L. I. Anatychuk *acad. of the NAS of Ukraine* [1,2]
R. R. Kobylianskyi *cand. phys.-math. sciences*[1,2]
R. V. Fedoriv [1,2]
I. A. Konstantinovych, *Ph.D (Phys and Math)*[1,2]

[1]Institute of Thermoelectricity of the NAS and MES of Ukraine,
1 Nauky str., Chernivtsi, 58029, Ukraine;
e-mail: anatych@gmail.com
[2]Yuriy Fedkovych Chernivtsi National University,
2 Kotsiubynsky str., Chernivtsi, 58012, Ukraine

ON THE PROSPECTS OF USING THERMOELECTRIC COOLING FOR THE TREATMENT OF CARDIAC ARRHYTHMIA

The paper presents the results of an analysis of various methods of treating cardiac arrhythmia. Among them, special attention is drawn to the ablation method, which boils down to the elimination of additional electrical stimuli of cardiac muscle contraction. The latter is achieved by surgical methods, high-frequency irradiation and cryodestruction with liquid nitrogen or the use of the Joule-Thomson effect. Cryotechniques have certain advantages over others, but their implementation is somewhat more complicated, which limits their clinical use. In recent decades, cooling by the Peltier effect has been increasingly used in medicine. It has proven itself to be simple, reliable and accurate in reproducing the required temperature conditions for treatment. This work is devoted to studying the possibility of using the Peltier effect for cryoablation. Bibl. 39, Fig. 2.

Key words: cardiac arrhythmia, atrial fibrillation, cryoablation, thermoelectric cooling.

Introduction

Arrhythmia is a fairly common cardiovascular disease, which is caused by various heart defects, toxic effects of harmful substances, nervous system disorders or thyroid gland diseases, etc. However, the most common cause is the ability of certain heart cells to generate electrical signals in an untimely manner. In doing so, the cardiac muscle tissue of the atria with altered electrical properties supports and conducts these pathological signals, which can lead to arrhythmia [1].

Many methods of combating heart arrhythmia are known. Among them, the treatment of open heart arrhythmia is important.

The first surgical procedures were based on the principle of reducing the mass of the pathological myocardium, this is the so-called left atrial isolation (LA) operation [2 – 3]. In 1981, one of the first successful operations of this type was performed in the treatment of left atrial flutter.

Guiraudon G.M. with co-authors in 1985 proposed the "corridor" procedure. This technique actually involved the creation of a corridor that should connect the sinus and atrioventricular nodes with the area of the atrial septum, which created surgical isolation of the left and right atria [4]. However, in the postoperative period, the transport function of the LA was disturbed, the tachyarrhythmia persisted, and there was a high need for electrocardiostimulation.

Due to the low efficiency, the "LA isolation" and "corridor" operations gave way to the more effective "labyrinth" procedure, which was proposed by Cox J. in 1987. The "labyrinth" operation became a classic in the surgical treatment of arrhythmia, and was subsequently improved and received a number of modifications : "labyrinth I - II - III" [5 – 8]. The operation includes the following actions:

- isolation of pulmonary veins as a single block;
- removal of the appendages of both atria;
- incision connection of the left atrial appendage suture with the collector of the pulmonary veins;
- incision connection of the right atrial appendage suture with the fibrous ring of the triscupid valve;
- connection of the collector of pulmonary veins with the posterior semicircle of the fibrous ring of the mitral valve;
- T-shaped section of the right atrium (vertical atriotomy from the atrioventricular groove + longitudinal section between the superior vena cava and the inferior vena cava);
- incision of the interatrial septum from the atriotomy to the coronary sinus; the atriotomy incisions are connected to each other.

It should be noted that Cox J. and co-authors identified five main conditions that are mandatory for complete elimination of arrhythmia and restoration of sinus rhythm (SR): 1) elimination of atrial fibrillation (AF); 2) restoration of SR; 3) restoration of atrioventricular synchronization and 4) atrial transport function; 5) reducing the risk of thromboembolism. Only the "labyrinth III" operation meets all these requirements and has become the standard of surgical treatment of arrhythmia [9 – 12].

However, despite its high efficiency, the "labyrinth" procedure is very rarely used by surgeons in open-heart surgery due to technical difficulties, significant duration and high risk of bleeding.

The introduction of new technologies into medicine made it possible to significantly facilitate such an operation. It was proposed to replace the traditional scalpel with linear ablation using different energy sources: radiofrequency ablation, cryoablation, etc. [13 – 17].

During radiofrequency ablation, heat is generated using an alternating electric current of medium frequency (in the range of 300 kHz - 1 MHz). Unmodulated monopolar or bipolar current is used for ablation of heart structures, since it is this that leads to coagulation necrosis, which is achieved in more than 90% of cases. To destroy biological tissue, it must be heated to temperatures above 50 °C, since at such temperatures irreversible cell death occurs. At temperatures above 100 C, evaporation of cell fluid occurs and damage to the cell membrane of myocytes, sarcoplasmic reticulum and mitochondria. If the temperature exceeds 140 C, carbonization of the tissue may occur. To ensure softer tissue coagulation, its temperature should be maintained in the range of $50 \div 100$ °C. The duration of radiofrequency ablation ranges from 10 to 20 minutes, which is several times less than the time of aortic cross-clamping during the original operation [5, 13, 18, 19]. The original operation "Maze III" lasts about 1 hour [11, 20].

Cryoablation is performed with the help of a hermetically isolated refrigerant (usually liquid nitrogen), which is delivered to the pathological area of the heart that is responsible for the irregular rhythm, with the aim of neutralizing it [21]. Cryoablation together with radiofrequency ablation gives approximately the same reduction in the time of surgery, clamping of the aorta, and artificial blood circulation compared to the classical option of "Labyrinth III" surgery [22]. The advantage over radiofrequency ablation is that due to transmural freezing of the atrium wall, the efficiency of the cryoablation procedure is higher. This is explained by the fact that freezing does not damage the collagen matrix; body tissues tolerate ultra-low temperatures (-120 -150 oC) better than a burn [25]. Therefore, cryoablation is devoid of the disadvantages of all methods of destruction based on the

influence of high temperature and leading to charring of tissues with subsequent thrombus formation or serious collateral damage to the heart and surrounding organs [23]. Another positive factor of cryodestruction is the often delayed restoration of sinus rhythm within a year after the intervention [24, 25, 26].

The main disadvantage of operations using cryodestruction is the high price of the equipment used to perform such operations. The use of such devices does not make it possible to ensure cooling with the necessary accuracy of temperature maintenance, it is necessary to use hoses and special conditions for the storage and transportation of refrigerants. They are dangerous and toxic substances, so work with them is carried out in a separate special room, away from explosive and flammable objects. If such substances get on the skin, there is a danger of getting all four degrees of frostbite and other complications [27].

However, among the sources of cold there is thermoelectric cooling, which has many advantages: a simple design, high reliability, precise control of temperature regimes, and the absence of dangerous refrigerants [27, 28]. Therefore, *the purpose of this paper* is to study the possibility of using thermoelectric cooling for the treatment of open-heart arrhythmia.

About temperature conditions and known methods of open heart cryodestruction

Cryomodification of the Labyrinth III operation has become widely used in modern medical practice for the treatment of arrhythmia. A number of companies that manufacture special equipment for such operations are known, and the results of clinical applications of this procedure have also been published.

One of the first devices for cryoablation was the cryoprobe from Medtronic (USA). This surgical ablation system consists of a control console that regulates time and temperature conditions, and disposable sterile probes containing a built-in thermocouple to monitor the temperature at the ablation site. The probes are made of specially heat-treated stainless steel and are designed to be flexible enough to be molded while maintaining sufficient rigidity to ensure stability during surgery. The dimensions of the working part of the probe are 60 mm. This device uses an argon-based cryogen for fast, controlled freezing. It is able to freeze biological tissue in the temperature range of -120 ÷ -160 oC and block electrical pathways, creating an inflammatory reaction and cryonecrosis. Ablation is carried out 1 minute after the probe has cooled to – 40 °C. The average time for a complete operation is about 17 minutes. With the help of such a device, 10 operations of the “Labyrinth III” type were performed using cryodestruction [24, 26, 27]. According to the results of this series of operations, there were no deaths or serious complications in patients. Sinus rhythm was restored on the operating table in all. As a result, when these patients were discharged, sinus rhythm was observed in 6 patients, others were on maintenance therapy due to repeated paroxysms of fibrillation. It should be noted that in 2 of them, the correct rhythm was restored after 3 and 6 months of treatment.

Another device actively used in medicine is the Atricure CryoFlex cryoprobe, developed by AtriCure (USA) and intended for cryosurgical treatment of cardiac arrhythmias by freezing tissues to block the passage of pathological electrical impulses. The device is a disposable sterile probe, the working part of which is corrugated and flexible, 10 cm long. N2O is used as a refrigerant. The device works together with the cryoICE BOX V6 control unit, with which you can adjust the temperature and ablation time. The work [32] provides data on the regular use of such a device for ablation of the left atrium during minimally invasive mitral valve procedures. A standard mini-maze procedure is performed, including bilateral pulmonary vein isolation, superior and inferior connecting lesions, mitral annulus lesions, and left atrial appendage lesions. The temperature of the cryoprobe during cryoablation is -140 oC, and the time to create each lesion is ¬ 2 minutes.

Reusable devices are also known. One of these is the "Cryo-01" device of the Russian company Elamed LPU. The principle of operation of the device is as follows. With excessive vapor pressure of the cryoagent (liquid nitrogen) in the Dewar vessel, which, together with the hermetically connected cryogenic block, form the cryostat, a regulated pulsed flow of the cryoagent from the cryostat through the pipeline to the cryoinstrument is formed. All cryotools are built according to the same principle and include a cylindrical working part with a threaded surface for attaching interchangeable nozzles and a docking unit with a connector and a ball seal of the liquid and gas channel of the cryoagent. The working part of cryoinstruments is made of thin-walled tubes and has vacuum thermal insulation, which protects the doctor's hands and the surface of the patient's body adjacent to the area of cryo action from hypothermia during the operation. The work [4] presents the result of using such a device for cryodestruction "Cryo-01". The patient was operated on in 6 stages: 1) local cryoaction between the inferior vena cava and the fibrous ring of tricuspid valve in the right atrium; 2) local cryoaction between the stump of the right atrium appendage and the fibrous ring of the tricuspid valve; 3) linear cryoimpact on the base of the left atrial stump; 4) linear cryoisolation of the mouths of the pulmonary veins; 5) local cryoaction between the line of ablation of the mouths of the pulmonary veins and the stump of the left atrium appendage; 6) local cryoimpact between the stump of the right atrium appendage and the Giradon incision. In this case, the time of artificial circulation was 210 minutes, and the time of aortic compression was 127 minutes. As a result, throughout the entire postoperative period the patient maintained a normal heart rhythm and after 10 days she was discharged in satisfactory condition.

Mechanism of cryodestruction

In modern medical practice, devices based on carbon dioxide, argon, or nitrogen are used for cryoablation to achieve ultralow temperatures in the range (–60 ÷ –200) °C. However, studies [29, 33 – 45] have confirmed that the use of such low temperatures is not necessary to achieve the necessary destruction of biological tissue. For the destruction of biological tissue, more moderate temperatures (-20 ÷ -50) °C can be used [30, 31].

A decrease in the temperature of biological tissue to (–5 ÷ –10) °C leads to the beginning of the process of crystal formation in the extracellular space, and with a decrease in temperature to (-15 ÷ -20) °C and below, the formation of ice crystals inside cells begins, which leads to death of biological tissue [30]. Cryonecrosis (destruction of biological tissue) occurs gradually, while cells and intracellular membranes are damaged by ice crystals. Blood circulation, supply of oxygen, nutrients, tissue respiration and all biochemical processes are completely stopped during freezing. As a result, the death of cells occurs in which all vital processes have been paralyzed for a long time. At the moment of ice crystal formation, a sharp increase in osmotic pressure in the cells occurs, since the extracellular fluid freezes faster and salt cations rush through the membranes into the cells. Biological cells cannot survive such an osmotic shock. The maximum damaging effect is achieved when biological tissue is cooled to -50 °C, and a further decrease in temperature does not increase the lethality of cells [30].

In addition, the intensity of cell destruction in the area of freezing depends not only on the minimum temperature, but also on the rate of cooling of biological tissue. Relatively fast freezing is optimal - (40–50) °C/min. The efficiency of cell cryodestruction is high, if it does not have time to displace the intracellular fluid through the membranes in the process of cooling the tissue before freezing [30]. Slower freezing (3–5) °C/min is impractical, since intracellular ice formation processes do not occur. It is also not rational to use ultra-fast freezing (more than 100 °C/min), since this forms amorphous ice that does not damage the structure of biological tissue [30].

It should be noted that the destruction of biological tissue occurs not only during cooling, but also during heating of the cooled tissue, and its effectiveness increases significantly during cyclic cooling-heating of biological tissue [27, 31].

Thus, the above research results indicate the following:

1. For cryodestruction, it is sufficient to reduce tissue temperatures to -20 ÷ -50 °C.
2. The optimal tissue cooling rate is 40–50 °C/min.

3. To increase the effectiveness of tissue cryodestruction, it is rational to use cyclic cooling and heating.

These conditions can be achieved through the use of thermoelectric cooling and heating method. Moreover, based on the capabilities of this method, its use may have advantages over others in terms of ease of use, accuracy of reproducing the required temperature conditions, cost of equipment, etc.

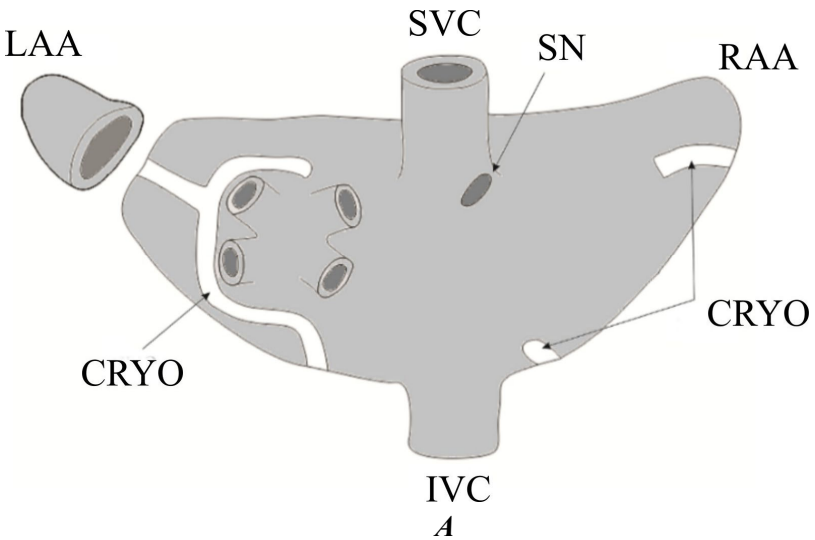
The principle of cryodestruction for arrhythmia and the method of its implementation

In order to achieve complete destruction of the pathological heart tissue, it is necessary that the lesion of the complete block of the conduction of pathological impulses be transmural, otherwise the electrical activity can cross the lesion line. For example, if a linear lesion is located on the endocardial side of the atrium and is not transmural, electrical activity may cross the lesion line on its epicardial side. Conversely, if a linear lesion is located on the epicardial side of the atrium and is not transmural, electrical activity may cross the lesion line on its endocardial side [32, 33].

The size of the lesion by cryoablation is proportional to the temperature of the probe, the area of he contact surface of the probe, the duration of energy supply and the number of freeze-thaw cycles [34 – 36].

Myocardial thickness varies considerably between different regions of the heart and between individuals (distal: range 1.4 – 7.7 mm, middle: range 1.2 – 4.4 mm, proximal: range 0 – 3.2 mm) [37]. However, from a clinical point of view, deep lesions are necessary only in a minority of cases. Currently, the majority of cryoablations are performed in atria with a typical muscle thickness of less than 3 mm [37].

For the treatment of open-heart arrhythmia using cryodestruction, a modification of the "Cox-Maze III" operation (Fig. 1) or a modification of the "Kosakai-Maze" operation (Fig. 2) is usually used [30, 38, 39].



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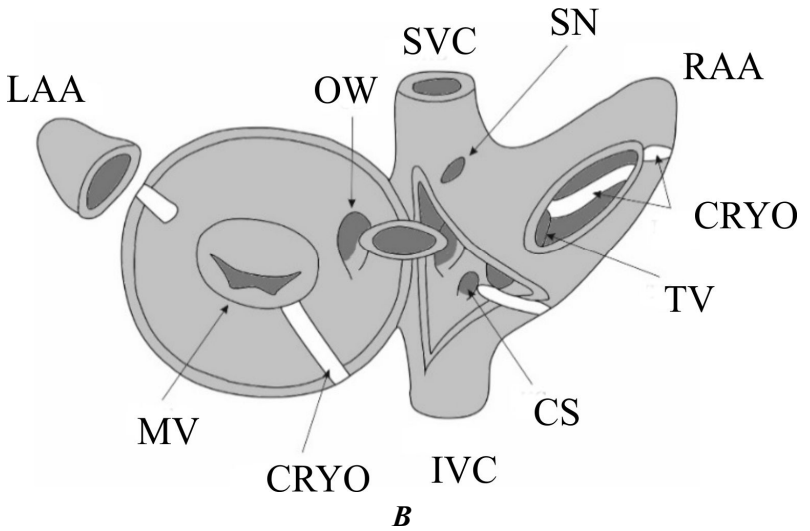

Fig. 1 Scheme of the "Cox-Maze III" operation (A - epicardial view, B - endocardial view).
LAA - left atrial appendage, SVC - superior vena cava, SN - sinus node,
RAA - right atrial appendage, IVC - inferior vena cava, OW - oval window,
TV - tricuspid valve, CS - coronary sinus, MV - mitral valve, CRYO - areas subject to cryodestruction

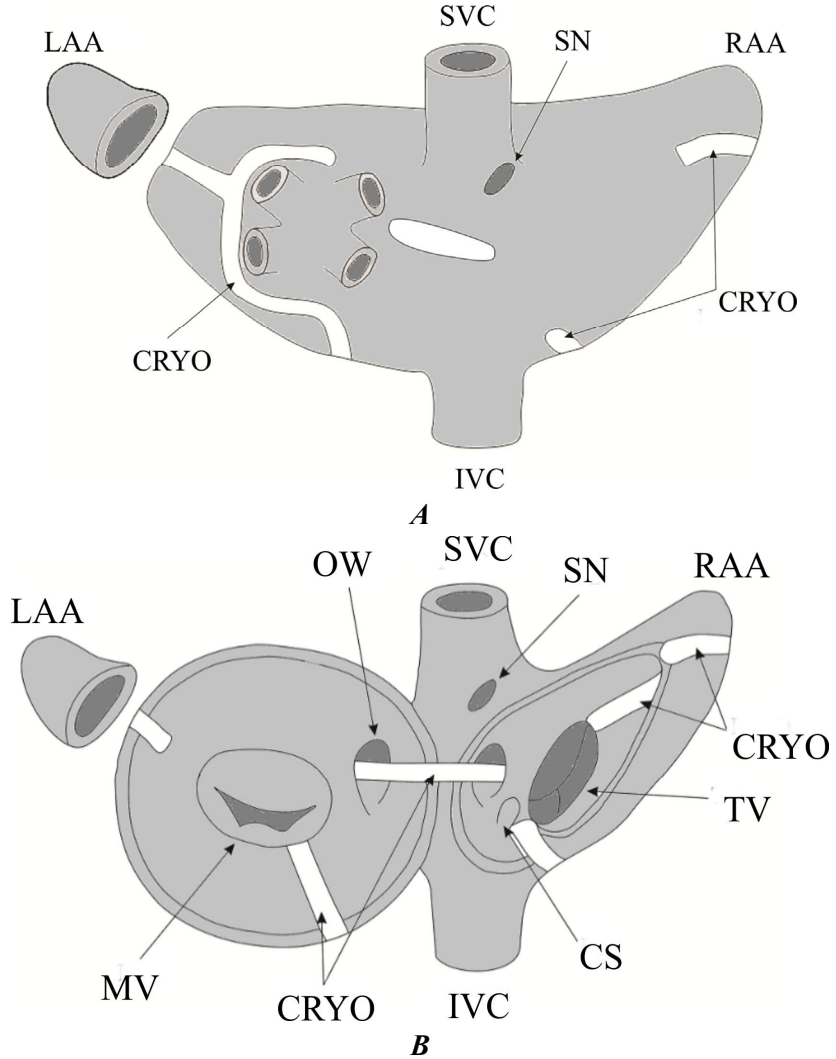

Fig.2. Scheme of the "Kosakai-Maze" operation (A – epicardial view, B – endocardial view).
LAA - left atrial appendage, SVC - superior vena cava, SN - sinus node, RAA - right atrium appendage,
IVC - inferior vena cava, OW - oval window, TV - tricuspid valve, CS - coronary sinus,
MV - mitral valve- sections subject to cryodestruction

Such procedures are carried out with special flexible probes, 4 to 10 cm long and 4 - 5 mm in diameter. They are able to provide cooling to (-60 ÷ -160)°C by using liquid nitrogen or argon. The duration of one cryo-lesion is 1 - 2 minutes [71 – 75].

Method of implementation of the "Cox-Maze III" operation

First, a cryo-lesion is performed on the inferior aspect of the pulmonary vestibule along the atrial ridge that separates the pulmonary vestibule from the mitral valve. The next cryo-lesion is created around the lateral aspect of the left pulmonary vein, between the left atrial appendage opening and the left superior pulmonary vein so as to cross the first lesion to form a connection between them. Next, the lesion is made on the upper aspect of the pulmonary vein, which connects to the left atriotomy incision, which is the only non-cryo lesion. After that, an endocardial lesion is created, which joins the previous lesions around the pulmonary veins to the mitral valve annulus. Next, an epicardial lesion is made, passing through the coronary sinus and the oblique sinus. And at the end, two lesions of the endocardium are created, 1 - to the tricuspid ring at the 2 o'clock position, and the other - between the right atrial appendage and the tricuspid ring at the 10 o'clock position [38].

Method of implementation of the "Kosakai-Maze" operation

At the first stage, cryoablation of the left atrial appendage is performed. Next, a cryo lesion is created on the back wall of the left atrium between the edge of the left atrial incision and the mitral annulus. The next lesion is made on the left side of the interatrial septum between the edge of the left atrium incision and the dorsum of the oval window, directed from the right atrium using forceps. Next, they move to the right atrium and perform cryoablation on the right side of the interatrial septum between the right atrium and the oval window. Cryoablation is then performed between the end of the right atriotomy and the tricuspid annulus. Finally, cryoablation is performed between the posterior edge of the right atrium incision and the junction with the fan [39].

Prospects for implementing temperature conditions of cryodestruction using thermoelectricity

From the above information, it can be concluded that the necessary conditions for the destruction of biological tissue can be achieved by using the thermoelectric method of cooling and heating. At the same time, based on the capabilities of this method, its use may have advantages over others in terms of ease of operation, accuracy of reproduction of the required temperature regimes, cost of equipment, etc.

In addition, the ability to reproduce multiple freezing-thawing makes it possible to reduce the temperature lethal for pathological tissue, to find a kind of compromise between the desire to freeze the pathogenic tissue as much as possible and the need to preserve healthy surrounding biological tissue [30].

It should be noted that in recent years research has been conducted on the use of thermoelectric cooling in medicine [27]. Many thermoelectric devices for cryodestruction have been created in the world, designed for the treatment of various diseases in various fields of medicine. Such devices are increasingly becoming widely used due to their advantages: simple design, high reliability, precise control of temperature regimes, and the absence of dangerous refrigerants [27, 28].

Conclusions

1. A review of the literature on open heart arrhythmia treatment methods has been made. It has been established that the promising method is the use of cryoablation.

2. The mechanism of cryodestruction was determined from the analysis of the literature and data was obtained that the use of excessive cooling is not necessary. It has been established that for cryodestruction, it is sufficient to reduce tissue temperatures to -20 ÷ -50 °C, and the optimal cooling rate of tissues should be 40–50 °C/min. To increase the efficiency of tissue cryodestruction, it is rational to use cyclic cooling and heating to (+39 ÷ +45) ºC, which indicates the prospects of using thermoelectric cooling in medical practice, since such conditions can be achieved by using the thermoelectric method of cooling and heating.
3. The most effective methods of treating arrhythmia using cryodestruction were studied and it was found that the depth of the lesion should be around 3 mm (the wall thickness is different in different parts of the heart). To create transmural damage to heart tissue, it is necessary to use the temperature of the working instrument T = -60 ºC, exposure time t = 2 minutes.
4. It was established that the use of the thermoelectric method of cooling is promising, as it provides the necessary conditions for the destruction of biological tissue, and its use may have advantages over other methods in terms of ease of operation, accuracy of reproduction of the required temperature regimes, cost of equipment, etc.

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Анатичук Л. І., *акад. НАН України* [1,2]
Кобилянський Р. Р., *канд. фіз.-мат. наук* [1,2]
Федорів Р. В. [1,2]
Константинович І. А., *канд. фіз.-мат. наук* [1,2]

[1] Інститут термоелектрики НАН та МОН України,
вул. Науки, 1, Чернівці, 58029, Україна;
[2] Чернівецький національний університет імені Юрія Федьковича,
вул. Коцюбинського 2, Чернівці, 58012, Україна
e-mail: anatych@gmail.com

ПРО ПЕРСПЕКТИВИ ВИКОРИСТАННЯ ТЕРМОЕЛЕКТРИЧНОГО ОХОЛОДЖЕННЯ ДЛЯ ЛІКУВАННЯ АРИТМІЇ СЕРЦЯ

У роботі наводяться результати аналізу різноманітних методів лікування аритмії серця. Серед них особливу увагу привертає метод абляції, що зводиться до ліквідації додаткових електричних подразників скорочення серцевих м'язів. Останнє досягається хірургічними методами, високочастотним опроміненням та кріодеструкцією рідким азотом або шляхом використання ефекту Джоуля-Томсона. Кріометоди мають певні переваги перед іншими, однак їх реалізація є дещо складнішою, що обмежує їх клінічні використання. В

останні десятиріччя у медицині все ширше використовується охолодження ефектом Пельтьє. Він зарекомендував себе як простий, надійний і точний у відтворенні необхідних температурних умов лікування. Дана робота присвячена дослідженню можливості використання ефекту Пельтьє для кріоабляції. Бібл. 39, рис. 2.

Ключові слова: аритмія серця, фібриляція передсердь, кріоабляція, термоелектричне охолодження.

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