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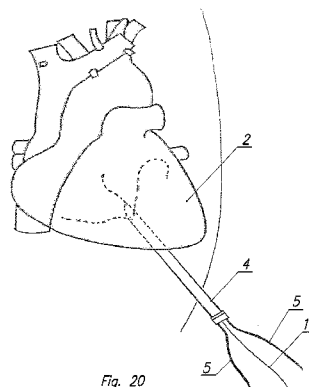
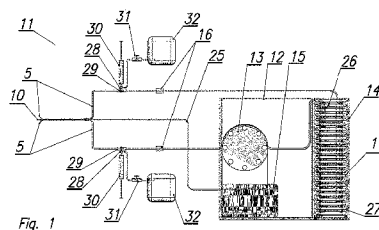
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(54) Title: COOLING LIQUID, METHOD, DEVICE AND PERICARDIAL CATHETER FOR THE HEART HYPOTHERMIA AND APPLICATION OF THE COOLING LIQUID



(57) Abstract: The cooling fluid (1) is designed to be introduced into the pericardium (3) of the heart (2) and contains either a crystalloid or a crystalloid with substances neutralizing harmful products of oxygen metabolism. In another version the cooling fluid (1) contains a dose of antiarrhythmic drug. The heart (2) is cooled down directly by the cooling fluid (1) introduced by a pericardial catheter (4) via cooling ducts (5) into the pericardium (3). The amount of cooling fluid (1) introduced in and withdrawn from the pericardium (3) as well as its temperature and pressure inside the pericardium (3) is monitored. The temperature in the pericardium (3) is regulated depending on the clinical requirements in the range from 10°C to 36°C. The subject of the invention is also another device (11), pericardial catheter (4) and another cooling fluid and its use which enables maintaining the temperature in the range from 10°C to 36°C inside the pericardium (3) during the cardiac hypothermia (2). The invention is used for a direct cardiac hypothermia (2) in case of cardiac arrest (2), arrhythmia and whenever it is necessary to decrease the oxygen metabolism of cardiac tissue (2), for example in the case of bridging, in advanced coronary artery disease (2), in heart transplantation (2), and can be used as cardioprotection in procedures such as TAVI and BAV, etc.



**Cooling liquid, method, device and pericardial catheter for the heart  
hypothermia and application of the cooling liquid**

The present invention is a cooling liquid, a method, a device and a pericardial catheter for heart hypothermia and an application of the cooling liquid, which are intended to reduce the temperature of the heart, and therefore change the level of metabolism of the heart muscle during myocardial infarction, arrhythmia and other need to reduce the oxygen metabolism of the heart tissue, for example in the bridging procedure in patients with advanced ischemic heart disease for heart transplant as well as cardio-protective therapy in such surgical treatments as TAVI, BAV, etc.

Myocardial infarction arises from sudden coronary artery occlusion. The myocardial area supplied by the artery is cut off from the blood supply and hence oxygen and nutrients, which causes necrosis of part of the heart. The larger vessel is occluded, the larger area of the heart undergoes necrosis. The larger area of the heart undergoes necrosis, the weaker becomes the heart and respectively shorter the patient survival.

Currently medical procedure for the treatment of myocardial infarction is limited to the modification of two factors that reduce the extent of necrosis: time from the coronary artery occlusion to its opening (the shorter the time, the less damage) and use of proper drug groups.

Previously used therapeutic hypothermia is the method for lowering the temperature of the entire body of the patient to about  $32 \div 34$  ° C and it has been known for several years. Currently, the most widely used therapeutic hypothermia is used to limit the brain damage in patients after cardiac arrest or cerebrospinal

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injuries. A clinical study clearly showed that the application of hypothermia therapy in patients after hospital cardiac arrest significantly reduces mortality, as shown in the publication by Bernard S. A. Jones, B. M., Horne M. K., Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med August 1997; 30:146-15. However, due to the systemic nature of the therapeutic hypothermia this procedure requires additional procedures, such as sedation of the patient, skeletal muscle relaxation, and application of mechanical ventilation.

As is known, treatment schedules currently used in the treatment of acute coronary syndromes and spectacular results of use of the invasive treatment in myocardial infarction significantly reduced mortality. Significant reduction in time of the patient transportation from home to the catheterization laboratory and the availability of invasive cardiology laboratory allow for quick treatment of myocardial infarction, aimed at restoring patency the occluded vessel with the appropriate instruments introduced into the patient's vasculature. The current European and US guidelines pay special attention to a maximum shortening of the time for cardiovascular intervention in the catheterization laboratory, where the recommended time is less than 1.5 hours in accordance with the - time is muscle - principle.

According to the invention, the cooling liquid for the heart hypothermia, intended to be placed into the heart pericardial sac, is characterized in that it comprises crystalloid or, depending on the clinical needs, crystalloid with substances neutralizing harmful by-products of ROS oxygen metabolism.

Crystalloid preferably is in the cooling liquid in the form of an aqueous solution of NaCl having a concentration of 0.9% by weight, and neutralizing substances contain the following per 100 ml of NaCl solution: glutathione GSH in an amount of 1200 mg, selenium Se in an amount of 14 mg, retinol (vitamin A) in an amount of 2 mg, alpha-tocopherol (vitamin E) in an amount of 100 mg and ascorbic acid in an amount of 100 mg.

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Further advantages are obtained if the cooling liquid contains a dose of the ant arrhythmic drug, which contains a mixture of amiodarone and glucose of a concentration of 5% ÷ 10% by weight.

According to the invention, the method of the heart hypothermia, is characterized in that the heart is cooled directly by the cooling liquid introduced through pericardial catheter, using cooling tubes, to the heart pericardial sac, wherein when introducing of the cooling liquid, its quantity introduced into the pericardial sac and discharged from it, and the temperature and pressure of the pericardial sac liquid mixture with cooling liquid inside the pericardial sac are monitored.

Preferably, during the heart cooling, the temperature inside the pericardial sac is, depending on the clinical needs, maintained in the range from 10 ° C to 36 ° C.

In the first stage, before the introduction of the cooling liquid into the pericardial sac, it is punctured with a needle having a central bore, whereupon, a guidewire is introduced into the pericardial sac through the axial bore of the needle, after removal of the needle from the guidewire pericardial catheter sealed with a guide with handle is slidden over it, and pericardial catheter is introduced into the pericardial sac, and then, after the proper placement of the pericardial catheter in the pericardial sac, the guide is detached, it is ejected from the pericardial sac, and then the guidewire is removed. In the second stage, before the introduction of the cooling liquid, cooling tubes and test probe are introduced into the pericardial sac through the pericardial catheter.

Further advantages are obtained if the cooling tubes and the test probe are sealed in the pericardial catheter, while forming a tight system closed for circulation of the cooling liquid in the pericardial sac and its outside.

According to the invention, the device for the heart hypothermia is characterized in that it comprises a pericardial catheter through which the cooling tubes with the cooling liquid and the test probe are with their ends introduced into

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the pericardial sac of the cooled heart, and their second ends are connected to the power supply and control unit, provided with at least one pump of the cooling liquid and cooling unit of the cooling liquid, and the controller of that pump and cooling unit, wherein the second ends of the cooling tubes are through the flow sensors connected with the pump and the cooling unit, and the second end of the test probe is connected to the input of the controller, and preferably outputs of that flow sensor are connected to further inputs of that controller.

Preferably, the pericardial catheter of the device is shaped like an elongated cylinder in front ended with a conical tip, and has main duct ended at the tip and located in its axis for the test probe and two lateral ducts parallel to the main duct, ended in front of the pericardial catheter, on its cylindrical surface, with lateral openings for cooling tubes, and in the rear part of the pericardial catheter the cooling tubes, and the test probe are sealed in it with a flexible valve covered by a cylindrical lid, which is snap mounted on the circumferential protrusion of the pericardial catheter, and moreover, after the introduction of the pericardial sac into the pericardial catheter it is sealed with a guide with a handle.

Further advantages are obtained if the cooling tube is ended at its end embedded in the pericardial sac with longitudinal apertures spaced around its circumference, and the test probe is at its end embedded in the pericardial sac ended with temperature and pressure sensors, and on the opposite side with a plug, whereby connection of the test probe with the input of the controller is through the test tube, and moreover the cooling unit of the power supply and control unit has a cooling coil placed in a tray for the cooling liquid.

Further advantages are obtained if in the cooling tubes of the device tees are mounted with the first taps, and each of the tees is connected to a second syringe via the second tap with the container for the cooling liquid and air, sucked from the cooling tubes, and moreover the apparatus further comprises a guide with a handle which is provided with a central passage duct for the guidewire, and the handle of the guide has two plugging lateral ducts of the pericardial catheter when introduced into the pericardial sac.

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According to the invention, the pericardial catheter, for hypothermia of the heart, is characterized in that, is shaped like an elongated cylinder in front ended with a conical tip, and has main duct ended at the tip and located in its axis and two lateral ducts parallel to the main duct, ended in front of the pericardial catheter, on its cylindrical surface, with lateral openings, and in the rear part of the pericardial catheter a flexible valve, with a covered cylindrical lid is embedded, which is snap mounted on the circumferential protrusion of the pericardial catheter, and moreover, after the introduction of the pericardial sac into the pericardial catheter it is sealed with a guide with a handle, which is provided with a central passage duct and has two plugging tubes lathered ducts of the pericardial catheter in its introduction into the pericardial sac.

Other cooling liquid for heart hypothermia, intended for mechanical introduction and removal from pericardial sac with the use of pericardial catheter for the purpose of direct heart cooling, based on the invention is characterized by the fact that it is a water solution of a substance with temperature lower than the organism to which it is introduced.

It is advantageous, that the cooling liquid contains as a substance at least one substance neutralizing Reactive Oxygen Species (ROS), and the advantageous content of neutralizing substances in 100 ml of solution occurs in the following: 1200 mg of glutathione (GSH), 14  $\mu$ g of selenium, 2 mg of retinol (vitamin A), 100 mg of alfa-tocopherol (vitamin E) and 100 mg of ascorbic acid.

Further advantages are achieved if the cooling liquid contains a dose of anti-arrhythmic drug, while as the dose of anti-arrhythmic drug it contains mixture of amiodarone and glucose of a concentration of 5% ÷ 10% by weight.

Application of the above described cooling liquid based on the invention is characterized by the fact that it is used for direct heart hypothermia by means of introduction of chilled cooling liquid to pericardial sac, monitoring the amount of cooling liquid introduced to pericardial sac and released therefrom as well as monitoring the temperature and pressure of the mixture of pericardial sac liquid

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and cooling liquid inside pericardial sac.

It is advantageous, that the cooling liquid maintains the temperature inside pericardial sac during heart hypothermia within the following limits: from 10 °C to 36 °C.

According to the invention, the described cooling liquids and method of direct heart hypothermia for the treatment of myocardial infarction have not previously been used in cardiology, and moreover it allows to affect the metabolic rate of muscle tissue of the heart, and by reducing the extent of necrosis it limits the damage to the heart after myocardial infarction, and thus affects the survival and the quality of life of patients.

According to the invention the method of the direct heart hypothermia using the device allows to keep the state of consciousness of the patient, eliminates the need for intubation and artificial ventilation. With the introduction of the cooled cooling liquid directly into the pericardial sac a direct effect on the heart muscle is possible. By lowering the temperature of the heart, the level of metabolism of the heart muscle will be reduced, and thus the area of damage in myocardial infarction will be limited. Recommendations for direct heart hypothermia include myocardial infarction, malignant arrhythmias and other needs for decreasing aerobic metabolism of heart tissue, such as e.g. bridge therapy for heart transplant in patients with advanced ischemic heart disease for heart transplant and also as cardio-protective therapy in surgical treatments such as: TAVI, BAV, etc.

Thanks to the invention, a system to be used in medicine (cardiology) was developed for quick and immediate reduction in the temperature of the heart muscle during myocardial infarction, and thus maximally quick release of the metabolism of the heart, which directly translates to the extent of myocardial infarction, and thus the survival of patients.

Innovation of solutions according to the invention is to optimize of further, except the time of intervention and introducing PCI (Percutaneous coronary

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Interventions) as a method of treating, mortality reducing factor - metabolism of the heart tissue. The reduced cooling liquid temperature in the pericardial sac (immediately surrounding the ischemic myocardial muscle) significantly slows the metabolic processes of the muscle, reducing the production of free radicals, slowing the production of other harmful products of metabolism and change of pH. Moreover, as demonstrated by tests, reduction of the heart tissue temperature stabilizes the cell membrane potential, thereby reducing the tendency to malignant arrhythmia in myocardial infarction. The invention is also applicable in the course of electrical storms, recurring arrhythmias, which are difficult to deal with by means of classical pharmacotherapy, as a bridge therapy for heart transplant in advanced ischemic heart disease. According to the invention the device was designed so that in addition to the possibility of "cooling the metabolism" of myocardium and antioxidant therapy, wherein the cooling liquid in addition to the cooling function can perform a reducing function, i.e., has the capacity to neutralize harmful products of ROS oxidative metabolism (Reactive Oxygen Species), for example, such as superoxide anion  $O_2^{\bullet-}$ , hydroperoxide radical  $HO_2^{\bullet}$ , it being possible to apply virtually any drug in the form of solution for injection by administering a suitable dose to the closed cooling liquid circuit of the device. This possibility is particularly important in patients with severe arrhythmias in the course of extensive myocardial infarction (such as amiodarone), or in the case of cardiogenic shock, when any number of catecholamines may be added to the system of direct hypothermia of the heart. The advantage of the invention is no need for sedation of the patients and sagging of skeletal muscles, as in the case of other therapeutic hypothermia. This feature allows maintaining a constant state of consciousness in the course of therapy in the intensive care ward and excludes any complications resulting from the use of sedatives, depolarizing neuromuscular junction and respiratorotherapy.

The solutions according to the invention are further clarified in embodiments on the drawing, in which: Fig. 1 shows the device according to the

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invention, as a scheme, Fig. 2 - pericardial catheter plugged with the guide with a handle in a perspective view from the front, side and top, Fig. 3 - the same pericardial catheter with the guide with a handle in a perspective dispersed view from the front, side and top, Fig. 4 ÷ 6 show pericardial catheter, respectively in a longitudinal section of the main duct, a longitudinal section of the lateral ducts and perspective front, side and top views, Fig. 7 ÷ 9 - guide with a handle and plugging tubes, respectively in front, side and top perspective views, and longitudinal cross section through the passage duct, Fig. 10 shows a pericardial catheter with the introduced cooling tubes and the test probe in front, side and top perspective view, Fig. 11 ÷ 13 showing the lid of the pericardial catheter, respectively in a perspective front and lateral view, front view and longitudinal section, Fig. 14 and 15 - pericardial catheter valve with openings for cooling liquid tubes, test probe and with recesses retaining its position within the pericardial catheter, respectively in front view and longitudinal section, Fig. 16 ÷ 18 - cooling tube, respectively, in lateral view, enlarged lateral view in longitudinal of openings and enlarged side view of the opposite end thereof, Fig. 19 shows the test probe with the connector in a side view, Fig. 20 - pericardial catheter with cooling tubes and probe inserted to the heart, as a scheme, Fig. 21 - chest with the location of the heart and its adjacent elements in longitudinal section, and Figures 22 ÷ 24 show sequential stages of the pericardial catheter introduction into the pericardial sac, in the longitudinal sections on Figures 22 and 23 and cross-section of the pericardial sac on Fig. 24.

According to the invention, the cooling liquid 1 for the heart 2 hypothermia in an embodiment is intended for its introduction into the heart 2 pericardial sac 3. In a preferred embodiment, the cooling liquid comprises crystalloid in the form of an aqueous solution of NaCl having a concentration of 0.9% by weight.

In a second embodiment the cooling liquid 1 further comprises substances neutralizing harmful by-products of ROS oxygen metabolism, which comprise the

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following per 100 ml of the NaCl solution: glutathione GSH in an amount of 1200 mg, selenium Se in an amount of 14 mg, retinol (vitamin A) in an amount of 2 mg, alpha-tocopherol (vitamin E) in an amount of 100 mg and ascorbic acid in an amount of 100 mg.

In a third embodiment, the cooling liquid 1, in addition to the aforementioned components, comprises a dose of the ant arrhythmic drug in the form of a mixture of amiodarone and glucose and a concentration of 5% ÷ 10% by weight.

The developed cooling liquid 1 is characterized by a high reducing potential. Its chemical composition outside the function of direct cooling of the heart muscle (myocardium) has the ability to neutralize harmful products of ROS oxygen metabolism. Reducing substances such as glutathione, selenium, retinol, alpha-tocopherol and ascorbic acid, used in optimum concentrations in an extremely efficient way absorb and inactivate reactive oxygen species (ROS) arising during acute myocardial ischemia. For maintaining a maximum buffering capacity of the cooling liquid 1, the maximum optimal duration of therapy with one portion of the cooling liquid 1 equal to 500 ml for about 24 hours of continuous therapy was determined. If the therapy requires a treatment longer than 24 hours, it is recommended to replace the cooling liquid 1 every 24 hours. It is only possible to conduct heart 2 hypothermia - to this end every available crystalloid is used as a cooling liquid 1. In certain cases of arrhythmia, requiring maximization of the ant arrhythmic therapy, 1 dose of the ant arrhythmic drug is injected in addition to the cooling liquid.

According to the invention, in the method of the heart 2 hypothermia in an embodiment, the heart 2 is cooled directly by the cooling liquid 1 introduced through pericardial catheter 4, using cooling tubes 5, to the heart 2 pericardial sac 3, When introducing of the cooling liquid 1, its quantity introduced into the pericardial sac 3 and discharged from it, and the temperature and pressure of the pericardial sac 3 liquid mixture with cooling liquid 1, inside the pericardial sac 3

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are monitored. During the heart 2 cooling, the temperature inside the pericardial sac 3 is maintained in the range from 10 ° C to 36 ° C, depending on the patient's clinical condition. In the first stage, before the introduction of the cooling liquid 1 into the pericardial sac 3, it is punctured with a needle 6 having a central bore, whereupon, a guidewire 7 is introduced into the pericardial sac 3 through the axial bore of the needle 6, after removal of the needle 6 from the guidewire 7 pericardial catheter 4 sealed with a guide 8 with handle is slid over it, and pericardial catheter 4 is introduced into the pericardial sac 3, and then, after the proper placement of the pericardial catheter 4 in the pericardial sac 3, the guide 8 is detached, it is ejected from the pericardial sac 3, and then the guidewire 7 is removed. In the second stage, before the introduction of the cooling liquid 1, cooling tubes 5 and test probe 10 are introduced into the pericardial sac 3 through the pericardial catheter 4. Cooling tubes 5 and the test probe 10 are sealed in the pericardial catheter 4, while forming a tight system closed for circulation of the cooling liquid 1 in the pericardial sac 3 and its outside.

The method of the invention involves direct cooling of myocardium in pericardial sac 3, which allows for cooling of the outer layer 2 of myocardium. Currently, studies are planned to determine the optimal target temperature of the heart 2.

The procedure of introducing the pericardial catheter 4 into the pericardial sac 3 consists of several stages. In the first stage, access to the pericardial sac 3 must be obtained by the same puncturing as for the pericardiocentesis. After puncturing the pericardial sac 3 with the needle 6 and the confirmation of the successful puncture by drawing a small amount of the liquid from the pericardial sac 3 to the first syringe (not shown on the figure) the guidewire 7 is introduced to the pericardial sac 3 through the needle 6. Then the needle 6 is removed from the pericardial sac 3 from the guidewire 7 and is completely slipped out of the guidewire 7 in the direction of the patient, and the pericardial catheter 4 sealed by the guide 8 with a handle 9 overlaps the distal part of the guidewire 7, coming out of the pericardial sac 3 through the body shell, and the pericardial catheter 4 is

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introduced into the pericardial sac 3. While stabilizing with one hand the guidewire 7, the guide 8 is with the other hand moved with pericardial catheter 4 towards the pericardial body shells so as to introduce the pericardial catheter 4 into the pericardial sac 3 of the patient. Before the introduction of the pericardial catheter 4 to pericardial sac 3 a small incision of the skin is performed, so that the pericardial catheter 4 with a guidewire 8 could be introduced into the pericardial sac 3 with the least resistance. After the proper placement of the pericardial catheter 4 in the pericardial sac 3 guide 8 is detached from the pericardial catheter 4, and then in one smooth movement it is removed after the guidewire 7, then the guidewire 7 itself is removed.

Once the pericardial catheter 4 is introduced into the pericardial sac 3 using known methods of the imaging testing (fluoroscopy, echocardiography), during the second stage cooling tubes 5 and test probe 10 are introduced to the pericardial sac 3 through the pericardial catheter 4. The cooling consists in injecting the cooling liquid 1 into the pericardial sac 3 via a cooling tube 5 (cooled to a predetermined temperature) and receipt of the same volume of the cooling liquid 1 per unit of time via the second cooling tube 5 in a closed circuit. Pericardial catheter 4 is designed as to match the pericardial sac 3 to create a tight closed circuit for the continuous circulation of the mixture of the pericardial sac 3 liquid and the cooling liquid 1, wherein it is also possible to introduce additional pharmacological substance into the circuit.

According to the invention, the device 11 for the heart 2 hypothermia in an embodiment, comprises a pericardial catheter 4 through which the cooling tubes 5 with the cooling liquid 1 and the test probe 10 are with their ends introduced into the pericardial sac 3 of the cooled heart 2, and their second ends are connected to the power supply and control unit 12, provided with one pump 13 of the cooling liquid 1 and cooling unit 14 of the cooling liquid 1, and the controller 15 of that pump 13 and cooling unit 14. The second ends of the cooling tubes 5 are through the flow sensors 16 connected with the pump 13 and the cooling unit 14, the

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second test probe 10 is connected to the input of the controller 15, and outputs of those flow sensors 16 are connected to further inputs of that controller 15. The pericardial catheter 4 is shaped like an elongated cylinder in front ended with a conical tip, and has main duct 17 ended at the tip and located in its axis for the test probe 10 and two lateral ducts 18 parallel to the main duct 17, ended in front of the pericardial catheter 4, on its cylindrical surface, with lateral openings 19 for cooling tubes 5. And in the rear part of the pericardial catheter 4 the cooling tubes 5, and the test probe 10 are sealed in it with a flexible valve 20 covered by a cylindrical lid 21, which is snap mounted on the circumferential protrusion of the pericardial catheter. The cooling tube 5 is ended at its end embedded in the pericardial sac 3 with longitudinal apertures 23 spaced around its circumference. And the test probe 10 is at its end embedded in the pericardial sac 3 ended with temperature and pressure sensors, and on the opposite side with a plug 24, whereby connection of the test probe 10 with the input of the controller 25 is through the test tube 25. The temperature sensor of the test probe 10 regulates the operation of the power supply and control unit 12 of the devices 11, and the pressure sensor of the test probe 10 is responsible for a continuous monitoring of the pressure of the cooling liquid 1 in the pericardial sac 3. The temperature of the cooling liquid 1 as the pressure in the pericardial 3 sets manually using the controller 15 as an integral part of the device 11. The cooling unit 14 of the power supply and control unit 12 in the device 11 has a cooling coil 26 placed in a tray 27 for the cooling liquid 1. In the cooling tubes 5 of the devices 11, tees 28 are mounted with the first taps 29, and each of the tees 28 is connected to a second syringe 30 via the second tap 31 with the container 32 for the cooling liquid 1 and air, sucked from the cooling tubes 5. Furthermore, the device 11 comprises a guide 8 with a handle 9, which is provided with a central passage duct 33 for a guidewire 7. Handle 9 of the guide 8 has two tubes plugging 34 the lateral ducts 18 of the pericardial catheter 4 when it is introduced into the pericardial sac 3.

According to the invention the pericardial catheter 4 in an embodiment, for hypothermia of the heart 2, is shaped like an elongated cylinder in front ended

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with a conical tip, and has main duct 17 ended at the tip and located in its axis and two lateral ducts 18 parallel to the main duct 17, ended in front of the pericardial catheter 4, on its cylindrical surface, with lateral openings 19, and in the rear part of the pericardial catheter 4 a flexible valve 20, with a covered cylindrical lid 21 is embedded, which is snap mounted on the circumferential protrusion of the pericardial catheter 4, and moreover, after the introduction of the pericardial sac 3 into the pericardial catheter 4 it is sealed with a guide 8 with a handle. 9, which is provided with a central passage duct 33 and has two plugging tubes 34 lathered ducts 18 of the pericardial catheter 4 in its introduction into the pericardial sac 3.

It is important that the cooling tubes 5 and the test probe 10 introduced into the pericardial sac 3 through the pericardial catheter 4 do not adhere too strongly to the cardiac wall and/or the inner surface of the pericardial sac 3, since with this arrangement a free circulation of the cooling liquid 1 in the pericardial sac 3 is possible and the risk of perforation is minimized. In the next stage cooling tubes 5 are connected to the tray 27 with the cooling liquid 1 and the test probe 10 with the test tube 25 of the controller 15, and then using the two second syringes 30 and containers 32 for the air and the cooling liquid 1 the air from the cooling tubes 5 is removed. After entering the manual setting on the controller 15 and connecting the tray 27 with cooling liquid 1 the process of direct heart 2 hypothermia begins. It should be noted that the device 11 has built-in sensors that continuously record the amount of the cooling liquid 1 entering into the pericardial sac 3, the amount of the cooling liquid 1 living the pericardial sac 3, the temperature of the cooling liquid 1 and the pressure of the pericardial sac 3. Thanks to the applied sensors an excellent control of the temperature of the myocardium of the ventricles, possibility of its smooth adjustment and adaptation to the current clinical condition of the patient are achieved, as well as the possibility of a dangerous increase or decrease in the pressure of liquid in the pericardial sac 3 is eliminated. Flow sensors 16, sensors of temperature and pressure installed on the device 11 after recording a significant deviation from the programmed settings cause the immediate stop of the device 11 and the activation

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of the audio signal.

On Fig. 21 the location of the heart 2 and its adjacent elements is shown in the form of pericardial cavity 35, spine 36, chest 37 wall and diaphragm 38, and Fig. 22 ÷ 24 show further stages of introducing the pericardial catheter 4 into the pericardial sac 3.

Other cooling liquid 1 for heart hypothermia 2, based on the invention in a fourth and a fifth example of execution is intended to be mechanically introduced and discharged from pericardial sac 3 with the use of pericardial catheter 4 to cause direct heart cooling 2, whereas cooling liquid 1 is a water solution of the substance and its temperature is lower than the organism to which it is introduced.

In the fourth example of execution, cooling liquid 1 contains substances neutralizing harmful products of aerobic metabolism (ROS), which contain the following in 100 ml of solution: 1200 mg of glutathione (GSH), 14 µg of selenium, 2 mg of retinol (vitamin A), 100 mg of alfa-tocopherol (vitamin E) and 100 mg of ascorbic acid, whereas cooling liquid 1 contains optional crystalloid.

In the fifth example of execution, cooling liquid contains identical components as in the first example, moreover, it contains a dose of anti-arrhythmia drug in the form of mixture of amiodarone and glucose with mass concentration of 5% ÷ 10%.

Application of the above described cooling liquid 1, based on the invention in the fourth example of execution is aimed at direct heart hypothermia 2 by means of introducing chilled cooling liquid 1 to pericardial sac 3 of the heart 2, monitoring the amount of cooling liquid 1 introduced to and discharged from pericardial sac 3, and monitoring temperature and pressure of the mixture of pericardial sac liquid 3 with cooling liquid 1, inside pericardial sac 3.

Application, based on the invention in the fifth example of execution, is the same as in the fourth example, moreover, it is aimed at maintenance during heart hypothermia 2 temperature inside pericardial sac 3 within the limits from

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10 °C to 36 °C.

The cooling liquid 1 in the fourth and fifth example of execution has similar properties to the cooling liquid 1, which is described in the examples from the first to the third, and it holds the same use.

The invention is applicable in lowering temperature of heart 2 in the course of myocardial infarction 2, arrhythmia and in other need to decrease aerobic metabolism of heart tissue 2, for example in bridge therapy in advanced ischemic heart 2 disease for heart 2 transplant and as cardio-protective procedure during surgical treatment such as TAVI, BAV, etc.

**List of designations**

|                                     |                            |
|-------------------------------------|----------------------------|
| 1 - cooling liquid,                 | 21 - lid,                  |
| 2 - heart,                          | 23 - longitudinal opening, |
| 3 - pericardial sac,                | 24 - plug,                 |
| 4 - pericardial catheter,           | 25 - test tube,            |
| 5 - cooling hose,                   | 26 - cooling water,        |
| 6 - needle,                         | 27 - tray,                 |
| 7 - guidewire,                      | 28 - tee,                  |
| 8 - guide,                          | 29 - first tap             |
| 9. handle                           | 30 - second syringe,       |
| 10 - test probe,                    | 31 - second tap,           |
| 11 - device,                        | 32 - container,            |
| 12 - power supply and control unit, | 33 - passage duct,         |
| 13 - pump,                          | 34 - plugging tube,        |
| 14 - cooling unit,                  | 35 - pericardial cavity,   |
| 15 - controller,                    | 36 - spine,                |
| 16 - flow sensor                    | 37 - chest,                |
| 17 - main duct,                     | 38 - diaphragm             |
| 18 - lateral duct,                  |                            |
| 19 - lateral opening,               |                            |
| 20 - valve,                         |                            |

### Patent claims

1. The cooling liquid for the heart hypothermia, intended to be placed into the heart pericardial sac, **is characterized in that** it comprises crystalloid or crystalloid with substances neutralizing harmful by-products of ROS oxygen metabolism.

2. Cooling liquid according to claim 1, **is characterized in that** crystalloid is in the form of an aqueous solution of NaCl having a concentration of 0.9% by weight, and neutralizing substances contain the following per 100 ml of NaCl solution: glutathione GSH in an amount of 1200 mg, selenium Se in an amount of 14 mg, retinol (vitamin A) in an amount of 2 mg, alpha-tocopherol (vitamin E) in an amount of 100 mg and ascorbic acid in an amount of 100 mg.

3. Cooling liquid according to claim 1 or 2, **is characterized in that** it comprises a dose of ant arrhythmic drug.

4. Cooling liquid according to claim 3, **is characterized in that** it contains as a dose of the ant arrhythmic drug, which contains a mixture of amiodarone and glucose of a concentration of 5% ÷ 10% by weight.

5. The method of the heart hypothermia, **is characterized in that** the heart (2) is cooled directly by the cooling liquid (1) introduced through pericardial catheter (4), using cooling tubes (5), to the heart (2) pericardial sac (3), wherein when introducing of the cooling liquid (1), its quantity introduced into the pericardial sac (3) and discharged from it, and the temperature and pressure of the pericardial sac (3) liquid mixture with cooling liquid (1), inside the pericardial sac (3) are monitored.

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6. The method according to claim 5, **is characterized in that** during the heart (2) cooling, the temperature inside the pericardial sac (3) is maintained in the range from 10 ° C to 36 ° C.

7. The method according to claim 5 or 6, **is characterized in that** in the first stage, before the introduction of the cooling liquid (1) into the pericardial sac (3), it is punctured with a needle (6) having a central bore, whereupon, a guidewire (7) is introduced into the pericardial sac (3) through the axial bore of the needle (6), after removal of the needle (6) from the guidewire (7) pericardial catheter (4) sealed with a guide (8) with handle (9) is slidden over it, and pericardial catheter (3) is introduced into the pericardial sac (4), and then, after the proper placement of the pericardial catheter (4) in the pericardial sac (3) the guide (8) is detached, it is ejected from the pericardial sac (3), and then the guidewire (7) is removed, in the second stage, before the introduction of the cooling liquid (1), cooling tubes (5) and test probe (10) are introduced into the pericardial sac (3) through the pericardial catheter (4).

8. The method according to claim 7, **is characterized in that** if the cooling tubes (5) and the test probe (10) are sealed in the pericardial catheter(4), while forming a tight system closed for circulation of the cooling liquid (1) in the pericardial sac (3) and its outside.

9. The device for the heart hypothermia **is characterized in that** it comprises a pericardial catheter (4) through which the cooling tubes (5) with the cooling liquid (1) and the test probe (10) are with their ends introduced into the pericardial sac (3) of the cooled heart (2), and their second ends are connected to the power supply and control unit (12), provided with at least one pump (13) of the cooling liquid (1) and cooling unit (14) of the cooling liquid (1), and the controller (15) of that pump (13) and cooling unit (14), and the second ends of the cooling tubes (5) are through the flow sensors (16) connected with the pump (13) and the cooling unit (14), and the second test probe (10) is connected to the input of the controller (15), and preferably outputs of those flow sensors (16) are

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connected to further inputs of that controller (15).

10. The device according to claim 9, **is characterized in that**, the pericardial catheter (4) is shaped like an elongated cylinder in front ended with a conical tip, and has main duct (17) ended at the tip and located in its axis and two lateral ducts (18) parallel to the main duct (17) on the test probe (10), ended in front of the pericardial catheter (4), on its cylindrical surface, with lateral openings (19) on cooling tubes (5), and in the rear part of the pericardial catheter (4) cooling tubes (5) and test probe (10) flexible are sealed in with a flexible valve (20), with a covered cylindrical lid (5) is embedded, which is snap mounted on the circumferential protrusion of the pericardial catheter (4), and moreover, after the introduction of the pericardial sac (20) into the pericardial catheter (4) it is sealed with a guide (21) with a handle (9).

11. The device according to claim 9 or 10, **is characterized in that** the cooling tube (5) is ended at its end embedded in the pericardial sac (3) with longitudinal apertures (23) spaced around its circumference,

12. The device according to claim 9 or 10 or 11, **is characterized in that** the and the test probe (10) is at its end embedded in the pericardial sac (3) ended with temperature and pressure sensors, and on the opposite side with a plug (24), whereby connection of the test probe (10) with the input of the controller (15) is through the test tube (25).

13. The device according to claim 9 or 10 or 11 or 12, **is characterized in that** the cooling unit (14) of the power supply and control unit (12) in the device (11) has a cooling coil (26) placed in a tray (27) for the cooling liquid (1).

14. The device according to claim 9 or 10 or 11 or 12 or 13, **is characterized in that** in its cooling tubes (5) tees (28) are mounted with the first taps (29), and each of the tees (28) is connected to a second syringe (30) via the second tap (31) with the container (32) for the cooling liquid (1) and air, sucked from the cooling tubes (5),

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15. The device according to claim 9 or 10 or 11 or 12 or 13 or 14, is **characterized in that** it comprises a guide (8) with a handle (9) which is provided with a central passage duct (33) for the guidewire (7), and the handle (9) of the guide (8) has two plugging (34) lateral ducts of the pericardial catheter (4) when introduced into the pericardial sac (3).

16. The pericardial catheter 4, for hypothermia of the heart, is **characterized in that**, is shaped like an elongated cylinder in front ended with a conical tip, and has main duct (17) ended at the tip and located in its axis and two lateral ducts (18) parallel to the main duct (17), ended in front of the pericardial catheter (4), on its cylindrical surface, with lateral openings (19), and in the rear part of the pericardial catheter (4) a flexible valve (20), with a covered cylindrical lid (21) is embedded, which is snap mounted on the circumferential protrusion of the pericardial catheter (4), and moreover, after the introduction of the pericardial sac (3) into the pericardial catheter (4) it is sealed with a guide (8) with a handle (9), which is provided with a central passage duct (33) and has two plugging tubes (34) lateral ducts (18) of the pericardial catheter (4) in its introduction into the pericardial sac (3).

17. Cooling liquid for heart hypothermia, intended for mechanical introduction and discharge from pericardial sac with the use of pericardial catheter for the purpose of direct heart cooling, is **characterized in that** it is a water solution of substance and its temperature is lower than the organism to which it is introduced.

18. Cooling liquid according to claim 17, is **characterized in that** it contains as substance at least one substance neutralizing harmful products of aerobic metabolism (ROS).

19. Cooling liquid according to claim 18, is **characterized in that** neutralizing substances contain in 100 ml of the solution: 1200 mg of glutathione (GSH), 14 µg of selenium, 2 mg of retinol (vitamin A), 100 mg of alfa-tocopherol

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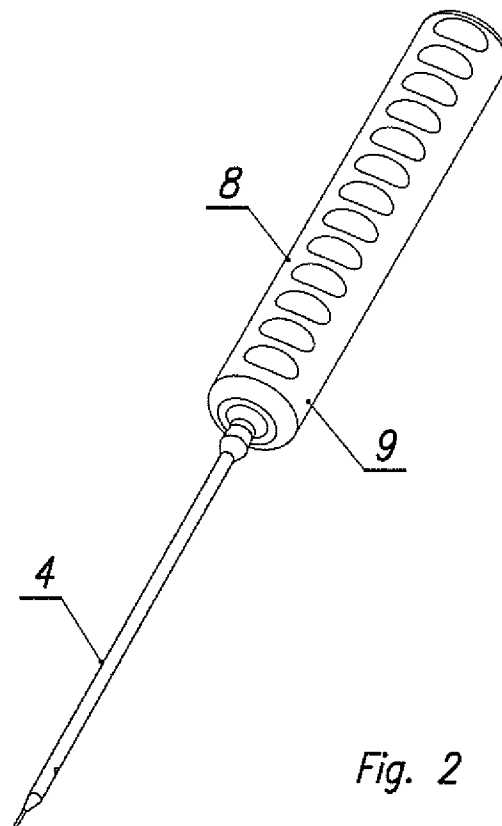
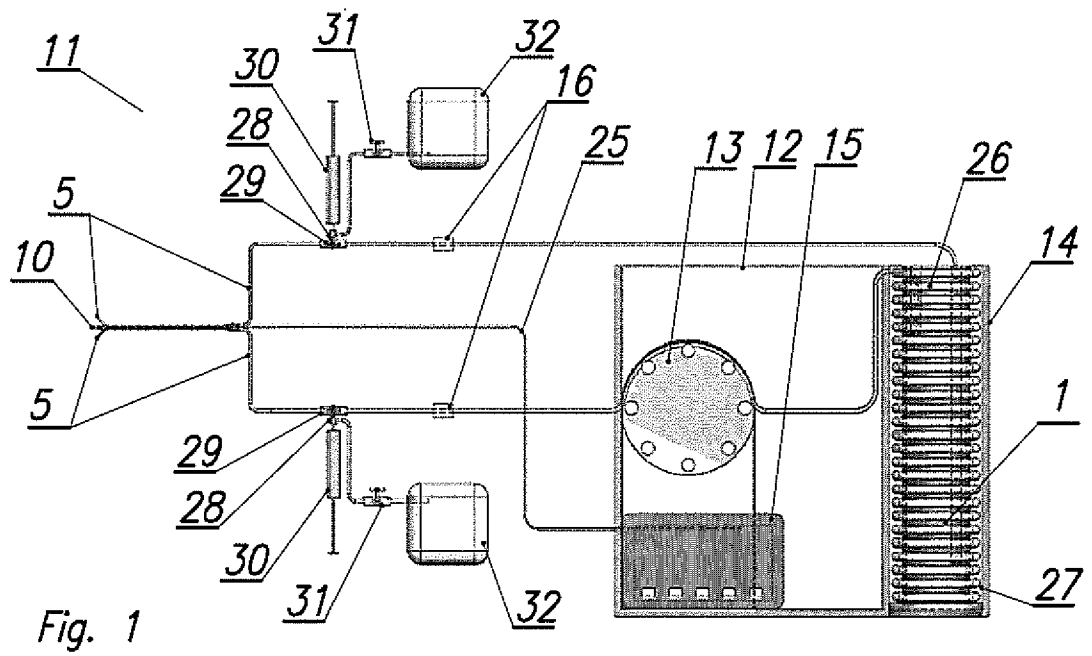
(vitamin E) and 100 mg of ascorbic acid.

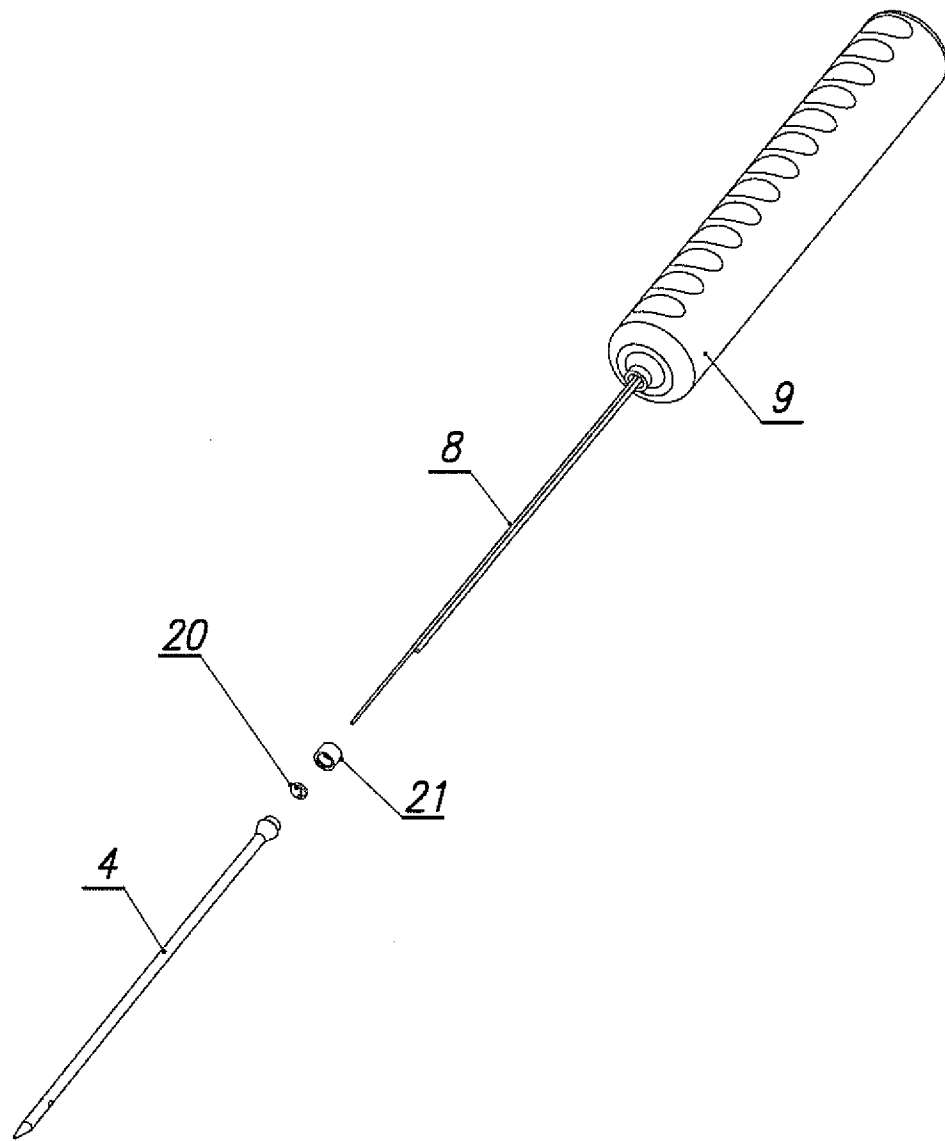
20. Cooling liquid according to claim 17 or 18 or 19, **is characterized in that** it contains a dose of anti-arrhythmic drug.

21. Cooling liquid according to claim 20, **is characterized in that** it contains mixture of amiodarone and glucose with mass concentration of 5% ÷ 10% as anti-arrhythmic drug.

22. Application of cooling liquid according to claim 17 for direct heart hypothermia (2) by introducing chilled cooling liquid (1) to pericardial sac (3) of the heart (2), monitoring the amount of cooling liquid (1) introduced to and discharged from pericardial sac (3) as well as temperature and pressure of the mixture of pericardial sac liquid (3) with cooling liquid (1) inside pericardial sac (3).

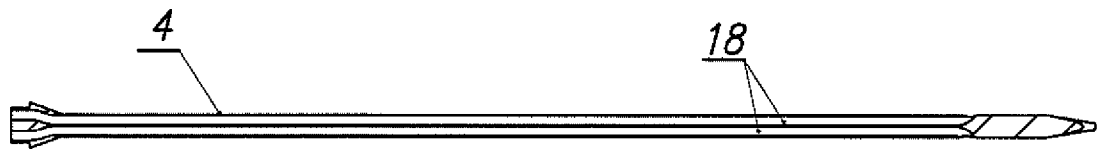
23. Application of cooling liquid according to claim 6 to maintain during heart hypothermia (2) temperature inside pericardial sac (3) within the limits from 10 °C to 36 °C.



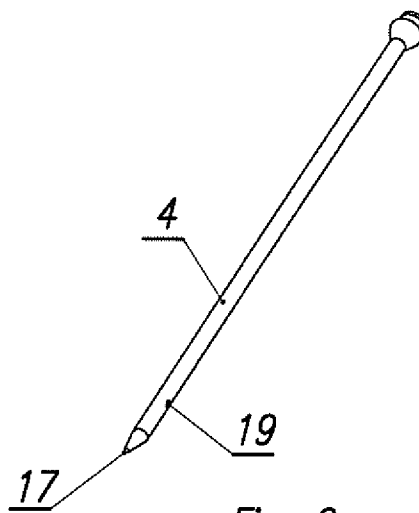
*Fig. 3*



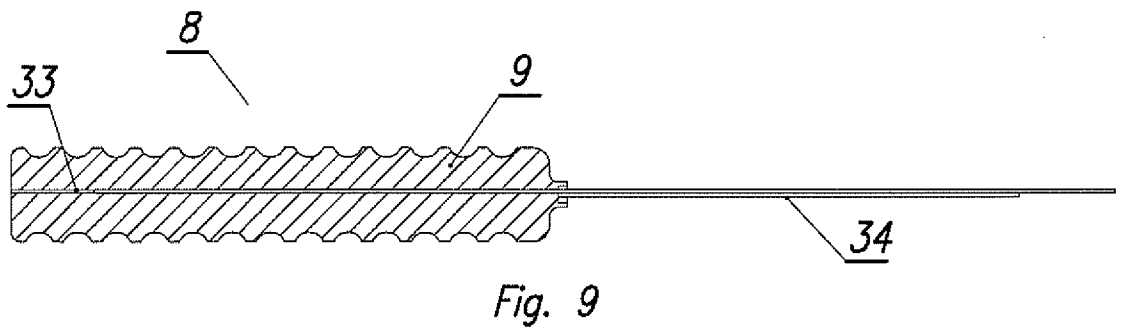
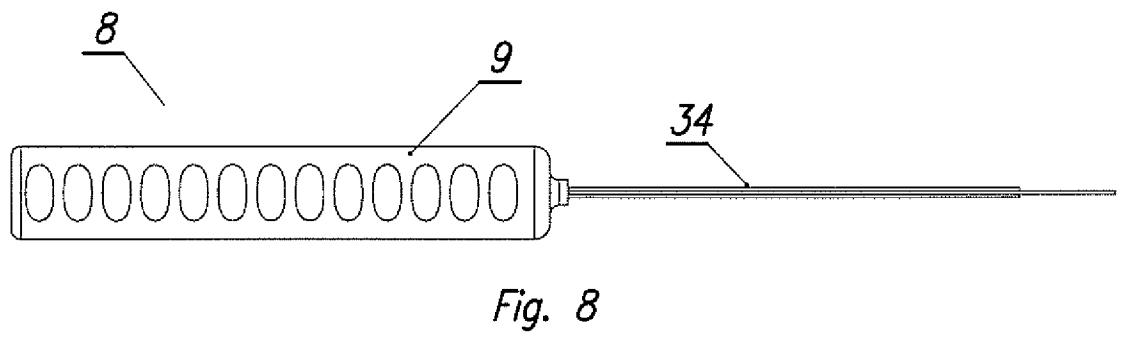
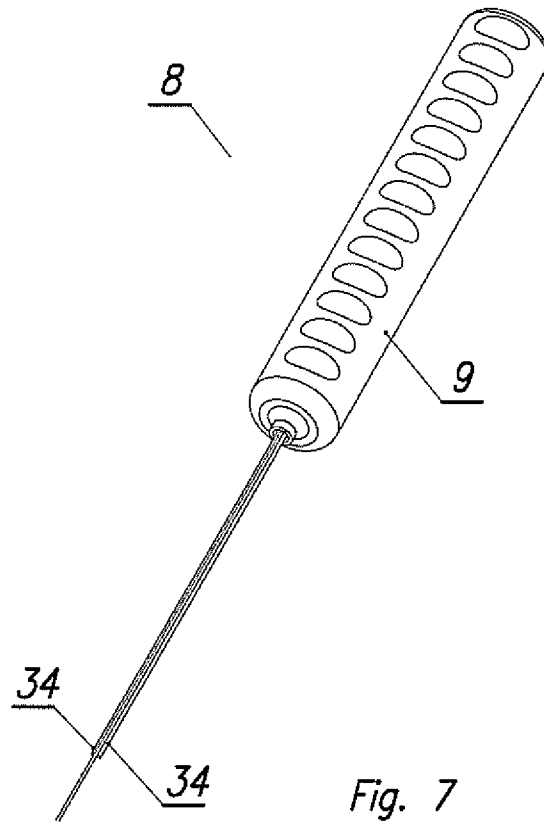
*Fig. 4*

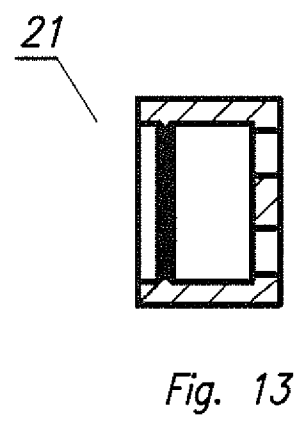
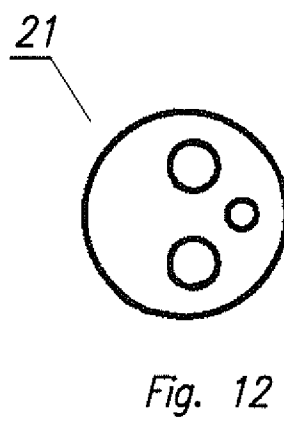
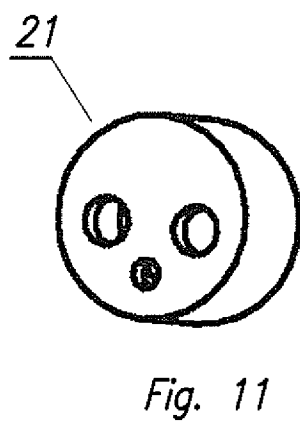
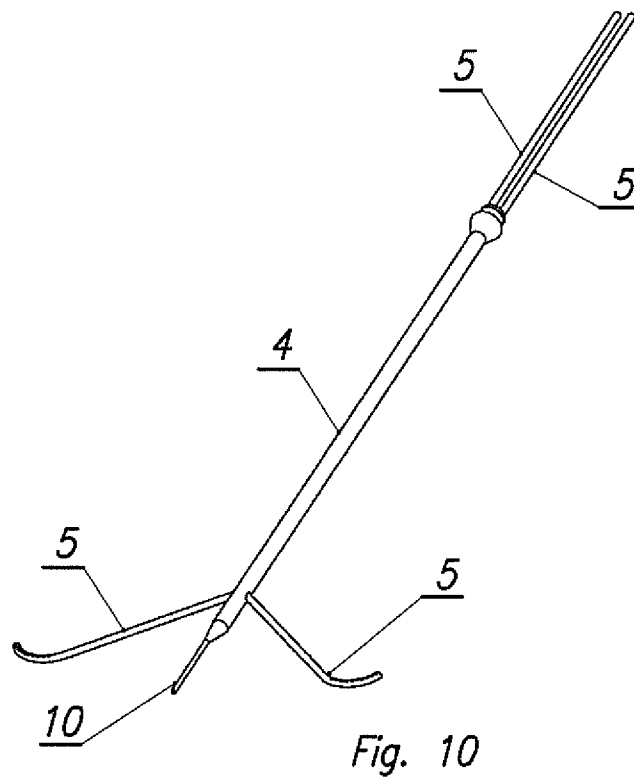


*Fig. 5*



*Fig. 6*





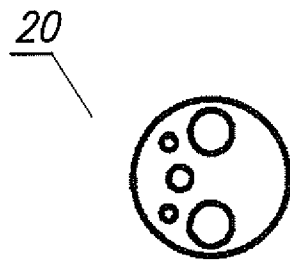


Fig. 14



Fig. 15

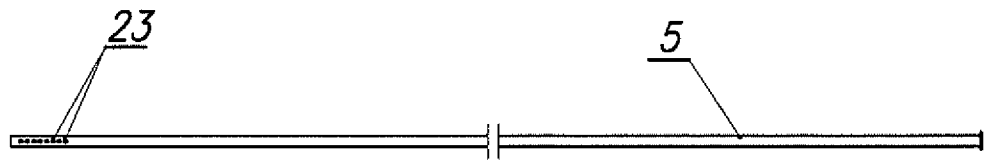


Fig. 16

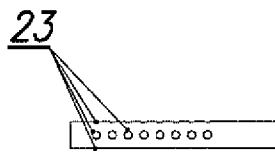


Fig. 17

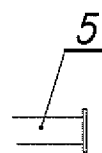
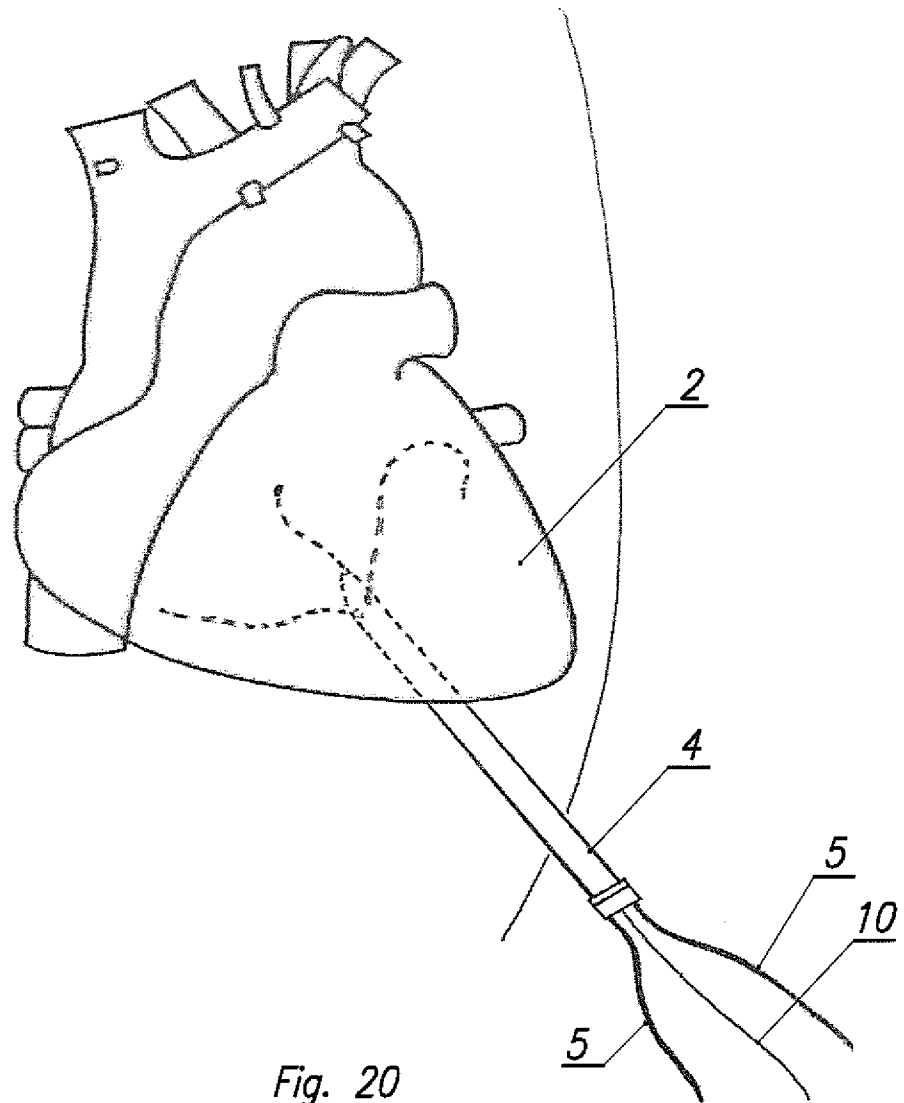


Fig. 18



Fig. 19



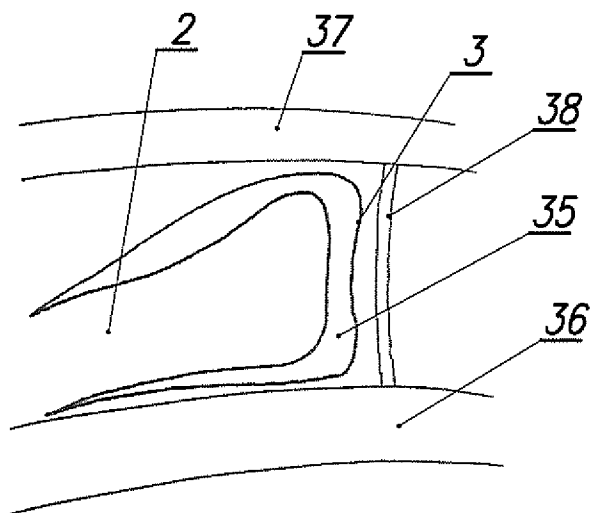


Fig. 21

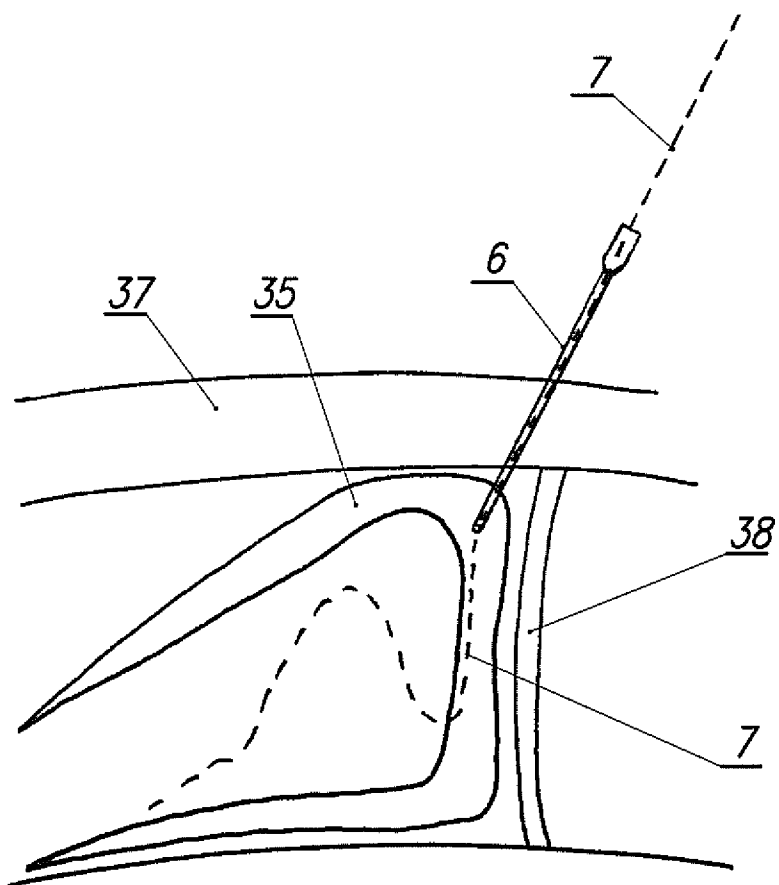
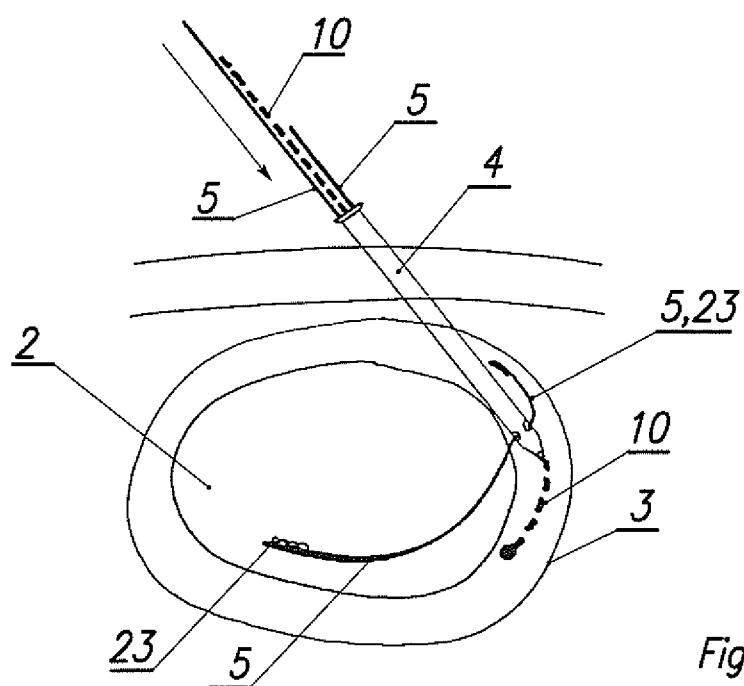
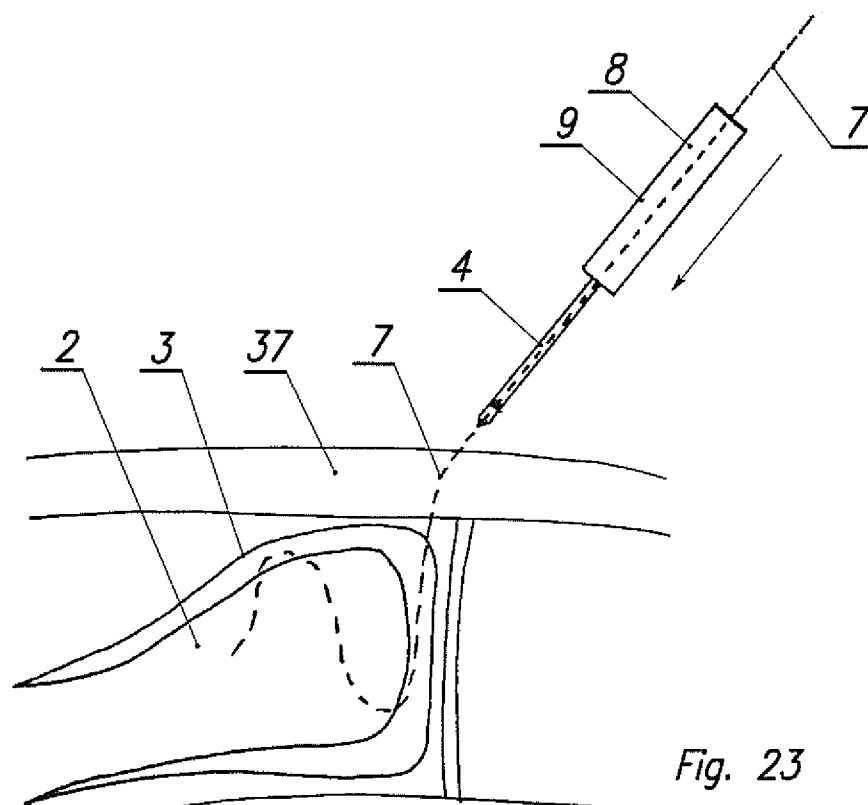


Fig. 22



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/PL2016/000159

## A. CLASSIFICATION OF SUBJECT MATTER

A61F7/12 (2006.01), A61B17/00 (2006.01), A61B18/02 (2006.01), A61M25/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61F7, A61B17, A61B18, A61M25

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Google, WPI, Google Patents

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                   | Relevant to claim No. |
|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | D1. D.R. Wheeldon, Et. Al. : "A simple cooling circuit for topical cardiac hypothermia" Thorax (1976), 31, pp. 565 - 571; see p. 570, left column, lines 16 - 30                                                                                                     | 1                     |
| X         | D2. Ravi H. Dave, ET. AL. : " Hypothermic, Closed Circuit Pericardioperfusion: A Potential Cardioprotective Technique in Acute Regional Ischemia", JACC Vol. 31, No 7, June 1998, pp. 1667 -1671; see p. 1668 left column, lines 32-33, p. 1670 left column, line 17 | 1                     |
| X         | D3. US 6 206 004 B1, Comedicus Incorporated, Columbia Heights, MN (US), Mar.27, 2001; column 2, "Summary of the invention" lines 12 - 19                                                                                                                             | 1                     |
| Y         |                                                                                                                                                                                                                                                                      | 3                     |



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

24 April 2017

Date of mailing of the international search report

25 April 2017

Name and mailing address of the ISA/  
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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/PL2016/000159

| C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                                                   |                       |
|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                             | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                                | Relevant to claim No. |
| X<br>Y                                                | D4. Paulina Kołat "Płynoterapia - Krystaloidy", 03.08.2009 r.<br>str. 3 - 4, 20<br><a href="http://www.machala.info/media/repository/Intensywna/34_Plynoterapia_w_oparciu%20o%20krystaloidy_Opr._Kol%C4%85t_P.pdf">http://www.machala.info/media/repository/Intensywna/34_Plynoterapia_w_oparciu%20o%20krystaloidy_Opr._Kol%C4%85t_P.pdf</a>                                                                      | 1 - 2<br>4            |
| Y                                                     | D5. RU 2270008 C1; 20060220; Doronin, Yu. G. 2006-02-20                                                                                                                                                                                                                                                                                                                                                           | 1 - 2                 |
| Y                                                     | D6. WO 2009 012 534 A1, Hibernation Therapeutics LTD [AU], Dobson Geoffrey, 2009-01-29                                                                                                                                                                                                                                                                                                                            | 1 - 4                 |
| Y                                                     | D7. CORDARONE: Charakterystyka produktu leczniczego, 2008-06-02; punkt 4.2 Dawkowanie i sposób podawania wiersz 10 - 13;<br><a href="http://www.sanofi-aventis.com.pl/produkty/Nasze%20produkty/Cordarone_50mg_ml_roztwor_do_wstrzykiwan_-_charakterystyka_produkту.pdf">http://www.sanofi-aventis.com.pl/produkty/Nasze%20produkty/Cordarone_50mg_ml_roztwor_do_wstrzykiwan_-_charakterystyka_produkту.pdf</a> ; | 4                     |

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/PL2016/000159

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 5-8, 22, 23  
because they relate to subject matter not required to be searched by this Authority, namely:  
Claims 5, 6, 7, 8, 22 and 23 relate to methods of treatment of humans or animals. Claims 22 and 23 relate to the application of the cooling fluid in direct cardiac hypothermia, and thus also relate to a method of treatment. According to Rule 39.1(iv), no International Searching Authority shall be required to search an international application if, and to the extent to which, its subject matter is methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☒ Claims Nos.: 17  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
Claim 17 does not fulfil requirements of Article 6 PCT. The product – cooling fluid from claim 17 is not stated in a concise and explicit way by means of indicating technical features referring to the composition of the product. The feature “water solution of a substance” is neither a concise feature nor does it distinguish the product from product group of cooling fluids known from prior art. This feature does not refer to the composition of the product.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Cooling fluid for cardiac hypothermia (claims 1 - 4)
2. The method of inducing cardiac hypothermia (claims 5-8): device for cardiac hypothermia (claims 9-15)
3. Pericardial catheter (claim 16)
4. Cooling fluid for inducing cardiac hypothermia (claims 17-21) and the use of the cooling fluid in accordance with claim 17 for cardiac hypothermia (claims 22 - 23)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT  
Information on patent family members

International application No.

PCT/PL2016/000159

| Patent document cited in<br>search report | Publication date | Patent family member(s) | Publication date |
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|                                           |                  | AU 5 372 698 A          | 1998-06-29       |
| -----                                     | -----            | -----                   | -----            |
| RU 2270008 C1                             | 2006-02-20       | None                    |                  |
| -----                                     | -----            | -----                   | -----            |
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