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REVIEW ARTICLE

Donor-recipient Matching in Heart Transplantation

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Abstract:

Heart transplantation remains the treatment of choice for end-stage Heart Failure (HF). Due to the shortage of organs for transplantation and the occurrence of perioperative complications, a key problem is donor matching, which should result in increased survival and improved quality of life for patients. The success of this procedure depends on various parameters such as gender, weight, ABO blood group and Human Leukocyte Antigen (HLA) system of both the recipient and the donor. Furthermore, non-HLA antigens may also be valuable in donor-recipient matching. The aim of this article is to summarize the recent knowledge on the impact of various factors on accurate donor-recipient matching to heart transplantation.

Keywords: Heart failure, Heart transplant, Donor-recipient matching, Non-HLA, Chronic graft vasculopathy, Ventricular assist device.

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1. INTRODUCTION

Heart Transplantation (HT) is the treatment of choice for suitable patients with advanced Heart Failure (HF), whose condition deteriorates despite optimal conventional treatment [1, 2]. The most common causes of severe HF that require HT are myocardial infarction (44%), post-inflammatory cardiomyopathy (44%), congenital heart failure (3%) and end-stage of acquired heart defects (2%) [3]. Other diseases, including heart tumors, together account for 4% of transplants, while re-transplants account for 2% [3]. As a result of the worldwide increase in life expectancy and significant progress in pharmacological and interventional treatment of HF, the percentage of patients reaching the advanced stage of the disease is constantly growing [4, 5]. Hence, an increasing number of patients qualify for HT, while the number of potential heart donors has remained unchanged for years [4, 5]. This contributes to an increased imbalance between the demand for organs that can be transplanted and the number of patients awaiting transplantation. Therefore, the precise identification of patients who are most likely to benefit from HT is necessary due to the mentioned lack of organs and to avoid complications perioperatively as well as long term.

The International Society for Heart Transplantation (ISHLT) guidelines consider an insufficient number of factors in the selection of the best donor [6]. They refer to the ratio

between donor and recipient Body Mass Index (BMI), although not to other parameters affecting the prognosis of heart transplantation, such as gender, age and proper matching of the human leukocyte antigen (HLA) and ABO systems. It is worth mentioning that certain factors such as non-HLA antigens are currently not used in matching, however, due to their impact on graft outcome, they may prove useful in the future.

Many complications after HT are related to insufficient donor and recipient matching. Complications related to HT can be divided into postoperative, early and late [7]. Postoperative complications occur during the first days after surgery, early complications occur up to 1 year after surgery and late complications occur >1 year after HT [3, 7].

Postoperative complications include hyperacute rejection, cardiac tamponade and primary graft dysfunction [7]. Hyperacute rejection is a rare complication that occurs shortly after transplantation when HLA and non-HLA antigens are attacked via binding of antibodies to the allograft [7]. Early complications include the development of right ventricular dysfunction, arrhythmia, acute rejection and infections [7]. The main early complication is acute rejection; the second most common are infections [3, 7]. The mechanism of acute rejection is most commonly cellular and less often associated with antibodies [7]. Infections occurring after HT may be opportunistic or reactivate latent infections and are related to administered immunosuppression [7, 8]. Cytomegalovirus (CMV) infection affects up to 80% of transplant recipients

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depending on the immunosuppression used and requires special consideration [7]. For example, CMV infection may indirectly affect the occurrence of cardiac allograft vasculopathy (CAV) [8]. Late complications include CAV, malignancy and renal dysfunction [7]. CAV is a form of chronic rejection induced by the development of atherosclerotic deposits and inflammatory cells within the coronary arteries [7]. This complication is the main cause of late morbidity and mortality after HT [7]. Both renal dysfunction and malignancy (mostly skin cancer) are complications associated with the chronic use of post-HT immunosuppression to prevent the rejection of graft [7]. Among the drugs used in post-HT immunosuppression, calcineurin inhibitors are particularly nephrotoxic [7].

The aim of this review is to summarize the recent knowledge on the impact of various factors on effective donor-recipient matching for HT.

2. GENDER

It is well known that there are differences in the function and structure of the myocardium between genders. The male heart has a larger volume of the right and left ventricle (LV), a larger LV mass and a lower LV ejection fraction than the female heart. This explains why a female heart transplanted into a male body cannot fulfill its circulation requirements, which leads to LV overgrowth, contractility impairment and anterograde graft failure [9 - 11].

The role of gender in HT is one of the best surveyed. Already in 1998, it was known that the increase in the number of episodes of rejection and a decrease in creatinine clearance in the first year after HT were mainly due to gender mismatch [9]. The gender difference is particularly important when the donor is female and the recipient is male. In the opposite situation, the studies did not reveal significant differences in mortality [10].

It has also been shown that male recipients who received female heart transplants reveal an increased progression of coronary vasculopathy. It is suggested that hemodynamic stress related to the smaller size of the transplanted heart and gender-related differences in the immune response after HT are the causes of this phenomenon; however, the exact pathophysiological basis of this problem has not been identified [11].

Ideally, these facts should exclude women as potential heart donors for men. However, in the real world, it seems reasonable to pay special attention to men, who are the recipients of the female heart, as well as to the condition of their grafts.

3. WEIGHT

Weight is a crucial parameter, which was one of the first to be considered during matching. In the early 1990s, the rules required that the donor/recipient body weight ratio should not be <0.8 [12]. BMI is included in the ISHLT guidelines, and, as before, it is said that the difference in BMI between donor and recipient should not be $>20\%$ [6]. The guidelines also recommend, more liberally than before, that no heart should be transplanted from a donor with the bodyweight $<70\%$ of the recipient unless the organ comes from a male donor with the

bodyweight >70 kg [6]. Nevertheless, many researchers indicate that weight is not an adequate parameter for donor/recipient matching due to the fact that the main goal when selecting an organ for HT is to provide sufficient perfusion in the recipient's vascular bed, which depends more on the graft function and its size than on the donor body weight [13]. Investigations of the effect of undersized organs on mortality have shown that even if the bodyweight ratio was <0.8 , this was not associated with worse results after transplantation, when transplanting male to male, female to female and male to female donors [14]. The only group with worse results after transplantation were female donors for male recipients [14]. To explain this phenomenon, Reeds *et al.* in 2014 calculated the predicted heart mass (PHM) of both genders [15, 16]. PMH is an innovative estimated LV mass measure based on weight, height, sex and age [16, 17]. This study revealed that even if the weight and height of the donor and recipient are the same, for opposite genders, the difference between their PHM is about 19% [15]. Together with other physiological differences between the hearts of men and women described above, it may seem that BMI should be the second parameter, after gender, to be taken into account in donor-recipient matching for HT. However, the most recent reports indicate that the optimal measure of matching donor size to recipient size is PMH [16, 17]. It has been shown that PMH is a better indicator than weight, height, BMI and body surface area [17]. These findings clearly suggest that in each case, PMH should be assessed and, where possible, the transplantation decision should be considered on the basis of this indicator.

The impact of oversizing in HT was also studied. Patel *et al.* observed no difference in the 5-year mortality rate between patients with undersized, properly sized or oversized heart in the weight ratio: <0.8 , 0.8 to 1.2 and >1.2 [18]. However, Schumer *et al.* reported that oversizing of the donor improves survival in patients with Left Ventricular Assist Device (LVAD) who underwent HT [19]. As an explanation for this phenomenon, two reasons are considered [19]. The first is the need for anticoagulants when using LVAD support, which leads to increased bleeding during surgery [19]. The second is the higher incidence of pulmonary hypertension in the group of LVAD patients, which leads to higher cardiac output after HT [19].

In the context of donor-recipient size matching, Bergenfeldt *et al.* reports seem to be the most crucial. Based on data from 52,455 adult heart transplants, a donor weight $<70\%$ of the recipient's weight increases mortality in non-obese recipients, but does not affect mortality in obese recipients [20]. Moreover, the same study showed that gender mismatch increases mortality, regardless of the weight match.

4. ABO BLOOD GROUP

Appropriate blood type matching is one of the most well-known factors in the search for the right donor. The need to match the recipient and the donor in terms of ABO blood groups affects not only the prognosis after HT, but also the waiting time for the procedure itself since the most common ABO blood groups in the world are O and A and the rarest are B and AB.

The following considerations use the division of blood groups into 3 ABO compatibility groups: ABO-identical, ABO-compatible and ABO-incompatible [21].

Previous studies demonstrated that the mismatch in ABO blood group negatively affects survival after HT [22]. At the same time, it was found that the compatibility of this parameter between donor and recipient reduces the risk of acute rejection [23]. Nevertheless, nowadays, due to a large shortage of donors, it was investigated whether a minor mismatch in the ABO group negatively impacts 1-year results. Neves *et al.* demonstrated that slight differences (interpreted as ABO-compatible) in ABO did not affect the prognosis of patients after HT and may shorten the HT waiting time in patients with rarer blood groups [23]. The results of others also confirmed that an identical match does not have to be preferable to a compatible, non-identical match of ABO blood group, especially in critically ill patients who can no longer wait for an identical donor [24]. A comparable observation was made by Jawitz *et al.* However, this study showed that special attention should be paid when the donor's blood group is O, as in this case, it is associated with decreased graft survival [21]. The pathophysiological background of this phenomenon is not exactly known. It was considered whether the cause is more related to the prevalence of each blood group in the population. Since hearts from blood group, O donors are mainly transplanted to blood group O or B recipients, and group B is less common in the population, patients wait longer for an HT, and this fact is associated with their worse condition until surgery. Moreover, it is said that blood group O is the "all-embracing donor", which may be the reason why even O-group recipients may have to wait longer for their ABO-identical donor. Additionally, Bergenfeldt *et al.* demonstrated that the survival of patients <55 years of age with AB blood group, in whom the heart was transplanted from an O donor group, improved compared with patients with ABO-identical donor group [25].

Although blood groups were one of the first parameters used in HT to properly match the donor and recipient, current research seems to support the thesis that a slight mismatch in ABO groups reduces mortality as it shortens the waiting time for HT [26]. Furthermore, there are reports of acceptable results of ABO-incompatible renal grafts in adults, ABO-incompatible HT in pediatric patients, as well as reports about no differences in the incidences of deaths and re-transplants between ABO-compatible and ABO-incompatible HT [27]. Such reports suggest that ABO-incompatible HT could also potentially be more widely used in adults. Nevertheless, nowadays, this kind of transplantation is performed exceptionally due to the lack of standardization of immunosuppression protocols, high risk of rejection and unclear long-term prognosis [27]. However, various innovative methods for ABO-incompatible HT are currently under investigation; for example, placing an anti-A/B immunoabsorption column in the cardiopulmonary bypass system to remove isohemagglutinins anti-A and anti-B [28]. The absence of detectable anti-A IgM titers has been shown to remain at least until the fifth day after operation, followed by a rebound to 1:4 on day 14 and a decrease to 1:1 on day 34, which lasted until the last test performed on day 54 after

operation [28]. Such methods have promising results, which allows us to believe that incompatible AB-O transplants may be further considered in the future [28].

5. HUMAN LEUKOCYTE ANTIGEN (HLA)

HLA matching in HT seems to be one of the most controversial issues. While the significance of this parameter for kidney transplantation is rather unquestionable [29], in the case of HT, it has not been clearly determined how an HLA mismatch affects the future of the transplanted patient.

Early studies by Frist *et al.* did not demonstrate the effect of HLA matching on early graft rejection; however, the authors have shown that infections were more common in patients with lower HLA compatibility [30]. Twenty years later, Almenar *et al.* disclaimed this thesis [31]. In their study, the degree of HLA matching was not found to significantly affect the survival of patients, development of infections or episodes of rejection [31]. Butts *et al.* noticed that the higher degree of donor-recipient HLA matching is associated with reduced graft loss in pediatric HT [32]. Nevertheless, this study showed no difference in the frequency of early rejection and the development of coronary artery vasculopathy [32]. Although earlier episodes of rejection have not been detected in pediatric transplantation, in adults after HT, Kilic *et al.* have observed them [33].

The most recent studies have reported the presence of HLA Donor Specific Antibodies (DSA), which have been recognized as the most important risk factors of rejection in HT [34, 35]. In this case, HLA is used to predict possible future rejection of the graft rather than as a parameter to be considered for the donor-recipient matching.

The effect of HLA matching in HT seems to be rather vague. However, it is possible that HLA may be used in this area in the future. Ansari *et al.* based on data from 25,583 heart transplants, showed a relationship between reduced long-term survival (>15 years) after HT and a higher degree of HLA-A compatibility in patients with HLA-B and/or HLA-DR incompatible grafts [36]. Although the HLA-A mismatch was related to lower mortality due to chronic rejection, this study showed that the HLA-DR or HLA-B mismatch was not associated with improved survival [36]. In any case, despite many years of research, it is not yet clear how matching the right donor and recipient in terms of HLA has changed the prognosis after HT. Further research is needed. Regardless of the unclear role in matching, HLA, as mentioned earlier, is a useful parameter in assessing the prognosis after HT.

The association of information about DSA with the clinical outcome after HT revealed that patients who were found to have DSA are at greater risk of antibody-mediated rejection (AMR) and have worse transplant outcomes [37, 38]. It was also demonstrated that circulating complement-activating anti-HLA DSA had particularly harmful effects on the survival of solid organ graft and the risk of rejection [39]. Therefore, they may be used in the future as a biomarker for individual non-invasive patient risk stratification [39].

6. NON-HLA ANTIGENS - IMPORTANT PARAMETERS IN DONOR-RECIPIENT MATCHING IN THE FUTURE?

An important aspect, however, which is currently not

directly related to donor-recipient matching, is the presence of non-HLA antigens. Despite the progress in immunosuppression and optimal patient management, antibody-mediated rejection is still the main barrier to the long-term survival of the transplanted heart [40]. As many as 40% of the antibody-mediated rejection (AMR) of heart transplants confirmed by biopsy showed no antibodies specific for HLA of the donor in peripheral blood of the recipient [41, 42]. Nevertheless, AMR in heart transplants in the absence of anti-HLA DSA is still not well documented. Many non-HLA-specific antigens are expressed in the vascular endothelium and often occur due to stress or graft damage, but it is still not feasible to detect many of them [43]. However, antibodies directed against non-HLA antigens have been shown to be associated with dysfunction or rejection of the graft.

The best-known non-HLA antigens include major histocompatibility complex class I chain-related gene A (MICA), angiotensin II type 1 receptor (AT1R), endothelin-1 type A receptor (ETAR), vimentin and myosin [43, 44]. Anti-MICA antibodies are linked to acute rejection and AMR [45 - 47]. On the other hand, the presence of anti-AT1R autoantibodies alone prior to transplantation is not associated with cell-mediated rejection (CMR) and AMR, but when anti-AT1R and *de novo* formed donor-specific anti-HLA antibodies are present, the incidence of both CMR and AMR increases [47, 48]. This suggests that damage to the transplanted heart by anti-HLA antibodies may cause increased exposure to neoantigens, which in turn leads to the formation of anti-HLA antigens. It is also worth noting that the presence of antibodies to non-HLA antigens may increase the risk of HLA-specific antibodies [49]. New discoveries suggest that non-HLA antibodies are associated with DSA-positive AMR, although, in this case, their role is not well known [42]. Increased levels of anti-AT1R and anti-ETAR antibodies are also associated with AMR and CMR processes [47, 50]. Non-HLA antigens further influence the occurrence of transplant-associated coronary artery disease, also called chronic graft vasculopathy (CGV). It has been reported that the presence of anti-vimentin antibodies is a predictor of CGV, whereas anti-myosin antibodies and myosin reactive T-cells are involved in the pathogenesis of CGV [44, 47, 51, 52].

Commercial reagents for the determination of antibody levels against MICA, AT1R and ETAR have been available for a relatively short time, and due to the previously described reports, their value should be highlighted, especially in the case of AMR unrelated to DSA [49, 53]. These findings also prove that both HLA and non-HLA antibodies should be taken into account when assessing the patient's immune risk. Currently, donor-recipient matching for non-HLA antigen compatibility is not available, although it may be possible in the future, as this could significantly improve graft outcome. However, this topic is not currently well understood and further research is needed.

CONCLUSION

It appears that ABO-identical matching is not necessary for HT. Similarly, there is no clear evidence of the negative impact of the HLA mismatch, although DSA detection is useful in assessing the risk of rejection after HT. The most important

parameter in donor-recipient matching seems to be gender, as the physiological differences between the cardiovascular systems of women and men are very difficult to overcome. Weight is also important in ABO-identical matching; however, recent studies indicate that PMH is a more appropriate parameter to use.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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