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Review

Mechanisms of Chronic Cardiac Allograft Rejection

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Chronic rejection in the form of cardiac allograft vasculopathy is one of the major factors that affects long-term graft and patient survival after heart transplantation. Whereas multiple factors contribute to the development of cardiac allograft vasculopathy, immunologic mechanisms play the predominant role in the chronic rejection process, because both alloimmune and autoimmune responses are causal factors. In addition, many nonimmune donor and recipient factors also affect the development of cardiac allograft vasculopathy, including hyperlipidemia, cytomegalovirus infection, baseline coronary artery disease, and the mechanism of brain death in the donor. Modern immunosuppression maintenance therapies have the potential to limit the development of cardiac allograft vasculopathy in the long term. Further research initiatives are needed to identify patient-specific immunosuppressive drug regimens and to elucidate factors that contribute to the chronic rejection of cardiac transplant allografts. ***(Tex Heart Inst J 2013;40(4):395-9)***

Key words: *Arteriosclerosis/etiology; alloimmunity; autoimmunity; brain death; graft rejection, chronic/immunology/prevention & control; heart transplantation/immunology/mortality/trends; immunity, cellular; vasculopathy/cardiac allograft/cardiac transplant*

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Solid-organ transplantation is often the sole therapeutic alternative for long-term survival of patients with end-stage organ disease. One of the major limiting factors of sustained allograft function and, by extension, of patient survival, is chronic organ rejection. In heart transplantation, this disease process is referred to as cardiac allograft vasculopathy (CAV). Although widely thought to be the result of immune-mediated processes, chronic rejection of cardiac allografts can also be caused, either in part or in whole, by nonimmune factors. This review summarizes the roles that various immune- and nonimmune-mediated factors have on the development and progression of CAV in heart-transplant recipients.

Chronic Rejection

Chronic rejection is a multifactorial process that significantly affects long-term graft and patient survival after solid-organ transplantation. It is identified as an evolving injury that results from repeated alloimmune attack on the transplanted organ. Although chronic rejection is a diffuse process within transplanted grafts, the alloimmune insult most commonly targets the epithelium, arteries, and capillaries.[1] This indolent process leads to replacement of the normal parenchyma of the allograft with fibrous scar tissue.[2] Ultimately, these fibroproliferative changes result in the occlusion of tubular structures within the allograft, manifesting in different organ tissues as pathologically similar yet separate clinical entities.[2]

Chronic Rejection in Cardiac Grafts

Cardiac allograft vasculopathy and malignancy are the most common causes of death in heart-transplant recipients beyond the 3rd year after transplantation.[3] After 5 years post transplantation, CAV affects over 30% of patients,[4,5] and ensuing allograft failure from CAV eventually accounts for 30% of recipient deaths after transplantation.[6] Cardiac allograft vasculopathy that is diagnosed within one year after transplantation, termed early CAV, is an independent predictor of death at 5 years after transplantation.[5]

Overall, CAV is characterized by occlusive narrowing of coronary vessels.[2,6] Although it manifests itself as coronary heart disease, CAV is pathologically distinct from the usual coronary atherosclerosis.[7] Common atherosclerosis is noncircumferential, focal, and most often presents proximally within epicardial vessels. Cardiac allograft vasculopathy is present both within the epicardial coronary arteries (causing

panarterial disease with concentric longitudinal intimal hyperplasia) and within the intramyocardial microvasculature (causing concentric disease of the media).[7,8] Histologic examination of the intramyocardial microvasculature reveals not only concentric intimal thickening but the presence of plump endothelial cells.[9] Overall, the classic histologic feature of CAV is diffuse concentric narrowing with luminal stenosis.[10]

Chronic rejection is a slowly evolving process, yet intravascular ultrasound imaging has shown that most coronary artery intimal thickening occurs, in fact, during the first 12 months after cardiac-allograft transplantation.[11] In specific regard to the immune reaction, CAV results from antigen-dependent and antigen-independent immune factors, and from autoimmune factors as well.[2-6] Although numerous nonimmune entities are also implicated in the development of CAV, immune factors are the most important causes, given that CAV occurs within the arteries of the donor but not the recipient.[12]

Clinical Immunosuppression after Heart Transplantation

Since the introduction of clinical transplantation and the recognition of the role that the immune system plays in rejection, immunosuppression has become the means to short- and long-term allograft survival. Immunosuppression can be classified as induction, maintenance, and anti-rejection on the basis of the timing of therapy during the different clinical stages of organ transplantation.

Induction immunosuppression therapy in cardiac transplantation is controversial. Rates of its use vary significantly between adult and pediatric heart-transplant recipients: approximately 47% of adult patients receive induction immunosuppression, in comparison with 70% of pediatric patients.[3,13] There are still concerns about the elevated risk of opportunistic infection and malignancy after induction immunosuppression therapy.

Whereas induction therapy is not universal, maintenance therapy is the mainstay of transplant immunosuppression. Substantial improvements in the selectivity of immunosuppressant drugs have been made since the early days of clinical transplantation, which enables more targeted treatment with fewer side effects. Survival has improved as a result of the lower episodic occurrence of both rejection and infection. Current maintenance immunosuppression relies on multiple drugs from different therapeutic classes. In cardiac transplantation, the 3 classes of drugs typically in use for this purpose are cell-cycle inhibitors, calcineurin inhibitors, and steroids.[3] Most regimens in clinical use today are 3-drug protocols that use one drug from each of these 3 classes.[14] According to the most recent published review of the International Society for Heart and Lung Transplantation (ISHLT) database, tacrolimus and mycophenolate mofetil are the most commonly used calcineurin inhibitor and cell-cycle inhibitor, respectively.[3] At one year after transplantation, steroids are still part of the maintenance immunosuppression regimen of 89% of heart-transplant recipients.[15] However, new data show that 51% of patients are free of steroid use 5 years after transplantation.[3]

Although developed to target immune cells responsible for rejection, maintenance immunosuppressants can also affect outcomes of chronic rejection at the vascular level. Rapamycin, a proliferative signal inhibitor, prevents vascular remodeling and neointimal proliferation, both of which are components of CAV.[16] It has been shown that this reduction in intimal hyperplasia by rapamycin can limit or prevent the progression of CAV in recipients after heart transplantation.[16]

Alloimmunity in Cardiac Allograft Vasculopathy

Recognized as the initiators of immune injury in allografts, T cells enable both B cell antibody production and cytotoxic cellular responses.[6] Clinically, chronic rejection in cardiac transplantation has been associated with the development of donor-specific human leukocyte antigen (HLA) antibodies.[17] After an initial period of direct allorecognition that leads to early acute rejection, the indirect pathway of allorecognition is the predominant driver of the immune response.[6] The indirect pathway consists of the presentation of processed donor antigens to recipient T cells by recipient antigen-presenting cells,[2] whereas the direct pathway involves the recognition by recipient T cells of intact donor major histocompatibility complex (MHC) molecules that are on the surface of donor antigen-presenting cells.[2] A proposed semi-direct pathway of allorecognition involves the acquisition of donor MHC through cell-to-cell contact with recipient antigen-presenting cells and the subsequent activation of a host T-cell response.[2]

Animal studies show that alloreactive T cells and antibodies that are reactive to donor MHC molecules play important roles in the pathogenesis of CAV.[18] Regardless of the cause, the duration and number of acute rejection episodes, as well as donor HLA mismatch, are independent risk factors of CAV.[19] Specifically, cardiac transplant recipients who experience antibody-mediated rejection (AMR) have both a higher incidence and shorter time to onset of CAV, and the severity and number of AMR episodes correlate with increased cardiovascular death.[20] The number and duration of acute cellular rejection (ACR) episodes also increase the risk of CAV development.[5]

Acute cellular rejection is defined as the histologic recognition of an inflammatory infiltrate (which comprises, mainly, T cells and macrophages), together with the presence of cardiac myocyte damage in endomyo-

cardial biopsy samples.[21] According to the ISHLT grading system,[21] ACR is graded as follows: Grade 0 R – no rejection; Grade 1 R, mild – interstitial and/or perivascular infiltrate with up to one focus of myocyte damage; Grade 2 R, moderate – 2 or more foci of infiltrate with associated myocyte damage; and Grade 3 R, severe – diffuse infiltrate with multifocal myocyte damage □ edema, □ hemorrhage, and □ vasculitis. Most patients are asymptomatic in early rejection,[22] which underscores the need for follow-up endomyocardial biopsies after transplantation. However, a significant number of recipients with early ACR can also present with signs and symptoms of cardiac allograft dysfunction.[22]

According to ISHLT guidelines, AMR is definitively recognized as histologic evidence of capillary injury caused by humoral responses, the presence of positive immunoperoxidase staining or immunofluorescence for CD68, C4d in endomyocardial biopsies, and the detection of circulating donor-specific antibodies, all in the setting of clinical evidence of cardiac allograft dysfunction.[21,23] The most common presentation of AMR is accompanied by clinical signs and symptoms of cardiac graft injury,[22] notably the onset of hemodynamic instability in the absence of graft atherosclerosis or ACR.[23] However, it is important to recognize that ACR and AMR occur concurrently in up to 25% of acute rejection episodes.[22,24]

There are differences in the prognosis of patients, depending upon the number of recurrences of ACR and AMR. After 3 episodes of AMR, there is an incremental increase in CAV and cardiovascular death with each subsequent occurrence of AMR.[20] Heart-transplant recipients who experience AMR have a higher incidence of death from cardiovascular causes, including CAV, than do patients who experience pure ACR.[20] In addition, AMR patients have a higher rate of cardiac graft loss related to CAV than do patients with ACR.[20] Overall, heart-transplant recipients with AMR (in comparison with ACR) have a 9-fold increased incidence of CAV.[20]

A recent single-institution review evaluating ACR, AMR, and combined ACR/AMR showed that the cardiovascular mortality rate is higher in both AMR and combined ACR/AMR than in ACR.[25] Regardless of the type of rejection, CAV and heart failure are the most common modes of death.[25] In addition, patients with combined ACR/AMR, including both stable and asymptomatic patients, have a higher risk of cardiovascular death than do patients with stable ACR.[25] It has also been shown that the cardiovascular mortality risk is increased in asymptomatic and subclinical AMR, when compared with ACR.[25]

Antiendothelial antibodies and anti-HLA antibodies increase the risk of CAV, each independently of AMR.[26,27] Multiple studies have shown that patients who develop and continue to exhibit anti-HLA antibodies after heart transplantation have both a higher incidence of CAV and a lower long-term (4-year) rate of survival.[26,27] The development of antiendothelial antibodies strongly correlates with an increased rate of coronary artery disease after cardiac transplantation.[28] Similar mechanisms of alloimmunity and subsequent chronic rejection are seen in the transplantation of other solid organs, including kidney and lung allografts.[2]

Autoimmunity in Cardiac Allograft Vasculopathy

Although the alloimmune response to cardiac transplantation is the leading factor in the development of chronic allograft rejection, autoimmunity also plays an important role in the process. Studies have shown that some solid-organ transplant patients develop chronic allograft rejection even in the absence of anti-HLA antibodies. In these patients, it is thought that the presence of antibodies against non-HLA antigens contributes to chronic rejection.[2] For example, the cardiac self-antigen myosin can be the target of T cell mediated attack. In the rejection process, tolerance to recipient self-antigen can be lost, and mouse studies have shown that anti-cardiac myosin autoimmunity can develop after cardiac transplantation.[29] Sensitization with cardiac myosin before transplantation can lead to accelerated rejection of allogeneic and syngeneic heart grafts.[2] This anti-self reactivity can remain for a long period after transplantation, raising concern about its role in the development of CAV.[6]

A 2nd self-antigen that is implicated in the autoimmune response is the cytoskeletal protein vimentin.[30] It has been shown that the presence of anti-vimentin antibodies after cardiac transplantation is an independent predictor of coronary atherosclerosis.[2] The development of anti-major histocompatibility complex class I chain-related A (MICA) antibodies has also been shown to be strongly associated with CAV in cardiac allografts.[31]

Nonimmune Mechanisms of Cardiac Allograft Vasculopathy

Several additional mechanisms of injury in transplanted allografts—separate from the immune response that leads to CAV—have been identified. Hyperlipidemia frequently occurs after heart transplantation and is probably associated with the immunosuppressive regimens that patients begin at the time of transplantation.[5] It has been observed that heart-transplant patients who undergo therapy with statin medications experience a reduction in CAV incidence and severity,[32] which provides evidence of hyperlipidemia's detrimental effects in this patient population.

Cytomegalovirus (CMV) seropositivity and infection have been implicated in the promotion of chronic rejection in solid-organ transplants and have been associated with a higher incidence of CAV in heart-transplant recipients.[5,6,33-35] Ganciclovir anti-CMV prophylaxis after

heart transplantation has been associated with a significantly lower likelihood of coronary artery disease development in human patients.[6,35] Murine data show that CAV can develop as a result of CMV infection even in the absence of B cells and T cells, which probably involves a mechanism of tissue damage that is dependent upon natural killer cells.[35] In addition, *Chlamydia pneumonia* infection in heart-transplant recipients has been associated with more severe CAV development.[6] In pediatric heart-transplant recipients, the presence of adenovirus and other viral genomes in myocardial biopsies is associated with the early development of CAV.[36]

Additional factors for which evidence exists to support their role in the development of CAV include hyperglycemia, insulin resistance, the presence of baseline coronary artery disease in the heart donor or recipient, a donor history of hypertension, and increasing donor age.[3,37,38] Another causal factor thought to be associated with CAV is donor brain death. Brain death can lead to the expression of inflammatory mediators,[6] and certain causes of brain death, including explosive brain death and intracranial hemorrhage, increase the development of CAV after cardiac transplantation.[39,40] Investigators have reported an increase in recipient mortality rates after heart transplantation from a donor who sustained traumatic brain death.[41] However, the rate of allograft rejection was found to be the same regardless of traumatic or nontraumatic cause of brain death.[41]

Conclusion

Alloimmunity, autoimmunity, and nonimmune factors all play significant roles in the development of CAV after cardiac transplantation. Ongoing research efforts will probably illuminate new subtleties in the mechanisms that lead to CAV development, thereby enabling more targeted therapeutic approaches to the reduction or prevention of chronic rejection. In this manner, the major limiting factor of long-term cardiac allograft and patient survival can be dealt with in a meaningful fashion that will ultimately lead to improved patient outcomes.

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