Cardiac transplantation is one of the most effective treatments of end stage heart failure to date, although it comes with risks. One of the major complications of cardiac transplantation is allograft failure, which is caused by ischemic injuries, pulmonary hypertension and chronic rejection. Recent animal and human studies have demonstrated that cardiac lymphatic obstruction leads to significant myocardial fibrosis and depression in contractile forces. We hypothesize that lymphatic interruption, which is almost inevitable after cardiac transplantation, is a major cause of cardiac allograft failure through direct damages to the myocardium and also through the formation of allograft coronary vasculopathy.
Cardiac lymphatic interruption is a major cause for allograft failure after cardiac transplantation

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ABSTRACT

Cardiac transplantation is one of the most effective treatments of end stage heart failure to date, although it comes with risks. One of the major complications of cardiac transplantation is allograft failure, which is caused by ischemic injuries, pulmonary hypertension and chronic rejection. Recent animal and human studies have demonstrated that cardiac lymphatic obstruction leads to significant myocardial fibrosis and depression in contractile forces. We hypothesize that lymphatic interruption, which is almost inevitable after cardiac transplantation, is a major cause of cardiac allograft failure through direct damages to the myocardium and also through the formation of allograft coronary vasculopathy.

Key word: cardiac lymphatics, allograft failure, ischemia, coronary vasculopathy, cardiac transplantation.
INTRODUCTION

Cardiac transplantation has become a mainstream treatment for end-stage heart failure. Early cardiac allograft failure, which accounts for up to 25% of perioperative deaths of transplant recipients, remains a major challenge for postoperative management after transplantation (1, 2). The causes of early cardiac failure are multi-factorial. The most important etiologies have been pulmonary hypertension, ischemic injury during preservation, and acute rejection (1, 2). Long-term survival of cardiac transplant recipients is primarily limited by the development of allograft coronary artery disease or allograft vasculopathy, the leading cause of allograft failure and death after the first post transplantation year (3, 4).

The cardiac lymphatic system plays an important role in interstitial fluid balance, lipid metabolism, and immune response. After heart transplantation, the cardiac lymphatics are inevitably disrupted. Emerging evidence has shown that the cardiac lymphatic obstruction has a detrimental effect on cardiac anatomy and function in the human or animal beating heart (5). We hypothesize that disruption of lymphatic vessels following heart transplantation plays a critical role in the early or chronic allograft failure.
Impact of lymphatic obstruction on cardiac anatomy and function

Early cardiac allograft failure was defined as acute allograft failure in the early transplant period. Early cardiac allograft failure may be caused by ischemic-reperfusion damage to the donor heart, increased pulmonary pressure and acute rejection (1, 2). Chronic left ventricular failure frequently is associated with elevated pulmonary vascular resistance, and the resultant pulmonary hypertension and right heart failure remain a leading cause of early mortality.

It has been assumed that the cardiac lymphatic system is surgically expendable, and that interruption of the lymphatics has no significant adverse physiological effect. Emerging evidence from animal and human studies strongly support the critical role of lymphatic disruption in the pathogenesis of allograft failure and chronic rejection. Previous animal studies have shown that acute or chronic obstruction of cardiac lymphatic flow is associated with significant anatomical and functional changes of the heart. A majority of myocardial tissue fluid exits the heart through the cardiac lymphatic system, thus, a reduction in lymph flow may lead to myocardial edema.

Within several hours of the ligation of cardiac lymphatics, subendocardial edema and hemorrhage, ischemia-type myocardial injuries, myofibrillar degeneration, disruption of Z-band and intercalated discs, and various mitochondrial derangements may occur (6). Chronic cardiac lymphatic obstruction also induces endocardial or subendocardial
fibrosis in animal (7) and human hearts (8). Lymphatic flow obstruction is also associated with significant fibrosis within the myocardial interstitial matrix, possibly through chronic edema within the interstitium (9).

In our recent rabbit heart study, permanent lymphatic vessel ligation resulted in significant interstitial edema and enhance expression of collagen type I and type III mRNA in the ventricular tissues surrounding the left coronary artery (5). Interstitial fibrosis was also found in these animal hearts (5). In addition, the pathological changes were associated with a significant reduction in left ventricular ejection (5).

**Lymphatic obstruction and vasculopathy**

Coronary allograft vasculopathy is a major risk factor to long-term survival in the heart transplant recipients. Coronary allograft vasculopathy is an accelerated form of obliterative coronary artery disease that occurs in the heart transplant recipients. The incidence of is 5% to 10% per year of the postoperative period, reaching 50% by 5 years post-transplant (10). Risk factors for recipients and vasculopathy include the presence of diabetes, peripheral vascular disease, dyslipidemia, and native heart disease (10). Risk factors for the early onset of vasculopathy are older donor age, sex, hypertension, recipient male sex, and black race (10).

Pathologically, allograft vasculopathy is characterized by (intimal) proliferation during the early phase of the disease, and ultimately luminal stenosis of the epicardial branches and the occlusion of smaller vessels and also myocardial infarction (14).
allograft coronary vasculopathy, the involvement of coronary vasculature is much more extensive than typical atherosclerotic coronary artery disease (13). In cardiac transplant recipients who have developed vasculopathy, concentric or diffuse intimal thickening occurs in both the proximal and distal epicardial vessels and their branches (13). In typical atherosclerotic coronary artery disease however, the intimal thickening mainly develops in the proximal epicardial coronary arteries.

The mechanisms of vasculopathy are still unclear, but most researchers believe the key element leading to vasculopathy is endothelial cell injury. This initially occurs at the time of organ procurement and reperfusion, which is directly related to ischemic time (11). Damages to the endothelium predispose the coronary arteries to arterial inflammation, thrombosis, vasoconstriction, and vascular smooth muscle proliferation (12), all of which contribute to atherosclerosis and stenosis or obstruction of the coronary arteries.

There are several immunologic and nonimmunologic factors that lead to the occurrence and progression of vasculopathy. It is believed that the allograft coronary endothelial cells are closely associated with allogeneic lymphyocyte reactivity (13). Allograft coronary endothelium first gets in contact with the recipient’s dendritic cells, which are the major antigen-presenting cells that identify foreign histocompatibility molecules on the allograft endothelium (14). Dendritic cells enter the coronary circulation, capture foreign antigens at the endothelium and migrate from coronary circulation to lymphatic vessels and lymph nodes (13). Heart transplantation
interrupts lymphatic system and alters the normal migration pathways of dendritic cells, channeling dendritic cells into the general blood circulation and activating T lymphocytes (13). Once activated, T lymphocytes interact with coronary endothelial cells and enter the vascular wall, leading to chronic immune injuries and development of allograft vasculopathy (13).

**Summary**

Apart from infection and allograft rejection, allograft failure constitutes another major cause of death after cardiac transplantation. Several mechanisms for acute or chronic allograft failure have been identified in recent years. However, little is known about the role of lymphatic vessel disruption in the pathogenesis of allograft failure. Several studies have demonstrated that permanent lymphatic obstruction in animal models and in patients is associated with extensive myocardial fibrosis and significant reduction in ventricular function. Recent evidence also suggests that lymphatic vessel or flow obstruction plays a critical role in the development of allograft vasculopathy, a known cause of ventricular dysfunction and death after cardiac transplantation.

We therefore hypothesize that lymphatic disruption after cardiac transplantation is a major cause for allograft failure and postoperative mortality. Within the first few months after the transplantation, obstruction of lymphatic vessels induces myocardial fibrosis and depresses myocardial contractility, contributing to the pathogenesis of early allograft failure. Over time the disrupted cardiac lymphatic system interferes with the normal dendritic migration pathways and mediates significant injuries to the
coronary endothelium, leading to coronary vasculopathy and allograft failure.

Further studies are warranted to assess the role of lymphatic insufficiency in the development of coronary vasculopathy and allograft failure after cardiac transplantation. Results from future studies may facilitate the development of new strategies in cardiac transplantation techniques, post-transplantation care, and eventually, improve the long time survival of patients.

REFERENCES


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