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CURRENT STATE OF THE PROBLEM AND RESULTS OF *EX VIVO* PERFUSION OF DONOR HEARTS

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Patients with drug refractory end-stage heart failure fall into the severe category of cardiological patients. Numerous studies have shown the superior efficacy of heart transplantation over other treatments for end-stage chronic heart failure. However, despite decades of achievements in transplantology, shortage of donor organs remains a pressing and unresolved issue. The only way to reduce shortage of donor organs is to use donors with advanced criteria, which requires the use of latest technologies in organ resuscitation and conditioning.

Keywords: heart failure, heart transplantation, ex vivo perfusion.

Over the past 15 years, heart failure has remained the leading worldwide cause of death. The disease affects 1 to 2% of the total population with the risk of development in people over 55 is 33 and 28% for men and women, respectively [1]. With the increasing life expectancy, such risk factors as arterial hypertension and coronary heart disease continue, and the predicted prevalence of heart failure will increase by 20% by 2030, thus remaining the primary cause of death [2].

Despite more than half a century of research in the treatment of chronic heart failure, the development of various devices for assisted circulation, stem cell therapy, etc., there is still no treatment comparable in effectiveness to a human donor heart transplant [3]. Heart transplant is the "gold standard" for treating patients with end-stage chronic heart failure. Unfortunately, an acute shortage of donor organs has been and remains the vulnerable spot of this treatment. Thus, due to donor organs shortage, the number of heart transplants performed in the United Kingdom and many Western countries has fallen sharply in recent decades, while the number of patients on the waiting list continues to grow [4].

In the UK, of the approximately 750,000 patients requiring heart transplant, only 0.02% receive it. Due to this discrepancy between the need and possibility, almost 10% of patients on the waiting list die annually [3]. According to the report by the Canadian Institute of Medical Information, in Canada for the past 10 years, the annual mortality rate of patients awaiting heart transplant has been 16% [5].

The first successful clinical cadaver heart transplant was performed with an organ donated after death from circulatory arrest in 1967 by Christian Barnard and his team at Groote Schuur Hospital [6]. In that time, before the criteria were established for brain death, a heart transplant could be performed only if the donor and recipient were in close proximity to each other. When the term "brain death" was introduced at the legislative level, it allowed the remote sampling of donor organs. At the same time, for years, the use of the hearts of donors who died from circulatory arrest has been discontinued.

However, in some time, the idea of using such organs for transplant returned to life. To meet the needs in donor organs, surgeons were forced to expand the criteria for donor organ collection, in particular through the use of organs received from donors who died from circulatory arrest or had an asystole episode. In the literature, such donor organs are called "organs from expanded criteria donors (ECD)", "organ donors after irreversible cardiac arrest" or "asystolic donors".

The strategy aimed at reducing the need for donor organs through the use of transplants from expanded criteria donors has proved safe and has been formed in protocols in accordance with national and international standards in Australia, Belgium, the Netherlands, Spain, the UK and the USA. According to G. Citerio et al., *ex vivo* restoration of a marginal donor organ would increase the donor pool by 15–30% [7, 8].

The use of such a donor pool became possible due to significant progress in the field of resuscitation and conditioning of donor organs, in particular due to the development of organ perfusion systems that are able to solve a number of such difficult tasks as assessing the functional status of the transplant, time of ischemia, and logistics of donor to recipient delivery.

The main issue of using hearts after donor death from circulatory arrest is the time of thermal ischemia, as well as the need to maintain myocardial viability during delivery. Despite the fact that pharmacological cold cardioplegia is the standard for preserving donor organs, after

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four hours the transplant function can be compromised by a long ischemic period, especially in patients of the older age group [9].

This technique of organ preservation is the greatest risk factor for primary allograft dysfunction and death [10, 11]. An increase in the time of cold ischemia from 3 to 6 hours doubles the risk of death one year after transplant, compared to 50% decrease in predicted one-year mortality, if the period of ischemia is less than one hour [12]. These data were also confirmed by US scientists, proving that reducing ischemic time by one hour increases survival by 2.2 years [13]. J. Kobashigawa et al. found that ischemia exceeding 4 hours significantly increases the risk of primary transplant dysfunction which is associated with 8% mortality after 30 days and increased mortality in 5 and 15 years after transplant [14].

The use of expanded criteria for the donor organs collection, though providing increase in the availability of heart transplants, can be accompanied by a number of complications [15]. Therefore, it became apparent that expanding the criteria for organ harvesting needs alternative, more physiological conditioning techniques. *Ex vivo* warm perfusion of the heart is an alternative technique of preserving the transplant, which allows improving the function of the donor organ and expanding the donor pool, neglecting the time required to deliver the organ from a donor to the recipient [16].

TransMedics (Massachusetts) system (TMS) is the first commercially available device to transport a donor heart in a normothermic perfusion state. Perfusate is a patented pouring solution with the addition of insulin, antibiotic, methylprednisolone, sodium bicarbonate, multivitamins and fresh donated blood [3].

A number of studies have proven the advantage of exothermic normothermic perfusion *ex vivo* over hypothermic preservation of donor hearts. It is important to note that thermal ischemia tolerance of the donor hearts donated after circulatory arrest is higher than that of hearts from donors with brain death [17]. TMS can be successfully used to assess the functional capabilities of "expanded criteria" organs, heart donors with low EF, previous cardiac arrest, long-term (>4 h) predicted ischemia and unknown coronary bed status due to the absence of coronary angiography before the implantation stage, thus avoiding the potential risk of dangerous complications and death for recipients [18, 19].

Heart EXPAND Trial results showed that 75 of 93 donor hearts perfused with TransMedics system were successfully transplanted, resulting in 81% utilization rate. The average OCS perfusion time was 6.35 h. 30-day and 6-month survival rates were 94.7 and 88%, respectively [20].

The use of TMS allows can solve another very important problem that reduces the donor pool: the problem of logistics of organ delivery to the recipient. According to various estimates, about 60% of potential allografts are considered unsuitable for transplant for various reasons, including the impossibility of the earliest possible organ delivery to the recipient [21]. In the United States, only 30–35% of donor hearts are used for transplant due to storage restrictions using standard pharmacological cold protection.

TMS extends the time for the donor organs outside the body to at least 8 hours, expands the potential geography of donor bases and allows angiography of the donor organ inside the system, which is especially important for donors of the older age group. For instance, in 2015 in Australia, a donor heart was successfully transplanted after 10.5 hours of TMS perfusion. In the UK, supposedly, this would provide for an international exchange of organs with Europe and the eastern United States. Such an expansion of the donor pool is one of TMS main potential advantages [22].

In 2018, Rymbay Kaliyev et al. reported the successful 16-hour perfusion of the donor heart followed by successful transplant to the recipient. The TransMedics donor organ support system made it possible to deliver the organ over a distance of 500 km by rail due to poor weather conditions and the inability to use air transport [23].

The use of TMS by the transplant team allows eliminating the urgency associated with the desire to shorten the ischemia period and avoiding the dangerous high-speed team traffic earlier associated with serious injuries and deaths among team members [3].

Every year, the number of cases using *ex vivo* perfusion systems is rising. In Diana García S. MD. et al., thirty hearts are reported to be saved with TMS from February 2013 to January 2014, 26 of which (86.7%) were transplanted. All these transplant procedures were classified as high-risk due to long delivery time: over 2.5 h with an estimated ischemia time of over 4 h, EF less than 50%, left ventricular hypertrophy, cardiac arrest donors, alcohol/drug abused donors, donors with coronary heart disease or increased pulmonary vascular resistance. According to 2015 data, the system for the donor organs transportation was used in 246 orthotopic heart transplants around the world [3].

M.A. Quader et al. did not find any differences in the results of heart transplants with good left ventricular function between the TransMedics system and the standard pharmacological cold protection in cases when the total period of ischemia was up to 2 h. Nevertheless, allografts with longer ischemia times showed worse left ventricular function and elevated troponin levels. Assessing the functional status of an organ *ex vivo* in combination with the decreased time of cold ischemia minimizes the risk of primary allograft dysfunction and potentially increases the donor pool [24].

According to J.M. Tikkanen et al., long-term survival, improved quality of life and graft function are comparable among recipients with the heart transplant, survived pharmacocholastic ischemia and *ex vivo* thermal perfusion [25]. Vipin Mehta et al. reported 100% 30-day survival rate of recipients who received hearts after *ex vivo* reperfusion and 86% 90-day survival rate. This result is comparable with S. Messer et al.; according to their data, the 30-day and 90-day survival rates were 100% and 93%, respectively [26]. According to Joshua L. Chan, MD et al., there was no significant difference in two-year survival between groups of patients who underwent cardiac transplantation after *ex vivo* perfusion and pharmacological cold ischemia. The two-year survival rate of the recipients was 72.2 and 81.6%, respectively (p 0.38) [27].

However, the wide use of TMS is limited by the high cost of the system. For the UK, the National Institutes of Health reports the cost of a one-time TMS perfusion kit of about £30,000 [28]. It should be noted that this estimate includes only the cost of the device and does not consider additional expenditures. It should be borne in mind that approximately 10–20% of the funds will be spent on hearts subsequently recognized as unsuitable for transplant. However, according to Vipin Mehta et al., the heart transplant from donors after blood circulation stop and using *ex vivo* perfusion can lead to a 23% increase in heart transplant activity and should be accepted by more institutions around the world [29].

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