution on a body surface, what can have significant meaning in medical diagnostics. All asymmetries in temperature distribution on a skin's surface are definitely partially connected with asymmetric anatomical structure of a man, however to a big extent they result from presence of pathological processes in particular organs. It is accepted that organs which are subject to inflammation have a temperature higher than surrounding and degenerative processes cause lowering of temperature in an area subjected to pathological process.

In another research [53] a time distribution of temperature in knee area in healthy, young volunteers and in patients with multiple sclerosis subjected to 3-minute lasting whole-body cryotherapy at temperature of -150°C was analysed. Temperature of knees before entering a cryochamber was from 28.8°C do 31.5°C and was the lowest at a central part of a knee joint. Also in this research, immediately after a completion of cryotherapy procedure, a temperature of knees lowered achieving from 5.7°C to 17°C. Then temperature increase was observed till the value of 27°C within 15 minutes after the end of procedure, and after 60 minutes the temperature exceeded initial values and it was from 29.5°C to 34°C. Temperature distribution after the procedure was more uneven and a temperature gradient in patients with multiple sclerosis was significantly lower comparing to a group of healthy volunteers.

In a research [65] the similar time course of temperature changes of cooled knee joints and neighbouring tissues of thighs and shanks during 3-minute cryostimulation using a local cryotherapy device Kriopol R with application of liquid nitrogen was confirmed. In this case, directly after a completion of cryostimulation, lowering of temperature from initial values within 29.1°C (patella area) – 32.0°C (front area of shins) to values on average of 5.6°C was observed. Then a quick increase in extremities temperature to 24.2°C in the 5th minute and to 32.3°C in two hours after a completion of this procedure was observed. The differences of temperature values in particular measurement places on extremities (the coolest area was the area of patella) together with substantial personal differences were proved.

In next research [149] in 78 healthy children after previous medical examination executed by paediatrician and neurologist, a single 2-minute lasting cryostimulation with liquid nitrogen steams of a palm part of a right hand was executed. Directly before the procedure of local cryotherapy and also directly after and in the 1st, 2nd and 5th minute after its completion, thermographic research of palm parts of both hands using a thermovision camera Agema 570 was executed. The analysis of obtained thermographic images shows that cooling of only one extremity caused not only lowering of its temperature (on average with 1÷2.4°C) but also lowering of a temperature (on average

with 1.8°C) on bulbs, palm parts of hand and forearm in the second extremity, which had not been cooled. In the 5th minute after a completion of the procedure a temperature in a cooled extremity was not achieving yet its initial values and on bulbs of fingers of not cooled extremity it was increasing even with 2.8°C, compared to the initial temperature. Obtained effects show existence of consensual reflex, which causes a reflex change of vascular game in non-cooled extremity and connected thereto constriction of vessels in a preliminary phase and their compensatory expansion in a secondary phase of described reaction. It seems that the phenomenon described in preceding section may have a significant influence on possibilities of using cryotherapy in curing of angiopathies and other diseases, in which anti-inflammatory, analgesic and antioedematous effects connected with increased blood supply to extremity are recommended, and for which a direct application of cryogenic temperatures is contraindicated (for instance at burns or trophic changes) [78].

The confirmation of existence of dermal-vascular reflex within a specified segment of spinal cord under influence of cryogenic temperatures action may be results of the researches [122,123]. In the first research 24 healthy volunteers were subjected to local cryotherapy procedures with using of liquid nitrogen vapours at temperature from -130°C to -160°C that were applied for 2 minutes at a back area of shanks and at sacral-lumbar area. As a result of cold application at an area of back surface of a shank a significant increase in maximum amplitude of rheographic wave was observed together with a significant decrease in values of standardized coefficient of susceptibility and of average minute blood flow in the cooled area, which is maintained for an hour after completion of the procedure. Received measurements results, together with a temporary temperature decrease of a cooled area skin, weigh in favour for increase in total blood amount with simultaneous decrease in its flow in a cooled area. Existence of similar, but much more weaker marked vascular reaction in the shank area in the case of cooling of sacral-lumbar area confirms ability of interacting of local cryostimulation procedures also on parts of a body that are distant from cold application. In the second research 30 healthy volunteers were subjected to local cryotherapy with application of liquid nitrogen stream of temperature within -160°C and -180°C, which was applied for 2 minutes on a back surface of left shank. Also in this case a decrease in medium blood flow intensity in a cooled extremity was observed together with increase in susceptibility co-efficient value (equalling a blood supply speed to a cooled body part), which was maintained up to 60 minutes from the end of the procedure. The existence of reflex contralateral reaction was confirmed again – this time on the second extremity, in a place corresponding to procedure location. The direction of change of resistance and flood parameters in this extremity was in compliance with observed direction of changes on extremity that was subject to cooling, but intensity of this changes was definitely lower. Simultaneously on an extremity that was subject to cooling a decrease in skin temperature with approximately 8.8°C directly after the procedure, with subsequent gradual increase to values slightly exceeding initial level in the 60th minute after the operation was observed, while the temperature of the second extremity lowered with only 0.3°C.

Two-phase character of intensity changes in local blood flow under the influence of low temperatures was shown also in the research [150], in which due to phlethysmogram use, a local blood flow was evaluated in 13 volunteers – in which a cooled gel dressing was used on the area of non-damaged tarsal joint. In a preliminary phase, after gel application a significant reduction of blood flow was observed achieving a maximum value at 13.5 minutes after application with a secondary phase of reactive vasodilatation. In turn, use of a similar therapeutical procedure in the case of 15 patients with distortion of tarsal joint led to reduction of local blood flow in the area of damaged joint, however without a secondary vasodilatation phase [160]. In another research [76] in 13 volunteers who were subjected to procedure of ice dressings, slowing down of blood flow was observed in vessels of forearm, and triple interrupted application of ice gave a stronger effect than a single application. Results of above-mentioned research indicate a possibility of using the cold in an acute phase of soft tissues injury.

Influence of low temperatures on metabolic processes – biochemical mechanism of thermoregulation

Extremely important issue is influence of cryotherapy on particular metabolic paths of living organisms deciding about homeostasis maintenance, which status during exposure to extremely low temperatures may decide about practical use of this method in a therapy. In spite of a growing interest of whole-body cryotherapy only few scientific publications present results of experimental and clinical researches in this scope.

A constant body temperature may be achieved only when a heat production is balanced by its loss. In biochemical thermoregulation an important role is played by liver, kidneys and muscles [20]. Blood temperature in hepatic vein is higher than in hepatic artery, what proves active heat production in a liver. Heat production in a liver significantly increases when organism is subjected to action of low temperatures. In those conditions organism uses energy coming from burning of carbohydrates, fats and proteins. However the main energy reserve material, which can be very quickly used at increased energy needs, are triglycerides. Properly functioning of thermoregulation mechanisms may cause temporary increase in triglyceride level through activation of lipolysis process [47].

The level of total cholesterol in organism is influenced by many factors. Except for genetic factors, the obvious role in this case is played by external factors, i.e. diet and energy expenditure of organism in specific environmental conditions.

In a research [55] significant changes of total cholesterol level as a result of cryotherapy procedure were not observed independently of used temperature. On the other hand in the paper [97] exposure to action of low temperature caused temporary increase in total cholesterol level directly after completion of cryostimulation, with subsequent decrease within 3 hours after the end of cryotherapy procedure.

In our own research [61] conducted in patients with ankylosing spondylitis, who were subjected to a cycle of whole-body cryotherapy procedures, beneficial changes

were observed in a scope of blood lipid profile connected with significant decrease in concentration of total cholesterol, HDL-cholesterol fraction and triglycerides. Decreasing tendency was also observed in these patients in a scope of LDL-cholesterol fraction concentration, however gained results were not statistically significant.

In another our experimental researches [133,134] on rats, exposed in cryogenic chamber to a temperature of -60°C and -90°C for 5 and 10 days, serum lipid profile (total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol and lipoproteins VLDL) was estimated. In all rats, which were subjected to cryostimulation, decrease in HDL and LDL fraction concentration was observed with unchanged total cholesterol concentration and in a group of animals, which were subjected to cooling at temperature of -60°C additionally for 10 days, increase in serum triglyceride concentration was observed. These changes were most likely connected with lipolysis intensity as one of mechanisms of maintaining heat homeostasis and activation of adrenergic system in a course of thermoregulation process. As it seems, decrease in HDL-cholesterol fraction level, observed in a research effect of cryostimulation influence on lipid metabolism results from the fact that HDL is the main fraction transporting cholesterol in rats.

As it was showed in a research [140], the key role in lipid metabolism, which decides about their participation in thermogenesis, is played by PPAR receptors (*peroxisome proliferator activated receptor*). PPAR receptors are nucleus receptors for steroid hormones. Activation of these receptors regulates expression of genes that are key for lipid metabolism connected with activation of numerous metabolic paths. Expression of these genes increases under the influence of low temperature leading to stimulation of UPC-1 protein production by brown fatty tissue, intensification of lipoprotein lipase expression in adipocytes and increase in pyruvate dehydrogenase kinase activity in tissues. In hepatocyte these receptors activate β -oxidation, what causes increase of triglyceride usage and at the same time decrease of VLDL synthesis. Mechanism of this reaction is connected with suppression of apo-CIII synthesis for VLDL, leading to increase of VLDL susceptibility to action of lipoprotein lipase. Increase in lipoprotein lipase activity in brown fatty tissue in rats was confirmed also in the research [23]. This increase was caused neither by extension of lipase half-life period nor by intensified activity of its proenzymes, but it was caused by adrenergic-dependant induction of genes transcription for lipoprotein lipase. Increase in activity of pyruvate dehydrogenase kinase, which is responsible for utilisation of carbohydronates in mechanism of suppression of pyruvate metabolism into acetylo-CoA, leads to activation of β -oxidation path [140]. All these processes may finally lead to changes of triglycerides concentration observed in conditions of low temperature action.

Changes in enzymatic activity have significant importance for stimulation of metabolic processes connected with thermoregulation under influence of low temperatures action.

Examinations of enzymatic systems reactions of living organisms to the cold were in the beginning executed in animals living in low temperatures. In research conducted on frogs [28] and it proved that during natural hibernation connected with seasons changing the frogs had shown changes of activity of enzymes taking part in glycoly-

sis, gluconeogenesis and in other metabolic changes of amino acids and fatty acids in a liver. Activity of majority of examined enzymes decreased under influence of the cold and increased after warming of animals, however some of liver enzymes showed paradoxically increase of activity in a low temperature. Higher sensitivity of kidney enzymes to lowering of environment temperature was proved along with higher sensitivity of skeleton muscles to increase of this temperature. It seems that observed changes of enzymatic activity, while influencing metabolism, show cytoprotective effect and protect amphibians against oxygen deficiency in tissues during hypothermia.

In a research [104] influence of external environment low temperature on activity of chosen enzymes of glycolysis cycle (hexokinase, phosphofructokinase and pyruvate kinase) and gluconeogenesis cycle (fructose-1.6-bisphosphatase and carboxylenolopyruvate carboxykinase) in laboratory animals was evaluated. During a gradual lowering of surrounding temperature, in the beginning researchers observed initial stimulation of particular enzymes activity – both of glycolysis and gluconeogenesis cycle – however after longer period of exposure to low temperature (when animals were introduced to stupor state) activity of evaluated enzymes was decreased by 30-50%. The relation of glycolysis cycle enzymes activity to gluconeogenesis cycle enzymes activity remained unchanged independently of surrounding temperature. A return to initial temperature caused significant increase in enzymes activity, exceeding even initial values. Slowing down of glycolysis and gluconeogenesis speed could be caused by suppression of key enzymes of these paths through a change of energetic potential and also by shift of metabolism in a direction of increased oxidation of fatty acids. It seems that the aforementioned metabolism changes are probably connected with development of adaptation and accommodation mechanism in a scope of vegetative nervous system and endocrine system under influence of extremely low temperatures.

In our own experimental researches [117], stimulating action of cryostimulation on activity of chosen enzymes having significant influence on energetic processes in a liver of rats subjected to a whole-body action of temperature of -90°C was proved.

Increase of sorbitol dehydrogenase activity (SDH) both in serum and in homogenate of liver tissue was observed. This enzyme is responsible for transformation of sorbitol into fructose. Fructose much quicker than glucose is subjected to glycolysis cycle in liver, it results from a fact that fructose avoids stage of glucose metabolism catalyzed by phosphofructokinase. This allows stimulation of metabolic paths in a liver contributing to extensive synthesis and esterification of fatty acids, production of VLDL and increase in serum triacylglycerol concentration by fructose [103,107]. Increase in triacylglycerol concentration (confirmed in cited own research) with accompanying increase of glycemia proves stimulation under influence of cold of alternative glucose metabolism path (sorbitol path) enabling utilization of glucose at saturation of glycolysis cycle. Increased activity of malate dehydrogenase observed in the research may prove an increased transport through a mitochondrion membrane of equivalents reducing in a process of tissue oxidation. This transport takes place through pairs of substrates coupled with malate and aspartate dehydrogenases (malate-aspartate bond) [102]. Activity of tissue oxidation reaction increased under influence of low temperatures le-

ads to increase of heat generation at expense of decrease in oxidative phosphorylation speed [103]. As confirmation of the mentioned thesis may serve results of a research [4] which prove that increase in PPARs expression observed in conditions of cold action leads to increase in malate enzymes activity in a liver.

In our own research [120] increase in activity of glycolytic enzyme – aldolase was also confirmed. Increase in this enzyme activity indicates stimulation of shivering thermogenesis mechanisms under influence of low temperatures [152]. Additional confirmation of muscles engagement in heat production is observed in a cited experiment increase of phosphocreatine kinase and also results of the research [16], in which in sportsmen making significant physical efforts during cryotherapy cycles significant decrease in serum lactate concentration was observed (exceeding standard limits prior to commencement of procedures) achieving maximum level on the 5th day of procedure cycle, and was normalized on the 14th day after completion of procedure cycle. This effect was not accompanied by any significant changes of phosphocreatine kinase concentration in a serum of examined sportsmen.

In turn increase in glutamate dehydrogenase activity gained in our researches both in serum and in liver tissue homogenates in rats may prove stimulation of proteins catabolism processes under influence of the cold, because increased activity of this enzyme occurs mainly at a high concentration of a basic product of proteins decomposition – ammonia [38,42].

As the confirmation of stimulating activity of low temperatures on proteins catabolism processes may also serve results of a research [18], during which in healthy men, who were subjected to a whole-body cryotherapy, decrease in total protein and albumin concentration was observed accompanied by a decrease in α_1 -globulin fraction share, together with an increase in α_2 , β and γ -globulin fractions share in a serum.

In our experimental researches [118], conducted on Wistar rats, which were subjected to a whole-body action of temperature of -90°C , one observed also decrease in total protein and albumine concentration, decrease in α_1 and α_2 -globulin fractions concentration and statistically insignificant increase in concentration of remaining fractions of globulines in a serum. Moreover a whole-body cryotherapy caused in exposed rats increase in urea concentration, and it also proves intensification of proteins catabolism in conditions of low temperatures action.

This effect is strictly connected with liver role in regulation of tissues supply with energetic material. The main factor regulating nitrogen changes in liver is blood concentration of amino acids. Anabolic hormones decrease blood concentration of amino acids through stimulation of their trapping by skeletal muscles. On the other hand catabolic hormones while causing increased decomposition of muscle proteins, increase supply of amino acids in liver and their usage in proteins resynthesis process and besides that they also stimulate urogenesis process. Taking into account a fact that action of low temperatures significantly influences activity of hormone system, what will be in details discussed in a further part of the chapter, it seems that one of basic mechanisms explaining increase of catabolic processes under influence of cold is connected with changes in hormone regulation mechanism.

Influence of low temperatures on generation of free oxygen radicals and activity of antioxidant enzymes

Free oxygen radicals are released in uncontrolled way both in metabolic processes which occurs in a cell and under influence of external factors. The main sources of free radicals are mitochondria, oxidizing reactions of thiol compounds, catecholamines, flavins and nucleotides, enzymatic systems and external factors such as xenobiotics, ionizing and ultraviolet radiation and also many chemical compounds.

Free oxygen radicals are responsible for:

- damage of a cell membrane,
- fragmentation of proteins (denaturation of enzymatic proteins, destabilization of collagen),
- damage of vascular glycocalyx (depolymerization of glycoaminoglycans),
- damage of nuclein acids (destabilization of genetic material),
- modification and change of antigenicity of plasma lipoproteins.

Free-radical oxygen compounds participate in etiopathogenesis of many illnesses. Among others, they have atherogenic influence through damaging of blood vessels endothelium, they also damage cells of pancreatic insula causing diabetes, they take part in aging process and also in pathomechanism of immunological diseases such as collagenosis and rheumatoid arthritis, neoplastic diseases, hemolytic syndromes and acute ischemic syndrome with subsequent reperfusion.

Living organisms have developed defensive mechanisms against action of free radicals and toxic compounds of their decomposition.

They include most of all enzymatic oxidizing factors [10]:

- superoxide dismutase,
 - catalase,
 - glutathione peroxidase,
 - glutathione reductase,
 - glutathione S-transferase,
- and non-enzymatic factors [10]:
- vitamins A,C, E ,
 - unsaturated fatty acids,
 - glutathione,
 - bilirubin,
 - mannitol,
 - albumins,
 - ceruloplasmin,
 - haptoglobin.

Homeostasis disorder leads to increased stationary concentrations of free oxygen radicals and is labelled as „oxidation stress“. An illustration of physiological oxidation stress may be activity of brown fatty tissue. Its obvious function is heat generation for thermoregulation purposes. As a result of an organism cooling, it is a subject to

stimulation and secondary a speed of its oxygen utilization increases, mainly due to intensification of oxygen metabolism in mitochondria. During this process superoxide anionradical generation by mitochondria increases as well. Adaptation of animals to decreased temperatures is connected with increase in production of free oxygen radicals by mitochondria and also by peroxisomes, in which oxidation process of fatty acids intensifies several times. A concentration of substances reacting with thiobarbituric acid increases as well [36]. The results of the research [83], in which in animals subjected to action of low temperature one estimated concentration of products of peroxidation of lipids reacting with thiobarbituric acid, a level of conjugated dienes and concentration of thiol proteins groups in homogenates of liver, heart and brain tissues, confirm the observation that a long-term action of low temperatures is one of the factors inducing oxidative stress. The results of this research prove increased production of lipid peroxidation products in examined tissues and their involvement in oxidative stress processes.

If activation of brown fatty tissues lasts longer, it is followed by adaptative increase in activity of that remove free oxygen radicals (superoxide dismutase, peroxidase and catalase).

In previous researches participation of free oxygen radicals in development of tissues inflammation and ischemia, after which restoration of blood and oxygen supply takes place, i.e. reperfusion after ischemia, has been documented very good [24]. A situation when organism is subjected to action of low temperatures may resemble ischemia – reperfusion condition. During cryotherapy procedure a vasoconstriction of peripheral vessels and transfer of blood to deeper located tissues and organs occurs. After completion of the procedure a secondary vasodilatation of these vessels and restoration of circulation appears. In the moment of reperfusion and within the first few following minutes free oxygen radicals are generated in a tissue. At the same time there is also increase in activity of many antioxidative factors. Experimental confirmation of free radicals reactions participation in a mechanism of ischemia-reperfusion provoked by cold was obtained among others in the research [89], in which it was proved that administration of S-adenosylmethionine prevented generation of oxidative stress and production of lipid peroxides in hepatocytes. Also results of researches [155] suggest that changes in concentration of glutathione may play a key role in apoptosis induced by cold.

In a research [41] it was proved that cryotherapy influences production of free oxygen radicals in cells of immunological system. In this research changes of oxidative metabolism of neutrophils under influence of local cryotherapy in patients with rheumatoid arthritis were analyzed. Generation of reactive oxygen intermediates – ROI was examined in a test of luminol-dependent chemiluminescence, what equals a total production of ROI and also in a test of lucigenin-dependent chemiluminescence, what equals extracellular oxidative activity. Whereas chemiluminescence of resting neutrophils isolated from articular fluid of patients with rheumatoid arthritis after local application of cold at area of this joint was decreased and it referred mainly to extracellular oxidative activity. On the other hand chemiluminescence of resting neutrophils

of healthy patients, who were subjected to stimulation and additionally incubated with articular fluid of patients with rheumatoid arthritis increased after using a local cryotherapy at a joint. Observed changes may prove that the cold has a stimulating effect on production of active oxygen forms in neutrophils.

In a research [93] a beneficial influence of a single whole-body cryotherapy procedure on prooxidative-antioxidative status in healthy, young men was proved. In the 30th minute after completion of the procedure and also on the following day, in examined men significant decrease in plasma total oxidative status (TOS) in comparison with initial values was noted. At the same time a significant decrease in plasma total antioxidative status (TAS) was proved in the 30th minute after completion of the procedure with secondary increase in this activity on the following day.

In another research of this team [94] one analysed influence of a single whole-body cryotherapy at temperature of -130°C , without secondary kinesitherapy, on activity of chosen antioxidative enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and S-glutathione transferase) in erythrocytes and also concentration of components of non-enzymatic antioxidative system of an organism: glutathione, uric acid, albumines and extra-erythrocyte derivatives of hemoglobin in a plasma of young, healthy men. After completion of the procedure an increase in peroxidase and glutathione reductase activity and decrease in catalase and S-glutathione transferase activity in erythrocytes was observed. In a plasma one could observe a significant increase in concentration of all examined non-enzymatic antioxidants and in particular of uric acid and extra-erythrocyte derivatives of hemoglobin, which concentration maintained at increased level also on the following day.

In a research [99] one examined influence of whole-body cryostimulation on activity of chosen antioxidative enzymes and on concentration of products of lipid peroxidation at 9 female canoeists, who were subjected to intensive 10-day typical training cycle and then after 4 months they were subjected to identical training cycle, in which physical loads used twice during a day were preceded with whole-body cryostimulation procedures at temperature from -120°C to -140°C (duration – 3 minutes). After first 6 days of a training cycle without using cryostimulation a significant increase in activity of superoxide dismutase and glutathione peroxidase in erythrocytes and also a significant increase in concentration of conjugated dienes in a serum and erythrocytes as well as in concentration of TBARS in serum was observed. On the 6th day of a subsequent training cycle, when physical exercises were preceded with whole-body cryostimulation procedures, one proved decrease in both activity of superoxide dismutase and glutathione peroxidase in erythrocytes and of concentration of conjugated dienes in serum and erythrocytes as well as in concentration of TBARS in serum, and it proved a beneficial influence of a whole-body cryostimulation on antioxidative capacity of an organism which was subjected to intensive physical efforts.

In another research conducted by these authors [166] was evaluated activity of chosen antioxidative enzymes in erythrocytes. 19 male canoeists of the Polish Olympic Team were subjected to two 10-day cycles of trainings with similar load of physi-

cal effort – conducted in 4-month intervals, in the beginning without and then with using of whole-body cryostimulation procedures, which had the same therapeutical parameters as in the previous research. After six days of training without cryostimulation activity of superoxide dismutase was significantly higher in comparison with values before commencement of a training cycle and after completion of this cycle it was not significantly different from initial values. During a training using cryostimulation activity of this enzyme was not significantly different from initial values. Catalase activity in any of training cycles did not differ from initial values. Activity of glutathione peroxidase on the 6th and 10th day of a training cycle without supporting cryostimulation was significantly higher compared to initial values, while during trainings which were preceded by cryostimulation, after transient increase on the 6th day of a cycle, activity of this enzyme got normalized after completion of a training cycle. Results of the research confirmed that a whole-body cryostimulation influenced positively on keep of prooxidant-antioxidant balance and reduced negative effects connected with increased production of reactive oxygen forms during physical efforts.

In a research [33] on healthy women who were subjected to a cycle of whole-body cryotherapy procedures at temperature of -110°C , within the first 4 weeks one could observe a significant increase of a total antioxidative capacity of serum to capture peroxy radical (TRAP) in the second minute after completion of an procedure, which was then normalized in the 35th minute after completion of an procedure. At the next stage of a cryotherapy cycle there was not any significant changes of TRAP values, and it proved against a persistent influence of cryogenic temperatures on oxidation-reduction processes in living organisms.

In the next research [100] one proved a beneficial influence of a whole-body cryotherapy on oxidative status at patients with multiple sclerosis. Patients were subjected to a cycle of 10 daily whole-body cryotherapy procedures (duration 2-3 minutes, at temperature in a cryochamber from -110°C to -120°C) with subsequent kinesitherapy. Prior to commencement of a cycle of procedures, a total antioxidant activity of a serum (total antioxidant status TAS) in those patients was significantly lower compared to a control group of healthy patients. After completion of a cycle of whole-body cryotherapy procedures in patients with multiple sclerosis one could observe a statistically significant increase in TAS values compared to a control group. One could not observe any significant changes of superoxide zinc-copper dismutase (CuZn-SOD) and of catalase in erythrocytes between both groups.

In our own experimental researches [121,135] which were conducted on Wistar rats one examined influence of multiple, whole-body exposure to action of low temperature of -90°C on activity of superoxide dismutase, glutathione peroxidase and catalase. One stated a significant increase in activity of these enzymes and decrease in concentration of a product of lipids peroxidation – malone dialdehyde. At the same time a total antioxidant capacity of serum increased. During cryostimulation one could not observe significant changes of vitamin E concentration, which is one of the main non-enzymatic antioxidant factors and therefore an important factor preventing lipid peroxidation.

Results of our clinical researches [141] confirm beneficial influence of whole-body cryotherapy on antioxidant status in patients with ankylosing spondylitis. After completion of a cycle of whole-body cryotherapy in those patients one could observe decrease of oxidative stress intensity (significant decrease in malone dialdehyde concentration in plasma and no changes of this marker concentration in erythrocytes) and also statistically significant increase in antioxidant enzymes activity (mainly superoxide dismutase) and a total antioxidant status.

In another our research [143], in which we observed influence of a whole-body cryotherapy on behaviour of inflammation status markers in 16 patients with ankylosing spondylitis and in 16 healthy volunteers, after completion of a cycle of 10 daily cryotherapy procedures at temperature of -120°C , in patients with ankylosing spondylitis one could observe a significant decrease in serum C-reactive protein, mucoproteids, fibrinogen and s-ICAM-1 concentrations and decrease in erythrocyte sedimentation rate (ESR.) values, while in healthy volunteers one could observe a significant decrease in serum mucoproteids and fibrinogen concentrations and decrease in ESR. value.

For safe functioning of an organism it is necessary to maintain prooxidant-antioxidant balance. Taking into account a fact that low temperatures used in cryostimulation do not cause very intensive oxidative stress, which may induce compensatory reactions – biosynthesis of enzymes removing free oxygen radicals and responsible for synthesis of low-molecule antioxidants or enzymes repairing DNA damage, it is worth considering a positive role of „oxidative stress“, which organisms are subjected to during cryotherapy [9]. Beneficial compensatory reactions triggered by oxidative stress caused by cryotherapy may be observed among others at patients with rheumatoid arthritis. In the course of rheumatoid arthritis a significant amount of activated phagocytes in synovial fluid of joints appears. They release O_2^- , which is one of free oxygen radicals. A synovial fluid in those patients shows increased concentration of lipid peroxidation products and decreased content of ascorbinian [50]. Using in such cases of cryotherapy may lead to increase of antioxidant enzymes activity decomposing free oxygen radicals caused by increase of enzymatic proteins synthesis and also to decrease of a level of lipid peroxidation products. What is very interesting is the fact that reactive oxygen species (ROS) – apart from unfavourable activities – may also fulfil useful functions. One emphasizes their role as metabolism regulators [48]. They have capacity of activating some of transport proteins. For instance, hydrogen peroxide stimulates glucose transport to cells. On the other hand serotonin transport to thrombocytes is stimulated by oxidation of thiol groups of transporting proteins. Sodium-calcium exchanger is activated on the basis of the same rule [1]. Increased during cryostimulation activity level of free oxygen radicals and of antioxidant enzymes at keeping prooxidant-antioxidant balance may cause many beneficial therapeutic effects.

Influence of low temperatures on hematopoietic and immunological systems

Only a few experimental works were dedicated to an issue of hematopoietic and immunological systems functioning in conditions of action of extremely low temperatures. The research [16] conducted on healthy volunteers who were subjected to 11-day lasting cycle of whole-body cryotherapy procedures proved both in women and men insignificant decrease in count of erythrocytes, leucocytes and thrombocytes and also decrease in hemoglobin concentration, hematocrit, MCV, MCHC and MCH values and decrease in thrombocyte count. These decreases did not go beyond reference values. At the same time authors observed increase in reticulocytes participation in peripheral blood smear which could result from releasing bone marrow reserve or stimulating its multiplication.

In another research [146] in healthy men, grass hockey players who were subjected to a cycle of 18 daily whole-body cryotherapy procedures at temperature varying from -120 to -130°C , directly after completion of a cycle one could observe significant decrease in erythrocytes count, hemoglobin concentration and hematocrit values with no change in a scope of leucocytes count and participation of particular cell fractions in blood smear. Within a week after completion of procedures a count of erythrocytes and hematocrit values in examined people returned to initial values and hemoglobin concentration even exceeded them.

Also in our researches [119] conducted on Wistar rats, which were subjected to multiple whole-body cryostimulation at temperature of -90°C one could observe a statistically significant decrease of in red blood cells erythrocytes, white blood cells leucocytes and thrombocytes count together with decrease of in hemoglobin concentration and of in hematocrit value, MCV, MCHC and MCH values. A total number of leucocytes did not change but significant changes in participation of particular white blood cell leucocyte fractions depending on exposition time of exposure to operation action of low temperatures could be proved. After a week of exposure, a significant increase of in granulocytes participation and decrease of in lymphocytes participation occurred. After two-week exposure participation of both granulocytes and lymphocytes did not differ significantly from values observed at in experimental control animals. In a microscopic picture of peripheral blood smear one could observe neither differentiation of red blood cells erythrocytes sizes nor any deviations in a scope of correct look image and number of morphotic elements of blood.

In our clinical research [142], in which one analysed a whole-body cryotherapy influence on behaviour of parameters of blood cells count at in 16 patients with ankylosing spondylitis and at in 16 healthy volunteers – after completion of a cycle of cryotherapy operations procedures conducted at temperature of -120°C at in examined men one could only observe only small changes in blood cell count parameter values, which were within a reference scope limits of binding norms and with a different character in both analyzed groups.

In patients with ankylosing spondylitis one observed statistically important significant decrease in hematocrit value and a medium volume of erythrocytes and increase of in a medium concentration of hemoglobin in erythrocytes (Tab. 3). Changes of blood cell count showed in patients with ankylosing spondylitis support improvement of blood rheologic properties.

Table 3. Parameters of blood cell count (medium value \pm standard deviation) in patients with ankylosing spondylitis before and after completion of a cycle of whole-body cryotherapy procedures.

<i>Parameter</i>	<i>Before a cryotherapy cycle</i>	<i>After a cryotherapy cycle</i>	<i>Statistical significance</i>
Number of leucocytes [G/l]	6.84 \pm 1.35	6.49 \pm 1.08	(NS)
Percentage share of lymphocytes [%]	31.16 \pm 5.27	30.94 \pm 5.38	(NS)
Percentage share of monocytes [%]	7.45 \pm 1.47	7.09 \pm 0.91	(NS)
Percentage share of granulocytes [%]	61.39 \pm 5.78	61.97 \pm 5.37	(NS)
Number of erythrocytes [T/l]	4.71 \pm 0.35	4.67 \pm 0.36	(NS)
Hematocrit [%]	43.91 \pm 2.96	42.12 \pm 3.04	p=0.004
Concentration of hemoglobin [g/dl]	14.28 \pm 1.02	13.98 \pm 1.02	(NS)
Mean corpuscular volume of erythrocyte (MCV) [fl]	93.06 \pm 2.64	90.19 \pm 2.66	p=0.002
Mean corpuscular hemoglobin in erythrocyte (MCH) [pg]	30.39 \pm 1.19	29.93 \pm 0.76	(NS)
Mean corpuscular hemoglobin concentration in erythrocyte (MCHC) [g/dl]	32.53 \pm 0.56	33.19 \pm 0.55	p=0.018
Number of thrombocytes [G/l]	248.0 \pm 38.71	243.8 \pm 29.88	(NS)

In healthy volunteers one could observe a significant increase in number of erythrocytes and hemoglobin concentration and decrease in hematocrit value and mean corpuscular volume of erythrocyte together with increase in number of thrombocytes and monocytes share in a peripheral blood smear (Table 4).

In a research [39] it was proved that resistance of red blood cell, which were subjected to action of low temperatures depended on age of circulating erythrocytes. Reconstruction of a cell membrane, functions of red blood cell enzymes and concentration of biochemical substances resulting out of a lifetime of red blood cells influence sensitivity of blood cells depending on value of acting temperature. The weakest reaction on action of low temperatures showed red blood cells in a middle-age. On the other hand the youngest and the oldest fractions of red blood cells, which are insignificant percent of a whole population of erythrocytes, were influenced by hemolysis most often.

Exposure to the cold significantly influences mobilization of leucocytes and it can also restrain their activity [62].

Table 4. Parameters of blood cell count (average value \pm standard deviation) in healthy volunteers before and after completion of a cycle of whole-body cryotherapy procedures.

<i>Parameter</i>	<i>Before a cryotherapy cycle</i>	<i>After a cryotherapy cycle</i>	<i>Statistical significance</i>
Number of leucocytes [G/l]	5.94 \pm 0.95	6.01 \pm 1.06	(NS)
Percentage share of lymphocytes [%]	33.86 \pm 6.53	33.21 \pm 5.68	(NS)
Percentage share of monocytes [%]	7.25 \pm 1.21	8.25 \pm 1.37	p=0.001
Percentage share of granulocytes [%]	58.89 \pm 6.83	58.41 \pm 5.98	(NS)
Number of erythrocytes [T/l]	5.02 \pm 0.31	5.23 \pm 0.36	p<0.001
Hematocrit [%]	43.98 \pm 1.67	47.34 \pm 2.75	p<0.001
Concentration of hemoglobin [g/dl]	14.86 \pm 0.59	15.39 \pm 0.77	p<0.001
Mean corpuscular volume of erythrocyte (MCV) [fl]	88.06 \pm 4.12	90.69 \pm 3.24	p=0.008
Mean corpuscular hemoglobin in erythrocyte (MCH) [pg]	29.74 \pm 1.42	29.47 \pm 1.32	(NS)
Mean corpuscular hemoglobin concentration in erythrocyte (MCHC) [g/dl]	33.81 \pm 0.57	32.55 \pm 1.03	p=0.003
Number of thrombocytes [G/l]	202.3 \pm 34.56	244.9 \pm 33.99	p<0.001

In a research [173] influence of a whole-body cryotherapy and kinesitherapy on participation of lymphocytes subpopulation in a peripheral blood in patients with rheumatoid arthritis and arthrosis was proved. Patients with rheumatoid arthritis were divided into two subgroups. The first subgroup was treated only with kinesitherapy and the second subgroup was subjected to both a whole-body cryotherapy and kinesitherapy. Patients who were subjected only to kinesitherapy also received small doses of non-steroidal anti-inflammatory drugs (NSAIDs). In patients with arthrosis whole-body cryotherapy and kinesitherapy were applied. A whole-body cryotherapy was conducted at temperature of $-140^{\circ}\text{C}\pm 10^{\circ}\text{C}$, and a duration of a single procedure was 180 s. After cryotherapy procedures the patients were subjected to kinesitherapy till physical exhaustion. In all patients who took part in the study blood was drawn on a day preceding a therapy cycle and on the 7th and 18th day of the therapy. In a drawn venous blood the following lymphocytes subpopulations were marked: CD3 (lymphocytes T), CD4 (auxiliary lymphocytes T), CD8 (cytotoxic suppressor lymphocytes T), CD19 (lymphocytes B), CD56 (lymphocytes NK „natural killers”). In the subgroup of patients with rheumatoid arthritis treated with a whole-body cryotherapy and kinesitherapy on the 7th day of a therapy one could observe a significant increase in number and percentage of lymphocytes CD3, CD4, CD8, CD 19 and CD56. A significant increase in percentage and number of CD56 cells (NK) was observed both in patients with arthrosis and in two subgroups of patients with rheumatoid arthritis. The authors surmise reasons

of that phenomenon in a mobilization of an organism under influence of whole-body action of cryogenic temperatures with a subsequent physical activity. It seems that immuno-modulating influence of a whole-body cryotherapy together with influence of kinesitherapy may result from inhibitive influence of cytokines and prostaglandins on NL cells observed in the case of chronic diseases with inflammatory background.

In another research [127] conducted in order to evaluate influence of the cold on function of immune system one proved suppression of some elements of humoral and cellular immunity under influence of low temperatures. One observed decrease in lymphocytes' proliferation, reduction of NL cells number and their cytolytic activity, activation of complement system and induction of thermal shock proteins.

In a research [5] one showed that a local cooling of rats' paws for a period of 10-20 s at temperature of -120°C stimulated a humoral immune response of an organism and this effect which was caused by release of cytokines from regional cells of lymph nodes could be multiplied by direct application of retinol acetate (vitamin A) to a cooled area of animal's body.

In the next research [57] healthy volunteers were subjected to three cycles of a whole-body cryotherapy at a temperature varying from -110°C to -150°C , including 5 everyday entries to a cryochamber each time for 2-3 minutes (totally 15 procedures were executed in each person). Before the beginning of a cryotherapy cycle, after the completion of each cryotherapy cycle and on the 30th day after completion of the last cryotherapy cycle in examined people one marked a concentration of C3 and C4 complement components and bactericidal activity of complement proteins expressed by percentage of bacteria surviving after 180 minutes of incubation in examined serum. Bactericidal activity of complement proteins significantly increased after each cycle of cryotherapy procedures and maintained at increased level also on the 30th day after completion of the last cryotherapy cycle. The concentration of C3 component and to a slightly less degree also a concentration of C4 complement component temporarily decreased till the end of two series of procedures and then systematically were increasing on the 30th day after completion of the last cryotherapy cycle achieved values exceeding initial once. Through the whole observation period these values, despite of some non-significant fluctuations, were within physiological norms.

In another research conducted by this team [56] in healthy volunteers who were subjected to a cycle of 15 whole-body cryotherapy procedures one proved a significant increase in concentration of immunoglobulin class IgA and C3 and C4 complement proteins in a preliminary phase of therapeutic cycle with a secondary decrease in concentrations these substances on the last day of the cycle and return to initial values on the 30th day after its completion. Concentration of immunoglobulins of classes IgG and IgM in these persons was higher than initial values for the whole period of a cryotherapy cycle duration and after its completion.

In a research [18], in which 14 athletes of both sexes were subjected to whole-body cryotherapy procedures at temperature from -110 to -150°C , in men a statistically significant increase in ESR values and in β and γ -globulin fraction share in men toge-

ther with a significant decrease in albumin fraction share were observed, while in women no such changes were noticed.

In a research [115] an increase of receptors expression for IL-1 i IL-6 and decrease of receptors expression for IL-1 β and TNF- α under influence of cryostimulation were observed. Some reports suggest as well that the cold may trigger changes in cytokines expression connected with non-specific reactions of severe phase [32,37]. Cytokines play a key role in two-direction communication between neuroendocrine and immune system [2]. It was suggested that mutual interaction between hormones and cytokines during exposure to the cold may condition immunological homeostasis in response to this factor of external environment.

In the previously cited research [115] one stressed a role of axis hypothalamus – hypophysis – adrenal gland and activation of sympathetic nervous system with a secondary increase in concentrations of cortisol and catecholamine, in modification of immune response to the cold stimulus. Expression of α and β adrenergic receptors and their bonding with catecholamins may stimulate or impede different routes of signals transduction, but stimulation of β_2 -adrenoreceptors causes inhibition of synthesis of proinflammatory cytokines (IL-1 β and TNF- α) and stimulation of anti-inflammatory cytokines (IL-6, IL-10) production, through increase in cAMP concentration [2,156,171]. Molecular mechanisms of immunological response to action of low temperatures require more detailed researches.

Influence of low temperatures on a structure of cytosol and biological membranes

As researches using cryomicroscopy techniques (it allows visualization and evaluation of processes taking part in a single cell) proved, local action of very low temperature was responsible for two basic biophysical mechanisms: intracellular creation of ice and cell dehydration [40,52,95,113,151]. It was proved, among others, that in a frozen cell (temperature -190°C) liquids crystallization and loss of solvent properties took place together with degradation of cytosol molecular structure. The effect of this phenomenon is a massive edema of tissues with its secondary necrosis and destruction of cell membranes, denaturation and protein dispersion in cytoplasm [40,52,95, 113,151]. In the research on processes which take part during freezing of tumor changes of fibroma character in uterus one stated that at very rapid lowering of temperature (above $50^{\circ}\text{C}/\text{min}$) a phenomenon of cells dehydration predominated and at slower cooling (below $50^{\circ}\text{C}/\text{min}$) intracellular creation of ice crystal predominated and more water was „kept prison” in a frozen tissue [29].

During cells freezing direct destruction of cytoskeleton takes place through creating of ice crystals. There is also a rapid increase in chemical compounds concentration dissolved in cytosol [109].

Cold spread in frozen tissue takes place at participation of so-called *gap junctions* (sternum, intercellular joints). In the research [54] using cryomicroscopic measurements

one proved that adding specific blocker of intracellular junctions caused a significant slowing down in intracellular ice spreading process.

Particular tissues differ by sensitivity to action of low temperatures this feature is probably connected with a different amino-acid composition of hydrophilic phase of cytoplasm membrane and presence of specific lipids in its hydrophobic layer. In a research [114] it was proved that excess of amino-acids such as phenylalanine or tryptophan may cause easier escape of cytoplasm and tendency to cell membranes fusion as a result of action of low temperatures. From reports of other scientists it results [96] that membranes of intracellular organellae are definitely more resistant to low temperatures and they are more difficult to destroy during cells freezing.

However, it is not only structure and cytoplasm membranes composition differences that condition resistance of some animal species to action of low temperatures. In some amphibians also presence in cytoplasm of specific proteins (so-called *antifreeze proteins*, AFPs) was proved, which not only resisted freezing but also controlled course of this process influencing its shape, size and aggregation of ice crystals inside cells and prevented their damage. Due to mechanism of these proteins activity it was postulated to change their name into *ice structuring proteins* [27].

The similar function compared is performed by *in vitro* agents preserving tissues in low temperatures. Substances such as for instance glycerol allow deep freezing of tissues without damage of their physiological structure and function. They have a significant influence on dynamics of ice creation, both intra- and extracellular and in this way they prevent tissue damage [109].

In mechanism of low temperatures action on human body important role seems to be played by cryostimulation influence on a state of biological membranes.

In a research [164], in canoeists of the Polish Olympic Team who were subjected to 31-day physical training (for the first 10 days was preceded with a whole-body cryotherapy), one evaluated serum activity of 3 lysosome hydrolases: arylsulphatase, acid phosphatase and cathepsin D. Cryotherapy procedures were performed twice a day for 3 minutes. On the first and the second day a temperature in cryochamber was -120°C , between the third and the sixth day -130°C , on the seventh day -140°C , on the eight and ninth day -150°C , and on the tenth day -160°C . Activity of enzymes was marked before the beginning of the trial, after the fifth and tenth day of intensive training connected with a whole-body cryotherapy and on the seventeenth, twenty fourth and thirty first day of further intensive training conducted after completion of a cycle of whole-body cryotherapy.

Activity of acid phosphatase and cathepsin D did not change significantly, both within the training period connected with a whole-body cryotherapy and also after its completion. One proved some tendencies to increase of acid phosphatase and cathepsin D activity after the fifth day of the training supported with cryotherapy (increase of acid phosphatase activity with approximately 15%, cathepsin D – with approxima-

tely 17%), however obtained differences did not show statistical significance. Activity of arylsulphatase decreased significantly after the fifth and the thirty first training day. Results show that a whole-body cryotherapy and a long-term exercise positively influence stability of lysosome membranes. It seems that mechanism of positive influence of a whole-body cryotherapy on stability of lysosome membrane is connected with increased releasing of ACTH and cortisol and with increased activity of antioxidant enzymes (catalase, glutathione peroxidase) in conditions of low temperatures action.

Confirmation for described observations may be results of the next research of this team [165], in which one evaluated influence of 3-minute lasting whole-body cryostimulation procedures at temperature from -120°C to -140°C applied three times within 24 hours directly before physical exercise in the course of 10-day lasting training cycle in 21 canoeists of the Polish Olympic Team and used as a single procedure in 10 untrained men, on activity of some lysosome enzymes and phosphocreatine kinase as well as concentration of cortisol in serum. In untrained men a single cryostimulation procedure caused a significant decrease in activity of phosphocreatine kinase and it did not significantly influenced activity of acid phosphatase, arylphosphatase, cathepsin D and concentration of cortisol in serum. In canoeists who trained without cryostimulation on the 6th and 10th day of training one did not observe significant changes of activity of acid phosphatase and arylphosphatase compared to values prior to commencement of a training cycle and during a training with supporting cryostimulation one observed a significant decrease in activity of these enzymes compared to initial values both on the 6th and on the 10th day of a training cycle. Activity of cathepsin D in the case of both forms of training was significantly higher in comparison with initial values, both on the 6th and on the 10th day and adequate values during cryostimulation support were lower than during training conducted without these operations. Activity of phosphocreatine kinase on the 6th and 10th day of training without preceding cryostimulation was significantly higher comparing to initial values and during the training supported with cryostimulation, after temporary increase in this enzyme activity on the 6th day of training one stated its normalization after completion of the training cycle. No significant changes in serum cortisol concentration, irrespective of a form of training were observed.

In our researches on rats, which for 10 days were subjected to a whole-body procedures at temperature of -90°C statistically significant increase in alkaline phosphatase activity was observed. Taking into account a fact that this enzyme occurs mainly in plasma membranes and that probably different fractions of alkaline phosphatase take part in through-membrane transport, obtained results could prove influence of low temperatures on membrane transport processes. On the other hand lack of changes of alanine and aspartate aminotransferase activity (enzymes being a marker of hepatocyte cell membranes integrity) in these animals proves against destabilizing influence of low temperatures on cell membranes [120].

Influence of low temperatures on regeneration processes in osteo-articular system and in soft tissues

There are many researches which prove beneficial influence of cryotherapy on a course of metabolic and regeneration processes in bone tissue, cartilage and synovial membrane of joints together with periarticular structures and skin.

In a research [148], in which in laboratory animals one used vapours of liquid nitrogen to dry cooling of burn injuries, a significant acceleration of treatment was obtained. Similarly beneficial effect of cryotherapy on healing process of burn injuries was also proved in the research [78]. In this research using of cryogenic temperatures caused decrease of edema and pain resulting out of injury and significant shortening of treatment.

In an experimental research [125] influence of local cooling of tissues on microcirculation, local inflammatory reaction and existence of tissues edema in rats after experimental damage of soft tissues of shin was analysed. One proved that cooling of tissues caused decrease in edema intensity and increase in capillary tube density and their permeability and also it decreased immunoreactivity in relation to neutrophils (HIS48). Influence of the cold on damaged soft tissues prevents severe effects of injury including disorder functions of microcirculation and endothelium leading to, among others, inflammation induced by granulocyte action and edema of skeletal muscles.

In another research [64] one examined influence of local cryotherapy on regeneration process of bone tissues in patients with patellar chondromalacia. In patients for three weeks one executed daily 3-minute lasting cryotherapy procedures on a knee joint and thigh muscles and directly after cryoprocedures patients were subjected to exercises (static and dynamic) saving cartilage. Basing on obtained results one formulated hypothesis that pain regression or reduction in those patients could indirectly prove influence of common using of cryotherapy and kinesitherapy on synthesis of substances of intercellular cartilage and stimulation of creation of cartilaginous-fibrous scar.

An analysis of cryotherapy influence on osteogenetic processes was conducted in the clinical research [167], in which in patients with early traumatic bone loss in the first and second phase of sickness (wrist, hand, tarsal joint, foot) one used a series of 20 daily local cryotherapy procedures lasting 2÷4 minutes. Directly after an procedure patients executed active exercises of a sick extremity. Beside that patients were recommended to use at home ice compresses on cured place within 6 hours after cryostimulation. In patients who were subjected to this form of therapy in X-ray examination executed from the 6th to the 8th week from commencement of a therapy one stated regression of macular atrophy and significant improvement in bone calcification with reconstruction of correct trabecular structure.

Anti-inflammatory and analgesic action of low temperatures

Positive therapeutic effects of cryotherapy are mostly connected with anti-inflammatory and analgesic action of low temperatures.

The basis of anti-inflammatory action is, among others, influence of low temperatures on blood vessels system, after which oscillation of their lumen diameter (so-called Lewis's waves) takes place and then their long-term (4÷6 hours) expansion with a secondary active hyperemia and warming occurs. In compliance with Dastre-Morat's law, blood vessels of muscles and internal organs behave contradictory to superficial vessels of a skin. The exceptions are vessels in brain, kidneys and spleen. Spasm of resistance vessels occurring under influence of cold and accompanying sealing up of these vessels cause stimulation of metabolism processes in tissues, it increases oxygen supply to tissues and enables their purification from products of tissue decomposition. This action effects in reduction of edema accompanying inflammatory status and in consequence decrease of compression of oedematous tissues on pain endings, and it gives analgetic effect.

This effect is intensified on the one hand by occurring under influence of cold improvement in patency of lymphatic vessels draining intercellular space and increase in capillary filtration, decrease in number of rolled and adjacent leucocytes and decrease in intracellular pressure and on the other hand – through impeding of enzymatic processes activity and particularly decrease in proteolytic enzymes activity taking part in inflammatory reaction [44,74]. Decrease in proteolytic enzymes activity causes inhibition of releasing of inflammatory process mediators, including histamine and lactates in the area of inflammatory focus, affecting chemoreceptors. At the same time one observes in this area increase in bradykinin and angiotensin concentrations giving analgesic effect. The afore-mentioned delay in tissue metabolism and sealing up of blood vessels together with metabolic effect is the next factor causing decrease of cell infiltration appearing in inflammatory focus [13,45,132].

Experimental confirmation of anti-inflammatory action of cryostimulation may be results of researches on animal model conducted on rats, in which inflammatory state was caused by injection of a small amount of diluted formalin in the area of a back paw [77]. As a result of a local action of low temperature in animals subjected to cryostimulation significantly faster – compared to control – decrease in a volume of tumid paw was observed.

In the next research [163] doctors examined influence of matched application of cryotherapy, kinesitherapy and administering anti-inflammatory drugs on a course of post-adjuvant inflammation in soft tissues in rats. The investigations were conducted on 96 male rats of a Brown Norway strain. Multiarticular inflammation was caused by injection of a complete Freund adjuvant in a cushion of a back paw. After two weeks animals were divided into 16 experimental groups (6 animals in each group), in which each of therapy methods was used separately or in different combinations. Cryostimulation as a blast of liquid nitrogen vapours at temperature of approximately –

120°C was used at a whole area of animal's body. Exposures to the cold were repeated for 14 days and a duration of a single exposure lasted 2 minutes. Kinesitherapy was also conducted for 14 days (5 minutes per day) on a specially constructed running track. Anti-inflammatory drugs (*Hydrocortisonum aceticum* 5 mg/kg, *Diclofenac* 5 mg/kg, *Movalis* 0.5 mg/kg) were administered intraperitoneally. After two weeks of a therapy animals were decapitated and then the following parameters were marked: oxidative status of granulocytes, histamine concentration, NO₂ concentration and cortisol concentration. The state of a stomach's mucous membrane was also evaluated with a use of microscope.

In animals, in which cryostimulation was used, significant reduction of joint edema was obtained. A drug blocking cyclooxygenase 2 activity – *Movalis*, turned to be the most efficient in this scope. Common application of cryotherapy with pharmacotherapy decreased to a higher extent symptoms of joints inflammation. Sole application of kinesitherapy did not have beneficial influence and in some cases intensified inflammatory symptoms.

In animals, in which cryotherapy and kinesitherapy was used, researchers observed increase in histamine concentration in blood and the highest values of histamine concentration were observed in animals, in which those two methods were used simultaneously. In turn common application of hydrocortisone with cryo- and kinesitherapy caused decrease in histamine concentration.

In animals, which were subjected to cryotherapy, response of neutrophil granulocytes to stimulation with opsonized molecules of zymosan increased significantly and it was not changed by anti-inflammatory drugs. In groups of animals, in which one used only anti-inflammatory drugs or pharmacotherapy together with kinesitherapy, metabolic activity of neutrophil granulocytes did not change significantly.

In animals, which were only subjected to cryostimulation one observed increase in cortisol concentration and in animals, which were subjected at the same time to pharmacotherapy with *Movalis* or with hydrocortisone, increase in this hormone concentrations was not observed.

In none of animal groups changes in NO concentration and pathological lesions in mucous membrane of stomach were observed.

Results of the cited research prove that anti-inflammatory action of cryotherapy is connected, among others, with stimulation of axis hypothalamus – hypophysis – adrenal glands, increase in histamine concentration in blood and increase in metabolic activity of neutrophil granulocytes. What is more, these results suggest that the most beneficial anti-inflammatory effect is achieved by application of cryotherapy together with inhibitors of cyclooxygenase 2.

Anti-inflammatory action of low temperatures was also verified in clinical trials evaluating influence of cryotherapy on a serum concentration of inflammatory status mediators.

In a research [69], in patients with active form of rheumatoid arthritis of a different advancement level (from the 1st to the 3rd stage of the disease according to Steinbrocker), one conducted medical crossed experiment, using in the first group of pa-

tients non-steroidal anti-inflammatory drugs, then for 3 weeks non-steroidal inflammatory drugs + cryotherapy +kinesitherapy and for further three weeks – non-steroidal anti-inflammatory drugs + kinesitherapy. In the second group of patients order of two last therapeutic cycles was reversed. The local cryotherapy was used in a form of extremely cold air supply at temperature from -160°C to -130°C and of ice compresses. Prior to cryotherapy, on the 21st and on the 42nd day of therapy the following parameters were marked: ESR, serum concentrations of seromucoid, α_2 -globulin and α_2 -macroglobulin and also serum and urine concentrations of free hydroxyproline, hydroxylysine and proteoglycans. In none of examined groups any statistically significant changes of inflammatory status markers and indices of damage of articular tissue or periarticular tissue were observed.

No changes in concentrations of C-reactive protein, seromucoid and total protein were stated in the research [139], in which a group of healthy volunteers was subjected to action of cryogenic temperatures.

In the next research [7], in which 10 players of the Italian National Rugby Team were subjected to a cycle of 5 daily, 2-minute lasting whole-body cryostimulation procedures, values of inflammatory status markers and activity of enzymatic markers of muscular damage was evaluated. For the whole period of investigation the players continued their routine training programme according to a scheme that had been executed for 6 weeks. After completion of a cryotherapy cycle in a serum of sportsmen a significant decrease in concentrations of the following mediators of inflammatory status: IL-2, IL-8, s-ICAM-1 and PGE_2 were noted. At the same time one proved significant increase in concentration of interleukin IL-10. Researchers did not observe significant changes in concentrations of CRP, immunoglobulins IgG, IgM and IgA and C3 complement component. Moreover after completion of cryostimulation cycle a significant decrease in concentrations of markers of miocyt damage: phopshocreatine kinase and lactate dehydrogenase were observed, compared to initial values before commencement of cryoprocedures.

In a research [159] in patients with rheumatoid arthritis and in our researches [130,136,162] in patients with ankylosing spondylitis, in which 2-week lasting cycle of a whole-body cryotherapy procedures was performed, one obtained respectively: statistically significant decrease in seromocoid concentration with accompanying increase in share of α_1 globulin fraction in proteinogram and statistically significant decrease in concentration of C-reactive protein (CRP) and seromucoid with accompanying statistically significant increase in share of β_1 globulin fraction in preteinogram.

Beneficial influence of low temperatures on a course of inflammatory process was also confirmed in clinical researches, in which one analysed behaviour of granulocytes in pathologically changed joints, which were subjected to cryotherapy.

In a research [116] in patients with rheumatoid arthritis of a different advancement level (from the 1st to the 4th stage of the disease according to Steinbrocker) that lasted from 4 months to three years, one evaluated influence of a local cryotherapy in a form of blast of nitrogen vapours at temperature of -150°C , used twice per day for three minutes and ice compresses used twice per day for 20 minutes on each joint, on

composition of cells in articular liquid. Before commencement of cryotherapy and after completion of a 5-week lasting cycle of local cryotherapy, in patient's articular liquid one evaluated a total number of cells and percentage of granulocytes in a smear of articular liquid's sediment. One observed statistically significant decrease in number of cells in liquid collected from cooled joint (from 8900 to 6100) and statistically insignificant decrease in granulocytes' percentage (from 55% to 53%), compared to initial values. Decrease in number of cells taking part in inflammatory process damaging a joint proves a beneficial influence of a local cryotherapy on a process of joints destruction occurring in rheumatoid arthritis.

In the next research [41] in patients with rheumatoid arthritis activity of neutrophils isolated from articular liquid prior to and after application of a local cryotherapy was one analyzed. All patients were treated with non-steroidal anti-inflammatory drugs and corticosteroides were discontinued for six months before commencement of cryotherapy. Using chemiluminescence test one examined both activity of neutrophils isolated from articular liquid in patients suffering from rheumatoid arthritis and activity of neutrophils of peripheral blood in healthy patients, which were incubated with articular liquid of patients with rheumatoid arthritis. One stated that articular liquid of patients with rheumatoid arthritis collected from a joint subjected to cryotherapy had caused higher activation of resting neutrophils of peripheral blood in healthy patients compared to liquid isolated from the same joint prior to commencement of cryotherapy. At the same time chemiluminescence of neutrophils isolated from articular liquid in patients with rheumatoid arthritis after a local cryotherapy procedure applied on the area of examined joint significantly lowered. Observed phenomenon may prove a change of inflammatory process dynamics in joints, which are subjected to a local cryotherapy as a result of cold influence on oxidant metabolism of neutrophils and modulation of releasing pro- and anti-inflammatory factors in a sick joint. The examination did not allow for a final identification of these factors although authors considered influence of cytokines and biogenic amines.

Final confirmation of anti-inflammatory effect of cryogenic temperature action may be brought by clinical results of cryostimulation in a form of regression of edemas and pains in pathologically changed joints in patients with rheumatoid arthritis, who were subjected to both a local and whole-body cryotherapy. These results will be specified in the next chapter.

Many observations seem to prove that decrease in pain intensity after application of cryotherapy procedure is not exclusively a result of anti-inflammatory activity, since analgesic effect appears very quickly, often even directly after a skin cooling.

Mechanism of analgesic effect of cold is complex. It is based in stimulating influence of cold on releasing of β endorphins in a central nervous system with simultaneous functional disconnection of sensory receptors and their connections with proprioceptors and release of conductivity in slowly conductive nerve fibres and also mechanism of „control gates“ selecting impulses coming to central nervous system.

Endogenic opioid peptides, which endorphines, enkephalines and dynorphins are part of, have strong and multidirectional biological activity. Action of β endorphin, which is produced by hypophysis of proopiomelanocortin, has been evaluated the most deeply. This peptide shows strong analgesic, anxiety-relieving and euphorizing features. Its role in organism adaptation to stress is well known together with a role in learning and memorizing process. One proved that even 2-3 minute stay in a cryochamber causes increase in concentration of β endorphins in a blood serum [157].

One also stated that under influence of the cold decrease in impulsation of non-receptive mechanoreceptors occurred together with delay in conductivity in nociceptive nerves, particularly in slowly conductive fibres type C characterizing with a high threshold of pain excitability [88].

Gate control theory was proposed by Wall and Melzack in 1965 when cells inhibiting impulses conduction to higher levels of a nervous system were discovered in gelatinous substance of posterior horn of the lateral cerebral ventricle of spinal cord. It is known that sensory impulses are transferred through conductive fibres type A and pain impulses – through slowly conductive fibres C. It causes impulsation of fibres A stimulates inhibiting cells of a spinal cord, which block impulses inflow through fibres C to a central nervous system. The result of this phenomenon is analgesic action, which drives a so-called reflex-therapeutic mechanism used in softening of pain through blocking afferent pain impulsation in the case of majority of physiotherapy methods, including probably cryotherapy [13,132].

In experimental researches on animal model [6] one observed existence of relation between analgetic action of local skin cooling and inhibiting nervous conduction with participation of VR1 receptor. One proved that lowering of temperature from 31°C to 14°C leads to inhibition of conduction induced by capsaicin in neurons of rat's dorsal ganglion. This phenomenon is probably caused by a significant decrease of functional potential of nerves leading to pain relief.

In our researches [129] analgesic effect caused by cooling of a whole body in rats placed in a cryogenic chamber for one minute per day for 8 days was evaluated. Intensity of analgesic effect was analysed with use of a „hot plate” method at a temperature of 56°C. One proved that both a single and repeated for few succeeding days exposure of animals to action of extremely low temperatures of –60°C and –90°C caused statistically significant analgesic effect. After a single cooling in a cryogenic chamber analgesic effect maintained for approximately 15 minutes. After four days of repeated exposure to temperature of –90°C this effect was significantly increased. On the 8th day of cryotherapy although similar values of analgesic index maintained, yet obtained differences did not show any statistical significance. Intraperitoneal administration of Naloxon (antagonist of endogenous opiate receptors) 40 minutes prior to exposure in a cryogenic chamber did not cause inhibition of analgesic effect and it rather proves against endogenous opiate system participation in a mechanism of analgetic action of low temperatures.

Influence of low temperatures on muscles and peripheral nervous system – neuromuscular effect

The direct effect of exposure to the cold is insignificant and slow decrease in temperature of skeletal muscles. Lower temperature and decreased blood flow in blood vessels supplying muscles with energy substances cause decrease in speed of local metabolism, what results in muscle shivering in low temperatures, being a way of local heat generation in muscles. Despite of big amounts of heat generated in this way (several times bigger than in conditions of basic metabolism), it is not stored in muscles because equivalent heat amount was lost through a convection [66].

A rapid dilatation of blood vessels occurring after completion of exposure to the cold leads to a strong hyperemia of skeletal muscles connected with increase in concentration of oxygen delivered to these muscles. This enables removing from muscles unnecessary metabolism products such as lactates and histamine. At the same time researchers observes accumulation of bradykinin and angiotensin in muscles. The aforementioned phenomenon significantly improves a muscle's „condition“ and decreases algesia. This effect is used among others in treatment of muscles injuries.

Influence of a local cryotherapy on muscles condition was examined among others in the research [71] evaluating activity of phosphocreatine kinase – a marker of muscle tissue damage in patients with active form of rheumatoid arthritis who were subjected to a single exposure of cold air at temperature from -160°C to -140°C supplied to the area of fine joints of one hand, and one carpal, ulnar or knee joint respectively. Activity of phosphocreatine kinase was evaluated before the procedure, directly after it and on the 10th, 20th and 60th minute after completion of cryostimulation. No significant changes of this marker values were observed and it proved lack of damaging influence of cryotherapy on muscles and possibility of safe using of this physiotherapy method in treatment of patients with diseases of motion system, which are accompanied by muscle pathologies.

The afore-mentioned mechanism with particular consideration of analgesic effect together with existing under influence of cold reduction of muscular tension resulting out of decrease in nerve conduction and decrease in reactivity of peripheral sensory and nerve endings and also modification of function of motor plate (nerve and muscle plate) and c-motoneurons allowing for execution of efficient kinesitherapy, are the basis of therapeutic application of cryostimulation particularly in the case of pathology of locomotor system resulting out of damages of nervous system [126].

Although mechanism of cold action on nervous system has not been fully recognized yet and many authors differently interpret results of researches. It was assumed that a physical impulse, such as a low temperature, might influence action of a central nervous system through cold receptors (numerously represented in skin) stimulating CNS in a way of afferent exteroceptive impulses. Short-term impulse action of the cold stimulates the most strongly activity of reticular system, and it leads to inhibition of activity of motoneurons of type α and stimulation of motoneurons of type γ . This causes increase in excitability of muscle spindle and increase in muscular tension, to-

gether with intensification of reflex excitability. In turn repeating impulses connected with a long-term action of low temperature cause a different reaction leading to reduction of muscular tension [147].

According to some authors, the cause of this phenomenon is decrease in frequency of discharges within nerve and muscle spindle occurring as a result of adequately long action of a low temperature. In a research [158] this effect was observed the most clearly at change of a body's surface temperature within a scope from $+30^{\circ}\text{C}$ to $+27^{\circ}\text{C}$, but it referred both primary and secondary sensory endings of muscle spindles. At the same time one stated that in primary endings of annular and spiral type frequency of impulsation decreased much more than in secondary endings of bouquet type.

On the other hand results of other researches [91] call into question the fact that secondary sensory endings of muscle spindles react to low temperature. According to the authors of this research, a phenomenon of decrease in frequency of discharges under influence of the cold is limited to primary endings of annular and spiral type. Moreover, based on conducted experiments they presented paradoxical increase in discharges frequency at temperature lowering of cooled tissue with $2\text{-}3^{\circ}\text{C}$ stating that just further decrease in body temperature to approximately $+28^{\circ}\text{C}$ caused decrease in this impulsation.

Confirmation of a theory concerning participation of sensory endings in muscle spindles in reaction of a nervous system to the cold action may also be results of observation on a group of patients with damage of a central nervous system treated with cryotherapy [15,144]. In the first research influence of cooling of extremities with water at temperature of $+8^{\circ}\text{C}$ within a period of 6 minutes with secondary physiotherapy on spastic muscles manifested in these patients with significant reduction of pathological muscular tension, what was explained by authors with decrease in excessive excitation of muscle spindles induced with even a small change of muscles length in spastic extremity. On the other hand in the second of the cited researches in electromiographic examination with using of Hoffman reflex from triceps muscle of calf, which was subjected to cooling at temperature of $+12^{\circ}\text{C}$, one unequivocally confirmed decrease in activity of muscle spindles.

Most of authors describing mechanism of thermal impulses action on sensory endings in muscle spindles, clearly distinguishes influence of cooling and heating on impulses conduction in a nervous system, although there are some reports postulating existence of medium thickness fibres within some nerve and muscle spindles reacting similarly to the cold and heat [144].

The reasons of reduction of muscle tone after cryotherapy procedures are suspected also in phenomenon of blocking pain receptors under influence of the cold. As a result of this effect, decrease in afferent impulsation takes place with temporary abolition of nervous conduction what results in a partial blockade in a system of γ motoneurons at a level of Granit's loop. In this way inhibition of nociceptive impulses reception takes place together with decrease in conduction in afferent tracts and decrease in muscular tension [46]. The similar view is presented by authors in a research [108], in which in patients with spasticity cooling of muscles with a mixture of water

and ethyl alcohol at temperature of -7°C was used. They think that as a result of action of low temperature in the beginning fast blocking of skin receptors takes place and in effect – reflex decrease in muscular tension. After some time and deeper penetration of the cold, number of discharges in nerve and muscle spindles decreases and a blocking phenomenon of afferent system takes place. The fact that a whole-body hypothermia of different duration causes inhibition of activity of acetylcholine esterase in cell membranes might also be important [79].

Despite the fact that majority of scientists focus on local action of the cold on nervous and muscular system, in some researches [31,87,105] also a role of cryostimulation in modifying activity of higher levels of a central nervous system is stressed. Possibility of cold therapy influence on higher levels of central nervous system is connected with proprioceptive impulsion occurring within nerve and muscle spindles that is reaching spinal cord and higher nervous centres. It is assumed that these impulses subjected to selection and inclusion to a system of feedback loops in control centres may participate in a process of programming and executing involuntary movements and in control of muscular tension. Taking into account plasticity of a human nervous system observed in the course of restoring movement functions for instance after apoplexy, at application of systematic and adequately long stimulation (including also stimulation with impulse cold action), use of cryotherapy may also cause occurrence of permanent repair changes in damaged central nervous system.

Significantly important for therapeutic action of low temperatures is also occurring under influence of this physical factor increase in muscular strength observed in patients with rheumatoid diseases, which one of symptoms is pathological decrease in muscular strength in the area of pathologically changed joints.

In a research [101], in which patients with active form of rheumatoid arthritis were subjected to ten local cryotherapy procedures in a form of blast of liquid nitrogen at temperature of -160°C directed at the area of inflammatory changed joint for the period from 30 seconds to 3 minutes, one proved significant increase in hand grip strength (in the case of a right hand – on average with 31.32% and left hand – on average with 31.50%).

A distinct improvement of grip strength in patients with rheumatoid arthritis appears after first local cryotherapy procedure and maintaining after two weeks of treatment, was also observed in the research [85].

In another research [19], in patients with rheumatoid arthritis one executed electromiographic examinations of ulnar flexor muscle strength of left wrist after a single local cryotherapy procedure with a flow of liquid nitrogen at a temperature in outlet place of -180°C , applied for 60 seconds on pathologically changed wrist joint and forearm. Electromiographic examination executed an hour after a local cryotherapy procedure showed increase in muscular strength reflected in increase in density and/or increase in amplitude of exercise record in 50% of patients with rheumatoid arthritis, and lack of similar increase in majority (60%) of healthy people from a control group.

On the other hand in the research [86], in which local cryotherapy procedures were applied for two weeks, in 3-hour intervals within a day for 60-180 seconds at the

area of knee joints of patients with rheumatoid arthritis, one proved significant changes of strength of muscles bending and straightening a knee joint. One observed a significant increase in active muscle strength and decrease in passive strength comparing to patients treated with terapeutic. Continuation of cryotherapy for subsequent two weeks caused further intensification of changes in examined muscular strength.

Influence of low temperatures on activity of higher levels of a central nervous system and on psyche

In a research [75], in which healthy volunteers were subjected to action of air at temperature of 8°C for 22 minutes one proved that feeling of thermal discomfort in examined men was accompanied by bilateral increase in activity of amygdaloid body, evaluated using functional analysis of images of nuclear magnetic resonance of particular brain structures, what could prove significant participation of amygdaloid body in mechanism of human body reaction to low temperatures action.

Evaluation of experimental animals behaviour in conditions of low temperature action has been so far a subject of only a few experimental researches. In a research [145], in which a whole body of rats was subjected to action of cold water, one observed a significant inhibition of motor activity of animals. In our preclinical researches on animal model [112] one evaluated influence of a long-term exposure to action of low temperatures on behaviour of rats based on a course of behavioral reactions. Whole body of animals located individually in specially constructed cages inside a cryogenic chamber was subjected to action of temperature of -90°C for one minute for the period of 10 days. Prior to cryostimulation cycle and after its completion one evaluated in animals motor activity in a test of „open field”, cognitive activity in a test of „hole”, motor coordination in a test of „spinning wheel”, spatial memory in a test of „water labyrinth” and irritability in Nakamura’s and Thoenen’s score test. One did not state any significant changes of particular tests results between a group of rats subjected to cryostimulation and a control group not subjected to the cold. Obtained results seems to prove a lack of significant influence of repeated exposures on action of cryogenic temperatures on activity of a central nervous system in experimental animals.

In turn in clinical research [124] influence of a whole-body cryotherapy on a mood and psyche of persons subjected to this form of stimulation was evaluated. Conducted observations proved that exposure to action of cryogenic temperatures had a beneficial influence on patients’ mood. Even after a short stay in a cryogenic chamber one stated in examined persons improvement of mood even to euphoria, which maintained for longer period of time after completion of the procedure with accompanying relaxation feeling together with higher psychical drive and mobilization.

Currently trials of evaluation of cryostimulation influence on activity of epileptogenic centres in a brain are at the stage of experimental preclinical researches on animal model. In a research [58] one proved that decrease in temperature of rats’ brain to 21°C lead to reversible inhibition of GABA-dependent fibres oscilation in hipocamp

structures and discontinuation of synchronization of neuronal network necessary to stimulate activity of epileptogenic centres. In turn in a research [170] tests executed on rats consisting in a local cooling of cerebral cortex with Pletier's method proved usefulness of cryostimulation for mapping of cerebral cortex from the point of view of location of epileptogenic centres what could enable to control attacks. Histopathological examinations of cerebral tissue of examined animals did not show any features of nervous joints damage as a result of applied cryostimulation.

Results of presented experimental researches indicate potential possibility of using cryostimulation in prevention of epilepsia attacks.

Influence of low temperatures on circulatory system

A circulatory system is one of organism systems, which functional changes and particularly disorders of microcirculation occurring under influence of low temperatures determine numerous effects from the side of other organs. During exposure to the cold the first of mentioned phenomena is constriction of skin and subdermic tissue vessels with inhibition of blood flow and lowering of these structures temperatures. One proved that within more than ten minutes after exposure to the cold a gradual return of integuments heat-insulation in a way of blood flow increase and significant, even multiple, expansion of skin vessels. This effect is observed for a few dozen minutes and leads to a change in blood distribution in a big circulation and in this way it may potentially cause disorders of many internal organs' functions including heart and big vessels [13,66,72].

Because a large group of patients subjected to a therapy with use of low temperatures are patients with diagnosed ischemic heart disease and arterial hypertension, a significant issue for therapy's safety is influence of cryogenic temperatures on function of a circulatory system.

Despite of the mentioned different changes in vascular placenta one has not proved so far that exposure to the cold caused significant influence on basic functional parameters of a circulatory system together with a value of arterial blood pressure and heart rate.

In a research [68] influence of a single local cryotherapy procedure and of 3-week lasting cycle of such procedures on electrocardiographic record, heart rate and values of arterial blood pressure in patients with rheumatoid arthritis was evaluated. A group of 20 patients was subjected to cryotherapy in form of blast of liquid nitrogen vapours at temperature of -160°C . Basing on obtained results one stated that local cryotherapy procedures applied on small hand joints did not cause acceleration of heart rate. Lack of expected Hines-Brown reflex, which was observed as a result of cold water action, resulted from – according to authors – using of a different type of cooling substance. Patients tolerate well using of extremely cold, dry gas as opposed to unpleasant, painful immersion of hand in icy water. During immersion in icy water a higher heat consumption takes place through conduction than through convention during application of vapours of liquid nitrogen. During investigation one did not ob-

serve occurrence of reflex of slowing down heart rate and increase in blood pressure (diving reflex). According to authors it results from the fact that impulse used in experiment in a form of cold gas is not strong enough to cause reflex excitation of vagus nerve.

In another research of this team [67] one conducted evaluation of a local cryotherapy influence on electrocardiographic changes and frequency of occurrence of anginal pain in a group of 20 patients with chronic arthritis (rheumatoid arthritis and ankylosing spondylitis) and stable form of angina pectoris. Cooling was performed using blast of vapours of liquid nitrogen at temperature from -160°C to -150°C and concerned joints of one hand together with a wrist joint. Prior to procedure, directly after it and on the 6th minute after its completion in patients electrocardiographic record was executed by means of Minnesota Code together with clinical evaluation of possible occurrence of anginal pain. In specified observation period one observed in none of patients occurrence of anginal pain or intensification of ischemic changes in EKG record was observed, which denies negative influence of cryogenic temperatures on functional state of coronary vessels.

Different conclusions are drawn from the research [110], in which one evaluated influence of 2-minute whole-body cooling in a cryogenic chamber on exercise capacity of healthy men. The examined group consisted of 6 men in the age of 23÷25 years, in whom in the first stage after 5-minute warming-up one evaluated exercise capacity using VITA MAXIMA test on a cycle ergometer starting from a load of 100 W, increasing in 3-minute intervals with 25 W. The next stage of examinations consisted in execution by examined persons of exercise to a threshold of anaerobic changes specified in the previous stage. Parameters evaluated in this stage were as following: exercise duration, frequency of heart rate, minute ventilation of lungs, oxygen intake and carbon dioxide elimination. In the last stage examined people entered a cryochamber (temperature of -120°C) for 2 minutes, and then on the 8th minute after leaving a cryochamber exercise load was repeated with renewed evaluation of the afore-mentioned parameters. Analysis of obtained results showed that oxygen and ventilation exercise cost increased after exposure to a temperature of -120°C in relation to an initial values. In all examined people one observed also increase in oxygen debt on average with 1.14 litre. A pulse cost behaved differently – in four examined people it decreased after cryotherapeutic procedure on average with 208 beats.

Obtained results show that single whole-body exposure to action of low temperatures is a load for a circulatory system and a respiratory system increasing a cost of physical exercise. With a moment of exercise commencement after the afore-mentioned exposure adaptative mechanisms of organism are engaged expressing in a fast acceleration of breath frequency and depth. It seems that observed changes of a circulatory system function may be a result of secondary dilatation of skin vascular placenta, decrease in muscular blood flow and resulting out of it decrease in exercise capacity.

In the next research [174] the team conducted a trial evaluating influence of a whole-body exposure to the cold in a cryogenic chamber on values of some hemodynamic parameters. A group of examined people consisted of 63 patients suffering from rheu-

matoid arthritis in the 2nd, 3rd and 4th stage of disease advancement. Patients were subjected to cooling of a whole-body lasting for two minutes at temperature from -110°C to -160°C , once per day for 14 consecutive days. Values of hemodynamic parameters were evaluated after a single exposure and on the 7th and 14th day of cryostimulation cycle. Conducted researches did not show any changes in frequency of heart rate, values of arterial blood pressure and values of transverse diameter of a left cardiac ventricle shortening index and heart ejection fraction. Cryostimulation did not cause arrhythmias.

In our researches [59,60] one analyzed influence of a whole-body cryotherapy on behaviour of some parameters characterizing a circulatory system function. Patients with ankylosing spondylitis were included in a trial and they were subjected to 10 daily two-minute whole-body cryotherapy procedures at temperature of -130°C , with two-day lasting break after first 5 procedures. Directly after each procedure one-hour kinesitherapy took place. Patients taking drugs of proved influence on behaviour of heart rate variability and drugs modifying efficiency of a cardiovascular system were excluded from a trial together with patients suffering from diseases of a circulatory system and diseases influencing value of ejection fraction of left ventricle. In patients on a day preceding the cycle of cryotherapy procedures one executed 24-hour ECG registration using Holter's method with a programme analyzing heart rate variability and 10-minute HRV registration in standard conditions together with sonographic examination of heart with evaluation of left cardiac ventricle ejection fraction. A set of examinations was repeated on the first day after completion of a cryotherapy cycle. After completion of a cycle of whole-body cryotherapy procedures one stated in examined patients increase of a total heart rate variability, but in the case of majority of analysed parameters of time domain this increase showed statistical significance. Analyzed parameters in a spectral domain showed insignificant increase of spectrum power in all analysed frequency ranges. Obtained results prove beneficial influence of a whole-body cryotherapy on adaptation processes of a vegetative nervous system. One did not observe statistically significant influence of cryogenic temperatures applied on a whole body on average values of ejection fraction of left cardiac ventricle.

In turn in a research [8] influence of a whole-body cryostimulation on values of some markers of heart muscle damage was evaluated. In 10 members of the Italian national rugby team, who were subjected to a cycle of 5 daily 2-minute whole-body cryostimulation procedures with simultaneous continuation of standard training programme that had been used for 6 weeks, one proved a significant decrease in activity of phosphocreatine kinase and a significant increase in concentration of N-terminal pro B-type natriuretic peptide (NTproBNP) at simultaneous lack of significant changes of troponin I and high sensitivity C-reactive protein (hsCRP) concentrations. Obtained results prove against harmful influence of a whole-body cryostimulation on heart structure and function in healthy people, even in conditions of increased physical exercise. Increased concentration in NTproBNP may be, according to the authors, a symptom of myocardium adaptation process to interaction of stressful factor, namely cryogenic temperatures.

In a literature there have been so far no reports on influence of cryogenic temperatures on function of lymphatic system fulfilling coordination functions in immunity processes of organism and in transport of proteins and other macromolecular compounds from area surrounding vessels to blood and to a small extent controlling also transport of body fluids. In our experimental researches [128] 40 mature male mice of strain BALB/C weighing on average 50 g were subjected to whole-body exposure to cold action in a cryogenic chamber at temperature of -60°C . In particular groups a single exposure and a cycle of 10 daily exposures in a cryogenic chamber were adequately used. A flow of lymph was evaluated after injection to inferior vena cava of 1% blue trephine solution. Since the moment of dye application one measured a time of a dye appearance in mesenteric lymphatic vessels and then a time of a dye getting to mesenteric lymph nodes. Evaluation of generation and speed of lymph transport was executed after a single exposure in a chamber (group 1), directly after a cryostimulation cycle (group 2) and in the third week since completion of this cycle (group 3).

After a single exposure in a cryochamber one stated statistically insignificant increase in speed of generating and flow of lymph compared to a control group (Table 5). Speed of lymph generation directly after completion of a cycle of ten cryostimulation procedures was also insignificantly higher compared to a control group, while a speed of lymph flow in an examined group decreased statistically significantly compared to a control group (Table 5). Evaluation of the afore-mentioned parameters conducted within three weeks after completion of a cryostimulation cycle showed in a group subjected to cold action insignificant shortening of speed of lymph generation and significant shortening of speed of its flow compared to a control group (Table 5).

Table 5. Average time of dye appearance in lymphatic vessels and in mesenteric lymphatic nodes. NS – statistically insignificant difference.

<i>Group</i>	<i>Average time of dye appearance in lymphatic vessels</i>	<i>Average time of dye appearance in mesenteric lymphatic nodes</i>
Control	44.75±9.26	124.42±18.47
Group 1	40.67±10.86 NS	120.00±14.19 NS
Group 2	48.67±13.36 NS	138.33±24.55 p<0.05
Group 3	43.50±14.74 NS	96.50±11.24 p<0.01

On the bases of presented preliminary data it may be assumed that cryogenic temperatures do not have significant influence on lymph generation time in mice but they change speed of its flow in lymphatic vessels and this effect seems to be long-term.

Influence of low temperatures on respiratory system

In a research [43] influence of a whole-body cryotherapy on ventilation function in patients with rheumatoid diseases was evaluated. 46 patients (35 women and 11 men in the age from 26 to 72 years) with rheumatoid arthritis and ankylosing spondylitis were subjected to a cycle of 14 daily procedures in a cryochamber at temperature

from -110°C to -160°C . After the first procedure and on the 7th and 14th day of cryostimulation cycle in patients doctors executed spirometry with evaluation of lung vital capacity VC, expiratory reserve volume ERV and inspiratory capacity IC together with measurements of maximum voluntary ventilation MVV and measurements of relation flow/volume of breathing air with evaluation of forced vital capacity (FVC) and 1-second forced expiratory volume (FVE_1). One proved that 14-day lasting whole-body cryotherapy did not cause in a whole examined group of patients any statistically significant changes of basic indicators of lungs ventilation: VC, MVV, FVC i FEV_1 . In more than 50% of patients ventilation parameters after treatment in cryochamber did not differ from equivalent values prior to commencement of treatment and were within physiological norms. In 20% of patients before commencement of cryotherapy procedures one showed different, most often mixed types of ventilation disorders with a high psychogenic component, which regressed after procedures in a cryochamber. The aforementioned effect may be connected both with a beneficial influence of cryostimulation on activity of chest bone scaffold disabled in a course of rheumatoid diseases and with beneficial influence of this therapy form on psychological sphere of patients. In turn in approximately 10% of patients did not show ventilation disorders prior to commencement of procedures, after a procedure in a cryochamber one observed temporary ventilation disorders, most often also of a mixed character, most probably of psychogenic or iatrogenic background, resulting probably out of hypersensitivity of a respiratory system to action of strongly cooled air.

Different results were obtained in a research [138], in which 25 healthy, non-smoking volunteers were subjected to a cycle of whole-body cryotherapy at temperature of -110°C including 2-minute lasting procedures repeated 3 times per week for the period of 12 weeks. In the 2nd and 30th minute after completion of the first procedure and then on the 4th, 8th and 12th week of treatment one executed measurements of peak expiratory flow PEF and of 1-second forced expiratory volume (FVE_1). In all measurements one proved insignificant decrease in PEF value comparing to initial values, which was expressed the most highly in the 1st and 3rd month of observation (decrease with 5.1 and 3.2%, respectively). In turn significant changes of FEV_1 values (reduction with 2.3%) were observed only in the 30th minute after the first procedure. Results of this examination proved a weak broncho-constricting effect of whole-body cryotherapy and resulting out of this fact necessity of thorough monitoring of patients' treatment with a case history of a respiratory system diseases.

In another research [70] one evaluated influence of a single local cryotherapy procedure with using of liquid nitrogen vapour at temperature of -180°C applied on a whole spine and near-spine area on some parameters of lungs ventilation. Measurements executed directly after procedure and within 30-minute lasting intervals until 240th minute after completion of a procedure did not show in these patients any significant changes in vital capacity (VC), one-second forced expiratory volume FEV_1 , forced vital capacity FVC, ratio $\text{FEV}_1\%$ and maximum voluntary ventilation MVV compared to values before commencement of a procedure. The authors of the research stress however that lack of changes in spirometric parameters values – despite objective improvement

of chest mobility in these patients – may result from the fact that spirometry is not probably sufficient way of objective evaluation of beneficial influence of cryotherapy on respiratory function in patients with restriction of chest mobility in the course of rheumatoid diseases.

In turn in a research [168], in which patients suffering from bronchial asthma were subjected to few weeks lasting treatment in a cryochamber at temperature of -160°C , one stated a significant improvement in ventilation function of lungs after procedures. Cryotherapy procedures caused in these patients a temporary bronchospasm with secondary, strong bronchodilatation effect. Beneficial influence of cryogenic temperatures on ventilation function of lungs may be proved also by results of the research [34], in which in persons subjected to cryotherapy one observed increase in partial O_2 pressure with simultaneous decrease in partial CO_2 pressure and significant sympatheticotonic and bronchodilatation effects of whole-body cryotherapy procedures.

Influence of low temperatures on endocrine system

One of the factors significantly influencing a final effect of low temperature influence on living organisms is stimulation of vegetative nervous system function and strictly connected with it endocrine system.

In a research [63] healthy, young volunteers were subjected to immersion in a cold water at a temperature of 14°C . In the case of a single exposure for one hour increase in activity of sympathetic part of a nervous system with secondary activation of hormones of adrenal medulla: noradrenalin and also to a smaller extent adrenaline and dopamine together with decrease in plasma activity of angiotensin, and insignificant changes of serum aldosterone concentration was observed. Water immersions repeated three times per week for six weeks did not cause significant changes of plasma renin-angiotensin activity or changes in serum concentration of aldosterone and catecholamines, what proved existence of adaptative reaction of a vegetative nervous system and endocrine system on action of low temperatures. Significant increase in serum concentration of noradrenalin maintaining at similar level both on the 5th and on the 10th day of observation was also stated in healthy men, who for eleven consecutive days were subjected to action of a cold air at a temperature of 10°C for one hour per day [81].

In turn in researches [157,174,175] one evaluated behaviour of concentrations of chosen hormones in blood serum in 32 healthy volunteers (18 men and 14 women) who were subjected to a single 2-minute lasting exposure in a cryochamber at temperature of -130°C and in 65 patients with rheumatoid arthritis (15 men and 50 women) who were subjected to a cycle of fourteen daily whole-body cryotherapy procedures of identical procedure, which for the first seven or subsequent seven days were accompanied by physiotherapy.

In the case of healthy men after a single cryostimulation one observed statistically significant increase in serum concentration of corticotrophin (ACTH), testosterone, adrenaline and noradrenalin compared to values prior to a procedure at lack of significant changes in serum cortisol concentration. In the case of healthy women after a sin-

gle cryostimulation one observed statistically significant increase in serum concentration of ACTH, adrenaline and noradrenalin compared to values before a procedure.

In turn, in patients with rheumatoid arthritis of both sexes, after a single cryostimulation and after a cycle of seven and fourteen procedures, one obtained a significant stimulation of axis hypothalamus – hypophysis – adrenal cortex in a form of statistically significant increase in serum concentrations of ACTH and cortisol compared to values prior to commencement of a cryotherapy cycle. Concentrations of these hormones after one, seven and fourteen procedures did not significantly differ between one another. Concentrations of growth hormone, triiodothyronine and thyroxin in none of observation days differed significantly between one another and compared to values before commencement of a cryotherapy cycle. Increase in secretion of cortisol under influence of a whole body cooling in a cryogenic chamber as potential stress impulse was also observed in another clinical research [169], in which cryotherapy was used in patients with rheumatoid arthritis. Results of the cited research show that cryogenic temperatures influence a human body as a typical stressor with a secondary stimulation of generation of ACTH, hormones of adrenal cortex and catecholamines.

In a research [137] one evaluated influence of two cold therapy forms: bath in a cold water with ice at temperature of 0-2°C (bath time 20 s) and 2-minute lasting whole-body cryotherapy procedures at temperature of -110°C on concentrations of a growth hormone, prolactin, thyrotrophic hormone and free fractions of thyroid hormones (fT3, fT4) in serum of healthy women. Women were subjected to cold therapy three times per week for 12 weeks. Concentrations of examined hormones were marked in the 1st, 4th and 12th week of examination (directly prior to exposure to the cold and in the 35th minute after its completion) and also on days of particular weeks, in which one did not make any procedures. In a group of women who were subjected to bath in icy water one stated only statistically significant increase in concentration of thyrotrophic hormone in the 1st and 4th week and statistically significant decrease in concentration of prolactin in the 12th week of examination, but observed concentration values were within reference range for healthy people. A whole-body cryotherapy did not show a significant influence on concentration of examined hormones. Received results show that cold therapy does not lead to disorders connected with changed secretion of a growth hormone, prolactin, thyrotrophic hormone and fT3, fT4, what guarantees security of conducted therapy.

In another research conducted by this team [90] one examined influence of the cold applied on whole-body using the same experimental model as specified above on concentration of ACTH, β -endorphins, catecholamines and cytokines IL-1 β , IL-6 and TNF- α in a serum of healthy women. Serum concentration of ACTH and cortisol in the 4th and 12th week of a cycle in both groups of women was significantly lower than in the 1st week of exposure, what can be a result of adaptation and lack of influence of both therapy forms on axis hypothalamus – hypophysis – adrenal glands. A significant influence of both cold therapy forms on plasma concentration of adrenaline and examined cytokines in women from both groups was not proved. In turn serum concentration of noradrenalin in both group of women subjected to the cold was signifi-

cantly higher (2-3 times) in relation to initial values through a whole 12-week exposure period. It seems that observed increase in noradrenalin concentration may play a specific role in a mechanism of analgesic effect of both forms of cold treatment.

While in a research [16] in 9 sportsmen training judo who were subjected to a cycle of 10 daily whole-body cryotherapy procedures at temperature of -140°C lasting 3 minutes, on the 5th day of a cryotherapy cycle one stated a significant decrease in cortisone concentration, which then gradually increased and on the 14th day after completion of procedures was again within upper norm limits. In examined sportsmen one did not state significant changes in concentrations of growth hormone and testosterone.

Different results were obtained in a research [73], in which in 54 patients with active form of rheumatoid arthritis were subjected for three weeks to a local cryotherapy with application of a dry air at temperature from -140°C to -160°C applied twice per day with a secondary application of 30-minute lasting ice compresses on small hand joints and the following joints: wrist, elbow and knee on one extremity. In this research after a single exposure to the cold, values of cortisol serum concentration directly after a procedure and in the 10th and 20th minute after its completion did not differ significantly from values before a procedure and in the 60th minute after completion of a procedure they were significantly lower compared to initial values. Further application of cryotherapeutic procedures did not cause significant changes in cortisol serum concentration. It seems that local cold action – contrary to a whole-body cryostimulation – is not sufficient impulse to stimulate axis hypothalamus – hypophysis – adrenal glands.

In turn in a research [82] in 22 healthy professional football players who were subjected to a cycle of 10 whole-body cryotherapy procedures one proved a significant decrease in concentrations of estradiol and testosterone at lack of significant changes in a scope of concentrations of dihydroepiandrosterone and LH, it may advocate inhibiting influence of cryogenic temperatures on activity of aromatase responsible for conversion of androsterone to estrogens.

In a few experimental researches [49] conducted on small mammals one proved that cryogenic temperatures caused a quick reaction of these animals' organism connected with stimulation of release of TSH with a secondary increase in release of thyroid hormones. Results of clinical researches in this scope show that increase in concentration of these hormones in people takes place just after a long-term cold action, what is probably connected with a different mechanism of thermogenesis regulation in humans [154]. In the previously cited works [73,81,157,174,175] one proved that a single and also repeated for more than ten days exposure to the cold in a form of frozen air as well as local and whole-body cryostimulation did not cause changes in activity of TSH and thyroid hormones.

Moreover in researches [157,174] one proved that whole-body influence of cryogenic temperatures does not significantly influence activity of growth hormone, gonadotropic hormones and testosterone in patients with rheumatoid diseases who were subjected to this form of therapy.

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Clinical applications of low temperatures

During last few years an increased interest in methods of using the cold in clinical practice has been observed. Systematic extension of life expectancy and thus aging of the population results in higher number of patients with mobility disorders resulting from degenerative changes of locomotor system that provide basic indications for cryotherapy. Because of high costs as well as side effects of e.g. drug therapy, such patients are more and more eager to try alternative methods of treatment. High therapeutic efficiency of cryotherapy, which – used as a part of complex rehabilitation – improves patients' mobility, no serious complications and relatively low costs, are behind its popularity within this group of patients. Another factor that is behind the development of this method is systematic increase in number of centres that offer local or whole-body cryotherapy. Great financial and organizational effort was made to equip these centres with modern equipment which enables to achieve higher efficiency and increase safety.

Cold treatment methods

Cold treatment methods used in medicine may be divided into two categories: on the basis of gained tissue effects and on the basis of patient's interaction.

Gained tissue effects : cryosurgery, during which low temperature is used to destroy pathologically changed tissues (cryodestruction) and cryotherapy, during which various physiological mechanisms are stimulated by the cold to achieve certain clinical effect (cryostimulation).

Cryosurgery

In cryosurgery, breaking tissues' integrity phenomenon by freezing is used in order to remove or destroy them. Under the influence of low temperatures on the cell level, there is intracellular and extracellular water crystallization, cell dehydration, increased concentration of electrolyte in cell and denaturation of cell membrane lipoprotein. On the other hand, tissue exposed to low temperature is affected by vasoconstriction of arteries and veins with secondary reduction of inner capillary hydrostatic

pressure and blood flow, increased endothelium permeability and blood viscosity. As a result of these changes, angiectasia is recorded on a margin of frozen tissue, causing blood retention and necrosis in frozen area [27,38,63,146,156].

Cryosurgery is based on a few basic therapeutic mechanisms [108]:

- cryodestruction related to necrosis of tissues affected by lethal temperature (-20 to -50°C),
- cryoadhesion involves sticking moist tissue to cooled metal,
- cryoextraction involves removal of pathologic tissue after „catching“ by frozen probe,
- cryostripping involves rapid removal of vessel of which moist walls stuck to cryoapplicator introduced to the vessels,
- cryoobliteration and cryopexy involve exertion of sterile inflammation resulting in closure of the vessel's lumen or integration of adjacent tissues,
- cryohemostasis involves vasospasms with secondary hemostatic effect,
- cryoimmunostimulation involves stimulation of immunological response of frozen tissue antigens with secondary lymphocytic infiltration and macrophage migration to the frozen point as well as destruction of cell's tumour beyond frozen point by activated cytotoxic lymphocytes,
- cryoanalgesia involves nerve destruction by freezing – it may be beneficial or side effect of long term freezing,
- cryoapoptosis involves stimulation by temperature -10°C programmed death of the cells (apoptosis) with no accompanying inflammation or single release of big necrosis mass.

Efficiency of cryosurgery treatment is determined by high freezing rate leading to tear of cell structures by created crystals of intracellular ice, free defrost enabling recrystallisation, which means aggregation of small crystals into larger lumps destroying cells' structure, freezing with adequate margin of healthy tissue, repeatable freezing to increase the number of affected cells as well as maximum extension of period of lowering temperature within tissue.

The final effect of treatment, connected with capacity of frozen tissue, depends on the following factors:

- heat exchange area,
- cryoprobe temperature,
- cryoprobe type,
- tissue thermal conduction,
- tissue vascularisation,
- different tissue sensitivity to cryodestruction.

The main advantages of cryosurgery as a therapeutic method [108] are:

- high therapeutic efficiency and safety of treatment,
- bloodlessness connected with no tissue integrity impairment,
- there is usually no need to use anesthesia, therefore treatment is commonly used in ambulant conditions,
- high treatment tolerance resulting from its low invasiveness,
- possibility for both single and repeated treatment,

- possibility to maintain correct functioning of organs in frozen area,
- good aesthetic effect (high elasticity or lack of scars) benefiting from no colloid-genetic side effects,
- possibility to combine with different forms of treatment, such as drug therapy, radiotherapy and classic surgery.

In practice, there is only one drawback of cryosurgery namely lack of possibility to gain material for histopathologic examination.

The cryosurgery methods are frequently used in dermatology, oncology, flebology, gastrology, cardiology, laryngology, ophthalmology and gynaecology.

Mucous membrane and skin diseases

Cryosurgery is a well accepted and popular method of removing skin and mucous membrane pathological changes [15,19,56,63,71,156].

The choice of tissue freezing technique depends on the type of pathologic changes. In case of mild and shallow changes, the most commonly used are tampons immersed in liquid nitrogen. The spray method, with application of liquid nitrogen or nitrous oxide, is used for disease focus no longer than 2 cm in diameter. The bigger lesions may be treated with superposed fields on the surfaces up to several cm². On the other hand, application method involving nitrous oxide and liquid nitrogen and special applicators (2,5 to 18 mm in diameter), is used for treatment in hard to reach places and enables to minimize freezing area to the planned point, reducing the risk of damaging surrounding tissues. It is mainly applied in stationary operating room conditions for freezing pathological changes of large mass or big thermal capacity (e.g. tumours). The single treatment time is 3 minutes for spray or 6 minutes for contact tip, while its temperature usually reaches from -65°C to -85°C.

Because of its simplicity and time-effectiveness and possibility of undertaking it without anaesthetic, very good cosmetic results, fast healing, low index of side effects as well as low costs of such treatment, cryosurgery is recommended for treating several dozen of disease classifications, while for many of them – despite implementation of new therapy methods – freezing is still a treatment of choice [19,44,58,113,156,166].



Fig. 8. Dermatology Spray Probe with stream regulation through cotton or limiters of freezing area.



Fig. 9. Cryosurgical treatment with usage of spray probe.

Freezing is a standard method for viral wart treatment. In this method liquid nitrogen streamed from a special “snout” is used. Application is continued until specific “hallo” sign appears around pathologically changed tissue. High efficiency of cryoablation while using refreeze technique (-60°C) in case of seborrheic wart, hand common wart, nail wart and feet wart of myrmecia type was proved in paper [113]. In case of rashes covered with hyperkeratotic epidermis for 10 days before freezing treatment, keratolytic procedure was taken with application of either collodion or salicyl and milk ointment while other keratosis build up was curettage or removed by scalpel directly just before treatment. In order to decrease the frequency of recurrence, more radical trials involving intensification of freezing process were conducted. There was used extended 10-second nitrous oxide. This modification of procedure improved therapeutic effect and limited recurrence, at the expense of increased sensation of pain and lower treatment’s tolerance by the patients [19].

The beneficial effects of cryosurgery were observed in the case of purulent inflammation of sudoriparous glands. In research, [15] 10 patients with chronic, painful tubercles after ineffective antibiotic therapy of this disease were treated. The changes were limited and affected small part of the skin’s surface. The total regression of changes with no local recurrence was observed in 8 patients. The average treatment time required for complete healing was 25 days. During and immediately after the treatment, the patients suffered from painful discomforts and in 8 cases the therapy caused shallow ulcers or secondary infections in freeze applied areas. Despite these side effects, 7 patients considered this method as more efficient than antibiotic therapy and were willing to repeat the treatment in case of recurrence.

Trials involving cryoablation in treatment of keloides were also conducted. In research [166], nitrous oxide (temperature -86°C) or liquid nitrogen (temperature -196°C) were used, and in some cases preliminary surgery was made. In 29% of cases the results were very good, in 33% – good and in 38% – only a little or no improvement was observed.

Beneficial effects of treatment were noticed in case of: *prurigo nodularis*, *syringoma*, *necrobiosis lipidica*, *xanthelasma*, *lichen ruber verrucosus*, discoid lupus erythematodes, senile keratosis and also senile and stellate haematoma [44,58,113,156,162].

Oncological cryosurgery

Cryosurgery is a method well respected in dermatological oncology [58,71,72, 156,162].

Many skin cancers are small focal with diameter not exceeding 2 cm and not accumulating deeper than 4 mm, cryosurgery may be applied both as radical therapy and palliative methods. Various cancers with different histological image may be treated – both local and metastasizing to skin whereby cryosurgery may be used as the only treatment or a part of complex therapy [58,72,96,156].

In case of cancers penetrating inside subcutaneous tissues, the best results are achieved by applying contact method, and in case of bigger tumours – superposed fields method is recommended. Frequently, in case of bigger tumours, surface freezing

of external tumour layer is combined with deep destruction with a closed applicator. Application of multiple freezing – refreezing cycles, compression during application, anaemisation of tumour surrounding tissues by means of noradrenaline added to anaesthetic, covering application surface with a drug free gel as well as application of thermocouple on the basis and margins of the tumour, increase area of freezing [55,156].

The results of many clinical trials indicate that in the patients treated with this therapy, during observation period (5 years), the number of relapses was not significantly different than after classic surgery or radiotherapy [72,156,162].

In research [59] the trials were made on the group consisting of 2316 patients with skin cancer (mainly basal cell carcinoma); the ulcers resulting from cryosurgery healed after 4 to 8 weeks leaving just a flat, hardly visible scar. The relapse of cancer was recorded in 2.9% of the cases, of which 83% occurred up to 12 months after treatment and concerned mainly tubercles up to 1 cm in diameter located near nasal-labial fold behind a nose ala. persistent side effects, such as auricle or nose cartilage defect, keloid or uneven scar bottom, were recorded in 41 patients.

Cryosurgery is more and more commonly used in internal organ cancer treatment. The trials involving low temperature application in cryoablation of liver, kidneys, bronchial tree, prostate and breast tumours brings very promising results [80,81,86,99,100,121,138,147,151].

In such cases, because of new imaging methods, cryosurgery tumour removal methods have more and more guided character and enable to reduce the area affected. One of the examples of such ultramodern therapeutic procedure is liver tumour percutaneous cryoablation controlled by magnetic resonance, in which a pathological change is precisely located, because of near-real-time MRI, and tumour freezing is controlled. There is no considerable tissue defect during procedure hence it is much easier to maintain the organ's physiological function [82]. The other example of the aforementioned technique is cryoablation of colon cancer metastasis in liver. In this case, the best results were achieved while treating changes no bigger than 3 cm with accompanying low values of carcinoembryonal antigen (CEA) before treatment. As the most significant drawback of the method its time-consumption was admitted [121,151].

One of the cryoablation side effects may be generalized thrombocytosis leading to serious coagulation system disorders [102].

According to the research [80], cryoablation is also effective, low invasive treatment method used for selected, small, peripheral kidneys' tumours. One of its advantages is application of laparoscopic technique with monitoring, thanks to ultrasonography and magnetic nuclear resonance, which reduces treatment affected area and maintains more secretory functions of the organ. Efficiency and safety of cryoablation in case of treating superficial layers of bigger tumours and tumours located nearby organ hilum is yet to be evaluated.

The good results were achieved by cryoablation in treatment of early stage prostate cancers. In research [101], only 14% of T3 prostate cancer patients with no metastasis to surrounding lymph nodes several days after cryoablation were diagnosed with cancerous changes in surgical margin of tumour surrounding tissues.

Cryoblation is also used in treatment of bronchial tree cancers [63] constricting trachea and bronchia lumen. In such cases, cryoablation is relatively easy to conduct thanks to bronchoscope, well tolerated by patients, reduces the number of side effects and is rather cost effective. The treatments are usually performed in general anaesthetic or neuroleptoanesthesia with application of both rigid tubes inserted by bronchoscope and flexible ones inserted by flexible fiberoptic bronchoscope. Application of this form of therapy usually secures considerable improvement in patient's condition enabling application of chemotherapy or radiotherapy in latter stages of treatment, which is beneficial for patient's clinical condition, respiratory efficiency and the quality of life [81]. The objective improvement of spirometric parameters is achieved in approximately 58% of cases and over 50% widening of trachea or bronchia lumen in 50-76% of patients treated with cryoablation [152]. The best results are achieved in the treatment of mild changes with coexistent both post-inflammatory granulation and granulation of foreign body adjoining type, where usually no recurrence is recorded [39]. The extension of life expectancy may be potentially achieved by combining cryotherapy with either radiotherapy or chemotherapy as cancerous tissue adjacent directly to the freezing zone is subjected to hypervascularisation and becomes more radiation sensitive [150]. The final assessment of combined therapy effects requires multicentre prospective research.

A trial using cryoblation in the treatment of breast cancer was undertaken in the research [100], in which 15 patients suffering from breast tumour of sizes 21 ± 7.8 mm were subjected to two cycles of freezing lasting adequately $7 \div 10$ and 5 minutes. Cryoapplicator was placed inside the tumor under control of ultrasonography. No significant complications of the procedure were observed. Within five days after executing of cryoblation in the case of five tumors of diameter below 16 mm one did not state neoplastic changes in tissues surrounding tumor. At the same time in the case of eleven tumors, of diameter exceeding 23 mm, one stated lack of complete necrosis of tumor tissues. According to the authors, cryoblation of breast tumours of dimensions exceeding 15 mm should be conducted at simultaneous using at least two cryoapplicators, in order to obtain extension of volume of necrotic tissues around tumor and in this way – to secure bigger margin of oncological safety.

In order to increase efficiency of oncological cryosurgery, trials of using joint therapy – a so-called cryochemotherapy – are conducted. One described very good effects of joint application of cryosurgical methods and bleomycin in the treatment of solid tumors. After a freezing procedure drug penetration to damaged cells increased and application of chemotherapy improved long-term treatment effects, prevented dissemination and recurrence of neoplastic process. Application of cryochemotherapy resulted in a significant reduction of bleomycin dose, which effected in lower toxicity and weaker side effects of chemotherapy [86].

Cryosurgery is also used as a method of palliative treatment in advanced forms of tumors. Cryoblation procedures are good alternatives in the cases of inoperable changes and may serve as a cytoreduction of tumor. They are often connected with other therapeutic methods in order to obtain higher treatment efficiency. Examples of simul-

taneous application of tumor cryoblation, regional immunotherapy and chemotherapy in patients with advanced breast carcinoma, with infiltration on a breast wall are described. In patients subjected to this complex therapy one observed tumor regression lasting few months, extension of survival time and improvement of life comfort. Patients had no problems with tolerating treatment. No one stated significant side effects and application of polytherapy allowed for inclusion of less aggressive chemotherapy schemes. The advantage of such a therapy is possibility of its multiple repeating [138].

Varices of lower extremities

Cryosurgical treatment of varices of lower extremities consists of a few stages including cryostripping of main venous trunks and their variciform collaterals or cryobliteration of varicoid vessels was conducted, among others, in researches [54]. 28 patients (37 extremities) qualified based on typical procedure including tests evaluating efficiency of superficial and deep venous system, status of arterial blood supply, presence of inefficient lancing veins and trophic lesions in legs were subjected to cryosurgical treatment. Cryostripping and cryobliteration procedures were executed using small and medium vascular cryoprobes introduced by single skin cuts into varicose vein lumen or along varicoid vein's route, respectively. In all patients positive therapeutic effect comparable with classic methods was obtained. In 30% of patients one observed skin hyperpigmentation and induration disappearing in further observation and in 60% of patients – haematoma in subdermic tissue but definitely less intensified than after classic cryostripping was noted. Only in one female patient functional paralysis of saphenous nerve branch occurred, which remitted naturally after approximately 6 weeks. The average hospitalization period was about 1-3 days and in majority of patients good, early cosmetic effect was observed. According to the authors, application of cryosurgical methods allows to decrease amount and extent of skin cuts together with tissues injury, which is connected with reduced pain intensity and amount of secondary infections. It also allows obtaining much better cosmetic effects and



Fig. 10. Mini-phlebectomy and haemorrhoids treatment – cryostripping probe set.

shorter hospitalization periods. Using in these cases cryoprobes of small and average diameters, enabling conducting operations in a full range, decreases a risk of damaging tissue elements as a result of skin and subdermic tissue frostbite together with nerves damage.

On the other hand in the research [20] presenting treatment results in more than 3000 patients with varices of lower extremities including also advanced stage (VI level of CEAP disease advancement level with accompanying venous ulceration) one proved a high efficiency of cryostripping method using a probe at temperature of -80°C , resulting in lack of necessity of using narcosis, a strong analgesic action, minimum scale of skin injury, possibility of perforators' removing, minimum bleeding scale during a procedure (connected with closing of small blood vessels under influence of low temperature) and also a small number of recurrences – not exceeding 6% in comparison with 40% in the case of classic operations. As the author's experience proves this method is the only one enabling varices removal after previous obliteration treatment (injection with chemical substances). An adequate structure of a probe enables surgical entrance to all varices and venous plexus from one skin cut, what secures beneficial esthetic effect (no postoperative scars).

Bleeding in the digestive tract

Cryoablation was also used successfully in the treatment of patients with bleeding from the digestive tract in the course of disseminated vascular anomaly of the gastric and duodenum mucosa as well as radiation-induced inflammatory changes of stomach and rectum [56]. The best results (complete bleeding regression) in all patients who underwent such therapy were achieved in postradiation proctitis. The therapeutic effectiveness of cryoablation in case of disseminated vascular anomaly of arterio-venous origin was 86%. The lowest effectiveness of cryoablation was recorded in radiation-induced changes in the stomach and duodenum, what was probably related to the considerable dissemination of the neoplastic process in the mucosa of both organs.

Cardiac dysrhythmia

Cryoablation is also an important non-pharmacological method of the cardiac dysrhythmia treatment [64].

Using in the surgery treatment cryoprobes that freeze pathologic tissue to temperature of -60°C often allows to destroy pathologic stimulogenic focuses from the epicardium side without the necessity to apply extracorporeal circulation, contributed to increasing both effectiveness of the procedure treatment as well as its safety.

Cryoablation is particularly useful in the treatment of the pathologic changes located in the areas which are hard to reach (e.g. adjacent to the coronary vessels), where using the classic surgery methods is related to the risk of serious complications.

Laryngologic diseases

Cryoablation was successfully used as a supplementary treatment to bilateral tonsillectomy performed due to the chronic palatine tonsillitis [107]. In 59 random patients aged 8-40, immediately after tonsillectomy, a postoperative bed was frozen up to -20°C and -32°C for one minute. In patients, who underwent cryoablation, reduced pain by over 28,3% assessed through the analogue visual scale and shorter time needed to return to the usual diet and hospitalization time (by 4 days) was observed, comparing to the control group that did not undergo such a therapy.

Moreover, cryosurgery was used successfully in the treatment of chronic rhinitis, papillomas located in nose and larynx, leucoplakia and neoplastic lesions of the nasopharynx [57,87].



Fig. 11. ENT cryosurgical treatment.



Fig. 12. ENT cryoprobe set.



Fig. 13. Ophthalmology cryoprobe set.



Fig. 14. Gynecology – cervix, endocervix, endometrial cryoprobe set.

Ophthalmologic diseases

One of the main applications of cryosurgery in the ophthalmology is treatment of retinopathy. In research [28] cryoablation was applied in ten premature infants with proliferative retinopathy in the stage III. As a result of applied therapy, in eight premature infants regression of the proliferative changes was observed and only in two infants increase in the severity of disease to stage IV was noted, what proves that the method is highly effective in the treatment of retinopathy in premature infants. In another research [134] in which cryoablation was applied in the treatment of premature retinopathy in 70 infants (129 eyes), positive, early results of therapy were observed in 119 eyes. After one-year observation in over 57% of eyes distinct improvement – both structural and functional was recorded. In another research [24] in thirteen premature infants (23 eyes) with retinopathy, therapeutic effectiveness of cryoablation and laser photocoagulation were compared. Results achieved with the use of each method applied individually and jointly were similar, while the simultaneous application of both methods secured shortening of procedure time and decrease in the number of complications. Clinical usefulness of cryopexy was also shown in the treatment of diabetic retinopathy, however, in this case photocoagulation is significantly more effective [141].

Cryopexy proved high therapeutic effectiveness in the treatment of small focuses of retinoblastoma. In research [65] in twenty-four children cancer focuses located on the margin of the eye's fundus were frozen with the use of a probe with temperature of -65°C for ca. 20 seconds repeated every 6-8 weeks. In over 25% of patients destruction and cicatrization of the neoplastic lesions even after first cryopexy procedure was achieved. Only in two cases expected therapeutic effect wasn't achieved.

Good effects of cryoablation were also observed in a treatment of corneal squamous cell carcinoma [137]. In patients treated with the cryosurgery method four times lower frequency of recurring neoplastic lesions comparing with the classical procedure methods was observed. The method was characterized by a slender number of complications.

Including cryoablation in the complex treatment that consists of tumorectomy preceded by diathermocoagulation of blood vessels, and followed by freezing the margins and bottom of postresective defect to temperature of -60°C for 30 seconds produced positive esthetic and functional effect in the treatment of eyelid and conjunctival neoplasms [109, 110].

Moreover, high therapeutic effectiveness of cryoablation was observed in curing the chemical and thermal burn of cornea (accelerated regeneration of epithelium, lower number of concretions in cornea, improved sight ability and shorter hospitalization time) [106] as well as in the treatment of viral corneal ulceration [79] and haemorrhage to the anterior chamber and vitreous body of eye [22].

Therapeutic usefulness of cryocoagulation was also proved in the treatment of glaucoma. In research [98] in treatment of 128 eyes of patients with glaucoma cryocoagulation of the ciliary body (8 procedures lasting 55 seconds with the use of a probe with 2.5 mm diameter) was applied. Using a probe with temperature of -70°C in 54% cases lower by 21 mmHg intraocular pressure was achieved, that remained

at the same level after one year and 30 months of observation, requiring additional adjuvant therapy and in 39% of cases reoperation as well. While using a probe with temperature of -82°C normalization of the intraocular pressure within the similar time of observation in 89% of cases was achieved, while the adjunctive therapy was necessary in 66% of cases and reoperation only in 7.9% of patients. Side effects of cryocoagulation were mainly related to rise in the intraocular pressure exceeding 55 mmHg, that occurred in 10% of cases and retreated after the osmotic therapy, as well as occurring fibrin exudates in the eye's anterior chamber in 4% of patients treated with a probe of temperature of -70°C and 60% of patients treated with a probe of temperature of -82°C .

Gynecologic diseases

Cryoablation with the use of liquid nitrogen (nitrous oxide) was also applied in treatment of many diseases of female reproductive organs. In research [62], in which treatment with the use of cryosurgery was performed in 182 women, a complete regression of pathologic changes was observed in 86% of patients with chronic cervicitis, 89% of patients with Nabothian cyst (within 6-8 weeks) and 84.9% of patients with cervical erosions (within 6-9 weeks). In patients with cervical dysplasia a complete regression of pathologic lesions occurred, within 7-11 weeks after cryoablation. Within 2-5 year observation period the recurrences were observed only in 15% of patients with cervicitis and in one patient with cervical dysplasia.

Expanding indications for applying cryosurgery results from many advantages of the therapeutic method such as:

- possibility to destroy completely previously determined tissue volume both on the skin surface and inside of any organ,
- possibility to gain access to pathologic lesions in tissue thanks to the application of cryoprobes with small diameter,
- possibility to freeze many times the recurrences after previous surgery treatment, radiotherapy as well as cryotherapy,
- occurrence of only minimum tissue reaction around the necrosis focus after freezing,
- possibility to perform a surgery almost without bleeding, even in highly vascularized organs,
- possibility to perform the majority of surgeries ambulatory due to their low burdening character,
- good cosmetic effect.

Cryotherapy

Cryotherapy is understood as an impulse stimulating surface application of cryogenic temperature (below -100°C) for a short time of 120-180 seconds in order to trigger and use human organism physiological reaction to the cold, as well as support background therapy and facilitate kinesitherapy [33,35,153].

Procedures of whole-body cryotherapy and therapeutic exercises are altogether main components of so-called cryorehabilitation (Fig. 15).

Cryotherapy can be applied locally on the selected body area or on the whole body – in cryochambers and cryosaunas.

Local cryotherapy

Due to the duration of local cryotherapy procedures, they are divided into:

- short-term procedures (single application lasts from 30 seconds to few minutes),
- periodically interrupted procedures (applications last a quarter of an hour or so, they are repeated after a break lasting a quarter of an hour or so),
- long-term procedures (single application lasts 48÷72 hours).

In local cryotherapy devices which use liquid nitrogen, carbon dioxide or cooled air to produce low temperature are applied.

The examples of devices for local cryotherapy are shown in Figures 16 and 17.

Local cryotherapy with the use of liquid nitrogen

In such a cryotherapy tissues are cooled by nitrogen vapour. Liquid nitrogen with a boiling point at -195.8°C transforms into gas after being heated inside of the tank. The pressure difference between a tank and atmospheric pressure causes discharging nitrogen vapour from a tank to a nozzle-ended hose, gas temperature at nozzle outlet ranges from -196°C to -160°C . The device is equipped with the controller of gas injection intensity.

Local cryotherapy with the use of carbon dioxide

Using carbon dioxide instead of liquid nitrogen allows obtaining temperature ca. -78°C at nozzle outlet. Methodology of performing such a procedure and safety rules are similar to the previous case [135].

Methodology of local cryotherapy procedures [48,122,132]

The main objective of local cryotherapy applied as a preparation for intensive kinesiotherapy is maximum cooling of the area adjacent to the organ (e.g. whole joint along with neighbouring muscles) to the value of 2 to 4°C in reference to skin surface. In order to obtain such a significant cooling of tissue, many factors have to be taken into account such as: type of used equipment and cryogen, jet speed of used gas dependant on the vapour pressure obtained from cryoliquid, heater power, length of the cryogenic pipe and cryogen level in dewar. The level of cooling the treated body area depends on its surface and jet speed of cryogen vapour that may be controlled through relevant selection of the cryoprobe cross-section and a distance of a cryoprobe from the skin surface. Moreover, a very significant factor affecting the intensity of cooling is the speed of shifting a cryoprobe over the cooled surface.

Each time before local cryotherapy procedure patients should dry thoroughly clean skin with a towel in the area, in which cryotherapy is to be applied. The procedure should be performed in anatomical position of patient or in case when it is not possi-

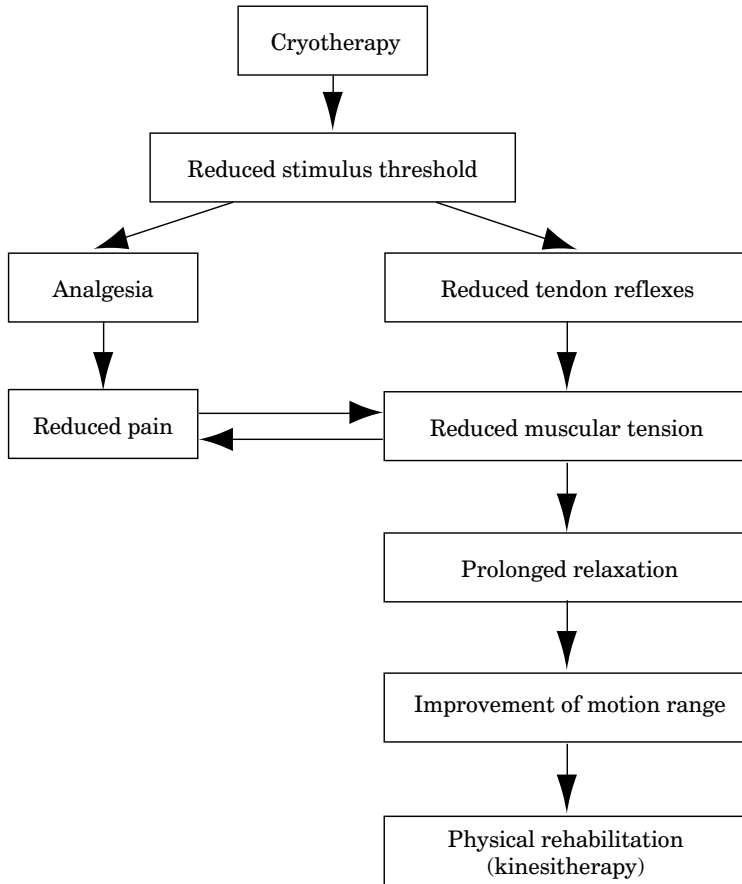


Fig. 15. Relationship between the application of cryotherapy and rehabilitation according to Knight [58] in own modification.



Fig.16. Cryostimulation device carbon dioxide system – Metrum Cryoflex.

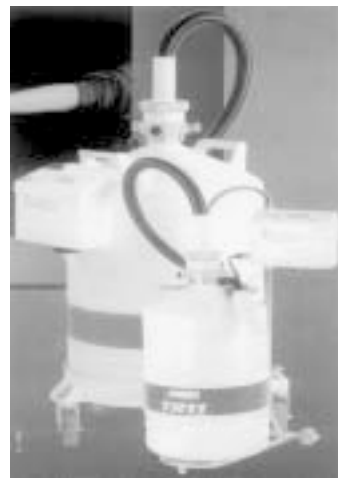


Fig.17. Device for local cryotherapy Kriopol.

ble, in lying-down or reclining position. The power of device heater should be set at maximum value, next slowly shifting of a cryoprobe nozzle turned towards skin should be made - from maximal distance of 15 cm in older types of device or 1-3 cm in modern ones that can control the application amount and speed of liquid nitrogen vapour. The distance and speed of shifting of a cryoprobe is controlled together with a patient on the basis of increasing feeling of subjective pain or burning in cooled skin surface.

Procedures are performed under visual control, with special attention to pigmentation, while skin pallor or lividity, occurring so-called cellulitis as well as intense feeling of pain or burning sensation, which do not disappear despite increasing of the distance between the nozzle and skin surface and speed of shifting of cryoprobe, indicate that a procedure should be interrupted. Therapist during performing procedure should make circular movements with a nozzle in order to avoid cooling the same area all the time, because it may lead to frostbite.

Time of procedure applied on one body area ranges from 30 seconds to 3 minutes, while in patients with fat deposition or large muscle mass may be extended to 5 minutes. When few areas are cooled at the same time, total time of procedure should not exceed 12 minutes [139]. Procedure of local cryotherapy can be performed at the same



Fig. 18. Metrum Cryoflex Cryostimulation device Nitrogen system – Metrum Cryoflex.



Fig. 19. Cryo S - Cryosurgery device Nitrous suboxide or Carbon dioxide System.



Fig. 20. Cryosurgery device Nitrous suboxide or Carbon dioxide System.

time on no more than five joints, while palm, foot and spine are counted as one group consisting of small joints [67].

It is crucial to cool down joint along with the dynamic groups of muscles responsible for a full range of movement in the joint with a particular attention paid to the trigger points and visible inflammatory focuses [49].

The cycle of local cryotherapy usually consists of 10-30 procedures performed once or twice a day. When it is performed twice a day, a break between them should be 4÷6 hours [95].

As local treatment with the cold is a component of cryorehabilitation, immediately after finishing the procedure of local cryotherapy, patients undergo 30÷60-minute lasting kinesitherapy, including individual exercises (at the beginning isometric muscle exercises and exercises against gravity of joints affected by the disease process and then active proper exercises and exercises with resistance of extensor and flexor muscles in these joints).

In Table 6 below are shown therapeutic parameters usually applied during the cycles of local cryotherapy procedures for particular diseases.

Table 6. Therapeutic parameters usually applied during local cryotherapy procedures in particular diseases.

<i>Disease</i>	<i>Gas temperature at patient's body surface</i>	<i>Time of procedure duration in minutes</i>	<i>Number of procedures in therapeutic cycle</i>
Ankylosing spondylitis	-130÷-160 °C	10-12*	10-20
Rheumatoid arthritis	-160÷-180 °C	2-3	10-20
Degenerative joint disease	-160÷-180 °C	3	10-20
Fibromialgia	-130÷-150 °C	10*	10-20
Post-traumatic disorders of locomotor system	-160÷-180 °C	3	20
Central nervous system disorders with increased spasticity	-160÷-180 °C	3-8*	30
Discopathies	-130÷-160 °C	3	10-20
Peripheral nervous system disorders e.g. trigeminal neuralgia	-130 °C	2-3	10

*Total time of procedure duration in case of simultaneous cooling of several (maximally 5) groups of joints or muscles affected by the pathologic process.

In local treatment with cold other methods that are not classified as the cryotherapy within a contemporary sense of the notion, are also used. This methods are: [135,163]:

Compresses with plastic bags filled with ice cubes

Plastic bags keep temperature of ca. 0°C even for an hour. Single procedure lasts 1÷60 minutes until ice melts. Expected positive results are observed even after 20 minutes.

Compresses with bags filled with cooled silicone gel

After cooling in a freezer, bags are put on selected joint or muscle. Manufacturer offers various sizes of bags with various heat capacity, what allows to match a bag to type and size of treated organ. It is recommended to put a piece of gauze or paper towel under the bag. Optimum temperature for such a procedure ranges from -5°C to 0°C. Single procedure lasts 20÷30 minutes. Due to greater likelihood of occurring frostbite, it is recommended to keep special caution during such a procedure.

Massage with an ice cube

The procedure, applied mainly in sports medicine to cure the overloading syndrome of the osteo-articular system or painful muscular tension, consists of massaging tendons, muscles or ligaments with an ice cube - it is done by circular movements. Recommended time of a single procedure is few (3÷5) minutes with 10-second break between succeeding procedures [36].

Ice slush

The procedure applied mainly in patients with diseases of the nervous system in order to reduce the excessive resting muscular activity, consists of multiple submersions of sick parts of the body in a container with partly melted snow. Single submersion usually lasts 3÷5 seconds [29].

Compresses with ice towels

Procedure, also applied to reduce excessive muscular tension, consists of putting directly on skin a well wrung wet cotton towel previously cooled in a freezer. Single procedure lasts 5÷10 minutes [29].

Cooling aerosols

Procedure consists of sprinkling skin surface with gaseous substances which in normal atmospheric conditions vapour heavily and take up heat from the skin and lying deeper tissues. Single application lasts 5 seconds, and when few areas are cooled at the same time total application time shouldn't exceed 30 seconds. Applicator should be kept in the distance of 15÷25 cm from the surface of uninjured skin.

Disposable cooling compresses

Procedure consists of cooling down the skin surface using bags with substances which trigger endothermic reaction when mixed. Such a reaction is to be triggered e.g. by hitting a bag with hand. Procedure usually lasts about 30 minutes.

Whole-body cryotherapy

Whole-body cryotherapy procedures are based on subjecting whole body of a patient to cryogenic temperatures action. They are performed in cryochambers.

Cryochamber is a large, closed, stationary and computerized device, using liquid nitrogen, synthetic air or triple cascading system for cooling air in a chamber. It enables to stay a few patients at the same time in a proper chamber at temperature below -110°C . Use of specific insulating materials and unique plastics ensures economical use of a chamber through fast cooling of the air inside the chamber [6].

Most of modern cryochambers uses synthetic air instead of nitrogen. Synthetic air-mixture of nitrogen and oxygen has temperature of -193°C and is easier in exploitation, and its use reduces costs of cryochamber construction up to 40% (most of cryochambers manufactured and used in Poland and all over the world are supplied with liquid synthetic air).

Cryochambers are usually covered with wood and have swing doors that a patient may easily open at any time to interrupt a procedure when a temporary indisposition occurs.

According to the authors of the research [3] the optimum effectiveness of the whole-body cryotherapy procedures may be achieved through using temperature ranging from -150°C to -130°C , what allows to reduce the integument temperature to ca. $-2,5^{\circ}\text{C}$, ensuring the highest effectiveness of cryostimulation at safeguarding the hypothermic safety and patient's high comfort. The calculations made in the quoted research show that increasing of temperature inside the chamber from -130°C to -120°C reduces the effectiveness of cryostimulation almost twice and at temperature -110°C the therapeutic effect is ten times lower.



Fig. 21. Picture of a standard cryochamber with cold retention – cryosauna.

Cryochamber construction and principle of operation („Wrocław type”)

Figures 22 and 23 show the construction of a cryochamber based on an example of low-temperature cryochamber of „Wrocław type” designed by Zbigniew Raczkowski, M.Sc. Eng. of the Low Temperatures and Structural Researches Institute of the Polish Academy of Sciences in Wrocław.

The main technical data of a cryochamber is shown below.

- Size: length– 4500 mm, width – 2500 mm, height – 2600 mm
- Number of doors – 3
- Temperature range: -110°C to -160°C
- Number of people in a chamber at the same time – 5
- Time of preliminary regeneration of cryopurifiers – 6 minutes
- Time of cooling a chamber from the ambient temperature to procedure temperature – 30 minutes
- Time of the working system regeneration – 15 minutes
- Consumption of liquid nitrogen to cool a chamber from ambient temperature to procedure temperature – 150 dm^3
- Consumption of liquid nitrogen during procedure – 100 dm^3
- Power consumption – 9 kW

Cryochamber consists of a pre-chamber with temperature of -60°C , where patients adapt to low temperature and a proper chamber with temperature below -120°C .

Crucial role in the cryochamber operation plays preparation of purified air in proper temperature. In „Wrocław” cryochamber, the system of preparing air (patent no. 157168) is based on cooling air to temperature -80°C to -160°C in one heat exchanger. Air compressed by a compressor to 1mPa is dried in adsorber, then conveyed to blow through cryopurifiers. Having blown through the system and having closed the valves conveying air, valves in the tank with liquid nitrogen are opened facilitating air flow from the tank to cool first cryopurifier to which is conveyed air compressed by a compressor. Air is purified in the adsorbent drier and reducer. When the first cryopurifier is cooled down, the second cryopurifier is cooled down as well. When temperature of air exhausted by the first cryopurifier reaches -100°C , it closes automatically and conveys air to the next cryopurifier. Thus, purified and cooled air, is conveyed to a cryochamber. At the same time the first cryopurifier is regenerated and cooled down once more. When the system finishes work it is regenerated at opened valves and heaters which are turned on. Such a way of two-stage air purification allows to eliminate completely water vapour as well as any organic, non-organic and mechanical contamination on sorbents, what allows to reach air dew-point at -75°C . Applying a double system of cryopurifiers ensures keeping stable temperature during procedure and increases its safety.

Cryochamber operation is completely automatic. After setting temperature of procedure and its duration on a computer keyboard and starting a controller, computer confirms device readiness to work. After patients enter a pre-chamber, then a proper chamber, doors are closed, a button, which starts to measure time of stay in a chamber, is pressed. During procedure any possible irregularities of the chamber operation are shown by a controller and notices are displayed on the computer screen. In case of



Fig. 22. Picture of a low-temperature cryochamber „Wroclaw type“.

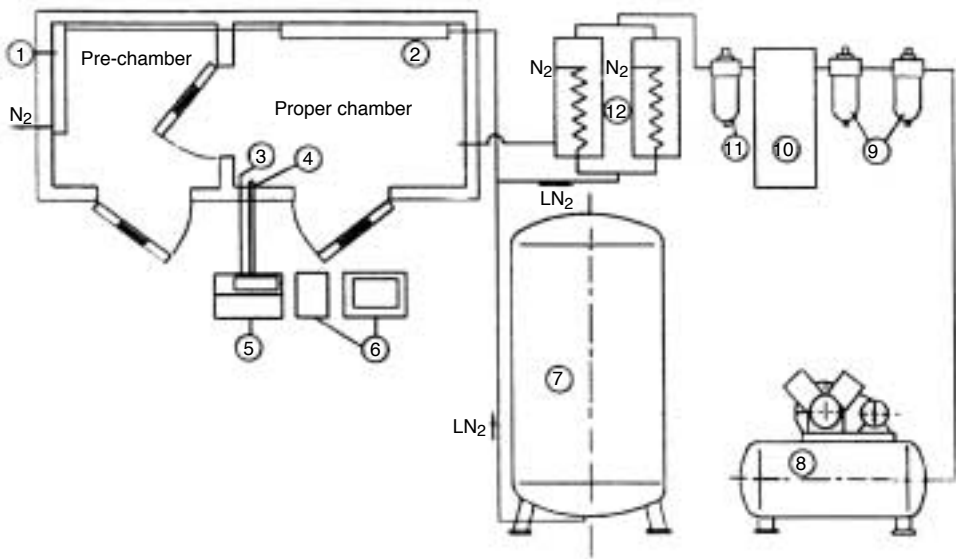


Fig.23. Schematic diagram of a cryochamber construction. 1 – pre-chamber exchanger, 2 – chamber exchanger, 3 – temperature sensor, 4 – pipe conveying air to oxygen meter, 5 – controller, 6 –computer, 7 – tank for liquid nitrogen, 8 – non-oil compressor, 9 – preliminary filters, 10 – drier, 11 – final filter, 12 – cryopurifiers.

device failure direct doors from a chamber may be used for immediate evacuation. When all the procedures scheduled for a certain day are completed, before turning a chamber off, final regeneration is always carried out.

Cryochambers supplied with liquid synthetic air (-193°C)

Cryochambers supplied with liquid synthetic air have similar construction to „Wrocław type” chambers. Its main advantage is lack of expensive, energy consuming, loud and requiring special room technical part. Direct injection of gas into procedure chamber allows quicker gaining of procedure temperature, what is more it also reduces consumption of freezing medium, failure frequency, exploitation and service cost. These cryochambers are also cheaper in purchase. They are fully automatized, and may be operated by only one person. What is unique, is a system of disinfection after procedure – ozone generator releases doses of gas destroying bacteria and viruses. It may be supplied by companies producing medical and technical gases in ordinary distribution.

Synthetic air supplied cryochambers are manufactured in two or more patients versions, with or without vestibule. Its construction may be classical one or with cooling retention. The first patented cryochamber with cooling retention system was designed in Poland by mgr inż. Wiesław Brojek from Metrum Cryoflex. Nowadays there are fifty synthetic air supplied cryochambers operating in the world (Poland, Czech Republic, United Kingdom, Ireland and Slovakia).



Fig 24. Arctica – Whole Body Cryochamber with cooling retention – LAIR system.



Fig. 25. Arctica Classic – Classic version with prechamber – LAIR system.

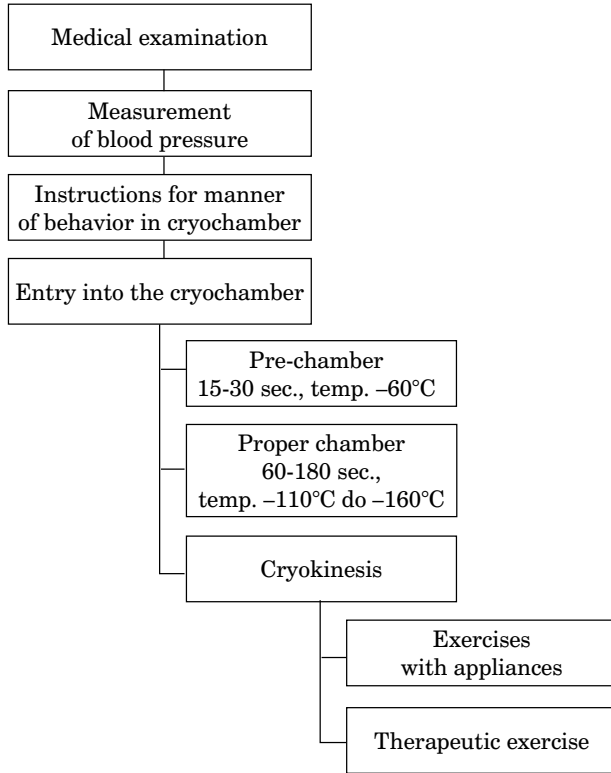


Fig. 26. Schematic diagram of conduct during preparing for and performing procedure of whole-body cryotherapy in a cryochamber.



Fig. 27. Standard wear and manner of protection during cryotherapy procedure for women.



Fig. 28. Standard wear and manner of protection during cryotherapy procedure for men.

Methodology of whole-body cryotherapy procedures [117,122,132]

Methodology of whole-body cryotherapy procedures performance in a cryochamber is shown in schematic diagram in Fig. 26.

Patients for whole-body cryotherapy procedures have to be examined by a doctor. Doctor's preliminary qualification should be based on collected medical history, physical examination including: blood pressure and pulse rate taking, urologic evaluation, as well as electrocardiographic investigation. On the basis of obtained data possible contraindications disqualifying patient from such a form of treatment are evaluated. For each patient qualified for whole-body cryotherapy therapeutic parameters and individual programme of kinesitherapy are determined, and also treatment record is created with noted down blood pressure taken before and after each procedure, number and duration of procedures, changes in therapeutic parameters of cryotherapy or course of kinesitherapy performed afterwards, as well as subjective feelings of patients and possible complications and side effects of procedure.

Patients admitted for the whole-body cryotherapy are instructed how to behave during a procedure. Special attention is paid to the way of breathing in the proper chamber during the procedure. Inhaling should be two times shorter than exhaling due to decompression of cooled air in lungs. Non-compliance with the recommendation may lead to serious breathing depression. Moreover, it is forbidden to touch other patients or rub own skin.

Cryogenic temperatures (-110°C to -160°C) applied during a procedure in a proper chamber require protecting parts of the body mostly exposed to low temperatures against injury. Hands are protected by gloves, while shanks and feet – by woolen knee-length socks. Moreover, feet are protected by wooden clogs. Then auricles are protected by a cap or headband. During a procedure women wear swimming costumes and men shorts. Such dress allows for contact of bigger body area with cold air. Mouths are protected by gauze-lined surgical masks. Standard wear for patients of both sexes worn during the whole-body cryotherapy procedure is shown in Figures 27 and 28.

At the same time chamber can be used by seven patients. Before each procedure control blood pressure is measured and written down in the treatment minute. Immediately before entering a cryochamber patients dry their skin with towel in order to remove sweat, as sweat drops turn into ice crystals in a chamber. Next, patient accompanied by a therapist dressed up in the cold-protecting wear enter a preliminary chamber called pre-chamber with temperature of -60°C . Adaptation time to low temperature is up to 30 seconds. Here, a therapist once more instructs how to behave during a procedure. Then, through linking doors patients enter one by one without any assistance a proper chamber where temperature ranges from -110°C to -160°C . Only patients with walking difficulties enter a proper chamber with staff assistance.

Temperature and time of staying in chamber depend on patient's individual reaction to the cold and are individually determined by a doctor supervising cryotherapy. Duration of a single procedure ranges from 60 to 180 seconds and a standard therapeutic cycle most often includes ten procedures.

Table 7. Therapeutic parameters usually applied during whole-body cryotherapy procedures in particular diseases.

Disease	Gas temperature at patient's body surface	Time of procedure duration in minutes	Number of procedures in therapeutic cycle
Ankylosing spondylitis	-120÷-130°C	2-3	10-20
Rheumatoid arthritis	-120÷-130°C	2-3	10-20
Degenerative joint disease	-120÷-130°C	2-3	10-20
Fibromyalgia	-120÷-150°C	2-3	20
Post-traumatic disorders of locomotor system, osteoporosis	-110÷-130°C	2-3	20
Diskopathies	-120÷-130°C	2-3	20
Central nervous system disorders with increased spasticity	-110 ÷-130°C	2	20
Multiple sclerosis	-110 ÷-150°C	2-3	20
Neurosis and depression	-110÷-130°C	2-3	10
Vital restitution, overtraining prevention in active sportsmen	-110÷-150°C	3	10

During a procedure patients walk slowly in circle, they don't touch any devices or walls in a chamber and breathe shallowly through their noses. During the entire procedure, patients are in eye contact, through a spyhole, with a doctor and the staff who may react when unwanted reactions occur.

When a procedure is finished, patients leave a proper chamber and go back to a pre-chamber, then after doors are closed, they leave a pre-chamber one by one.

Immediately after leaving a cryochamber, taking off gloves, caps and clogs and changing wear and shoes (to tracksuit and trainers), patients undergo kinesitherapy lasting 30-60 minutes that include individual gymnastics (active and passive exercises as well as active-passive exercises, at the beginning they are isometric exercises and exercises against gravity and in the further stages of rehabilitation – supportive exercises including proper active exercises and active exercises with resistance) and collective gymnastics, special attention was paid to joints and certain groups of muscles affected by the disease process as well as exercises with the use of equipment according to individually adjusted programme, which take into account patient's age, diagnosis, stage of disease and present efficiency of the locomotor system and physical fitness.

After finishing a cycle of whole-body cryotherapy procedures it is necessary to do once more medical examination with evaluation of obtained clinical data and consideration of possible continuation of cryotherapy [4,33,153].

In Table 7 below are shown therapeutic parameters usually applied during the cycle of whole-body cryotherapy procedures for particular diseases.

Therapeutic applications

Local and whole-body cryotherapy is currently applied in the treatment of many diseases such as:

- diseases of the locomotor system of various etiology,
 - diseases of the central and peripheral nervous system,
 - diseases of the mental origin – neurosis and depression syndrome,
 - diseases of the autoimmunological origin,
- and in sports medicine and widely understood spa and wellness.

Diseases of locomotor system

The largest group of patients qualified for cryotherapy procedures are patients with diseases of locomotor system of various etiopathogenesis and symptomatology.

The main groups of locomotor system diseases with substantiated beneficial influence of the treatment with cold are the following diseases [1,4,33,41,42,47, 53,67,69,88,153,159,160,161]:

- diseases of the locomotor system of autoimmunological origin: e.g. rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and Reiter's syndrome,
- diseases of soft tissues with accompanying dysfunction of the locomotor system of autoimmunological origin: e.g. *myositis*, *fibromyositis* and collagenosis,
- diseases of the locomotor system related to non-specific inflammatory process: periarticular tendinitis, periarticular inflammation of joint capsules and muscles,
- spondyloarthrosis and peripheral arthrosis along with secondary inflammatory reaction,
- diseases of the locomotor system of metabolic origin: e.g. gout,
- diseases related to disorder of the calcium and phosphate metabolism with loss of the osseous mass: osteoporosis of various etiopathogenesis,
- disease of the locomotor system caused by trauma and overloading: traumatic Sudeck's atrophy (Reflex Sympathetic Dystrophy Syndrome)
- diseases of intervertebral disk,
- diseases of the locomotor system caused by injury of the central and/or peripheral nervous system: e.g. spastic paresis,
- diseases of the locomotor system of fibromyalgia type.

Opportunities and practical applications of cryotherapy (both local and whole-body in certain diseases of the locomotor system are described in details below.

Ankylosing spondylitis

In our own researches [123,128,158] behaviour of selected markers of the inflammatory status was evaluated on the group of patients with ankylosing spondylitis (AS). Patients with diagnosed ankylosing spondylitis were sent by the Rheumatologic Out-patient Clinic to the Department and Clinic of Internal Diseases, Angiology and Physical Medicine of the Medical University of Silesia in Bytom in order to qualify for whole-body cryotherapy procedures. On the basis of their medical history, physical

examination and additional tests seven men were qualified for the whole-body cryotherapy procedures. Each of the examined patients was instructed about the examination character and its objective, as well as expressed a written consent to it. Patients' average age was 45.2 ± 5.4 years and average duration time of disease since its diagnosis was 17.3 ± 6.0 years.

On a day preceding the beginning of whole-body cryotherapy cycle, in patients' blood concentrations of the following biochemical parameters that characterize the activity of the immunological system were determined:

- C-reactive protein (CRP) determined by means of the turbidimetric method,
- seromuroid determined by means of the colorimetric method modified by Winzler,
- fibrinogen determined by means of the turbidity method,
- immunological panel (immunoglobulins IgG, IgA, IgM, complement components C3 and C4) determined by means of the turbidimetric method,
- proteinogram determined by means of the biuret colorimetric method.

Next, the patients were subjected to a cycle of daily, whole-body cryotherapy procedures at temperature of -130°C lasting two minutes, for ten consecutive days with two-day break after first five procedures. Immediately after each cryotherapy procedure the patients received 60-minute lasting kinesitherapy conducted according to the individual rehabilitation scheme. Whole-body cryotherapy procedures and kinesitherapy were performed at the Silesia Rehabilitation and Physical Medicine Centre in Ruda Śląska.

In all the patients who received kinesitherapy, a significant clinical improvement was observed, it was showed in following symptoms: reduced pain in the vertebral joints, what allowed to introduce a suitable kinesitherapy programme, improvement in patients general feeling and mood, as well as improvement in mobility of spine and chest with increase in breathing capacity indicated in performed measurements.

At the beginning of cryotherapy cycle the patients were recommended to continue pharmacologic treatment, that they have received so far, however, during the whole-body cryotherapy procedures cycle significantly lower demand for analgesic and anti-inflammatory drugs was observed.

Whole-body cryotherapy procedures were well tolerated by the patients, no significant complications nor were side effects observed in any of them after applied therapy.

One day after completing full cryotherapy cycle, biochemical laboratory tests according to the above-mentioned scheme were performed on the group of patients.

Obtained values of immunological parameters are shown in Tables 8, 9 and 10.

Table 8. Concentration of selected markers of the inflammatory status (mean value \pm standard deviation) in AS patients' serum before and after a cycle of whole-body cryotherapy procedures.

<i>Parameter</i>	<i>Before a cycle of cryotherapy</i>	<i>After a cycle of significance</i>	<i>Statistical cryotherapy</i>
C-reactive protein (CRP) [ng/ml]	7.13 \pm 1.10	4.90 \pm 0.77	p = 0.0003
Seromuroid [g/l]	1.07 \pm 0.12	0.94 \pm 0.17	p = 0.0137
Fibrinogen [g/l]	4.03 \pm 0.79	3.91 \pm 0.59	(IS)

IS – statistically insignificant difference.

Table 9. Concentration of selected complement components and immunoglobulins (mean value \pm standard deviation) in AS patients' serum before and after a cycle of whole-body cryotherapy procedures.

<i>Parameter</i>	<i>Before a cycle of cryotherapy</i>	<i>After a cycle of significance</i>	<i>Statistical cryotherapy</i>
Complement Component C3 [mg/dl]	108.15 \pm 12.42	104.23 \pm 9.44	(IS)
Complement Component C4 [mg/dl]	27.10 \pm 5.76	26.05 \pm 5.36	(IS)
IgA [mg/dl]	291.00 \pm 38.29	253.50 \pm 32.29	p = 0.0006
IgG [mg/dl]	975.66 \pm 139.54	880.83 \pm 129.26	p = 0.0010
IgM [mg/dl]	103.30 \pm 69.59	96.25 \pm 50.32	(IS)

IS – statistically insignificant difference.

Table 10. Concentration of total protein and share of particular protein fractions (mean value \pm standard deviation) in AS patients' serum before and after a cycle of whole-body cryotherapy.

<i>Parameter</i>	<i>Before a cycle of cryotherapy</i>	<i>After a cycle of cryotherapy</i>	<i>Statistical significance</i>
Protein concentration [g/l]	70.50 \pm 2.16	68.02 \pm 4.37	(IS)
Albumin [%]	57.96 \pm 4.55	52.30 \pm 8.48	(IS)
α_1 globulin [%]	5.44 \pm 0.81	5.36 \pm 1.07	(IS)
α_2 globulin [%]	11.26 \pm 2.33	12.38 \pm 1.62	(IS)
β_1 globulin [%]	6.78 \pm 1.35	8.26 \pm 1.65	p = 0.0009
β_2 globulin [%]	5.40 \pm 1.75	6.16 \pm 2.29	(IS)
γ globulins [%]	12.76 \pm 2.68	15.14 \pm 3.38	(IS)

IS – statistically insignificant difference.

Conducted tests showed statistically significant decrease in C-reactive protein (CRP), seromuroid and immunoglobulins IgA and IgG serum concentrations, as well as statistically significant increase in the share of β_1 globulin in the proteinogram. Observed decrease in patient's serum concentrations of the acute phase proteins and im-

munoglobulins may confirm indirectly the anti-inflammatory action of whole-body cryotherapy in the patients with ankylosing spondylitis.

In other researches conducted in our centre [130,131,133] on bigger clinical material of 16 AS men in third and fourth stage of disease (mean age 47.4 years) an impact of whole-body therapy followed by kinesitherapy on parameters of spine mobility and patients' subjective evaluation of the treatment effectiveness was analysed. Gained results were compared with the results of 16-men group with AS in similar age and similar stages of disease, who received only kinesitherapy.

The procedures cycle included, depending on tested group, ten (applied every week for 5 days with weekend break) two-minute lasting stay in a cryochamber at temperature -120°C and/or 60-minute lasting set of therapeutic exercises.

On a day preceding the beginning of cycle of whole-body cryotherapy and/or kinesitherapy, and once more one day after the cycle completion, every patient received routine that measured: flexion of the thoracic spine measured by the Ott's test, flexion of the lumbar spine measured by Schober's test, finger to floor distance, chest expansion, rotation of cervical spine, chin to chest distance, lateral flexion of lumbar spine and occiput to wall distance.

Moreover, after the completion of the therapy cycle, patients filled in anonymously a questionnaire evaluating subjectively the treatment effectiveness of whole-body cryotherapy and kinesitherapy.

The questionnaire included questions on date of falling ill, possible pharmacological therapy applied prior to the trial, determination of the treatment effectiveness (options: significant improvement, improvement, lack of improvement, deterioration). In two last sections, the patients determined a type of improvement or deterioration and possible negative subjective feelings experienced during the therapy.

After the treatment in both groups of patients, statistically significant improvement in the values of all examined parameters of spine mobility was noted.

In the group of patients who received kinesitherapy only, the range of improvement of particular spine mobility parameters was similar and amounted to 6.1-25.9% of the output value (Table 11).

Whereas in the group of patients who received whole-body cryotherapy, the percentage change in the values of spine mobility parameters was significantly higher (by 2-7 times) than relevant values in the group of patients who received only kinesitherapy (Table 11). It was mostly related to the thoracic and lumbar spine mobility parameters such as: flexion of the thoracic spine measured by the Ott's test, chest expansion, flexion of the lumbar spine measured by Schober's test and lateral flexion of lumbar spine. Changes in these parameters in comparison with the output values in the group were 75.9%, 46.6%, 62.5% and 28.9% respectively.

In the group of AS patients who received whole-body cryotherapy along with kinesitherapy a significant subjective improvement was experienced by 56.25% and improvement by 37.5% of patients. Lack of improvement was experienced by only 6.25% of patients. Whereas in the group of AS patients who received kinesitherapy only a significant subjective improvement was experienced by 25% and improvement

by 68.75% of patients. Lack of improvement in this group was experienced by 6.25% of patients.

In patients who received whole-body cryotherapy followed by kinesitherapy the most visible in statistic significant improvement was related mainly to decrease in the intensity and frequency of occurring of pain, as well as relaxation and improvement in the quality of falling asleep and sleep. Moreover, a significant clinical improvement

Table 11. Values of spine mobility parameters in AS patients before and after the end of whole-body cryotherapy procedures with subsequent kinesitherapy or kinesitherapy solely.

<i>Parameter</i>	<i>Type of therapy</i>	<i>Before a therapy</i>	<i>After a therapy</i>	<i>Statistical significance</i>
Ott's test	Cryotherapy with kinesitherapy	0.91±0.61	1.59±0.61	p<0.001
	Kinesitherapy	1.36±0.88	1.51±0.97	p=0.003
Schober's test	Cryotherapy with kinesitherapy	1.50±1.13	2.44±1.24	p<0.001
	Kinesitherapy	1.43±0.95	1.61±1.04	p=0.002
Finger-floor distance	Cryotherapy with kinesitherapy	30.75±18.13	26.13±16.17	p=0.003
	Kinesitherapy	29.13±7.02	26.75±5.43	p=0.003
Chest expansion	Cryotherapy with kinesitherapy	1.81±0.95	2.66±1.01	p<0.001
	Kinesitherapy	2.22±1.21	2.79±1.23	p=0.001
Left lumbar lateral flexion	Cryotherapy with kinesitherapy	7.34±4.18	9.56±4.58	p=0.001
	Kinesitherapy	6.90±2.44	7.36±2.54	p=0.008
Right lumbar lateral flexion	Cryotherapy with kinesitherapy	7.94±4.65	10.13±4.75	p<0.001
	Kinesitherapy	6.33±2.87	6.83±2.80	p=0.003
Left cervical rotation	Cryotherapy with kinesitherapy	38.94±16.97	44.56±14.28	p=0.002
	Kinesitherapy	24.63±12.67	29.25±11.95	p<0.001
Right cervical rotation	Cryotherapy with kinesitherapy	39.06±15.16	44.25±13.47	p=0.002
	Kinesitherapy	25.75±13.63	29.06±12.65	p<0.001
Chin-chest distance	Cryotherapy with kinesitherapy	3.38±3.04	2.81±2.52	p=0.012
	Kinesitherapy	5.64±1.69	5.07±1.48	p=0.008
Occiput-wall distance	Cryotherapy with kinesitherapy	7.09±5.56	6.13±5.42	p<0.001
	Kinesitherapy	8.90±8.06	8.36±7.91	p=0.005

was observed in relation to reduced size of periarticular edemas and reduced time of morning stiffness, as well as improved physical efficiency (Fig. 29).

Therapy effects related to the above mentioned symptoms were obviously better in comparison with the group of patients who received kinesiotherapy only.

No patient who received whole-body cryotherapy experienced negative feelings during the procedures or any significant complications or side effects of applied therapy.

In other research [52] 52 patients with ankylosing spondylitis local cryotherapy were subjected to the complex treatment that consisted of alternate (combined) pharmacotherapy with non-steroidal anti-inflammatory drugs and movement rehabilitation. Cryostimulation was applied twice a day as blast of cooling gas at temperature ranging from -130°C to -160°C to the area of entire spine along with sacroiliac joints and peripheral joints affected by the inflammatory process. The result of applying local cryotherapy was strong analgesic effect that made movement rehabilitation much easier, however, significant anti-inflammatory action was not confirmed.

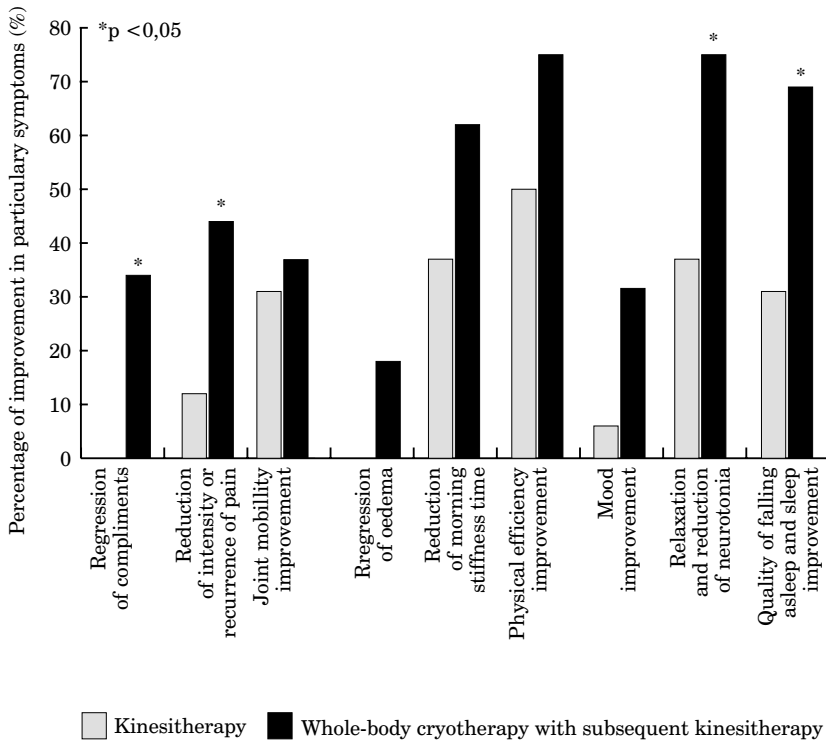


Fig. 29. Comparison of subjective estimation of clinical improvement using percentage regression of particular clinical symptoms in patients with ankylosing spondylitis exposed to whole-body cryotherapy procedures or kinesiotherapy procedures solely.

Rheumatoid arthritis

Beneficial effect of cryotherapy (both local and whole-body one), in the treatment of rheumatoid arthritis is well known and applied in medical practice for a long time. Positive therapeutic effects of cryotherapy are noticed in various forms and stages of disease.

In rheumatoid arthritis, similarly to other inflammatory diseases of the locomotor system and systemic diseases of connective tissue, selection of the cryostimulation manner depends on intensity of the disease changes and general condition of a patient. Local cryostimulation is mainly applied in the first stage of disease, when maximum 2-4 joints are affected by the pathologic process, in severe and acute conditions, when a patient is immobilized during hospitalization and in elderly patients with ravaged body and with some diseases of the cardiovascular system for whom a stay in a cryochamber would endanger their health, as well as in home rehabilitation. In other situations the whole-body cryotherapy is preferred [49].

In a research [83] usefulness of whole-body cryotherapy in treatment of pain related to rheumatic diseases was evaluated, in the group of 120 patients, most of them suffered from rheumatoid arthritis and from primary and secondary fibromyalgia, chronic lumbalgia, spondyloarthritis and osteoporosis. Patients were subjected to the cold in a cryochamber at temperature of -105°C , each procedure lasted 2.5 minutes. After each procedure strong analgesic effect which lasted for ca. 90 minutes was observed. Although intensification of the analgesic action did not rise during the cryotherapy cycle and long-term analgesic effect was relatively weakly, particularly important for the final rehabilitation outcomes was the fact that strong, however transient, analgesic action was helpful in applying more intensive scheme of kinesitherapy. Researches also proved that the procedure is completely safe and is well tolerated. Among the patients were not observed serious side effects of cryotherapy, and in patients' opinion procedures were an important component of the rehabilitation programme.

While research [78] analyzed the impact of whole-body therapy on the pain intensity, disease activity, functional condition of the locomotor organ and concentration of proinflammatory cytokines (the tumour necrosis factor α – TNF- α , interleukin IL-1) in patients with rheumatic diseases (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis) in the active phase. Patients were subjected to 9 procedures of whole-body cryotherapy within 5 days (first procedure lasted for 90 seconds, next were gradually extended up to 2.5 minutes). In patients statistically significant reduction of pain, reduced activity of disease and statistically significant decrease in the concentration of proinflammatory cytokines were observed. Side effects of whole-body cryotherapy (headache and cold sensation) were observed only in 2 patients.

In a randomized research conducted with the method of double blind test [37] 60 patients with seropositive rheumatoid arthritis in the active stage of disease were receiving for 7 days (2-3 times a day) alternatively whole-body cryotherapy procedures at temperature -110°C or -60°C and local cryotherapy with blast of cold air at temperature of -30°C followed by conventional kinesitherapy. In all groups decreased intensity of joint pain was observed and the most noticeable analgesic effect was observed in the patients, who rece-

ived whole-body cryotherapy at temperature of -110°C . Moreover, in all groups of patients a slight reduction of the activity of disease assessed by means of DAS scale was observed and differences between the groups were not statistically significant.

In a research [88] in 36 patients (32 women and 4 men aged 23 to 72) with active stage of rheumatoid arthritis cryotherapy was applied. Patients with renal, heart and hepatic failure, with organic diseases of the central nervous system and patients with senso-motor disorders and trophic changes in skin, as well as with extra-articular inflammatory focuses were excluded from the research. Patients received local cryotherapy applied to the most painful and tumid joints. Procedures were performed with Kriopol device, which uses a jet of liquid nitrogen at temperature of -160°C pointed to the area of inflammatory joint for the time ranging from 30 seconds to maximum 3 minutes. All patients received also kinesitherapy immediately after completion of the cryotherapy procedure. In the research changes in the intensity of swelling through measurement of joint circumference, flexion of joints under treatment and strength of handgrip with the use of the sphygmomanometer were analyzed. Subjective pain sensation at passive movements and compression of examined joint as well as morning stiffness in joints affected by the disease were also assessed. After the completion of a cycle of ten cryotherapy procedures, distinct shortening of morning stiffness duration time, decrease in joint circumference, increased strength of handgrip (for right hand by 31.32% on average, for left hand by 31.50% on average) were observed in patients exposed to cryotherapy. After the end of cryotherapy cycle, a significant increase in mobility of joints affected by inflammation was found. Moreover a beneficial analgesic effect of cryotherapy was observed [4].

Also the research [68] proved the improvement in strength of handgrip in patients with rheumatoid arthritis, even after first procedure of local cryotherapy, as well as after two-week lasting treatment.

In another research [9] in 26 patients with rheumatoid arthritis aged 23 to 72 electromyography (EMG) of muscle strength was conducted after a single procedure of local cryotherapy applied with the use of blast of liquid nitrogen at temperature of -180°C at nozzle mouth for 60 seconds to wrist joint and forearm affected by the disease. Evaluation of the muscle strength was made by means of determination of mean density of electromyographic record obtained during maximum exercise of elbow flexor muscle in left wrist. Electromyography which was made one hour after the local cryotherapy procedure showed increased muscle strength expressed in increased density and/or increased amplitude of exercise record in 50% of patients with rheumatoid arthritis, while a similar increase was not recorded in the majority (60%) of healthy people of the control group. The obtained result was accompanied by a noticeable improvement of patients' locomotor activity, reduced stiffness of joints and noticeable decrease of pain intensity.

In a research [69] impact of local cryotherapy on the strength of flexor and extensor muscles of knee joint was evaluated in patients with rheumatoid arthritis. The research was conducted on 134 knee joints in 68 patients with rheumatoid arthritis in stage 2 and 3 according to Steinbrocker. Cryotherapy was applied in 48 patients, ano-

ther 20 patients (control group) were treated with therapulse. Local cryotherapy procedures were applied twice a day in 3-hour intervals and lasted from 60 to 180 minutes. Each cryotherapy and therapulse procedure was followed by kinesitherapy. Two-week cryotherapy resulted in higher increase of the active strength of muscles comparing with the therapulse treatment. Continuation of cryotherapy for next two weeks resulted in further increase in the muscle strength while passive strength of flexor and extensor muscles of knee joint decreased after two-week lasting therapy in both groups, however there were no statistically significant differences between both groups. Continuation of cryotherapy for the next two weeks resulted in the further decrease in the passive strength of muscles.

In a research [55] effects of applying local cryotherapy procedures and treatment with the peat paste in patients with various stages of rheumatoid arthritis were compared. The research was conducted on 78 selected at random patients, divided into two groups. In one group the peat paste was used, in another one – local cryotherapy. The final analysis included 73 patients, as due to the occurrence of disease aggravation (increase in ESR) two patients were excluded from the first group and three patients from another one. The majority of patients in both groups were women and average age of patients was 53.0 ± 11.6 years in the first group and 55.4 ± 9.8 years in the second one. In both groups patients received eighteen procedures in total, five procedures a week with a weekend break. In the first group, procedures were based on application of the peat paste compresses at temperature of 38°C on the disease-affected joints put every day for 30 minutes. In the second group, liquid nitrogen vapour at temperature -160°C generated by Kriopol device was applied on the area of joint affected by disease for $2 \div 3$ minutes every day. Regardless which physical therapy was used, both groups of patients received kinesitherapy (including: individual passive and active exercises and group exercises with particular attention paid to joints in upper and lower limbs) lasting for $45 \div 60$ minutes every day. Moreover, suitable pharmacological treatment was applied depending on the stage of the inflammatory process. Before the therapy cycle and after its completion in patients 100-score functional test of the motor system was performed, assessing in all joints in lower and upper limbs the following parameters: intensity of edema in each joint affected by the disease process in scale from 0 to 3 points (maximum 72 scores), intensity of pain in each joint affected by disease in scale from 0 to 3 points (maximum 72 scores) and morning stiffness in all the joints altogether (also scale from 0 to 3 points). The better functional condition of joints was observed, the higher scores were assessed. Regardless of functional tests, in both groups of patients before and after the procedure cycle following laboratory tests in blood were conducted: ESR and morphology with assessment of thrombocyte number. As a result of applied procedure cycles in both groups statistically significant decrease of the intensity of pain in joints and decrease in the intensity of edema as well as improvement in the movability of the joints affected by disease were observed. At the same time in both groups of patients decrease in ESR value was observed, which was statistically significant only in the group treated with the peat paste compresses, particularly in case of significantly advanced lesions of joints.

Also a very good analgesic effect of the treatment with cold was proved by a research [155], where in patients with rheumatoid arthritis cryotherapy was applied as a part of complex rehabilitation therapy and in research [1], in which 23 patients received local cryotherapy with the use liquid nitrogen vapour generated by Kriosan device to all dolorous joints and in majority of patients decrease of pain intensity (rated by specially determine score scale) was observed.

In a prospective study [16] in patients with rheumatoid arthritis and ankylosing spondylitis who received whole-body cryotherapy applied twice a day, a beneficial impact of the whole-body cryotherapy on patients' clinical condition was proved – in RA patients statistically significant decrease in the score value in the Disease Activity Score (DAS28) and visual analog scale rating the pain intensity and in AS patients statistically significant decrease in the value of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Statistically significant decrease in pain intensity was maintained for 2 months period. In 21.3% of patients, interrupting of the therapeutic cycle period on account of observed side effects was necessary.

Beneficial impact of the cryogenic temperatures was also proved in children with dysfunction of hip and knee joints in the course of juvenile chronic arthritis [70]. The research was conducted on the group of 40 children aged 7÷18 who had not been subjected to any physiotherapy since two months. The pharmacological treatment applied so far was not changed during the study. The patients received physical therapy such as cryotherapy or therapulse followed by kinesitherapy. After 2-week lasting treatment comparing the therapeutic effectiveness of local cryotherapy with therapulse weights in favour of cryotherapy.

Regardless of the improvement in patients' clinical condition related to strong analgesic and antioedematous action leading to the improvement in efficiency and range of mobility of disease-affected joints, potential impact of cryotherapy on the immunologic system is significantly important to the final treatment effect in patients with rheumatoid arthritis. Research results in this aspect are ambiguous. In a research [129], in which cryogenic temperatures were applied to the group of healthy volunteers, no significant changes in the concentration of C-reactive protein, seromucoid or total protein were found comparing with the output values before the cryotherapy cycle. Research of other centre [51] showed that 3-week lasting cycle of local cryotherapy in patients with rheumatoid arthritis does not cause any statistically significant differences in the concentration of seromucoid and share of α_2 globulin comparing with the output values before the cryotherapy cycle. While in a research [153] patients with rheumatoid arthritis after 2-week cycle of whole-body cryotherapy achieved statistically significant decrease in the concentration of seromucoid and increase in the share of α_1 globulin in proteinogram.

Arthrosis

Arthrosis of various origins and accompanying pain are one of the main indication to cryotherapy, both local and whole-body. Type of joint affected by disease seems to be not important for application of the therapy with the cold, as beneficial

treatment effects were achieved regardless of the location and size of joints treated by cryotherapy.

In a research [31] local cryotherapy was applied on the group of 30 people (17 women and 13 men aged 25÷70) with diagnosed arthritic changes in hip and/or knee joints in the course of arthrosis or rheumatoid arthritis. Local cryotherapy was applied in three versions: procedure applied to disease-affected area, procedure applied to lumbar and sacral area and procedure applied to disease-affected area as well as lumbar and sacral area at the same time. It was proved that each version of cryotherapy procedures caused noticeable analgesic effects and improvement in the mobility of disease-affected joints with accompanying reaction of skin vessels with various intensity.

The authors of another work [26] evaluated impact of applying local cryotherapy on size of edema in disease-affected joint, active and passive mobility range in disease-affected joint and subjective pain sensation. Research included 24 women aged 45÷72 with arthrosis of knee joints (one knee joint or both). Degenerative changes in 10 women were of post-traumatic origin, and in 14 women resulted from rheumatoid arthritis. In the majority of patients occurred gait disorders caused by strong pain. Six patients walked on crutches, fourteen limped and in eleven swaying gait was observed. All the patients received a cycle of ten local cryotherapy procedures combined with rehabilitation exercises. During research following parameters were evaluated in patients: measurement of circumference of knee joint along with patella through the centre of patella and under it, measurement of relative and absolute length of limb, evaluation of active and passive mobility range in knee joint with the use of goniometer, as well as function test based on walking up- and downstairs, kneeling down and doing deep knee bends was performed. During functional tests, the patients were asked to rate intensity of pain according to 5-score Laitinen's scale and a distance was measured by number of stairs or knee bends done before pain occurred. During each 3-minute procedure knee joint of disease-affected limb put in the position of 25% bend in knee joint received a jet of mixture of atomized liquid nitrogen and air at temperature of -190°C with the use of a special applicator from the distance of 10÷20 cm. Local cryotherapy was followed by kinesitherapy in form of exercises for knee joint against gravity, isometric exercises for quadriceps muscle and active exercises of flexors and extensors of knee joint.

After 10 local cryotherapy procedures followed by kinesitherapy, in patients decrease in intensity of edema determined by decrease in joint circumference by 1 cm on average was obtained. Moreover, in all a significant increase in the mobility range of disease-affected joint was observed. Functional test „walking stairs” showed that only two patients felt pain during walking upstairs and in seven patients pain during walking downstairs occurred, whereas before procedures all of them experienced pain during the test. During deep knee bends only four patients suffered from pain in the first phase of full knee bend and seven - in the second phase, while 23 patients suffered from such pain before the therapy. During the kneel test done before the procedures, all patients suffered from pain, while after the procedures only six patients felt pain during starting to kneel, 14 – during kneeling and 16 – during rising from kneel. Also analgesic effect of procedures was beneficial as all patients experienced a significant decrease in pain in-

tensity as pain rated according to Laitinen's scale changed from unbearable to severe or mild. Also patients' gait improved after procedures, the majority of them stopped limping and four of six stopped using crutches.

In a research [46] local cryotherapy was applied to 35 patients with arthrosis in knee joints (in 14 patients lesions occurred in both joints, in the others – only in one joint). As a result of applied cycle consisting on average of 15 daily cryostimulation procedures applied for 3 minutes on each joint, followed by kinesitherapy, a significant increase in the muscle strength of extensors was achieved and to a lesser extent also flexors in knee joint, almost three times higher than respective values in the group of patients who underwent traditional physical therapy including paraffin compresses, infrared rays irradiation, ultrasounds and impulse magnetic field of high frequency. Individual differences in the growth of muscles mass were observed that probably were caused by various stage of arthrosis advancement in knee joints.

In another research [50] in 32 patients with the patella and thigh overloading syndrome local cryotherapy (20 procedures with blast of nitrogen vapour at temperature of -196°C lasting for 3 minutes) or whole-body cryotherapy (20 procedures at temperature of -110°C lasting for 3 minutes), followed by properly planned rehabilitation programme lasting for 35 minutes was applied 5 times a week. Distinct differences in the circumference of lower limbs in 66% of patients in the group which received local cryotherapy and even in 90% of patients in the group which received whole-body cryotherapy were observed. In the group of patients who received local cryotherapy, results of diagnostic tests (static test – Clark's symptom, Waldron's dynamic test and percussion test – Frund's symptom) improved from respectively 88, 100 and 100% of positive results, before the treatment to respectively 12, 12 and 20% of positive results after treatment. Outcomes of functional tests showing the stability of patella (test for patella dislocation, Zohlen's symptom, McConnell's test) in this group of patients improved from respectively 87, 67 and 67% of positive results before the treatment to respectively 33, 33 and 73% of positive results after the treatment completion. In the group of patients that received whole-body cryotherapy, the results of diagnostic tests improved from respectively 100, 70, 100% of positive results before the treatment to 20, 20, 12% of positive results after the treatment, and results of functional tests in this group improved from 88% of positive results before the treatment to 45% of positive results after the treatment completion. Those results prove comparable effectiveness of both forms of cryotherapy in the treatment of pain and disorders of the knee joint function in the course of the overloading syndrome.

Researches [43] showed that cryogenic temperatures also have a beneficial therapeutic impact on patients with degenerative lesions of cervical spine. In thirty patients with pain of cervical spine and typical irradiation of pain to the occiput or upper limbs a 6-week lasting cycle of local cryotherapy was applied, in form of cold gel compresses followed by kinesitherapy or thermal procedures followed by the same kinesitherapy. In the group of patients who received treatment with the cold more intense regression of muscular hypertonia of paravertebral muscles was observed, resulting in noticeable decrease in pain sensation level.

In research [127] in 37 patients with diagnosed chronic degenerative and diskopathic lesions in spine who received a cycle of 10-30 cryotherapy procedures at temperature range from -110°C to -150°C lasting for 1-3 minutes and followed by 45-minute kinesitherapy, an improvement in the activity of extensors and flexors of spine determined at the isokinetic test stand at two different speed of movement, respectively in 84 and 73% of patients (at speed $90^{\circ}/\text{s}$) and in 78 and 73% of patients (at speed $120^{\circ}/\text{s}$) was obtained. At low speed of movement, maximum moment of force in flexors increased by 16.7 Nm and in extensors by 50.1 Nm. Total work of flexors increased by 46.2 J and extensors by 167.9 J. At higher speed of movement, the parameters increased respectively by 12.7 Nm and 47.9 J for flexors and by 44.2 Nm and 143 J for extensors. Moreover, in 97% of patients significant decrease in pain intensity from 6 to 3 scores according to VAS scale was observed.

In another research [143] in 20 patients with the spine overloading syndrome who received a cycle of 20 whole-body cryotherapy procedures at temperature -130°C lasting for 3 minutes and followed by kinesitherapy and exercises with ergometer in the lying position, lessening of tenderness of the pelvis ligaments (by 20%) and reduction of intensified muscular tension in cardinal pelvis muscles (by 30%) were achieved.

In another work [84] in which 496 patients of both sexes aged 18-82 with diseases of the locomotor system of various etiology (mostly arthrosis of spine and limbs) received a cycle of 20-30 daily procedures of whole-body therapy (temperature -130°C , duration 2-3 minutes) followed by 15-30 minute kinesitherapy, after one month of the therapy completion the following results were observed: decrease in the intensity of pain rated in the visual and analogue scale VAS by 54.8% on average, improvement of walking ability rated in the subjective 3-score scale in 88.9% of patients as well as higher level of patients' satisfaction from applied therapy which was 6,7 scores on average in 10-score scale. The best therapeutic effects were achieved in patients with the post-traumatic lesions – a decrease in pain was 63.8% on average.

Beneficial effects of whole-body cryotherapy in the treatment of lumbalgia were also proved in research [18] in which, in patients who received 10 cryotherapy procedures, changes in the temperature profile of skin in the disease-affected area being indicative of regression of the inflammatory process were confirmed with the use of thermographic camera.

Comparison of therapeutic effectiveness of 20 procedures of local and whole-body therapy followed by kinesitherapy in 16 patients with chronic pain in the course of arthrosis in numerous joints, lasting for at least 2 years and treated with conservative therapy only, confirmed a decrease in the pain intensity rated by 10-score scale of McGill's questionnaire and 4-score scale of functional pain assessment occurring during selected basic life activities with the impact of both cryotherapy methods while whole-body cryotherapy proved to be more effective. In patients who received whole-body cryotherapy pain intensity decreased from 6.9 to 2.3 points, whereas in patients who received local cryotherapy from 6.5 to 3.5 points in 10-score scale [85].

Research [17] compared effectiveness of whole-body therapy in 46 patients of both genders with pain syndrome in the course of spondyloarthrosis treated with the use

of cryochamber and cryochamber with cold retention. Patients received a cycle of 10 daily procedures lasting for 2-3 minutes followed by kinesitherapy. Temperature in the proper chamber of two-level cryochamber ranged from -107°C at the height of 60 cm to -68°C at the height of 180 cm, while in a chamber with cold retention the temperature range was broader from -125°C to -67°C respectively. In such a type of chamber temperature during a procedure was more stable. The questionnaire filled in by the patients after completion of cryotherapy cycle proved, that the therapeutic effects achieved through the treatment in both chambers were similar - a significant decrease in pain intensity in 54.6% of patients and an improvement in the motor activity in 60.7 patients was observed. Repetition of a procedure cycle resulted in the increased share of patients with noticeable lower intensity of pain to 83.3% and share of patients with a noticeable improvement in their fitness, also to 83.3%. Patients' age did not have any impact on the intensity of the analgesic effect of the therapy, while in elderly patients (older than 55 years) improvement of fitness was not as spectacular as in younger patients.

Another research [60] was conducted in order to evaluate effectiveness of whole-body cryotherapy procedures with the use of single-person cryochamber in 49 patients professionally active (31 men and 18 women) with the pain syndrome in the course of arthrosis of lumbosacral spine. As a part of complex rehabilitation programme patients received 10 cryotherapy procedures at temperature -153°C lasting for 1.5-4 minutes. The results proved high therapeutic effectiveness of single person cryochamber in form of decrease in the intensity of pain rated in VAS scale by 69.4% and improvement in the flexion of lumbar spine measured by Schober's test by 53.6%.

Treatment with the cold was also applied in the therapy of arthrosis accompanying plasmatic diathesis. Research [76] showed that cryogenic temperatures are the especially effective in the rehabilitation of patients with hemophilic arthropathy, in whom applying other methods of rehabilitation causes problems due to complications resulting from the primary disease.

Periarticular inflammations

Positive effects were achieved by applying local cryotherapy using liquid nitrogen vapour at temperature -170°C in 15 patients with painful shoulder syndrome in the course of *periarthritis humeroscapularis* [8]. Each patient received 20 daily procedures of local cryostimulation lasting for 3 minutes followed by rehabilitation gymnastics lasting for 30-60 minutes each time including at the beginning active exercises with balanced shoulder joint, then in the further stage of rehabilitation also additional exercises. The results of applied therapy included improved flexion in the shoulder joint (the most visible in the bending, then abduction movements, the poorest in rotation movements), which although did not cause any physiological values, it allowed to obtain enough flexion to do main activities without pain. Mentioned therapeutic effects caused noticeable removal of pain and its early introduction of therapeutic exercises was possible and it contributed to positive subjective evaluation of applied therapy.

Beneficial impact of 15 daily procedures of local cryotherapy (lasting for 3 minutes) followed by active exercises of the shoulder joint against gravity (in sagittal, frontal, and vertical planes) in 18 patients with painful shoulder syndrome was also proved in the other research [13]. After completing treatment such effects were observed: decrease in the intensity of pain by 2.5 points on average in 6-score Domzal's scale, improvement in the flexion of shoulder girdle joints rated by SFTR method: bending in the vertical plane (33.3°), external rotation in the frontal plane (17.7°) and slight improvement in bending in the sagittal plane (3.3°), abduction in the frontal plane (2.9°), rectification in the vertical plane (2°) and internal rotation (1.5°).

Gout

Clinical observations conducted so far have shown beneficial impact of cryotherapy on decreasing inflammatory reaction in the course of the gout seizure. The research [53] including ten patients with the gout seizure, who received during first three days of the disease aggravation only local cryotherapy, alternately in form of blast of liquid nitrogen vapour at temperature ranging from -160°C to -140°C and ice compresses. During a day patients were receiving four procedures of local cryotherapy with 3-hour breaks between them. Since the fourth day patients have taken only pharmacological therapy i.e. colchicine in average dose of 2 mg a day. Research results proved that local cryotherapy causes short-term decrease in the intensification of the local inflammatory reaction, however, it does not interrupt the gout seizure. Application of colchicine has significantly better effect than local cryotherapy.

Diseases related to disorder in osseous structure

The research [47] evaluated an impact of local cryotherapy on patients with patellar chondromalacia. The research included 23 patients aged 14 to 40 years. Each patient received daily for 3 weeks, cycles of 3-minute lasting cryotherapy applied to knee joint and thigh muscles. Immediately after the cryoprocedures patients executed static and dynamic exercises sparing the patella. For the evaluation of treatment effects the following methods were used: walking on the distance up to 1 km, walking upstairs to 1st floor and downstairs, Waldron's test (dynamic test), Clark's symptom (static test) and Frund's symptom (percussion test). Regression of pain was recorded in 47.8÷87.0% of patients depending on used test. It seems that regression or decrease of pain intensity in those patients may indirectly confirm stimulatory impact of combined cryotherapy and kinesitherapy on the synthesis of cartilage intercellular substance and stimulating creation of cartilage and fibrous cicatrix.

Another trial [73] included 2-minute lasting local cryotherapy procedures followed by rehabilitation exercises in 25 patients suffering from pain in the course of osteomalacia in patella and thigh joint. Occurrence of patellar chondromalacia syndrome and activity of knee joint was evaluated with the use of S. Wernear's scale. Applying cryostimulation caused in the majority of patients regression or significant alleviation of pain which allowed introducing early rehabilitation treatment and resulted in improving of strength of the knee joint extensor.

Beneficial effects of cryotherapy such as: of strong analgesic action, decrease in intense muscle tone, particularly in paravertebral muscles and improvement in the efficiency of motor system, mainly spine, are used also in the osteoporosis treatment [67]. Decrease in the pain intensity (that occurred due to cryotherapy), and regulation of the tone in muscles related to spine, buttocks and abdomen favours keeping correct posture and prevents wedging of vertebral bodies of spine, which lead to irreversible posture deformation in patients with osteoporosis.

Fibromyalgia

In the treatment of fibromyalgia, except from using pharmacology aimed mainly at alleviating pain which accompanies disease, more often are used physical methods allowing for not only alleviating pain but also for effective limitation of chronic fatigue, improvement in muscle strength and elimination of sleep disorder and general weakness caused by chronic disease process.

Beneficial treatment effect of both local and whole-body cryotherapy that was included in the complex treatment of fibromyalgia was showed in research [97]. Both methods caused strong analgesic effects leading to a decrease in the intensity of both local and generalized pain and contributed to effective slowing down of the disease course. Usefulness of cryogenic temperatures in the treatment of fibromyalgia was also proved in research [118] in which twenty patients with primary fibromyalgia received local cryotherapy to shoulder and cervical spine area in form of 10-minute lasting blast of liquid nitrogen at temperature of -150°C followed by kinesitherapy, once a day for two weeks. After the treatment completion, in all patients statistically significant reduction of the pain intensity, muscle rigidity and feeling fatigue was observed.

Research [120] compared effectiveness of whole-body cryotherapy treatment and peat compresses in patients with generalized fibromyalgia. Therapy effectiveness was evaluated on the basis of subjective pain sensation according to visual analogue scale and so-called pain index as well as results of dolorimetry performed in 24 points of measurement of sensitiveness to pressure. In patients who received cryotherapy significant improvement in dolorimetric measurements and lowering of subjective pain sensation was observed, lasting for 2 hours after completing application of cold as well as occurring noticeably even after 24 hours from cryostimulation completion. Whereas in patients who had peat compresses only slight decrease in the pain index occurring immediately after the procedure completion was observed.

In another research carried out by the same centre [119] 37 patients with primary fibromyalgia (32 women and 5 men aged 25-64) received a complex treatment programme including local cryotherapy in form of blast of liquid nitrogen vapour and air at temperature of -150°C , applied twice a day for 3÷5 minutes, classical massage, general gymnastics and general exercises in a swimming pool. Before therapy and after the end of 4-week lasting complex treatment the following parameters were assessed: pain intensity with the use of visual analogue scale (VAS), tenderness of anatomic tender points measured by dolorimeter, intensity of the vegetative and functional symptoms in score scale (feeling of cold hands and feet, xerostomia, hyperhidrosis, dizziness,

sleep disorders, constipation or diarrhoea, feeling arrhythmic heart beat, feeling lack of air, paresthesia, dysuria, headaches or migraine), spine mobility (distance finger-floor, lumbo-sacral spine mobility range – Schober's symptom, lateral flexion – Dornian's symptom) as well as muscle strength measured by dynamometer (isometric strength, isokinetic strength, endurance and muscle work). The following effects were proved: statistically significant decrease in pain intensity (almost by 25%), slight decrease in the tender points sensitivity, decrease in the intensity of vegetative and functional symptoms, slight increase in spine lateral flexion, decrease in the distance finger-floor measurement value, intensification of isometric and isokinetic strength and endurance as well as increase in parameters related to the work of muscles.

In a research [126] 15 women with primary fibromyalgia received a cycle of 20 procedures of whole-body cryotherapy at temperature ranging from -110°C to -150°C lasting for 2-3 minutes followed by 1-hour lasting kinesitherapy. After the treatment completion the following effects were observed: decrease in the pain intensity in 10-score VAS scale (it was 6.4 points before treatment, 5.2 after 10 procedures and 3.1 points after 20 procedures), decrease in the number of tender points from 12.4 before treatment to 8.1 after 10 procedures and 5.9 after 20 procedures. All patients reported subjective improvement of their health.

Post-traumatic lesions of locomotor system and post-operative complications

Cryotherapy has been applied in the treatment of post-traumatic lesions of locomotor system for a long time.

Research [14] showed a beneficial effects of local cryotherapy in 26 patients with post-traumatic lesions in ankle joints, in which 10 procedures with the use of carbon dioxide blast at temperature of -75°C lasting for 3 minutes were applied. The treatment resulted in complete regression of pain in 75% of patients and decrease in pain intensity to 2 scores in 10-score VAS scale in remaining 25% of patients. Moreover, in those patients significant increase in the range of active plantar and dorsal flexion in the upper tarsal joint was observed.

In turn in the randomized research [12] 44 sportsmen and 45 patients with acute dislocation of tarsal joint with moderate intensity received treatment with plastic bags filled with ice with temperature of 0°C . In patients who received interrupted ice application within the first week after treatment statistically significant decrease in pain intensity during active movements of tarsal joint was observed, comparing with the group who received classical 20-minute ice application. Later on, no significant differences between both groups were observed in the range of resting pain intensity, swelling intensity and activity of injured joint. Results of meta-analysis [11] of clinical researches related to the therapeutic effectiveness of low temperature application in the treatment of injured soft tissues in the course of tarsal joint dislocation do not allow to recommend unequivocally such method as treatment of choice in case of soft tissue injury.

In research [161] in 60 patients with early post-traumatic osseous dystrophy (Sudeck's syndrome) in first and second disease stage, after fractures of radius, wrist and

hand bones, both ankles in the lower limb, heel and other foot bones, 20 local cryotherapy procedures were applied. Procedures applied once a day lasted for 2÷4 minutes. Patients exercised injured limb immediately after procedure. Moreover, patients were recommended to use at home ice compresses on the cured area within 6 hours after a cryotherapy procedure. In majority of patients, X-ray examination carried out in 6÷8 week after treatment beginning showed a regression of maculate atrophy and significant improvement in bone calcification with reconstruction of proper trabecular structure.

Another research [159] was conducted to analyse therapeutic effect of local cryotherapy in patients with diagnosed algodystrophy resulted from injury of upper limb, that was conservatively treated before. Research was done on 113 patients in whom the size of swelling in hand and forearm was evaluated, that is one of the main algodystrophy symptoms. Local cryotherapy applied to disease-affected area resulted in significant decrease in swelling intensity compared with the conservative treatment.

Whereas the research [124] evaluated cryotherapy effectiveness as non-pharmacological method of reducing pain in patients after arthroscopy procedure on the shoulder joint. Patients who received cryotherapy, more rarely felt pain in the shoulder after surgery and suffered from sleep disorder as well as reported lower pain intensity. Analgesic effects occurred as early as after first application of the cold. Within few days after the procedure patients who received cryotherapy tolerated rehabilitation far better and more willingly participated in rehabilitation. Thus, cryotherapy may be an important additional treatment to surgical treatment of the locomotor system as it helps to alleviate post-operative and rehabilitation pain.

In a research [2] in 24 patients after operative prosthetic restoration of knee and hip joints local cryotherapy was applied. Cooling skin surface of operated limbs to 8°C in the post-operative period resulted in 50% decrease in the demand for analgesic drugs and 20% increase in active movement range of the operated joints. In another research [89] in 41 patients within the period of 3-5 weeks after prosthetic restoration of knee joints local cryotherapy was applied as a part of complex treatment including also isometric exercises for quadriceps muscle, and then passive and active exercises of extension and flexion. In more than a half of the patients who received cryotherapy a decrease in deficit of active extension in knee prosthesis by ca. 10% and increase in the range of knee flexion by 20% on average were achieved.

In another research [157] 25 patients, with arthrosis in knee joint within 5 and 25 day after arthroplasty with the use of complete endoprosthesis with swelling and pain in the operated limb, as a part of complex kinesitherapy programme received 10 daily local cryotherapy procedures with the use of device generating carbon dioxide vapour at temperature -74°C. The applied therapy resulted in a decrease in pain intensity (from 5-10 to 1-4 scores in 10-score VAS scale) and retreating (in 84% of patients) or decrease (in 16% of patients) in the intensity of swelling in the operated lower limb what favored for improvement in the kinesitherapy effectiveness. Finally a decrease in the flexion range (by 23.6°), decrease in deficit of extension range (by 4.68°) in knee joint, augmentation of the strength of muscles related to knee joint (by 0.78° in Lovett's sca-

le) and as a consequence on improvement of efficiency and aesthetics of gait as well as subjective assessment of results in the rehabilitation process were obtained.

Diseases of nervous system

Cryotherapy and whole-body cryotherapy in particular, is more and more frequently applied in the treatment and rehabilitation of diseases with neurological origin.

Diseases of nervous system with increased spasticity

In the treatment of spasticity which results from damage in the central nervous system, physical methods, among them thermotherapy, have been used for a long time. Such methods as electrostimulation, thermal procedures and cryostimulation are highly effective as the factors decreasing pathological muscular tension. Their main advantage over pharmacotherapy is that they allow for selective decreasing of tension in the groups of spastic muscles without affecting healthy muscles. This enables to avoid many side effects related to using drugs decreasing muscular tension and, what is equally important, favors efficient rehabilitation.

The majority of researchers agree that effectiveness of using cold in the spasticity treatment is higher than observed effects of warming muscles. In order to decrease pathologically intensified muscular tension cold water, cold compresses or massage with an ice cube were used successfully. Good results were also achieved through cooling spastic limbs with specially designed cooling blanket, mixture of water and ice, water and ethyl alcohol and ethyl chloride or gas vapour (mainly nitrogen vapour) [74].

At present in the local treatment of spasticity devices of cryo-air type are used more frequently, which have system cooling air to temperature of -34°C . Maintenance costs of such procedures are lower, and at the same time the risk of occurring frostbites in patients is relatively lower in comparison with local blasts of nitrogen vapours [30].

In disorders of neurological origin, similarly to other diseases, type of applied cold, area and application manner must be adjusted to occurring symptoms and individual patient's tolerance to low temperature. Personalization of cryotherapy scheme taking into account not only type of disease but also patient's motivation and ability allows for optimum use of cryostimulation procedure action and intensification of kinesiotherapy that follows procedure.

Equally important are patients' feelings during cold application; majority of them report pleasant relaxation, decrease in pain sensation and sensation of warm in cooled limbs. Research [154] tested an impact of cold applied with the use of specially designed blanket cooling spastic limbs. As a result of cooling procedures relaxation of muscles that maintained even up to two weeks after cryotherapy completion was observed. Electromyography tests confirmed improvement in the bioelectric activity of muscles measured as shorter time of appearing muscle relaxation after its maximum contraction. In patients who received cryotherapy procedures also an improvement of gait phases in EMG record was observed.

Similar effect of reduction of pathologically intensified muscular tension was also proved in patients after cerebral stroke who received procedure of cooling spastic up-

per limbs for 10÷15 at temperature of -8°C [140]. This form of treatment with cold caused in patients significant decrease in muscular tension in limbs what made rehabilitation easier.

Also researches [21] conducted on patients with symptoms of damaged central nervous system who received complex rehabilitation proved effectiveness of cryotherapy applied to achieve long-term (lasting even up to few hours) relaxation of pathologically intensified muscular tension, what resulted in significantly improved effectiveness of kinesitherapy.

In research [142] 13 children with damaged central nervous system and scoliosis received 4-week cycle of whole-body therapy followed by training of motor activities. During procedures children were staying in cryochamber with their guardians. After treatment completion the following effects were observed: increase in frequency of proper values of objective indices of gait efficiency from 54% for left lower limb and 48% for right lower limb to 66 and 69% respectively, as well as increase in mean values for individual gait indices. Moreover, frequency of gait rated on the basis of time of walking certain distance and number of steps increased significantly from 8.9 to 9.7 Hz, it was. Beneficial changes in rated visually gait stereotype in children were also observed.

In another research [93] 26 children and teenagers with infantile cerebral palsy received a cycle of 10 whole-body cryotherapy procedures at temperature of -110°C lasting for 1.5-2 minutes followed by individual revalidation programme, what resulted in the mood improvement (in 14 patients), decrease in spasticity (in 16 patients) and increase in spontaneous motor activity (in 18 patients).

Whereas in a research [144] in 32 children with infantile cerebral palsy who received local cryostimulation with the use of nitrogen vapour blast indeed significant decrease in spasticity of lower limbs rated by Ashworth scale was not obtained, yet an improvement in spontaneous motor activity rated by Brunnström's test was observed.

Researches from another centre [104,105] included cryostimulation in the general therapy scheme as an integral component of patients rehabilitation with spasticity related to damaged central nervous system of various etiopathology, mainly with spastic paresis after cerebral stroke. Cryotherapy in the form of cooling limbs with nitrogen vapour blast was applied twice a day for 3 minutes and a completed cycle lasted for 3 weeks on average. In patients treated with the cold significant decrease in pathological muscular tension, increase in walking speed and improved motor activity of cooled limbs rated by Brunnström's test were observed. In the group of patients with similar characteristics effectiveness of cryostimulation with the use of cold air blast at temperature -35°C and regulated flow was also tested. The procedures resulted in a decrease in spasticity by one degree in Ashworth scale on average, which maintained for about 3 hours in the majority of patients.

In another work [77] in 15 patients with post-stroke spasticity application of local blast of nitrogen vapour resulted in statistically significant decrease in muscle tension assessed by Ashworth scale.

In turn in a research [145] patients with spastic hemiparesis received cryostimulation as carbon dioxide blast along with mobilization according to PNF method what resulted in decrease in muscle tension by 1 degree in Ashworth scale on average.

Clinical observations carried out for many years and conducted electromyography tests proved that treatment with use of low temperature has a beneficial impact not only on muscular spasticity but also on decrease in the intensity of muscular clonus and weaken stretching reflex [25]. According to the authors in a treatment of pathological muscular tension first of all thermotherapy with cold or warm (depending on individual demand of particular patient) should be used and pharmacotherapy should be used only as a extremity. However, a significant limitation of using thermotherapy in these cases is providing access to professional equipment and participation of medical staff as well as difficulty in applying this method at home on patient's own.

In other researches a beneficial impact of local cryotherapy on increasing muscle strength was also observed. In a research [9] neurophysiologic tests were carried out in patients with rheumatoid arthritis who received local cryotherapy in form of nitrogen vapour blast at temperature -180°C at wrist and forearm. Then exercise tolerance test was done and electromyographic record showed increase in density of EMG record, what confirms improvement in the muscle strength of tested muscles.

Cryostimulation methods in form of cooling paretic limbs by flowing water at temperature ranging from 9.4°C to 11.1°C for 30 minutes are also applied to alleviate pain and swelling symptoms in the paresis-affected hand in patients after cerebral stroke [90].

For the final assessment of cryotherapy usefulness in the treatment of patients with pathological spasticity, of significant importance is the fact that there are almost no side effects of the method which are often observed when pharmacotherapy or surgical procedures are used. In researches [104, 105] describing results of experiments carried out over many years in applying cryostimulation in rehabilitation of patients with damaged central nervous system, only in a few patients there was a necessity to interrupt treatment due to cold sensation reported by patients that lasts for few hours after cryoapplication. Also no serious complications or side effects of applied therapy were reported, on the contrary, physical procedures contributed to introducing a complete rehabilitation programme.

Due to effectiveness of cryostimulation procedures in patients with spasticity symptoms regardless of their pathomechanism, there are attempts to treat with the cold also patients with spasticity of spinal origin, among others, in the course of cervical myelopathy, abscess of spinal cord, after operation on spinal or brain tumour as well as after craniocerebral injuries [75].

Diseases of intervertebral disk – diskopathies

Due to confirmed analgesic, anti-swelling and relaxant effects of local and whole-body therapy in the treatment of rheumatoid arthritis and spondyloarthritis, there are attempts to treat with the cold other diseases of similar symptomatology, among them diskopathies remaining a serious problem particularly those related to lumbar spine.

In the course of disease compression and dislocation of vertebral disk occur and as consequence hyperemia and swelling of nerve roots with strong pain reaction appears. Reflex contracture of paravertebral muscles is also observed, and it leads to restricted spine flexion and secondary intensification of pain.

Research [136] tested cryotherapy effectiveness in the treatment of pain in 163 patients with lumbosacral radicular syndrome in the course of spondyloarthrosis complicated with hernias of disk. The following parameters were evaluated in patients: intensity of pain, range of restricted flexion in lumbar spine, tension of paravertebral muscles and level of restoration of nerve roots function on the basis of neurological examination before and after a complex treatment and rehabilitation programme also including cold application. Patients were divided into subgroups depending on the type of pain and nerve root syndrome. Cryostimulation procedures were applied to patient's whole body (2÷3 minutes at a temperature below -100°C) as well as locally to lumbar spine (blast of cooled liquid nitrogen at temperature -130°C). In patients with dominating radicular syndrome application of cryotherapy as a component of complex rehabilitation resulted in significantly better treatment effects related to both: pain decrease and increased flexion in lumbar spine. Whereas in pseudoradicular syndrome similar effects were not found. Obtained results allow to draw conclusion that although cryotherapy can't be applied routinely in the treatment of arthrosis in lumbar spine, it is recommended to patients with dominating radicular pain and functional restriction of spine flexion. What is more a good tolerance to such physical method was proved, as after local procedures no complications were observed and during whole-body cooling there were slight skin lesions similar to frostbite in three patients only.

Positive therapeutic effect of cryogenic temperatures was also shown in a research [114] in which cryotherapy was applied in 15 patients with complications related to creating periradicular scar in vertebral canal after operative treatment of diskopathy in lumbar spine, that were previously treated ineffectively with other physical methods. Assessment of analgesic effect by means of the pain questionnaire according to Laitinen was made. After cryotherapy, in two patients very good analgesic effect was achieved, in eleven- satisfactory or good, while only in two patients no improvement was observed.

In our own and so far not published research, cryotherapy was applied in 40 patients with dorsal pain syndrome due to diskopathy treated at the Silesia Rehabilitation and Physical Medicine Centre in Ruda Śląska. Patients received a cycle of daily whole-body cryotherapy procedures at temperature of -130°C lasting two minutes for ten consecutive days with two-day break after five procedures. Immediately after each cryotherapy procedure the patients underwent 60-minute lasting kinesitherapy conducted according to the individual rehabilitation scheme. After the procedure, patients filled in a questionnaire about subjective evaluation of therapy effects. Analysis of achieved therapeutic effects was made independently in a group of patients who received 1÷10 procedures (20 persons) and in a group of patients who received 11÷20 procedures (20 persons) taking into account patients' sex and age group (2 age groups of pa-

tients: 20-40 years old and older that 40). Reduction of the pain intensity and motor activity of patients was assessed in three-level scale: lack of improvement, slight improvement and significant improvement.

Subjective assessment of therapeutic effects related to regression of pain and improvement in motor activity resulting from questionnaire, taking into account gender and age of patients as well as number of applied procedures are shown in tables 12 and 13.

In all patients significant improvement in clinical condition related to pain alleviations and intensification of motor activity was achieved, while therapeutic effect of whole-body cryotherapy related to both regression of pain and intensification motor activity was proportional to the number of received procedures.

Table 12. Therapeutic effect related to pain regression and improvement in motor efficiency in patients with diskopathy who received whole-body cryotherapy taking into account sex and number of received procedures.

Number of procedures	Level of subjective improvement	Regression of pain sensation		Improvement in motor activity	
		Women	Men	Women	Men
1-10	Lack of improvement	10%	10%	10%	20%
	Slight improvement	50%	40%	70%	50%
	Significant improvement	40%	50%	20%	30%
11-20	Lack of improvement	0%	0%	0%	0%
	Slight improvement	10%	30%	20%	40%
	Significant improvement	90%	70%	80%	60%

Table 13. Therapeutic effect related to pain regression and improvement in motor efficiency in patients with diskopathy who received whole-body cryotherapy taking into account patients' age.

Age of patients	Level of subjective improvement	Regression of pain sensation	Improvement in motor activity
20-40 years	Lack of improvement	0%	0%
	Slight improvement	33.3%	22.2%
	Significant improvement	66.7%	77.8%
Older than 40	Lack of improvement	6.4%	9.7%
	Slight improvement	32.3%	54.8%
	Significant improvement	61.3%	35.5%

After first cryotherapy cycle (10 procedures) 25% of patients felt a significant improvement, 60% – slight improvement and only 15% of patients did not observe any improvement in their motor activity. Significant regression of pain was reported by 45% of patients, slight regression felt 45% of patients and lack of regression was observed

by only 10% of patients. After second cryotherapy cycle (20 procedures in total) all the patients reported improvement in motor activity: 70% – significant and 30% – slight. All the patients also felt pain reduction: 80% – significant and 20% – slight.

In younger patients greater improvement in motor activity was observed while in this group of patients obtained analgesic effect was only slightly bigger comparing with the elderly group. Better effect of therapy, after longer procedure cycle, was observed in women. Patients tolerated procedures well. The majority of patients felt improvement in general feeling and relaxation after stay in cryochamber. Significant majority of patients continued willingly procedures, some of them received another cryotherapy without significant complications.

Multiple sclerosis

Use of whole-body cryotherapy in the treatment of multiple sclerosis is a very interesting issue from the clinical point of view. Such research was a subject of a work [125] in which 29 patients (35% of women – mean age 38 years and 65% of men – mean age 40 years) with multiple sclerosis in the remission stage were included. Average duration of disease was 7.2 years, all the patients could walk (1.5- 6.5 in EDSS scale) while in 25 patients dominated spinal symptoms and in 3 – cerebellar symptoms. All patients received whole-body therapy for 5 consecutive days in cryogenic chamber at temperature ranging from -110°C to -130°C lasting each time for 1.5÷3 minutes. Immediately after cryotherapy, patients took exercises according to individual scheme determined on the basis of Frenkel's exercises including assisted exercises (proper active and active with resistance), relaxant exercises (Jakobsen's training, Schulz's autogenous training) and redressing exercises. Cryotherapy applied in 20 patients resulted in a improvement of motor activity by 0.5 score in the functional scale EDSS, in 13 patients decreased spasticity in lower limbs and in 5 patients– retreated nystagmus. Also a tendency of improvement in psychomotor functions was observed.

In another work conducted by the same team [91] 25 patients with multiple sclerosis received 20 daily procedures of whole-body cryotherapy at temperature ranging from -110°C to -150°C lasting for 2-3 minutes each time followed by kinesitherapy, that was individually scheduled to each patients according to the scheme, taking into account: improvement in muscle strength and fitness, coordination and coherence of active movements as well as gait equilibrium and efficiency. In each patient following tests were performed: neurological examination, functional evaluation with the use of EDSS scale, evaluation of spasticity with the Ashworth scale and posturegraphic tests assessing dislocation of centre of gravity in the view of XY plane. Conducted research proved that whole-body cryotherapy along with relevant set of exercises cause significant improvement of most of analyzed parameters in the patients.

In another research [92] 26 patients (16 men and 10 women) with diagnosed multiple sclerosis received a cycle of 20 procedures of whole-body cryotherapy with exactly the same kinesitherapy as above. After the whole-body cryotherapy cycle in 19 patients decrease in spasticity by 1 degree in 6-score Ashworth scale was observed, while the best results were achieved in patients with lowest spasticity 1 i 1+ before start of

the procedure. At the same time in more than half of patients an improvement in muscular tension was observed.

In a research [34] 23 patients with diagnosed multiple sclerosis (disease duration 2÷40 years, mean duration 13.8 years) were receiving for 14 days whole-body cryotherapy at temperature ranging from -110°C to -150°C , twice a day for 2÷3 minutes followed by individual and group kinesitherapy. Also in this research in the majority of patients noticeable decrease in spasticity level was observed, moreover, a significant increase in physical fitness assessed in the exercise tolerance test on stepper with registration of made steps until pulse 120/min or refusal of further continuation of test.

Also beneficial therapeutic effects were achieved in research [94] where 115 patients with multiple sclerosis received a cycle of 20 whole-body cryotherapy procedures at temperature ranging from -110°C to -130°C lasting for 1.5-3 minutes followed by individual and group kinesitherapy. The effects were as follows: noticeable functional improvement resulting from a decrease in spasticity intensity (in 57 patients) and improvement in body stability when standing.

Diseases of central nervous system

Local cryotherapy was applied successfully, among other in the treatment of trigeminal neuralgia [103]. The classical treatment of the disease based on pharmacotherapy using carbamazepine as a drug of first choice often does not bring expected results. In the cited work, application of local cryotherapy resulted in strong analgesic effect in the mechanism of long-term reversible nerve blockade. It seems that such method is particularly beneficial in those patients with contraindications for possible surgery treatment after unsuccessful pharmacological therapy.

Diseases of psychogenic origin – neurosis

There are only a few reports on the impact of physical stimulus as cold on psyche of patients who received whole-body cryotherapy. Research [115] showed that exposure of patients to extremely low temperature significantly affects their mood. In patients who received cryotherapy noticeable improvement in mood, relaxation and even euphoria were observed. Such effects occurred immediately after leaving cryochamber and were maintained for a long time after a procedure.

In another research conducted by the same team [116] 34 patients with depression and anxiety syndromes except from routine pharmacological treatment received a cycle of 15 daily whole-body cryostimulation procedures lasting for 2-3 minutes at temperature -110°C (at the beginning) and -160°C (at the end). Before start of cryostimulation cycle and then in 7th, 14th and 21st day of a cycle as well as in 3rd and 6th month after its completion in patients intensity of depression and anxiety syndromes was rated, using HDRS-17 scale (*17-item Hamilton's Depression Rating Scale*) and HARS scale (*Hamilton's Anxiety Rating Scale*), respectively. Results were compared with results of the control group of 26 patients who received pharmacological treatment only, without cryotherapy. In the group of patients who were subjected to whole-body cryotherapy significantly lower scores in both scales were observed, after 1 and 2 weeks

of procedures as well as after cryostimulation completion, comparing with the control group. In depression syndrome a 50% decrease in scores of HDRS-17 scale comparing with initial values was observed in 34.6% patients who received cryostimulation as opposed to 2.9% of patients from the control group. As to anxiety symptoms a 50% decrease in scores of HARS scale was observed in 46.2% of patients who received cryostimulation as opposed to no such improvement in the control group. Long-term 6-month observation after the completion of the therapeutic cycle did not show any significant differences in the intensity of disease symptoms between the groups.

Although, the mechanism of changes in mental condition of patients who received cryotherapy has not been known in details (at present it is considered impact of the hypothalamus-hypophysis axis and endogenous opiate system related to regulation of the biological rhythm and pain reduction that have a significant impact on patient's mood), it seems that whole-body cryotherapy may be used to a possible alternative to the pharmacological treatment of neuroses in the future.

Biological regeneration and professional sport

Cryotherapy is applied in sports medicine in the treatment of both acute and chronic injuries of soft tissue in sportsmen although a mechanism of beneficial impact of low temperature on muscle injuries caused by training overloading has not been known in details yet [7,61,139,148,164].

Treatment of acute injuries in sportsmen is based on the traditional principle so-called RICE (*Rest-Ice-Compression-Elevation*). In sport, effect of the cold may be significantly increased by using nitrogen spray instead of ice compress applied on routine basis. Here liquid nitrogen vapour at temperature -196°C is blasted to the post-injury area from the distance of 15-20 cm. Analgesic and antioedematous effect after 3-minute cryostimulation usually maintains for over 3 hours [164].

Cryotherapy has a vast scope of application in post-traumatic rehabilitation of injured locomotor system and preparing of active professional sportsmen for exercises. Significant component seems to be a decrease in the intensity of post-traumatic pain and edema, for which people during professional training are especially exposed, as well as subjective improvement in general condition and better exercise tolerance.

Beneficial effect of local cryostimulation frequently applied (even 2÷3 times a day), along with light muscles and joints exercises, was observed in muscle injuries (detachment of muscles, acute syndrome of fascial compartment also after operative treatment, extension of muscles, excessive elongation and rupture of muscle fibers, painful muscular contraction), tendon injuries (detachment, distortion, extension of tendons, tendinosis, tendinopathy) as well as overloading syndromes resulting from too strenuous training (sterile inflammation of tendon in popliteal muscle and Achilles tendon, inflammation of tendon attachment to epicondyles of shoulder bone so-called „tennis player elbow” and „golf player elbow”, rotation muff syndrome, „frozen shoulder syndrome”, chondromalacia of patella so-called „housemaid's knee”, syndrome of muscles of back thigh and lumbar muscles so-called „weightlifter's back” and inflammation of plantar aponeurosis) [164]. A lot

of those lesions regressed just after single procedure and obtained improvement was usually persistent.

When post-traumatic injuries have to be operated (e.g. tendorrhaphy) cryotherapy is applied after operation as it makes healing faster, mainly due to improvement in perfusion of tissue that are usually ischemic, due to protracted training.

Beneficial effect of cold on the course of injuries in muscles caused by protracted training was observed, among other, in research [23] that assessed an impact of immersion in water at temperature of -15°C on injured during strenuous exercises (including 8 sets of 5 maximal flexions) elbow flexors. In 15 women (control group) no physiotherapy was applied, while in other 8 women limbs participating in exercises received local cryotherapy in form of water immersion lasting for 15 minutes each time, immediately after exercises and after each 12 hours (in total 7 exposures). The following parameters were assessed: muscular expansibility, isometric strength of muscular spasm, degree of relaxation of elbow angle, intensity of local swelling (based on the measurement of arm circumference) and activity of creatine kinase. In both groups of women relevant measurements and analysis of biochemical tests, which were done on the third day after muscle exercises showed significant increase in pain sensitivity (tenderness) of muscles, increase in arm circumference, increase in activity of creatine kinase as well as decrease in strength of muscular spasm and degree of relaxation of elbow angle. In group of women who received cryotherapy higher level of relaxation of elbow angle and lower activity of creatine kinase was observed in comparison with the control group that did not receive any therapy. On the basis of obtained results it was observed that cryotherapy applied as cold water immersion results in decrease of stiffness and degree of muscle damage after strenuous overloading physical exercises, however, it does not affect tenderness and loss of muscular strength, that are typical of such physical activity.

In research [165] 14 judo competitors aged 17 to 33 with complete dislocation of acromioclavicular joint (III degree according to Toss-Heppenstal) received local cryotherapy as conservative treatment and immobilization of upper limb in Velpeau's bandage for two weeks. Then intensive rehabilitation was applied. After 3-7 years (4.5 years on average) from the injury all the patients filled in a questionnaire in which with the use of special 100-score scale they rated occurred pain, flexion of humeral joint, muscular strength and return to the previous level of sports activity. In eight treatment result was acknowledged as very good (90-100 scores), in five – good (80-89 scores) and in one – satisfactory (70-79 scores).

Significant increase of the tolerance to a strenuous training was observed, among others, in research [5] which included a group of 24 sportsmen practicing professionally martial arts (mean age 21.3): two women and eleven men practiced karate and eleven men practiced judo. Sportsmen received 10 daily whole-body cryotherapy procedures lasting for 3 minutes in a cryogenic chamber at temperature ranging from -110°C to -150°C . Before beginning of procedures, then after the first, third, fifth and tenth procedure as well as on the tenth day after completion of exposure to the cold, sportsmen filled in a questionnaire in which they rated pain occurrence and its intensity in

joints and muscles, impact of procedures on the tolerance of training and intensity of post-traumatic swelling. Assessment rated by sportsmen was subjective in its character and was related to each day listed in questionnaire. On the basis of questionnaire significant change in sportsmen's subjective feelings in consecutive days of exposure was observed. As to the tolerance to training, first three days of cryotherapy did not produce any results. On the fifth day a significant decrease in the tolerance was observed, while on the ninth day – a significant increase in the tolerance to overloading was noted, which was maintained in 75% of sportsmen also on the tenth day after procedure completion. Since the fifth day of procedure cycle gradual decrease in the intensity of pain in injured joints was observed, that was particularly noticeable in knee and hand joints and to lesser extent in brachial and elbow joints. Equally beneficial results were achieved in decreasing swellings and chronic pain syndrome. Moreover, in the half of the sportsmen an improvement in mood on the tenth day after the cryotherapy cycle was observed.

Indications for applying cryotherapy

Clear assessment of therapeutic effectiveness of cryotherapy based on the Evidence-Based Medicine principle is difficult, mainly due to the character of cryotherapy procedures that virtually makes carrying out clinical research through double-blind trial impossible as well as wide diversity of applied therapeutic procedures and vague description of the clinical material and methodology of researches in available literature [40].

To sum up described above results of clinical researches related to treatment application of low temperatures, it should be emphasized that, as the majority of authors agree, that whole-body cryotherapy has significantly higher therapeutic effectiveness in comparison with local procedures applied in the majority of analyzed diseases.

Based on contemporary literature reports and authors' own experience, the following indications for cryotherapy should be considered, both as an independent method and a component of the complex rehabilitation [4,6,10,33,35,41,42,47,53,66,67,69, 88, 139,153, 159,161,163]:

1. Diseases of locomotor system:

- inflammatory diseases of locomotor system: rheumatoid arthritis, ankylosing spondylitis,
- arthrosis and secondary degeneration of spine and peripheral joints,
- diseases of metabolic origin: gout,
- periarticular inflammation in ligaments and joint capsule,
- some skin diseases with affected joints: psoriatic arthritis,
- inflammatory diseases of soft tissues: *myositis*, *fibromyositis* and collagenosis,
- post-traumatic or overloading changes in joints and soft tissues,
- diskopathies,
- fibryomalgia,
- osteoporosis.

2. Diseases of nervous system:

- radicular syndromes,
- multiple sclerosis
- spastic paresis.

3. Biological regeneration of overloaded muscles.

4. Professional sport:

- adjunctive biological regeneration (biostimulating effect),
- adjunctive endurance and strength training,
- acceleration of post-endurance restitution,
- prophylaxis of locomotor system overloading,
- adjunctive post-traumatic treatment of soft tissues and joints (contusion, hematomas, distortion),
- adjunctive treatment of overloading syndromes in muscles, muscle attachments, joints and spine.

Regardless of the classical cryotherapy using radiation cooling with cryogenic temperature, in the clinical practice cold is also applied (although quite rarely) as cooling through conveyance of cold (convection) in order to decrease body temperature in the following clinical conditions accompanied by hyperthermia:

- heat stroke,
- malignant hyperpyrexia,
- thyrotoxic crisis,
- infectious disease with fever reaction,
- diseases of central nervous system with excessive heat production,
- condition with impaired physical thermoregulation

and as various forms of cooling through conduction, conveyance and vaporization in form of compresses, poultices and cooling aerosols (described at the beginning of the chapter) used mainly in the treatment of overloading syndromes of locomotor system and intensified muscular tension [135, 163].

Contraindications for applying cryotherapy

Although therapy using low temperature is a relatively safe method, we have to bear in mind these conditions in which using low temperature may produce adverse health results.

During qualification of patients following parameters should be taken into account: patient's age, existing diseases, nutritional status, efficiency of blood vessels, time of exposure to the cold and its intensity, drugs taken by patients, drinking alcohol, individual sensitivity to the cold effect. All those parameters determine possibility of safe application of cryogenic procedures and may be a reason for patient's disqualification for cryotherapy procedures.

According to the present knowledge, absolute contraindications for applying cryotherapy are 6,10,33,35,41,42,66,67,139,163]:

- cold intolerance,
- cryoglobulinemia,
- cryofibrinogenemia,
- Raynaud's disease,
- thrombotic, embolic and inflammatory lesions in the venous system,
- some diseases of central nervous system,
- neuropathies of sympathetic system,
- mental diseases restricting communication with patient,
- claustrophobia,
- taking some drugs, particularly neuroleptic drugs and alcohol,
- hypothyroidism,
- local disorders of blood supply,
- open wounds and ulcerations,
- advanced stage of anemia,
- organism cachexy and hypothermia,
- neoplastic disease,
- active tuberculosis,
- acute disease of respiratory system,
- diseases of cardiovascular system including:
 - unstable angina and advanced stage of stable angina,
 - defects in valvular apparatus in form of semilunar aortic valve stenosis and mitral valve stenosis,
 - other diseases of cardiac muscle and valvular apparatus in stage of circulatory failure,
 - cardiac rhythm disorder, *among them*, sinus tachycardia above 100/minute,
 - arterio-venous shunts in lungs.

Also obvious absolute counter indication is lack of conscious consent to apply cryotherapy procedures.

Except for absolute contraindications, there also are relative contraindications [33,67,153]:

- age above 65 years,
- excessive emotional instability that is expressed, among others in form of hyperhidrosis.

Significant issue from the perspective of contraindications is applying cryotherapy in patients with implanted cardiostimulators. In ca. 30% of patients after stimulator implementation, in the place of surgery, most often in the area of humeral joint and acromioclavicular joint pain ailments occur, what result in restriction of brachial joint activity and condensation of collagen fibers adjacent to passive and active joint structures. Due to asymmetric work of muscles in the shoulder girdle and nape there is also disorder in cervical spine statics. A serious therapeutic difficulty is the fact that the majority of physical therapy procedures are contraindicated in patients with implemented cardiostimulator due to possible disturbance in proper function of electronic components in a stimulator, also including producing false stimulation.

Research [111,112] proved full safety of applying local cryotherapy in patients at early phase after cardiostimulator implementation. Applied in those patients cryotherapy didn't affect pacemaker function, what was confirmed by ECG with the use of Holter's method. Thus, presence of implemented cardiostimulator is not a contraindication for applying treatment with cold.

At the same time, taking into account high therapeutic effectiveness of the method related to significant alleviation of pain intensity after a procedure and when followed by kinesitherapy also making easier return of physiological mobility in brachial joint, cryotherapy should be considered as a valuable alternative to pharmacological treatment in such patients.

In recent years, some controversy has been risen in the literature and related to using cryotherapy in the treatment of diseases with etiology, where hypersensitivity to the cold (e.g. Raynaud's syndrome) plays a significant role and that are traditional contraindications for applying such method of treatment. In research [45] in fourteen patients with symptoms of Raynaud's syndrome accompanied by rheumatoid arthritis, scleroderma and lupus erythematoses local cryotherapy was applied as adjunctive treatment of the mentioned diseases. After a cycle of procedures, in all the patients increase in joint mobility as well as temporary hand warming maintaining for almost all day were achieved. Moreover, in nine patients a significant lowering of hand tenderness was observed. At the beginning of therapy (2÷5 day) in patients intensification of pain occurred and then it suddenly disappeared. Further, a gradual improvement of sensation in hands and their functional activity related to return of ability to do complicated manual activities was observed. In no patient complications or significant side effects of cryotherapy were observed. Although too small group of patients subjected to research does not allow to draw ambiguous conclusions, but results obtained in the research prove the necessity to carry out further detailed researches in order to verify finally a list of contraindications for applying cryotherapy, with a particular emphasis to Raynaud's syndrome and other diseases of similar etiopathogenesis.

As authors' own experience and literature data show, whole-body cryotherapy is well tolerated by patients, including children and the elderly. The method was successfully, without any complications, applied in 81-year old as well as in 12-year old patient [4,10,33,35,41,42,67,153].

During first days of procedure, there may occur slight aggravation of disease symptoms what is generally promising prognosis. Positive reaction of body to the cold, at the same time potential usefulness of cryotherapy in a certain patient, may usually be evaluated after some 10 procedures. When after 10 procedures there is no improvement in patient's status (it happens only in ca. 1-2% of patients), a chance for improvement in further therapy is very slim and therefore usefulness of further cryotherapy application should be reconsidered [6].

When qualification for treatment was carried out correctly and all the procedures are followed, particularly during cryotherapy, then complications occur very rarely. In single cases only surface frostbites caused by device failure or contamination of nitrogen used to cool cryochamber were observed.

Patients who receive whole-body cryotherapy most frequently report subjective heat sensation, relaxation and sedation. Sometimes, during first phase of cryotherapy cycle temporary pain intensification may occur, however, it should **not** be a reason for interrupting treatment.

Scheduling an individual rehabilitation programme for patients that is a continuation of cryotherapy, it should be taken into account that for a dozen or so minutes after cryostimulation there is intense stiffness and disorder of position perception, among other in knee joints, what in case of intensive exercises performed immediately after procedure completion may cause injuries [149].

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