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Revisiting the transplantation of donor heart with left ventricular myocardial hypertrophy

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Despite the widespread use of mechanical circulatory support systems, modern optimal drug therapy and various interventional methods of heart transplantation remain the "gold standard" for the treatment of end-stage heart failure patients.

At the same time the required number of heart transplants is significantly increasing due to the progressively increasing number of patients needing transplants and the actual donor pool. In recent years there has been a trend towards the increase in the number of recipients and the decrease in the number of donor organs. However, the use of donor hearts with pathological changes, including left ventricular myocardial hypertrophy, remains a controversial topic. It is believed that the use of expanded criteria significantly increases the risk of graft failure in the post-transplant period and leads to deterioration of immediate and long-

term results. This work aimed to analyze the data on using donor hearts with left ventricular myocardial hypertrophy for allotransplantation.
Keywords: heart transplantation, left ventricular myocardial hypertrophy, expanded criteria organs, expanded criteria donor, terminal heart failure

ACEi, angiotensin-converting enzyme inhibitors
BP, arterial blood pressure
HT, Heart transplantation
IVS, Interventricular septum
LV, Left ventricle
LVMH, Left ventricular myocardial hypertrophy
TNF-α, Tumor necrosis factor alpha

Introduction

Complications arising due to left ventricular myocardial hypertrophy (LVMH) of the native heart are well known. Meantime, this issue has not adequately been studied in heart transplant recipients.

In donors, this pathology may be due to the presence of diseases such as hypertension, coronary heart disease, and a number of others [1, 2]. The increase in myocardium mass associated with its hypertrophy leads to remodeling of the left ventricle (LV), the impairment of its diastolic function, and, ultimately, affects the survival [3].

It is known that LVMH is one of the main compensatory responses of the heart to an increased hemodynamic load (by pressure, volume) both at physical exercise and in pathological processes [4].

According to the recommendations of the American Society of Echocardiography, LVMH is defined as an increase in the thickness of the interventricular septum (IVS) and LV wall more than by 1.2 cm.

LVMH severity has been graded into mild (thickening up to 1.2–1.3 cm), moderate (1.4–1.7 cm) and severe (over 1.7 cm) [5].

Traditionally, two types of LVMH are distinguished: concentric and eccentric hypertrophy. Concentric LVMH is characterized by the LV wall thickness increase due to the functional overload by pressure; meanwhile, cardiomyocyte hypertrophy develops mainly due to the increased thickness of myofibrillar bundles, while the length of cardiomyocytes does not noticeably change. This type of LVMH is characterized by a high total peripheral vascular resistance, subnormal stroke volume, and an increased pulse blood pressure due to a significant stiffness of the arterial bed. Eccentric LVMH develops as a result of the volume overload and is characterized by an increased LV cavity, meanwhile cardiomyocytes lengthen by adding new sarcomeres to the previous myofibrils, and the transverse dimensions of the cardiomyocytes and the length of the sarcomere in this case do not change. Patients with eccentric hypertrophy are characterized by a high stroke volume, a relatively low pulse blood pressure, which is due to the arterial bed compliance in the absence of pronounced vasospastic reactions.

According to the classification proposed by Hill et al., an asymmetric form of LVMH has also been distinguished, which is characterized by the increased thickness of predominantly IVS.

LVMH is of particular interest in heart transplant recipients. This pathology may be observed in them in two versions: the first implies that a donor heart with LVMH has been used, in the second, the LVMH is the result of a pathological process that occurred in the post-transplant period. Both versions deserve a separate consideration.

Expanded Criteria Donors

Currently, the disparity between the demand for donor organs and the real donor pool has led to a revision of the criteria for the use of donor organs. There appeared such a concept as "expanded criteria donors", which implies a retreat from the previously accepted "strict" limits of the donor organ suitability for transplantation in favour of their liberalization to a reasonable limit. This also applies to changing the attitude to LVMH and its severity in a donor.

The initial experience of using expanded criteria donor organs involved transplanting them only to high-risk recipients. Otherwise, these patients had not been considered as candidates for heart transplantation (HT) [6].

Over the recent decade, the analysis of large HT registries has shown a cautious approach to selecting the eligibility criteria for a donor heart. For example, the analysis of the United Network for Organ Sharing (UNOS) Heart Transplant Registry in the United States demonstrated equivalent 30-day to 3-year survival rates in recipients with donor hearts without LV hypertrophy (less than 1.1 cm) versus mild LVMH (1.1–1.3 cm) and moderate LVMH (no less than 1.4 cm); however, the analysis in subgroups showed an increased risk of death in the recipients who used organs with LVMH and aged more than 55 years, as well as with transplant ischemia time no less than 4 hours, which emphasizes the need for a thorough assessment of donor risk factors in aggregate. [7].

Many donor hearts are still not used due to LV systolic dysfunction or myocardial hypertrophy [8]. A significant proportion of donors have a reversible LV dysfunction that occurs due to neurogenic stunned myocardium. This condition is caused by a high release of catecholamines, which is characteristic after brain death [9].

There is convincing evidence that donor hearts with initially reduced LV systolic function often restore this function with proper donor

conditioning and give acceptable results after transplantation [10, 11]. In fact, even the hearts of donors who have a decreased LV function during organ harvesting can be safely transplanted. A recent UNOS Registry study has analyzed postoperative outcomes of using donor hearts with LV ejection fractions less than 40%, 40–50%, and no less than 50%. The equivalent probability of the graft primary failure and death within 1 year was the same in all 3 groups. One year after transplantation, the normalization of systolic function was observed in recipients with an initial low donor LV ejection fraction [12].

The first studies with the analysis of HT operations where donor hearts with LVMH had been used showed an early transplant dysfunction and decreased survival [13, 14]. D. Marelli et al. assessed the transplant results in 37 patients with LVMH, but the wall thickness measurements using echocardiography were only shown in 6 patients. At the same time, a low 1-year survival was seen in the recipients who had a history of hypertension and the graft ischemia time more than 180 min [13]. S.Aziz et al. showed 30-day results in 9 patients who underwent transplantation of a LVMH heart (LV wall thickness more than 11 mm). That study also showed the impact of LVMH on early graft dysfunction [14]. Correspondingly the data from two studies dated from 2000 and 1997 highly likely influenced the expansion of the donor pool at the time. At least, the recommendations of those years proposed that only donors with a mild form of LVMH (less than 1.3 cm) could be used. But given the advances in therapy, as well as the ever-increasing need for donor organs, new studies have appeared showing opposed data.

In 2008, S. Goland et al. retrospectively analyzed and compared 2 groups of patients in whom HT was performed. So, 62 patients underwent the transplantation of heart with LVMH (interventricular septum or posterior wall thickness no less than 1.2 cm), and 365 patients had the

heart free of hypertrophy transplanted. The follow-up period was 3.8 years. Patients of the two groups had the same 30-day, 1-year, and 5-year survival rates. An independent analysis comparing the survival between the patients who had a heart transplant with mild or moderate LVMH and severe LVMH did not reveal any significant differences. The leading cause of mortality in the group with LVMH was not due to cardiac causes. There was also a pronounced regression of MH in response to the therapy with angiotensin-converting enzyme inhibitors (ACEi) and/or beta-blockers. That was the first study to evaluate a long-term outcome of HT with the use of donor LVMH hearts. The main conclusion of that study stated that donor LVMH did not adversely affect a short-term or long-term survival [15].

In a very recent study from 2019, M. Kittleson et al. analyzed the data of 54 patients with the donor heart LVMH of more than 1.2 cm. There were no significant differences between the recipients of hearts with and without the presence of LVMH in terms of a 1-year survival and a 1-year freedom from different types of the graft rejection and dysfunction. The authors concluded that donor's LVMH does not lead to a risk of adverse outcomes after HT [16].

Etiopathogenesis of acquired left ventricular myocardial hypertrophy

The mechanisms responsible for the development of the graft LVMH are still poorly understood, and the hypertrophy impact on HT outcome remains significant. The causes of systolic and diastolic dysfunctions of the graft include the potential mediators of hypertrophy: systemic arterial hypertension that often occurs after transplantation; an immune response due to the exposure to cytokines; as well as a response to immunosuppressive therapy. Under these conditions, myocardial

hypertrophy contributes to the diastolic dysfunction occurrence, an increased filling pressure and, as a result, to myocardial remodeling. LVMH progresses due to an increase in LV afterload caused by systemic arterial hypertension, as well as the damage to cardiomyocytes associated with ischemia and a graft rejection. The excessive production of neurohormones and arterial hypertension caused by immunosuppressants further aggravate this vicious mechanism.

S.J. Stetson et al. suggested that LVMH in patients after HT might be the consequence of a continuous expression of tumor necrosis factor-α (TNF-α) that induced the expression of angiotensin II, a known mediator of hypertrophic heart fibrosis. The levels of total collagen, of collagen type I and type III were also increased in the post-HT patients who had elevated TNF-α levels. In this regard, the authors concluded that TNF-α was a direct mediator of LV hypertrophy [17].

T. Yokoyama et al. also confirmed the role of TNF-α in myocardial hypertrophy. In their study, they showed that TNF-α stimulated the synthesis of actin and myosin as much as by several times [18].

Immunosuppressive therapy is also a significant factor in the LVMH development in the post-transplant period. The study by McKoy et al. has shown that the treatment with cyclosporine A provokes systemic hypertension, increasing the myocardium mass, compromising LV systolic and diastolic functions, and ultimately, leading to a graft dysfunction [19]. A number of studies have confirmed this conclusion [20–23].

Discussion

Despite present-day optimal pharmacological therapy, various advanced interventional and mechanical circulatory support systems, HT remains the "gold standard" in the treatment of patients with end-stage

forms of the heart failure. The main constraint to its widespread use is the pervasive shortage of donor organs. The most realistic way to solve this problem is to expand the criteria for the use of donor organs, which, with a reasonable approach, will lead to an increased number of HTs and improved treatment results in this severely ill patient population.

The HT indications and donor organ suitability parameters considered not fitting the “strict” criteria previously, have recently been revised [24–28].

In 1999, the so-called expanded criteria donor list was proposed, which allowed the extension of the indications for organ selection without a significant deterioration of HT results [29]. One of the possibilities in that list was the use of donor hearts with LVMH. Based on the studies, the permissible severity degree of LVMH in donor hearts has been changed time and again, and at present it is not an absolute contraindication for their use in HT, provided the certain conditions for selecting a donor–recipient pair are met.

Special attention should be paid to the assessment of LVMH in donors. LV walls might be thickened due to various causes: hypovolemia, myocardial edema induced by a “catecholamine storm”, which can lead to unreasonable refrain from using the organ.

However, with actual severe hypertrophy and a decrease in the volumetric characteristics of the left ventricle, which cause diastolic and systolic dysfunctions, the decision on using the organ should be made with careful consideration of each individual case.

One of the ways to slow down the myocardial hypertrophy progression, as well as the development of critical graft dysfunction, is to use ACE inhibitors after HT. ACE inhibitors have actively been used in the early postoperative period as a method to reduce preload and postoperative myocardial edema, as well as to suppress angiotensin II

formation, reduce the aldosterone synthesis, reduce the salt and water retention in the body, increase the bradykinin bioavailability. The doses of ACE inhibitors depend on patient's condition and hemodynamic parameters [30].

Thus, the introduction and use of the expanded criteria donor strategy for HT, including those in our country, have led to an increase in the number of HTs and improved treatment outcomes in severely ill patient population compared to pharmacological therapy and mechanical support of blood circulation [31]. This applies to using both the grafts with LVMH, and also those with corrected structural cardiac pathology: valvular and coronary heart disease.

Also noteworthy is the expansion of age limits in donors of an older age group with a preserved heart function when using donor organs for HT.

Conclusion

Given all of the above, the situation dictates an inevitable reasonable implementation of using the organs for heart transplantation from expanded criteria donors in order to improve the treatment outcomes in extremely severely ill patient population with end-stage forms of heart failure.

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