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Atrial fibrillation after heart transplantation

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Arrhythmias in heart transplant recipients remain an important but under-studied issue in transplant medicine. One of the most common arrhythmias, atrial fibrillation can cause cardioembolic complications in transplant recipients, in the same way as in general population and, accordingly, affect the quality of life and the prognosis. This review discusses epidemiology, classification, mechanisms of development, and therapy of atrial fibrillation after heart transplantation.

Keywords: heart transplantation, atrial fibrillation, denervation

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OHT – orthotopic heart transplantation

Epidemiology

Heart transplantation is the unique surgical radical treatment of chronic cardiac failure (insufficiency). Surgical technique of such operation implies complete transplant denervation pulmonary veins isolation and postoperative therapy administration preventing allograft rejection. These three factors define mechanisms of cardiac rhythm disturbances development in recipients and approaches to their therapy as in common population atrial fibrillation in this category of patients is independent factor, which increases the risk of ischemic insult, hospitalization frequency, worsen the prognosis and quality of life [1]. Atrial fibrillation is one of the most frequent tachyarrhythmia in patients after heart transplantation. According to the data of different authors atrial fibrillation frequency in donor recipient is from 0.3 to 24% [2-4].

It can be explained by different follow-up period and amount of patients taking part in the research. It is interesting that atrial fibrillation spreading after orthotopic heart transplantation (OHT) according to bicaval methods is lower than while using biatrial methods: 9.7% and 37.1% correspondingly [5]. Probable cause of these differences may be less frequency of tricuspid regurgitation and more complete atrial architecture. Conservation (preservation) while using bicaval technique [6]. Frequency of postoperative atrial fibrillation after transplantation is lower in comparison with other cardiosurgical procedures. Organ denervation and lung veins isolation with their trigger activity [7] promoting formation and fibrillation support cause (stipulate) less risk of these arrhythmia development after heart transplantation.

Classification

Taking into account prognostic significance and mechanisms of this arrhythmia in patients after (OHT) atrial fibrillation is classified into early postoperative (during 1 month after operation) and late (in 1 month and more after OHT) [7].

According to the data of the largest investigations (Chang et al 2013, Noheria et al 2013. Dasari et al 2010, Dison et al, 2009, Vaseghi et al 2008) early postoperative atrial fibrillation occurs in 6% of cases in 1/3 patients, it was associated with allograft rejection and is not connected with bad prognosis. Late postoperative atrial fibrillation is observed more seldom (4%) but is associated with significantly worse prognosis [3, 8-10]. According to Pavri et al atrial fibrillation in recipients is associated with three-fold increase of death risk [11]. The most frequent pathological conditions resulting in atrial fibrillation are the reaction of transplant rejection (50%); disease of allograft coronary arteries (25%) sepsis and polyorganic insufficiency (25%) [12]. Transplanted heart is considered to be the classic example of complete vegetative blockade**.** Denervation promotes sensitivity increase to the endogenous catecholamines and adenosine due to the receptors amount increase produced on the myocardium cell surface.

The absence of central nervous influence on allograft function and also surgical isolation of lung veins which takes place in the framework of transplantation allows to confirm the hypothesis that atrial fibrillation after heart transplantation is the indicator of myocardium pathological changes having ischemic or immunological genesis and also non-adequate neurohumoral background. A number of investigations [3, 7-9, 11] allowed

to identify the main causes resulting in post transplanted atrial fibrillation development (table 1).

Table 1. Causes of posttransplant atrial fibrillation

Posttransplant atrial fibrillation	
Early **(within 1 month after surgery)**	**Late** **(at 1 month expiry after surgery)**
Allograft rejection reaction Inotropic support Pericardial exudate Sepsis Primary graft dysfunction	Allograft rejection reaction Allograft vasculopathy Sepsis Delayed graft dysfunction Valve regurgitation Trigger activity in the region of superior vena cava, inferior vena cava and coronary sinus

The most frequent factors causing the development of this arrhythmia in early postoperative period is mechanical impact on heart, pericarditis, using of inotropic therapy in postoperative period, disturbance of autonomic nervous system balance and of reaction on allograft rejection [2, 4].

Duration of allograft ischemia. Long transplant ischemia promotes the damage of conductive myocard system: damaged myocard sites being substituted by connective tissue provide its myocard electrical

heterogeneity. Patients with transplant ischemia duration for more than 4 hours had higher 30 days and one year mortality [13, 14].

Denervation and reinnervation of transplantat. As mentioned above transplanted heart is characterized by complete denervation. The absence of parasympatic regulation causes high frequency of cardiac contractions in the rest and absence of heart rate variability [15, 16]. As a rule in a year after operation signs of partial reinnervation are noted, however the reinnervation degree and correlation of sympathetic and parasympathetic components differ greatly both in different patients and in the same patient in the course of time such heterogeneity makes the basis for cardiac rhythm disturbance [17].

Vasculopathy of allograft is a pathological process the basis of which is endothelial dysfunction and multiple foci development of vessel wall intima hyperplasia which results in obstructive coronary artery lesion [18]. Later myocard ischemia caused by transplant coronary arteries lesion is the trigger element for heart rhythm lesion development. Most often it leads to the development of the rhythm ventricle lesion and more seldom is the cause of atrial fibrillation [19].

Non-specific late transplant dysfunction. This term is used to denote dysfunction of cardiac transplant in the absence of allograft vasculopathy and rejection signs according to endomyocardial biopsy data. Disturbance of heart rhythm occurs due to the dilation of its chambers and electric heterogeneity development [20].

Reaction of transplant rejection. Lymphocytic infiltration, myocardial necrosis and edema developing in case of acute rejection lead to fibrosis sites in atrial myocard which are the morphological substrates for arrhythmia development [21-23].

Treatment

Treatment of donor heart recipients with atrial fibrillation depends on concrete causes and mechanisms having led to this arrhythmia in concrete patient.

Early postoperative atrial fibrillation. The approach to the treatment of this form of postoperative atrial fibrillation depends on the results of endomyocardial biopsy. If there are signs of transplant rejection, immunosuppressive therapy is intensified and repeated biopsy confirming reaction rejection resolution is performed. In case of persisting form of atrial fibrillation and if previous biopsy result did not identify rejection signs it is necessary to make repeated endomyocardial biopsy in a week. Intensive therapy of rejection reaction, normalization of electrolyte balance and discontinuation of inotropic support often promotes arrhythmia relief. Electrical cardioversion is the main method of sinus rhythm reconstitution in donor heart recipients with atrial fibrillation which in spite of the rejection treatment preserves. This method allows to eliminate the causes of arrhythmia emergence and also it is used in case of hemodynamic instability.

Antiarrhythmic drugs administration is connected with the risk of pharmacological interaction with calcineurin inhibitors and danger of severe bradycardia development requiring pacemaker usage. It is important to note that after conversion and antiarrhythmic drugs discontinuation in the absence of recurrence of rejection reaction or severe disease of allotransplant coronary arteries atrial fibrillation recurrence usually does not develop (Vaseghi et al., 2008). Thus according to many observations antiarrhythmic therapy can be stopped maximally early with following anticoagulant abolishing in a month [17].

Late postoperative atrial fibrillation

As in the case of early postoperative atrial fibrillation the development of this arrhythmia is the indicator for special endomyocardial biopsy and ultrasound research. As rejection reaction is the frequent cause of late postoperative atrial fibrillation, stress-therapy by glucocorticoids administration is recommended before getting endomyocardial biopsy results. As allograft vasculopathy risk increases with time after heart transplantation coronarography must be made with endomyocardial biopsy especially in case of combination vasculopathy with left ventricular dysfunction identified by ultrasound research. At present there is no similar opinion about anticoagulant therapy choosing and duration. Patients after heart transplantation have significant risk of bleeding in early postoperative period and they need endomyocardial biopsy to be made. A number of authors consider that all patients with atrial fibrillation need anticoagulant therapy administration not depending on CHA_2DS_2-VASc –risk [7]. One should prefer the use of new anticoagulant oral or heparins. A number of investigations demonstrated good results of catheter ablation in case of paroxysmal and persisting forms of atrial fibrillation [19, 26, 27]. If catheter ablation is made, anticoagulant therapy discontinuation is recommended in 1 month after successful surgery [27].

Features of some drugs administration

As a rule in most of donor heart recipients after the relief of the first case of atrial fibrillation, in future arrhythmia does not recur [28] and therefore antiarrythmic therapy is not indicated. Most often Amiodarone is used, and Procainamide and Flecainid are used more rarely [28].

Amiodarone. Amiodarone has long half time elimination causing longer drug interaction with calcineurin inhibitors. Amiodarone is metabolized in liver with cytochrome P450, inhibiting isoenzymes IA2, 2C9, 2D6, 3A4 and P glycoprotein activity. Tacrolimus, everolimus and cyclosporine metabolism takes place also in liver with isoenzyme CY P3A4 and protein transmitter P-Glycoprotein. Thus Amiodarone administration leads to the increasing of immunosuppressive drugs concentration in blood [29–31].

Frequent monitoring and correction of immunosuppressive drug doses need to be performed. Amiodarone optimal administration duration is not more than 3 months due to the high risk of complications in the drug interaction [28].

Taking into account long period of Amiodarone half time elimination it is necessary to continue immunosuppressive level monitoring during several weeks after Amiodarone discontinuation.

Beta-adrenoblockers and undigidroperedine blockers of calcium channels. As is was mentioned before, heart denervation causes high frequency of heart rate in rest and non-significant increase of heart rhythm in case of physical load. It is necessary to administrate such drugs with great care because they have negative chronotropic action and risk of significant decrease of physical tolerance load.

Anticoagulant therapy. Early after surgery it is reasonable to prescribe low molecular heparines or new oral anticoagulants in view of the frequent endomyocardial biopsy necessity. Varfarine administration besides its strict monitoring requires frequent analysis of cyclosporine or tacrolimus to possible drug interaction.

Conclusion

Patients after heart transplantation is a unique group of patients requiring special approach to the treatment choice in case of atrial fibrillation. Atrial fibrillation in such patients can indicate the conditions requiring immediate therapy.

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