Transplant coronary artery disease in children

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Abstract

Transplant coronary artery disease is an accelerated vasculopathy that occurs in adult and pediatric heart transplant recipients, and it is a leading cause of death among late survivors. This form of coronary disease, also known as graft coronary disease, differs from classical atherosclerosis in both histologic and angiographic features and it progresses much more rapidly. Although its pathogenesis has not been determined precisely, both immune and non-immune mechanisms appear to contribute, with a final common pathway of endothelial injury due to both antigen-dependent and antigen-independent factors. Many investigators believe both cellular and/or humoral rejection play a direct role in its etiology. In children the true incidence of the condition is unknown, although a multicenter survey identified 58 (7.2%) patients among 815 transplant recipients at 17 centers. Detection remains difficult. In the past, non-invasive methods have been unsatisfactory, although recent experience has suggested that Dobutamine stress echocardiography may be promising. Once a diagnosis is made, treatment has been limited to palliation by either intracoronary interventional procedures or surgical coronary bypass grafting, and to cardiac retransplantation with its own set of problems. Current efforts are directed at prevention. Blood levels of cholesterol have been reduced in adults treated with Pravastatin, but there have been no reports of its use in children. In adults additional agents with potential benefit have included calcium channel blockers and ACE inhibitors. A multicenter trial in children is needed to answer the many remaining questions regarding transplant coronary disease in this age group. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Transplant coronary artery disease is an accelerated coronary arterial vasculopathy that occurs in heart transplant recipients, both children and adults, and it is a leading cause of death among late survivors [1–3]. The pathogenesis is unclear, although numerous theories have been proposed. The exact prevalence of the condition in children has not been de-termined, but in adults the complication has been found in 5–10% of recipients each year after transplantation [4]. Current treatment is limited to palliation or retransplantation, and preventive medical strategies are in clinical trials.

1.1. Terminology

Transplant coronary artery disease has been referred to by several different terms (Table 1). Although there is certainly an overlap, using these terms interchangeably can be confusing for several reasons. Humoral rejection should be reserved for episodes with specific histologic changes in complement and fibrin deposition, as described by Hammond et al. [5].

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Table 1
Synonyms for TCAD[a]

Chronic rejection
Vascular rejection
Humoral rejection
Graft arteriopathy
Allograft vasculopathy

[a] TCAD: transplant coronary artery disease.

Chronic rejection can refer either to coronary disease or to refractory or recurrent cellular rejection. Vascular and humoral rejection are used interchangeably, but vascular rejection has been equated with transplant coronary artery disease. Both graft arteriopathy and allograft vasculopathy are acceptable terms, although transplant coronary artery disease is preferred.

1.2. Pathology

The classic allograft lesion consists of progressive concentric myointimal proliferation that involves the entire length of the coronary artery, including small branches, and ultimately results in luminal occlusion (Fig. 1) [6]. There is smooth muscle proliferation and increased production of matrix leading to fibrosis. Platelet-derived growth factor, basic fibroblast growth factor, and other substances are produced that sustain the vicious cycle, and cytokines cause additional damage to the allograft cells [7,8]. Transplant coronary artery disease has histologic and angiographic characteristics that are quite different from classical atherosclerosis (Table 2) [2,8].

1.3. Pathogenesis

Research is ongoing to determine its exact pathophysiology. Previously, some clinicians thought that coronary disease in the allograft was related to immune factors, with implications for both cellular and humoral arms of the immune system. Others believed that traditional risk factors for atherosclerosis played the leading role. Most likely both immune and non-

Table 2
Pathology

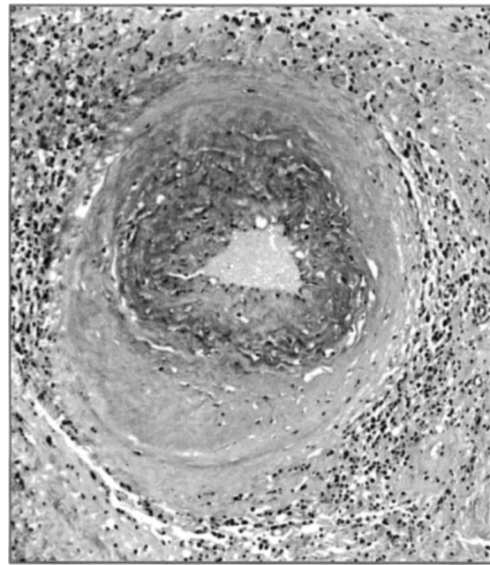| TCAD lesions	Atherosclerotic lesions
Concentric	Eccentric
Diffuse	Focal
Distal	Proximal
Major and small	Epicardial
IEL[a] intact	Disrupted IEL[a]
Rapid progression + Vasculitis	Indolent
	No inflammation

[a] IEL = internal elastic laminus.

Fig. 1. Postmortem histopathologic section of left anterior descending coronary artery from patient who died suddenly 8 years after heart transplantation. Note the extensive myointimal proliferation with obliteration of the coronary lumen. A mononuclear cell infiltrate is evident in the adventitia and a small number of lymphocytes infiltrate the vascular wall. Hematoxylin and Eosin, 20 × .

immune mechanisms are contributory, and the final pathway of endothelial injury is due to both antigen-dependent and antigen-independent factors.

A heterotopic animal model, using two strains of rats (Lewis and F344) with only minor mismatches, has been used extensively to study transplant coronary artery disease. Russel, who implicates activated macrophages producing cytokines as a mechanism of allograft injury, describes the model in a detailed review [9]. A summary of other basic research in this area is found in the proceedings of an international symposium on allograft coronary disease [10].

1.4. Immune-related factors

1.4.1. Cellular rejection
In 1987 Uretsky demonstrated that two or more major rejection episodes were associated with the development of transplant coronary artery disease [1]. Others have shown similar associations. In a review of 2138 adult patients in 38 centers, the Cardiac Transplant Research Database found two risk factors for the development of transplant coronary disease: the number of rejection episodes during the first year after transplant and the development of rejection associated with hemodynamic compromise during that same period of time [11]. In pediatric recipients we confirmed the relationship between cellular rejection and the development of transplant coronary artery disease [3]. Autopsies in children demonstrated obliterative intimal proliferation, areas of fibrosis, and

variable lymphocytic infiltration [2]. Nevertheless, some studies in adults have not conclusively linked cellular rejection to the subsequent development of transplant coronary artery disease [12].

1.4.2. Humoral rejection

Some investigators have related the type of rejection to the occurrence of transplant coronary artery disease. Using endomyocardial biopsies, Hammond et al. found that deposition of immunoglobulin and complement in coronary arteries — a sign of humoral rejection — was associated with transplant coronary disease [5]. However, in adults this association remains controversial and it has not been demonstrated in children.

1.5. Non-immune mechanism

The contributions of immune and non-immune factors account for the rapid progression of transplant coronary artery disease. In recipients with significant traditional risk factors for coronary artery disease, the placement of an allograft will lead to progression of coronary damage at a much faster rate. A large multicenter adult study that focused on pre-operative risk factors and detection of transplant coronary artery disease found incidences of 11%, 22% and 45% at 1, 2 and 4 years after transplantation [4]. On multivariable analysis, the strongest risk factor was advanced donor age. Because of this finding, hearts from male donors older than 35 years are often avoided for pediatric recipients because of the higher risk of pre-existing atherosclerosis. Although severe disease occurred in only 5% of the multicenter adults, it was highly predictive of subsequent coronary events. Recipient characteristics such as older age, gender, obesity, hypertension, blood lipid levels, smoking, and diabetes can all contribute to transplant coronary artery disease (Table 3). Identification and evaluation of specific risk factors for pediatric patients is planned as part of a prospective multicenter investigation of transplant coronary artery disease by the Pediatric Heart Transplant Study (PHTS). Adult studies have found an association between active cytomegalovirus (CMV) infection and the development of transplant coronary artery disease, but the mechanism is speculative and evidence is conflicting [13]. A report by Johnson et al. reviews the non-immune risk factors in adults [14].

2. Incidence

We reported the findings of a multicenter study of children with transplant coronary artery disease identified by either autopsy or angiography [3]. The true

Table 3
Non-immune risk factors

Age	Blood lipids
Gender	Smoking
Obesity	Diabetes
Hypertension	CMV infection

incidence and prevalence of transplant coronary artery disease could not be determined from this retrospective survey, since only the worst cases were identified. This complication was reported as the primary cause in 24% of all deaths. The 17 centers performed 815 transplants and identified 58 patients (7.1%) with transplant coronary disease. Affected patients included 16 children under the age of 2 years and several neonates. The mean age at diagnosis in this group was 9.9 (0.2–26) years and the mean interval of time between transplant surgery and diagnosis was 2.2 (0.1–7.7) years. Mortality was high with only nine of 58 patients alive, although by design the study identified only the most severe cases. Cellular rejection correlated with transplant coronary artery disease. Moreover, 60% of affected patients had a history of four or more treated cellular rejection episodes as well as lympholytic treatment of rejection. Recently, data obtained from the PHTS registry indicated an incidence of transplant coronary artery disease of 0.4% per year based on angiographic detection, and a risk of death from the complication of only 2.1% during the first 5 years after transplantation [15].

3. Detection

Often patients are asymptomatic until they develop heart failure or sudden death as the initial presentation of transplant coronary artery disease. Because they have denervated hearts, transplant patients seldom experience warning signs of angina. Transplant centers have focused on better methods for early detection and modification of risk factors.

3.1. Non-invasive methods

Most non-invasive methods for the diagnosis of transplant coronary artery disease, such as exercise echocardiography and nuclear stress imaging, are insensitive because the disease is diffuse and most isolated perfusion defects are not imaged, leading to false-negative studies [16]. Dobutamine stress echocardiography, the most promising of the non-invasive techniques, compares the regional wall motion of 16 left ventricular segments at rest and stress. Adult studies have correlated Dobutamine echocardiography with angiography and more recently with

intravascular coronary ultrasound [17]. The sensitivity, specificity, positive and negative predictive values of these studies are fairly high and superior to any other non-invasive methods previously used in adults. Two studies in children have found a high correlation between abnormal Dobutamine stress echocardiographic results and poor outcomes of death or need for retransplantation [18,19]. In Larsen's study of 72 children, Dobutamine stress echocardiography was compared to coronary angiography with a sensitivity of 72% and a specificity of 80% [19]. Dobutamine stress echocardiography is a safe and useful screening technique, which may play an increasing role in risk stratification, even in pediatric patients. Its biggest limitation is its requirement of a high level of skill and experience for both the echocardiography technician and cardiologist to avoid false-negative studies [18].

3.2. Invasive methods

Although traditionally considered the gold standard, angiographic detection of transplant coronary artery disease is fraught with problems. The types of angiographic coronary lesions seen in children are similar to those in adults. They include focal lesions, diffuse concentric lesions, and abrupt obliteration with loss of distal branches [2]. The recognition of coronary angiographic abnormalities is insensitive and findings of severe disease are associated with a poor prognosis, as in the patient with severe coronary obstruction shown in Fig. 2. The angiogram was a routine annual study in an asypmtomatic 3-year-old child who had heart transplantation at 8 months of age. This patient died 17 days after the angiogram was obtained while the family was considering retransplantation. In another patient moderate obstruction on angiogram (Fig. 3) corresponded to near total obstruction (Fig. 4) when the coronary arteries were examined histologically at explant 6 weeks later. Although the angiographic lesions did not appear severe, he had significant hemodynamic impairment 5 years after initial transplant and was listed for retransplantation. A third patient, now 9 years after transplantation, remains alive almost 2 years after a coronary angiographic study showing severe diffuse disease (Fig. 5).

Once the disease is recognized by coronary angiography, survival rates are dismal, as confirmed in a large multicenter study of adults [4]. At 5 years after transplant coronary disease was mild in 27% of patients, moderate in 8%, and severe in 7%. Costanzo et al. found that 91% of patients were free of severe transplant coronary artery disease, including significant clinical events. Once mild disease was diagnosed, the likelihood of progression to severe disease was 19% by 5 years [4]. Some pediatric centers advocate relisting at the time of diagnosis of any coronary angiographic abnormality, because of the poor prognosis with severe disease and the tendency for angiography to underestimate the degree of involvement. Other centers are more conservative and relist only children with either abnormal hemodynamics, rapid progression, a positive stress echo, or systolic left ventricular dysfunction. Since natural history data is not yet available in children, if patients are not relisted

Fig. 2. Selective cineangiogram of right coronary artery. Note the severe narrowing of the mid-portion of the vessel.
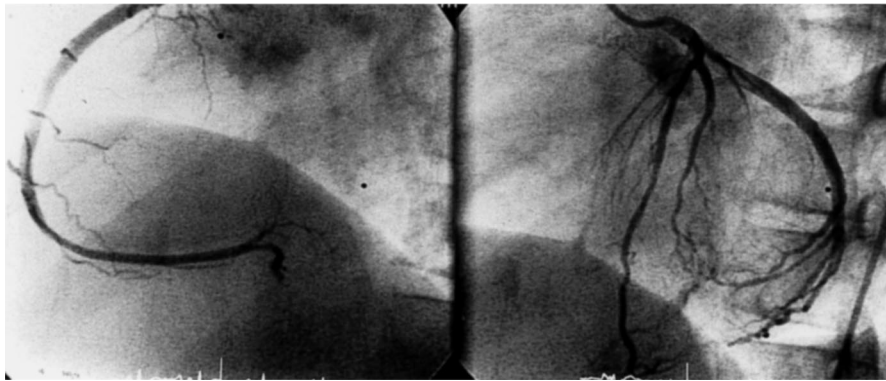
Fig. 3. Selective right and left coronary angiograms showing graft dysfunction in a patient 5 years after transplant.

when 'mild' disease is recognized it seems appropriate to follow them closely with serial angiography.

Intravascular coronary ultrasound, in conjunction with coronary angiography, has the greatest sensitivity and is routinely used in many adult transplant centers. In adults intracoronary abnormalities have been demonstrated despite normal appearing coronary angiograms [20]. In one study the prevalence of any coronary disease was 88% by coronary ultrasound but only 15% by angiography, making the diagnosis of 'mild' disease suspect [21]. This study found that patients with an intimal thickness of less than 0.3 mm were less likely to have angiographic evidence of coronary disease, whereas in others an intimal thickness greater than 0.5 mm was correlated with clinical events. Attempts to classify the severity of disease using intracoronary ultrasound may be important in the ability to predict more accurately the prognosis of these patients. In the only report in children, 44

studies compared intracoronary ultrasound to coronary angiography. With intravascular ultrasound 25% of the children had severe disease, although only one demonstrated signs of severe disease by angiography [22]. In our center intracoronary ultrasound is performed in all transplant patients over 30 kg. Experiences with additional studies in children will be necessary before conclusions can be made.

4. Treatment

Because of the diffuse nature of the disease, coronary angioplasty and surgical bypass have limited use in the treatment of transplant coronary artery disease [23]. Nevertheless, the reduction in luminal obstruction is similar to that achieved in non-transplant patients, and both treatments can be appropriate in selected cases. A more recent study reports favorable experiences with coronary stenting for transplant coronary artery disease when compared to angioplasty alone [24]. Directional atherectomy and laser techniques, although palliative, may be even more effective. None of these procedures has been reported in pediatric transplant recipients so far.

Retransplantation remains a difficult choice to consider, particularly in a compliant patient with severe coronary artery disease. Because of the scarcity of donors, especially for the adolescent, retransplantation is feasible in very few patients. Survival after retransplantation has improved in adults, and there have been reports of its success in children. The first series of pediatric heart retransplantation described 17 patients from four centers, including 11 children with graft coronary disease. Coronary disease developed in the new allograft 3–16 months post-operatively in three patients, and survival rates at 1 and 3 years were only 71% and 47% [25].

Recently Razzouk et al. reported on retransplantation for transplant coronary artery disease in 14 pediatric patients with survival rates of 83% at 1 and 4
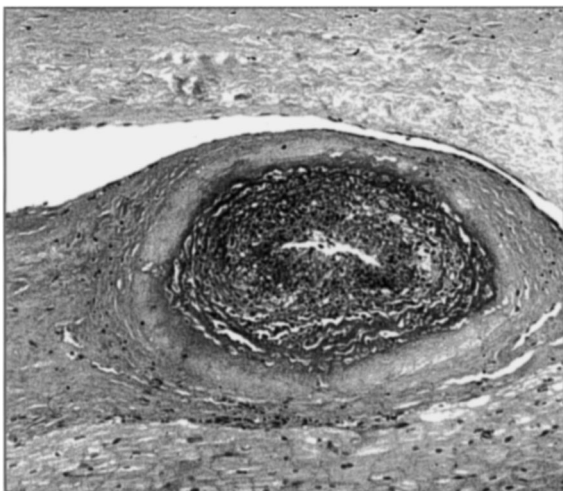

Fig. 4. Histology of the explanted heart from the patient whose angiograms are shown in Fig. 3 demonstrates severe luminal narrowing of the proximal left anterior descending coronary artery due to neointimal proliferation. A sparse lymphocytic infiltrate is present within the perivascular fibrous tissue. Hematoxylin and Eosin, 20 ×.
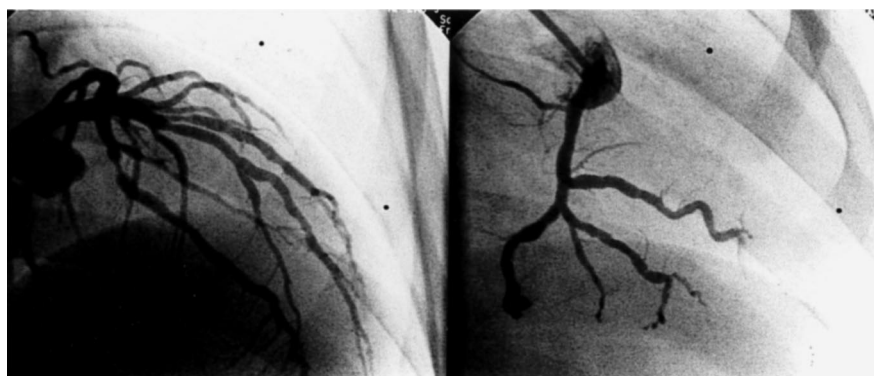
Fig. 5. Selective right and left coronary angiograms demonstrating diffuse coronary disease in all major and minor branches.

years after surgery, which compared favorably with survival after primary transplantation [26]. Once a diagnosis of transplant coronary disease is made, the decision to offer retransplantation should be individualized on the basis of the extent of disease, evidence of graft dysfunction (left ventricular systolic dysfunction) or inducible ischemia (abnormal stress echocardiography), and the likelihood of compliance with medical management during long-term follow-up.

5. Prevention

Several pharmacological strategies have been aimed at prevention and treatment of transplant coronary disease, with accumulating evidence of benefits in both animal and human trials. Unfortunately, introduction of Cyclosporine and Tacrolimus have not made an obvious impact on the prevalence of transplant coronary artery disease, despite fewer episodes of acute rejection than with Azathiaprine and corticosteroid regimens. The new immunosuppressive agent, mycophenolate mofetil (Cellcept), may have both immunosuppressive and antiproliferative effects.

Animal and clinical studies of ACE-inhibitors and calcium channel blockers have been reviewed by Mehra et al. [27]. A slightly lower incidence of angiographic evidence of coronary artery disease has been found in patients receiving long-term treatment with Diltiazem [28]. In an animal model, however, Diltiazem failed to suppress intimal proliferation [29]. ACE inhibitors have been shown to have a beneficial effect in reducing intimal proliferation in a heterotopic rat model, and rats treated with Captopril had much less cellular rejection and transplant coronary artery disease then controls [30]. The authors speculated that the mechanism for reduced intimal proliferation was either a direct inhibition of angiotensin II or a suppression of platelet derived growth factor.

HMG-COA reductase inhibitors, Pravastatin in particular, may be useful in the treatment of transplant recipients for several reasons. In a randomized study, Kobashigawa et al. demonstrated effective lowering of blood lipid levels with Pravastatin [31]. Recently this same group of patients, re-evaluated up to 5 years later, demonstrated persistent benefits, including a reduction in acute rejection and a diminution in intimal thickness measured by serial coronary ultrasound studies.

In a recent study of children who had heart transplants at our center, 40% had fasting levels of total cholesterol greater than 200 mg/dl, regardless of the dosage of Prednisone or the interval of time since transplant [32]. Among our patients with transplantation we use Pravastatin in those children with fasting total cholesterol levels greater than 200 mg/dl, LDL-cholesterol levels greater than 110 mg/dl, or the presence of transplant coronary artery disease. Whereas this policy is probably not routinely used in the management of pediatric transplant patients, many adult transplant centers treat all patients with HMG-COA reductase inhibitors, regardless of the blood lipid profile.

6. Conclusions

Transplant coronary artery disease is a serious problem that develops in many young transplant recipients. It can be insidious and its first manifestation can be sudden death. The pathogenesis appears to be multifactorial and preventive strategies are under development. Treatment involves palliation with interventional intracoronary procedures and/or retransplantation in selected individuals. A further understanding of the true prevalence, quantitative analysis of risk factors, and the natural history of transplant coronary artery disease will require significant additional prospective multicenter studies.

Acknowledgements

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