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Technologies of donor organ storage by the example of a donor heart. Status and prospects

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The authors studied the world experience in technologies and devices for the donor organ storage, the current status and prospects, innovative developments. The status of the issue in Russia and the CIS countries was specifically reviewed. The need in special devices for the donor organ storage was assessed using a donor heart as an example.

Keywords: transplantation, heart transplantation, technologies and devices for donor organ preservation.

Introduction

Transplantation is the branch of medicine that studies the problems of organ (e.g., heart, kidney, liver, lung, pancreas, small intestine) and tissue transplantation. The main factors that determine the success in transplantation include: the preservation period for donor organs and tissues, their reliable protection against ischemic damage.

By 2030, according to WHO, about 23.3 million people will have died from cardiovascular diseases, mainly from heart disease and stroke which remain the main causes of death [1].

In Russia, the standardized mortality ratio for cardiovascular diseases (CVD) has been significantly higher than in the developed countries of Europe, in Belarus, and Kazakhstan. Mortality from the coronary heart disease (CHD) in 2012 rose to 53.3% of CVD mortality. The CHD mortality rates among working-age population made 49.7% of all CVD deaths. The proportion of deaths from heart disease in the US was 24.1% in 2010 [2].

Overview

The number of patients in need for organ transplantation can be conceived from the data presented by National Transplant Societies. General data on all organ transplants are shown in Table. 1, the data on heart transplantation are presented separately (Table. 2).

Table 1. General information on cumulative organ transplantation (for all organs).

Country / Community	Population, million people (1)	Period, year	Waiting list		Transplants performed		
			thous. people (2)	per 1 million population, number of people	thous. procedures (3)	per 1 million population, procedures	% of the Waiting list
USA	320	2014	123	384	29	91	24
Eurotransplant (4)	134	2014	15	112	7.2	54	48
Russia	143	2013	5.4	38	1.4	10	26

Notes: (1) https://ru.wikipedia.org; (2), (3) United States: https://www.unos.org/data/; Eurotransplant: http://www.eurotransplant.org; Russia: http://transpl.ru; (4) the Eurotransplant Community includes Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands, Slovenia.

Table 2. General information on heart transplantation.

Country / Community	Population, million people (1)	Period, year	Transplants performed			
			all organs, thous. procedures (2)	including heart transplants (3)	heart transplants per 1 million population, procedures	Heart transplants,%
USA	320	2014	29532	2655	8	9
Eurotransplant	134	2014	7194	617	4.6	9
Russia	143	2013	1400	164	1.1	12

Notes: (1) https://ru.wikipedia.org; (2), (3) United States: https://www.unos.org/data/; Eurotransplant: http://www.eurotransplant.org; Russia: http://transpl.ru.

The United States of America have been the leader in organ transplantation: there are 384 patients registered in the Waiting list for transplantation per 1 million population, 91 of them received transplants, i.e. 24% of those in the waiting list. In Russia, the figures are much lower: there are 38 people registered in the Waiting list for organ transplants per 1 million population, 10 of those in the waiting list receive transplants, i.e. 26%. The data from the Eurotransplant International Foundation are twice more modest than in the USA. The heart transplantation accounts for 1/10 of all transplantations (See Table 2) and makes 8 transplants per 1 million population in the USA, 4.6 transplants per 1 million in Eurotransplant countries, and 1.1 in Russia [3- 5].

Thus, organ transplantation provides for about 25% of those on the Waiting list only. However, the number of patients on the waiting list in transplant centers is greatly limited by the center transplantation activity and by the number of such centers; though, the actual need in organ transplantation is significantly higher [6]. This causes the urgency of the

problem and dictates the necessity of implementing a set of public measures for the development of organ donation and transplantation in Russia, and worldwide.

Expected number of transplantations in 2020 in developed countries and the BRICS countries are shown in Tables 3 and 4. The prognosis is based on the following assumptions: the waiting list and the number of transplants will continue to grow from now to 2020 at a rate of 5% in the USA (already very advanced), 10% in Japan and the European Union (will catch up with the US numbers); the BRICS countries will have the growth by 5.5% in the waiting list, and by 10% in the number of transplant procedures [3-5].

Table 3. Expected number of transplantations in 2020: the developed countries.

Country	Population, million people (1)	Waiting list, people		The number of transplants, people		Including heart transplants, people	
		per 1 million population (2)	Total	per 1 million population (2)	Total	per 1 million population (2)	Total
USA	320	490	156800	116	37120	12	3712
EC	503	180	90540	87	43761	9	4376
Japan	127	180	22860	87	11049	9	1105
Total	950	284	270200	97	91930	10	9193

Notes: (1) https://ru.wikipedia.org; (2) with regard to growth: 5% in the USA, 10% in the EU and Japan; http://www.transmedics.com (the number of organ donors in the USA has been growing by 10% per year since 2013).

Table 4. Expected number of transplantations in 2020: BRICS countries

Country	Population, million people (1)	Waiting list, people		The number of transplants, people		Including heart transplants, people	
		per 1 million population (2)	Total	per 1 million population (3)	Total	per 1 million population (3)	Total
Brazil	203	50	40803	67	13601	6.7	1360
Russia	143	50	7150	16	2288	1.6	229
India	1275	50	63750	16	20400	1.6	2040
China	1371	50	68550	16	21936	1.6	2194
South Africa	55	50	2750	16	880	1.6	88
Total	3047	50	183003	19	59105	1.9	5911

Notes: (1) https://ru.wikipedia.org, (2) The growth in Russia is 5.5% per year, the other countries follow this result, (3) The growth in Russia is 10% per a year, the other countries follow this result.

Thus, in 2020, there will be about 140,000 transplants in the world, including 92,000 in the developed countries, and 48,000 in the BRICS countries. World waiting lists will be 270,000 patients in the developed countries and 150,000 in the BRICS countries. The number of heart transplants will be at a level of 10% of all transplantations, i.e. about 15,000, including 9,000 in the developed countries, and 6,000 in the BRICS countries [3-5].

State of the art in heart transplantation and its relevance

Over 100,000 heart transplants were undertaken worldwide for 45 years from 1967 to 2013. Virtually, all of them were performed using a hypothermic heart preservation technique involving the organ cooling

followed by the administration of the heart preservation solution at a temperature of 4-6° C that ensured a heart protection for about 180 minutes [7].

The trend that has emerged in the developed countries in the recent decade demonstrates a steadily increasing gap between the growing number of the patients and inadequate donor heart supply. In the UK, 10% of the patients on the waitlists annually die while awaiting for the donor heart. On the other hand, 7 hearts of 10 organ donors in the United States are ineligible for transplantation because of inadequate preservation; a donor heart with left ventricular hypertrophy can not be adequately preserved under cold storage, it can be well preserved for only a few hours (jets and helicopters will not save the situation). Brain death consequences may lead to a poor quality of the donor organ preservation [8]. Due to ischemia and donor age, only 25% of donor hearts are suitable for transplantation in the UK. Statistics for the recent 20 years in the UK has demonstrated that with a 1-hour decrease in the ischemia time, the risk of dying in the first year after transplantation drops by 25% [9]. In the USA, a 1-hour decrease of ischemia time results in 2.2-year survival increase [10]. According to the International Society for Heart and Lung Transplantation (ISHLT), the risk of transplanted organ rejection increases significantly if ischemia time extends more than 3 hours [11].

Mortality in the first month after heart transplantation makes 8% and is accounted for by the primary graft rejection that is mainly caused by a donor-recipient mismatch, the donor age, and ischemia duration. Since 2003, the growth rate of donor heart pool in the US has made 10% per year. However, more than half of donor hearts could not be used due to cool storage technique [3, 12].

An increasing demand in and a limited supply of applicable donor organs have led to a seriously unmet demand constituting 3/4 of patients in need for transplant. Moreover, the doctors' strive to expand the donor pool by reducing the requirements to the donor organ quality results in a steadily high post-transplant mortality: only half of the heart transplant recipients survive over 10 years [13].

The presented data clearly demonstrate that moving away from the cool storage technique would give us the chance to considerably increase the donor organ pool and significantly reduce the growing gap between the demand and supply of donor hearts.

Russian scientists have determined the prospects of increasing the donor pool via expanding the donor eligibility criteria. They have elucidated in-detail the role of ischemia-reperfusion in organ transplantation, described the strategies adopted to reduce the consequence of ischemia-reperfusion injury of donor organs, reviewed extensive literature data on the role of perfusion methods for organ preservation in modern transplantation. The necessity of the donor organ management prior to transplantation has been well-grounded, a number of theoretical propositions have been given for the development of new donation types to provide a wider access to transplantation for the population. The question about changing the paradigm of organ donation has been set up implying the switch from the donor organ cooling and preservation to their constant normothermic perfusion with oxygen-rich autologous blood. This will provide an effective diagnosis, organ management, its prolonged preservation that would generally greatly expand the number of organs available for transplantation [14, 15].

Heart transplantation appears the most effective treatment for patients with end-stage heart disease. With advances in heart transplantation, the eligibility criteria to donor organs are constantly expanding. Nevertheless, transplantation is restrained by the shortage of eligible donor hearts. Age of the donor and the ischemia severity are the major limiting factors. Donors who have significant impairments of cardiac function due to their brain death are not currently used because there is no reliable way to predict the graft function recovery after transplantation. To circumvent these limitations, we have developed a technological system of donor organ management that minimizes the cold ischemia time and allows the restoration of the cardiac function to estimate the parameters of heart function in natural conditions. The experience has shown that a wider use of new perfusion techniques would contribute to expanding the organ eligibility criteria and increasing the organ donor pool [16].

Current trends

Currently, transplantation research is being conducted in the following areas:

• Search for the ways to overcome the immune system incompatibility between donor organs/tissues and the recipient.

• Development of artificial organs for transplantation.

• Donor organ culturing.

• Monitoring the status and function of transplanted donor organs.

• Donor organ safe preservation for longer time period.

In the developed countries, the current legislation in the filed of transplantation supports this sector and there is no competition between

manufacturers of the equipment for donor heart preservation. Barriers to foreign market entry are virtually absent.

A key factor in the success of transplantation is a long-term organ preservation ensuring a high-degree protection. [3, 14, 17, 18].

Modern solutions

Modern technologies in transplantation have concentrated on moving from cold storage technique to normothermic techniques of donor organ preservation and transportation by using autonomous mobile equipment for ensuring the organ perfusion with an oxygen- and nutrient-enriched solution. The choice of a normothermic perfusion is dictated by the need to protect the donor organ from ischemia and cold stress.

The TransMedics Organ Care System (OCS™) from TransMedics Inc., USA, has been designed to preserve the donor heart in a state of ex vivo normothermic machine perfusion with donor's autologous blood and is based on the principle of the donor's heart "not feeling" that its host (the donor body) has been replaced by the perfusion device. From the moment of organ retrieval from the donor body until the moment when the surgeon starts its implantation to the recipient, the organ is functioning as if it has never left the body. During this period the organ "lives" in the machine that has replaced the human body. Heart beats, kidneys produce urine, and liver produces bile. The warm oxygenated blood is pumped through the organ. TransMedics is actively promoting its equipment for the donor heart storage and transportation. The OCS™ is being tested in the clinics of the USA and Europe. It was used for 128 heart transplantation procedures. Clinical trials to test it for lung transplantation are under way. Further trials are planned in liver and kidney transplantation. The claimed maximum amount of time that

a donor heart can be maintained outside the body using the OCS™ is up to 12 hours, the actual time was limited to 8 hours, as per clinical trial results. Bulk sales of the device are not available [5, 19]. The OCS™ Heart was used in the first heart transplant procedures in Kazakhstan.

It should be noted that the widespread introduction of these systems in the clinical practice around the world will be limited due to its high cost: the traditional "cooler box" used to transport a donor heart overlaid with ice costs about $100, and the "beating heart" machine will cost around 200,000 dollars [20]. In addition, the disposable insides of the "beating heart" container have to be replaced prior every new heart transportation. Clinical studies have shown that the cost of consumables per transport is 49,000 US dollars [20]. TransMedics believes these expenditures are cost-effective, since the method contributes to significant reductions in patient's waiting time for the donor organ in clinic, and postoperative complication rates, resulting in shortened length of hospital stay [5, 19-21]. It should be stated that virtually lacking the home market of devices for donor organ preservation, we have to create it. However, it is clear that many countries of the world will not be able to afford such mass expenditures for transplantation development. National research and developments in this area are necessary.

Conclusion

One can draw the following analogy. Only few surgical procedures were performed on the stopped heart before the heart-lung machine (HLM) had been introduced. With the advent of HLM mass-production, the number of such operations experienced a rapid and considerable growth worldwide.

The current problem could be solved by the creation of a perfusion device that, unlike all the existing devices, and the technologies under development, would allow a donor heart preservation as long as for 24 hours.

Today, there are no devices to preserve donor organs long enough providing their acceptable protection, so the modern transplant industry can satisfy no more than 25% of the existing registered needs only. Should the long-term organ preservation system be created, we would expect a similar rapid growth in the global transplantation branch that had its beginnings from experiments of a Russian surgeon V.P.Demikhov [22]. This would help to create a single Waiting list for the optimal donor-recipient selection, improve the outcomes and quality of care, raise the level of protection and recovery of preserved organs, reduce mortality and morbidity rates, and increase the overall transplantation efficacy.

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