Pediatric Coronary Allograft Vasculopathy—A Review of Pathogenesis and Risk Factors

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ABSTRACT

Coronary allograft vasculopathy is the current leading cause for late graft loss following cardiac transplantation. Its pathogenesis is multifactorial, including immune, constitutional and genetic factors, metabolism, infection, as well as potential injury from routine immunosuppressive therapy. Children represent a patient group with unique differences: their pretransplant history rarely includes ischemic heart disease and risk factors for atherosclerotic heart disease, but many are presensitized from use of allograft material during reconstructive cardiac surgeries. Compared with older children and adults, infants and young children show significantly lower rates of graft vasculopathy that may be related to the relative immaturity of their immune system.

This review summarizes the current concepts of coronary allograft vasculopathy derived mainly from animal models and adult clinical observations. It provides an overview of confirmed risk factors and explains their interactions. The characteristics and unique clinical findings among pediatric transplant recipients will be explored within the context of recent, albeit limited, scientific investigations.

Key Words. Heart Transplant; Coronary Vasculopathy; Polymorphisms

Introduction

Coronary allograft vasculopathy (CAV) is an accelerated form of arteriopathy affecting the coronary vessels of both pediatric and adult heart transplant (HTx) recipients.[1,2] It is characterized by heterogeneous intimal proliferation, medial wall thickening, and progressive luminal stenosis.[3–5] Despite recent improvements in early and midterm post-HTx survival, CAV develops in approximately one third of pediatric patients within 10 years of transplant and continues to be an immutable barrier to longer-term graft survival.[6] This review will outline the current pathophysiologic understanding of this complex disease process and detail commonly reported constitutional, infectious, and immunogenetic risk factors in order to provide a framework from which current therapies have been and may be developed. While much of the following discussion will focus on pediatric risk factors, the reader should be cognizant that published data on childhood risk factors is less robust than in adults. Therefore, some factors may be notably absent not because they are necessarily irrelevant in pediatrics, but rather because of limited data or an unknown association with disease.

CAV Pathogenesis

CAV shares many aspects of its pathogenesis and many risk factors with arteriosclerosis of the nontransplanted heart.[3] In adults, ischemic heart disease is the leading cause necessitating heart transplantation. In these patients, the partial persistence of the atherosclerotic process after transplantation partly explains the higher frequency of CAV compared with children. However, the difference in incidence is only marginal when comparing adults with teenagers, an age group that in nontransplanted individuals usually does not experience significant atherosclerotic vascular disease.[7]

In addition to these constitutional factors, which include mainly genetic and metabolic predispositions, a large contribution to CAV stems from the immune response toward an immunologically foreign organ. The operative procedure of transplantation from a deceased donor enhances
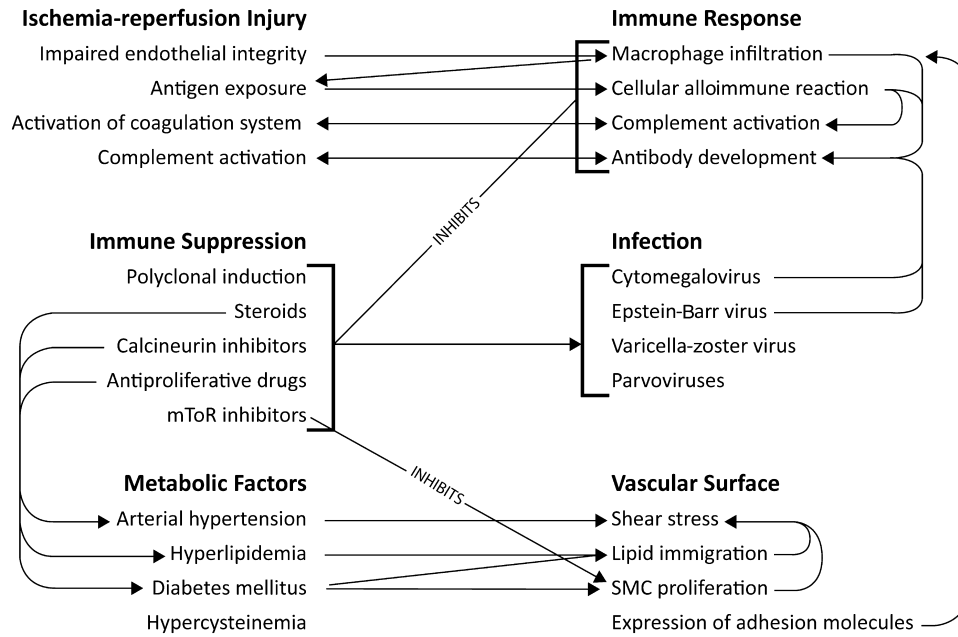
Ischemia-reperfusion Injury
Impaired endothelial integrity
Antigen exposure
Activation of coagulation system
Complement activation

Immune Response
Macrophage infiltration
Cellular alloimmune reaction
Complement activation
Antibody development

INHIBITS

Immune Suppression
Polyclonal induction
Steroids
Calcineurin inhibitors
Antiproliferative drugs
mToR inhibitors

Infection
Cytomegalovirus
Epstein-Barr virus
Varicella-zoster virus
Parvoviruses

INHIBITS

Metabolic Factors
Arterial hypertension
Hyperlipidemia
Diabetes mellitus
Hypercysteinemia

Vascular Surface
Shear stress
Lipid immigration
SMC proliferation
Expression of adhesion molecules

Figure 1. Overview of the pathogenetic factors of CAV and their interaction: Arrows symbolize enhancing effects, bars inhibition. Ischemia-reperfusion injury includes damage to the endothelium facilitating macrophage invasion and leading to exposure of graft antigens and activation of the complement system. This triggers an early response of the adaptive immune system, which is enhanced if preformed graft specific antibodies are present, but also yields their development if no appropriate immune suppression is introduced. Adverse effects of the immune suppressants include enhancement of constitutional factors of atherosclerosis and increased risk for infections with negative impact on CAV. Viral infections under immune suppression may enhance antibody production (Epstein-Barr virus) and have additional direct effects on endothelium integrity (cytomegalovirus). Formation of plaques in the lumen perpetuates itself through increasing shear stress and further disturbance of the endothelial integrity and subsequent enhanced immune response. mTOR inhibitors have antiproliferative effects on small muscle cell delaying the progression of graft vasculopathy. For details, see text.

this response. To further complicate matters, immunosuppressive medications and certain infectious complications of immune suppression also contribute to CAV pathogenesis. These factors show significant overlap and interaction as schematically shown in Figure 1 and detailed in the following sections.

Ischemia-reperfusion Injury and Early Immune Activation

The process of CAV in HTx recipients can be traced to the time of graft transplantation when donor-derived factors, which may likely contribute to future CAV, have already been activated.[8] Because the basis for heart donation is brain death, the vast majority of donated hearts have undergone a period of significantly impaired circulation and oxygen delivery often including a cardiac arrest. Inotropic support and fluctuations of the blood pressure are common, if only transiently, in

many patients. Subsequent apoptotic processes in the tissue and activation of the donor immune system and coagulation are initiated, including complement, macrophages, and thrombocytes. In addition, the process of brain death is associated with multiple neurohormonal changes that may adversely affect the coronary endothelium. Immediately following brain death, circulating plasma catecholamines markedly rise resulting in an imbalance between oxygen delivery and consumption.[9,10] The resulting ischemic damage to the graft leads to impaired integrity of the endothelium and activation of the innate immune system[11] causing endothelial alteration that persists post-HTx.[12,13] Following organ harvest, a period of cold ischemia further contributes to this process and especially enhances the disturbance in the endothelial cell function and the vessel wall integrity.[14] In animal models, loss of smooth muscle cells (SMCs) in the intima media at this stage is significantly associated with the degree of later CAV.[15] A

recent study observed the SMC reduction to occur in two waves, one at the initial day post-HTx and one 7 days later.[16] The decrease of SMC density occurred significantly less in absence of neutrophil granulocytes (NCs).

These models confirm the current understanding of the early events: preexplantation damage and preservation-associated ischemia induce disturbed integrity of the endothelial barrier[17] promoting invasion of components of the innate (NCs, macrophages) and adaptive immune system in both donor and recipient.[4,18] Apoptosis occurs in various cells in the intima yielding exposure of human leukocyte antigen (HLA) and other antigens[17] that are recognized and processed by the recipient adaptive immune system including both CD8 and CD4 positive T cells[18] and B cells.[19] At the same time, a highly immunogenic environment persists within the graft through activation of the complement and the coagulation system and secretion of cytokines and chemotactic factors by the injured endothelium.[14] Microscopic changes within the vascular wall accompanying these processes include interstitial fibrosis, invasion of NC, macrophages and lymphocytes, primarily reduced numbers and secondarily increased proliferation of SMC, and infiltration of lipids with formation of foam cells.[4,16]

Mechanical Factors and Atherosclerotic Impact

Once changes are initiated, the vessel narrowing, plaque development, and local activation of thrombocytes perpetuates the endothelial injury. Shear stress associated with the altered vessel geometry and perfusion hemodynamics is further enhanced by increased arterial blood pressures.[20–22] The latter is a very common finding in post-HTx patients. In children, hypertension is often attributed to the immunosuppressive medication (steroids, calcineurin inhibitors [CNI])[23] but is also due to progressive renal impairment as observed in the majority of patients.

Mammalian target of rapamycin inhibitors sirolimus and everolimus play an ambivalent role in the pathogenesis of CAV: their antiproliferative capacity does not only impair the adaptive immune response but additionally reduces proliferation of SMC and NC, hampering the progression of the vascular narrowing. On the flipside, particularly in combination with CNI, the majority of patients experience an unfavorable shift in plasma triglyceride and cholesterol levels and profile,[23] increasing the risk for development of

atheroma-associated vasculopathy. Similar concerns accompany other immune suppressive agents. As described previously, steroids and CNI induce hypertension in a significant proportion of patients through direct effects but also secondary to renal injury. Both drugs may also alter metabolism leading to less favorable lipid profiles and development of diabetes mellitus.[23] However, the use of synergistic effects in combined immunosuppressive regimens was found to reduce incidence of CAV[24–26] with the latest trials showing less new development and progression of CAV when combining a CNI with an mammalian target of rapamycin inhibitor compared with mycophenolate.[27] The adverse effect of infection, particularly virus-induced enhanced generation of antibodies against the graft, will be discussed later. Finding the right balance between sufficient immune suppression and adverse effects of the medication is therefore crucial, but often challenging.

Chronic Rejection and Antibody-mediated Immune Response

In any organ transplantation not originating from an identical twin, the alloimmune response occurs from the moment of reperfusion of the organ. Significant concentrations of preformed antibodies against the donor HLA or blood group antigens induce immediate massive activation of all arms of the immune system, a situation clinically experienced as "hyperacute rejection." Antibody-mediated activation of the complement system leads to direct graft damage but also chemotaxis, attracting antigen presenting cells as well as lymphocytes including CD8+ cytotoxic T cells. Surfaces covered in antibodies are opsonized to antigen presenting cells facilitating activation of the adaptive immune system. This includes generation of antigen specific CD4+ T cells, B cells, and plasma cells and yields further antibody production and direct cytotoxic effects on the graft.

Consistent with findings in adults[28] and other transplanted organs,[29] clinical studies in heart transplanted children found not only a higher mortality in presence of donor-specific HLA antibodies (DSAs) but a higher incidence and accelerated progression of CAV.[30–33] Compared with adults, development of DSA is less frequent in children and associated with older age at transplant.[34]

Multiple investigators have linked acute allograft rejection with pediatric CAV,[24,35] particularly recurrent rejection during the first post-HTx

year.[2,36] In the Pediatric Heart Transplant Study group analysis, Pahl and colleagues found that two or more episodes of acute rejection in the first year correlated with CAV.[37] Late rejection (>1 year post-HTx), including that associated with hemodynamic compromise, is also a well-established risk factor for CAV development.[2,24,36,38–40] In a large, single-center experience, Mulla and colleagues reported that both frequent (regardless of severity) and severe episodes (even in the absence of other rejection episodes) of late rejection are independent predictors of CAV development, and the resulting CAV can have a rapid onset and accelerated course.[38]

Most of these studies have not investigated the presence of DSA in their patient cohorts. Development of DSA is associated with the frequency of acute cellular rejection.[41] In part, the detrimental effect of repeated acute cellular rejection may be mediated through de novo DSA. However, graft vasculopathy occurs in absence of DSA. The development of DSA as well as repeated acute rejection may both be surrogates for insufficient suppression of the immune system. Every episode of rejection will, to some extent, result in an episode of vascular damage comparable with the previously described cascade during reperfusion and the early post-HTx phase.

Genetic Predispositions

Variations in small sections of DNA, including single nucleotides, between individuals that occur with some regularity in the human population—typically at least 1%—are known as genetic polymorphisms.[42] The presence of a polymorphism does not imply that it is pathologic, and much research is currently ongoing to determine which of these naturally occurring genetic variations may be disease-causing. In recent years, an increasing awareness of potentially pathologic polymorphisms affecting the inflammatory response has led to several publications describing the role of polymorphisms in determining the risk of CAV. Because there have been no large-scale pediatric publications examining polymorphisms and CAV, the following discussion will review currently available adult data assuming some pediatric relevance to encourage new hypothesis-driven investigations.

Immune System Polymorphisms

Intracellular adhesion molecule-1 (ICAM-1) is an adhesion molecule present on the surface of leukocytes and endothelial cells. When stimulated by inflammatory cytokines, ICAM-1 expression is markedly increased.[43] When Borozdenkova et al. studied ICAM-1 polymorphisms in both HTx donors and recipients, they found that donor hearts expressing a particular ICAM-1 polymorphism had significantly decreased incidence of CAV at 2 years post–orthotopic heart transplant.[44]

Interleukin-6 (IL-6) is a proinflammatory cytokine released by myocardial and endothelial cells.[45,46] It has many effects that may contribute to the development of CAV including SMC growth,[47] production of C-reactive protein,[48] modulation of endothelial permeability,[49] and triggering neutrophil oxidative burst.[46] The IL-6 gene is known to be polymorphic with a single nucleotide exchange resulting in a phenotype with increased IL-6 production.[50] Densem and colleagues sequenced adult HTx recipients and found that being homozygous for the high-production IL-6 allele was significantly associated with an earlier onset of CAV.[51]

Transforming growth factor-beta 1 (TGF-β1) is a cytokine that influences the accumulation and function of leukocytes and fibroblasts at sites of injury while enhancing production of extracellular matrices,[52] which may contribute to the development of CAV. However, TGF-β1 also inhibits smooth muscle and endothelial cell proliferation,[53] which may be protective against CAV. The gene encoding TGF-β1 has multiple polymorphisms, and, as such, reports on the effects of these polymorphisms are contradictory. Holweg and colleagues found that in HTx recipients, a specific polymorphism at locus site +869 was a risk factor for accelerated CAV, while a polymorphism at locus site +915 was not a significant predictor.[52] To the contrary, Densem and colleagues found directly opposing results.[54] The explanation for this discrepancy is unclear, but nevertheless, TGF-β1 appears to have a role in the pathogenesis of CAV, and additional studies may further elucidate its significance.

Tumor necrosis factor-alpha (TNF-α) is a cytokine released primarily by macrophages that initiates a host of responses that can precipitate coronary endothelial dysfunction,[55,56] and some CAV patients have been found to have high levels of circulating TNF-α.[57] However, when Densem and colleagues evaluated the influence of TNF-α polymorphisms on CAV development, they found no relationship between recipient or donor genotype and CAV development, despite a significant proportion of recipients and donors having high

TNF-α producing genotypes.[55] In contrast, Ternstrom and colleagues studied recipient TNF-α and its linked cytokine gene, TNF-β,[58] finding an increased CAV prevalence and decreased 3-year post-HTx survival among patients homozygous for high cytokine producing polymorphisms of either TNF-α or TNF-β. The discrepant results between the two studies may be due to methodologic differences. While more compelling data is needed, polymorphisms in TNF-α and TNF-β could become important pretransplant markers with TNF-α suppression as a potential therapeutic target in at-risk recipients.

Coagulation and Thrombocyte Activation

Alterations in fibrinolytic activity may also be important in CAV intimal proliferation as the involved enzymes promote vascular cell migration, cellular infiltration, and matrix regeneration.[59] Enhanced fibrinolytic activity can result from excessive tissue plasminogen activator (TPA) or decreased activity of plasminogen activator inhibitor-1 (PAI-1), a TPA inhibitor.[60] Polymorphisms of both the TPA and PAI-1 genes have been previously described.[60–62] In one such study, Benza and colleagues[60] found significantly increased freedom from CAV at 24 months for PAI-1 high-expression homozygotes (100% freedom) and heterozygotes (92%) compared with low expression homozygotes (45%). No association was found between TPA polymorphisms and CAV. In a recent follow-up study, the same investigators corroborated their previous findings and demonstrated severe CAV in transplanted PAI-1 knockout mice.[59] Thus, PAI-1 activity appears to prevent CAV development and may be a future therapeutic target.

Platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) both regulate differentiation of vascular progenitor cells.[63] PDGF regulates progenitor cell differentiation into SMCs, while VEGF regulates differentiation into endothelial cells. Both factors may contribute to CAV pathogenesis by expanding sites of coronary injury through smooth muscle and endothelial cell proliferation.[64] Both genes have polymorphisms at multiple sites.[65,66] Tambur and colleagues[64] recently demonstrated that specific PDGF and VEGF polymorphisms were significantly associated with an increased incidence of CAV and decreased 3-year patient survival.[64]

The renin-angiotensin system has been postulated to be a significant contributor to the pathogenesis of CAV,[67] and inhibition of the renin-angiotensin system is now standard therapy to prevent progression of CAV.[68,69] A component of that system, angiotensin converting enzyme (ACE) has well-recognized polymorphisms, ACE-D and ACE-I, in humans,[70] and a specific genotype (ACE-DI) may increase atherosclerotic coronary disease and myocardial infarction in non-HTx adults.[71,72] Pethig and colleagues ACE genotyped 146 patients and serially assessed them for onset and progression of CAV finding that the three ACE genotypes had differing freedoms from CAV by 6 years post-HTx.[73] In ACE-II and ACE-DI patients, freedom from CAV was 85% and 77%, respectively, while ACE-DD patients had only a 55% freedom from CAV ($P = 0.015$). Cunningham and colleagues[74] evaluated donor ACE polymorphisms and found ACE-DI grafts had significantly increased prevalence of CAV.[74]

Clinical Relevance

The current role of genetic polymorphisms in clinical decision making is very limited, and, with few exceptions, the study of polymorphisms has been limited to single genes. However, multiple inflammatory pathways and cytokines interact during the inflammatory response. Given the complex interplay and high level of redundancy of the immune system, understanding how a single polymorphism modulates expression of a single cytokine adds little to understanding how the inflammatory cascade affects CAV pathogenesis. Until studies evaluate large numbers of patients comparing both genetic and nongenetic risks of CAV, the clinical utility of polymorphisms for risk stratification or treatment guidance will remain limited.

Metabolism

While hypercholesterolemia is a risk factor for CAV in adult patients and treatment with statins may ameliorate its effects,[75] cholesterol levels have not been associated with CAV in pediatric patients. Nonetheless, hypercholesterolemia is prevalent in pediatric HTx patients, particularly those on cyclosporine immunosuppression, and statin therapy decreases both low-density lipoprotein cholesterol and total cholesterol levels in these patients.[76,77] In a single-center study by Mahle and colleagues, treatment with pravastatin in post-HTx children was associated with a lower incidence of CAV.[39] As high low-density lipoprotein cholesterol has been associated with coronary disease in adults, including CAV, so, too, has low

high-density lipoprotein cholesterol.[78,79] A recent, small pediatric study demonstrated an association between low serum levels of high-density lipoprotein cholesterol and CAV in patients already on statin therapy.[80] However, small patient numbers and an abnormally early onset of CAV in these study patients limit the generalizability of these results to a larger pediatric HTx population. While the relative contribution of cholesterol chemistry to pediatric CAV is unclear, because of the beneficial effects of statins on CAV noted in adult studies their use has nevertheless become routine in many pediatric transplant centers.

Finally, elevated plasma homocysteine (Hcy) levels are a recognized independent risk factor for coronary atherosclerosis.[81–83] Both adult and pediatric HTx patients have been demonstrated to have elevated plasma Hcy.[84,85] Further, adult HTx recipients with severe CAV have significantly higher plasma Hcy levels when compared with HTx recipients without evidence of CAV.[86,87] No association between pediatric Hcy levels and CAV has been established. The exact mechanism through which Hcy affects CAV remains unclear; however, Hcy is known to damage vascular endothelium through prooxidative pathways leading to impaired endothelial vasodilation and intimal hyperplasia.[86,88,89] Treatment of both adult and pediatric patients with folic acid has been shown to decrease Hcy levels in patients with abnormally high Hcy levels.[90,91] In adults, this led to improved survival 7-years posttreatment, although the benefit may not be exclusively related to a decrease in cardiovascular events.[92] Hcy and treatment of hyperhomocysteinemia warrant further study in pediatric CAV.

Infection

Cytomegalovirus Infection

The role of cytomegalovirus (CMV) infection in pediatric CAV remains controversial. CMV may contribute to atherosclerotic plaques by modulating chronic inflammation in arterial walls.[93] A similar process may contribute to CAV lesions in transplanted patients. In adults, multiple studies have demonstrated an increased risk of CAV after both CMV seroconversion and symptomatic CMV infection.[94–97] Notably, most adult data cites "CMV mismatch," a CMV-negative recipient of a CMV-positive heart, as a CAV risk factor. A large, single-center retrospective pediatric study demonstrated that recipients who are CMV-positive prior

to transplant have a significantly higher rate of CAV.[98] Post-HTx CMV replication appears to impair recipient endothelial function, and this may provide a substrate for the development and progression of CAV.[99] A recent clinical study evaluating intravascular ultrasound as a modality to detect CAV found that CMV-positive patients had significantly increased coronary maximal intimal thickness compared with CMV-negative patients.[35] To the contrary, a recent multicenter study of 1568 patients from the Pediatric Heart Transplant Study group found no correlation between donor or recipient CMV status and CAV.[100] These discrepant results may be partially explained by differences in the proportion of infants in each study, differences in CMV prophylaxis and differences in CAV detection methods. A definitive role for CMV infection in the pathogenesis of pediatric CAV remains unclear.

Non-CMV Viral Endomyocarditis

Other viral endomyocardial infections have also been associated with CAV. In a large study of pediatric HTx patients, polymerase chain reaction identification of viral genome in myocardial biopsies, particularly adenovirus, was associated with adverse clinical events including increased rejection, graft loss, and early CAV development.[101,102] Moulik and colleagues recently found that viral endomyocardial infection is an independent predictor of graft loss in children likely secondary to premature development of CAV.[103] Historically, many of these viruses have been causally linked to acute rejection that can accelerate CAV (as previously described). It is unclear whether the viruses themselves led to the development of CAV, or if CAV was indirectly associated with virally mediated rejection. In the study by Moulik et al., parvoviral endomyocarditis was not associated with rejection but was a significant risk factor for CAV.[103] The precise mechanisms by which viral infections are associated with CAV, whether independent of rejection or not, remain elusive. However, many investigators suspect these active myocardial viruses may lead to an inflammatory state that potentiates ongoing coronary inflammation and subsequent CAV. In this setting, natural killer (NK) cells may be important mediators of CAV. Graham and colleagues developed a model for CAV using post-HTx mice that lacked functioning B and T cells.[104] Virally infected mice subsequently developed CAV, while noninfected mice did not. Furthermore, infected mice in which NK cells were depleted had a significantly lower inci-

dence of CAV supporting the role of NK cells in virally mediated CAV development.

Constitutional Factors

Hypertension

Hypertension is a well-established risk factor for cardiovascular disease in adults.[105,106] In concordance with the pathophysiologic mechanisms described previously, hypertension is significantly associated with CAV in post-HTx adults,[107] and treatment with antihypertensive medication delays CAV progression.[108] Despite the lack of published data for pediatric CAV, given its strong association with coronary disease in other populations, blood pressure control is a mainstay of post-HTx therapy.

Age

Compared with adults, the cited incidence of CAV is lower in children with reported 5-year freedom from CAV of 50%[109] and 85%[110] in adult and pediatric transplant recipients, respectively. Pahl and colleagues demonstrated that recipient age was a relative risk for CAV. They found that a patient aged ≥12 years at transplant had a 2.9-fold increased likelihood of developing CAV compared with a child transplanted at ≤5 years.[37] This corroborates data from other studies showing an increased incidence of CAV among older age transplant patients.[40] The incidence of CAV in adolescent patients is similar to adults.[6] As a corollary, there is a lower risk of CAV in infant transplant recipients.[35,111] The higher freedom from CAV in pediatric patients may be related to a lack of donor/recipient atherosclerotic risk factors or preexisting coronary endothelial injury that usually predisposes adult patients to an increased incidence of disease.[7] As such, older donor age has also been recognized as a risk for pediatric CAV with incremental increases as donor age increases to an ultimate threefold increase if using donors >30 years old compared with younger donors.[37] This may be partially attributable to older donors frequently having increased cardiovascular risk factors for atherosclerosis, but in addition, intact immune function within the donor myocardium may affect endothelial function after transplantation thereby increasing the potential for donor-mediated CAV.[37] Detection methods may also affect reported frequencies of disease as widespread use of intravascular ultrasound has significantly increased detection rates among adult patients.

Pediatric patients, especially infants and toddlers, are immunologically privileged in the setting of organ transplantation due to various immaturities of the immune system reflected in an annual CAV incidence of only 3% in children transplanted in the first year.[6] Children demonstrate a decreased incidence of immune-mediated endothelial injury,[7] lack immune memory,[112] are unable to mount T-independent B cell immune responses under 2 years old,[113] are less likely to develop donor-specific HLA antibodies post-HTx,[34] and are able to persistently tolerate blood group incompatible organs.[114,115] Thymectomy, which routinely occurs in children with congenital heart disease for reasons of surgical access, may also contribute to the better graft acceptance of infant recipients. The thymus plays a crucial role in the development of adaptive immunity and self-tolerance, and this procedure alters the total number and the phenotype of T cells for many years.[116,117]

Retransplantation

Although patients retransplanted for CAV fare better than those retransplanted for early graft failure, overall survival after pediatric retransplantation is inferior to survival after primary transplant.[118] The International Society for Heart and Lung Transplantation 2010 pediatric HTx report found that retransplantation was significantly associated with early onset CAV.[6] The reasons for this are not completely clear; however, the proportion of sensitization against HLA or minor antigens is likely higher due to the exposure to nonself-antigens and the previous development of a "successful" immune response against the first graft. Further, the higher likelihood of cofactors having developed through years of immune suppression and associated adverse events may contribute. In particular, children with early graft failure show poor graft survival following retransplantation in registry data;[6] however, this is likely impacted by their overall poorer clinical condition going into the surgery.

Summary

CAV pathogenesis represents the complex interplay of a variety of factors. Medical intervention for one factor may increase the risk of another developing or worsening. Close monitoring of the various contributors to CAV is required and therapy must be adapted to changes in the balance of risk factors. The intensity of immune suppression needs to be carefully balanced with potential adverse effects of the medication. Contribution of

altered lipid profiles, arterial hypertension, and diabetes mellitus, whether caused by genetic predisposition or subsequent to medication, have to be addressed by appropriate medication. Infectious disease monitoring as adapted in the recent decade allows more timely intervention when required. Donor-specific antibodies represent a major contribution to CAV; however, despite increasing evidence that acute antibody-mediated rejection can successfully be treated with invasive antibody removal and therapies to inhibit antibody development, the impact of these treatments on the progression of CAV remains indeterminate.

CAV remains the leading challenge for long-term graft survival. An incomplete understanding of its pathogenesis has limited the development of therapies directed at process reversal or avoidance. Further study, particularly in the pediatric HTx population, is necessary to better elucidate mechanisms of disease and potential targets for future therapeutic intervention.

Author Contributions

Dr. Schumacher was responsible for article concept and design, comprehensive review of the literature, drafting the article, and critical revision of the article.

Dr. Gajarski was responsible for article concept and design and critical revision of the article.

Dr. Urschel was responsible for article concept and design, comprehensive review of the literature, drafting the article, and critical revision of the article.

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