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MODERN IDEAS IN HEART DONOR SELECTION CRITERIA

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With the limited capacity of the available donor pool and the simultaneously growing demand for heart transplantation, expanding the heart donor selection criteria as one of the ways of increasing the availability of organ transplantation, and particularly donor heart, has become a challenge. On one hand, the use of expanded criteria donors increases the number of transplants and reduces the time spent on the waiting list. On the other hand, however, it increases the risk of adverse transplant outcomes. Accordingly, high-risk donors require a more thorough objective assessment using predictive models, while organs obtained from expanded criteria donors, require optimal selection of a donor-recipient pair. Analysis of global and national studies presented in this review reveals the depth of the current problem of heart donor selection.

Keywords: expanded criteria heart donors, cardiac donor selection, donor heart assessment criteria, prognostic models.

INTRODUCTION

The efficacy of heart transplantation is directly dependent on the maximum use of the available donor resource and suggests that each donor heart should be considered for transplantation by all existing programs in order to avoid the loss of a "working" donor organ. Assuming that all proposed donor hearts are successfully transplanted, the problem of organ shortages will become less acute [1]. However, clinicians, when faced with hearts from donors with extended criteria, tend to make decisions more often on rejection, fearing the negative impact of donor risk factors on the outcome of heart transplantation [2]. Despite the lack of organs, only 39.2% of the donors declared in Eurotransplant in 2010 were considered as possible heart donors, and only 66.6% of them became effective donors [3]. In addition, unlike the United States, where there has been no increase in the number of effective heart donors with extended criteria since the 2000s, the average age of heart donors in Europe continues to increase, reaching 34 years in 1996, 36 years in 2000, in 2010 – an increase to 43 years [3, 4].

Thus, there is a reasonable need for an objective assessment of the donor heart based on modeling the degree of influence of donor risk factors on the outcome of heart transplantation. In modern conditions, when the number of "ideal" donors is extremely small and the majority of donors are in the so-called gray zone, that is, between "ideal" and "unsuitable", verified criteria for assessing the donor heart are needed, which will help in an objective decision-making – to use or refuse a donor heart [2].

SELECTION OF HEART DONORS. EXPANDED CRITERIA HEART DONORS AND THEIR EFFECT ON HEART TRANSPLANTATION RESULTS

Currently, the selection criteria for a donor heart vary widely depending on the country, the medical institution performing the heart transplant, the experience of working with donors with extended criteria, etc. The most noticeable differences relate to the donor's age, cause of death, history of tobacco smoking, the state of the donor's hemodynamics, as well as circulatory arrest, episodes of hypotension, their number and duration [5, 6].

The traditional selection criteria for heart donors include age <55, no chest injury and heart disease, no prolonged hypotension and hypoxemia, stable hemodynamics, mean arterial pressure (MAP) >60 mm Hg. Art., central venous pressure (CVP) from 8 to 12 mm Hg. Art., inotropic support less than 10 mg/kg/min (dopamine or dobutamine), ECG and Echo-CG without pathological changes, the state of the coronary arteries according to coronary angiography (CAG) according to the age and history of the donor [7].

Modern approaches to the selection of a donor heart, first of all, donor risk factors should be considered that can negatively affect the results of transplantation. Donor age is widely regarded as the most important risk factor, along with left ventricular (LV) ejection fraction <50%, which does not improve after donor conditioning, and LV myocardial hypertrophy [8].

Donors with characteristics associated with an increased risk of graft failure are referred to as expanded criteria donors (ECD). According to Kilic (2014), in order to

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reduce the deficit of donor hearts, it is necessary to pay special attention to working with donors with extended criteria (DRC). Such donors require careful selection of the recipient, which contributes to the achievement of optimal survival results for recipients who received a heart from ECDs [6].

Donor factors that are most often found in publications as independent risk factors for transplantation outcome include donor age, female gender and cold ischemia duration [9].

Despite the fact that the clinical characteristics of the recipient are more significant in predicting survival after transplantation, donor risk factors also have a proven influence on the results of transplantation [9–11].

Accordingly, in the process of deciding on transplanting a donor heart, it is necessary to consider the donor and recipient factors in a complex manner. Heart transplants obtained from high-risk donors and transplanted to recipients with the least number of aggravating factors demonstrate higher survival rates; in addition, optimized donor and recipient selection is one of the possible ways to reduce the shortage of donor organs for transplantation [9, 11].

PREDICTIVE EFFECT OF DONOR AGE ON HEART TRANSPLANTATION RESULTS

One of the recent studies by Bergenfeld (2019) demonstrates the prognostically unfavorable effect of the donor's age with a difference with the recipient of +10 years in the form of an increase in the risk coefficient (RR) of the recipient's death in a 30-day period after transplantation to 1.19, in 1th year after transplantation – 1.16, in the time periods after transplantation 1–3 years, 3–5 years, 5–10 years, the risk coefficient is 1.12; 1.07 and 1.07, respectively. The study included 64,354 heart transplant cases in 1988–2013 [12]. Another study performed in the USA (Lushaj, 2019) retrospectively analyzed 755 heart transplant patients and found that the long-term survival of recipients who received a heart from a donor <45 years is significantly higher compared to recipients who received a heart from a donor >45 years. The risk of death was also higher in heart recipients from donors >45 years old [13]. At the same time, a study by Ravi (2019) using the UNOS register for the period 2008–2017. (19 514 heart transplants), shows that when a heart transplant from a donor over 50 years old to a recipient in the age range of 18–39 years, there is no decrease in survival. Recipients in the 40–49 age group who received hearts from donors 40–49 years old and over 50 years old have a 10-year survival rate decrease by 43 and 75%, respectively, compared to the group of recipients who received donor hearts in the 18–29 age range. Similarly, in recipients <50 years old who received donor hearts 30–39, 40–49, >50 years old, there was a decrease in 10-year survival by 14, 27 and 47%, respectively. Thus, it is important to note that donor age does not decrease survival in young recipients [14].

GENDER AND ANTHROPOMETRIC CONFORMITY OF DONOR AND RECIPIENT

A number of studies have revealed that the female gender of the donor is considered as an independent factor in increasing mortality in recipients of the opposite sex [15–21]. Men who received hearts from male donors had the highest cumulative survival rate in 5 years [22]. The mechanisms underlying the obtained results of gender mismatch are not entirely clear but may be associated with a mismatch in the size of the heart, despite the coincidence of the weight of the donor and recipient of the opposite sex [23].

A weight difference in the range of 20–25%, or a donor to recipient weight ratio in the range of 0.8–1.2, are generally considered acceptable for transplantation. D.O. Taylor et al. (2007) found that a decrease in the donor to recipient body mass index ratio is a significant risk factor for an increase in 5-year mortality [24]. However, N.D. Patel et al. (2008) by analyzing the combined database of the Registry of Donor Organs for the period 1999–2007. found that 30-day mortality was highest in recipients with a donor/recipient weight ratio <0.8, but the finding was not statistically significant [25]. R.M. Reed et al. (2014) demonstrated that there was no difference in survival between underweight donor, overweight donor and the group in which the ratio by weight to the recipient was optimal. In modern clinical practice, the weight ratio between donor and recipient is considered in combination with the presence of other risk factors, such as the clinical condition and history of the donor, and the time of graft ischemia. Similarly, the body mass index (BMI) is considered most often in cases of severe obesity, both donor and recipient [16]. Thus, in the selection of a donor and the selection of a donor-recipient pair, donor weight in the absence of other risk factors is not a contraindication for heart transplantation. Recently, attention has been paid to the ratio of the mass of the left ventricle of the donor and the recipient since a decrease in survival was revealed with a mismatch in LV mass by more than 10–15% [23].

EFFECT OF CAUSE OF DONOR'S DEATH ON THE RESULTS OF HEART TRANSPLANTATION

Some single-center studies demonstrate a decrease in recipient survival and an increase in the incidence of vasculopathy of a heart transplant in the event that the death of the donor is due to non-traumatic brain damage. Suarez-Pierre et al. (2019) studied 20,244 patients who underwent heart transplantation in 2007–2016 and found no statistically significant difference in the 1- and 5-year survival rates of recipients who received hearts from donors with traumatic brain injury and donors wi-

thout traumatic brain injury. brain (vascular or another genesis). Also, no differences were found between the groups of recipients in the incidence of transplanted heart vasculopathy [26]. A study by Barac et al. (2019) and having the same goals as the above study included 58 474 patients after heart transplantation. There was no difference in patient survival, the median survival was identical between groups of patients and amounted to 12.3 years [27]. This study is the largest to date in terms of the number of patients included in it, and the results obtained should remove concerns about the influence of the cause of death of the donor on the results of heart transplantation. An earlier study by Singhal et al. (2009), devoted to the study of the influence of the cause of death of the donor on the results of organ transplantation – heart, lungs, liver, kidneys. The study looked at such causes of death of the donor as cerebrovascular disease (stroke), traumatic brain injury, anoxic brain injury, brain tumor, and other causes. The results of the univariate model of proportional risks of death of a patient (Cox) after heart, lung, and liver transplantation show that the risk ratio (RR) of death of the recipient after heart transplantation from a donor with traumatic brain injury is a reference value and is 1.0, while the risk coefficient the death of a recipient who received a heart from a donor with cerebral vascular injury is 1.20, with the death of a donor from hypoxia, the risk coefficient is less than the reference one – 0.96. The results of a multifactorial model of proportional risks, adjusted for age, sex, the presence of cytomegalovirus (CMV) infection, diabetes mellitus, dependence on tobacco and cocaine, hypertension, etc., demonstrated the preservation of survival rates of recipients depending on the cause of death of the donor [28]. Swiss researchers led by Rizzi (2016) found no effect of the cause of death of the donor on the survival of patients after heart transplantation. The study included 114 patients who underwent heart transplantation in 1997–2009. Notably, this study used known indicators of the medical status of a critically ill patient such as APACHE II, SAPS II and SOFA to classify a donor as an extended criteria donor. No difference in survival was found between recipients who received hearts from a donor with standard and extended criteria in accordance with the values of the indicated critical condition indicators [29].

HEART DONORS WITH CARDIOPULMONARY REANIMATION. DURATION OF TRANSPLANT ISCHEMIA

There is currently concern regarding the use of a donor heart from a donor with cardiac arrest and subsequent cardiopulmonary resuscitation (CPR). The key question is whether such a heart can withstand further ischemic damage that accompanies brain death, subsequent conservation, transportation, and what is important is the survival rate of recipients after transplantation of such a heart. The effect of circulatory arrest in donors on the results of heart transplantation is reflected in a retrospective study, which included 19,980 donors for the period 1994–2011, of which in 856 cases cardiac arrest was observed [30]. It was found that 1-, 5-, 10-year survival rates between standard donors and donors with circulatory arrest did not differ significantly. The same authors found that patients who received heart transplants from donors with short-term cardiac arrest (0–8 min) had better survival rates compared to other groups, including those who received a donor heart from a standard donor. As an explanation for the reason, the authors put forward the hypothesis of ischemic preconditioning, which was first described by C.E. Murry et al. (1986) [31]. A short episode of ischemia slows down the rate of ATP depletion, contributes to the preservation of intracellular structure, a decrease in oxygen consumption, retention and a decrease in cell necrosis during subsequent ischemic episodes. Thus C.E. Murry et al. (1986) suggested that multiple short-term ischemic episodes may protect the heart from subsequent ischemic exposure. Nevertheless, an increase in the duration of cardiac arrest in the donor, exceeding 25 minutes, demonstrated a decrease in the survival of recipients [30].

Similar results of the absence of a negative effect of cardiac arrest in donors on the survival rate of recipients after heart transplantation were obtained by A. Galeone et al. (2017). The study included 584 cases of heart donation in 2004–2012, of which 117 donors had cardiac arrest with an average duration of 15 minutes (5–25 minutes). The authors found that the rates of 30-day and 1-year survival in the groups with CPR and without CPR did not differ significantly, while the 10-year survival rate had a significantly better result in donors with CPR (69.4% vs 50.4%) [32]. A possible explanation for the obtained results, suggested by A. Galeone (2017), that the CPR group included younger donors. It is well known that the young age of the donor is a proven factor that has a positive effect on the survival of heart recipients [33]. In addition, the ischemic preconditioning effect of short-term cardiac arrest, described above, was not excluded [31].

Russian authors (Poptsov V.N., 2019) also studied the effect of cardiac arrest of the donor on the survival rate of recipients after heart transplantation. The study included 28 recipients who underwent heart transplantation (HT) from donors who underwent CPR from 01.01.2011 to 31.12.2017, which amounted to 4.0% of the total number of HTs for the analyzed period (n = 698). In terms of the incidence of early heart transplant dysfunction, which required the use of post-transplant mechanical circulatory support (BMC), the recipients of the “donor with CPR” and “donor without CPR” groups did not differ significantly. Comparative analysis did not reveal any significant differences in 1-, 3- and 5-year survival

rates of recipients in the two groups [34]. Thus, when analyzing the above studies, no convincing evidence was found for a decrease in the survival rate of recipients after heart transplantation from a donor with cardiac arrest. Donor CPR should not exclude the possibility of considering the donor heart for transplantation [35].

Speaking of ECDs, it is necessary to know the acceptable time limits for ischemia of the donor heart (conservation), since exceeding the time of conservation is a factor that negatively affects the survival of recipients.

There are two degrees of duration of ischemia of a cardiac transplant, optimal and long-term. The optimal ischemia is less than 180 minutes, and prolonged, more than 240 minutes. The 1-year survival rate of recipients is comparable for optimal and prolonged ischemia, although long-term data (10-year survival) are still insufficient for analysis [36]. There are studies demonstrating that longer ischemia time is associated with increased mortality in recipients [37–39]. The threshold value of ischemia of the donor heart is considered to be a value of 300 minutes with insufficient clinical data exceeding this value. In the presence of other risk factors – the elderly age of the donor, cardiovascular factors, high doses of inotropic and vasopressor support – the specified threshold for the duration of ischemia cannot be exceeded [40, 41].

MANAGED RISK IN HEART TRANSPLANTATION FROM EXPANDED CRITERIA DONORS

The selection of a donor heart is often rather difficult and subjective, despite the guidelines available for deciding whether to use a donor heart for transplantation. If one transplant center finds the donor heart unsuitable for transplant, it can and should be offered to other centers [42].

Table

Reasons Why Hearts Were Declined by first centre (n = 93)

Reasons	Primary	Secondary
Inotropic support (%)[1]	23.6	4.3
Hemodynamic instability (%)[2]	10.7	8.6
ECG changes (%)[3]	10.7	5.3
Age (%)[4]	5.3	12.6
Aggravated history	16.1	13.9
X-ray changes (%)[5]	4.3	3.2
Smoking (%)[6]	6.5	38.7
Other (%)[7]	22.8	13.1

Note. [1] – dopamine >10 μg/kg/min or noradrenalin >0.2 μg/kg/min or adrenaline >0.5 μg/kg/min; [2] – high filling pressures and low systemic blood pressure; [3] – abnormal rhythm, bundle branch block, or ST wave changes; [4] – up to a maximum of 65 years; [5] – abnormal cardiac size/cardiothoracic ratio or pulmonary oedema; [6] – up to 20 pack-years (i. e. 1 pack/d for 20 years); [7] – cerebral astrocytoma grade IV, brain tumour with unknown histological findings, hypernatremia and hyperkalemia of unknown cause and significant history of drug abuse.

A 2007 study carried out in Manchester, UK, presents an analysis of the "primary" and "secondary" reasons for refusal from a donor heart when the first and subsequent transplant centers refused. It is noteworthy that the range of failure rates of the second center according to such criteria as high doses of inotropic support, unstable hemodynamics, ECG changes is 1.5–6 times lower than that of the first center. However, according to such donor criteria as the age of the donor and smoking, the second center refused 2.5 to 6 times more often than the first, which once again underlines the serious difference between the centers in the criteria for selecting a donor heart and demonstrates the need for donor evaluation by several centers in order to achieve full use of donor resource in conditions of its deficit (Table) [43].

In the course of this study, two groups of recipients were also identified, in one (group B) hearts were transplanted from the first distribution attempt, in the second (group A) – after the failure of other transplant centers. The study found no significant difference in 30-day mortality, length of stay in the intensive care unit (ICU), and total length of hospital stay between the two groups. There was no statistically significant difference in the incidence of death from cardiac causes: 30% in group A and 22% in group B. Early graft dysfunction was the leading cause of death in 75% of cases in group A and 69% in group B. Kaplan–Meyer survival curves showed no significant difference in long-term survival (6 years of follow-up), log rank test = 0.30.

In all cases of heart donation according to extended criteria, the balance of risks and benefits associated with performing heart transplantation in a particular recipient is of paramount importance, as well as an assessment of the risk of death in case of refusal of transplantation and further stay of the recipient on the waiting list. Therefore, each decision must be made individually and carefully. Some surgeons transplant borderline hearts into high-risk recipients, believing that high-risk recipients have a chance in the event of such a transplant. Other surgeons transplant suboptimal organs into recipients with a lower risk of death, relying on the evidence that the severity of the recipient's condition is a determining factor in early survival after transplantation [44].

PREDICTIVE MODELS FOR ASSESSING DONOR HEART

As noted above, many donor and recipient factors can influence the outcome of heart transplantation. Accordingly, an objective assessment of the donor heart from the standpoint of the survival rate of recipients at different times after transplantation is an important joint task of the donor service and specialists in the field of heart transplantation. In the world for this purpose, various prognostic models are used, including both donor and recipient factors. The outcome points for which the risk is

quantified are the recipient's survival after transplantation and the decision to refuse or use a donor heart. Among the most well-known models, it is necessary to name the Index for Mortality Prediction After Cardiac Transplantation (IMPACT), the Index for predicting mortality after cardiac transplantation, developed in the USA (Weiss ES, 2011), considers 12 preoperative factors of the recipient and is maximum 50 points, allows predicting the annual survival of recipients after heart transplantation [45, 46].

J. Segovia et al. (2011) retrospectively investigated the results of heart transplants performed in one clinic in 621 recipients in the period 1984–2006. The use of multivariate analysis made it possible to identify six independent factors that increase the risk of death in recipients after transplantation, four of which are recipient factors – right atrial pressure ≥10 mm Hg. Art., recipient age ≥60 years, diabetes mellitus, dependence on inotropic support, and two donor factors – donor age ≥30 years, ischemic time ≥240 min. Based on these results, the RADIAL risk calculator was developed. The maximum number was 6 points. Each subsequent increase of one point was associated with an increased risk of primary graft failure (PGF). A score of 4–6 was associated with a more than 5-fold increase in the PGF risk (OR = 5.33, p = 0.01) [47].

French researchers led by C. Jasseron (2015) proposed their model for predicting risks after heart transplantation, considering both donor and recipient factors. The model, validated on a national pool of heart donors, has shown the effect on the annual survival rate of such recipient factors as age >50, congenital valvular heart disease, and, as a consequence, the development of cardiomyopathy, increased bilirubin levels, low glomerular filtration rate, among donor factors only female donor sex [9]. A group of researchers from the United States already known to us, led by E.S. Weiss (2012) developed the first predictive model for assessing a donor heart, considering only donor factors. During the logistic regression and multivariate model, 4 donor factors were identified that significantly affect the annual survival rate after heart transplantation – the time of cold ischemia (conservation), donor age, racial differences between donor and recipient, and urea/creatinine ratio ≥30 [10].

Using the European Registry of Donor Organs, J.M. Smits et al. (2012), created a donor heart assessment model using more than 20 donor factors. With the logistic regression method, the degree of influence of donor factors on the level of 3-year survival of recipients was revealed [2, 47].

Mention should be made of the risk stratification assessment developed using the UNOS Organ Transplant Registry to predict annual survival after heart transplantation. The assessment includes 13 recipient factors, 3 donor factors, and 2 common factors [38].

The International Heart Transplant Survival Algorithm is a predictive model of short-term and long-term survival after heart transplantation using complex modeling of 32 recipient risk factors and 11 donor risk factors [48]. Also, the combined assessment of the recipient and the donor was used in the study by J.R. Trivedi (2016), where it was shown that heart transplantation from a high-risk donor to a low-risk recipient is associated with good 5-year survival, while heart transplantation from a high-risk donor to a high- or very high-risk recipient leads to a low five-year survival rate – from 65 up to 49% [49].

CONCLUSION

With the increasing number of donors with extended criteria, the need to revise the approaches to the selection of heart donors is of paramount importance. In order to increase the efficiency of heart transplantation, select the optimal recipient for transplantation, improve the algorithms for the distribution of the donor heart, maximize the use of the donor resource, donor service specialists and clinicians need a modern tool in the form of a prognostic model for a comprehensive objective assessment of the donor heart and the recipient's risk factors in the context of the outcome of heart transplantation… For Russia, where over the past 12 years (2006–2018) the number of heart transplants has increased 25.6 times, including due to the work with donors with extended criteria, the development and use of such a prognostic model becomes extremely urgent.

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